Introduction to Neurobiology

Avinash Bala Singh, PhD

Introduction to Neurobiology

INTRODUCTION TO NEUROBIOLOGY

Open Edition

AVINASH SINGH

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INTRODUCTION

Introduction to Neurobiology is aimed at undergraduate students new to the field of neurobiology. The first edition specifically targets students enrolled in **BI360 Neurobiology** at the **University of Oregon** and primarily contains topics covered in that course. The textbook is modified from a combination of from two existing open texbtooks: Foundations of Neuroscience by Casey Henley, and Introduction to Neuroscience by Valerie Hedges. An introduction to Bioelectricity has been added. Figures and text have been added, and edited or modified as needed. Citations are being added as appropriate.

As established by Casey Henley, original text follows principles of Universal Design for Learning: multiple means of representation will be provided for students to engage with the content. Clear, accessible text will be divided into short, easily digestible chapters that focus on one concept. Numerous images and animations will be paired with the text, and a captioned video version of the text is shared for each chapter. The text is written with the undergraduate student that is new to neuroscience in mind. Neuroscience terminology will be introduced in an easy-to-understand manner, and supporting content will be clear and concise to minimize cognitive load not associated with understanding new material.

Each chapter will end with an interactive quiz for student self-evaluation of the content. All quiz answers (i.e. both correct and incorrect) will provide feedback, so students can self-check their understanding at the end of each concept and receive immediate feedback about their learning.

Find errors or have suggestions? Email avinash at uoregon dot edu.

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ADAPTATION STATEMENT

This book is an adaptation of two introductory neuroscience OER. Chapters 3-8, 10-17, 19-29, 35-38 and 44 were adapted from *Foundations of Neuroscience* by Casey Henley which is licensed CC BY NC SA. Chapters 1, 2, 9, 18, 30-34, 38-43, 45-49 were adapted from *Introduction to Neuroscience* by Valerie Hedges which is licensed CC BY NC SA. Valerie Hedges's book is also an adaptation of Casey Henley's book and another introductory neuroscience OER. Many chapters from both Henley's and Hedges' versions were excluded from this book.

Avinash Singh, the author of *Introduction to Neurobiology*, made significant changes to several chapters, added citations as needed, and contributed a new *Bioelectricity* chapter. He also made significant changes to many of the figures in this book. All the figures that he contributed are licensed under the same license as the text. Figures by Henley and Hedges have license statements included in the caption.

WHAT IS NEUROBIOLOGY?

What is Neurobiology?

Neurobiology is the study of the structure and function of the nervous system, the collection of nerve cells that interpret all sorts of information which allows the body to coordinate activity in response to the environment.

Neurobiology has taught us that the brain is a complicated organ with several connection routes, both between different bodily organs and within itself. Some of those connections communicate information down towards the body, such as signals that allow us to control the movements of our muscles or to change the activity of our internal organs. Other connections ascend into the brain, conveying all sorts of information from the world around us into a representation of our surroundings. Still, other routes communicate between brain areas, such as when the sudden detection of a threat passes through our visual system and turns into a "get ready" signal that then prepares the rest of our body for conflict. Because of this complex system of communication, the nervous system can be thought of as a series of highways and roads that connect different cities (organs).

Resources

- Scientist links to learn more
- Glossary Terms
- Key Takeaways
- Test Yourself

The nervous system conveys all of these different types of information using a combination of electrical and chemical signals. The main active cellular units of the nervous system, the **neurons**, are highly sensitive to changes in their environment. A wide variety of chemicals called **neurotransmitters** are responsible for passing information between neurons.

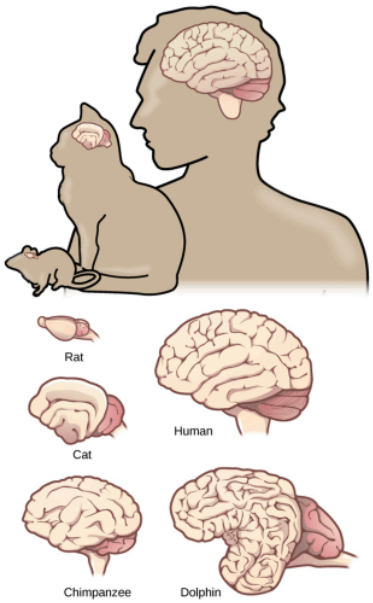


Figure 1.1. Brain size comparison between different vertebrate mammals. Brain images are shown for a rat, cat, chimpanzee, human, and dolphin. There are similarities in the layout of the structure of the brain across all species.

Neurobiology is the biology of the brain, while Neuroscience is an integrative field of study

Realistically, our modern understanding of "neuroscience" is a combination of several academic disciplines, all using their strengths to understand some aspect of the nervous system. Because of this integrative nature, it is possible to study neuroscience from many different perspectives, each of them more fitting for answering different types of questions. These "angles" of analysis are described below.

Biology

At the root of the study is biology. Whenever you are studying living processes, such as learning, visual perception, or consciousness, you dip into the realm of biology. The broad field of biology can be subdivided into smaller, more precise categories. Molecular neurobiologists study proteins and gene regulation, cellular neurobiologists examine how networks of neurons communicate with one another, and cognitive neuroscientists study the underlying causes of behaviors. Understanding neuroscience involves genetics, such as the autosomal dominant neurodegenerative condition Huntington's disease. Other biological sub-disciplines, such as

ecology and evolution, are also considered in neuroscience as well, such as the parasite Toxoplasma, which changes an animal's response to fearful stimuli, allowing the organism to reproduce as it moves through different species in the food web.

Psychology

Psychology provided the earliest explanations about the brain and ideas about the origin of the mind. Some questions in this field branched off from philosophy as people began thinking about the "mind–body problem", the discussion that centered around the question of whether a function as complex as consciousness could result from the activity of a clump of cells. Psychologists also wondered whether parts of the brain in isolation have different properties than when those parts are working together. This property, called emergence, is the idea that the whole is greater than the sum of its parts. Psychologists examine neuroscience from a top-down view, aiming questions at understanding the whole organism before looking at smaller components of the organism (compare this with biological approaches, often a bottom-up view that starts at the level of cells or molecules).

Chemistry

Chemistry is a strong influencer of nervous system function—just ask anyone who forgot their morning cup of coffee! We use a variety of endogenous (originating from within the body) chemicals that act as signaling molecules, allowing communication between cells. These chemicals exist in many different structures, which determine their function; some are acidic while others are basic, some are polar, others are fat-soluble, and some are even gases. The nervous system is also highly sensitive to influence by exogenous chemicals (meaning they originate from outside the body), such as caffeine and cocaine.

Physics

Many principles of physics can be observed through the functioning of neurons. For example, neurons maintain a negative electrical charge, usually measured on the scale of tens of millivolts (a millivolt is a thousandth of a volt.) The main way for neurons to send signals depends on a temporary change in this voltage; this signal is called an **action potential**. This change in voltage is brought on by the movement of charged ions across the cell membrane, and they closely follow the rules of magnetism: opposite charges attract while like charges repel.

Mathematical Modeling

The field of computational neuroscience has grown from the use of mathematical modeling to describe or predict some aspect of the nervous system. If our current estimates are correct, we have around 86 billion neurons in the brain, a number so large that it is difficult to conceptualize. It would be nearly impossible to understand that many components of a system without taking advantage of the sheer mathematical strength of a computer.

Healthcare Providers

Healthcare providers, like neurologists and psychiatrists, work from a different angle. They coordinate closely with researchers to apply scientific knowledge from the field or laboratory to treat patients, thus using biological principles as therapies. For example, neurologist Dr. Oliver Sacks used his knowledge of the dopamine neurotransmitter system to treat patients with a paralysis-like condition in the 1960s, leading to the development of levadopa treatment for **Parkinson's disease**. Other healthcare providers use imaging strategies like a CT scan to assess the extent of a head injury or the location of a brain tumor, while an **EEG** can be helpful for the diagnosis of **epilepsy**.

Engineers

Engineers help develop the tools needed to understand questions in neuroscience, such as the patch clamp rig or electron microscope, highly specialized pieces of lab equipment. They also work closely with healthcare providers to translate science into therapy, such as the deep brain stimulator devices for the treatment of conditions such as **Parkinson's disease**. Collectively, all the people who participate in neuroscience in some way are united by their interest in the workings of the body. Because of the overwhelming complexity of the nervous system, there are many questions still unanswered. The continual appearance of new questions in neuroscience keeps us wondering, inspires curiosity, and promises a multitude of fascinating career paths for centuries to come.

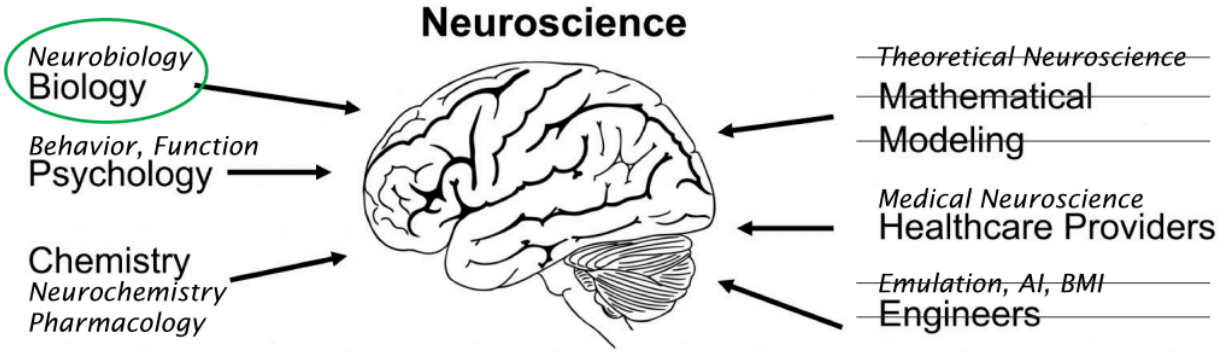


Figure 1.2 Neurobiology is one of the areas of study that contribute to our understanding of how our brains work. Many fields contribute to our understanding of modern neuroscience including biology – which we will focus on, and others that we will only cover when they impact biology – psychology, chemistry, mathematical modeling, healthcare providers, and engineers.

How do we learn about neurobiology?

Experimental design

The gold standard in science is the use of **experimental design**. In an experiment, the scientist uses a stepwise process of developing a research question and hypothesis, then answering that question by performing tests. The main goal of an experiment is to establish a causal relationship between one factor that is being changed, the independent variable, and the factor that is influenced, the dependent variable. A well-designed experiment has variables that are carefully controlled, which minimizes the influence of extraneous variables, often called confounding variables. The influence of confounding variables can be eliminated by comparing the experimental group with a control group, a group that is as similar as possible in every way except for the manipulation of the independent variable. Importantly, subjects or patients are generally assigned to the experimental or control group at random.

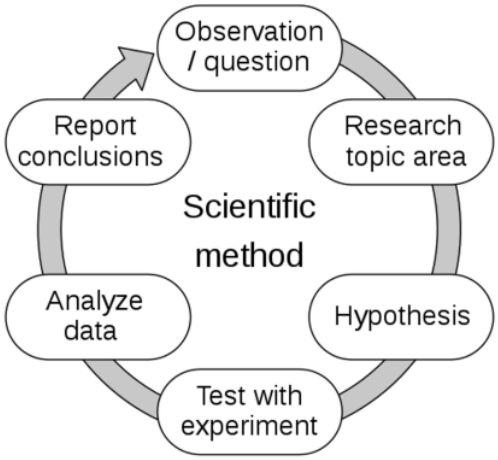


Figure 1.3 The Scientific Method. The Scientific Method starts with the development of a research question or observation that will lead to a research topic area and hypothesis. The hypothesis is tested through experimentation and analysis. The results of the experiment are then communicated via a report, which can further support additional observations or questions.

Case Studies

Another strategy is the **case study**, a highly detailed description of a single patient and their condition. A case study documents the details regarding a specific deficit or enhancement and is an opportunity to examine individuals with very rare conditions, which are useful for informing about the functions of different brain structures. Like a quasi-experimental study, case studies only show correlation, not causation. It is difficult to generalize the findings from a case study to the population at large.

Perhaps the most famous case study in all of neuroscience is the 1848 story of the railroad worker Phineas Gage. Gage was a construction foreman working on the railroad when an unfortunate explosive workplace accident caused a iron rod to be driven through his left frontal lobe, largely destroying it. Remarkably, Gage survived this accident and lived another 12 years. However, Gage's acquaintances described subsequent changes in his personality, teaching us that one of the functions of this area of the brain is regulating our inhibitions.

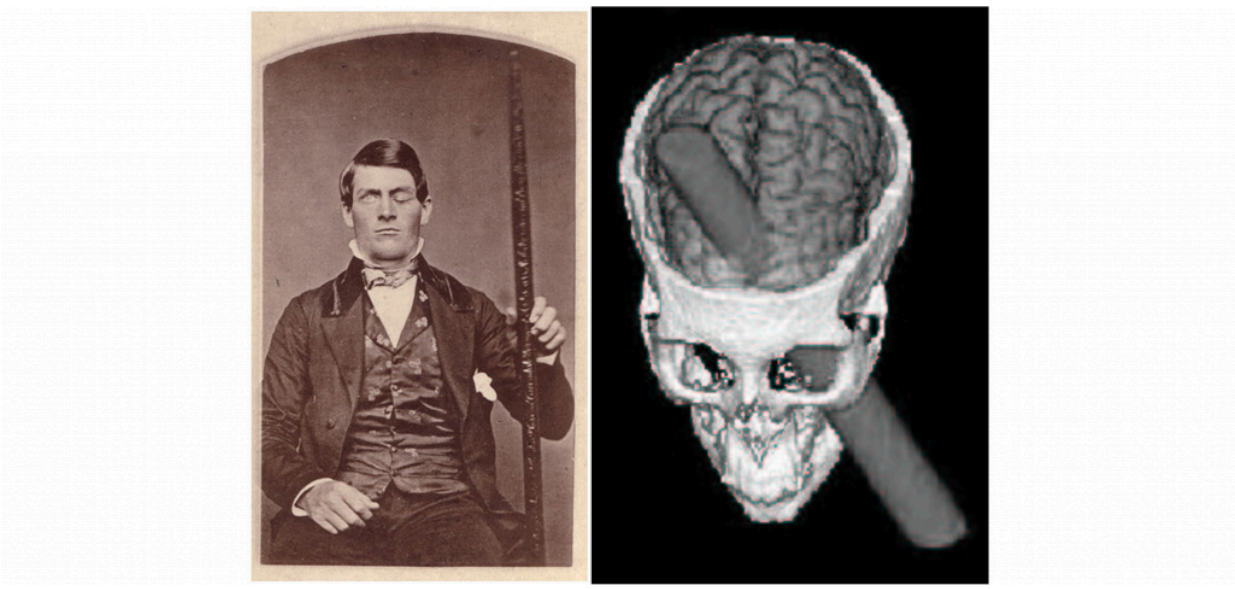


Figure 1.4 Image of Phineas Gage and his site of injury. The figure on the left is an image of Phineas Gage holding the iron rod that caused his injury. The image on the right shows a Magnetic Resonance Image rendering of the location of the rod in the injury. The rod entered below the left eye and damaged much of the left frontal cortex.

Case studies can be helpful for the development of hypotheses that can later be tested experimentally. For example, consider another famous case study of Patient HM, the man who had his left and right hippocampus surgically removed and couldn't create certain types of memory. A research question based on this case study might be: "Is the hippocampus needed for the creation of navigational memory?" Then, an experimental study could be performed in rodents, where we surgically remove the hippocampus (experimental group) or a different part of the brain (control group) and see how well the rodents perform on a memory task.

The Use of Animals in Research

Though there are many ways that we can directly study humans through experimentation or case studies, it is often impossible to test every question in humans. Instead of always studying humans, scientists often use nonhuman model organisms, the most common organisms being the worm *C. elegans*, fruit flies (*Drosophila melanogaster*), zebrafish (*Danio rerio*), song birds, mice, rats, and macaque monkeys.

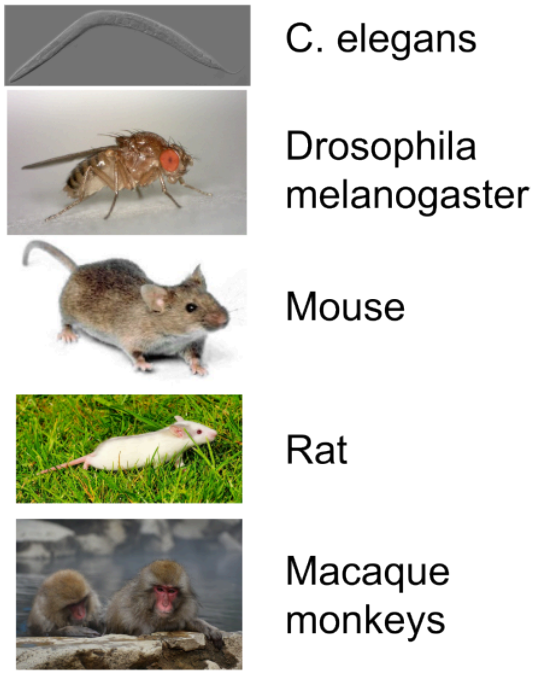


Figure 1.5 Experimental Animal Models. Images of C. elegans (worms), Drosophila melanogaster (fruit flies), mice, rats, and Macaque monkeys.

The closer we move towards the human, the more similarities the model organism shares with us. Of the commonly used model organisms, macaque monkeys are the non-humans that are most similar to humans. We share 93% of our genetic material with macaques, but we still have different metabolic and physiological processes, and our behaviors are much different from theirs. Ethical constraints prevent us from performing experiments that may cause physical or psychological harm if performed in humans. We would never conduct a test on humans to assess what concentration of neurotoxin leads to brain damage (these experiments aren't done very frequently in nonhumans anyway). Invertebrates, such as worms and fruit flies are not as heavily regulated by ethics oversight committees, allowing scientists to conduct a wider set of experiments on these animals.

Our moral responsibilities toward animal subjects are that:

1. Animals should only be used in worthwhile experiments.
2. All steps are taken to minimize pain and distress.
3. All possible alternatives to animal research are considered.

Research facilities at colleges and universities are monitored by an Institutional Care and Use Committee (IACUC). The IACUC consists of fulltime veterinarians, scientists, and community members. They must follow federal laws when approving animal research.

Experimental Preparations

Performing an experiment in an intact, living organism, whether human or nonhuman, is described as an **in vivo** (Latin meaning "within life") preparation. The main strength of this strategy is that the data collected here are more predictive of the human condition, which is one of the main goals of biomedical research. However, the in vivo preparation has challenges, because thousands of variables within a living system are uncontrolled or still unknown. There are also very strict ethical limitations on the nature of experiments that can be done in vivo.

On the other hand, an **in vitro** (Latin meaning "within glass") preparation is an experiment performed on cultured cells or isolated molecules of DNA, RNA, or protein. These preparations have the opposite strengths and weaknesses of in vivo preparations. They allow for extremely good control over variables, but the results are less reliable in translating to a therapy. The regulations on these experiments are much more lax compared to in vivo experiments; most of the regulatory guidelines are to protect the experimenter rather than the patient or the experimental subject.

Falling in between these two preparations is an **ex vivo** experiment. In this kind of experiment, a section of the living organism is taken, such as a slice of brain, a tissue biopsy, or a detached frog leg. The strengths and limitations of these experiments are somewhere in between that of the other two preparations.

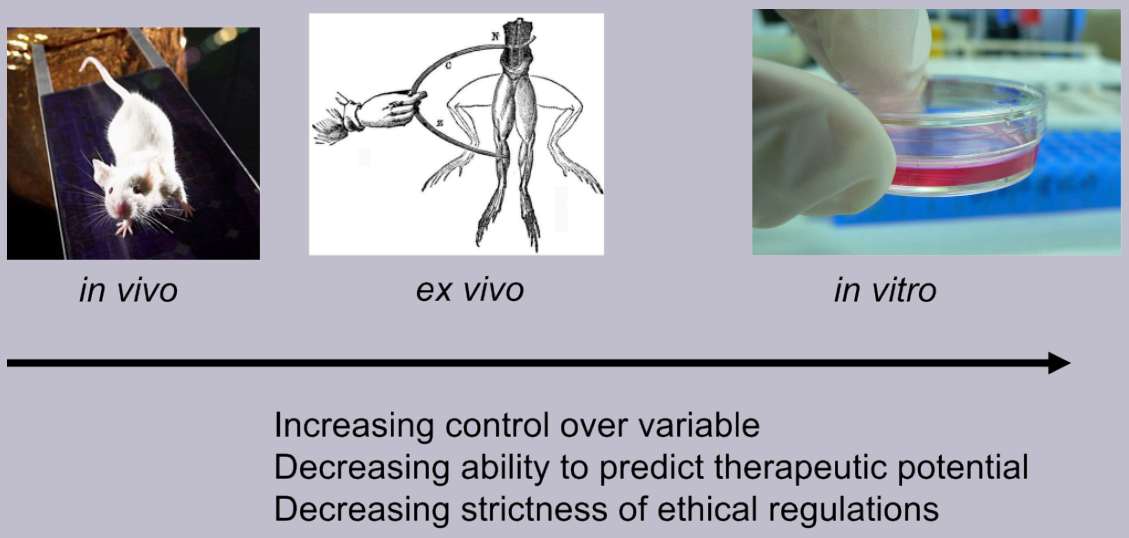


Figure 1.6 Experimental Preparations. Details of the in vivo, ex vivo, and in vitro preparations can be found in the text. The in vivo preparation has the least control over variables, but increased ability to predict therapeutic potential and increased strictness of ethical regulations. The ex vivo preparation has more control over variables, and decreasing ability to predict therapeutic potential and strictness of ethical regulations. The in vitro preparation has the most control over variables but the least ability to predict therapeutic potential and the least strict ethical regulations.

What the brain is not!

As complex as the brain is, naturally misconceptions make their way into popular culture. It's valuable to address these myths about neuroscience and explain the evidence that refutes these statements .

Myth 1: "We only use 10% of our brain."

This wildly inaccurate statistic has been the foundation for several fictional movies, TV shows, and books. The truth is that we use every part of the brain, and most of our brain is active most of the time—just not at the same time. Neurologist V.S. Ramachandran uses a great analogy to describe the fallacy of this myth: does a traffic light only use 33% of its lights? A properly functioning traffic light

will use all three lights at very precise times. The activity of the brain is closely regulated by multiple mechanisms which prevent unusual electrical activity. In fact, if too many cells were active at the wrong times, just like a traffic light showing both green and red, chaos ensues—one cause of seizures is excessive neural activity.

Myth 2: "Forming memories causes new neurons to be born."

Another misconception is the idea that each new cell in our brain represents a new memory. While we are far from understanding the process of exactly how memories are formed in the brain, we do have a few clues. Most likely, memories are stored at the sites of close contact between neurons, called synapses. Changes in ways neurons connect and communicate with one another is likely the mechanism behind how memories are formed and stored, rather than the creation of new neurons. Even though the process of cell reproduction is halted in the majority of adult neurons, we are still capable of new neuronal growth, a process called **neurogenesis**. A few brain areas in particular, like the hippocampus (used in learning and memory functions and the olfactory epithelium (used for smelling), do exhibit frequent birth and death of new neurons.

Myth 3: "The brain cannot repair itself."

If neurons aren't being replaced in adulthood, then how do people spontaneously recover from neurological injuries like a **stroke**? One of the most amazing features of the brain is the phenomenon of **plasticity**, the ability to change over time. Even if critical brain areas are damaged, it is theorized that the brain learns how to "rewire itself", essentially figuring out how to carry out these functions without using the damaged connections. Unfortunately, there are some conditions that are neurodegenerative, meaning that their symptoms get progressively worse over time. Many of these disorders, like **Parkinson's disease** and **Alzheimer's disease**, currently do not have any simple cures or treatments that don't carry risks and side effects. For people with these conditions, there is not strong evidence that the brain can recover from the destruction caused by these diseases.

Myth 4: "If you are analytical, you are left brain

dominant, but if you are creative, you are right brain dominant."

A common misconception is that the two hemispheres of the brain are responsible for wildly different functions. The truth is that nearly every function that the left half of the brain can do, the right half can do just as well, and vice versa. Sensory information, voluntary control of the muscles, memories, and many other behaviors can be performed equally well by both the left and right halves of the brain. A major exception to the "left vs. right" component is the processing and production of language. For some reason unknown to scientists, these functions are heavily lateralized in the left hemisphere for most people.

Fascinatingly, we do have one strange quirk about signaling between the brain and the rest of the body: signaling pathways from the left brain crosses over to communicate with the right half of the body, and vice versa. This contralateral organization is an unintended consequence of evolution, and is one of the major distinguishing features of the vertebrate brain.

Neurobiology is ever-changing

One of the most exciting and satisfying aspects of modern science is the rapidity of new discoveries in the field. New findings are often communicated by publishing academic studies in scientific journals. More neurobiology studies were published between 2015 and 2020 than in the previous seventy years! But the study of the brain hasn't always advanced so quickly: for hundreds, perhaps thousands of years, neurobiology like all other sciences was a static field of study, with intellectuals looking back to the ancient Greeks for inspiration, rather than nature. This meant that all sorts of superstitious rituals and beliefs flourished unchecked – and some unfortunately survive to this day.

Trepanation was a surgical intervention that involved drilling a hole into an individual's skull. It is believed to be one of the oldest surgical procedures according to archaeological evidence. Interestingly, skulls that show evidence of trepanation have been dated to 6500 BCE and show evidence of healing, indicating that the patient survived the surgery.



Figure 1.7 Trepanated Skull. This image shows an example of trepanation, or drilling holes in the skull of individuals as a form of treatment. The growth of the skull around the site of surgery suggests healing and that this procedure was performed while the individual was still alive.

Localizationism

For hundreds of years, physicians attempted to correlate behaviors with changes in the brain. In the mid 1800s, the physician **Paul Broca** contributed to **localization** theory by concluding that specific areas of the brain were responsible for carrying out specific functions. This idea was supported by **ablation** studies that demonstrated that when different brain structures were ablated, or lesioned, there were specific associated functional losses. Further, electrically exciting specific brain structures resulted in eliciting specific behaviors.

Most likely, some behaviors are more localized than others, but still rely on signals from across many other brain areas. As with most fields of biology, absolutes are rare in neuroscience.

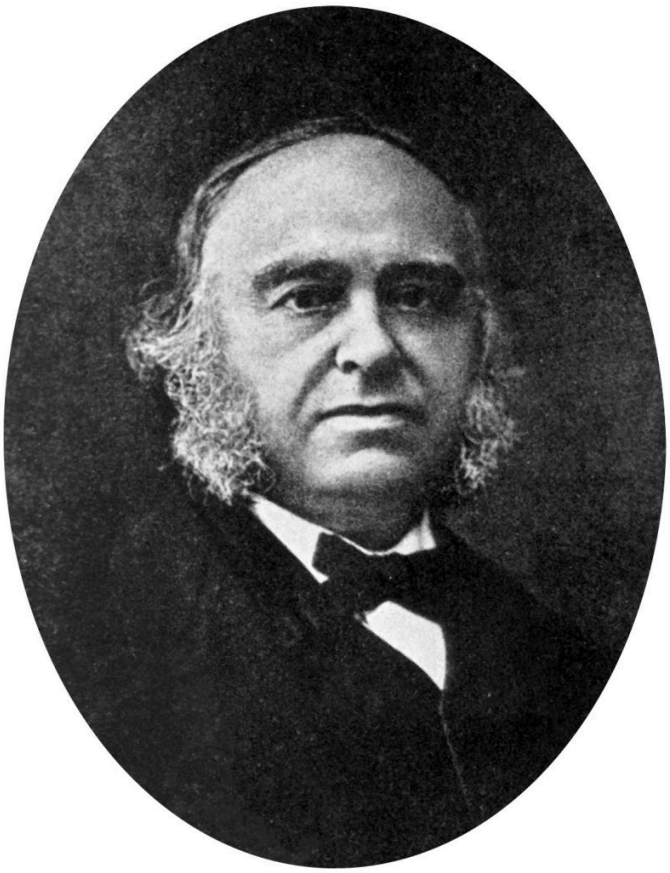


Figure 1.8. Image of Paul Broca.

Plasticity

The real strength of our brain is its flexibility: brains are capable of changing and adapting to a wide variety of circumstances. Blind people use their visual areas of the brain while echolocating, **stroke** survivors can regain lost motor functions using the unaffected brain circuits, and babies can effortlessly learn two languages simultaneously in a bilingual household.

Plasticity is based on the idea that not only is the brain capable change, but that our experiences change the structure and function of our nervous system.

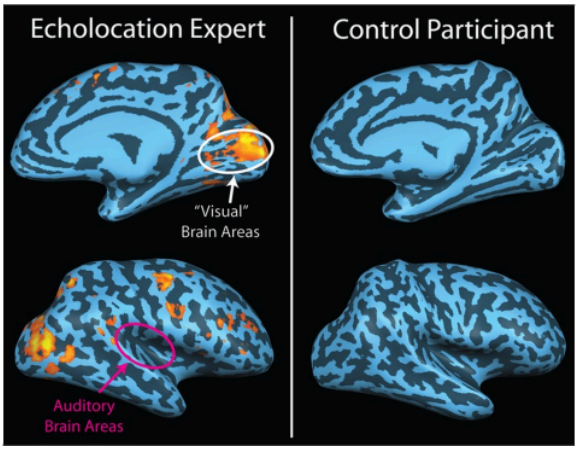


Figure 1.9 Example of Brain Plasticity. Brain images are shown of two different individuals, a blind individual that is an echolocation expert and a control participant. The blind echolocation expert shows an increase in activity within areas of the brain that typically respond to visual information, but no activation in areas of the brain that respond to auditory information. The brain is plastic and has allowed for the blind individual to use areas of the brain that typically process sight to instead process echolocation information.

Key Takeaways

- Neuroscience is the study of the nervous system and is an integrative field of study that incorporates biology, psychology, chemistry, physics, mathematical modeling, and health care providers.
- The study of neuroscience is accomplished through experimental studies, case studies, and the use of experimental animal models.
- There are many popular myths concerning neuroscience and it is important to analyze data that refutes these myths.
- Though the field of neuroscience is relatively young and ever-changing, humans have been interested in the brain and its function for centuries.

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=497#h5p-42

Attributions

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PART I

NEURON STRUCTURE & FUNCTION

1.

CELLS OF THE NERVOUS SYSTEM: THE NEURON

There are 2 major cell types within the nervous system: **Neurons** and **Neuroglia**. Neurons are cells that transmit electrical information. Neuroglia are supporting cells of the nervous system.

Neurons are the cells or basic units of the brain, and were first, and beautifully described by Camillo Golgi who stained nervous system tissue using a new silver staining method, revealing the structure of neurons. This discovery sparked a boom in neuroscience, and Golgi, along with Santiago Ramon-y-Cajal, won both a Nobel Prize for Physiology and Medicine, 1906, and the joint title of fathers of neurobiology. The main function of neurons is to send electrical signals over short and long distances in the body, and they are electrically and chemically excitable. The function of the neuron is dependent on the structure of the neuron. The typical neuron consists of the dendrites, cell body, axon (including the axon hillock), and presynaptic terminal.

Resources

- Scientist Links to Learn More
- Glossary Terms
- Key Takeaways
- Test Yourself

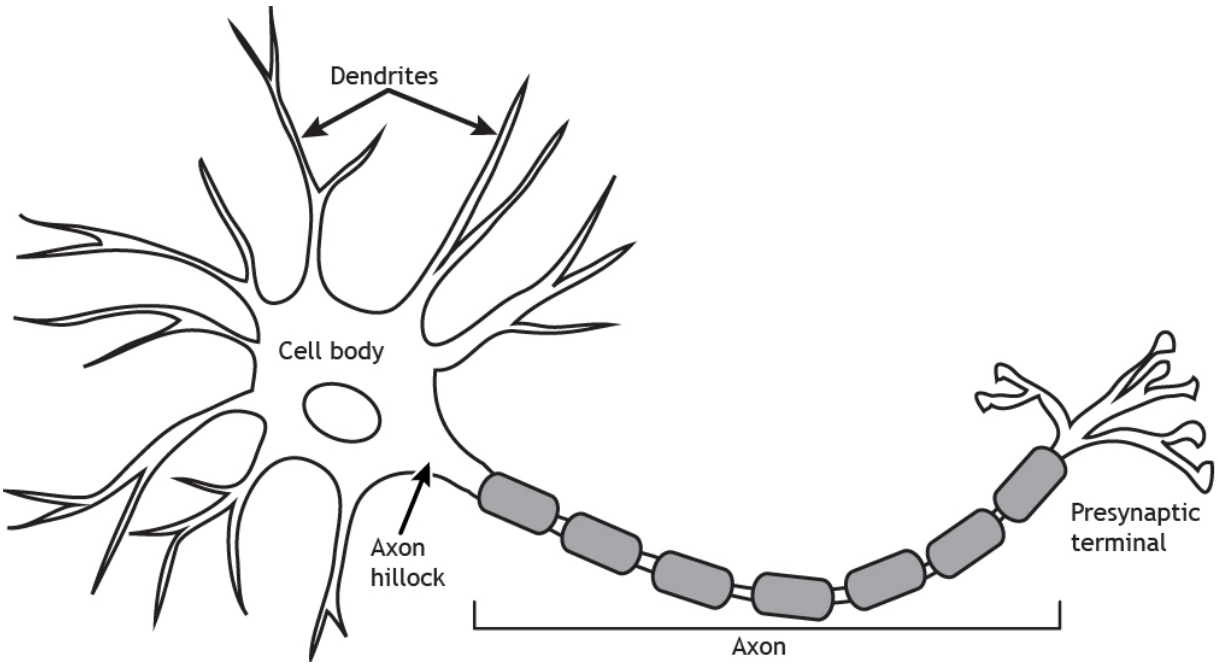


Figure 1.1. A typical neuron. Dendrites branch out from the cell body, where the nucleus is located. The axon hillock is located where the cell body transitions into the axon. The axon begins at the axon hillock and ends at the presynaptic terminal, which can branch into multiple terminals. 'Neuron' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Although neurons do have a variety of adaptations that make them unique from other types of cells in the body, they are still cells. Therefore, they contain all of the basic features of a typical mammalian cell.

For example, they are made up of an aqueous cytoplasm bounded by a cell membrane. This cell membrane, also called a plasma membrane or lipid membrane, consists of a sheet of several individual molecules called phospholipids, which consist of two hydrophobic (water-fearing) tails and a hydrophilic (water-loving) end. These phospholipids arrange themselves into a bilayer, with the hydrophobic tails touching each other and the hydrophilic sides facing the cytoplasm and the extracellular space, which are both mostly water. Because of the chemical properties of the cell membrane, it is very effective at keeping ions and charged molecules separated, while allowing small molecules like water and oxygen across the cell.

Neurons also have all the organelles that you would see in other cell types, like a nucleus and mitochondria. The number of neurons in the adult human brain, according to our current best

estimate, is close to 86 billion. This number was calculated using a revolutionary technique, the isotropic fractionator or "brain soup", developed by Brazilian neuroanatomist Suzana Herculano-Houzel. To put this number in context, we have about 37 trillion cells in the whole body, so neurons in the brain make up about 0.2% of all cells in the body. Below are some unique characteristics that neurons have in common.

1. **Neurons are electroactive**, which means that they are charged cells that can change their charge.
2. **Neurons are specialized for rapid communication.**

   Many cells are capable of sending and receiving chemical signals across long distances and time scales, but neurons are able to communicate with a combination of electrical and chemical signals in a matter of milliseconds. Additionally, the shape of neurons and the organization of the neurons on a microscopic level make them effective for sending signals in a very specific direction.
3. **Neurons are "forever" cells.**

   We are constantly replacing non-neuronal cells. For example, the cells in our bones replace themselves frequently at a rate of about 10% each year. Our body makes new skin cells to replace the dying skin cells on the surface so that we have a "new" skin every month. The cells along the inside of our stomachs, exposed to very harsh acidic conditions, get replaced about every week. About 100 million new red blood cells are created every minute! On the other hand, the mature nervous system generally does not undergo much neurogenesis: the creation of new neurons.

   The neurons that we have after development are the ones that we will keep until we die and this permanence of neuronal count makes them different from almost every other cell of the body. However, the idea of adult neurogenesis is a topic of debate among neuroscientists since some areas, like the olfactory system and the hippocampus, display new nerve cell production.
4. **...But, neurons can change.**

   Even though new neurons are not created in most areas of the brain, neurons still have the capability to change in their structure and function. Some of these changes, such as physical changes to the structures of the input sites of the neurons, are believed to last for a lifetime.

   We use the word *plasticity* to describe the ability for the brain to alter its morphology. This term is derived from the Greek *plastikos*, meaning "capable of being shaped or molded"—think of plastic surgery, where a person changes their physical appearance.

   Also, neurons do have the capacity to repair themselves to some extent. Neurons of the Peripheral Nervous System may get injured or completely destroyed as a result of trauma to the

body. Afterwards, those injured neurons can regrow to connect once again with their original partner. This regrowth seems to depend on a few chemical signals that the body produces, such as nerve growth factor and brain derived neurotrophic factor. However, this process is often very slow, and does not always successfully restore the nervous system to the way it was pre-injury.

Dendrites

The main function of neurons is to use changes in electrical properties in order to communicate with connected cells. This communication usually moves in one direction, and we will use this pathway as an outline for discussing the anatomical structures of the neurons.

Dendrites, shown here in green, are processes that branch out in a tree-like fashion from the cell body. They are the main target for incoming signals received from other cells. The number of inputs a neuron receives depends on the complexity of the dendritic branching. Dendrites may also have small protrusions along the branches known as **spines**. Spines (illustrated in the inset box) are the sites of some synaptic contacts. Spines increase the surface area of the dendritic arbor, which may be an important factor in receiving communication.

We believe that spines are one of the most important sites where the nervous system is able to change. For example, neurons change shape after exposure to various environmental conditions, such as stress or exposure to drugs. Tiny changes to the surface of the neuron at the level of dendritic spines is an example of **plasticity**.

Dendritic plasticity is thought to underlie the reason that we can learn new facts or maintain memories about our childhood over long periods of time. Some set of tiny, submicroscopic changes to the morphology of dendritic spines may represent a single complex memory that you form. A neuron does not need spines for receiving information or for plasticity to take place. Many cells lack spines but are still capable of permanently changing. The input site may be anywhere along the dendrite, or even at the cell body—the "center" of the neuron.

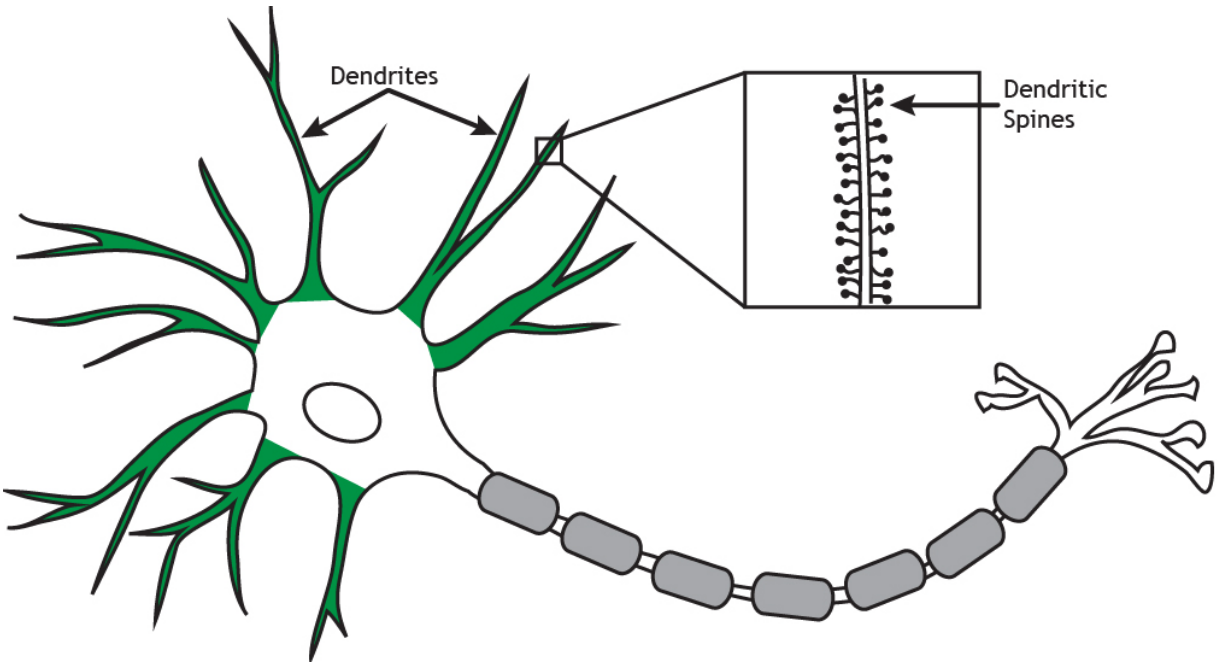


Figure 1.2. Dendrites branch out from the soma. Their function is to receive information from other neurons. Some dendrites have small protrusions called spines that are important for communicating with other neurons. 'Dendrites' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Cell Body

Information that arrives through the many dendrites of a neuron eventually filters into the cell body, or the **soma**, of the neuron. The cell body (shown below in green) contains the nucleus and cellular organelles, including the endoplasmic reticulum, Golgi apparatus, mitochondria, ribosomes, and secretory vesicles. The nucleus houses the DNA of the cell, which is the template for all proteins synthesized in the cell. The organelles (illustrated in the inset box) in the soma are responsible for cellular mechanisms like protein synthesis, packaging of molecules, and cellular respiration.

The cell body is responsible for deciding whether to pass a signal onto the next cell. The cell membrane of the soma performs a complex set of "cellular arithmetic" that weighs all of the incoming signals: excitatory, inhibitory, and modulatory signals. After all of the calculations have been performed, the membrane decides to send a signal, either a "yes" or "no" output, which travels down the axon.

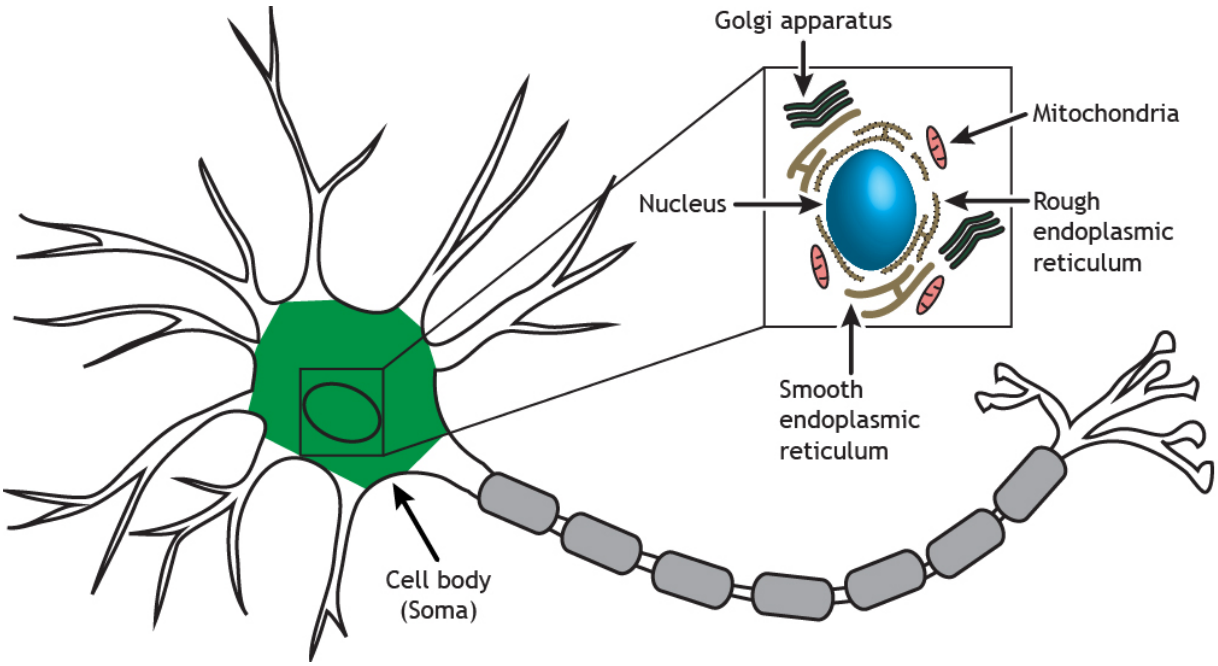


Figure 1.3. The cell body, or soma, of the neuron contains the nucleus and organelles that are commonly found in other cell types and are important for basic cellular functions. These organelles include mitochondria, endoplasmic reticulum, and Golgi apparatus. 'Soma' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Axon

The **axon** is the main output extension of the neuron. The axon (highlighted in green) is usually a long, single process that begins at the axon hillock and extends out from the cell body. The axon hillock is located where the cell body transitions into the axon. Axons can branch in order to communicate with more than one target cell.

Several axons can bundle and travel together; these are **nerves**. Axons can be very long; the longest axon in the human body is part of the sciatic nerve that runs from the posterior end of the spinal cord down the leg to control the muscles of the big toe.

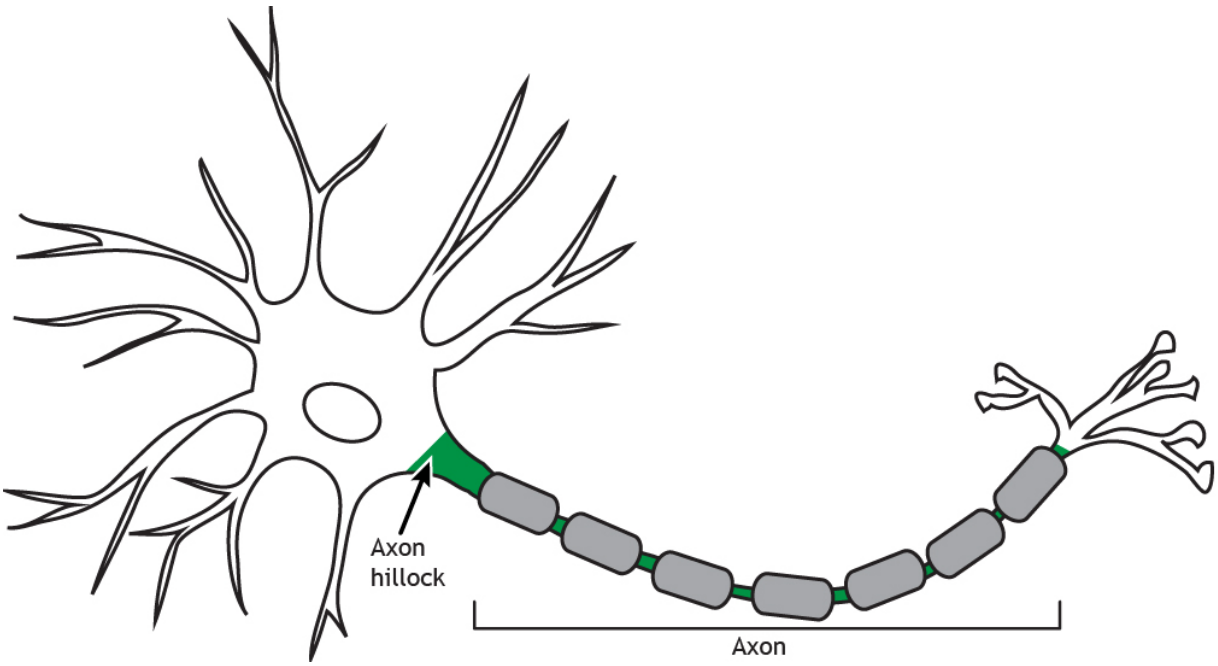


Figure 1.4. The axon is a long single projection that begins at the axon hillock, the region between the cell body and the axon. The axon terminates at the presynaptic terminal. 'Axon' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Action Potential

The axon transmits an electrical signal—called an **action potential**—from the **axon hillock** to the presynaptic terminal, where the electrical signal will result in a release of chemical **neurotransmitters** to communicate with the next cell. The action potential is a very brief change in the electrical potential, which is the difference in charge between the inside and outside of the cell. During the action potential, the **electrical potential** across the membrane moves from a negative value to a positive value and back.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=510#video-510-1

Animation 1.1. The action potential is a brief but significant change in electrical potential across the membrane. The membrane potential will move from a negative, resting membrane potential, shown here as -65 mV, and will rapidly become positive and then rapidly return to rest during an action potential. The action potential moves down the axon beginning at the axon hillock. When it reaches the synaptic terminal, it causes the release of chemical neurotransmitter. 'Action Potential Propagation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Myelin

Many axons are also covered by a **myelin sheath**, a fatty substance that wraps around portions of the axon and increases action potential speed. There are breaks between the myelin segments called **Nodes of Ranvier**, and this uncovered region of the membrane regenerates the action potential as it propagates down the axon in a process called saltatory conduction. There is a high concentration of voltage-gated ion channels, which are necessary for the action potential to occur, in the Nodes of Ranvier.

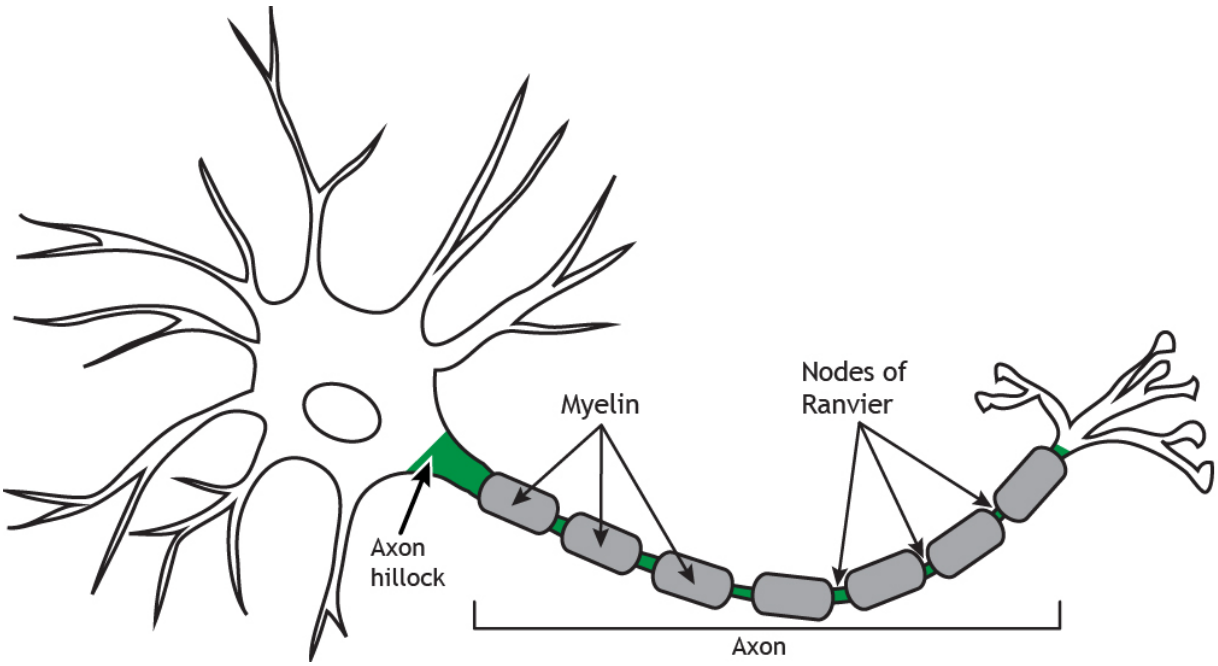


Figure 1.5. Myelin wraps around and insulates the axon. The spaces between the myelin sheath, where the axon is uncovered, are call the Nodes of Ranvier. 'Myelin' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Axon Characteristics

Axon Length

The length of an axon is variable depending on the location of the neuron and its function. The axon of a sensory neuron in your big toe needs to travel from your foot up to your spinal cord, whereas an interneuron in your spinal cord may only be a few hundred micrometers in length.

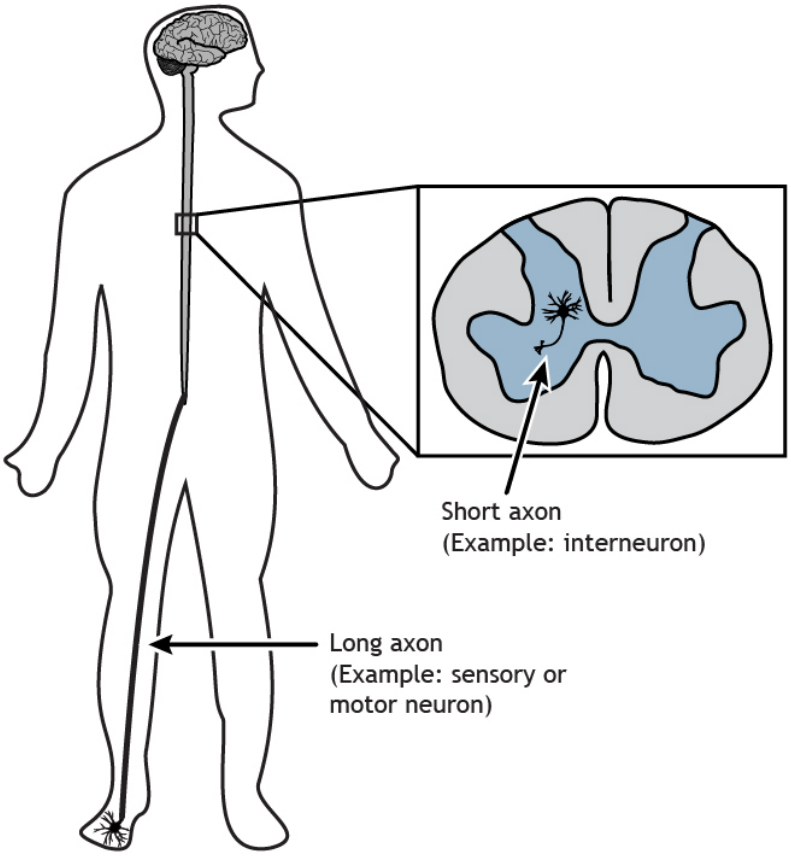


Figure 1.6. Axons vary in length. Spinal interneurons, neurons that fully exist within the spinal cord, can have short axons, whereas sensory or motor neurons, which need to reach from the spinal cord to the appropriate body region, for example the toe, have long axons. 'Axon Length' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Axon Diameter

Axon **diameter** is also variable and can be used to differentiate different types of neurons. The diameter affects the speed at which the action potential will propagate. The larger the diameter, the faster the signal can travel. Additionally, larger diameter axons tend to have thicker myelin.

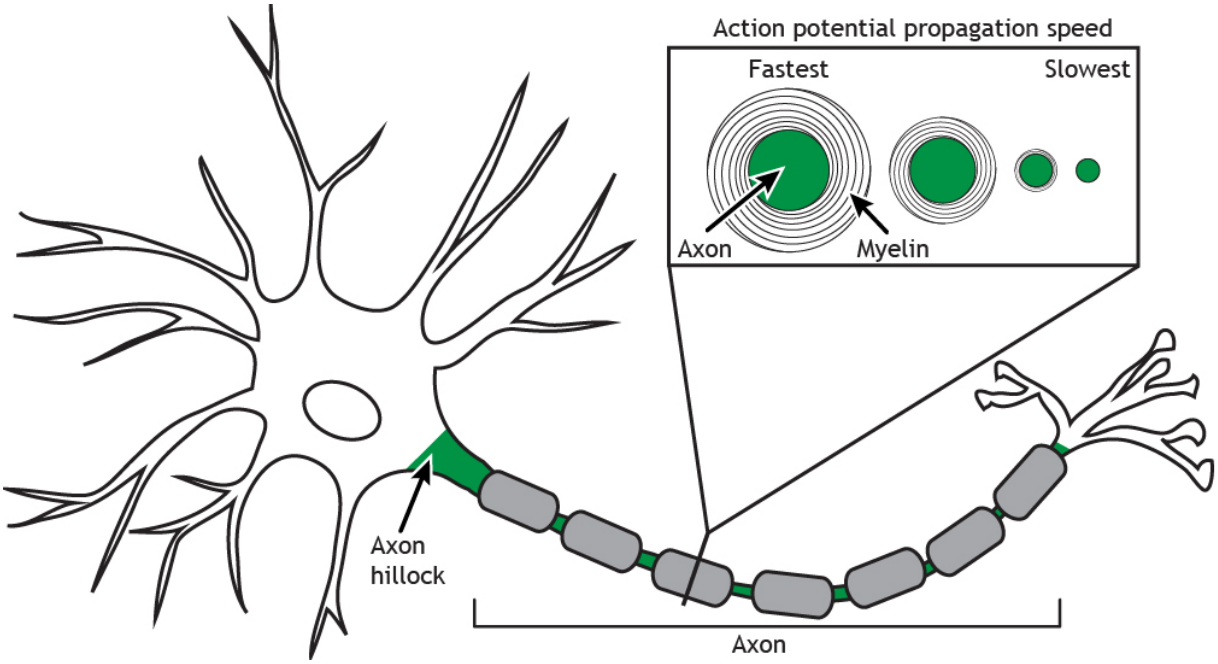


Figure 1.7. The diameter of the axon and the amount of myelination varies. Large diameter axons typically have thicker myelin sheath, which results in fast action potential speed. Small diameter axons may have no myelin present, resulting in slow action potential speed. 'Axon Diameter' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Axoplasmic Transport

Axoplasmic transport refers to the movement of material within the axon. Organelles, vesicles, and proteins can be moved from the cell body to the terminal via **anterograde** transport or from the terminal to the cell body via **retrograde** transport. Anterograde transport can be either fast or slow.

Microtubules run the length of the axon and provide the cytoskeleton tracks necessary for the transportation of materials. Proteins aid in axoplasmic transport. **Kinesin** is a motor protein that uses ATP and is used in anterograde transport of materials. **Dynein** is another motor protein that also uses ATP, but is used in retrograde transport of materials.

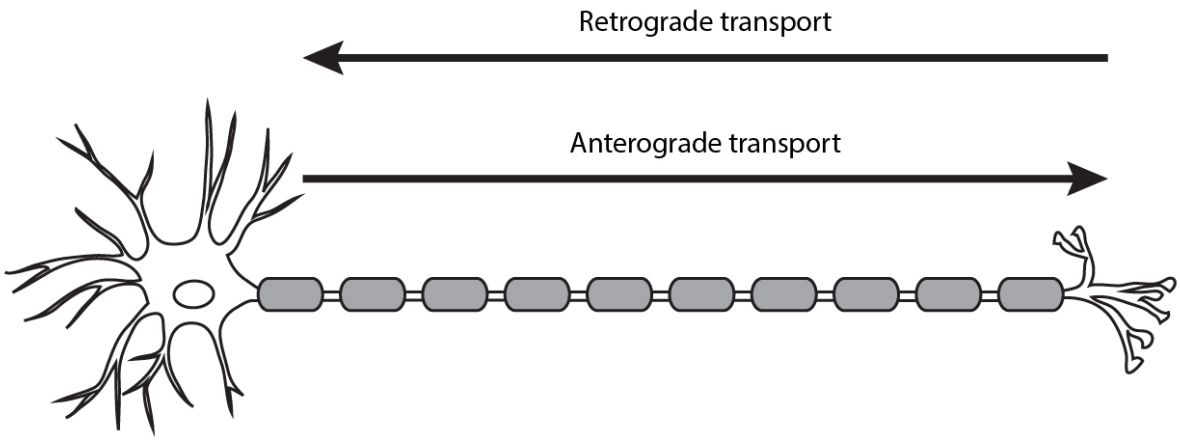


Figure 1.8. Cellular components need to be able to move throughout the cell to have proper functioning. Anterograde transport moves components from the cell body toward the terminal. Retrograde transport moves components from the terminal toward the cell body. 'Axonal Transport' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The Synapse

The **synapse** is the physical distance that separates two neurons.

Electrical Synapse

Electrical synapses physically share cytoplasm. An electrical synapse may be less than 5 nanometers apart. Cells connected by electrical synapses share cytoplasm, but have two separate cell membranes.

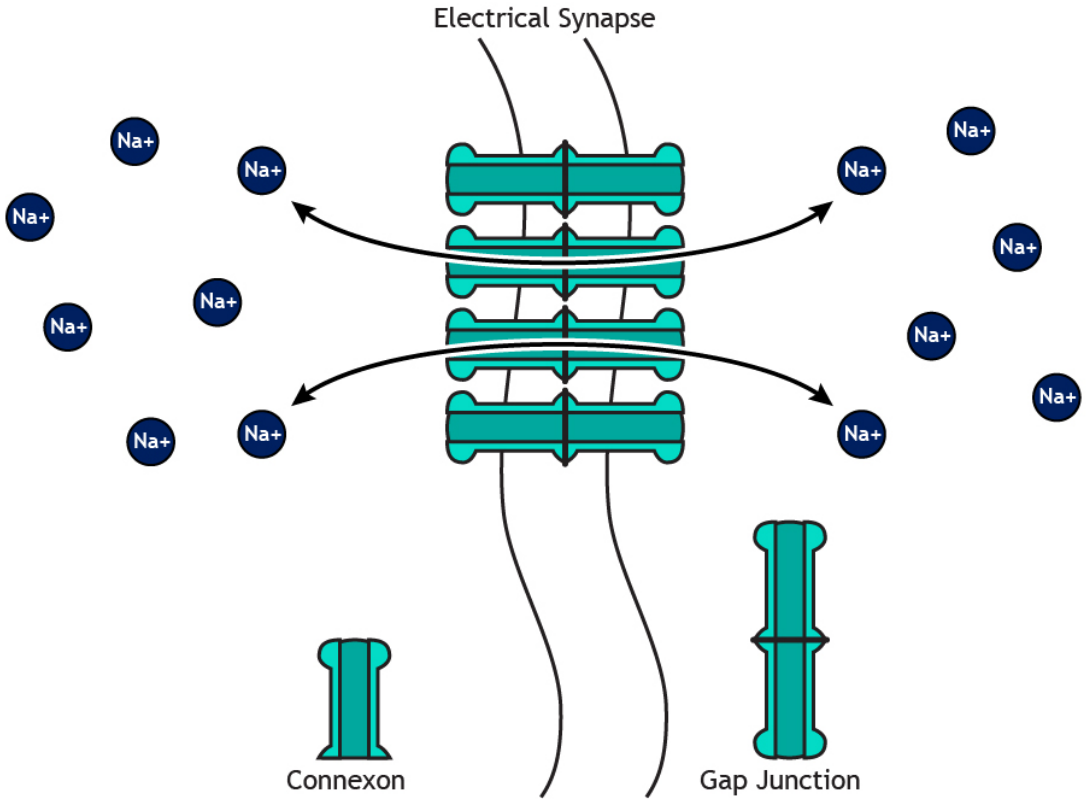


Figure 1.9. Since an electrical synapse is a direct, physical connection between the cytoplasm of two neurons, ions are able to flow in either direction across the gap junction. 'Bidirectional Electrical Synapse' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Chemical Synapse

Chemical synapses use neurotransmitters to communicate. Chemical synapses can vary depending on the nature of the synapse. A chemical synapse is a larger distance, about 15–40 nm across. Adjacent neurons connected by chemical synapses do not share cytoplasm.

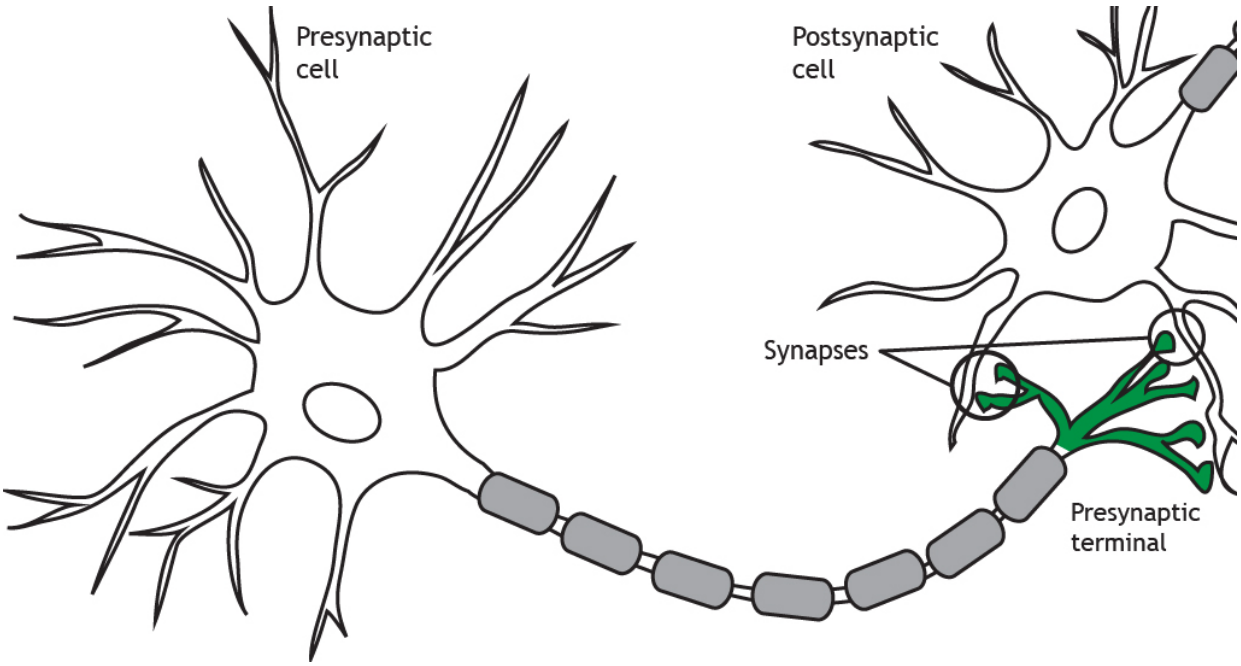


Figure 1.10. Synapses are found between two adjacent cells. In this image, the axon terminals (presynaptic terminals) are synapsing on the dendrites of another neuron (postsynaptic cell). "Presynaptic Terminal' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Presynaptic versus Postsynaptic

The axon terminates at the **presynaptic terminal** or terminal bouton. The terminal of the presynaptic cell forms a synapse with another neuron or cell, known as the postsynaptic cell. When the action potential reaches the presynaptic terminal, the neuron releases neurotransmitters into the synapse. The neurotransmitters act on the postsynaptic cell. Therefore, neuronal communication requires both an electrical signal (the action potential) and a chemical signal (the neurotransmitter). Most commonly, presynaptic terminals contact dendrites, but terminals can also communicate with cell bodies or even axons. Neurons can also synapse on non-neuronal cells such as muscle cells or glands.

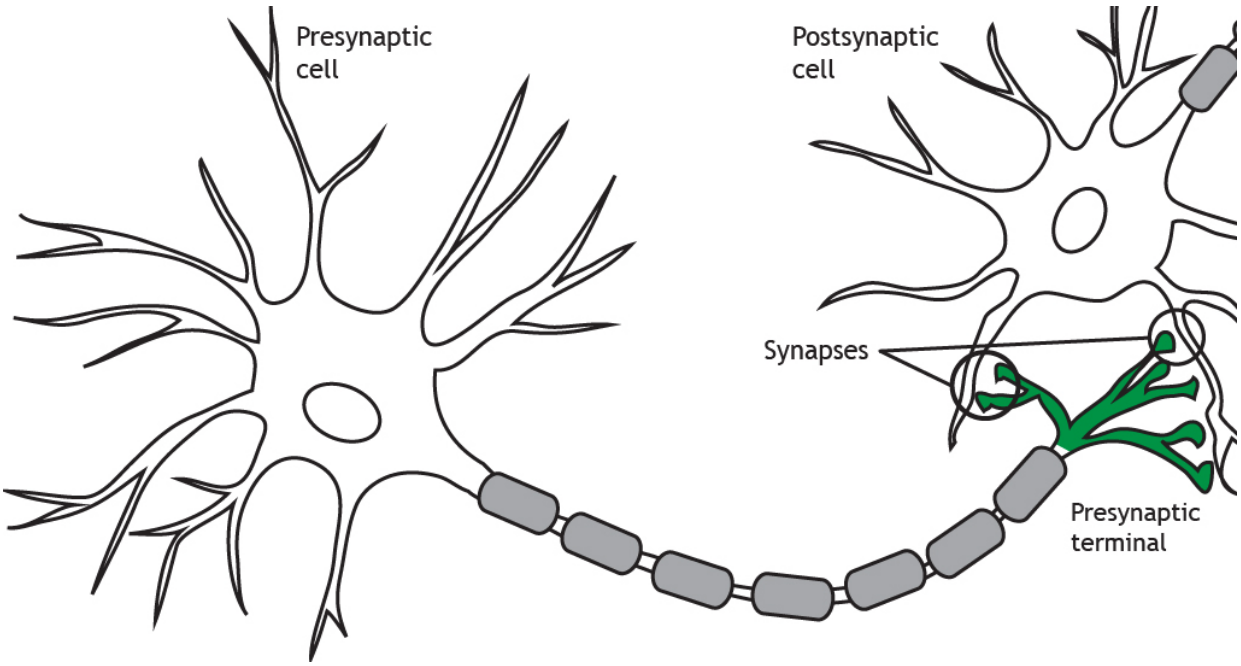


Figure 1.11. The presynaptic terminal forms synaptic contacts with a postsynaptic cell. 'Presynaptic Terminal' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

The terms presynaptic and postsynaptic are in reference to which neuron is releasing neurotransmitters and which is receiving them. **Presynaptic cells** release neurotransmitters into the synapse and those neurotransmitters act on the **postsynaptic cell**.

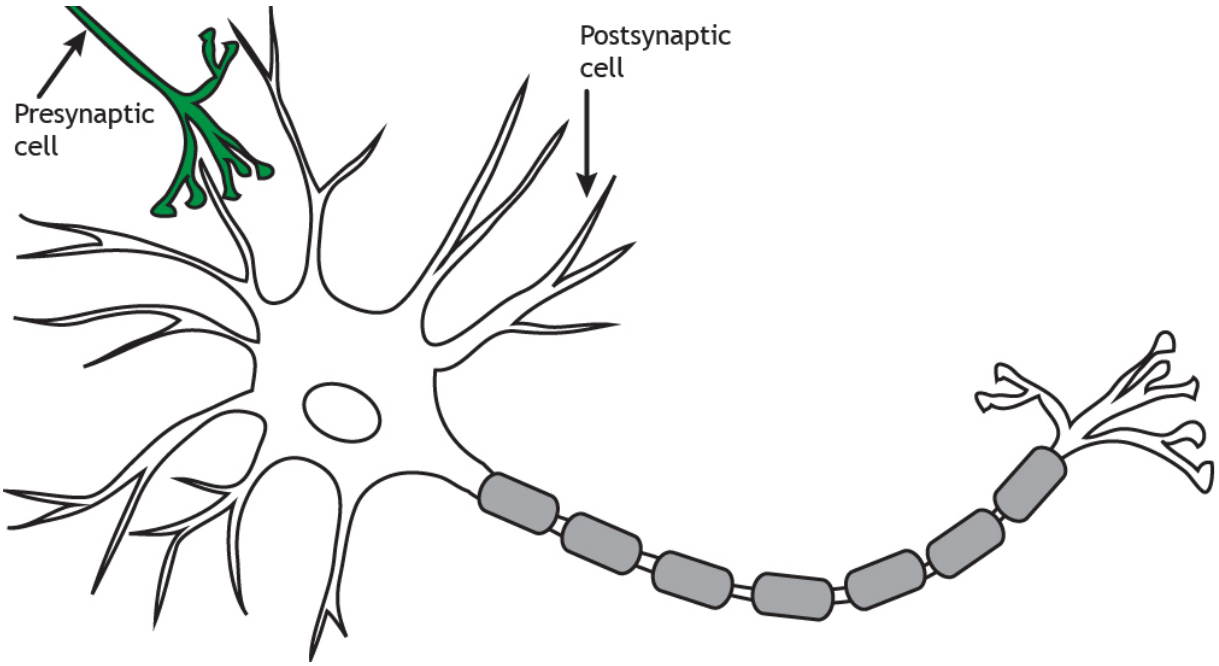


Figure 1.12. The presynaptic cell is the neuron that releases neurotransmitters into the synapse to act upon the postsynaptic cell. 'Postsynaptic Cell' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Variations in Structure

Although these typical structural components can be seen in all neurons, the overall structure can vary drastically depending on the location and function of the neuron. Some neurons, called unipolar, have only one branch from the cell body, and the dendrites and axon terminals project from it. Others, called bipolar, have one axonal branch and one dendritic branch. Multipolar neurons can have many processes branching from the cell body. Additionally, each of the projections can take many forms, with different branching characteristics. The common features of cell body, dendrites, and axon, though, are common among all neurons.

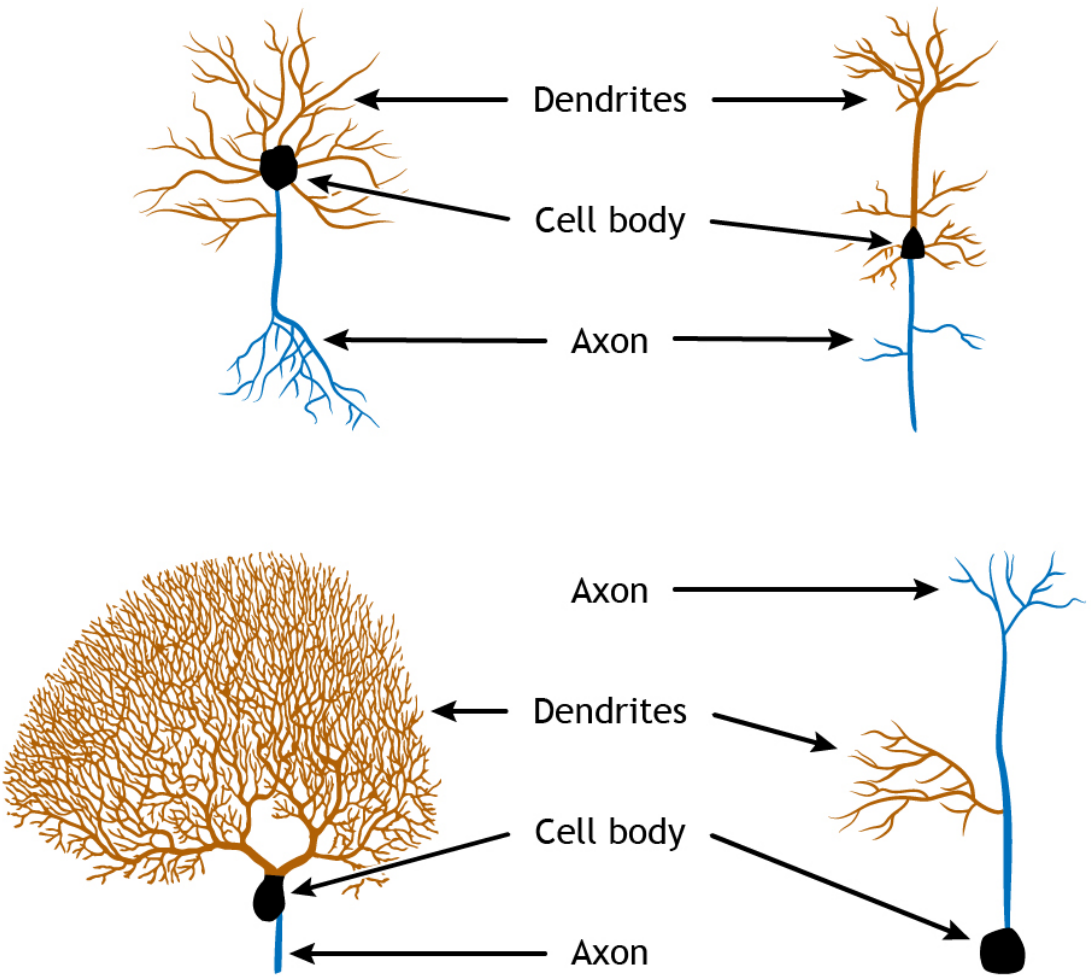


Figure 1.13. Neuron structure is variable, but the main components of cell body (shown in black), dendrites (shown in brown), and axon (shown in blue) are common among all neurons. 'Neuron Types' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Key Takeaways

- Each structural component of the neuron has an important function

- Overall structure of the cell can vary depending on location and function of the neuron

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=510#h5p-43

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2.

CELLS OF THE NERVOUS SYSTEM: GLIA

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

Although most of neuroscience is concerned with understanding the functions of neurons, there are other cells in the nervous system that are just as interesting. These cells are grouped together under the umbrella classification of **glia**. Historically, when these non-neuronal cells were visualized under the microscope, the **histologists** and anatomists had no idea about their function. They were seen all around the neurons, so the assumption was that these cells were structural elements, a sort of living glue, that held the nervous system together. Today, we know that these glia serve a variety of functions; unfortunately, the misnomer "glia"—derived from the Latin word for "glue"—is still used to describe these non-neuronal components of the nervous system.

Astrocytes

Astrocytes are named for their characteristic star-shaped morphology. One of the main functions of astrocytes in the brain is to help maintain the **blood-brain barrier**. At the end of the extensions of the astrocyte are protrusions called "endfeet". These endfeet are often wrapped around the endothelial cells that surround the blood vessels. The endfeet release important biological compounds that allow the endothelial cells to remain healthy as they function in maintaining the blood-brain barrier. Astrocytes are also very closely associated with **synapses**.

Astrocytes also synthesize and produce a variety of **trophic factors**, which are helper molecular signals that serve several different functions. For one, trophic factors signal to neurons that the neuron

should continue to live, or that specific synapses should be maintained. They help guide the neurons as they reach out, forming synapses where appropriate.

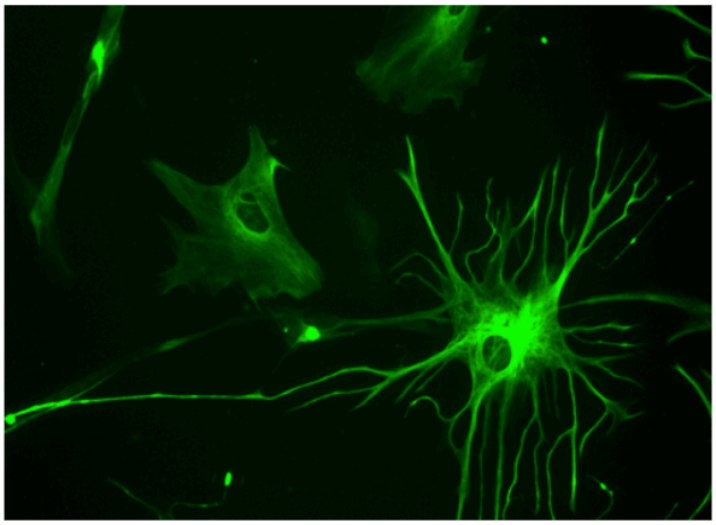


Figure 2.1 Astrocyte. A green fluorescent marker has been used to stain astrocytes within brain tissue. The astrocytes has star-like projections off the cell body.

Oligodendrocytes

The main function of the oligodendrocytes is to add a layer of **myelin** around the axons of nearby neurons in the **central nervous system**. A single oligodendrocyte is able to myelinate up to 50 segments of axons. As cells that produce myelin, they are responsible for increasing the conduction speed of nearby neurons as they send signals. Oligodendrocytes only exist in the **central nervous system**.

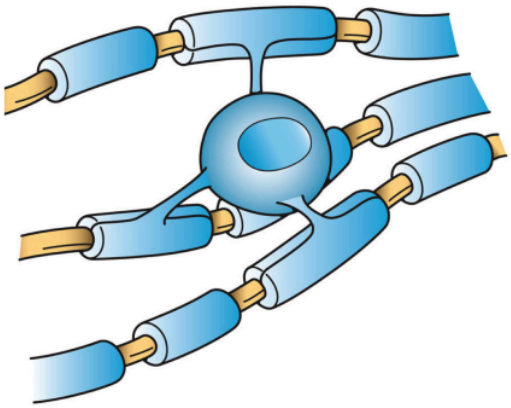


Figure 2.2 Image of an oligodendrocyte. A single oligodendrocyte shown in blue covers axons from multiple neuron axons with myelin sheath.

Schwann Cells

Schwann cells can only be found in the **peripheral nervous system**. The main action of Schwann cells is to provide a section of **myelin** sheath for peripheral nervous system neurons, and in this way, they function similarly to the oligodendrocytes. Schwann cells produce only a single section of myelin, compared to oligodendrocytes, which myelinate multiple sections. Schwann cells also function in the regeneration of injured axons. When nerves in the peripheral nervous system are damaged after trauma, Schwann cells rapidly mobilize to the site of injury.

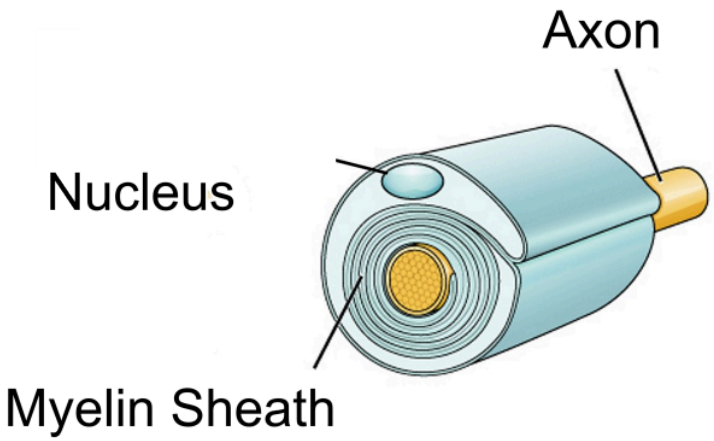


Figure 2.3 Schwann Cell. The Schwann cell is shown in blue. A single Schwann cell wraps myelin around a neuron axon, shown in yellow. Multiple Schwann cells are needed to myelinate one neuron axon.

Microglia

Microglia are a bit different from the other glial cell populations. For one, microglia are more immune cells rather than neural. They act as cellular scavengers that travel throughout the brain and spinal cord. It is estimated that microglia make up 10-15% of all cells in the brain.

As immune cells, microglia identify and destroy clumps of proteins, dead/dying cells, or foreign pathogens that enter into the brain. After an injury to the **central nervous system**, like a traumatic blow to the head, microglia rapidly react to the area of the insult.

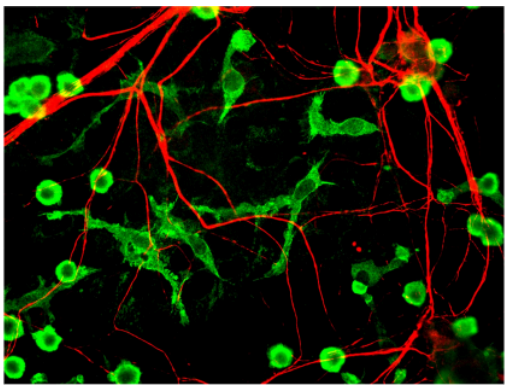


Figure 2.4 Photograph of microglia and neurons. In this microscope photograph, microglia are stained with a green fluorescent stain and neurons are stained with a red fluorescent stain. Microglia are much smaller than neurons.

Ependymal Cells

Along the inside of the **ventricles** are a lining of glia called ependymal cells. These ependymal cells are **columnar** with small fingerlike extensions called **cilia** that extend into the ventricles and into the central canal that runs down the inside of the spinal cord. The cilia have motor properties that allow for them to rhythmically beat to create a current in the surrounding fluid.

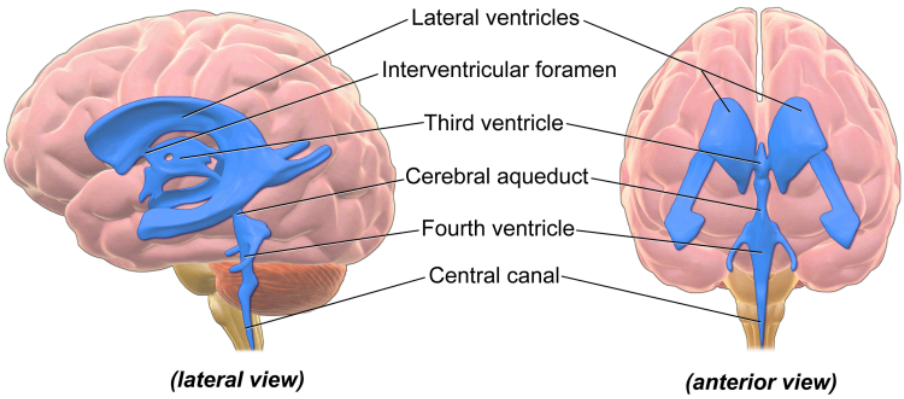


Figure 2.5 Image of brain ventricles. The brain ventricles (shown in blue) are hollow areas within the brain that are interconnected and filled with cerebrospinal fluid. The ventricles are connected to the central canal of the spinal cord. The ventricles are show in a lateral view (left) and anterior view (right).

Ependymal cells produce **cerebral spinal fluid** (CSF). In total, the body can make about half a liter of CSF each day (a little more than two cups.) The ependymal cells are part of a structure called the choroid plexus, the network of blood vessels and cells that form a boundary between the blood and the CSF.

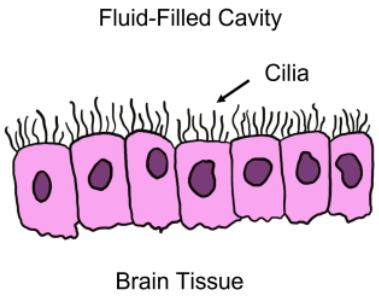


Figure 2.6. Ependymal Cells. Ependymal cells are ciliated columnar cells that line the ventricles and other fluid-filled spaces of the central nervous system. The rhythmic beating of the cilia create movement of the surrounding cerebral spinal fluid. 'Ependymal Cells' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Key Takeaways

- There are multiple different types of glia cells that each have their own functions

Test Yourself!

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3.

ION MOVEMENT

Ion flow into and out of the neuron is a critical component of neuron function. The control of **ion movement** affects the cell at rest and while sending and receiving information from other neurons.

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

Phospholipid Bilayer Prevents Ion Movement

The neuronal membrane is composed of lipid molecules that form two layers. The hydrophilic heads of the molecules align on the outside of the membrane, interacting with the intra- and extracellular solution of the cell, whereas the hydrophobic tails are arranged in the middle, forming a barrier to water and water-soluble molecules like ions. This barrier is critical to neuron function.

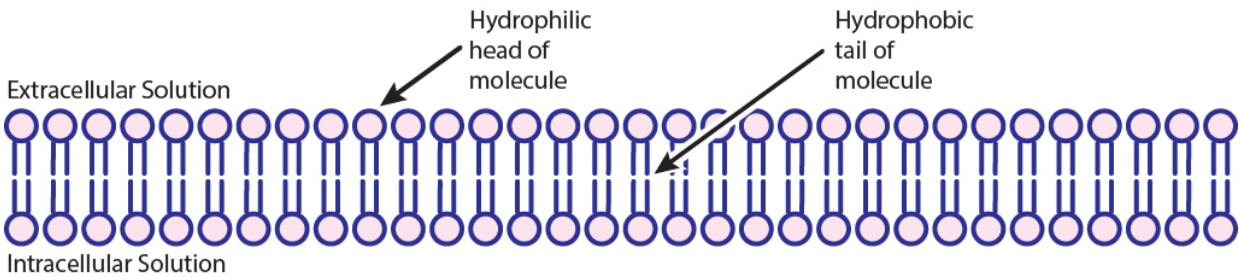


Figure 3.1. The neuronal membrane is composed of two layers of phospholipid molecules that form a barrier to water and water-soluble molecule due to the organization of the hydrophilic heads and hydrophobic ends of the molecules. 'Phospholipid Bilayer' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial (CC-BY-NC) 4.0 International License.

Ions move in predictable ways

Ion Channels Allow Ion Movement

Embedded throughout the neuronal membrane are ion channels. Ion channels are proteins that span the width of the cell membrane and allow charged ions to move across the membrane. Ions cannot pass through the phospholipid bilayer without a channel. Channels can be opened in a number of different ways. Channels that open and close spontaneously are called leak or non-gated channels. Channels that open in response to a change in membrane potential are called voltage-gated. Channels that open in response to a chemical binding are called ligand-gated. Other mechanisms like stretch of the membrane or cellular mechanisms can also lead to the opening of channels. Channels can be specific to one ion or allow the flow of multiple ions.

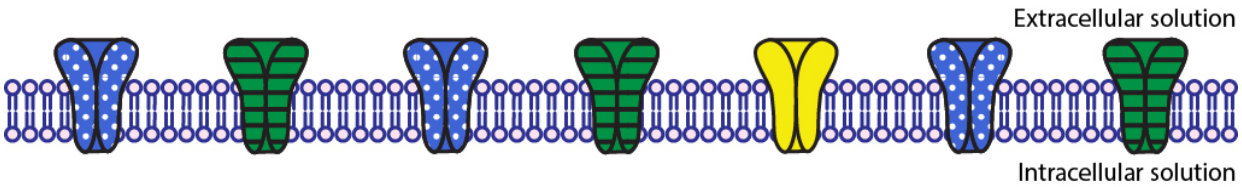


Figure 3.2. The phospholipid bilayer with embedded ion channels. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. 'Membrane with Channels' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial (CC-BY-NC) 4.0 International License.

Ion channels control ion movement across the cell membrane because the phospholipid bilayer is impermeable to the charged atoms. When the channels are closed, no ions can move into or out of the cell. When ion channels open, however, then ions can move across the cell membrane.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=37#video-37-1

Animation 3.1. When ion channels in the membrane are closed, ions cannot move into or out of the neuron. Ions can only cross the cell membrane when the appropriate channel is open. For example, only sodium can pass through open sodium channels. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. 'Ion Movement' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial (CC-BY-NC) 4.0 International License. View static image of animation.

Gradients Drive Ion Movement

Ions move in predictable ways. Concentration and electrical gradients drive ion movement. Ions will diffuse from regions of high concentration to regions of low concentration. Diffusion is a passive process, meaning it does not require energy. As long as a pathway exists (like through open ion channels), the ions will move down the concentration gradient.

In addition to concentration gradients, electrical gradients can also drive ion movement. Ions are attracted to and will move toward regions of opposite charge. Positive ions will move toward regions of negative charge, and vice versa.

For discussion of ion movement in this text, the combination of these two gradients will be referred to as the electrochemical gradient. Sometimes the concentration and electrical gradients driving ion movement can be in the same direction; sometimes the direction is opposite. The electrochemical gradient is the summation of the two individual gradients and provides a single direction for ion movement.



One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=37#video-37-2

Animation 3.2. Concentration and electrical gradients drive ion movement. Ions diffuse down concentration gradients from regions of high concentration to regions of low concentration. Ions also move toward regions of opposite electrical charge. 'Gradients' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial (CC-BY-NC) 4.0 International License. View

static image of animation.

When Gradients Balance, Equilibrium Occurs

When the concentration and electrical gradients for a given ion balance, meaning they are equal in strength but in different directions, that ion will be at equilibrium. Ions still move across the membrane through open channels when at equilibrium, but there is no net movement in either direction meaning there is an equal number of ions moving into the cell as there are moving out of the cell.



One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=37#video-37-3

Animation 3.3. When an ion is at equilibrium, which occurs when the concentration and electrical gradients acting on the ion balance, there is no net movement of the ion. The ions continue to move across the membrane through open channels, but the ion flow into and out of the cell is equal . In this animation, the membrane starts and ends with seven positive ions on each side even though the ions move through the open channels. 'Ion Equilibrium' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial (CC-BY-NC) 4.0 International License. View static image of animation.

Key Takeaways

- The phospholipid bilayer prevents ion movement into or out of the cell
- Ion channels allow ion movement across the membrane

- Electrochemical gradients drive the direction of ion flow
- At equilibrium, there is no *net* ion movement (but ions are still moving)

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=37#h5p-2

1. Explain how chemical and electrical gradients affect ion flow.
2. Explain ion movement at equilibrium.

Video Lecture

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=37#oembed-1

Attributions

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4.

MEMBRANE POTENTIAL

The membrane potential is the difference in electrical charge between the inside and the outside of the neuron. This is measured using two electrodes. A reference electrode is placed in the extracellular solution. The recording electrode is inserted into the cell body of the neuron.

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

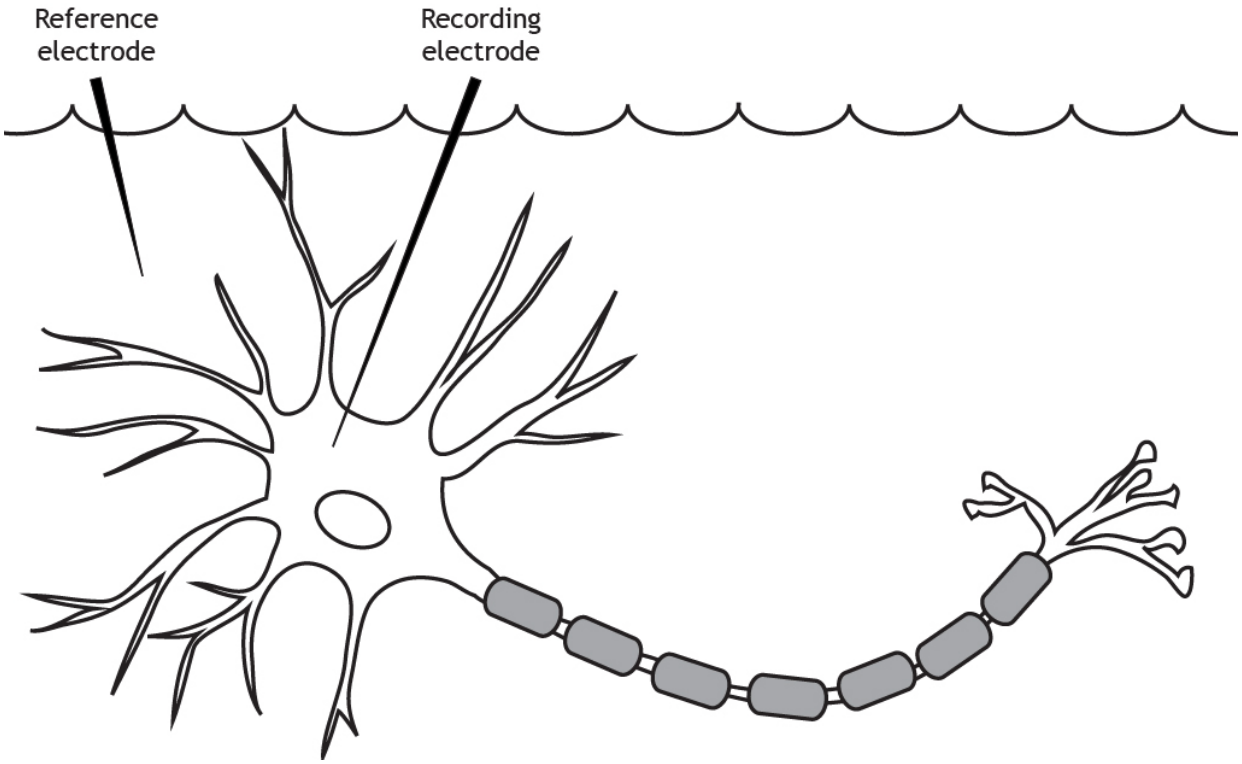


Figure 4.1. The membrane potential is measured using a reference electrode placed in the extracellular solution and a recording electrode placed in the cell soma. The membrane potential is the difference in voltage between these two regions. 'Measuring Membrane Potential' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Terminology

There is more than one way to describe a change in membrane potential. If the membrane potential moves toward zero, that is a depolarization because the membrane is becoming less polarized, meaning there is a smaller difference between the charge on the inside of the cell compared to the outside. This is also referred to as a decrease in membrane potential. This means that when a neuron's membrane potential moves from rest, which is typically around -65 mV, toward 0 mV and becomes more positive, this is a *decrease* in membrane potential. Since the membrane potential is the difference in electrical charge between the inside and outside of the cell, that difference decreases as the cell's membrane potential moves toward 0 mV.

If the membrane potential moves away from zero, that is a hyperpolarization because the membrane is becoming more polarized. This is also referred to as an increase in membrane potential.

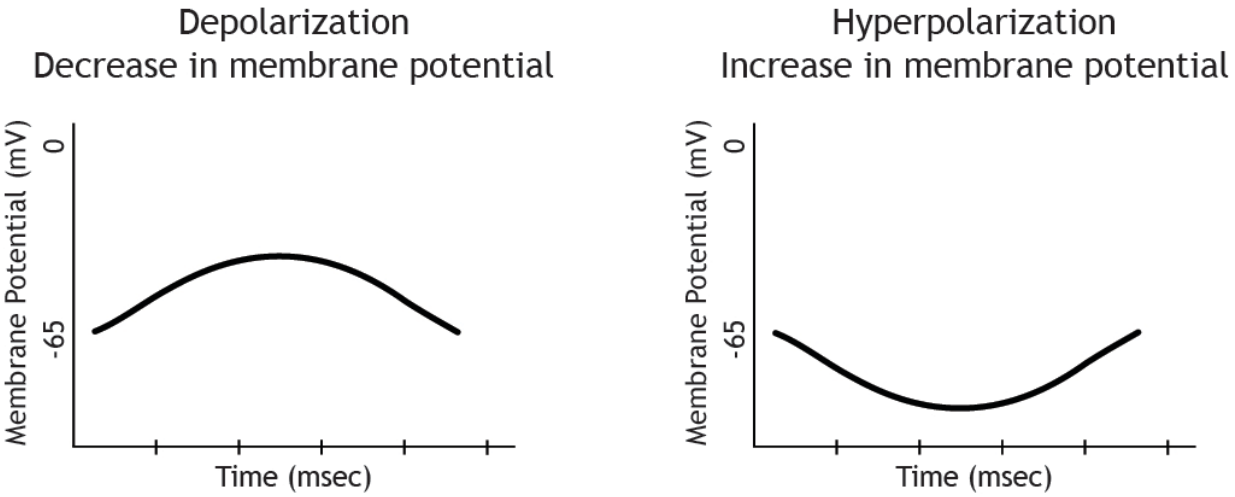


Figure 4.2. A decrease in membrane potential is a change that moves the cell's membrane potential toward 0 or depolarizes the membrane. An increase in membrane potential is a change that moves the cell's membrane potential away from 0 or hyperpolarizes the membrane. 'Membrane Potential Terms' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The solution inside of the neuron is more negatively charged than the solution outside

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Voltage Distribution

At rest, ions are not equally distributed across the membrane[1]. This distribution of ions and other

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1. Hille B. Ionic channels in nerve membranes. Prog Biophys Mol Biol. 1970;21:1-32. doi: 10.1016/0079-6107(70)90022-2. PMID: 4913288.

charged molecules leads to the inside of the cell having a more negative charge compared to the outside of the cell.

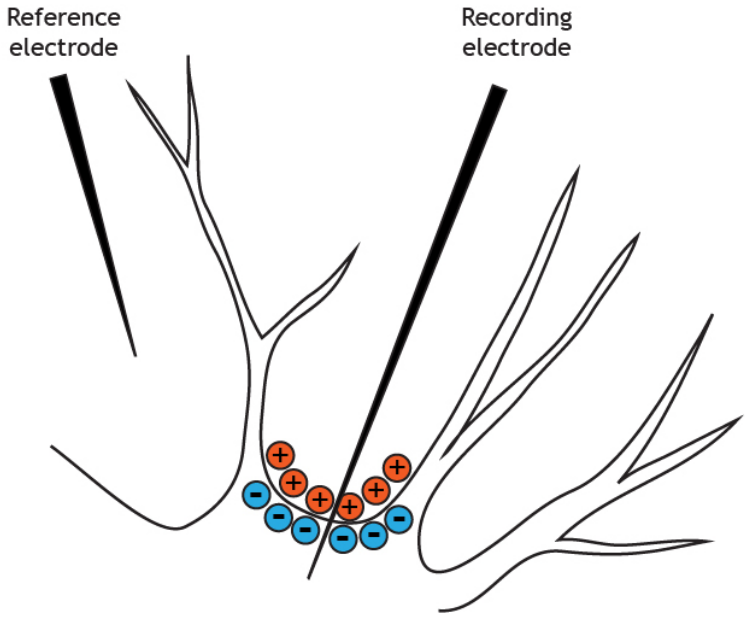


Figure 4.3. The inside of the neuron has a more negative charge than the outside of the neuron. 'Membrane Potential' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

A closer look shows that sodium, calcium, and chloride are concentrated outside of the cell membrane in the extracellular solution, whereas potassium and negatively-charged molecules like amino acids and proteins are concentrated inside in the intracellular solution.

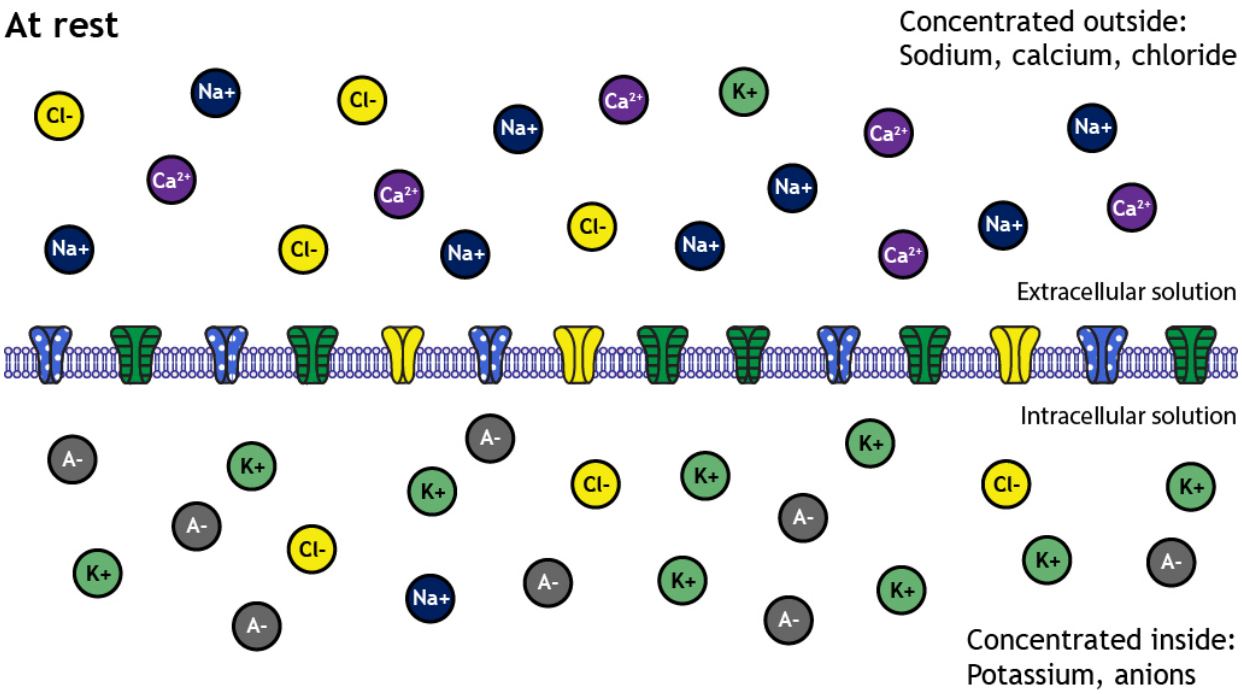


Figure 4.4. For a typical neuron at rest, sodium, chloride, and calcium are concentrated outside the cell, whereas potassium and other anions are concentrated inside. This ion distribution leads to a negative resting membrane potential. The dotted, blue channels represent sodium leak channels; the striped, green channels represent potassium leak channels; the solid yellow channels represent chloride leak channels. 'Membrane at Rest' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The distribution of the different ions across the membrane creates electrochemical gradients that drive ion movement

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These concentration differences lead to varying degrees of electrochemical gradients in different directions depending on the ion in question. For example, the electrochemical gradients will drive potassium out of the cell but will drive sodium into the cell.

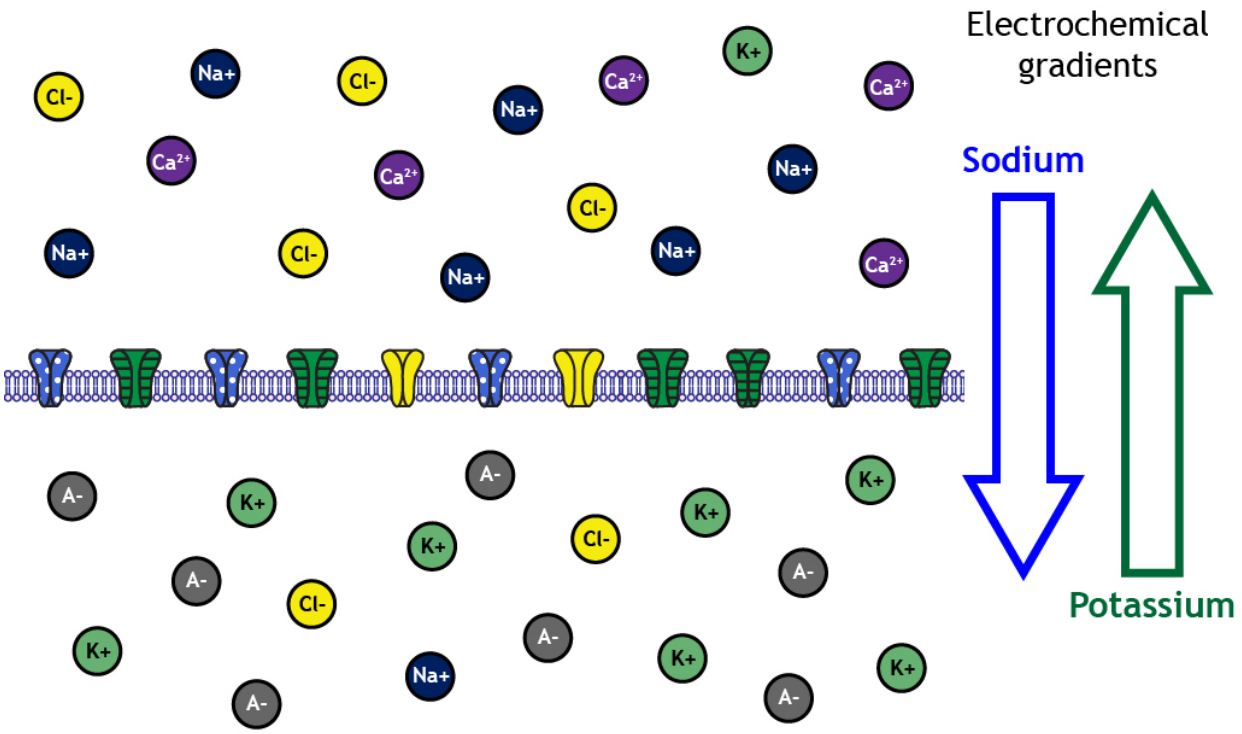


Figure 4.5. The distribution of ions on either side of the membrane lead to electrochemical gradients for sodium and potassium that drive ion flow in different directions. If the membrane is permeable to sodium, ions will flow inward. If the membrane is permeable to potassium, ions will flow outward. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. 'Gradients Across Membrane' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Equilibrium Potential

The neuron's membrane potential at which the electrical and concentration gradients for a given ion balance out is called the ion's equilibrium potential. The ion is at equilibrium at this membrane potential, meaning there is no *net* movement of the ion in either direction. Let's look at sodium in more detail:

Example: Driving Forces on Sodium Ions

When sodium channels open, the neuron's membrane becomes permeable to sodium, and sodium will begin to flow across the membrane. The direction is dependent upon the electrochemical gradients. The concentration of sodium in the extracellular solution is about 10 times higher than the intracellular solution, so there is a concentration gradient driving sodium into the cell. Additionally, at rest, the inside of the neuron is more negative than the outside, so there is also an electrical gradient driving sodium into the cell.

As sodium moves into the cell, though, these gradients change in driving strength. As the neuron's membrane potential become positive, the electrical gradient no longer works to drive sodium into the cell. Eventually, the concentration gradient driving sodium into the neuron and the electrical gradient driving sodium out of the neuron balance with equal and opposite strengths, and sodium is at equilibrium. The membrane potential of the neuron at which equilibrium occurs is called the equilibrium potential of an ion, which, for sodium, is approximately +60 mV.



One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=46#video-46-1

Animation 4.1. At rest, both the concentration and electrical gradients for sodium point into the cell. As a result, sodium flows in. As sodium enters, the membrane potential of the cell decreases and becomes more positive. As the membrane potential changes, the electrical gradient decreases in strength, and after the membrane potential passes 0 mV, the electrical gradient will point outward, since the inside of the cell is more positively charged than the outside. The ions will continue to flow into the cell until equilibrium is reached. An ion will be at equilibrium when its concentration and electrical gradients are equal in strength and opposite in direction. The membrane potential of the neuron at which this occurs is the equilibrium potential for that ion. Sodium's equilibrium potential is approximately +60 mV. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. 'Sodium Gradients' by Casey Henley is licensed under a Creative Commons

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Calculate Equilibrium Potential with Nernst Equation

The gradients acting on the ion will always drive the ion towards equilibrium. The equilibrium potential of an ion is calculated using the Nernst equation:

The Nernst Equation

$$E_{ion} = \frac{61}{z} log \frac{[ion]_{outside}}{[ion]_{inside}}$$

The constant 61 is calculated using values such as the universal gas constant and temperature of mammalian cells

Z is the charge of the ion

$[Ion]_{inside}$ is the intracellular concentration of the ion

$[Ion]_{outside}$ is the extracellular concentration of the ion

An Example: Sodium's Equilibrium Potential

$$E_{ion} = \frac{61}{z} log \frac{[ion]_{outside}}{[ion]_{inside}}$$

For Sodium:

z = 1

$[Ion]_{inside}$ = 15 mM

$[Ion]_{outside}$ = 145 mM

$$E_{ion} = \frac{61}{1} \log \frac{145}{15} = 60mV$$

It is possible to predict which way an ion will move by comparing the ion's equilibrium potential to the neuron's membrane potential

Predict Ion Movement by Comparing Membrane Potential to Equilibrium Potential

Let's assume we have a cell with a resting membrane potential of -70 mV. Sodium's equilibrium potential is +60 mV. Therefore, to reach equilibrium, sodium will need to enter the cell, bringing in positive charge. On the other hand, chloride's equilibrium potential is -65 mV. Since chloride is a negative ion, it will need to *leave* the cell in order to make the cell's membrane potential more positive to move from -70 mV to -65 mV.

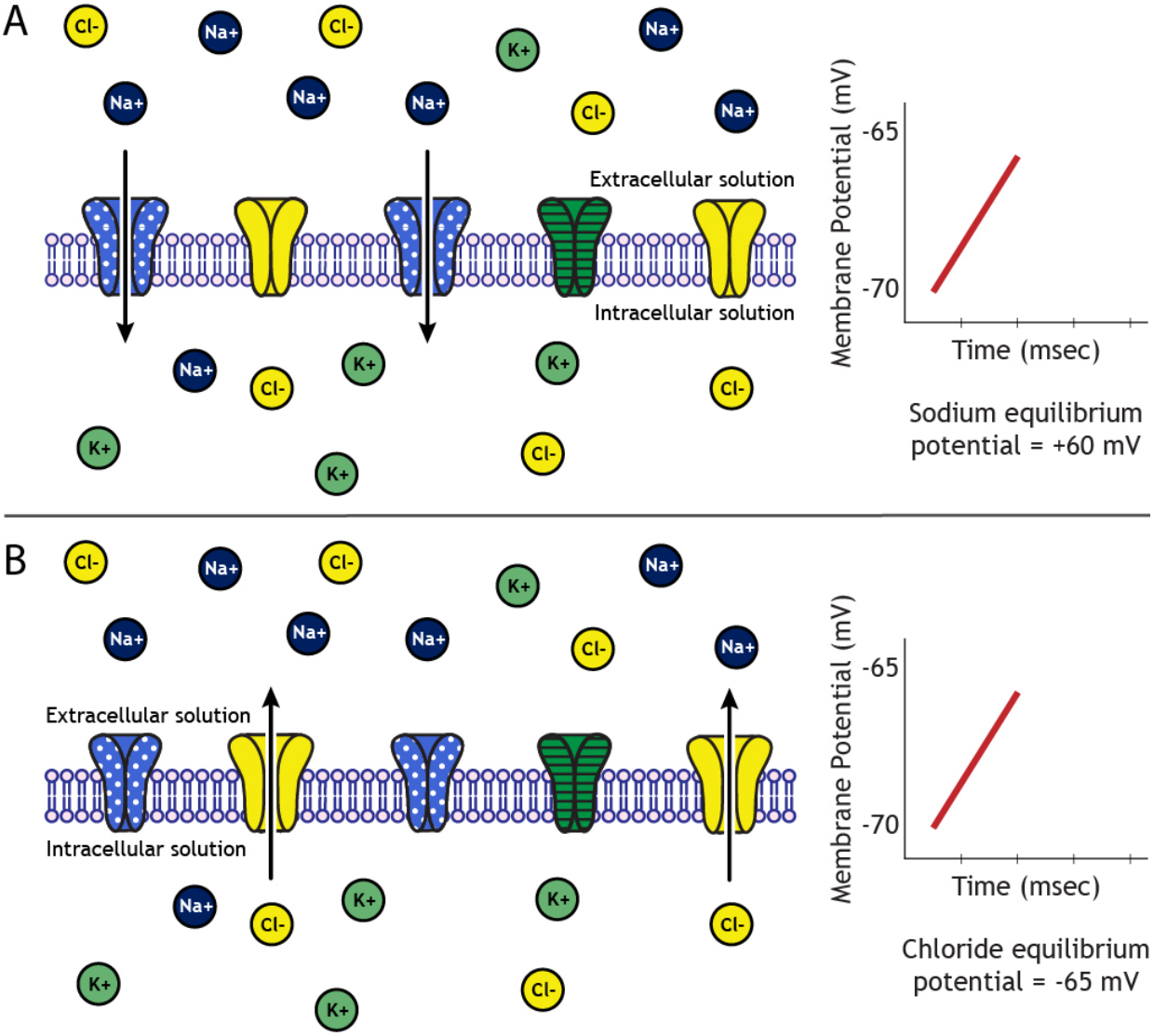


Figure 4.6. A) If a cell is at rest at -70 mV, sodium ions will flow into the cell to move the cell's membrane potential toward sodium's equilibrium potential of +60 mV. B) At the same resting membrane potential, chloride would flow out of the cell, taking away its negative charge, making the inside of the cell more positive and moving toward chloride's equilibrium potential of -65 mV. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. 'Moving Toward Equilibrium' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Concentration and Equilibrium Potential Values

We will use the following ion concentrations and equilibrium potentials:

[table id=1 /]

Key Takeaways

- Moving the membrane potential toward 0 mV is a decrease in potential; moving away from 0 mV is an increase in potential
- The distribution of ions inside and outside of the cell at rest vary among the different ions; some are concentrated inside, some are concentrated outside
- Equilibrium potentials are calculated using the Nernst equation
- To predict ion movement, compare the current membrane potential of the neuron with the ion's equilibrium potential. Determine which way the ion needs to move to cause that membrane potential change (i.e. does the ion need to move into the cell or out of the cell?)

Test Yourself!

Try the quiz more than once to get different questions!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=46#h5p-3

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=46#h5p-4

1. Define resting membrane potential (Vm) of a cell.
2. Explain the differences between the resting membrane potential and the equilibrium potential.
3. Using the concentration values from the table below, calculate the equilibrium potential of potassium using the Nernst equation. [table id=4 /]

Video Lecture

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=46#oembed-1

Attributions

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5.

THE MEMBRANE AT REST

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

As covered in the previous chapter, at rest there is an uneven distribution of ions on either side of the membrane. The inside of the membrane is more negatively charged than the outside, which is expressed as a negative membrane potential.

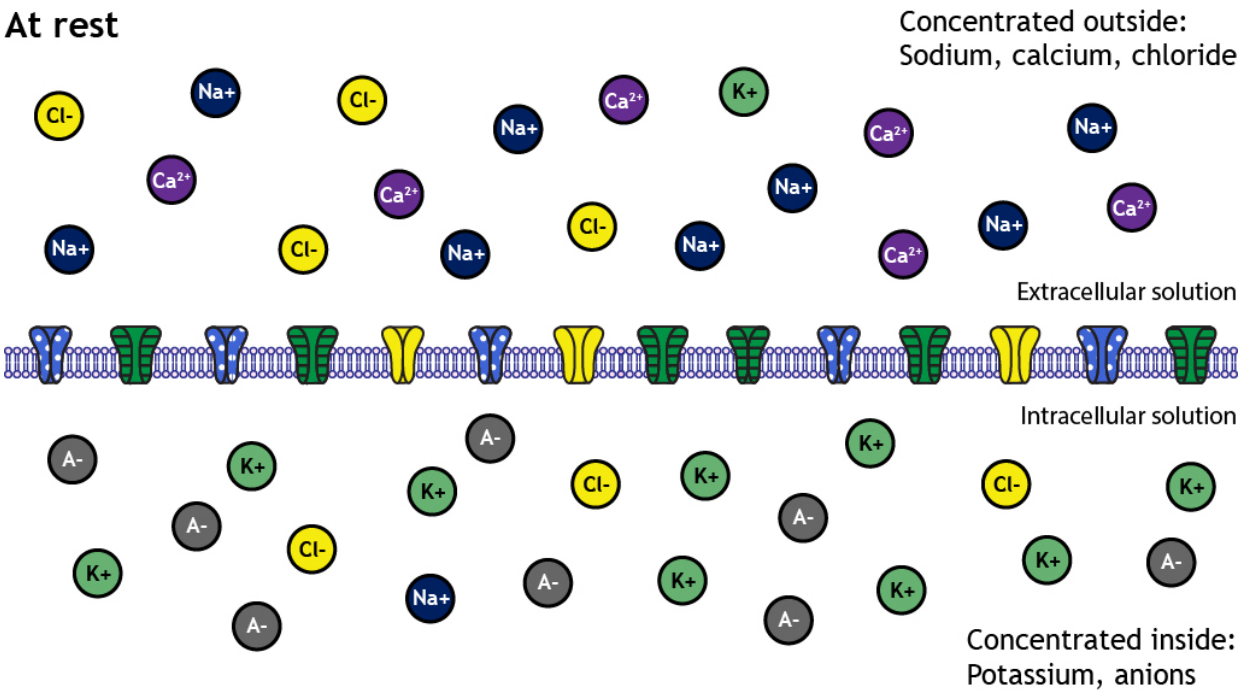


Figure 5.1. For a typical neuron at rest, sodium, chloride, and calcium are concentrated outside the cell, whereas potassium and other anions are concentrated inside. This ion distribution leads to a negative resting membrane potential. The dotted, blue channels represent sodium leak channels; the striped, green channels represent potassium leak channels; the solid yellow channels represent chloride leak channels. 'Membrane at Rest' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The membrane at rest is most permeable to potassium. Permeability for other ions, like chloride and sodium, is significantly lower.

Permeability at Rest

How the ions are distributed across the membrane plays an important role in the generation of the resting membrane potential. At rest a type of non-gated ion channels, called leak channels are actually

open. Significantly more potassium channels are open than sodium channels, and this makes the membrane at rest far more permeable to potassium than sodium.

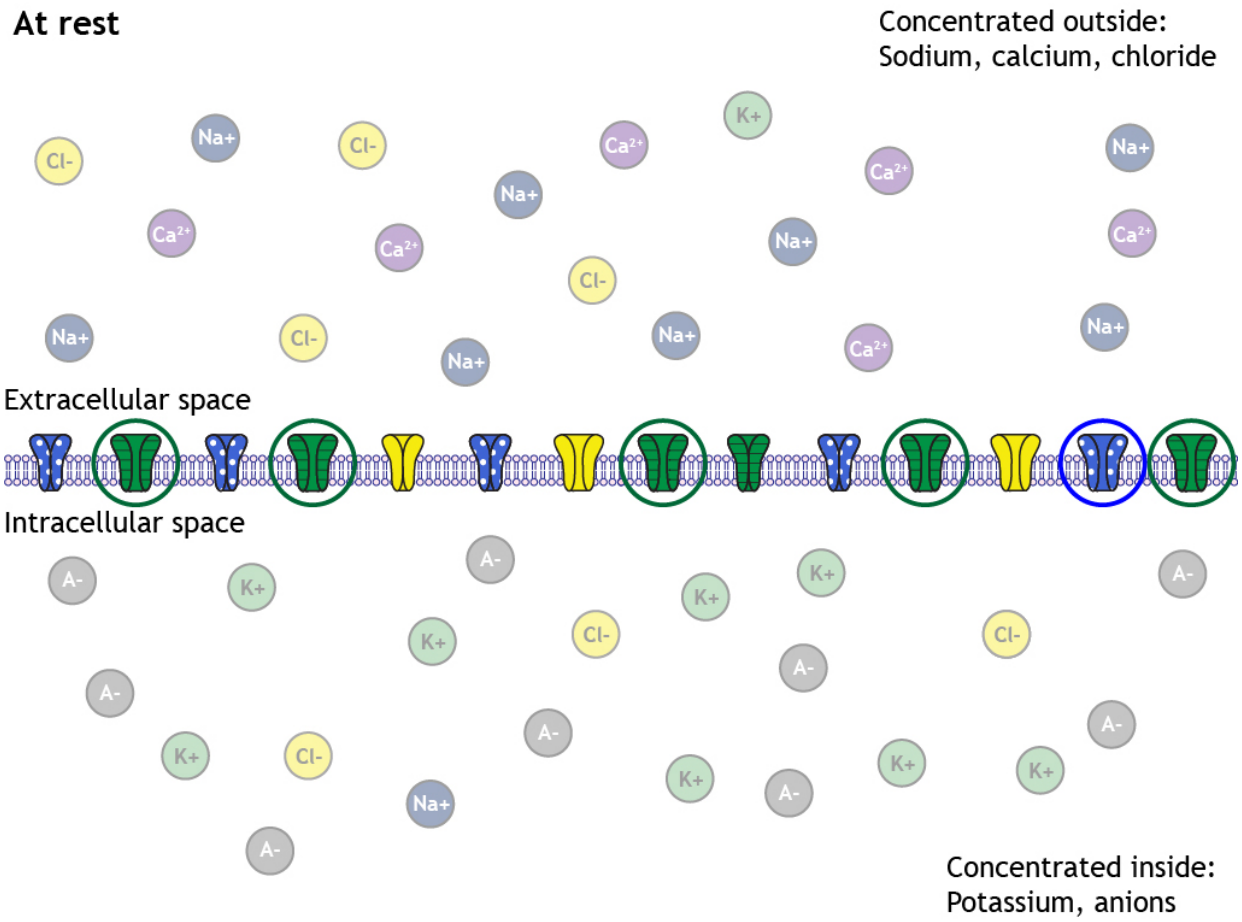


Figure 5.2. At rest, the distribution of ions across the membrane varies for different ions. Additionally, at rest, more potassium non-gated ion channels (emphasized by green circles) are open than sodium channels (emphasized by the blue circle). The dotted, blue channels represent sodium leak channels; the striped, green channels represent potassium leak channels; the solid yellow channels represent chloride leak channels. 'Channels at Rest' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Potassium Can Cross Membrane at Rest

Since the membrane is permeable to potassium at rest due to the open non-gated channels, potassium

ions flow across the membrane. Since permeability to potassium is hundreds of times more than that to sodium, the electrochemical gradients at work will cause potassium to flow out of the cell in order to move the cell's membrane potential toward potassium's equilibrium potential of -80 mV.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=52#video-52-1

Animation 5.1. Electrochemical gradients drive potassium out of the cell, removing positive charge, making the cell's membrane potential more negative, in the direction of potassium's equilibrium potential. The dotted, blue channels represent sodium leak channels; the striped, green channels represent potassium leak channels; the solid yellow channels represent chloride leak channels. 'Potassium Flow at Rest' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Resting Membrane Potential Value

You might ask, though, if the cell has these open non-gated ion channels, and ions are moving at rest, won't the cell eventually reach potassium's equilibrium potential if the membrane is only permeable to potassium?

If the only structural element involved in ion flow present in the cell membrane were the open non-gated potassium channels, the membrane potential would eventually reach potassium's equilibrium potential. However, the membrane has other open non-gated ion channels as well. There are fewer of these channels compared to the potassium channels, though. The permeability of chloride is about half of that of potassium, and the permeability of sodium is about 25 to 40 times less than that of potassium. This leads to enough chloride and sodium ion movement to keep the neuron at a resting membrane potential that is slightly more positive than potassium's equilibrium potential.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=52#video-52-2

Animation 5.2. The membrane is most permeable to potassium at rest, and this leads to potassium efflux. However, the membrane is also permeable to chloride and sodium, and the flow of these ions keep the resting membrane potential more positive than potassium's equilibrium potential. The dotted, blue channels represent sodium leak channels; the striped, green channels represent potassium leak channels; the solid yellow channels represent chloride leak channels. 'Ion Flow at Rest' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

The sodium-potassium pumps work to keep the ion concentrations stable even as ions cross the membrane at rest.

Maintenance of Gradients

As ions move across the membrane both at rest and when the neuron is active, the concentrations of ions inside and outside of the cell will change. This leads to changes in the electrochemical gradients that are driving ion movement. What, then, maintains the concentration and electrical gradients critical for the ion flow that allows the neuron to function properly?

The key mechanism for maintaining gradients across the neuronal membrane is the sodium-potassium pump. The pump uses energy in the form of ATP to move three sodium ions out of the cell and two potassium ions in. This moves the ions against their electrochemical gradients, which is why it requires energy. The pump functions to keep the ionic concentrations at proper levels inside and outside the cell. The sodium-potassium pump is so critical to function, that it uses fully 30-40% of the brain's energy consumption.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=52#video-52-3

Animation 5.3. The sodium-potassium pump is embedded in the cell membrane and uses ATP to move sodium out of the cell and potassium into the cell, maintaining the electrochemical gradients necessary for proper neuron functioning. Three intracellular sodium ions enter the pump. ATP is converted to ADP, which leads to a conformational change of the protein, closing the intracellular side and opening the extracellular side. The sodium ions leave the pump while two extracellular potassium ions enter. The attached phosphate molecule then leaves, causing the pump to again open toward the inside of the neuron. The potassium ions leave, and the cycle begins again. 'Sodium-Potassium Pump' by by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Calculating Membrane Potential with Goldman Equation

It is possible to calculate the membrane potential of a cell if the concentrations and relative permeabilities of the ions are known. Recall from the last chapter, the Nernst equation is used to calculate one ion's equilibrium potential. Knowing the equilibrium potential can help you predict which way one ion will move, and it also calculates the membrane potential value that the cell would reach if the membrane were only permeable to one ion. However, at rest, the membrane is permeable to potassium, chloride, and sodium. To calculate the membrane potential, the Goldman equation is needed.

The Goldman Equation

Like the Nernst equation, the constant 61 is calculated using values such as the universal gas constant and temperature of mammalian cells

P_{ion} is the relative permeability of each ion

$[Ion]_{inside}$ is the intracellular concentration of each ion

$[Ion]_{outside}$ is the extracellular concentration of each ion

Example: The Neuron at Rest

[table id=2 /]



Key Takeaways

- At rest, the membrane is most permeable to potassium because Non-gated (leak) potassium channels are open at resting potential
- Other ion channels (chloride and sodium) are also open, but fewer are open than potassium

- Therefore, the resting membrane potential of a typical neuron is relatively close to the equilibrium potential for potassium (E_K)
- Electrochemical gradients needed for normal neuronal function are maintained, despite constant flow through leak channels, by the sodium-potassium pump, which expends energy to translocate K^+ into the cell, and Na^+ out of the cell.

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=52#h5p-5

- From memory, draw a diagram of a neuronal membrane at rest that includes the non-gated ion channels in their correct state (i.e., open, closed, inactivated).
- If all other conditions (see purple box above) are unchanged, but P_{Na} is 0.004 instead, how will the resting potential change?

Video Lecture

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=52#oembed-1

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6.

GRADED POTENTIALS

When the neuron is at rest, there is a baseline level of ion flow through leak channels. However, the ability of neurons to function properly and communicate with other neurons and cells relies on ion flow through channels other than the non-gated leak channels. We will cover how these channels open in a later lesson. This chapter will examine ion flow through these channels after a stimulus and how the membrane potential changes in response.

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

Postsynaptic Potentials

Postsynaptic potentials are changes in membrane potential that move the cell away from its resting state. For our purposes, postsynaptic potentials are measured in the dendrites and cell bodies. Ion channels that are opened by a stimulus allow brief ion flow across the membrane. A stimulus can range from neurotransmitters released by a presynaptic neuron, changes in the extracellular environment like exposure to heat or cold, interactions with sensory stimuli like light or odors, or other chemical or mechanical events. The change in membrane potential in response to the stimulus will depend on which ion channels are opened by the stimulus.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=63#video-63-1

Animation 6.1. A stimulus can cause ion channels in the membrane of the cell body or dendrites to open, allowing ion flow across the membrane. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. 'Postsynaptic Ion Flow' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Incoming signals can cause either an excitatory response or an inhibitory response in the neuron

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Excitatory Postsynaptic Potentials (EPSPs)

An excitatory postsynaptic potential (EPSP) occurs when sodium channels open in response to a stimulus. The electrochemical gradient drives sodium to rush into the cell. When sodium brings its positive charge into the cell, the cell's membrane potential becomes more positive, or depolarizes. This change is called a depolarization because the cell's membrane potential is moving toward 0 mV, and the membrane is becoming less polarized. At 0 mV, there is no potential or polarization across the membrane, so moving toward 0 would be a decrease in potential. This depolarization increases the likelihood a neuron will be able to fire an action potential, which makes this ion flow excitatory. Therefore, an EPSP is an excitatory change in the membrane potential of a postsynaptic neuron.

A postsynaptic potential is typically brief, with ion channels closing quickly after the stimulus occurs. If there is not another stimulus, the cell will return to the resting membrane potential.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=63#video-63-2

Animation 6.2. When a stimulus opens sodium channels, sodium rushes into the cell because the equilibrium potential of sodium is +60 mV. This causes an excitatory depolarization called an excitatory postsynaptic potential (EPSP). After the stimulus, the ion channels close, and the membrane potential returns to rest. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. 'EPSP' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Inhibitory Postsynaptic Potentials (IPSPs)

An inhibitory postsynaptic potential, or IPSP, on the other hand, is caused by the opening of chloride channels. The equilibrium potential of chloride is -65 mV, so if the neuron is at rest at -60 mV, when chloride channels open, the electrochemical gradients drive chloride to flow into the cell. Chloride brings its negative charge into the cell, causing the cell's membrane potential to become more negative, or hyperpolarize. This change is called a hyperpolarization because the cell's membrane potential is moving away from 0 mV, and the membrane is becoming more polarized. An IPSP decreases the likelihood a neuron will be able to fire an action potential, which make this ion flow inhibitory. Therefore, an IPSP is an inhibitory change in the membrane potential of a postsynaptic neuron.

Like an EPSP, an IPSP is also typically brief, and the membrane potential will return to rest if not additional stimulation occurs.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=63#video-63-3

Animation 6.3. When a stimulus opens chloride channels, and the resting membrane potential is more positive than chloride's equilibrium potential of -65 mV, chloride rushes into the cell. This causes an inhibitory hyperpolarization called an inhibitory postsynaptic potential (IPSP). After the stimulus, the ion channels close, and the membrane potential returns to rest. The dotted, blue channels represent

sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. 'IPSP' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

The Resting Membrane Potential is Critical

The direction of ion movement depends on the membrane potential of the cell

---

In the previous example, the resting membrane potential of that cell was -60 mV, so chloride moved into the cell. If the resting membrane potential was instead equal to chloride's equilibrium potential of -65 mV, then chloride would be at equilibrium and move into and out of the cell, and there would be no net movement of the ion. Even though this would lead to no change in membrane potential, the opening of chloride channels continues to be inhibitory. Increased chloride conductance would make it more difficult for the cell to depolarize and to fire an action potential.



One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=63#video-63-4

Animation 6.4. If the cell is at rest at chloride's equilibrium potential, when a stimulus opens the chloride channels, there will be no net movement of chloride in either direction because chloride will be at equilibrium. Since there is no net movement, there will also be no change in membrane potential because there is an equal amount of ion flow into and out of the cell. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. 'IPSP at Equilibrium' by Casey Henley is licensed under a

Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

If the resting membrane potential of the cell was more negative than chloride's equilibrium potential, for example, at -70 mV, then chloride would *leave* the cell, in order to move the membrane potential toward -65 mV. This would result in a depolarization of the membrane potential. However, the overall effect is still inhibitory because once the cell reaches -65 mV, the driving forces acting on chloride would try to keep the cell at that membrane potential, making it more difficult for the cell to depolarize further and fire an action potential.

A good rule of thumb is to remember that opening of sodium channels is excitatory whereas opening of chloride channels is inhibitory.



One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=63#video-63-5

Animation 6.5. If the cell is at rest at chloride's equilibrium potential, when a stimulus opens the chloride channels, chloride will leave the cell, removing its negative charge. This causes a depolarization in the membrane potential, but it is still inhibitory since chloride movement will try to keep the cell near -65 mV. TThe dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels.'Inhibitory Depolarization' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Summation of Inputs

Postsynaptic potentials combine when more than one stimulus is present

---

If an excitatory stimulus is followed by additional excitatory stimuli, the sodium channels will either remain open or additional sodium channels will open. The increased sodium conductance will cause the EPSPs to summate, depolarizing the cell further than one EPSP alone. Each neuron has a threshold membrane potential at which the cell will fire an action potential. The summation of EPSPs causes the neuron to reach that threshold.



One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=63#video-63-6

Animation 6.6. Excitatory stimuli that occur quickly in succession lead to summation of EPSPs. This leads to increased depolarization of the membrane potential compared to a single EPSP. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. 'Summated EPSP Ion Flow' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Summation can occur in two ways. Temporal summation occurs when one presynaptic input stimulates a postsynaptic neuron multiple times in a row. Spatial summation occurs when multiple presynaptic inputs each stimulate the postsynaptic neuron at the same time. Both types of summation result in a depolarization of a higher magnitude that when only on excitatory input occurs.

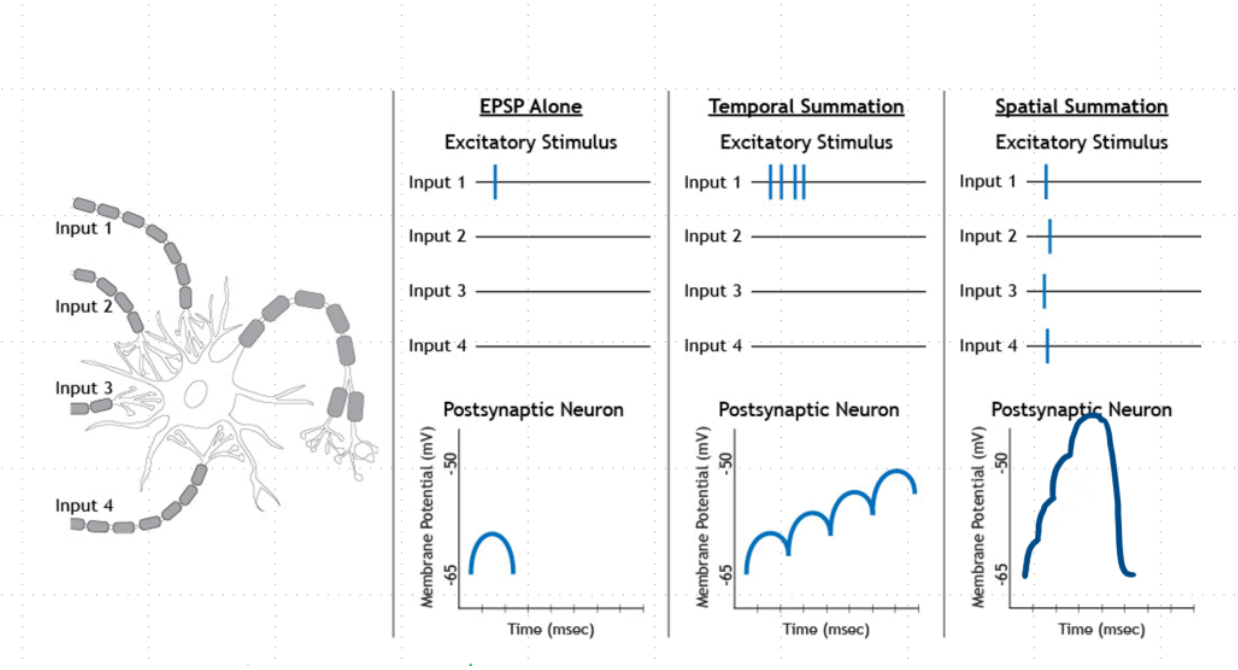


Figure 6.1 EPSPs can summate via temporal or spatial summation. Temporal summation occurs when a presynaptic neuron, Input 1 in the figure, stimulates the postsynaptic neuron multiple times in a row. Spatial summation occurs when more than one presynaptic neuron, Inputs 1 through 4 in the figure, each stimulate the postsynaptic neuron at the same time. The EPSPs of each stimulation will add together to cause a stronger depolarization of the membrane potential of the postsynaptic neuron than one excitatory stimulus alone. Modified from Synaptic Summation" by Casey Henley

In addition to the summation of excitatory inputs, EPSPs can also summate with inhibitory inputs. The addition of an inhibitory stimulus will result in either a weaker depolarization compared to a single excitatory stimulus or possibly no depolarization at all, depending on the strength of the inhibitory input.

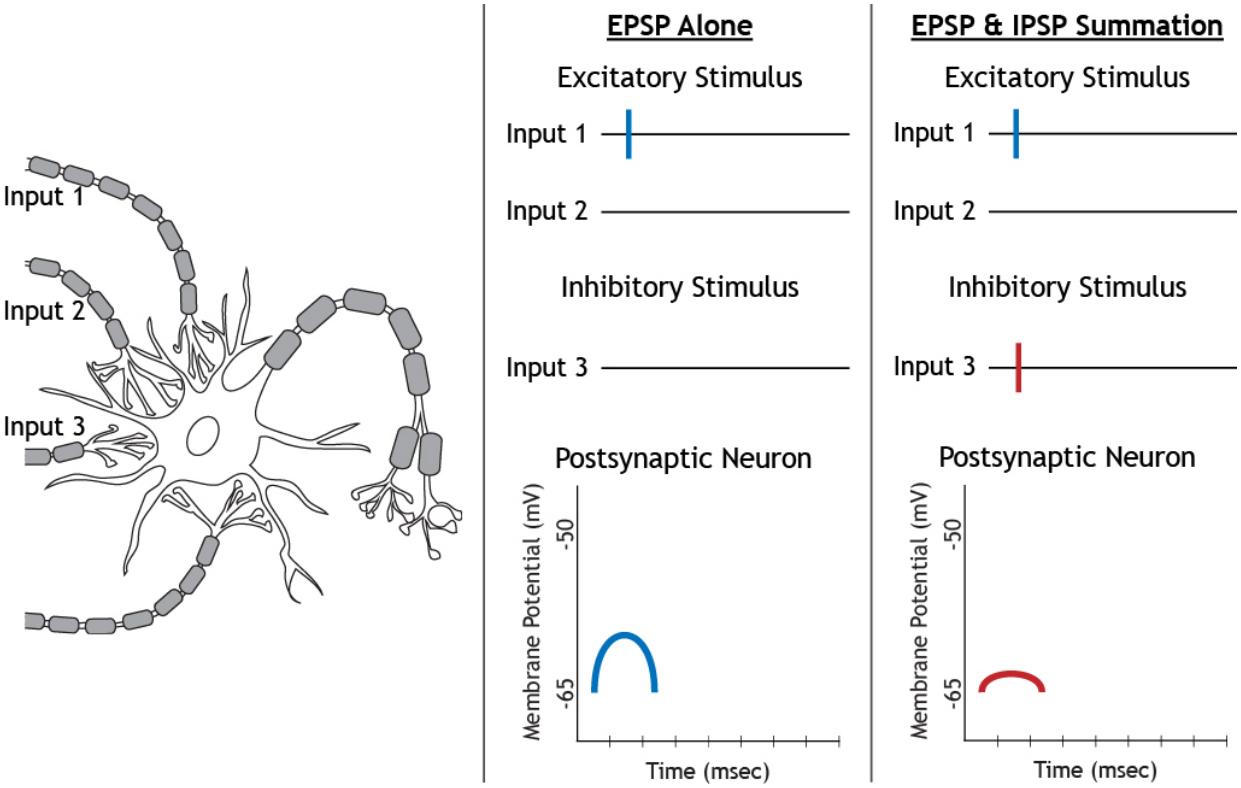


Figure 6.2. If an inhibitory input, Input 3 in the figure, stimulates the postsynaptic neuron at the same time as an excitatory input, Input 1 in the figure, the result is a decrease in the amount of depolarization or the complete prevention of depolarization, depending on the strength of the inhibitory input. 'EPSP and IPSP Summation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

In the case of combined inhibitory and excitatory stimuli, both chloride and sodium channels will open. As sodium enters the cell trying to move the membrane potential to +60 mV, the equilibrium potential of sodium, chloride will also enter, trying to keep the cell near -65 mV, the equilibrium potential of chloride.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=63#video-63-7

Animation 6.7. When an inhibitory input and an excitatory input stimulate a postsynaptic neuron at the same time, chloride and sodium channels open. Due to the equilibrium potentials of the two ions, both will flow into the cell. Sodium tries to depolarize the cell, whereas chloride tries to keep the cell near rest. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. 'EPSP and IPSP Ion Flow' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Post-synaptic potential magnitudes are thus **graded**, varying from small to large enough to trigger an action potential, and their magnitude depends on the number and intensity of input. Graded potentials diffuse along the membrane, eventually reaching the axon hillock. resulting in action potentials. Note that unlike action potentials, where gated channels in flanking regions of the membrane open to maintain the action potential, diffusion along the membrane is passive. Thus, as the potential diffuses along the membrane, its size and shape change. How far a graded potential can travel depends on the trans-membrane resistance as well as the resistance along the length of the axon. Higher trans-membrane resistance allows current to travel further, while higher resistance along the length of the axon (inside the axoplasm) will diminish the distance to which a graded potential can travel.

The graded nature of post-synaptic potentials is an important difference from the binary nature of action potentials – an action potential is either triggered fully, or not at all. One other circumstance in which graded potentials are seen is in receptor cells, where the depolarization induced by sensory input is proportional to stimulus intensity. A graded receptor potential diffuses along the membrane of the receptor cell, and causes a proportional release of synaptic vesicles at the synapse between a receptor cell and the primary sensory neuron.

Key Takeaways

- Postsynaptic potentials occur in the dendrites or cell body
- Excitatory postsynaptic potentials are caused by sodium channels opening
- Inhibitory postsynaptic potentials are caused by chloride channels opening
- Since the resting membrane of a typical neuron is usually very close to chloride's

equilibrium potential, knowing and comparing these two values is important for determining direction of ion flow when chloride channels open
- Input effects, whether excitatory or inhibitory, can summate and affect the postsynaptic neuron's membrane potential

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=63#h5p-6

Video Lecture

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=63#oembed-1

Attributions

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7.

ACTION POTENTIALS

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

As covered in Chapter 1, the action potential is a very brief change in the electrical potential, which is the difference in charge between the inside and outside of the cell. During the action potential, the electrical potential across the membrane moves from a negative resting value to a positive value and back. Alan Hodgkin and Andrew Huxley shared the Nobel Prize in 1963[1] for their discoveries about the generation and propagation of the action potential. They shared the prize with John Eccles, who worked out how synapses work.

1. https://www.nobelprize.org/prizes/medicine/1963/summary/

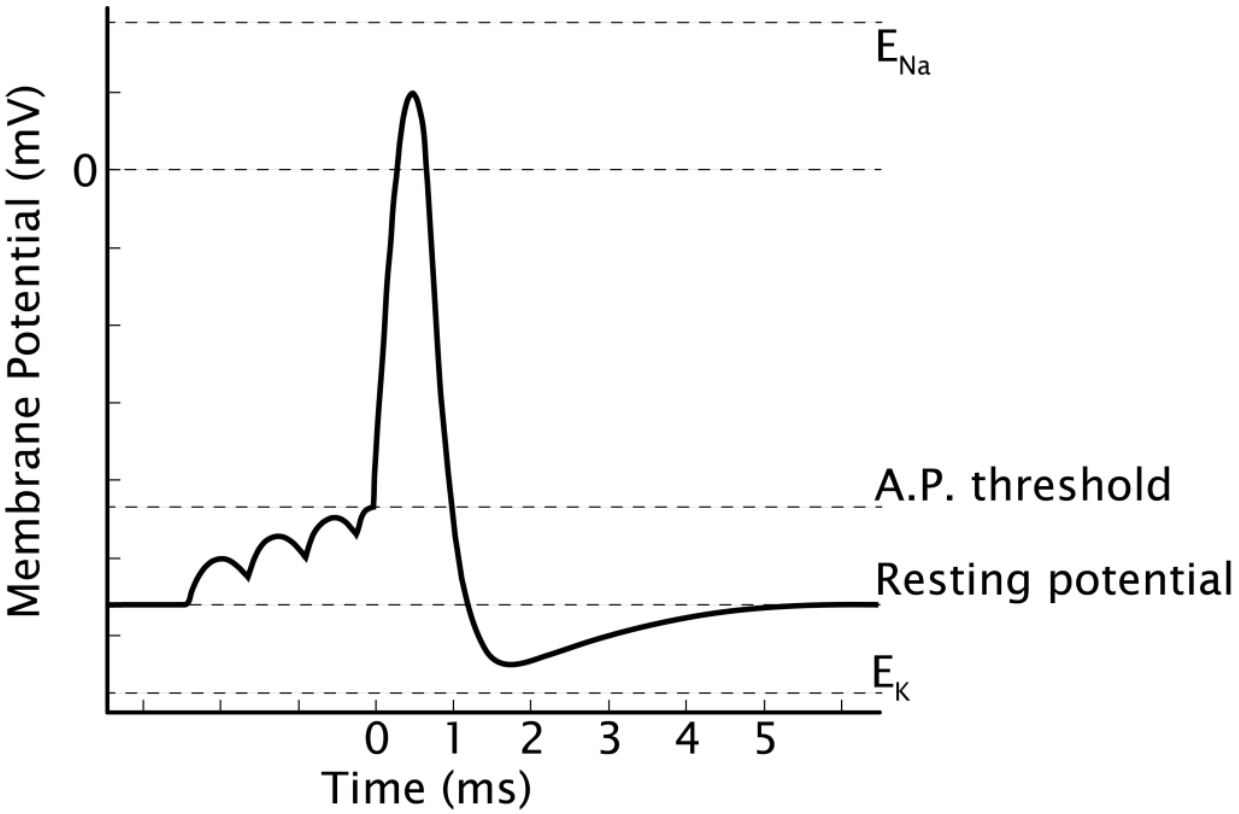


Fig 7.1 An action potential. The action potential is triggered when graded potentials (from a receptor or from dendrites) accumulate and the membrane reaches a trigger level, and a sudden cascade of channel openings produces a depolarization all the way to a positive potential. After potential reaches a peak, a different set of channels open, repolarizing the membrane. After about one ms, repolarization overshoots resting potential and leads to a relatively long period of hyperpolarization. Intracellular action potentials were first reported by Hodgkin & Huxley.

2

Propagation

The propagation of the action potential from the axon hillock down the axon and to the presynaptic

2. HODGKIN, A., HUXLEY, A. Action Potentials Recorded from Inside a Nerve Fibre. Nature 144, 710–711 (1939). https://doi.org/10.1038/144710a0

terminal results in release of chemical neurotransmitters that communicate with a postsynaptic neuron.

> *One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=79#video-79-1*

Animation 7.1. The action potential moves down the axon beginning at the axon hillock. The action potential moving down a myelinated axon will jump from one Node of Ranvier to the next. This saltatory conduction leads to faster propagation speeds than when no myelin in present. When the action potential reaches the synaptic terminal, it causes the release of chemical neurotransmitter. 'Action Potential Propagation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Voltage-Gated Ion Channels

The change in membrane potential during the action potential is a function of ion channels in the membrane. In the previous lessons, we have learned about the principles of ion movement and have discussed non-gated (leak) channels at rest, as well as ion channels involved in the generation of postsynaptic potentials. In this chapter, we will examine a different type of ion channel: voltage-gated ion channels. For our purposes, these channels are located primarily at the axon hillock, along the axon and at the terminal. They are necessary for the propagation of the action potential.

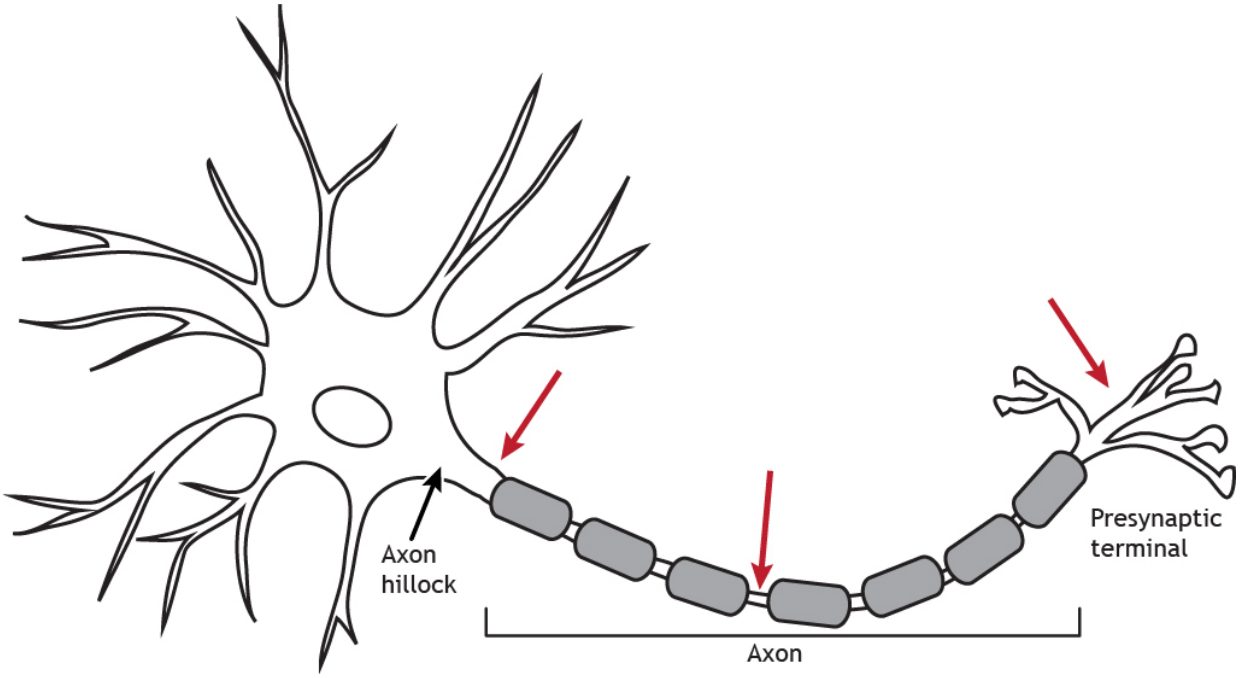


Figure 7.2. Voltage-gated channels critical for the propagation of the action potential are located at the axon hillock, down the axon at the Nodes of Ranvier, and in the presynaptic terminal. 'Voltage-Gated Channel Location' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Voltage-gated channels allow ions to cross the membrane using the same ion movement principles covered in previous lessons. The main difference between voltage-gated channels and leak channels are how they are opened or "gated". Voltage-gated channels open when the cell's membrane potential reaches a specific value, called threshold. The neuron reaches threshold after enough EPSPs summate together.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=79#video-79-2

Animation 7.2. As EPSPs summate, a result of ion movement not shown in the animation, the cell's membrane potential will depolarize. Reaching threshold causes voltage-gated ion channels to open.

Once the channels are open, ions will move toward equilibrium. In the animation, sodium ions flow inward. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels; the solid yellow channels represent chloride channels. 'Voltage-Gated Channel' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

The actions of the voltage-gated channels cause the different phases of the action potential

---

The action potential begins when the cell's membrane potential reaches threshold, caused by the summation of EPSPs (Chapter 5). Once initiated in a healthy, unmanipulated neuron, the action potential has a consistent structure and is an all-or-nothing event. It will run through all the phases to completion[3].

The rising phase is a rapid depolarization followed by the overshoot, when the membrane potential becomes positive. The falling phase is a rapid repolarization followed by the undershoot, when the membrane potential hyperpolarizes past rest. Finally, the membrane potential will return to the resting membrane potential.

3. HODGKIN AL, HUXLEY AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol. 1952 Aug;117(4):500-44. doi: 10.1113/jphysiol.1952.sp004764. PMID: 12991237; PMCID: PMC1392413.

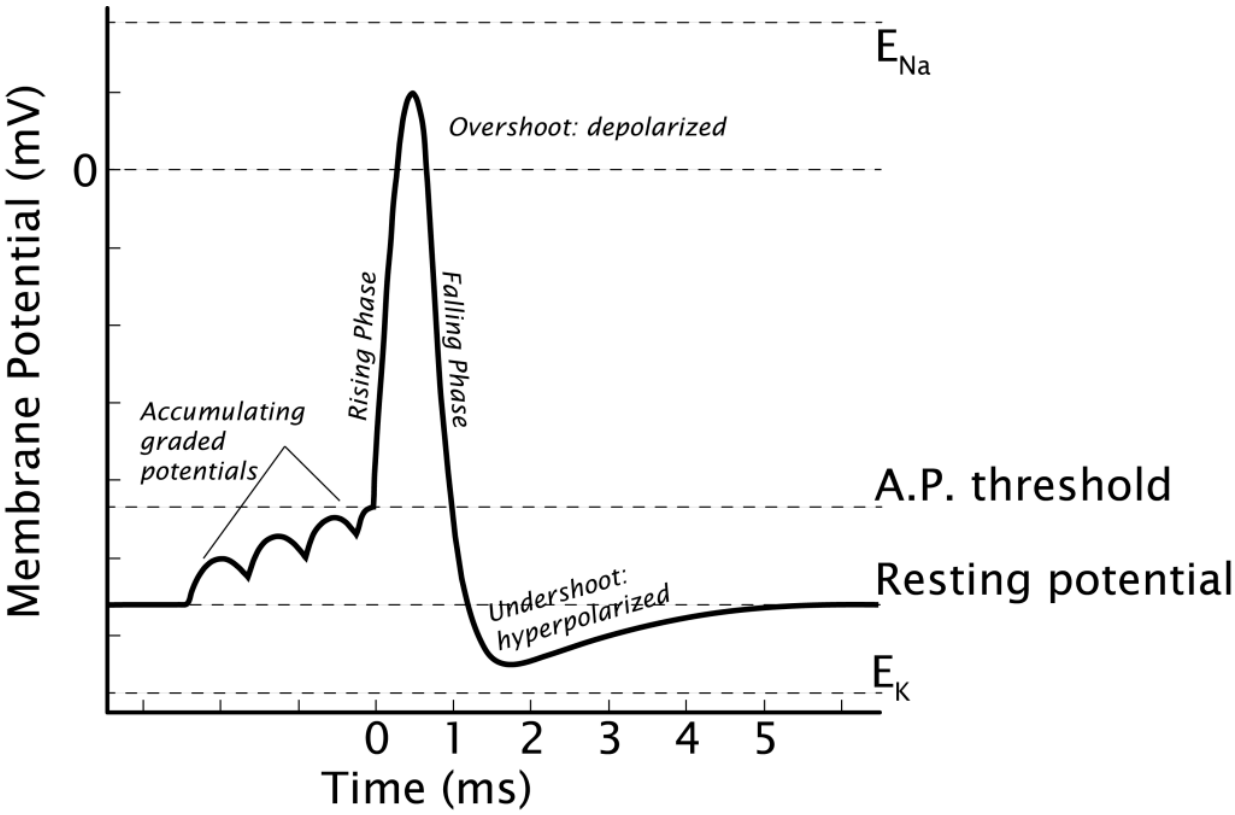


Fig 7.3 Phases of an action potential. EPSPs summate over space and time to reach threshold potential. Once a spike is initiated, voltage-gated sodium channels open exponentially, leading to a rising phase is initiated. This increase in potential is offset by the opening of voltage-gated potassium channels, leading to the falling phase. Potassium channels start to close at the threshold voltage, continuing past resting potential, leading to an undershoot. Slow ion exchange through sodium-potassium pumps eventually restores membrane potential.

Rising Phase

The rising phase is caused by the opening of voltage-gated sodium channels. These ion channels are activated once the cell's membrane potential reaches threshold and open immediately. The electrochemical gradients drive sodium into the cell causing the depolarization.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=79#video-79-3

Animation 7.3. Voltage-gated sodium channels open once the cell's membrane potential reaches threshold. The rapid influx of sodium results in a large depolarization called the rising phase. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels; the solid yellow channels represent chloride channels. 'Rising Phase' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Falling Phase

The falling phase of the action potential is caused by the inactivation of the sodium channels and the opening of the potassium channels. After approximately 1 msec, the sodium channels inactivate. The channel becomes blocked, preventing ion flow. At the same time, the voltage-gated potassium channels open. This allows potassium to rush out of the cell because of the electrochemical gradients, taking its positive charge out of the cell, and repolarizing the membrane potential, returning the cell's membrane potential back near rest.

Like the voltage-gated sodium channels, the voltage trigger for the potassium channel is when the cell's membrane potential reaches threshold. The difference is that the sodium channels open immediately, whereas the potassium channels open after a delay.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=79#video-79-4

Animation 7.4. After approximately 1 msec, the voltage-gated sodium channels inactivate, which prevents any further ion flow into the cell. Although the voltage-gated potassium channels are activated

in response to the cell reaching threshold, their opening is delayed and occurs alone with the sodium channel inactivation. This allows an efflux of potassium ions, which causes the repolarization of the falling phase. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels; the solid yellow channels represent chloride channels. 'Falling Phase" by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Undershoot

As the membrane potential returns to resting level, the sodium channels will de-inactivate, returning to the closed position, ready to be opened by a voltage change again. The potassium channels will also close, but they remain open long enough to cause a hyperpolarizing undershoot as potassium continues to move toward its equilibrium potential of -80 mV.

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Animation 7.5. Once the cell's membrane potential repolarizes, the voltage-gated sodium channels de-inactivate and return to their closed state. The voltage-gated potassium channels remain open long enough for the undershoot to occur as potassium continues to flow out of the cell. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels; the solid yellow channels represent chloride channels. 'Undershoot' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Return to Rest

Once the voltage-gated channels close, the sodium-potassium pumps will reestablish the proper ionic concentrations needed for the electrochemical gradients. This action along with open leak channels in

the membrane will return the cell to its resting membrane potential, ready to fire another action potential.

> *One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=79#video-79-6*

Animation 7.6. Once the voltage-gated potassium channels close, the sodium-potassium pump will work to re-establish the electrochemical gradients and return the cell to its resting membrane potential. 'Return to Rest' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Speed of Propagation

Presence of Myelin

The presence of myelin leads to a significant increase in action potential conduction speed compared to an unmyelinated axon. For a myelinated axon, the action potential "jumps" between Nodes of Ranvier in a process called saltatory conduction. The nodes have a high density of voltage-gated channels, and the action potential is able to skip the axon segments covered by the myelin. In an unmyelinated axon, the action potential moves in a continuous wave. In additional to the saltatory conduction process, the presence of myelin also insulates the axon, preventing charge loss across the membrane, which also increases speed of the action potential.

> *One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=79#video-79-7*

Animation 7.7. The action potential moves down an unmyelinated axon like a wave, opening voltage-gated channels along the length of the axon. In a myelinated axon, though, the action potential is able to skip portions of the axon that are covered by the myelin; the action potential jumps from node to node and travels further down the axon in the same amount of time. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels. 'Action Potential Speed' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Diameter of Axon

The diameter of the axon also affects speed. The larger the diameter of the axon, the faster the propagation of the action potential down the axon. A larger axon leads to less resistance against the flow of ions, so the sodium ions are able to move more quickly to cause the regeneration of the action potential in the next axon segment.

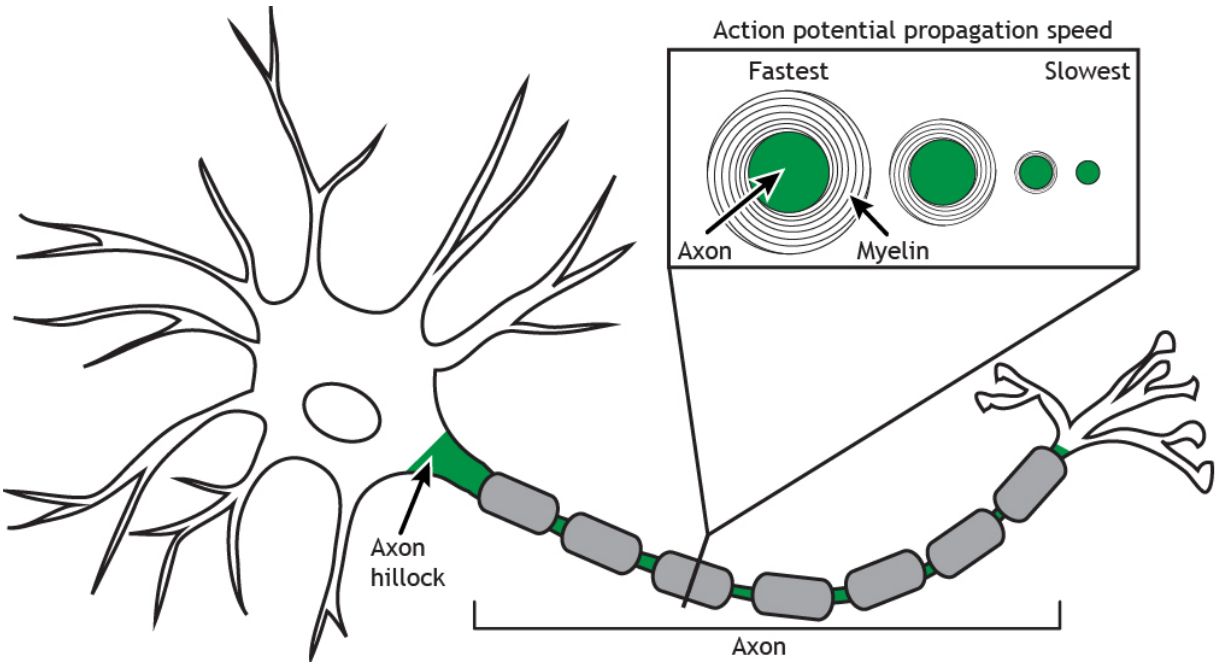


Figure 7.4. The diameter of the axon and the amount of myelination varies. Large diameter axons typically have thicker myelin sheath, which results in fast action potential speed. Small diameter axons may have no myelin present, resulting in slow action potential speed. 'Axon Diameter' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Direction of Propagation

The action potential moves down the axon due to the influx of sodium depolarizing nearby segments of axon to threshold.

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Animation 7.8. A voltage change that reaches threshold will cause voltage-gated sodium channels to open in the axonal membrane. The influx of sodium causes the rising phase of the action potential, but

the ion flow also depolarizes nearby axon regions. As the depolarization reaches threshold, the action potential moves down the axon. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels. 'Action Potential Movement' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Action potentials only move in one direction, though, from the cell body to the presynaptic terminal. The refractory period keeps the action potential from moving backward down the axon. As the action potential moves from one Node of Ranvier to the next, the inactivated sodium channels in the previous axon segment prevent the membrane from depolarizing again. Therefore, the action potential can only move forward toward axon segments with closed sodium channels ready for rising phase depolarization.

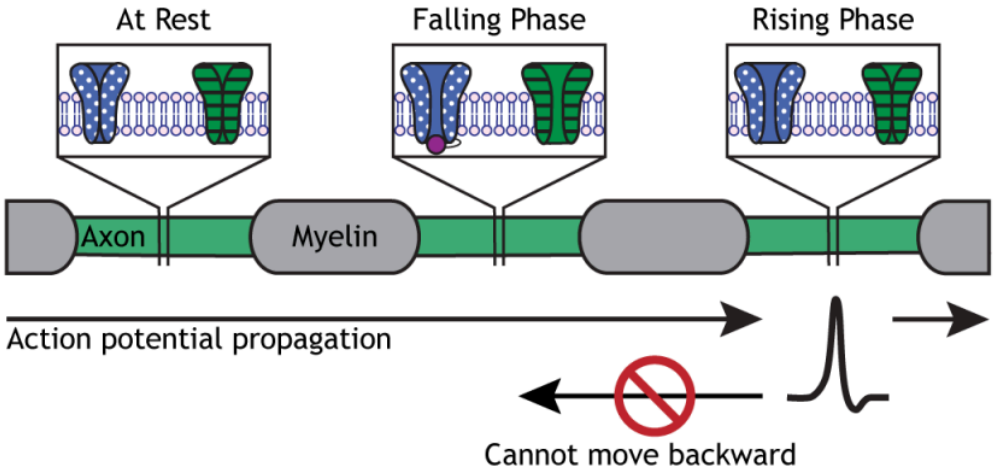


Figure 7.5. Action potentials only travel in one direction. The inactivated sodium channels prevent the action potential from moving backward down the axon. Blue dotted channels: sodium channels; green striped channels: potassium channels. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels. 'No Backward Propagation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Speed of Firing Rate

Stimulus Strength

The strength of a stimulus needs to be encoded by the neurons. We need to be able to perceive the

difference, for example, between a dim light and a bright one. The frequency or rate of action potential firing informs the nervous system of stimulus strength.

Since the height of the action potential is always the same for a given neuron, the strength of the stimulus is determined by the frequency of action potential firing. A weak stimulus would cause fewer action potentials to be fired than a strong stimulus.

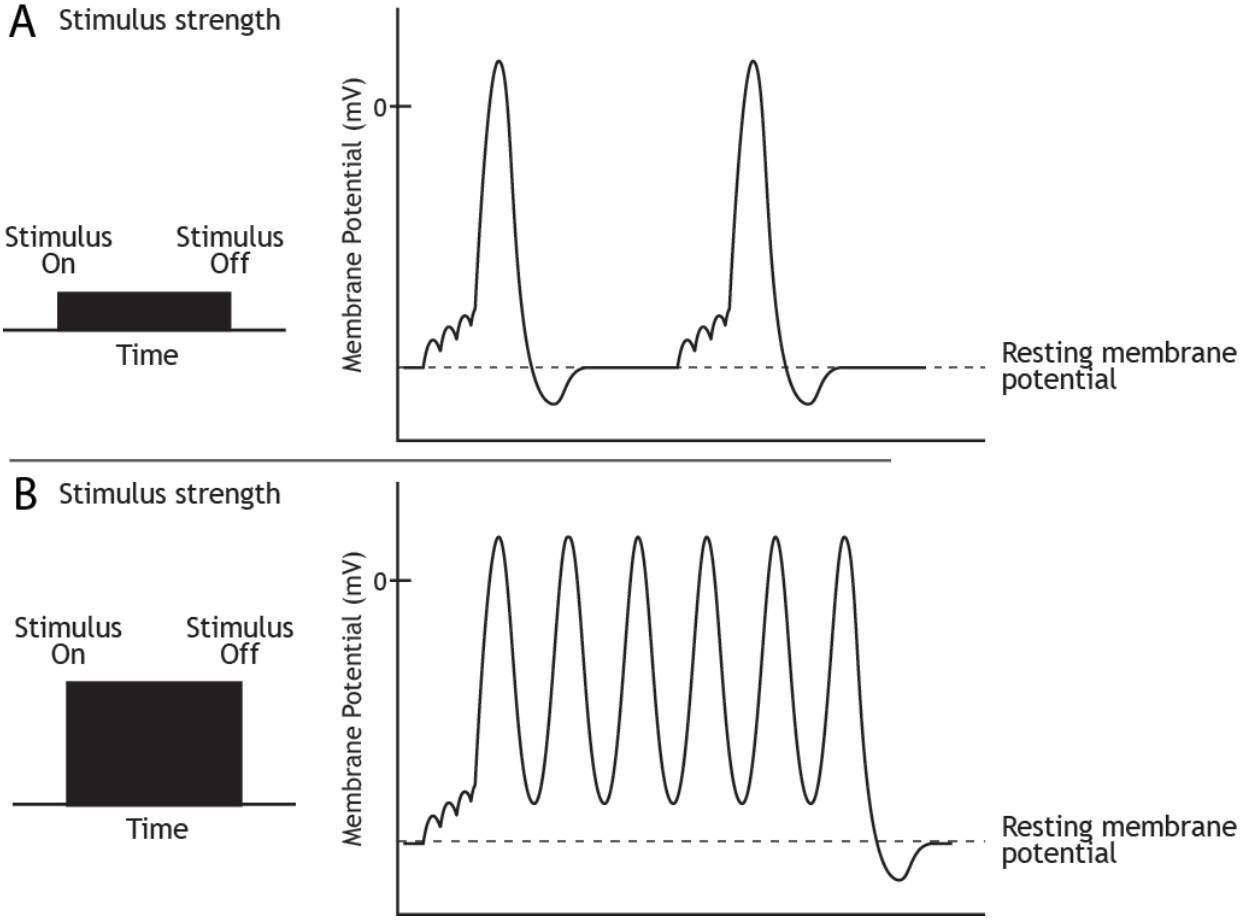


Figure 7.6. Information about the strength of a stimulus is encoded by the rate of action potential firing. A) A weak stimulus results in few action potentials being fired. B) A strong stimulus results in many action potentials firing in a row. 'Stimulus Strength' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

The Absolute Refractory Period

At some point, even if the stimulus continues to increase in strength, the neuron cannot fire at a

higher frequency. This is the cell's maximum firing rate. The maximum firing rate of a cell is determined by the status of the ion channels in the neuronal membrane during the different phases of the action potential. During the absolute refractory period, a second action potential cannot be fired under any circumstances regardless of the strength of the stimulus. The voltage-gated sodium channels are either open (during the rising phase) or inactivated (during the falling phase). Therefore, the cell cannot fire faster than the time it takes to pass through the absolute refractory period.

The Relative Refractory Period

When the cell repolarizes and the voltage-gated sodium channels de-inactivate and return to a closed state, the cell is again able to fire another action potential. However, during the end of the falling phase and the during the undershoot, voltage-gated potassium channels are still open. During the undershot, while the neuron is hyperpolarized, a larger-than-normal stimulus is needed to make the cell reach threshold again. This segment of the action potential is called the relative refractory period. Action potentials can be fired, but a stronger stimulus is needed than when the cell is at rest.

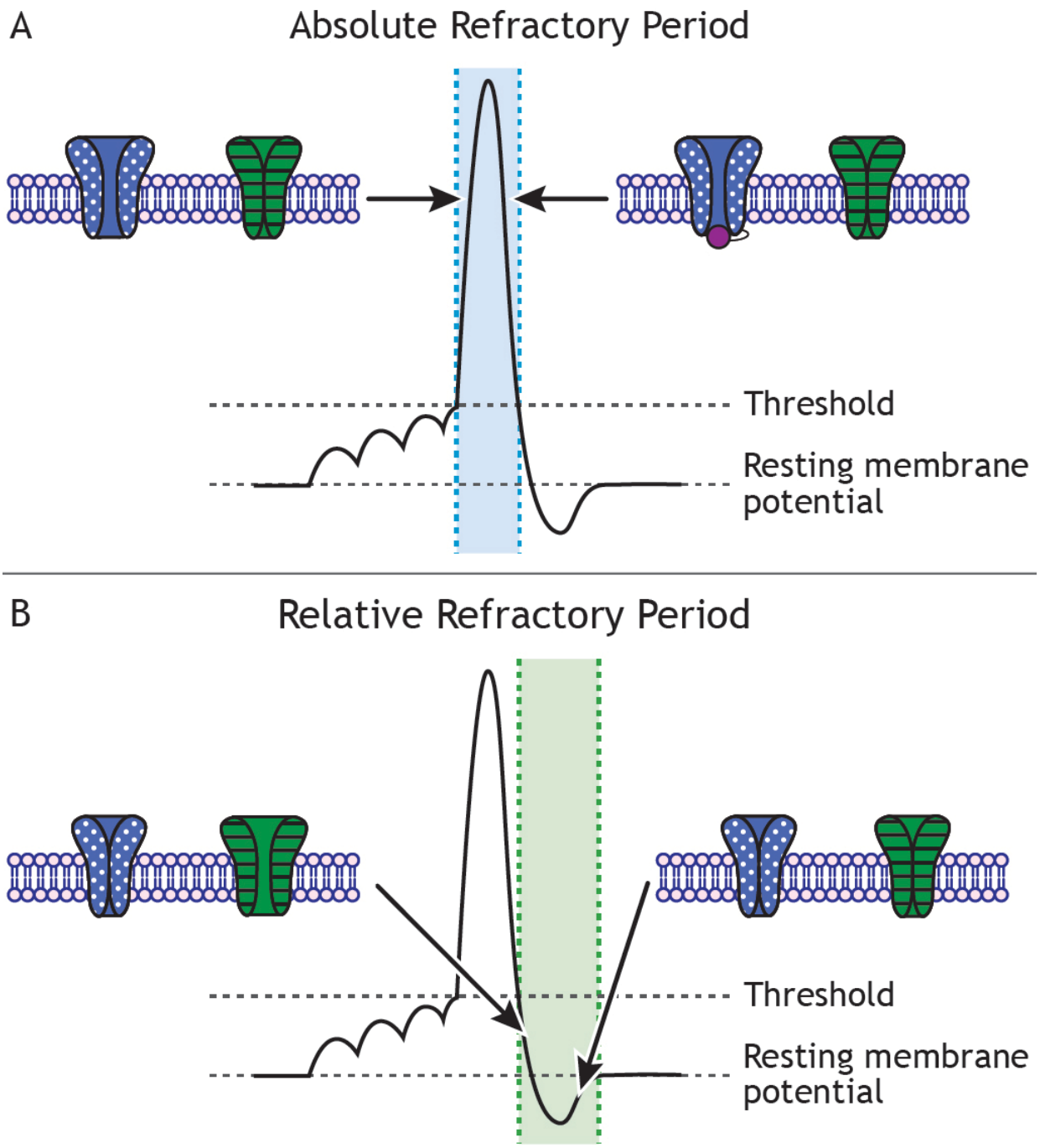


Figure 7.7. The maximum firing rate of a neuron is determined by the refractory periods. A) During the absolute refractory period no additional action potentials can be fired because the voltage-gated sodium channels are either already open (rising phase) or inactivated (falling phase). In these states, they cannot be opened again to begin a second action potential. B) The relative refractory period occurs when the voltage-gated sodium channels are closed, but the open voltage-gated potassium channels cause a hyperpolarization of the membrane. After the potassium

channels close, it takes a short period of time for the membrane potential to return to rest. Action potentials can be fired during this time, but a stronger stimulus is required to reach threshold compared to when the cell is at rest. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels; the solid yellow channels represent chloride channels. 'Refractory Periods" by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Action Potential Characteristics Can Change

For a given cell, all action potentials have the same characteristics; they depolarize to the same membrane potential value and take the same amount of time. However, different neurons may exhibit different action potential characteristics. Likewise, if a neuron has a change in its environment, like altered extracellular ion concentrations, the shape of the action potential would change due to a change in the electrochemical gradients. For example, if the external concentration of sodium is decreased, the equilibrium potential of sodium, as well as the strength of the electrochemical gradients will change, which will result in a slower rate of rise and a lower amplitude of the action potential.

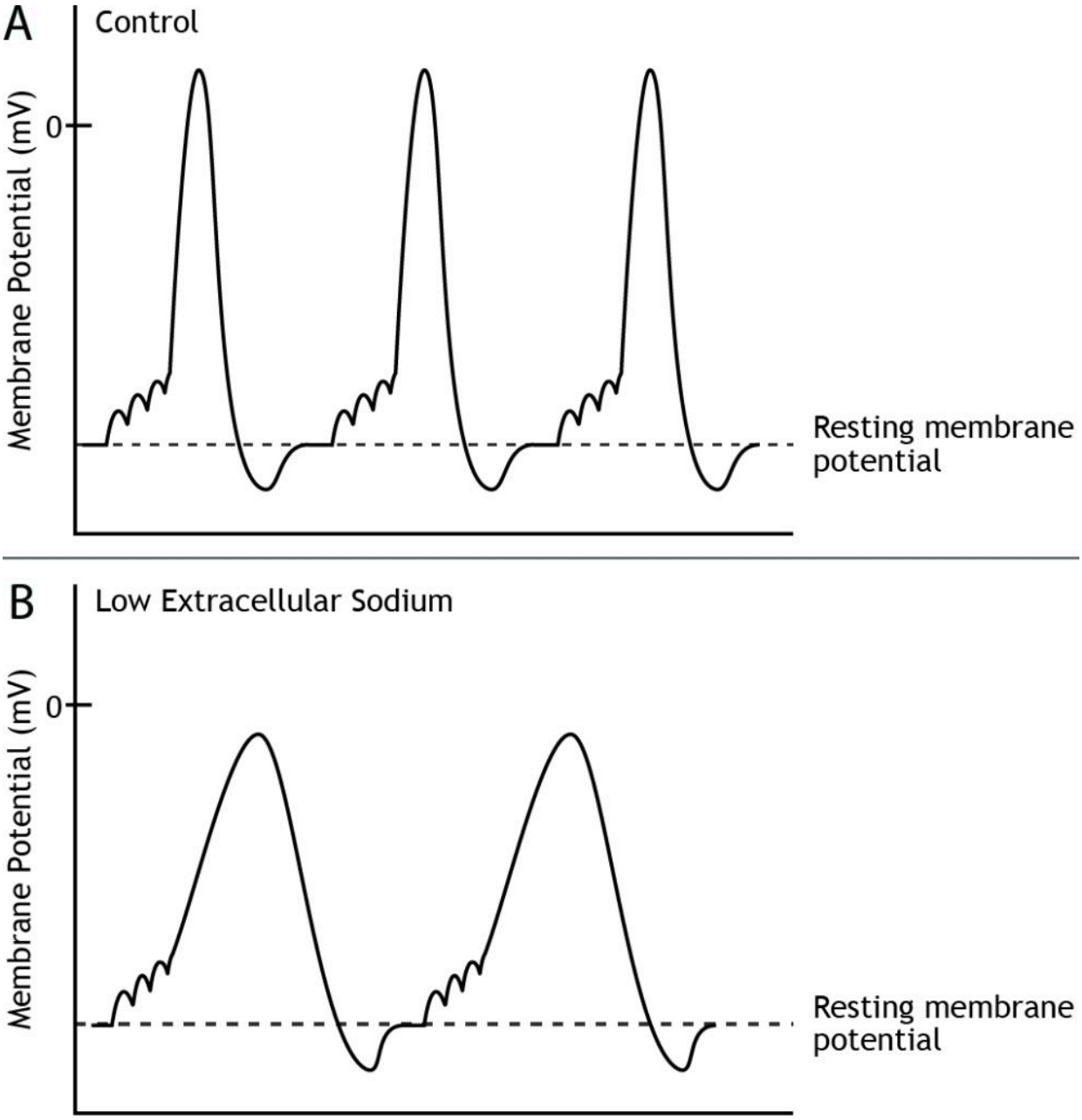


Figure 7.8. A) A neuron kept under the same conditions will display action potentials of similar height and length. B) However, if cellular conditions change, so will the action potential characteristics. If extracellular sodium levels are decreased compared to control levels, the action potential will show a slower rate of rise and a decreased height. 'Low Sodium Action Potential' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Key Takeaways

- The voltage-gated ion channels are located along the axon hillock and axon; they open in response to the membrane potential reaching a threshold value
- The rising phase of the action potential is a result of sodium influx
- The falling phase of the action potential is a result of potassium efflux
- Action potentials are all-or-none (postsynaptic potentials are graded)
- Action potential have the same height of depolarization for a given cell under typical conditions, but can change if extracellular conditions change
- Speed of propagation relies on presence and thickness of myelin and diameter of axon
- Action potential travel in one direction due to the presence of inactivated voltage-gated sodium channels
- Stimulus strength is coded by frequency of action potential firing
- The neuron cannot fire a second action potential during the absolute refractory phase
- The neuron can fire a second action potential during the relative refractory phase, but it requires a stronger stimulus than when the neuron is at rest

Test Yourself!

Try the quiz more than once to get different questions!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=79#h5p-7

- From memory, draw an action potential diagram, label each phase, identify the change in membrane potential (depolarization, repolarization, and hyperpolarization), and label threshold.
- From memory and for each phase of the action potential, draw a diagram of a neuronal membrane that includes the voltage-gated ion channels in their correct state (i.e., open, closed, inactivated).
- Compare and contrast non-gated (leak) channels and voltage-gated channels.

Video Lecture

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Attributions

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8.

VOLTAGE CLAMP

In the previous chapter, we covered ion flow and membrane potential changes that occur during the action potential in the neuron. We have this level of understanding about how ions move during the action potential because of a special technique called a voltage clamp experiment that was used in the 1950s[1]. The voltage clamp method allows researchers to study voltage-gated ion channels by controlling the membrane potential of a neuron.

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

The Voltage Clamp Experiment

Initial Set-Up

To conduct a voltage clamp experiment, a portion of the axon, which would include the cell membrane and all the voltage-gated ion channels located there, is removed from a neuron and placed into a solution that mimics that of physiological extracellular solution. The ion concentrations across the membrane, as well as the electrochemical gradients, would remain the same.

1. HODGKIN AL, HUXLEY AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol. 1952 Aug;117(4):500-44. doi: 10.1113/jphysiol.1952.sp004764. PMID: 12991237; PMCID: PMC1392413.

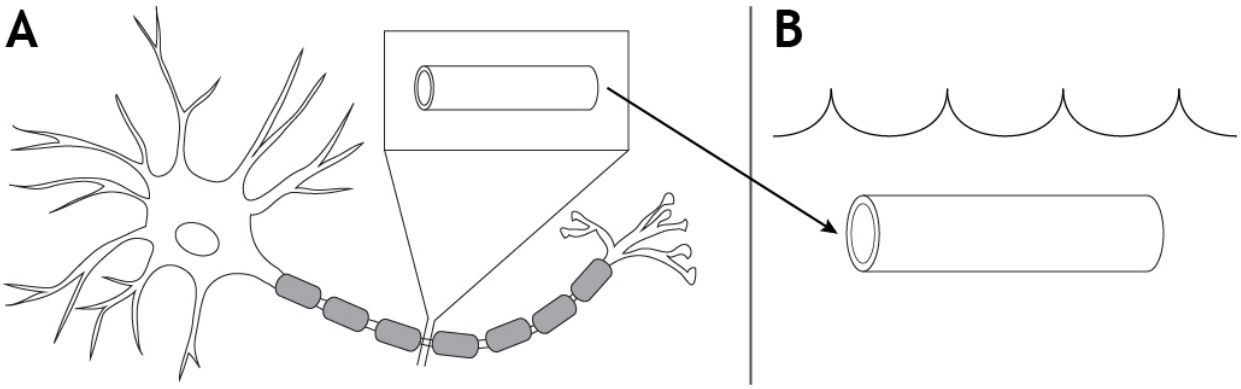


Figure 8.1. To conduct a voltage clamp experiment, a portion of the axon is removed from the neuron. The axon is placed in a special solution that is similar to physiological extracellular solution. '*In Vitro* Axon' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Measuring the Membrane Potential

The initial step in the voltage clamp method is to measure the membrane potential of the axon. A recording electrode is placed into the axon, and a reference electrode is placed into the extracellular solution. The voltage difference between these two electrodes is the membrane potential of the axon.

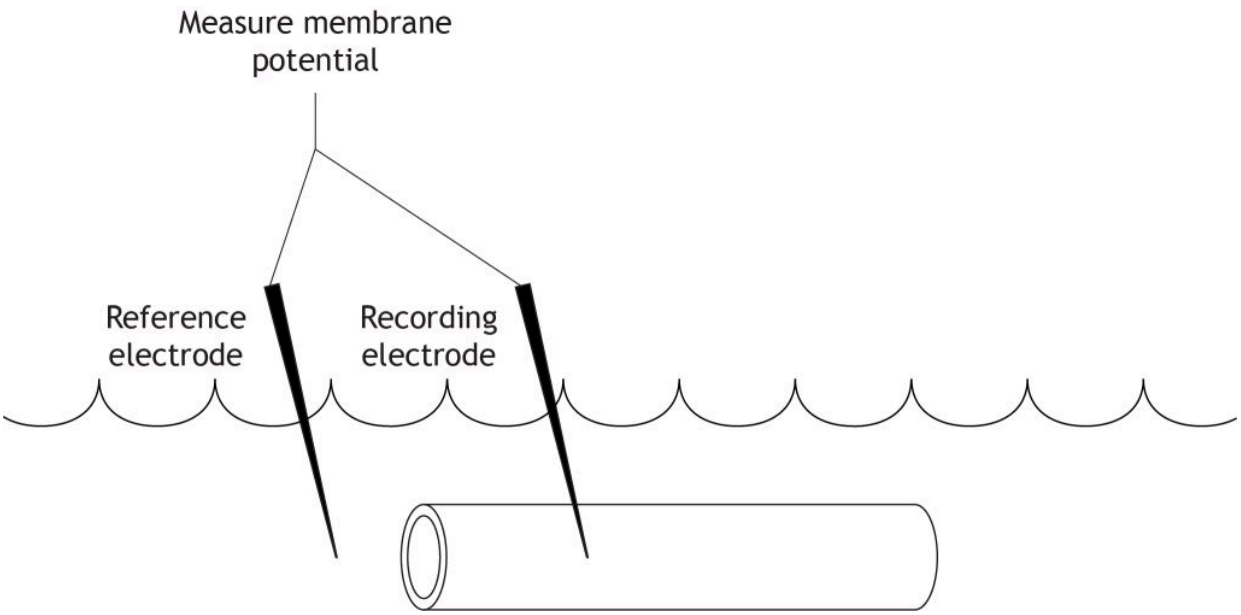


Figure 8.2. Measuring the membrane potential of the axon segment is the first step in the voltage-clamp experiment. The membrane potential is the difference in voltage between the intracellular recording electrode and the extracellular reference electrode. 'Measure Membrane Potential' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Clamping the Voltage

The researchers running the experiment can set a desired membrane potential for the cell. The equipment then compares the desired membrane potential with the measured membrane potential from the electrodes. If these values differ, current is injected into the cell to change the measured membrane potential and make it equal to the desired potential.

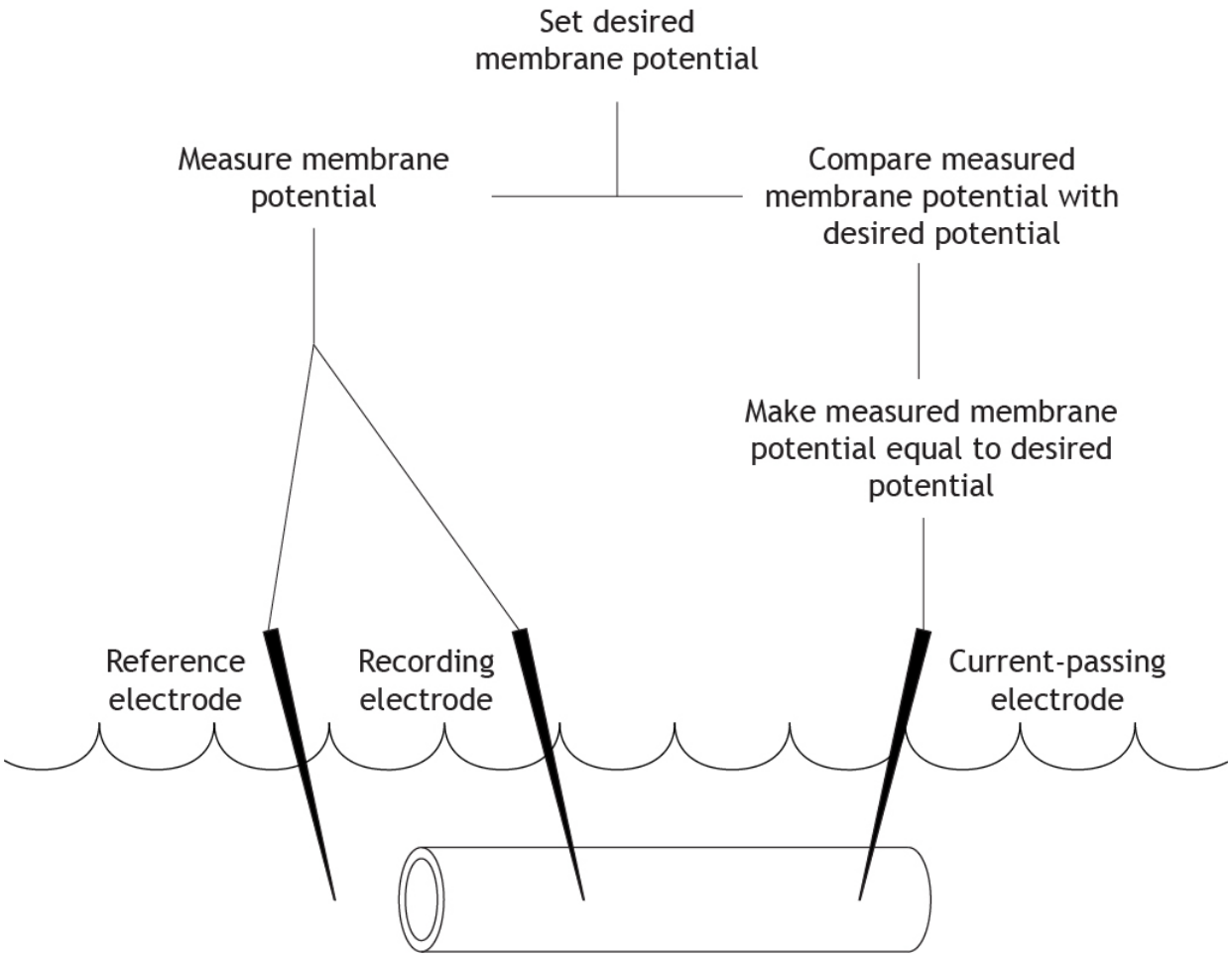


Figure 8.3. A desired membrane potential is set for the experiment. The voltage-clamp experimental equipment then compares the measured membrane potential with the desired potential. Current is then injected into the axon through a current-passing electrode to make the measured membrane potential equal to the desired potential. 'Clamping Voltage' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Repeat

The equipment continues this cycle for the length of the experiment. It constantly measures and compares the actual membrane potential with the desired potential, and then uses current to correct any changes, "clamping" the potential at one value.

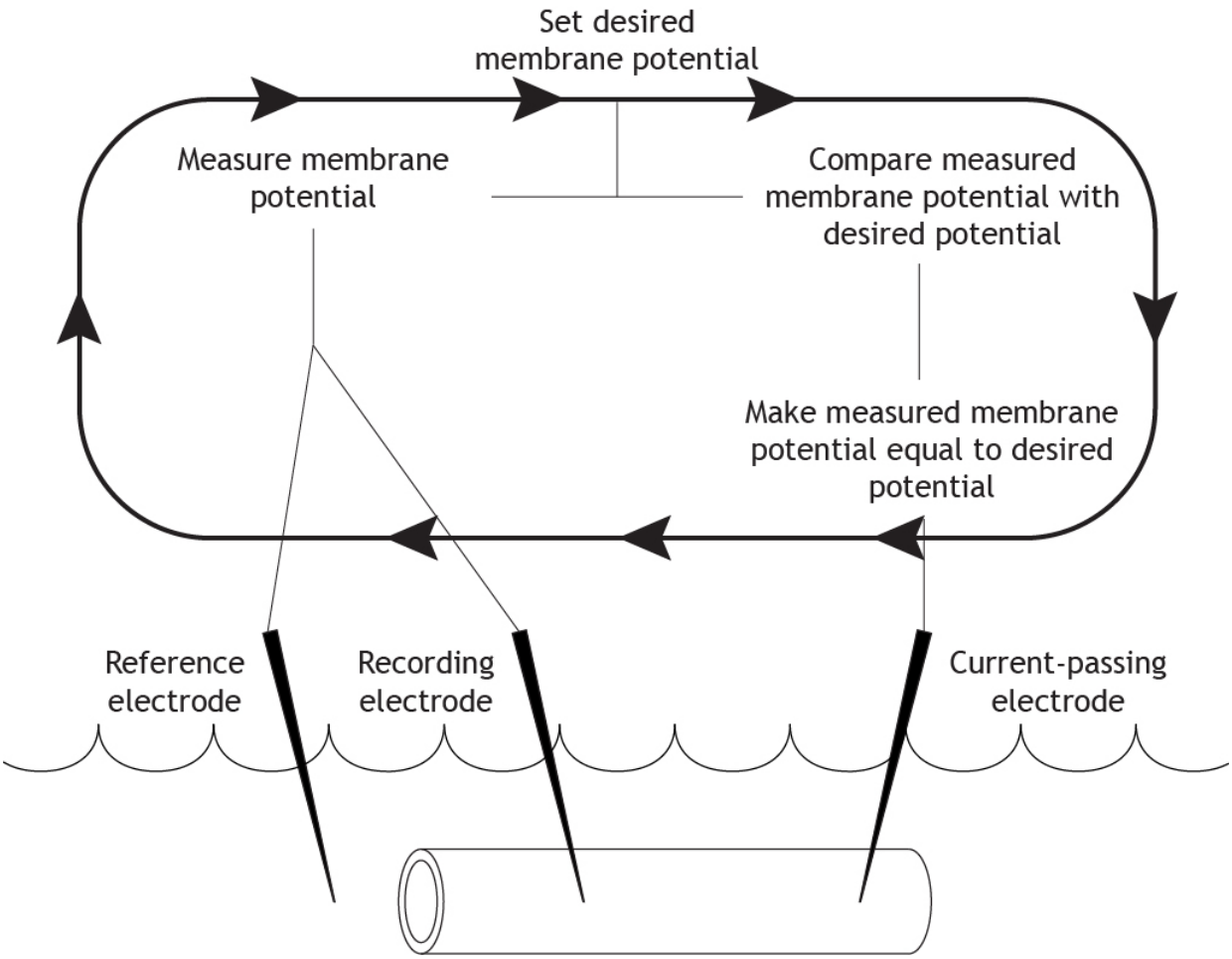


Figure 8.4. The voltage clamp cycle repeats continuously. The actual membrane potential of the axon is measured, compared to the set desired potential value, and then current is passed into the axon to keep the actual membrane potential equal to the desired potential. 'Voltage Clamp Cycle' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Voltage Clamp Experiment Example

At Rest

Let's work through the system with an example. Here is an axon bathed in the extracellular solution. The resting membrane potential is measured at -65 mV.

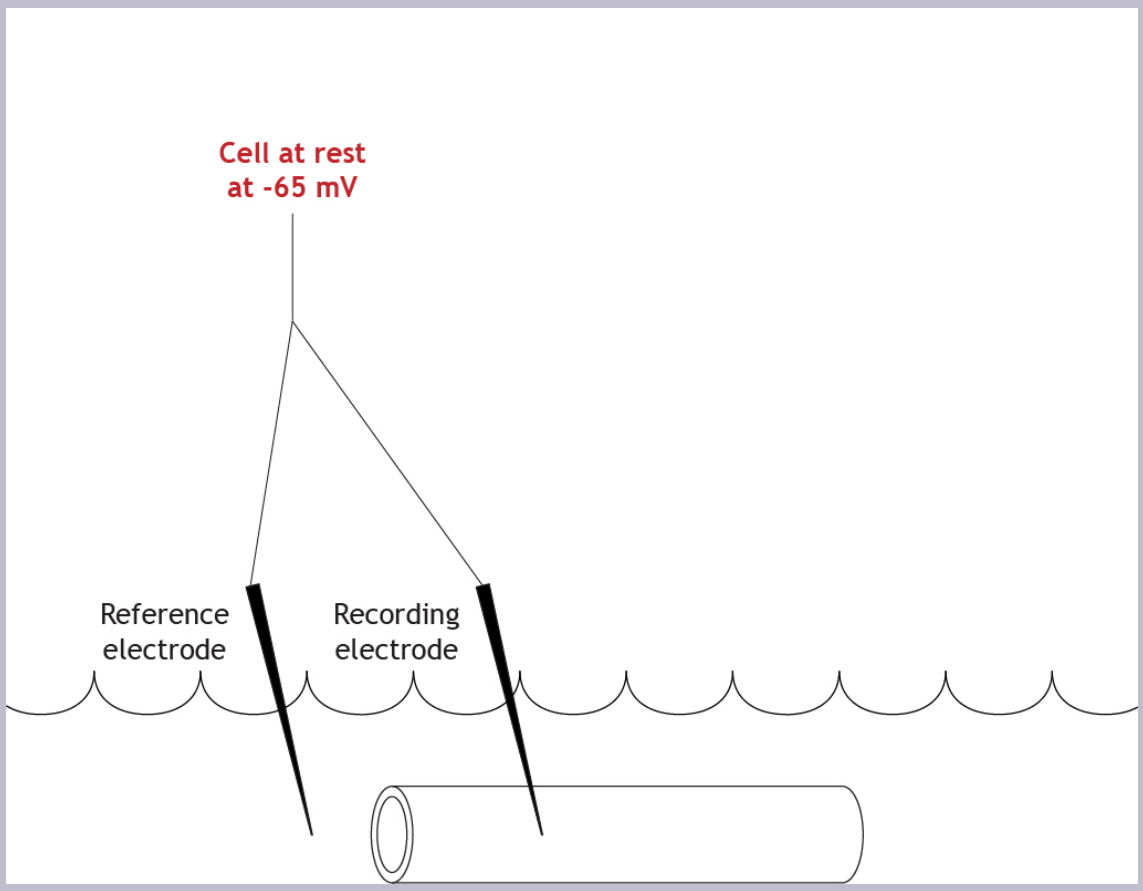


Figure 8.5. Measure the membrane potential. The membrane potential of this axon at rest is -65 mV. 'Voltage Clamp Example at Rest' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Set Clamped Membrane Potential Value

For this experiment, the desired membrane potential value is 0 mV.

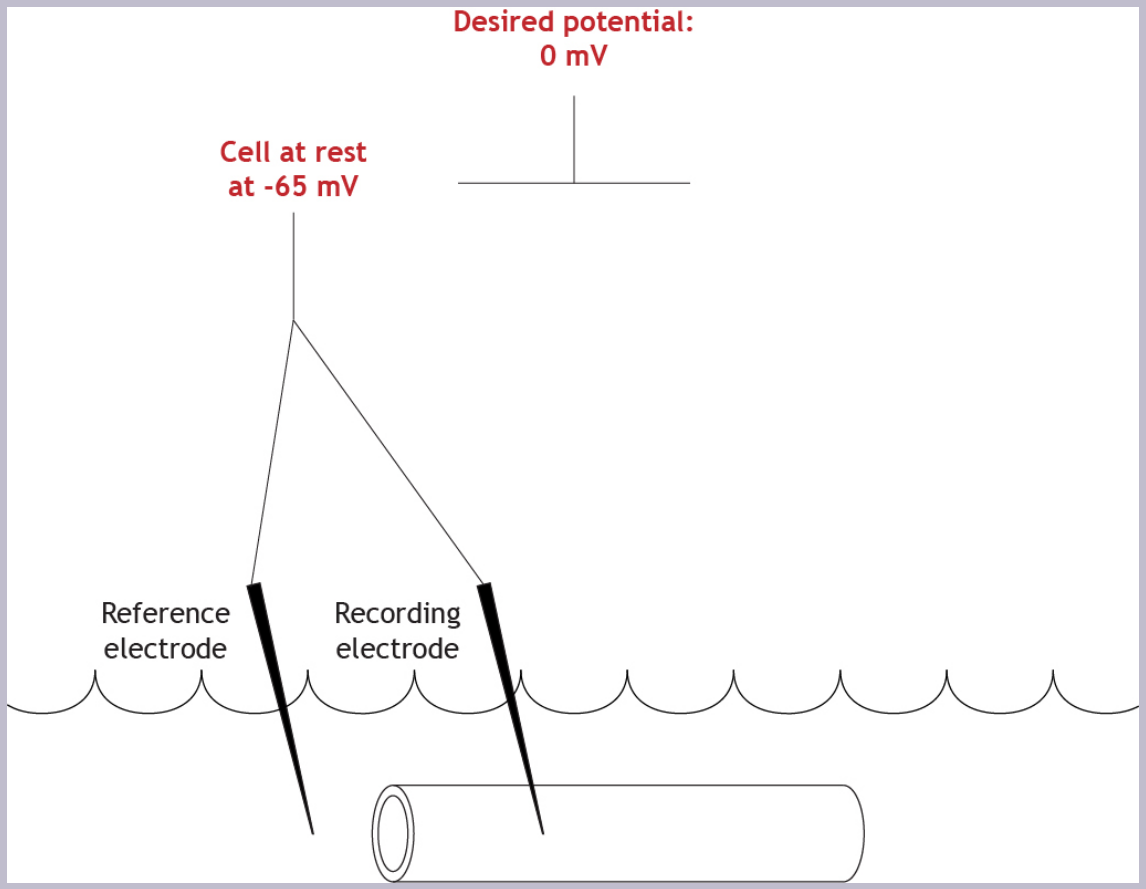


Figure 8.6. Set desired membrane potential. The set value for this experiment is 0 mV. 'Voltage Clamp Example Set Value' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Compare Actual and Set Membrane Potential Values

The equipment will determine that the actual membrane potential of the cell is not correct (-65 mV compared to 0 mV), so the cell must depolarize to reach the set value.

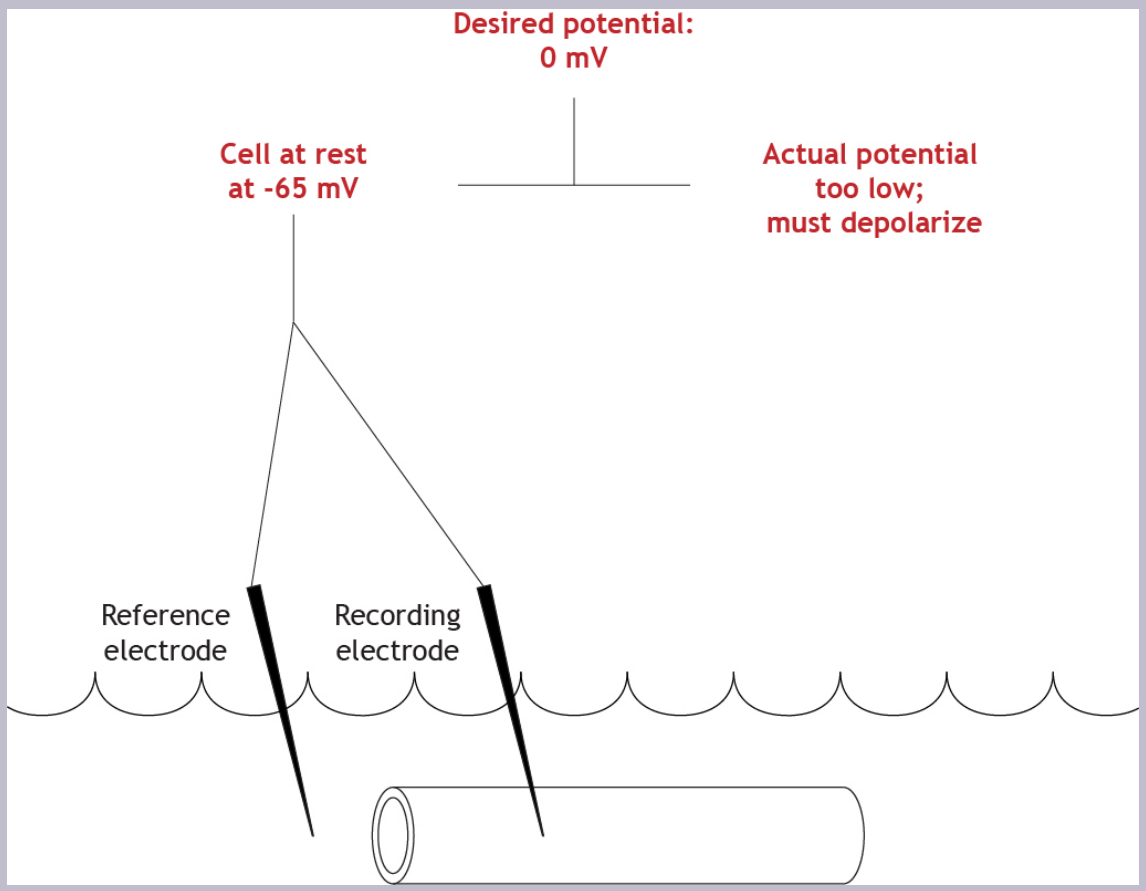


Figure 8.7. Compare measured membrane potential to desired potential. The actual membrane potential of the axon is at -65 mV, so the cell needs to be depolarized to reach the desired potential of 0 mV. 'Voltage Clamp Example Comparison' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Adjust Membrane Potential

To make the axon move from its resting membrane potential to 0 mV, the current electrode will pass positive current into the cell, depolarizing the cell until the membrane potential reaches the set value.

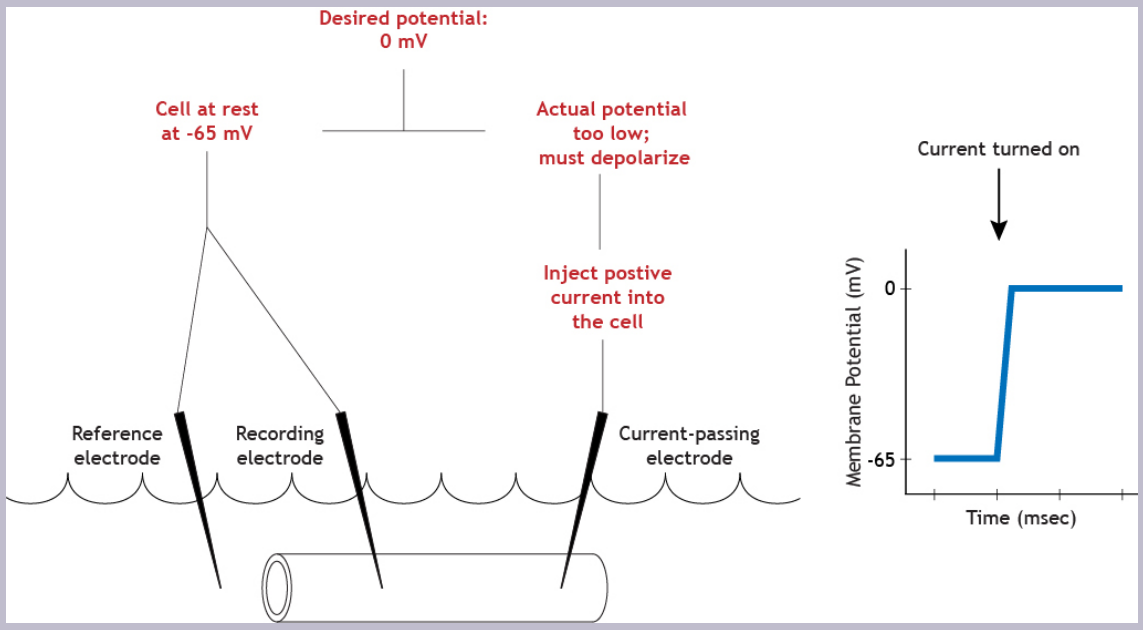


Figure 8.8. Correct actual membrane potential. To depolarize this axon from rest at -65 mV to the desired clamp value of 0 mV, positive current will be injected into the cell. The membrane potential will then depolarize to 0 mV and remain there. 'Voltage Clamp Example Current' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Ion Channels Continue to Function During Voltage Clamp

The important aspect of the depolarization seen in the example is that it is above threshold. Moving the membrane potential above threshold will activate the voltage-gated ion channels. Sodium channels will open immediately, and sodium will begin rushing into the cell. This influx of positive ions would normally cause change the membrane potential to depolarize, but the voltage clamp equipment will measure the ion flow and inject a current of equal strength and opposite charge into the axon to maintain the membrane potential at 0 mV. This happens almost instantly and is a constant process, so as the ion flow changes, so does the injected current.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=91#video-91-1

Animation 8.1. Clamping the cell at 0 mV will result in current being passed into the axon to depolarize the membrane potential. This depolarization is above threshold, so the voltage-gated ion channels in the membrane will be activated. Sodium will enter the axon through the open sodium channels. The voltage clamp equipment will inject current equal in strength and opposite in charge to the sodium influx in order to keep the membrane potential of the axon at 0 mV. The membrane potential will remain at 0 mV because the injected current offsets any change that would normally occur due to ion flow. 'Voltage Clamp Sodium Flow' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Since the ion channels function as expected during the voltage clamp experiment, the voltage-gated sodium channels will inactivate, and the delayed voltage-gated potassium channels will open because, like the sodium channels, they are also activated when the membrane potential reaches threshold. This causes the ion flow to change from inward to outward. Normally, potassium efflux would cause a repolarization of the membrane potential, but the voltage clamp equipment will again inject a current that is equal in strength and opposite in charge to the potassium flow to keep the membrane potential steady at 0 mV.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=91#video-91-2

Animation 8.2. The voltage-gated sodium channels will inactivate, and the potassium channels will open. Potassium will then flow out of the axon. Similar to the sodium influx, the voltage clamp equipment will inject current equal in strength and opposite in charge to the potassium efflux in order to keep the membrane potential of the axon at 0 mV. 'Voltage Clamp Potassium Flow' by Casey

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Data Collection

Researchers can determine how much current is moving through the voltage-gated ion channels by observing how much current the equipment must inject into the cell to keep the membrane potential steady. If the equipment has to inject negative current in for 2 milliseconds, then the researchers know that positive ions were flowing in for 2 milliseconds. So the voltage-clamp set up allowed researchers in the 1950s to learn about how the voltage-gated ion channels were functioning during an action potential.

Key Takeaways

- The membrane potential does not change during a voltage clamp experiment
- Voltage-gated ion channels are still able to function normally and allow ion flow
- If the clamped membrane potential is above threshold, the voltage-gated channels will act as if the cell is firing an action potential
- The equipment must compensate for the neuron's ion flow by injecting current into the axon. The amount of current needed to keep the membrane potential steady is equal and opposite to the current actually flowing in the cell

Test Yourself!

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https://opentext.uoregon.edu/neurobiology/?p=91#h5p-8

Video Lecture

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Attributions

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PART II
NEURONAL COMMUNICATION

9.

STEPS IN SYNAPTIC SIGNALING

Steps in Chemical Signaling

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

As we have covered, when an action potential **propagates** down the axon to the presynaptic terminal, the electrical signal will result in a release of chemical neurotransmitters that will communicate with the postsynaptic cell.

At a chemical synapse, the process of neurotransmitter release is very tightly regulated. If there were no mechanisms to control the release of chemicals at the synapse, nerve cells would deplete their entire stock of neurotransmitter. Regulation of release depends on several proteins that are important parts of the process. These proteins are often embedded within cell membranes of the vesicles or the neuronal membrane.

Step 1: An action potential arrives at the axon terminal

There are a series of steps that take place during chemical synaptic transmission.

First, an action potential propagates down the axon until it arrives at the axon terminal, depolarizing the membrane of the presynaptic terminal.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=522#video-522-1

Animation 10.1. The action potential is a brief, but significant, change in electrical potential across the membrane. The membrane potential will move from a negative, resting membrane potential (shown here as -65 mV) and will rapidly become positive and then rapidly return to rest during an action potential. The action potential moves down the axon beginning at the axon hillock. When it reaches the synaptic terminal, it causes the release of chemical neurotransmitter. 'Action Potential Propagation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation

Step 2: Membrane depolarization from action potential causes influx of calcium ions

When the action potential reaches the terminal, there is an influx of sodium ions. This inward positive current causes a depolarization of the terminal, activating **voltage-gated** calcium channels that are embedded in the cell membrane of the axon terminals. Due to the electrochemical gradient of calcium, when the voltage-gated calcium channels are opened, calcium will rush into the cell. The concentration of intracellular calcium, generally in the range of 100 nM, is much lower than the concentration outside the cell, therefore there is a strong electrochemical gradient that moves calcium into the terminal. As it turns out, an elevation of Ca^{2+} in the intracellular space is the "go ahead" signal that causes neurotransmitter release.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=522#video-522-2

Animation 10.2. An action potential causes an influx of sodium in the terminal. The depolarization opens voltage-gated calcium channels, and calcium ions flow into the terminal down their electrochemical gradient. The blue, dotted channels represent voltage-gated sodium channels, and the purple, striped channels represent voltage-gated calcium channels. 'Terminal Calcium Influx' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Active Zones

The voltage-gated calcium channels are concentrated in the presynaptic terminal at **active zones**, the regions of the membrane where small molecule neurotransmitters are released. At active zones, some synaptic vesicles are docked and are ready for immediate release upon arrival of the action potential. Other neurotransmitter-filled vesicles remain in a reserve pool outside of the active zone.

Vesicles filled with neuropeptides do not dock at active zones. They are located outside of the active zone, further away from the membrane and the high density of voltage-gated calcium channels. They are, therefore, slower to release than the small molecule transmitters.

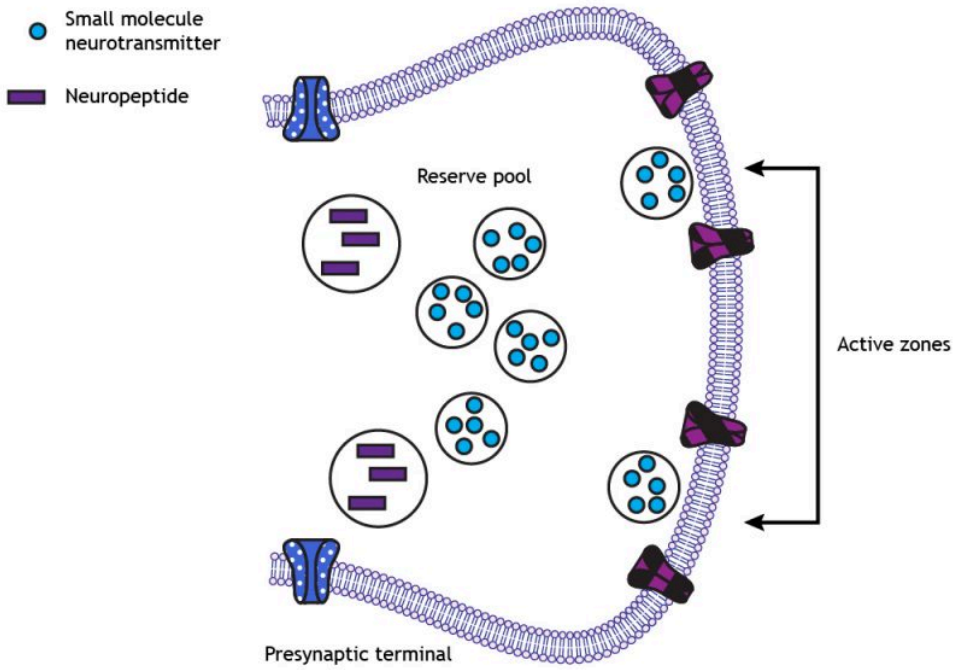


Figure 10.1. Some synaptic vesicles filled with small molecule neurotransmitters dock at active zones on the presynaptic membrane, ready for immediate release. Other synaptic vesicles remain nearby in reserve pools, ready to move into empty active zones. Neuropeptide-filled vesicles do not dock at active zones. The blue, dotted channels represent voltage-gated sodium channels, and the purple, striped channels represent voltage-gated calcium channels. 'Active Zones' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Location of vesicles

Synaptic vesicles can be found in one of three places at the axon terminal.

1. **Readily releasable pool**. These vesicles are located close to the cell membrane at the axon terminal. In fact, many of them are already "docked", meaning that their coat proteins are already interacting closely with the proteins on the inside of the cell membrane. When the depolarizing charge of an action potential reaches the terminal, these vesicles at the readily releasable pool are the first ones that fuse with the cell membrane and release their contents.
2. **Recycling pool**. These vesicles are the ones that have been depleted due to release. They are currently in the process of being refilled or reloaded with neurotransmitter. They are farther

from the cell membrane, and the protein machinery is not primed for release, so it requires a more intense stimulation to release the contents of these vesicles.

3. **Reserve pool**. These vesicles are the farthest from the surface of the cell membrane, and most vesicles are held in this reserve pool. For these neurotransmitters to be released, very intense stimulation is required.

Step 3: Docking of synaptic vesicles at the membrane

Docking of synaptic vesicles packaged with small molecule neurotransmitters occurs through the interaction of three membrane-bound proteins called SNARE proteins. **Synaptobrevin** is called a *v-SNARE* because it is located on the *Vesicular* membrane. **Syntaxin** and **SNAP-25** are called *t-SNARES* because they are located on the terminal membrane, which is the *Target* membrane. The interaction of these three proteins leads to vesicle docking at the **active zone**.

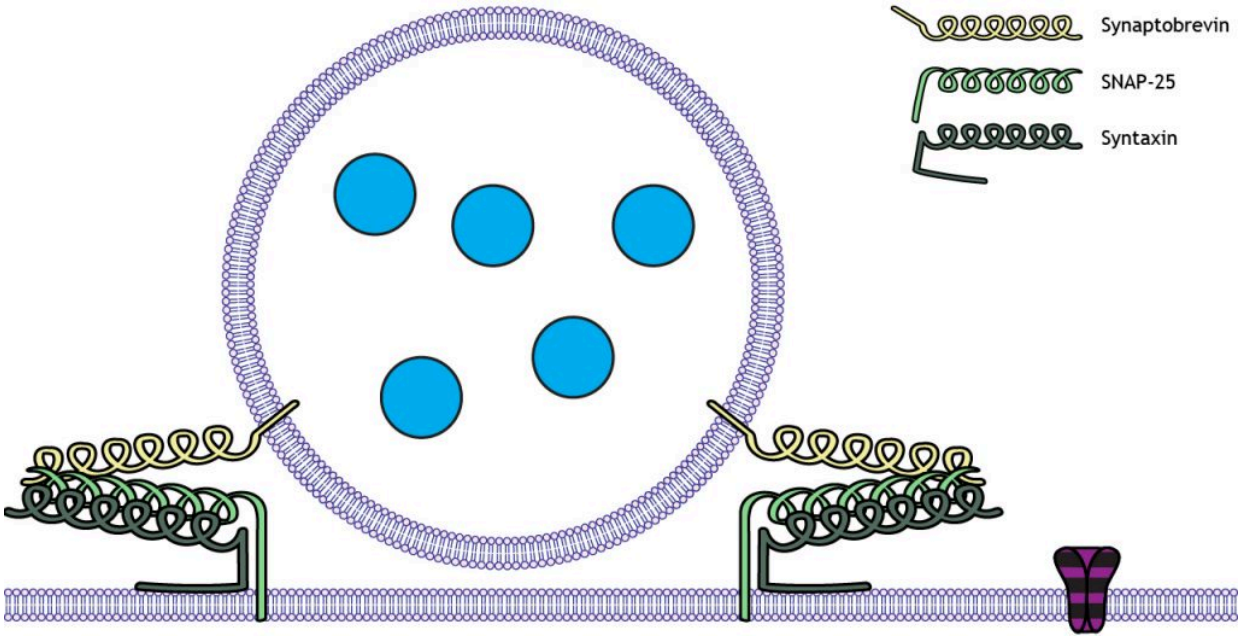


Figure 10.2. Synaptic vesicles filled with small molecule neurotransmitters are able to dock at active zones by the interaction of v- and t-SNARE proteins. Synaptobrevin is embedded in the membrane of the vesicle whereas SNAP-25 and Syntaxin are embedded in the presynaptic terminal membrane. The purple, striped channels represent voltage-gated calcium channels. 'SNARE proteins' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

The influx of calcium through the voltage-gated calcium channels initiates the exocytosis process that leads to neurotransmitter release. Calcium enters the cell and interacts with a vesicle-bound protein called **synaptotagmin**. Synaptotagmin is a calcium sensor that detects elevated levels of calcium in the axon terminal.

In the presences of calcium, the *v-SNAREs* and the *t-SNAREs* interact with one another, forming a molecular structure called a SNARE complex. The SNARE complex looks a lot like two twist ties that are wound tightly together. As they twist tighter together, it causes the vesicle membrane to approach the inside of the cell membrane, which results in vesicular fusion.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=522#video-522-3

Animation 10.3. Calcium enters the cell when the voltage-gated channels open. In the presence of calcium, synaptotagmin, a protein bound to the vesicular membrane interacts with the SNARE proteins. The purple, striped channels represent voltage-gated calcium channels. 'Synaptotagmin' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation

Step 4: Release of neurotransmitters into the synapse

The last step of neurotransmitter release is the fusing of the cell membrane. In order to release their chemical contents into the synapse, vesicles need to fuse with the cell membrane. As the vesicular membrane merges with the interior of the neuronal membrane, the membranes fuse and the contents of the vesicle become exposed to the extracellular space. The neurotransmitters then float across the aqueous synapse, giving them the opportunity to interact with postsynaptic receptors.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=522#video-522-4

Animation 10.4. Once the synaptotagmin-SNARE protein complex forms, the synaptic vesicle membrane fuses with the terminal membrane, and the neurotransmitters are released into the synaptic cleft through exocytosis. The purple, striped channels represent voltage-gated calcium channels.

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Step 5: Receptor Activation

After exocytosis of the transmitter molecules, neurotransmitters traverse across the synapse and bind to **receptors** on the postsynaptic membrane. Receptors fall into two main categories: **ionotropic receptors** (also called ligand-gated channels) and **metabotropic receptors** (also called G-protein coupled receptors). These two types of receptors will be covered in upcoming chapters.

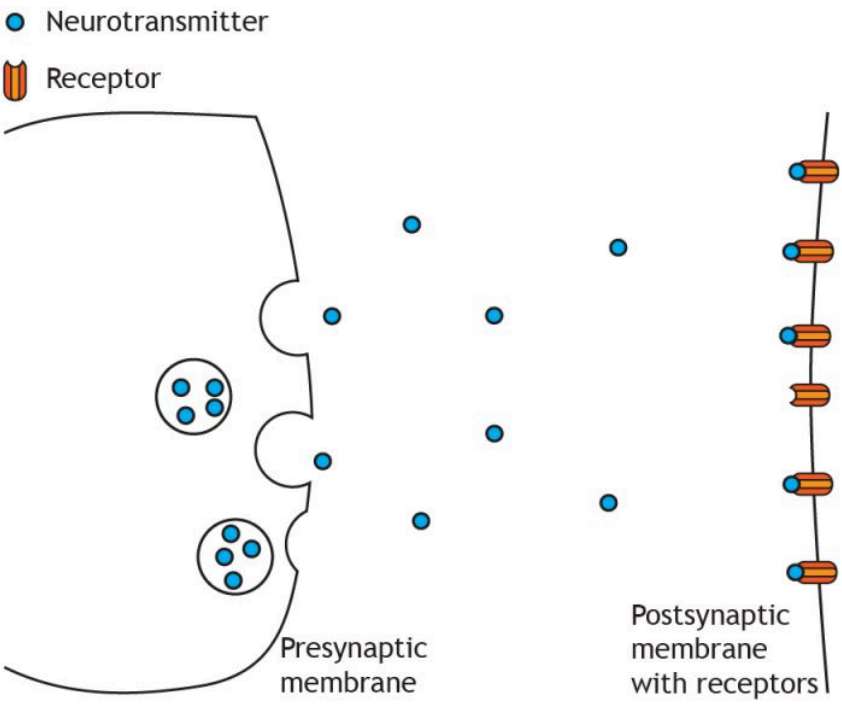


Figure 10.4. After exocytosis of the neurotransmitters into the synaptic cleft, the transmitters bind to receptors present on the postsynaptic membrane. 'Neurotransmitter in Synapse' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Step 6: Postsynaptic potentials generated in postsynaptic cell summate

Recall the process of summation from Chapter 8. The postsynaptic potentials generated from neurotransmitter binding **summate** at the axon hillock. If the membrane potential is over **threshold** potential for the cell, then a new action potential will be generated in the postsynaptic cell.

Postsynaptic potentials (graded potentials) can occur following different types of stimulation.

When neurotransmitters bind to receptors on postsynaptic cells, they cause the receptor proteins to undergo a conformational change, and open ligand-gated ion channels that produce depolarization or hyperpolarization.

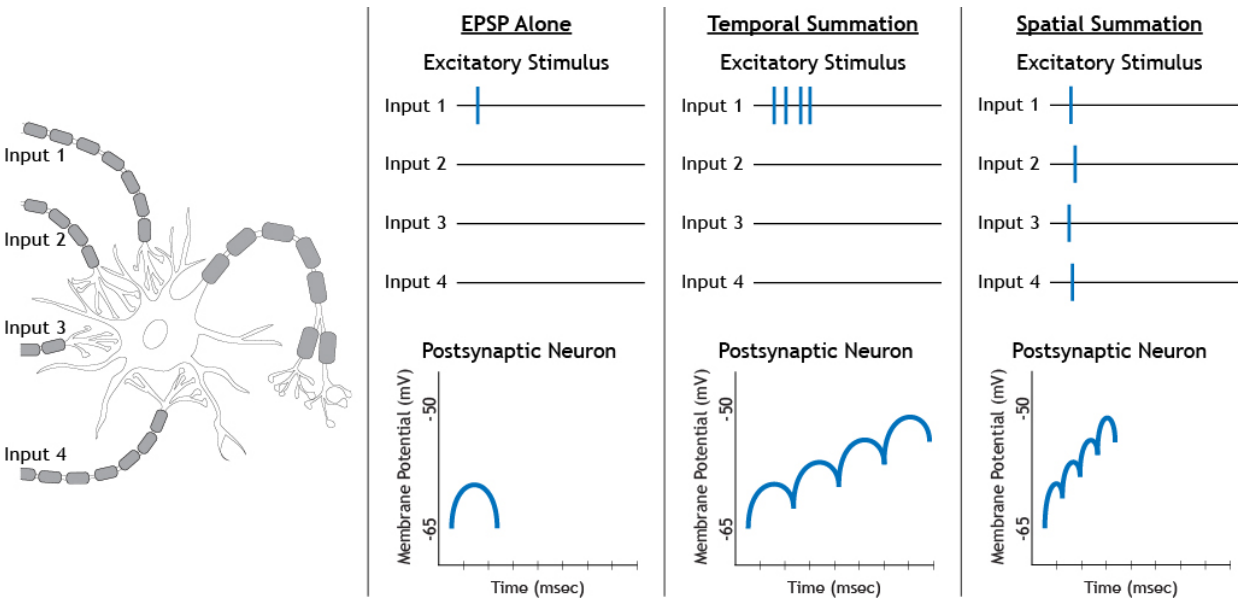


Figure 10.5. EPSPs can summate via temporal or spatial summation. Temporal summation occurs when a presynaptic neuron (Input 1 in the figure) stimulates the postsynaptic neuron multiple times in a row. Spatial summation occurs when more than one presynaptic neuron (Inputs 1 through 4 in the figure) each stimulate the postsynaptic neuron at the same time. The EPSPs of each stimulation will add together to cause a stronger depolarization of the membrane potential of the postsynaptic neuron than one excitatory stimulus alone. 'Synaptic Summation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Step 7: Neurotransmitter Inactivation

It is important that neurotransmitter signaling be tightly regulated. This means that there needs to be ways to terminate chemical signaling. Inactivation can be accomplished in three different ways.

1. After being released, neurotransmitters can be altered into inactive substances.
2. Neurotransmitters can go through the **reuptake** process, where they are recycled by being transported back into the presynaptic cell and repackaged into synaptic vesicles.
3. Some neurotransmitters simply float away from the synapse due to the aqueous environment surrounding neurons.

Key Takeaways

- In order for neurotransmitter release to be initiated, an action potential (depolarizing stimulus) needs to arrive at the axon terminal to open voltage-gated calcium channels
- Neurotransmitter release is dependent on the influx of calcium into the terminal through voltage-gated calcium channels
- SNARE proteins are important for vesicle docking at active zones and exocytosis of neurotransmitters into the synapse
- Synaptotagmin is a calcium sensor
- Neurotransmitters bind to postsynaptic receptors and cause postsynaptic potentials that summate within the postsynaptic cell
- Neurotransmitter signaling is terminated through chemical inactivation, reuptake, or through diffusion away from the synapse.

Test Yourself!

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10.

SYNAPSE STRUCTURE

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

For the nervous system to function, neurons must be able to communicate with each other, and they do this through structures called synapses. At the synapse, the terminal of a presynaptic cell comes into close contact with the cell membrane of a postsynaptic neuron.

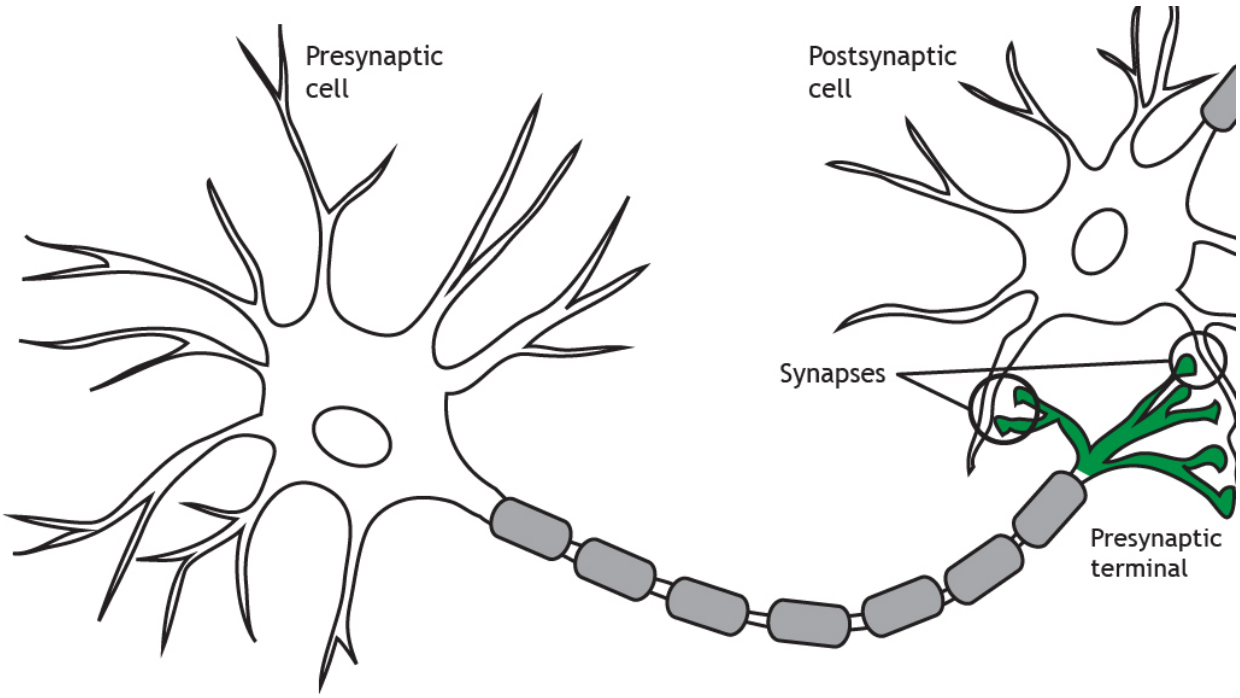


Figure 9.1. The terminal of a presynaptic neuron comes into close contact with a postsynaptic cell at the synapse. 'Synapse' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Synapse Types

There are two types of synapses: electrical and chemical.

Electrical

Electrical synapses outnumber chemical synapses in the developing nervous system

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Electrical synapses are a physical connection between two neurons. Cell membrane proteins called connexons form gap junctions between the neurons. The gap junctions form pores that allow ions to

flow between neurons, so as an action potential propagates in the presynaptic neuron, the influx of sodium can move directly into the postsynaptic neuron and depolarize the cell. The response in the postsynaptic cell is almost immediate, with little to no delay between signaling in the pre- and postsynaptic neurons. Electrical synapses play an important role in the development of the nervous system but are also present throughout the developed nervous system, although in much smaller numbers that chemical synapses.



One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=101#video-101-1

Animation 9.1. Membrane-bound proteins called connexons form gap junctions between presynaptic and postsynaptic neurons. This allows for direct exchange of ions between neurons. An action potential in the presynaptic neuron will cause an immediate depolarization of the postsynaptic membrane because the sodium ions will cross the membrane through the gap junctions. 'Electrical Synapse – Ion Flow' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Since the gap junctions allow diffusion of ions without any obstruction, the signal can flow bidirectionally through an electrical synapse. The electrochemical gradients will drive direction of ion flow.



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Animation 9.2. Since an electrical synapse is a direct, physical connection between two neurons, ions are able to flow either direction across the gap junction. 'Bidirectional Electrical Synapse' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Additionally, small molecules like ATP or second messengers can also move through the gap junctions. These signaling molecules play an important role in cellular mechanisms, which we will see in a later chapter.



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Animation 9.3. Gap junctions are large enough to allow the flow of small cellular molecules like ATP or second messengers. 'Electrical Synapse – Small Molecules' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Chemical

Chemical synapses outnumber electrical synapses in the fully developed nervous system

Chemical synapses are the primary synapse type in the developed nervous system and do not form physical connections between the pre- and postsynaptic neurons. Instead, a space called the synaptic cleft exists between the presynaptic terminal and the postsynaptic membrane.

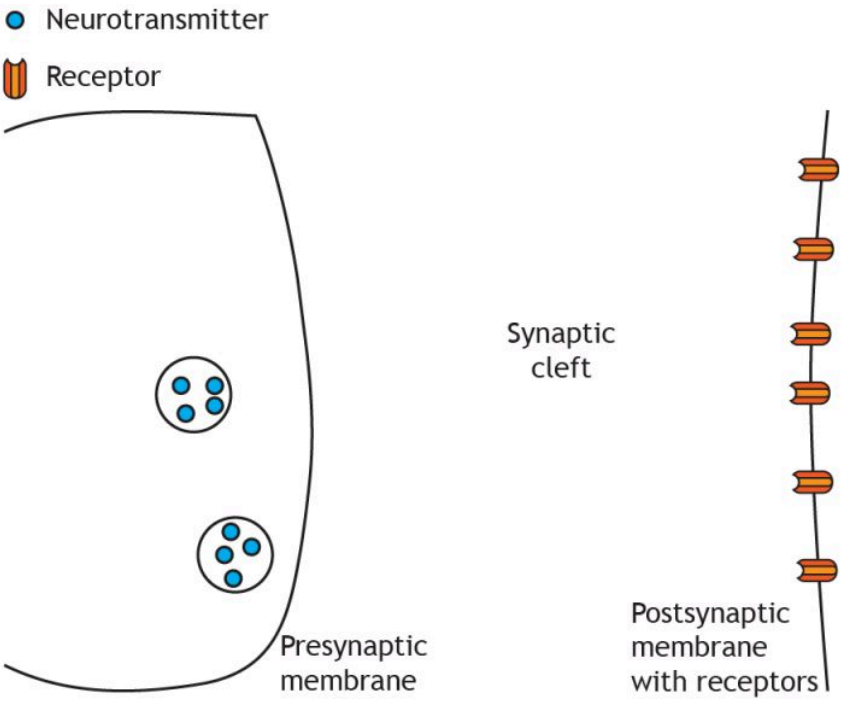


Figure 9.2. A chemical synapse does not make direct contact between the two neurons. The presynaptic terminal and the postsynaptic membrane are separated by the synaptic cleft. Neurotransmitters are stored in the presynaptic cell, and the postsynaptic cell has neurotransmitter receptors in the membrane. 'Chemical Synapse' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

At a chemical synapse, the depolarization of an action potential reaching the presynaptic terminal causes release of neurotransmitters, which act on specialized receptors located in the cell membrane of the postsynaptic neuron. The structure and function of chemical synapses make them slower than electrical synapses and permit signaling in only one direction.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=101#video-101-4

Animation 9.4. An action potential causes release of neurotransmitters from the presynaptic terminal into the synaptic cleft. The transmitters then act on neurotransmitter receptors in the postsynaptic

membrane. 'Chemical Synapse – Neurotransmitter Release' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Synapse Location

As we discuss synaptic transmission, we will focus mainly on axodendritic synapses, in which the presynaptic terminal synapses on the dendrites of the postsynaptic cell. But synapses can also be located between the terminal and the cell body of the postsynaptic cell, called axosomatic, or even between the terminal and the axon of the postsynaptic cell, called axoaxonic.

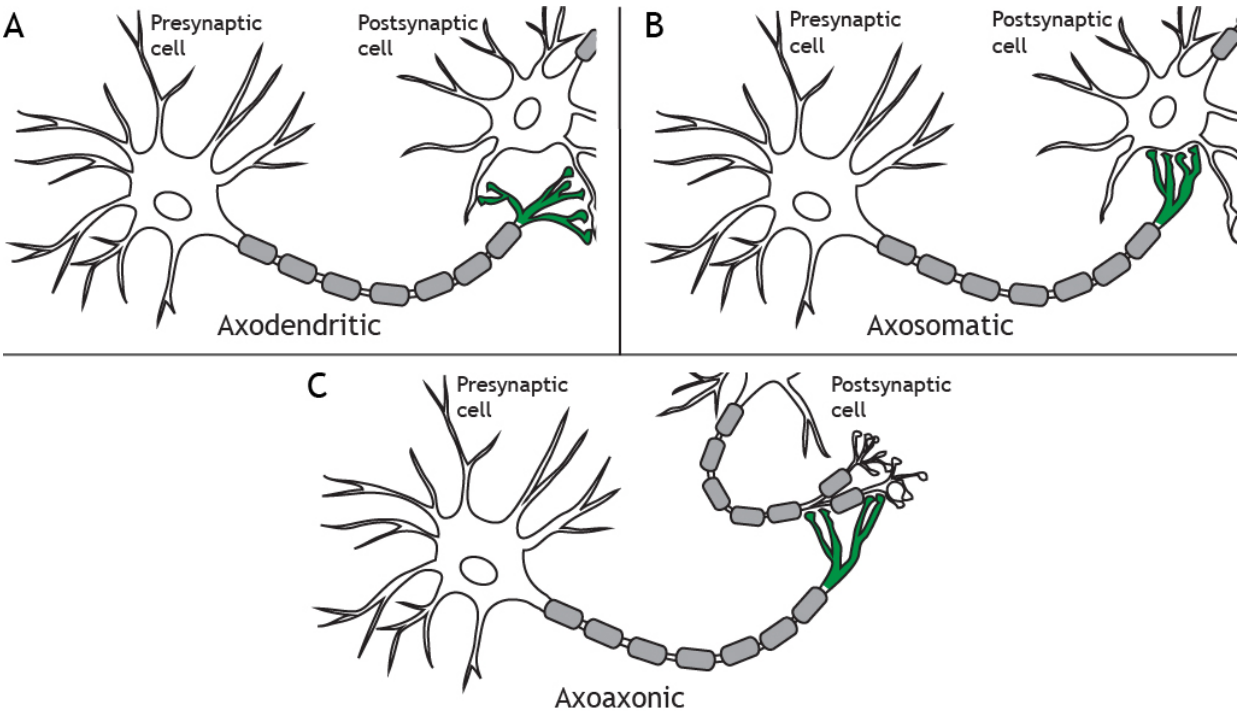


Figure 9.3. A) Axodendritic synapses occur when the presynaptic terminal makes a synaptic connection with the dendrite of a postsynaptic neuron. B) Axosomatic synapses occur when the presynaptic terminal makes a synaptic connection with the cell body of a postsynaptic neuron. C) Axoaxonic synapses occur when the presynaptic terminal makes a synaptic connection with the axon of a postsynaptic neuron. 'Chemical Synapse Types' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- Electrical synapses make direct contact between neurons, are faster than chemical synapses, and can be bidirectional
- Chemical synapses form a synaptic cleft between the neurons and are unidirectional
- Synapses can occur between the presynaptic terminal and the postsynaptic dendrites (axodendritic), cell body (axosomatic), or axon (axoaxonic)

Test Yourself!



An interactive H5P element has been excluded from this version of the text. You can view it online here:
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Video Lecture



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Attributions

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11.

NEUROTRANSMITTER SYNTHESIS AND STORAGE

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

A few criteria must be met for a molecule to be called a neurotransmitter. First, the transmitter must be synthesized within in the presynaptic neuron. Second, the transmitter must be released by the presynaptic neuron in response to stimulation. Third, when a postsynaptic neuron is treated with the transmitter by a researcher, the molecule must cause the same effect in the postsynaptic neuron as when it is released by a presynaptic neuron.

There are two main categories of neurotransmitters: small molecule transmitters and peptide transmitters. Synthesis and storage of these neurotransmitter groups differ. Small molecule neurotransmitters are synthesized and stored in the terminal for fast release. Neuropeptides are synthesized in the cell body and must be transported to the terminal, which can lead to slower release. Additionally, a neuron typically will synthesize and release only one type of small molecule neurotransmitter but can synthesize and release more than one neuropeptide.

Small Molecule Transmitters

Small molecule transmitters are synthesized in the synaptic terminal

The small molecule transmitters can be divided into two main groups: amino acid neurotransmitters and biogenic amines, also called monoamines. In addition to acting as neurotransmitters, the amino acids glutamate and glycine are used to synthesize proteins in all cell types throughout the body. GABA (γ-Aminobutyric acid) is a metabolite of glutamate but is not used in protein synthesis in the body. The biogenic amines include serotonin and histamine, and the subgroup the catecholamines dopamine, norepinephrine, and epinephrine. Acetylcholine does not fit into either division but is still considered a small molecule neurotransmitter.

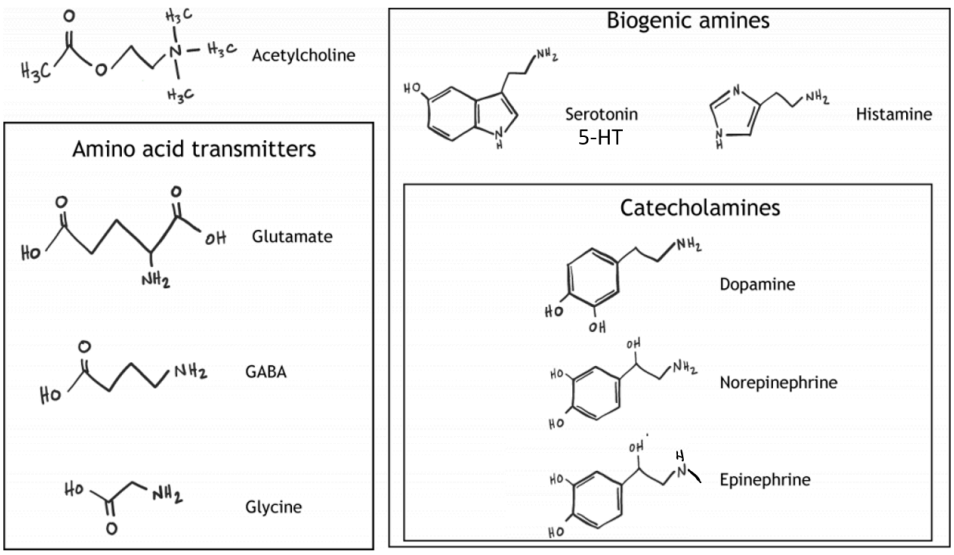


Figure 11.1. Small molecule neurotransmitters can be subdivided into groups based on chemical structure. Amino acid transmitters include glutamate, GABA, and glycine. The biogenic amines include serotonin and histamine, and the catecholamines, a subgroup of the biogenic amines, include dopamine, norepinephrine, and epinephrine. Acetylcholine does not fit into a group. Modified by Avinash Singh from 'Small Molecule Neurotransmitters' by Casey Henley

Synthesis and Storage of Small Molecule Transmitters

Most small molecule neurotransmitters are synthesized by enzymes that are located in the cytoplasm (the exception is norepinephrine, see below). This means that small molecule neurotransmitters can be synthesized and packaged for storage in the presynaptic terminal using enzymes present in the terminal.

Acetylcholine

Acetylcholine is best known for its role at the neuromuscular junction, the synapse between a motor neuron and the muscle fiber. In the presynaptic terminal, acetylcholine is synthesized from acetyl coenzyme A (acetyl CoA) and choline via the enzyme choline acetyltransferase. The level of enzyme activity is the rate-limiting step in the synthesis pathway. Acetylcholine is packaged into vesicles for storage in the terminal via the vesicular acetylcholine transporter (VAChT).

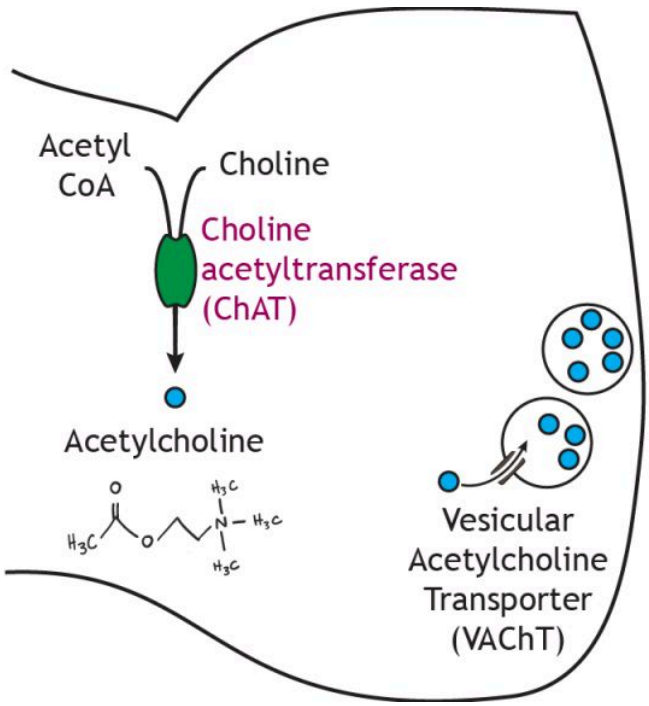


Figure 11.2. Acetylcholine is synthesized from acetyl CoA and choline by choline acetyltransferase, the rate-limiting step in the pathway. Acetylcholine is then packaged into vesicles by vesicular acetylcholine transporter. 'Acetylcholine Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Glutamate

Glutamate is an amino acid transmitter and is the primary excitatory neurotransmitter in the brain. In the presynaptic terminal, glutamine is converted into glutamate via the enzyme glutaminase, which is the rate-limiting step in the synthesis pathway. Glutamate is packaged into vesicles for storage via the vesicular glutamate transporter.

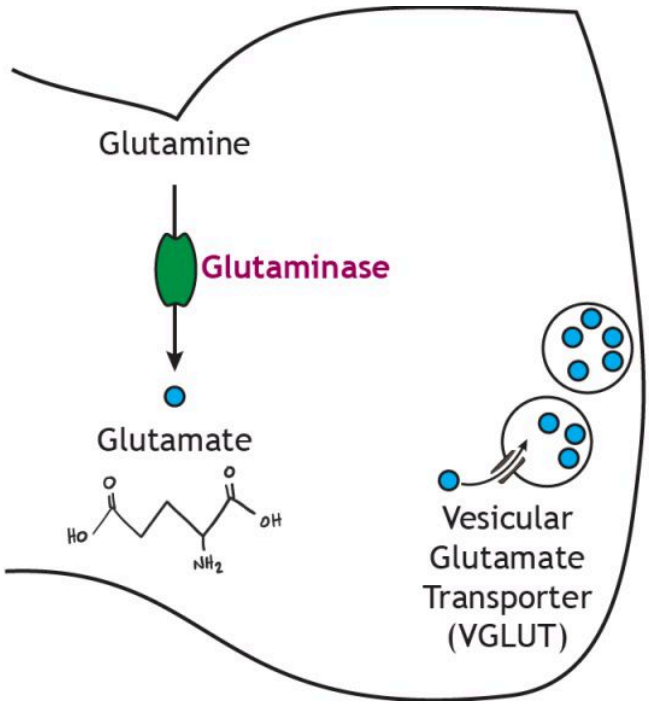


Figure 11.3. Glutamate is synthesized from glutamine by glutaminase, the rate-limiting step in the pathway. Glutamate is then packaged into vesicles by vesicular glutamate transporter. 'Glutamate Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

GABA

Glutamate is then used to synthesize GABA, another amino acid transmitter and the primary inhibitory neurotransmitter in the brain. In the presynaptic terminal, glutamate is converted into GABA via the enzyme glutamic acid decarboxylase, which like the other synthesis pathways is the rate-limiting step. GABA is packaged into vesicles for storage in the terminal via the vesicular inhibitory amino acid transporter.

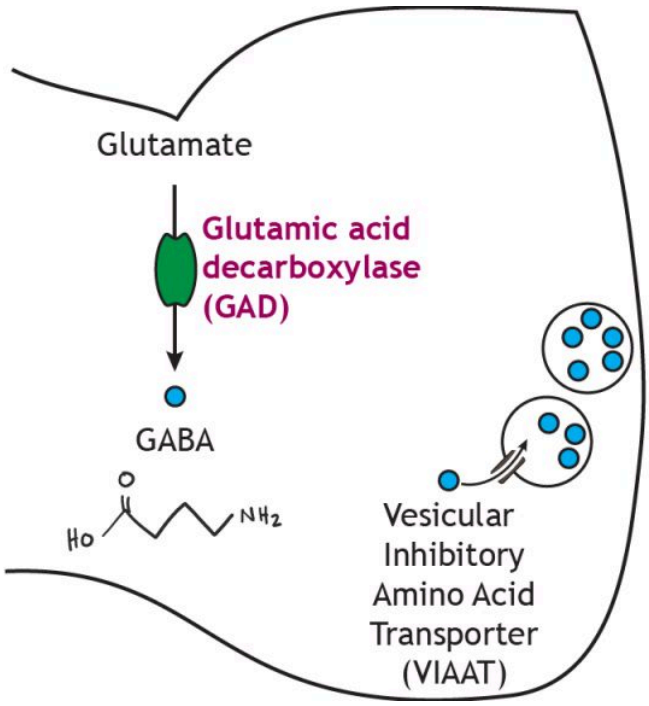


Figure 11.4. GABA is synthesized from glutamate by glutamic acid decarboxylase, the rate-limiting step in the pathway. GABA is then packaged into vesicles by vesicular inhibitory amino acid transporter. 'GABA Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Glycine

Glycine is another inhibitory amino acid neurotransmitter, but unlike GABA, it is more common in the spinal cord than in the brain. Serine hydroxymethyltransferase converts the amino acid serine into glycine in the presynaptic terminal. The rate limiting step for glycine synthesis occurs earlier in the pathway prior to serine synthesis. Glycine is packaged into vesicles by the vesicular inhibitory amino acid transporter like GABA.

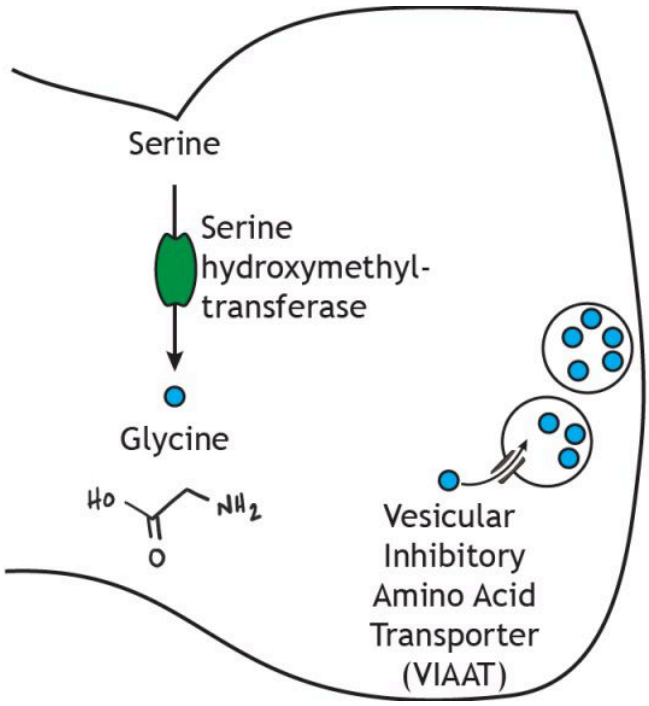


Figure 11.5. Glycine is synthesized from serine by serine hydroxymethyltransferase. Glycine is then packaged into vesicles by vesicular inhibitory amino acid transporter. 'Glycine Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Dopamine

Dopamine, a catecholamine transmitter, plays many roles in the nervous system, but it is best known for its roles in reward and movement. In the presynaptic terminal, the amino acid tyrosine is converted into DOPA via tyrosine hydroxylase, which is the rate limiting step in the synthesis of all the catecholamines. DOPA is then converted to dopamine by DOPA decarboxylase. Dopamine is packaged into synaptic vesicles by the vesicular monoamine transporter.

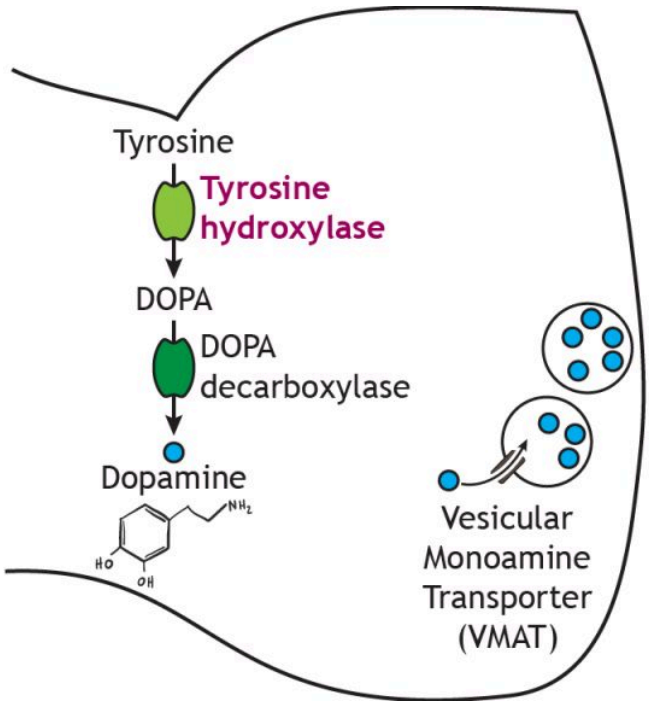


Figure 11.6. Dopamine is synthesized in a two-step process. Tyrosine is converted into DOPA by tyrosine hydroxylase, the rate-limiting step in the pathway. Then dopamine is synthesized from DOPA by DOPA decarboxylase. Dopamine is then packaged into vesicles by vesicular monoamine transporter. 'Dopamine Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Norepinephrine

In neurons that release norepinephrine, which is another catecholamine transmitter, once dopamine is packaged into the synaptic vesicles, a membrane-bound enzyme called dopamine beta-hydroxylase converts dopamine into norepinephrine. Therefore, unlike the other small molecule neurotransmitters, norepinephrine is synthesized within the vesicles, not in the cytoplasm. Like dopamine, the rate limiting step of this synthesis pathway is the activity of tyrosine hydroxylase.

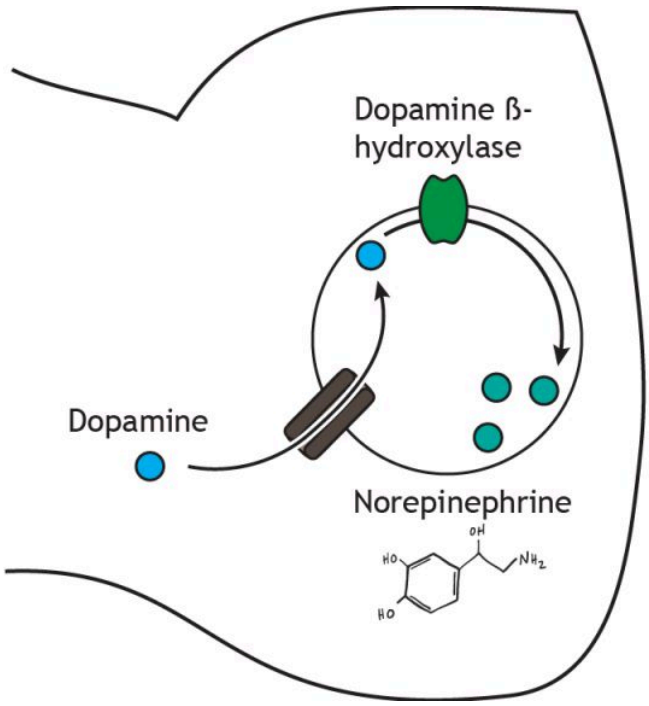


Figure 11.7. Norepinephrine is synthesized from dopamine by dopamine beta-hydroxylase. Unlike other neurotransmitters, synthesis occurs after the precursor, dopamine, has already been packaged into vesicles. 'Norepinephrine Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Epinephrine

Epinephrine, also called adrenaline, is a catecholamine, but it is often considered a hormone instead of a neurotransmitter. Epinephrine is primarily released by the adrenal medulla into the circulation; it is used as a neurotransmitter in only a small number of neurons. Epinephrine is synthesized from norepinephrine in the cytoplasm by the enzyme phenylethanolamine-N-methyltransferase, so epinephrine synthesis requires norepinephrine to exit the vesicles where it was synthesized. After synthesis in the cytoplasm, epinephrine is repackaged into vesicles via the vesicular monoamine transporter.

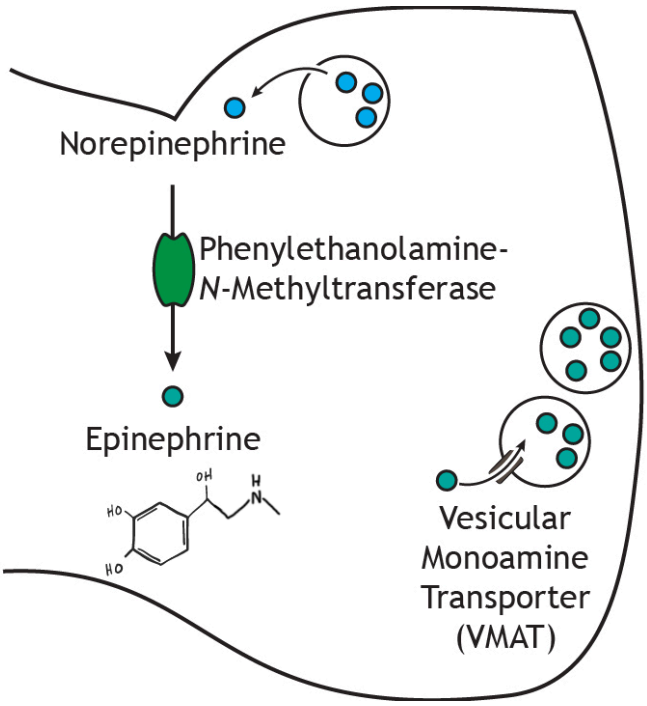


Figure 11.8. Epinephrine is synthesized from norepinephrine by phenylethanolamine-N-methyltransferase in the cytoplasm. As the name suggests, the n-methyltransferase adds a methyl group to the amine group. Epinephrine is then packaged into vesicles by vesicular monoamine transporter. Modified by Avinash D Singh Bala from 'Epinephrine Synthesis' by Casey Henley

Serotonin

Serotonin, a biogenic amine neurotransmitter, is known for its role in mood. Tryptophan is converted into 5-hydroxytryptophan by tryptophan hydroxylase. This is also the rate-limiting step of the synthesis pathway. Then aromatic L-amino acid decarboxylase converts the 5-hydroxytryptophan into serotonin. Serotonin is packaged into vesicles by the vesicular monoamine transporter similar to the other monoamine neurotransmitters: dopamine and epinephrine.

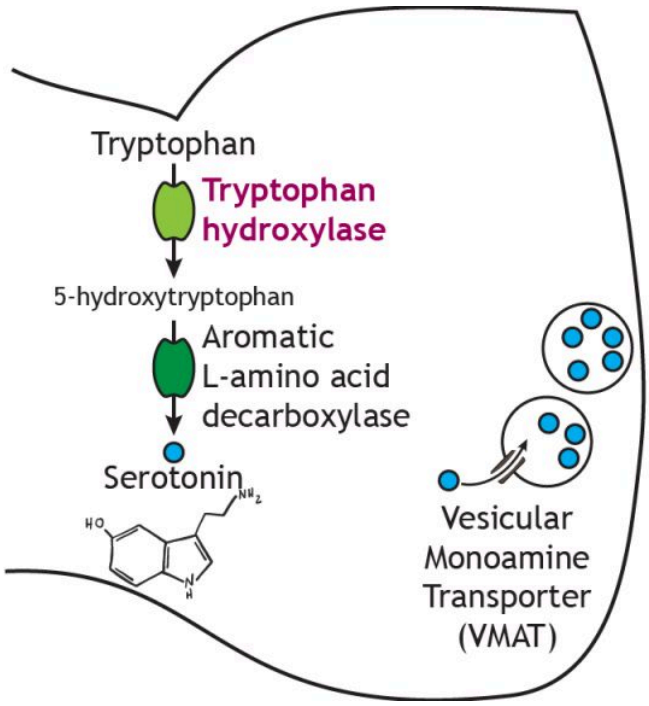


Figure 11.9. Serotonin is synthesized in a two-step process. Tryptophan is converted into 5-hydroxytryptophan by tryptophan hydroxylase, the rate-limiting step in the pathway. Then serotonin is synthesized from 5-hydroxytryptophan by aromatic L-amino acid decarboxylase. Serotonin is then packaged into vesicles by vesicular monoamine transporter. 'Serotonin Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Histamine

Finally, histamine is another biogenic amine transmitter that is synthesized from histidine through the action of histadine decarboxylase, the rate limiting step of the pathway. Like the other monoamine neurotransmitters, it is packaged into synaptic vesicles via the vesicular monoamine transporter.

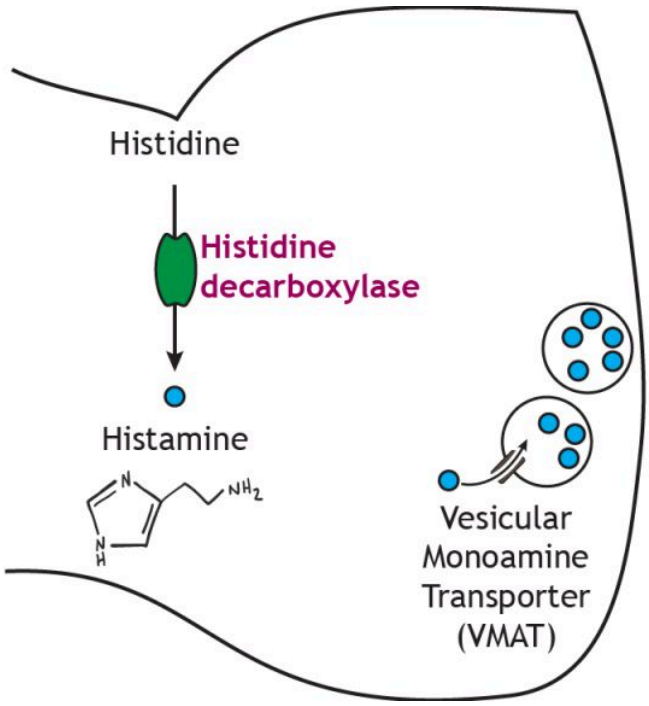


Figure 11.10. Histamine is synthesized from histadine by histadine decarboxylase, the rate-limiting step in the pathway. Histamine is then packaged into vesicles by vesicular monoamine transporter. 'Histamine Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Synthesis and Storage of Neuropeptides

Neuropeptides are synthesized in the cell body and transported to the synaptic terminal

Neuropeptides are a short string of amino acids and are known to have a wide range of effects from emotions to pain perception. Unlike small molecule neurotransmitters, neuropeptides are synthesized in the cell body and transported to the axon terminal. Like other proteins, neuropeptides are synthesized from mRNA into peptide chains made from amino acids. In most cases, a larger precursor molecule called the prepropeptide is translated into the original amino acid sequence in the

rough endoplasmic reticulum. The prepropeptide is processed further to the propeptide stage. The remaining processing and packaging of the final neuropeptide into a vesicle occurs in the Golgi apparatus. The peptides are packaged into vesicles that are significantly larger that the vesicles that store the small molecule transmitters. These large vesicles must then move from the soma to the terminal.

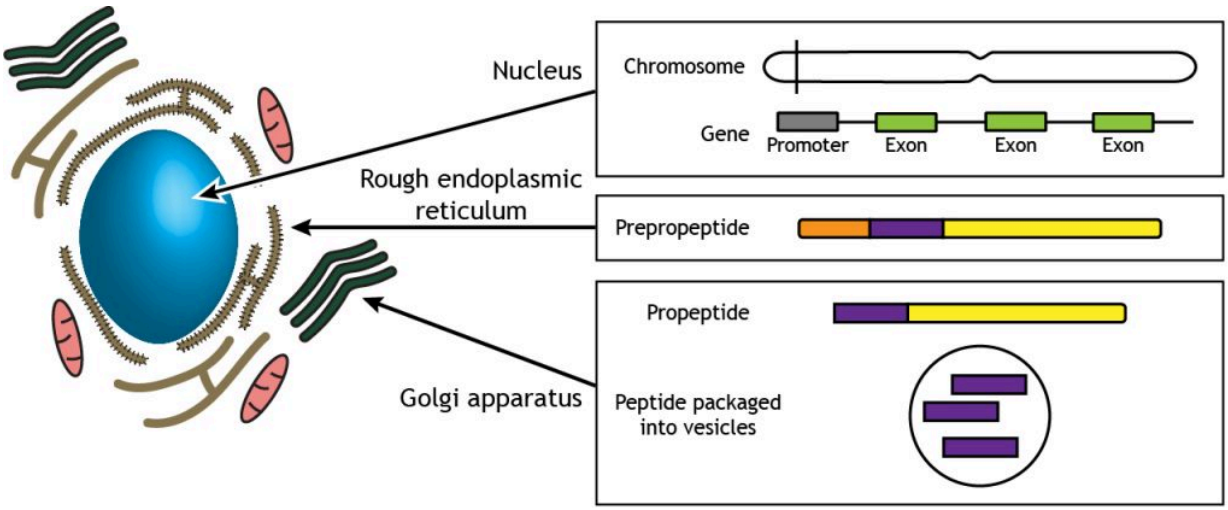


Figure 11.11. Neuropeptide synthesis occurs in the cell body. Each neuropeptide is encoded by a gene on the DNA located in the nucleus. mRNA is translated into an amino acid sequence for a precursor molecule called a prepropeptide in the rough endoplasmic reticulum. Further processing and packaging of the neuropeptide into vesicles occurs in the Golgi apparatus. 'Neuropeptide Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Axonal Transport

The packaged peptides need to be transported to the presynaptic terminals to be released into the synaptic cleft. Organelles, vesicles, and proteins can be moved from the cell body to the terminal via anterograde transport or from the terminal to the cell body via retrograde transport. Anterograde transport can be either fast or slow.

The packaged neuropeptides are transported to the synaptic terminals via fast anterograde axonal transport mechanisms.

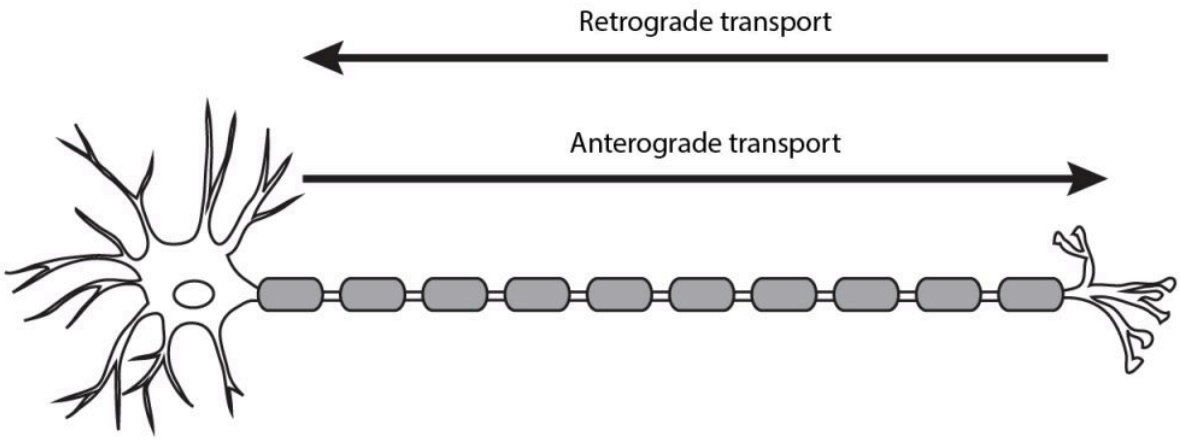


Figure 11.12. Cellular components need to be able to move throughout the cell to have proper functioning. Anterograde transport moves components from the cell body toward the terminal. Retrograde transport moves components from the terminal toward the cell body. 'Axonal Transport' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- Small molecules neurotransmitters are synthesized and packaged into vesicles in the presynaptic terminal
- Neuropeptide transmitters are synthesized and packaged into vesicles in the cell body and are transported to the terminal via fast axonal transport
- Each small molecule neurotransmitter has a rate limiting step that controls the rate of synthesis
- Neuropeptides rely on axonal transport mechanisms to move from the soma to the terminal

Test Yourself!

Try the quiz more than once to get different questions!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=115#h5p-10

- For each neurotransmitter below, which enzyme is responsible for the rate-limiting step in the synthesis pathway, which enzyme is responsible for the final step of the synthesis pathway, and which enzyme is responsible for packaging of the transmitter into vesicles
    - Acetylcholine
    - Glutamate
    - GABA
    - Glycine
    - Dopamine
    - Norepinephrine
    - Epinephrine
    - Serotonin
    - Histamine

Video Lecture

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12.

NEUROTRANSMITTER RELEASE

Action Potential

As we have covered, when an action potential propagates down the axon to the presynaptic terminal, the electrical signal will result in a release of chemical neurotransmitters that will communicate with the postsynaptic cell.

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=123#video-123-1

Animation 12.1. The action potential is a brief but significant change in electrical potential across the membrane. The membrane potential will move from a negative, resting membrane potential, shown here as -65 mV, and will rapidly become positive and then rapidly return to rest during an action potential. The action potential moves down the axon beginning at the axon hillock. When it reaches the synaptic terminal, it causes the release of chemical neurotransmitter. 'Action Potential Propagation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation

Ion flow in Terminal

Depolarization of the terminal causes voltage-gated calcium channels to open

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When the action potential reaches the terminal, there is an influx of sodium ions, just like when the action potential moves down the axon. This inward current causes a depolarization of the terminal, and that depolarization activates voltage-gated calcium channels. There is a strong electrochemical gradient that moves calcium into the terminal.



One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=123#video-123-2

Animation 12.2. An action potential causes an influx of sodium in the terminal. The depolarization opens voltage-gated calcium channels, and calcium ions flow into the terminal down their electrochemical gradient. The blue, dotted channels represent voltage-gated sodium channels, and the purple, striped channels represent voltage-gated calcium channels. 'Terminal Calcium Influx' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Active Zones

The voltage-gated calcium channels are concentrated in the presynaptic terminal at active zones, the regions of the membrane where small molecule neurotransmitters are released. At active zones, some synaptic vesicles are docked and are ready for immediate release upon arrival of the action potential. Other neurotransmitter-filled vesicles remain in a reserve pool outside of the active zone.

Vesicles filled with neuropeptides do not dock at active zones. They are located outside of the active zone, further away from the membrane and the high density of voltage-gated calcium channels and are therefore slower to release than the small molecule transmitters.

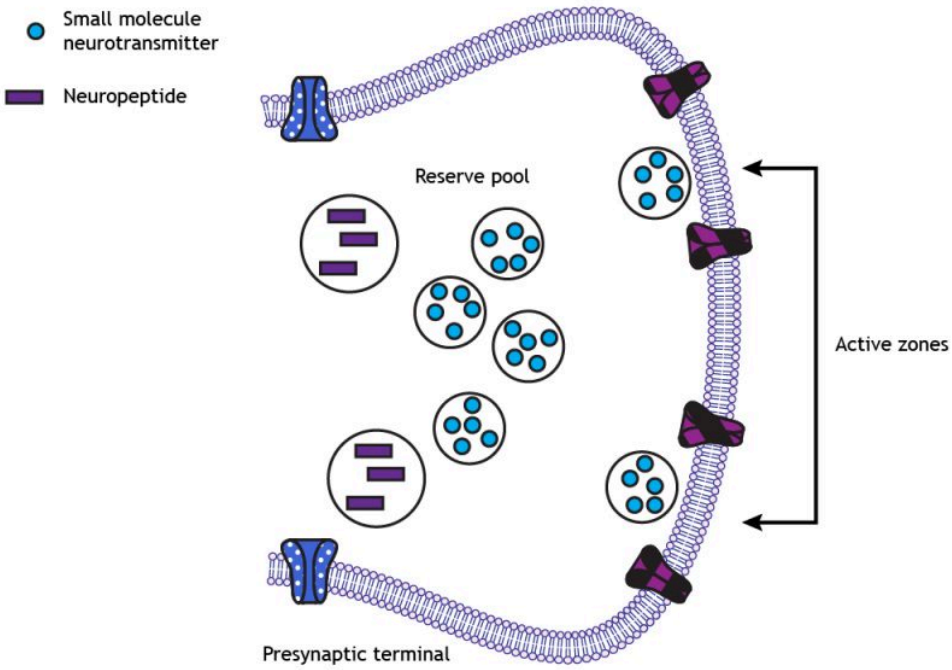


Figure 12.1. Some synaptic vesicles filled with small molecule neurotransmitters dock at active zones on the presynaptic membrane, ready for immediate release. Other synaptic vesicles remain nearby in reserve pools, ready to move into empty active zones. Neuropeptide-filled vesicles do not dock at active zones. The blue, dotted channels represent voltage-gated sodium channels, and the purple, striped channels represent voltage-gated calcium channels. 'Active Zones' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Vesicle Docking

Docking of synaptic vesicles packaged with small molecule neurotransmitters occurs through the interaction of three membrane-bound proteins called SNARE proteins. Synaptobrevin is called a v-SNARE because it is located on the Vesicular membrane. Syntaxin and SNAP-25 are called t-SNARES because they are located on the terminal membrane, which is the Target membrane. The interaction of these three proteins leads to vesicle docking at the active zone.

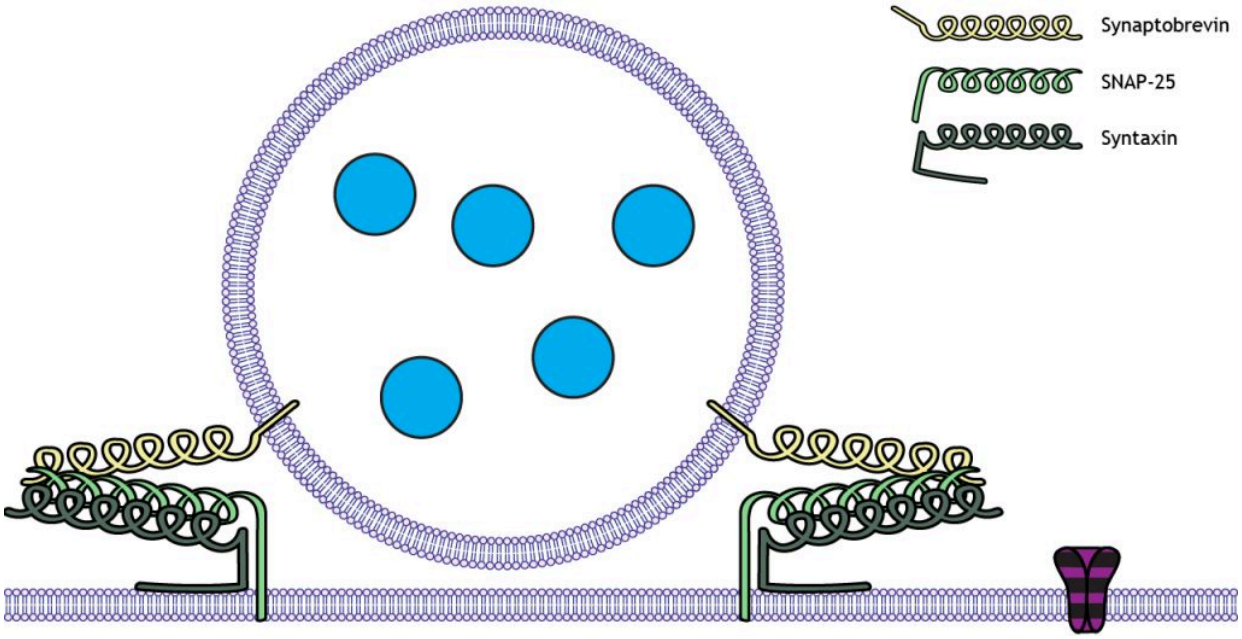


Figure 12.2. Synaptic vesicles filled with small molecule neurotransmitters are able to dock at active zones by the interaction of v- and t-SNARE proteins. Synaptobrevin is embedded in the membrane of the vesicle whereas SNAP-25 and Syntaxin are embedded in the presynaptic terminal membrane. The purple, striped channels represent voltage-gated calcium channels. 'SNARE proteins' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Exocytosis

Exocytosis of neurotransmitters is dependent on calcium

The influx of calcium through the voltage-gated calcium channels initiates the exocytosis process that leads to neurotransmitter release. Calcium enters the cell and interacts with another vesicle-bound protein called synaptotagmin. This protein is a calcium sensor, and when calcium is present at the active zone, synaptotagmin interacts with the SNARE proteins. This is the first step toward exocytosis of the synaptic vesicle.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=123#video-123-3

Animation 12.3. Calcium enters the cell when the voltage-gated channels open. In the presence of calcium, synaptotagmin, a protein bound to the vesicular membrane interacts with the SNARE proteins. The purple, striped channels represent voltage-gated calcium channels. 'Synaptotagmin' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation

Once synaptotagmin interacts with the SNARE proteins, the synaptic vesicle membrane fuses with the presynaptic terminal membrane, exocytosis occurs, and the neurotransmitters released.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=123#video-123-4

Animation 12.4. Once the synaptotagmin-SNARE protein complex forms, the synaptic vesicle membrane fuses with the terminal membrane, and the neurotransmitters are released into the synaptic cleft through exocytosis. The purple, striped channels represent voltage-gated calcium channels. 'Transmitter Exocytosis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Neurotransmitter Action

After exocytosis of the transmitter molecules, they enter the synaptic cleft and bind to receptors on the postsynaptic membrane. Receptors fall into two main categories: ligand-gated channels and G-protein coupled receptors. The next two chapters cover these receptors.

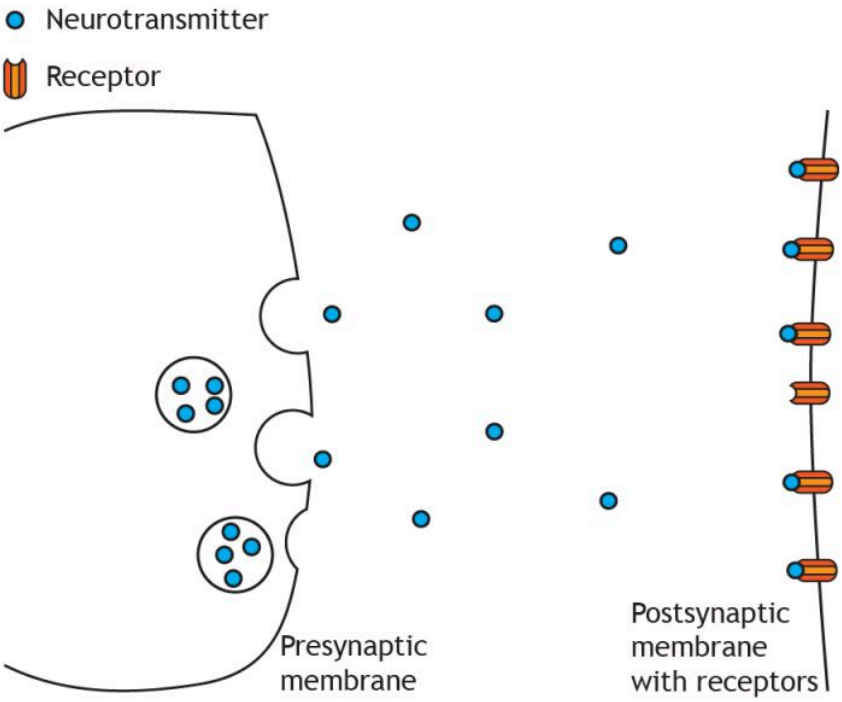


Figure 12.4. After exocytosis of the neurotransmitters into the synaptic cleft, the transmitters bind to receptors present on the postsynaptic membrane. 'Neurotransmitter in Synapse' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Key Takeaways

- Neurotransmitter release is dependent on the influx of calcium into the terminal
- SNARE proteins are important for vesicle docking at active zones and exocytosis
- Synaptotagmin is a calcium sensor

Test Yourself!

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- Describe the events that occur in the presynaptic terminal when an action potential arrives. Include the role of Ca2+.

Video Lecture

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Attributions

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13.

NEUROTRANSMITTER ACTION: IONOTROPIC RECEPTORS

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

Ionotropic receptors, also called neurotransmitter-gated or ligand-gated channels, are ion channels that open in response to the binding of a neurotransmitter. They are primarily located along the dendrites or cell body, but they can be present anywhere along the neuron if there is a synapse. Ligand-gated channels are important for receiving incoming information from other neurons.

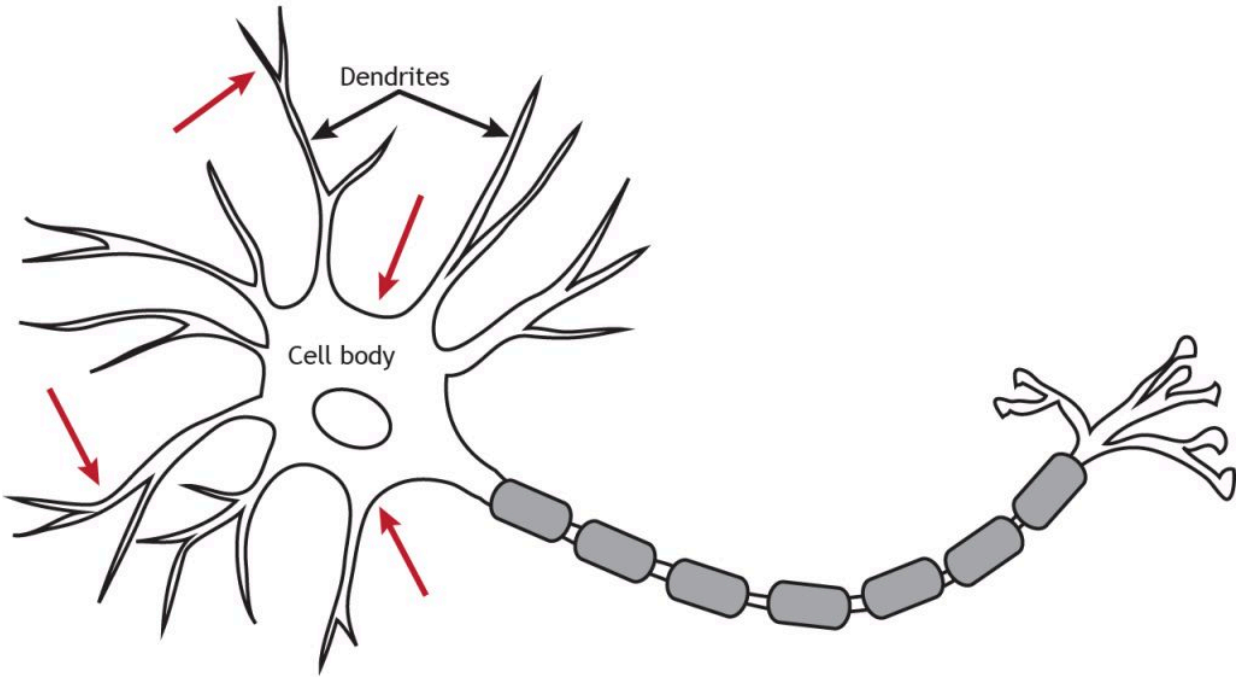


Figure 13.1. Ligand-gated channels critical for receiving incoming synaptic information are primarily located along the dendrites and cell body. 'Receptor Location' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Although ionotropic receptors are ion channels, they open in a different way than the voltage-gated ion channels needed for propagation of the action potential. The ionotropic receptors are ligand-gated, which means that a specific molecule, such as a neurotransmitter, must bind to the receptor to cause the channel to open and allow ion flow. As seen in previous chapters, the voltage-gated channels open in response to the membrane potential reaching threshold.

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Animation 13.1. Ionotropic receptors, also called ligand-gated channels, are ion channels that are opened by the binding of neurotransmitters. Voltage-gated channels are opened by the membrane

potential of the cell reaching threshold. Both types of channels allow ions to diffuse down their electrochemical gradient. The lined, teal channels represent glutamate receptors; the solid yellow channels represent GABA receptors; the dotted, blue channels represent voltage-gated sodium channels. 'Ion Channel Gating' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

The receptors can only be opened by a specific ligand. Neurotransmitters and receptors fit together like a lock and key; only certain neurotransmitters are able to bind to and open certain receptors.



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Animation 13.2. Since neurotransmitter receptors can only bind specific neurotransmitters, glutamate binds to and opens glutamate receptors but has no effect on GABA receptors. The lined, teal channels represent glutamate receptors; the solid yellow channels represent GABA receptors. 'Ligand and Receptor' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Ion movement through ligand-gated ion channels follows the same principles covered in previous chapters

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Glutamate Receptors

Glutamate causes EPSPs by opening cation channels that increase sodium permeability across the membrane

Glutamate is the primary excitatory neurotransmitter in the central nervous system and opens non-selective cation channels. There are three subtypes of glutamate receptors. The AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainate receptors allow both sodium and potassium to cross the membrane. Although potassium can leave the cell when the receptors open, the electrochemical gradient driving sodium ion movement is stronger than the gradient driving potassium movement, resulting in a depolarization of the membrane potential.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=137#video-137-3

Animation 13.3. AMPA and kainate glutamate receptors are non-selective ion channels that allow both sodium and potassium to flow across the membrane. When glutamate binds, sodium flows in and potassium flows out. The lined, teal channel represent sAMPA receptors; the checkered, teal channel represents kainate receptors. 'AMPA and Kainate' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

The NMDA (N-methyl-D-aspartate) receptor requires the binding of glutamate to open, but it is also dependent on voltage. When the membrane potential is below, at, or near rest, a magnesium ion blocks the open NMDA receptor and prevents other ions from moving through the channel. Once the cell depolarizes, the magnesium block is expelled from the receptor, which allows sodium, potassium, and calcium to cross the membrane. The voltage change needed to open the NMDA receptor is usually a result of AMPA receptor activation. Released glutamate binds to both AMPA and NMDA receptors, sodium influx occurs through open AMPA channels, which depolarizes the cell enough to expel the magnesium ion and allow ion flow through the NMDA receptors.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=137#video-137-4

Animation 13.4. NMDA receptors are opened by a combination of glutamate binding and a voltage trigger. At low levels of stimulation, when the the membrane potential is near rest, a magnesium ion blocks the open NMDA receptor channel preventing ion flow. Ions can flow through open AMPA receptors, which begins to depolarize the membrane. The voltage change eventually expels the magnesium ion from the channel, allowing sodium, potassium, and calcium to cross the membrane. The lined, teal channel represents AMPA receptors; the dotted, violet channel represents NMDA receptors. 'AMPA and NMDA' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Nicotinic Acetylcholine Receptors

Like glutamate receptors, nicotinic acetylcholine receptors are non-selective cation channels. Nicotinic receptors, though, are located primarily outside of the central nervous system and are primarily used at the neuromuscular junction.

GABA and Glycine Receptors

GABA and Glycine cause IPSPs by opening chloride channels that increase chloride permeability across the membrane

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GABA and glycine receptors are chloride channels. Since an increase chloride permeability across the membrane is inhibitory, the binding of GABA or glycine to their respective ionotropic receptor will cause inhibition.

> *One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=137#video-137-5*

Animation 13.5. GABA and glycine are inhibitory receptors that are selective to chloride. The solid yellow channel represents a GABA receptor; the patterned, yellow channel represents a glycine receptor. 'GABA and Glycine' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Ionotropic Receptors Cause Postsynaptic Potentials

Postsynaptic potentials (Chapter 5) are a result of ionotropic receptors opening. Excitatory ionotropic receptors increase sodium permeability across the membrane, whereas inhibitory ionotropic receptors increase chloride permeability. Ion flow through the ionotropic receptors follows the same principles as other ion channels covered so far.

Equilibrium Potential Review

Previously, we covered ion movement through voltage-gated channels and discussed that electrochemical gradients will drive ion movement toward equilibrium. The neuron's membrane potential at which the chemical and electrical gradients balance and equilibrium occurs is the ion's equilibrium potential.

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Animation 13.6. Ions move through open voltage-gated channels trying to reach equilibrium. As the ions cross the membrane, the neuron's membrane potential moves closer to the ion's equilibrium potential. In the animation, a voltage-gated sodium channel opens, and sodium flows in until the membrane potential equals approximately +60 mV, sodium's equilibrium potential. The blue, dotted channel represents a voltage-gated sodium channel. 'Equilibrium Potential' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Reversal Potential

This same principle is used for ion movement through ionotropic receptors. The membrane potential at which ion flow through a receptor is at equilibrium is called the reversal potential of the receptor. The direction of ion movement can be predicted if the reversal potential of the receptor is known.

You can think of a reversal potential as being the equilibrium potential for a receptor, which may allow more than one ion to move across the membrane

---

GABA and Glycine – Receptors Selective to One Ion

When an ionotropic receptor that is selective to only one ion opens, the reversal potential of the receptor is the same as the equilibrium potential of the ion. GABA and glycine receptors only allow chloride ions to cross the membrane. Therefore, the reversal potential of a GABA or glycine receptor

is equal to the equilibrium potential of chloride, and the binding of GABA or glycine to their respective ionotropic receptor will cause an inhibitory postsynaptic potential (IPSP).

> *One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=137#video-137-7*

Animation 13.7. Ions move through open ligand-gated channels trying to reach equilibrium. As the ions cross the membrane, the neuron's membrane potential moves closer to the receptor's reversal potential. When the ionotropic receptor only increases permeability for one ion, the receptor's reversal potential is the same as the ion's equilibrium potential. In the animation, a GABA receptor open, and chloride flows in until the membrane potential equals approximately -65 mV, GABA's reversal potential and chloride's equilibrium potential. Increased chloride permeability causes an IPSP and inhibits the neuron. The yellow, checkered channel represents a GABA receptor. 'GABA Reversal Potential' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Glutamate – Reversal Potential for Receptors that are Non-Selective

However, if the ionotropic receptor allows the flow of more than one ion, or is non-selective, the reversal potential of the receptor does not equal the equilibrium potential of either ion but is somewhere in between. The equilibrium potential of sodium is approximately +60 mV, and the equilibrium potential of potassium is approximately -80 mV. A glutamate receptor is a non-selective cation channel that allows the flow of both ions, and the reversal potential of the receptor is 0 mV. This means that if the neuron's membrane potential is negative, the driving forces acting on sodium are stronger than the driving forces acting on potassium, so more sodium will flow in than potassium will flow out, and the membrane potential will depolarize, causing an excitatory postsynaptic potential (EPSP).

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Animation 13.8. The reversal potential of an ionotropic receptor that is not selective to one ion will fall between the equilibrium potentials of the permeable ions. Glutamate receptors allow the flow of both sodium and potassium ions, so the reversal potential for the receptor is approximately 0 mV. More sodium will flow into the cell than potassium flows out, resulting in a depolarization of the membrane. The line, teal channel represents a glutamate receptor. 'Glutamate Reversal Potential – Rest' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

If the membrane potential reached the reversal potential of the glutamate receptor, the electrochemical gradients acting on sodium and potassium would balance, so overall ion flow in both directions would be equal, and the membrane potential would not change.

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Animation 13.9. At the reversal potential, there is no net ion flow in either direction. An equal number of sodium ions enter the cell as potassium ions leave. Since there is no change in voltage at the reversal potential, if the receptor remained open, the membrane potential would stay at 0 mV. 'Glutamate Reversal Potential – 0 mV' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License. View static image of animation.

Key Takeaways

- Ionotropic receptors are ligand-gated ion channels that open when a specific neurotransmitter binds
- For receptors selective to one ion, the reversal potential equals the ion's equilibrium potential
- For receptors not selective for only one ion, the reversal potential is a value between the ions' equilibrium potentials
- Glutamate is an excitatory neurotransmitter that opens non-selective cation channels that allow the influx of sodium, causing an EPSP
- GABA and glycine are inhibitory neurotransmitters that open chloride channels, causing an IPSP

Test Yourself!

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https://opentext.uoregon.edu/neurobiology/?p=137#h5p-12

The following questions refer to a mythical cell, the Thinking Cell. The properties for this cell are given in the table. In all cases, the postsynaptic membrane is a dendrite. Use the information in the table to answer the following questions.

[table id=4 /]

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Video Lecture

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14.

NEUROTRANSMITTER ACTION: G-PROTEIN-COUPLED RECEPTORS

G-protein-coupled receptors (GPCRs), also called metabotropic receptors, are membrane-bound proteins that activate G-proteins after binding neurotransmitters. Like ionotropic receptors, metabotropic receptors are primarily located along the dendrites or cell body, but they can be present anywhere along the neuron if there is a synapse. Metabotropic receptors are also important for receiving incoming information from other neurons. GPCRs have slower effects than ionotropic receptors, but they can have long-lasting effects, unlike the brief action of a postsynaptic potential.

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

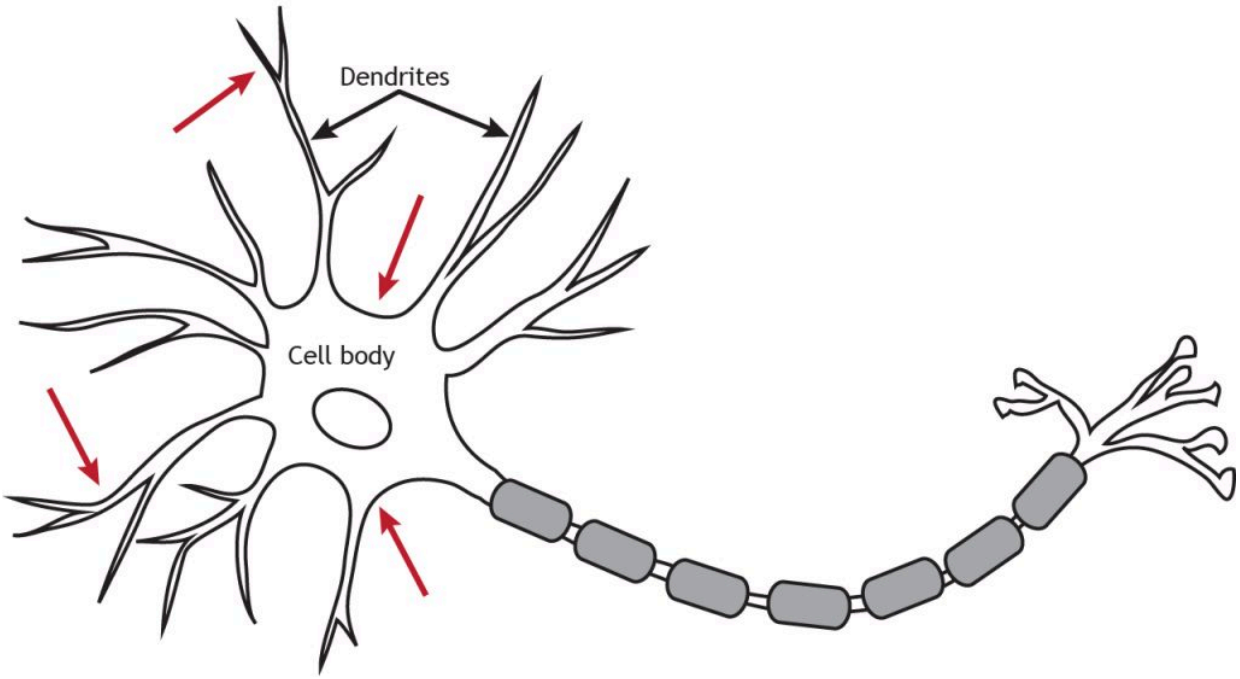


Figure 14.1. Metabotropic receptors critical for receiving incoming synaptic information are primarily located along the dendrites and cell body. 'Receptor Location' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

G-Proteins

G-proteins are enzymes with three subunits: alpha, beta, and gamma. In the resting state of the G-protein complex, the alpha subunit is bound to a GDP molecule. There are multiple types of alpha subunits, and each initiate different cellular cascades in the neuron.

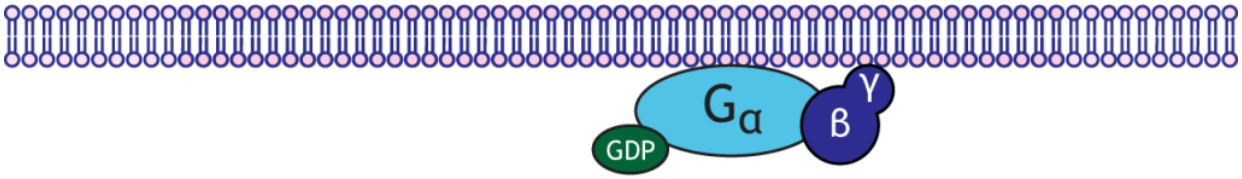


Figure 14.2. The unactivated G-protein complex in the cell consists of three subunits (alpha, beta, and gamma) and a bound GDP molecule. 'G-protein Complex' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

G-Protein Coupled Receptors

When a neurotransmitter binds to a GPCR, the receptor is able to interact with an inactivated G-protein complex. The complex that binds is specific to the receptor; different metabotropic receptors for the same neurotransmitter can have different effects in the cell due to which G-protein binds. Once coupled to the receptor, the GDP molecule is exchanged for a GTP molecule, and the G-protein becomes activated.

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Animation 14.1. Neurotransmitter binding to a G-protein-coupled receptor causes the inactivated G-protein complex to interact with the receptor. The GDP molecule is then exchanged for a GTP molecule, which activates the G-protein complex. 'G-protein Binding' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

After activation, the G-protein complex will separate into the alpha-GTP subunit and the beta-gamma subunit. Both components can alter the function of effector proteins in the cell. Effector protein functions can range from altering ion permeability across the membrane by opening ion

channels to initiating second messenger cascades. Second messenger cascades can have long-term, widespread, and diverse cellular effects including activation of cellular enzymes or altering gene transcription.

> *One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=149#video-149-2*

Animation 14.2. Once activated, the G-protein complex will separate into the alpha-GTP subunit and the beta-gamma subunit. These subunits can stimulate or inhibit effector proteins within the cell. 'G-protein Effects' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Cellular Effects of G-Proteins

Open Ion Channels – Beta Gamma Subunit

Metabotropic receptors can indirectly open ion channels; this process is slower than ionotropic receptors

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In certain situations, the activated beta-gamma subunit can open or close ion channels and change membrane permeability. Muscarinic acetylcholine receptors in the heart use this pathway. When acetylcholine binds to a muscarinic receptor in the heart muscle fiber, the activated beta-gamma subunit opens a type of potassium channel called G-protein-coupled inwardly-rectifying potassium (GIRK) channel, hyperpolarizing the cell. This inhibitory effect explains why acetylcholine or an agonist like atropine slow the heart rate.

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Animation 14.3. Some GPCRs, like the muscarinic acetylcholine receptors in the heart, alter cellular permeability by opening ion channels. The activated beta-gamma subunit of the muscarinic receptor opens GIRK potassium channels and allows the efflux of potassium. 'Beta-Gamma Ion Channels' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Second Messenger Cascades

Metabotropic receptors can alter protein function in the cell through second messenger cascades; these cascades may lead to changes in gene transcription

In addition to direct effects like the activated beta-gamma subunit opening ion channels, G-proteins can have many indirect actions in the cell through the use of second messenger cascades. The specific second messenger pathway that is activated or suppressed by G-protein action depends on the type of alpha subunit.

For example, norepinephrine can act on either alpha- or beta-adrenergic receptors. Beta-adrenergic GPCRs couple to a stimulatory G-protein, or G_s, which initiates the cyclic AMP (cAMP) second messenger system by activating the enzyme adenylyl cyclase. Alpha 2-adrenergic receptors, however, couple to an inhibitory G-protein, or G_i, and suppress the activity of adenylyl cyclase. Alpha 1-adrenergic receptors couple to a third type of G-protein, G_q, which activates the phospholipase C pathway. One neurotransmitter can, therefore, cause a wide range of cellular effects after binding to

GPCRs, unlike the single function of ion flow through the ionotropic receptors. The pathway initiated by norepinephrine will depend on the type of receptor a specific cell expresses.

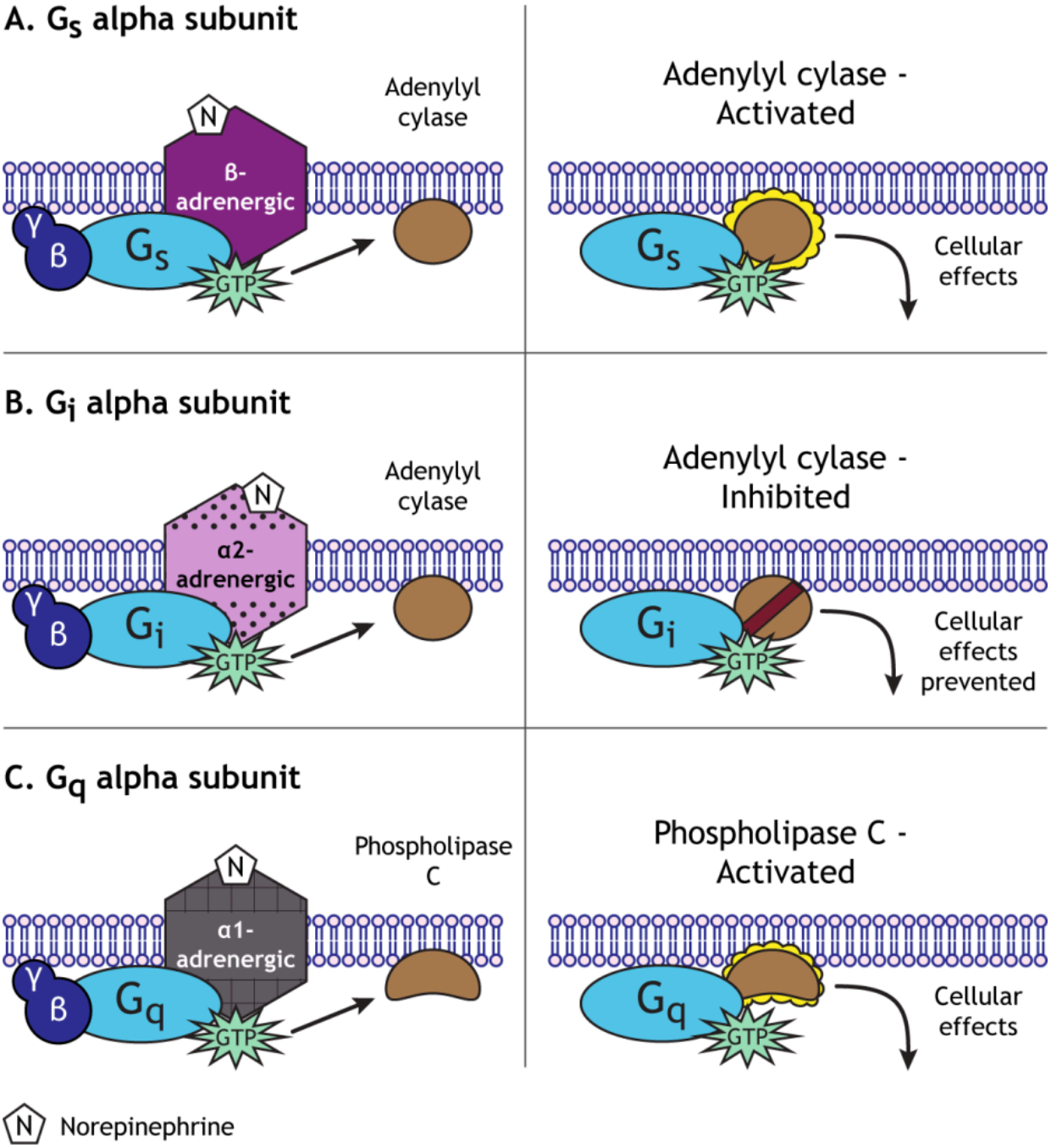


Figure 14.3. The second messenger pathway use and whether that pathway is stimulated or inhibited depends on the type of alpha subunit in the G-protein complex. Different receptors couple to different G-protein complexes. This allows one neurotransmitter to initiate multiple types of signaling cascades. A) The norepinephrine beta-adrenergic receptor couples to the G_s subunit and activates adenylyl cyclase, which initiates downstream cellular effects. B) The norepinephrine alpha 2-adrenergic receptor couples to the G_i subunit and inhibits adenylyl cyclase, which prevents

downstream cellular effects. C) The norepinephrine alpha 1-adrenergic receptor couples to the G_q subunit and activates phospholipase C, which initiates downstream cellular effects. 'Alpha Subunit Effects' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Adenylyl Cyclase / cAMP Second Messenger Cascade

The cyclic AMP (cAMP) second messenger pathway is used by many GPCRs. Activation of the pathway is caused by the G_s alpha subunit and inhibition of the pathway is caused by the G_i alpha subunit. When activated, adenylyl cyclase converts ATP to cAMP in the cytoplasm. cAMP then activates another enzyme called protein kinase A (PKA) by binding to the regulatory subunits, allowing the catalytic (functional) subunits to separate and become active. Protein kinases add a phosphate molecule to proteins, a mechanism called phosphorylation. The addition of the phosphate changes the activity of the protein and how it functions in the cell.



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Animation 14.4. GPCRs that couple to the G_s alpha subunit initiate the adenylyl cyclase / cAMP pathway. The G_s subunit activates adenylyl cyclase, which then converts ATP to cAMP. cAMP binds to and activates protein kinase A (PKA), which phosphorylates proteins in the cell. 'Adenylyl Cyclase Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

The end effects of this pathway will depend on which proteins are targeted. For example, cAMP can gate ion channels and PKA can phosphorylate ion channels altering permeability and membrane potential. Phosphorylation can open the channel, or it may modulate the activity of the channel, making the channel easier to open or remain open longer.



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Animation 14.5. The adenylyl cyclase / cAMP pathway can alter many cellular functions. One example is that both cAMP and PKA can open ion channels. Like ligand-gated channels, there are also cAMP-gated channels, which open after cAMP binding. PKA is able to phosphorylate and modulate ion channel function by converting ATP to ADP. 'Second Messenger Ion Channel Action' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

In addition to altering ion channel function, PKA can phosphorylate other proteins important for neuron function, such as proteins involved with neurotransmitter synthesis and release. One other critical target of PKA phosphorylation is the transcription factor CREB (cAMP response element binding-protein). Transcription factors bind to DNA in the nucleus and change the rate of gene transcription. Phosphorylation by PKA can cause CREB to initiate transcription of genes, creating new proteins for the neuron. Depending on which genes are transcribed, the effects on the neuron can be long-lasting.

Overall, neurotransmitters working through GPCRs and second messenger cascades like the adenylyl cyclase pathway can cause a diverse range of cellular effects: from opening ion channels, to changing protein activity via phosphorylation, to altering the proteins synthesized in the neuron.

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Animation 14.6. PKA can phosphorylate a number of proteins involved with neuron function. It can target proteins involved with neurotransmitter synthesis, packing, and release, or it can enter the nucleus and phosphorylate CREB, a transcription factor that can initiate gene transcription and

protein synthesis. 'PKA Targets' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Phospholipase C / IP_3 / DAG Second Messenger Cascade

The Gq alpha subunit initiates a separate signaling pathway in the cell by activating phospholipase C. Phospholipase C targets PIP_2 (phosphatidylinositol 4,5-bisphosphate), which is a phospholipid present in the plasma membrane of the cell. PIP_2 is split into two cellular molecules: IP_3 (inositol 1,4,5-trisphosphate) and DAG (diacylglycerol). DAG remains in the membrane and interacts with protein kinase c (PKC). IP_3 moves to the endoplasmic reticulum where it opens calcium channels and allows calcium to flow into the cytosol.

Calcium is also a second messenger in the cell. One important effect is the binding of calcium to calmodulin protein. This complex can then activate another kinase, the calcium/calmodulin-dependent protein kinase (CaMK). Both PKC and CaMK can phosphorylate specific cellular and nuclear proteins like PKA.

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Animation 14.7. The G_q G-protein subunit activates phospholipase C, which converts the phospholipid PIP_2 in the cell membrane into DAG, another membrane-bound molecule, and IP_3, a cytoplasmic molecule. DAG can interact with PKA, initiating phosphorylation of cellular proteins. IP_3 opens calcium channels in the endoplasmic reticulum, allowing calcium to flow into the cytoplasm. Calcium, another second messenger can have many cellular effects. It can bind to calmodulin, which then activates CaMK, causing phosphorylation of more protein targets. 'IP_3-DAG Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Signal Amplification

One characteristic of GPCR activation is the signal amplification that takes place. One receptor is able to activate more than one G-protein complex. The effector protein activated by the G-protein can create many second messengers, and the activated protein kinases can each phosphorylate multiple cellular proteins. This means that one neurotransmitter can have a significant effect on cellular function.

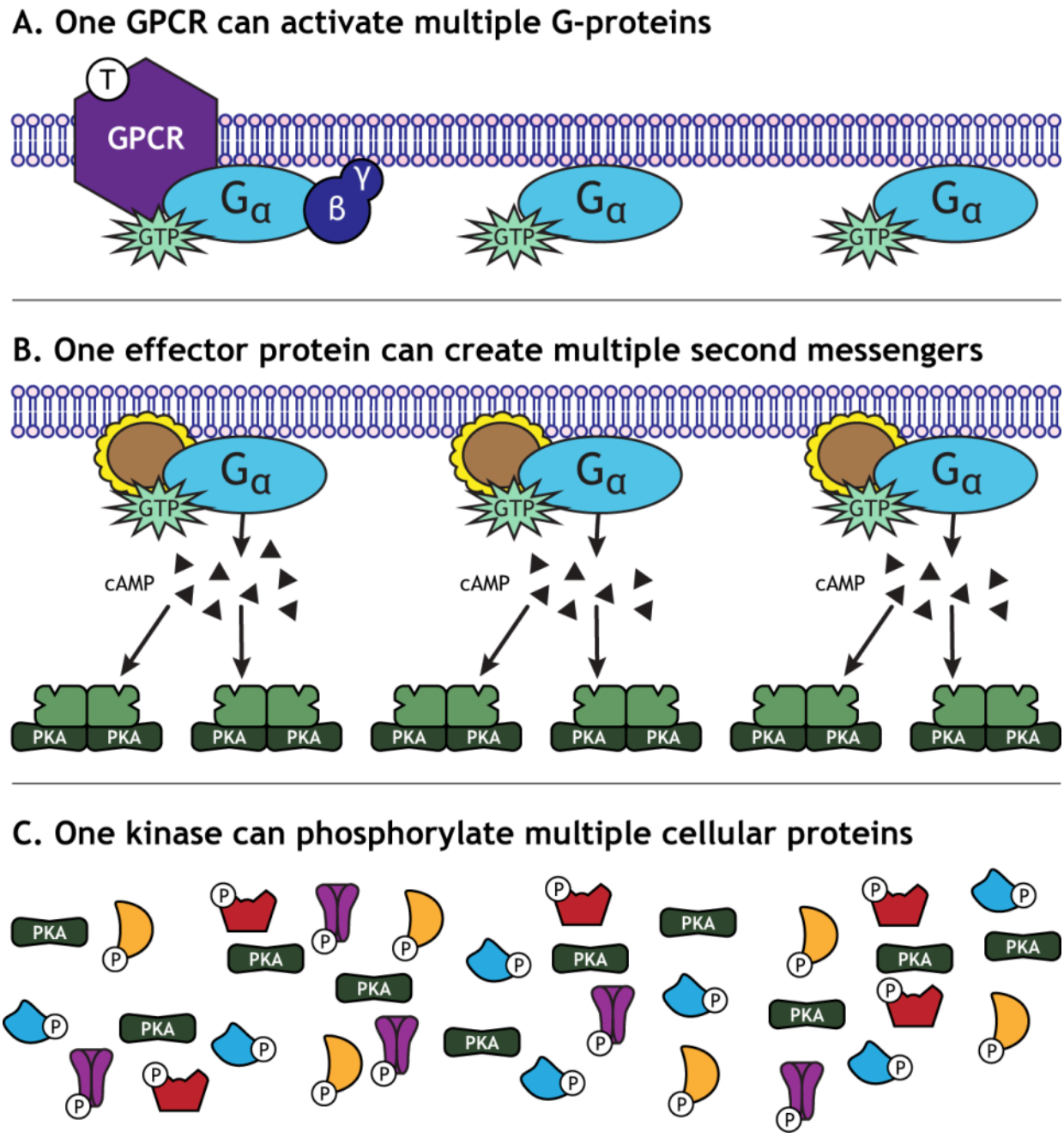


Figure 14.4. The second messenger cascades initiated by GPCRs undergo significant signal amplification. A) Multiple G-proteins can be activated by a GPCR. B) Each effector protein is able to synthesize numerous second messenger molecules. C) Each protein kinase activated by the second messengers can phosphorylate various cellular proteins. 'Signal Amplification' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Signal Termination

Eventually, the cascade initiated by binding of the neurotransmitter to the GPCR needs to end. The alpha subunit of the G-protein is able to convert the bound GTP back to GDP after a short period of time, inactivating the G-protein. The alpha subunit will then interact with a beta-gamma subunit and stay in the resting state until activated by another GPCR. Enzymes in the cell called protein phosphatases find and remove the phosphate groups added to cellular proteins by the protein kinases. And finally, other cellular mechanisms exist to remove calcium from the cytoplasm and degrade other second messengers.

Key Takeaways

- G-protein-coupled receptors rely on the activation of G-proteins to cause cellular changes
- G-protein-coupled receptors have slower effects than ligand-gated receptors
- G-proteins can open ion channels, alter protein function via phosphorylation, and alter gene transcription
- The G_s subunit initiates the adenylyl cyclase / cAMP signaling pathway
- The G_i subunit inhibits the adenylyl cyclase / cAMP signaling pathway
- The G_q subunit initiates the phospholipase C / IP_3 / DAG signaling pathway

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
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- What are some differences between ionotropic and metabotropic neurotransmitter receptors?

Video Lecture

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Attributions

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15.

NEUROTRANSMITTER CLEARANCE

After neurotransmitters have been released into the synaptic cleft, they act upon postsynaptic receptors, as covered in the previous chapters. That action must be terminated in order for proper neuronal communication to continue. This is accomplished mainly through two processes: neurotransmitter transport and/or degradation. Transport physically removes the neurotransmitter molecule from the synaptic cleft. Degradation breaks down the neurotransmitter molecule by enzyme activity.

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

Neurotransmitters can be degraded by enzymes in the synapse

Acetylcholine

Acetylcholine action is terminated by acetylcholinesterase, an enzyme present in the synaptic cleft. Acetylcholinesterase degrades acetylcholine into choline and acetate molecules. Choline is then transported back into the presynaptic terminal and used in the synthesis of new acetylcholine.

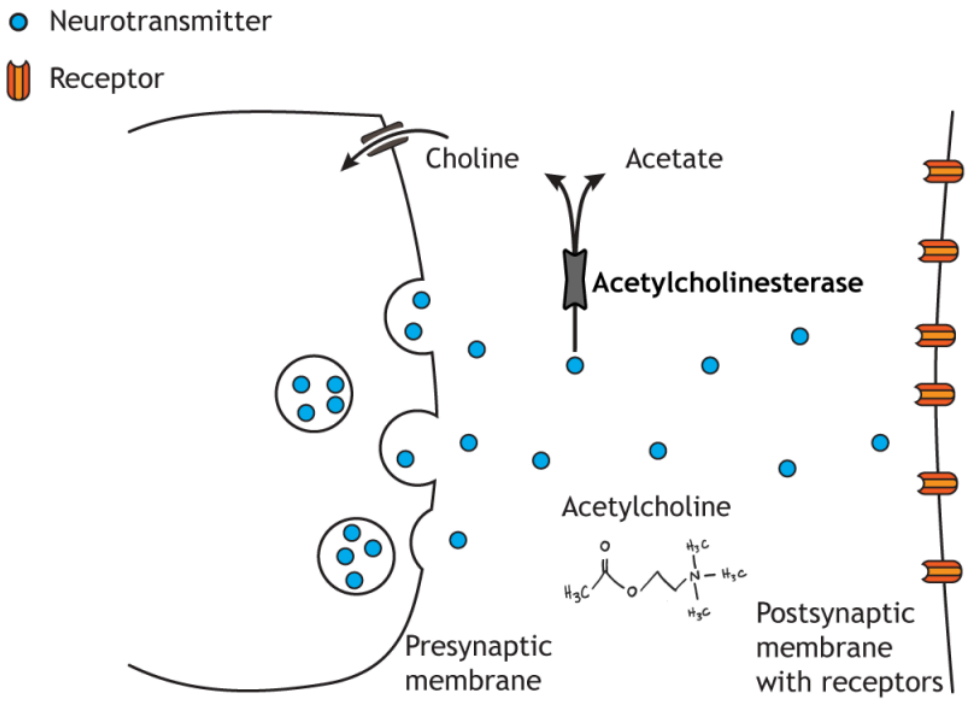


Figure 15.1. Acetylcholine is degraded into choline and acetate within the synaptic cleft via acetylcholinesterase. Choline is then transported back into the presynaptic terminal. 'Acetylcholine Degradation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Neurotransmitters can be transported into glial cells and degraded by enzymes

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Glutamate

Glutamate action is terminated by two mechanisms. Reuptake of glutamate molecules into the presynaptic terminal can occur, or glutamate can be transported into nearby glial cells. The excitatory amino acid transporters are sodium co-transporters and use the sodium electrochemical gradient to drive neurotransmitter transport. Within glial cells, glutamate is converted into glutamine by glutamine synthetase. Glutamine is then transported out of the glial cell and back into the presynaptic

terminal for use in future glutamate synthesis. If glutamate is transported back into the presynaptic terminal, it can be repackaged in synaptic vesicles.

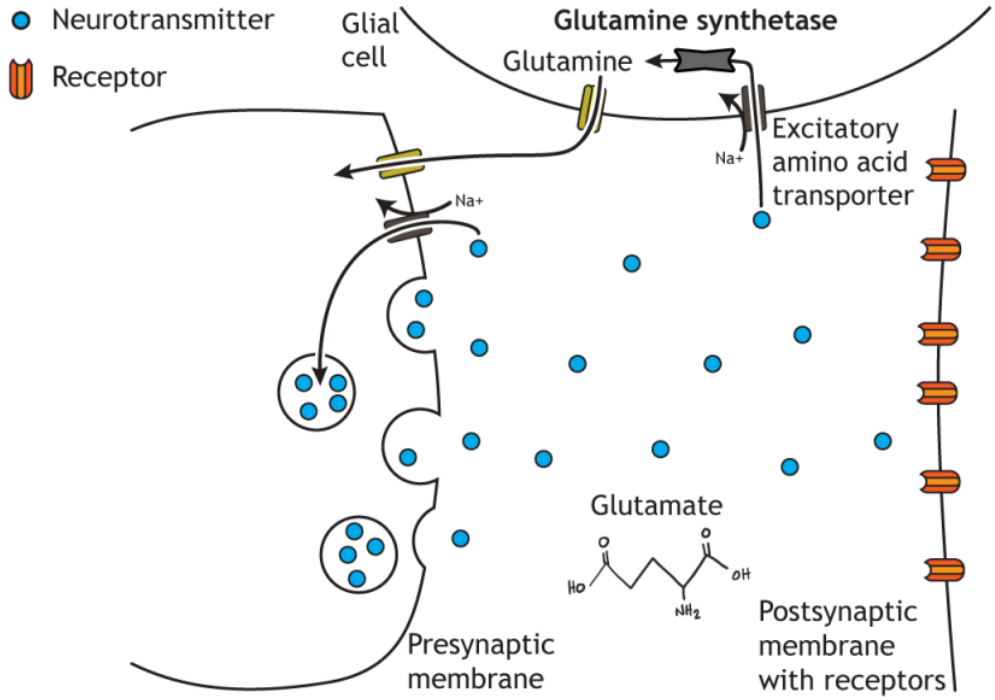


Figure 15.2. Glutamine needs to removed from the synapse. The excitatory amino acid transporter that uses sodium to drive glutamate movement across the membrane can move glutamate into glial cells or back into the presynaptic terminal. In the terminal, glutamate is repackaged into synaptic vesicles. In the glial cells, glutamate is broken down into glutamine by glutamine synthetase. 'Glutamate Degradation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

GABA and Glycine

Like glutamate, GABA and glycine action are terminated by either reuptake into the presynaptic terminal and packaging in synaptic vesicles or through transport into glial cells where breakdown can occur. The GABA and glycine transporter also use the sodium electrochemical gradient to drive the movement of the transmitter across the membrane.

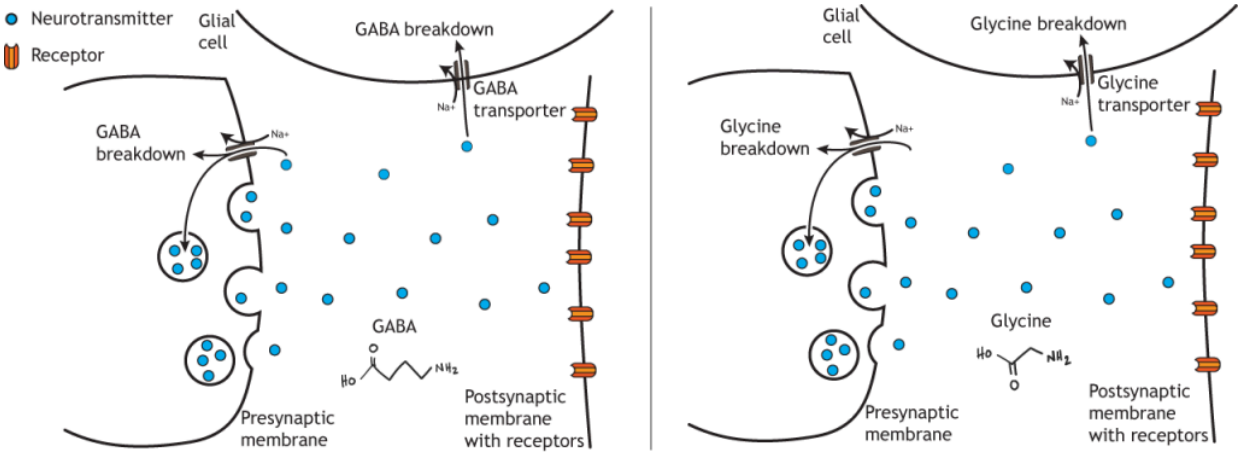


Figure 15.3. GABA and glycine action is terminated by reuptake by sodium co-transporters into either glial cells or back into the presynaptic terminal. In both locations, the neurotransmitters can be broken down by enzymes, whereas in the presynaptic terminal, the transmitters can be repackaged in synaptic vesicles. 'GABA and Glycine Degradation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Neurotransmitters can be transported back into the terminal and either degraded or repackaged

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Dopamine

Dopamine action is terminated by reuptake into the presynaptic terminal via the dopamine transporter (DAT). Once inside the cell, dopamine is either degraded via the actions of either monoamine oxidase (MAO) or catechol-O-methyltransferase (COMT), or it is repackaged into vesicles.

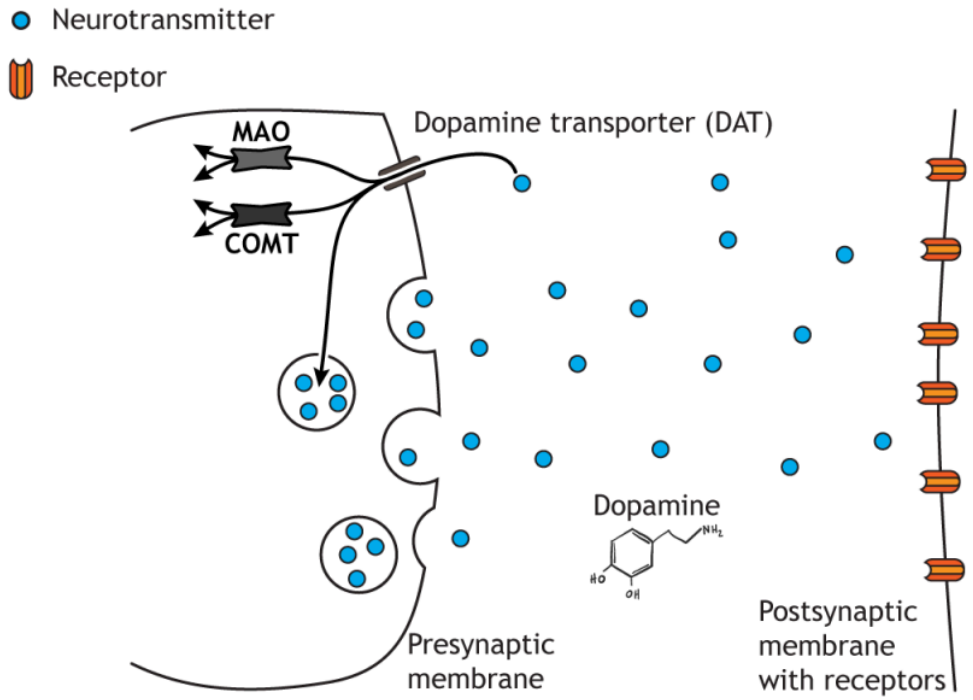


Figure 15.4. Dopamine action is terminated by reuptake into the presynaptic terminal via DAT. Dopamine is then either degraded by MAO or COMT or repackaged into synaptic vesicles. 'Dopamine Degradation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Norepinephrine

Norepinephrine follows the same pathway as dopamine. Reuptake into the presynaptic terminal occurs via the norepinephrine transporter (NET), and then the transmitter is either degraded within the cell by MAO or COMT or repackaged into synaptic vesicles.

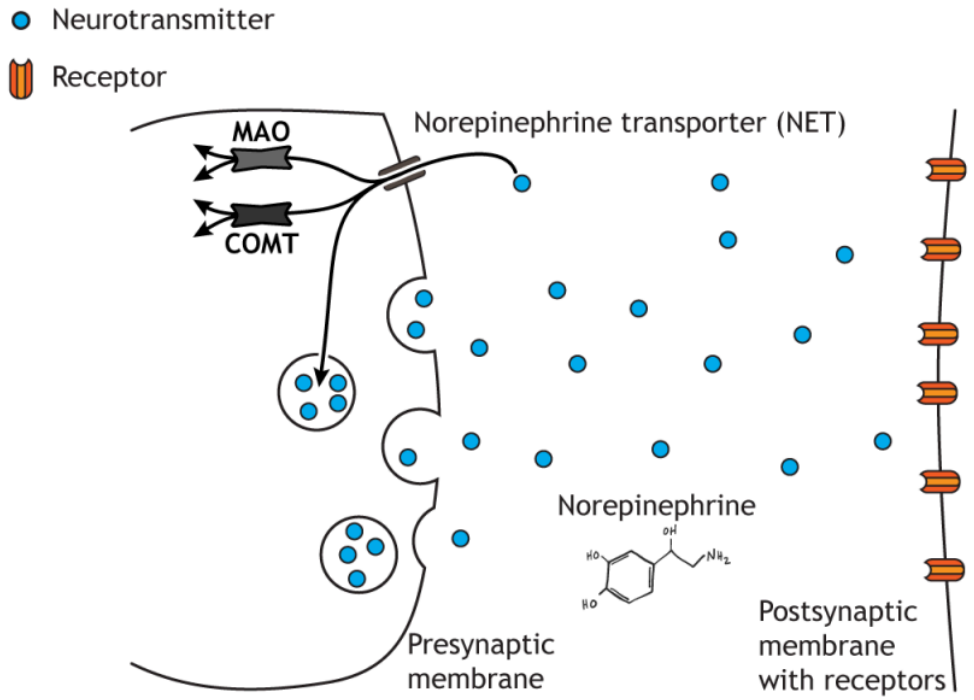


Figure 15.5. Norepinephrine action is terminated by reuptake into the presynaptic terminal via NET. Norepinephrine is then either degraded by MAO or COMT or repackaged into synaptic vesicles. 'Norepinephrine Degradation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Serotonin

Like the other monoamines, serotonin is transported back into the presynaptic terminal via the serotonin transporter (SERT). The difference between serotonin and the catecholamines dopamine and norepinephrine is that monoamine oxidase is the only enzyme used for degradation.

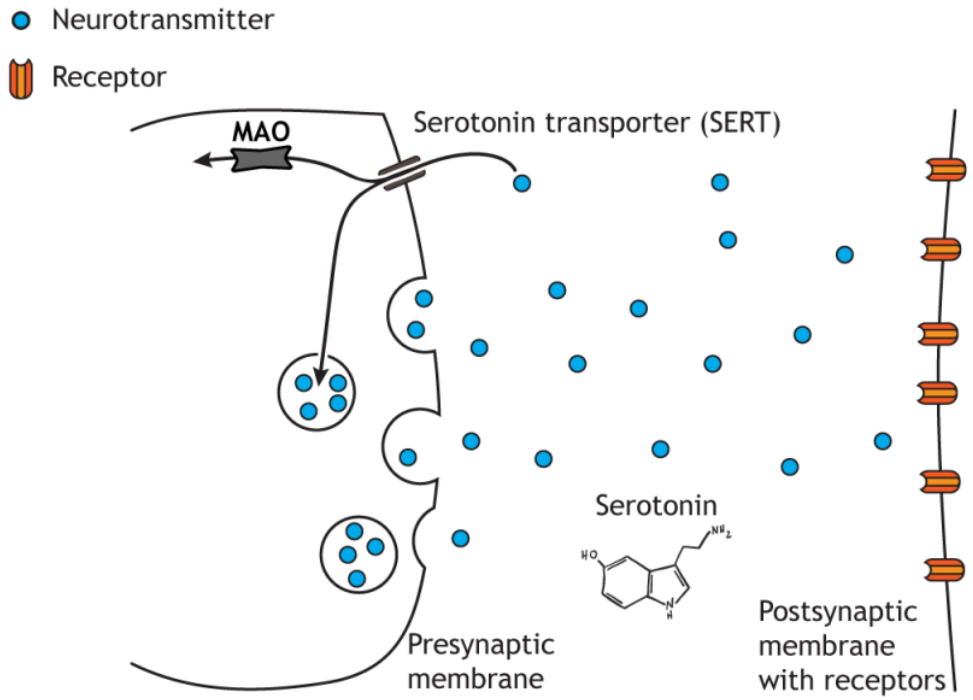


Figure 15.6. Serotonin action is terminated by reuptake into the presynaptic terminal via SERT. Serotonin is then either degraded by MAO or repackaged into synaptic vesicles. 'Serotonin Degradation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Key Takeaways

- Neurotransmitter action in the synapse must be terminated
- This occurs by either
  - reuptake into the presynaptic terminal where enzymatic degradation or repackaging into vesicles occurs
  - transport into glial cells where enzymatic degradation occurs
  - enzymatic degradation in the synapse

Test Yourself!

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Video Lecture

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16.

DRUG AND TOXIN EFFECTS

Drugs and toxins can alter neuron functioning in a range of ways, from activation to inhibition and all levels of modulation. Although many drugs exist that alter molecular process typical of many cells, this lesson will focus on neuron-specific targets.

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

Drug and toxin effects can be excitatory, inhibitory, or modulatory

Synaptic Effects

As we have seen, the synapse is an incredibly complex structure, and for small molecule neurotransmitters, the entire "lifecycle" of the transmitter occurs in this space – synthesis, packaging, release, action, and termination. This means there are numerous targets upon which drugs and toxins can act and alter synaptic communication.

Drug Effects on Neurotransmitter Release

Drugs can alter neurotransmitter synthesis pathways, either increasing or decreasing the amount of neurotransmitter made in the terminal, affecting how much transmitter is released. An example of this is administration of L-DOPA, a dopamine precursor molecule that results in increased dopamine production; it is used as a treatment for Parkinson's Disease.

Neurotransmitter packaging is another site of possible drug action. Reserpine, which has been used to treat high blood pressure, blocks the transport of the monoamine transmitters into vesicles by inhibiting the vesicular monoamine transporter (VMAT). This decrease the amount of neurotransmitter stores and the amount of neurotransmitter released in response to an action potential.

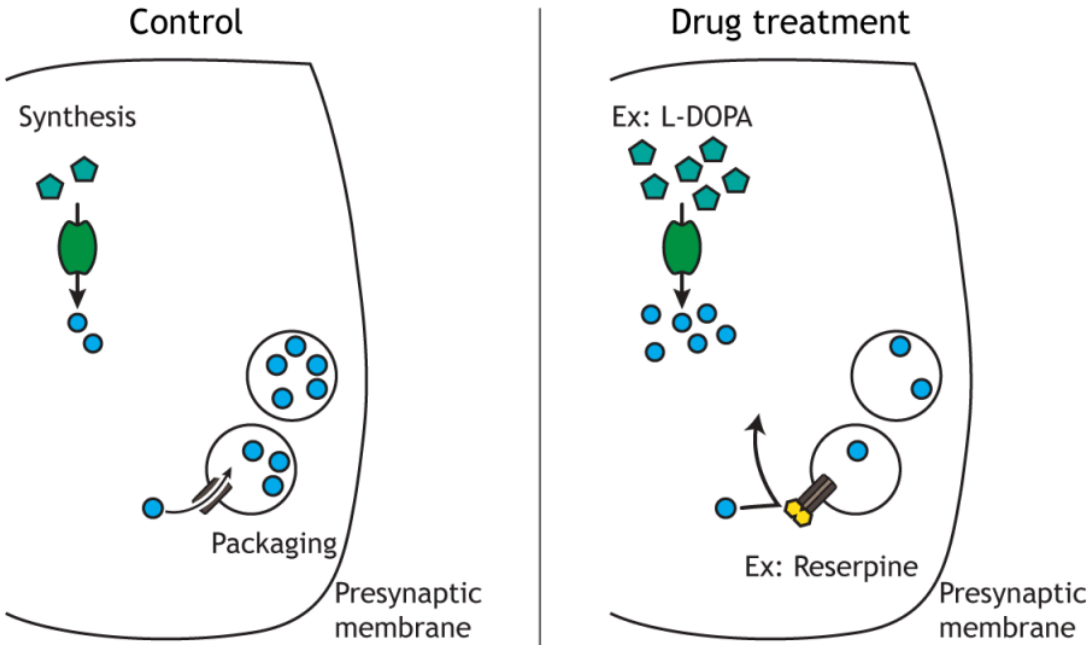


Figure 16.1. Drugs and toxins can alter neurotransmitter synthesis and packaging into synaptic vesicles. L-DOPA increases the synthesis of dopamine in the terminal. Reserpine prevents packaging of the biogenic amines, resulting in low concentrations of transmitter stored in synaptic vesicles. 'Drug Effects on Neurotransmitter Release' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Drug Effects on the Postsynaptic Membrane

The neurotransmitter receptors are another critical location for drug and toxin action. Agonists mimic neurotransmitter effects, whereas antagonists block neurotransmitter effects. Muscimol, a component of some mushrooms, is an agonist for the ionotropic GABA receptor. Bicuculine, a component of some plants, is an antagonist to this receptor and blocks the action of GABA. Additionally, many chemicals are able to modulate receptors in either a positive or negative fashion. Alcohol binds to the GABA receptor and increases the time the receptor is open when GABA binds.

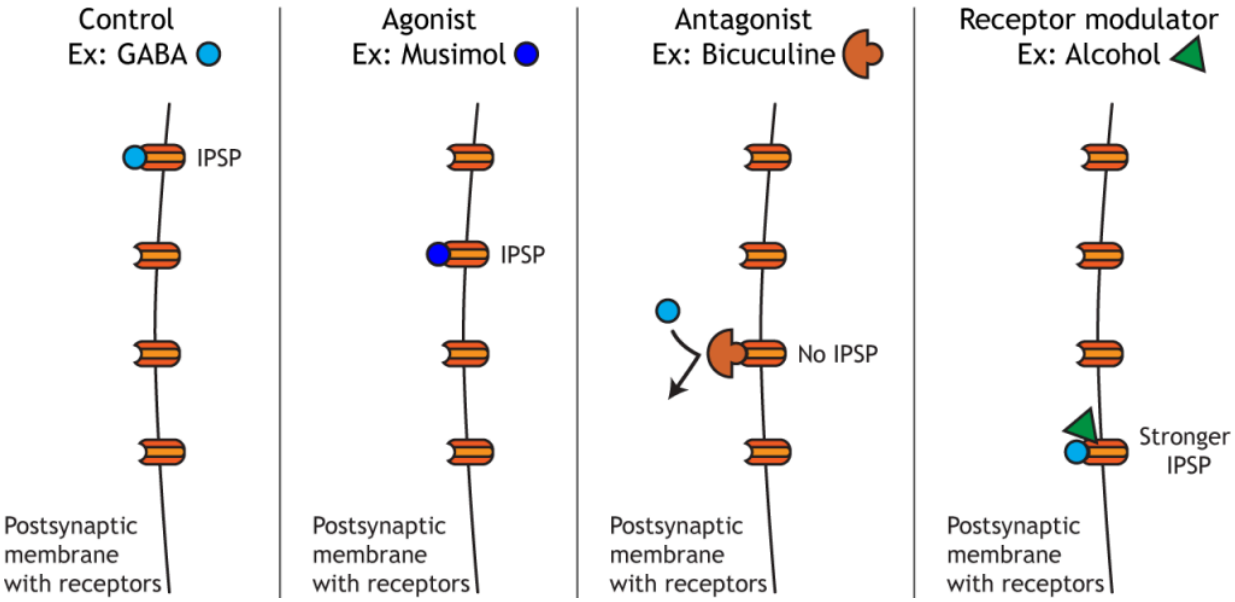


Figure 16.2. Drugs and toxins can alter neurotransmitter receptors on the postsynaptic neuron. A GABA agonist, muscimol, would replicate the actions of GABA and cause an IPSP. A GABA antagonist, bicuculine, would prevent GABA actions resulting in no IPSP. Modulators such as alcohol, alter how the receptor works, so when GABA binds the response is a stronger IPSP than when alcohol is not present. 'Postsynaptic Drug Effects' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Drug Effects on Neurotransmitter Clearance

Finally, neurotransmitter degradation and reuptake can also be altered by drugs and toxins. Depending on the neurotransmitter, enzymes located in either the synapse or in the terminal are responsible for degradation of the transmitter, and these enzyme can be blocked by drugs.

Organophosphates are found in many pesticides and prevent the action of acetylcholinesterase, the enzyme that breaks down acetylcholine in the synapse. This inhibition increases acetylcholine action on the postsynaptic neuron. Monoamine oxidase inhibitors (MAOIs) prevent monoamine oxidase from degrading the biogenic amine neurotransmitters. MAOIs have been used as antidepressants since they increase the amount of transmitter available. Additionally, drugs can prevent the reuptake of neurotransmitters into the presynaptic terminal. Cocaine blocks the dopamine transporter, which results in increased action of dopamine in the synapse.

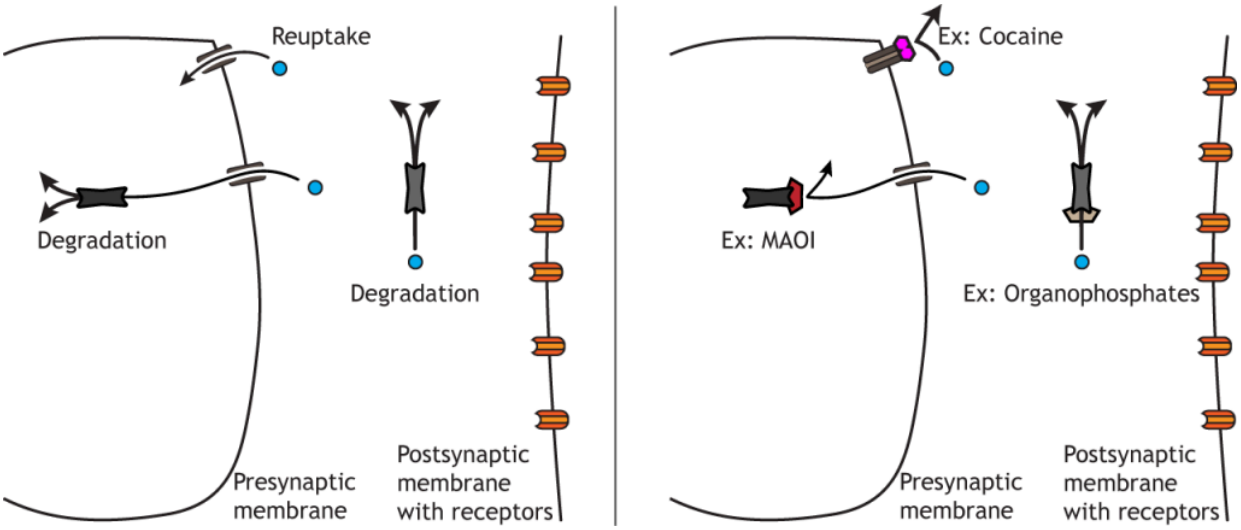


Figure 16.3. Drugs and toxins can alter neurotransmitter degradation and reuptake into the presynaptic terminal. Organophosphates prevent the degradation of acetylcholine in the synapse. MAOIs prevent the degradation of monoamine transmitters in the terminal. Cocaine prevents dopamine from being transported into the presynaptic terminal. All of these effects lead to increased neurotransmitter action and availability. 'Drug Effects on Neurotransmitter Clearance" by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Non-Synaptic Effects

Drugs and toxins can also affect neuron function by acting outside of the synapse. For example, some chemicals change voltage-gated ion channel dynamics. Veratridine, a compound found in plants from the lily family, prevents voltage-gated sodium channels from inactivating. Initially, this causes an increase in neurotransmitter release, but it can quickly lead to excitotoxicity.

Key Takeaways

- There are many ways in which drugs and toxins can alter neuron function
- Effects can be excitatory, inhibitory, or modulatory

Test Yourself!

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Video Lecture

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PART III

NERVOUS SYSTEM ORGANIZATION

17.

ANATOMICAL TERMINOLOGY

Familiarity with the terminology used to describe location and relationships within the nervous system is critical as we move forward into examining brain systems.

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

Directional Terms

Directional terms are used to locate one structure, usually in relation to another structure. Some terms, like dorsal or ventral, are relative to the axis of the central nervous system, so the direction these terms define changes if used for brain regions versus other body regions. Other terms, like superior or inferior, keep their meaning across the entire body.

- Anterior: In front of; toward the face
- Posterior: Behind; toward the back
- Superior: Above; toward the head
- Inferior: Below; toward the feet
- Medial: Toward the middle
- Lateral: Toward the edge
- Dorsal: Toward the top of the brain or the back of the spinal cord
- Ventral: Toward the bottom of the brain or the front of the spinal cord
- Rostral: Toward the front of the brain or the top of the spinal cord
- Caudal: Toward the back of the brain or the bottom of the spinal cord

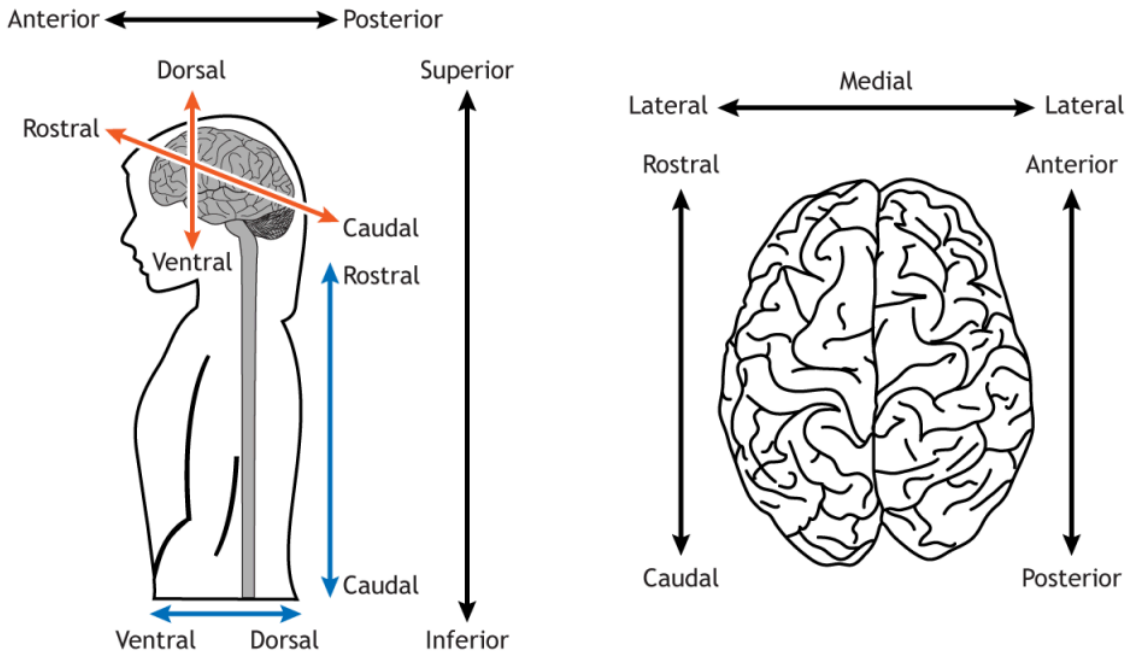


Figure 17.1. Directional terms used to locate nervous system structures. The dorsal / ventral and rostral / caudal pairs point in different directions depending on if they are referring to the axis of the brain (orange arrows) or the axis of the spinal cord (blue arrows). The definitions of each term are described in the text. 'Anatomical Directions' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Anatomical Planes

There are planes or axes that can be used to examine the nervous system. The frontal or coronal plane is a vertical plane in a medial to lateral direction, dividing objects into front and back pieces. The sagittal plane is also a vertical plane but in a rostral-caudal direction, meaning it divides objects into right and left regions. Finally, the horizontal plane divides objects into top and bottom regions.

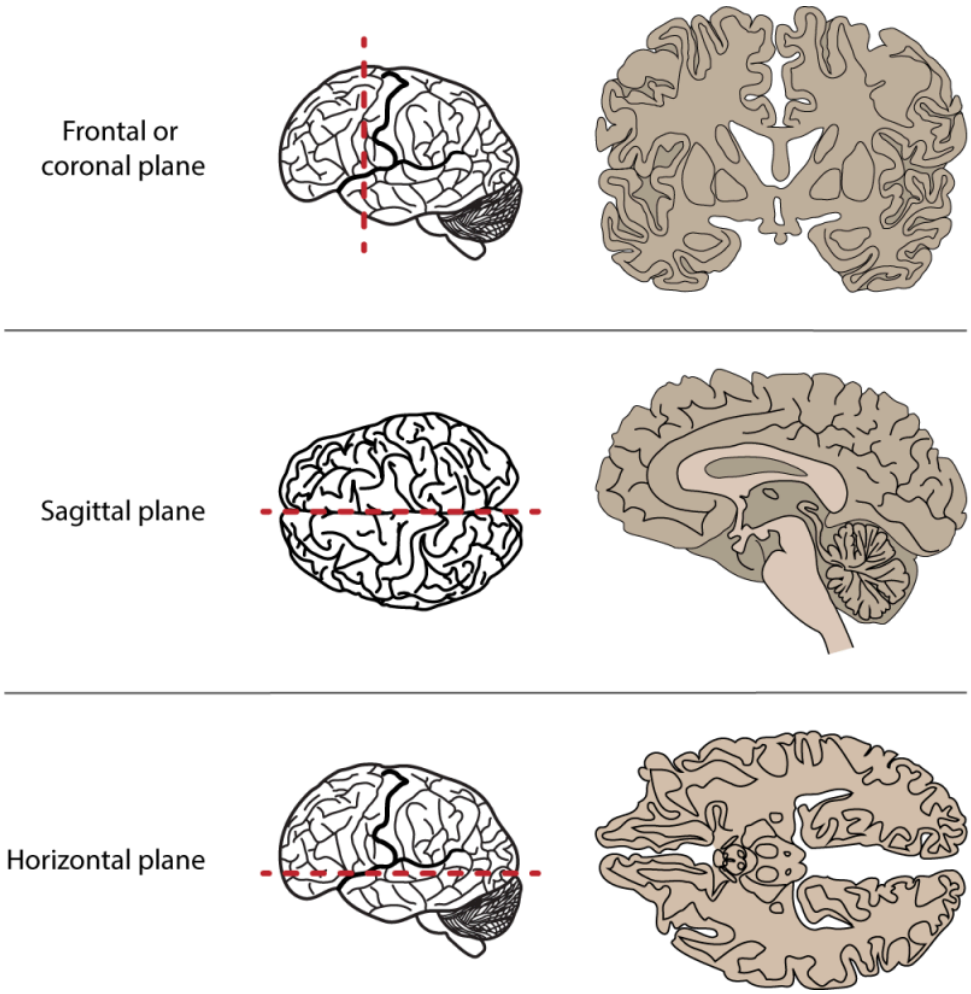


Figure 17.2. Three anatomical planes are used to divide the nervous system to be able to view internal regions and structures. The frontal or coronal plane is a vertical plane that runs parallel to the eyes or ears and will divide the body into front and back regions. The sagittal plane is a vertical plane that runs perpendicular to the eyes or ears and will divide the body into left and right regions. The horizontal plane runs parallel to the ground and will divide the body into top and bottom regions. 'Anatomical Planes' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Nervous System Divisions

The nervous system is divided into two primary components. The central nervous system (CNS) is comprised of the brain and the spinal cord. The peripheral nervous system (PNS) is comprised of the cranial and spinal nerves. When information flow is described in the nervous system, it can either be

afferent communication, meaning it is moving from the periphery to the brain, or efferent communication, meaning it is moving from the brain to the periphery.

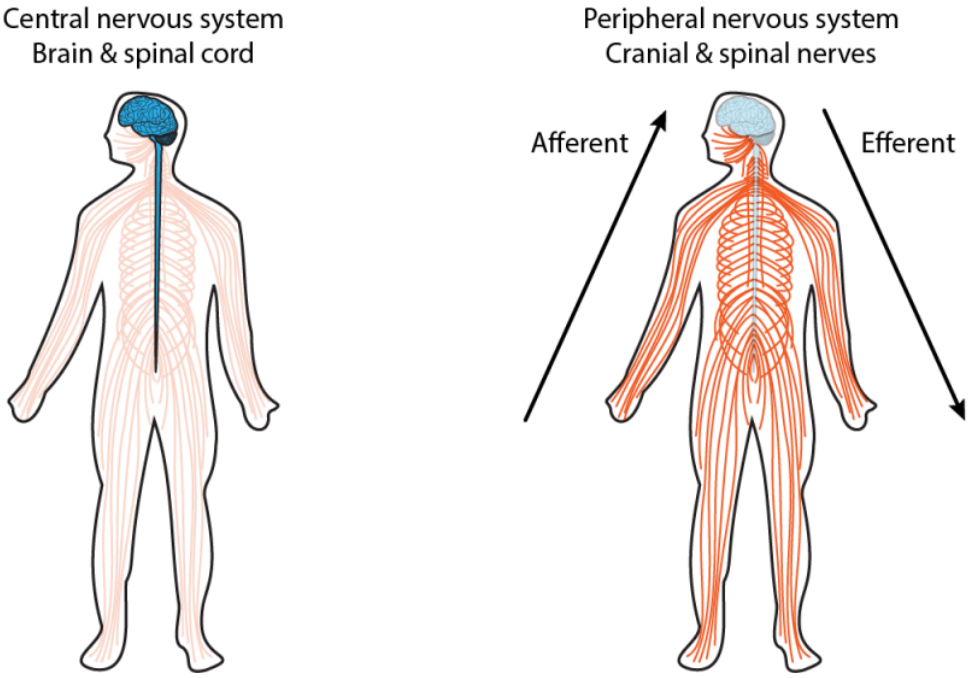


Figure 17.3. The nervous system is divided into the central nervous system, which includes the brain and spinal cord, and the peripheral nervous system, which includes the cranial and spinal nerves. Information traveling toward the brain is called afferent, whereas information traveling from the brain is called efferent. 'CNS and PNS' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Tissue in the central nervous system can be further divided into either white matter or gray matter. White matter regions are comprised of axons. It appears white due to the myelin sheath on the axons. Gray matter regions are comprised of cell bodies and dendrites. Gray matter is the location of most synapses.

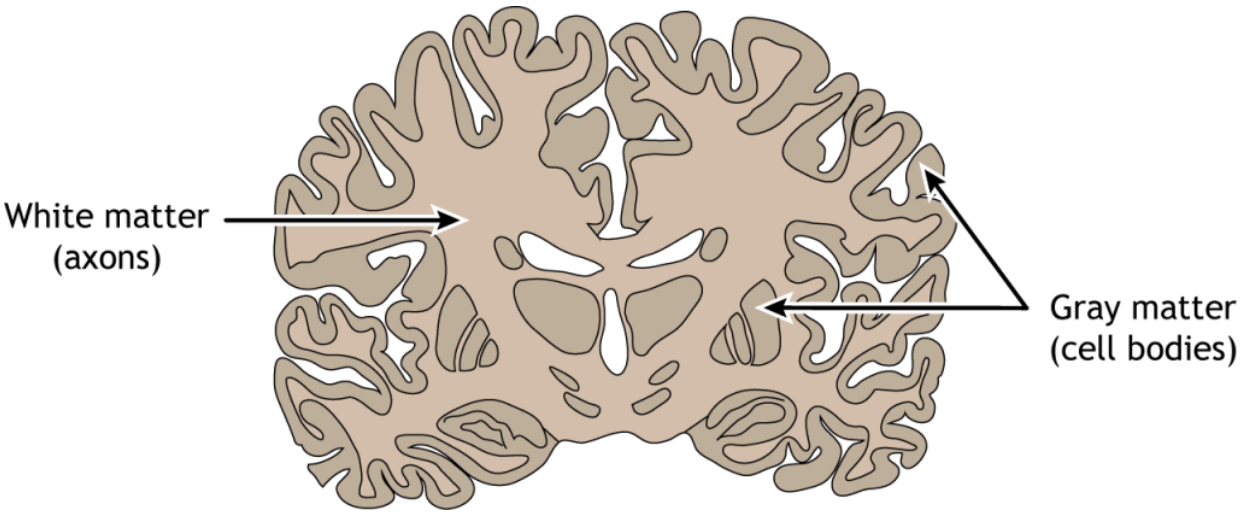


Figure 17.4. The central nervous system tissue can be divided into white and gray matter. White matter is primarily myelinated axons. Gray matter is primarily neuronal cell bodies and dendrites. In the brain, the surface of the cerebral cortex is a layer of gray matter. White matter can be found below the gray matter layer and is the location of the axons traveling to and from the cortical cell layer. Gray matter can also be found deep in the brain in subcortical regions that play critical roles in behavior. 'White and Gray Matter' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- Anatomical terminology is critical for determining neurological landmarks

Test Yourself!

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Video Lecture

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18.

NERVOUS SYSTEM DEVELOPMENT

In the following chapters, some of the many structures that make up the brain will be introduced. To begin this discussion, we will identify some of the basic development of the nervous system to understand how different areas of the brain are organized. An extremely simplified view of early development is presented below.

The first stage after fertilization is **cleavage**, involving a series of synchronized cell divisions. Cells develop and divide together, because embryonic transcription has not yet started, and it's the maternal transcripts that are being translated. Embryonic cell division becomes asynchronous when embryonic cell division starts, at the blastula stage. Eventually, the zygote develops into a flat layer of cells called the **epiblast.**

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

The next step of development, shared across many different animal clades, is **gastrulation**. During gastrulation, cells rotate and fold inwards to create multiple layers. The place through which cells **ingress** is called the primitive streak. Cells that fail to ingress express a set of ectodermal precursor genes, while ingressing cells are stimulated to express a different set of genes, turning them into endoderm or mesoderm. Over the course of gastrulation, the primitive streak moves from anterior to posterior. Right below the streak, a mesodermal structure, called the **notochord**, develops, forming a signaling center.

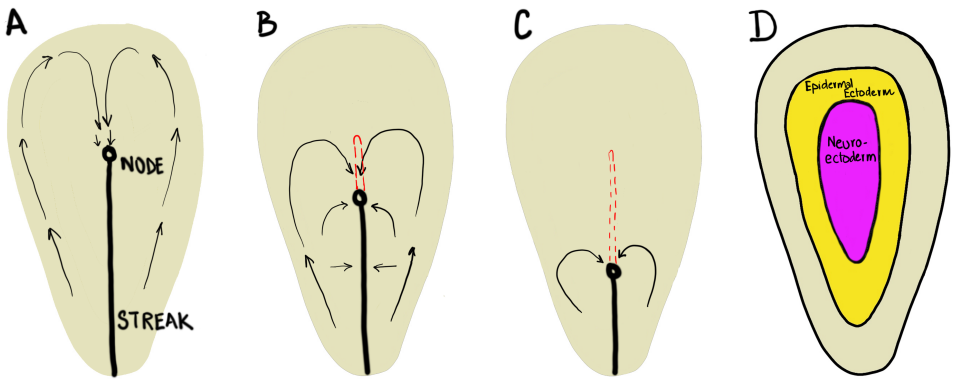


Figure 18.1. Amniote gastrulation. (A) At the start of gastrulation, precursor cells are arranged in a single layer, the epiblast. Gastrulation starts with ingression, where epiblast cells start to move forward and then to the middle, eventually ingressing below the eplblast, passing through the node and the primitive streak. (B) The node reaches to about 60% anterior, and then retracts. The node is a signaling center, turning on a set of genes that mark ingressing cells as mesodermal. The primitive streak and node retracts, leaving behind a cylinder of mesodermal cells along the midline (dotted red line) called the notochord. Other mesodermal cells migrate laterally.

(C) Further regression of the primitive streak during gastrulation, leaving behind a growing notochord. (D) At the end of gastrulation, the embryo is transformed from from a single layered epiblast to a three-layered gastrula with ectoderm on top, mesoderm below, and endoderm at the bottom. At the same time, ectodermal cells close to the midline are specified as neuroectoderm, while the remaining ectoderm will develop into epidermal cells. Figure was adapted from Fig 22.1 by Casey Henley.

After gastrulation, the embryo is 3-layered, with a central primitive streak and an underlying notochord. Ectodermal cells closer to the primitive streak become neural, while cells on the periphery develop into epidermal precursors. The notochord, being a signaling center, secretes molecular signals that diffuse to the ectoderm above, and stimulate the formation of the neural tube.

Very early in development, an embryo looks like a flat disc with 3 different layers of cells.

1. Endoderm: will eventually develop into the viscera (organs of the body)
2. Mesoderm: will eventually develop into the bones and muscles
3. Ectoderm: will eventually develop in the nervous system and the skin

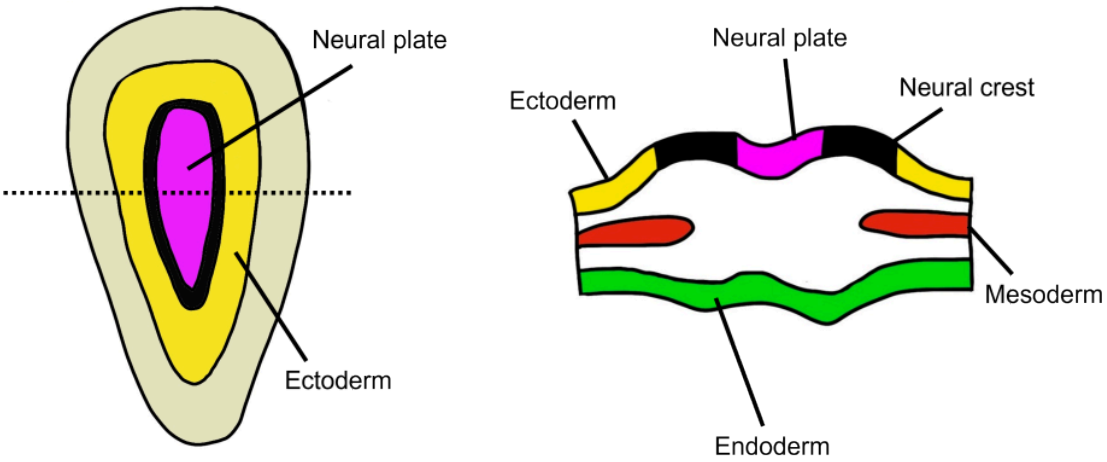


Figure 18.2. Developmental layers of the embryo. Early in development, the embryo looks like a flat disc made up of three different layers (left image). The ectoderm layer is what will develop into the nervous system. A cross section of the embryo (right image) reveals the endoderm, mesoderm, and ectoderm layers. 'Developmental layers of the embryo' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The Neural Tube

Next, part of the **ectoderm** will fold to form a nervous system precursor, a hollow neural tube, via the process called **neurulation**. Just prior to neurulation, the ectodermal layer has already been specified into centrally located neural precursors (magenta), flanking neural crest precursors (black), and epidermal precursors (yellow). Neural precursors will fold to form a **neural tube (magenta)**. Neurulation occurs within the first month following conception in humans. Neurulation starts at the anterior end, and progresses toward the posterior, though it leaves the neural tube open both at the anterior and all the way at the posterior. At the end of neurulation, the embryo has a hollow neural tube, separated from the remaining ectodermal cell layer above (yellow) which will form the epidermis. The flanking neural crest precursors come to lie between the neural tube and the epidermis, and will eventually migrate away from the midline. Below the neural tube lies mesodermal tissue, primarily in

the form of a solid cylinder of cells called the notochord. Epidermis and notochord cells both secrete diffusible signals, which guide further differentiation of cells in the neural tube.

During neurulation, the middle of the neural plate folds first, followed by the anterior and posterior ends. The central nervous system will develop from the walls of the neural tube and the hollow lumen of the tube will become the cerebral **ventricles** and spinal canal within the central nervous system.

The neural tube is initially only one cell thick. These are the progenitor cells, which divide to create multiple layers, increasing in complexity from posterior (spinal cord) to the midbrain and at the anteriormost, the forebrain. Epidermal signals result in differentiation of cells in the dorsal part of the neural tube into sensory cells and interneurons, while the mesodermal signals from notochord result in ventral neural tube cells differentiating into motor neurons and interneurons.

FInally, neural crest cells (black, Fig 22.2) migrate away from the midline, differentiating into melanophores, Schwann cells, and neurons with cell bodies that are located outside the CNS – sensory neurons and cells of the enteric nervous system.

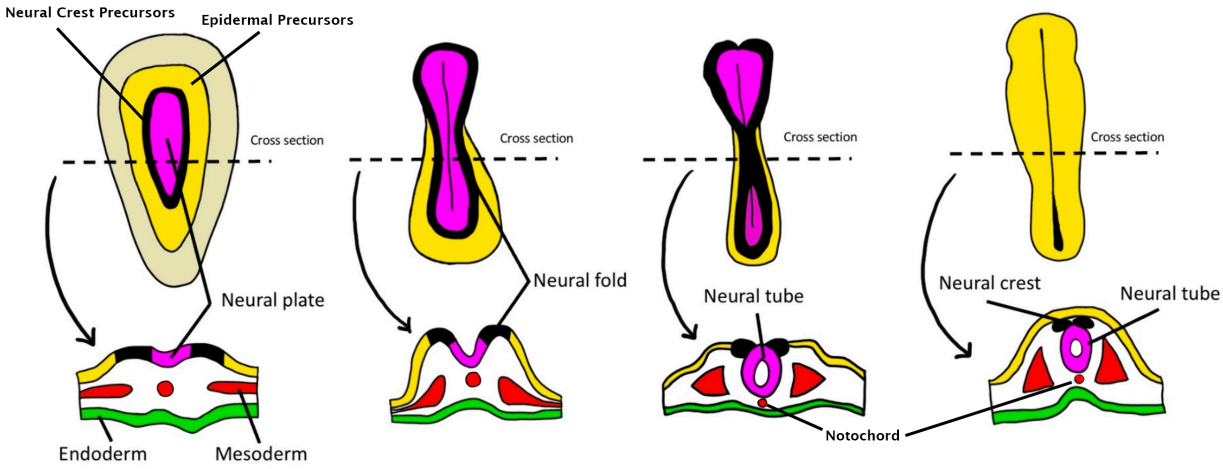


Figure 18.3. Neurulation. During the process of neurulation, the neural plate pinches together at the neural fold in the middle, and then closes at the anterior and posterior ends to form a neural tube. The structures of the central nervous system will form from the walls of the neural tube and the lumen of tube will become the ventricles of the brain and central canal of the spinal cord. Modified from 'Neurulation' by Valerie Hedges.

Neural Tube Defects

Early in pregnancy, there can be problems with the process of neurulation and the formation and closure of the neural tube. Collectively, these are referred to as **neural tube defects** that include defects that occur within the brain, spine, or spinal cord. One of the more common neural tube defects is **spina bifida**. In spina bifida, the neural tube fails to close completely, and as a result the backbone that typically protects the spinal cord also does not form appropriately. This event can occur anywhere along the spine, and will typically result in nerve damage at that particular site that will potentially lead to physical and / or intellectual disability ranging in severity with the degree of damage.

Anencephaly is a neural tube defect that is caused by the failure of the **anterior** portion of the neural tube to close. Anencephaly is a serious birth defect that typically prevents the development of the anterior portion of the brain and associated skull.

Unfortunately, many neural tube defects occur very early in pregnancy, such that many women do not yet know that they are pregnant. As a result, daily folic acid supplements or a diet that includes foods rich in folate is recommended to all women of reproductive age to help prevent neural tube defects in the event of a pregnancy.

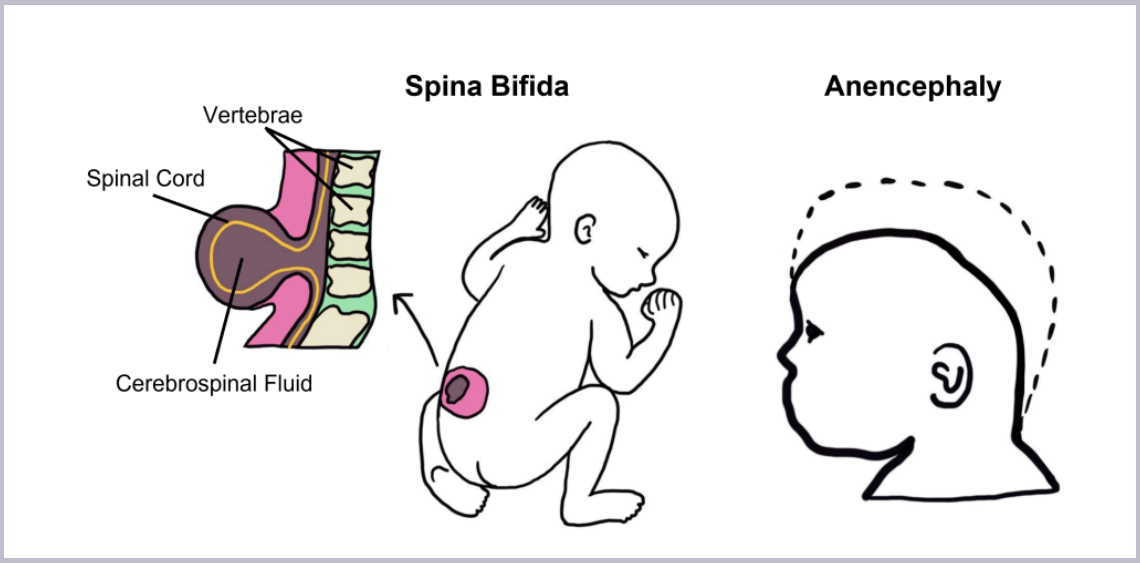


Figure 18.4. Neural Tube Defects. Spina bifida (left) occurs when the posterior neural tube fails to close. Anencephaly (right) occurs when the anterior neural tube fails to close, causing decreased development of the brain and skull. 'Neural Tube Defects' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Three Vesicle Stage of Development

Early in development, the anterior portion of the neural tube has three distinct vesicles, which will each develop into different structures. These vesicles, from most anterior to most posterior, are the **prosencephalon (forebrain)**, the **mesencephalon (midbrain)**, and the **rhombencephalon (hindbrain)**.

Through development, the walls of these vesicles will differentiate into adult brain structures. Differentiation is the process by which structures become more complex and functionally specialized during development. The names of these early vesicles can be used to describe either the stages through development, or a grouping of structures that eventually form in adulthood. In the following chapters, we will learn more about some of these anatomical structures.

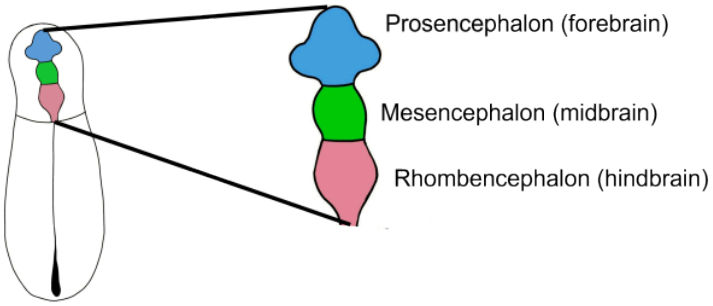


Figure 18.5. Three vesicle stage of embryonic development. Early in development the anterior portion of the neural tube can be divided into three vesicles: the prosencephalon, the mesencephalon, and the rhombencephalon. 'Three vesicle stage' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Prosencephalon (Forebrain)

The prosencephalon, or the forebrain, is most **anterior** in the neural tube and eventually develops into the "higher order" brain regions, including the cerebral cortex. Most of the time, when you see an image of an intact brain from the side or the top, the structures that are visible to you are the forebrain structures. The prosencephalon is made up of the **telencephalon** and the **diencephalon**.

As the prosencephalon continues to develop, additional structures will form that are associated with the cerebral hemispheres. For instance, the optic vesicles that bud off the surface of the prosencephalon will differentiate into the retinas of the eyes—thus, the retina is made up of neural tissue. The olfactory bulbs will differentiate from the ventral surface of the cerebral hemispheres.

Note that as the walls of the tube develop into these structures, the lumen of the tube remains and will become the fluid-filled **ventricles** of the brain. The lateral ventricles will form from the tube within the cerebral hemispheres and the third ventricle will be found ventrally surrounded by the diencephalon.

Structures of the Telencephalon: Cerebral Cortex and the Basal Ganglia

The **cerebral cortex** makes up the outermost layer of the brain. The word "cortex" comes from the word meaning "bark", the outer layer of a tree. The cerebral cortex is the most evolved structure of the human brain and is responsible for higher order thinking. Here, the brain processes behaviors such as attention, memory, and language.

The **basal ganglia** are made up of a series of brain structures (including the caudate and putamen, globus pallidus, substantia nigra, and subthalamic nucleus) that are used for such behaviors as motor and habit learning, emotional processing, and action selection.

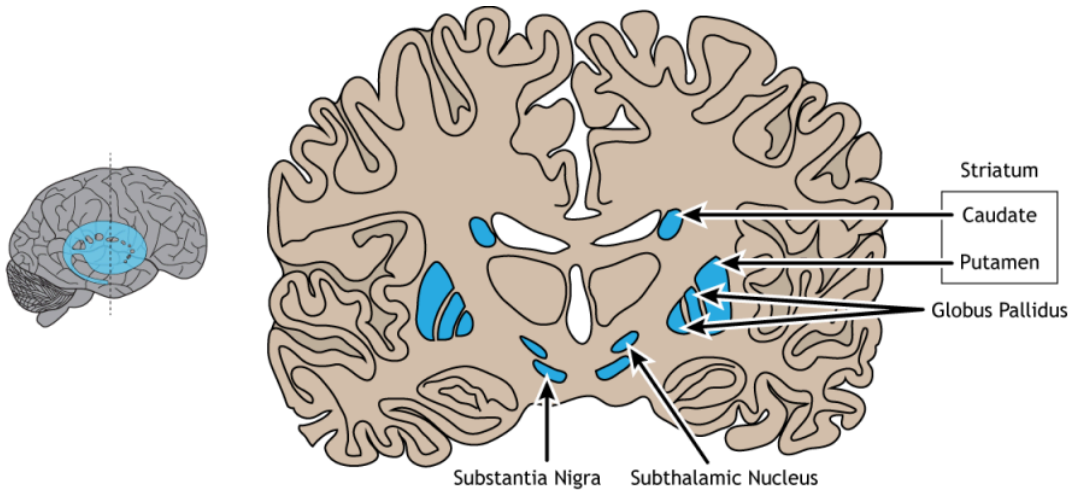


Figure 18.6. The basal ganglia are subcortical structures located at the base of the forebrain. They are comprised of the caudate and putamen, which both make up the striatum, as well as the globus pallidus, substantia nigra, and subthalamic nucleus. 'Basal Ganglia' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Structures of the Diencephalon: Thalamus and Hypothalamus

The thalamus is often referred to as a "sensory relay station" in the brain, since almost every sensory

modality (sight, taste, touch, and hearing) passes information through the thalamus before being directed to the appropriate area of the cortex.

The hypothalamus is also within the diencephalon. This structure serves as an autonomic control center to alter visceral function and a communication route to the body's endocrine system through control of anterior pituitary hormones and production of posterior pituitary hormones. Neural signals originating in the hypothalamus have the capability to influence the chemistry and function of the entire body. The hypothalamus also has nuclei that function in emotional responses, and regulate body temperature, food intake, water balance, and sleep.

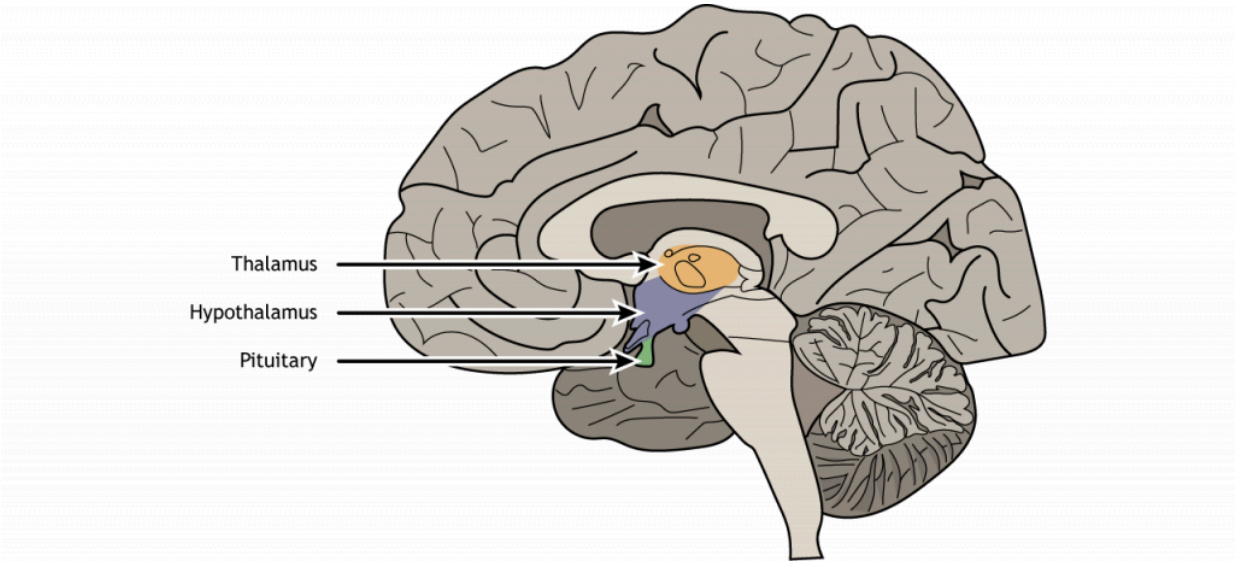


Figure 18.7. The pituitary, shown in green in a mid-sagittal section, lies inferior to the hypothalamus, shown in blue. 'Hypothalamus and Pituitary' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Mesencephalon

Moving more caudally, the mesencephalon (or the midbrain) differentiates into the tectum and the tegmentum.

Tectum

The tectum (which means "roof") is the dorsal portion of the midbrain and it has two major

structures: the superior colliculus and inferior colliculus. The **superior colliculus** is important in reflexive eye movements that allow you to quickly orient to something changing in your environment. The **inferior colliculus** relays auditory information to the thalamus for auditory function.

Tegmentum

The tegmentum (which means "floor") is the ventral portion of the midbrain. There are many structures in the tegmentum and they can perform a wide variety of functions. For example, the **periaqueductal gray** allows us to respond to painful stimuli, the **red nucleus** and **substantia nigra** coordinate complex movements, and the **ventral tegmental area** is important for the processing of reward and motivation.

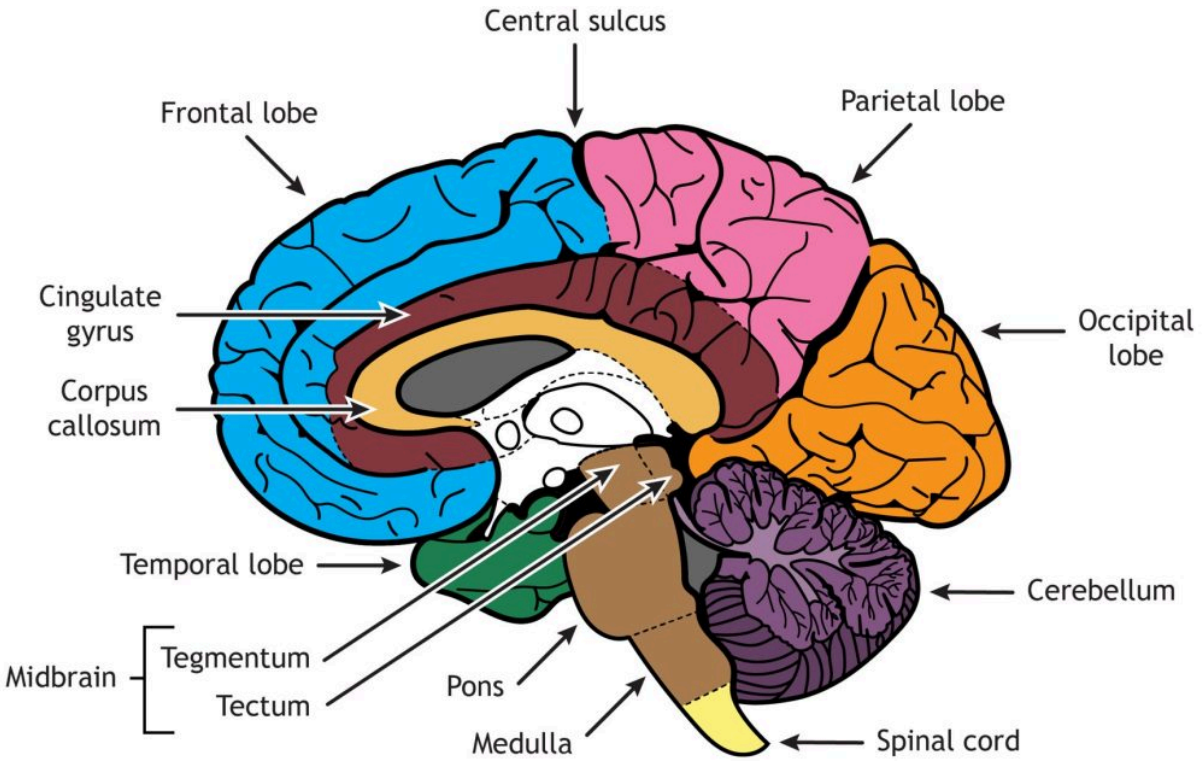


Figure 18.8. A midsagittal section of the brain. The midbrain (tectum and tegmentum) are located anterior to the pons. 'Internal Brain Regions' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Rhombencephalon

The most posterior/caudal portion of the neural tube is the **rhombencephalon** (or **hindbrain**). Evolutionarily speaking, the rhombencephalon represents the oldest part of the central nervous system. These structures likely evolved some 570 million years ago.

Rostral Hindbrain

The more rostral portion of the hindbrain differentiates into two structures: the **cerebellum** and the **pons**. The cerebellum, or "little brain", is best known as a structure that enables motor control functions, such as balance, coordination, posture, and learning physical actions. The cerebellum helps us recognize and predict sequences of events during motor learning. More recently, the cerebellum has also been recognized to play a role in non-motor functions like learning. The pons (which means "bridge") is an important structure that relays impulses between the motor cortex and the cerebellum. It has a critical function to help us perform involuntary functions like breathing.

Caudal Hindbrain

The caudal portion of the hindbrain differentiates into the **medulla**. The medulla is found at the far posterior end of these three early developmental vesicles. The medulla contains many clumps of neurons that are responsible for functions that an organism carries out unconsciously. It contains a cardiovascular center that is especially important in maintaining and changing blood pressure and heart rate, and also has connections to the pons to help regulate breathing. The medulla contains areas that can detect toxins in the blood that come from dietary sources, triggering vomiting. Other behaviors like hiccupping, swallowing, coughing, and sneezing are also controlled by the medulla.

Moving beyond this anterior portion of the neural tube that contains the prosencephalon, mesencephalon, and rhombencephalon, the neural tube continues down the length of the embryo. The remainder of the neural tube will differentiate into the **spinal cord**, with the lumen of the tube becoming the central canal of the spinal cord. The spinal cord is important in relaying information to and from the body.

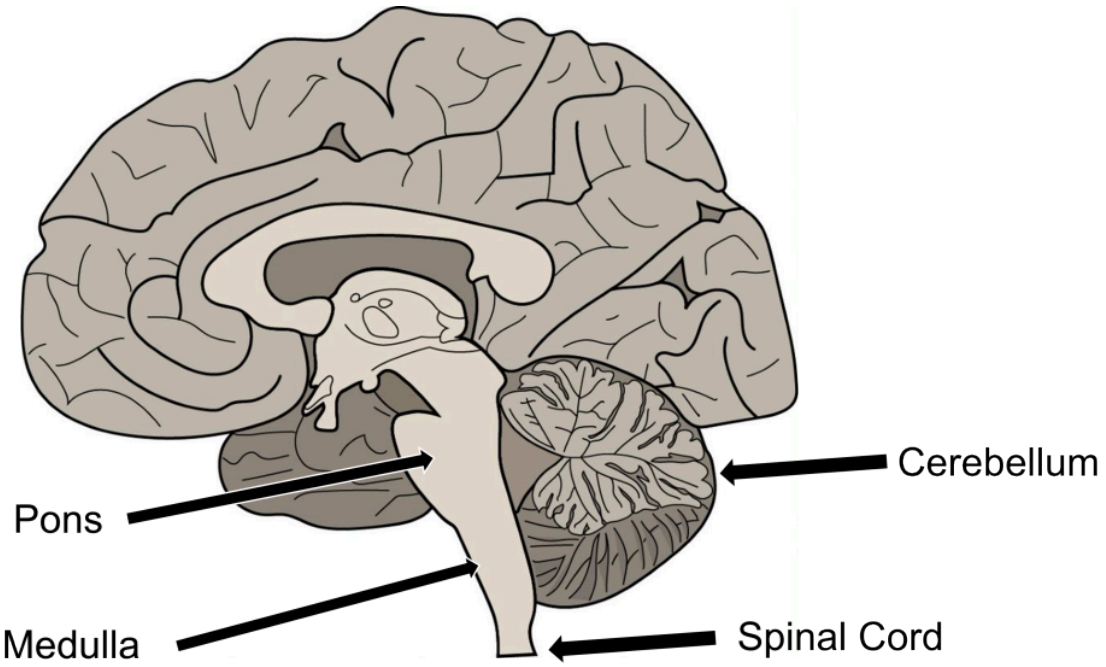


Figure 18.9. Structures of the rhombencephalon. The rostral portion of the rhombencephalon develops into the cerebellum and pons. The caudal portion of the of the rhombencephalon develops into the medulla. The spinal cord is connected to the posterior end of the medulla and continues down the length of the spine. 'Structures of the rhombencephalon' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- The ectoderm layer of the embryo develops into the nervous system
- Neurulation is the process that forms the neural tube and failure for portions of the neural tube to close can cause neural tube defects
- The prosencephalon, mesencephalon, and rhombencephalon are the three vesicles at

the anterior end of the neural tube. They will develop into structures in the adult brain.

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=531#h5p-35

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19.

EXTERNAL BRAIN ANATOMY

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

The brain is comprised of the cerebrum, cerebellum, and brainstem. The cerebrum is the most prominent region of the brain. It is divided into left and right hemispheres. The hemispheres have many of the same functions, for example, each perceives touch on one side of the body, but some functions, like language, demonstrate laterality, meaning they are primarily controlled on one side of the brain. The cerebral hemispheres in humans have many folds to increase the surface area of the brain. The ridges are called gyri and the grooves are called sulci. Large sulci are often called fissures.

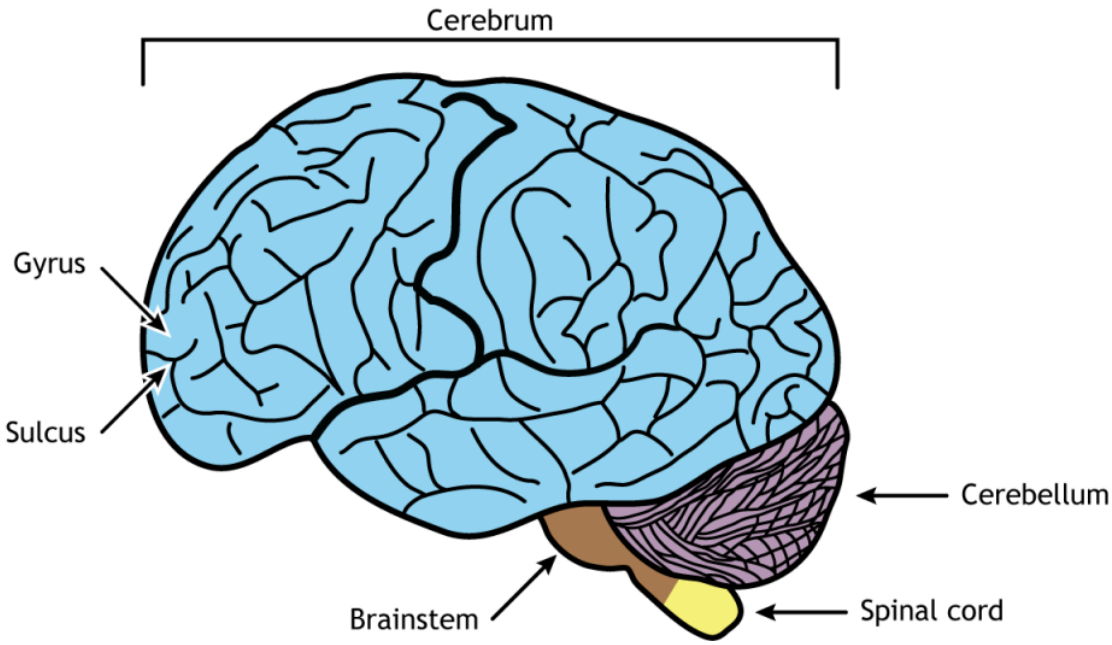


Figure 19.1 An external, side view of the parts of the brain. The cerebrum, the largest part of the brain, is organized into folds called gyri and grooves called sulci. The cerebellum sits behind (posterior) and below (inferior) the cerebrum. The brainstem connects the brain with the spinal cord and exits from the ventral side of the brain. 'External Brain Regions' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The four lobes of the brain are each responsible for specific functions

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Frontal Lobe

The cerebral hemispheres of the brain are divided into four lobes. The frontal lobes are the most rostral, located in the front of the brain and are responsible for higher level executive functions, like attention, critical thinking, and impulse control. They are the last brain region to fully develop, not completing development until individuals reach their 20s. The frontal lobes are also the location of

the primary motor cortex, the region of the brain responsible for planning and executing movement. The primary motor cortex is located in the precentral gyrus.

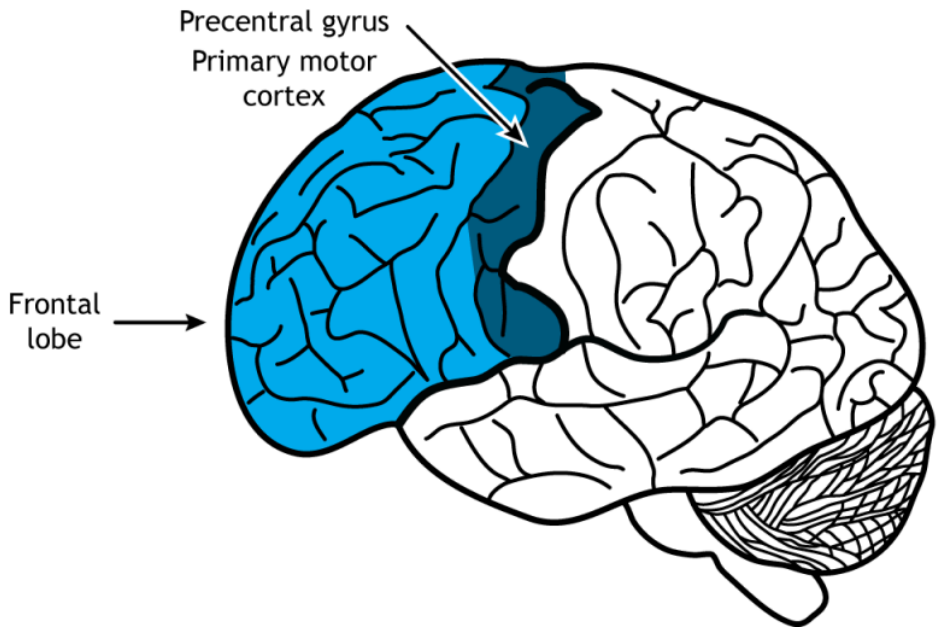


Figure 19.2. The frontal lobe is located in the front of the brain. It includes the precentral gyrus, the location of the primary motor cortex. 'Frontal Lobe' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the frontal lobe using the BrainFacts.org 3D Brain

Parietal Lobe

The central sulcus lies caudal to the frontal lobe and divides the frontal lobes from the parietal lobes. The parietal lobes are important for processing sensory information. The primary somatosensory cortex is located in the postcentral gyrus of the parietal lobe and is responsible for the perception of touch and pain. The parietal lobes also perform higher-level visual processing.

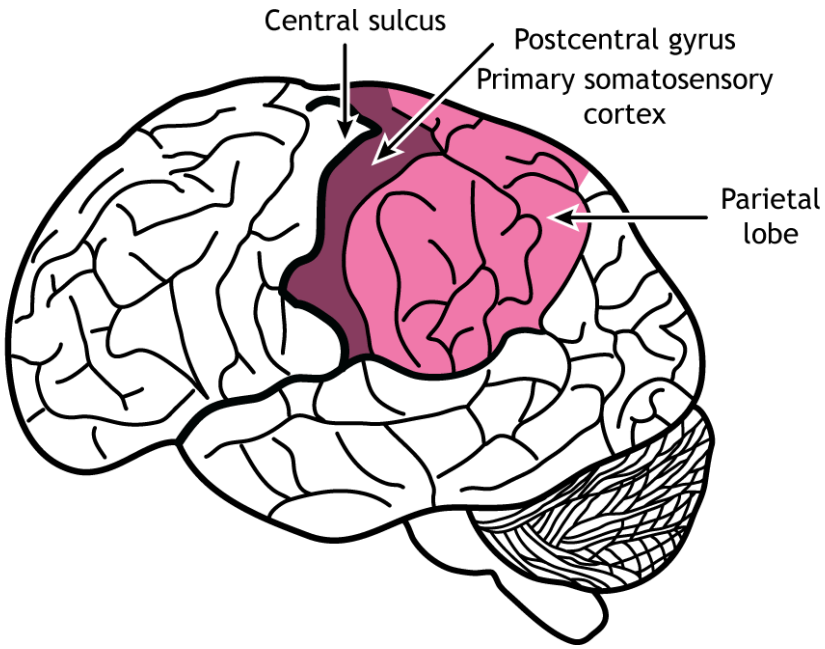


Figure 19.3. The parietal lobe is located on the top of the brain. It includes the postcentral gyrus, the location of the primary somatosensory cortex. The central sulcus divides the parietal lobe from the frontal lobe. 'Parietal Lobe' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the parietal lobe using the BrainFacts.org 3D Brain

Temporal Lobe

The temporal lobes are located on the side of the brain, separated from the frontal and parietal lobes by the lateral fissure. Like the parietal lobe, the temporal lobe plays a role in sensory processing, specifically with hearing, smell, taste, and higher-level visual processing. The temporal lobe is also important for speech and memory. Beneath the cerebral cortex, deep in the temporal lobes, lie the hippocampus and amygdala, two regions of the limbic system, a circuit important for emotion and memory.

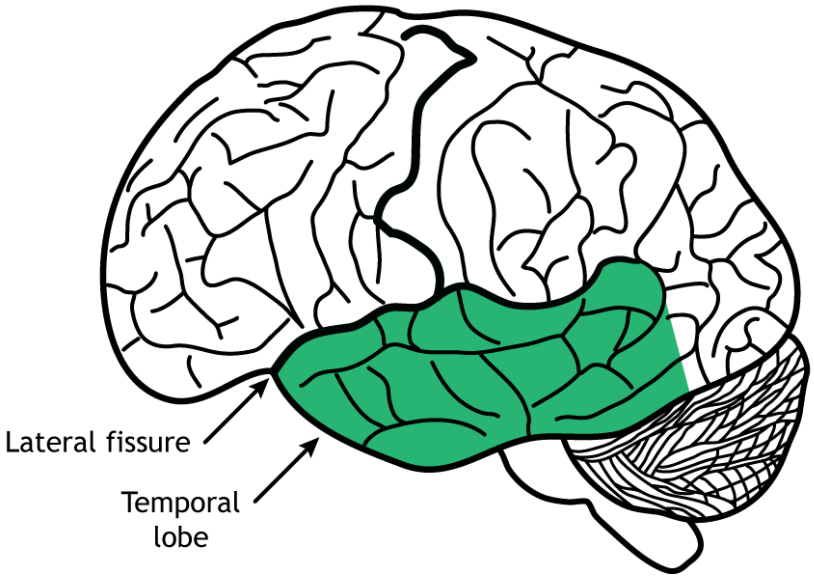


Figure 19.4. The temporal lobe is located on the side of the brain. The lateral fissure divides the temporal lobe from the frontal and parietal lobes. 'Temporal Lobe' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the temporal lobe using the BrainFacts.org 3D Brain

Occipital Lobe

The last lobes are the occipital lobes, the most caudal lobes located in the back of the brain. The occipital lobes' primary function is processing of visual information.

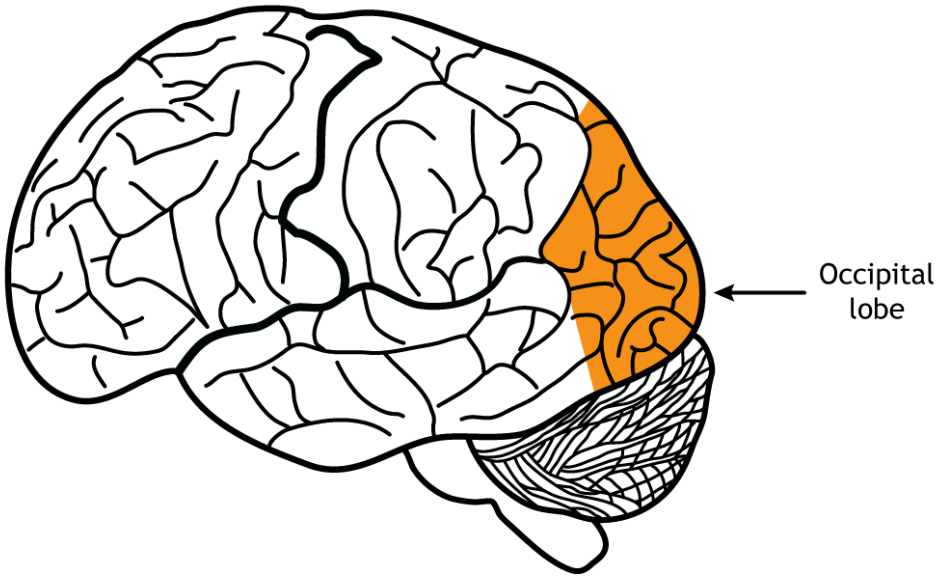


Figure 19.5. The occipital lobe is located in the back of the brain. 'Occipital Lobe' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the occipital lobe using the BrainFacts.org 3D Brain

Non-Cerebral Components

The cerebellum lies inferior to the occipital lobes. The cerebellum is also divided into two hemispheres, like the cerebral cortex. The cerebellum is best known for its role in regulation and control of movement, but it is also involved in cognitive functions like emotions.

The brainstem is located between the cerebrum and the spinal cord. It is important for regulating critical functions like heart rate, breathing, and sleep. It is also the location of most of the cranial nerves.

The spinal cord, which is part of the central nervous system but not part of the brain, is responsible for receiving sensory information from the body and sending motor information to the body. Involuntary motor reflexes are also a function of the spinal cord, indicating that the spinal cord can process information independently from the brain.

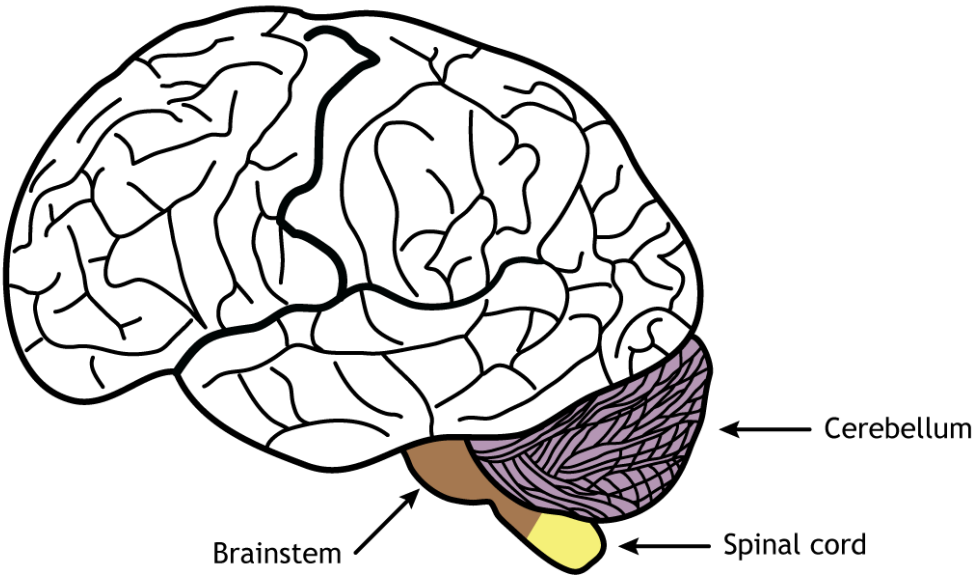


Figure 19.6. The cerebellum, brainstem, and spinal cord are located below the brain. 'Hindbrain' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the brainstem using the BrainFacts.org 3D Brain
View the cerebellum using the BrainFacts.org 3D Brain

Landmarks on the brain can be seen from different planes of view

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Dorsal View

Viewing the brain from above shows the bilateral symmetry of the left and right cerebral hemispheres, which are separated by the longitudinal fissure. The frontal, parietal, and occipital lobes can be seen. Similar to the lateral view, the central sulcus divides the frontal lobe from the parietal lobe. The precentral gyrus, which is the location of the primary motor cortex, sits rostral to the central sulcus,

whereas the postcentral gyrus, which is the location of the primary somatosensory cortex, lies caudal to the central sulcus.

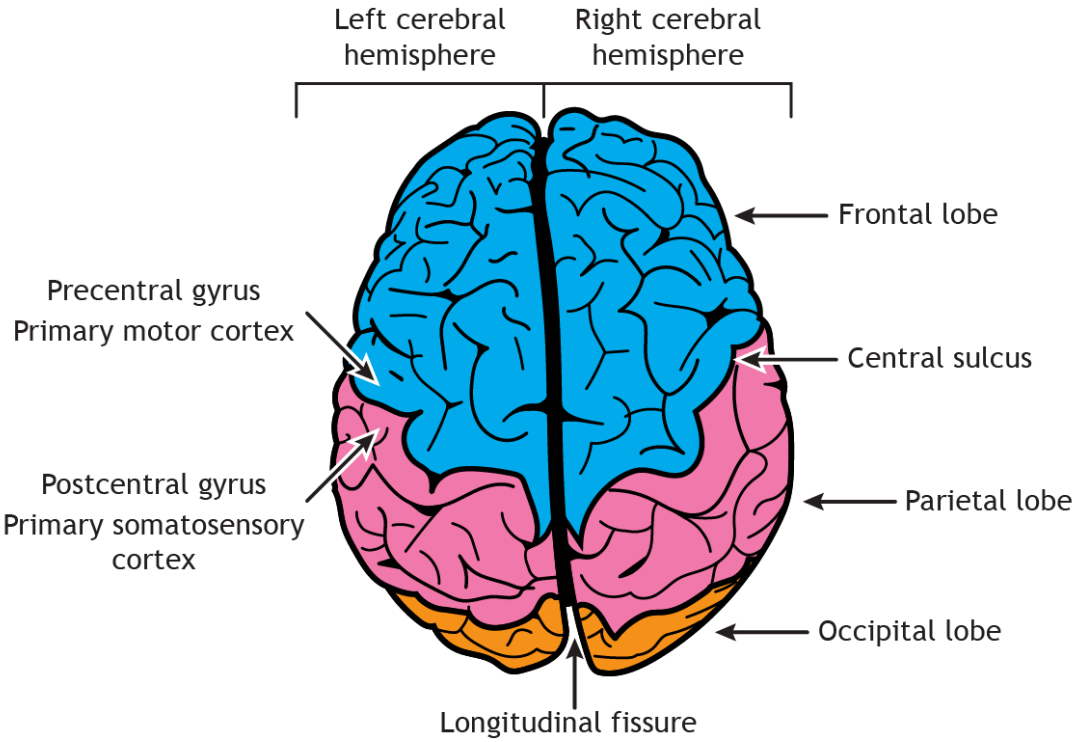


Figure 19.7. The dorsal view of the brain. The left and right cerebral hemispheres are separated by the longitudinal fissure. Three of the four lobes, the frontal, parietal, and occipital can be seen in this view. 'Dorsal Surface of Brain' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Ventral View

Underneath the brain, the frontal and temporal lobes are visible, as is the cerebellum. Like the dorsal view, the longitudinal fissure divides the cerebrum into right and left hemispheres. The pons and medulla, components of the brain stem, connect the cerebrum to the spinal cord.

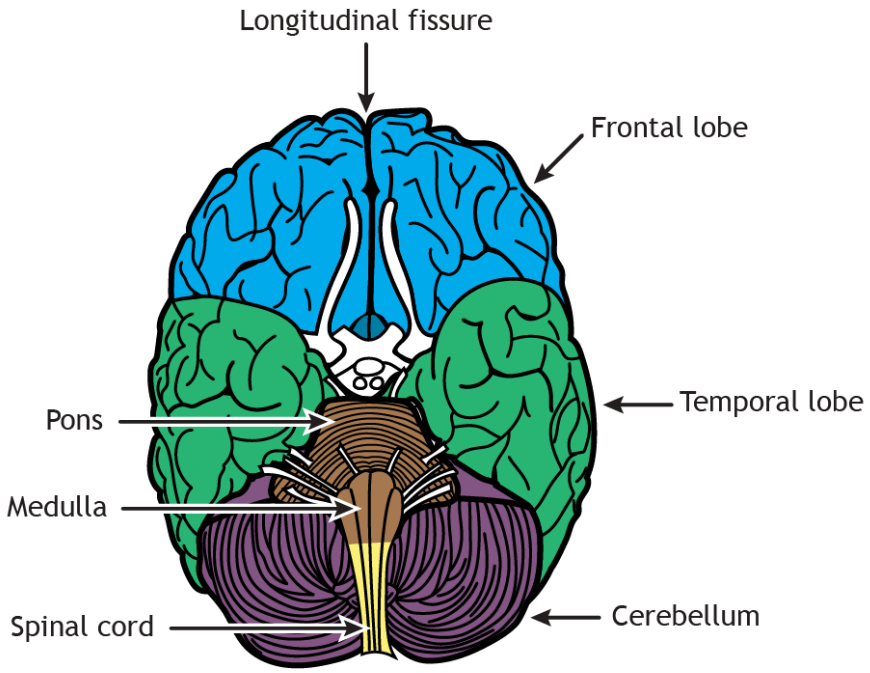


Fig 19.8. Ventral Surface of the Brain. The frontal lobe, temporal lobe, cerebellum, pons, medulla, spinal cord and longitudinal fissure can be seen when viewing the bottom of the brain. "Ventral Surface of the Brain" by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Cranial nerves are also visible on the ventral surface of the brain. The olfactory tract leads out to the olfactory bulb, which connects to the olfactory nerve. The optic tract crosses the midline at the optic chiasm, and then the optic nerve projects to the retina. Other cranial nerves enter or leave the brain at the level of the brainstem. The hypothalamus is located caudal to the pons, and the mammillary bodies project out from the hypothalamus.

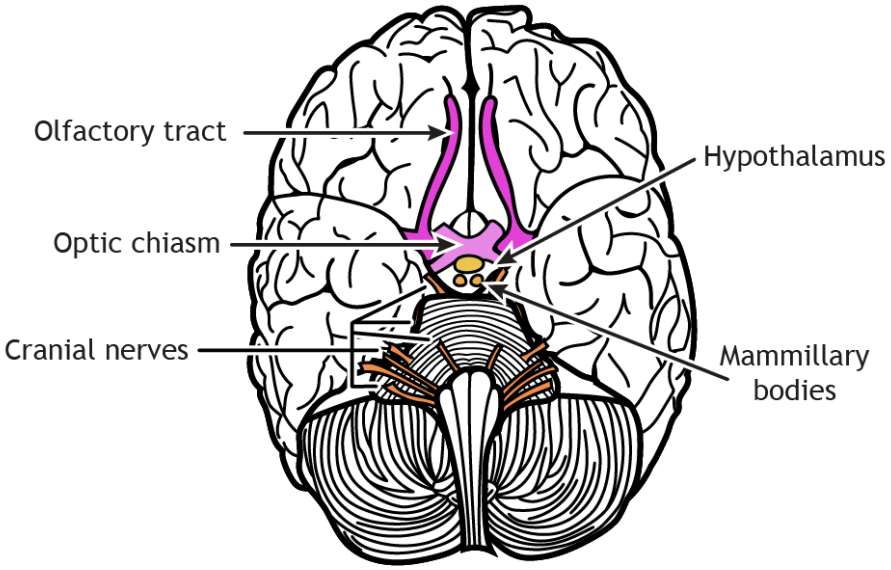


Figure 19.9. Cranial nerves, optic chiasm, and olfactory tract are visible on the bottom of the brain. In the center, the hypothalamus and mammillary bodies can also be seen. "Ventral Surface Cranial Nerves" by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- The four lobes of the cerebral cortex each have specific functions
- The cerebral cortex has gyri and sulci to increase the surface area
- The cerebral cortex, underlying structures, cerebellum, brainstem, and spinal cord form the central nervous system

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=188#h5p-19

Video Lecture

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20.

INTERNAL BRAIN ANATOMY

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

A mid-sagittal section slices the brain through the longitudinal fissure and separates the right hemisphere from the left. It also reveals more structures. In a mid-sagittal view, all four cortical lobes are visible. The frontal lobe is separated from the parietal lobe by the central sulcus, the occipital lobe is in the posterior region of the brain, and the temporal lobe can be seen behind the brainstem. The cerebellum, pons, medulla, and spinal cord are seen caudal to the cerebrum, but in this view, the midbrain, which is made up of two regions, the tegmentum and tectum, are also visible superior to the pons. The corpus callosum is located in the center of the cerebrum and is a white matter bundle made up of axons crossing from one hemisphere to the other. Surrounding the corpus callosum is the cingulate gyrus, a region important for emotion.

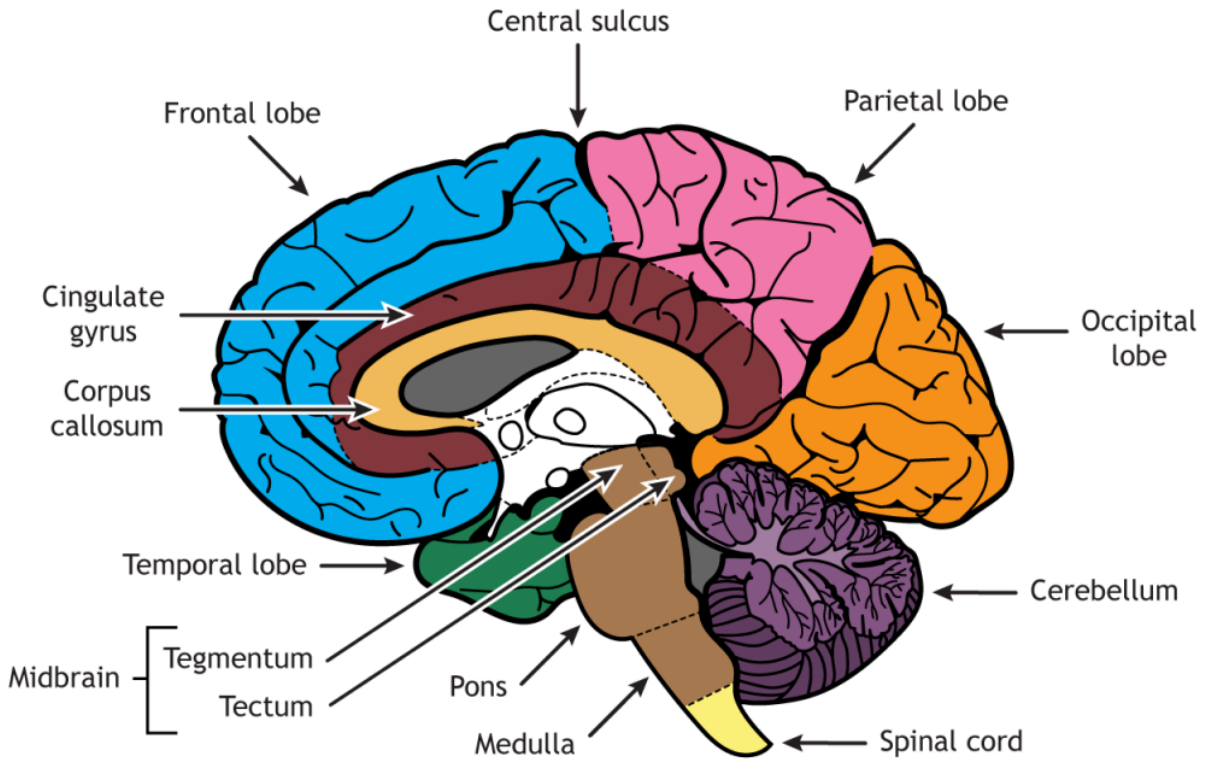


Figure 20.1. A midsagittal section of the brain. All four cerebral lobes are visible, as in the cingulate gyrus, which extends through the medial aspects of the frontal and parietal lobes. The corpus callosum sits beneath the cingulate gyrus. Below the cerebrum lies the midbrain, pons, medulla and cerebellum. 'Internal Brain Regions' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The diencephalon consists of subcortical structures and connects the forebrain to the midbrain

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The diencephalon region of the brain consists of the region around the thalamus and hypothalamus. It is located inferior to the fornix and lateral ventricle, posterior to the anterior commissure, and superior to the brainstem. The fornix is a nerve fiber bundle containing primarily output from the hippocampus. The anterior commissure sits above the hypothalamus and is white matter tract, like the corpus callosum, that allows information to cross from one hemisphere to the other. The thalamus

is best known for its role as a relay and processing location for the sensory and motor systems. The hypothalamus has a variety of functions including control of stress and the "fight or flight" response of the autonomic nervous system, reproduction, sleep, thirst, hunger, and other homeostatic functions. The mamillary bodies sit in the posterior part of the hypothalamus and are important for memory. The optic nerves from the retina cross at the optic chiasm, and then the optic tracts continue back into the diencephalon.

In the brainstem, the tectum of the midbrain consists of the superior and inferior colliculi, which are important for vision and hearing, respectively. The reticular formation is located throughout the brainstem. Networks within the reticular formation are important for regulating sleep and consciousness, pain, and motor control. The fourth ventricle lies between the brainstem and the cerebellum.

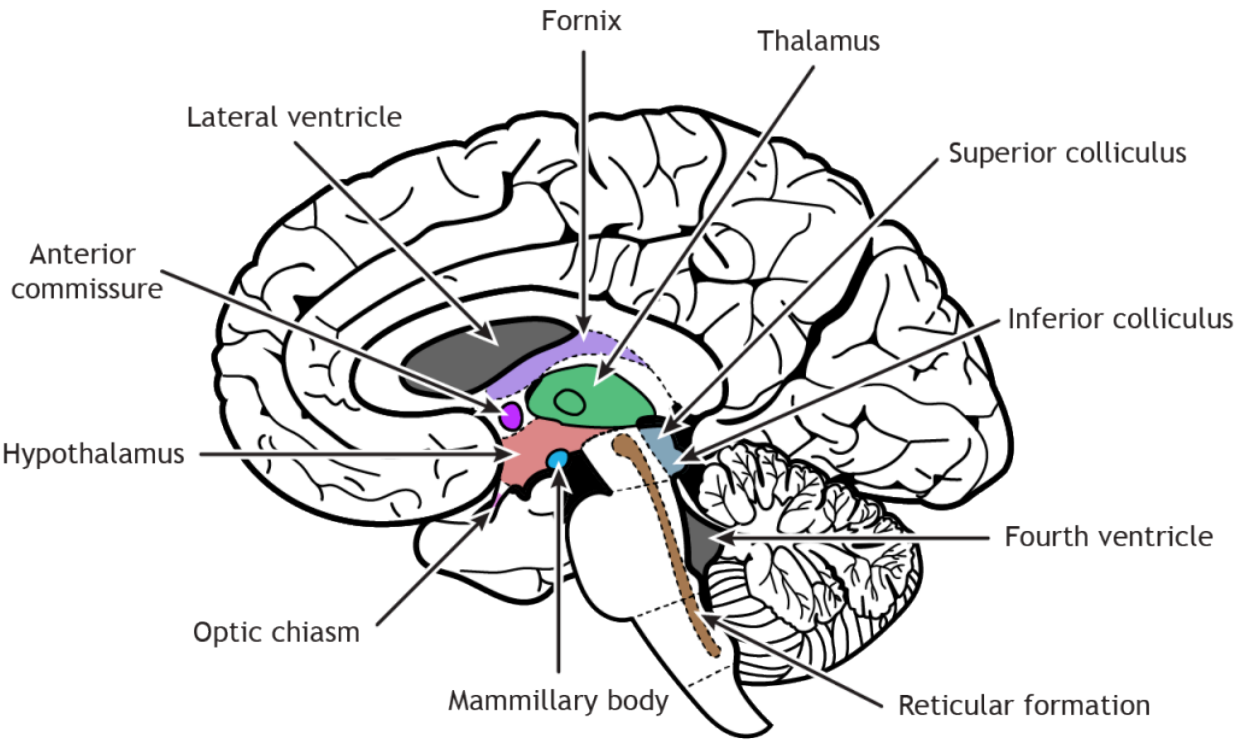


Figure 20.2. Regions of the diencephalon and brainstem in a midsagittal section. The thalamus, hypothalamus, and mammillary bodies are part of the diencephalon. The optic tracts leave the diencephalon, cross at the optic chiasm, and continue as the optic nerves out to the retina. The anterior commissure and fornix create the front and upper border of the diencephalon. The superior and inferior colliculi are part of the midbrain tectum, and the reticular formation is located throughout the brainstem. 'Midsagittal Diencephaon and Brainstem' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The basal ganglia, amygdala, and hippocampus are subcortical forebrain structures with a range of functions

Coronal sections of the brain allow deep tissue structures to be visible. A cut through the anterior portion of the temporal lobe shows the amygdala, a region important for emotion, located in the medial temporal lobe. The regions of the basal ganglia are also visible; the striatum, which consists of the caudate and the putamen, and the globus pallidus. The basal ganglia has multiple functions but is best known for its role in regulation of movement. The lateral ventricle sits medial to the basal ganglia, and above the lateral ventricle is the corpus callosum. The third ventricle is located in the middle of the brain, inferior to the lateral ventricle, and the optic chiasm lies inferior to the third ventricle. The longitudinal fissure separates the left and right cerebral hemispheres, and the lateral sulcus is the border between the frontal and temporal lobes.

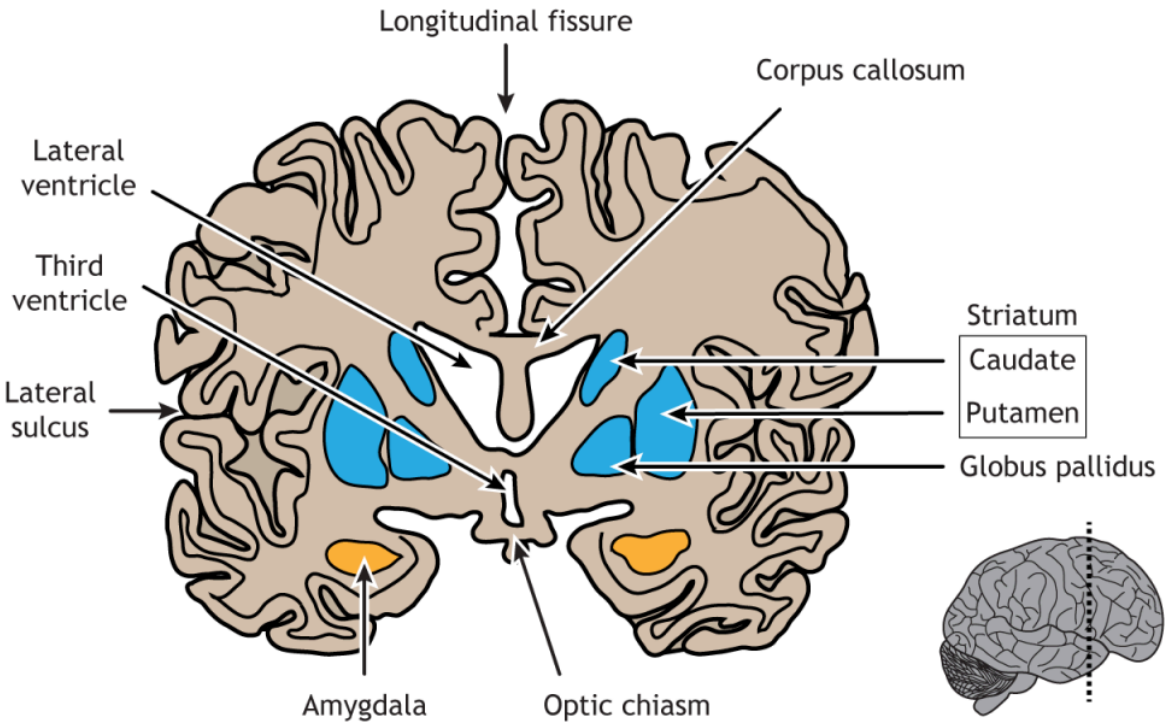


Figure 20.3. A coronal section at the location of the amygdala. The amygdala is located in the temporal lobe, and the basal ganglia is a subcortical structure located near the lateral ventricle. The corpus callosum, third ventricle, longitudinal fissure, and lateral sulcus can also be seen. 'Amygdala and Basal Ganglia' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

A coronal section taken closer to the central sulcus will make the hippocampus visible. The hippocampus is known for its role in memory and spatial awareness. At this location, the basal ganglia is more defined; the caudate and putamen are still present, but the two separate regions of the globus pallidus, the internal and external segments, can be seen, as well as the subthalamic nucleus and the substantia nigra. The thalamus is located on either side of the third ventricle. The corpus callosum is superior to the lateral ventricle. The cerebrum is divided in half by the longitudinal fissure, and the lateral sulcus separates the temporal lobe from the frontal and parietal lobes.

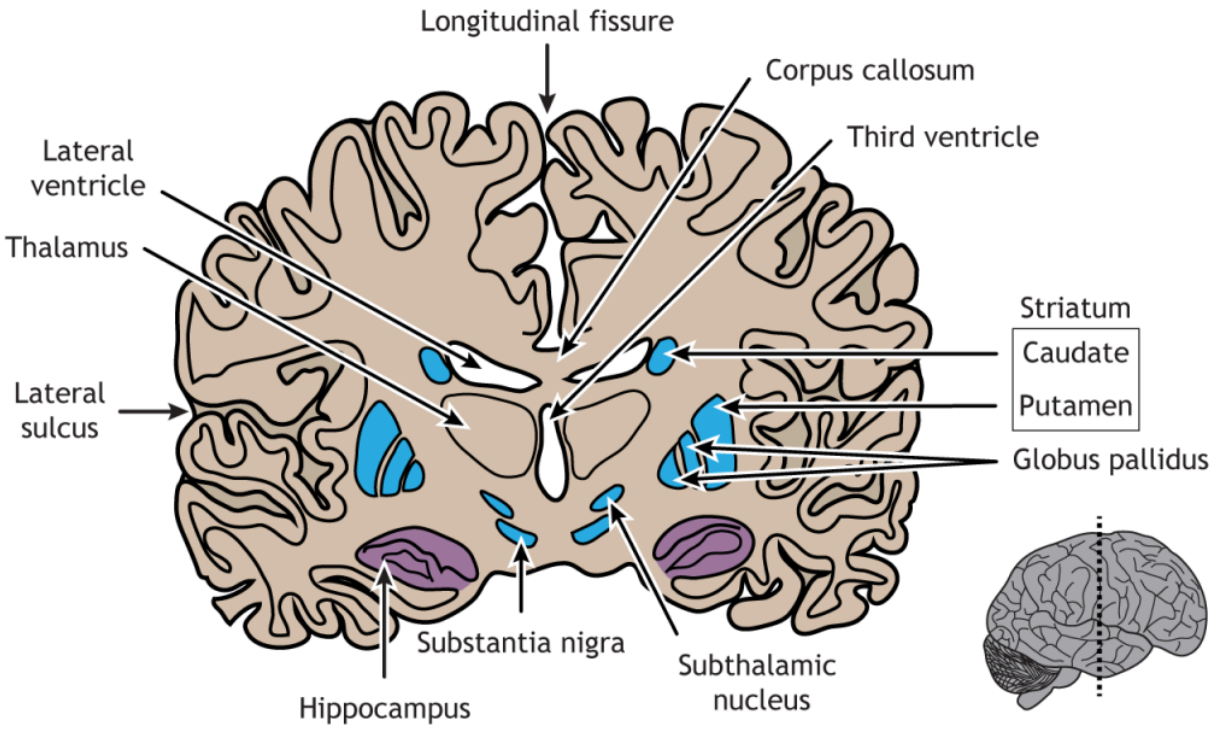


Figure 20.4. A coronal section at the location of the hippocampus. The hippocampus is located in the temporal lobe, and the basal ganglia is a subcortical structure located lateral to the thalamus and lateral ventricle. 'Hippocampus and Basal Ganglia' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- Like the external anatomy, internal structures also have specific functions
- Sectioning the brain in different ways provides views of subcortical regions

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=194#h5p-20

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21.

BRAINSTEM AND SPINAL CORD

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

Brainstem

The brainstem is made up of the midbrain, pons, and medulla. It is located between the diencephalon (thalamus and hypothalamus region) and the spinal cord. All connections between the brain and the body must travel through the brainstem. The brainstem also plays an important role in the regulations of consciousness and regulates critical functions like heart rate and breathing.

The mammillary bodies are located on the ventral side of the hypothalamus. The infundibulum is the stalk between the hypothalamus and the pituitary and is located caudal to the mammillary bodies. The optic tract leaves the diencephalon and crosses the midline at the optic chiasm.

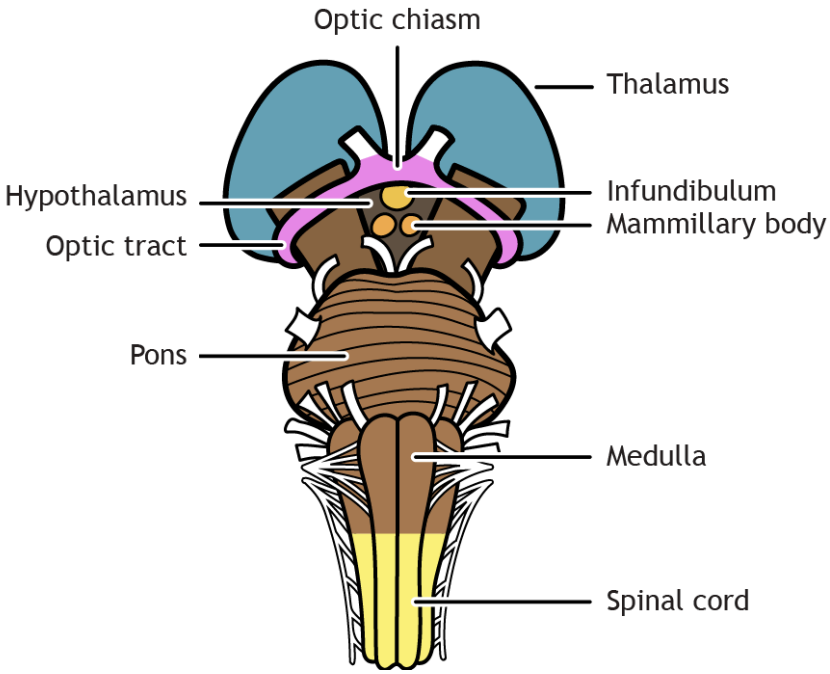


Figure 21.1. The brainstem and diencephalon. The pons and medulla are parts of the brainstem. The diencephalon consists of the thalamus, hypothalamus, infundibulum, mammillary body, and the optic tract and chiasm. 'Brainstem' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Cranial Nerves

A critical component of the brainstem is the presence of the twelve pairs of cranial nerves, which provide sensory and motor innervation to the head, face, and neck, as well as autonomic innervation to the organs in the abdomen. The first two cranial nerves (olfactory [I] and optic [II]) are part of the central nervous system. They carry sensory information, smell and vision, respectively. They enter the forebrain and not the brainstem. The remaining nerves, like spinal nerves, have their axons in the peripheral nervous system. The oculomotor [III] and trochlear nerves [IV], whose functions are to move the eye, exit the brainstem from the midbrain. The trochlear nerve is the only cranial nerve to exit on the dorsal surface of the brainstem. The trigeminal nerve [V] is the largest cranial nerve and carries both sensory and motor information from the face; axons in this nerve enter and exit from the pons. The abducens nerve [VI], another eye movement nerve, exits at the junction of the pons and medulla, as do the facial [VII] and vestibulocochlear [VIII] nerves. The facial nerve contains both sensory and motor axons, whereas the vestibulocochlear nerve carries only sensory information

related to hearing and balance. The glossopharyngeal [IX] and vagus [X] nerves also carry both sensory and motor information and enter/exit from the medulla. The glossopharyngeal nerve is responsible for movement of the throat muscles and taste; the vagus nerve is the primary autonomic cranial nerve and contains parasympathetic fibers that innervate the heart, lungs, and abdominal organs. Finally, the spinal accessory [XI] and hypoglossal [XII] are motor nerves with the hypoglossal exiting the brainstem from the medulla and the spinal accessory nerve exiting from the cervical spinal cord. The spinal accessory innervates muscles in the throat, shoulder, and neck, and the hypoglossal innervates muscles of the tongue.

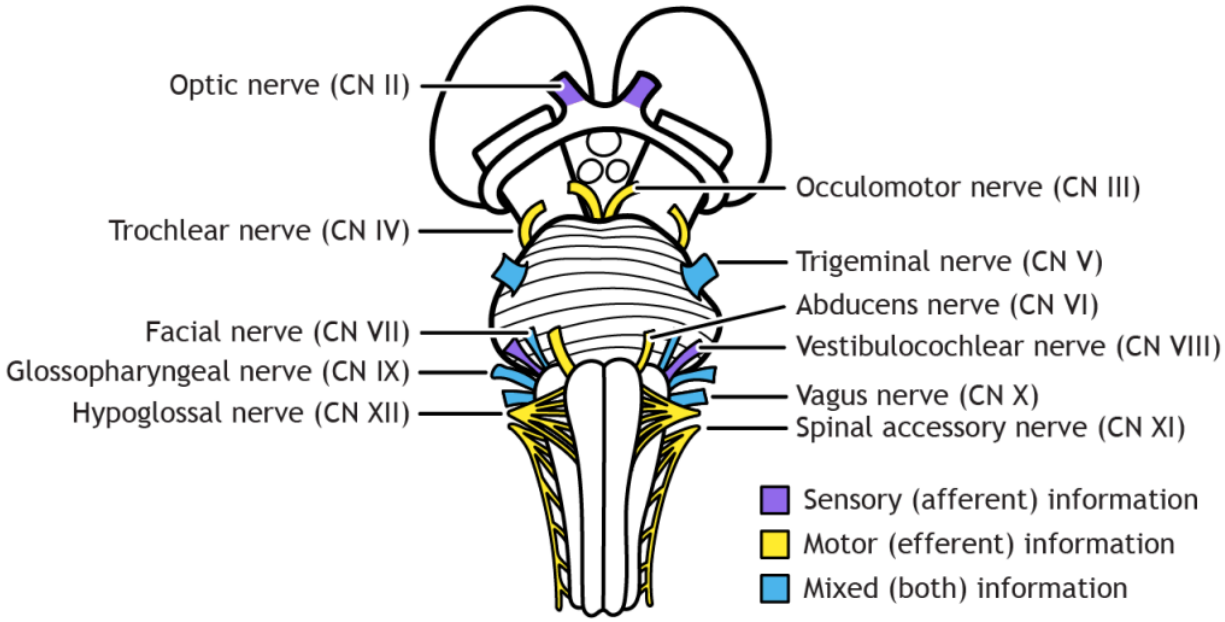


Figure 21. 2. The cranial nerves receive sensory information and send motor information to the head and neck and also carry parasympathetic fibers. The olfactory [I] (not shown), optic [II], and vestibulocochlear [VIII] nerves carry sensory information only. The oculomotor [III], trochlear [IV], abducens [VI], spinal accessory [XI], and hypoglossal [XII] carry motor output only. The trigeminal [V], facial [VII], glossopharyngeal [IX], and vagus [X] carry both sensory and motor information. Cranial nerves three through twelve exit or enter the central nervous system at the level of the brainstem. 'Cranial Nerves' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Spinal Cord

The spinal cord begins at the base of the brainstem. The vertebral column is divided into four main regions: cervical, thoracic, lumbar, and sacral. The spinal cord and spinal nerves that enter and exit the

vertebral column are divided into these regions as well. The cervical division consists of seven segments (C1-C7), the thoracic consists of twelve segments (T1-T12), the lumbar consists of five segments (L1-L5), and the sacral division consists of five segments (S1-S5). The shape of the spinal cord changes over the length of the vertebral column, a result of the function of the spinal nerves. For example, motor information to the hands and arms, so the region where motor neurons are located (ventral horn) is larger than segments with minimal motor output.

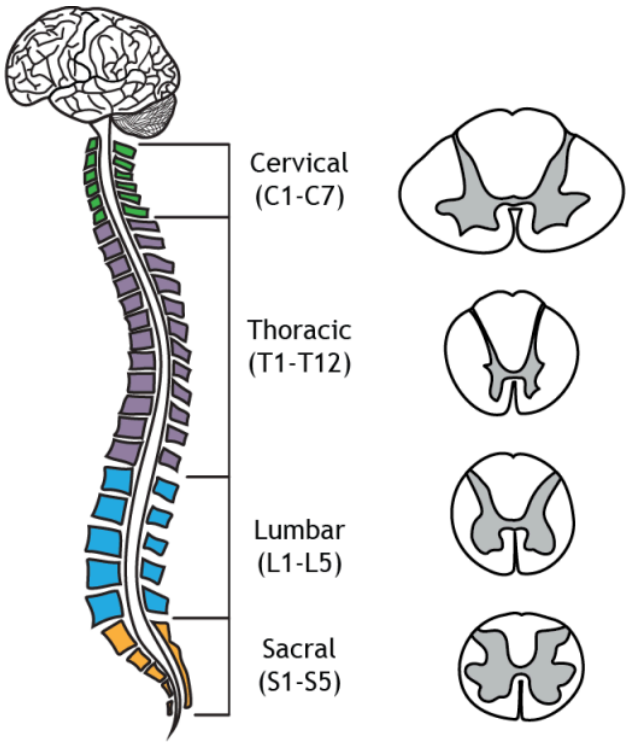


Figure 21.3. The vertebral column and representative spinal cord cross-sections. The vertebral column and corresponding spinal cord and spinal nerves are divided into four regions. The cervical division is the most rostral, starting at the base of the brainstem. The thoracic is the largest division, just caudal to the cervical. The lumbar is the next division, and the sacral is the most caudal. 'Spinal Cord' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The spinal cord is part of the central nervous system, but the fibers that leave and enter the spinal cord are located in the peripheral nervous system. These spinal nerves can then extend to or from target tissue throughout the body.

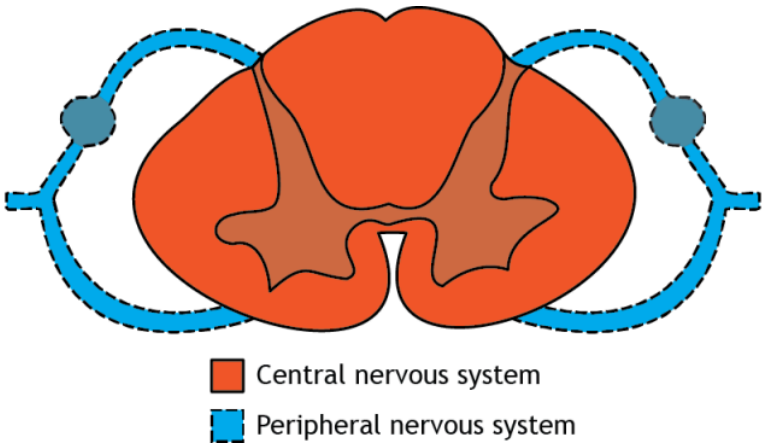


Figure 21.4. The spinal cord is part of the central nervous system, but the axons that exit and enter the spinal cord are in the peripheral nervous system. 'Spinal Cord CNS and PNS' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Like the brain, the spinal cord is also made up of regions of white matter and gray matter. White matter regions are comprised of axons. It appears white due to the myelin sheath on the axons. Gray matter regions are comprised of cell bodies and dendrites. Gray matter is the location of most synapses.

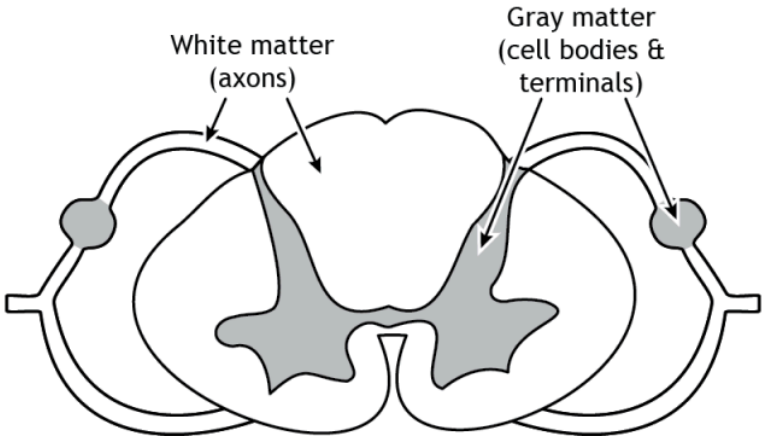


Figure 21.5. The spinal cord can be divided into white and gray matter. White matter is primarily myelinated axons. Gray matter is primarily neuronal cell bodies and dendrites. In the spinal cord, the inner part is gray matter, whereas the surround tissue is white matter. The regions that extend from the central nervous system and into the peripheral nervous system contain primarily axons traveling to or from peripheral targets and therefore are mainly white matter except for ganglia, which are clusters of cell bodies in the periphery. 'Spinal Cord White and Gray Matter' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The white matter in the spinal cord is divided into structures called columns because the axons in these regions are either ascending toward the brain or descending toward the appropriate spinal nerve. The dorsal column is on the dorsal or posterior side of the spinal cord, the ventral column is on the ventral or anterior side of the spinal cord, and the lateral column lies between them. The gray matter is likewise divided into regions called horns. The dorsal horn is the location of sensory synapses, the ventral horn is the location of motor neuron cell bodies, and the lateral horn is the location of cell bodies of the autonomic nervous system. The dorsal root and ventral root consist of the axons of afferent (dorsal) and efferent (ventral) fibers. They combine to form the spinal nerves. Sensory neuron cell bodies are located in the dorsal root ganglion, a gray matter region of the dorsal root.

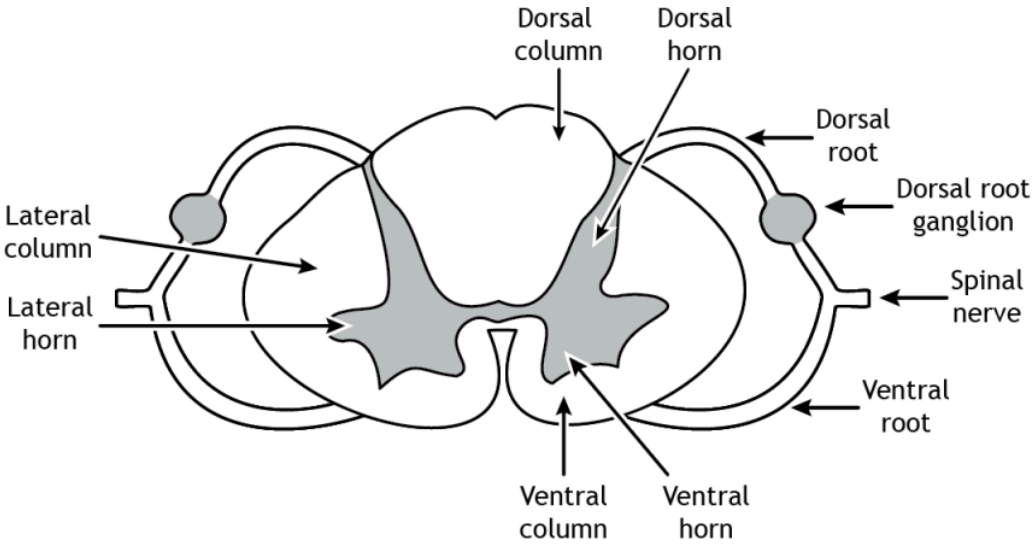


Figure 21.6. The spinal cord is comprised of white and gray matter. The dorsal column and dorsal horn are on the posterior side of the spinal cord. The ventral column and ventral horn are located on the anterior side of the spinal cord. The lateral column and lateral horn are located in the middle. The spinal nerves that extend into the periphery consist of fibers that split into the dorsal root and the ventral root to enter (dorsal) or exit (ventral) the spinal cord. The dorsal root ganglion is a gray matter region of the dorsal root. 'Spinal Cord Anatomy' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Afferent fibers coming from the periphery through the spinal nerves enter the spinal cord via the dorsal root. The cell bodies of sensory neurons are located in the dorsal root ganglion, and the axons continue into the spinal cord and typically synapse in the dorsal horn. Interneurons are very short neurons that are a communication link between cell types in the spinal cord. They can be either excitatory or inhibitory depending on their role. They can also cross the midline of the spinal cord. The cell bodies of motor neurons that innervate skeletal muscles are located in the ventral horn. The efferent axons of these neurons leave the spinal cord via the ventral root and then enter the spinal nerve on their way to their target tissue.

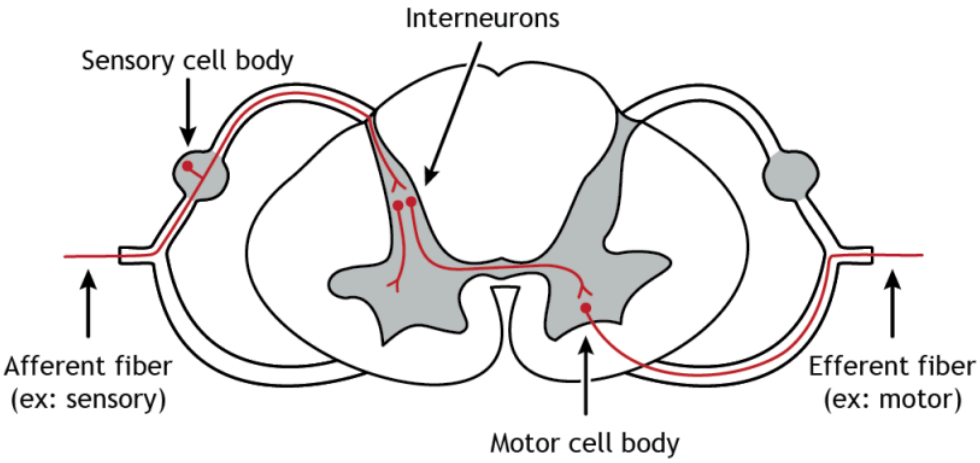


Figure 21.7. Afferent axons coming from the periphery travel through the dorsal root to enter the spinal cord. These axons can synapse on interneurons, cells with short axons which communicate with other cell types. Efferent fibers, like those of the skeletal muscle motor neurons located in the ventral horn, leave the spinal cord through the ventral root. 'Spinal Cord Fibers" by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- The brainstem connects the diencephalon to the spinal cord and is responsible for critical body functions
- The cranial nerves enter and exit the central nervous system primarily through the brainstem
- The spinal cord is part of the central nervous system and spinal nerves are part of the peripheral nervous system
- Like the brain, the spinal cord is made up of both white and gray matter

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
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22.

PERIPHERAL NERVOUS SYSTEM

The **Peripheral Nervous System** (PNS) functions as the intermediary between the **central nervous system** (CNS) and the rest of the body, including the skin, internal organs, and muscles of our limbs. The PNS can be divided into three main branches:

1. Somatic nervous system
2. Autonomic nervous system
3. Enteric nervous system

In this chapter, the somatic and autonomic nervous systems will be compared and contrasted. An overview of the enteric nervous system will also be provided.

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

Somatic vs. Autonomic Nervous System

The somatic and autonomic nervous system differ in their:

- Target/effector organs
- **Efferent** pathways and the neurotransmitters that are used
- How the target/effector organ responds to the neurotransmitter

Peripheral Nervous System: Somatic Nervous System

The **somatic nervous system** represents all the parts of the **PNS** that are involved with the outside environment, either in sensing the environment or acting on it. For example, the nerves that detect pressure or pain on the foot are part of the **afferent** somatic nervous system. We also think of the somatic nervous system as the branch that sends signals to our skeletal muscles. The nerves that innervate the muscles of the legs as we run are part of the efferent somatic nervous system. The somatic nervous system is also called the "voluntary nervous system" since it is used to cause muscle movement related to intentional actions.

The somatic nervous system has an efferent path from the central nervous system to the target / effector organ that is made up of one neuron. The axon of this neuron is heavily **myelinated**, which allows for fast delivery of messages. This somatic motor neuron has its cell body in the central nervous system and has an axon that extends all the way to the target/effector organ, which—for the somatic nervous system—will be a **skeletal muscle**.

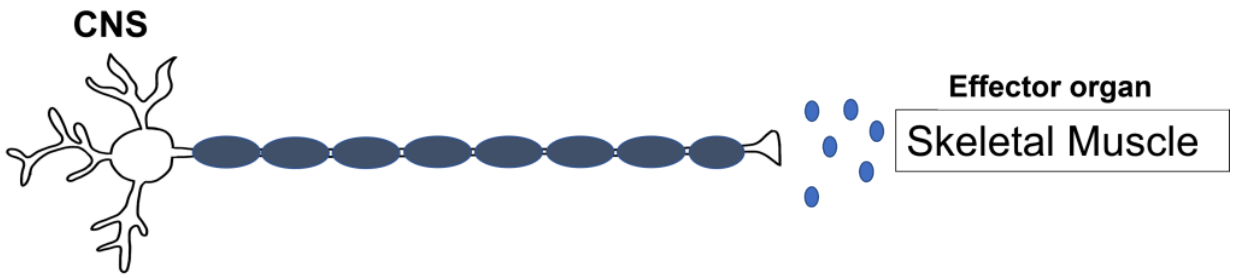


Figure 22.1. Somatic nervous system efferent pathway. The somatic nervous system efferent path consists of a neuron that has a cell body within the central nervous system that extends all the way to the target tissue: skeletal muscles. The neurotransmitter released onto the skeletal muscle is acetylcholine. 'Somatic Nervous System' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Synapse: Neuromuscular Junction

All somatic motor neurons release the same neurotransmitter, **acetylcholine**, onto the skeletal muscle target/effector organ at the **neuromuscular junction** (NMJ). The NMJ is one of the largest synapses in the body and one of the most well-studied because of its peripheral location. Acetylcholine is the

neurotransmitter released at the NMJ and it acts upon **ligand-gated**, non-selective **cation** channels called nicotinic acetylcholine receptors that are present in postjunctional folds of the muscle fiber. **Acetylcholinesterase**, an enzyme that breaks down acetylcholine and terminates its action, is present in the synaptic cleft of the neuromuscular junction.

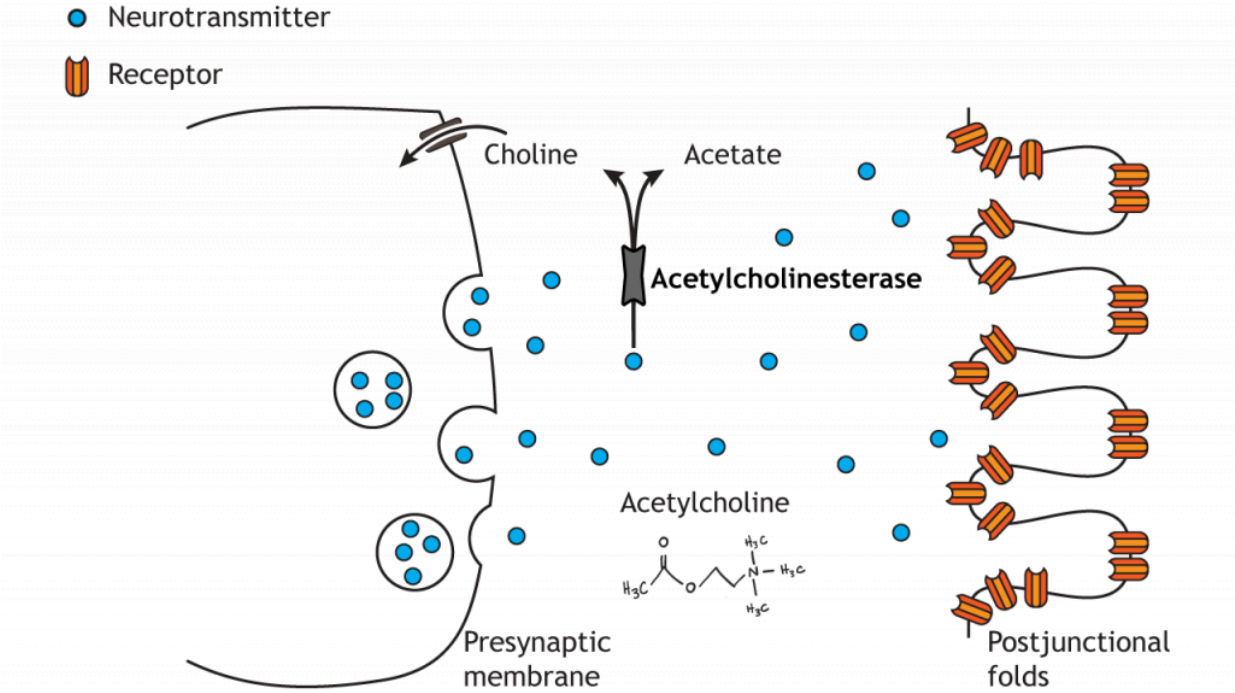


Figure 22.2. The neuromuscular junction (NMJ) is the synapse between a motor neuron and a muscle fiber. Acetylcholine is released at the NMJ and acts on nicotinic acetylcholine receptors located in the postjunctional folds of the muscle fiber. Neurotransmitter action is terminated through breakdown by acetylcholinesterase. 'Neuromuscular Junction' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Nicotinic acetylcholine receptors allow for the influx of sodium ions into the muscle cell. The depolarization will cause nearby **voltage-gated channels** to open and fire an action potential in the muscle fiber. In a healthy system, an action potential in the motor neurons always causes an action potential in the muscle cell. The action potential leads to contraction of the muscle fiber.

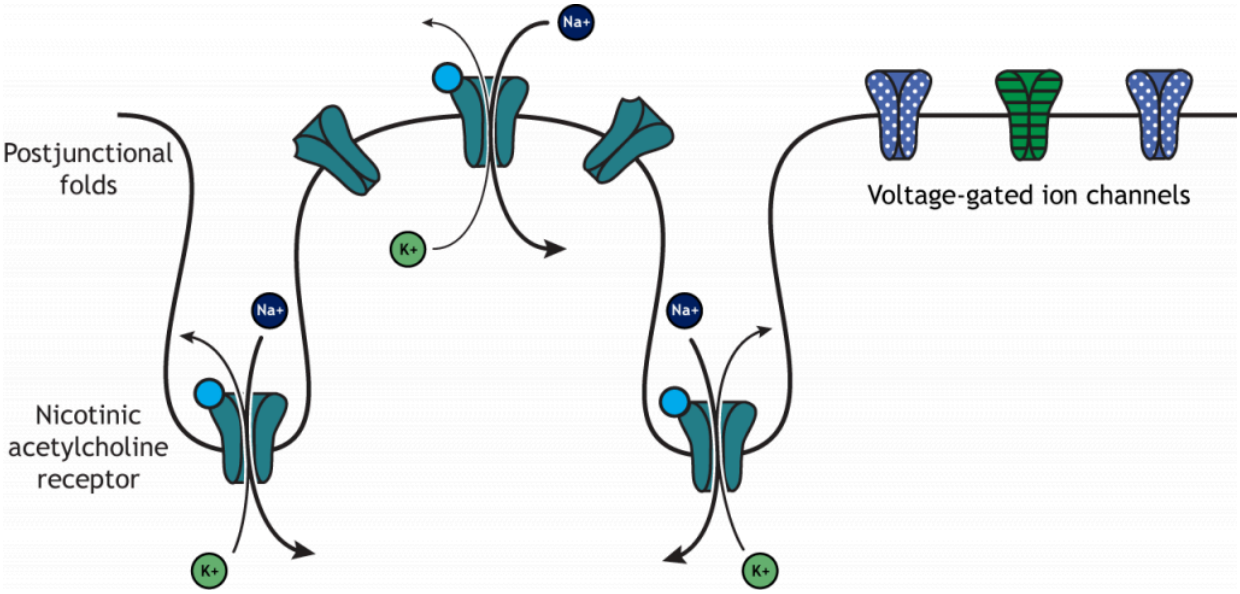


Figure 22.3. The ionotropic nicotinic acetylcholine receptors in the postjunctional folds of the muscle fiber are non-selective cation channels that allow the influx of sodium and the efflux of potassium. The depolarization of the cell by the sodium influx will activate nearby voltage-gated ion channels. 'NMJ Ion Flow' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Peripheral Nervous System: Autonomic Nervous System

The **autonomic nervous system** encompasses all the branches of the peripheral nervous system that deal with the internal environment. As with the somatic nervous system, the autonomic nervous system is comprised of nerves that detect the internal state as well as nerves that influence the internal organs. The body carries out all sorts of functions and responses unconsciously without any intentional control. It can do so by sending signals to smooth muscles and glands. The signals that cause us to sweat when it is hot, our pupils to dilate when it is dark, and our blood pressure to adjust when we stand up too quickly are all driven by the nerves of the autonomic nervous system.

The autonomic nervous system has an efferent path from the central nervous system to the target/effector organ that is made up of a chain of two neurons with a ganglion in the middle. Recall that a **ganglion** is a collection of neuron cell bodies in the periphery.

The neuron that has its cell body in the central nervous system is called the **preganglionic neuron**. The preganglionic cell axon is lightly myelinated and extends to a ganglion in the periphery where it synapses on the second neuron in the chain called the **postganglionic neuron**. The postganglionic neuron has its cell body in the ganglion and its unmyelinated axon extends from the ganglion to the target/effector organ, which for the autonomic nervous system will be: smooth muscle, cardiac muscle, glands, or organs.

The first synapse happens at the site of the ganglion. All preganglionic cells release **acetylcholine** onto the postganglionic cells. The acetylcholine binds to nicotinic acetylcholine receptors, which results in the generation of an **excitatory postsynaptic potential** for the postganglionic cell body. This effectively passes the message between the preganglionic and postganglionic cells.

The second synapse occurs between the postganglionic cell and the target/effector organ. Postganglionic neurons in the autonomic nervous system release either norepinephrine or acetylcholine (more on this later). These neurotransmitters can have either stimulatory or inhibitory activity at the target organs, dependent on the properties of the postsynaptic receptor that they bind to.

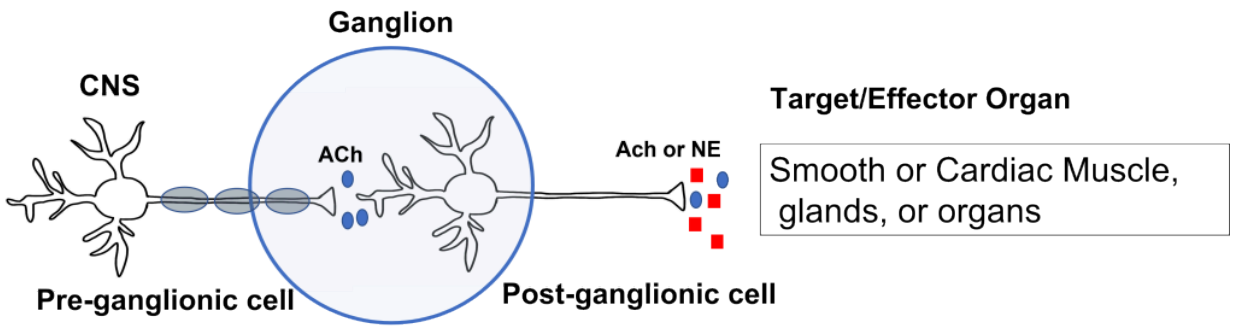


Fig 22.4. Autonomic nervous system efferent path. The efferent path for the autonomic nervous system consists of two neurons. The first neuron is called the preganglionic neuron and it starts in the central nervous system and extends to a ganglion in the periphery where it releases acetylcholine onto the postganglionic neuron. The postganglionic neuron extends to the target tissue where it releases either acetylcholine or norepinephrine. Target tissues include smooth muscle, cardiac muscle, glands, and organs. 'Autonomic two neuron chain' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Autonomic Effector Synapse

Within the autonomic nervous system, synapses have a different structure than what is observed at the **NMJ** of the somatic nervous system. Instead, autonomic axons are highly branched and have enlarged **varicosities** that are spread along the axon. These varicosities contain synaptic vesicles that are filled with neurotransmitters. The varicosities form synapses **'en passant'** (literally meaning 'in passage') with the target organ. These axon branches with varicosities drape over the cells of the target tissue, allowing a single axon branch to affect change over a greater area of the target tissue and better distribute autonomic activation at the target tissue.

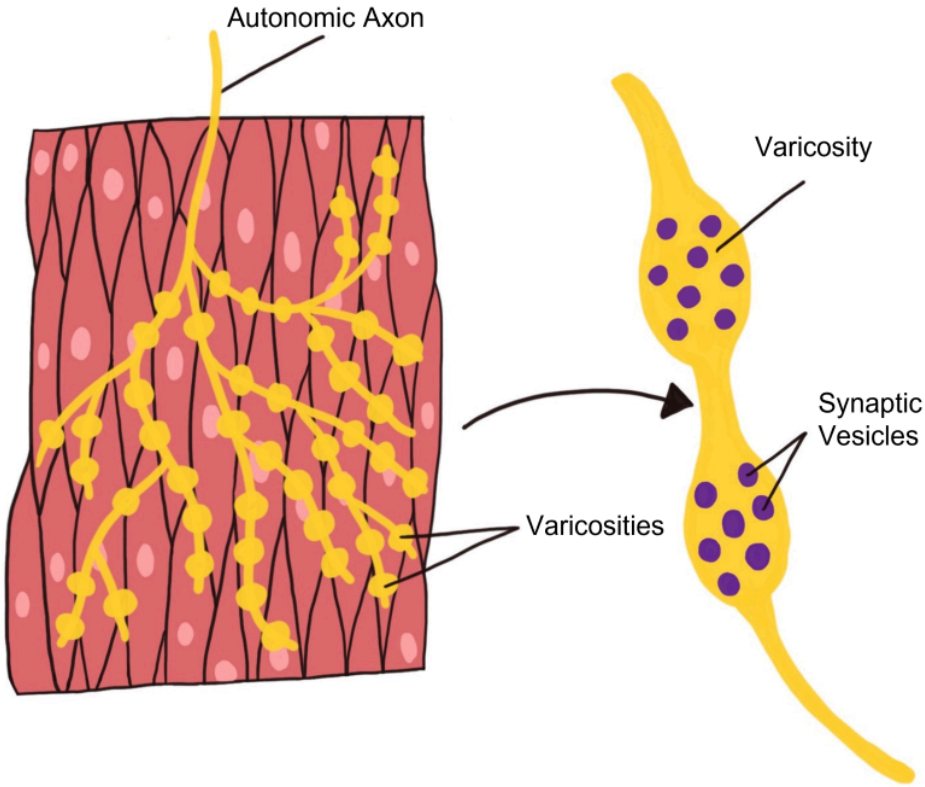


Figure 22.5. An autonomic axon branches extensively to cover effector tissues like a net. Multiple varicosities have synaptic vesicles that release neurotransmitters onto effector cells. 'Synapse en passant' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Comparing Somatic to Autonomic Nervous System

In summary, the somatic nervous system has a one neuron path that originates in the central nervous system. That neuron extends all the way to the skeletal muscle (target tissue) where it releases acetylcholine. The acetylcholine binds to nicotinic acetylcholine receptors that cause EPSPs in the muscle fibers and giving a stimulatory effect. The autonomic nervous system (both branches) use a two neuron pathway between the CNS and the target tissues that are smooth muscle, cardiac muscle, glands, and organs. The sympathetic division consists of short presynaptic neurons that synapse on longer postsynaptic neurons in peripheral ganglia that are situated close to the spinal cord. The parasympathetic division consists of long presynaptic neurons that synapse on shorter postsynaptic neurons in peripheral ganglia that are situated close to the target organ. Like the somatic motor system, the primary neurotransmitter in the parasympathetic division is acetylcholine. In the sympathetic division, the preganglionic neuron releases acetylcholine, but the postganglionic neuron releases norepinephrine. The effects of these neurotransmitters at the target tissue can be either stimulatory or inhibitory depending on the properties of the postsynaptic receptor. This information is summarized in the figure and table below.

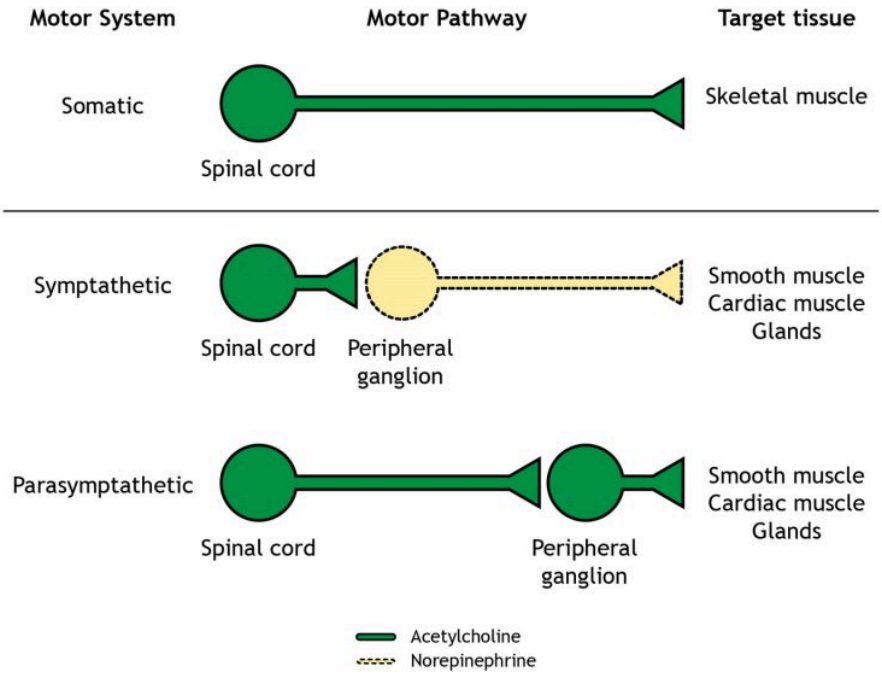


Figure 22.6. The somatic motor system consists of single neuron that extends from the central nervous system directly to skeletal muscle where it releases acetylcholine. The autonomic nervous system uses a two-neuron pathway. The preganglionic cell extends from the central nervous system to a peripheral ganglion where it synapses on the postganglionic cell body and releases acetylcholine. The postganglionic neuron then innervates the target tissue, which could be smooth muscle, cardiac muscle, or a gland. In the sympathetic division, the postganglionic neuron releases norepinephrine onto the target tissue, whereas in the parasympathetic system, the postganglionic neuron releases acetylcholine onto the target tissue. 'Somatic vs SNS and PNS Motor' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Table 22.1. Table comparing the somatic nervous system to the autonomic nervous system specifically identifying the efferent path, the target / effector organ, the neurotransmitter released at the ganglion and effect, the neurotransmitter released at the target organ, and the response of the target organ to the neurotransmitter.

Branch of PNS	Efferent Path	Target / Effector Organ	Neurotransmitter Released at Ganglion and Effect	Neurotransmitter Released at Target Organ	Target Organ Response to Neurotransmitter
Somatic	1 Neuron	Skeletal Muscle	None- No Ganglion	Acetylcholine	Stimulatory
Autonomic	2 Neuron Chain	Smooth / Cardiac Muscle, Glands, Organs	Acetylcholine, excitatory	Acetylcholine or Norepinephrine	Can be stimulatory or inhibitory

Two Branches of the Autonomic Nervous System

There are two branches of the autonomic nervous system, called the sympathetic nervous system and the parasympathetic nervous system, that typically have opposite effects at target tissues.

Consider a scenario in which you encounter a bear on hike through Yellowstone National Park. Your heartrate would likely increase and your breathing rate would increase as you contemplate how to survive your encounter. This complex set of physiological reactions are due to activation of one of the branches of the autonomic nervous system: **the sympathetic nervous system**. The sympathetic nervous system mobilizes a set of physiological changes to a threat that is sometimes called the fight-or-flight response, which is activated when we are faced with a threat, either perceived or real. All of these rapid bodily responses result in the body preparing to attack or defend itself. Increased respiration allows the body to take in more oxygen, and dilation of blood vessels in the muscles allows that oxygen to get to the muscles, which is needed for muscle activation.

Now, consider a completely opposite scenario. You've just eaten a large meal and you are spending the evening watching television on your couch. You would probably feel relaxed, satisfied, and more than a little sluggish. A different physiological response is happening, a behavior called the rest-and-digest response. These physiological changes are driven by the other main branch of the autonomic nervous system, called the **parasympathetic nervous system**.

Targets and Effects of the 2 Branches of the Autonomic

Nervous System

The sympathetic nervous system and the parasympathetic nervous system are referred to as antagonistic. These branches are called 'antagonistic' because they typically have opposite effects at target tissues.

There is dual innervation at many target organs of the autonomic nervous system. This means that target organs receive connections from both sympathetic and parasympathetic neurons. In a sense, this dual innervation provides both a 'break' and an 'accelerator' for changing the activity of our internal organs, offering a good amount of control.

Both the sympathetic nervous system and parasympathetic nervous systems influence the internal organs simultaneously. At all times, the heart is getting signals from the sympathetic nervous system which increase heart rate, and signals from the parasympathetic nervous system which decreases heart rate. However, this seesaw-like balance can shift quickly in either direction, such as inducing a sympathetic response if a fearful stimulus is encountered.

Table 22.2. Comparison between sympathetic and parasympathetic action at various target organs.

Target Organ	Sympathetic Action	Parasympathetic Action
Eye	Pupil dilation	Pupil constriction
Salivary glands	Prevents saliva secretion	Increases saliva secretion
Lungs	Airway dilation	Airway constriction
Heart	Increases heart rate	Decreases heart rate
Blood vessels	Constriction	No innervation
Stomach, liver, intestines, pancreas	Decreases digestion	Increases digestion
Kidneys	Sodium and water retention	No innervation
Adrenal gland	Increases epinephrine and norepinephrine secretion	No innervation
Reproductive organs	Orgasm and ejaculation	Blood vessel dilation leading to erection

Anatomical Differences between 2 Branches of Autonomic Nervous System

The sympathetic and parasympathetic nervous systems differ anatomically as well. The sympathetic preganglionic neurons are short and the sympathetic postganglionic neurons are long. The parasympathetic preganglionic neurons are long and the parasympathetic postganglionic neurons are short.

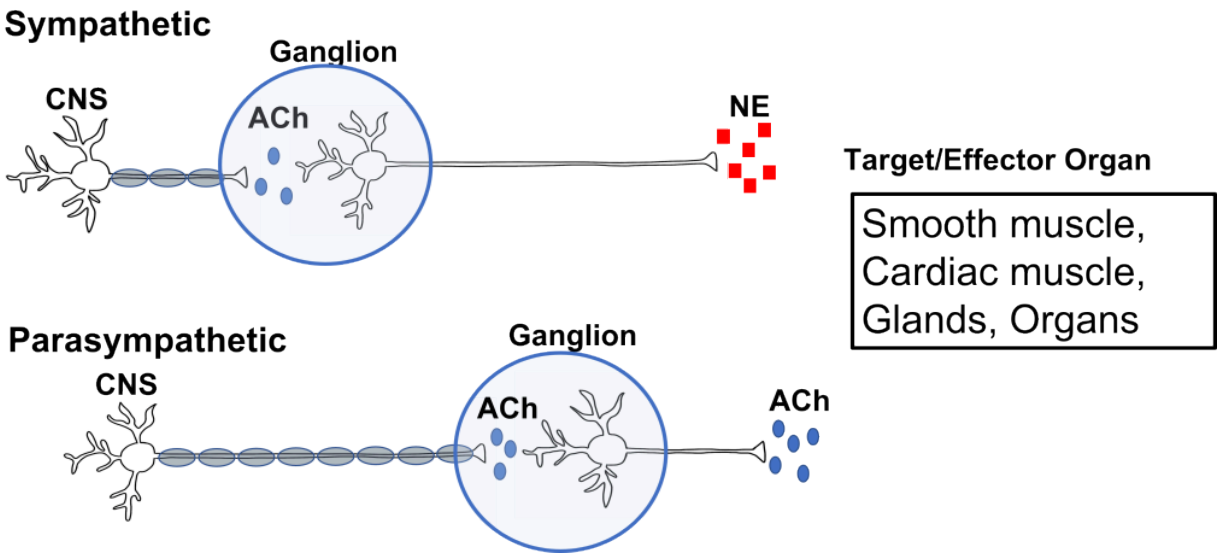


Figure 22.7. Anatomical differences between the sympathetic and parasympathetic nervous system. The sympathetic nervous system has short preganglionic neurons due to the proximity of the ganglion to the spinal cord (central nervous system). The sympathetic nervous system has long postganglionic neurons that release norepinephrine (red squares) onto target tissues. The parasympathetic nervous system has long preganglionic neurons due to the ganglions being close to target tissues. The postganglionic neurons of the parasympathetic nervous system are short and release acetylcholine (blue ovals) onto target tissues. 'Anatomical differences between sympathetic and parasympathetic nervous systems' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Sympathetic Anatomy

The cell bodies of the preganglionic neurons of the sympathetic nervous system are located in the thoracic and lumbar sections of the spinal cord, so we can use thoracolumbar to describe the site of origin. The axons leave the central nervous system and travel only a short distance to the peripheral

ganglion. In the sympathetic system, most of the ganglia are located along the spinal cord in the sympathetic paravertebral chain. A few sympathetic ganglia, called prevertebral, are located slightly more laterally. The preganglionic neurons synapse on the postganglionic neurons in the sympathetic ganglia. The postganglionic neurons then travel the rest of the distance to synapse on the target organs.

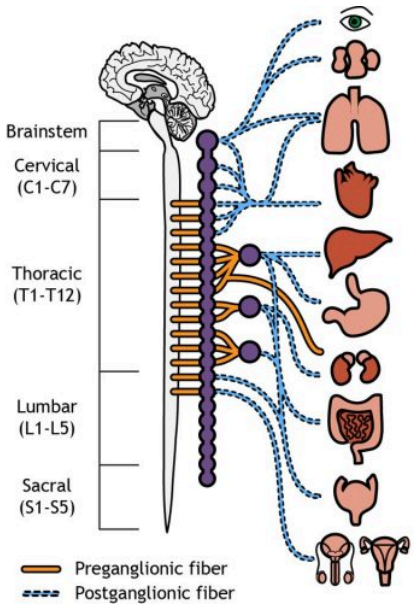


Figure 22.8. The preganglionic neurons of the sympathetic nervous system arise from the thoracic and lumbar sections of the spinal cord and terminate in paravertebral and prevertebral ganglia. The preganglionic neurons synapse on postganglionic neurons, which then extend to the target organ tissue and innervate the muscle and gland cells. 'Sympathetic nervous system' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

One exception to this structure is the innervation of the adrenal medulla. The adrenal gland is a structure located at the top of each kidney. The gland has an outer portion called the **cortex** and an inner portion called the **adrenal medulla**, which is made up of cells called **chromaffin cells**. The sympathetic preganglionic cell releases acetylcholine at the synapse with the chromaffin cells of the medulla and releases acetylcholine onto the chromaffin cell that is serving as a modified post-ganglionic neuron. Then the chromaffin cells of the adrenal medulla release epinephrine and norepinephrine into the bloodstream. Within the bloodstream these neurotransmitters can act as hormones affecting change throughout the body leading to a rapid onset of sympathetic activity and sustained activation.

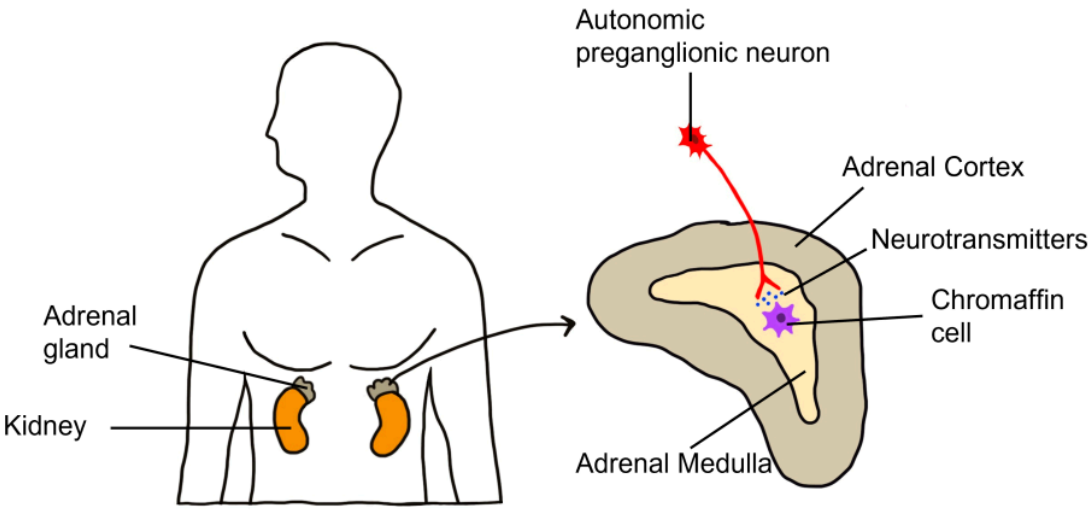


Figure 22.9. Autonomic control of the adrenal medulla. The adrenal glands are located on top of the kidneys and consist of outer cortex and an inner medulla. Sympathetic preganglionic neurons release acetylcholine onto chromaffin cells that serve as modified postganglionic neurons. The chromaffin cells of the adrenal medulla release epinephrine and norepinephrine into the blood stream. 'Sympathetic control of the adrenal medulla' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

The sympathetic preganglionic cell bodies are located in the intermediolateral cell columns in the lateral horn of the spinal cord, a gray matter region between the dorsal and ventral horns. The neurons send their axons out through the ventral root, and then can take one of multiple pathways. The axon can terminate in the paravertebral ganglion at the same spinal level as the cell body, or the axon can extend up or down the sympathetic chain to synapse on a postganglionic fiber at a different spinal level. Another possible pathway is to enter and exit the sympathetic chain without synapsing and continue on to terminate in a prevertebral ganglion located closer to the target organ.

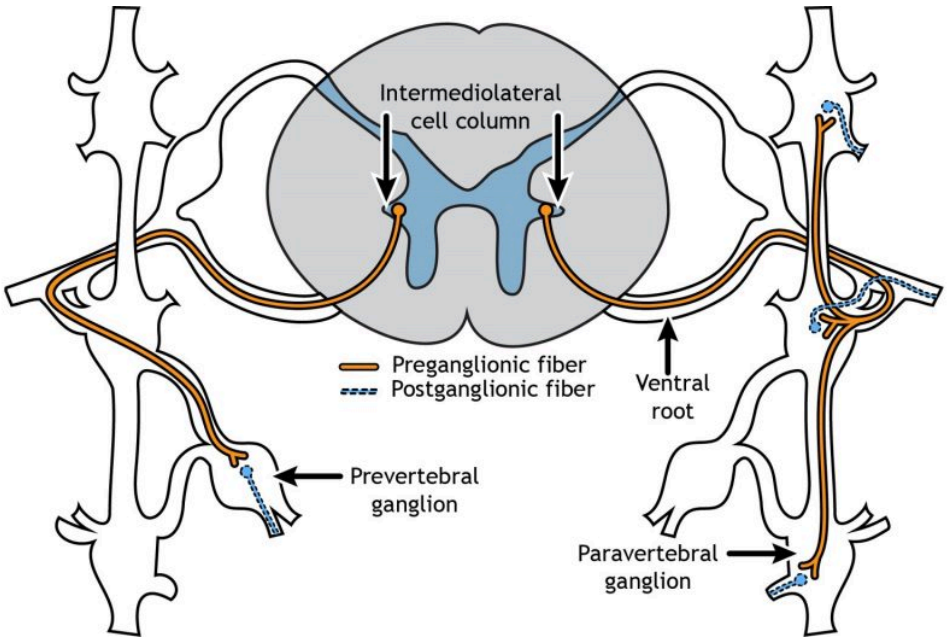


Figure 22.10. The cell bodies of the sympathetic preganglionic neurons are located in the intermediolateral cell column of the spinal cord. The preganglionic neurons leave the spinal cord via the ventral root and can synapse in paravertebral ganglion at the same spinal level as the cell body location or can travel rostrally or caudally along the sympathetic chain to a different spinal level (right side of image). Preganglionic neurons can also leave the spinal cord, pass through the paravertebral ganglia without synapsing and instead synapse on a postganglionic neuron in a prevertebral ganglion (left side of image). 'Sympathetic Preganglionic Fibers' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Parasympathetic Anatomy

On the other hand, parasympathetic neurons originates predominantly in the cervical spinal cord (near the neck), with some signals originating in the sacral areas (near the tail bone). The parasympathetic nervous system usually receives signals from several cranial nerves. Cranial nerve X, also called the vagus nerve innervates multiple bodily organs in the midsection of the body. For the parasympathetic nervous system, the ganglia are located very close to the target tissues. Therefore, the preganglionic neuron must be very long to reach all the way to the ganglion to makes its first synapse. But due to the proximity of the ganglion to the target tissue, the postganglionic neuron is very short.

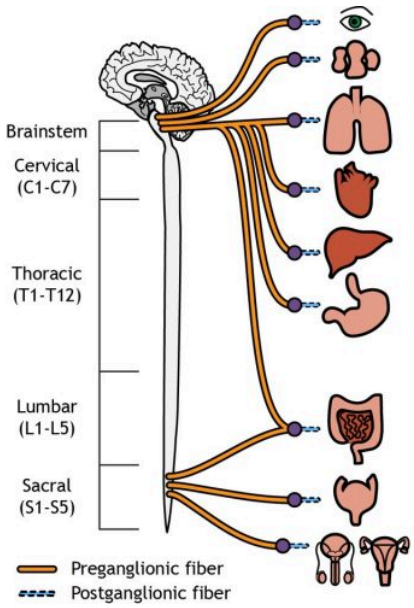


Figure 22.11. The preganglionic neurons of the parasympathetic nervous system arise from the brainstem and sacral sections of the spinal cord and terminate in ganglia located on or near the target organs. The preganglionic neurons synapse on postganglionic neurons, which then innervate the muscle and gland cells. 'Parasympathetic nervous system' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Neurotransmitters of the Autonomic Nervous System

We have already established that at the first synapse in the chain of autonomic neurons, all preganglionic neurons release acetylcholine, which binds to excitatory nicotinic receptors on the postganglionic neurons. This is true of both the sympathetic and parasympathetic nervous system. However, the two branches of the autonomic nervous system have different effects at target tissues because they use different neurotransmitters that produce either stimulatory or inhibitory effects at target tissues.

The sympathetic postganglionic neurons release norepinephrine at target tissues. Norepinephrine (and epinephrine) binds two major classes of adrenergic receptors: alpha adrenergic receptors and beta adrenergic receptors. The effects of norepinephrine (and epinephrine) can be either excitatory or inhibitory depending on the properties of the postsynaptic receptor.

The parasympathetic postganglionic neurons release acetylcholine at target tissues. The target tissues express muscarinic acetylcholine receptors. The effect of the acetylcholine can be either

excitatory or inhibitory depending on the subtype of muscarinic (metabotropic) receptors. The location of function of these transmitters and receptors are critical for clinical use, for example, when treating high blood pressure or sexual dysfunction.

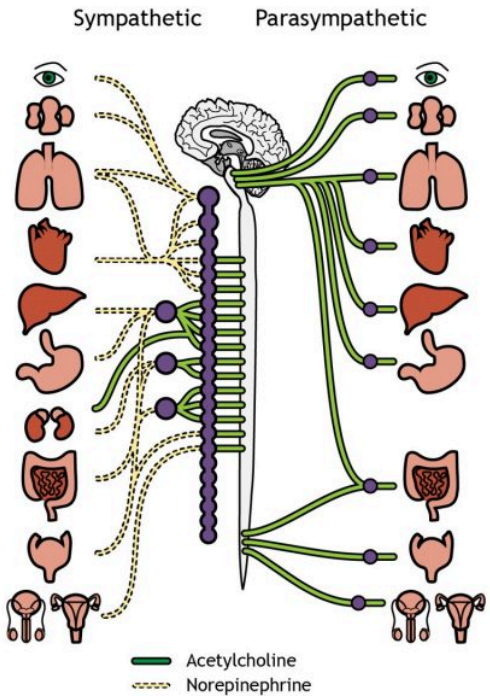


Figure 22.12. Acetylcholine is the primary neurotransmitter in both the pre- and postganglionic fibers of the parasympathetic nervous system and in the preganglionic neurons in sympathetic system. The sympathetic postganglionic fibers release norepinephrine onto their targets. 'Autonomic Neurotransmitters' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Autonomic Control Centers in the Brain

Visceral functions are regulated through a number of autonomic reflexes, but they can be directly controlled by higher brain areas. Within the brain stem, the medulla most directly controls autonomic activity. The medulla receives most of its information via the vagus nerve (a mixed nerve that contains both sensory and motor fibers). Within the medulla are a variety of control centers that regulate functions such as cardiovascular activity, respiratory rate, vomiting, and swallowing. The pons, another brain stem structure also serves as an autonomic control center for respiration.

In addition to brain stem structures, there are also higher order brain areas that are important for autonomic control. The hypothalamus can directly regulate the medulla, and is also critical for the

regulation of water balance, temperature control, and hunger. The Limbic System, made up of a number of structures including the the hippocampus and amygdala, functions in our expression of emotion. The limbic system structures are responsible for visceral responses associated with emotional states, including blushing, fainting, pallor, nervous cold sweats, racing heart rate, and uneasy feelings in the stomach.

Further, the cerebral cortex and cerebellum also function in autonomic control. The cerebral cortex has been shown to regulate lower brain structures especially in autonomic control associated with emotion and personality. The cerebellum has connections to the medulla that are critical for the control of autonomic functions such as sweating and nausea.

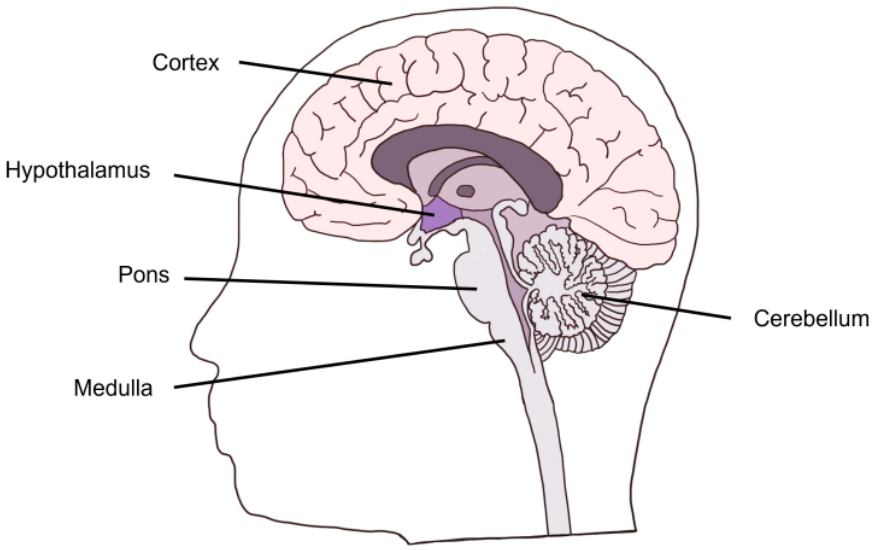


Figure 22.13. Autonomic control centers of the brain. Various higher order brain structures control autonomic nervous system function including the medulla and pons within the brain stem, the hypothalamus, the limbic system, cortex, and cerebellum. 'Autonomic control centers of the brain' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Enteric Nervous System

The internal organs that carry out digestive functions, such as the esophagus, stomach, and intestines, are surrounded by a dense mesh of neurons that regulate their activity. Consisting of half a billion

nerve cells, this net of neurons cause the digestive tract to increase or decrease the rate of these processes depending on the body's demands The enteric nervous system receives signals from both the sympathetic and parasympathetic nervous systems, and functions without our conscious knowledge. Historically, these digestive functions have been classified as part of the autonomic nervous system, but these responses do not share the same reflex pathway, and the enteric signals can work entirely independent of the vagus nerve, for example.

Key Takeaways

- There are 3 main divisions of the peripheral nervous system: the somatic nervous system, the autonomic nervous system and the enteric nervous system.
- The somatic and autonomic nervous systems different in their efferent path, how they synapse on target tissues, the neurotransmitters that are used, and the action of those neurotransmitters at target tissues.
- The autonomic nervous system can be subdivided into the sympathetic and parasympathetic nervous systems.
- The sympathetic nervous system is the "fight or flight" system and the parasympathetic nervous system is the "rest and digest" system.
- There are anatomical differences between the sympathetic and parasympathetic nervous system.
- Several brain areas serve as autonomic control centers.
- The enteric nervous system controls the gut and receives connections from both autonomic nervous system branches.

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=545#h5p-46

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PART IV
SENSORY SYSTEMS

23.

GENERAL PRINCIPLES OF SENSORY SYSTEMS

Each sensory system is obviously quite different in the type of stimulation that it responds to and the manner in which environmental stimuli is converted to neuronal signaling. However, there are many principles that can be generalized across sensory systems.

Sensory transduction

Our sensory systems work by converting different types of stimuli in the environment (i.e. visible light, sound waves, chemical molecules) into action potentials in the nervous system. This conversion is called sensory transduction and occurs in all sensory systems.

Sensory receptors

Sensory transduction begins at the sensory receptors. Each sensory system has specialized cells that are able to detect the environmental stimuli. Photoreceptors detect light, chemical receptors in the tongue and nose detect odors and taste, mechanoreceptors detect touch, and hair cells detect sound.

Receptor Potentials

We have learned about postsynaptic potentials in neurons, receptor potentials are similar membrane potential changes that happen in sensory receptors in response to a stimulus.

Receptive fields

Receptive fields are easiest to understand in the visual and somatosensory systems. The receptive field for a neuron is the region of the retina or skin where a stimulus (light or touch) will evoke a response in the neuron. Receptive fields in the auditory system can consist of a certain frequency of sound and/or the location of sound in space.

Receptive fields can vary in size and shape depending on the characteristics of neuron (i.e. type, location in body, location in pathway). Receptive fields become more complex as information travels to the brain.

Lateral Inhibition

Lateral inhibition is a process used by sensory systems to enhance the perception of signals, particularly at edges, points, or other changes in the stimulus. It occurs because overlapping receptive fields can inhibit each other. This inhibition enhances the perceived differences between the stimulus and the area not stimulated.

Neural Coding

There are a number of different ways in which the nervous system encodes complex information. Two that are common within the sensory systems are line coding and population coding.

Labeled Line Coding

In the labeled line coding of information, one cell encodes for one type of sensory quality. Pain is a good example of this. If a pain receptor is activated, the resulting sensation will be pain, regardless of the manner in which the receptor is stimulated. In other words, the sensory neurons are specifically tuned to one sensory stimulus. If that receptor-cell type was dysfunctional, the sensation will not be perceived. For example, there is a mutation that prevents sodium channels in pain receptors (but not other cell types) from working. When this mutation occurs, the subject cannot feel pain.

Population Coding

In populating coding, one cell can encode more than one sensory modality, and it is the combination of many cells that make up the perception. An example of this is color vision. Each color photoreceptor is most sensitive to a specific color (blue, green, or red), but a range of wavelengths can elicit changes in firing rates in the neuron. Therefore, the responses from a population of color photoreceptors must be combined to perceive the full spectrum of color.

Higher level processing of taste and olfaction also uses population coding – sometimes the sense of smell is needed in addition to the sense of taste to fully perceive a flavor. Have you ever been congested from a cold and food just doesn't taste the same? That's due to this combining of the senses for a full perception.

Pathways

In general, the route sensory information takes from the periphery to the central nervous system is similar among most of the systems. Environmental stimuli become encoded by a specialized receptor in the periphery. Information then enters the central nervous system via the spinal cord or brainstem and relays through the thalamus, a structure that sits deep in the forebrain. The only sensory system that does not relay through the thalamus is the olfactory system. The thalamus then sends projections out to the primary cortical regions for each sensory system.

Role of the Thalamus

It's common to hear that sensory information "relays" through the thalamus on the way to the cortex (for example, in the paragraph above). This language can give the impression that the thalamus is only responsible for making sure the sensory signal gets from periphery to the cortex. This greatly underestimates the thalamic role. The thalamus is known to contribute to the processing and modification of the sensory signal.

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24.

VISION: THE RETINA

Anatomy of the Retina

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

The front of the eye consists of the cornea, pupil, iris, and lens. The cornea is the transparent, external part of the eye. It covers the pupil and the iris and is the first location of light refraction. The pupil is the opening in the iris that allows light to enter the eye. The iris is the colored portion of the eye that surrounds the pupil and along with local muscles can control the size of the pupil to allow for an appropriate amount of light to enter the eye. The lens is located behind the pupil and iris. The lens refracts light to focus images on the retina. Proper focusing requires the lens to stretch or relax, a process called accommodation.

The retina is the light-sensitive region in the back of the eye where the photoreceptors, the specialized cells that respond to light, are located. The retina covers the entire back portion of the eye, so it's shaped like a bowl. In the middle of the bowl is the fovea, the region of highest visual acuity, meaning the area that can form the sharpest images. The optic nerve projects to the brain from the back of the eye, carrying information from the retinal cells. Where the optic nerve leaves, there are no photoreceptors since the axons from the neurons are coming together. This region is called the optic disc and is the location of the blind spot in our visual field.

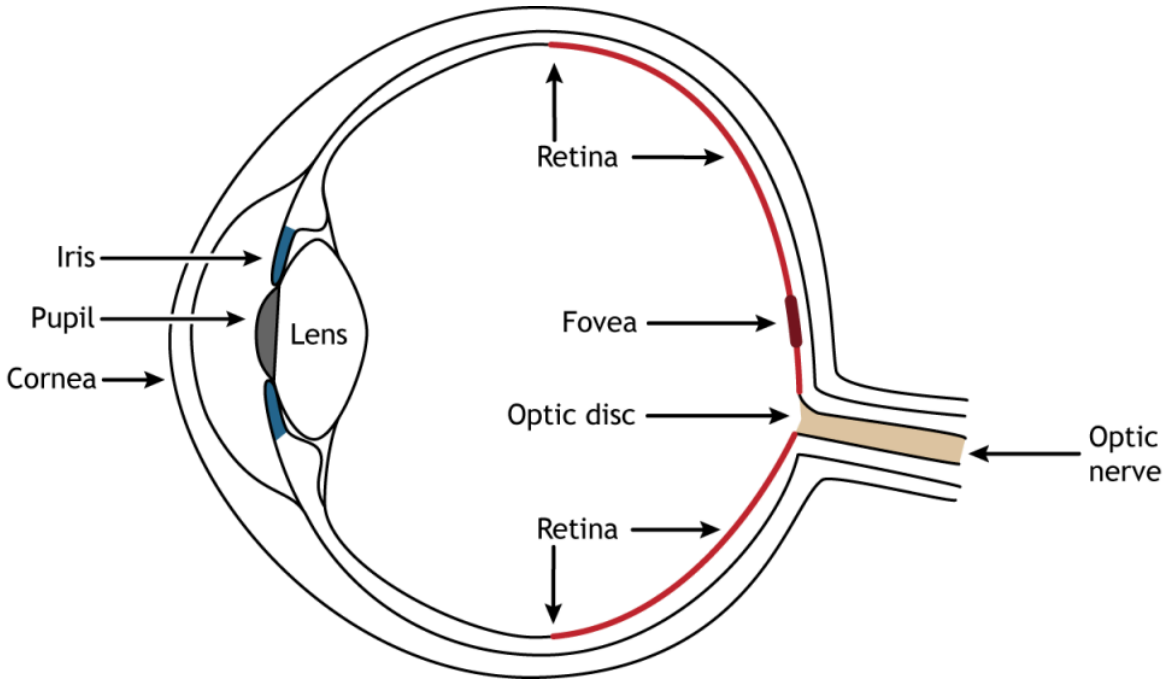


Figure 24.1. Cross section of the eye. The visible regions of the eye include the cornea, pupil (gray region), and iris (blue region). The lens sits behind the pupil and iris. The retina (red line) is located along the back of the eye. The fovea (dark red section) is a small portion of the retina where visual acuity is highest, and the optic disc is located where the optic nerve (tan region) leaves the eye. Details about the functions of each region are in the text. 'Eye Anatomy' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Retinal Cells

There are 5 primary types of cells in the retina

In addition to the photoreceptors, there are four other cell types in the retina. The photoreceptors synapse on bipolar cells, and the bipolar cells synapse on the ganglion cells. Horizontal and amacrine cells allow for communication laterally between the neurons.

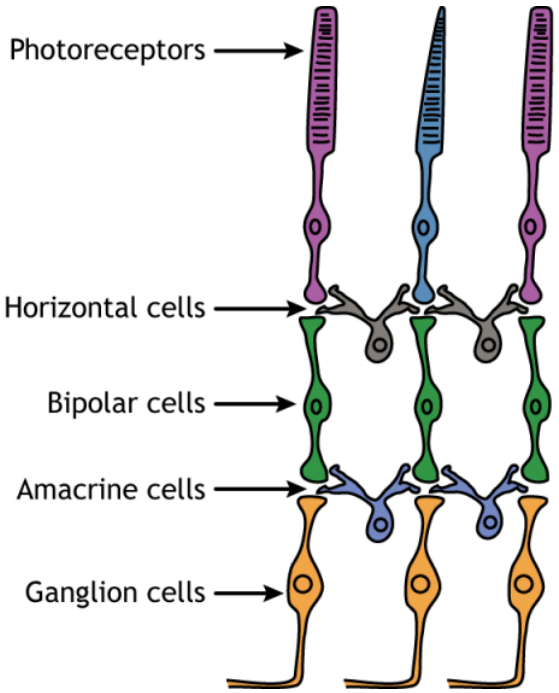


Figure 24.2. There are five cell types in the retina. The photoreceptors synapse on bipolar cells, and the bipolar cells synapse on ganglion cells. The horizonal cells allow for communication between photoreceptors by interacting with the photoreceptor-bipolar cell synapse, and the amacrine cells allow for communication between bipolar cells by interacting at the bipolar cell-ganglion cell synapse. 'Retinal Neurons' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Direction of Information

When light enters the eye and strikes the retina, it must pass through all the neuronal cell layers before reaching and activating the photoreceptors. The photoreceptors then initiate the synaptic communication back toward the ganglion cells.

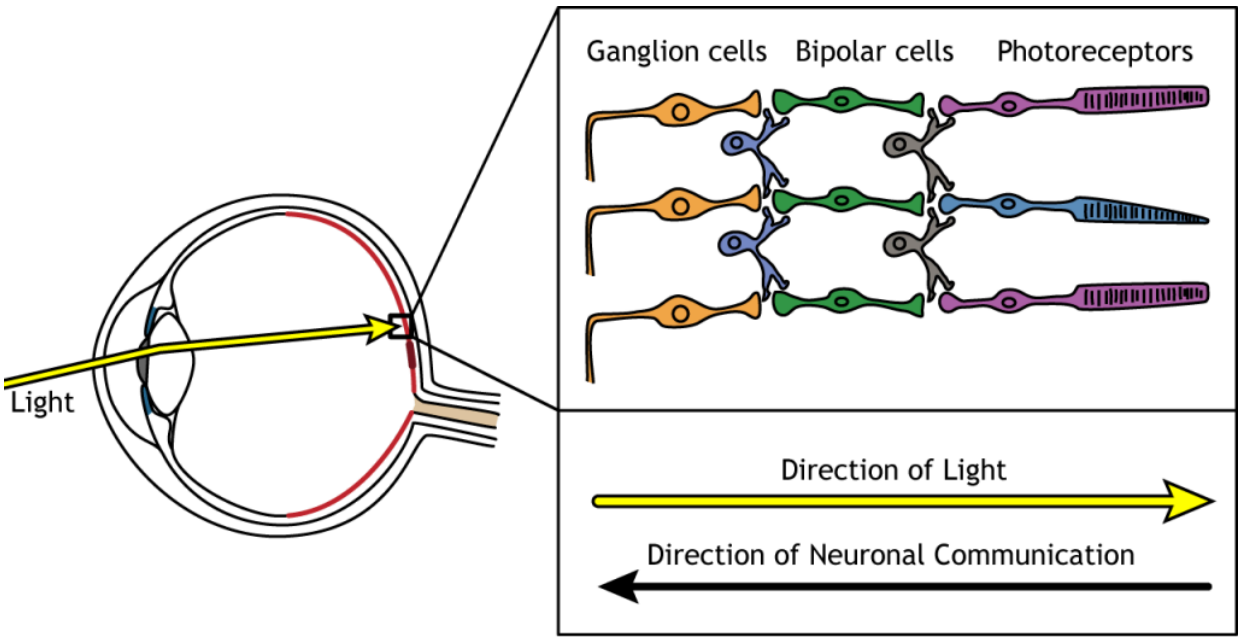


Figure 24.3. When light enters the eye, it must pass through the ganglion and bipolar cell layers before reaching the photoreceptors. The neuronal communication travels in the opposite direction from the photoreceptors toward the ganglion cells. 'Light in the Retina' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Receptors

The photoreceptors are the specialized receptors that respond to light. There are two types of photoreceptors: rods and cones. Rods are more sensitive to light, making them primarily responsible for vision in low-lighting conditions like at night. Cones are less sensitive to light and are most active in daylight conditions. The cones are also responsible for color vision.

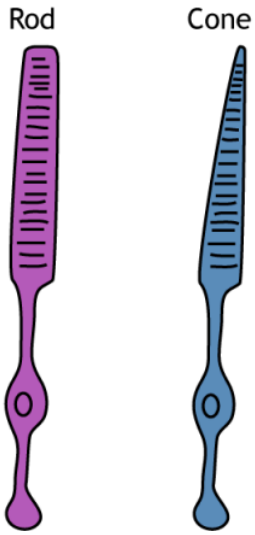


Figure 24.4. The rods and cones have different physical appearances and play separate roles in visual processing. 'Rod and Cone' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Receptor Density

In addition to having different visual functions, the rods and cones are also distributed across the retina in different densities. The cones are primarily found in the fovea, the region of the retina with the highest visual acuity. The remainder of the retina is predominantly rods. The region of the optic disc has no photoreceptors because the axons of the ganglion cells are leaving the retina and forming the optic nerve.

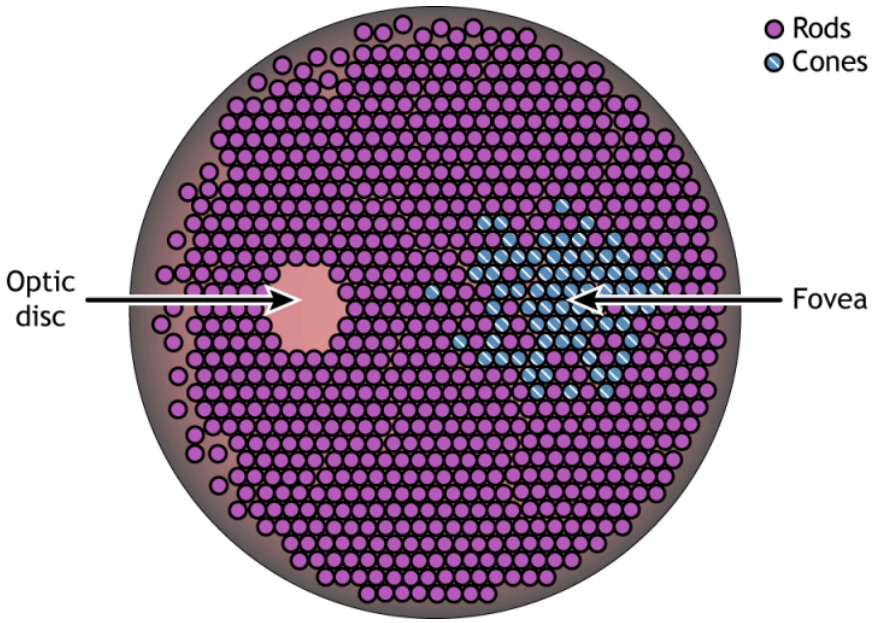


Figure 24.5. Rods and cones are distributed across the retina in different densities. Cones are located at the fovea. Rods are located everywhere else. The optic disc lacks all photoreceptors since the optic nerve fibers are exiting the eye at this location. 'Retinal Receptor Density' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Phototransduction

Photoreceptors hyperpolarize in response to light, do not fire action potentials, and release glutamate

The photoreceptors are responsible for sensory transduction in the visual system, converting light into electrical signals in the neurons. For our purposes, to examine the function of the photoreceptors, we will A) focus on black and white light (not color vision) and B) assume the cells are moving from either an area of dark to an area of light or vice versa.

Photoreceptors do not fire action potentials; they respond to light changes with graded receptor

potentials (depolarization or hyperpolarization). Despite this, the photoreceptors still release glutamate onto the bipolar cells. The amount of glutamate released changes along with the membrane potential, so a hyperpolarization will lead to less glutamate being released. Photoreceptors hyperpolarize in light and depolarize in dark. In the graphs used in this lesson, the starting membrane potential will depend on the initial lighting condition.

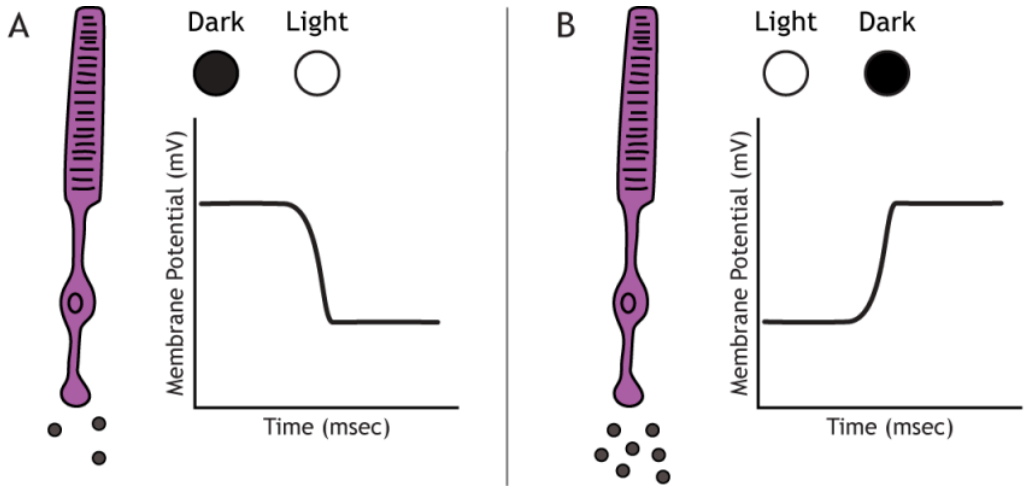


Figure 24.6. Photoreceptors respond with graded potentials when moving from light to dark or vice versa. A) When moving from dark to light, the photoreceptor will hyperpolarize, and glutamate release will decrease. B) When moving from light to dark, the photoreceptor will depolarize, and glutamate release will increase. 'Photoreceptor Receptor Potentials' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

In the dark, the photoreceptor has a membrane potential that is more depolarized than the "typical" neuron we examined in previous chapters; the photoreceptor membrane potential is approximately -40 mV. Photoreceptors have open cation channels that allow the influx of sodium and calcium in the dark. These channels are gated by the presence of cyclic GMP (cGMP), a molecule important in second-messenger cascades that is present in the photoreceptor in the dark.

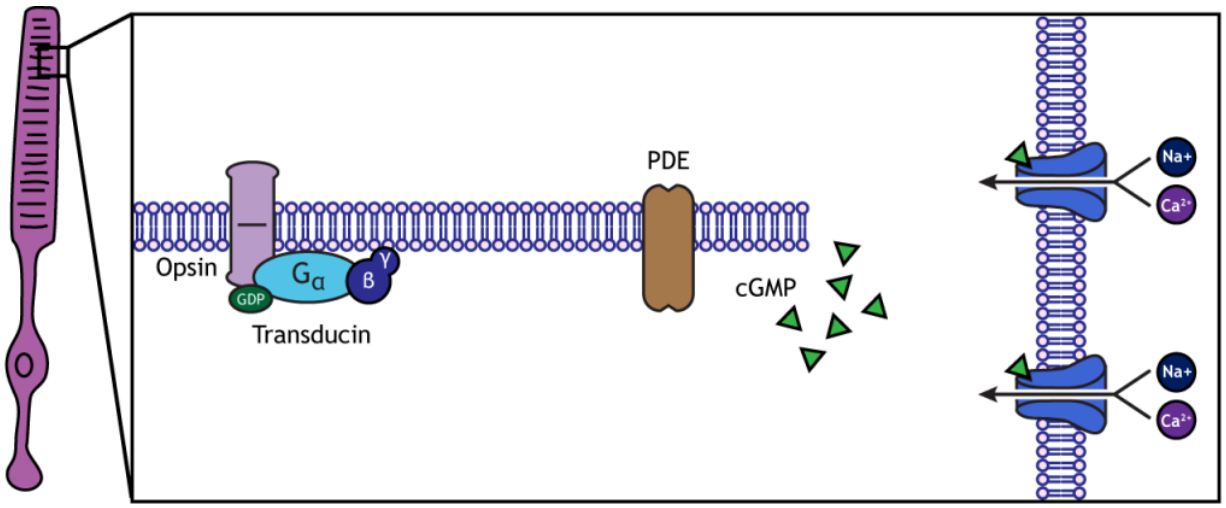


Figure 24.7. In the dark, the photoreceptor is depolarized due to an influx of sodium and calcium through open ion channels that are gated by cGMP. The photoreceptor has high levels of cGMP when it is in the dark. Additionally, the opsin proteins, the G-protein transducin, and phosphodiesterase (PDE) are all inactivated. 'Retinal Dark Current' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

When the photoreceptor moves into the light, the cell hyperpolarizes. Light enters the eye, reaches the photoreceptors, and causes a conformational change in a special protein called an opsin. This change activates a G-protein called transducin, which then activates a protein called phosphodiesterase (PDE). PDE breaks down cGMP to GMP, and the cGMP-gated ion channels that were open in the dark close. The decrease in cation flow into the cell causes the photoreceptor to hyperpolarize.

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=224#video-224-1

Animation 24.1. Light reaching the photoreceptor causes a conformational change in the opsin protein, which activates the G-protein transducing. Transducin activates phosphodiesterase (PDE), which converts cGMP to GMP. Without cGMP, the cation channels close, stopping the influx of positive ions. This results in a hyperpolarization of the cell. 'Phototransduction' by Casey Henley is

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Transmission of Information within Retina

Photoreceptors synapse onto bipolar cells in the retina. There are two types of bipolar cells: OFF and ON. These cells respond in opposite ways to the glutamate released by the photoreceptors because they express different glutamate receptors. Like photoreceptors, the bipolar cells do not fire action potential and only respond with graded postsynaptic potentials.

OFF bipolar cells depolarize in the dark; ON bipolar cells depolarize in the light

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OFF Bipolar Cells

In OFF bipolar cells, the glutamate released by the photoreceptor is excitatory. OFF bipolar cells express ionotropic glutamate receptors. In the dark, glutamate released by the photoreceptor activates the ionotropic receptors, and sodium can flow into the cell, depolarizing the membrane potential. In the light, the absence of glutamate causes the ionotropic receptors to close, preventing sodium influx, hyperpolarizing the membrane potential.

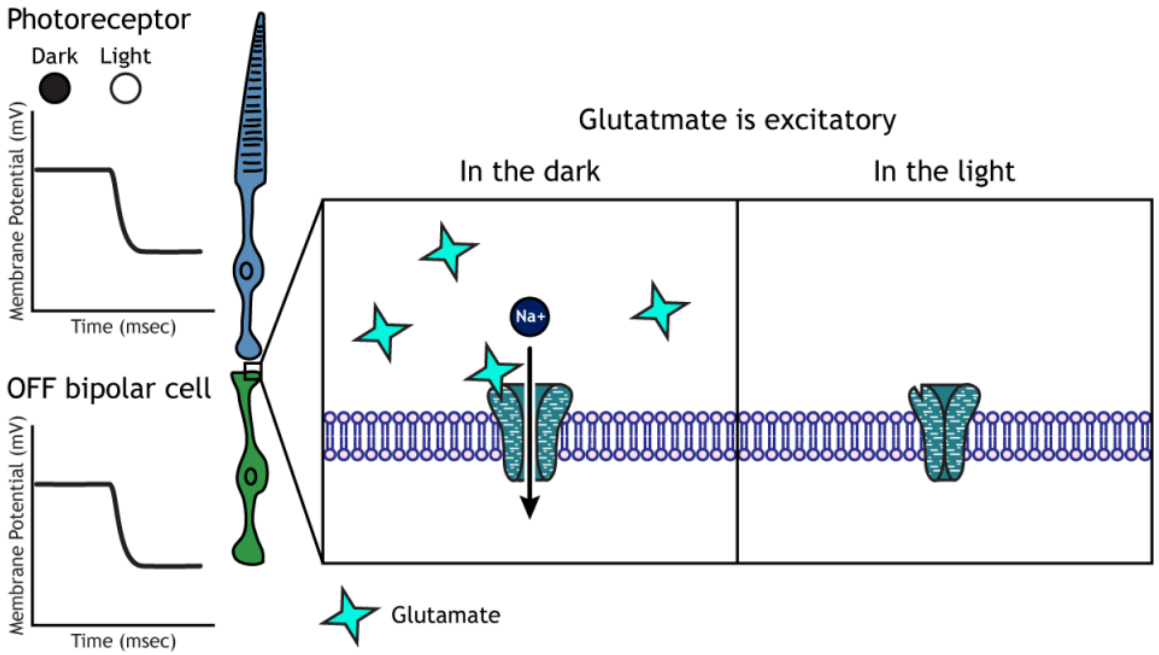


Figure 24.8. Photoreceptors hyperpolarize in light and decrease the amount of released glutamate. Glutamate is excitatory in OFF bipolar cells, opening ionotropic receptors and allowing sodium influx. In the dark, the OFF bipolar cells are depolarized, and in the light the OFF bipolar cells are hyperpolarized. 'Off Bipolar Cells' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

ON Bipolar Cells

In ON bipolar cells, the glutamate released by the photoreceptor is inhibitory. ON bipolar cells express metabotropic glutamate receptors. In the dark, glutamate released by the photoreceptor activates the metabotropic receptors, and the G-proteins close cation channels in the membrane, stopping the influx of sodium and calcium, hyperpolarizing the membrane potential. In the light, the absence of glutamate results in the ion channels being open and allowing cation influx, depolarizing the membrane potential.

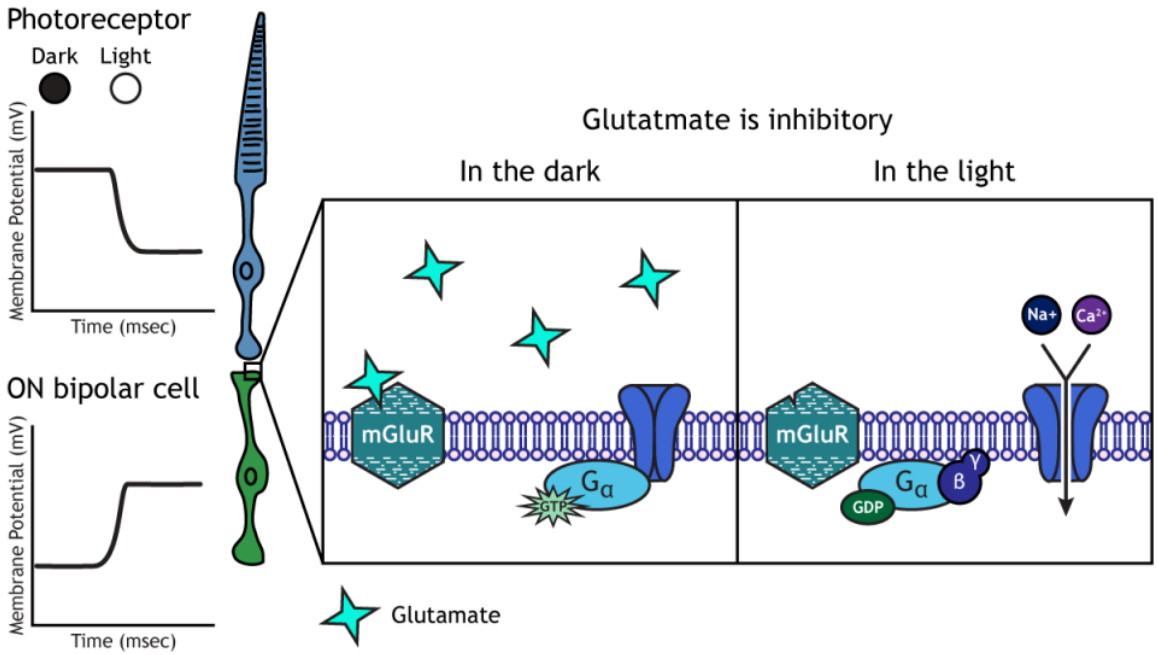


Figure 24.9. Photoreceptors hyperpolarize in light and decrease the amount of released glutamate. Glutamate is inhibitory in ON bipolar cells, activating metabotropic receptors, which closes cation channels. In the dark, the ON bipolar cells are hyperpolarized, and in the light the ON bipolar cells are depolarized. 'ON Bipolar Cells' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Ganglion Cells

OFF-center ganglion cells increase firing rate in the dark; ON-center ganglion cells increase firing rate in the light

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OFF and ON bipolar cells synapse on OFF-center and ON-center ganglion cells, respectively. Ganglion cells are the only cell type to send information out of the retina, and they are also the only cell that fires action potentials. The ganglion cells fire in all lighting conditions, but it is the relative firing rate that encodes information about light. A move from dark to light will cause OFF-center ganglion cells to decrease their firing rate and ON-center ganglion cells to increase their firing rate.

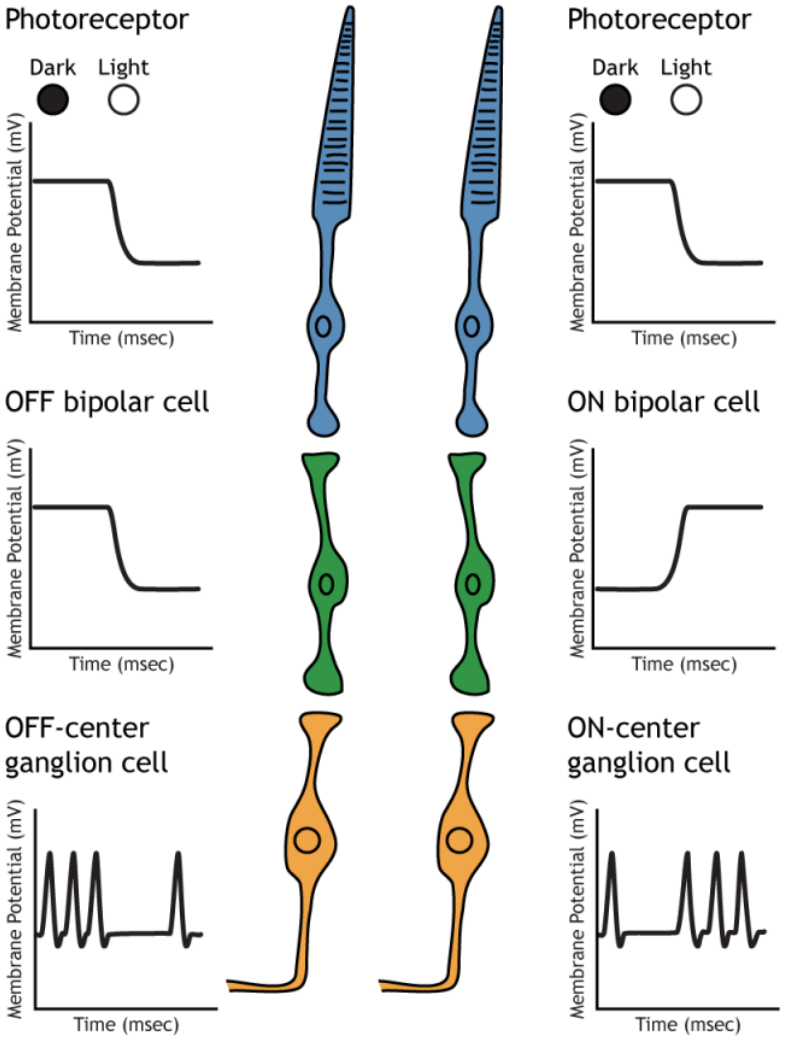


Figure 24.10. A move from dark to light will hyperpolarize all photoreceptors. OFF bipolar cells will also hyperpolarize in light, which will lead to a decreased firing rate in OFF-center ganglion cells. ON bipolar cells will depolarize in light, which will lead to an increased firing rate in ON-center ganglion cells. 'Retinal Ganglion Cells' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Receptive Fields

Each bipolar and ganglion cell responds to light stimulus in a specific area of the retina. This region of retina is the cell's receptive field. Receptive fields in the retina are circular.

Size of the receptive field can vary. The fovea has smaller receptive fields than the peripheral retina.

The size depends on the number of photoreceptors that synapse on a given bipolar cell and the number of bipolar cells that synapse on a given ganglion cell, also called the amount of convergence.

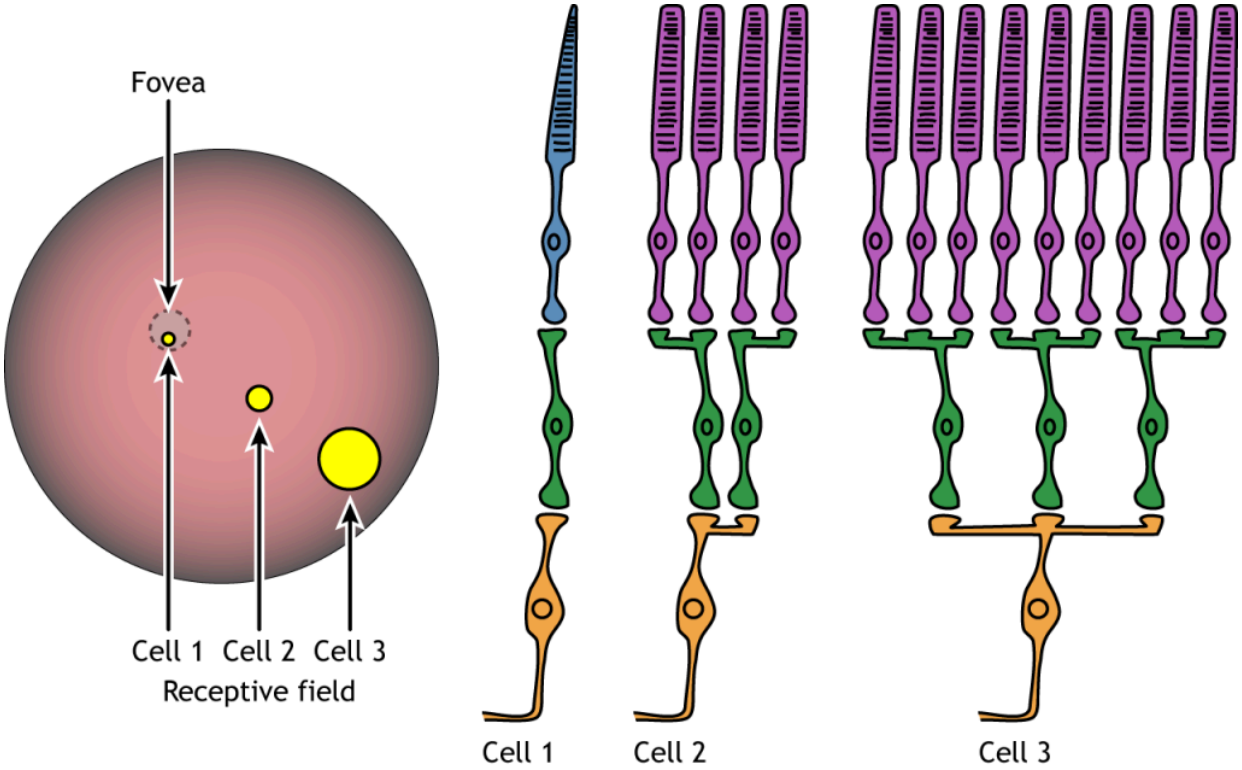


Figure 24.11. Ganglion receptive field sizes can vary depending on location of the bipolar and ganglion cells and the amount of convergence onto those cells. When the photoreceptors are in or near the fovea (Cell 1), the receptive fields are small. In the fovea, each bipolar cell receives input from only one photoreceptor and then synapses on only one ganglion cell. Toward the periphery (Cells 2 and 3), more photoreceptors synapse on each bipolar cell, and more bipolar cells synapse on each ganglion cell, making the surface area of the receptive field larger. 'Retinal Receptive Field' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Receptive Field Example

Let's use an example of an ON bipolar cell to look at the structure of receptive fields in the retina. The bipolar and ganglion cell receptive fields are divided into two regions: the center and the surround. The center of the receptive field is a result of direct innervation between the photoreceptors, bipolar cells, and ganglion cells. If a light spot covers the center of the receptive field, the ON bipolar cell would depolarize, as discussed above; the light hits the photoreceptor, it hyperpolarizes, decreasing glutamate release. Less glutamate leads to less inhibition of the ON bipolar cell, and it depolarizes.

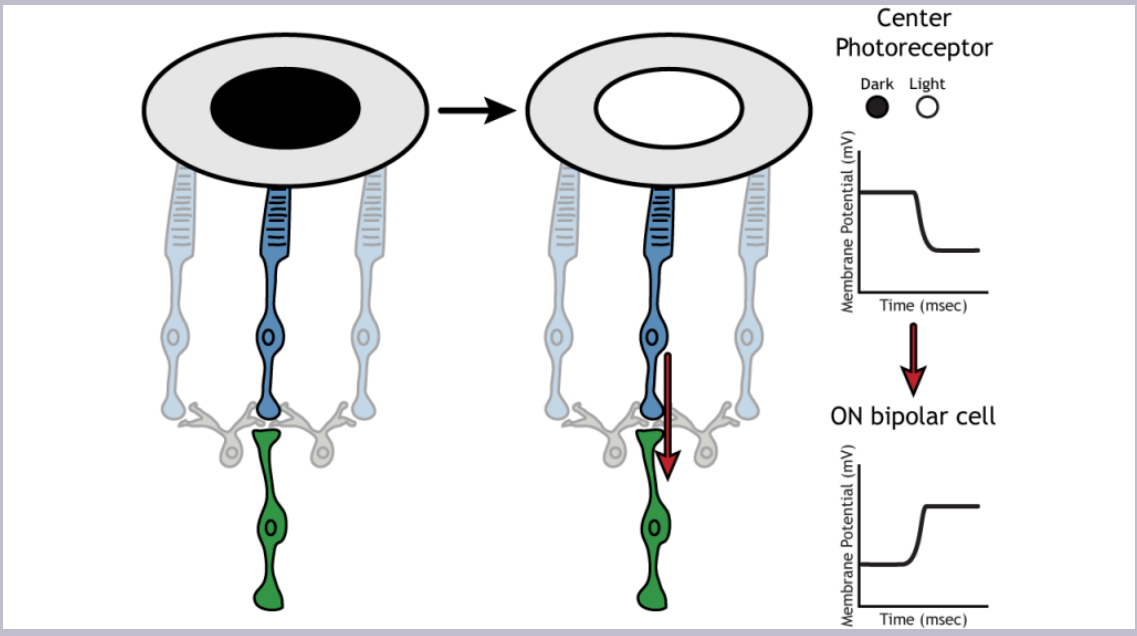


Figure 24.12. A photoreceptor in the center of an ON bipolar cell's receptive field moves from dark to light. The photoreceptor will hyperpolarize, and the ON bipolar cell will depolarize. The red arrows show the direct synaptic communication from photoreceptor to ON bipolar cell. 'Light in Center' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The surround portion of the receptive field is a result of indirect communication among the retinal neurons via horizontal and amacrine cells. The surround also has an opposing effect on the bipolar or ganglion cell compared to the effect of the center region. If a light spot covers the surround portion, the ON bipolar cell would respond by hyperpolarizing. The light would cause the photoreceptor in the surround to hyperpolarize. This would cause the

horizontal cell to also hyperpolarize. Horizontal cells have inhibitory synaptic effects, so a hyperpolarization in the horizontal cell would lead to a depolarization in the center photoreceptor. The center photoreceptor would then cause a hyperpolarization in the ON bipolar cell. These effects mimic those seen when the center is in dark. So even though the center photoreceptor is not directly experiencing a change in lighting conditions, the neurons respond as if they were moving toward dark.

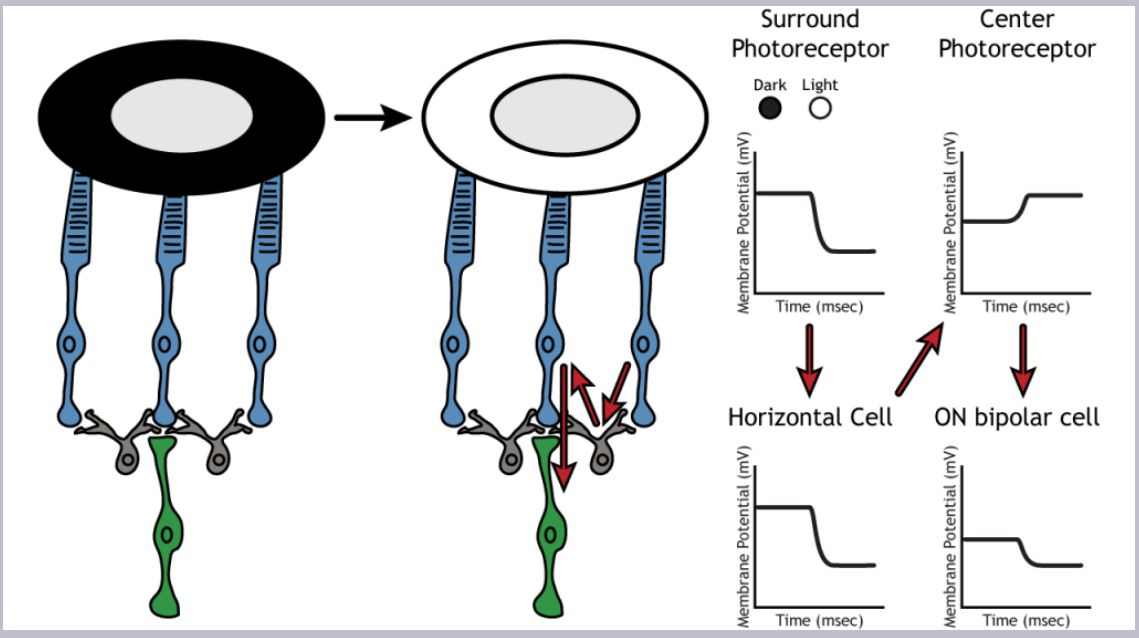


Figure 24.13. A photoreceptor in the surround of an ON bipolar cell's receptive field moves from dark to light. The photoreceptor will hyperpolarize, and the postsynaptic horizontal cell will hyperpolarize. This will cause the center photoreceptor to depolarize, and the ON bipolar cell to hyperpolarize. The red arrows show the indirect synaptic communication between the surround photoreceptor and the ON bipolar cell. The surround photoreceptor synapses on the horizontal cell, which synapses on the center photoreceptor, which synapses on the bipolar cell. 'Light in Surround' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Lateral Inhibition

Lateral inhibition is critical for the enhance perception of edges and borders

The center-surround structure of the receptive field is critical for lateral inhibition to occur. Lateral inhibition is the ability of the sensory systems to enhance the perception of edges of stimuli. It is important to note that the photoreceptors that are in the surround of one bipolar cell would also be in the center of a different bipolar cell. This leads to a direct synaptic effect on one bipolar cell while also having an indirect effect on another bipolar cell.

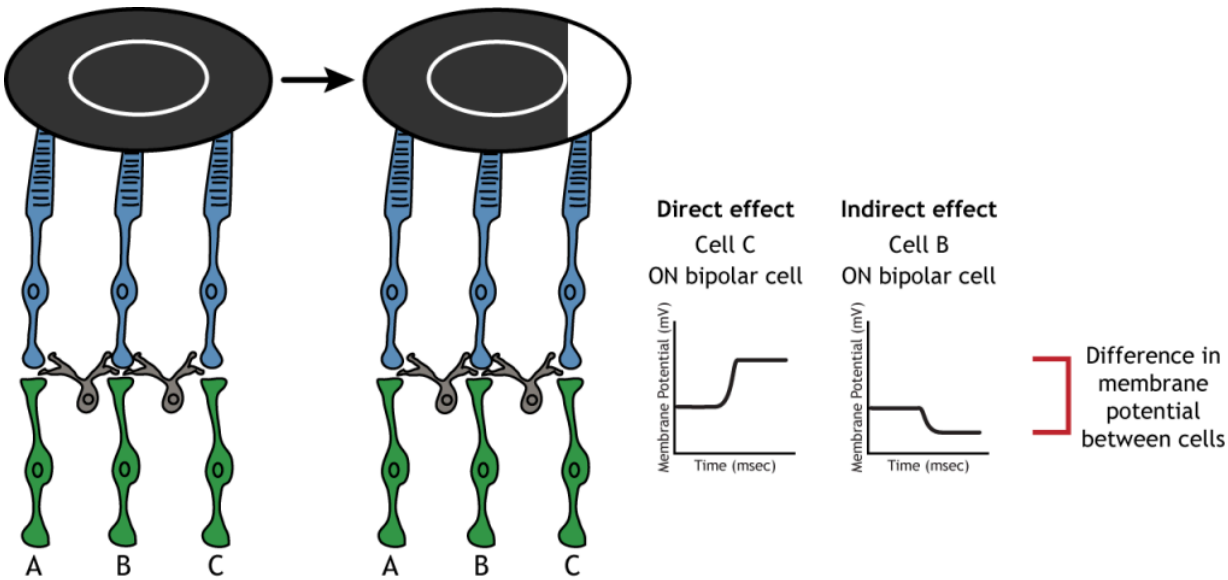


Figure 24.14. An edge of a light stimulus moves into the receptive field surround of ON bipolar cell B. This edge is also falling on the receptive field center of ON bipolar cell C. The light will cause bipolar cell C to depolarize because of the direct synapse with the photoreceptor. The light will also cause bipolar cell B to hyperpolarize because of the indirect synapses through the horizontal cell. This hyperpolarization causes a larger membrane potential difference between cells B and C that would occur if the horizontal cells were absent. The larger membrane potential difference between the cells will lead to an enhancement in the perception between the dark and light side of the edge. 'Lateral Inhibition' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Although some of the images used here will simplify the receptive field to one cell in the center and a couple in the surround, it is important to remember that photoreceptors cover the entire surface of

the retina, and the receptive field is two-dimensional. Depending on the level of convergence on the bipolar and ganglion cells, receptive fields can contain many photoreceptors.

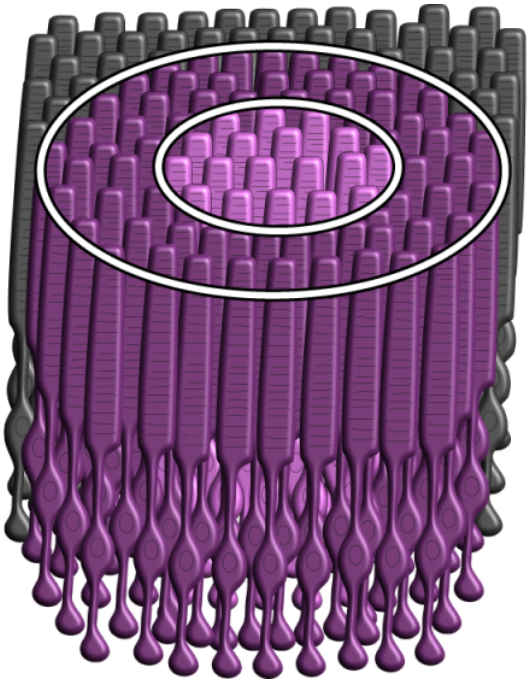


Figure 24.15. The receptive fields exist in two-dimensions along the surface of the retina. Depending on the location of the receptive field, and the amount of convergence that occurs at the bipolar or ganglion cell, the receptive field may contain many photoreceptors. 'Retinal surface' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

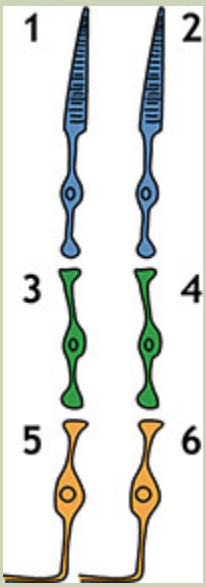
- Photoreceptors and bipolar cells do not fire action potentials
- Photoreceptors hyperpolarize in the light
- ON bipolar cells express inhibitory metabotropic glutamate receptors
- OFF bipolar cells express excitatory ionotropic glutamate receptors

- Receptive fields are circular, have a center and a surround, and vary in size
- Receptive field structure allows for lateral inhibition to occur

Test Yourself!

Try the quizzes more than once to get different questions!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=224#h5p-22



An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=224#h5p-23

- Compare and contrast rods and cones.
- Compare and contrast the fovea and the optic disc.

Video Lecture

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=224#oembed-1

Attributions

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25.

VISION: CENTRAL PROCESSING

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

Visual Fields

Before learning the pathway that visual information takes from the retina to the cortex, it is necessary to understand how the retina views the world around us. The full visual field includes everything we can see without moving our head or eyes.

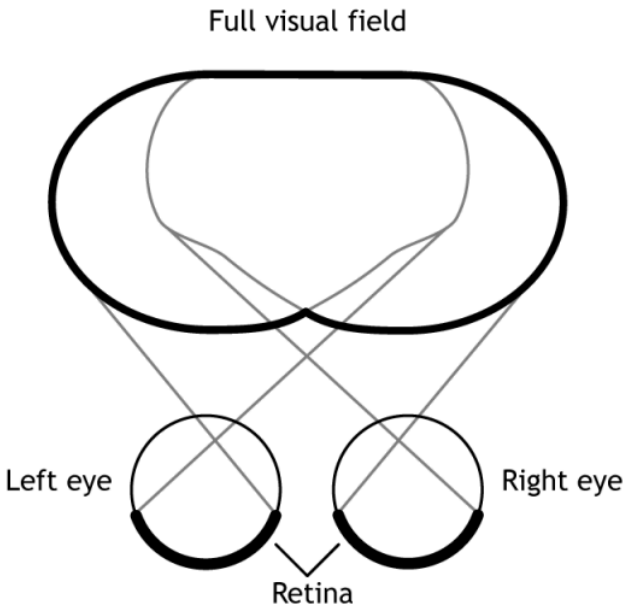


Figure 25.1. The two eyes together can view the entire visual field, which is all the visual space we can see without moving our head or eyes. 'Full Visual Field' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Visual fields can be divided in multiple ways, each dependent on different regions of the retina

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The full visual field can be divided in a few ways. Each individual eye is capable of seeing a portion of, but not the entire, visual field.

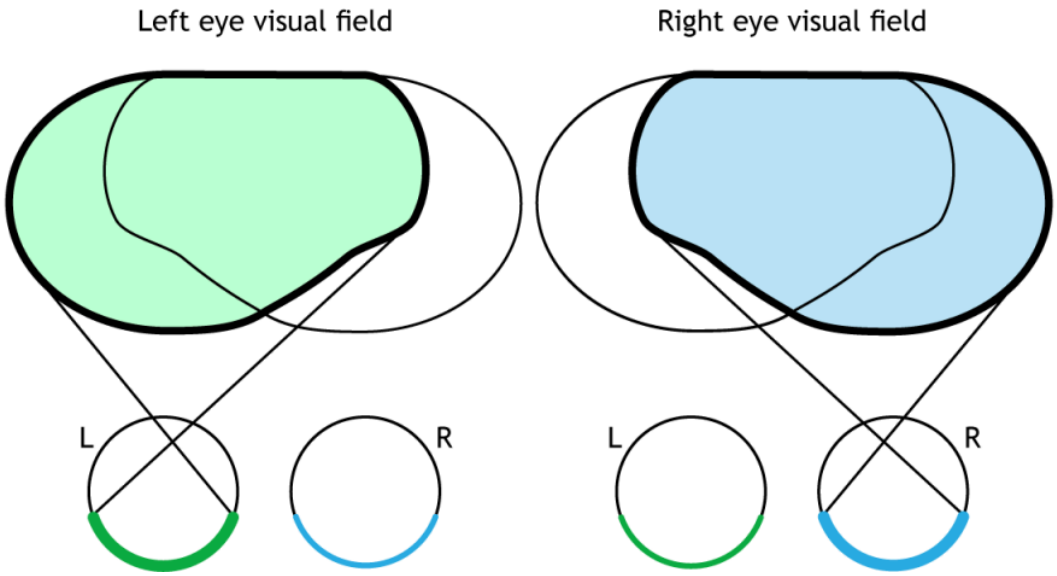


Figure 25.2. Each eye individually can view only a portion of the full visual field. 'Single Eye Fields' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The full visual field can also be divided into the right and left hemifields. The hemifields range from the most peripheral point to the center point, splitting the full visual field into two equal regions. Both eyes are involved in viewing each hemifield. The fovea separates the retina into two sections: the nasal retina and the temporal retina. The nasal retina is the medial portion that is located toward the nose. The temporal retina is the lateral portion that is located toward the temples and temporal lobe. The nasal retina from one eye along with the temporal retina from the other eye are able to view an entire hemifield.

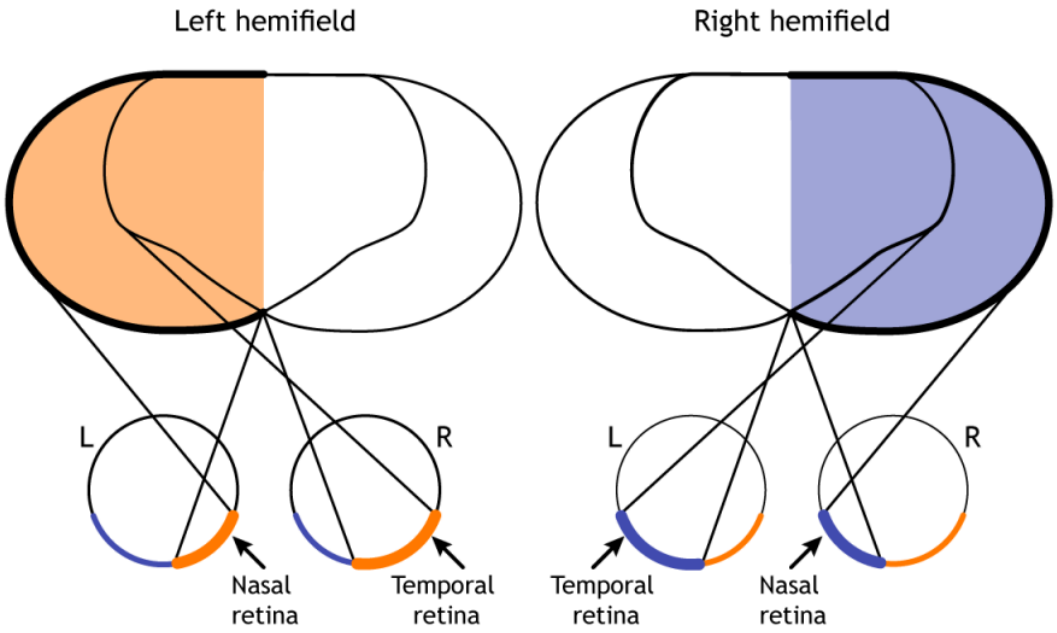


Figure 25.3. The full visual field can be divided into left and right hemifields. Both eyes contribute to viewing these regions. The nasal retina of the left eye and the temporal retina of the right eye view the left hemifield. The nasal retina of the right eye and the temporal retina of the left eye view the right hemifield. 'Visual Hemifields' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Finally, the full visual field can be separated into monocular and binocular regions. Each monocular field is visual space that can only be viewed by one eye. The binocular region is visual space that can be viewed by both eyes.

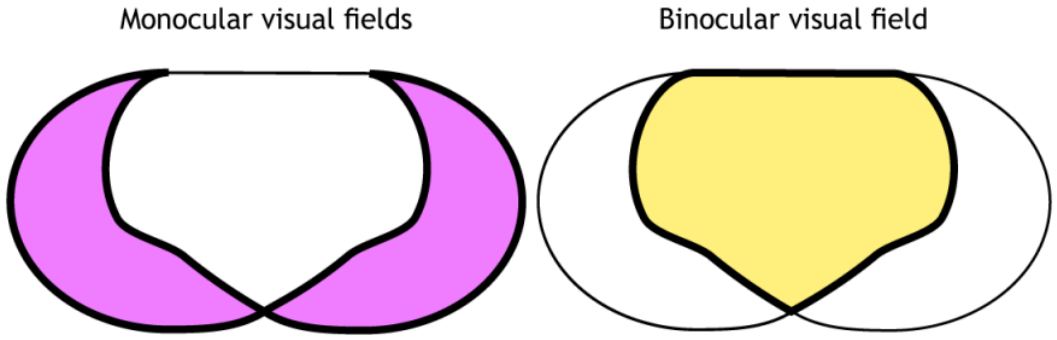


Figure 25.4. Monocular visual fields are viewed by only one eye and are located toward the periphery of the full visual field. The binocular visual field is viewed by both eyes and is located in the center of the full visual field. 'Monocular and Binocular Fields' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Pathway to Brain

The right visual field is processed by the left side of the brain; the left visual field is processed by the right side of the brain

Visual information from each eye leaves the retina via the ganglion cell axons at the optic disc, creating the optic nerve. Prior to entering the brain, axons from the nasal portion of each retina cross the midline at the optic chiasm. Since the axons from the nasal retina cross to the opposite side of the nervous system but the temporal retina axons do not, this leads to the brain processing input from the contralateral (opposite side) visual hemifield. Therefore, the right side of the brain receives visual information from the left hemifield and vice versa.

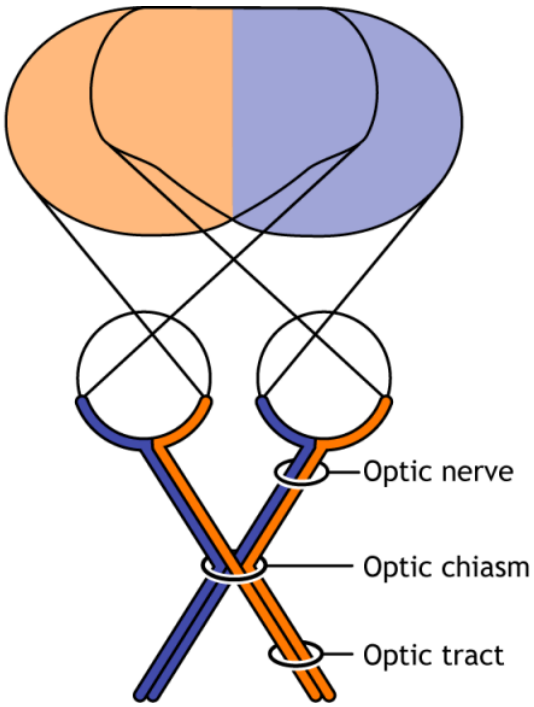


Figure 25.5. Information from each eye is carried away from the retina by the optic nerve. Information perceived by neurons in the nasal retina of each eye crosses the midline at the optic chiasm. Information from the contralateral visual hemifield then travels to the brain. 'Pathway from Retina' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the optic nerve (cranial nerve II) using the BrainFacts.org 3D Brain

The optic tract enters the brain and ascends to synapse in the lateral geniculate nucleus of the thalamus. From there, axons project to the primary visual cortex, also called the striate cortex or V1, located in the occipital lobe.

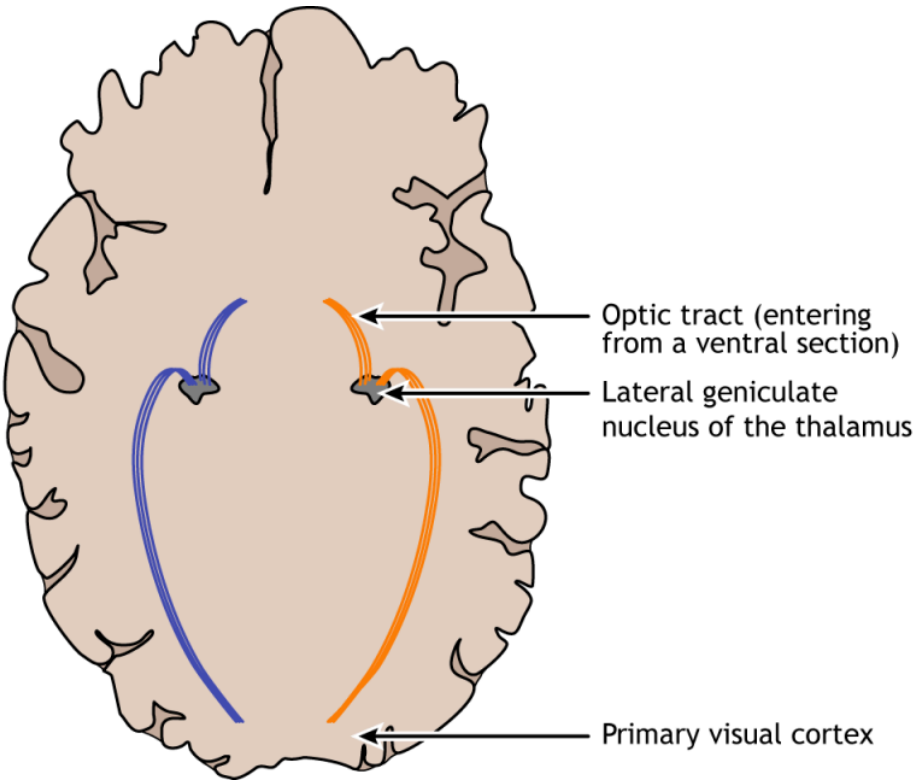


Figure 25.6. A horizontal section of the brain. The optic tract enters the brain and projects dorsally to the thalamus. Information is then sent to the primary visual cortex in the occipital lobe. 'CNS Visual Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

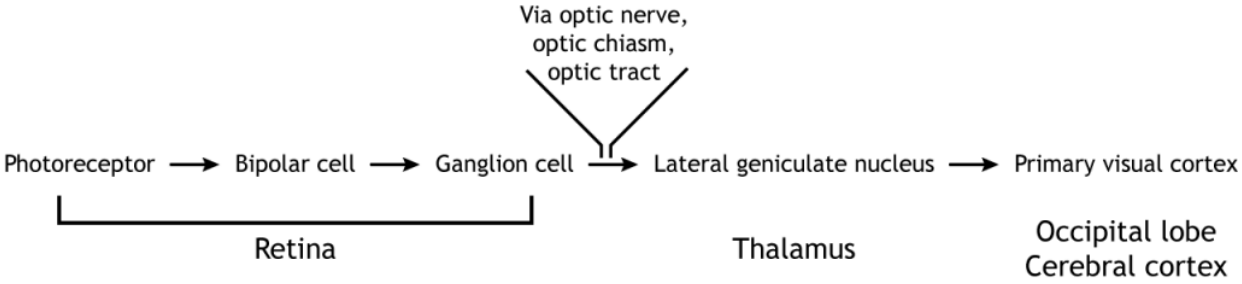


Figure 25.7. Visual information that is sent through the full visual pathway, therefore, moves from photoreceptor to bipolar cell to ganglion cell in the retina. It leaves the retina via the optic nerve, optic chiasm, and optic tract to the lateral geniculate nucleus of the thalamus and then travels to the primary visual cortex. 'Visual Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the thalamus using the BrainFacts.org 3D Brain

View the primary visual cortex using the BrainFacts.org 3D Brain

Receptive Fields

Receptive fields transition to circular to lines and then to more complex forms (like faces), orientation, and direction of movement

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As information moves from the retina to the cortex, receptive fields become larger and more complex. Receptive fields in the thalamus continue to be circular in shape like the receptive fields of the retinal neurons. However, once information reaches the primary visual cortex, these circular receptive fields combine to create receptive fields that are activated by lines.

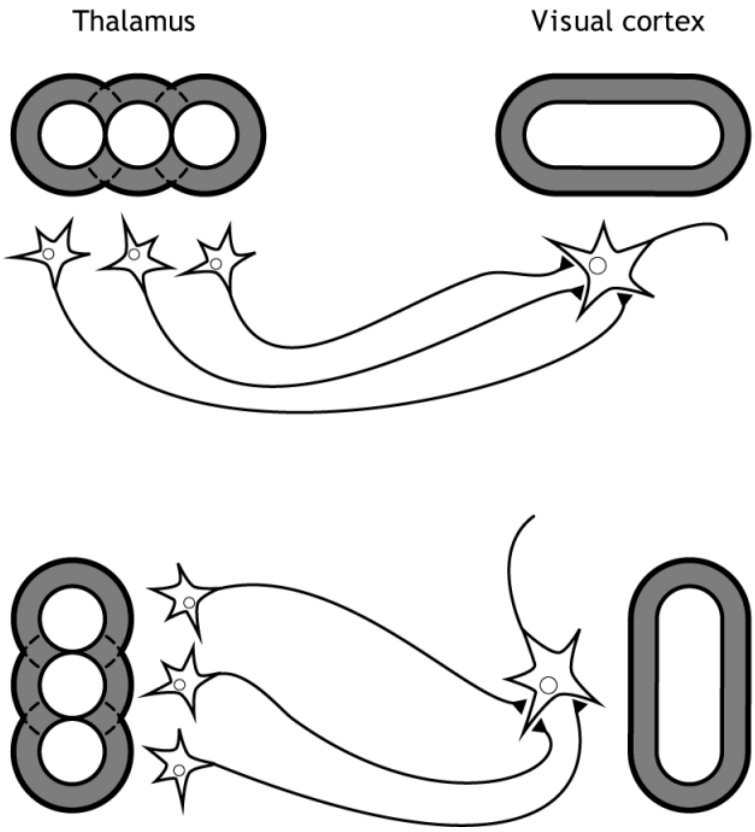


Figure 25.8. Circular receptive fields located in the thalamus combine to form straight receptive fields in the visual cortex. The orientation of the line direction in the visual cortex depends on the location of the thalamic retinal fields. 'CNS Receptive Fields' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

These receptive fields cause neurons in the primary visual cortex to respond best to a line in a specific orientation. The firing rate of the neuron will increase as the line rotates toward the "preferred" orientation. The firing rate will be highest when the line is in the exact preferred orientation. Different orientations are preferred by different neurons.

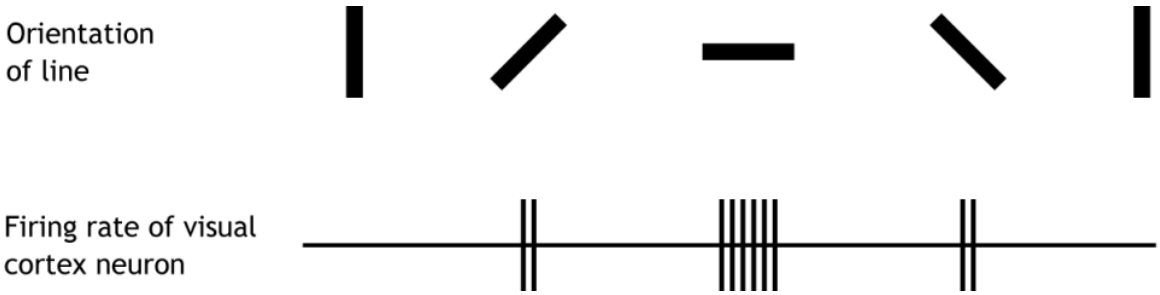


Figure 22.9. Neurons in the primary visual cortex show increased firing rates in response to a preferred line orientation. Lines rotated away from the preferred orientation will not cause activity. 'CNS Receptive Field Responses' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Higher-Level Processing of Sensory Information

Sensory system processing of input does not end upon reaching the primary sensory cortex in any sensory system. Information typically gets sent from the primary sensory cortex to other sensory association regions throughout the brain. The characteristics of sensory information becomes more complex as this higher-level processing occurs.

Post-Striatal Processing

The dorsal stream recognizes movement; the ventral stream recognizes objects

---

In the visual system, there are two broad streams of information that leave the striate cortex. Information that travels from the primary visual cortex down through the inferior temporal lobe is responsible for determining object recognition, or what an object is. Differentiating between an apple and a person occurs in this stream. Information that travels from the striate cortex up through the parietal lobe is responsible for motion or spatial components of vision.

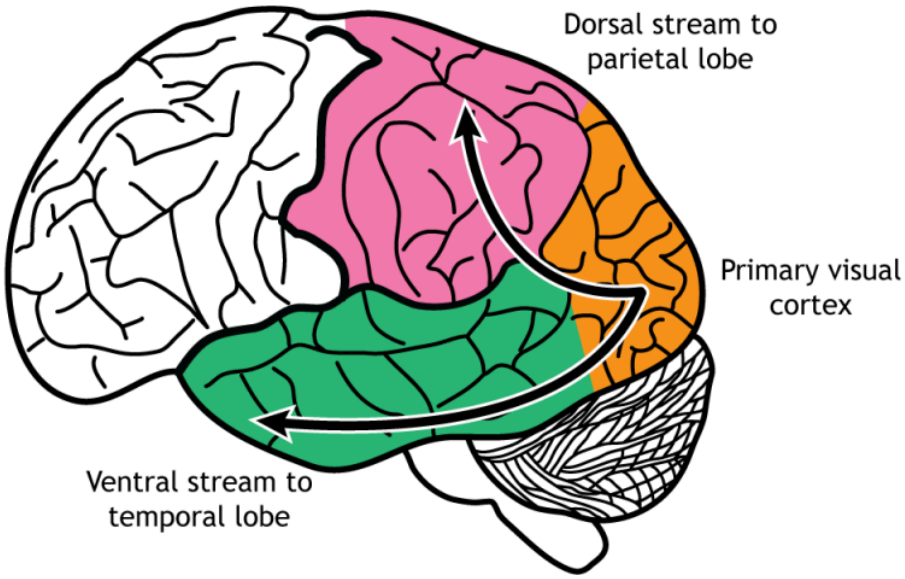


Figure 25.10. Information continues to be processed after reaching the primary visual cortex. The dorsal stream travels to the parietal cortex and is important for spatial components of vision. The ventral stream travels to the temporal lobe and is important for object recognition. 'Visual Streams' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Dorsal Stream

One of the most important regions in the dorsal pathway is region MT, also called V5. In this region, neurons are preferentially activated by a specific direction of movement by an object – for example, left to right or up to down. As an example, remember the receptive fields in the primary visual cortex were activated by lines at a specific orientation. Like that, in V5, the neurons would be activated by lines moving in a specific direction.

As information continues to be processed through the dorsal stream, the neurons become selective for more complex motions. The dorsal stream is also important for processing our actions in response to visual stimulation, for example, reaching for an object in the visual field or navigating around objects while walking.

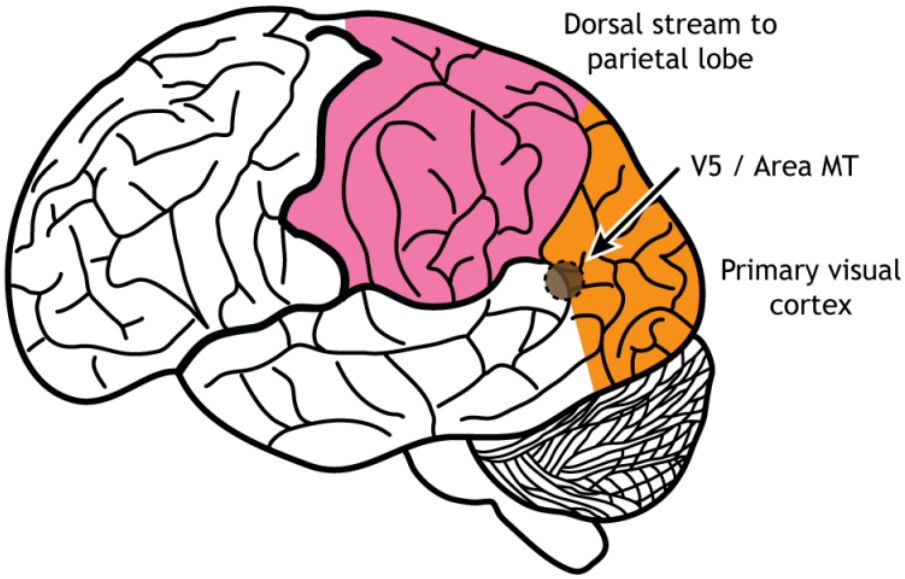


Figure 25.11. Area MT, also called V5, is an early processing region of the dorsal stream through the parietal lobe. Neurons in the region are activated by direction of an object in a specific direction. 'Area MT' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Ventral Stream

Object identification is a key function of our visual system. The ventral visual stream is responsible for this process. Like the more complex activation characteristics of region MT in the dorsal stream, neurons in Area V4 in the ventral stream show more complex receptive fields and show sensitivity to shape and color identification. As visual information continues to be processed through the inferior temporal lobe, differentiation of objects occurs. For example, in a region called the fusiform face area, located in the fusiform gyrus, which lies on the ventral aspect of the temporal lobe, neurons are activated by faces and can be specialized to one specific face.

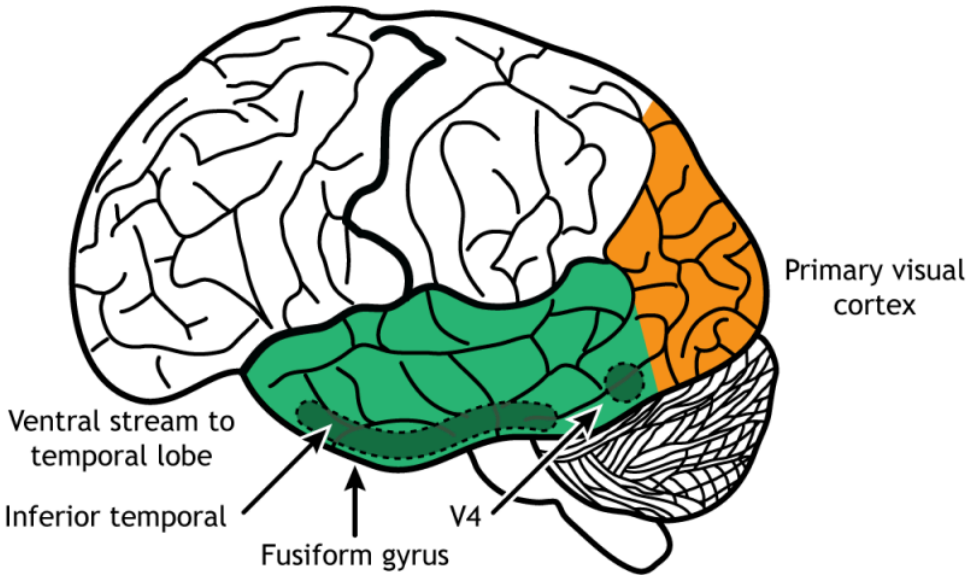


Figure 25.12. The ventral stream is first processed by area V4, which recognizes shapes and color. Information the continues through the inferior temporal lobe and sends information to regions like the fusiform gyrus, which is an area responsible for the recognition of faces. 'Ventral Stream' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The inferior temporal lobe also makes reciprocal connections with the structures in the limbic system. The limbic system plays an important role in processing emotions and memory, both of which are significant components to visual perception. The amygdala ties visual stimuli with emotions and provides value to objects. A family member will have emotional ties that a stranger will not. The hippocampus is responsible for learning and memory and helps establish memories of visual stimuli.

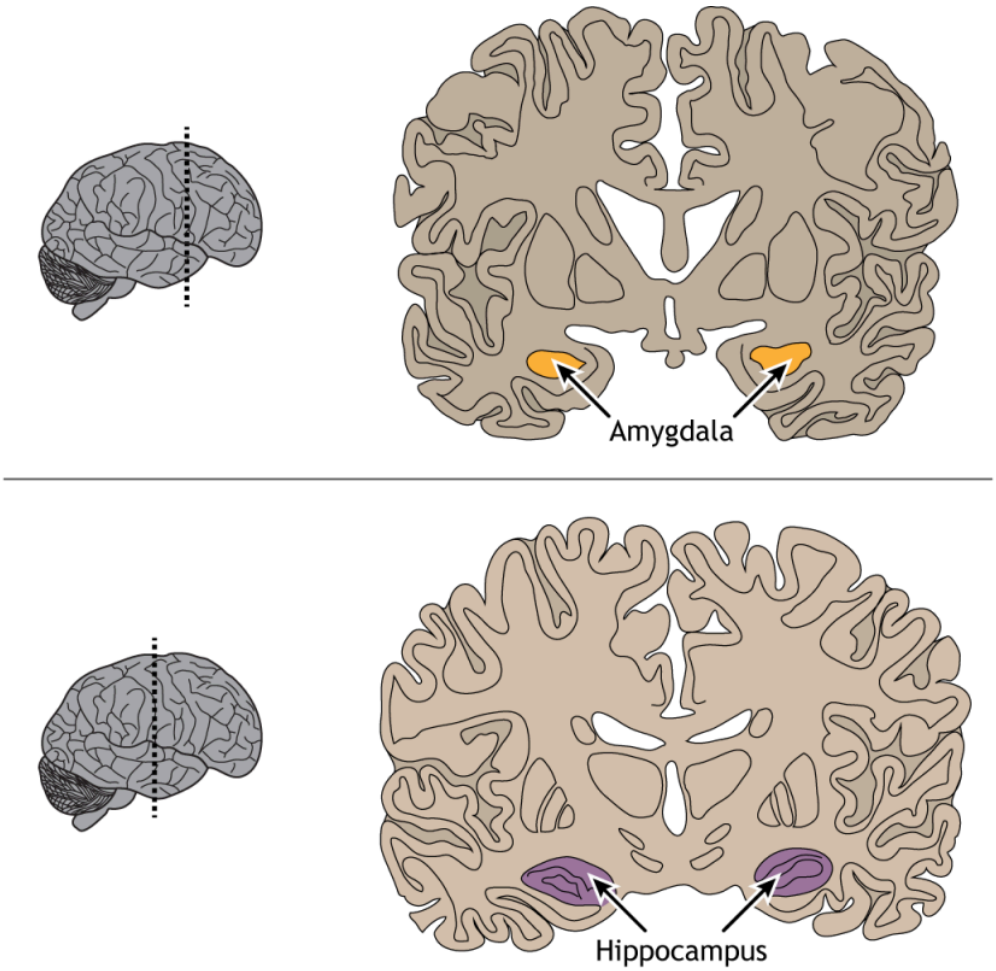


Figure 25.13. The limbic system structures, the amygdala and the hippocampus, also play important roles in visual processing. Both regions are located deep in the temporal lobe and have reciprocal connections with the ventral stream as is it moves through the temporal lobe. 'Deep Temporal Lobe' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the amygdala using the BrainFacts.org 3D Brain

View the hippocampus using the BrainFacts.org 3D Brain

Pathways through the Amygdala

The amygdala receives visual information through multiple pathways

In addition to the projections to the amygdala via the ventral stream, the amygdala also appears to rely on input from the thalamus that is independent of the ventral stream pathway. A shorter pathway travels from the retina to the amygdala via the thalamus. It is believed that this pathway allows for a rapid responses to the threats and allows visual stimuli to activate the amygdala quicker than processing through the visual cortex. In fact, studies have shown that pictures of angry or fearful faces can cause amygdala activation without conscious awareness of seeing the image, a result of images being shown for only milliseconds to the subject.

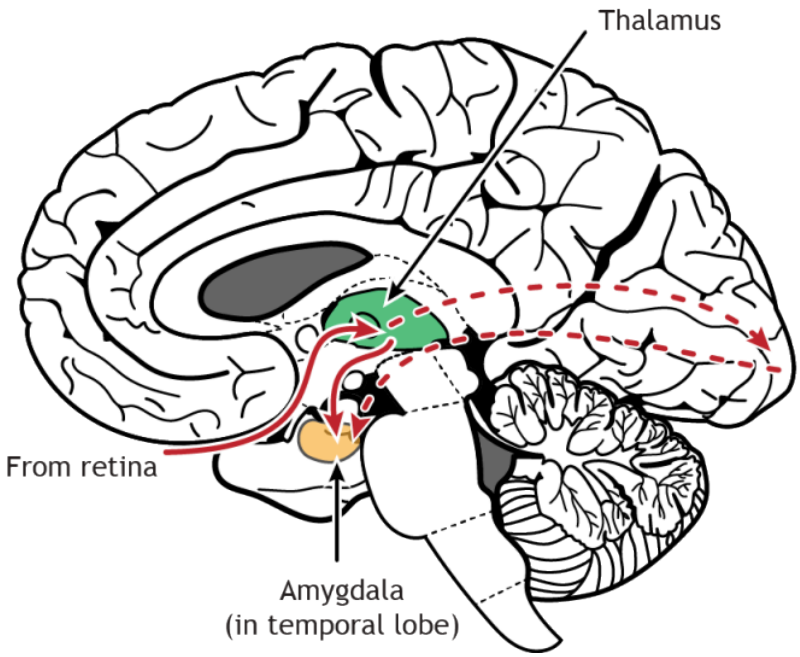


Figure 25.14. Information from the retina travels to the thalamus. From the thalamus, there is a direct pathway to the amygdala (solid red arrows) in addition to the pathway to the occipital lobe and ventral stream (dashed red arrows). 'Amygdala Visual Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Non-Thalamic Pathways

The retina sends projections to more regions than just the thalamus

Although most retinal output projects to the lateral geniculate nucleus of the thalamus and then to the primary visual cortex, there are some axons that project to other areas of the brain. A subset of specialized retinal ganglion cells project to the suprachiasmatic nucleus in the hypothalamus. This region is critical for circadian rhythms and the sleep/wake cycle. Other retinal neurons send axons to the pretectum, a midbrain region that communicates with motor nuclei and is responsible for pupillary control. Finally, other ganglion cells project to the superior colliculus, another midbrain region. This pathway is responsible for movements that will orient the head and eyes toward an object to focus the object in the center of the visual field, the region of highest visual acuity.

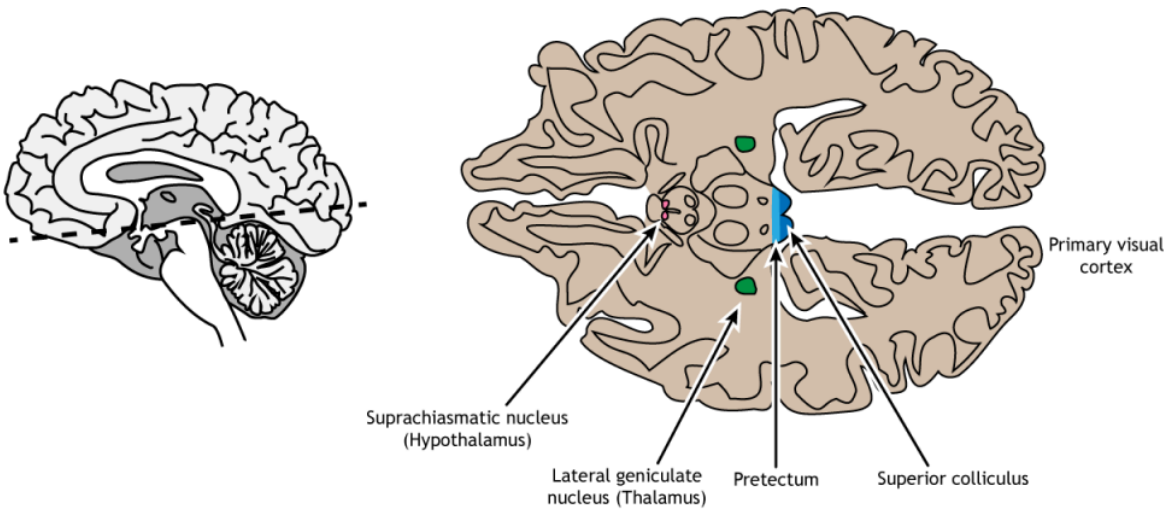


Figure 25.15. In addition to the thalamus, the retinal neurons send projections to other regions of the brain. The suprachiasmatic nucleus (pink) is located in the hypothalamus and is important for biological rhythms. The pretectum (light blue) is a midbrain structure that plays a role in muscle control of the pupil. Finally, the retina projects to the superior colliculus (blue), another midbrain region important in eye and head movements. The lateral geniculate nucleus of the thalamus (green) is also shown. 'Non-Thalamic Retinal Pathways' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the hypothalamus using the BrainFacts.org 3D Brain

View the midbrain using the BrainFacts.org 3D Brain

Key Takeaways

- The nasal and temporal retinal regions are responsible for viewing specific regions of the visual field
- Some retinal projections cross the midline at the optic chiasm, causing the left side of the brain to process the right visual hemifield and vice versa
- The retinal axons synapse in the lateral geniculate nucleus of the thalamus. Information then travels to the primary visual cortex
- Receptive fields and the preferred visual stimuli for neuron activation become more complex as information moves through the visual pathway
    - Retinal cells and thalamic neurons have circular receptive fields with inhibitory surround
    - Primary visual cortex neurons have linear receptive fields are are activated by a line in a specific orientation
    - Area MT / V5 is activated by motion in a specific direction
    - Area V4 is activated by specific shapes and colors
    - The fusiform gyrus is activated by faces
- The retina also projects to midbrain regions

Test Yourself!

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https://opentext.uoregon.edu/neurobiology/?p=241#h5p-24

Video Lecture

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Attributions

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26.

SOMATOSENSORY SYSTEMS

Resources

- Key Takeaways
- Test Yourself

The somatosensory system is regulated by receptors that are spread throughout the body and measure a number of different sensory modalities in the body. These sensations can be divided into three main divisions: external stimuli, internal stimuli , and the sense of where the body is in space.

Perception of external stimuli can include the sense of touch (via mechanoreceptors), pain (via nociceptors), and temperature (via thermal receptors). Perception of internal stimuli can include organ (visceral) sensation and pain (via multiple receptor types) and blood chemical composition (via chemoreceptors). Proprioception (via proprioceptors) is the sense of where the body is in space. The ability of an individual to touch their nose easily while their eyes are closed is an example of the proprioception system. Finally, equilibrioception is the sense of head and body orientation relative to gravity, which is mediation both via somatosensory and middle-ear receptors.

Somatosensory Cell Bodies

All somatosensory receptor neurons have their cell bodies located in the dorsal root ganglion, a structure found just outside the dorsal aspect of the spinal cord. The receptor neurons, also called primary afferent fibers, of the somatosensory system are bipolar neurons, meaning they have one process from the cell body that splits into two branches. One travels to the location of the receptor (e.g. the skin for touch) via the spinal nerves, and one travels into the spinal cord at the dorsal horn via the dorsal root. The axon can either synapse in the spinal cord or ascend to the brain in the dorsal column.

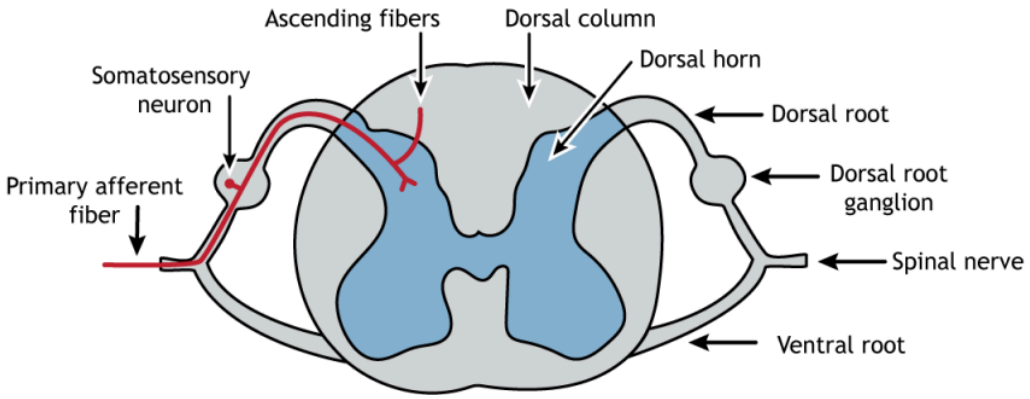


Figure 26.1. Primary afferent fibers travel from the periphery or target organs through the spinal nerve to the dorsal root ganglion where the cell body of the neuron is located. The axons then continue through the dorsal root into the dorsal horn of the spinal cord. Axons can branch and synapse in the spinal cord, or they can ascend to the brain via the dorsal column. 'Somatosensory Spinal Cord' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Primary Afferent Axons

Primary afferent axons are divided into four groups based on size and conduction speed. The groups, unfortunately, have different names depending on if the axons come from the skin (Aα, Aβ, Aδ, and C fibers; examples are touch or pain) or the muscles (Group I, II, III and IV fibers; example is proprioception). The fastest axons are the Aα or Group I type; they have the largest diameter and are heavily myelinated. The next fastest myelinated axons are the Aβ or Group II fibers, followed by the Aδ or Group III fibers. Finally, the C fibers have the smallest diameter, are unmyelinated, and are the slowest at conducting action potentials.

[table id=3 /]

Different sensory information is sent via the different types of axons. Proprioceptive information from the skeletal muscles is sent to the spinal cord via Group I fibers. Touch information from the mechanoreceptors travels along Aβ fibers. Aδ fibers carry pain and temperature sensation, and C fibers convey information about pain, temperature, itch, and chemoreception.

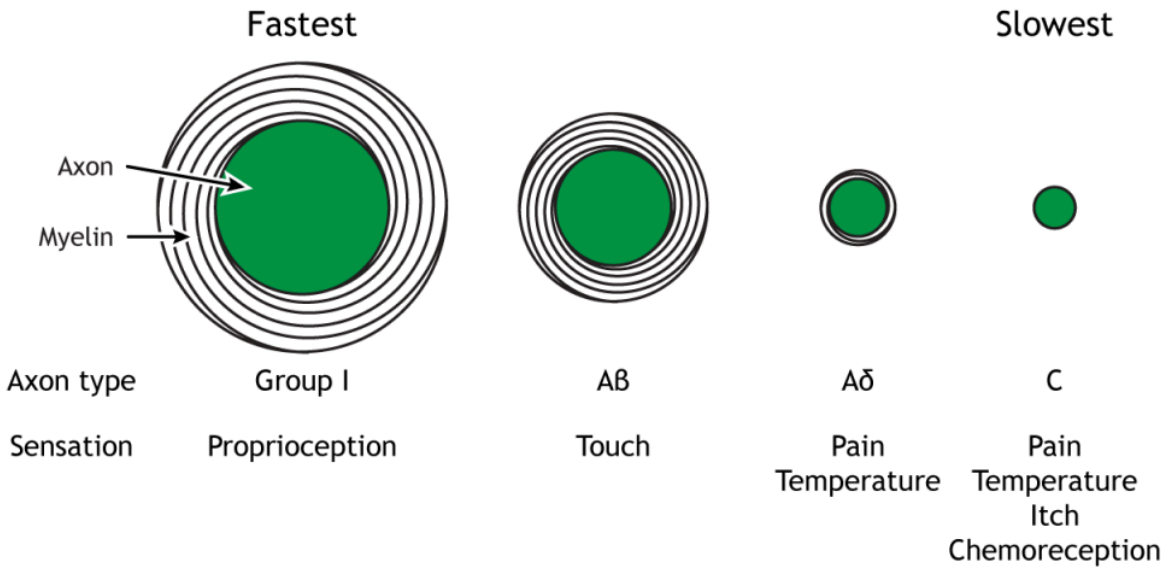


Figure 26.2. Primary afferent fibers differ in diameter and myelination, and therefore have different conduction speeds. A alpha fibers convey proprioception and are the largest and fastest of the axon types. Mechanoreception, or touch, is sent via A beta fibers, the next largest. Some aspects of pain and temperatures are sent by A delta fibers, which have small diameter and little myelination. C fibers are unmyelinated and sensory axons that detect pain, temperature, itch and chemoreception (chemical composition). These are the slowest of the somatosensory axons. 'Somatosensory Axon Types' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Dermatomes

The afferent axons from the dorsal root ganglion enter the spinal cord via the spinal nerves. Axons from nearby regions of the body enter the spinal cord together, and this forms regions of skin that are innervated by the same spinal nerve. These regions are called dermatomes. Damage to a spinal nerve will cause dysfunction along the innervated dermatome. The dermatomes and spinal nerves are divided into 4 groups. The seven cervical spinal segments are the most rostral and are located in the neck. The twelve thoracic spinal segments are located along the chest and abdomen. The five lumbar segments are located below the thoracic segments, and the five sacral segments are the most caudal.

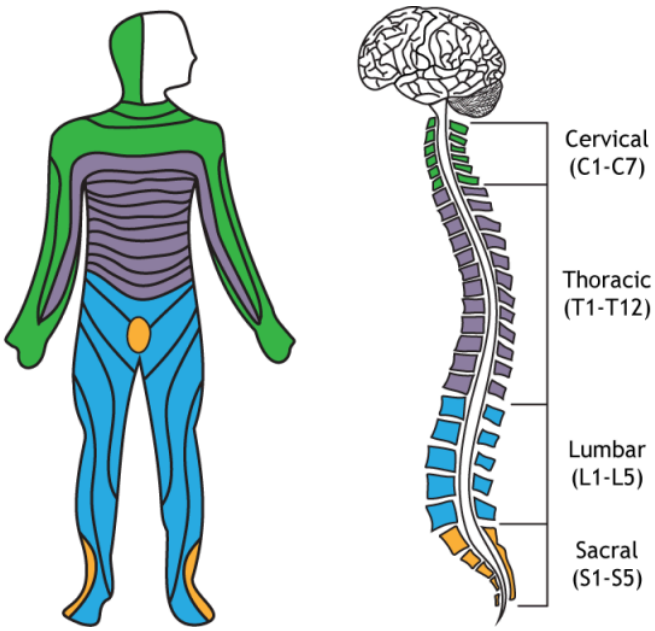


Figure 26.3. Spinal nerves exit the spinal cord and innervate a region of skin called a dermatome. There are five cervical, twelve thoracic, five lumbar, and five sacral spinal segments. 'Dermatomes' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- Somatosensory neuron cell bodies are located in the dorsal root ganglion
- Somatosensory primary afferent axons ascend to the brainstem via the dorsal column white matter tract
- Primary afferent axons vary in diameter and myelination, both of which affect action potential speed
- Different somatosensory information is carried by the different sizes afferents
- Dermatomes are the region of skin innervated by one spinal nerve

Test Yourself!

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27.

TOUCH: THE SKIN

Touch can come in many forms: pressure, vibration, stretch, motion, edges, points, etc. Receptors in the skin allow for perception of these different characteristics, and when this information is combined in the central nervous system, we are able to determine the location, strength, duration, movement, shape, and texture of the object interacting with the skin.

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

Receptors

We can feel different modalities of touch because of the presence of specialized sensory receptors, called mechanoreceptors, located in the skin.

The Pacinian corpuscles are located deep in the dermis of the skin and are responsible for perception of vibration.

Ruffini endings detect skin stretch and are also located within the dermis layer of the skin.

The Meissner corpuscles are stimulated by skin motion and are located in the epidermis layer.

The Merkel cells are located at the border between the dermis and epidermis and are specialized to detect edges and points.

Multiple types of mechanoreceptors allow for perception of different qualities of touch

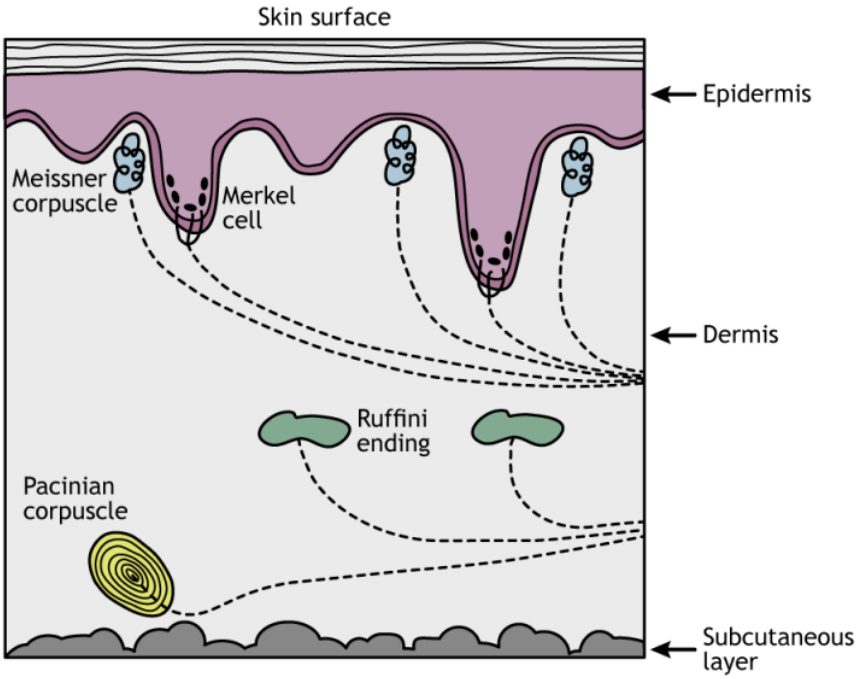


Figure 27.1. The different mechanoreceptor types are located in different regions of the skin and are responsible for perception of different characteristics of a touch timulus. Pacinian corpuscles and Ruffini endings are located deep in the dermis. Meissner corpuscles are located in the dermis near the epidermis, and Merkel cells are located in the epidermis, near the surface of the skin. 'Mechanoreceptors' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Receptive Fields

Each mechanoreceptor responds to a touch stimulus in a specific area of the skin, a region called the receptive field of the receptor. When the receptive field is touched, the mechanoreceptor will be activated.

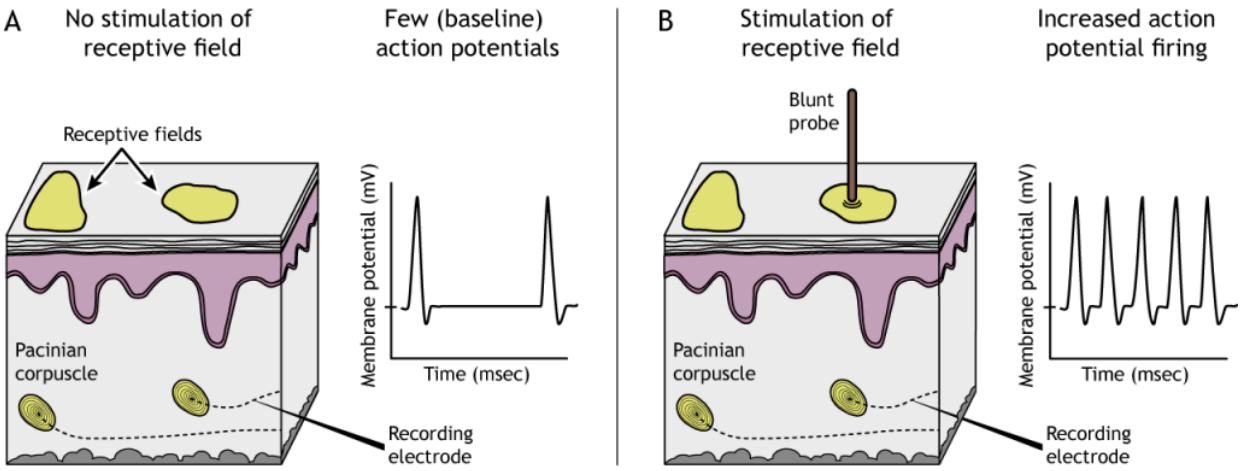


Figure 27.2. Each mechanoreceptor will be activated by a specific region of skin, the receptive field. When no stimulation of the receptive field occurs on the surface of the skin, the mechanoreceptor will show a baseline firing rate. When stimulation of the receptive field occurs, the firing rate of the mechanoreceptor will increase. 'Receptive Field Activation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Receptive field characteristics differ depending on the type of mechanoreceptor and location on the body

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Receptive Field Size

Merkel cells and Meissner corpuscles, both of which are located near the skin surface, have small receptive fields. Ruffini endings and Pacinian corpuscles, located deeper in the skin layers, have larger receptive fields than the Merkel cells and Meissner corpuscles.

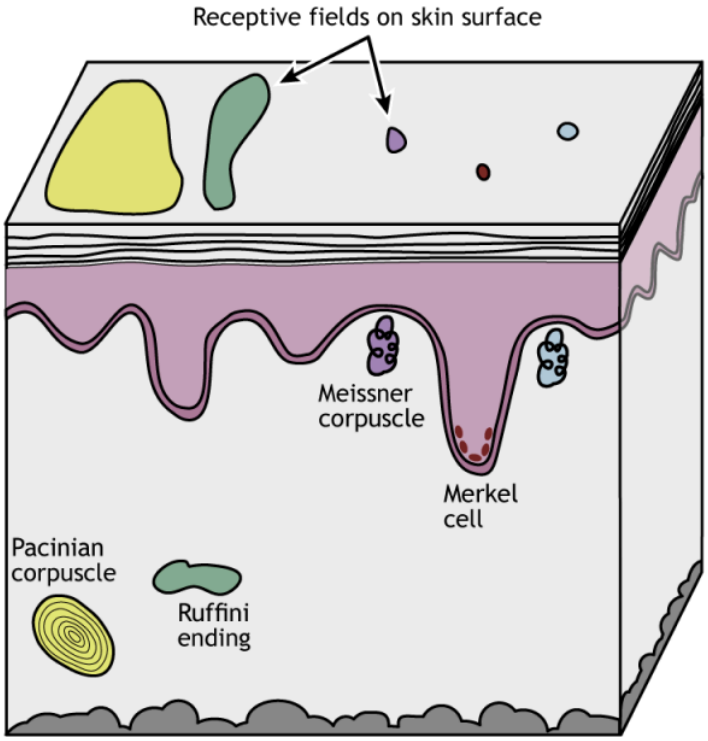


Figure 27.3. Receptive field sizes vary depending on the underlying mechanoreceptor type and location. Merkel cells and Meissner corpuscles have small receptive fields, whereas Pacinian corpuscles and Ruffini endings have large receptive fields. 'Mechanoreceptor Receptive Fields' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Receptive field sizes are different among the different mechanoreceptors, but they also vary among different body regions. Even within one receptor type (e.g. Meissner corpuscles), receptive fields in regions like the fingers or lips are smaller than in regions like the back or leg. This allows us to have finer spatial resolution with locating and identifying objects using our fingers. The smaller receptive fields in these regions are a result of a higher density of receptors in the skin.

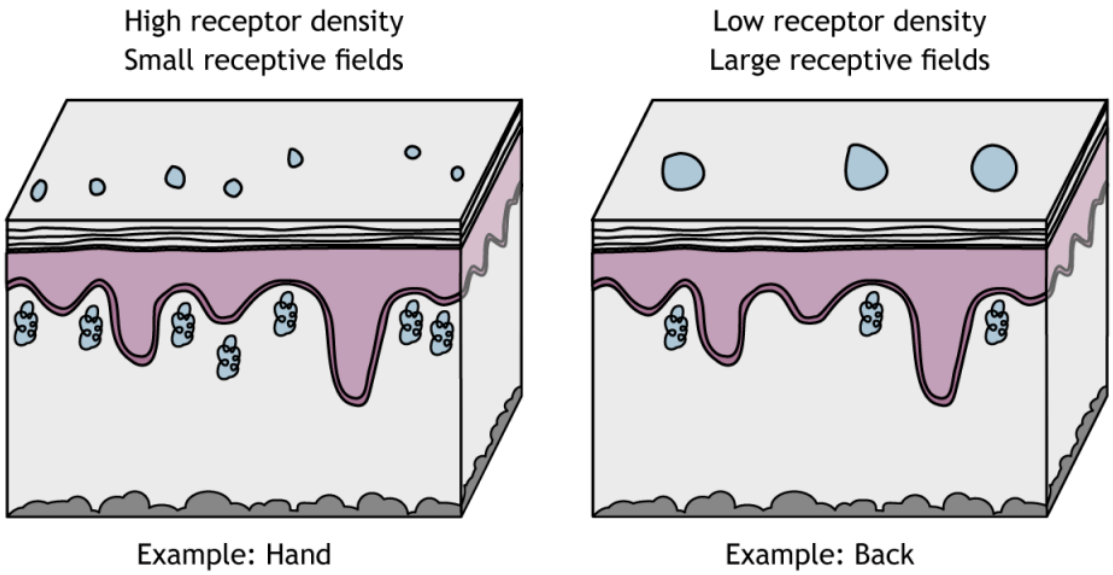


Figure 27.4. Density of mechanoreceptors can affect the size of the receptive field for each receptor. High density leads to smaller receptive fields. Density and receptive field size varies by location on the body. Regions like the hands and face have smaller receptive fields than regions like the back. 'Receptive Field Location' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Two-Point Discrimination

Receptive field sizes are important because they allow us to locate a stimulus on our bodies. Larger receptive fields are not as precise as smaller receptive fields. One measure of receptive field size is two-point discrimination (try it at home!), which determines the minimum distance needed between two stimuli to perceive two separate points on the skin and not one. The hand has a smaller threshold for discerning between two points than does the back, a result of the different sized in receptive fields.

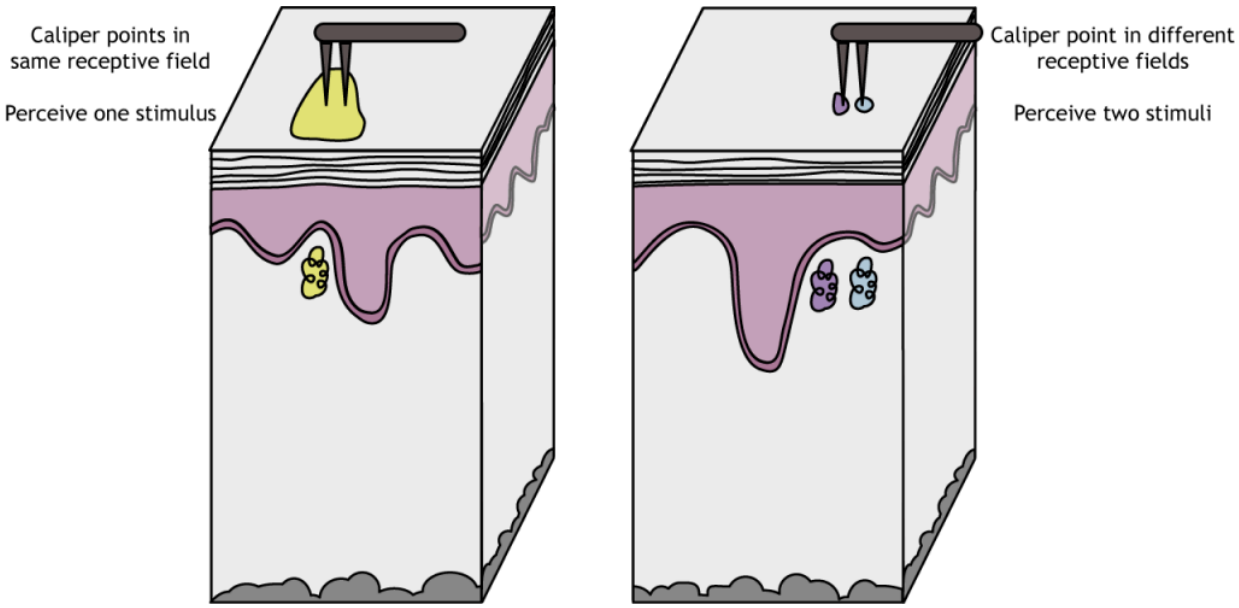


Figure 27.5. The size of the receptive fields affect the sensitivity of the skin, which can be measured by the two-point discrimination test. Tools like calipers or even a paperclip can be used to measure two-point discrimination. If the two points of the caliper feel like one point, they are both activating the same receptive field, indicating the receptive field is large. If, however, it is possible to perceive two separate points on the skin, then the calipers are activating two different receptive fields. 'Two-Point Discrimination' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Adaptation Rate

Another important characteristic of the somatic sensory receptors is that of adaptation rate. Fibers that are slowly adapting show action potential firing throughout the entire time a stimuli is present. Merkel cells and Ruffini endings are both slowly adapting fibers. Slowly adapting fibers are most useful for determining the pressure and shape of a stimulus.

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Animation 27.1. Slowly adapting mechanoreceptors continuing firing action potentials throughout the duration of a stimulus. As the stimulus moves from not present, to weak, to strong, the action potential firing of the Ruffini ending fires throughout the entire stimulus. 'Slowly Adapting Receptor' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Rapidly adapting fibers fire action potentials when a stimulus changes (e.g., starts, stops, gets stronger or weaker) but not when a stimulus is constant. This firing makes rapidly adapting fibers specialized for detecting movement and vibration. Meissner and Pacinian corpuscles are rapidly adapting.



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Animation 27.2. Rapidly adapting mechanoreceptors firing action potentials when the strength of the stimulus changes. As the stimulus moves from not present, to weak, to strong, the action potential firing of the Pacinian corpuscle only fires when the stimulus changes strength. 'Rapidly Adapting Receptor' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Sensory Transduction

In previous chapters we discussed ion channels that are gated by voltage changes in the neuron and channels that are gated by neurotransmitters. In the somatosensory system, we find ion channels that are gated by physical distortion or stretch of the membrane. These channels can open by stretch of the membrane itself or indirectly through movement of intra- or extracellular proteins that are linked to the channels. Sodium and calcium flow into the cell, causing both a depolarization and the initiation of second messenger cascades. If enough stimulus is applied, the depolarization reaches threshold of the axon and an action potential is sent toward the spinal cord.

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Animation 27.3. Mechanoreceptors respond to touch stimuli via stretch-gated non-selective cation channels. The channels can either open due to stretch of the membrane itself which stretches open the channel or due to proteins associated with the channels that pull the channel open. 'Stretch-Gated Ion Channels' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License. View static image of animation.

Key Takeaways

- There are multiple types of mechanoreceptors in the skin that are activated by different types of touch stimuli
- The receptive field size differs among the types of mechanoreceptors
- The adaptation rate differs among the types of mechanoreceptors
- Receptive field is a region of skin that activate a given mechanoreceptor
- Receptive field size for a specific type of mechanoreceptor can vary in size across the body
- Mechanoreceptors express stretch-gated non-selective ion channels that depolarize the cell during sensory transduction

Test Yourself!

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https://opentext.uoregon.edu/neurobiology/?p=256#h5p-26

- Describe the relationship between density of receptors, receptive fields, and two-point discrimination.

Video Lecture

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28.

TOUCH: CENTRAL PROCESSING

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

Receptive Fields and Lateral Inhibition

The receptive fields of the sensory neurons become more complex as information moves up the pathway. We saw in the last lesson that mechanoreceptors have receptive fields that, when touched, activate the neuron. The mechanoreceptors synapse on neurons in the dorsal column, and those neurons have more complex receptive fields. The dorsal column nuclei have receptive fields that are divided into center and surround regions. The center of the receptive field is a result of direct innervation from the mechanoreceptors. If a stimulus touches the skin in the center of a dorsal column neuron's receptive field, the neuron will increase its firing rate. The center / surround structure is like that of bipolar and ganglion cells in the vision system.

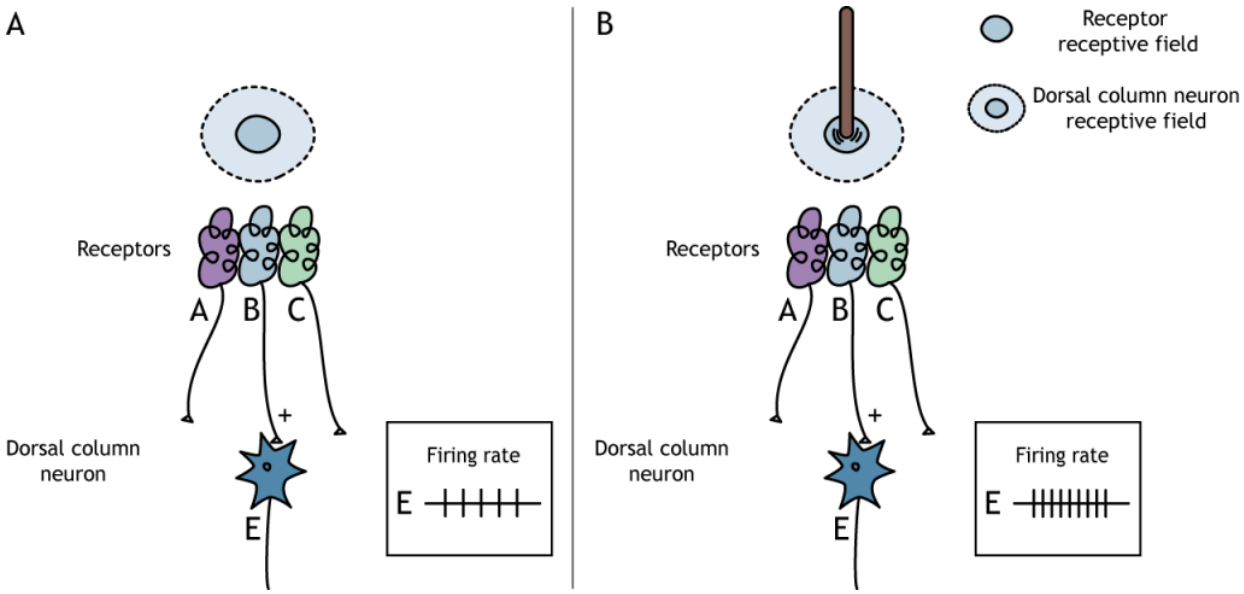


Figure 28.1. The receptive field of a dorsal column neuron has an excitatory center that is generated by the mechanoreceptors that synapse directly on the dorsal column neuron. A) When no stimulus is present, the dorsal column neuron fires at a baseline rate. B) When a stimulus touches the center of the receptive field of Cell E, the firing rate increases. 'Touch Receptive Field Center' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The surround region of the receptive field is a result of indirect communication between the receptor neurons and the dorsal column neurons via inhibitory interneurons. The surround has an inhibitory effect on the dorsal column neuron. If a stimulus touches the skin in the surround of a dorsal column neuron's receptive field, the neuron will decrease its firing rate.

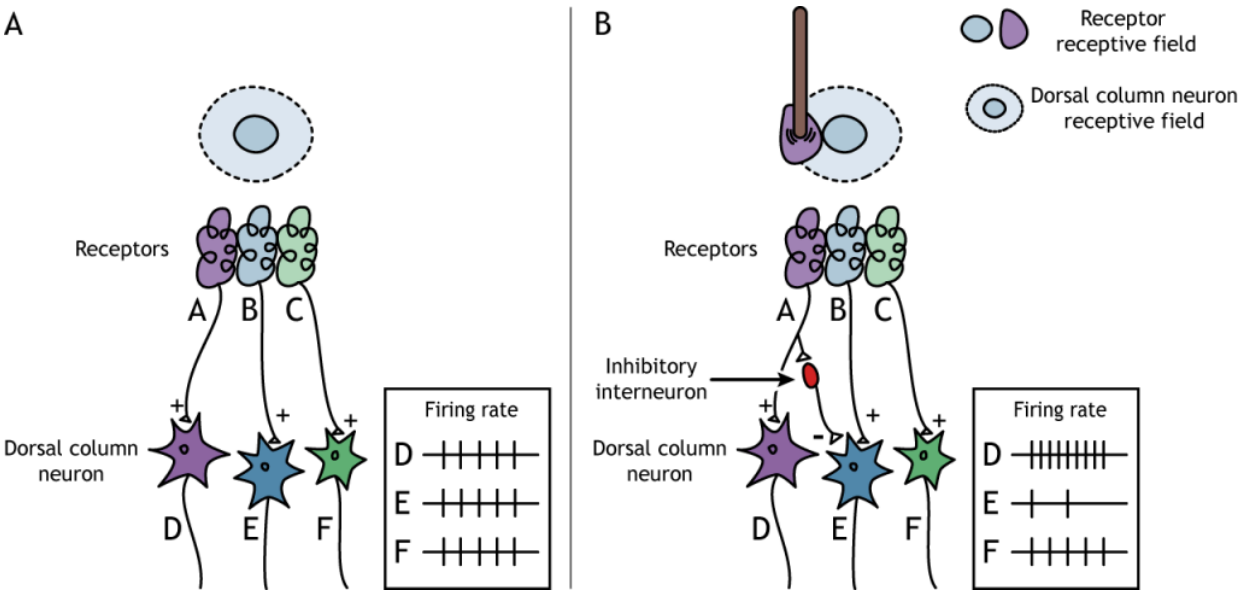


Figure 28.2. The receptive field of a dorsal column nucleus has an inhibitory surround, which is a result of the indirect connections between mechanoreceptors and the dorsal column neuron via inhibitory interneurons. A) When no stimulus is present, the dorsal column neurons fire at a baseline rate. B) When a stimulus touches the surround of the receptive field of Cell E, the firing rate decreases. Note that the stimulus is in the surround of Cell E's receptive field but is also in the center of Cell D, so the firing rate of Cell D will increase. 'Touch Receptive Field Surround' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Lateral inhibition results from overlapping receptive fields and increases perception of stimuli at edges and borders

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Lateral Inhibition

The center-surround structure of the receptive field is critical for lateral inhibition to occur. Lateral inhibition is the ability of the sensory systems to enhance the perception of edges of stimuli. At a point or an edge of a stimulus, because of the inhibitory interneurons, the perceived stimulus strength will be enhanced compared to the actual stimulus strength.

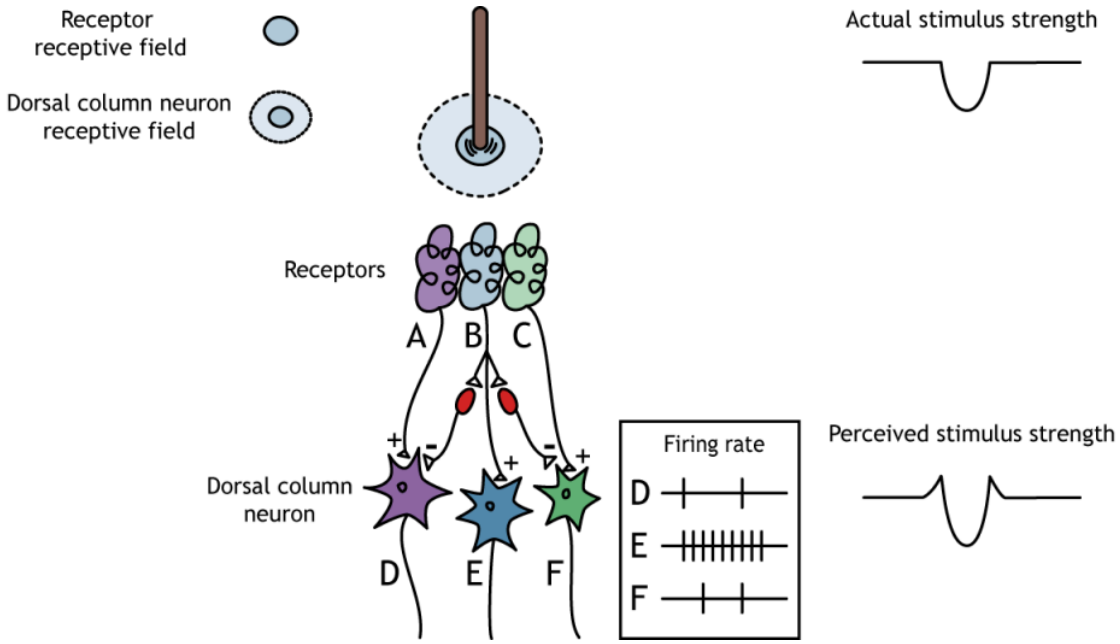


Figure 28.3. Lateral inhibition heightens the perception of edges or points on the skin. The point of a blunt probe pressing on the receptive field of Cell B will cause an increase in the firing rate of Cell E, but will also cause a decrease in the firing rate of Cells D and F. This increases the perceived difference between the point and the area next to the point that is not being stimulated. 'Touch Lateral Inhibition' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Pathway to Brain

The right side of the brain processes touch on the left side of the body; the left side of the brain processes touch on the right side of the body.

Dorsal Column-Medial Lemniscus Pathway

Primary afferent sensory fibers have their cell bodies located in the dorsal root ganglion, a structure that lies just outside of the spinal cord. The axons of these first-order neurons enter the ipsilateral

dorsal side of the spinal cord. Some axon collaterals terminate in the spinal cord and are important for reflexes. The main axon branch ascends the spinal cord toward the brain, via the dorsal column, terminating in the dorsal column nuclei located in the brainstem. The axons of sensory neurons in the lower body remain separate from the axons of sensory neurons in the upper body throughout the pathway. These two populations of neurons synapse in different regions of the brainstem. The lower body axons terminate in the gracile nucleus, whereas the upper body axons terminate in cuneate nucleus. Projections from the second-order neurons in the dorsal column nuclei cross the midline, or decussate, and ascend via a white matter tract called the medial lemniscus. The axons terminate in the ventral posterior lateral nucleus of the thalamus. The thalamic neurons then project to the primary somatosensory cortex located in the postcentral gyrus in the parietal lobe.

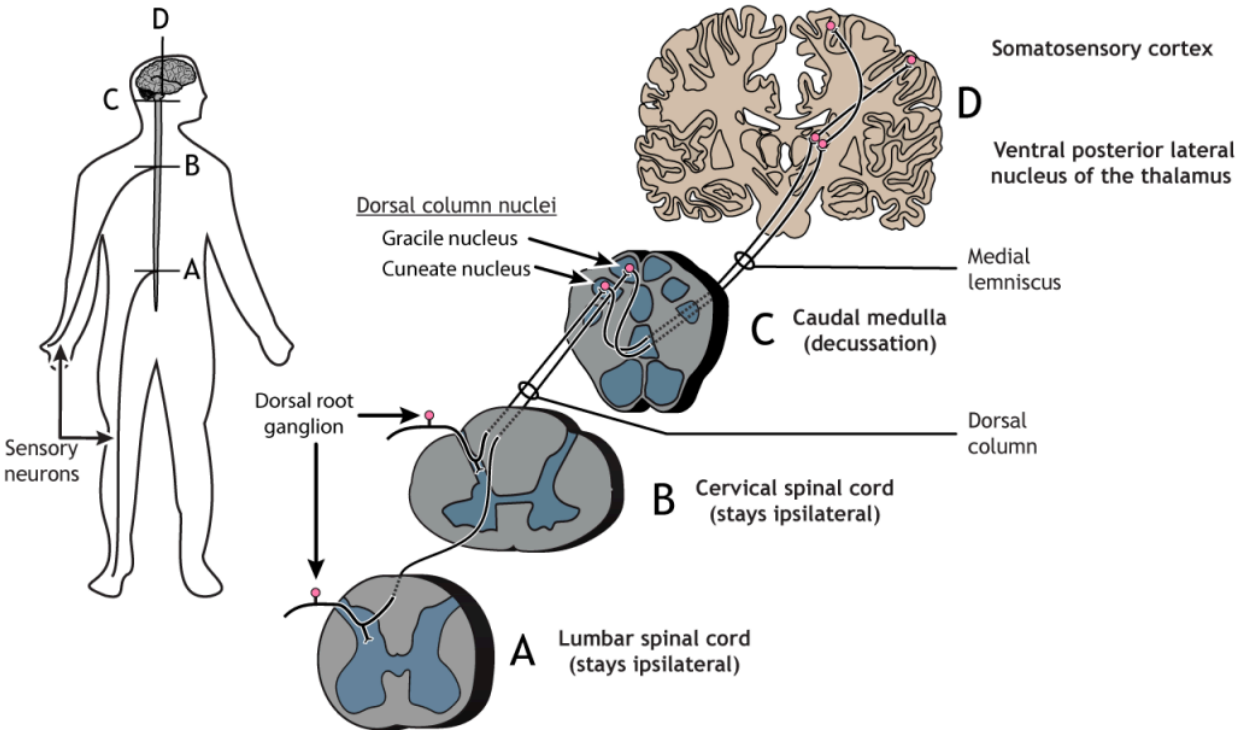


Figure 28.4 Somatosensory information from the neck and body travels through the dorsal column – medial lemniscus pathway, named for structures within the pathway. Axons enter the spinal cord and ascend through the dorsal column to the medulla where decussation, or crossing the midline, occurs. Information continues to the thalamus via the medial lemniscus, and then reaches the somatosensory cortex. Details of the pathway are found in the text. 'Touch Pathway from Body' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the thalamus using the BrainFacts.org 3D Brain

View the primary somatosensory cortex using the BrainFacts.org 3D Brain

Trigeminal Pathway

Sensory receptors in the face and head send information to the brain via cranial nerve V, the trigeminal nerve. The first-order neurons have their cell bodies in the trigeminal ganglion, located just outside of the brainstem, and they project to the ipsilateral trigeminal nucleus in the pons. The second-order neurons cross the midline and project up to the ventral posterior medial nucleus of the thalamus. These neurons then send projections to the face region of the somatosensory cortex.

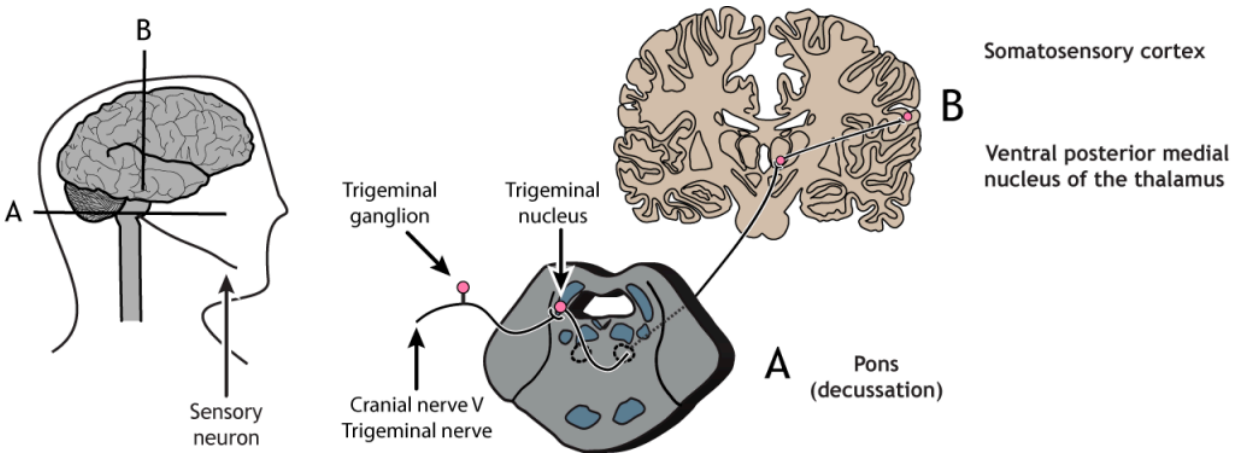


Figure 28.5. Somatosensory information from the head and face travels through the trigeminal pathway. Axons enter the brainstem at the level of the pons and decussate before traveling to the thalamus and somatosensory cortex. Details of the pathway are found in the text. 'Touch Pathway from Face' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

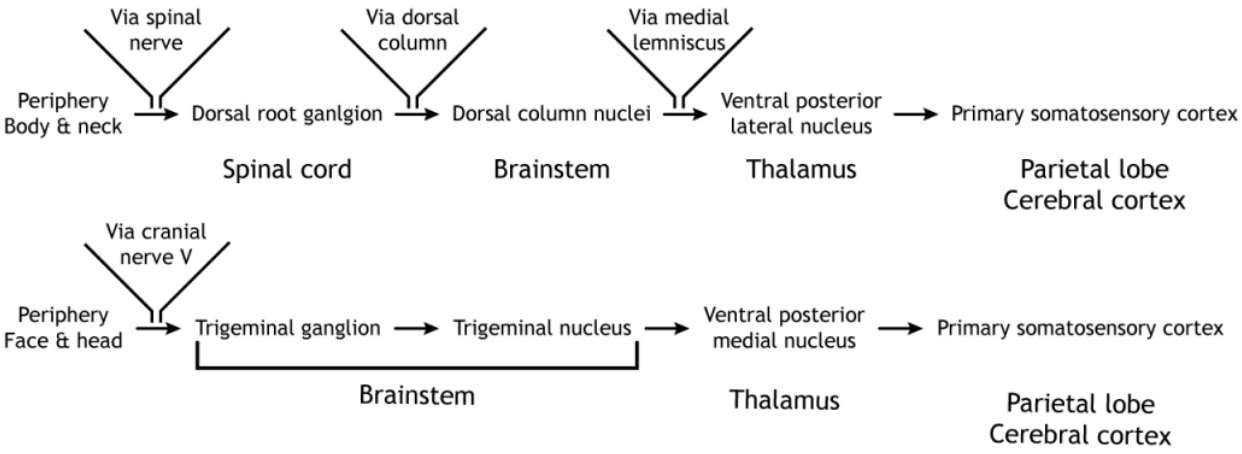


Figure 28.6. To compare the two pathways, sensory information comes in from the periphery. For the body, the peripheral axon branch travels via a spinal nerve to the cell body located in the dorsal root ganglion, which sits just outside the spinal cord. The central axon branch then enters the spinal cord and ascends via the dorsal column to the dorsal column nuclei in the brainstem. The second-order neuron crosses the midline and then projects to the ventral posterior lateral nucleus of the thalamus via the medial lemniscus tract. The thalamic third-order neuron projects to the primary somatosensory cortex in the parietal lobe. For sensory information from the face, the peripheral axon branch travels to the trigeminal ganglion via cranial nerve V. The ganglion sits outside of the brainstem, and the axons then enter the brainstem and synapse on the trigeminal nucleus. The second-order neuron travels to the ventral posterior medial nucleus of the thalamus, and the third-order neuron projects to the primary somatosensory cortex in the parietal lobe. 'Touch Pathways' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Primary Somatosensory Cortex

Anatomy

The primary somatosensory cortex is divided into four regions, each with its own input and function: areas 3a, 3b, 1, and 2. Most touch information from mechanoreceptors inputs to region 3b, whereas most proprioceptive information from the muscles inputs to region 3a. These regions then send and receive information from areas 1 and 2. As processing of somatosensory information continues, the stimuli required to activate neurons becomes more complex. For example, area 1 is involved in sensing texture, and area 2 is involved in sensing size and shape of an object. The posterior parietal cortex, an important output region of the somatosensory cortex, lies caudal to the postcentral gyrus; areas 5 and 7 are downstream structures that continue to process touch.

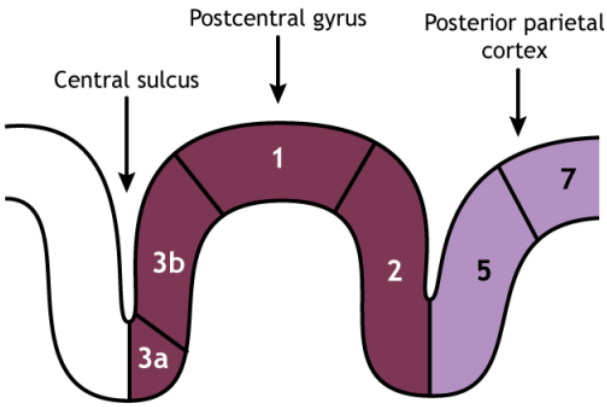


Figure 28.8. The somatosensory cortex, located in the postcentral gyrus, just posterior to the central sulcus, is divided into 4 areas: 3a, 3b, 1, and 2. The posterior parietal cortex, an output region of the somatosensory cortex, lies just posterior to the postcentral gyrus and is divided into areas 5 and 7. 'Postcentral Gyrus' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Somatotopic Map

Information from the skin is organized into a map of the body on the primary somatosensory cortex

The receptive fields of each higher order neuron increases in size and complexity, but even cortical neurons are associated with a specific region of the body. Cortical neurons are organized by the region of the body they represent, so neurons that respond to sensation in the fingers are located close to the neurons that respond to sensation in the hand. Remember from above that axons in the dorsal column from the lower body run next to, but remain separate from, the axons from the upper body. This separation, which occurs for all body regions and at all levels of the pathway, creates a somatotopic map of the body in the primary somatosensory cortex. Each area of the somatosensory cortex (Figure 23.7) has its own, but similar, map of the body.

Regions with high receptor density in the skin, and, therefore, fine two-point discrimination, have more cortical space devoted to them. This means that the cortical representation of the body is not

true to actual physical proportions. A homunculus is a cartoon representation of what a body would look like if actual body size was proportional to the cortical representation. The hands and lips would be excessively large while the torso, arms, and legs, would be relatively small.



Figure 28.8. The body is mapped onto the somatosensory cortex. Regions with high touch sensitivity, and therefore high mechanoreceptor density, have more cortical space dedicated to their processing. The feet and legs are represented in the medial superior region of the cortex; the face is represented on the lateral side of the cortex; the hand and fingers fall in between. 'Somatotopic map' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Higher-Level Processing of Touch Information

The primary somatosensory cortex sends projections to other parietal lobe regions for higher-level processing of touch information.

Secondary Somatosensory Cortex

The secondary somatosensory cortex (SII) is located in the inferior parietal lobe, just above the lateral fissure. This region, like the dorsal stream of visual processing, is responsible for object recognition,

discerning texture, shape, and size. The SII also has receptive fields that represent bilateral regions of the body, so both hemispheres will be activated by touch on either side of the body. The SII sends projections to the posterior parietal cortex, the premotor cortex, the amygdala, and the hippocampus.

Posterior Parietal Cortex

The posterior parietal cortex recognizes touch characteristics like orientation and movement. It is also important for combining the touch and motor components of actions like grasping. The posterior parietal cortex outputs to the frontal motor cortex.

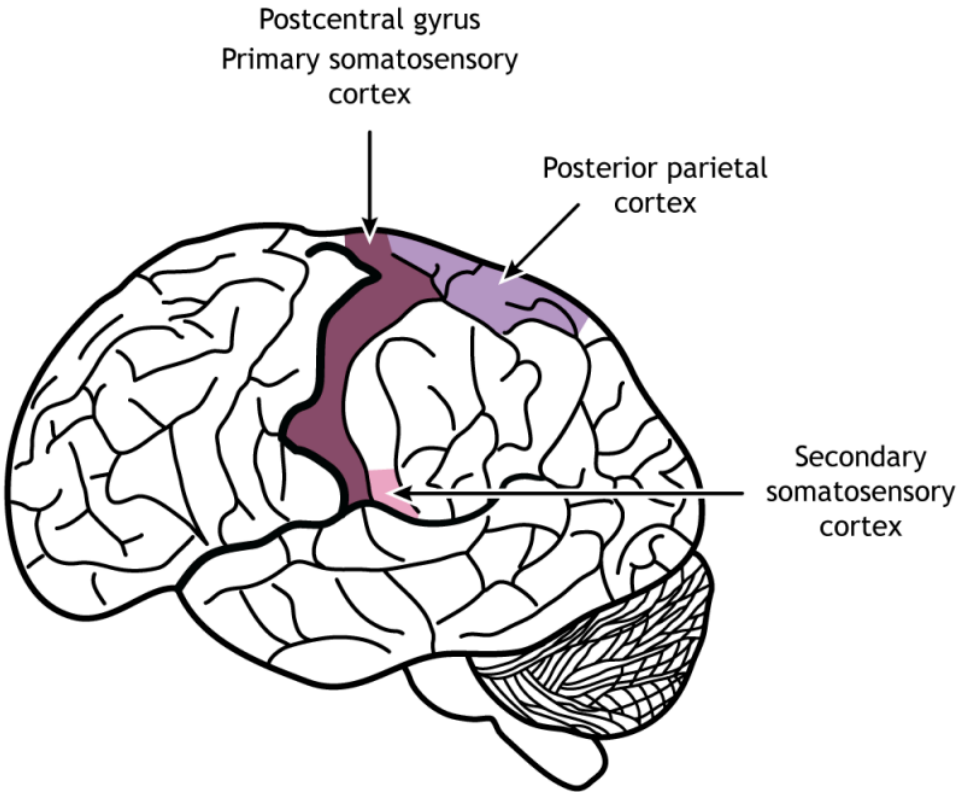


Figure 28.9. The primary somatosensory cortex is located in the postcentral gyrus. The posterior parietal cortex regions important for somatosensory lie caudal to the postcentral gyrus in the superior parietal lobe. The secondary somatosensory cortex is located dorsal to the lateral fissure, caudal to the postcentral gyrus. 'Somatosensory Streams" by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the posterior parietal cortex using the BrainFacts.org 3D Brain

Cortical Plasticity

The brain can show plasticity when sensory input changes over time

In adulthood, the brain is plastic, meaning synaptic connections can rearrange under certain conditions. Amputation or loss of a finger, for example, will lead to the associated cortical space to be functionally remapped by input from neighboring regions of the hand. The cortical neurons do not die, they begin to be activated by a different region of the body. Likewise, cortical representation can expand with use or practice. Repeated training of certain fingers can lead to an increase in cortical space mapped to those digits. Cortical plasticity is believed to underly the phenomenon of the perception of phantom limbs after amputation. In these cases, subjects that have lost a region of their body can sometimes still "feel" the missing part.

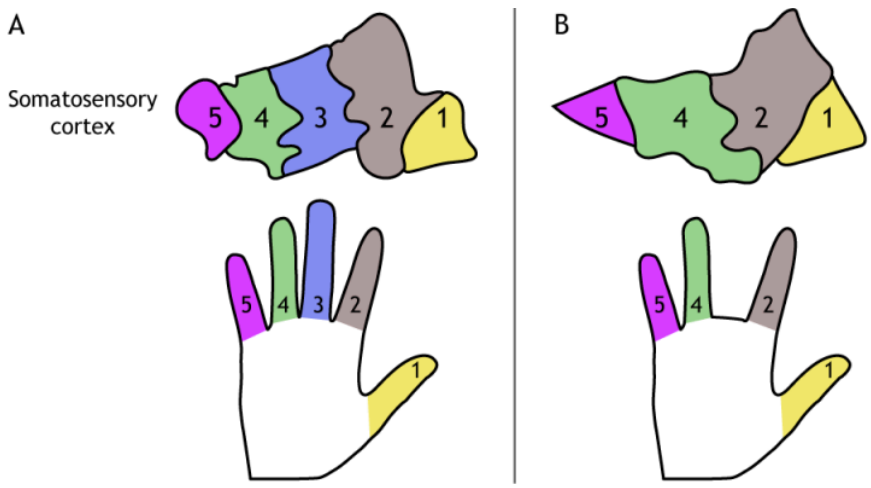


Figure 28.10. It is possible to map cortical space to regions of skin. A) The cortical space mapped to each finger for an imaginary individual is shown as an example. B) If this individual were to lose a finger, in this case digit 3 or the middle finger, and the cortical space was remapped after time had passed, the region that had once responded to touch on digit 3 would instead respond to touch on either digit 2 or 4. The brain does not let that cortical space die or go to waste; it rearranges connections to make use of all the neurons. Based on Merzenich et al., 1984. 'Cortical Plasticity' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- Receptive fields become more complex as information moves through the touch pathway
- Lateral inhibition enhances edges and borders by affecting the perceived stimulus strength
- Mechanoreceptor afferents synapse in the dorsal column nuclei in the medulla. Information then decussates and synapses in the ventral posterior nucleus of the thalamus before traveling to the primary somatosensory cortex
    - Sensory axons from the lower body synapses in the gracile nucleus in the dorsal column
    - Sensory axons from the upper body synapses in the cuneate nucleus in the dorsal column
    - Information from the neck and body synapse in the ventral posterior lateral nucleus of the thalamus
    - Information from the head and face synapse in the ventral posterior medial nucleus of the thalamus
- The primary somatosensory cortex is organized in a somatotopic map
- The cortex is plastic and connections can change with experience

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=268#h5p-27

- What is the anatomical name of the primary somatosensory cortex?
- After somatosensory information leaves the brainstem, it must relay through which structure before reaching the primary somatosensory cortex?

Video Lecture

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=268#oembed-1

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29.

PAIN

Pain or **nociception** is the sensation we feel in response to activation of special branching, bare nerve endings called **nociceptors**. Activation of nociceptors usually occurs in response to tissue damage or the threat of damage. Depending on the type of stimulus, either lightly myelinated Aδ fibers or unmyelinated C fibers transmit information to the CNS. Nociceptors are located throughout the body in skin, muscles, and viscera, but there are no nociceptors in the CNS.

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

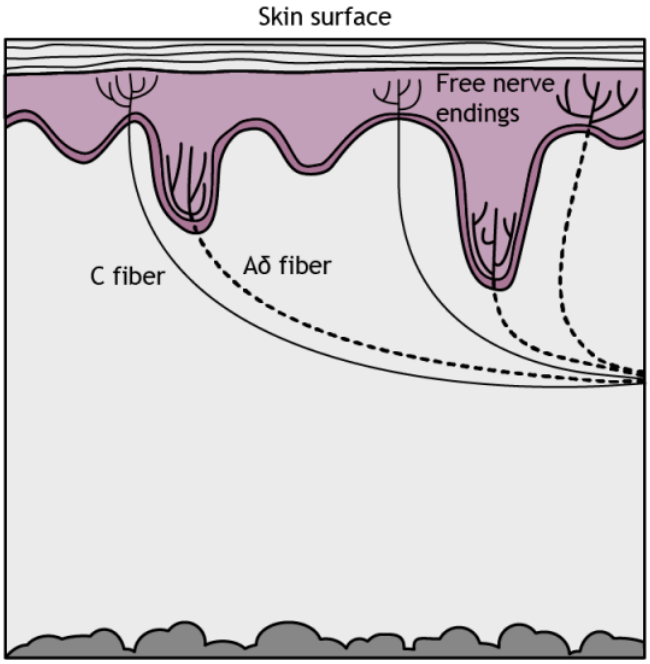


Figure 29.1. Free nerve endings in the skin and other tissues respond to tissue damage. Activation of these nociceptors lead to perceived pain sensation. Nociceptor fibers can either by unmyelinated (C fibers) or lightly myelinated (A delta fibers). 'Nociceptors' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Receptors

The type of pain perceived depends on which receptor type is activated.

There are three types of nociceptors that are each activated by different types of harmful stimuli. Type Aδ I fibers have a low threshold for mechanical stimulation, such as intense pressure or an incision on the skin. Type Aδ II fibers have a low threshold for thermal stimulation and activate in extremely hot or extremely cold environments. Type C fibers tend to be polymodal or activated by a range of stimuli including mechanical, chemical, and thermal.

The Aδ and C fibers transmit information to the CNS at different speeds because of their different myelination levels. We can often perceive this difference in the form of "first pain" and "second pain". Think about a time where you were injured, perhaps you hit your thumb with a hammer. Immediately, you might have felt an intense, sharp pain – first pain, but then a milder, burning or aching pain that continue longer – second pain. A delta fibers are responsible for first pain transmission whereas C fibers are responsible for second pain transmission.

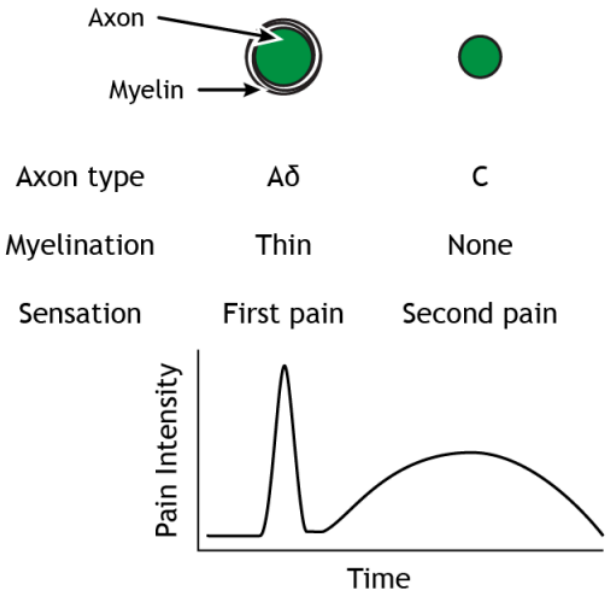


Figure 29.2. Aδ pain fibers have thin myelination, whereas C fibers have none. This allows Aδ fibers to transmit information to the CNS faster, resulting in the perception of the sharp, first pain after an injury. C fibers transmit information slower, causing the dull, aching, second pain perception. 'Pain fibers' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Pain Transduction

Like the other sensory systems, specialized proteins in the cell membrane of nociceptors convert noxious stimuli into electrical potentials in the neurons. A family of ion channels called transient receptor potential (TRP) channels can be expressed in the nociceptor nerve endings and have been shown to be activated by thermal and chemical components. For example, TRPV1, a non-selective cation channel found in nociceptors, can be activated by temperatures above 45 degrees C and can

also be activated by a chemical in hot peppers called capsaicin. Another family of receptors called Piezo is believed to be responsible for some mechanical pain transduction.

Once depolarization occurs in response to a painful stimulus, action potential propagation depends on the action of voltage-gated sodium and potassium channels. Lidocaine, a common local anesthetic, dulls pain by blocking these voltage-gated sodium channels, preventing signal transmission. A special type of sodium channel, Na1.7, is present only in nociceptor fibers. A mutation in this ion channel that prevents it from functioning can results in the inability to feel pain.

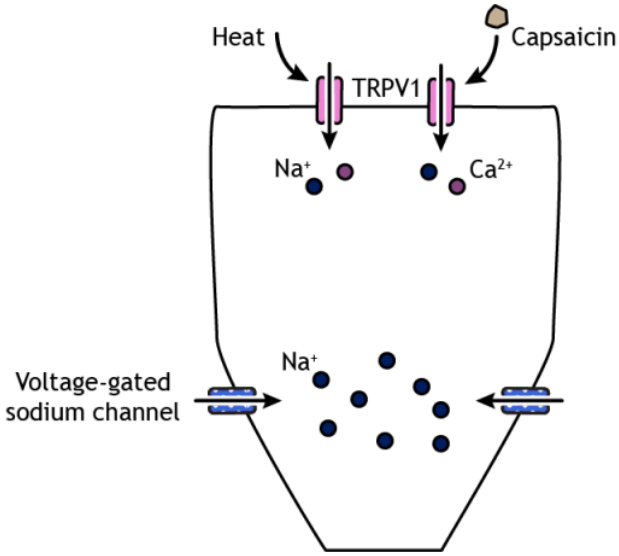


Figure 29.3. Pain transduction occurs when specialized ion channels that open in response to harmful stimuli cause depolarization and eventually activation of voltage-gated sodium channels, initiating the action potential. Different channels are responsive to different stimuli. Here, the TRPV1 channel can allow influx of sodium and calcium when opened by either heat or capsaicin, the molecule responsible for the perception of heat when eating hot peppers. 'Pain Transduction' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Pathway to Brain

Spinal Cord Branching

Primary afferent pain fibers have their cell bodies located in the dorsal root ganglion, like the fibers of the mechanoreceptors responsible for touch. The axons of these first-order neurons enter the

ipsilateral dorsal side of the spinal cord, and then they branch and travel up and down the spinal cord a couple of segments in a white matter region of the spinal cord just posterior to the dorsal horn called Lissauer's tract. All the branches terminate in the dorsal horn.

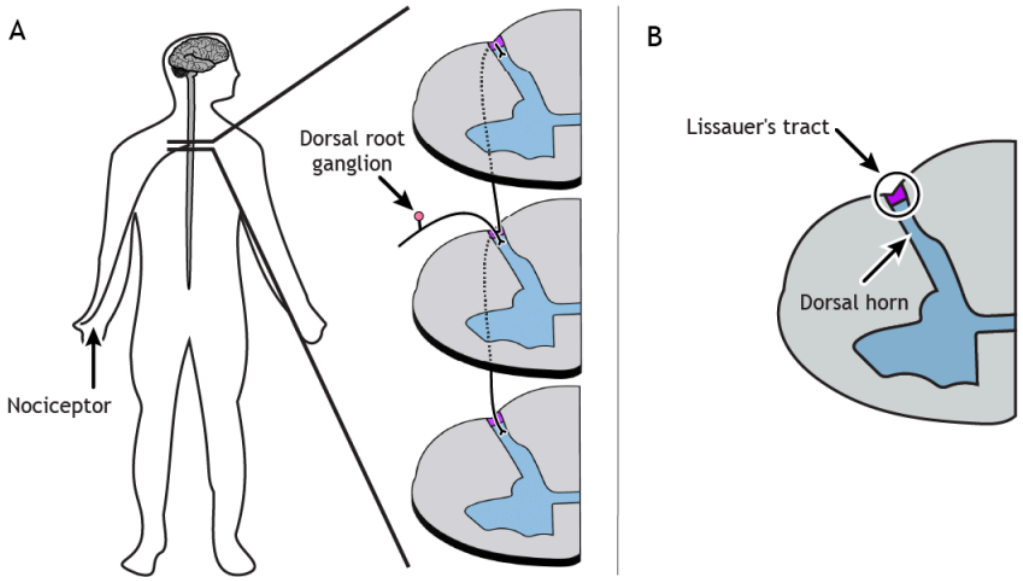


Figure 29.4. Nociceptors cell bodies are located in the dorsal root ganglia. Axons enter the spinal cord and then branch and ascend and descend a short distance. These branches travel in a region called Lissauer's tract. The neurons make synaptic connections in the dorsal horn. 'Lissauer's tract; by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Spinothalamic Pathway

The nociceptor fibers make synaptic contact with second-order neurons in the dorsal horn of the spinal cord. These neurons immediately cross the midline, or decussate, and then ascend to the brain through the anteriolateral aspect of the spinal cord and brainstem via the spinothalamic tract. The axons terminate in the ventral posterior lateral nucleus of the thalamus. The thalamic neurons then project to the primary somatosensory cortex located in the postcentral gyrus in the parietal lobe.

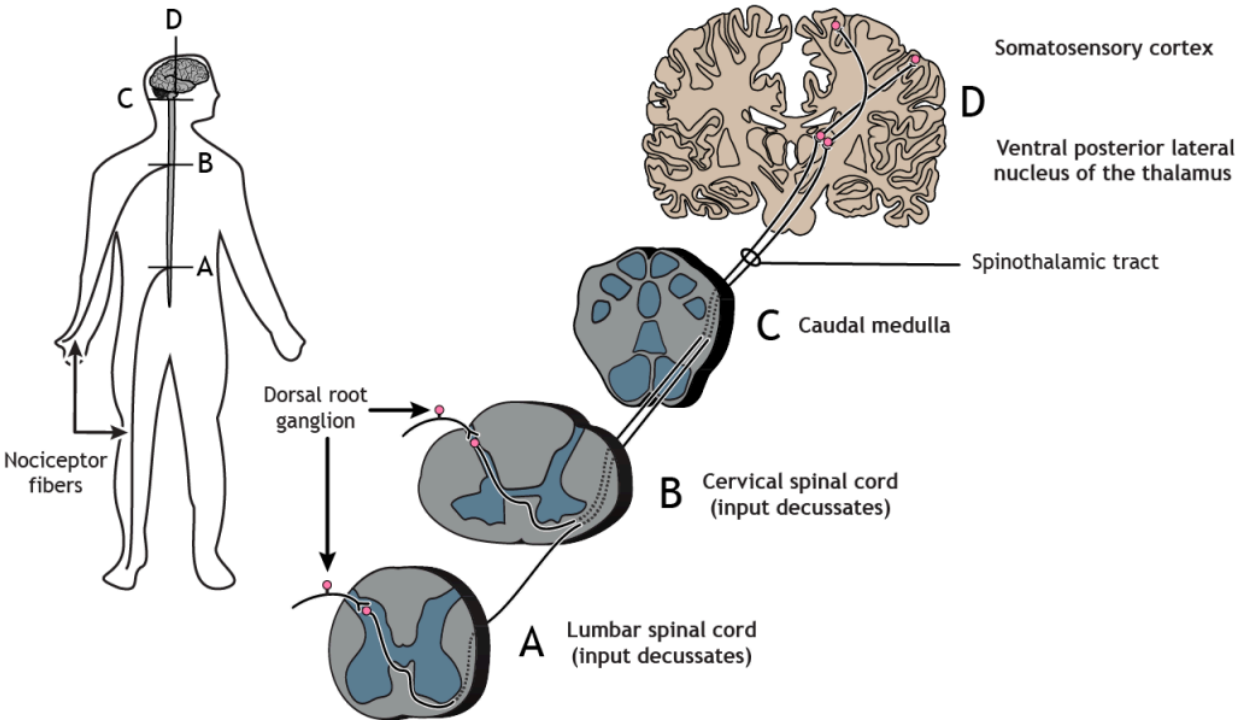


Figure 29.5. Pain and temperature information from the neck and body travels through the spinothalamic pathway, named for structures within the pathway. Axons enter the spinal cord and terminate in the dorsal horn. Second-order neurons decussate and ascend to the brain. Information continues to the thalamus, and then reaches the somatosensory cortex. Details of the pathway are found in the text. 'Pain Pathway from Body' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Trigeminothalamic Pathway

Nociceptors in the face and head send info to the brain primarily through cranial nerve V, the trigeminal nerve. The first-order neurons have their cell bodies in the trigeminal ganglion, located just outside of the brainstem. The fibers enter the brainstem and descend to the spinal trigeminal nucleus in the medulla, where they synapse on a second-order neuron. The second-order neurons cross the midline and project up to the ventral posterior medial nucleus of the thalamus. These neurons then send projections to the face region of the somatosensory cortex.

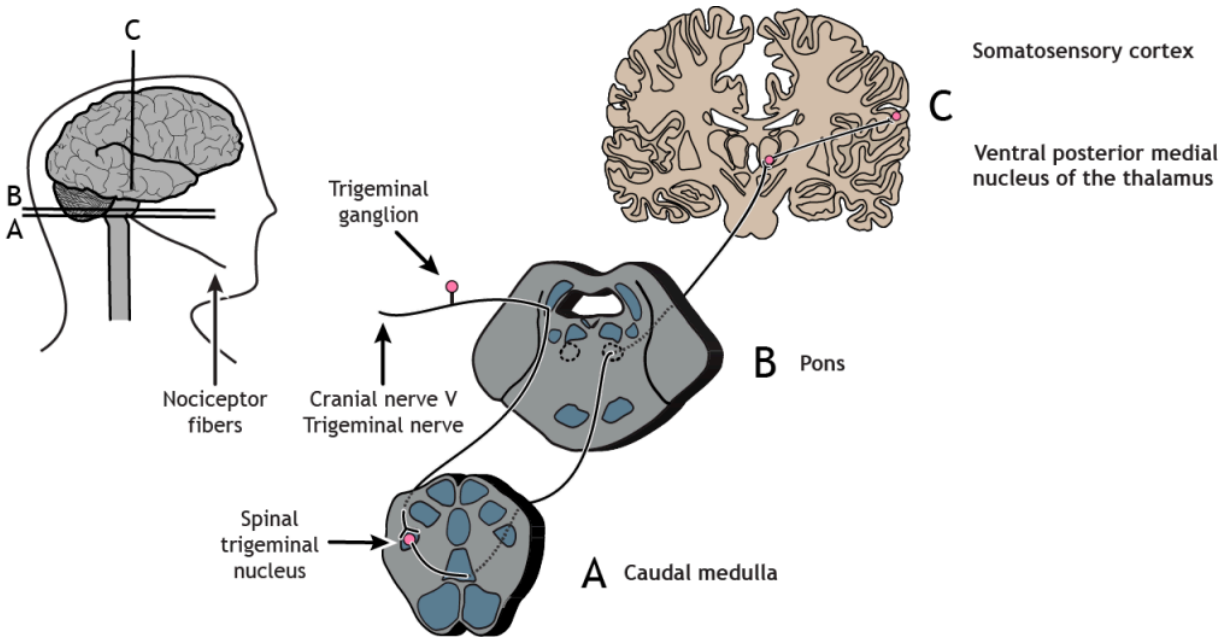


Figure 29.7. Pain and temperature information from the head and face travels through the trigeminothalamic pathway. Axons enter the brainstem at the level of the pons and descend to the medulla. They then decussate before traveling to the thalamus and somatosensory cortex. Details of the pathway are found in the text. 'Pain Pathway from Face' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Sensitization

Pain sensitization occurs after injury and causes the feeling of pain in situations that would not normally cause pain. Tissue damage causes pain signals to be sent to the CNS, as seen above, but the injured tissue also releases substances like prostaglandins, neurotransmitters, substance P, cytokines, and protons, which cause inflammation and begin the healing process. Additionally, non-neuronal cell types such as mast cells and macrophages come to the injured site, releasing more inflammatory substances. These chemicals, particularly prostaglandins, however, can act on nociceptors and cause cellular changes that allow the receptors to be more sensitive to stimuli. This results in a decreased threshold for pain sensation. There are two types of pain sensitization. Hyperalgesia is increased pain in response to a stimulus that normally causes pain but less intensely, like having a second injury at or near a previously injured site. Allodynia is pain sensation in response to a stimulus that would normally not cause pain, like a light touch on a sunburn.

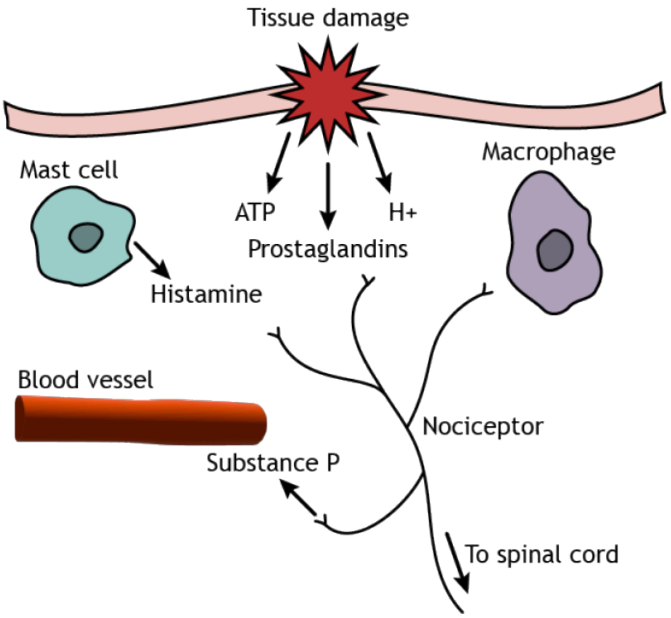


Figure 29.8. Tissue damage causes the release of chemicals including prostaglandins, neurotransmitters, and ions. Mast cells and macrophages move to the site of injury and release substances like histamine. These chemicals act upon the nociceptors and decrease stimulus threshold. Substance P, released from the nociceptor, along with the other substances causes inflammation in the area. 'Peripheral Sensitization' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Modulation of Pain

Pain signals that enter the CNS can be modified.

Peripheral

Think of a time when you cut a finger or stubbed a toe. It is common after an injury like this to put pressure at or near the injured location – squeeze the hurt finger or toe. This touch stimulation can decrease the pain sensation felt because sensory mechanoreceptors send signals through inhibitory

interneurons in the dorsal horn of the spinal cord to pain neurons that ascend to the brain. This effect is known as the gate theory of pain.

One type of therapy that is believed to activate this process is transcutaneous electrical nerve stimulation (TENS) therapy. TENS units, which use small electrical impulses at the site of the pain, are often used to minimize both long- and short-term pain in joints and muscles.

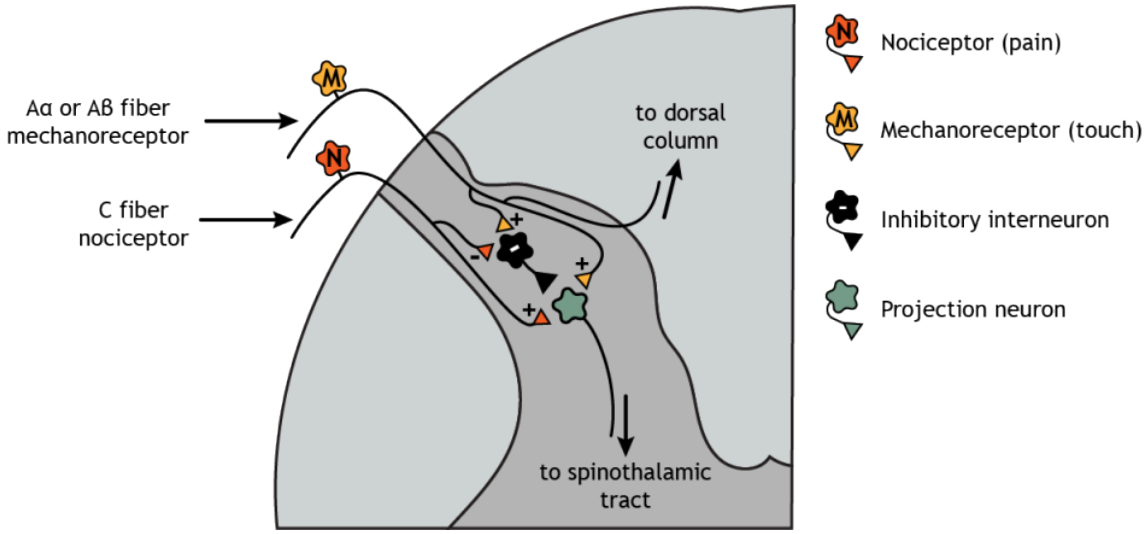


Figure 29.9. In the dorsal horn of the spinal cord, nociceptor axons enter and synapse on second-order neurons, which ascend via the spinothalamic tract, as covered earlier in this chapter. Afferent mechanoreceptor fibers also enter the dorsal horn and ascend via the dorsal column, but axon branches can also activate inhibitory interneurons, which then inhibit the second-order pain neurons, reducing the pain signal transmitted to the brain. 'Gate Theory of Pain' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Central

Descending regulation of pain also occurs. In this case, neurons from the medulla, which are innervated by the periaqueductal gray (PAG), descend and synapse in the dorsal horn of the spinal cord. The medulla neurons release either serotonin or norepinephrine onto enkephalin-releasing interneurons. These interneurons inhibit both the nociceptors and the second-order pain neurons that project to the brain. External stimulation of the PAG results in widespread analgesia.

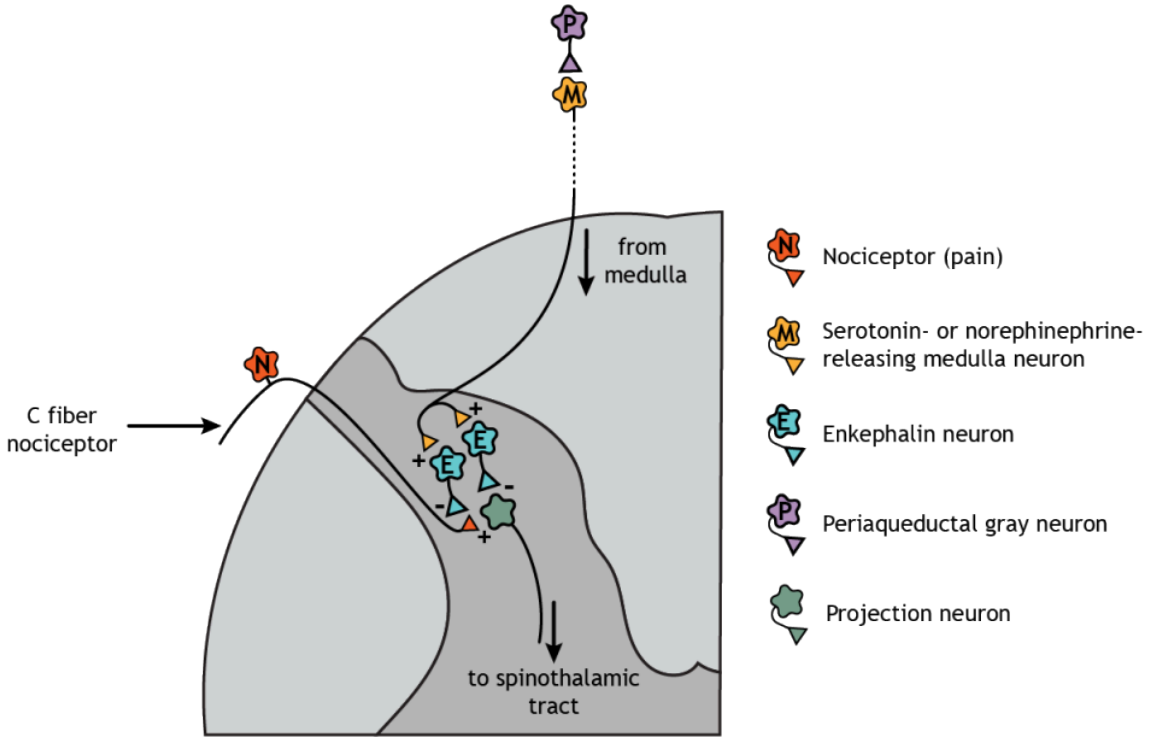


Figure 29.10. In the dorsal horn of the spinal cord, nociceptor axons enter and synapse on second-order neurons, which ascend via the spinothalamic tract, as covered earlier in this chapter. Descending medulla neurons, innervated by the periaqueductal gray, release serotonin and norepinephrine onto interneurons that release enkephalins and inhibit signal transmission in the nociceptors and projection neurons, decreasing pain sensation. 'Descending Pain Modulation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- There are multiple types of nociceptors in the skin that are activated by different types of damaging stimuli
- Nociceptors express specialized proteins that convert noxious stimuli into electrical potentials during sensory transduction

- Nociceptor afferents synapse in the dorsal horn of the spinal cord. Information immediately decussates and synapses in the ventral posterior nucleus of the thalamus
    - Information from the neck and body synapse in the ventral posterior lateral nucleus of the thalamus
    - Information from the head and face synapse in the ventral posterior medial nucleus of the thalamus
- Pain sensitization occurs after injury and causes the feeling of pain in situations that would not normally cause pain
- Pain signals can be modified via peripheral and central nervous system processes

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
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30.

GUSTATORY SYSTEM

Your gustatory system, which mediates your sense of taste, helps you walk the line between health and illness. It acts as a short-range detection system, as you must actually put something in your mouth to taste it.

The gustatory system guides you towards foods that are energy rich and keeps you away from food that could make you sick. Humans can perceive five basic tastes: salty, sour, bitter, sweet, and umami. These specific taste modalities all support this balance. Sweet foods taste good because foods rich in sugar, such as fruit and wheat, contain large amounts of usable energy, and humans have evolved to find these foods appetizing. In contrast, toxic compounds are often bitter, causing you to respond with feelings of disgust. Salty taste indicates a substance with high salt content and sour taste indicates an acidic food, and umami taste indicates a high protein food.

Resources

- Glossary Terms
- Key Takeaways
- Test Yourself

Some of our taste is innate, like sweetness, whereas other tastes are learned like bitterness. This explains why many individuals do not initially like the taste of coffee, and why many individuals prefer to have their coffee with sugar when they first start drinking it. Our tastes can also be modified by our dietary needs, like craving a salty food.

Organs of Taste

Although taste receptor cells are most prevalent on the tongue, there are other regions of the mouth and throat, including the palate, pharynx, and epiglottis, that also are sensitive to food and play a role in taste perception.

Other sensory information is also tightly linked to our sense of taste. Smell is important in our sense

of taste as odorant compounds from food can reach odor receptors in the nasal cavity. How a food looks (sense of vision) is also important to how it tastes. The texture and temperature of the food is also important (somatosensory information). Even a sense of pain, related to the spicy level of the food relates to our sense of taste.

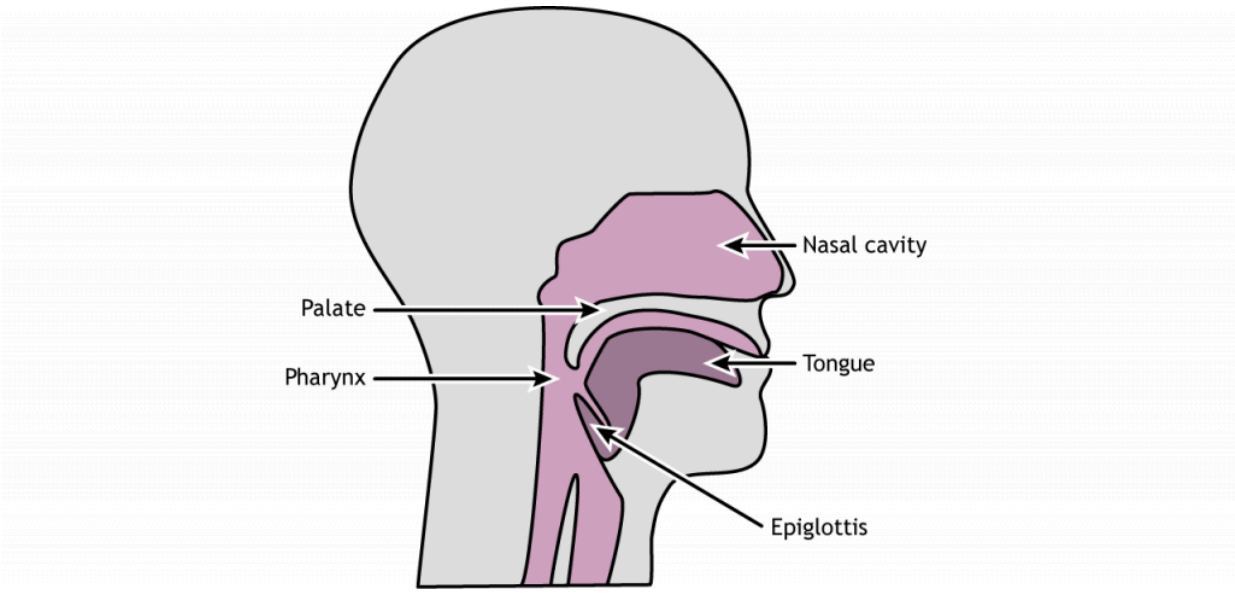


Figure 30.1. The tongue is the primary location for taste receptors cells, but receptors are also located along the palate, pharynx, and epiglottis. Additionally, airborne compounds from food can reach odor receptors in the nasal cavity. The sense of smell plays an important role in the perception of flavor. 'Throat Anatomy' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Tongue anatomy

The surface of the tongue is covered in small, visible bumps called papillae. Taste buds are located within the papillae, and each taste bud is made up of taste receptor cells, along with supporting cells and basal cells, which will eventually turn into taste receptors cells.

The taste cells have a lifespan of approximately two weeks, and the basal cells replace dying taste cells. The taste cells have microvilli that open into the taste pore where chemicals from the food can interact with receptors on the taste cells. Although taste cells are not technically neurons, they synapse and release neurotransmitters on afferent axons that send taste perception information to the brain.

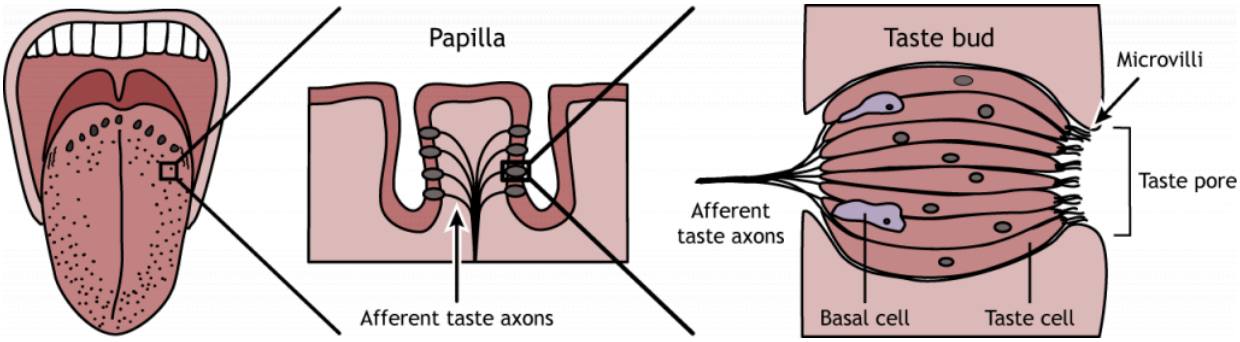


Figure 30.2. The visible bumps on the surface of the tongues are papillae that house taste buds. Taste buds are made up of taste cells and basal cells. The taste cells synapse on afferent axons that send information to the central nervous system. Tastants in food access the taste cells via the taste pore, where the food particles interact with the microvilli of the taste cells. 'Tongue Anatomy' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The entire tongue is capable of perceiving all five tastes, meaning there are taste receptors for each taste present across the entire surface. However, some regions of the tongue have a slightly lower threshold to respond to some tastes over others. The tip of the tongue is the region most sensitive to sweet, salt, and umami tastes. The sides are most sensitive to sour, and the back of the tongue to bitter tastes.

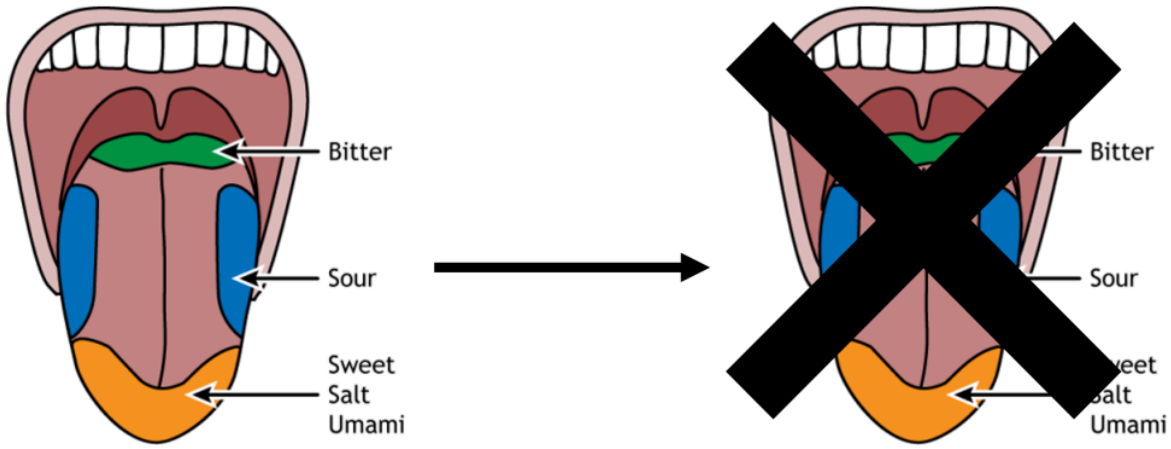


Figure 30.3. Although all tastes can be perceived across the entire tongue, sensitivity levels vary for each taste. The front of the tongue has the lowest threshold for sweet, salt, and umami tastes; the side of the tongue has the lowest threshold for sour tastes, and the back of the tongue has the lowest threshold for bitter tastes. It is inaccurate to map each of the tastes to a single region of the tongue because each area of the tongue is capable of sensing each type of taste.

Taste transduction

Currently, it is believed that humans sense five basic tastes: Salty, sour, sweet, bitter, and umami. Salty and sour taste are both mediated by ionotropic taste receptors, while sweet, bitter, and umami taste are mediated by metabotropic taste receptors.

Salt

Salt taste is mediated by the presence of epithelial sodium channels. These receptors are usually open, and when foods are ingested with high salt concentrations, sodium flows into the cell causing a depolarization. This change in membrane potential opens voltage-gated sodium and calcium channels. The increased calcium influx causes the release of serotonin-filled vesicles. The serotonin acts on the afferent taste axon causing depolarization and action potentials.

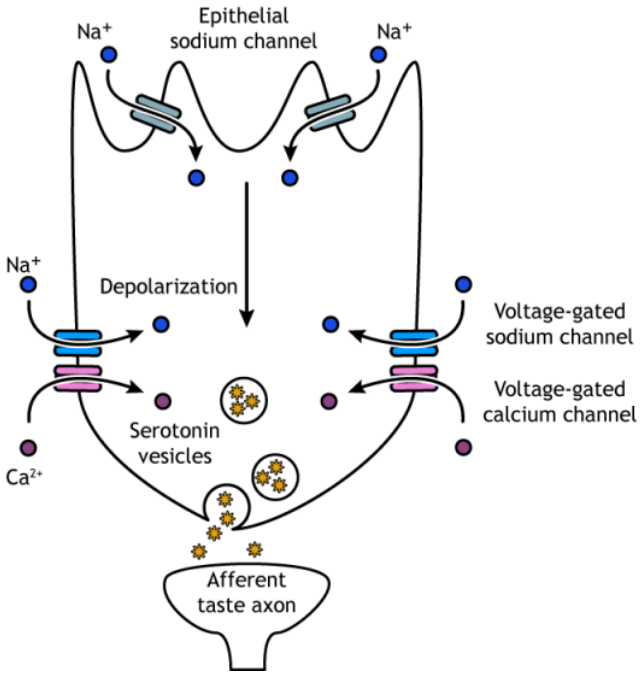


Figure 30.4. When salty foods are ingested, the sodium from the food enters the taste cell via open epithelial sodium channels. The resulting depolarization opens voltage-gated sodium and calcium channels, leading to release of serotonin onto the afferent taste axon. 'Salt Taste Transduction' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Salty foods elicit a biphasic response depending on concentration. Foods cooked with a low concentration of salt taste bland and are not very appetizing; however, high salt concentrations elicit a strong aversive reaction – imagine how disgusted you were when you first tried to cook and were overly generous with the salt!

Additionally, the appeal of salt at a given moment depends on our body's need for salt at the time. Several hormones such as the appetite-stimulating hormone ghrelin contribute to regulating the concentration of salt in the body by mediating Na+ absorption. Current salt levels can also impact appetite for salt. For example, in chronically-sodium deprived animals, high salt solutions are highly rewarding.

Why are we so sensitive to the taste of salt? As it turns out, both sodium and chloride are essential nutrients. They are critical for maintaining blood volume and pressure, for regulating body water, for maintaining muscle contractions, and mediating action potentials.

Sour

Foods taste sour because of their acidity, and when acids are present in water, they produce hydrogen ions (protons). Therefore, a sour food has high acidity and a high concentration of hydrogen ions, thus a low pH. The exact mechanism for sour taste transduction has yet to be worked out, but it is believed that protons enter the cell through an ion channel, and then block potassium channels. The decreased efflux of potassium, along with the presence of the protons, depolarizes the cell causing voltage-gated sodium and calcium channels to open. Like salt taste transduction, the increase in intracellular calcium causes release of serotonin into the synapse.

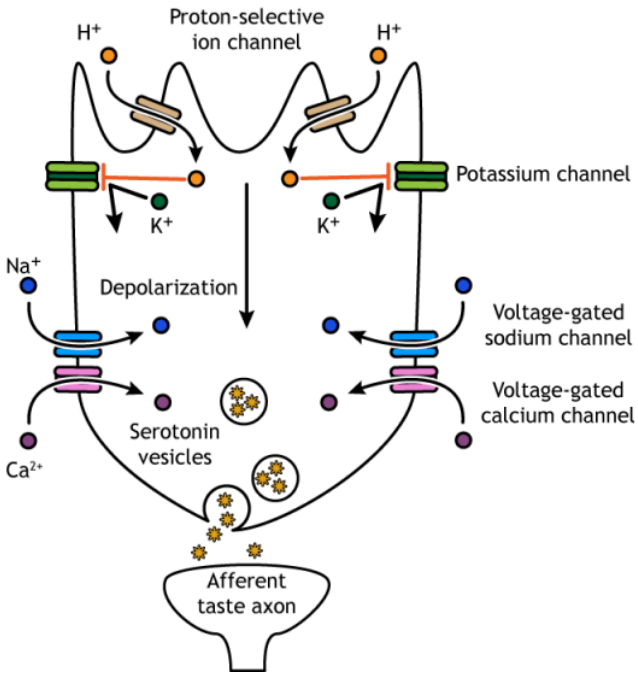


Figure 30.5. When sour foods are ingested, the protons from the acid enter the cell via open ion channels. The protons then block potassium channels. The resulting depolarization opens voltage-gated sodium and calcium channels, leading to release of serotonin onto the afferent taste axon. 'Sour Taste Transduction' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The purpose for our ability to sense acids in our food is under debate. Sour tastants do not inherently provide any nutritional value, except in the case of Vitamin C. Humans and other higher primates cannot synthesize Vitamin C on their own, so it's possible that we evolved to find a combination of sourness and sweetness attractive enough to consistently consume Vitamin C-rich fruits. However, sour can be aversive, motivating us to avoid spoiled or unripe foods that might contain pathogens.

Bitter

Bitter, sweet, and umami compounds all activate taste receptor cells via G-protein coupled receptors. The bitter receptors are from the T2R family of receptor proteins; humans have over 25. Each taste cell can express most or all of the different receptor types, allowing for the detection of numerous molecules, which is important when wanting to avoid dangerous substances like poisons and toxins.

Activation of the G-protein receptor activates phospholipase C, which in turn increases production of the second messenger inositol triphosphate. Inositol triphosphate causes the release of calcium from intracellular stores. Calcium causes the opening of ion channels, allowing the influx of sodium. These ion changes depolarize the cell and cause ATP-specific channels to open, allowing ATP to flow out of the cell and enter the synapse to act on the afferent taste axon by binding to purinergic receptors on the postsynaptic cell.

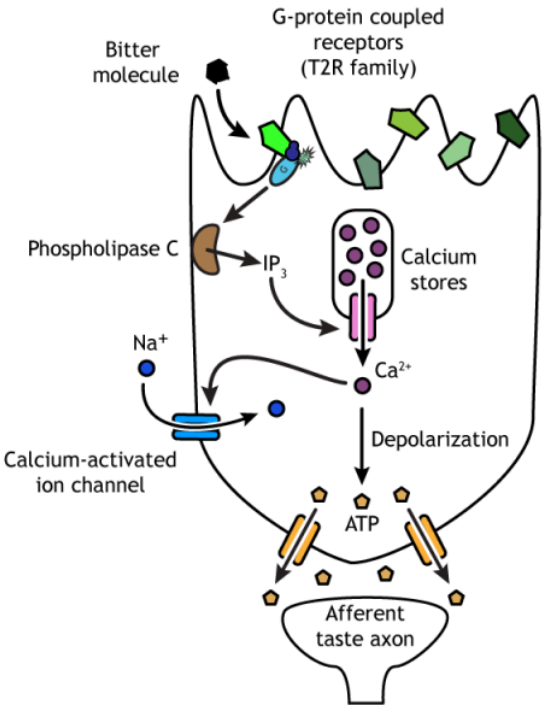


Figure 30.6. Bitter foods activate G-protein receptors, which initiate the phospholipase C second messenger system. IP3 releases calcium from intracellular stores, and the calcium opens ion channels that allow sodium influx. The resulting depolarization causes ATP release onto the afferent taste axon. 'Bitter Taste Transduction' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Sweet

Sweet and umami receptors are comprised of G-protein coupled dimers, meaning two separate proteins function together as one. The receptors are encoded by the T1R family of receptor proteins. Sweet receptors are dimers of the T1R2 and T1R3 proteins. Both proteins need to be present and functioning for activation of a sweet taste cell. Like bitter cells, activation of the G-protein receptor

uses a second messenger system to release calcium from intracellular stores and increase the influx of sodium. These ion changes depolarize the cell and cause ATP-specific channels to open, allowing ATP to enter the synapse and act on the afferent taste axon.

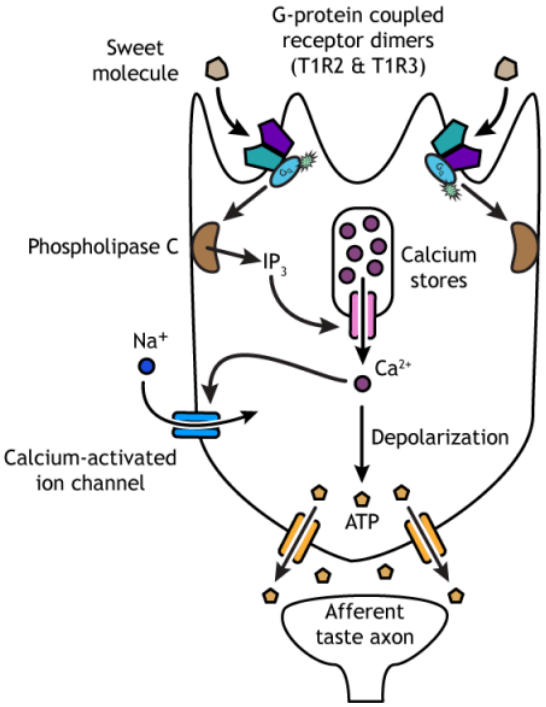


Figure 30.7. Sweet foods activate G-protein receptor dimers, which initiate the phospholipase C second messenger system. IP3 releases calcium from intracellular stores, and the calcium opens ion channels that allow sodium influx. The resulting depolarization causes ATP release onto the afferent taste axon. 'Sweet Taste Transduction' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Sugars like glucose and sucrose are essential for the survival of a species, since they are the main source of cellular energy. Therefore, our ability to detect sweetness plays a central role in regulating how much energy we take into our bodies. Of all the taste modalities, sweet is the strongest driver of food selection.

Umami

Umami is the taste of savory deliciousness, such as the taste of rich chicken broth, a perfect medium-rare steak, or aged cheese. The word is derived from the Japanese word umai, which means "delicious."

Umami is signaled when a molecule of glutamate (chemically the same as the neurotransmitter) binds to T1R1/T1R3 receptors.

Umami receptors are comprised of the T1R3 protein, like the sweet receptor, but it is paired with the T1R1 protein. Once the G-protein coupled receptor is activated, the transduction pathway is the same as bitter and sweet taste cells.

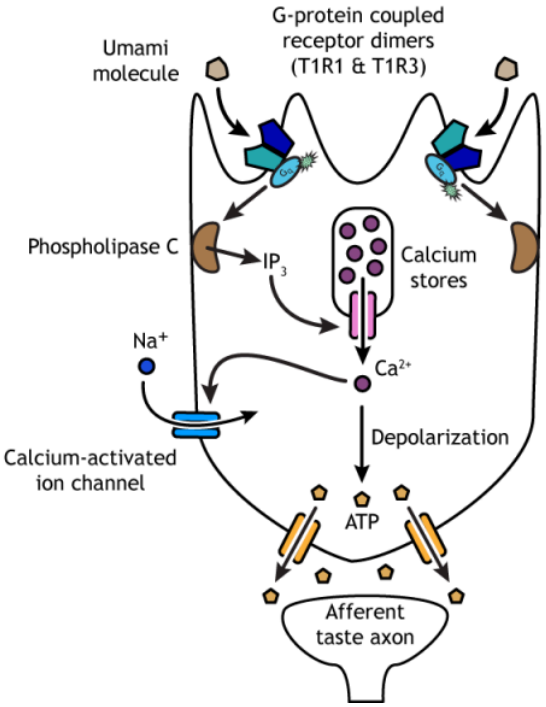


Figure 30.8. Umami compounds activate G-protein receptor dimers, which initiate the phospholipase C second messenger system. IP3 releases calcium from intracellular stores, and the calcium opens ion channels that allow sodium influx. The resulting depolarization causes ATP release onto the afferent taste axon. 'Umami Taste Transduction' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Through evolution, we have come to prefer the taste of umami because glutamate is a byproduct of cooking food. Cooking foods changes their chemical properties, thereby improving digestion, reducing toxicity, and increasing absorption of nutrients. Glutamate is one of the byproducts in the process of heating a food, and so it benefits us to appreciate these flavors.

Coding Properties of Taste

Of the five tastes, only two neurotransmitters are used to communicate information to the central nervous system, so how does our brain know what tastes to perceive? The answer is how the information is encoded. Most taste cells use a labeled line coding method, which means that each cell and the related afferent taste axon only responds to one type of taste. For example, bitter cells only express bitter receptors and are only activated by bitter molecules. These bitter taste cells activate bitter sensory neurons and bitter regions of the taste cortex.

A small portion of taste cells do use population coding as well, meaning more than one tastant can activate the cell, and perception is based on a combination of multiple cells each with a different response. Most information, however, is encoded via labeled line at the level of the taste cell.

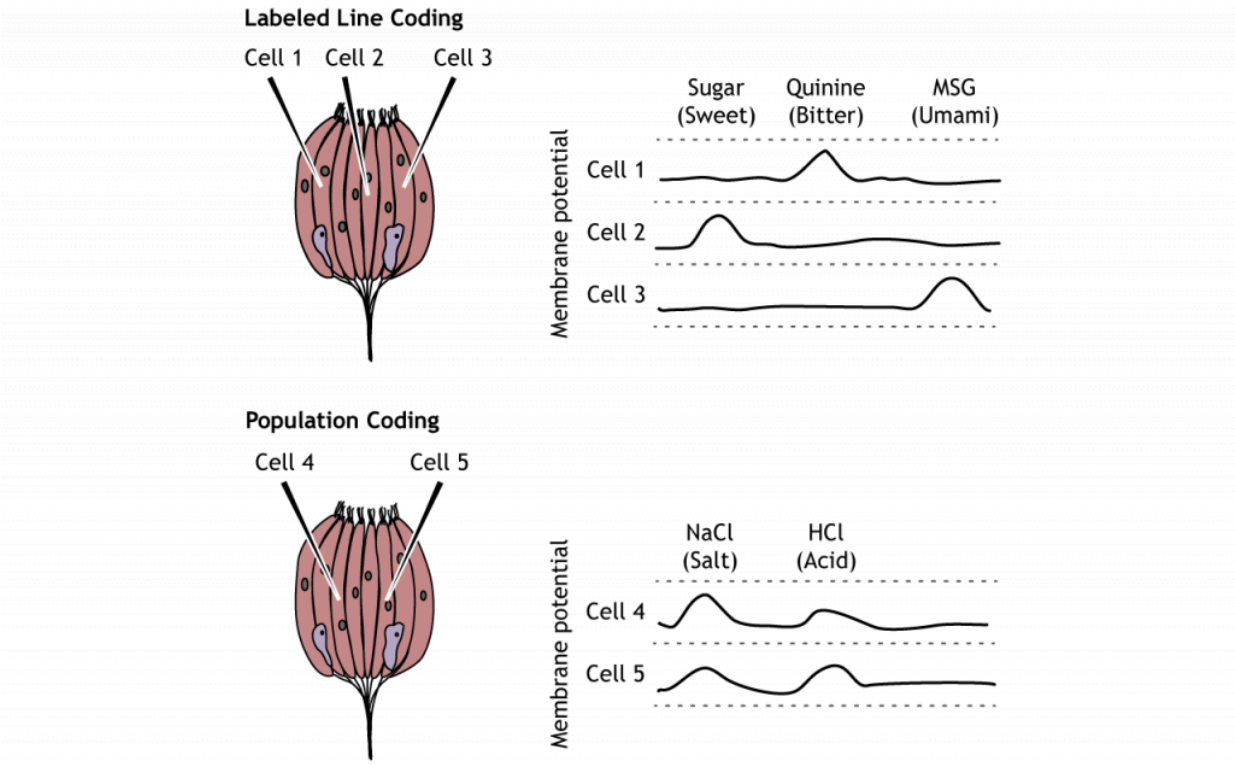


Figure 30.9. Labeled lined coding occurs when one sensation (in this case, a specific taste) leads to activation of the sensory cell. In this example, Cell 1 is activated only by quinine, a bitter compound, Cell 2 is activated only by sugar, a sweet compound, and Cell 3 is activated only by MSG, an umami compound. Most taste cells in the tongue use labeled line coding. Population coding results from broader activation, where multiple sensations can activate a sensory cell and perception is a result of information from a population of cells. In the example, Cells 4 and 5 are activated by both salt and acid compounds. 'Taste Coding' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Pathway

The tongue is innervated by three cranial nerves. The front two-thirds of the tongue is innervated by cranial nerve VII (Facial nerve). The back third is innervated by cranial nerve IX (Glossopharyngeal nerve). Finally, the epiglottis and pharynx are innervated by cranial nerve X (Vagus nerve). All three cranial nerves enter the brainstem at the medulla and synapse in the nucleus of the solitary tract. From there, information is sent to the ventral posterior medial nucleus of the thalamus. Thalamic neurons send projections to the gustatory cortex. The gustatory cortex is located deep in the lateral fissure in a region called the insula. Information processing taste stays primarily on the ipsilateral side of the

nervous system that is to say, taste information from the left half of the tongue gets represented in the left hemisphere of the brain, and visa versa.. Projections within the brain also exist between the taste regions and the hypothalamus and amygdala.

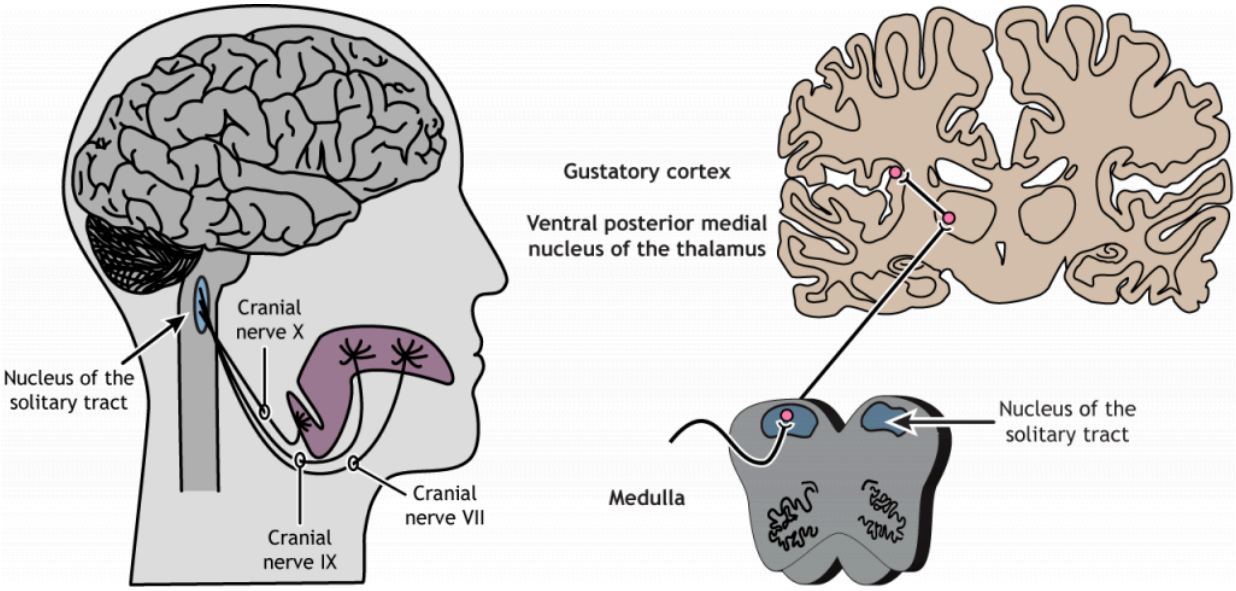


Figure 30.10. Taste information from the tongue travels through cranial nerves VII, IX, and X to the nucleus of the solitary tract in the medulla. Neurons in the brainstem project to the ventral posterior medial nucleus of the thalamus and then on to the gustatory cortex. 'Taste Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

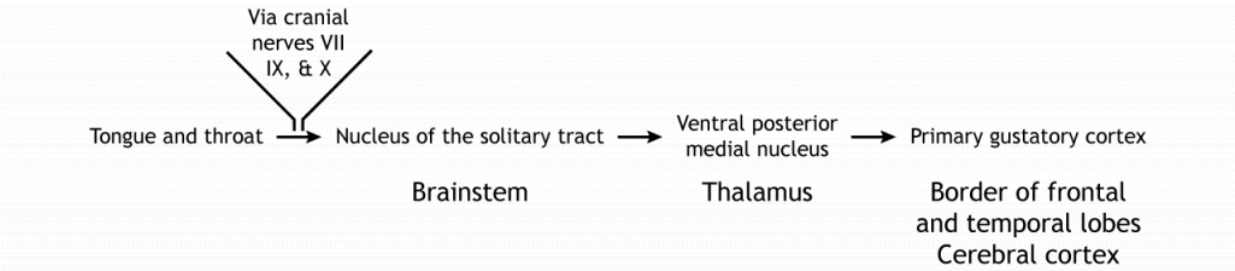


Figure 30.11 Axons from sensory afferents from the tongue and throat travel to the nucleus of the solitary tract in the brainstem via cranial nerves VII, IX, and X. The second-order brainstem neurons project to the ventral posterior medial nucleus of the thalamus. The thalamic third-order neuron projects to the primary gustatory cortex, which is located at the border of the frontal and temporal lobes. 'Taste Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the facial nerve (cranial nerve VII) using the BrainFacts.org 3D Brain
View the glossopharyngeal nerve (cranial nerve IX) using the BrainFacts.org 3D Brain
View the vagus nerve (cranial nerve X) using the BrainFacts.org 3D Brain
View the thalamus using the BrainFacts.org 3D Brain

Flavor

How do 5 basic tastes turn into the myriad complex taste sensations we experience when eating food? Olfaction plays an important role in the perception of flavor, as do vision and touch. Taste information combines with information from these other sensory systems in the orbitofrontal cortex located in the frontal lobe. This region is believed to be important for the pleasant and rewarding aspects of food. Additionally, as taste is processed in higher-order regions of the CNS, information is combined using population coding mechanisms. Test how your senses combine to create flavor at home!

View the orbitofrontal cortex using the BrainFacts.org 3D Brain

Key Takeaways

- Taste cells express specific taste receptors and are located in taste buds within the papillae
- Salt and sour taste cells rely on ion channels to depolarize the cell and release serotonin
- Bitter, sweet, and umami taste cells rely on G-protein coupled receptors and second messengers that open ATP channels
- At the level of the taste receptor cells, taste is perceived by using labeled line coding
- Multiple regions in the mouth and throat play a role in processing of taste
- Three cranial nerves innervate the tongue and throat
- The cranial nerves synapse in the nucleus of the solitary tract in the medulla. Information then travels to the ventral posterior medial nucleus of the thalamus and

then to the gustatory cortex
- To perceive complex flavors, information from other sensory systems is combined with taste information in the orbitofrontal cortex

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=557#h5p-41

Attributions

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- Posterior Parietal © Casey Henley adapted by Valerie Hedges is licensed under a CC BY-NC-SA (Attribution NonCommercial ShareAlike) license

31.

OLFACTORY SYSTEM

Olfaction is the ability to sense and perceive volatile chemicals that are suspended in the air. The typical human can distinguish up to 10,000 distinct odors, ranging from the sweet aroma of esters produced by apples and oranges, to the putrid smells of sulfurous compounds produced by skunks and rotten eggs. Because odors can drift along in the air, some chemicals can be detected long before the source is within eyesight: think about smelling a burning bonfire from miles away.

Smells affect our conscious behavior. They can motivate us to approach freshly-baked bread or avoid a rotting animal carcass. These chemicals serve as survival cues: bread gives us energy-rich carbohydrates while a decaying carcass can expose us to disease.

Resources

- Glossary Terms
- Scientist links to learn more
- Key Takeaways
- Test Yourself

Smell is often used in communication between animals, especially in reproductive behaviors, territory marking and identification of individuals. Olfaction is one of the oldest functions we possess as animals. While our sense of smell has seemed to take a backseat to other senses relative to other animals (about 2% of the total mouse brain mediates smell, while only a scant 0.01% of the volume of the human brain is dedicated to this function), scientists now appreciate that our olfactory system is simply more specialized. For example, humans use the smells of sweat to clue us into the emotional state of others, and we can even subconsciously detect sickness through body odor.

Anatomy of the Olfactory System

Your sensation of smell begins when odorant molecules travel through your nostrils and pass through the nasal cavity, an empty, air-filled space just behind the front of the skull.

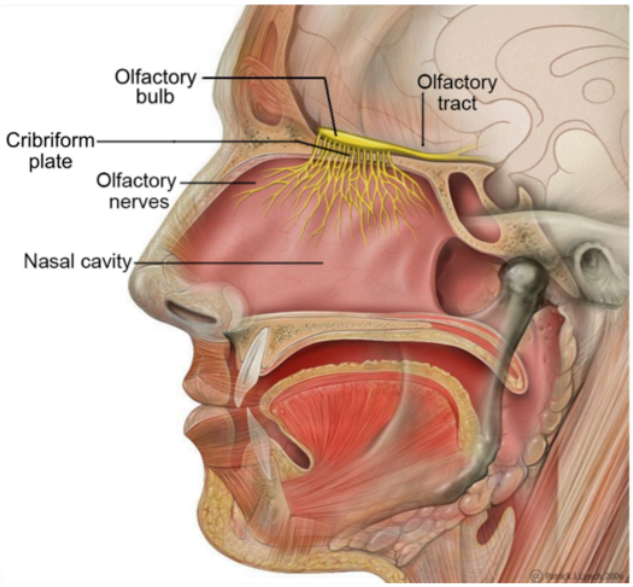


Figure 31.1. Olfactory system structures. Odorants enter through the nostrils into the nasal cavity, which is a large air-filled chamber. The olfactory epithelium is located at the dorsal most portion of the nasal cavity. This is where the odorants interact with olfactory receptor neurons (labeled as olfactory nerves in this image).

The odorants dissolve in the mucus covered dorsal-most portion of the nasal cavity, an area called the **olfactory epithelium**. Embedded within the olfactory epithelium are olfactory receptor neurons, supporting cells, and basal cells.

The axons of the olfactory receptor neurons travel through a sheet of bone called the **cribiform plate** before going to the **olfactory bulb**. Collectively, the axons of the olfactory receptor neurons make up **Cranial Nerve 1 (Olfactory Nerve)**.

Also found within the olfactory epithelium and surrounding the olfactory receptor neurons are **supporting cells** and **basal cells**. The supporting cells help dispose of dead and dying cells, metabolize pollutants, and may also help to physically maintain the epithelium by producing mucus. The basal cells function to replace the olfactory receptor neurons.

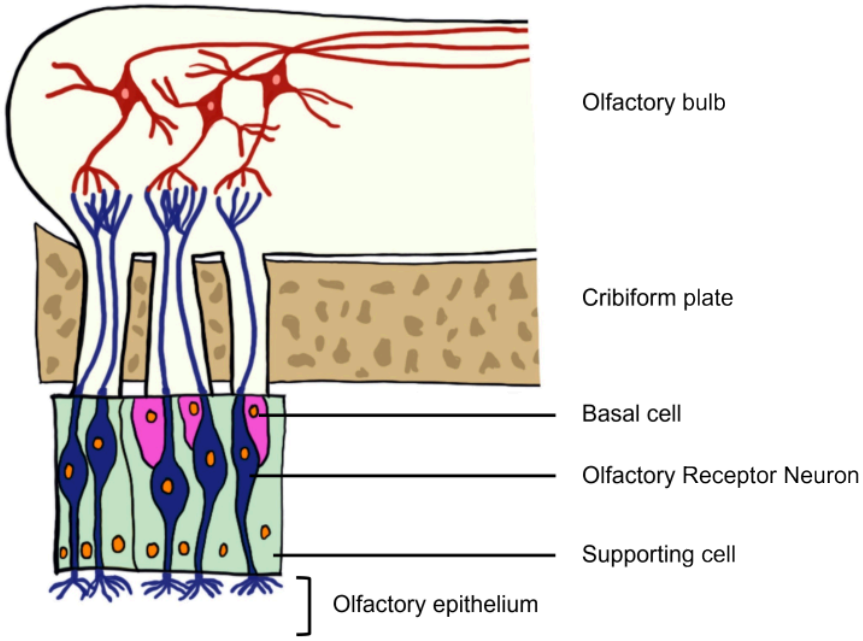


Figure 31.2. Olfactory receptor neurons in the olfactory epithelium. Olfactory receptor neurons are embedded within the olfactory epithelium. In addition to the olfactory receptor neurons, there are also basal cells and supporting cells. The axons of the olfactory receptor neurons exit through holes within the cribiform plate and then synapse within the olfactory bulb where they synapse onto the secondary cells (mitral cells). 'Olfactory receptor neurons and olfactory epithelium' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Olfactory Receptor Neurons

The **olfactory receptor neurons** begin processing smell. They serve as the sensory neurons for the olfactory system. Olfactory receptor neurons are **bipolar** neurons, that have a single dendrite with many **cilia** that are exposed to the epithelial surface. The cilia stretch into the mucus of the olfactory epithelium and act to increase the surface area of the neurons, providing increased space for odorants to interact with the olfactory receptor neurons. When the odorants dissolve in the mucus they interact with **odorant receptor proteins** on the cilia of the olfactory receptor neuron.

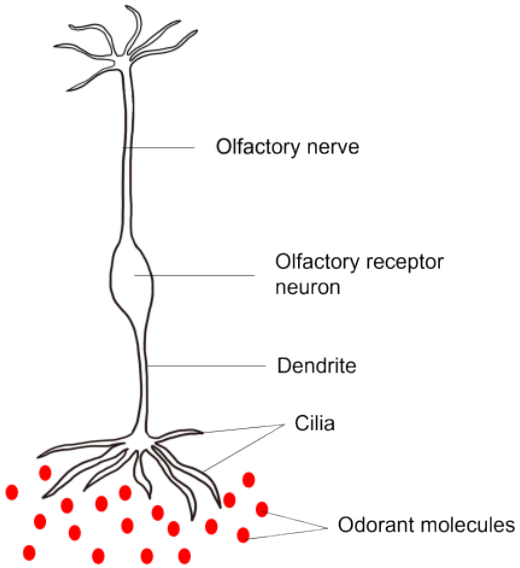


Figure 31.3. Structure of olfactory receptor neuron. Olfactory receptor neurons are bipolar and have a single dendrite that extends into the olfactory epithelium. Projecting from the dendrite are cilia that spread out into the olfactory epithelium to increase the surface area of the cell that can interact with odorants. The odorants bind to odorant receptor proteins on the cilia of the cells. 'Structure of olfactory receptor neuron' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Their proximity to the air make them the only neurons that are directly exposed to the outside world. Unfortunately, this causes them to encounter all sorts of dangers such as toxins, particulates, and microbes. They are one of the few known populations of neurons where adult **neurogenesis** regularly occurs, each having a lifespan in the range of 30 days to a year. The average human olfactory system has somewhere between 6-20 million olfactory receptor neurons.

Olfactory Transduction

Though taste uses different signaling systems for transduction of each of the different tastes, olfaction uses a single system for transduction. First, odorants bind to **odorant receptor proteins** (a G-protein-coupled receptor) on the cilia of the olfactory receptor neurons.

Odorant Receptor Proteins

It is estimated there are about 1,000 different genes (about 3% of the total human genome) that code for roughly 400 different odorant receptor proteins[1]. Each olfactory receptor neuron expresses only one type of odorant receptor protein. The initial research into the genetics underlying these neurons helped reveal the mechanism underlying olfactory transduction and specificity, and earned Drs. Linda Buck and Richard Axel a Nobel prize in 2004[2],.

Odorant receptor proteins are transmembrane G protein-coupled receptors that have extracellular binding sites on their surface that bind to odorants. Each receptor differs in their specific binding pockets. Importantly, the receptor does not bind to one specific odorant, but rather binds to a specific molecular feature of the odorant. This means that many odorants can activate more than one odorant receptor protein, ultimately allowing each odorant to generate a unique pattern of activity across the olfactory receptor neurons.

Thus, analyzing the activity of a single olfactory receptor neuron is not sufficient to understand how that odorant alters neural signaling. Rather, the olfactory system uses **population coding**.

1. Buck L, Axel R. A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. Cell. 1991 Apr 5;65(1):175-87. doi: 10.1016/0092-8674(91)90418-x. PMID: 1840504.

2. https://www.nobelprize.org/prizes/medicine/2004/summary/

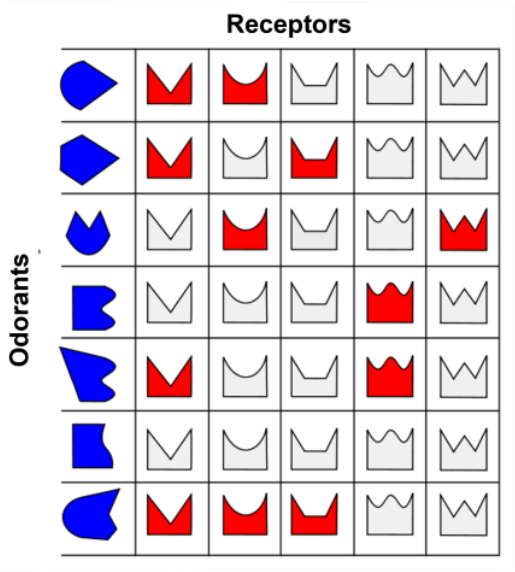


Figure 31.4. Odorant receptor proteins. Odorants are shown as the blue shapes on the left of the image. Each odorant has different features that allows for it to act with different odorant receptor proteins. The odorant receptor proteins are shown in red if the odorant can bind to that odorant receptor protein. The binding pocket within the odorant receptor protein does not need to match the entire shape of the odorant molecule, but rather just one structural feature of the odorant. In the top row of image, the odorant can bind to the two left-most odorant receptor proteins.

Odorant Receptor Protein Example

In this example we are looking at three different olfactory receptor neurons that express different types of odorant receptor proteins labeled Cell 1 ('blue' odorant receptor), Cell 2 ('orange' odorant receptor), and Cell 3 ('purple' odorant receptor). These neurons are exposed to four different odorants (vanilla, lavender, mint, and rose), and their neural activity is measured via an electrode.

When looking at the response to the 'Vanilla" odor, cell 1 shows an increase in the rate of action potentials, cell 2 shows very little activity, and cell 3 shows an increase in action potentials. Whereas the 'Lavender' odor only causes a response in cell 2. The 'Mint' odor causes very little activity in cell 1, and increased activity in both cell 2 and cell 3. Lastly, the 'Rose' odor causes an increase in activity in cell 1 and cell 2, but very little activity in cell 3. These recordings demonstrate that a single odorant can cause changes in activity in more than one type of olfactory receptor neuron, due to the receptor proteins recognizing more than one type of molecular feature of the odorant molecules.

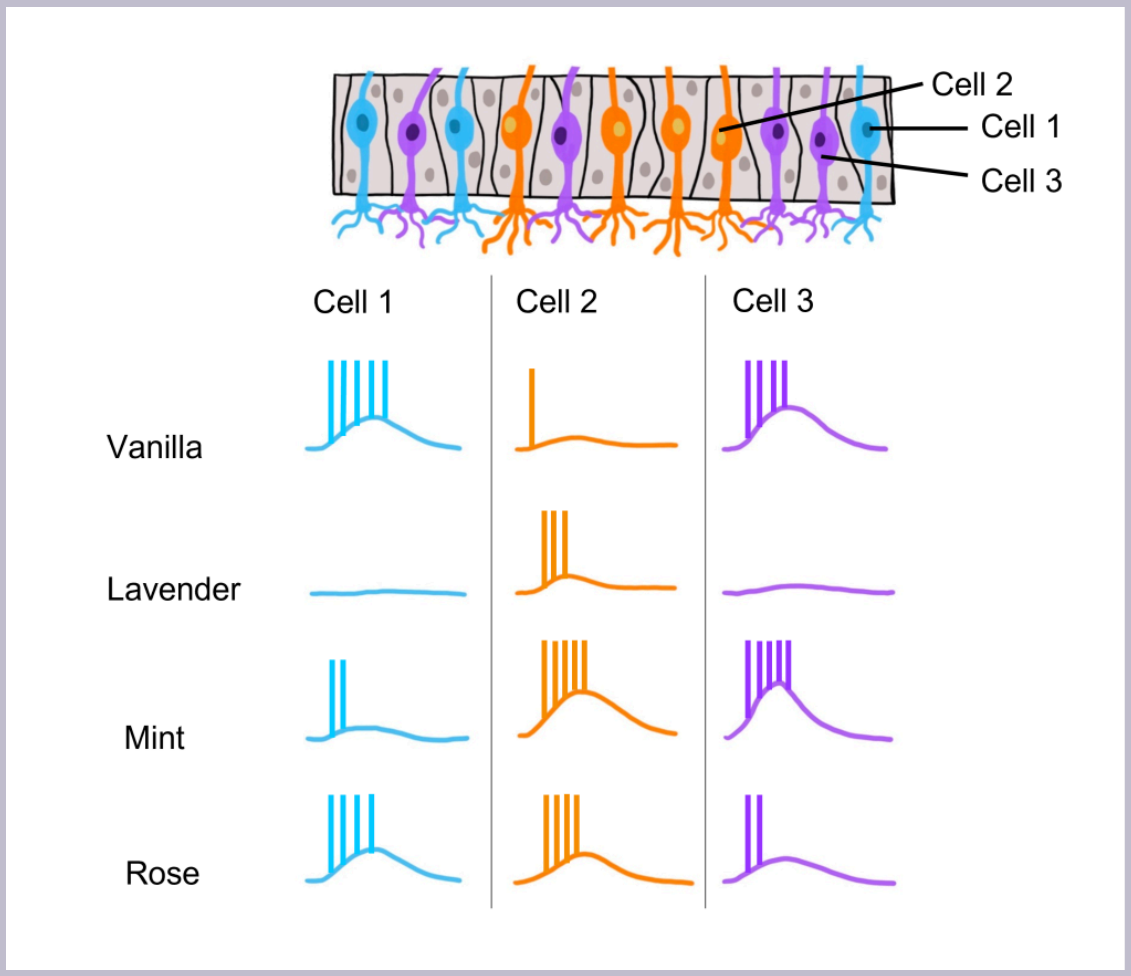


Figure 31.5. Example of population coding for olfactory receptor neurons. Three different cells are labeled within the olfactory epithelium (cell 1- blue, cell 2,- orange, and cell 3- purple). Recordings of action potentials for each of the three cells are shown when presented with different odorants (vanilla, lavender, mint, and rose). Each of the cells responds to more than one different odorant. Some cells respond preferentially to a single odorant. For example cell 2 preferentially responds to lavender odors. Odorant receptor proteins use population coding to code for different odorants. This means that the activity of a population of cells must be measured to determined how an odorant ultimately alters neuronal signaling. 'Population coding for olfactory receptor neurons' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Transduction Pathway

After the odorant binds to the odorant receptor protein, the receptor activates an associated G protein called G_{olf}. This protein complex is 90% similar to the stimulatory G protein G_s , and likewise triggers activation of adenylyl cyclase, elevating the intracellular concentration of cyclic AMP. cAMP binds to cyclic nucleotide-gated cation channels that when opened, allow for the influx of calcium and sodium. The influx of calcium opens calcium-activated chloride channels. Olfactory receptor neurons have high intracellular chloride concentration, so the opening of the chloride channel results in chloride flowing out of the cell. Together, this causes the olfactory receptor neuron to **depolarize**, leading to membrane depolarization within the dendrite. This change in membrane potential is called a "**receptor potential**". If depolarization crosses threshold potential within the olfactory receptor neuron cell body, then the olfactory receptor neuron will fire action potentials down its axons that make up the olfactory nerve toward the olfactory bulb.

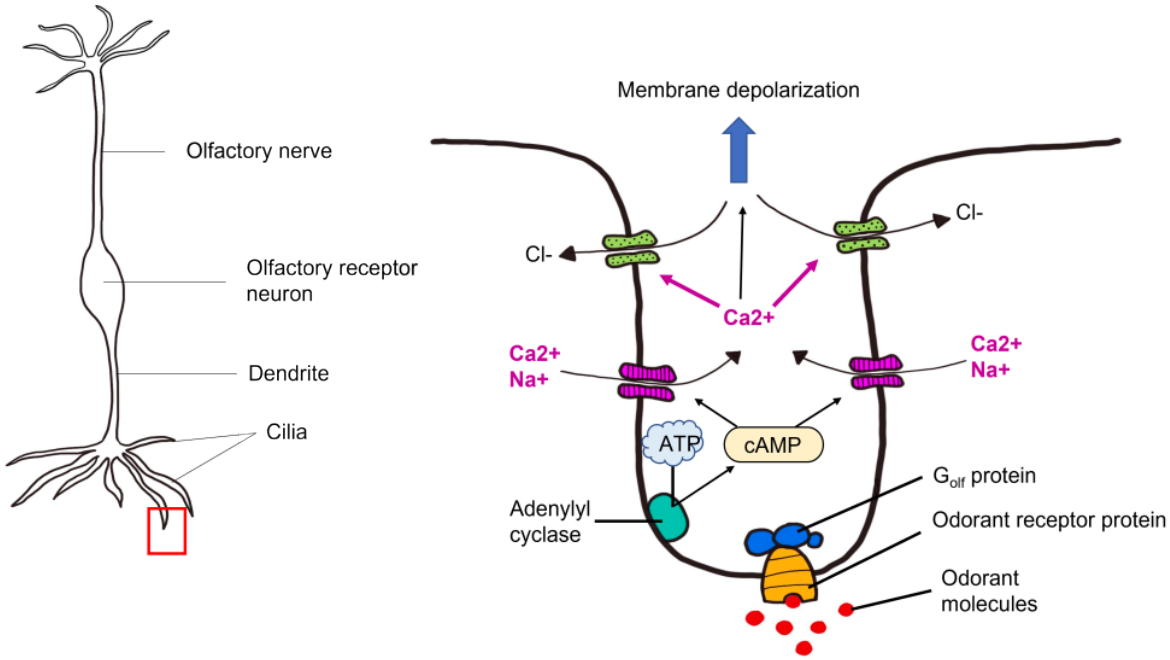


Figure 31.6. Olfactory receptor neuron transduction. Odorant molecules binds to odorant receptor proteins located on the cilia of olfactory receptor neurons. Odorant receptor proteins are G-protein coupled receptors that are coupled to Golf. Similar to activation of Gαs, activation of Golf increases activity of adenylyl cyclase, which in turn increases cAMP production within the cell. cAMP causes the opening of cation channels in the cell membrane that allow for the influx of both calcium (Ca2+) and sodium (Na+). The calcium influx opens chloride channels. Chloride concentration is high within the olfactory receptor neurons, so chloride flows out of the cell. The increase in positively charged ions combined with the loss of negatively charged ions from inside the cell leads to membrane depolarization. 'Olfactory receptor neuron transduction' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Olfactory receptor neurons encode the intensity of smells through the frequency of action potential firing, which changes in accordance with the concentration of odorant molecules. Imagine standing over a fresh-baked pizza and inhaling deeply. Due to the high concentration of odorant molecules in the air, several receptors will be activated, leading to frequent neuronal firing. Now, imagine you are down the block from a pizza restaurant, getting only a slight whiff of those same scents. Here, the concentration of odorants is low, meaning that the Olfactory receptor neurons fire less frequently.

Termination of Olfactory Signaling

Because odorants are found in the air, they are highly mobile and can easily diffuse away, no longer having the ability to activate odorant receptor proteins. Olfactory signaling can also be terminated through the activity of enzymes located within the mucus of the olfactory epithelium.

Our perception of smells can also fade, even if the odorant is still present in the air. The odorant receptor neurons can adapt to the presence of an odorant, and thus no longer signal its presence.

Central Olfactory Pathway

The axons of the olfactory receptor neurons pass through the skull through a tiny series of holes at the cribriform plate. These primary neurons form synaptic connections onto neurons in the olfactory bulb called **mitral cells**, forming the beginning of the olfactory nerve (CN I). Like the optic nerve, the olfactory nerve runs along the **ventral** surface of the brain.

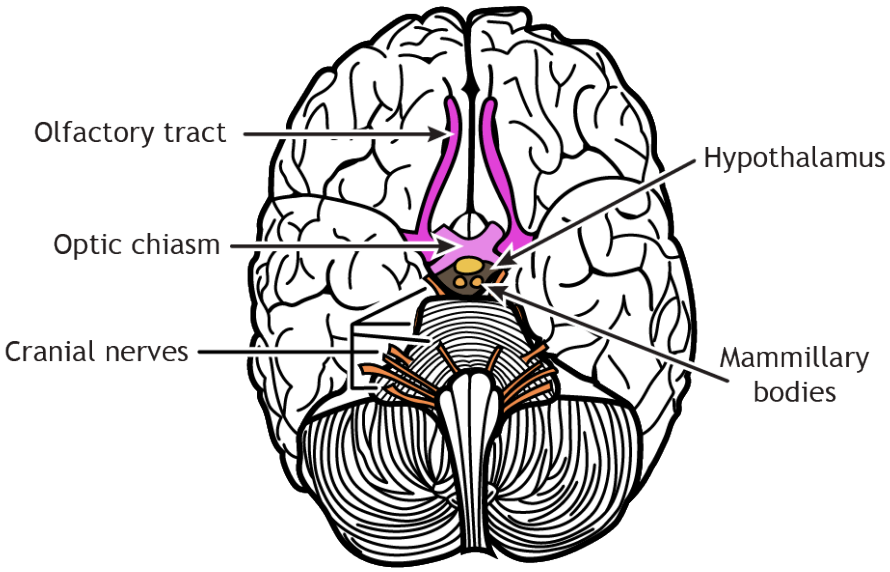


Figure 31.7. Human olfactory bulbs and tracts. In this ventral view of the brain, the optic bulbs and tracts (colored pink) run along the ventral surface of the brain.

Glomeruli within the Olfactory Bulb

The site of synaptic connectivity between the olfactory receptor neurons and the secondary neurons in the olfactory bulb (mitral cells) is a highly specialized clump of tissue called a **glomerulus**. The typical human has a little under 2,000 glomeruli, and each glomerulus only receives inputs from olfactory receptor neurons that express the same type of odorant receptor proteins. This means that even through the olfactory receptor neurons that express the same type of odorant receptor protein are spread out throughout the olfactory epithelium, the axons of those neurons all converge within the same glomerulus.

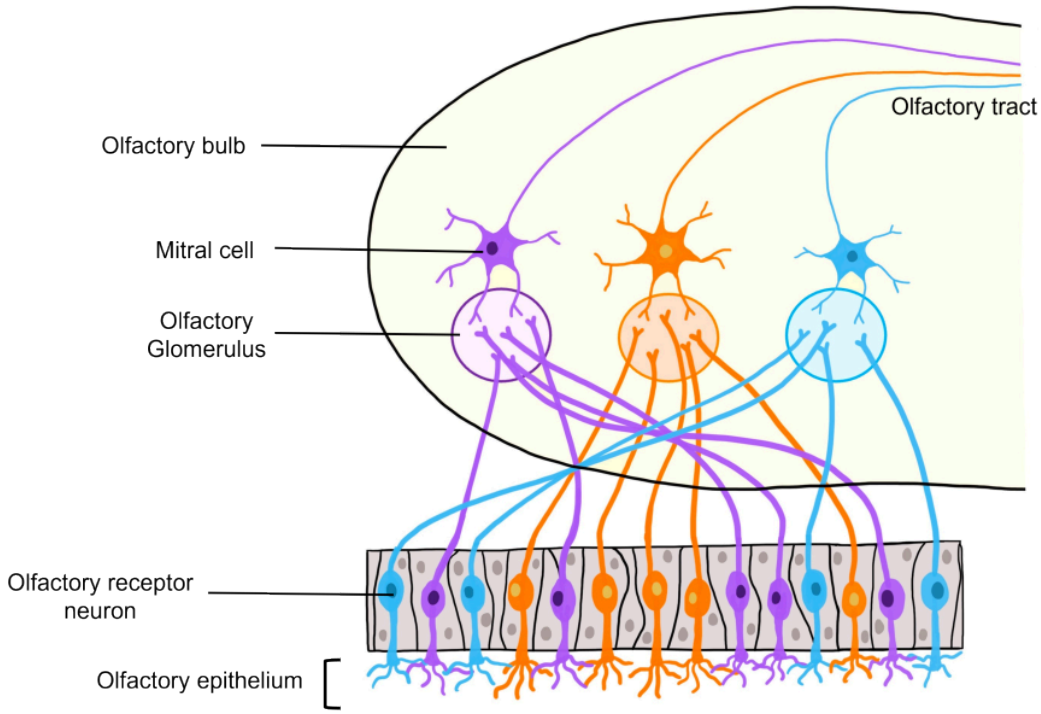


Figure 31.8. Olfactory glomeruli. Olfactory receptor neurons that contain the same type of odorant receptor protein are spread throughout the olfactory epithelium. All neurons that contain the same odorant receptor protein all synapse onto a common olfactory glomerulus within the olfactory bulb. Within the olfactory glomerulus is a synapse onto the secondary mitral cells. The axons of the mitral cells make up the olfactory tract that will carry the olfactory signal into the brain. 'Olfactory glomeruli' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Brain Targets of Olfactory Neurons

Axons leave the olfactory bulb via the olfactory tracts and project to two different targets.

First, some cells project to the **olfactory tubercle**, are routed through the **medial dorsal nucleus of the thalamus** and then to the **orbitofrontal cortex**. This pathway is responsible for our conscious perception of smell.

Other cells project directly to the **olfactory cortex** and other related structures found within the **temporal lobes, like the hippocampus**. This makes the olfactory system the only sensory system that does not have to first pass signals through the thalamus before cortical processing. This pathway may play roles in discriminating odors, and the emotional, motivational, and memory-related aspects of smell.

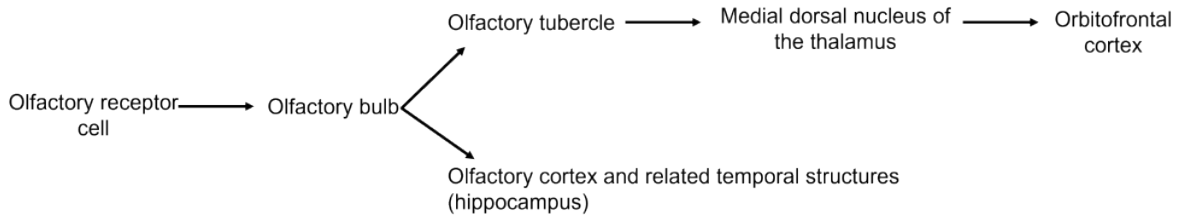


Figure 31.9. Projection of olfactory information. Olfactory receptor neurons send information to the olfactory bulb. From the olfactory bulb information can be routed through the olfactory tubercle, then to the medial dorsal nucleus of the thalamus, and finally the orbitofrontal cortex for processing of olfactory information. Alternatively, olfactory information can leave the olfactory bulb and be routed directly to the olfactory cortex and other related temporal structures like the hippocampus. This makes the olfactory system the only sensory system that does not necessarily need to be routed through the thalamus prior to cortical processing. 'Projection of olfactory information' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Disorders of the Olfactory System

Like other sensory systems, the structures involved in olfaction can be injured. An injury to the olfactory system can result in **hyposmia**, a reduced ability to smell, or **anosmia**, a complete loss of smell.

The most common insult to the olfactory system is simple nasal congestion, a temporary, physical blockage of the entry to the nasal cavity that decreases airflow and, therefore, the number of particles that reach the olfactory epithelium. Congestion can be caused by allergies, the common cold, upper respiratory bacterial or viral infections, or sinus infections.

Hyposmia is also one of the main neurological symptoms of COVID-19. Hyposmia is common among healthy, older adults, affecting about half of the population between 65 and 80 years old. As a person ages, spontaneous calcification causes the holes in the cribriform plate to shrink, which can impinge on and damage olfactory receptor neuron axons. Hyposmia can also be caused by abrupt head injuries. The olfactory receptor neuron axons that project through the holes of the cribriform plate are particularly sensitive to blows to the head. Neurodegenerative disorders, such as Parkinson's disease and Alzheimer's disease, contribute to smell deficiency. Usually, hyposmia precedes the major clinically observed symptoms of these disorders, hinting that smell deficiency may serve as an early diagnostic biomarker.

Another olfactory deficit, **phantosmia**, is when a person perceives "phantom" scents, or in other words, experiences an olfactory hallucination. Phantosmia may be triggered by a temporal lobe seizure or a stroke. It can also be caused by a brain tumor affecting the olfactory nerve (CN I), or the subsequent surgical removal of the tumor, leading to injury. Schizophrenia, a psychiatric condition characterized by auditory hallucinations, may also cause phantosmia.

Key Takeaways

- Odorants dissolve in the mucus of the olfactory epithelium and bind to odorant receptor proteins on olfactory receptor neurons.
- A single odorant can bind to multiple different odorant receptor proteins because the odorant receptor protein binds to a molecular feature of the odorant.
- Odorant receptor proteins are G protein-coupled receptors that cause accumulation of cAMP within the cell, and ultimately membrane depolarization of the olfactory receptor neuron.
- Olfactory information is carried from the olfactory receptor neuron axons through the cribiform plate and into the olfactory bulb where it synapses with the olfactory glomeruli. From there, the information travels through the olfactory tracts and can either be routed through the thalamus and then to olfactory brain areas, or can be directly routed to olfactory cortical areas, bypassing the thalamus.

Test Yourself!



An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=567#h5p-40

Attributions

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PART V
MOTOR SYSTEM

32.

SPINAL MOTOR CONTROL AND PROPRIOCEPTION

The motor system refers to the nerve cells that are used to control our body. The key roles of the motor system are to plan, control, and execute voluntary (deliberate) movements, and to control involuntary (subconscious or automatic) functions, such as digesting food. The motor system is sometimes described as a top-down process: in a voluntary movement, neural activity in the frontal lobe sends commands down to motor neurons located in the brainstem or spinal cord, which in turn activate muscle groups. In reality, motor control is more of a loop, rapidly communicating between the sensory cortex and motor cortex. Sensory information about limb position, posture, and objects in contact with the skin inform the descending motor plan. Simultaneously, the motor plan provides predictions about upcoming movement.

Resources

- Glossary terms
- Key Takeaways
- Test Yourself
- Additional Review

There are multiple levels of control. Within the spinal cord, simple reflexes can function without higher input from the brain. Slightly more complex spinal control occurs when central pattern generators function during repetitive movements like walking. The motor and premotor cortices in the brain are responsible for the planning and execution of voluntary movements. And finally, the basal ganglia and cerebellum modulate the responses of the neurons in the motor cortex to help with coordination, motor learning, and balance.

This lesson explores the lowest level of control at the level of the spinal cord.

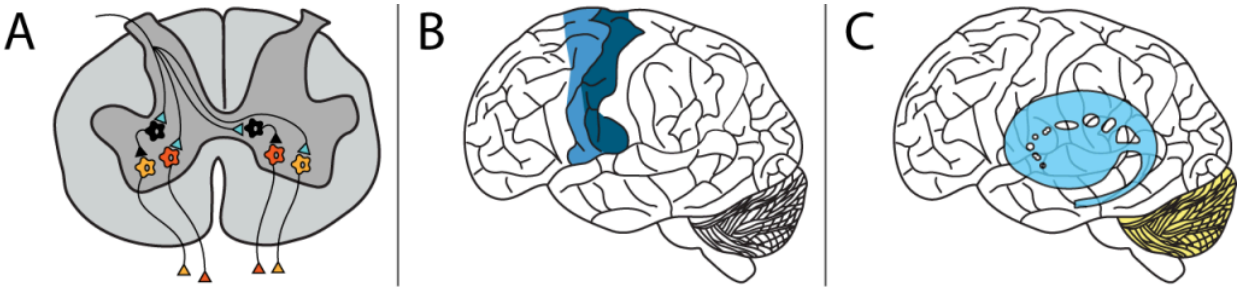


Figure 32.1. Motor output is controlled at multiple levels: A. Spinal cord and spinal neurons, B. Motor (dark blue) and premotor (light blue) cortices, C. Basal ganglia (a subcortical structure shown in light blue) and cerebellum (yellow). 'Motor Control Levels' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Alpha Motor Neurons

Muscle fibers are innervated by **alpha motor neurons**. Alpha motor neurons are also called lower motor neurons because they are not located in higher brain areas. These cells are the only cells that directly command muscle contraction. The cell bodies of the alpha motor neurons are located in the central nervous system in the ventral horn of the spinal cord. Their axons leave the spinal cord via the ventral roots and travel to the muscle via **efferent** peripheral spinal nerves.

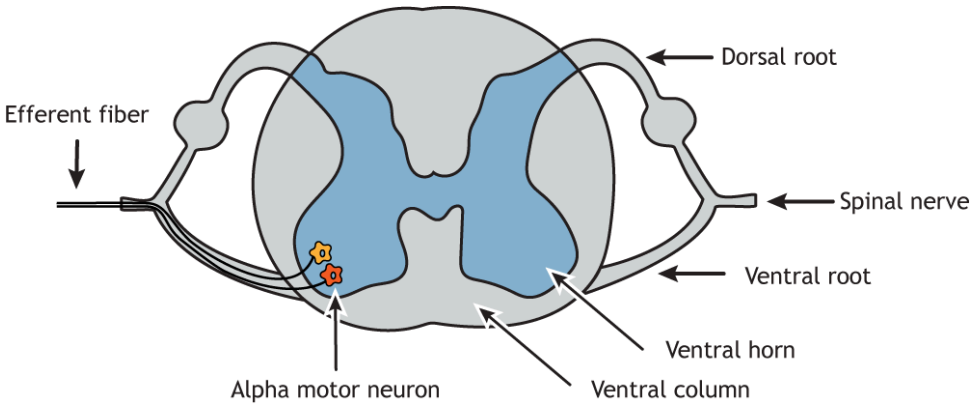


Figure 32.2. Alpha motor neurons are located in the ventral horn of spinal cord. Their axons, which are efferent fibers, travel to the muscles via spinal nerves. 'Alpha Motor Neurons' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Like the sensory systems, the motor system is also organized in a topographic fashion, referred to as

'somatotopic organization'. Within the spinal cord, alpha motor neurons that innervate muscles in the arms and legs are located in the **lateral** portion of the ventral horn, whereas alpha motor neurons that innervate muscles in the trunk are located in the **medial** portion.

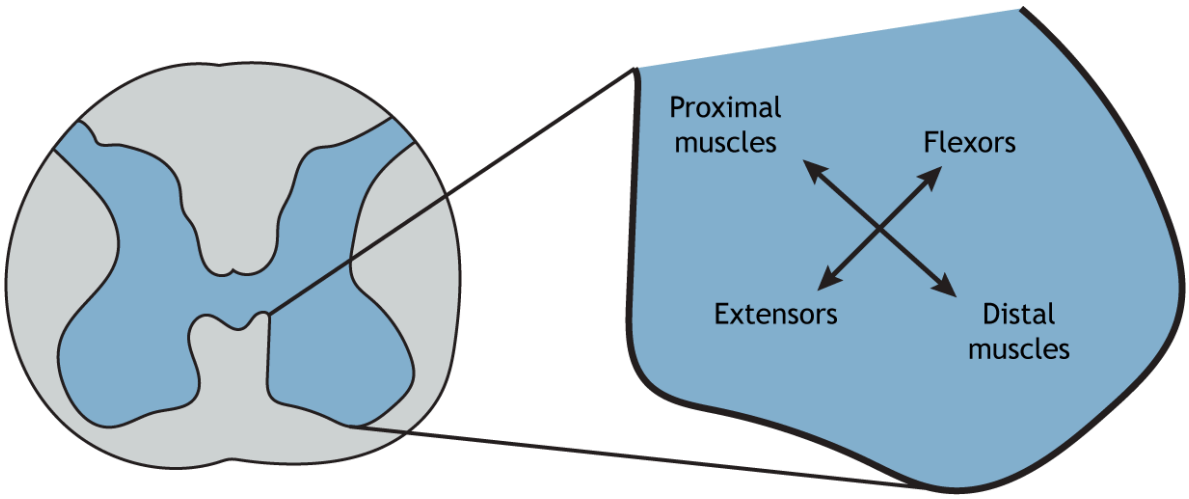


Figure 32.3. The ventral horn is organized in a topographic manner, with proximal muscles (like those in the trunk) located more medially than distal muscles (like the arms or legs). Additionally, motor neurons are organized by function with extensor motor neurons located together and flexor neurons located together. 'Spinal Cord Map' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Location of Alpha Motor Neurons

The structure of the spinal cord is reviewed in Chapter 26. Examining cross sections of the spinal cord at different levels reveals that there is a non-uniform distribution of lower motor neurons. This is determined by the size of the ventral horn at the different levels of the spinal cord. At the cervical enlargement the larger ventral horns are due to the presence of more lower motor neurons that function in movement of the arms. At the lumbar enlargement the larger ventral horns are due to the presence of more lower motor neurons that function in movement of the legs.

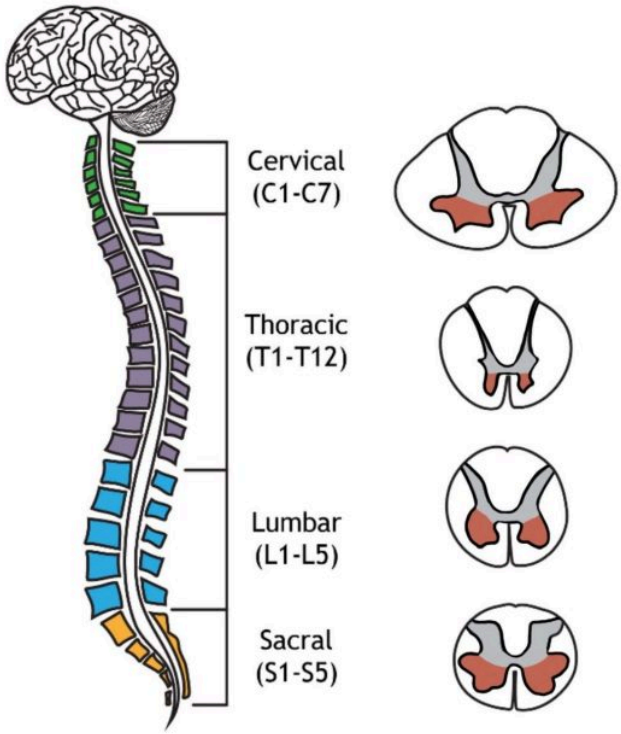


Figure 32.4. Ventral horn anatomy at different levels of the spinal cord. There are 4 divisions of the spinal cord: cervical, thoracic, lumbar, and sacral. The size of the ventral horn (colored in red), where α motor neuron cell bodies are located, changes at the different levels of the spinal cord. The ventral horn is enlarged in the cervical and sacral regions of the spinal cord due to the increased number of motor neurons that are needed for motor control of the arms and legs. The ventral horn is smaller in the thoracic region due to decreased muscle innervation in this area.

Neuromuscular Junction

The lower motor neurons communicate with muscle fibers (muscle cells) at the **neuromuscular junction** (NMJ). The NMJ is similar to other chemical synapses, however the postsynaptic cell is a muscle cell separated by about 30 nm. The presynaptic cell is the motor neuron and the postsynaptic site is the sarcolemma, the cell membrane of the long cylindrical muscle fibers (muscle cells). The neuromuscular junction is one of the largest synapses in the body and one of the most well-studied because of its peripheral location.

The neuromuscular junction is located midway down the length of the muscle fiber. The muscle fiber will contract in response to depolarization traveling down the sarcolemma of the muscle fiber.

The synapse is located midway down the length of the muscle fiber so that the postsynaptic signal can travel in both directions down the long muscle fiber and quickly activate a contraction along the entire cell.

Acetylcholine is the neurotransmitter released at the neuromuscular junction (NMJ), and it acts upon ligand-gated, non-selective cation channels called nicotinic acetylcholine receptors that are present in postjunctional folds of the muscle fiber. Nicotinic acetylcholine receptors allow the influx of sodium ions into the muscle cell. The depolarization will cause nearby voltage-gated channels to open and fire an action potential in the muscle fiber. In a healthy system, an action potential in the motor neurons always causes an action potential in the muscle cell. The action potential leads to contraction of the muscle fiber.

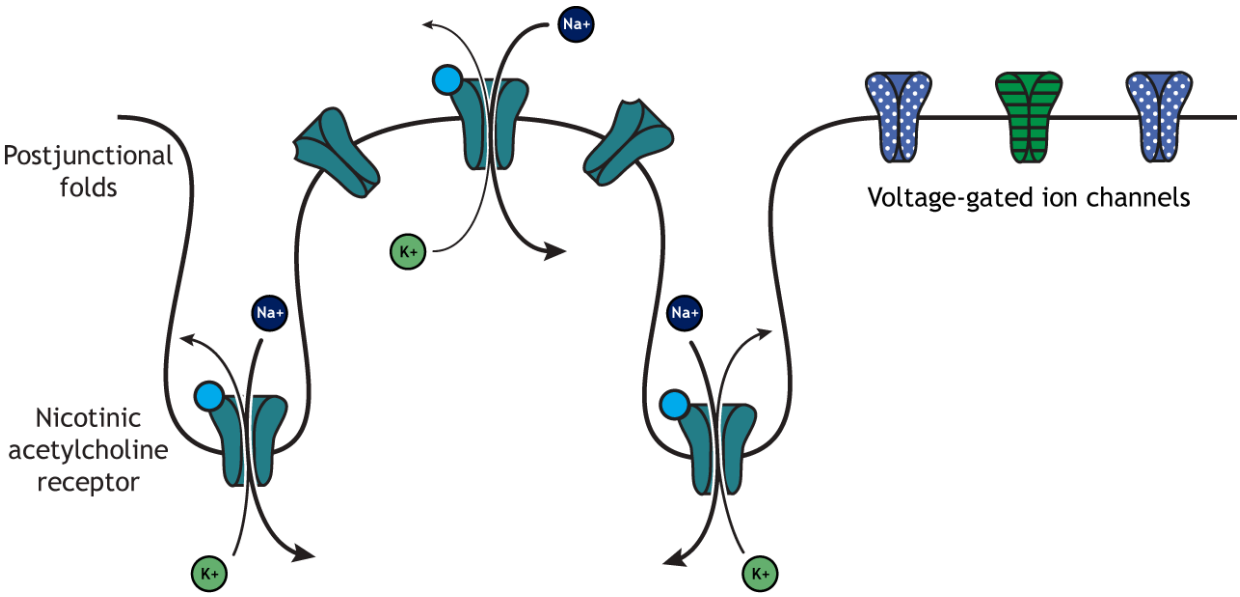


Figure 32.5. The ionotropic nicotinic acetylcholine receptors in the postjunctional folds of the muscle fiber are non-selective cation channels that allow the influx of sodium and the efflux of potassium The depolarization of the cell by the sodium influx will activate nearby voltage-gated ion channels. 'NMJ Ion Flow' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

To review, an action potential traveling down the motor neuron (presynaptic cell) will cause the release of acetylcholine into the synapse. Acetylcholine binds to postsynaptic nicotinic acetylcholine receptors that are located in the folded sarcolemma (increasing surface area), causing depolarization of muscle fibers and ultimately muscle contraction.

Acetylcholinesterase, an enzyme that breaks down acetylcholine and terminates its action, is

present in the synaptic cleft of the neuromuscular junction. Muscle contraction must be tightly controlled. Thus, the actions of acetylcholinesterase are very important to cease muscle contraction quickly.

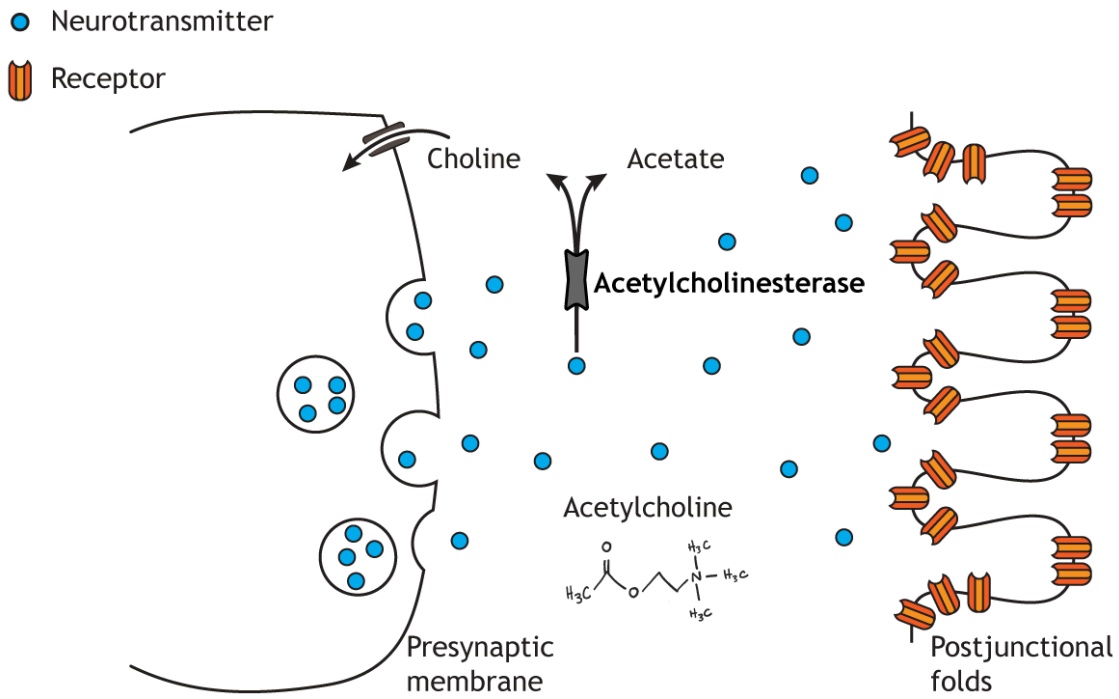


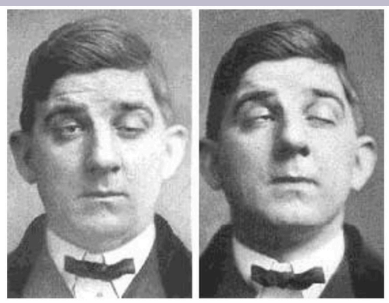
Figure 32.6. The neuromuscular junction (NMJ) is the synapse between a motor neuron and a muscle fiber. Acetylcholine is released at the NMJ and acts on nicotinic acetylcholine receptors located in the postjunctional folds of the muscle fiber. Neurotransmitter action is terminated by breakdown by acetylcholinesterase. 'Neuromuscular Junction' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Clinical Application: Myasthenia gravis

Myasthenia gravis (MG) is an autoimmune disorder characterized by muscle weakness, resulting in difficulty with speech, trouble with movement and swallowing, drooping eyelids, and double vision. Each year, an estimated 20 out of a million people get diagnosed with MG.

The muscle weakness seen in MG results from immune system-mediated destruction of the nicotinic acetylcholine receptors expressed at the NMJ. Thus, when the lower motor neuron releases acetylcholine, the muscle cells are unable to detect this release, so they fail to contract appropriately.

One therapeutic strategy involves inhibition of acetylcholinesterase, the enzyme that degrades acetylcholine. This causes the synaptic acetylcholine to remain in the synapse longer, increasing the chance that receptors get activated. Alternatively, autoimmune diseases like MG can be improved with immunosuppressant therapy. With successful treatment, MG usually does not result in changes in lifespan.



32.7. Myasthenia Gravis. Individuals with Myasthenia Gravis can have symptoms such as drooping eye lids and weak facial muscles.

Motor Units

Importantly, there are many more muscles cells than there are motor neurons. One alpha motor neuron can innervate multiple fibers within one muscle due to the branching of motor neuron axons. Each axon terminal synapses (innervates) a single muscle fiber. A motor neuron and all the fibers innervated by it are called a **motor unit**. The muscle fibers within one motor unit are often spread throughout the muscle to spread the contraction throughout the full muscle. Further, motor units in a muscle usually contract asynchronously to help protect the muscle from fatigue. A graded contraction of the muscle is produced by activating varying numbers of motor units.

Motor units differ in size. Small motor units are motor units that innervate fewer muscle fibers and thus control fine movements. Small motor units are located in the eyes and fingers, both of which function in fine and precise movements. Large motor units innervate many muscle fibers and are typically found in weight-bearing muscles like the thighs.

The group of motor neurons that innervate all the fibers of one muscle is called a **motor pool**.

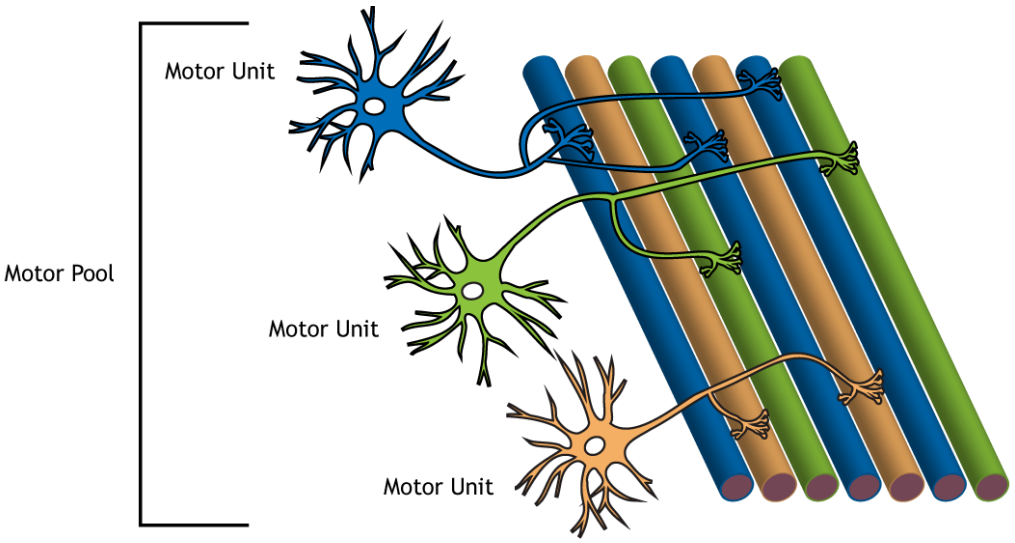


Figure 32.8 Motor neurons can innervate more than one muscle fiber within a muscle. The motor neuron and the fibers it innervates are a motor unit. Three motor units are shown in the image: one blue, one green, one orange. Those three motor units innervate all the muscles fibers in the muscle and are the motor pool for that muscle. 'Motor Unit and Pool'by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Types of Motor Units

In addition to the size of the motor unit, the types of muscle fibers that are innervated by motor units can also differ. There are three different types of motor units:

1. **Slow motor units**. Slow motor units are slow to contract and generate less force but can work for a long time. They are used in endurance exercise like jogging.
2. **Fast fatigue-resistant motor units**. Fast fatigue-resistant motor units are quick to contract (though not as fast the fast fatigable motor units). These motor units generate more force that then slow motor units, but are much more resistant to fatigue than the fast fatigable motor units.
3. **Fast fatigable motor units**. Fast fatigable motor units are quickest to contract and generate the most force. These motor units are more prone to fatigue due to decreased number of mitochondria within the muscles. Fast fatigable motor units generate a lot of force quickly, but also tire quickly. They are used mostly in high intensity exercise like lifting weights and sprinting.

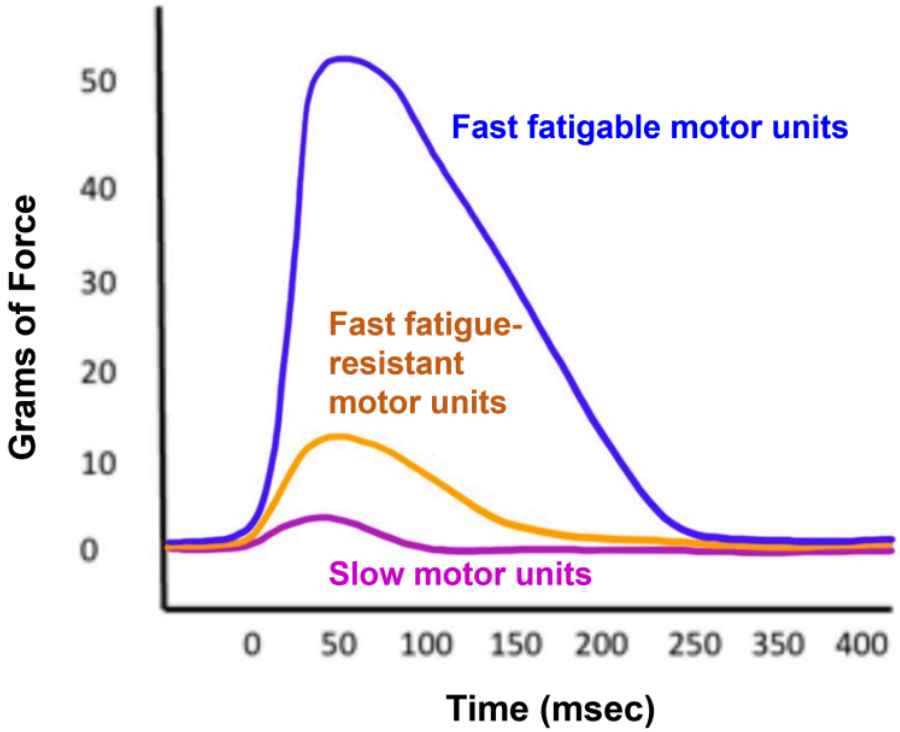


Figure 32.9. Force generated by different types of motor units. Slow motor units are slow to contract and exert very little force (shown in pink). Fast-fatigue resistant motor units are quicker to contract and generate more force than slow motor units. Fast-fatigable motor units are fastest to contract and generate the most force. 'Motor unit force' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Muscle Activation

Action Potential Triggered in a Muscle

When an action potential is triggered in a muscle it causes a **muscle twitch** (contraction) that is followed by a period of relaxation. A muscle twitch shows an increase in tension after a short delay (latent period). During the contraction period, the muscle tension increased, and then has a long relaxation period, causing the muscle tension to be increased long after the initial stimulus.

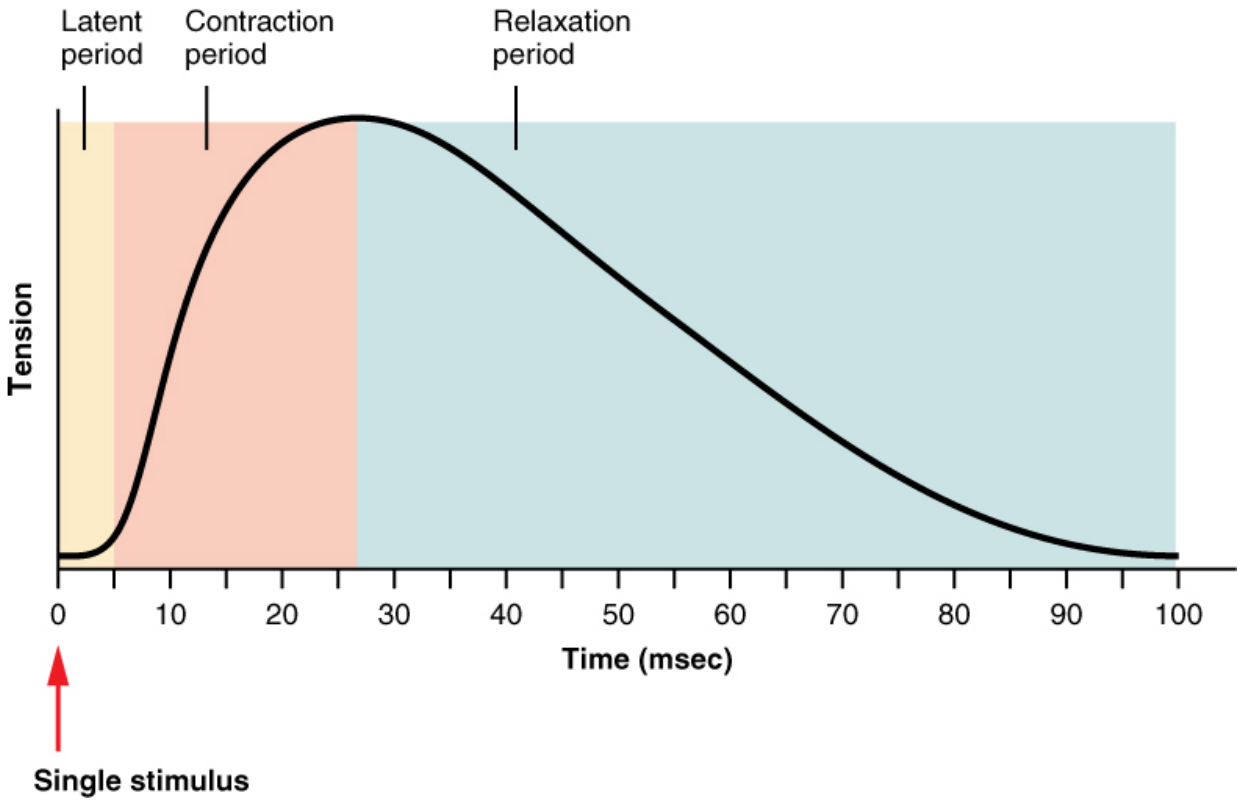


Figure 32.10. Muscle twitch. A stimulus will cause a muscle to experience a twitch. A twitch is characterized by a short latent period following the stimulation, followed by contraction, which increases muscle tension. Following contraction, the muscle has a longer relaxation period until tension returns to baseline.

When a stimulus occurs during the long relaxation period following a muscle twitch, the newly generated muscle twitch will summate to increase the strength of the overall muscle contraction. Shortening the time between stimuli will result in **unfused tetanus** and if stimuli are very close together will result in **fused tetanus**. Therefore, a higher rate of action potentials in the alpha motor neuron will generate more muscle contraction.

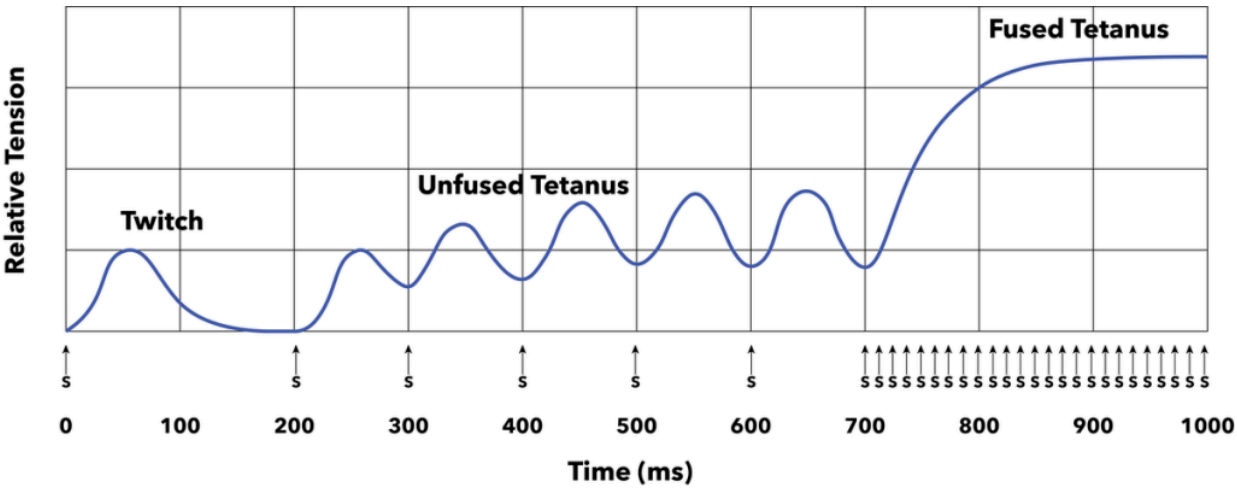


Figure 32.11. Unfused and fused tetanus in muscles. Due to the long relaxation period in muscles, if another stimulus is delivered during the relaxation period, the muscle twitches summate to produce an increase in muscle tension, referred to as 'unfused tetanus'. When stimuli are delivered very close together in time, such that the muscle does not have time to relax, then maximal muscle tension results, also called 'fused tetanus'.

Muscle Recruitment

In addition to the rate of action potentials changing the force of the muscle contraction, **muscle recruitment** can also increase the strength of contraction within a muscle. When generating motor activity, the smallest motor units will be activated to contract first due to their size and increased excitability to move the load. Increasingly larger motor units are recruited to lift heavier loads. Recruitment of motor units allows for us to generate appropriate muscle tension to move a given load. For example, if you need to pick up a pencil, then we do not need to use the same force as if we were trying to pick up a 20-pound weight. Only smaller motor units would be activated to pick up the pencil, and increasingly larger motor units would be recruited to lift the heavier load of the 20-pound weight.

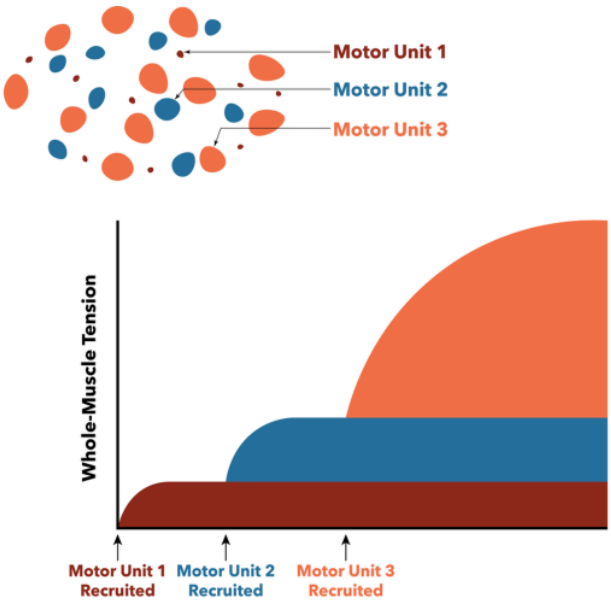


Figure 32.12. Muscle Recruitment. Motor units are recruited in size order to move increasingly heavier loads. For a light load that requires minimal muscle tension, only Motor Unit 1 (shown in red) is recruited. For a medium-heavy load, Motor Unit 2 (shown in blue) is recruited, in addition to Motor Unit 1. The heaviest loads require the additional recruitment of Motor Unit 3 (shown in orange).

Alpha Motor Neuron Inputs

The alpha motor neurons that directly cause muscle contraction receive inputs from three different sources.

1. **Sensory cells from the dorsal root ganglion** that provide sensory information from the muscles through proprioception.
2. **Upper motor neurons from the motor cortex in the brain and brain stem** that are responsible for initiating voluntary movement.
3. **Interneurons in the spinal cord.** These represent the largest input to the alpha motor neurons and can either provide excitation or inhibition to the alpha motor neuron.

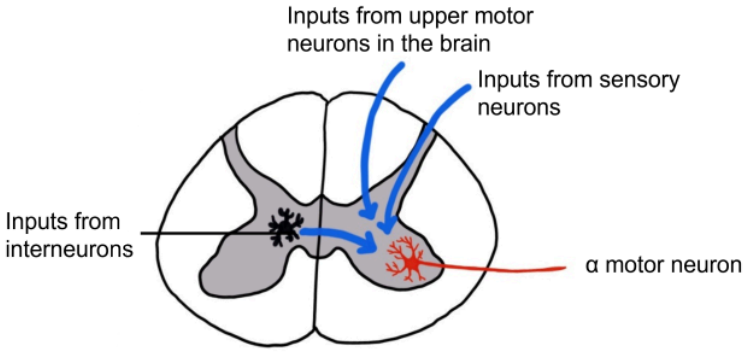


Figure 32.13. Alpha motor neuron inputs. Alpha motor neurons located in the ventral horn of the spinal cord receive inputs from the sensory neurons collecting information from the periphery, upper motor neurons from the brain and brainstem, and from a population of interneurons within the spinal cord. 'Alpha motor neuron inputs' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Proprioception

Raise your arms above your head. Even without seeing your arms, your nervous system has mechanisms that inform you about the location and position of your body parts, including how much your joints are bent. This sense is called **proprioception** and is critically important for coordinated movement and motor reflexes that contribute to those tiny, rapid adjustments that are made while maintaining balance. Proprioceptive information ascends through the spinal cord and into the brain via the **dorsal column-medial lemniscus tract**. Proprioception is also processed in the primary somatosensory cortex.

Proprioception refers to the "body sense" that informs us about how our bodies are positioned and moving in space. **Proprioceptors** are receptors that provide proprioception information.

There are two main types of proprioceptors:

1. **Muscle spindles** measure muscle stretch (muscle length) and transmit this sensory information via 1a sensory afferent fibers. Muscle spindles are nested within and arranged parallel to the extrafusal muscle fibers.
2. **Golgi Tendon Organs** measure muscle tension and transmit this sensory information via 1b sensory afferent fibers. Golgi tendon organs are located between the extrafusal muscle fibers and their points of attachment at the bone.

Muscle Spindles

Extrafusal and Intrafusal Muscle Fibers

Muscle spindles are fibrous capsules that are located within muscles. **Intrafusal muscle fibers** are special muscle fibers that are located within the fibrous capsule of the muscle spindle. The intrafusal muscle fibers are innervated by **gamma motor neurons** that will cause them to contract.

Extrafusal muscle fibers, however, make up the bulk of the muscle and are located outside of the muscle spindle. The extrafusal muscle fibers are stimulated to contract by the **alpha motor neurons**.

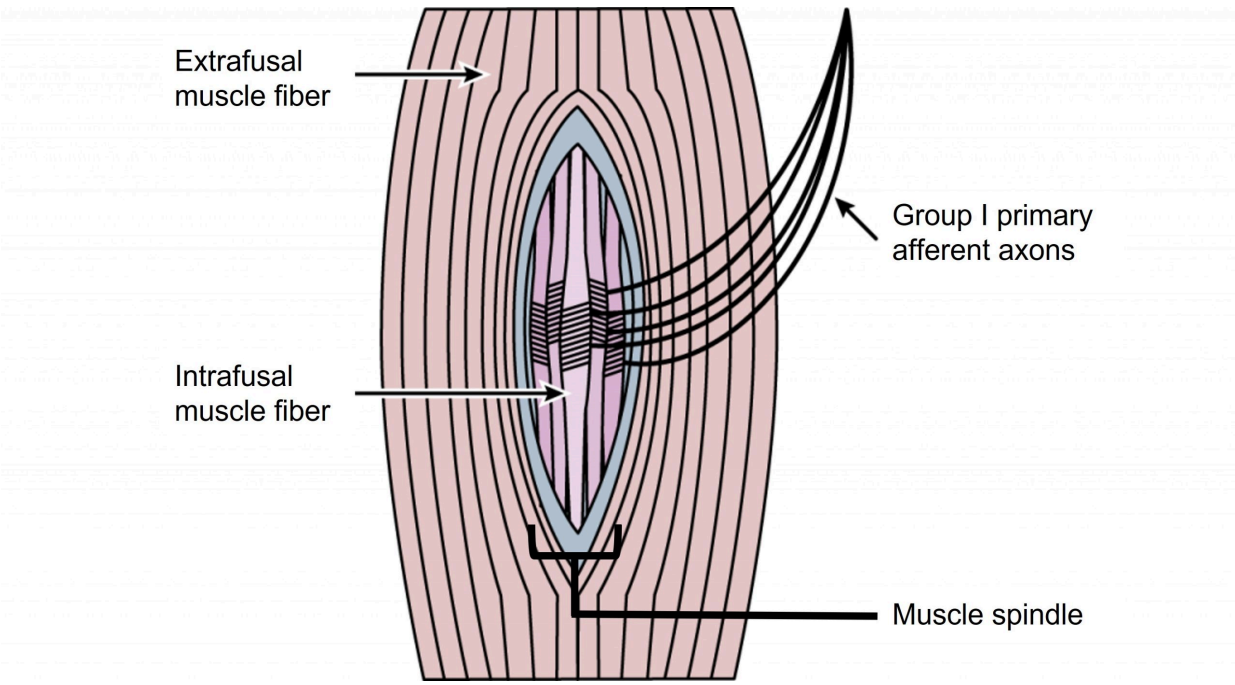


Figure 32.14. Type I primary afferent sensory axons wrap around the intrafusal fibers within the muscle spindle, located deep in the muscle. When the muscle stretches, these sensory neurons are activated. Extrafusal muscle fibers are located outside of the muscle spindle and make up the bulk of the muscle. 'Muscle Spindle' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Muscle Spindles Function

Group 1a sensory afferent axons, which have a large diameter and are heavily myelinated, wrap around the **intrafusal fibers** contained within the muscle spindle. These sensory afferent fibers will

signal when the intrafusal fibers of the muscle spindle are experiencing stretch and communicate information about muscle length.

Within the spinal cord, a single sensory 1a afferent axon synapses on every alpha motor neuron within the **motor pool** that innervates the muscle that contains the muscle spindle. This allows for a fast and powerful contraction of the muscle in response to a change in muscle stretch.

Gamma Motor Neuron Function

When the muscle experiences a stretch and the extrafusal fibers are stretched, the muscle spindle and the intrafusal fibers are also stretched (due to being within the muscle and surrounded by the **extrafusal fibers**). When the **muscle spindle** stretches, the 1a sensory axon will start to fire action potentials. The sensory axon synapses with an alpha motor neuron that will then cause the extrafusal muscle fibers to contract. As the extrafusal fibers contract and the muscle shortens, the muscle spindle goes slack, and the 1a axon will no longer fire action potentials as it is no longer being stretched. The **gamma motor neuron** is then activated that innervates the **intrafusal muscle fibers**, causing the intrafusal fibers to contract, allowing the muscle spindle to sense stretch again. Therefore, the gamma motor neuron is critical for allowing the muscle spindle to continue providing information about muscle stretch even when the muscle has experienced contraction.

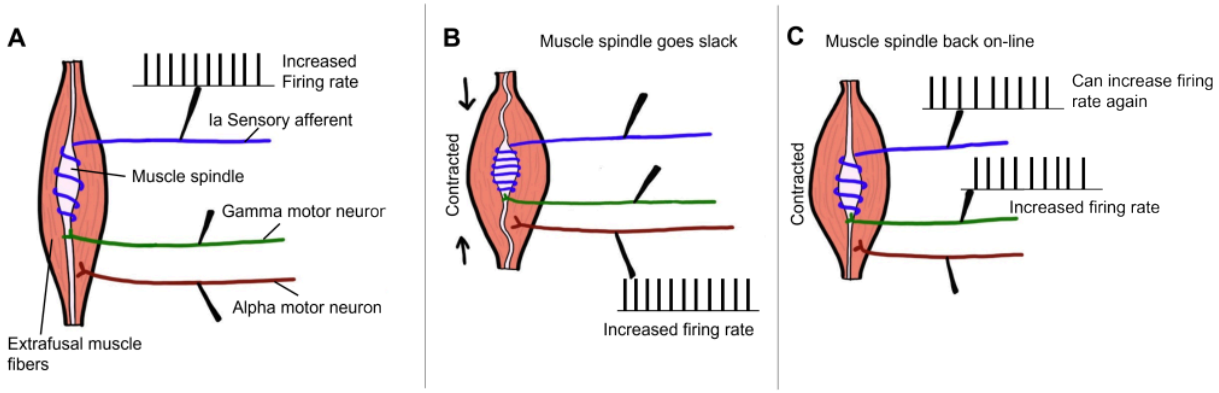


Figure 32.15. Gamma motor neuron function. A. A muscle spindle is shown within a muscle. A 1a sensory afferent is wrapped around the muscle spindle. An electrode is measuring an increase in 1a sensory afferent firing rate when the muscle is stretched. B. In response to stretch, the alpha motor neuron that innervates the extrafusal muscle fibers has an increase in firing rate. At this time, the muscle spindle goes slack and can no longer communicate muscle stretch information via the 1a sensory afferent. C. Gamma motor neuron activity increases to contract intrafusal muscle fibers within the muscle spindle. This allows for the muscle spindle to continue to communicate muscle length that is then sensed by the 1a sensory afferent. 'Gamma motor neuron function' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Golgi Tendon Organ

The **Golgi tendon organ** is a proprioceptor that measures muscle tension, or the force of contraction. They also contribute to our detection of weight, as we lift something heavy for example. Golgi tendon organs are located in the tendon that connects the muscle to bone. The tendon is made up of collagen fibrils and the **Group 1b sensory axons** are intertwined within the collagen fibrils. When the muscle experiences an increase in tension, the collagen fibrils surrounding the 1b sensory axon physically squeeze the 1b axon, opening mechanically-gated ion channels within the 1b sensory axon.

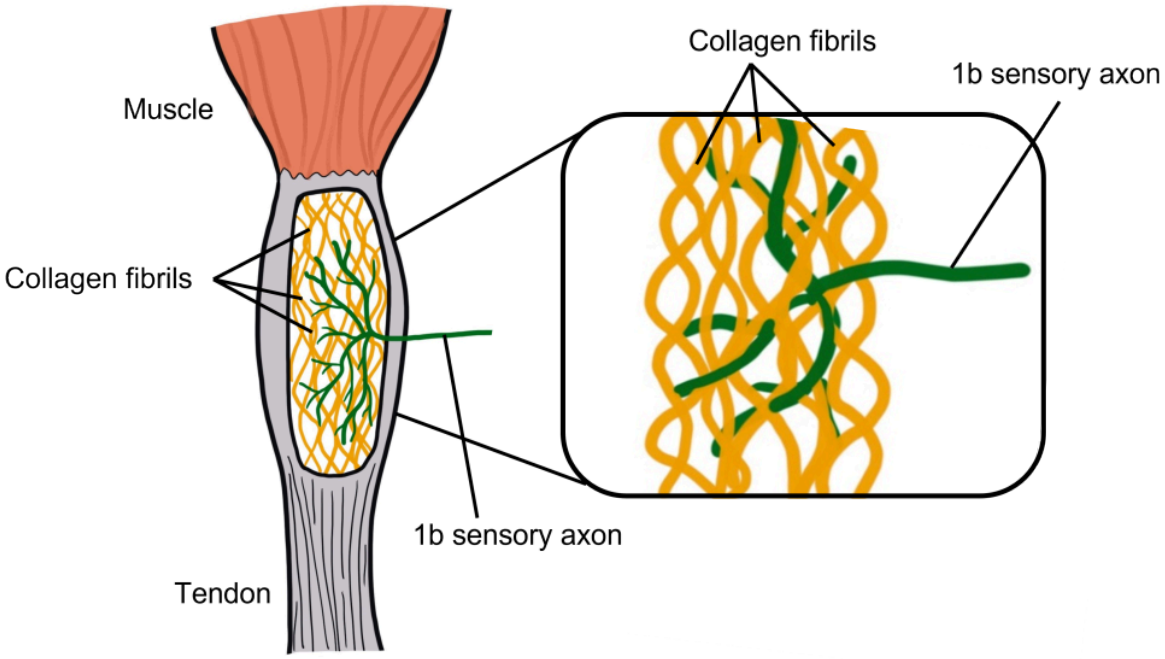


Figure 32.16. Golgi tendon organ. Golgi tendon organs are located within muscle tendons. A Group 1b sensory axon intertwines within the collagen fibrils of the muscle tendon. When the muscle experiences an increase in tension, the collagen fibrils squeeze the 1b sensory axon, causing a signal to travel down the 1b axon toward the spinal cord. 'Golgi tendon organ' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The purpose of the Golgi tendon organ is to allow for an optimal range of tension for the muscle and to protect the muscle from injury due to being overloaded. This is accomplished through a negative feedback loop controlled by the Golgi tendon organ. When the muscle experiences an increase in muscle tension, the 1b sensory axon starts to fire action potentials. The sensory neuron synapses onto an inhibitory interneuron within the spinal cord, which when active will release GABA onto the alpha motor neuron that innervates the same muscle that experienced the increase in muscle tension to begin with. When GABA binds to the alpha motor neuron, it will decrease firing of the alpha motor neuron, leading to a decrease in contraction of the muscle. This is an example of negative feedback as the increased muscle tension ultimately leads to physiological changes that decrease muscle tension.

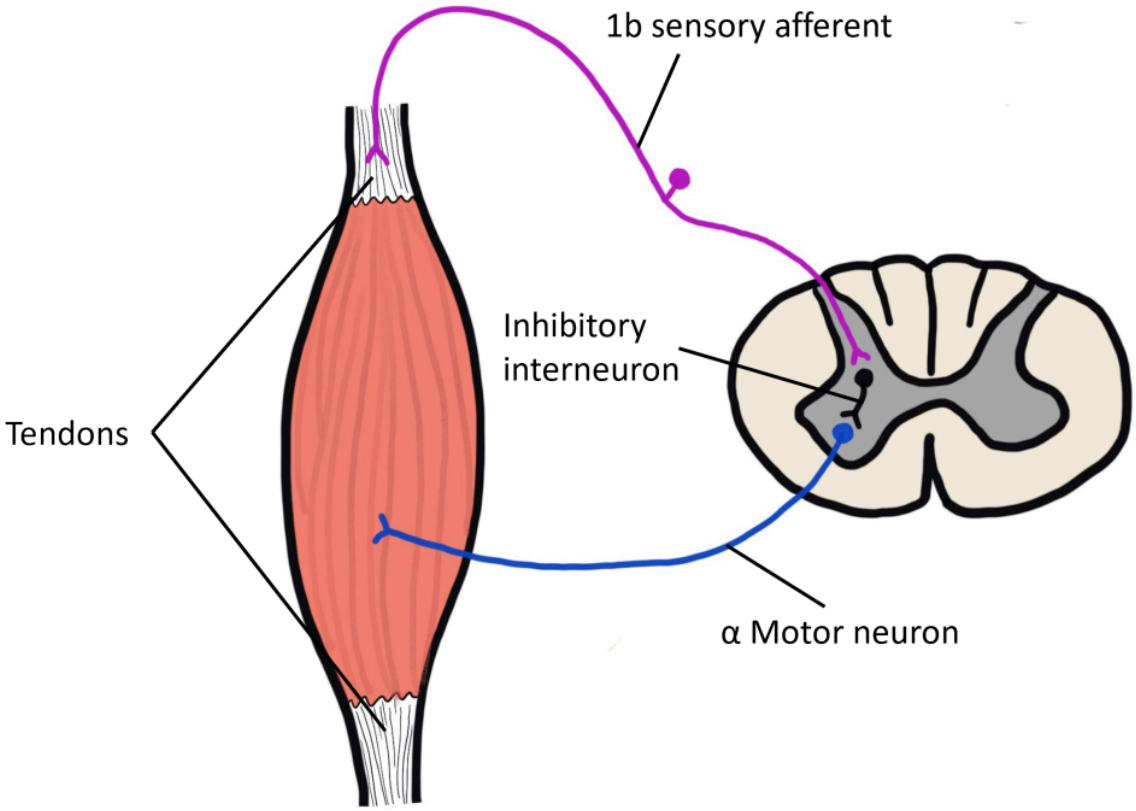


Figure 32.17. Golgi tendon organ signaling. An incrase in tension within the muscle, will cause activity of a 1b sensory axon that travels through the dorsal side of the spinal cord, where it synapses onto an inhibitory interneuron within the spinal cord. Activation of the inhibitory interneuron will cause it to release GABA onto the α motor neuron within the ventral horn of the spinal cord, inhibiting the α motor neuron from firing. This will lead to a decrease in contraction of the muscle that is innervated by the α motor neuron. 'Golgi tendon organ signaling' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- Motor neuron cell bodies are located in the ventral horn of the spinal cord.
- Motor neuron axons are located in the peripheral nervous system and travel to muscles via spinal nerves.
- Acetylcholine is released at the neuromuscular junction and acts upon ionotropic nicotinic acetylcholine receptors.
- The spinal cord is topographically organized.
- Muscle twitches can summate to increase muscle tension.
- A motor unit is an alpha motor neuron and all of the motor fibers that it innervates. Motor units differ in size, recruitment, and power.
- Muscle spindles and Golgi tendon organs are proprioceptors that communicate information about the location and position of the body.

Test Yourself!

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Additional Review

1. What is the difference between a motor unit and a motor pool?

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33.

SPINAL REFLEXES

Reflexes

Reflexes are involuntary motor responses that are performed automatically and independent of brain signals (although some can be suppressed voluntarily, with extra effort). Reflexes involve very simple circuits, sometimes consisting of only two populations of neurons: Sensory information comes in from the periphery, synapsing onto motor neurons in the brainstem or spinal cord. Reflexes can take place as quickly as 1/100th of a second!

Resources

- Glossary terms
- Key Takeaways
- Test yourself!

Stretch Reflex

When a muscle is stretched, this stretches the associated **muscle spindle**, which activates a 1a sensory afferent neuron that has its cell body located in the dorsal root ganglion. The sensory axon enters the dorsal side of the spinal cord where it makes two synapses:

1. A direct synapse onto a motor neuron in the spinal cord gray matter. The axon of the motor neuron exits the spinal cord and innervates the stretched muscle, causing it to contract.
2. A synapse onto an inhibitory interneuron that then synapses onto a separate motor neuron that innervates the antagonistic muscle.

The **myotatic reflex**, also called the patellar, or knee-jerk reflex, is an example of a stretch reflex and occurs in response to activation of the **muscle spindle** stretch receptors. This reflex is commonly tested at a doctor's visit when the doctor taps your knee with a little hammer. This usually results in the lower

leg kicking up slightly. The synaptic communication for this reflex takes place completely within the spinal cord and requires no input from the brain.

The knee is tapped on the tendon that connects to the quadriceps muscle. The tapping of the tendon stretches the tendon and as a result causes the quadriceps muscle to stretch, activating the stretch receptors. Sensory information travels to the dorsal horn of the spinal cord where it synapses on alpha motor neurons that innervate the quadriceps muscle. Activation of the motor neurons contracts the quadriceps, extending the lower leg. This is called a monosynaptic communication because there is only one synapse between the sensory input and the motor output. The reflexive kick is controlled at the level of the spinal cord and cannot be intentionally suppressed by descending motor pathways no matter how hard you concentrate.

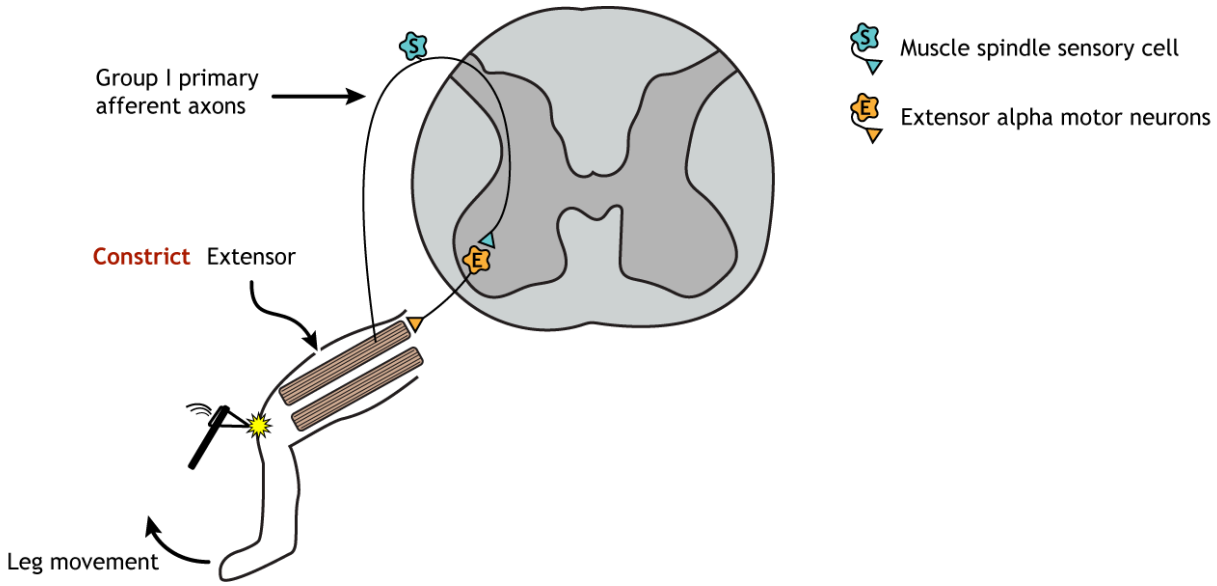


Figure 33.1. When the tendon in the knee is tapped, the extensor muscle is stretched slightly. This stretch activates the Group I sensory afferent axons (blue S neuron in dorsal root ganglion) from the muscle spindles. The sensory neurons synapse on and activate motor neurons (yellow E neuron) that constrict the extensor muscle, causing the leg to kick upward. The stretch reflex is a monosynaptic reflex. 'Stretch Reflex Extensor' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The sensory neurons also synapse on interneurons within the spinal cord that are inhibitory (this means that these neurons make and release GABA). These inhibitory interneurons then synapse on alpha motor neurons that innervate the hamstring, the antagonistic flexor muscle to the quadriceps.

When these motor neurons are inhibited, the hamstring muscle relaxes, allowing the contraction of the quadriceps to occur with more ease. This is called **reciprocal inhibition**.

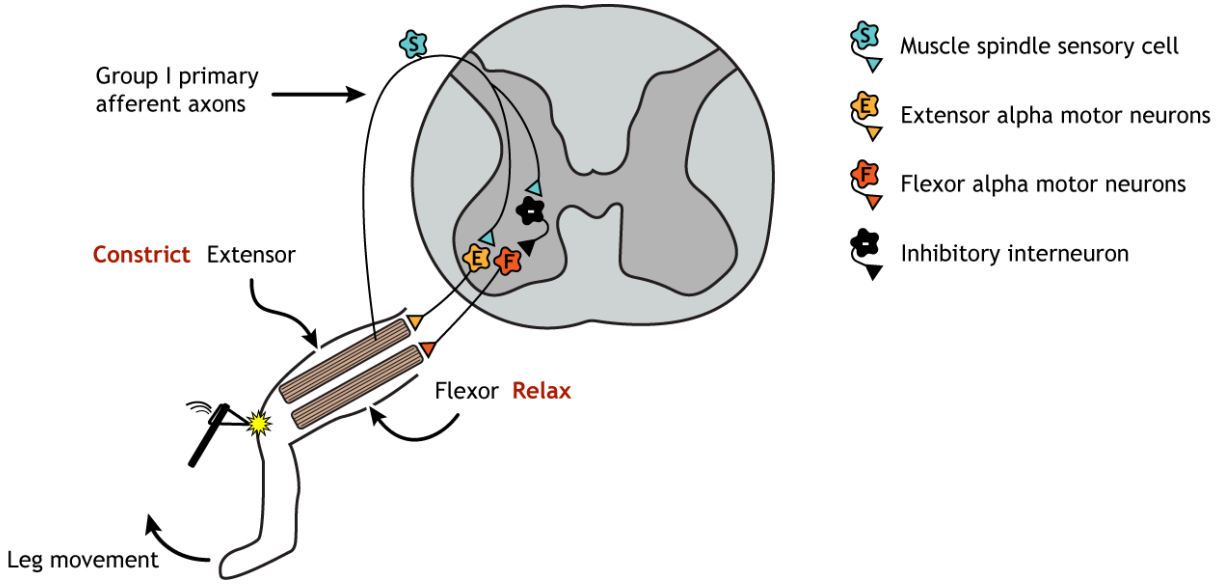


Figure 33.2. In addition to the monosynaptic extensor reflex, the sensory information from the muscle spindle sensory cell (blue S neuron) also activates inhibitory interneurons (black – neuron) in the spinal cord. These interneurons then inhibit the motor neurons (orange F neuron) that innervate the flexor muscle, causing the flexor muscle to relax. This relaxation allows the extensor muscle to kick the leg up with less opposition from the flexor muscle. 'Stretch Reflex' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Withdrawal (Flexor) Reflex

A similar process can be seen in the **withdrawal reflex**. In this case, instead of an extension, the muscles lead to muscle flexion in response to a stimulus. If, for example, you step on something painful, the reflex will be to lift the injured foot. The sensory information that initiates this reflex is activation of pain receptors, or nociceptors. Like with the stretch reflex, the sensory information enters the spinal cord at the dorsal horn. Unlike the stretch reflex, the withdrawal reflex is a polysynaptic reflex, meaning interneurons are present between the sensory neurons and the motor neurons. Excitatory interneurons communicate with the alpha motor neurons of the flexor muscle, whereas inhibitory interneurons communicate with the alpha motor neurons of the extensor muscle. The behavioral response is flexing of the leg upward (the opposite action of the stretch reflex).

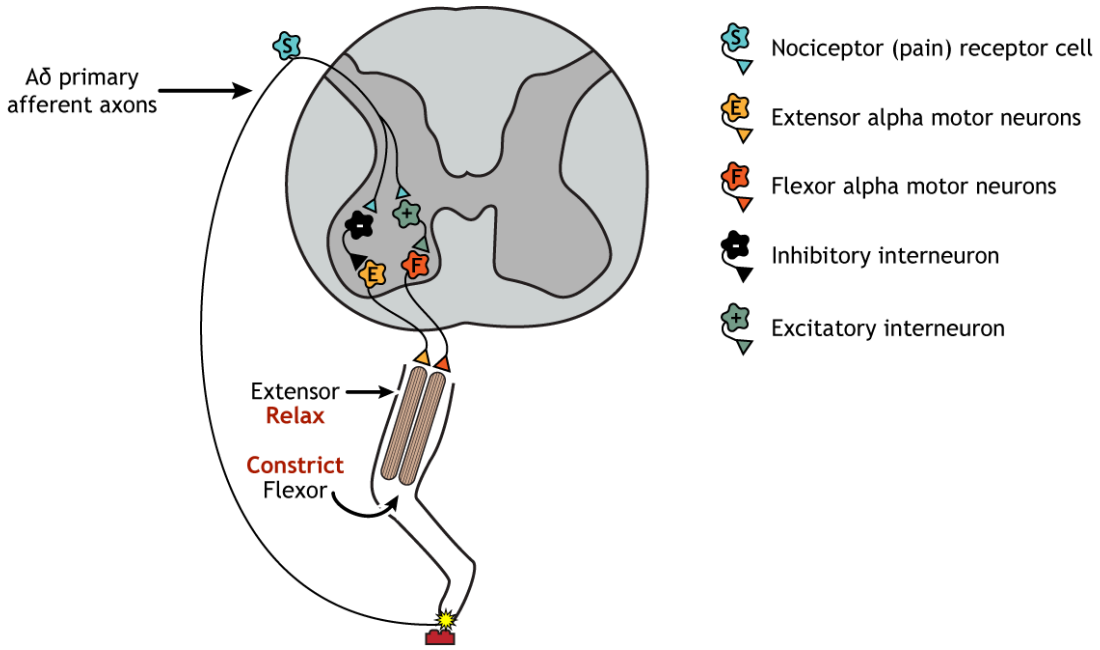


Figure 33.3. Pain information is sent from the periphery to the spinal cord via a nociceptor receptor cell (blue S neuron in dorsal root ganglion). The A delta sensory axons synapse on interneurons within the spinal cord. Excitatory interneurons (green + neuron) activate motor neurons (orange F neuron) that constrict the flexor muscle. Inhibitory interneurons (black – neuron) inhibit motor neurons (yellow E neuron) that innervate and relax the extensor muscle. The leg lifts in response. 'Withdrawal Reflex' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Crossed-Extensor Reflex

Running in parallel to the withdrawal reflex is the **crossed-extensor reflex**. If you step on something sharp and lift that leg, your other leg needs to be able to support your weight shift, or you would fall. This is accomplished by interneurons that cross the midline of the spinal cord and communicate with motor neurons on the contralateral side of the body. The painful sensory information that initiated the withdrawal reflex also initiates the crossed-extensor reflex. In addition to the **ipsilateral** interneurons active in the withdrawal reflex, the sensory axons also synapse on excitatory interneurons that cross the midline. These interneurons then synapse on excitatory interneurons that activate the alpha motor neurons of the extensor muscle and inhibitory interneurons that inhibit the alpha motor neurons of the flexor muscle (the opposite configuration to the withdrawal reflex). This leads to the leg extending, providing a stable base for the weight shift.

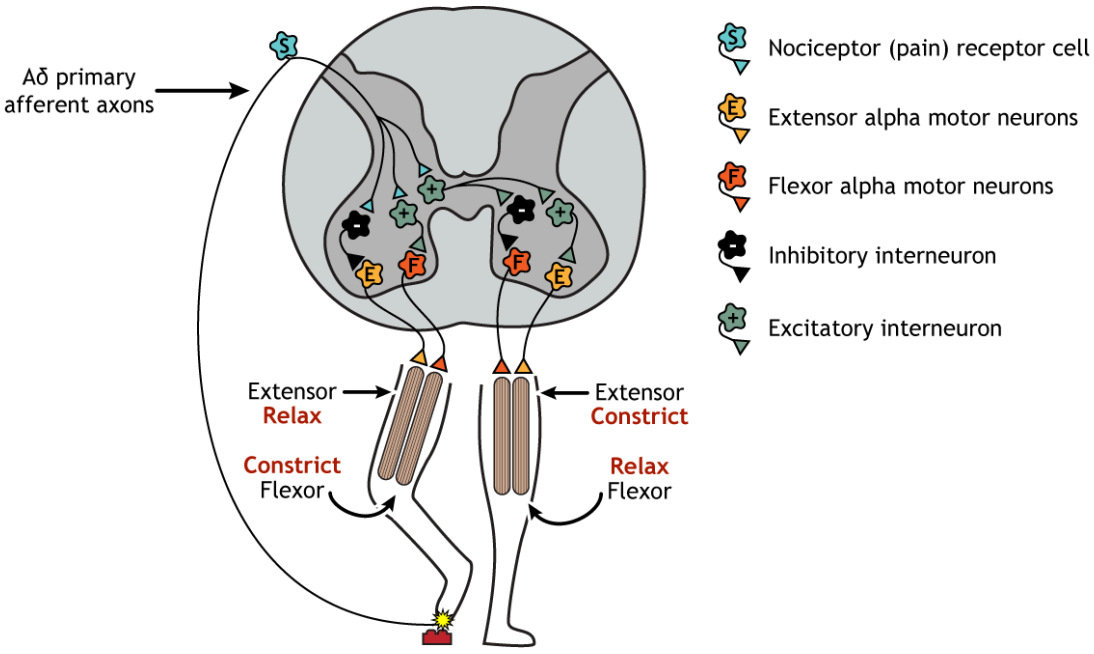


Figure 33.4. If the leg lifts due to the withdrawal reflex, the opposite leg must stabilize via contraction of extensor muscles to balance the body. This is accomplished by excitatory spinal interneurons that cross the midline and communicate the sensory information to the contralateral side of spinal cord. Inhibitory interneurons cause relaxation of the contralateral flexor muscles, and excitatory interneurons cause constriction of the contralateral extensor muscles. 'Crossed-Extensor Reflex' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- Control of reflexes occurs within the spinal cord and input from the brain is not needed.

Test Yourself!

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34.

CENTRAL PATTERN GENERATORS

Central pattern generators (CPGs) are networks of cells that are capable of producing intrinsic motor responses even in the absence of sensory or brain inputs. These motor responses are usually well-rehearsed, repetitive, and happen at the unconscious level, meaning that certain behavioral outputs can be performed independently of signals upstream in the motor cortex.

Resources

- Glossary Terms
- Key takeaways
- Test yourself!

CPGs have been observed in several organisms, ranging from insects, crayfish, birds, and mammals including humans, hinting that their evolution was highly adaptive for survival. Imagine how difficult it would be to survive if every breath required a conscious thought! The CPG is not a standalone driver of motor activity, however. The circuits receive signals from higher brain areas which can modify their characteristics. Imagine that you want to consciously hold your breath, or intentionally walk in some unusual or goofy way. In both cases, the descending signals from the brain are able to override the output motor command pattern that the CPG normally produces. Once you stop intentionally changing your motor behavior, the muscles return to their normal activity in response to CPG output.

Central Pattern Generators in Different Species

Many earlier studies of spinal cord CPGs were conducted in different animal groups with unique locomotor patterns. Mollusks have crawling activity that is rhythmic, fish swim by sending alternative patterns of muscle activity through their body, and birds fly by rhythmic flapping of their wings.

In mammals, spinal CPGs were demonstrated in cats with a thoracic-level spinal cord transection. Following this surgery, the signals from the brain were unable to be communicated down to the hind

legs, eliminating voluntary movement. They exhibited weakened muscular power, but were still able to stand for short times. If their front paws were put onto a stable platform while their hindlegs were put on a moving treadmill, the cat would involuntarily walk to keep up.

Humans also have CPGs for movement. One remarkable study looked at 37-year-old man who had injured his spinal cord in a football accident as a young man. His injury was at the level of C5, resulting in complete paralysis and a loss of sensation from the neck down. Over the following years, he gradually recovered a small amount of function. Fine manipulation skills and bladder bowel control never recovered, and he had not walked unassisted for ten years, experiencing tremendous weakness after taking a few steps. Just days after beginning a physical therapy regimen consisting of assisted upright walking, upon lying down, the man reported alternating muscle flexion and relaxation of the hips, knees, and ankles similar to the pattern of activity seen in locomotion. He was unable to voluntarily stop these motions, and could only get some rest by turning to the side. This muscle activity was smooth and rhythmic, as would be seen in a healthy person walking.

Locomotion

Some example motor responses driven by CPGs include diaphragm movement (respiration), alternating leg swinging and foot flexing (walking), and the progressive contraction of up to 25 pairs of muscles in the tongue and mouth (swallowing). Some CPGs are located in the brain stem (respiration) and others throughout the spinal cord (locomotion). Locomotion is one example of a basic, rhythmic movement that requires coordination of a number of muscle groups to work properly.

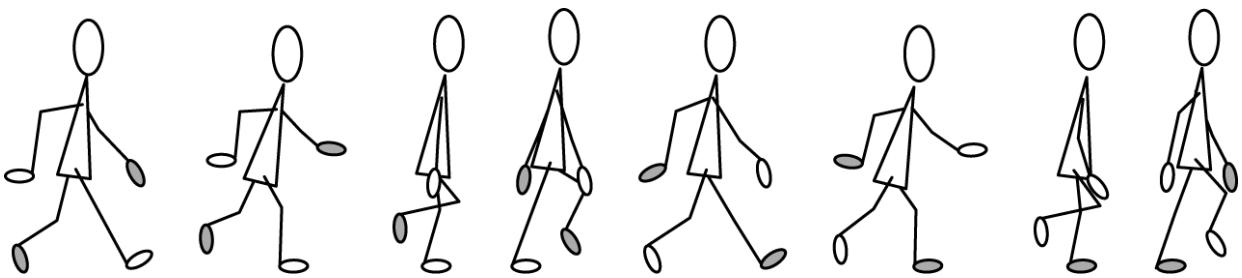


Figure 34.1. Walking cycle of a human. The arms and legs must be coordinated in opposing fashion during locomotion. The gray hand and foot are left side limbs. When one is in front of the body, the other is behind. 'Walking Cycle' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Activity of extensor and flexor muscles in both legs must be coordinated to allow smooth locomotion

without falling. These rhythmical movements are controlled at the level of the spinal cord by circuits called central pattern generators. The spinal cord has circuitry that, in the case of walking, moves the legs in opposite patterns. When one leg is lifting up to move forward, the other leg is stable, touching the ground.

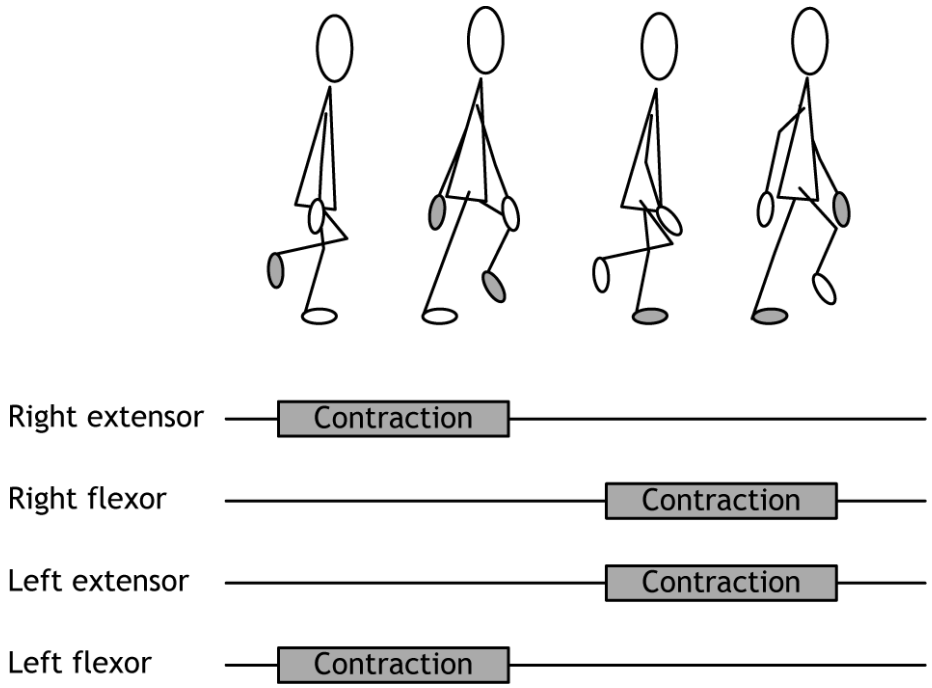


Figure 34.2. While walking, there must be coordinated, reciprocal activation of the extensor and flexor muscles of each leg; as an extensor is contracted (gray bar) the flexor must relax. Additionally, the muscle activation of one leg must be the opposite of the other leg, so the right extensor and the left flexor are activated at the same time. 'Walking Cycle Muscle Activation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Spinal Circuitry

The control of this system has multiple levels. Neurons themselves may have pacemaker properties that allow for a continuous cycle of depolarization and repolarization. These neurons are then located within multi-cell circuits involving a collection of excitatory and inhibitory interneurons that results in reciprocal inhibition of contralateral muscles. Additional networks of spinal interneurons would cause reciprocal inhibition of ipsilateral antagonistic muscles.

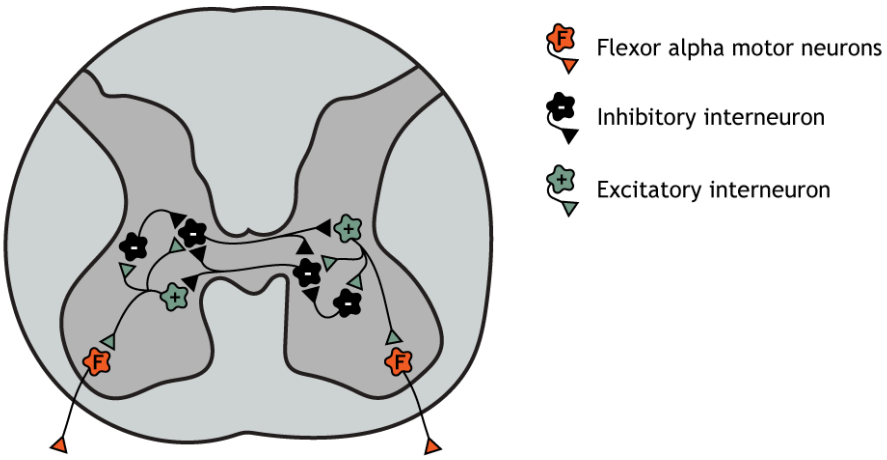


Figure 34.3. Central pattern generators are controlled by interneuron circuitry within the spinal cord. The circuit would require the motor neurons on the opposite side of the spinal cord to be activated in a reciprocal fashion. This is accomplished through a network of excitatory and inhibitory interneurons that allow for the flexor (or extensor) muscle on one side of the body to control while the contralateral muscle relaxes. 'Central Pattern Generator Circuit' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Although the spinal cord is able to control these movements on its own, there is input from both the brainstem and sensory neurons which can have an effect on modulating the pattern of neuronal activity in the spinal cord. For example, when an animal needs to slow down, speed up, or turn away from a danger, for example, those inputs can alter the spinal cord circuit.

Key Takeaways

- Central pattern generators are circuits in the spinal cord that control repetitive, consistent movements like walking.

Test Yourself!

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35.

PLANNING OF MOVEMENT

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

There are a number of steps that must take place for voluntary movement to occur. Assessment of the surrounding environment and the body's location in space, followed by determining what action is appropriate, and then initiating that action. We will first focus on the cortical regions involved in planning of voluntary movement.

After work, you sit down on the couch to watch one episode of your favorite show. As the end credits appear, you realize it is now time to head to your study space and start working on class. To do this, you need to leave the couch, grab your computer from the table, get your coffee from the kitchen and head to a different room. All of these voluntary movements take a great deal of processing by the brain. You must assess your surrounding environment and your body's location in it, determine which actions need to be completed, and then actually initiate those actions. In this chapter we will focus on how the planning of voluntary movement occurs.

Cortical Anatomy

Much of the cortex is actually involved in the planning of voluntary movement. Sensory information, particularly the dorsal stream of the visual and somatosensory pathways, are processed in the posterior parietal lobe where Visual, tactile, and proprioceptive information are integrated.

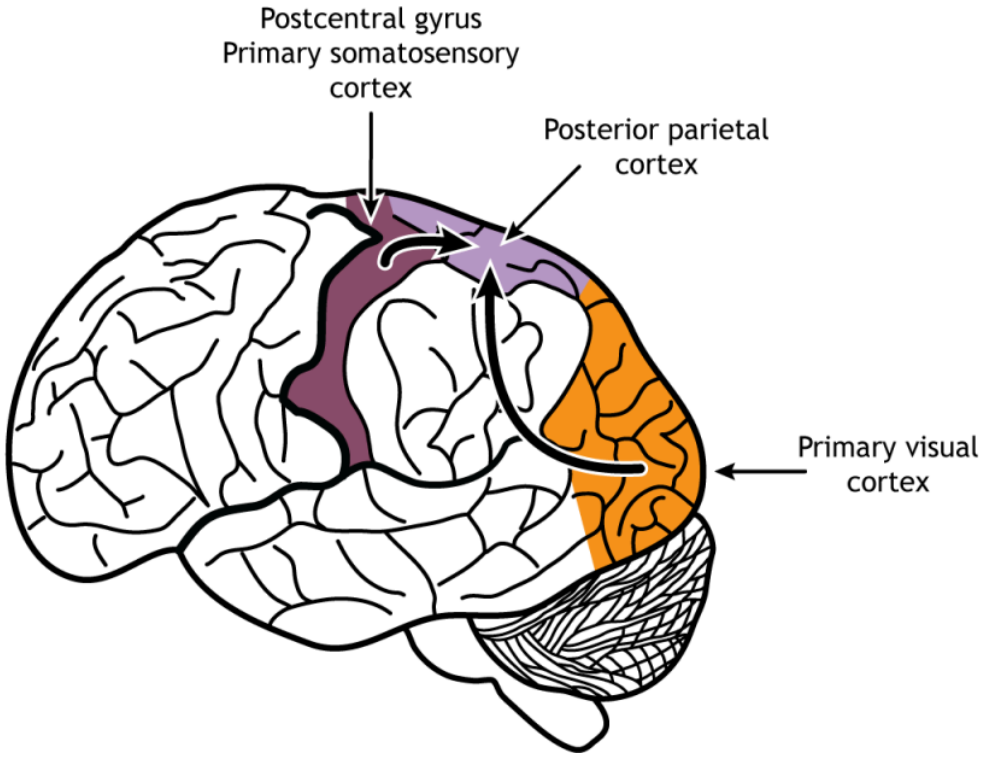


Figure 35.1. Information from multiple sensory systems are processed in the posterior parietal lobe. Projections are sent from the primary somatosensory and primary visual cortices. 'Posterior Parietal by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Connections from the posterior parietal lobe are then sent to both the premotor regions and the prefrontal cortex. The prefrontal cortex, which is located in the front of the brain in the frontal lobe, plays an important role in higher level cognitive functions like planning, critical thinking, and understanding the consequences of our behaviors. The premotor area lies just anterior to the primary motor cortex. This region helps plan and organize movement and makes decisions about which actions should be used for a situation.

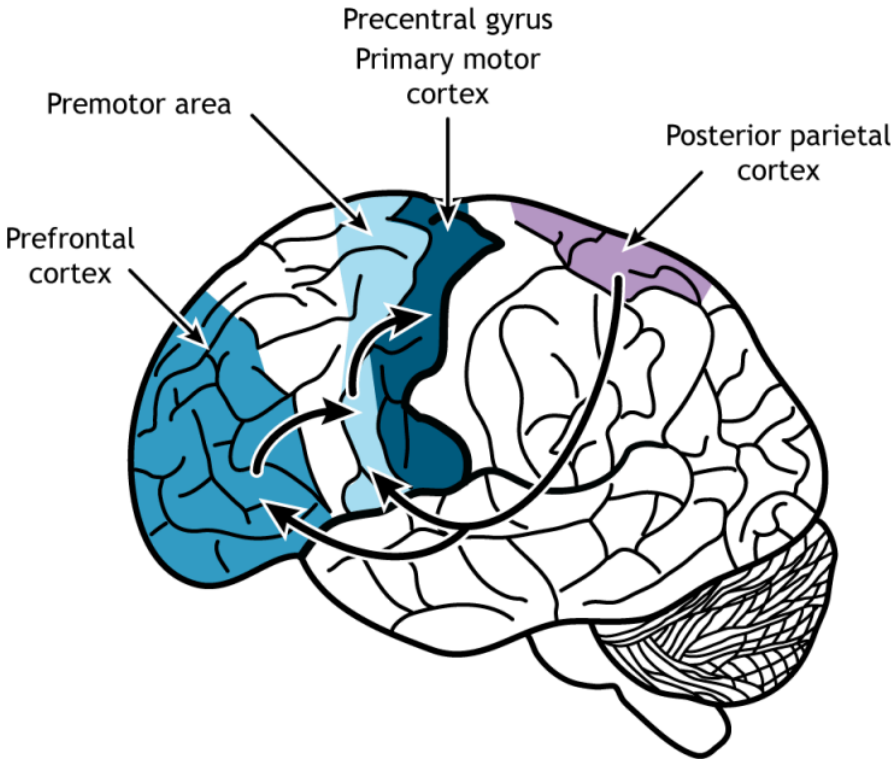


Figure 35.2. Sensory information from the posterior parietal is processed in the prefrontal cortex and premotor area, both located in the frontal cortex. These areas then send information to the primary motor cortex located in the precentral gyrus. 'Motor Regions' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the primary motor cortex using the BrainFacts.org 3D Brain

View the premotor cortex using the BrainFacts.org 3D Brain

View the prefrontal cortex using the BrainFacts.org 3D Brain

Role of Premotor Area

The premotor regions do send some axons directly to lower motor neurons in the spinal cord using the same pathways as the motor cortex (see Execution of Movement chapter). However, the premotor cortex also plays an important role in the planning of movement. Two experimental designs have demonstrated this role. Monkeys were trained on a panel that had one set of lights in a row on top and one set of buttons that could also light up in a row on the bottom. The monkeys would watch

for a top row light to turn on. This would indicate that within a few seconds, the button directly below would light up. When the button turned on, the monkeys were supposed to push the button.

Therefore, there were two light triggers in the experiment. The first required no motor movement from the monkey but did give the monkey information about where a motor movement would be needed in the near future. The second required the monkey to move to push the button. When brain activity was measured during this study, neurons in the premotor cortex became active when the first light trigger turned on, well before any movement actually took place (Weinrich and Wise, 1928).

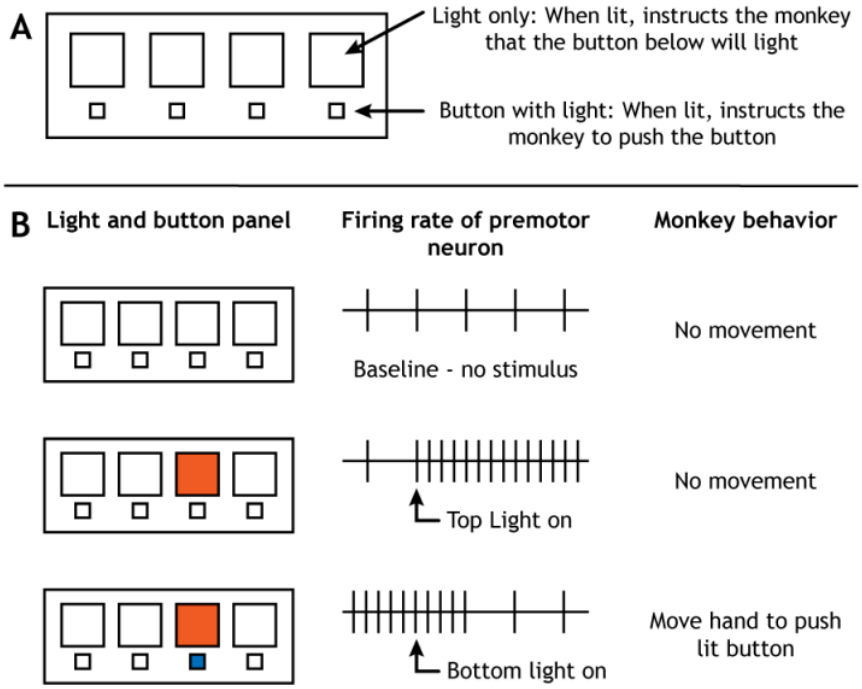


Figure 35.3. (A) Monkeys were trained to use a light panel. When lit, a light located in the top row informed the monkey that the button directly below would light up soon. Shortly after one of the top row lights turned on, the button directly below it would turn on, and the monkey would need to push that button for a reward. (B) When no lights are lit, premotor neurons fire at a baseline rate, and the monkey does not move. Neurons located in the premotor cortex increase action potential firing rate when the top row light turns on, even though the monkey makes no movement. The firing stops shortly after the monkey moves to push the bottom button after it turns on. (Based on Weinrich and Wise, 1928) 'Light Panel Experiment' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

In another experiment, people were trained to move their fingers in a specific pattern. Cerebral blood flow was then measured when they repeated the finger pattern and when they only imagined repeating

the finger pattern. When the movement was only imagined and not actually executed, the premotor regions along with parts of the prefrontal cortex were activated (Roland, et al, 1980).

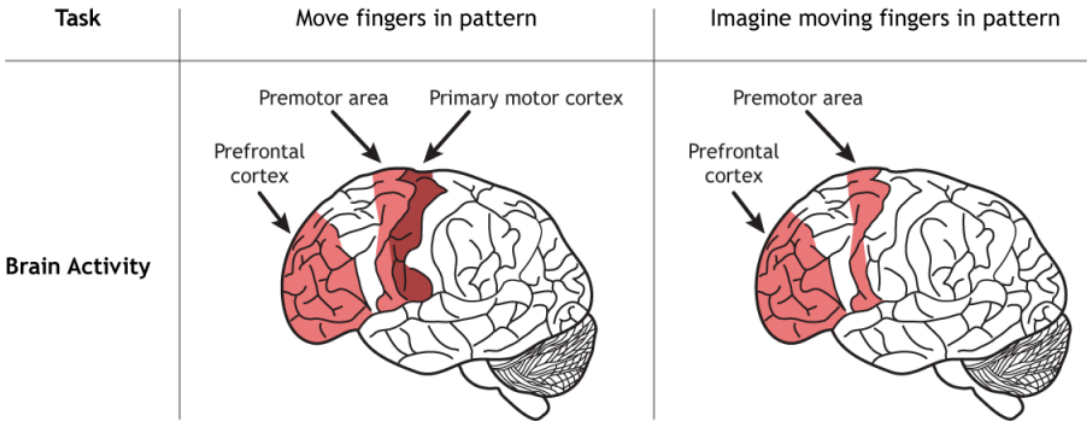


Figure 35.4. People were trained to move their fingers in a pattern. When the pattern was repeated, brain activity was seen in the primary motor cortex, along with the premotor area and prefrontal cortex. When the pattern was only imagined, and no finger movement took place, brain activity was seen in the premotor area and prefrontal cortex. (Based on Roland, et al, 1980) 'Finger Movement Experiment' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

These studies show that the premotor cortex is active prior to the execution of movement, indicating that it plays an important role in the planning of movement. The posterior parietal, prefrontal, and premotor regions, though, also communicate with a subcortical region called the basal ganglia to fully construct the movement plan. The basal ganglia are covered in the next chapter.

Key Takeaways

- Sensory information is processed in the posterior parietal before being sent to motor regions of the brain
- The prefrontal cortex and premotor cortex are critical for creating a movement plan

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=315#h5p-31

Video Lecture

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References

Roland PE, Larsen B, Lassen NA, Skinhøj E. Supplementary motor area and other cortical areas in organization of voluntary movements in man. J Neurophysiol. 1980 Jan;43(1):118-36. doi: 10.1152/jn.1980.43.1.118. PMID: 7351547.

Weinrich M, Wise SP. The premotor cortex of the monkey. J Neurosci. 1982 Sep;2(9):1329-45. doi: 10.1523/JNEUROSCI.02-09-01329.1982. PMID: 7119878; PMCID: PMC6564318.

Attributions

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36.

BASAL GANGLIA

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

The basal ganglia are a group of subcortical nuclei, meaning groups of neurons that lie below the cerebral cortex. The basal ganglia is comprised of the striatum, which consists of the caudate nucleus and the putamen, the globus pallidus, the subthalamic nucleus, and the substantia nigra The basal ganglia are primarily associated with motor control, since motor disorders, such as Parkinson's or Huntington's diseases stem from dysfunction of neurons within the basal ganglia. For voluntary motor behavior, the basal ganglia are involved in the initiation or suppression of behavior and can regulate movement through modulating activity in the thalamus and cortex. In addition to motor control, the basal ganglia also communicate with non-motor regions of the cerebral cortex and play a role in other behaviors such as emotional and cognitive processing.

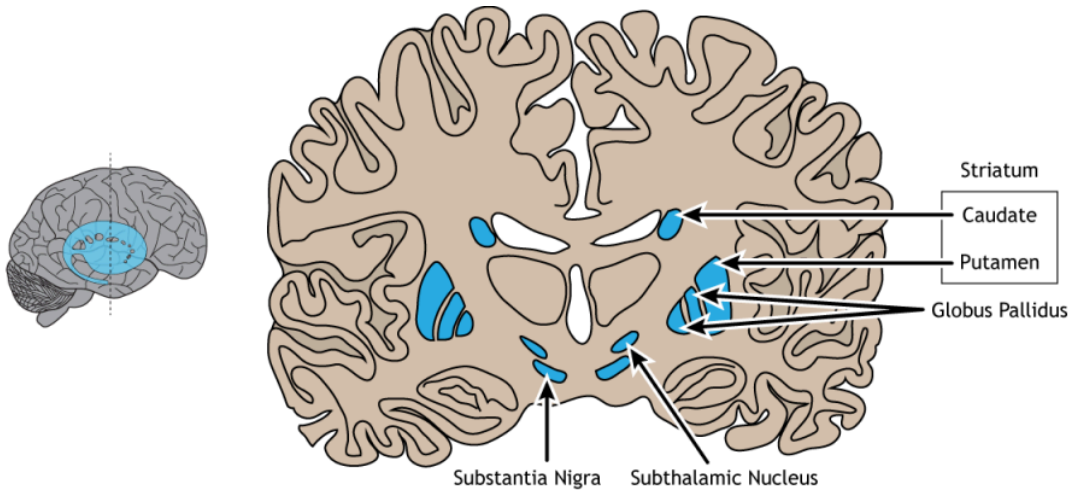


Figure 36.1. The basal ganglia are subcortical structures located at the base of the forebrain. They are comprised of the caudate and putamen, which both make up the striatum, as well as the globus pallidus, substantia nigra, and subthalamic nucleus. 'Basal Ganglia' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the basal ganglia using the BrainFacts.org 3D Brain

Basal Ganglia Input

The majority of information processed by the basal ganglia enters through the striatum. The principal source of input to the basal ganglia is from the cerebral cortex. This input is glumatergic and therefore, excitatory. The substantia nigra is also a region with critical projections to the striatum and is the main source of dopaminergic input. Dopamine plays an important role in basal ganglia function. Parkinson's disease results when dopamine neurons in the substantia nigra degenerate and no longer send appropriate inputs to the striatum. Dopamine projections can have either excitatory or inhibitory effects in the striatum, depending on the type of metabotropic dopamine receptor the striatal neuron expresses. Dopamine action at a neuron that expresses the D1 receptor is excitatory. Dopamine action at a neuron that expresses the D2 receptor is inhibitory.

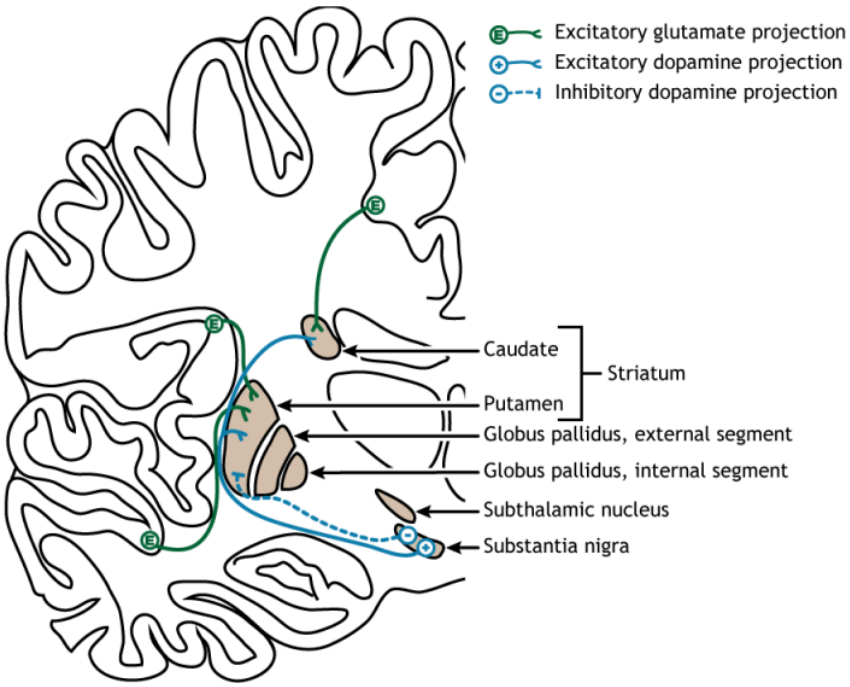


Figure 36.2. Inputs to the basal ganglia enter through the striatum (the caudate and putamen). Cortical projections (shown in green) release glutamate and are excitatory. Substantia nigra projections (shown in blue) release dopamine and can be either excitatory or inhibitory. 'Basal Ganglia Input' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

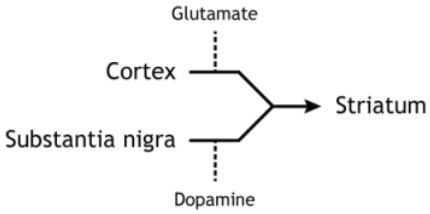


Figure 27.3. The cortex sends glutamate projections to the striatum. The substantia nigra sends dopamine projections to the striatum. 'Basal Ganglia Input – Text' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Basal Ganglia Output

The primary output region of the basal ganglia is the internal segment of the globus pallidus. This region sends inhibitory GABAergic projections to nuclei in the thalamus. This inhibitory output has a tonic, constant firing rate, which allows the basal ganglia output to both increase and decrease depending on the situation. The thalamus then projects back out to the cerebral cortex, primarily to motor areas.

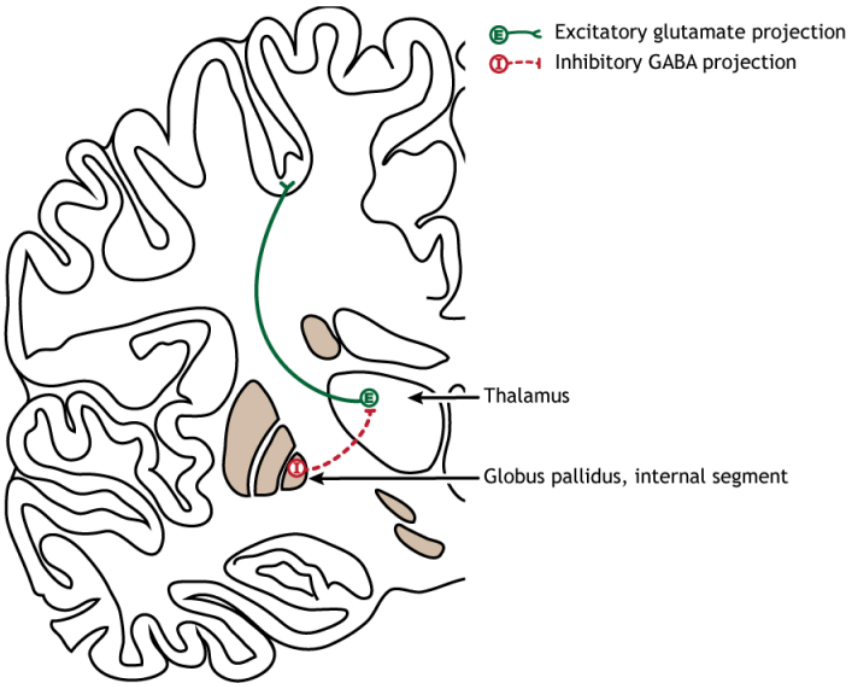


Figure 36.4. Output from the basal ganglia leaves through the internal segment of the globus pallidus. Inhibitory projections (shown in red) release GABA onto the thalamus. Excitatory thalamic projections (shown in green) communicate with the cerebral cortex. 'Basal Ganglia Output' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.



Figure 36.5. The internal segment of the globus pallidus sends GABA projections to the thalamus. The thalamus sends glutamate projections to the cortex. 'Basal Ganglia Output – Text' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Basal Ganglia Internal Processing

Direct Pathway

There are multiple connections within the basal ganglia structures as well. For motor control, there are two main circuits: the direct pathway and the indirect pathway. These circuits have opposing actions when activated by cortical neurons. The circuits are also modulated by dopamine release by the substantia nigra into the striatum. It is believed that the different control mechanisms allow a finely tuned balance between the direct and indirect circuits, which allows for refined control of movement.

The direct pathway begins in the striatum, which sends inhibitory projections to the internal segment of the globus pallidus (GPi). The GPi then sends inhibitory output to the thalamus.

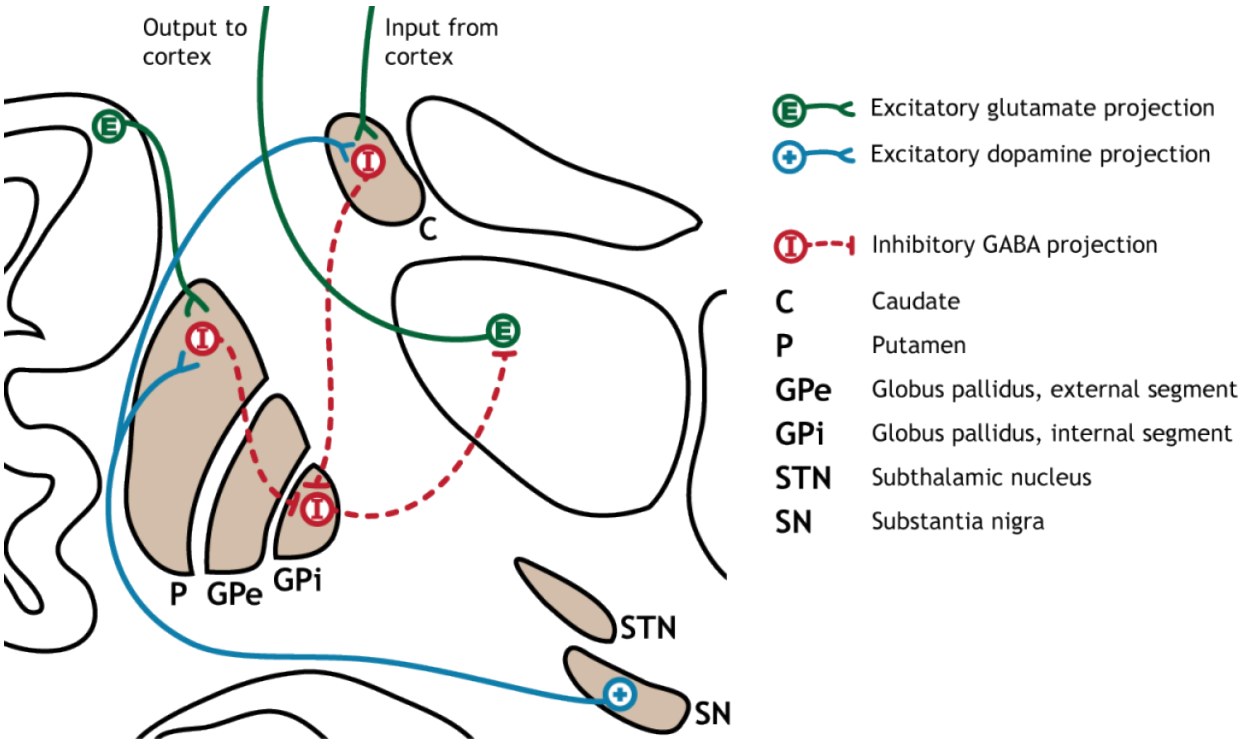


Figure 36.6. The direct pathway in the basal ganglia consists of excitatory input from the cortex via glutamate action or substantia nigra via dopamine action that synapses on inhibitory neurons in the striatum. The striatal neurons project to the internal segment of the globus pallidus (GPi). The GPi then sends inhibitory output to the thalamus. 'Basal Ganglia Direct Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

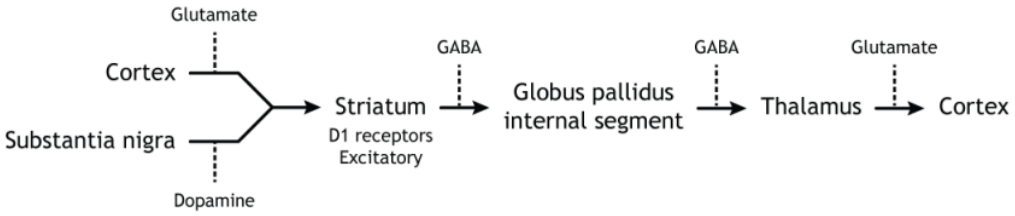


Figure 36.7. The cortex sends glutamate projections to the striatum. The substantia nigra sends dopamine projections to the striatum, which are excitatory, acting on D1 receptors in the neurons involved in the direct pathway. The striatum sends GABA projections to the internal segment of the globus pallidus (GPi). The GPi sends GABA projections to the thalamus. The thalamus sends glutamate projections to the cortex. 'Basal Ganglia Direct Pathway – Text' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Activation of the Direct Pathway

When input from either the cortex or substantia nigra increases in intensity, the direct pathway is activated. The neurons in the striatum involved in the direct pathway express the D1 metabotropic dopamine receptor, and the activation of this receptor is excitatory. Therefore, projections from both the cortex and the substantia nigra activate the neurons in the striatum. Those neurons are inhibitory and release GABA onto the internal segment of the globus pallidus (GPi). As described above, the neurons in the GPi are inhibitory, releasing GABA onto the thalamus. Activation of the striatum neurons inhibit the neurons in the GPi, releasing the inhibition on the thalamus. Inhibition of an inhibitory region is called disinhibition. Therefore, the activation of the direct pathway results in increased output from the thalamus because it is disinhibited.

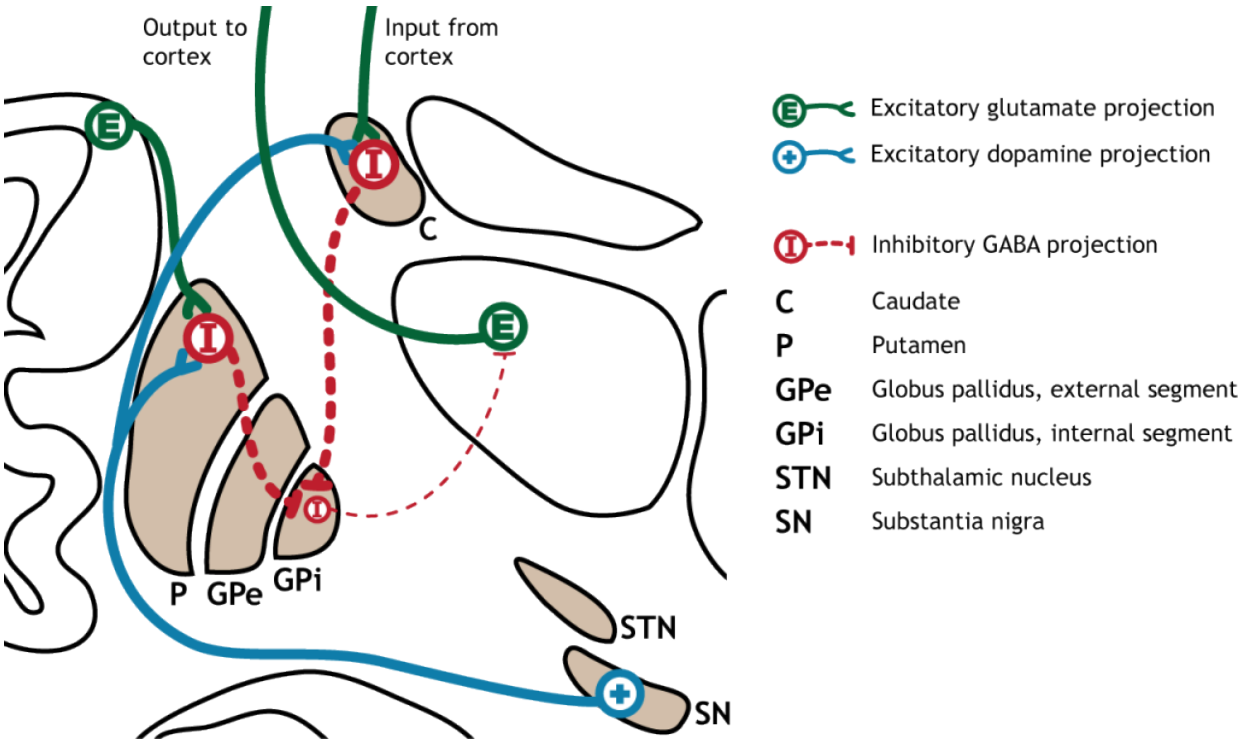


Figure 36.8. Activation of the direct pathway by either increased input from either the cortex or substantia nigra leads to increased inhibitory output from the striatum to the GPi. The inhibition on the GPi leads to less inhibitory input to the thalamus, causing increased output from the thalamus to the cortex. 'Direct Pathway Activation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

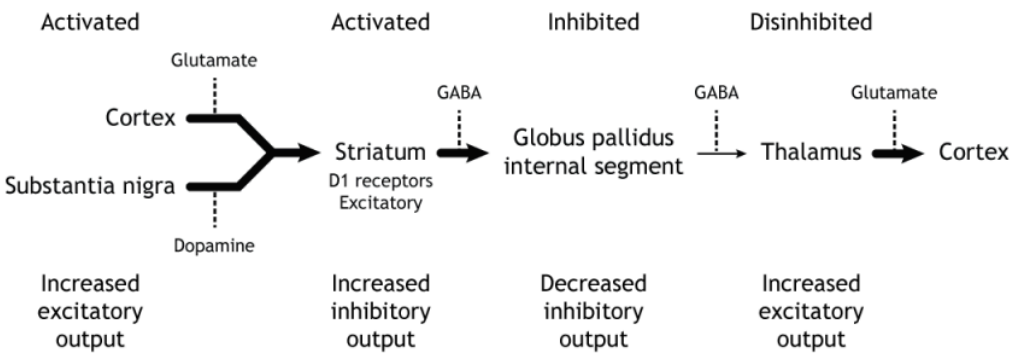


Figure 36.9. When either the cortex or the substantia nigra are activated, they send increased excitatory output to the striatum, which expresses excitatory D1 receptors in the neurons involved in the direct pathway. This input activates the striatum, which sends increased inhibitory projections to the GPi. The inhibited GPi sends decreased inhibitory projections to the thalamus, disinhibiting the thalamus. The thalamus then sends increased excitatory output to the cortex. 'Direct Pathway Activation – Text' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Indirect pathway

The indirect pathway is a little more complex. Like the direct pathway, input into the basal ganglia arises from the cortex and substantia nigra, but there are more internal connections within the basal ganglia that what occurs in the direct pathway. Inhibitory neurons in the striatum involved in the indirect pathway project to the external segment of the globus pallidus (GPe). GABA-ergic neurons in the GPe project to the subthalamic nucleus, which then sends excitatory output to the GPi, which outputs to the thalamus.

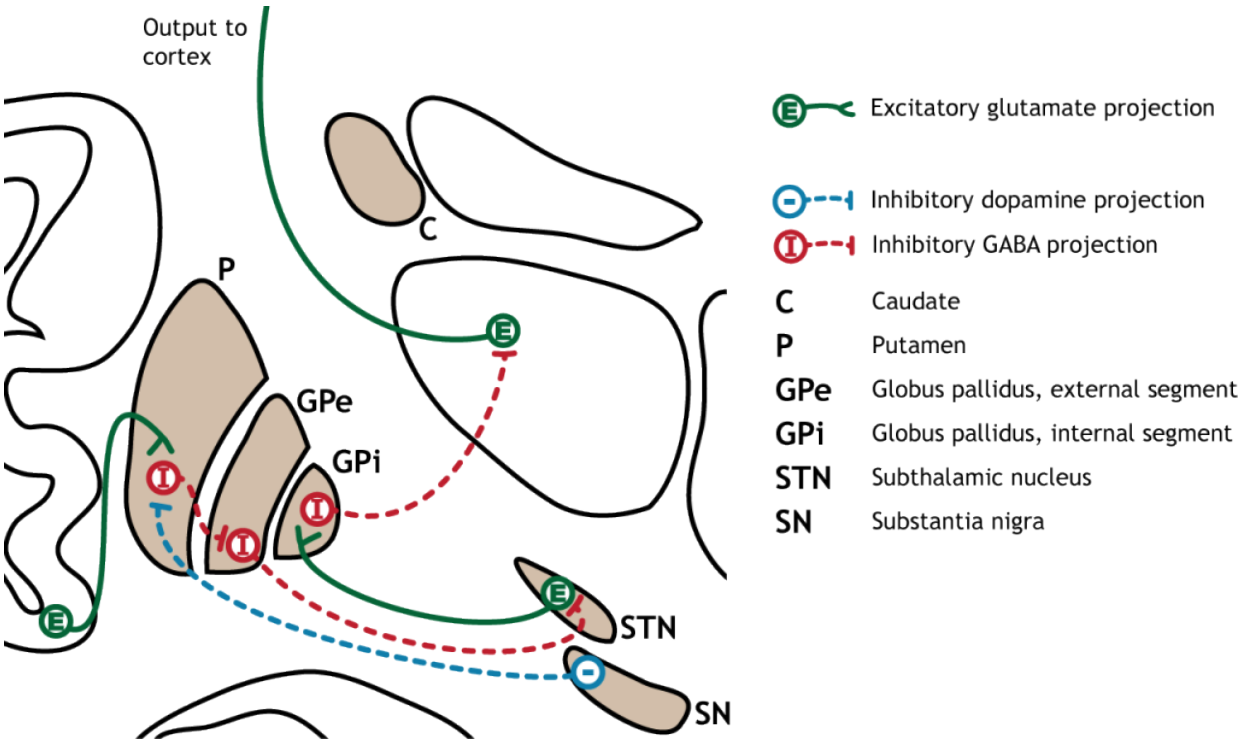


Figure 36.10. The indirect pathway in the basal ganglia consists of excitatory input from the cortex via glutamate action or inhibitory input from the substantia nigra via dopamine action that synapses on inhibitory neurons in the striatum. The striatal neurons project to the external segment of the globus pallidus (GPe). The GPe the sends inhibitory output to the subthalamic nucleus, which had excitatory projections to the GPi. The GPi then sends inhibitory output to the thalamus. 'Basal Ganglia Indirect Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

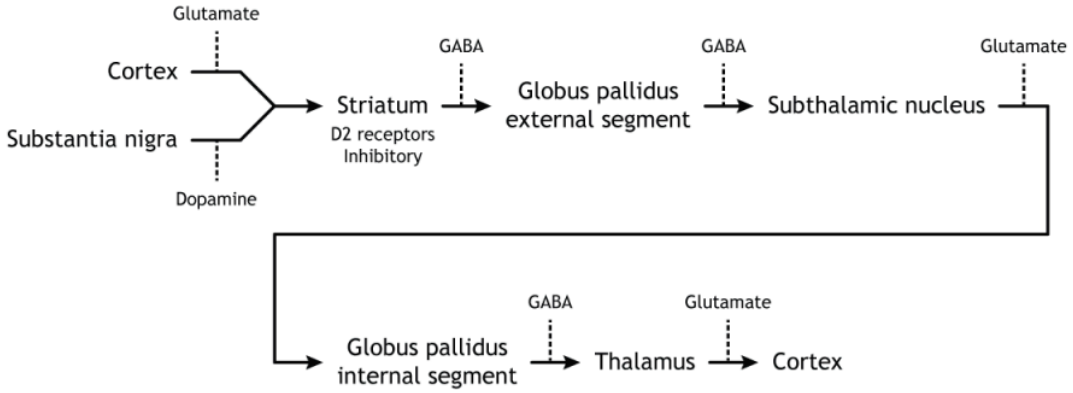


Figure 36.11. The cortex sends glutamate projections to the striatum. The substantia nigra sends dopamine projections to the striatum, which are inhibitory, acting on D2 receptors in the neurons involved in the indirect pathway. The striatum sends GABA projections to the external segment of the globus pallidus (GPe). The GPe sends GABA projections to the subthalamic nucleus. The subthalamic nucleus sends glutamate projections to the GPi. The GPi send GABA projections to the thalamus. The thalamus sends glutamate projections to the cortex. 'Basal Ganglia Indirect Pathway – Text' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Activation of the Indirect Pathway

The indirect pathway is activated by excitatory cortical input, activating the inhibitory striatal neurons. This leads to inhibition of the GPe neurons, resulting in disinhibition of the excitatory neurons in the subthalamic nucleus. The excitatory output from the subthalamic nucleus to the GPi increases inhibition of the thalamus, leading to decreased thalamic output to the cortex.

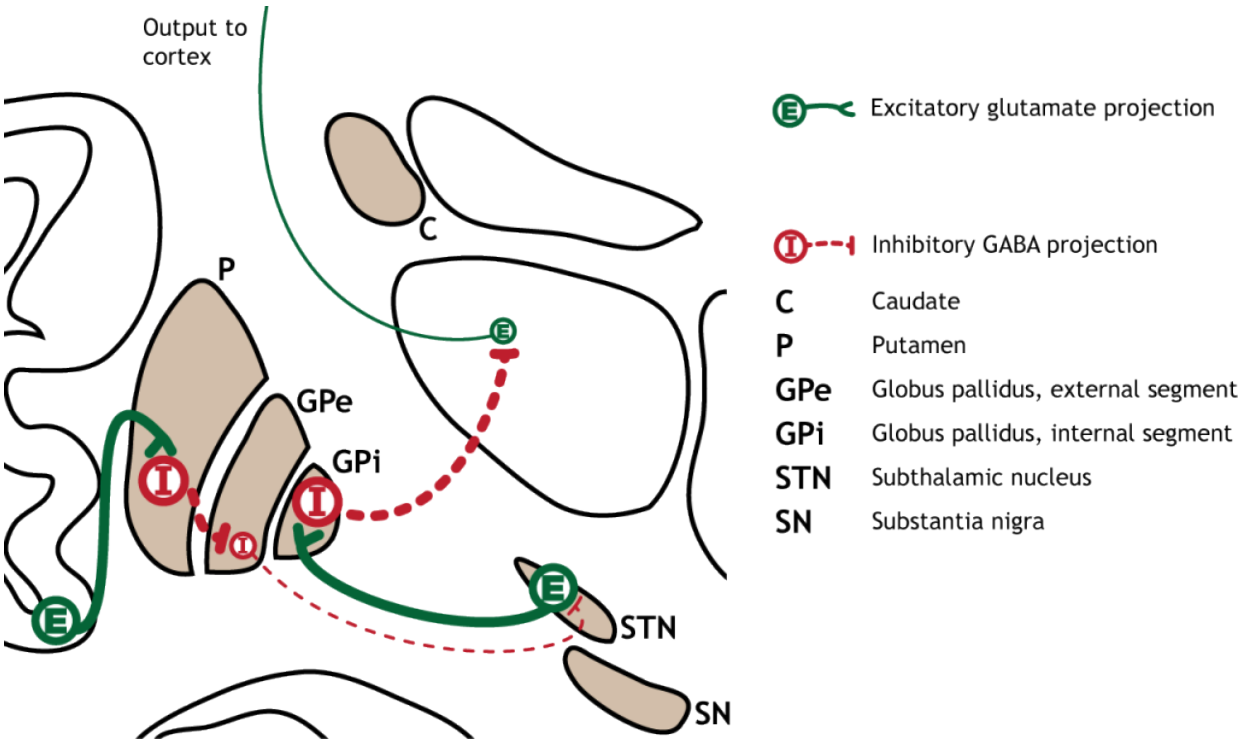


Figure 36.12. Activation of the indirect pathway by excitatory cortical input to the striatum leads to increased inhibitory output to the GPe. The inhibited GPe sends decreased inhibitory output to the subthalamic nucleus, causing increased excitatory output from the subthalamic nucleus to the GPi. Activation of the GPi inhibits the thalamus, resulting in decreased output from the thalamus to the cortex. 'Indirect Pathway Activation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

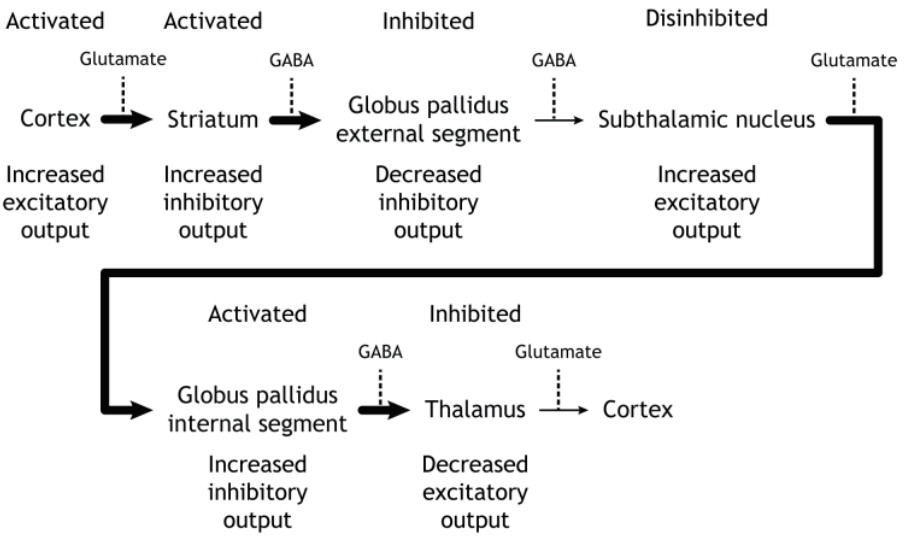


Figure 36.13. When the cortex is activated, it sends increased excitatory output to the striatum. This input activates the striatum, which sends increased inhibitory projections to the GPe. The inhibited GPe sends decreased inhibitory projections to the subthalamic nucleus, disinhibiting the region. The subthalamic nucleus then sends increased excitatory output to the GPi. The activated GPi sends increased inhibitory projections to the thalamus, which sends decreased excitatory output to the cortex. 'Indirect Pathway Activation – Text' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Inhibition of the Indirect Pathway

The indirect pathway can be inhibited by dopamine release from the substantia nigra. The neurons in the striatum involved in the indirect pathway express the D2 metabotropic dopamine receptor. The activation of this receptor is inhibitory. If the indirect pathway is inhibited by dopamine projections from the substantia nigra, the inhibitory striatal neurons are inhibited. This leads to disinhibiton of the GPe neurons, resulting in inhibition of the excitatory neurons in the subthalamic nucleus. This decreased excitatory output to the GPi decreases inhibition of the thalamus, leading to increased thalamic output to the cortex.

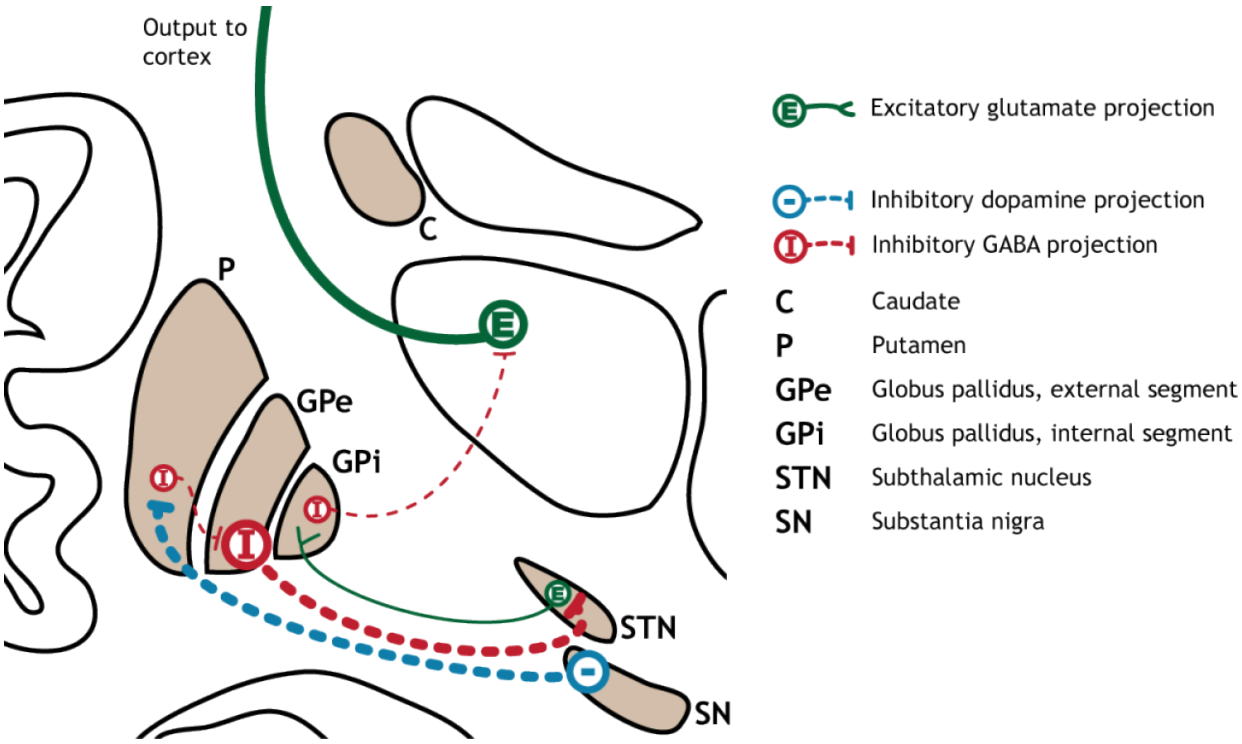


Figure 36.14. Inhibition of the indirect pathway by inhibitory input from the substantia nigra to the striatum leads to decreased inhibitory output to the GPe. The disinhibited GPe sends increased inhibitory output to the subthalamic nucleus, causing decreased excitatory output from the subthalamic nucleus to the GPi. A decrease in activation of the GPi releases the inhibition on the thalamus, resulting in increased output from the thalamus to the cortex. 'Indirect Pathway Inhibition' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

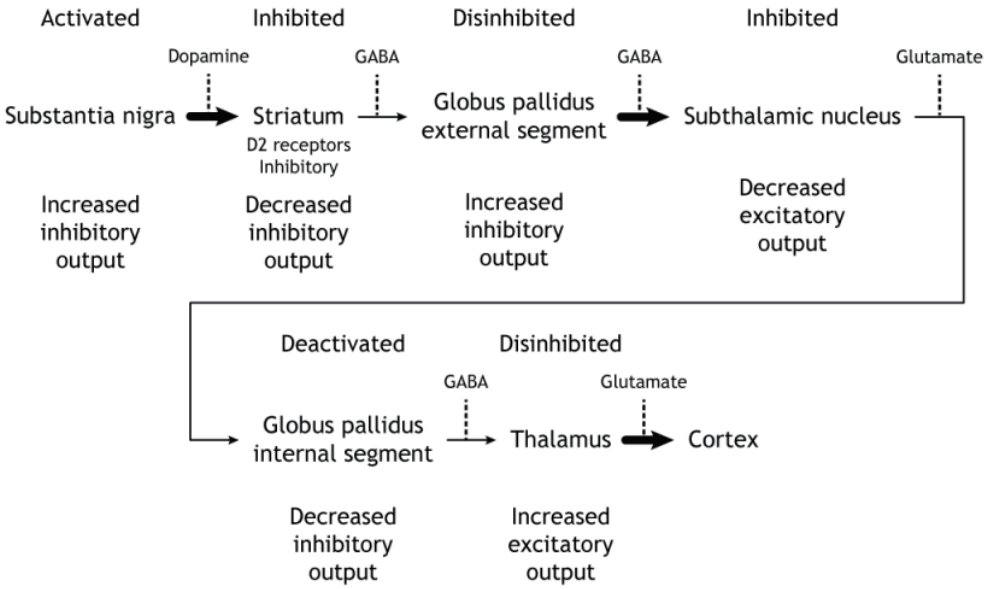


Figure 36.15. When the substantia nigra is activated, it sends increased inhibitory output to the striatum, which expresses inhibitory De receptors in the neurons involved in the indirect pathway. This input inhibits the striatum, which sends decreased inhibitory projections to the GPe. The disinhibited GPe sends increased inhibitory projections to the subthalamic nucleus, inhibiting the region. The subthalamic nucleus then sends decreased excitatory output to the GPi. The deactivated GPi sends decreased inhibitory projections to the thalamus, which sends increased excitatory output to the cortex. 'Indirect Pathway inhibition – Text' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Summary of Internal Processing

To put it all together, there is input to the striatum from two different locations: cortex (glutamate) and substantia nigra (dopamine).

- Cortical activation of the direct pathway leads to increased thalamic output
- Cortical activation of the indirect pathway leads to decreased thalamic output
- Substantia nigra activation (via D1) of the direct pathway leads to increased thalamic output
- Substantia nigra inhibition (via D2) of the indirect pathway leads to increased thalamic output

It is the combination of these pathway that allows for precise control of motor movement.

Loops through the Basal Ganglia

There are multiple circuits that pass through the basal ganglia:

- The motor circuit, which plays a role in voluntary movement
- The oculomotor circuit, which plays a role in eye movement
- The associative circuit, which plays a role in executive functions like behavioral inhibition (preventing impulsive behaviors) planning and problem solving, and mediating socially appropriate behaviors
- The limbic or emotional circuit, which plays a role in the processing of emotion and reward.

Although the circuits each use different circuits within the basal ganglia, the general loop is the same: cortical input to the striatum leads to internal processing within the basal ganglia structures. Basal ganglia output projects from the pallidum to the thalamus, which then projects back to the cortex. It is important to recognize that the basal ganglia plays an important role in a number of functions. For example, medications that are used to treat Parkinson's can sometimes lead to the presentation of impulse control disorders, a result of dopaminergic changes in the limbic loop through the basal ganglia.

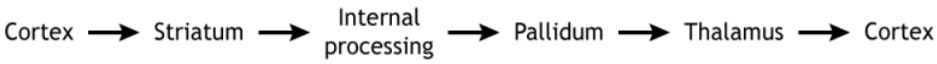


Figure 36.16. Loops through the basal ganglia have different functions but follow the same general circuit. The cortex inputs to the striatum. Internal processing through basal ganglia circuits occurs, and then the output from the pallidum projects to the thalamus, which sends output to the cortex. 'Basal Ganglia Loops' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- The subcortical basal ganglia nuclei receive information from the cortex and send output to the thalamus
- Motor control through the basal ganglia occurs through both the direct and indirect pathways
- Disinhibition is when an inhibitory region is itself inhibited
- The basal ganglia are best known for their role in motor control but are also critical for emotion and behavioral inhibition

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
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Video Lecture

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37.

EXECUTION OF MOVEMENT

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

Motor cortex

Once the plan for movement has been created, the primary motor cortex is responsible for the execution of that action. The primary motor cortex lies just anterior to the primary somatosensory cortex in the precentral gyrus located in the frontal lobe.

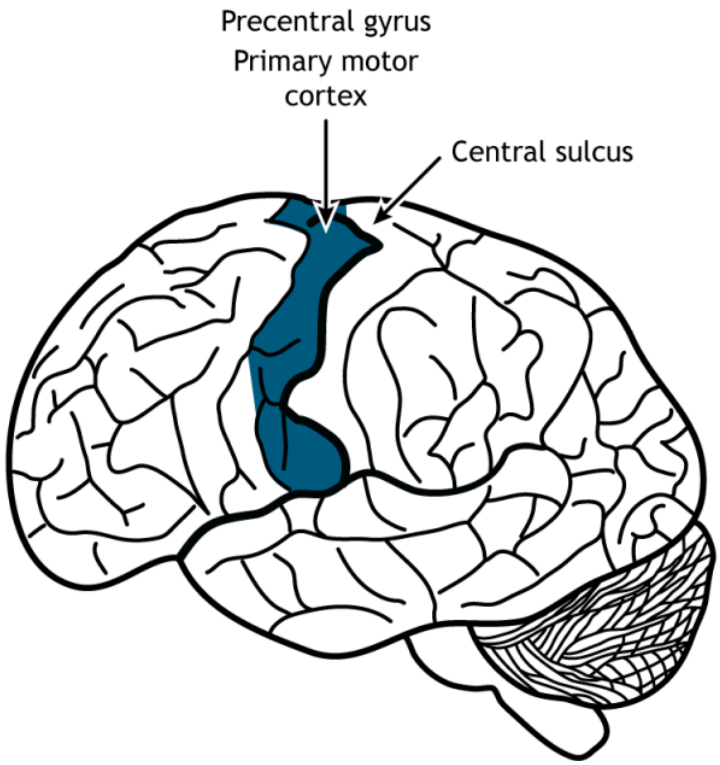


Figure 37.1. The primary motor cortex is located in the frontal lobe in the precentral gyrus, just anterior to the central sulcus. 'Primary Motor Cortex' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Like the somatosensory cortex, the motor cortex is organized by a somatotopic map. However, the motor cortex does not map onto the body in such an exact way as does the somatosensory system. It is believed that upper motor neurons in the motor cortex control multiple lower motor neurons in the spinal cord that innervate multiple muscles. This results in activation of an upper motor neuron causing excitation or inhibition in different neurons at once, indicating that the primary motor cortex is responsible for movements and not simply activation of one muscle. Stimulation of motor neurons in monkeys can lead to complex motions like bringing the hand to the mouth or moving into a defensive position (Graziano et al, 2005).

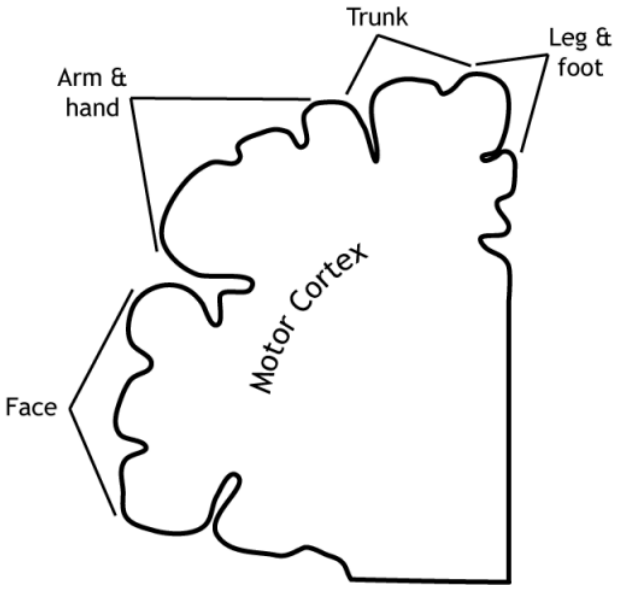


Figure 37.2. The map of the body that exists on the motor cortex is less specific than the somatosensory map because cortical neurons control multiple muscles at the same time. Instead, regions of the cortex are associated with larger body regions, such as the face, arm and hand, trunk, or leg and foot. 'Motor Cortex Map' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Population coding

The motor cortex controls movement by using population coding mechanisms. Upper motor neurons are broadly tuned to a certain movement in a certain direction, meaning firing rate is highest when moving in one direction, but firing also occurs when moving in nearby directions. For example, when a monkey is trained to move its hand toward the left, neurons "tuned" toward left movement will be active immediately before and during the movement. Neurons tuned to other directions will also be active but at lower rates (Georgopoulos, et al, 1982). This means that the firing rate of one specific neuron does not give enough information to know direction of movement. It is the combined firing rates of an entire population of neurons that indicates direction.

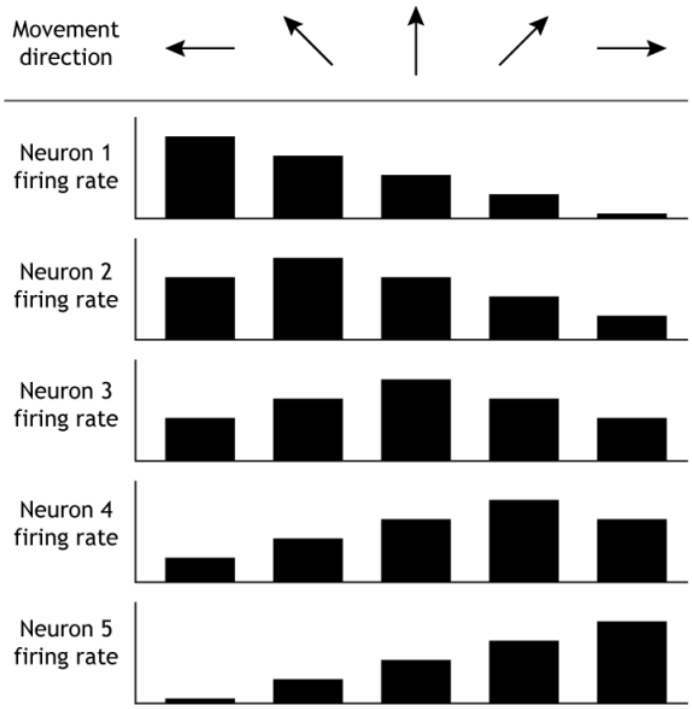


Figure 37.3. Motor movement is coded via population coding in the primary motor cortex. Information from one neuron is not enough to determine the direction of movement; a population of neurons must be used. Some neurons will be "tuned" to fire most rapidly in response to a specific direct. For example, Neuron 1 in the figure shows the highest firing rate when movement of the hand is to the left and a low firing rate when the hand is moving to the right, whereas Neuron 3 fires the most when the movement is forward. The combination of the firing patterns of many neurons provides a precise direction for the movement. 'Population Coding' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Descending Spinal Tracts

There are multiple descending tracts within the spinal cord that send information from the brain to the motor neurons in the ventral horn. The lateral tracts are responsible for carrying information about voluntary movement of the arms and legs. The ventromedial pathways are responsible for carrying information about posture and balance.

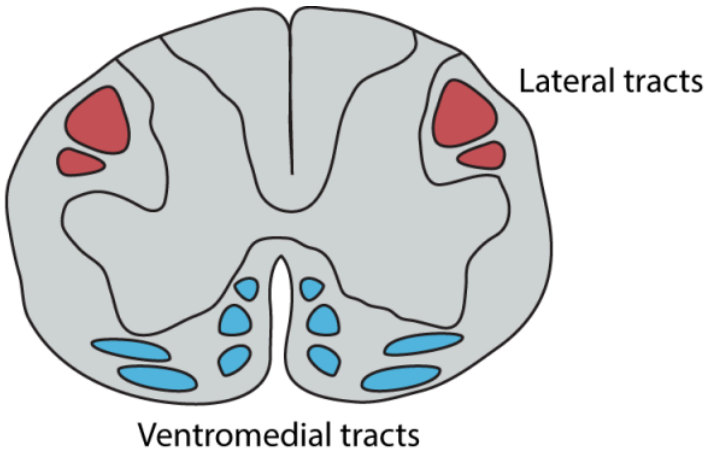


Figure 37.4. The descending motor tracts travel from the brain through the white matter in the spinal cord. The lateral tracts descend in the dorsolateral white matter, and the ventromedial tracts descend in the ventromedial white matter. 'Descending Spinal Tracts' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Lateral Tracts

Coticospinal Tract

The largest of the lateral pathways is the corticospinal tract. This pathway sends information directly from the motor and premotor cortices down to the motor neurons in the spinal cord. Cortical axons travel through the brainstem and then cross the midline at the base of the medulla; like the somatosensory system, the right side of the cortex processes information for the left side of the body and vice versa. In the spinal cord, the axons travel through the lateral column and synapse in the ventral horn on motor neurons that typically innervate distal muscles.

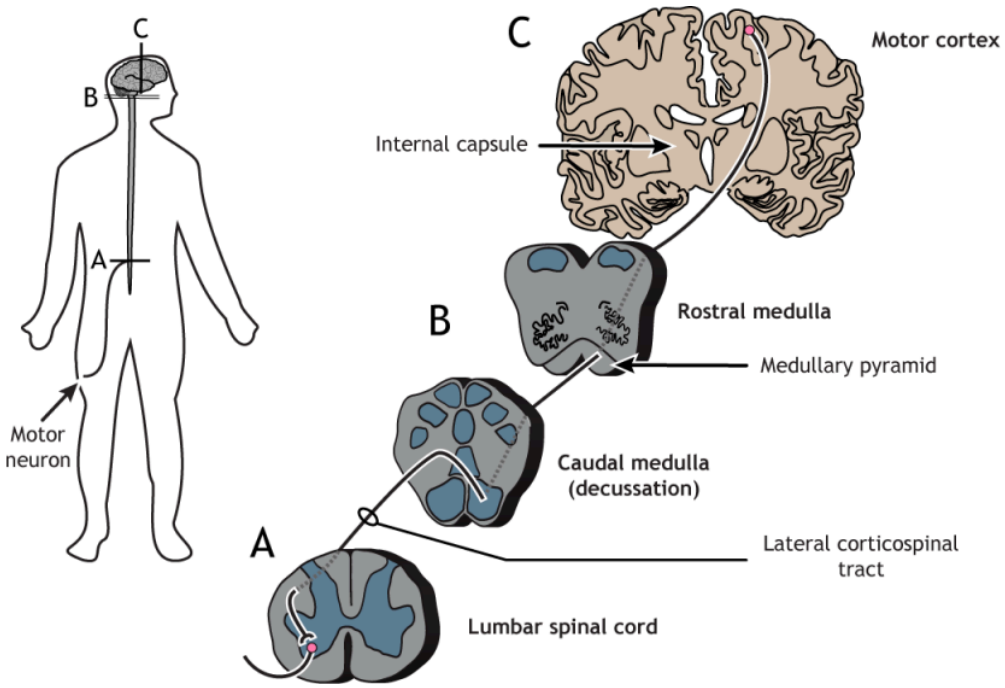


Figure 37.5. Motor information to the arms and legs travels from the primary motor cortex to the medulla via the internal capsule, a white matter structure in the brain. The corticospinal tract passes through the medullary pyramids and then decussates in the caudal medulla. The axons continue traveling through the lateral corticospinal tract and synapse on an alpha motor neurons in the ventral horn of the spinal cord. 'Corticospinal Tract' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Corticobulbar Tract

The corticobulbar tract is another lateral tract and sends motor information to cranial nerves for motor control of the face. This path travels ipsilateral from the cortex into the brainstem where it branches off at the appropriate cranial nerve level in either the pons or the medulla and then innervates cranial nerve neurons bilaterally.

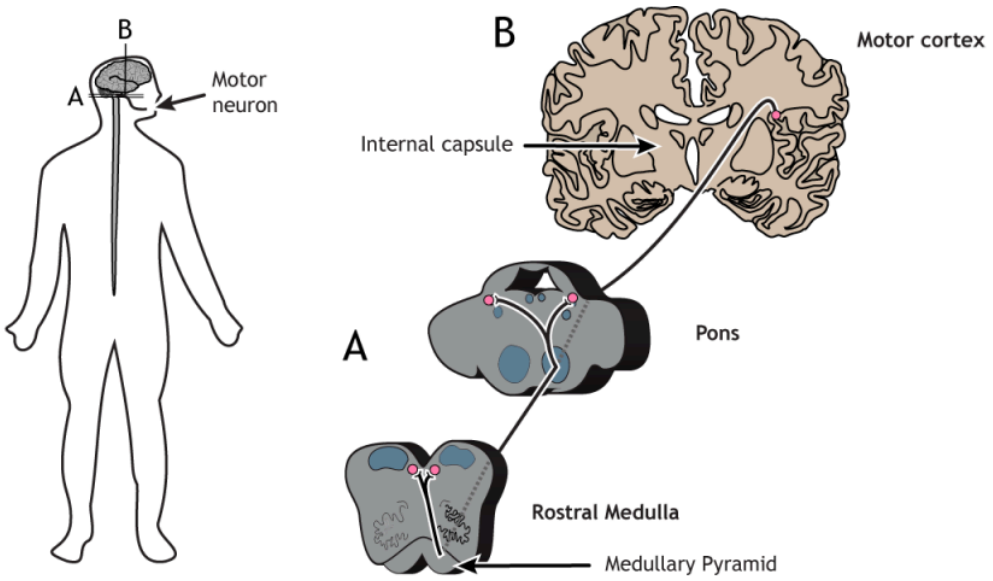


Figure 37.6. Motor information to the face travels from the primary motor cortex through the internal capsule to the pons and medulla where it branches to synapse on cranial nerve nuclei on both sides of the brainstem. 'Corticobulbar Tract' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Ventromedial Tracts

There are four ventromedial pathways that travel in the spinal cord as well. These tracts begin in the brainstem and descend through the ventromedial columns. They receive input from motor areas of the cortex as well as integrating information from multiple sensory regions.

- The vestibulospinal tract is important for head balance as we move. This tract begins in the vestibular nucleus.
- The tectospinal tract is responsible for moving the head in response to visual stimuli. This tract begins in the superior colliculus.
- The two reticulospinal tracts play a role in managing anti-gravity reflexes needed for posture and standing. These tracts begin in the reticular formation.

Key Takeaways

- The motor cortex is located in the frontal lobe
- The motor map is not as detailed as the somatosensory homunculus
- The motor cortex uses population coding to encode direction of movement
- The lateral tracts carry information about voluntary movement of the arms and legs
- The ventromedial pathways carry information about posture and balance

Test Yourself!



An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=342#h5p-33

Video Lecture



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References

Georgopoulos AP, Kalaska JF, Caminiti R, Massey JT. J Neurosci. 1982 Nov;2(11):1527-37.

Graziano et al, 2005 J Neurophysiol 94: 4209-4223.

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38.

NEURODEGENERATIVE DISEASES: MOTOR

Neurodegenerative diseases cause neurons to lose either their function or structure over time, potentially leading to cell death in either the central or peripheral nervous system. These diseases can be devastating because there are no known ways to reverse the neurodegeneration. There are multiple diseases that are classified as neurodegenerative diseases and affect millions of people worldwide. We will focus on the two most prevalent neurodegenerative diseases: The motor disease **Parkinson's disease** that affects the basal ganglia, and **Alzheimer's disease**.

Resources

- Glossary Terms
- Key Takeaways

Parkinson's Disease

Symptoms and Risk Factors

Parkinson's disease is a neurodegenerative movement disorder that causes **bradykinesia** (slowness of movement), **akinesia** (difficulty initiating movement), a resting tremor, muscle rigidity, and changes to posture and locomotion. Although most symptoms are motor, there are mild cognitive and psychiatric changes, such as apathy, **anhedonia**, mood disturbances, or depression.



Figure 38.1. Parkinson's disease. This drawing depicts the stooped posture and shuffling gait that are both symptoms of Parkinson's disease.

Advanced age is the primary risk factor, as an estimated 2% of people over the age of 60 develop Parkinson's disease. It is also shows a sex difference with men being diagnosed more than women. Other environmental factors contribute to risk, such as repeated traumatic brain injury (suspected in Muhammad Ali) or occupational exposure to heavy metals, insecticides, or other neurotoxins. A small percentage of cases are early onset (21 – 50 years old; Michael J. Fox was diagnosed at 30), and have a strong genetic component. The disease causes significant decreases in life expectancy and quality of life.

Basal Ganglia Dysfunction

A loss of dopaminergic neurons within the **substantia nigra** (a midbrain structure) contributes to basal ganglia circuitry disruption in Parkinson's disease. This loss of substantia nigra cells can be visualized postmortem without the use of histology due to the natural black pigmentation of the substantia nigra cells.

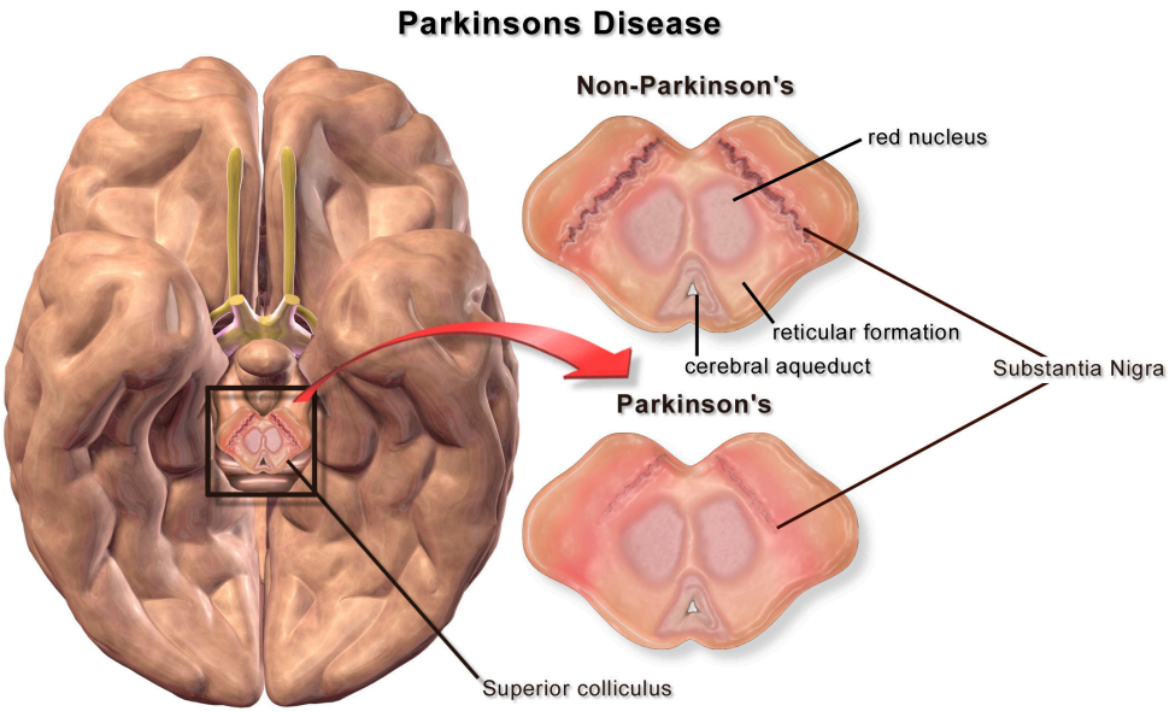


Figure 38.2. Substantia nigra. The substantia nigra is a midbrain structure made up of dopaminergic neurons that project to the striatum. These dopaminergic cells are naturally pigmented black (substantia = substance, nigra = black). In Parkinson's disease, these dopaminergic cells die, and a loss of the black pigmented cells can be observed in human cadavers.

When the substantia nigra cells die, they are no longer able to release dopamine at the striatum appropriately. When less dopamine is released into the striatum, the two populations of striatal neurons are affected differently dependent on the type of dopamine receptor that they express. Recall the basal ganglia circuitry from the previous chapter.

Direct Pathway Dysfunction

Within the **direct pathway**, striatal cells (within the **caudate**) express **excitatory D1 receptors** that project directly to the globus pallidus internal segment. In the direct pathway, typically, dopamine binds to D1 receptors on striatal neurons, increasing caudate activity. These striatal neurons release GABA onto the globus pallidus internal segment (GPi) neurons, causing the GPi neurons to be less active. When the Gpi neurons are less active, they release less GABA onto the thalamic neurons,

increasing thalamic neuron activity and the excitatory projections to the motor cortex, thus increasing movement.

In Parkinson's disease, there is *decreased* release of dopamine onto the striatal caudate neurons that express D1 receptors, making them less active. Now that the striatal neurons are not as active, they release less GABA onto GPi neurons, disinhibiting them. The GPi is now more active, releasing more GABA onto thalamic neurons. In response, the thalamic neurons are less active and send less excitatory messages to the cortex, thus causing a decrease in movement overall.

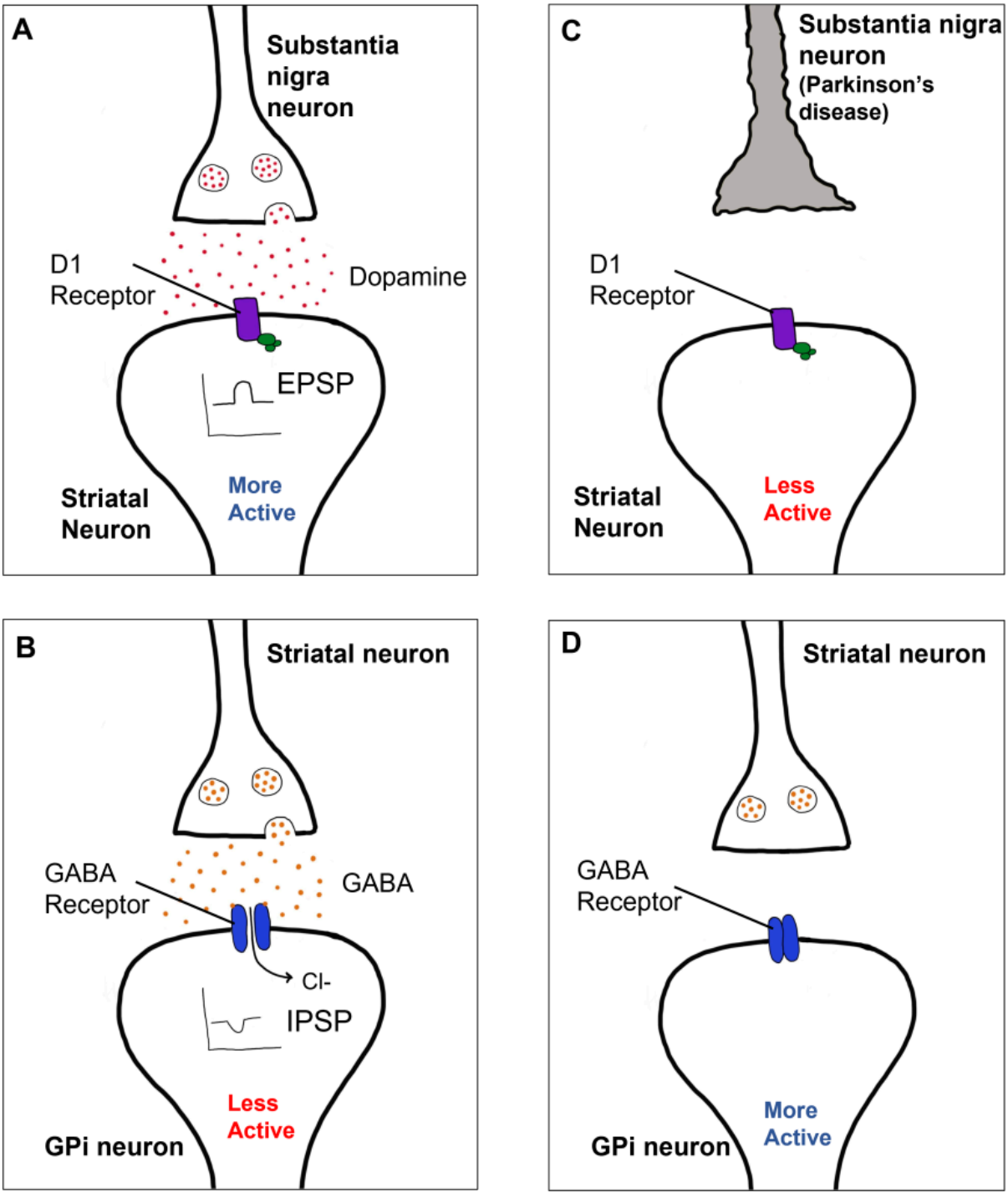


Figure 38.3. Changes in D1 Receptor activity in Parkinson's disease. A. In healthy individuals, the substantia nigra releases dopamine onto striatal cells in the caudate. The caudate expresses D1 receptors that are excitatory. When dopamine binds to D1 receptor it causes EPSPs in the caudate neurons, and an increase in activity of the caudate neuron. B. The striatal neurons are GABAergic, so

when activity is increased in healthy individuals, they release more GABA onto GPi neurons. GABA binds to receptors on the GPi neurons, causing an influx of Cl- ions and membrane hyperpolarization, leading to less activity. C. In individuals with Parkinson's disease, the dopaminergic substantia nigra cells die, and as a result do not release dopamine onto caudate neurons. This causes a decrease in activity of the caudate neurons. D. Decreased activity of the caudate neurons leads to decreased release of GABA onto the GPi neurons. As a result, the GPi neurons have increased activity. 'Changes in D1 Receptors activity in Parkinson's disease' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

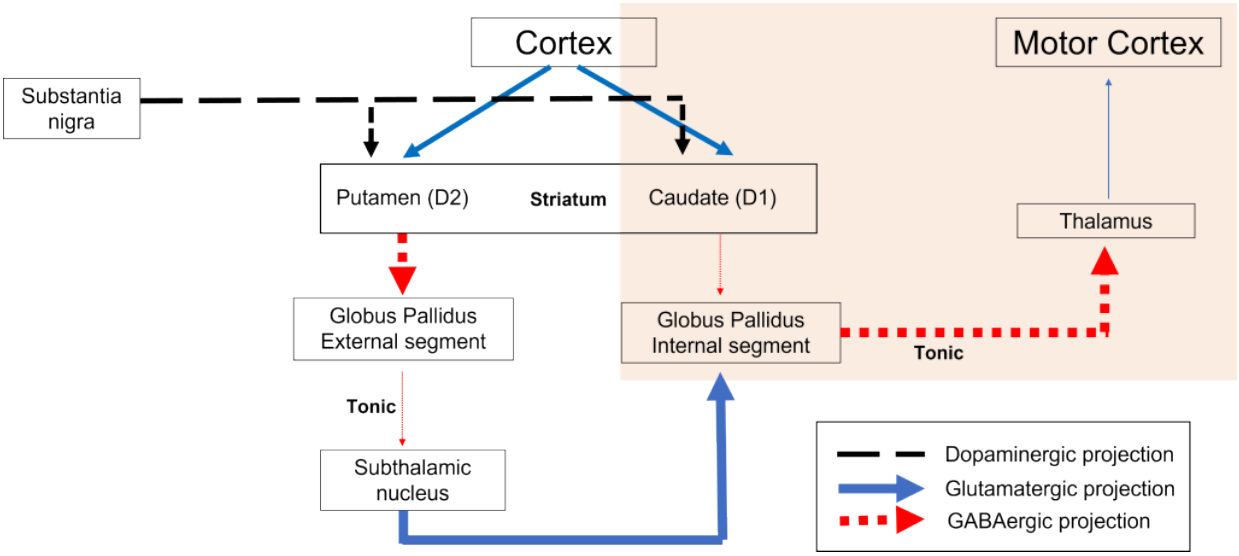


Figure 38.4. Model of Basal Ganglia Circuitry in Parkinson's disease- Direct Pathway. This model shows the dopaminergic, glutamatergic, and GABAergic connections within the basal ganglia circuitry. Tonically active connections are indicated. The direct pathway is highlighted with orange. Larger arrows indicate increased activity, and smaller arrow indicated decreased activity. The cortex provides glutamatergic input to the striatum, which also receives dopaminergic projections from the substantia nigra. In Parkinson's disease, the dopaminergic neurons die and there is a loss of dopaminergic input into the striatum. As a result, the decreased D1 receptor activation in the caudate causes the caudate cells to be less active, releasing less GABA onto the globus pallidus internal segment. The globus pallidus internal segment is disinhibited, and thus increases its firing rate, releasing more GABA onto the thalamus. The decreased D2 receptor activation in the putamen causes the putamen cells to be more active, releasing more GABA onto the globus pallidus external segment. The globus pallidus releases less GABA onto the subthalamic nucleus. The subthalamic nucleus is disinhibited, and increases its release of glutamate onto the GPi. This causes the GPi to increase its firing rate, releasing more GABA onto the thalamus. Together, the decreased activity of the thalamus decreases activity of the motor cortex and thus decreases movement. 'Model of Basal ganglia circuitry in Parkinson's disease- direct pathway' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Indirect Pathway Dysfunction

In the indirect pathway, dopamine typically binds to **inhibitory D2 receptors** on striatal (**putamen**) neurons, inhibiting striatal neuron activity. These striatal neurons then release *less* GABA onto the globus pallidus external segment neurons (GPe), causing the GPe neurons to be more active. When the GPe neurons are more active, they release more GABA onto the subthalamic nucleus neurons, decreasing subthalamic neuron activity and the excitatory projections to the GPi. Decreasing activation of the GPi causes the GPi to release less GABA onto the thalamus, which then causes more activation of the motor cortex, thus increasing movement.

In Parkinson's disease, there is decreased release of dopamine onto the striatal neurons that express D2 receptors, making them more active. Now that the striatal neurons are more active, they release more GABA onto GPe neurons. This inhibits the GPe neurons, causing them to release less GABA onto subthalamic nucleus neurons, disinhibiting the subthalamic nucleus. Increasing the excitatory inputs from the subthalamic nucleus onto the GPi will cause the GPi to release more GABA onto the thalamus. In response, the thalamic neurons are less active and send less excitatory messages to the cortex, thus causing a decrease in movement overall.

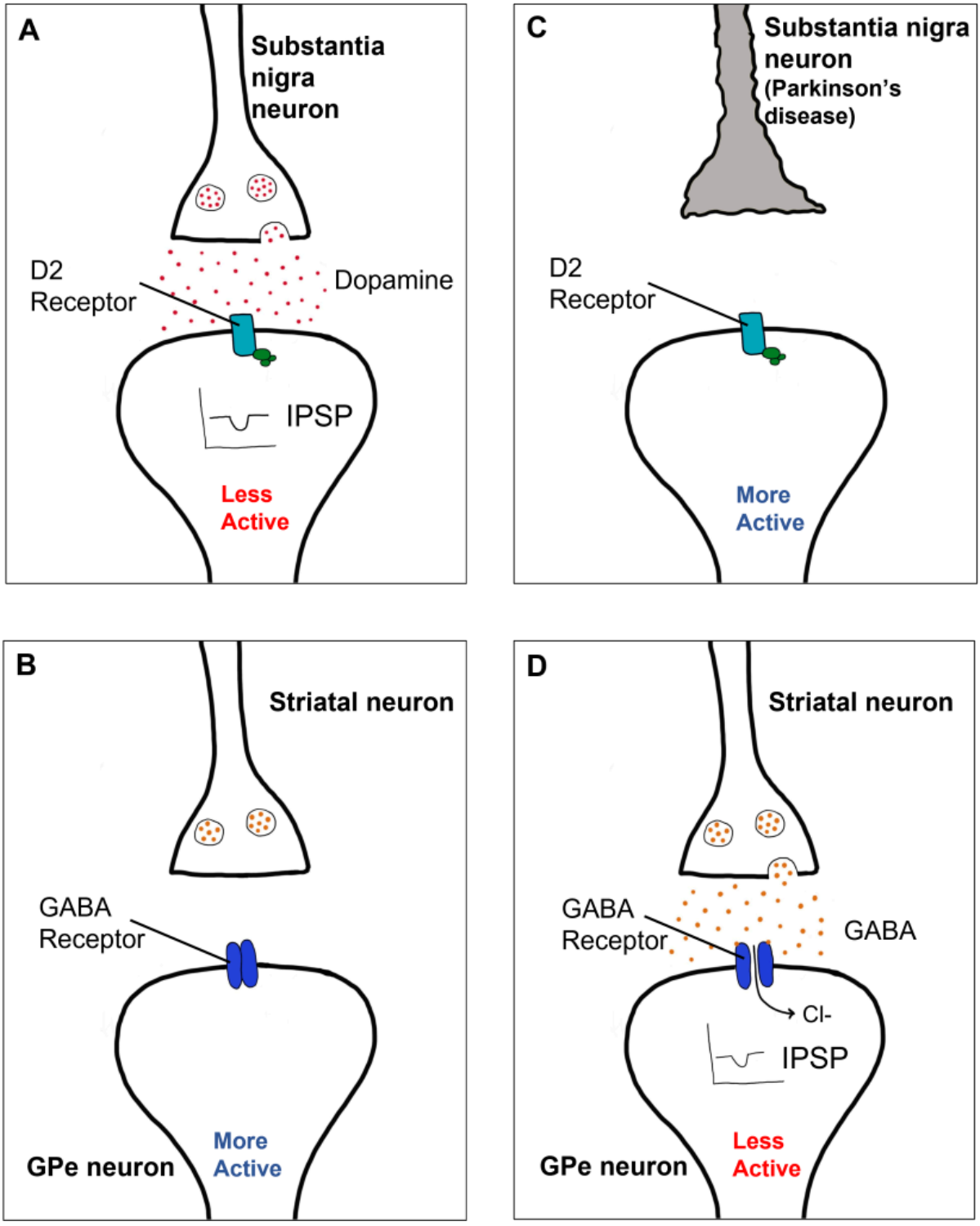


Figure 38.5. Parkinson's disease effect on indirect pathway. Changes in D2 Receptor activity in Parkinson's disease. A. In healthy individuals, the substantia nigra releases dopamine onto striatal

cells in the putamen. The putamen expresses D2 receptors that are inhibitory. When dopamine binds to D2 receptor it causes IPSPs in the putamen neurons, and an decrease in activity of the putamen neuron. B. The striatal neurons are GABAergic, so when activity is decreased in healthy individuals, they release less GABA onto GPe neurons. Decreased activity of the caudate neurons leads to decreased release of GABA onto the GPi neurons. As a result, the GPe neurons have increased activity. C. In individuals with Parkinson's disease, the dopaminergic substantia nigra cells die, and as a result do not release dopamine onto putamen neurons. This causes an increase in activity of the putamen neurons. D. Increased activity of the putamen neurons leads to increased release of GABA onto the GPe neurons. As a result, the GPe neurons have decreased activity. 'Changes in D2 Receptors activity in Parkinson's disease' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

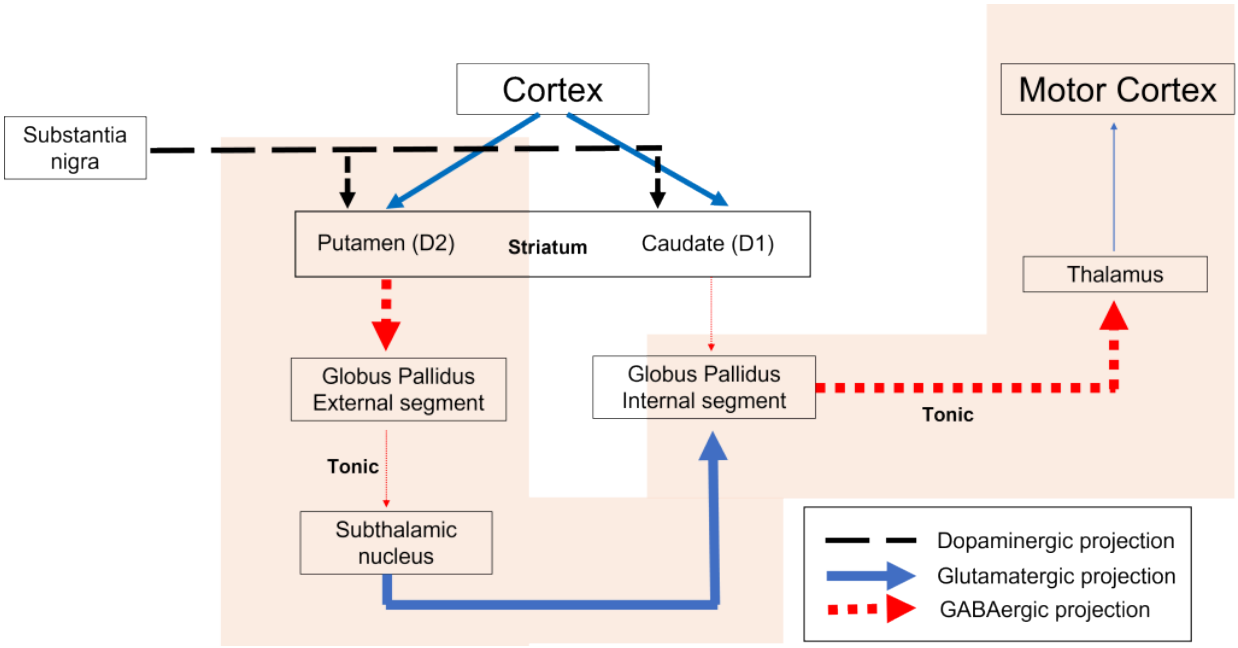


Figure 38.6. Model of Basal Ganglia Circuitry in Parkinson's disease- Indirect Pathway. This model shows the dopaminergic, glutamatergic, and GABAergic connections within the basal ganglia circuitry. Tonically active connections are indicated. The indirect pathway is highlighted with orange. Larger arrows indicate increased activity, and smaller arrow indicated decreased activity. The cortex provides glutamatergic input to the striatum, which also receives dopaminergic projections from the substantia nigra. In Parkinson's disease, the dopaminergic neurons die and there is a loss of dopaminergic input into the striatum. As a result, the decreased D1 receptor activation in the caudate causes the caudate cells to be less active, releasing less GABA onto the globus pallidus internal segment. The globus pallidus internal segment is disinhibited, and thus increases its firing rate, releasing more GABA onto the thalamus. The decreased D2 receptor activation in the putamen causes the putamen cells to be more active, releasing more GABA onto the globus pallidus external segment. The globus pallidus releases less GABA onto the subthalamic nucleus. The subthalamic nucleus is disinhibited, and increases its release of glutamate onto the GPi. This causes the GPi to increase its firing rate, releasing more GABA onto the thalamus. Together, the decreased activity of the thalamus decreases activity of the motor cortex and thus decreases movement. 'Model of Basal ganglia circuitry in Parkinson's disease- indirect pathway' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Diagnosis and Treatment

Parkinson's disease is considered idiopathic because there is not a single known cause. Unfortunately, there are not measurable biomarkers (blood tests, brain scans) to diagnose Parkinson's disease. Rather, diagnosis of individuals is typically done by a neurologist and a detailed exam. This can be further

confirmed by giving medications that are used to treat Parkinson's disease and determining if symptoms decrease.

A diagnosis of Parkinson's disease is confirmed post-mortem through:

1. The loss of dopaminergic substantia nigra cells.
2. Presence of Lewy bodies.

Lewy bodies are intracellular alpha-nuclein protein aggregates that are believed to potentially displace healthy neurons and lead to the neurodegeneration observed in the disease.

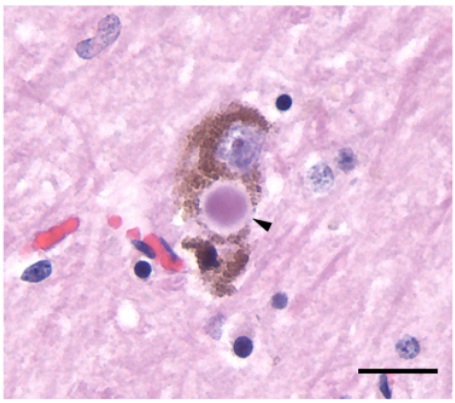


Figure 38.7. Lewy bodies. This microscope image is showing a Lewy body (denoted by the black triangle) in the substantia nigra of an individual with Parkinson's disease.

Dopamine cannot be administered as a treatment to those with Parkinson's disease to replace the loss of dopamine from the substantia nigra due to the inability of dopamine to cross the **blood-brain-barrier**. Instead, the major drug treatment for the motor symptoms of Parkinson's disease has been administration of the drug **levodopa (L-DOPA)**. L-DOPA is an intermediate in the synthesis of dopamine. Typically, it is converted into dopamine through the activity of DOPA decarboxylase. It is typically co-administered with other drugs to help prolong its effects. Unfortunately, there are many side effects of L-DOPA including nausea, joint stiffness, **dyskinesias** (involuntary movements and tics), and psychosis.

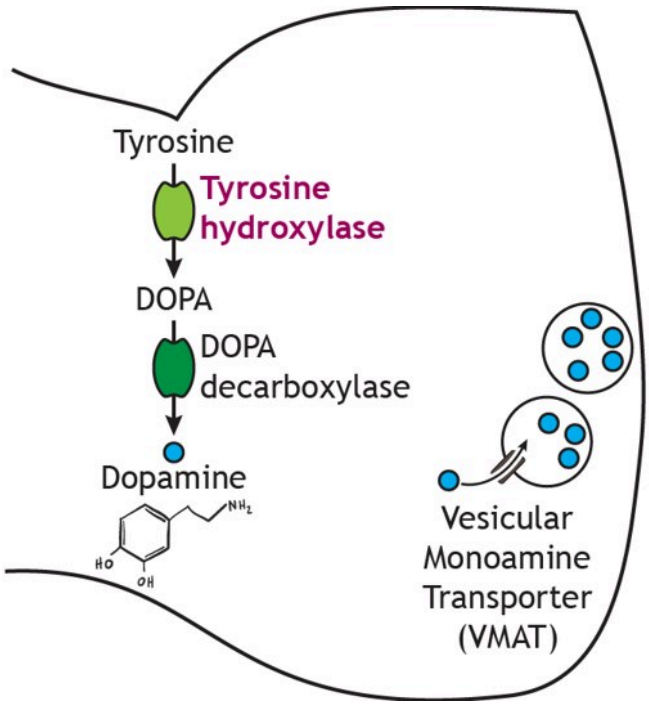


Figure 38.8. Dopamine synthesis pathway. Tyrosine is converted into L-DOPA through tyrosine hydroxylase. L-DOPA is then converted into dopamine by the enzyme DOPA decarboxylase. 'Dopamine Synthesis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

In a medical intervention called **deep brain stimulation (DBS)**, a surgeon implants permanently indwelling electrodes directly into brain tissue. These electrodes are controlled by an external battery pack that delivers preprogrammed stimulation protocols. DBS in the STN is used to alleviate the symptoms of Parkinson's disease.

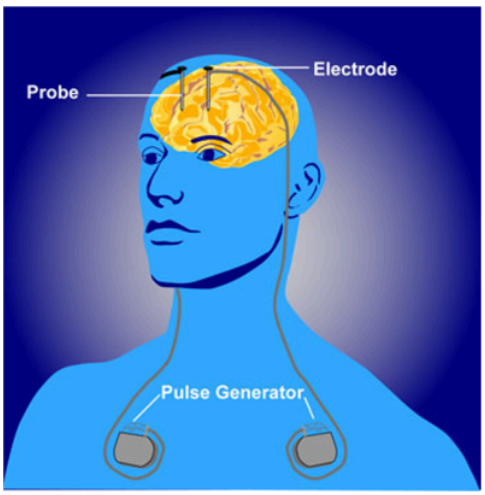


Figure 38.9. Deep brain stimulation. A deep brain stimulator device must be implanted surgically. Electrodes are positioned in specific brain areas for the delivery of electrical impulses. The impulses come from an external battery pack that is typically implanted beneath the skin on the chest. Deep brain stimulation can be used to treat disorders such as Parkinson's disease, obsessive compulsive disorder, and depression.

Key Takeaways

- Parkinson's disease is a neurodegenerative disease that causes dopaminergic substantia nigra cells to die, causing dysfunction in the basal ganglia circuitry.
- L-DOPA and deep brain stimulation are treatments for Parkinson's disease.

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PART VI
BEHAVIOR

39.

MOTIVATED BEHAVIOR: REWARD PATHWAY

Having a sense of reward is a valuable adaptive trait. Consider two similar organisms living in the distant geologic past, both involved in Darwin's struggle to pass their genetic material to the following generation. One of these creatures gets an internal rewarding sensation whenever it drinks water while thirsty, eats high-caloric-content food, or successfully reproduces. As can be expected, this organism is highly motivated to seek out those rewarding stimuli in the world. It is are more likely to crave sugary foods to maximize daily caloric intake necessary for activity and growth. The other creature does not experience pleasure from its actions, resulting in little motivation to seek out calories or to reproduce, for example. It stands to reason that the first of these two creatures has an evolutionary advantage to survive. As can be expected, the regions of the brain that are concerned with reward are highly conserved through evolution.

Resources

- Glossary terms
- Scientist links to learn more!
- Key Takeaways

Reward Circuit

For us humans, our reward signaling neural circuitry starts with the **ventral tegmental area (VTA)**. Located in the midbrain, the VTA contains neurons that synthesize the neurotransmitter **dopamine (DA)**. This population of DA cells is similar to the cells in the substantia nigra, the midbrain neurons that are lost in **Parkinson's disease**.

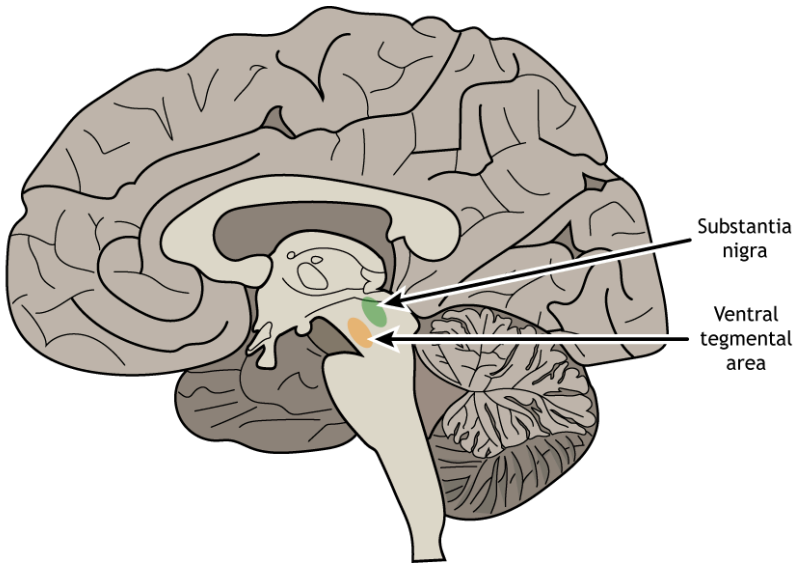


Figure 39.1. The ventral tegmental area (orange region) is located in the midbrain region near the substantia nigra (green region). Both regions release dopamine onto downstream targets. 'Ventral Tegmental Area' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

There are two primary pathways from the VTA that are important for reward.

The **mesolimbic pathway** consists of dopamine-producing neurons that release dopamine onto the cells in the **nucleus accumbens** (NAc; also sometimes called the ventral striatum). This seems to be the major pathway by which reward is mediated by the brain. Using microdialysis, it is possible to measure the dopamine concentration in the NAc during performance of some behavioral tasks. In studies with rats, engaging in rewarding activities such as eating or sex results in increased release of dopamine in the NAc. Similarly we see that release of dopamine into the human NAc is enhanced when we engage in activities we enjoy: binge eating sugary stuff, having sex, even playing video games. Notably, many drugs of abuse such as cocaine or amphetamine can induce a similar overflow of dopamine release when an animal is exposed to the drug.

The second area that receives VTA innervation is the **prefrontal cortex (PFC)**, and this projection is called the **mesocortical pathway**. We think of the PFC as being involved in the conscious, decision making and inhibition of action.

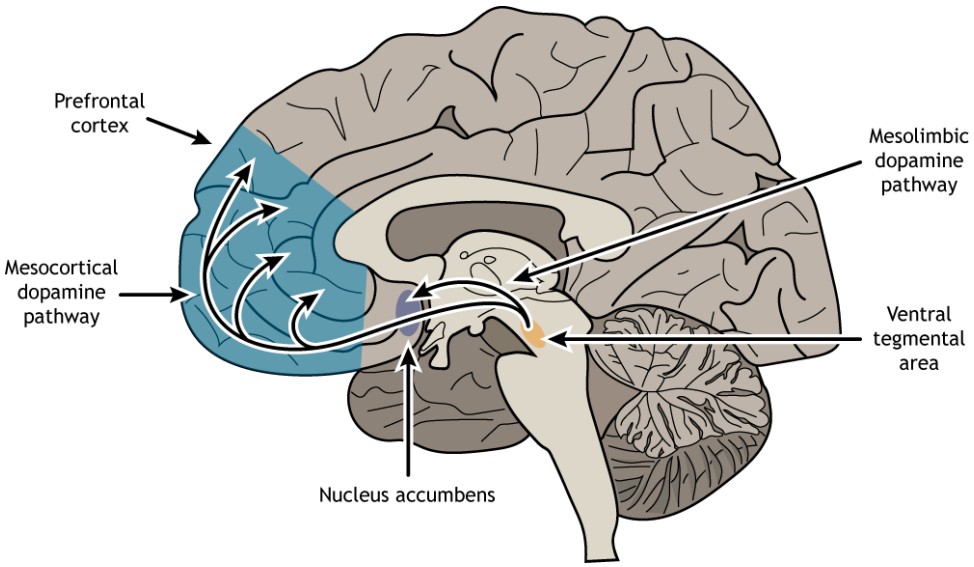


Figure 39.2. The ventral tegmental area (orange region) releases dopamine into the nucleus accumbens (purple region) via the mesolimbic pathway and releases dopamine into the prefrontal cortex (blue region via the mesocortical pathway. 'Mesolimbic and Mesocortical Pathways' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the amygdala using the BrainFacts.org 3D Brain

View the amygdala using the BrainFacts.org 3D Brain

One of the earliest experiments demonstrating functional evidence of a "reward circuit" was conducted at McGill University in the early 1950's. Drs. James Olds and Peter Milner carried out surgery on anesthetized rats to implant metal electrodes into different areas of the brain. After recovery, the rats were placed into an operant conditioning chamber, also called a Skinner box. These special cages are equipped with a device which the subject can physically manipulate. For example, the cage may have a lever which the animal can push, or a hole into which they can poke their nose.

In the case of Olds and Milner's experiments, a lever press led to activation of the implanted electrodes, resulting in neuronal activation. They had found that when the electrode was implanted into brain areas such as the corpus callosum or the hippocampus, the rats did not spend significant time pressing on the lever. However, the rats which had the electrodes implanted in the medial forebrain bundle that is located in the VTA to NAc pathway, responded frequently on the lever. One such rat pressed the lever almost 2000 times in less than an hour, averaging nearly one response every two seconds! Electrical activation of reward centers is so desirable, rats will choose electrical stimulation over food even to the point of starvation. This experimental paradigm is also called **intracranial-self**

stimulation (ICSS). Treatment with drugs that block the receptors for dopamine reduce the self-stimulating behavior, indicating that dopamine is the critical neurotransmitter involved in making the stimulation of these brain regions rewarding.

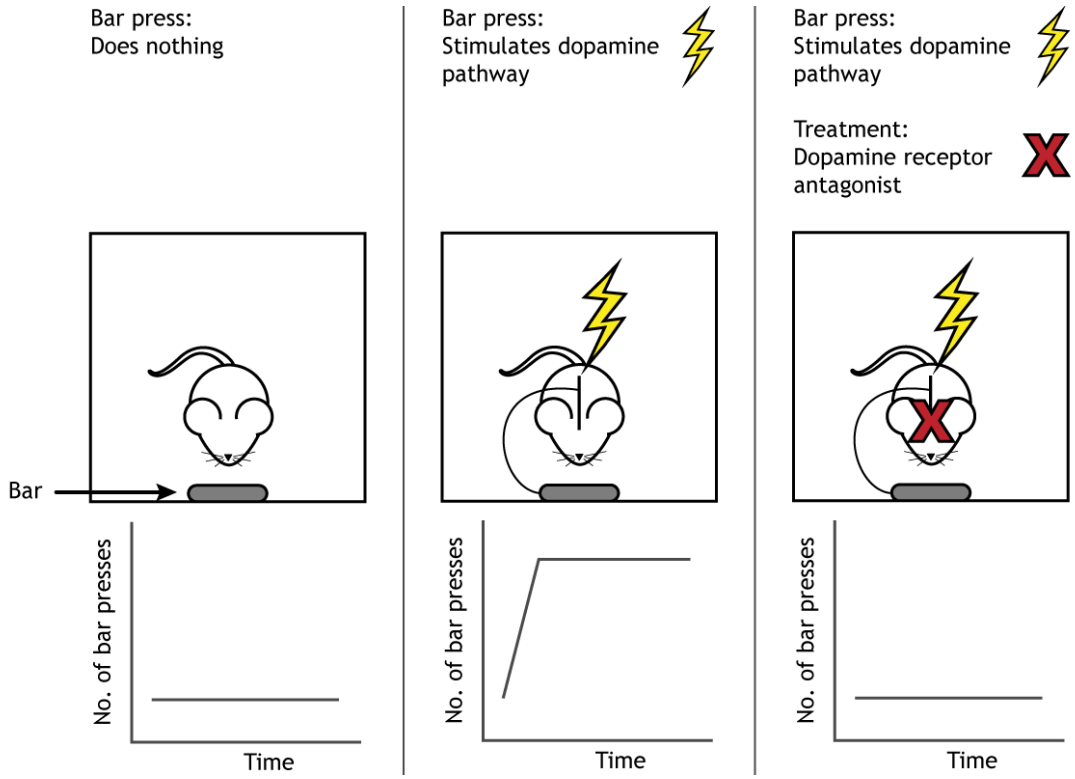


Figure 39.3. When an activity like bar pressing is paired with stimulation of the reward system circuitry, rats will show a marked increased in the behavior (center panel) compared to controls (left panel). If a dopamine receptor antagonist is given in addition to the bar press stimulation, the behavior decreases, presumably because dopamine cannot have its reward effect (right panel). 'Dopamine Pathway Stimulation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

And while the original studies were conducted on rats, clinicians soon after tested their model in humans, with similar indwelling electrodes in different brain regions. Unsurprisingly, humans also have areas of the brain that are responsible for encoding reward, and when given the chance to electrically activate those areas, they do so extensively. When the experimenters brought in a tray of delicious food to the test chamber, the hungry patients—who hadn't eaten for upwards of seven hours—simply looked at the meal, but couldn't pull themselves away from the stimulation button

long enough to eat. Artificial stimulation of these reward centers of the brain was more valuable to the patients than nutrition.

However, continued research suggests the connection between dopamine release and reward may not be as simple as the self-stimulation studies imply. It appears that it is not the reward itself that increases dopamine, but the predicted expectation of the reward . Dopamine signaling increases during anticipation of a predicted reward. If the level of reward is more than predicted, reward learning occurs, and dopamine signaling and motivation to repeat that behavior increases. If the level of reward is less than predicted, then dopamine signaling decreases as does motivation to repeat the behavior.

Rewarding Stimuli

Natural rewards that increase survival and fitness of a species activate the reward circuit. These behaviors and stimuli include certain food (like those containing high sugar or fat levels), social bonding, parental bonding, and sex. Most drugs of abuse also activate the reward circuit and dopamine signaling, which plays a critical role in the formation of addiction. For example, cocaine blocks dopamine reuptake into presynaptic VTA terminals; heroin and nicotine increase dopamine release from the VTA. These alterations increase dopamine effect on neurons in the nucleus accumbens.

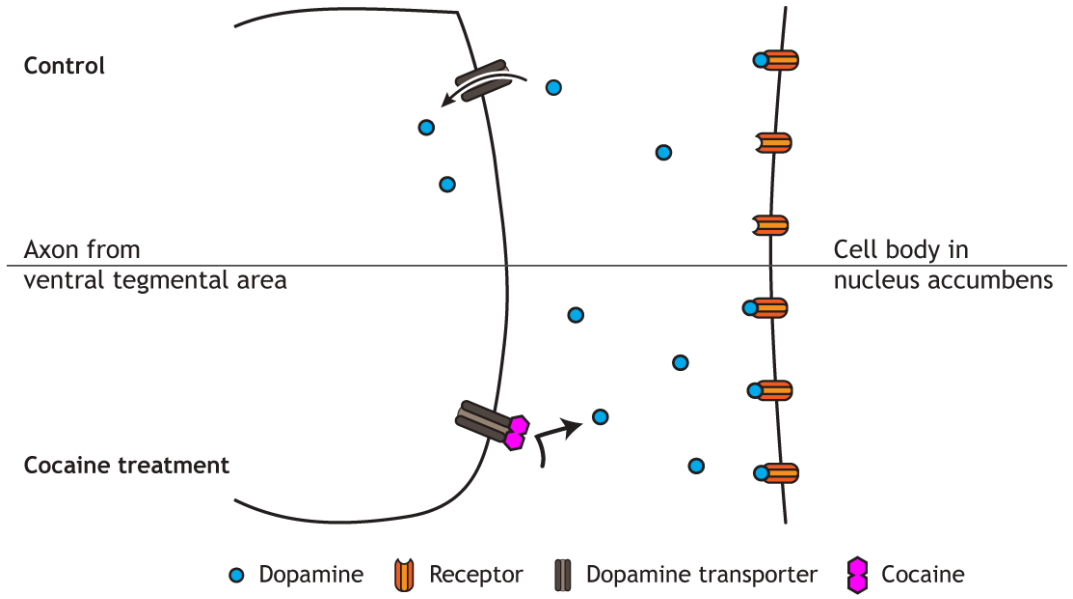


Figure 39.4. Control (top) panel: Dopamine effects are typically terminated by reuptake into the presynaptic terminal via the dopamine transporter (DAT). Cocaine treatment (bottom) panel: Cocaine blocks DAT, preventing reuptake of dopamine. The increased action of dopamine on the nucleus accumbens leads to increased activation of the reward circuit, a mechanism underlying addiction to the drug. 'Cocaine Effects' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- The reward circuit involves dopamine release from the ventral tegmental area into the nucleus accumbens and prefrontal cortex.
- Self-stimulation experiments demonstrate the role of dopamine and the reward circuit.
- Dopamine signaling likely predicts reward value and can be altered if predicted outcomes differ from actual outcomes.

- Drugs of abuse act upon the reward circuit.

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40.

MOTIVATED BEHAVIOR: FEEDING BEHAVIOR

Resources

- Scientist links to learn more!
- Glossary Terms
- Key Takeaways

Motivated behaviors are voluntary behaviors that individuals find rewarding or pleasurable. Motivation varies in intensity which will correlate to the probability of performing the associated behavior. Certain behaviors or stimuli, like food or sex, are naturally rewarding because they are necessary for the survival of a species; they are adaptive, and the nervous system has evolved to make these behaviors pleasurable. Rewarding stimuli increases brain activation in brain regions that comprise the reward circuit.

Homeostasis

Homeostasis is maintenance of the body's internal environment within a physiological range. The hypothalamus is important in regulating many homeostatic processes by responding to sensory input when a deviation from homeostatic set point is detected.

Role of Hypothalamus in Homeostasis and Motivated Behavior

The **hypothalamus** is located ventrally on the brain and surrounds the third ventricle. Sensory neurons within the hypothalamus measure changes in parameters that need to be regulated within the body, such as temperature, water balance, and feeding. When that parameter is sensed to be outside

the normal physiological range, these hypothalamic neurons will initiate a three component process that will act to bring that parameter back within range (restore homeostasis): humoral response, visceromotor response, and somatic motor response.

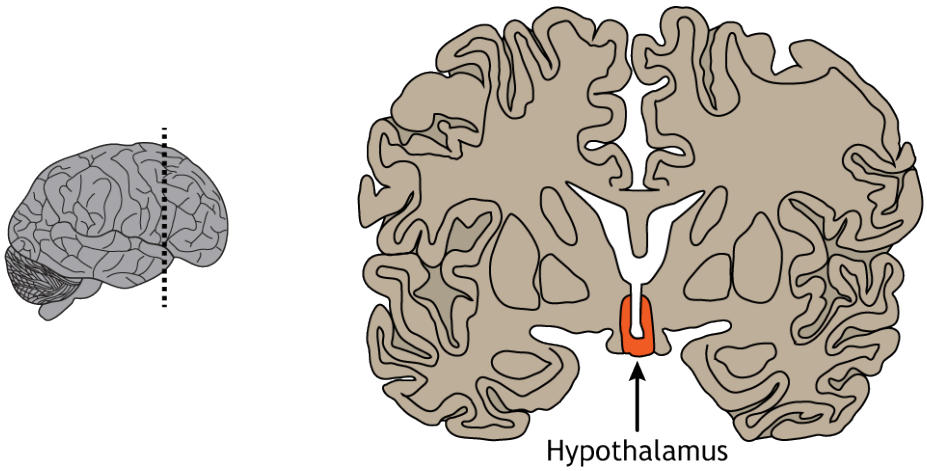


Figure 40.1. The hypothalamus, shown in orange in this coronal view, is located adjacent to the third ventricle. 'Hypothalamus Coronal View' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the hypothalamus using the BrainFacts.org 3D Brain

Humoral Response

In the humoral response, neurosecretory cells within the hypothalamus regulate release of pituitary hormones into circulation. The word 'humoral' comes from the word 'humor' which is an older word that refers to different fluids within the body. In the case of the humoral response, the bodily fluid is in reference to the blood where the hormones are being released.

Hypothalamic Control of the Pituitary Gland

The hypothalamus contains two types of neurons that secrete hormones into the pituitary: parvocellular neurosecretory cells and magnocellular neurosecretory cells. **Magnocellular neurosecretory cells**, the larger type of neurosecretory cell compared to parvocellular neurons, send

axons from the hypothalamus down to the pituitary stalk where they terminate on capillaries of the general circulation located within the posterior pituitary. Therefore, the hormones that are released by the posterior pituitary gland are actually made within the hypothalamus. For this reason, the posterior pituitary is considered neural tissue, rather than endocrine tissue.

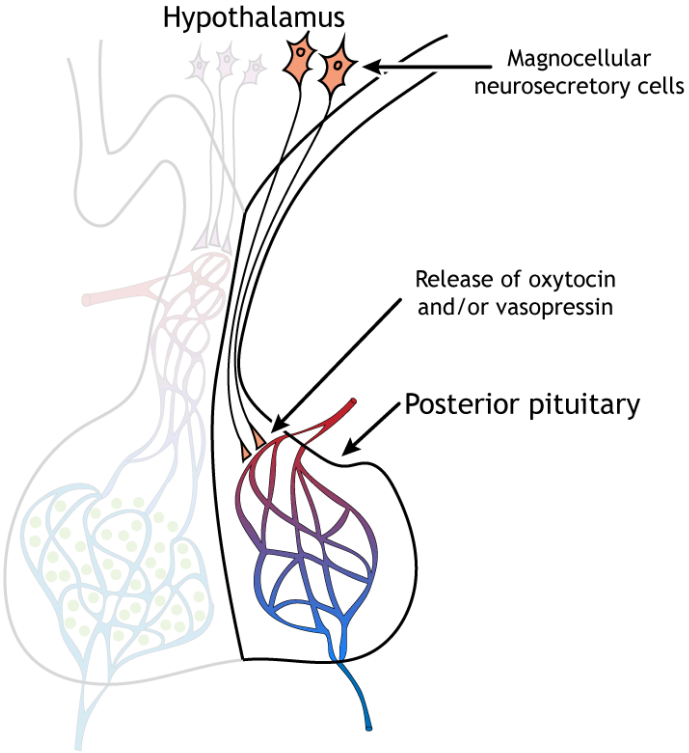


Figure 40.2. The hypothalamic magnocellular neurosecretory neurons release oxytocin and/or vasopressin into the general circulation via capillaries located in the posterior pituitary. 'Oxytocin and Vasopressin Release' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The magnocellular neurons synthesize and release oxytocin and vasopressin, two neuropeptides, into the blood. **Oxytocin**, often referred to as the love hormone, promotes social bonding. It is released during reproduction and also causes uterine contractions during labor and the milk letdown reflex after birth. Vasopressin, also called antidiuretic hormone, plays a role in regulating salt concentration in the blood by acting on the kidneys to promote water retention and decrease urine production. **Vasopressin** has also been shown to be involved in bonding, parenting, territoriality, and mate guarding in some animals.

Parvocellular cells are smaller than the magnocellular neurons (parvus means "small" in

Latin). These neurons release **hypophysiotropic hormones** into a specialized capillary system that lies between the hypothalamus and the anterior pituitary gland called the **hypophyseal portal circulation**. The hypophysiotropic hormones cause anterior pituitary cells to make and release their own hormones. The anterior pituitary gland is therefore endocrine tissue because the cells make their own hormones. There are multiple hormones that are made and released by the anterior pituitary gland. They act on multiple target tissues throughout the body, including the gonads, thyroid glands, adrenal glands, and mammary glands.

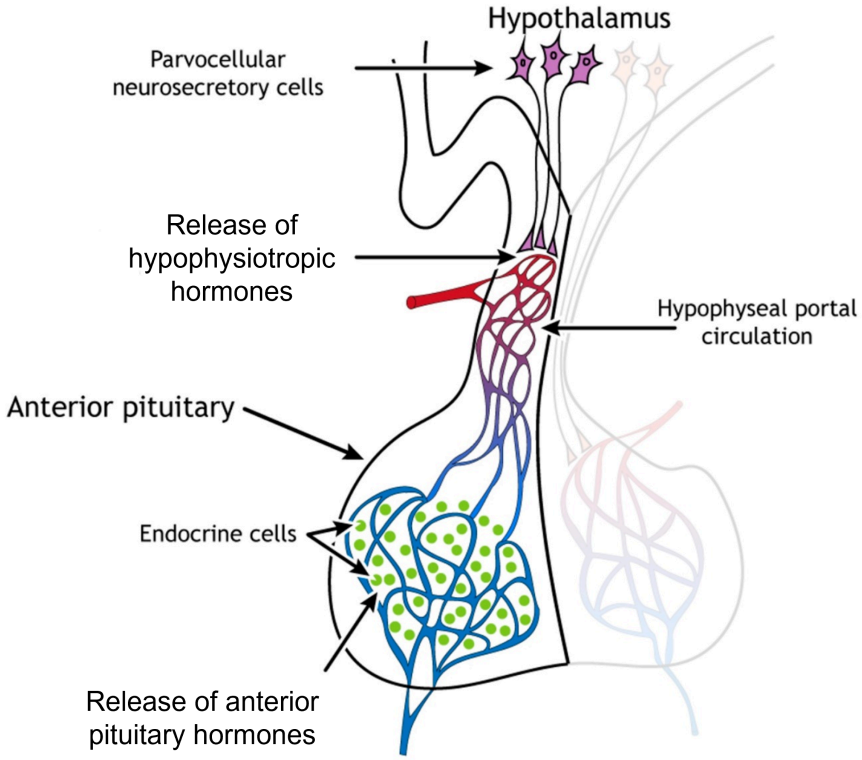


Figure 40.3. The hypothalamic parvocellular neurosecretory neurons release hypophysiotropic hormones into the hypophyseal portal circulation, causing the hormone-releasing endocrine cells in the anterior pituitary to release hormones. 'CRH and ACTH Release' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Visceromotor Response

The visceromotor response involves hypothalamic neurons that adjust **sympathetic** and **parasympathetic** activity to regulate internal organs.

Somatic Motor Response

The somatic motor response involves hypothalamic neurons that trigger an appropriate behavioral response.

Using a drop in temperature as an example, the humoral response will cause the release of hormones into circulation that will allow you to metabolize energy in a different way that will allow for more generation of heat. The visceromotor response would increase sympathetic nervous system activity to ensure that internal organs stay warm. Lastly, the somatic motor response would cause a behavioral change that would result in getting warmer (e.g. getting a coat, moving closer to the fire, or getting out of the cold outside).

Homeostatic Regulation of Body Weight and Food Intake

We obtain energy from our diet and consumption of glucose, which serves as our energy source within the body. The body depends on access to glucose for normal function and survival. To ensure access to glucose when needed, our body stores glucose within the body in fat stores. We are motivated to eat and maintain these body fat stores.

Energy Balance

Body fat stores are regulated after we eat a meal. When we consume more glucose than we can use, the excess glucose is stored within the body as fat stores. Over time, this repeated pattern leads to increased adiposity and can lead to obesity. If energy demands exceed the consumption of glucose, then glucose must be broken down from fat stores and fat is lost. Over time, this leads to decreased adiposity and starvation.

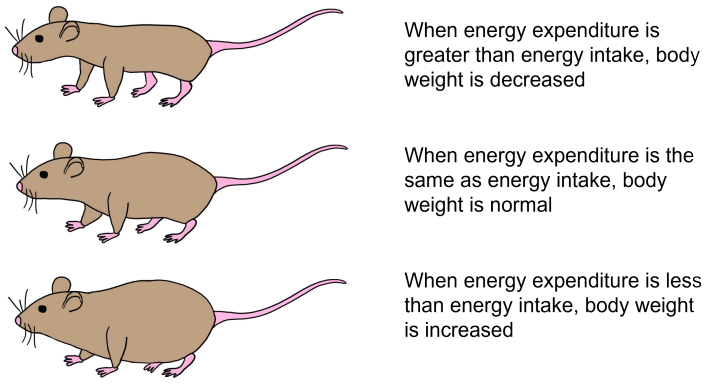


Figure 40.4. Energy Balance. Glucose is used as energy within the body. If glucose intake is equal to energy expenditure, then a normal body weight will result. When dietary intake of glucose is less than the amount of energy expended, then glucose stores will be broken down and there will be a loss of fat and a loss of body weight. When dietary intake of glucose is more than the amount of energy expended, then excess glucose will be stored in the body as fat, increasing body weight. 'Energy Balance' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

The body tries to defend fat stores and body weight around a particular set point. When rodents have restricted access to calories they experience a decrease in body weight, however when food is freely available again, they gain weight back to their weight prior to calorie restriction. Conversely, animals that are force fed to consume more calories than normal will gain weight, but will lose that gained weight when they are free to regulate their own feeding.

To maintain a balance of fat stores and expended energy, we regulate our feeding behavior. There are both short-term and long-term mechanisms that contribute to feeding regulation and maintenance of fat stores.

Long-Term Regulation of Feeding Behavior

Leptin

The level of fat within the body must somehow be communicated to the brain in a way that ultimately controls feeding behavior. The discovery of genetically obese mice by Dr. Douglas Coleman and

colleagues helped determine the source of this signal. The DNA of the genetically obese mice found that these animals were missing both copies of the *ob* gene. These mice are referred to as *ob / ob* mice.



Figure 40.6. Normal mouse vs ob / ob mouse. This pictures shows an ob / ob mouse on the left and a normal mouse on the right. The ob / ob mouse has significantly more fat store than the normal mouse.

It was theorized that the *ob* gene must produce a hormone that typically signals that fat reserves are sufficient. Without this gene, and thus without this hormone, the obese mice were not receiving the appropriate signal to stop eating, causing them to over eat and increase fat stores. It was determined that the *ob* gene codes for the hormone **leptin**, which is secreted by fat cells. The *ob* mice had sufficient levels of fat, but did not have the hormone leptin released by the fat cells that would typically decrease feeding behavior. In fact, when ob mice are treated with leptin, they no longer over eat and restore a normal body weight.

More **leptin** is secreted when fat levels are high. Leptin acts to decrease appetite and increase energy expenditure, which will ultimately decrease levels of fat, and maintain normal fat stores levels in the

body. Though it may seem that leptin administration would be an effective treatment for obesity, leptin treatment is only effective for individuals with an identified leptin deficiency. Those without a leptin deficiency have increased levels of leptin due to increased fat stores, but ultimately have neurons with decreased sensitivity to leptin levels.

Role of Hypothalamus in Feeding Behavior

Two areas of the hypothalamus have been historically described with regard to their role in feeding behavior through lesion studies. If the **lateral hypothalamus** is bilaterally lesioned, it results in **lateral hypothalamic syndrome and anorexia**, whereas bilateral lesions of the **ventromedial hypothalamus** results in **ventromedial hypothalamic syndrome and overeating/obesity**. Though it follows that the lateral hypothalamus causes feeding behavior to increase and the ventromedial hypothalamus causes feeding behavior to decrease, leptin signaling within these structures underlies these behavioral changes.

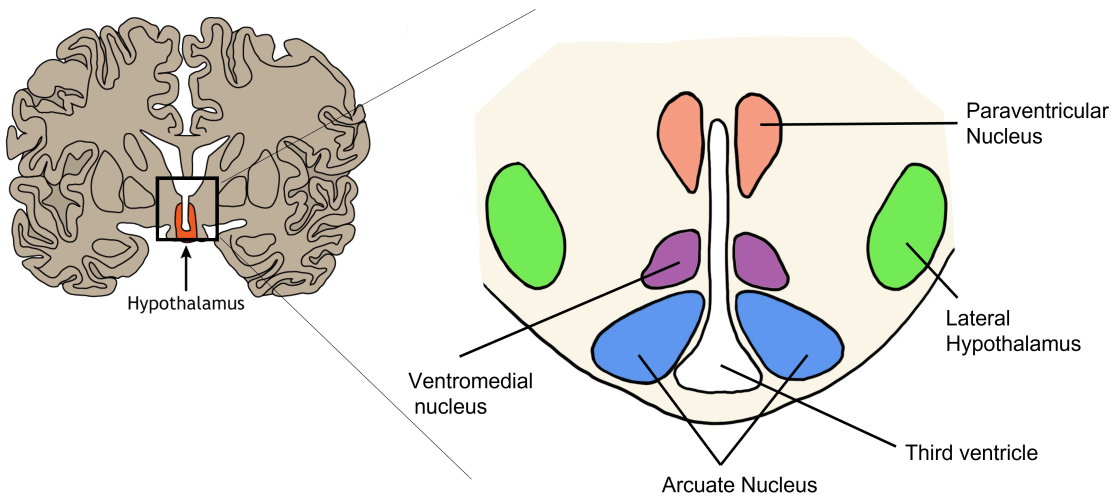


Figure 40.5. Hypothalamic Nuclei. A coronal section of the brain showing the location of the hypothalamus. The hypothalamus is then enlarged to show the location of multiple hypothalamic nuclei. There are multiple nuclei within the hypothalamus that regulate feeding behavior. The arcuate nucleus (shown in blue) is adjacent to the third ventricle. Dorsal to the arcuate nucleus is the ventromedial nucleus (shown in purple). The paraventricular nucleus sits adjacent to the dorsal area of the third ventricle (shown in orange). The lateral hypothalamus is not a nucleus, but has cells that all perform the same function (shown in green). 'Hypothalamic Nuclei' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Arcuate Nucleus

The neurons within the **arcuate nucleus** of the hypothalamus have receptors that detect levels of circulating **leptin**. The arcuate nucleus neurons produce peptide neurotransmitters called **αMSH** (alpha-melanocyte-stimulating hormone) and **CART** (cocaine- and amphetamine-regulated transcript). Note, that the names of peptides are typically derived from the first identified function of the peptide, but that additional functions are later discovered, which can lead to the names of the peptides being somewhat confusing.

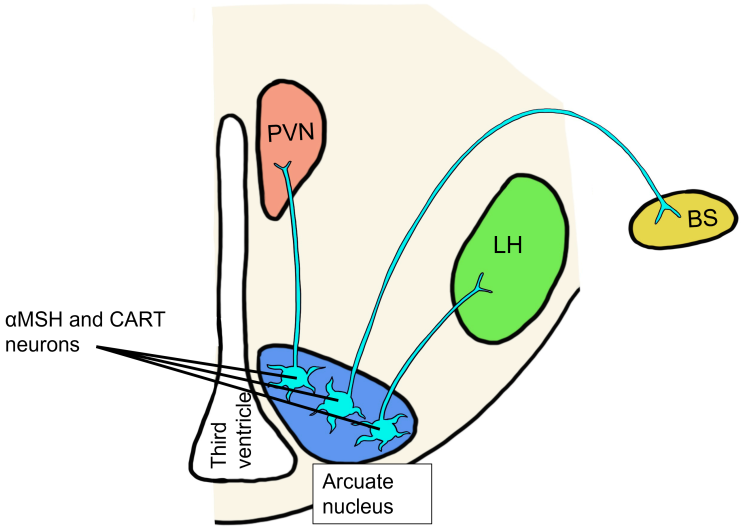


Figure 40.7. αMSH and CART arcuate neuron projections. A population of αMSH and CART-producing arcuate neurons (blue colored neurons) are activated by high levels of leptin. These neurons project to three different locations to bring about the humoral, visceromotor, and somatic motor responses of the hypothalamus. Projections from the arcuate to the paraventricular nucleus (PVN) controls the humoral response. Projections from the arcuate to the brainstem (BS) controls the visceromotor response. Lastly, projections from the arcuate to the lateral hypothalamus (LH) controls the somatic motor response. 'αMSH and CART arcuate neuron projections' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Humoral Response to Increased Leptin

Changes in leptin levels will lead to the humoral, visceromotor, and somatic motor hypothalamic responses.

When fat levels are increased, leptin levels are also increased. In the humoral hypothalamic response, leptin binds to neurons in the arcuate nucleus. This population of arcuate neurons project to the paraventricular nucleus (PVN) and release αMSH and CART onto the PVN neurons. In response to the binding of αMSH and CART, the PVN neurons cause the release of the hypophysiotropic hormones. The anterior pituitary gland will then release thyroid stimulating hormone (TSH) and adrenocorticotropic hormone (ACTH), which will both act to raise the metabolic rate within the body.

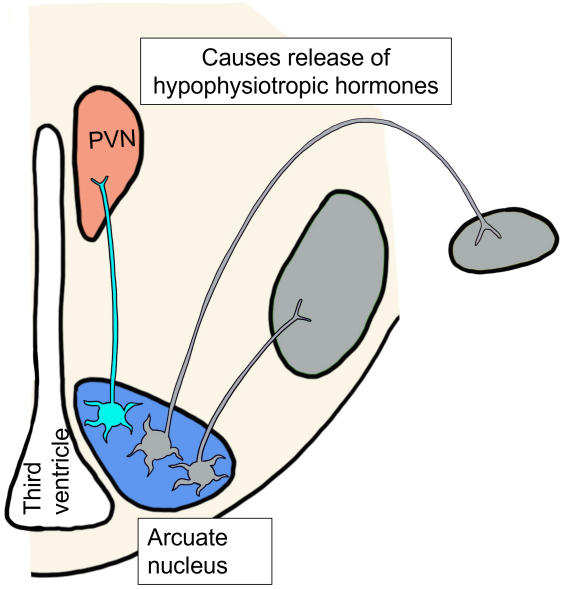


Figure 40.8. High leptin humoral response. When leptin levels are high neurons within the arcuate nucleus release αMSH and CART onto neurons within the paraventricular nucleus (PVN), controlling the humoral response of the hypothalamus. In response to αMSH and CART, the PVN neurons cause the release of the hypophysiotropic hormones. The anterior pituitary gland then releases thyroid stimulating hormone (TSH) and adrenocorticotropic hormone (ACTH), which will both act to raise the metabolic rate within the body. 'High leptin humoral response' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Visceromotor Response to Increased Leptin

When leptin levels are high, leptin will also bind to a separate population of arcuate neurons that project to the brainstem and control the hypothalamic visceromotor response. These arcuate neurons release αMSH and CART onto brainstem neurons that will act to increase **sympathetic nervous system** activity, raising the metabolic rate and increasing body temperature.

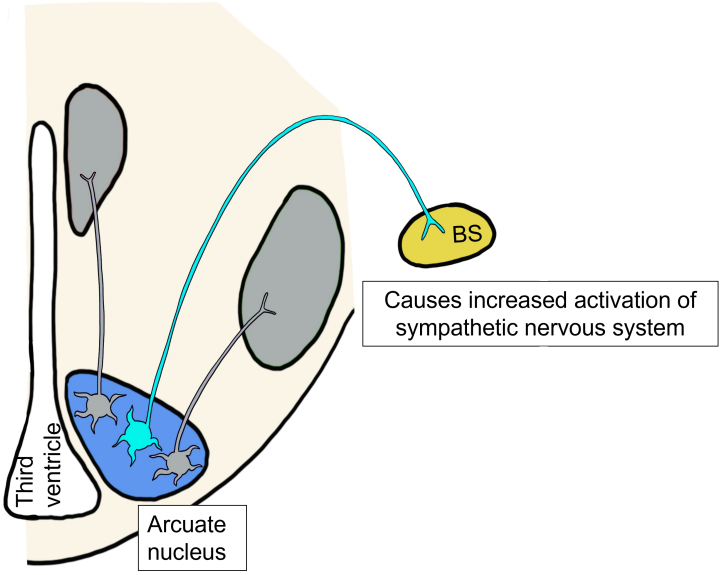


Figure 40.9. High leptin visceromotor response. When leptin levels are high neurons within the arcuate nucleus release αMSH and CART onto neurons within the brainstem (BS), controlling sympathetic nervous system activity and the visceromotor response of the hypothalamus. αMSH and CART cause increased sympathetic nervous system activity, which will increase body temperature and increase metabolic rate within the body. 'High leptin visceromotor response' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Somatic Motor Response to Increased Leptin

Lastly, when leptin levels are high, leptin binds to a third population of arcuate neurons that project to the lateral hypothalamus and control the hypothalamic somatic motor response. These arcuate neurons release αMSH and CART onto lateral hypothalamus neurons. αMSH and CART inhibit the lateral hypothalamus, inhibiting feeding behavior.

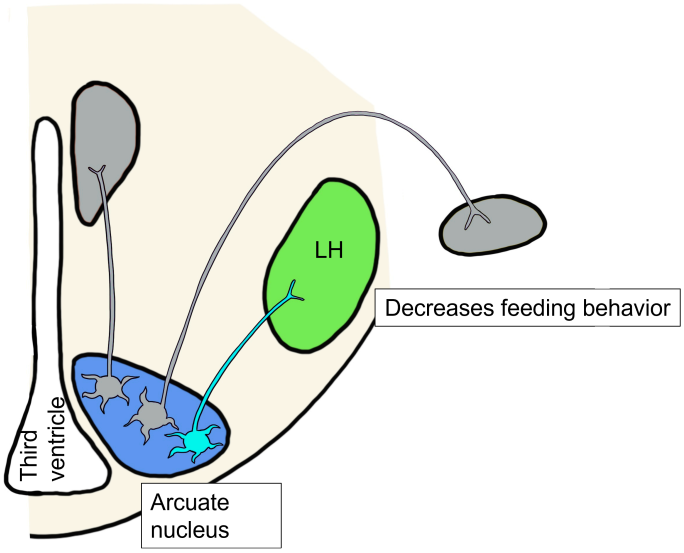


Figure 40.10. High leptin somatic motor response. When leptin levels are high neurons within the arcuate nucleus release αMSH and CART onto neurons within the lateral hypothalamus (LH) controlling the somatic motor response of the hypothalamic. αMSH and CART inhibit the neurons within the lateral hypothalamus that normally promote feeding behavior, thereby causing decreased feeding. 'High leptin somatic motor response' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Overall, the increase in metabolic rate, increase in body temperature, and decreased feeding will all ultimately lead to a decrease in body fat and thus a decrease in leptin levels, bringing fat and leptin levels back within the physiological setpoint range. αMSH, CART, and Leptin are all examples of **anorexigenic**, or satiety, signals. Collectively, **anorexigenic signals** decrease feeding behavior and decrease body weight in response to increased adiposity.

Humoral Response to Decreased Leptin

When fat levels are decreased, leptin levels are also decreased. When leptin levels drop, an entirely different set of neurons within the arcuate nucleus are activated that release the neuropeptides **neuropeptide Y (NPY)** and **agouti-related peptide (AgRP)**.

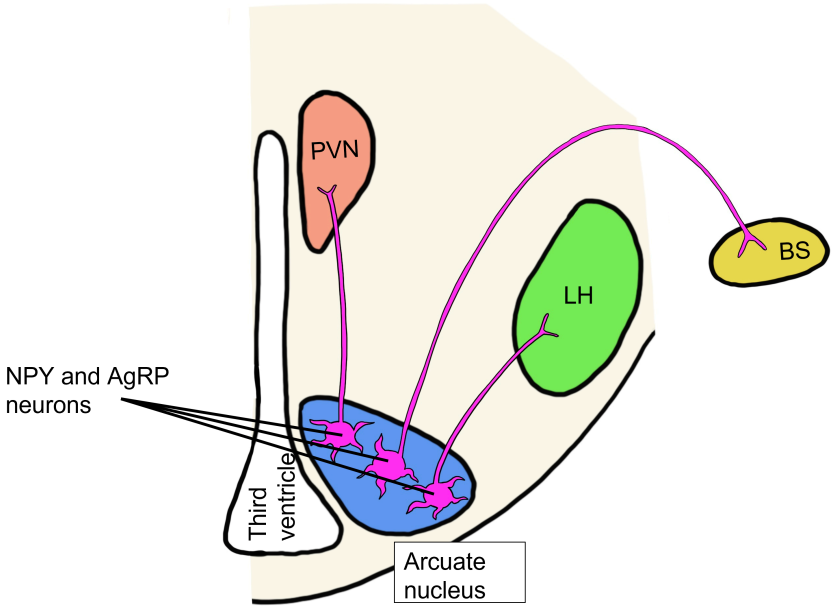


Figure 40.11. AgRP and NPY arcuate neuron projections. A population of AgRP and NPY- producing arcuate neurons (pink colored neurons) are activated by low levels of leptin. These neurons project to three different locations to bring about the humoral, visceromotor, and somatic motor responses of the hypothalamus. Projections from the arcuate to the paraventricular nucleus (PVN) controls the humoral response. Projections from the arcuate to the brainstem (BS) controls the visceromotor response. Lastly, projections from the arcuate to the lateral hypothalamus (LH) controls the somatic motor response. 'AgRP and NPY arcuate neuron projections' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

In the humoral hypothalamic response, the drop in leptin activates neurons in the arcuate nucleus. This population of arcuate neurons project to the paraventricular nucleus (PVN) and release NPY and AgRP onto the PVN neurons. These neuropeptides inhibit the PVN, thereby inhibiting release of the hypophysiotropic hormones, and ultimately inhibiting release of TSH and ACTH. As a result, metabolic activity in the body is decreased.

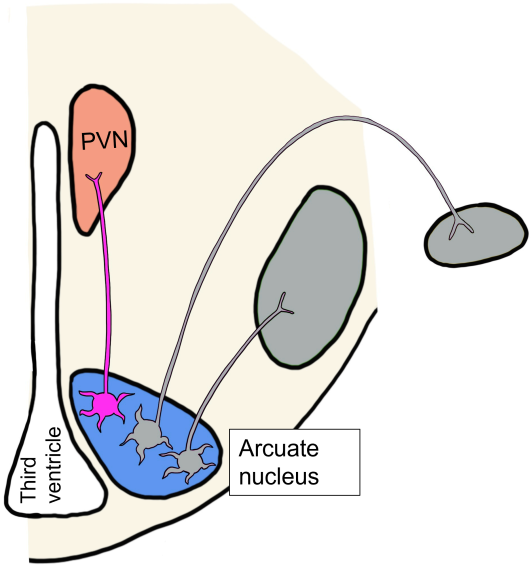


Figure 40.12. Low leptin humoral response. When leptin levels are low, neurons within the arcuate nucleus release AgRP and NPY onto neurons within the paraventricular nucleus (PVN), controlling the humoral response of the hypothalamus. In response to AgRP and NPY, the PVN neurons are inhibited, and thus do not release hypophysiotropic hormones. As a result, -the anterior pituitary gland does not release thyroid stimulating hormone (TSH) and adrenocorticotropic hormone (ACTH), causing metabolic rate within the body to decrease. 'Low leptin humoral response' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Visceromotor Response to Decreased Leptin

When leptin levels are low, arcuate neurons are activated that project to the brainstem and control the hypothalamic visceromotor response. These arcuate neurons release NPY and AgRP onto brainstem neurons that will act to increase parasympathetic nervous system activity, decreasing the metabolic rate and decreasing body temperature.

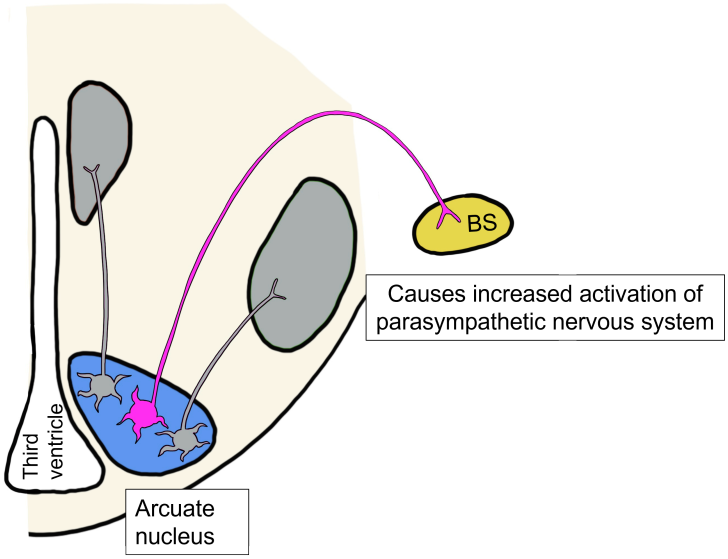


Figure 40.13. Low leptin visceromotor response. When leptin levels are low, neurons within the arcuate nucleus release AgRP and NPY onto neurons within the brainstem (BS), controlling parasympathetic nervous system activity and the visceromotor response of the hypothalamus. AgRP and NPY cause increased parasympathetic nervous system activity, which will decrease body temperature and decrease metabolic rate within the body. 'Low leptin visceromotor response' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Somatic Motor Response to Decreased Leptin

Lastly, when leptin levels are low, the drop in leptin activates a population of arcuate neurons that project to the lateral hypothalamus and control the hypothalamic somatic motor response. These arcuate neurons release NPY and AgRP onto lateral hypothalamus neurons. NPY and AgRP stimulate the lateral hypothalamus, stimulating feeding behavior.

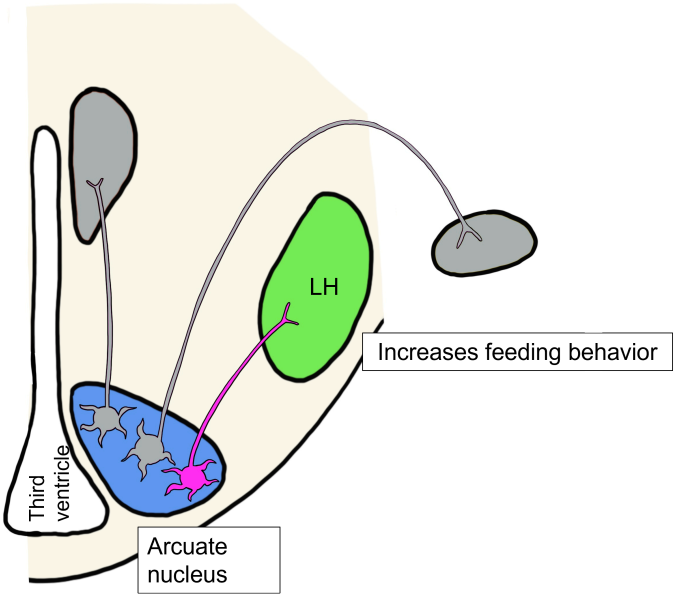


Figure 40.14. Low leptin somatic motor response. When leptin levels are low, neurons within the arcuate nucleus release AgRP and NPY onto neurons within the lateral hypothalamus (LH) controlling the somatic motor response of the hypothalamic. AgRP and NPY activate the neurons within the lateral hypothalamus that promote feeding behavior, thereby causing increased feeding. 'Low leptin somatic motor response' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Overall, the decrease in metabolic rate, decrease in body temperature, and increased feeding brought about by the three hypothalamic responses will all ultimately lead to an increase in body fat and thus an increase in leptin levels, bringing fat and leptin levels back within the physiological setpoint range.

NPY and AgRP are examples of orexigenic signals. **Orexigenic signals** increase feeding behavior and increase body weight in response to changes in adiposity. AgRP and αMSH are considered antagonistic neurotransmitters because they both bind to the MC4 receptor on hypothalamic neurons, but exert opposite effects on feeding behavior.

Key Takeaways

- Motivated behaviors are voluntary behaviors that individuals find rewarding.
- Certain behaviors or stimuli are naturally rewarding because they are necessary for the survival of a species.
- The hypothalamus has three responses to help maintain homeostasis: humoral response, visceromotor response, and somatic motor response.
- Leptin levels are controlled by fat levels in the body.
- Leptin interacts with 2 different populations of neurons within the arcuate nucleus of the hypothalamus to bring about homeostasis.

Attributions

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41.

MOTIVATED BEHAVIOR: SEXUAL BEHAVIOR

Here we will examine an additional rewarding behavior. Rodents, such as rats, are used as a model for studying sexual behavior and reward.

Resources

- Glossary terms
- Key Takeaways

Rodent Sexual Behavior

When in the presence of a sexually receptive female rat, a male rat will engage in male sexual behavior, called **mounting behavior**. Mounting behavior is controlled by the **medial preoptic area (mPOA) of the hypothalamus** in males.

Female rats display their own sexual behavior called **lordosis**. Lordosis behavior is displayed as an arched-back posture that is controlled by the **ventromedial hypothalamus (VMH)**. Female rats also have the ability to pace their sexual interactions by controlling the timing of the sexual interaction. The female rat will run around the cage and choose when they will stop and allow the male to engage in mounting behavior.

Steroid hormones such as testosterone, estrogen, and progesterone regulate activity of the mPOA and VMH.

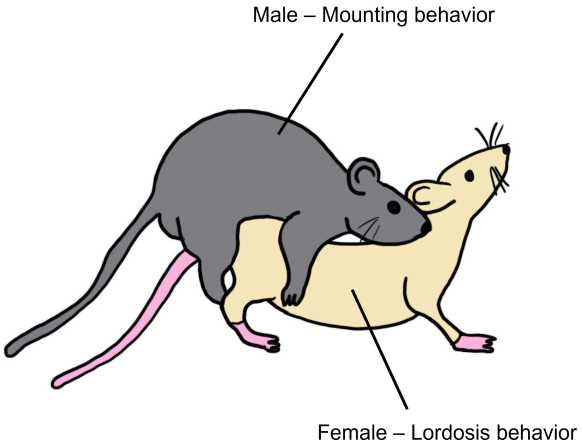


Figure 41.1. Rat Sexual Behavior. The male rate (gray) displays mounting behavior and the white rate (female) displays lordosis behavior, which involves arching of the back. 'Rat Sexual Behavior' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

When considering sexual behavior as a model for motivated behaviors, it is important that we understand *why* an animal engages in sexual behavior.

A modified operant chamber was constructed by Everitt and colleagues (1990) that helped to answer this question. A male rat was trained to press a lever within the chamber that when pressed would open a door and allow for access to a sexually-receptive female rat, with whom the male could engage in a sexual bout. Males easily learned this paradigm and consistently pressed the lever to gain access to the female (Everitt, 1990).

When the mPOA was lesioned in the male rats and they were tested in this same operant chamber, the male rats still pressed the lever to gain access to the female rat, even though they no longer had the ability to perform sexual mounting behavior. However, when the nucleus accumbens was lesioned and the mPOA remained intact, the male rats no longer pressed the lever. They had lost the motivation associated with the prospect of sexual experience, thus demonstrating that the nucleus accumbens, and the reward pathway drive the motivation for sexual behavior in rodents, not the brain structure that controls sexual behavior. It follows that in female rats, the motivation to engage in sexual behavior is dependent on activity of the nucleus accumbens, and not on activity within the VMH.

Nucleus Accumbens Dopamine in Sexual Behavior

Measuring extracellular dopamine concentrations outside the nucleus accumbens through microdialysis techniques has demonstrated that extracellular dopamine increases during many different behaviors considered to be rewarding, including male and female sexual behavior.

Measuring Reward: Conditioned Place Preference

Conditioned place preference (CPP) is a behavioral test that can be used as way of measuring the reward associated with different stimuli. CPP is commonly used as a way to measure reward associated with different drugs of abuse, but the paradigm can also be used to measure the rewarding aspects of natural rewards, such as sexual behavior. In a CPP paradigm, a CPP appartus is used that typically has two distinct testing chambers that have different colors or patterns on the walls, and different tactile surfaces on the floor of the chamber. Additionally, there is a neutral compartment between the two testing chambers. As an example, one testing chamber might have white walls and hard bedding on the floor, whereas the other testing chamber has gray walls and soft bedding.



Figure 41.2. Conditioned place preference apparatus. This conditioned place preference apparatus has a clear central compartment that serves as a neutral area. There are two testing chambers that differ in color and tactile sensation on the floor of the chamber. The gray chamber has soft aspen bedding and the white chamber has hard corncob bedding. During testing, a potentially rewarding stimulus is paired with a specific environment (eg. gray chamber) whereas the opposite environment is not paired with any substance or behavior. 'Conditioned place preference apparatus' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

An experimental male animal can be placed in the neutral central compartment and then given 10 minutes to explore the entirety of the apparatus. The amount of time that the animal spends in each chamber is recorded as a pre-test measurement. Next, the chambers are sectioned off from each other and the experimental male animal is placed with a sexually-receptive female animal in the gray chamber with soft bedding. The experimental male then has a 10-minute sexual experience within the gray chamber. After the sexual experience, they are also placed alone in the white chamber with hard bedding. This is repeated for several weeks, such that the animals learn to associate sexual

experience with the gray chamber environment and learn to associate nothing with the white chamber environment. Lastly, the experimental animal is placed alone in the central neutral compartment and again permitted to access the entire apparatus. The amount of time spent in each of the chambers is recorded as a post-test measurement.

By comparing the time spending in the conditioning chamber during the pre-test to the time spent in the conditioning chamber during the post-test, it can be determined if the animal spends significantly more time in the chamber that was paired with the sexual experience. Researchers interpret a significantly increased time spent in the conditioning compartment as a measurement of the reward that the animal feels being in that environment. If no significant difference is observed between the pre-test and post-test times in the conditioning compartment, then the testing substance or behavior is not considered to be rewarding to the animal.

Using this paradigm, administration of a dopamine antagonist to animals prior to the conditioning sessions prevents the formation of a conditioned place preference, indicating that dopamine within the reward pathway underlies the reward associated with sexual behavior.

Key Takeaways

- Male rodent sexual behavior is called mounting behavior, and it is controlled by the medial preoptic area of the hypothalamus.
- Female rodent sexual behavior is called lordosis behavior, and it is controlled by the ventromedial hypothalamus.
- Lesions to the areas of the brain that control the ability to perform the sexual behavior does not impact the desire that the animal has to engage in sexual behavior. Only lesions to the nucleus accumbens removes the desire to engage in sexual behavior.
- Conditioned place preference is a behavioral paradigm that is used to determine whether a substance or a behavior is rewarding.

- Dopamine within the reward circuit underlies the reward associated with sexual behavior.

References

"Sexual Motivation: A Neural and Behavioral Analysis of the Mechanisms Underlying Appetitive and Copulatory Responses of Male Rats" 1990. Everitt BJ. Neuroscience and Biobehavioral Reviews, Vol 14 pp 217-232.

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42.

SEX STEROID HORMONES

Control of gonadal hormone release relies on activation of the **hypothalamic-pituitary-gonadal (HPG) axis**. Gonadal hormones are important for development of the body and brain, changes during puberty, and the activation of some behavior in adulthood like reproductive behavior and aggression.

Resources

- Glossary terms
- Key Takeaways

Hypothalamus

As a refresher, the hypothalamus, which is located **inferior** to the thalamus, integrates information from many regions of the central nervous system and maintains homeostasis in the body. The hypothalamic regulation of gonadal hormones and sex behavior is managed via hormone release by the pituitary gland.

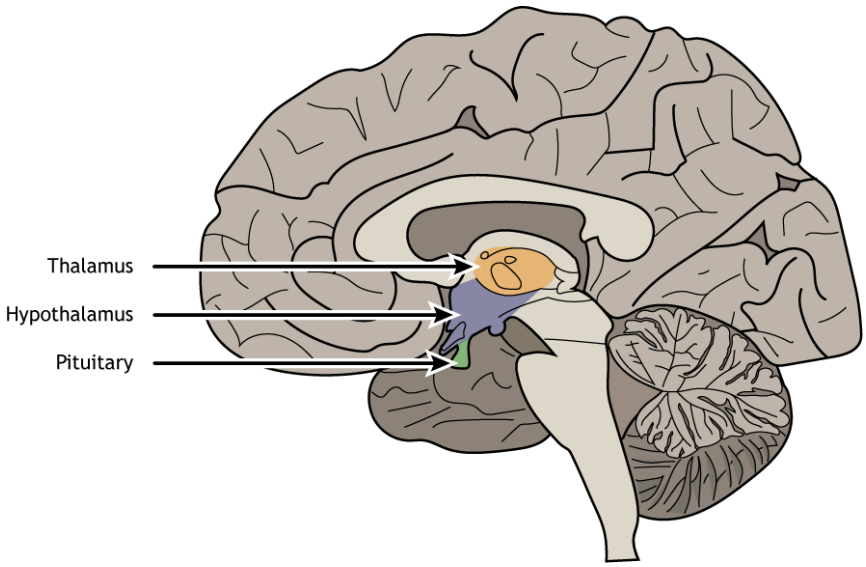


Figure 42.1. The pituitary, shown in green in a mid-sagittal section, lies just below the hypothalamus, shown in blue. 'Hypothalamus and Pituitary' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the hypothalamus using the BrainFacts.org 3D Brain

View the pituitary using the BrainFacts.org 3D Brain

Hormone Release

Gonadal hormone release relies on anterior pituitary function. In the hypothalamus, the parvocellular neurosecretory cells release a hormone called **gonadotropin-releasing hormone (GnRH)** into the hypophyseal portal circulation. When GnRH reaches the anterior pituitary, it causes the endocrine cells of the pituitary to release **luteinizing hormone (LH)** and **follicle-stimulating hormone (FSH)** into the general circulation.

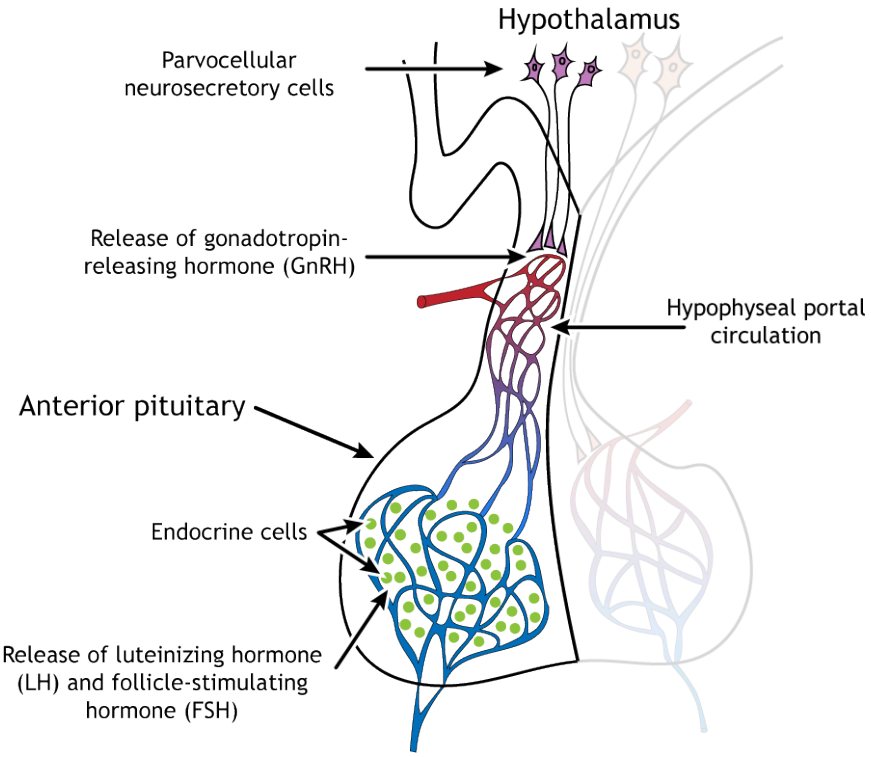


Figure 42.2. In the HPG axis, the hypothalamic parvocellular neurosecretory neurons release gonadotropin-releasing hormone (GnRH) into the hypophyseal portal circulation, causing the hormone-releasing endocrine cells in the anterior pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). 'LH and FSH Release' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The LH and FSH travel through the circulatory system and can act on the gonads, either the testes in males or ovaries in females. In response to the pituitary hormones, the **testes release testosterone**, an androgen, and the **ovaries release estradiol**, an estrogen, into the blood stream. After puberty, the LH and FSH are also critical for the maturation of sperm and egg cells.

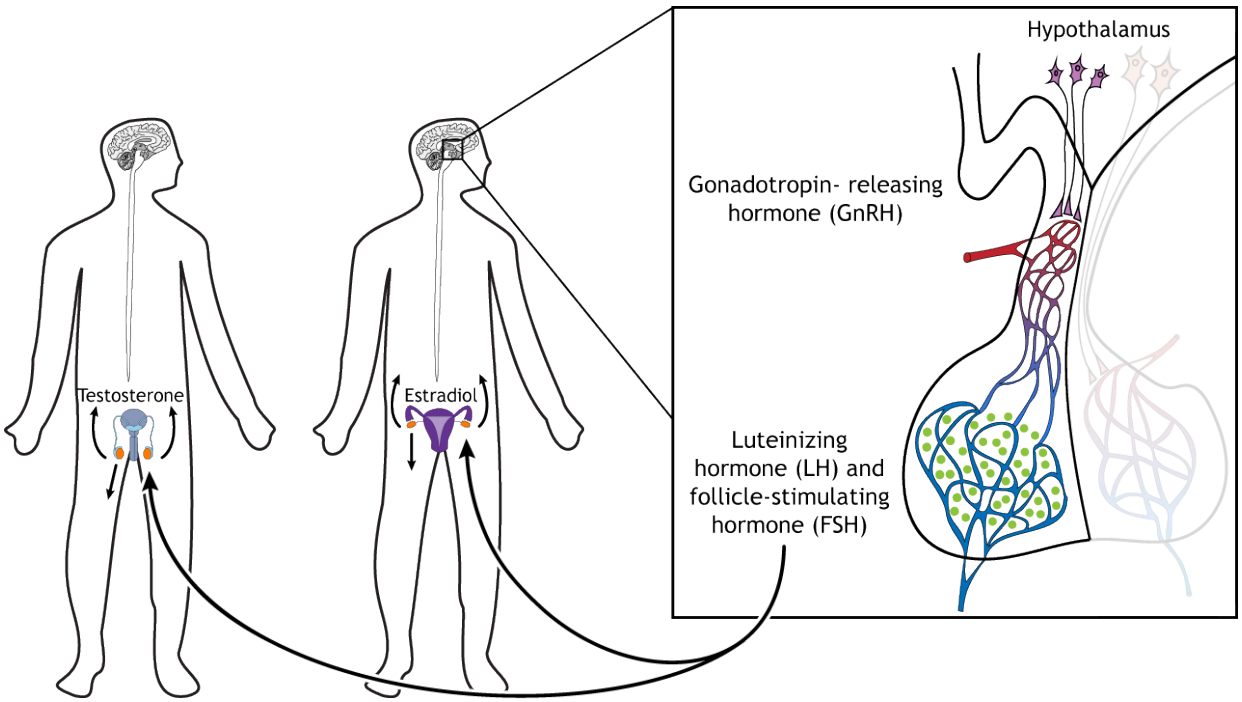


Figure 42.3. The gonads release either testosterone (testes) or estradiol (ovaries) into the bloodstream in response to release of LH and FSH by the anterior pituitary. 'HPg Axis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Sex Steroid Hormone Synthesis

Sex steroid hormones are produced by the gonads (ovaries or testes). All sex steroid hormones are originally generated from cholesterol. Males typically have higher concentrations of androgen sex steroid hormones, such as **testosterone** and **5-alpha-dihydrotestosterone (DHT)**. Androgens are primarily released from the testes. Females typically have higher concentrations of **estrogens (such as estradiol)** and **progesterone** that are primarily released from the ovaries. Importantly, males also have estrogens and progesterone, and females have androgens. The only difference is the relative concentration between males and females.

In the synthesis pathway, enzymes are responsible for converting one hormone into another hormone. The enzyme **5-α reductase** converts testosterone into DHT. DHT is important for masculinization of the body structures. Through just one chemical reaction, the enzyme **aromatase** converts testosterone into estradiol.

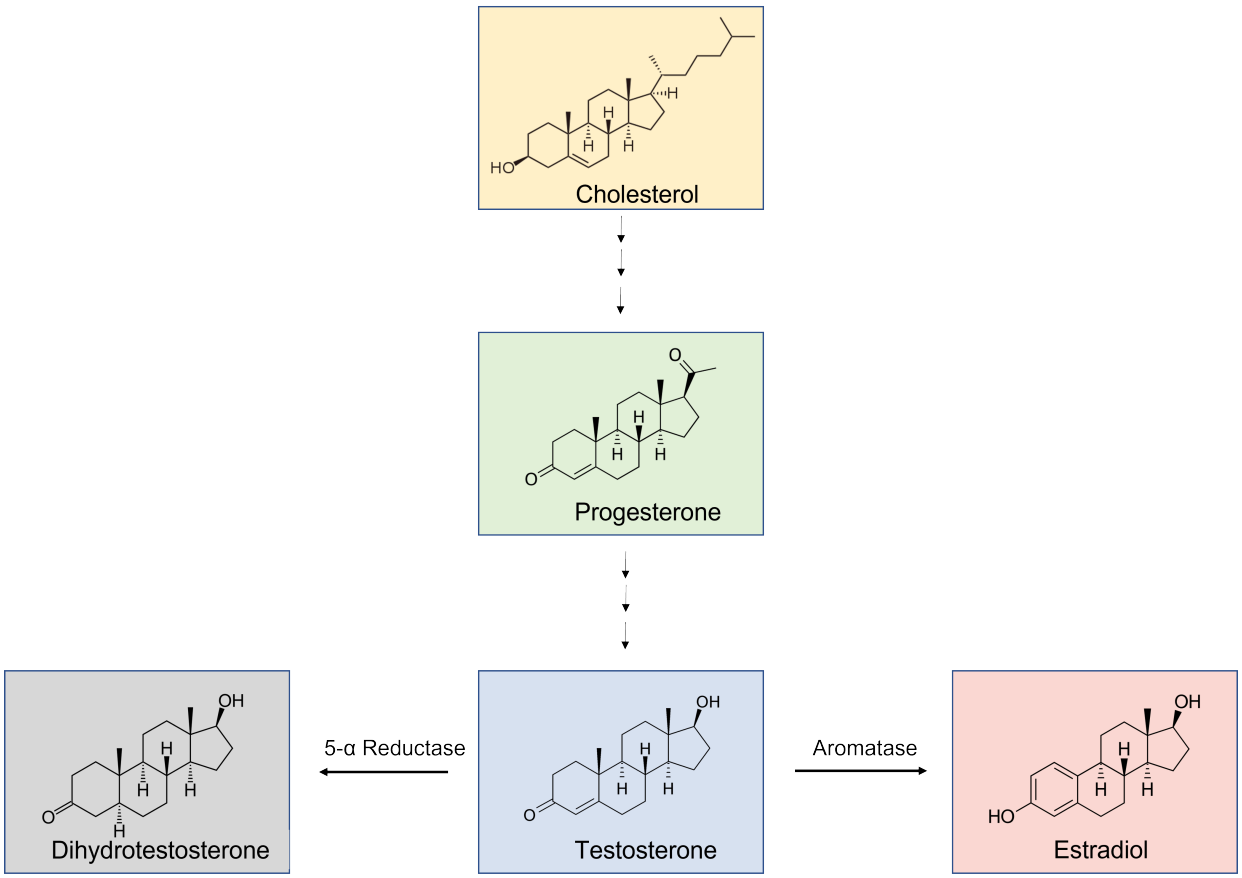


Figure 42.4 Sex steroid hormone synthesis. The sex steroid hormones are all synthesized from cholesterol. Through a number of chemical reactions, cholesterol is converted into progesterone. Through a series of additional chemical reactions, progesterone is converted into testosterone. One chemical reaction converts testosterone into estradiol through the actions of the enzyme aromatase. One chemical reaction converts testosterone into dihydrotestosterone (DHT) through the actions of the enzyme 5-α reductase.

Hormone Action

Once the gonadal hormones are synthesized and enter the circulation, they are able to act on cells that express either androgen receptors or estrogen receptors. Testosterone and estradiol are steroid hormones that can affect target cells through two different mechanisms:

1. **Classical mechanism:** Steroid hormones like testosterone and estradiol are able to pass through the phospholipid membrane of a neuron because they are **lipophilic**. Some neurons express

receptors for these hormones. Androgen receptors bind androgens like testosterone while estrogen receptors bind estrogens like estradiol. When a hormone binds to a receptor in the neuron, the hormone-receptor complex dimerizes and moves into the nucleus where it can bind to specific promoter sites on the DNA and act as a transcription factor to turn on or off certain genes (genomic effects).

2. **Rapid mechanism:** Sex steroid hormones can also bind to membrane-bound receptors and can exert more rapid effects within the cell.



One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=1120#video-1120-1

Animation 42.1. Steroid hormones can cross the phospholipid bilayer and bind to hormone receptors. The receptors dimerize, move to the nucleus, and interact with DNA, altering transcription of certain genes. 'Estradiol Action' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The testes secrete testosterone during the prenatal critical period. The effect of this testosterone is to masculinize and defeminize the brain, body, and behavior, and this is accomplished through the transcription of a specific set of genes. However, many of those genes are not transcribed by the action of androgen receptors interacting with the DNA. Instead, when testosterone enters the cell, it does not always bind to androgen receptors. Some neurons also express the enzymes 5-α reductase and aromatase that break testosterone down into its metabolites: DHT and estradiol.



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Animation 42.2. After testosterone enters the cell, if it does not bind to an androgen receptor, it can

be metabolized by enzymes in the cell. 5-α reductase converts testosterone into dihydrotestosterone. DHT, like testosterone, can bind to and activate androgen receptors. The enzyme aromatase converts testosterone into estradiol. Estradiol is an estrogen and can bind to and activate estrogen receptors. During developmental critical periods, the aromatization of testosterone to estradiol leads to the transcription of masculinizing genes in some animals like rodents. 'Aromatization' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

In some mammals, like rodents, this conversion of testosterone to estradiol through the actions of the enzyme aromatase is the main process by which neurons and the brain are masculinized. The estrogen receptors cause the transcription of masculinizing genes. Therefore, somewhat surprisingly, even though estrogen is typically thought of as a 'female' hormone, its actions during development are responsible for much of the masculinization that occurs in the brain in some animals.

The brain is by default "female" during development, and requires the testosterone secreted by the testes and converted into estradiol for "male" development. It should be noted, though, that estrogen does not appear to have these same masculinizing effects during human development.

Key Takeaways

- The hypothalamus directly controls release of gonadal hormones by controlling hormone release from the anterior pituitary.
- The hypothalamus releases gonadotropin-releasing hormone (GnRH).
- The anterior pituitary releases luteinizing hormone (LH) and follicle-stimulating hormone (FSH).
- The ovaries release estradiol.
- The testes release testosterone.
- Gonadal hormones bind to receptors and alter DNA transcription.

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43.

ORGANIZATIONAL AND ACTIVATIONAL EFFECTS OF STEROID HORMONES

In addition to differentiating the reproductive duct system, the presence or absence of gonadal steroid hormones during development also differentiates the rest of the body, including the brain. Testosterone causes the brain, body, and behavior of the individual to be masculinized and defeminized. The quiescent ovaries do not release hormones which causes the brain, body, and behavior of the individual to be feminized and demasculinized.

Resources

- Glossary terms
- Key Takeaways

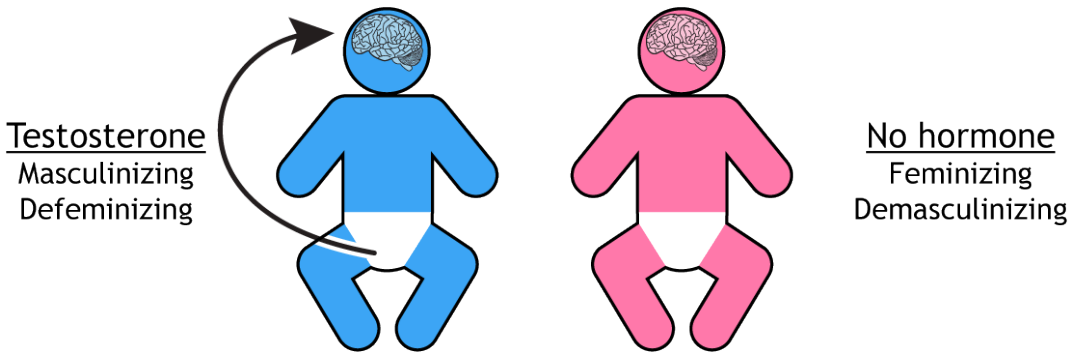


Figure 43.1. Testosterone presence during development masculinizes and defeminizes the brain, body, and behavior. No hormone exposure during development feminizes and demasculinizes the brain, body, and behavior. 'Developmental Hormones' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Sexual Dimorphisms

In the brain, gonadal hormones bind to receptors to alter neuronal function and overall behavior. In many species, males and females have different roles in sexual reproduction when it comes to finding a mate, copulation, birth, nursing, and nurturing offspring. It follows that there are differences in structure and function between male and female brains.

A **sexual dimorphism** is a distinct difference in the size or appearance of a structure between the sexes of an animal. In rodents, a **sexual dimorphism** has been described in the **sexually dimorphic nucleus of the preoptic area (SDN-POA) within the hypothalamus**. The SDN-POA is generally 5-8 times larger in male rodents than it is in female rodents.

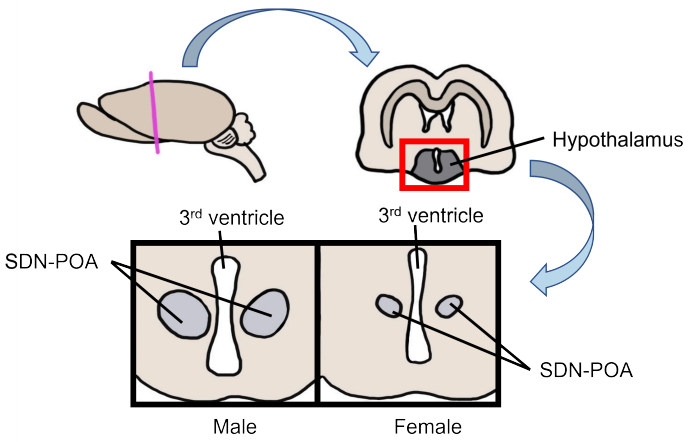


Figure 43.2 SDN-POA. A coronal (frontal) section of a rodent brain reveals the hypothalamus on the ventral surface of the brain surrounding the third ventricle. The sexually dimorphic nucleus of the preoptic area (SDN-POA) is a nucleus within the hypothalamus. This nucleus is sexually dimorphic in rodents and is 5-8x larger in males than in females. 'SDN-POA' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Are there sexual dimorphisms in the human brain? This answer is not clear. There may be differences in structures, but the differences are small and controversial. A set of nuclei within the human brain has been studied with regard to sexual dimorphisms called the **interstitial nuclei of the anterior hypothalamus (INAH)**. Within this collection of nuclei, INAH-1, INAH-2, and INAH-3 have been reported to be larger in men than in women, with INAH-3 having the largest difference. The function of INAH in sexual behavior is still not well-understood. Importantly, there is a large degree

of variability between human brains. This means that even when a sexual dimorphism is observed, it is being observed "on average" across many brains. Within this comparison group, there will be brains that do not show a sexual dimorphism or potentially show the exact opposite difference in size.

Critical Period

The hormonal effects of secreted testosterone on the brain must take place during a specific time in development, called a **critical period**. **Organizational effects** of hormones lead to major, generally irreversible, aspects of cell and tissue differentiation. Organizational effects take place during critical periods like prenatal development and puberty.

In adulthood, the same hormones trigger physiological or behavioral responses called **activational effects** that are reversible and short-lived.

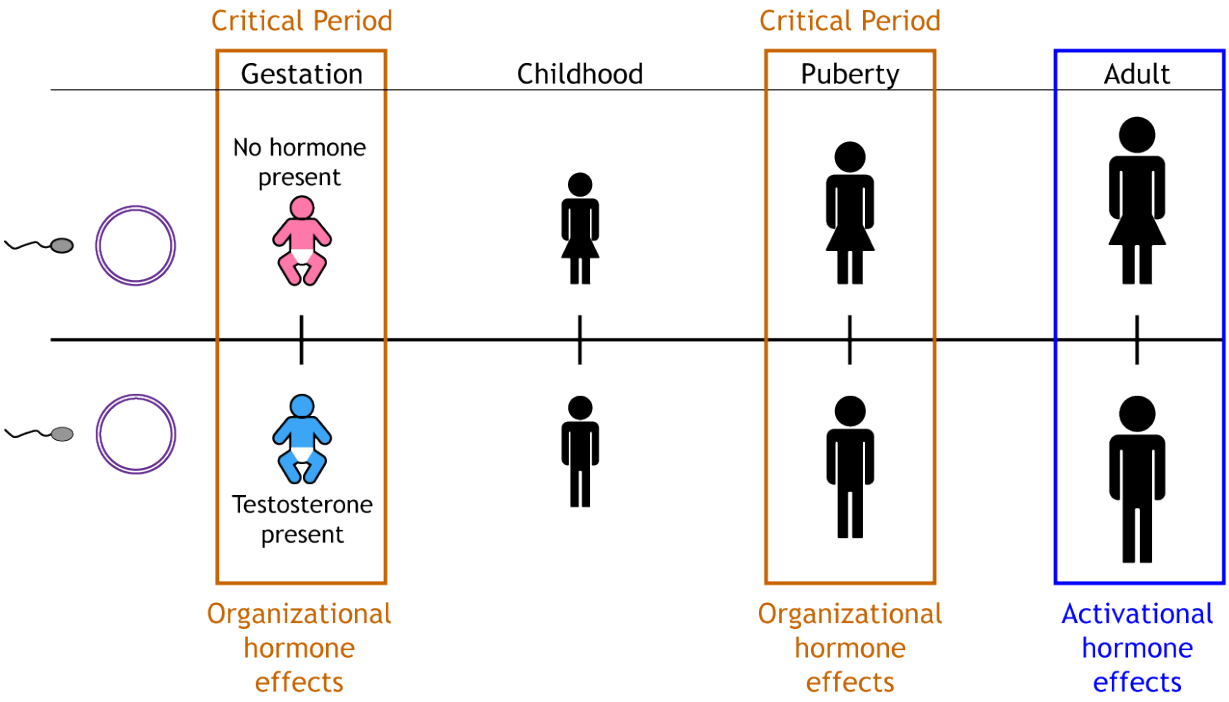


Figure 43.3. Hormones can have long-lasting, organizational effects when present during critical periods such as during the prenatal period or puberty. During these critical periods, hormones will alter the structure of the nervous system, setting up cells and circuits needed to display sex-typical behaviors later in life. Those sex-typical behaviors are then activated in adulthood by the presence of gonadal hormones. 'Organizational versus Activational' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Organizational Effects of Steroid Hormones

The early role of testosterone is an **organizational effect** and results in a permanent change in the nervous system and therefore behavior. The androgens released by the testes enter cells of the SDN-POA and are converted into estradiol through the actions of the enzyme aromatase. The estradiol within the SDN-POA acts to masculinize the structure of the SDN-POA by preventing cell death, causing the SDN-POA to be larger in males than in females. Due to the female ovaries being inactive during development (do not secrete estradiol), the female SDN-POA has a smaller, feminized structure due to the normal cell death that occurs during development. If testosterone is experimentally administered to a female during the organizational critical period, the SDN-POA will be masculinized

and larger, however if the testosterone is experimentally administered to a female after the organizational critical period, the structure of the SDN-POA will remain small and feminized.

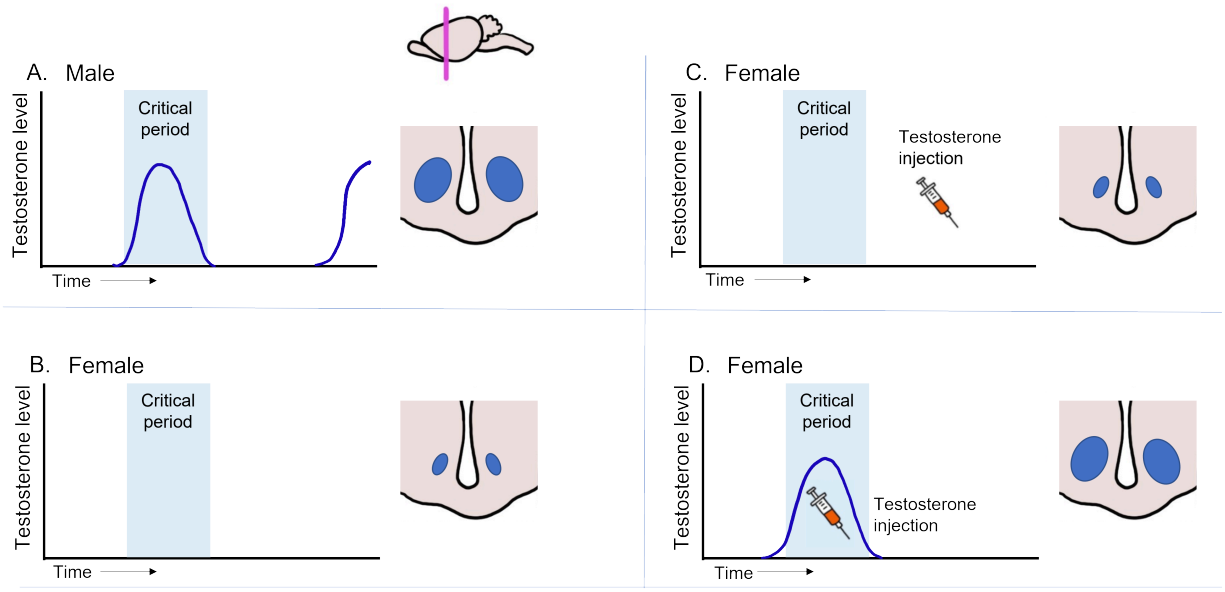


Figure 43.4. Testosterone during the critical period masculinizes the SDN-POA. A. During the critical period of male development, the testes release testosterone. This testosterone is aromatized into estradiol in the rodent brain, and estradiol masculinizes the SDN-POA structure, causing it to be larger. B. During female development, the ovaries are quiescent and do not release any hormones. The lack of hormones causes the structure of the SDN-POA to be feminized and smaller. C. If testosterone is administered to female rodents outside of the critical period of development, the testosterone will not cause a change in SDN-POA structure. D. However, if testosterone is administered to females during the critical period, the structure of the SDN-POA is masculinized and larger, similar to the structure of the SDN-POA in typical males. 'SDN-POA testosterone' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Hormone Change in Humans: Organizational Effects

Clearly, the presence of hormones during the organizational critical period is critical for the masculinization of the rodent brain. Below are examples of conditions in humans that demonstrate the organizational effects of gonadal steroid hormones on both the brain and body.

Androgen Insensitivity Syndrome (AIS) (also known as Testicular Feminization Syndrome) affects the development of the reproductive organs. Individuals with this syndrome do not have functional androgen receptors. Therefore, circulating androgens cannot bind to androgen receptors which affects the development of secondary sexual characteristics, causing these individuals to have a feminized appearance. They have an XY genotype but have genitalia that look female at birth, with the presence of a vagina, but do not have ovaries or a uterus. As a result, they do not menstruate and cannot become pregnant. Due to the presence of the Y chromosome, individuals with AIS have undescended, but typically functional testes. Many XY individuals that have AIS only discover their syndrome during puberty when they do not experience their first menses. Upon understanding their biology, many still prefer to call themselves women, dress like women, and choose men as their sexual partners.

Congenital Adrenal Hyperplasia (CAH) affects individuals with an XX genotype. During development, the adrenal glands of these individuals produce an excess of androgens. The higher circulating androgen levels results in masculinization of the external genitalia to varying degrees resulting in intersex conditions with ambiguous genitalia structure. These individuals still have ovaries and do not have testes (due to the lack of Y chromosome). In many cases, these individuals are treated medically with hormones and raised as female.

Lastly, a group of individuals in the Dominican Republic referred to as the “Guevedoces” are XY genotypic individuals that are born with a feminized appearance and undescended testes that are assigned a female sex at birth. These individuals have a deficiency in the

activity of the enzyme 5-α-reductase. 5-α-reductase is typically responsible for converting testosterone into dihydrotestosterone (DHT), the hormone that is responsible for the development of male external genitalia. However, at puberty there is a surge in testosterone in these individuals that overcomes the 5-α-reductase enzyme deficiency, allowing in the growth of male sex organs. This causes these individuals that were raised as females to start growing a penis. "Guevedoces" literally translates to "penis at 12 years" in Spanish. This phenomenon has also been observed in a small population with Papua New Guinea. Culturally, this has major implications in gender roles for these individuals as only 2 genders are typically recognized, though they are described as a third sex.

Activational Effects of Steroid Hormones

Activational effects of gonadal steroid hormones occur during adulthood and are short-lived and reversible. Examples of activational effects of gonadal steroid hormones include sexual behavior patterns and ovulation. Removal of the activating hormone will cause the behavior to stop, but replacement later will cause the response to begin again because the brain has previously been organized to produce those behaviors when hormones are present. Interestingly, maternal and paternal behavior have both been shown to change the brain in various ways such as changes in dendritic branching and somatosensory maps through experiential plasticity.

The role of activational hormones can be demonstrated by adult **castration** in male rats. Healthy males with intact testes will show sexual behavior when placed with a female rat. Castration, the removal of the testes, will cause males to stop showing sexual behavior because the activating hormone, testosterone, is no longer present. However, if the castrated males receive testosterone replacement, they will resume showing sexual behavior. The sexual behavior brain circuit was organized during development by exposure to gonadal hormones, and in adulthood that circuit can be activated by testosterone. The adult behavior can only be seen when the activating hormone is present.

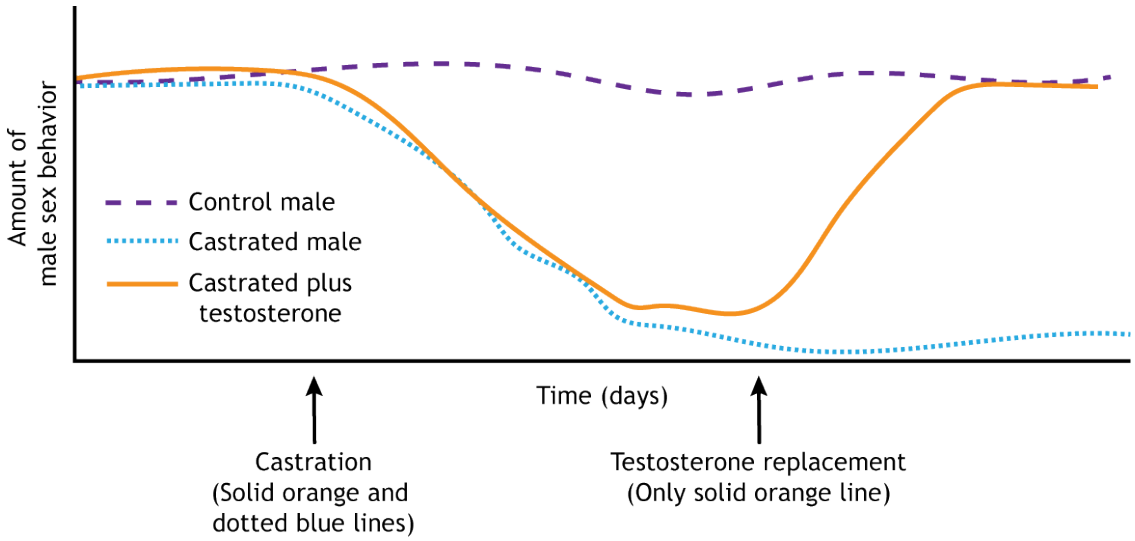


Figure 43.5 Removing testosterone by castrating an adult male rat will decrease the amount of sexual behavior displayed because the hormone can no longer activate sexual behaviors (solid orange and dotted blue lines). However, if the castrated animal is treated with testosterone, sexual behavior returns (solid orange line). 'Castration Effects' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- Testosterone released from the testes during development masculinizes and defeminizes the brain and body.
- The ovaries do no release hormones during development, causing the default feminized brain and body.
- Sexual dimorphisms are differences in the size or appearance of a structure between males and females.
- Gonadal steroid hormones cause a sexual dimorphisms in the sexually dimorphic nucleus of the preoptic area in male rodents.

- The interstitial nuclei of the anterior hypothalamus might be sexually dimorphic in the human brain, however the differences in size are small and controversial.
- A critical period is a period of time in development where hormones have the most effect in determining the structure and function of the brain and body.
- Organizational effects of gonadal steroid hormones occur early in life during development and result in permanent changes in brain and behavior.
- Activational effects of gonadal steroid hormones occur later in life during adulthood and result in temporary changes in brain and behavior that come and go as hormones levels change.
- Androgen Insensitivity Syndrome is a condition in humans in which XY genotypic individuals have dysfunctional androgen receptors.
- Congenital Adrenal Hyperplasia is a condition in humans in which XX genotypic individuals have excess secretion of androgens during development.
- The Guevedoces of the Dominican Republic are XY genotypic individuals that have deficient activity of the enzyme 5-α-reductase.

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44.

SOCIAL BONDING

Long-term attachment, which includes pair bonding with a sexual partner and parental bonding with offspring, are naturally rewarding behaviors in some species of mammals.

Resources

- Glossary Terms
- Scientist links to learn more
- Key takeaways

Animal Model

Much of the research on social attachment and mammalian pair bonding has been done using voles as the animal model. Voles are useful because there are closely related species that display considerably different reproductive behavior. The **prairie vole** (Microtus ochrogaster) that is indigenous to central North America is an atypical rodent that displays highly social behavior, has monogamous relationships after mating, and will cohabitate and share parental duties such as mutual resource collections, nest building, and care for their young. The **montane vole**, on the other hand, has a slightly different geographical location and is a non-social species. They do not form pair bonds and only the female cares for the young.



Figure 44.1. Prairie Voles. Prairie voles are a monogamous species of vole that forms pair-bonds with their mating partners and display biparental care of young.

An experimental test called the **partner preference paradigm** can be used to assess vole monogamy. Here, a three-chamber testing apparatus is used where a test vole is placed in a central chamber. In the other two chambers are voles who have been harnessed into their rooms, unable to leave. The test vole is then free to move between any of the three chambers. When a prairie vole has mated with one of the harnessed voles, they will choose to spend more time with their "partner" vole compared to the novel "stranger" vole, whereas a montane vole will choose to spend most of their time alone and spend very little time with any other animal. Differences in brain and behavior can be studied between these species to determine why they display these different reproductive behaviors.

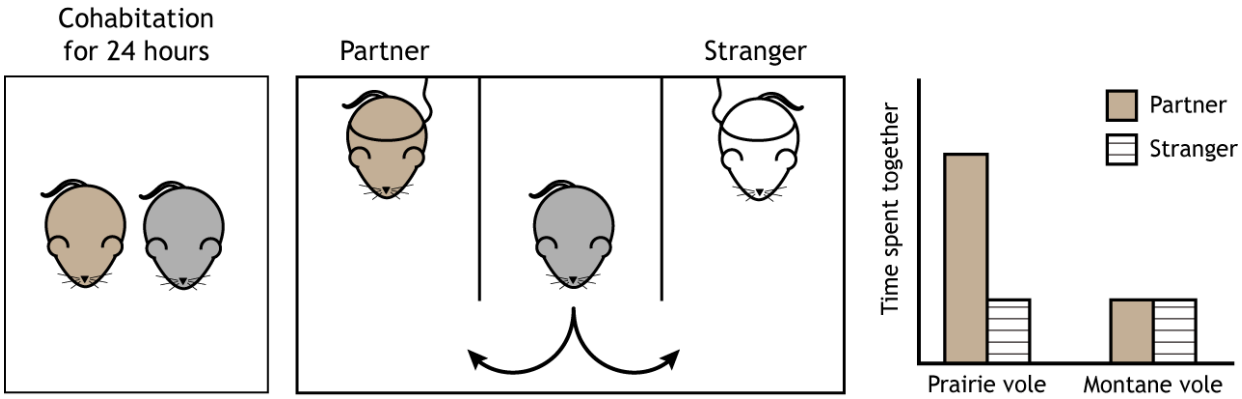


Figure 44.2. Partner preference tests can be conducted to examine social bonds in voles. First, voles are allowed to cohabitate and mate for 24 hours. Then, one of the pair is placed into a preference testing chamber and is allowed to spend time with either the partner animal or a novel stranger. In social voles like the prairie vole, mating will induce a strong preference for the partner animal over a stranger. This effect is not seen in non-monogamous voles like the montane vole. 'Vole Preference' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Not only do mated prairie voles prefer the company of their partner, they also demonstrate behaviors similar to some human romantic relationships. For example, mated prairie voles living together display selective aggression against a stranger, "intruder" voles, a behavior called "mate-guarding". They also spend significant time mutually caring for their young, their pair bonding can be modified by psychoactive substance use, and they show increased anxiety when they are separated from their partner vole.

Role of Oxytocin and Vasopressin in Pair Bonding

Comparing between monogamous and promiscuous species has allowed researchers to identify several neurotransmitter signals that are implicated in pair bonding. Oxytocin and vasopressin seem to play important roles in vole pair bonding, as inhibition of either of these signals decrease partner preference. Additionally, differences in dopamine receptor levels and corticotropin releasing factors are observed between vole species.

Hormone Control

The **hypothalamus** is a critical region for the formation of social bonds. **Magnocellular neurosecretory cells**, the larger type of neurosecretory cell compared to parvocellular neurons, send axons from the hypothalamus down to pituitary stalk where they terminate on capillaries of the general circulation located within the posterior pituitary. Therefore, unlike the control of stress and gonadal hormones, where the hypothalamic neurons release hormones onto anterior pituitary endocrine cells, release of hormones from the posterior pituitary comes directly from hypothalamic neurons.

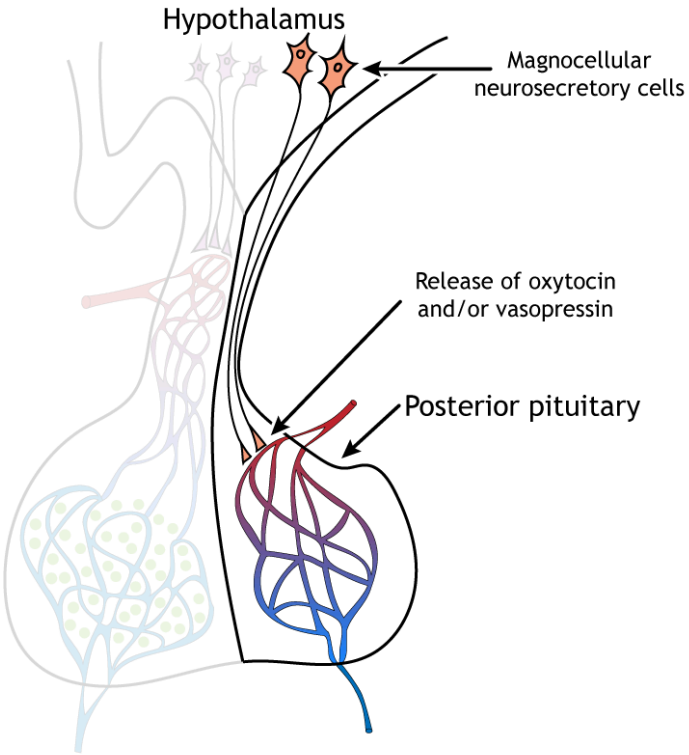


Figure 44.3. The hypothalamic magnocellular neurosecretory neurons release oxytocin and/or vasopressin into the general circulation via capillaries located in the posterior pituitary. 'Oxytocin and Vasopressin Release' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The magnocellular neurons synthesize and release **oxytocin** and **vasopressin**, two neuropeptides, into the blood. **Oxytocin**, often referred to as the love hormone, promotes social bonding. It is released during reproduction and also causes uterine contractions during labor and the milk letdown reflex after birth. **Vasopressin**, also called antidiuretic hormone, plays a role in regulating salt concentration in the blood by acting on the kidneys to promote water retention and decrease urine production. Further, it constricts blood vessels, raising blood pressure. Vasopressin has also been shown to be involved in bonding, parenting, territoriality, and mate-guarding in some animals. Biochemically, vasopressin is very similar to oxytocin, as they are both nine amino acid peptides differing by only two residues.

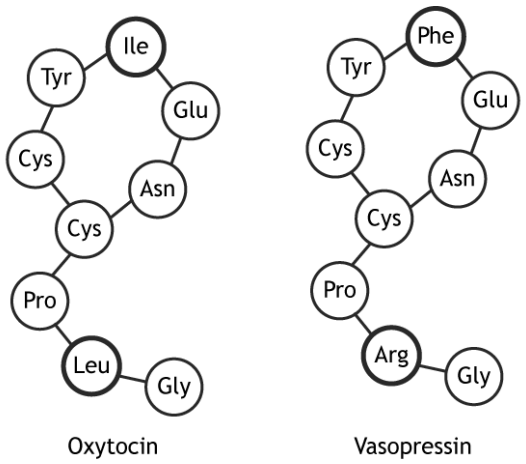


Figure 44.4. Amino acid sequences of oxytocin and vasopressin. The amino acids that are different between the two neuropeptides are bolded. 'Oxytocin and Vasopressin' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

In the social prairie voles, oxytocin and vasopressin are released by the hypothalamus in response to mating and act on regions of the reward and limbic systems. Specifically, there are increases in oxytocin release in female prairie voles following mating. Female prairie voles express higher levels of oxytocin receptors in the nucleus accumbens compared to montane voles. Oxytocin binding to oxytocin receptors within the nucleus accumbens is necessary for females to form pair bonds and may reinforce the association of reward with a partner. This is supported by experimental evidence that when oxytocin is administered to females, there is an increase in pair bond formation. Female montane voles have decreased oxytocin receptors within the nucleus accumbens, and thus do not form pair bonds. Oxytocin does not have the same effects in male prairie voles.

Male prairie voles have an increase in vasopressin release following mating. The male prairie voles express higher levels of vasopressin receptors in the ventral pallidum compared to montane voles. When vasopressin is given to males, it increases pair bond formation, and when a vasopressin antagonist is administered prior to mating, pair bond formation is prevented. Vasopressin has no effect on female prairie voles. The nucleus accumbens and ventral pallidum are both located in the basal ganglia and are involved in the limbic loop, which is responsible for processing of emotions, rewards, and motivation.

An interesting experiment was done that overexpressed vasopressin receptors in the ventral pallidum of male montane voles. The simple manipulation of this one protein completely changed the behavior of the monogamous montane voles such that they now behaved like prairie voles by forming pair bonds and helping to take care of young.

Human Bonding

Oxytocin, vasopressin, and the reward system also appear to be important for bonding in humans. When presented with pictures of either their own children or partners, subjects in an fMRI show increased activation in regions like the ventral tegmental area and striatum compared to when viewing pictures of friends. These regions are also known to express oxytocin and vasopressin receptors, and the hormones are released during times of bond formation, like breastfeeding and intercourse.

Love

Love can be thought of as an intensely strong attachment towards a person (romantic love, lust), a thing (passion project), or concept (patriotism as a love for country, or altruism as a love for fellow humans). However, it is very difficult to put a strict biological definition on these varied concepts of love. This section focuses on interpersonal love, of which there are several unique forms, each resulting in different behavioral outcomes. For example, romantic love drives physical attraction, lust, and sexual activity. Parental love, on the other hand, encourages self-sacrifice and hyper-attentiveness towards a newborn. Some behaviors are shared between the two forms of love, such as respect.

Romantic Love

Romantic love drives much of human behavior and has been documented thoroughly in the arts all the way from Homer's *Iliad,* through Shakespeare's *Romeo and Juliet,* up to modern Taylor Swift.

The majority of human societies have embraced social monogamy, the romantic relationship characterized by a pair of people who share resources, parenting duties, and exhibit preferential mating. Outside of humans however, only 9% of mammalian species form socially monogamous pairs, while at least 75% of bird species maintain socially monogamous relationships (which may explain the origin of the phrase "love birds").

Dr. Helen Fisher, an anthropologist and a leader in the field of love research, suggests that love can be divided into three closely interconnected components. These three are guided in part by different signaling pathways, and lead to somewhat different behavioral outcomes.

Lust (or libido) refers to a very strong desire for sexual gratification. These behaviors are largely driven by the actions of the sex hormones testosterone, estradiol, and progesterone, released

downstream of activation of the HPG axis. Both testosterone and estradiol contribute to sex-seeking behaviors in men and women, where increasing testosterone levels drive up sexual desire. The amygdala also plays a significant role in mediating lust, and lesions may either result in hypersexuality (Kluver-Bucy syndrome) or a decrease in response to socially-derived sex cues.

Attraction is characterized by high energy-investment and preoccupation towards a small number of people. From an evolutionary perspective, attraction may have developed to discriminate between multiple reproductive partners, allowing the focusing of limited resources towards fewer partners. In Fisher's theory, attraction is strongly related to the action of dopamine and norepinephrine. In humans, the reward circuitry is involved in feelings of love. Using fMRI, Fisher presented pictures of a patient's romantic partner to them and identified increases in the blood flow to dopaminergic midbrain areas such as the ventral tegmental area and the striatum. This finding compares with imaging studies that observed increases in blood flow to insula, premotor, and hypothalamus as well as striatum in response to highly erotic, sexual imagery. These studies suggest that romantic love and lust have different driving neural structures underlying these behaviors. Norepinephrine functions to increase attention, alertness, and energy, which accounts for the exhilarated feeling you may feel when spending time with a potential partner.

Attachment is the long-term association with an individual accompanied by feelings of comfort and emotional stability. Attachment also contributes to behaviors that maximize offspring survivability, such as sharing parenthood responsibilities and protectiveness towards offspring. The major neurochemical drivers of this form of love are oxytocin and vasopressin.

Parental Love

Parental love refers to instinctive affection towards one's offspring. Parental love behaviors include nurturing (collecting and sharing resources), protecting (promoting aggression against "intruders"), and preparing one's young for their adult life (risk assessment training). In evolutionary theory, parental love serves to improve the odds of passing of one's genes through the following generation. Most large mammals (humans included) are K-selected species, which benefit most from a small number of high-quality offspring that require substantial parental investment, as opposed to large numbers of offspring with little investment.

An extension of parental love is familial love or kinship, the protection and preferential support of one's extended genetic relations. Because blood relatives share common genes, increasing the

survivability of these family members has benefits for passing genes to the next generation. In the words of the geneticist Jack Haldane, "I'd gladly give my life for two brothers or eight cousins."

Many behaviors related to mammalian motherhood are accompanied by changes in neural activity. Nursing, for instance, is feeding behavior that is regulated through a positive feedback cycle. Offspring suckling activates the mother's somatosensory afferents. Through a series of oxytocin-dependent circuits across the hypothalamus, suckling ultimately increases lactation through the milk letdown reflex. Auditory sensory inputs, such as the sounds of a crying baby, can also trigger this reflex. Sometimes, just thinking about the baby can induce letdown. Some changes are dependent on neural plasticity. For example, after childbirth, the auditory areas of rodents rewire to become more sensitive to high frequency sounds. This adaptation allows the mothers to better detect the ultrasonic vocalizations that are emitted by offspring when they are distressed or hungry. Olfactory areas also change in order to become more sensitive to the particular odorants given off by their young, allowing them to better identify their offspring. In humans, these olfactory changes result in decreased aversion towards traditionally aversive stimuli (urine or fecal matter) when they originate from their children.

Key Takeaways

- Prairie voles are a socially monogamous species that forms pair bonds with their mating partners and display biparental care of young.
- Montane voles are a closely related species that display a promiscuous mating strategy, do not form pair bonds, and do not show biparental care of young.
- Female prairie voles have increased oxytocin receptors within the nucleus accumbens compared to montane voles.
- Male prairie voles have increased vasopressin receptors within the ventral pallidum compared to montane voles.
- Oxytocin and vasopressin are both neuropeptides released from the posterior pituitary.
- Human bonding and love (romantic and parental) has also been shown to involve oxytocin, vasopressin, and reward circuitry.

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45.

SLEEP AND EEG

Resources

- Glossary terms
- Key Takeaways

Sleep is such an important part of our lives that a lack of it strongly correlates with negative outcomes on nearly every measure of health. People who sleep less than approximately 7 hours a night are at a greater risk for heart disease, stroke, asthma, arthritis, depression, and diabetes. Nearly 20% of all car crashes, both fatal and nonfatal, are attributed to drowsy driving. The cancer research branch of the World Health Organization has determined that disruption of regular sleep is "probably carcinogenic to humans", putting it in the same risk category as the infectious agents malaria and human papillomavirus (HPV), as well as the biochemical weapon mustard gas. Sexual health is affected by sleep deprivation as well, as men with the worst sleeping habits have significantly lower sperm counts, decreased circulating testosterone, and even testicular shrinkage.

Despite all that we know about the benefits of sleep, sleep is often the first time commitment to get cut, often getting squeezed as people stay awake later while waking up sooner. Consider that the CDC estimates that more than a third of American adults fail to get enough sleep each night. Almost 70% of college students fail to get the recommended amount of nightly sleep, and half of all college students report experiencing daytime sleepiness as a result.

The current medical recommendation is 7-9 hours of sleep each night. But why is sleep so important? It is possible to study sleep using a combination of techniques; the output of sleep studies are visualized on a **polysomnogram** (pahle-SOM-nuh-gram; somn- is the prefix referring to sleep). Several physiological measures are taken in a polysomnogram, including heart rate, blood pressure and oxygenation level, respiratory depth and pattern, muscle activity, eye movement, and one of major interest to neuroscientists: brain wave activity. While everyone knows what sleep is, it is useful to try to more precisely define sleep as a biological function.

Sleep is characterized by a decrease in physical activity, a decoupling from external inputs, and changes in brain wave activity.

Compared to waking behavior, a person's physical activity is greatly decreased when they sleep. While asleep, people are relatively inactive and as a result, the body uses about 10% less energy. This is not to say that people do not completely cease all movement during sleep. It is very common to readjust posture many times in the middle of the night. Some people may grind their teeth together or talk in their sleep, sometimes carrying on full conversations by themselves! About 15% of people have experienced **somnambulism**, or sleepwalking: full on wake-like behaviors, such as navigating down a flight of stairs or preparing a sandwich, performed entirely in the absence of intent of memory recall. Despite these rare occurrences of physical activity, the average movement of the person over a night's rest is still less than their average activity when awake.

When we sleep, our conscious brains are "distanced" from the outside world. Sleep causes a heightened threshold for detection of stimuli, so we do not receive the same magnitude of inputs from our sensory systems as when we're awake. This is why someone else might have to talk loudly or even shake you physically to wake you up.

Lastly, sleep was once thought to be a period of time characterized by low brain activity. After all, the person looks like they are not moving. Shouldn't brain activity be reflective of that decreased state of activity? With the advancement of EEG technology in 1924, and the rise of sleep laboratories in the 1970s, scientists who studied brain activity noticed that, at different times throughout the night, the brain of a sleeping person was very similar in activity to the brain of an awake person!

EEG

Electroencephalography (EEG) is used to measure brain rhythms through recording electrical activity at the scalp, making it a non-invasive and painless tool to detect brain activity. EEG detects the general activity of the cortex by measuring small (~10 uV) fluctuations in voltage. This technique does not measure electrical activity of a single neuron, but rather measures the electrical activity of a large population of neurons, on the order of thousands of cells, in order to generate a signal that is large enough to detect.

An EEG reading depicts differences in both **amplitude** and **frequency** over time. An increase in amplitude on an EEG indicates a higher degree of synchronous activity of cortical neurons, whereas the frequency of an EEG indicates how often neural synchrony occurs. EEG is used to measure

patterns of brain activity during different behavioral states and is used in both research and in the diagnosis of various neurological conditions such as sleep disorders and **epilepsy**.

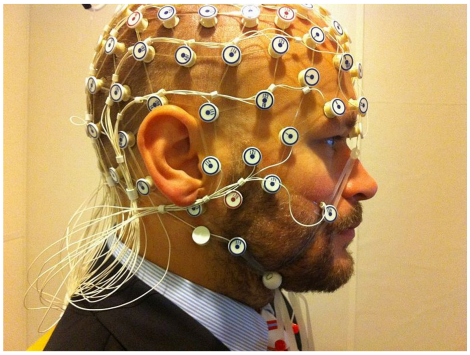


Figure 45.1. EEG recording setup. In an EEG, electrodes are placed on the head that can detect and record neuronal activity of the cortex.

How is synchronous activity generated?

Though EEG is used to measure brain rhythms, the function of these rhythms is unknown, but they have been correlated to different behavioral states such as wakefulness, sleep, attentiveness, and various pathologies. Brain rhythms generated through synchronous neuron activity can be created through two different mechanisms.

1. Cells within the thalamus have been demonstrated to have pacemaker properties that allow it to generate rhythmical cortical activity.
2. Collections of cells can also generate intrinsic rhythms through their collective activity.

EEG patterns during sleep

Each night when we go to sleep, our brains undergo a very stereotyped pattern of activity changes. At times, neurons in the cortex exhibit synchronized patterns of firing. And at other times, cortical activity looks very similar to an awake brain. We can divide sleep roughly into two different phases depending on one of the first physiological measures that sleep scientists studied: eye movement. A study published in 1953 used a device to detect eye movement while a person was asleep. Interestingly, they noticed that at some points in the night, usually first occurring around three hours after falling

asleep, the patient's eyes would dart rapidly and jerkily back and forth, a pattern of activity that the University of Chicago researchers called **rapid eye movement (REM)**. This first period of REM activity lasted for about 20 minutes, after which the eyes would stop moving again. This activity pattern repeated every hour or two for the rest of the night. They used eye movement to separate sleep into two phases: **REM sleep**, and **nonREM sleep (NREM sleep).**

In addition to eye movement, they observed and measured other physiological behaviors. Respiration rate and heart rate both increased during the REM phase of sleep and dipped during NREM sleep. They also (rudely) woke up patients throughout the two phases of sleep and found that patients were more likely to recall dreams with visual imagery if their REM sleep was interrupted. Those woken during NREM sleep were less likely to recall dreams, hinting that dreaming is more likely to happen during REM sleep. While eye movement could differentiate between two phases of sleep, EEG could further subdivide NREM sleep. Using EEG, scientists discovered three distinct NREM phases based on neuron activity patterns: NREM1, NREM2, and NREM3 sleep.

Currently, readings collected via EEG are considered to be the gold standard for measuring the stages of sleep. But before we describe EEG traces while asleep, we should describe the EEG of a person who is awake. Usually, the awake EEG is dominated by high-frequency waves that increase with attention and mental activity.

NREM1 is the earliest stage of sleep. It's also described as relaxed wakefulness, drowsiness, or light sleep. During NREM1, mostly alpha waves are present and a person's muscles are still somewhat active. Their eyelids may open and close every so often, and they may still respond to questions. Basically, the deeper into NREM1 sleep a person becomes, more waves with lower and lower frequencies start to emerge. NREM1 transitions into **NREM2**, which mostly has theta waves.

Lastly, **NREM3** occurs, which is also called deep sleep. At this phase of the night, a person's physiological activity drops to its lowest point of the night: heart rate, respiration, blood pressure, and metabolism all reach minimum during NREM3. In this stage of sleep, many of the cortical neurons fire in synchronicity with one another, and the subsequent change in potentials cause large amplitude deflections in the EEG, called delta waves.

The EEG trace of a person in **REM sleep** is quite the opposite of what is seen in deep sleep. Instead of large amplitude events at a low frequency, the REM brain has a lot of low amplitude events at a high frequency. In fact, the brain in REM sleep has a pattern of activity that is more similar to a person who is awake than asleep! Because of this asynchronous firing activity, REM sleep is sometimes also called paradoxical sleep.

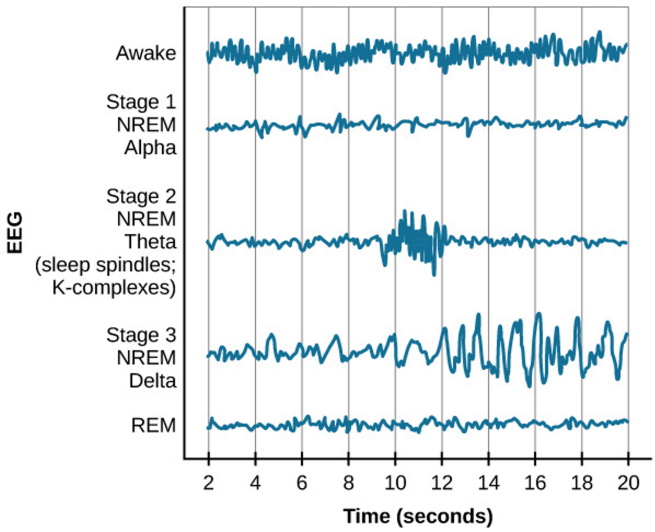


Figure 45.2. EEG activity during different stages of sleep. Brainwave activity changes drastically over the course of the different stages of sleep. REM sleep brain activity most closely resembles brain activity while awake.

Progression through the stages of sleep

To illustrate the stages of sleep that a person experiences each night, we can use a **hypnogram**. These charts plot time on the x-axis and stage of sleep on the y-axis. Awake is represented at the top, and deep sleep is at the bottom. For an average night's rest, neural activity will fluctuate through the four phases relatively predictably. When a person first falls asleep, they will move from NREM1 down through NREM2 then NREM3, before coming back out of deep sleep progressively back to NREM1. After NREM1, they may enter REM sleep before transitioning back through the stages to NREM3 again. This cycle of activity repeats roughly every one and a half hours. People spend a larger percentage of each cycle in deep sleep and very little time in REM sleep early in the night. On the other hand, in the last few cycles before waking up from a full night's rest, people spend a larger percentage of each cycle in REM sleep, and almost no time in deep sleep.

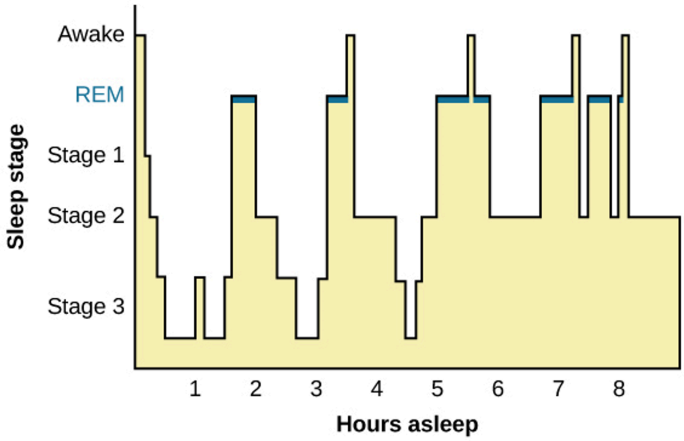


Figure 45.3. Hypnogram showing progression of sleep stages through the night. After falling asleep, an individual starts in REM sleep, and then progresses through Stage 1, Stage 2, and Stage 3 of NREM sleep. They then progressively return to REM sleep. As the night progresses, an individual spends less time in deep sleep and more time in REM sleep.

Why do we sleep?

All organisms that we know of experience some type of sleep. But we still haven't figured out exactly why animals sleep. Here, we will discuss three theories that have been proposed to explain sleep. None of these theories alone fully explains the complex phenomenon of sleep, and they are not mutually exclusive. The most likely reason we sleep is probably some combination of the following three theories.

Recuperation Theory

The recuperation theory of sleep is centered around the idea that being awake is stressful and exerts a physically demanding toll on the body. The body therefore needs a period of time when energy usage decreases and the body's natural repair systems can work without disruption. Sleep is how the body "wipes the slate clean" and resets. Evidence for the recuperation theory comes from experiments tailored around the idea of looking at what happens when a person doesn't get sufficient sleep.

As anyone who has ever pulled an all-nighter can attest, a single night of sleep deprivation often leads to significant psychological changes, including anxiety, irritability, and mood swings. Staying awake

even longer than 24 hours can cause more severe changes in mind state, such as temporary psychosis, hallucinations, or delusions.

While the support for the recuperation theory is generally true for almost all people, there are about 1% of people who seemingly gain the restorative benefits of sleep, even with fewer than 6 hours of sleep each night. They may wake up at 4:30 in the morning feeling completely refreshed. And yet, despite getting so little sleep, these short sleepers have similar health outcomes with respect to body mass index and psychiatric measures such as depression and overall optimism. Something about the circadian rhythms of these short sleepers allows them to "maximize" their sleep efficiency. Many have very short sleep latencies, meaning they fall asleep within minutes after lying down—as quickly as someone with narcolepsy. They also spend a larger percentage of their night in deep sleep and REM sleep while minimizing NREM1 and NREM2.

Evolutionary Adaptation Theory

The evolutionary adaptation theory is the idea that animal sleep patterns are different across species for reasons that most efficiently benefit each animal. Over millions of years of evolution, individuals with the most ideal sleep patterns have an advantage, and their sleep habits will be selected for in the following generation. For example, consider humans. As an animal highly dependent on light and the visual system for navigation and accurate performance of tasks, the dark is a very dangerous time to be active. The risks of wandering off a cliff, running head-first into a tree while escaping a predator, or eating a wrong-colored poisonous berry would all be elevated in the dark. We benefit from behaviors that minimize those risks, such as inactivity until the sun rises. During this inactive period, sleeping decreases our metabolism and our body's need for energy.

Humans are just one animal that has an evolutionarily fine-tuned sleep pattern. If you look across the animal kingdom, you'll find all varieties of sleep behaviors that are best fitted to the needs of the individual species. In the wild, for example, dolphins are generally prey. They evolved with the ability to put one half of their brain to "sleep" at a time, allowing the "awake" half to keep an eye out for potential predators. Small prey animals, like squirrels, are faced with the threat of being attacked at night. For them, remaining very still, quiet, and hidden improves their survival. Tigers, the top alpha predators in any ecological niche, have almost no predators to hide from, allowing them the luxury of sleeping up to 20 hours a day.

This evolutionary adaptation theory argument has a major weakness, however. In almost all animals, sleep represents a period of time when an organism's ability to use their sensory organs to detect the

hallmark signs of an approaching predator, like the flurry of feathers from a hungry owl or the soft padding of a wolf footsteps, decreases drastically. For an animal that can't hide very effectively, sleep represents a period of vulnerability, as they would be unable to sense incoming threats.

Brain Plasticity Theory

The brain plasticity theory suggests that the brain needs some period of time for critical changes to occur. During sleep, circuits in the brain undergo consolidation processes that are important for memory formation. For example, academic performance and examination grades worsen as a person's nightly sleep decreases. Both the REM and NREM3 phases of sleep are important for different types of memories and studies suggest that **declarative memory**, pieces of information about facts, benefits more from slow-wave sleep while **procedural memory**, the learning of motor skills, is enhanced by REM sleep.

Although the exact mechanisms about how sleep improves memory are unknown, we theorize that brain activity during sleep helps move memories held in "temporary" areas into areas of stable, long-term storage. The evidence in support of this theory starts with looking at the brains of newborns. When you were first born, during those first few weeks of life, you slept close to nearly 70% of the day, almost 17 hours! At this point in your life, your brain starts to experience all sorts of new sensations: your eyes detect visible light for the first time, the skin feels the air blow past it, and the ears sense new frequencies and combinations of sound waves. As a result of these stimuli, scientists hypothesize that your brain undergoes as many learning events as rapidly as possible. This rapid learning helps you remember what you learned each day so you can respond to your environment as you grow up.

Sleep Disorders

Insomnia

Almost everyone has experienced difficulty sleeping at some point in their lives, often as a result of stress or anxiety. For example, it might be difficult to fall asleep the night before a big interview, or you may wake periodically in the hours before an important early morning flight. There is no strict definition for insomnia. The major clinical symptoms are self-reported measures, such as a dissatisfaction with nightly sleep or a change in daytime behavior, such as sleepiness, difficulty

concentrating, or altered mood states. The lack of clear diagnostic criteria makes estimating prevalence difficult, but some guesses put the number of people with insomnia close to one third of the US population. Common triggers for insomnia include heightened anxiety, stress, or advanced age. It may also be downstream of other diseases, such as Parkinson's disease, diabetes, depression, or chronic pain conditions. Lifestyle can also be a major risk factor for insomnia, as jet lag and working late-night shifts can disrupt sleep patterns.

We can describe insomnia as acting at two stages. Onset insomnia is defined as a difficulty with initially falling asleep. People with onset insomnia will frequently lie in bed for a long time before finally drifting off. Maintenance insomnia, however, is a difficulty with remaining asleep. People with maintenance insomnia experience many waking events throughout the middle of the night, or they may wake up very early in the morning and be unable to get back to sleep. The two are not exclusive, and people may experience both forms of insomnia in a single night.

The most effective treatments for insomnia begin at the level of behavioral changes. Improving sleep habits, such as minimizing arousal states before bedtime, developing a reliable pattern of sleep-wake timing, eliminating caffeine intake in the afternoon and evening, and increasing daytime physical activity can decrease insomnia. Prescription medications are less preferred for insomnia treatment, since these drugs are more effective at inducing unconsciousness rather than biological sleep. These drugs can also have adverse psychological side effects such as mood swings and depression, and those adverse effects may be more severe than insomnia itself. Prolonged use of prescription sleep medications can lead to a "rebound effect", causing a person to experience even worse insomnia when they are unable to get sleep drugs. This is called iatrogenic insomnia, and can lead to a cycle of dependence.

Narcolepsy

Unlike the previous two sleep disorders, which result in a deficit of sleep, narcolepsy can be thought of as an "excess" of sleep. More accurately, narcolepsy is inappropriate sleep, and it manifests as frequent sleep attacks throughout the day, each event lasting for seconds or minutes at a time. An estimated 1 in 2000 people experience narcolepsy. One of the life-threatening symptoms that appears in narcolepsy is **cataplexy**, which is the sudden weakening of muscle tone that accompanies a sleep attack. A cataplectic attack may cause someone to physically fall over during a narcoleptic incident. Cataplexy often happens during high emotional states, such as excitement. As with other sleep disorders, changes in lifestyle can improve the course of narcolepsy. Introducing short daily naps can be helpful, as can

general good sleep habits (minimal digital device usage before sleep, regular sleep-wake timing, and physical activity). Drugs such as amphetamines (Modafinil) can be used in the daytime to stimulate activity in the CNS and can be prescribed to treat severe cases of narcolepsy. Some antidepressant drugs can be used to treat cataplexy.

The exact cause of narcolepsy has not yet been identified. However, there are many clues that point to a dysregulation of the signaling molecule orexin produced by cells in the lateral hypothalamus. These neurons die off in people with narcolepsy, but the cause of why the neurons die is unknown. Also, having a genetic predisposition to narcolepsy does not guarantee that a person will experience the symptoms, indicating that there is some combination of genetic and environmental factors that lead to narcolepsy.

Fatal familial insomnia

While many cases of sleeplessness last a day or two, and some cases are clinically significant and treatable with behavioral changes, a very small fraction of cases of insomnia are incurable and deadly. In people with **fatal familial insomnia (FFI)**, they experience severe insomnia. Some patients stay awake for up to six months at a time. As a result of either the disease or the sleep deprivation, they experience altered mood states, hallucinations, dementia, and eventually death, usually within two years after a diagnosis is made. The cause of FFI is unknown. There is a strong genetic component associated with it, as it appears frequently within certain family trees. But, there have also been a few cases of sporadic FFI, people with no apparent family members with the disease. One observation in common among people with FFI is significant damage to the thalamus, as a result of misshapen proteins called prions, a similar disease-causing agent that is responsible for mad cow disease.

REM sleep behavior disorder

One very rare sleep disorder called **REM sleep behavior disorder (RBD)** can cause people to carry out complex, highly coordinated motor actions while they are sleeping, sometimes acting out their dreams as if they were reality. People with RBD are at risk of injuring themselves or others. Their sleep actions may be in response to a violent nightmare, causing them to jump out of bed, kick or punch the air, run through the house, or throw things. One of the most shocking instances of parasomnia-induced sleepwalking was the 1987 case of Kenneth James Parks, a Canadian man who, in his sleep,

drove 23 km to the house of his in-laws and stabbed both of them with a kitchen knife. After his arrest, scientists discovered that his brain activity was highly abnormal during sleep. As a result of the medical examination, the Supreme Court of Canada acquitted him of murder in 1992.

Key Takeaways

- EEG is used to measure brain activity through the scalp and is used to measure brain activity during sleep.
- Sleep can be divided into REM and NREM sleep (NREM1, NREM2, NREM3).
- REM sleep EEG readings most closely resemble awake EEG readings.
- The progression of the stages of sleep starts in REM sleep, then progresses through NREM 1, NREM2, and NREM3 before cycling back to REM sleep. As the night progresses, an individual spends more time in REM sleep and less time in deep sleep.
- The reason why we sleep is not fully understood but is likely a combination of three theories: recuperation theory, evolutionary adaption theory, brain plasticity theory.
- There are disorders of sleep that can cause either lack of sleep or excessive sleep.

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46.

CIRCADIAN RHYTHMS

Resources

- Glossary terms
- Scientist links to learn more
- Key takeaways

Almost every living organism that we know of on Earth exhibits some sort of cyclic pattern of activity that closely matches the rising and setting of the sun.

Retinohypothalamic Tract

Our sleep and wake cycles are associated with the day/night cycle. Previously, we discussed the retinal ganglion cells that transmit signals from the rods and cones of the retina into the brain for processing within the lateral geniculate nucleus and primary visual cortex. A separate population of retinal ganglion cells do not process signals from the rods and cones, but rather serve as photoreceptors and are directly sensitive to light, communicating whether or not it is daytime.

These cells send their axonal projections separately from the optic nerve that sends most visual information. Rather, they project through a pathway called the **retinohypothalamic tract**, synapsing on a clump of cells in the hypothalamus called the **suprachiasmatic nucleus (SCN)**. In turn, these cells of the SCN have projections to a gland in the brain called the **pineal gland**, so named for its pinecone-like shape. The pineal gland converts the amino acid tryptophan into **melatonin**, an endogenous hormone, which is then secreted into the bloodstream. Melatonin helps the brain regulate the sleep-wake cycle with increased melatonin levels helping to signal the body to prepare for sleep.

The production of **melatonin** is heavily dependent on exposure to sunlight. In the daytime, the SCN tonically inhibits activity of the pineal gland, resulting in low production of melatonin. But when daylight starts to decrease, the retinohypothalamic tract sends a weaker excitatory signal onto the

SCN, which allows increased pineal gland activity. Light exposure is the main environmental influence that decreases melatonin levels.

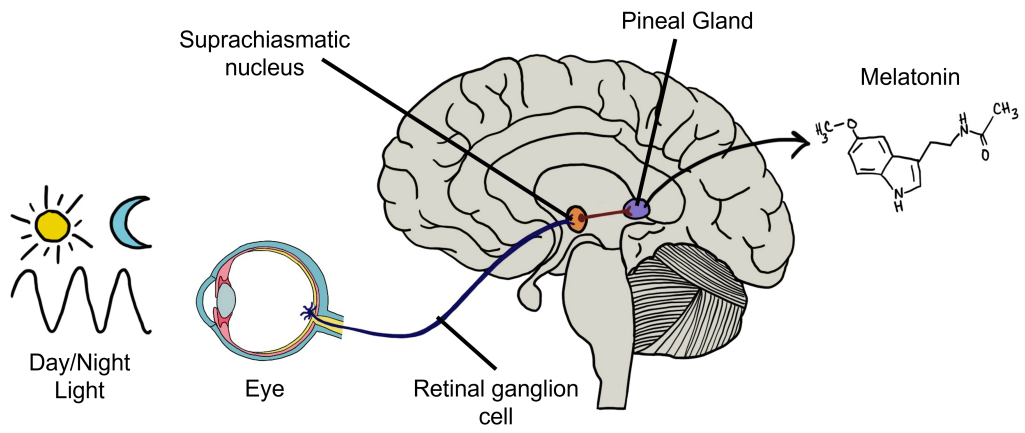


Figure 46.1. Pineal gland and melatonin. A group of retinal ganglion cells within the retina are photosensitive and are able to communicate day/night lighting conditions through the retinohypothalamic tract. The photosensitive retinal ganglion cells synapse on the suprachiasmatic nucleus. The pineal gland produces the neurohormone melatonin. The suprachiasmatic nucleus inhibits activity of the pineal gland and production of melatonin. Under nighttime lighting conditions, there is weaker activation of the retinhypothalamic tract, and thus decreased inhibition of the pineal gland, leading to increased melatonin production. 'Pineal gland and melatonin' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Not all wavelengths of light are equally potent at dampening melatonin production. The shorter wavelengths of light, down in the violet-blue range, are much more efficient at activating the retinohypothalamic tract compared to longer, yellow-red wavelengths. Increased retinohypothalamic tract activation leads to decreased melatonin production, which can delay the onset of sleep. Fluorescent or LED lighting and digital devices, such as computer screens and cell phone screens, use blue wavelengths of light. Therefore, the best advice to optimize your sleep habits is to eliminate exposure to all digital devices about one hour before your intended bedtime.

Circadian Rhythms

The discovery of 24-hour patterns of behaviors began in 1729 with the French scientist Jean-Jacque d'Ortous de Mairan, who documented the movement of the *Mimosa pudica* plant. This unique organism was chosen since the plant exhibits **heliotropism**, light-seeking movements. In particular, this plant opened up the leaves in the daytime to capture sunlight, then closed at night, minimizing predation. When the plants were put into a dark room with no exposure to sunlight, to his surprise they still opened and closed their leaves in time with the clock. Mairan concluded that the plant did not change its behavior in response to light, but rather in response to some internal 24-hour clock. His work laid the foundations for future **chronobiologists**, scientists who study day-night dependent periodic phenomena in living beings.



Figure 46.2. The *Mimosa pudica* plant displays light-seeking movements, with the leaves of the plant opening during daylight and the leaves closing at night. During an experiment in which the plants were put in a dark environment for 24 hours, surprisingly, the plant still opened and closed its leaves on a 24-hour cycle, demonstrating that the plant had an internal clock controlling the opening and closing of leaves.

Any behavior or physiological measure that intrinsically cycles on a 24-hour pattern is said to be a **circadian rhythm**. The word circadian comes from the Latin words 'circa' meaning "around", and 'diem' meaning "day". Compare this with an **ultradian rhythm**, any cycle that is faster than 24 hours, such as the cycling between deep sleep and REM sleep every 90 minutes. Alternatively, compare with **infradian rhythms**, patterns that are longer than 24 hours, like the 4-week-long human menstrual cycle.

Although we mostly think of the circadian rhythm in the context of sleep and wake, many other

physiological measures fluctuate reliably throughout the day. Body temperature dips late in the evening, putting the body into a low-energy state that helps promote sleep. Withdrawal reflexes peak around midnight, hunger-driving hormone production rises before lunch and dinner, attention is usually highest in the morning—all manner of behaviors that rise and fall depending on the time of day can be said to be a part of a circadian rhythm.

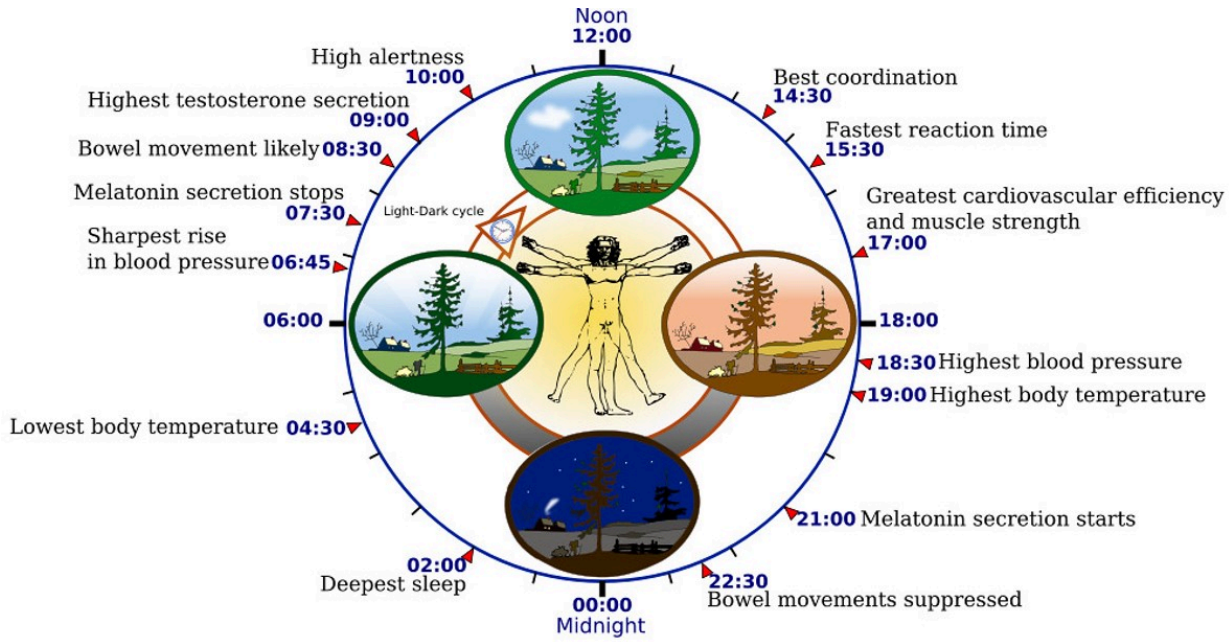


Figure 46.3. Circadian rhythms in the body. Throughout a 24-hr period of time, there are many behavioral and physiological changes that occur through the day.

Circadian Rhythms are Entrainable

Luckily, a person's circadian rhythm is not permanent. Anyone who has traveled overseas to a different time zone for more than a few days has experienced that uncomfortable sensation called jet lag, where a person experiences psychological symptoms such as difficulty concentrating and mood swings, and physical symptoms like daytime fatigue, insomnia, and gastrointestinal distress (nausea, constipation, or diarrhea). Jet lag happens when there's a mismatch between the internal environment and the signals that the brain receives from the outside world.

If you flew east from Chicago to Cairo, for example, your circadian clock will be off by 7 hours. When your internal "Chicago" clock is telling you to start getting sleepy around 11 PM, the sun will be rising in Cairo, as the locals are starting to wake up. You may be eating when you're not hungry or

laying down in bed when you're not sleepy, and this mismatch contributes to jet lag. However, with a few days of adjustment, you will be able to overcome jet lag. You will start sleeping as the sun sets, you will get hungry at the same time as the Egyptians, and your physiological measures will start to align with your time zone.

This adjustment is only possible because our circadian rhythms are **entrainable**, meaning they are able to change and fit the surroundings. Our circadian rhythms entrain in response to **zeitgebers**, the German word for "time givers": environmental cues, such as increased light exposure when the sun comes up, or social cues, such as increased sensory input from heightened activity of the people around you. A rise in the neurohormone **melatonin** is an important signal that contributes to helping the brain entrain, which is why taking a melatonin supplement late at night when in a new time zone may help someone get over jet lag more quickly.

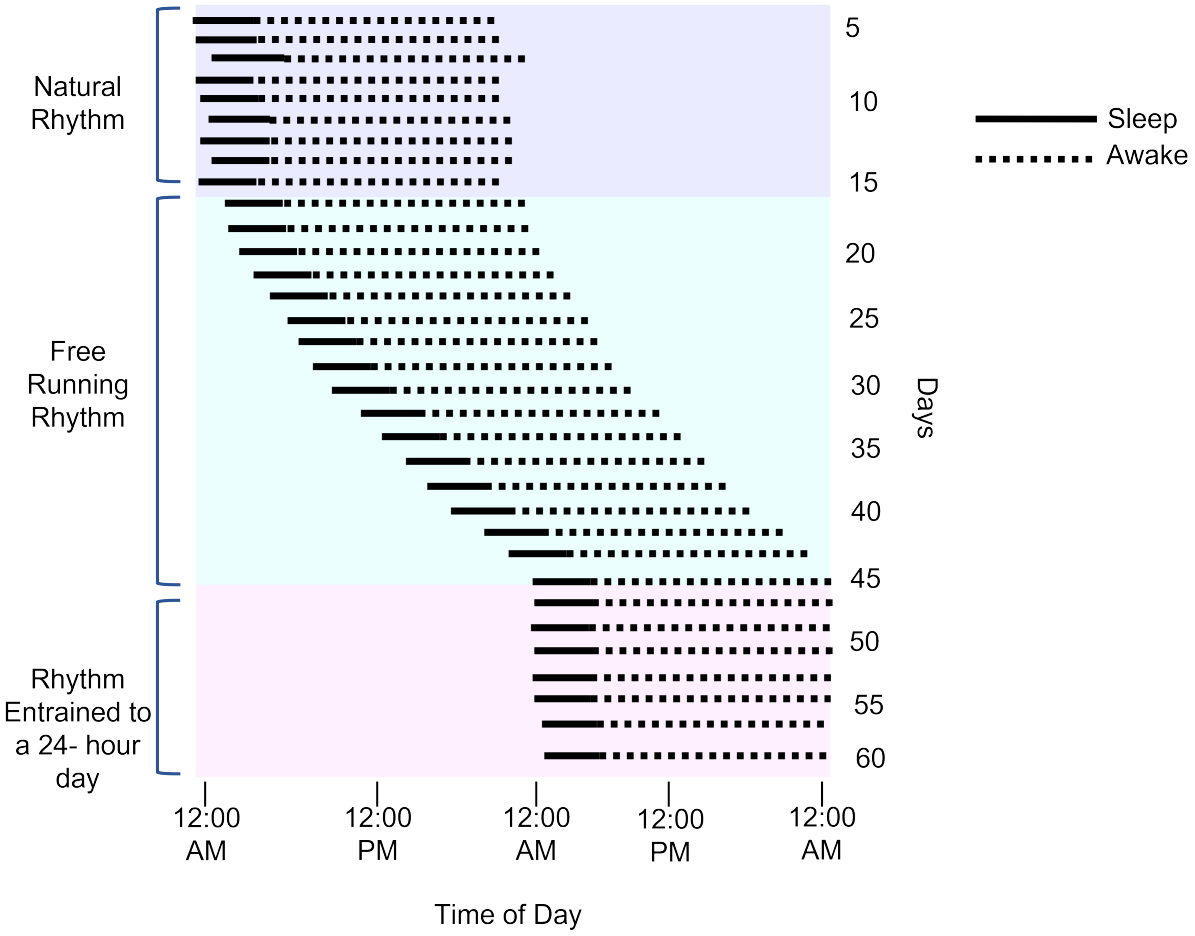


Figure 46.4. Free-running and entrained circadian rhythms. In the absence of zeitgebers, circadian rhythms will free run. Typically, this means that the 24-hour cycle will shift 2 hours later each day. When the cycle is entrained again to a 24 hour rhythm, the circadian rhythm will no longer free run and will be consistent. 'Free-running and entrained circadian rhythms' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

If sunlight is a trigger that helps a person entrain their circadian rhythm to new environments, what would happen if a person is completely isolated from sunlight? In other words, what does a **free-running circadian rhythm** look like? One of the early documented case studies addressing this curiosity was conducted by a French cave explorer named Michel Siffre. In 1972, Siffre (voluntarily) spent six months deep in a Texan cave to evaluate what would happen to a person completely isolated from zeitgebers. At the end of the experiment, he found his circadian cycle was much longer than 24 hours, and very unpredictable—some of his so-called days would consist of being awake for 36 hours and asleep for 12.

A more rigorous scientific study, conducted in a group of people living in an underground bunker with unchanging lighting conditions for several days estimates the typical free-running circadian cycle to be close to 26 hours. In other words, a person absent from external cues begin to fall asleep and awaken 2 hours later each day. Free-running circadian disruption is a potential issue for scientists aboard the International Space Station, who experience about 16 sunsets and sunrises per day, since the orbiting space vessel completes one trip around the earth every 90 minutes. In order to minimize the negative effects of jet lag on the researchers aboard, NASA has the inside of the vessel set to an artificial 24-hour cycle. Bright blue LEDs illuminate the cockpit in the "daytime," while dim, red-shifted wavelengths are used in the evening to induce sleepiness.

Key Takeaways

- The retinohypothalamic tract signals lighting conditions to the suprachiasmatic nucleus.
- Activity in the suprachiasmatic nucleus inhibits the pineal gland and production of melatonin.
- A 24-hour cycle is called a circadian rhythm
- Circadian rhythms are entrainable to zeitgebers, or external cues.
- Without zeitgebers circadian rhythms free-run, and will shift.

Attributions

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47.

MEMORY SYSTEMS

Resources

- Glossary Terms
- Scientist links to learn more!
- Key Takeaways

Think back to your favorite birthday party. Which of your friends were there? What did you do, where did you go, and did you have cake? Did you get gifts? The ability to perform this task depends on our ability to create and recall memories. According to our current best understanding of the neuroscience of learning, the underlying biology of a memory mainly consists of subtle changes among synapses distributed across several brain areas. Our ability to learn new facts, recount the events of last week, or to perform new motor skills is the result of learning-induced neural plasticity. In our discussion of learning and memory, we will consider different aspects of learning and memory, starting from the behavioral level down to the molecular changes responsible for memory formation.

Types of Memory

First, it is important to distinguish between different types of memories.

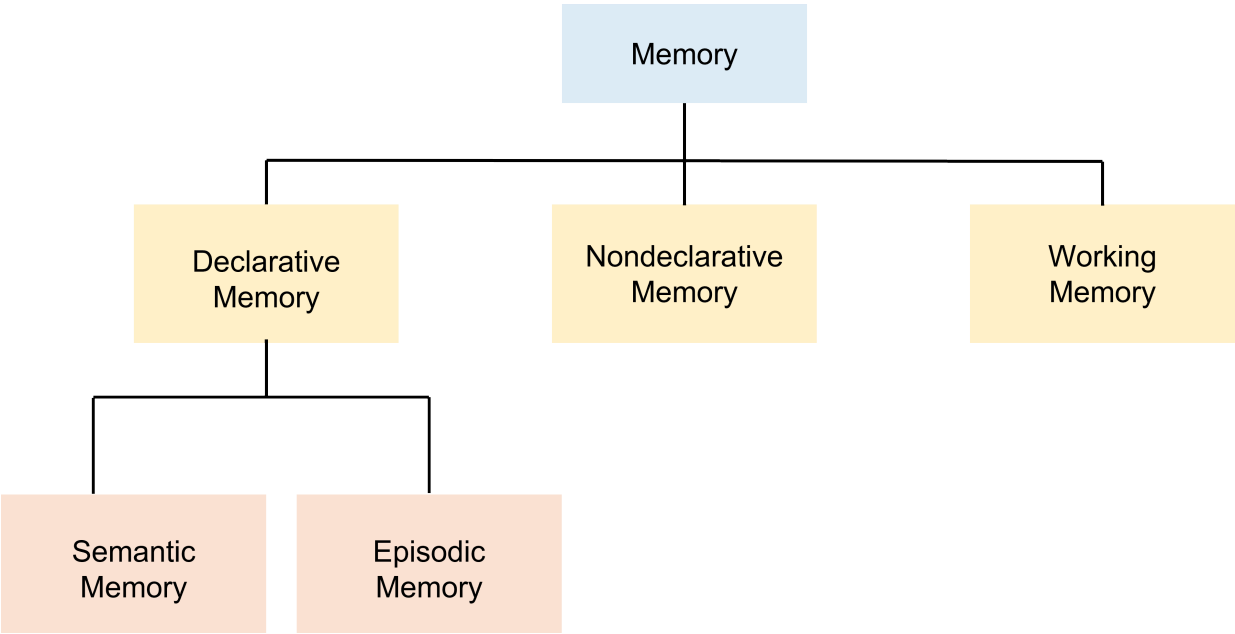


Figure 47.1. Different types of Memory. Declarative memory, nondeclarative memory and working memory are distinct from each other. Declarative memories, also called explicit memories, are memories of piece of information that can be stated explicitly. Declarative memories can be further subdivided into semantic memory, memory of facts, and episodic memory, memory of autobiographical events. Nondeclarative memories encompass "knowing how" memories and include procedural memories, emotional memories, and skeletal muscle memories. Working memory involved temporarily storing information that you are simultaneously working on. 'Types of Memory' by Valerie Hedges is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Declarative Memory

Declarative memories, also called explicit memories, are the pieces of information that can be consciously declared or stated explicitly. Declarative memories are thought of as a "knowing what". Declarative memories can be further subdivided into **semantic memory** and **episodic memory**. Semantic memories are pieces of factual information. Some examples include: 1. "Jupiter is the largest planet of our solar system." 2. "Rosalind Franklin discovered the doublehelix structure of a DNA molecule." 3. "The actor Keanu Reeves played the protagonist of the movie The Matrix."

An **episodic memory**, sometimes also called an autobiographical memory, is the recollection of a discrete moment in a person's life. It can be thought of as "mental-time travel"—what was it like when. The following memories are examples of episodic memories: "When I got home, I put my wallet

and phone on the table.", "I ordered pizza last night.", "In 2019, I went to see my favorite musicians perform live.".

Declarative memories can either be a short-term memory or a long-term memory, which are distinct from each other. The process of **memory consolidation** takes facts and events and converts them from short-term memory into a long-term memory, which is supported by structural and functional change within the neurons that hold the long-term memory.

Nondeclarative Memory

Nondeclarative memory encompasses all other types of memory outside of semantic and episodic memory including procedural memories, skeletal muscle memory, and emotional response memory.

Procedural memories, (or implicit memories) are unconscious memories, and can't be explicitly stated. These can be thought of as "knowing how". Some examples of procedural memories include, for example, performance of a series of motor actions without conscious thought such as an experienced musician playing a simple scale (sometimes commonly called "muscle memory", even though the muscles do not store any actual memory!), or a **priming effect** (such as when a person sees pictures of bananas, they are more likely to answer the fill-in-the-blank prompt "b _ _ _ _ _" with "banana", whereas other people might guess "bubble" or "badger".

There are two different types of procedural learning: non-associative learning and associative learning.

Non-Associative Learning

Non-associative learning involves a change in behavioral response over time in response to a single type of stimulus and includes habituation and sensitization. In **habituation**, responses decrease after repeated presentation of a stimulus as the individual learns that the stimulus lacks meaning. For example, if someone poked you in the back, you will initially jump in surprise. However, if someone repeatedly pokes you in the back over and over again, your response will decrease and you realize that the stimulus is meaningless.

In **sensitization**, responses increase following presentation of a strong stimulus. For example, a sound of a door opening in your house typically will not cause a strong response. However, if you are home alone and hear a loud bang followed by a door opening, you will likely be on high alert.

Associative Learning

Associative memories are the types of information that we learn through traditional **Pavlovian conditioning**. For example, recall the classic Nobel prize-winning experiment in physiology conducted by Ivan Pavlov in the late 1800s. Normally, the presentation of dog food, an unconditioned stimulus (US), causes a dog to salivate, a naturally occurring behavior, called the unconditioned response (UR). Dogs are not particularly interested in the sound of a bell: this neutral stimulus will produce a minor response, such as a head turn and attentional shift towards the origin of the sound, but not much more than that. However, when this stimulus is repeatedly paired with the presentation of food, dogs quickly learn to associate that the bell signals food. After multiple pairings, upon hearing the bell, a conditioned stimulus (CS), the dogs begin to salivate, a conditioned response (CR), independent of any food being presented.

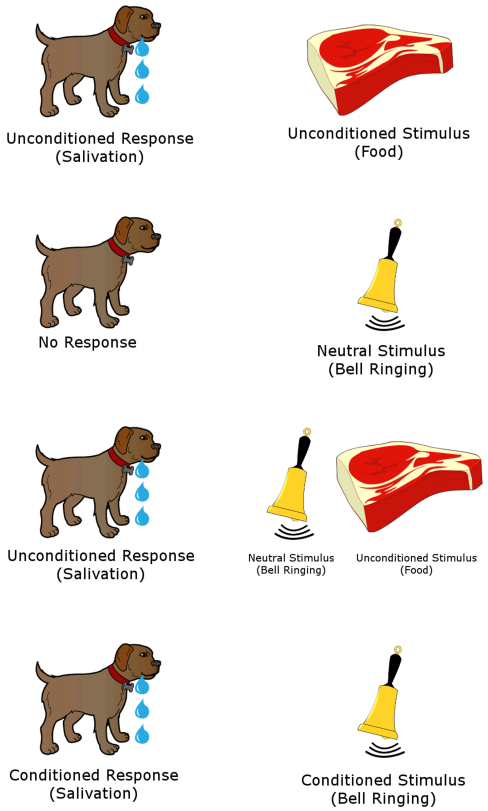


Figure 47.2. Associative Learning. Initially, in the presence of an unconditioned stimulus (food) the dog will salivate, however in the presence of a neutral stimulus (a ringing bell), the dog will not salivate. During conditioning, the unconditioned stimulus is paired with the bell, causing the dog to salivate. Following conditioning, the dog will salivate from only the presence of the bell.

Associative learning can also be measured with **instrumental conditioning** where a rodent, for example, learns to associate a response with a meaningful stimulus. For example, a rodent will learn to press a lever for access to food.

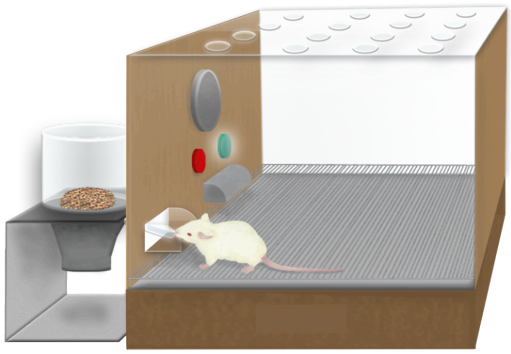


Figure 47.3. Instrumental conditioning. In instrumental conditioning a rodent can learn to associate pressing a lever with a meaningful stimulus, such as access to food.

Working Memory

Separate from declarative or procedural memories, a different form of memory called **working memory** involves processes of storing information temporarily while simultaneously manipulating those pieces of information. This type of memory can be thought of as a "short-term memory on overdrive." For example, a test of working memory is the **digit span test**, where a person is given a series of numbers to remember, then they are asked to repeat the numbers in reverse order. After successfully completing this task, a different series of numbers, this time one digit longer, is presented to the patient until they first start making errors in recall. A related task is called the **Corsi block tapping test**, where an experimenter sets up several blocks on a table. The experimenter then taps a series of blocks in a specific order, then the subject is asked to tap on the blocks in reverse order. As with the digit-span test, the experimenter then makes the series of blocks longer until they make mistakes in the tapping.

Brain Structures in Memory

Declarative Memory—Cortex

In the 1950's, the scientist Karl Lashley was interested in finding a location in the brain where memories were stored. His experiments searched for the location within the cortex of what he called an "**engram**" or memory trace. He trained rats to run in a complex maze to reach a food reward, which took the animals time to learn. After the animals had learned how to successfully run the maze, Lashley would lesion different areas of the rat cortex and then test the rats in the maze again. He found that regardless of the location of the lesion, which was done at different areas of the cortex for each rat, that cortical lesions resulted in decreased ability to remember the location of the food reward and run the maze. Instead of finding a specific location where the memories were being stored, Lashley discovered that the size of the lesion corresponded to the amount of memory deficit in the animal, but that the location of the lesion did not have an effect, demonstrating that the engram was widely spread across the cortex.

Memory Consolidation and Spatial Memory—Medial Temporal Lobes, Including the Hippocampus

The main structures of the medial temporal lobes include the **hippocampus**, the **entorhinal cortex**, the **perirhinal cortex**, and **parahippocampal cortex**. Together, these structures are important in both consolidation and storage of declarative memories.

The hippocampus, meaning "seahorse" in Greek, was named based on its morphology and resemblance to a seahorse. The hippocampus is located along the ventral and medial surface of the brain. The hippocampus is one of the critical structures of the limbic system, a series of subcortical brain structures that are involved in several different complex behaviors, such as emotions and memory. The limbic system is an evolutionarily ancient brain network.

The hippocampus is involved in spatial memories, memories involved in navigation of our surroundings, and the creation of a mental map of our world. Spatial memories are developed when we enter a new building for the first time and we search for a new classroom. We also use our spatial memory whenever we are walking around campus, making our way from one building to another, thinking about the streets you'd need to cross or the buildings you can cut through. While the volume

of the hippocampus is not a reliable indicator of the strength of a healthy person's spatial memory, injury to the hippocampus causes deficits in spatial memory.

Patient HM

One of the most influential case studies in the neuroscience of memory is the story of **Patient HM**. Since his death in 2008, we now know that Patient HM's name was Henry Molaison. HM was born in 1926 in a small Connecticut town. In his childhood, HM began having severe seizures, possibly the result of a head injury. In his teenage years, he started having tonic-clonic seizures, the most severe form of seizures that produces a loss of consciousness and convulsions (extreme muscle contraction or extension). In his early adulthood, he was having a tonic-clonic seizure monthly and several minor seizures daily, preventing him from working a normal job or living a normal life, despite taking a cocktail of anti-epileptic medications.

Neurosurgeon William Scoville proposed a "frankly experimental operation" to treat HM. It was known that most epilepsy originates in patches of neurons of the medial temporal lobe, and HM's epilepsy was typical in this respect. Scoville suggested to surgically resect, or remove, the medial temporal lobe. In 1953, Scoville removed about 8 cm of the medial temporal lobe bilaterally, including part of the amygdala, and notably the hippocampus, the seahorse-shaped structure of the brain. The surgery succeeded at its primary goal: HM's seizures were less frequent and less severe. However, HM was left with a highly unusual and life-altering side effect: He was unable to create new declarative memories, a memory deficit called **anterograde amnesia**. For example, he could not remember what he had eaten for lunch just minutes after finishing the last bite. Despite being an avid fan of watching the news, HM couldn't remember the names or the faces of different celebrities or public figures. It was as if he was permanently living in the present. (In contrast, **retrograde amnesia** affects the ability to successfully retrieve memory from one's past.)

However, despite his pervasive memory deficits, HM did not display any deficits in intelligence. His language and speech were unaffected, and word recall was excellent, as he loved completing crossword puzzles and often did so successfully late in life, with only the occasional spelling errors. He could learn to acquire new skills, such as keeping a pen still on a moving circular platform, or a tapping task (these skills are a different form of memory called **procedural memory**). He was also capable of recalling things from his early childhood, such as geography facts he had learned in elementary school.

The fact that HM's medial temporal lobe surgery disrupted some types of memories (e.g., memory for facts) while others were still intact (e.g., motor skills) inspired neuropsychiatrists to try to define the

different forms of memory. Much of the research was led by Dr. Brenda Milner, who carried out several behavioral tests on HM to figure out what types of memories are dependent on the intact medial temporal lobe and which ones can function without the medial temporal lobe.

Several tests concluded that HM had lost his ability to create new **semantic memories**. In one such study, HM was asked to determine if a word was made up or real. He was shown words with very old origins, such as "shepherd" or "butcher." On these words, he performed as well as the control group. When he was shown words that are made up, such as "phlage" or "thweise", he likewise performed as well as the controls. However, when shown words that were added into the dictionary after his 1953-surgery, such as "granola" or "jacuzzi," he scored about 50% correct—consistent with guessing at random, as if he never acquired the knowledge that these words have a meaning.

HM was also unable to create autobiographical memories. When asked to recall one of his birthday celebrations as an adult, he wouldn't be able to give any significant details about the event. Instead, his answers were often vague and generic. One interesting observation was that HM's memory about details from his childhood were still intact. The inability to recall memories from the past, in this case, from before HM's surgery, is called **retrograde amnesia**. Patient HM's retrograde amnesia was temporally graded, meaning that the farther back you examine, the more complete his memories were. Many of his memories for the two years before his surgery were completely lost, but memories from his youth and teenage years were intact as much as healthy individuals (there is contention about this observation, because HM was taking several anti-epileptic drugs, which may have impacted memory formation.)

From this observation, memory researchers concluded that the **medial temporal lobe** functions as short-term storage site for memories, but after some years, those memories get relocated to other brain areas outside of the medial temporal lobe. Currently, the scientific evidence suggests that memories are distributed across several networks of cortical and subcortical brain areas.

While HM lost the ability to create new declarative memories, he was still able to maintain a different class of memories, called procedural memories (or implicit memories). The original test of procedural memory conducted by Dr. Brenda Milner was called the mirror tracing task. In this test, the patient is told to draw a third star in between the two stars as quickly as possible without making any mistakes. The challenge is that the tracing is to be done while watching their hand and the star in their reflection in a mirror. Because of these unusual circumstances, completing this task is difficult. But over multiple days of practice, people become better at this mirror tracing task, completing it faster with fewer errors. Improvement on this task indicates that a person is learning or gaining some memory about how to better perform the task. After practicing this mirror tracing task, HM was able to finish drawing the

star about ten times faster than when he first began. He improved his performance within each day's worth of training, and he also improved day-to-day. There is evidence that he maintained these skills up to one year later, despite not having regular training on this task.

Surprisingly, each day Milner examined HM, she would need to reintroduce herself since he forgot who she was. She also had to re-explain what HM was supposed to do in the mirror tracing task. Hence, while HM was unable to form declarative memory about the experiment or the people involved, learning of the procedural memories and motor actions involved in this task remained intact.

Based on the deficits seen in Patient HM and other experimental manipulations of the hippocampus, we conclude that the hippocampus is strongly implicated in the process of declarative memories and spatial navigation. Since some of HM's memory functions were still intact, such as procedural memories and working memory, it is believed that these functions are independent of hippocampus function.

Tests of Hippocampal Function in Rodents

To test **spatial memory** behaviorally in nonhuman animals, one test that is regularly used in rodents is called the **Morris water maze**. In this test, a shallow pool is filled with an opaque liquid, making it difficult to see through. Hidden somewhere in this pool is a clear plexiglass platform, and surrounding the pool are different environmental cues that can be seen from the surface of the water, such as different shapes or colors. The water is deep enough that when a rodent is put into the Morris water maze, they have to swim to stay afloat. The rodents swim around aimlessly until they find the platform, the time it takes for this to happen is recorded, and the trial ends. Over time, the animals learn that the platform is located near certain navigational cues, and on future trials, the animals spend more time near those cues, and the latency to find the platform decreases. When the hippocampus is surgically removed from rodents or inactivated, they perform poorly in the Morris water maze.

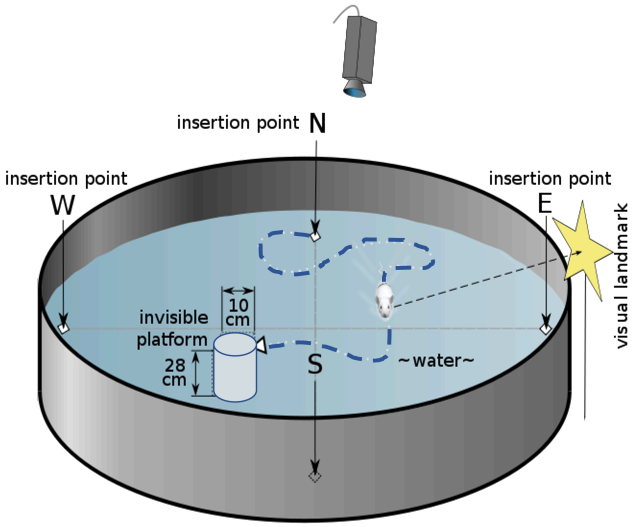


Figure 47.4. Morris water maze. The Morris water maze is used to test spatial memory in rodents. A tub of water is filled with an opaque liquid that the rodent cannot see through. Hidden within the pool is a clear plexiglass platform. A camera is placed above the pool to track the rodent's path through the pool. When the rodent is put in the pool, it has to swim around looking for an escape. Visual cues are placed around the pool that can be seen from the surface of the water, such as different shapes or colors. During a trial, the time it takes for the rodent to find the hidden platform is recorded. Over time and additional trials, the animals learn that the platform is located near certain navigational cues, and on future trials, the animals spend more time near those cues, decreasing the amount of time it takes for the animal to find the platform.

Another non-human behavioral test used to assess the capacity for learning navigational cues is the **radial arm maze**. In this test, a rodent is placed on a circular platform. Extending from this platform are eight or more "arms", at the end of each is a small dish. In one of the dishes is a morsel of food ("rewarded arm"), while the other dishes contain nothing ("non-rewarded arms"). The maze is designed so that the food cannot be seen from the end of each arm, so the animal must return to the starting platform before exploring another arm. The number of entries into a non-rewarded arms is counted as an error. Over time, the animals make fewer errors as they learn which arm is rewarded and which ones are not. Alzheimer's disease model organisms perform poorly on this task.

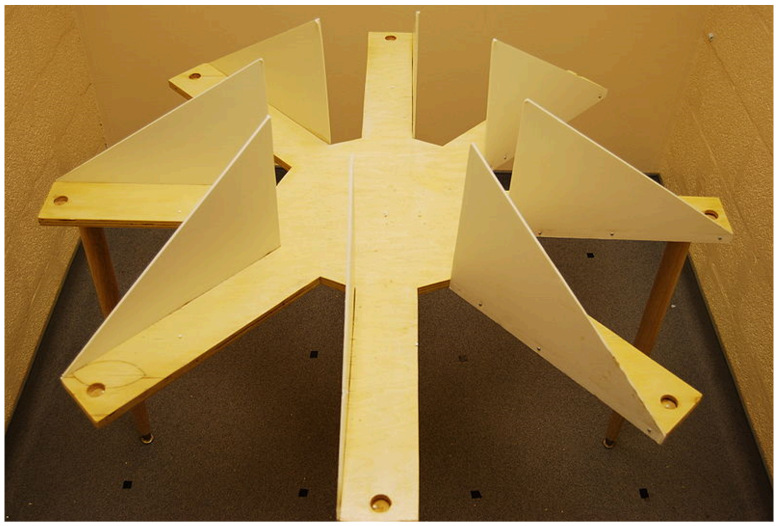


Figure 47.5. Radial arm maze. A radial arm maze is a test of hippocampal function. A central platform is surrounded by several arms radiating away from the center. At the end of one arm is a small dish that contains food, but the other arms do not have food. The rodent must explore the arm to discover if it has food or not. When an animal travels down a non-rewarded arm it is counted as an error. Animals with a damaged hippocampus commit more errors in this task than animals with an intact hippocampus.

Special Populations of Neurons

An individual memory is likely distributed widely across several different parts of the brain. However, there are a few special populations of neurons mainly in the medial temporal lobe that contribute to highly specific types of memories.

Place Cells

Place cells are a special population of pyramidal cells of the hippocampus. These neurons increase their firing activity when the animal is in a particular location in an environment, indicating that they contribute strongly to location and navigational memory. There is no apparent topographical arrangement of these place cells, meaning that adjacent areas of an environment do not necessarily activate adjacent hippocampal place cells. The place cells, when firing at the right times, help the animal create a spatial map of their surroundings.

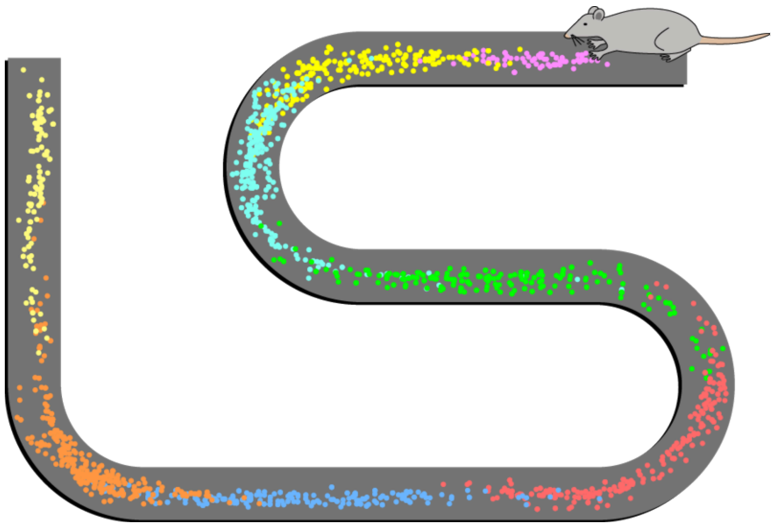


Figure 47.6. Place Cells. Place cells, a special population of neurons located within the hippocampus, fire action potentials when an animal is in a specific location and are believed to be important in navigational memory. Here a rat is placed in a maze and place cells within the hippocampus are being recorded. Where each place cell fires is indicated on the maze with colored dots. All dots of the same color indicate that the same place cell is firing.

Grid cells

Grid cells are located in the entorhinal cortex, the main input structure to the hippocampus. Closely related to the place cells described above, grid cells increase their firing properties periodically when an animal is at an intersection of a "grid" in a wide-open, previously-explored environment. The grid itself is roughly hexagonal, and spans the whole environment an animal is in. The overlap of multiple grids gives the animal an idea of the surroundings. The scientific description of grid cells earned three scientists, Edvard Moser, May-Britt Moser, and John O'Keefe, a Nobel Prize in Physiology or Medicine in 2014.

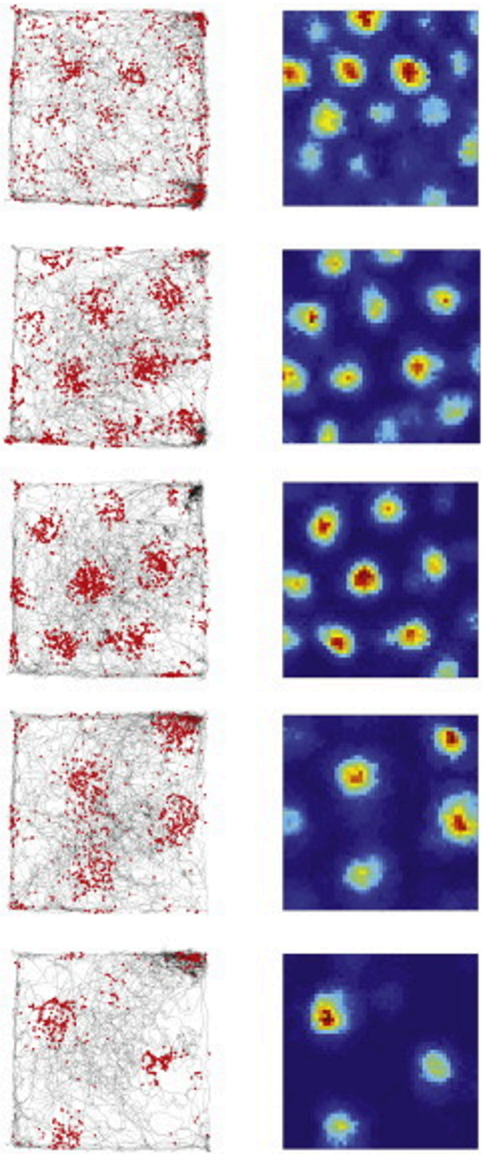


Figure 47.7. Grid cells are a special population of neurons located in the entorhinal cortex, which serves as the main input structure to the hippocampus. Similar to place cells, grid cells fire when an animal is at an intersection of a "grid" in a wide-open, previously-explored environment. These images on the left show the movement of a rat through a square environment depicted by a black line. The red dots indicate locations within the environment where a specific entorhinal grid cell fired. The images on the right show a spatial autocorrelogram that corresponds to the neuronal activity of the grid cell from the figures on the left.

Concept cells

Concept cells are a series of cortical neurons in the temporal lobe that increase their firing exclusively in response to highly-specific stimuli, such as the idea of Jennifer Aniston, Halle Berry, or the Tower of Pisa. These concept cells respond to much more than just pictures: for example, a Luke Skywalker neuron that responded to a picture of young Mark Hamill (the actor who played Luke Skywalker) will also respond to text that reads "LUKE SKYWALKER" and the sound of a person saying "Luke Skywalker". Although this particular neuron probably won't fire in response to pictures of athlete Manu Ginobili or actress Marilyn Monroe, the neuron might fire in response to pictures of Yoda or Darth Vader, indicating that the neuron may encode an even broader concept, such as "Star Wars characters" or "Jedi", or is a part of a network that encodes concepts related to the Star Wars franchise.

Working Memory—Prefrontal Cortex

As part of the frontal lobe, the prefrontal cortex is involved in higher order decision making and personality. In the context of memory, neural circuits in the prefrontal cortex are important for short-term and working memory.

A **delayed-response task** relies on prefrontal cortex activity. In this task, a monkey is shown a cue of food placed into a randomly selected compartment outside their cage. A screen is then lowered and the compartments are covered for a standard period of time. The screen is then raised again and the monkey is tasked with correctly uncovering the compartment that contains the food. Animals with a lesion to the prefrontal cortex perform worse than animals with an intact prefrontal cortex in this task.

Patients with injuries to their prefrontal cortex after stroke, tumors or aneurysm, performed worse on a variety of working memory tasks such as the **digit span test**. Additionally, people with frontotemporal dementia, a neurodegenerative disorder characterized by a degradation of the frontal lobe, often have difficulty with working memory. The prefrontal cortex also has strong projections with the hippocampus, and these circuits are likely also involved in the formation of hippocampal-dependent memories.

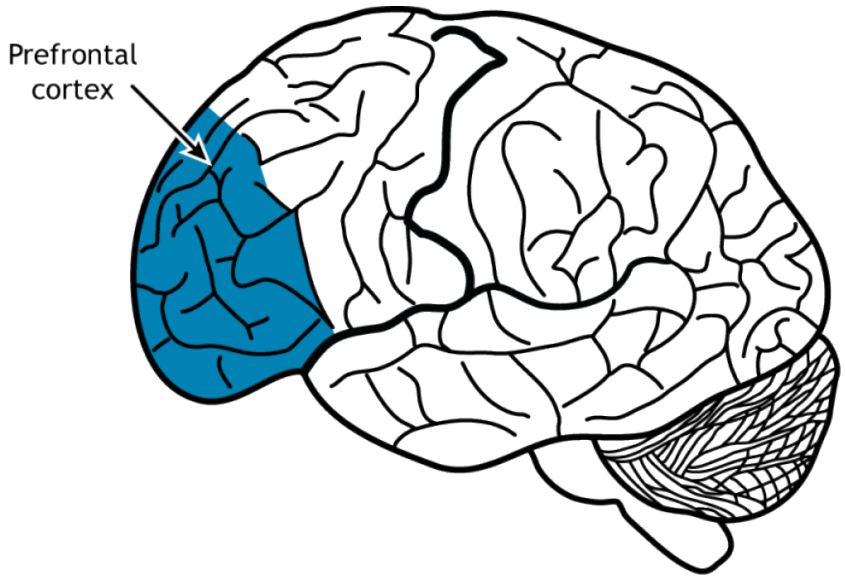


Figure 47.8. Prefrontal Cortex. The prefrontal cortex, shown in blue in an external view of the brain, is located in the anterior portion of the frontal lobe.

Habit or Procedural Memory—Striatum

The **striatum**, made up of the caudate nucleus and putamen, is important for habit or procedural memory and reward in learning. A **T-maze** is used to test procedural learning. In this task, a rodent is placed at the area of the maze that corresponds to the bottom of the T. The animal is trained to turn either left (with a high frequency tone) or right (with a low frequency tone) once they reach the cross of the T. If the animal completes the task successfully, they are rewarded with a treat. The ability of the animal to learn this task is dependent on activity within the striatum. Animals that have striatal lesions have impaired performance on the T-maze, but not on tasks that rely on other types of memory.

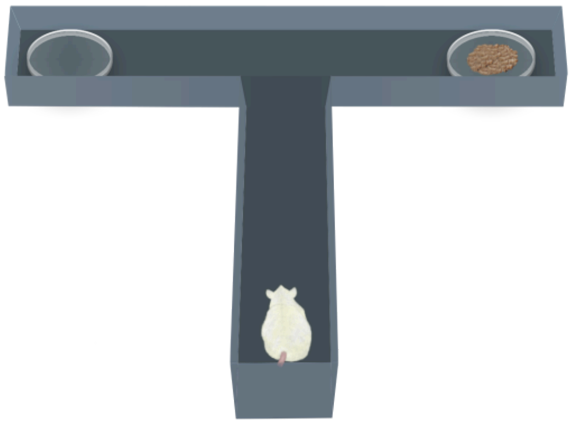


Figure 47.9. T Maze. A T maze is used to test habit, or procedural memory and reward in learning. In this task a rodent is placed at the area of the maze that corresponds to the bottom of the T. The animal is trained to turn either left or right. If the animal completes the task successfully, they are rewarded with a treat.

Cellular Memory

In the late 1800s, around the time when Golgi and Ramon y Cajal were engaged in intense debate about the organization of the nervous system, many neuroscientists came to a strange observation: the weight of the brain increases dramatically over the first 10 years of life, but not much more after that. Even though we learn lots of new facts and make lots of new memories in adulthood, the brain itself doesn't grow in size. So how is it possible to store new knowledge if the brain is not making many new neurons? Most likely, new pieces of information are held in the connections between cells, not just in the cells themselves. If our estimate of 150 trillion synapses per adult brain is correct, then it is possible that we could store all the knowledge and memories that we collect over our lifetime through some combination of activity across certain connections.

The activity at the cellular level is believed to take place on at least three different levels enabling us to build, store, and retrieve memories.

1. Memory Encoding

Encoding refers to the ability for brain circuits to store some piece of information. In real life, you are presented with countless stimuli simultaneously. Imagine walking down a busy street, and think

of the number of different sights, smells, and tactile stimuli you experience. Storing memories is an energetically costly process, and we are limited in the fact that all of our sensory inputs cannot possibly get encoded. Instead, evolution has preferred to encode stimuli that are the most salient pieces of information, such as perceptual cues associated with predators. Alternatively, information that we pay strong attention to can get encoded more strongly, like when we repeat a phone number to ourselves until we have a chance to write it down. It is also easier to encode novel information that "builds" on previous bits of knowledge, or information that is closely related to other well-established information, which is why analogies are such an effective way to learn new facts.

2. Memory Consolidation

The process that enables memory storing is called **consolidation**, which makes the memory more permanent. In 1949, a student of Karl Lashley, the neuropsychologist Donald O. Hebb, offered an explanation for how changes in synapses could possibly lead to a phenomenon as complex as learning. His theory, published in his text *The Organization of Behavior*, can be summed up in the phrase: "Cells that fire together, wire together." In Hebb's framework, repeated activity at a synapse within a circuit of neurons acts as a reinforcer signal that strengthens this synapse for future communication, making the next incoming signal more robust. Hebb also implies the inverse is true: when cells do not fire together, they weaken their connection. Through fine tuning of synaptic connections, some strengthening and others weakening, a lifetime of memories can be stored across a wide distribution of neurons. After a memory has been created, the specific circuit of neurons that represent that piece of information is called a memory trace or an engram. A cellular process called reverberation is thought to be the mechanism that allows for consolidation.

Reverberation is the process by which networks of neurons fire repeatedly. Each time that circuit is activated, the strength of the network is increased, meaning that it becomes easier for that circuit to be activated in the future. Throughout the process of consolidation, memory traces are thought to become more represented in the neocortex and less in the subcortical structures like the hippocampus or amygdala.

Recall Patient HM's temporally graded **retrograde amnesia**, where he had lost declarative memories in the two years leading up to this surgery, and yet his memories from the long past were maintained. This finding suggests that some aspects of declarative memory consolidation depends at least partially on medial temporal lobe and hippocampus for a period of time, maybe up to two years, before those memories get stored in the cortex more permanently. However, we cannot conclude

how long consolidation takes in healthy humans based on findings from HM, who had pervasive and frequent seizures, which might have negatively impacted memory consolidation before the surgery.

Consolidation seems to occur predominantly during sleep. Specifically, declarative memory is enhanced during non-REM sleep, while procedural memory is enhanced during REM sleep. Studies investigating sleep consolidation are often done by letting participants learn or perform behavioral tasks, after which they are deprived of a specific phase of sleep. To wake participants at the right moment, researchers commonly use EEG signatures, which are unique for different phases of sleep: sleep deprivation early in the night denies non-REM slow wave sleep, while late-sleep deprivation decreases time spent in REM sleep. Some speculate that the hallucinations we sometimes experience during dreaming are a consequence of consolidation processes, but it is inconclusive as to what role dreaming plays in memory formation.

3. Memory Retrieval

Finally, for the stored memories to be recalled, a cellular process called **retrieval** happens which brings back the specific engram. Retrieval happens for both declarative and procedural memories. The writing of memories can be differentiated from the retrieval of memories using specific priming-related behavioral tests. One example is a **vocabulary recall test**. Consider if you were given a list of 50 words to memorize, words that belong to a handful of different conceptual categories (such as cinnamon, pepper, or curry, which fall under the category "food flavors"). When asked to write down as many words as possible from the list using your memory, a test called **free-recall**, you may be able to successfully remember about a third of them. However, if you were prompted with the category titles, a related test called **cued-recall**, you would perform much better at retrieving those memories, possibly recalling up to 75% of the words. The fact that cued-recall scores are often higher than free-recall scores indicate that there is a distinction between the encoding / consolidation of memories and the retrieval of memories.

Retrieval is not a passive function. When an engram is retrieved, it is **reconsolidated**, which is an act similar to replaying the activity of the circuit. During this reconsolidation, it is possible that some aspects of the memory are emphasized, while others are lost. This is likely the main reason why we experience **false memories**, memories that are not true to reality—one reason why eyewitness testimonies are notoriously unreliable. We may imagine our good memories as better than they actually were, while simultaneously dampening the negative aspects of those memories. A dysregulation of this

reconsolidation process could lead to the symptoms seen in post-traumatic stress disorder, where the negative emotional components of a particular memory are exaggerated rather than being blunted.

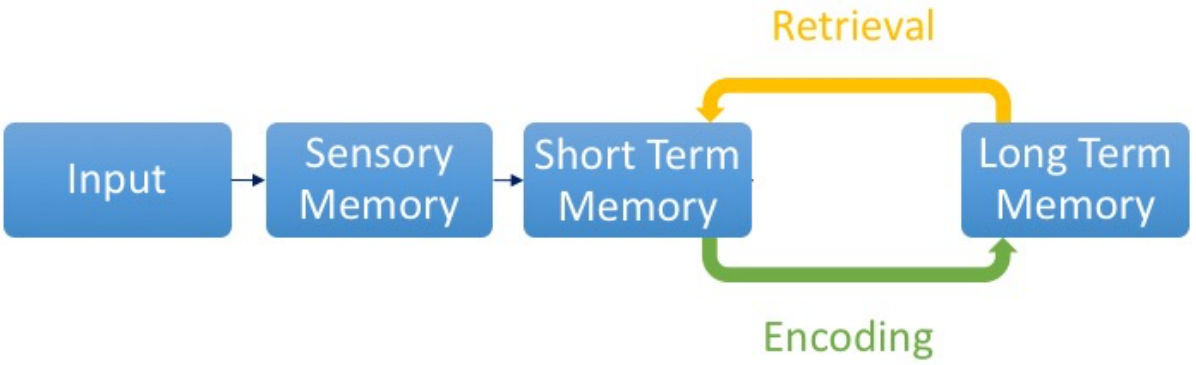


Figure 47.10. Memory encoding and retrieval. Short term memory goes through the process of encoding to be converted into long term memory. Retrieval brings back a specific engram for both declarative and procedural memories.

Key Takeaways

- Memory can be divided into declarative memory, nondeclarative memory, and working memory. Declarative memory can be further subdivided into semantic memory and episodic memory.
- The cortex, hippocampus, striatum, and prefrontal cortex are all structures with specific roles in memory.

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48.

MOLECULAR MECHANISMS OF MEMORY: APLYSIA

Resources

- Glossary terms
- Scientist links to learn more!
- Key Takeaways

Through the 1960s, psychiatrist Eric Kandel and his colleagues Arvid Carlsson and Paul Greengard worked with the marine mollusk Aplysia californica. Their work uncovering the neural mechanisms of learning and memory earned them the Nobel Prize in Physiology or Medicine in 2000.

With a nervous system of only 20,000 cells, Aplysia is orders of magnitude simpler than the other model organisms used at the time. Additionally, some Aplysia neurons are huge, up to a millimeter in diameter, which took away the need for highly precise equipment.



Figure 48.1. Aplysia californica. Picture of an Aplysia californica specimen.

Aplysia also has a relatively simple anatomy. It breathes using a half-circle of delicate tissue called the **gill**, which is guarded by the **mantle shelf**. They also have an organ called the **siphon**, a small tube that is used for moving water through the animal.

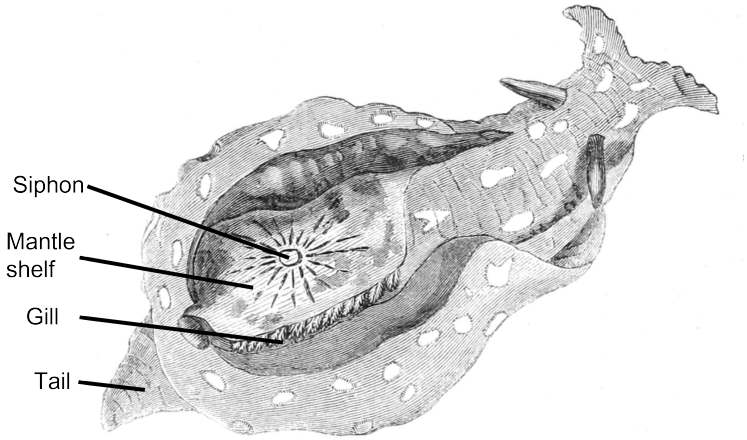


Figure 48.2 Aplysia anatomy. Aplysia is a sea slug that has anatomical features that have been utilized by neuroscientists to learn more about the processes of learning and memory. The Aplysia uses their delicate gill to breath, which is protected by the mantle shelf. The siphon is a small tube that is used to move water through the animal and the tail helps the animal move in the water.

Kandel and his colleagues began their exploration of memory by studying the **gill-withdrawal reflex**, a defensive motor response behavior. When a stimulus, such as a hungry predator (or an experimenter's paintbrush), grazed the siphon, the Aplysia would reflexively withdraw their gill, as if to protect this vital organ by shrinking away from the threat. However, after repeated brush strokes to the siphon, the sea slugs figured out that the stimulus was completely innocuous and decreased the strength of gill withdrawal. Kandel and team suggested that this change in behavior was a form of learning. Kandel and colleagues used Aplysia to learn about the processes of **habituation** and **sensitization**.

Habituation

The gill-withdrawal reflex circuit relies heavily on two different populations of neurons: the glutamatergic sensory neurons that receive somatosensory information from the skin of the siphon, and the motor neurons that control the muscles of the gill. By using two different tiny glass pipettes,

they could impale these neurons, inducing action potential firing in the sensory neuron, and observe changes in membrane potential of the motor neurons. Activation of the sensory neuron causes release of glutamate onto the motor neuron that controls the gill, binding to glutamatergic receptors and causing an EPSP response in the motor neuron.

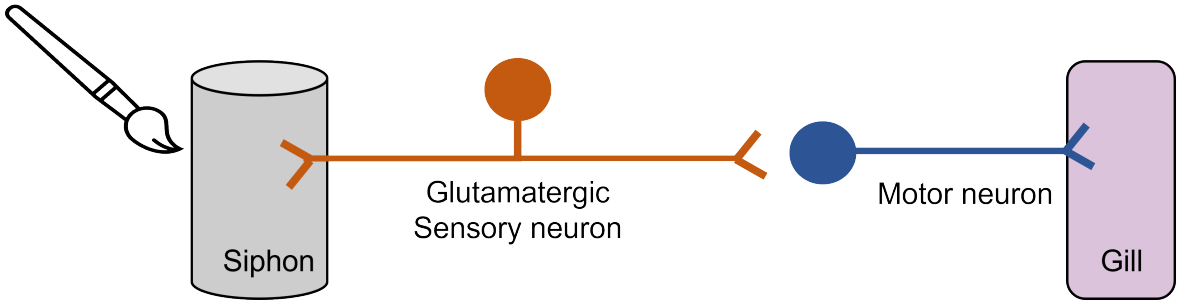


Figure 48.3. Synapse between siphon sensory neuron and gill motor neuron. The siphon sensory neuron is glutamatergic, which results in the release of glutamate onto the motor neuron that serves the gill when the siphon is touched with a paintbrush. When glutamate binds to the motor neuron it causes excitation of the motor neuron and contraction of the gill.

Although there was a strong gill withdrawal reflex following the one poke, Kandel and colleagues observed that after repeated pokes to the siphon, the gill withdrawal reflex got weaker. They found that the activity of the siphon neuron remained unchanged, however, the activity of the motor neuron supplying the gill decreased. The reflex had been habituated. This habituation was due to a decreased release of glutamate from the siphon sensory neuron onto the gill motor neuron.

Sensitization

The group went about seeing if they could modify this habituated response, curious if a stored memory can be modified by stimuli from the outside world. When they paired the mild siphon touch with a painful electric shock to the tail, the Aplysia began responding with a strong motor reaction, withdrawing the gill very intensely, indicating that the inhibited response disappeared. They called this observation sensitization. In electrophysiological studies, they observed that the EPSP at the motor neuron was much larger following the tail shock.

On a molecular level, presentation of sensitization is downstream of the action of a third population of neurons, serotonergic interneurons that synapse onto the siphon sensory neurons. The noxious stimulus triggers these interneurons to release the neurotransmitter serotonin, which binds to

receptors on the terminals of the siphon sensory neurons, increasing adenylyl cyclase activity and cAMP production. cAMP activates protein kinase A, which in turn increases the release of glutamate from the sensory neuron and strengthening the gill withdrawal reflex.

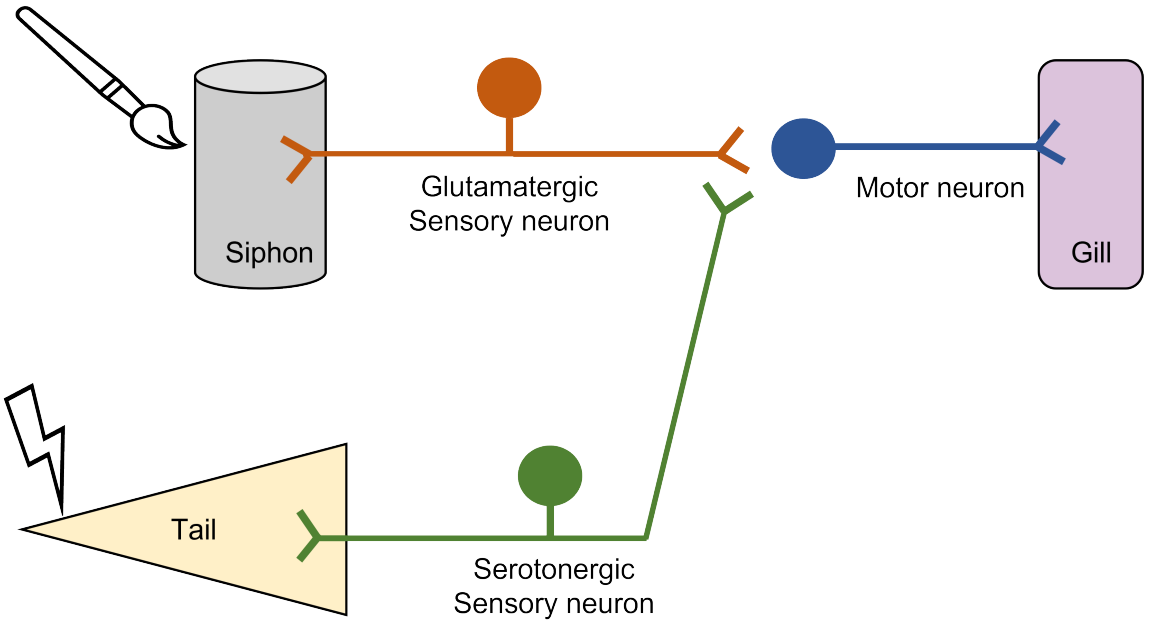


Figure 48.4. Shocking the tail produces sensitization of the gill withdrawal reflex. After producing a habituated response by touching the siphon repeatedly, a tail shock was provided, which results in the return of a strong gill withdrawal reflex. Shocking the tail excites a serotonergic neuron that synapses on the siphon sensory neuron. This facilitates the release of glutamate from the siphon sensory neuron onto the gill motor neuron.

Repeating the sensitization protocol multiple times results in plastic changes at the synapse between the sensory siphon neuron and the motor neuron. These plastic changes are long-lasting and dependent on new gene expression. The activated protein kinase A can translocate to the siphon sensory neuron nucleus to activate gene expression and the production of proteins that can remodel the anatomy of the synapse through the growth of additional sensory neuron axons, increasing synaptic connections.

Key Takeaways

- Aplysia is a simple animal model that has been used to study learning and memory.
- Touching the siphon activates the gill withdrawal reflex through the release of glutamate on to the gill motor neuron.
- Repeatedly touching the siphon results in habituation of the gill withdrawal reflex, and a weaker gill withdrawal.
- Shocking the tail following habituation activates a serotonergic neuron that facilitates glutamate release from from the siphon neuron, producing a strong gill withdrawal reflex.
- Over the long-term, this produces long lasting plasticity within this synapse.

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49.

MOLECULAR MECHANISMS OF MEMORY: HIPPOCAMPUS

Resources

- Glossary terms
- Key Takeaways
- Scientist links to learn more!

Zooming in beyond the level of anatomy, the substrates of learning can be found at the level of synapses. Synapses change in a phenomenon called plasticity. The word "**plasticity**" refers to a change in synaptic strength, which may be an increase or a decrease. This change may persist for minutes, hours, days, or in some cases, even a whole lifetime.

When synaptic strength is increased and remains elevated, we call this long-term potentiation (**LTP**). A prolonged weakness of a synapse is called long-term depression (**LTD**). In our current limited understanding of plasticity, both phenomena are important for a healthy brain, and neither one is always good or always bad. It is also important to clarify that both excitatory synapses and inhibitory synapses can be subject to either LTP or LTD.

The Hippocampus

The **hippocampus**, meaning "seahorse" in Greek, was named based on its morphology. It is located along the ventral and medial surface of the brain. The hippocampus serves as one of the critical structures of the limbic system, a series of subcortical brain structures that are involved in several different complex behaviors, such as emotions and memory. The synaptic connectivity of the hippocampus is very well characterized. Hippocampal synaptic connectivity was first described by

Ramon y Cajal, and is made up of three main synaptic connections; sometimes called the **trisynaptic circuit**.

First, the **entorhinal cortex** serves as the major input to the hippocampus. This white matter signaling tract is called the **perforant pathway**, and the neurons synapse onto the granule cells within an area of the hippocampus called the **dentate gyrus**. The dentate gyrus neurons send their axons, called **mossy fibers**, to the pyramidal cells of the **CA3** region of the hippocampus. The CA3 neurons have axonal projections called **Schaffer collaterals** that project out of the hippocampus via the **fornix** and also to neurons within an area of the hippocampus called **CA1**, which are also neurons that serve as an output of the hippocampus.

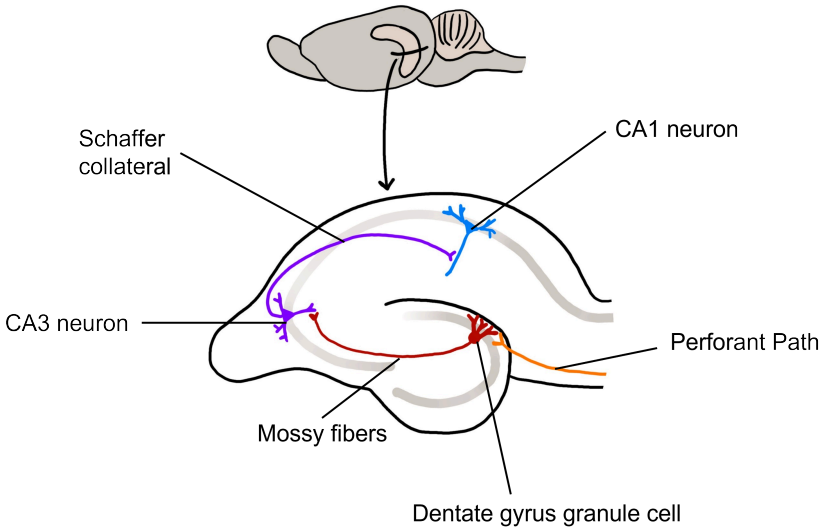


Figure 49.1. Rodent hippocampal trisynaptic circuit. Neurons from the entorhinal cortex serve as the input to the hippocampus. The axons of these cells form the perforant path (orange). The entorhinal cortex neurons synapse onto granule cells in the dentate gyrus (red). The dentate gyrus cells extend their axons, called mossy fibers, to cells in a region of the hippocampus called CA3. The CA3 neurons (purple) extend axons, called Shaffer collaterals, to another area of the hippocampus called the CA1 region (blue). 'Rodent hippocampal trisynaptic circuit' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Long-Term Potentiation (LTP)

Long-term potentiation (LTP) is a long-lasting increase in synaptic strength, measured by the

amplitude of the post-synaptic potential. Plasticity can be measured throughout these connections, but for our purposes we will examine how to create LTP within the **Schaffer collateral**.

To create LTP within the Schaffer collateral, a brief electrical stimulus must be provided to the presynaptic axons coming from the CA3 cells via a stimulating electrode. The EPSP generated in the postsynaptic CA1 neurons is then measured with a recording electrode to establish a baseline.

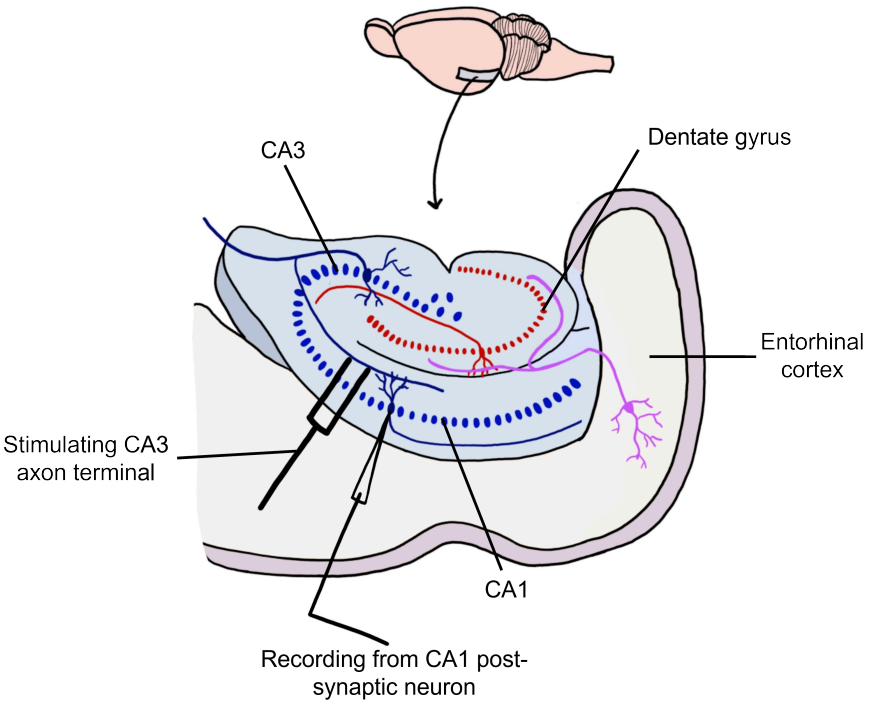


Figure 49.2. Inducing Schaffer collateral LTP. To induce LTP through the Schaffer collateral, a stimulating electrode is positioned to electrically excite the Schaffer collaterals, which are also the axon terminal of the CA3 neurons. A recording electrode is placed postsynaptically in the CA1 neurons. First, baseline measurements are taken by providing brief stimulation to the CA3 neurons and recording the amplitude of the EPSP postsynaptic response. After establishing a baseline, a tetanus is delivered the the CA3 neuron, consisting of short burst of high frequency stimulation. Following the delivery of the tetanus, a single brief stimulation is provided to the CA3 neuron and the postsynaptic response in the CA1 neuron is measured. An increased amplitude of the EPSP in the CA1 neuron indicates LTP. 'Inducing Schaffer collateral LTP' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Using Hebb's theory about plasticity, if "cells that fire together, wire together," then it stands that repeated stimulation of that synapse would induce a rewiring of the connection, resulting in LTP.

To induce LTP within these cells, a **tetanus**, or a very intense electrical stimulation consisting of 100 stimulations a second (100 Hz) is delivered to the presynaptic CA3 cells for 3 seconds. Following the delivery of tetanus, a single stimulus is provided again and the EPSP is then measured in the postsynaptic CA1 neuron. The delivery of the high frequency stimulation results in an increased amplitude of the postsynaptic EPSP in response to a single stimulus, demonstrating that LTP is a measurable phenomenon.

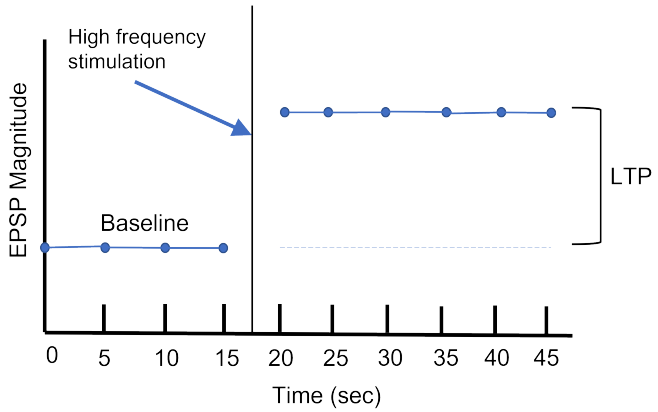


Figure 49.3. Graphing LTP. In this graph the magnitude of the postsynaptic EPSP is being measured on the y-axis over time. After establishing a baseline, a high frequency stimulation (tetanus) is delivered. After the high frequency stimulation, the magnitude of the postsynaptic response increases and remains elevated for a long-period of time, indicating LTP. 'Graphing LTP' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

In many cases, **LTP** is shown graphically by measuring the EPSP amplitude as a percent of the control EPSP amplitude. Prior to **tetanus** delivery, the **amplitude** will be measured as 100%, or the same as control. Following tetanus, the amplitude of the EPSP will be larger than it was baseline, for instance 130% indicating a 30% increase in amplitude. Increasing the amplitude of the postsynaptic EPSP increases the likelihood of a neuron firing an action potential by increasing the neuron membrane potential such that it is closer to the **threshold** potential for the cell.

It has been demonstrated in rodents that the elevated postsynaptic EPSP response is long-lasting and can remain elevated for upwards of one year. In humans, we theorize that some synaptic connections may remain potentiated for our entire lifetime, however investigating this is in humans is ethically constrained.

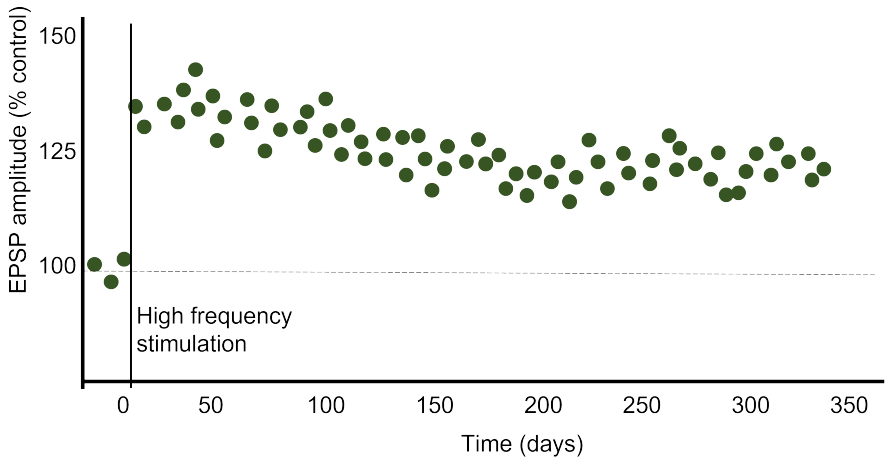


Figure 49.4. Graphing postsynaptic response as a percent of control. Here, the postsynaptic EPSP amplitude is being measured as a percent of the control measurements. Prior to the high frequency stimulation, the EPSP amplitude is 100%. Following the high frequency stimulation, the EPSP amplitude is increased above the control, indicating that there is a larger postsynaptic response. In this example, the EPSP amplitude remains elevated for upwards of one year of time, indicating that LTP can be long-lasting. 'Graphing postsynaptic response as a percent of control' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Glutamate Receptors and LTP

Long-lasting changes in synaptic strength, such as the LTP, are made possible through a series of molecular and cellular level changes. One form of LTP results from a change in the types of glutamatergic receptors. Of the three classes of ionotropic glutamate receptors, two are important for this form of LTP: the AMPA and the NMDA receptors (Chapter 16).

When a molecule of glutamate binds to the active site of the **AMPA** (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor, the ligand-gated ion channel changes to the open conformation and allows the cations, sodium and potassium, to cross the cell membrane. Sodium moves into the cells more than potassium leaves the cell, leading to depolarization. The **NMDA** (N-methyl-D-aspartate) receptor requires the binding of glutamate to open, but it is also dependent on voltage. The pore of the NMDA ligand-gated ion channel is blocked by a molecule of **magnesium** when the membrane potential is below or near resting membrane potential, preventing ions from moving through the channel. Once the cell depolarizes, the magnesium block is expelled from the receptor, which allows sodium, potassium, and calcium to cross the membrane.

The voltage change needed to open the NMDA receptor is usually a result of AMPA receptor activation. Released glutamate binds to both AMPA and NMDA receptors, and sodium influx occurs through open AMPA channels, which depolarizes the cell enough to expel the magnesium ion and allow ion flow through the NMDA receptors.

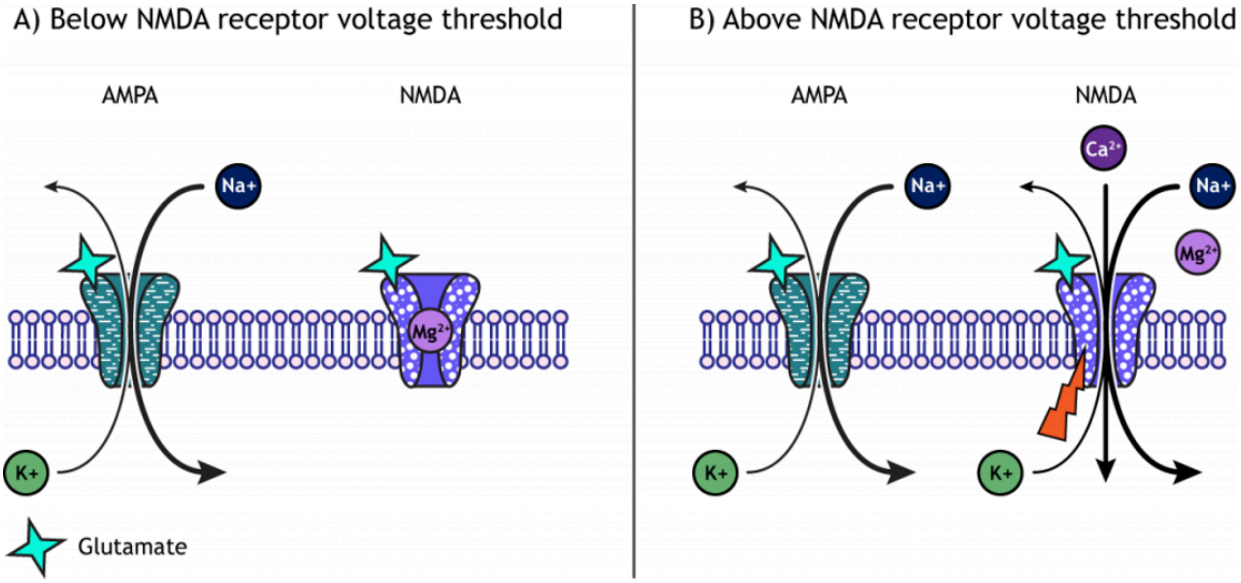


Figure 49.5. AMPA and NMDA. (A) When below the voltage threshold, glutamate binds to AMPA receptors, causing the ionotropic receptor to open and allow passage of both sodium and potassium. The movement of sodium into the cell dominates, indicated by the bold arrow. However, the binding of glutamate to the NMDA receptor does not allow the movement of ions across the membrane due to a magnesium ion blocking the pore of the channel. (B) When the membrane is depolarized above the threshold voltage of the NMDA receptor, the magnesium ion is expelled from the pore of the channel, allowing movement of calcium, sodium, and potassium through the NMDA channel. The movement of calcium and sodium into the cell dominates, indicated by the bold arrows.

LTP and Intracellular Calcium

The calcium that enters the cell through the open NMDA receptors activates various **kinase**s including, **protein kinase A** (PKA), **protein kinase C** (PKC), and **calcium-calmodulin-dependent kinase II** (CAMKII). Kinases phosphorylate target proteins within the cell, including AMPA receptors. Phosphorylation of AMPA receptors increases their conductance, allowing more ions to pass through the receptors and leading to a greater degree of depolarization. Further, increased intracellular

calcium can lead to the insertion of additional AMPA receptors into the postsynaptic cell membrane, which will also allow more sodium to move into the cell and lead to increased depolarization.

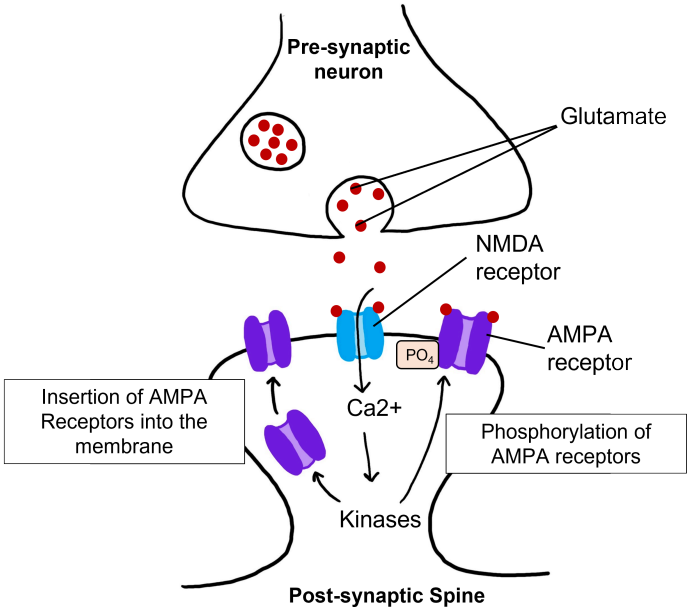


Figure 49.6. Calcium and LTP. Calcium enters the cells through NMDA receptors. When intracellular calcium levels are high, the calcium activates protein kinases within the cell. The protein kinases phosphorylate AMPA receptors expressed on the cell surface, increasing their conductance and allowing more sodium to enter the cell. Kinases also cause additional AMPA receptors to be inserted into the membrane of the cell, thereby increasing the available receptors that glutamate can bind. 'Calcium and LTP' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Long-Term Depression (LTD)

Long-term potentiation increases the strength of synapses. Changes in activity can also cause synapses to be weakened through the process of long-term depression (**LTD**). Again, using the Schaffer collateral as an example, long-term depression can be induced at the synapses between the CA3 and CA1 neurons by replacing the tetanus stimulation with **low-frequency stimulation** for longer periods of time. For instance, a 15 min exposure to 1 Hz stimulation will lead to a decreased EPSP amplitude.

Through LTP and LTD, synapses demonstrate bidirectional plasticity that is dependent on the type of stimulation that the synapse receives.

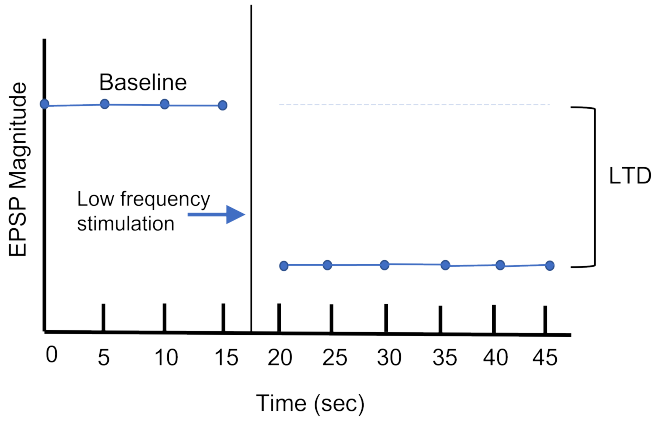


Figure 49.7. Graphing LTD. In this graph the magnitude of the postsynaptic EPSP is being measured on the y-axis over time. After establishing a baseline, a low frequency stimulation is delivered. After the low frequency stimulation, the magnitude of the postsynaptic response decreases and remains lowered for a long-period of time, indicating LTD. 'Graphing LTD' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

LTD and Intracellular Calcium

Even with low-frequency stimulation of the synapse, glutamate will bind to post-synaptic NMDA receptors and allow for the influx of calcium into the cell. Weak depolarization of the membrane leads to a low amount of calcium entering the cell, which activates a separate class of enzymes call **protein phosphatases**, specifically **protein phosphatase 1** and **protein phosphatase 2**, that remove phosphate groups from target proteins. Further, LTD causes AMPA receptors to be internalized, or removed from the postsynaptic membrane. Removal of AMPA receptors will decrease excitability.

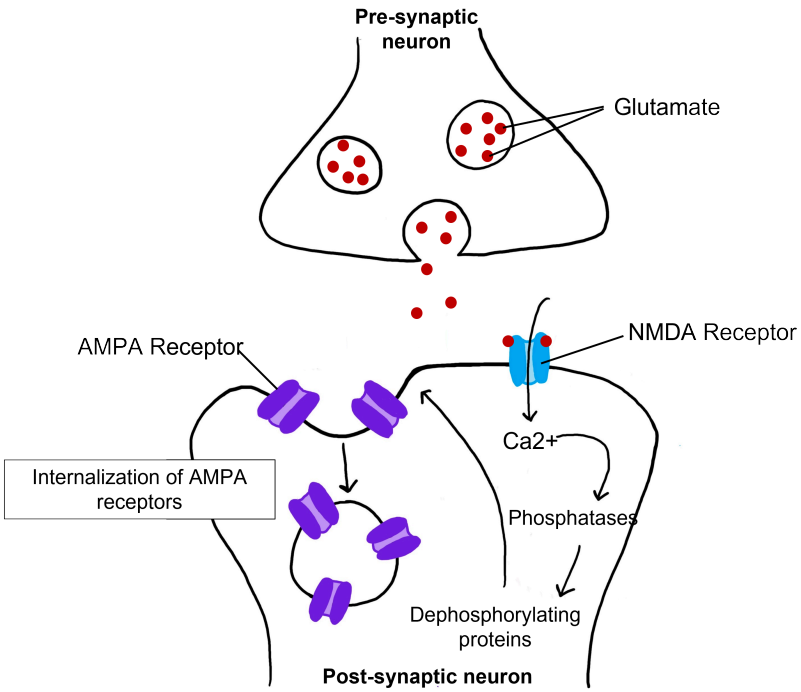


Figure 49.8. Calcium and LTD. Calcium enters the cells through NMDA receptors. When intracellular calcium levels are low, the calcium activates protein phosphatases within the cell. The protein phosphatases de-phosphorylate AMPA receptors expressed on the cell surface, decreasing their conductance of sodium. Further, phosphatases cause AMPA receptors to be internalized and removed from the cell surface, thereby decreasing the available receptors that glutamate can bind. 'Calcium and LTD' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Relating LTP to Learning

To test how LTP And LTD are directly related to memory, a robust model of learning is used called **Inhibitory Avoidance**. In an inhibitory avoidance task, a rat learns to associate an environment with an aversive experience. Typically, a two-chamber compartment is used with one light side and one dark side. The animal is permitted to move from the light chamber to the dark chamber, where it receives an electric foot shock. After just one trial with this protocol, the animal will learn to avoid the dark chamber where it received the foot shock.

One trial of inhibitory avoidance led to measurable LTP within the Schaffer collaterals, demonstrating that the behavioral learning corresponded to LTP during this task. Administration

of an NMDA receptor blocker to the hippocampus prior to inhibitory avoidance training results in the animals being unable to learn that the dark chamber leads to a foot shock and inhibition of the corresponding LTP.

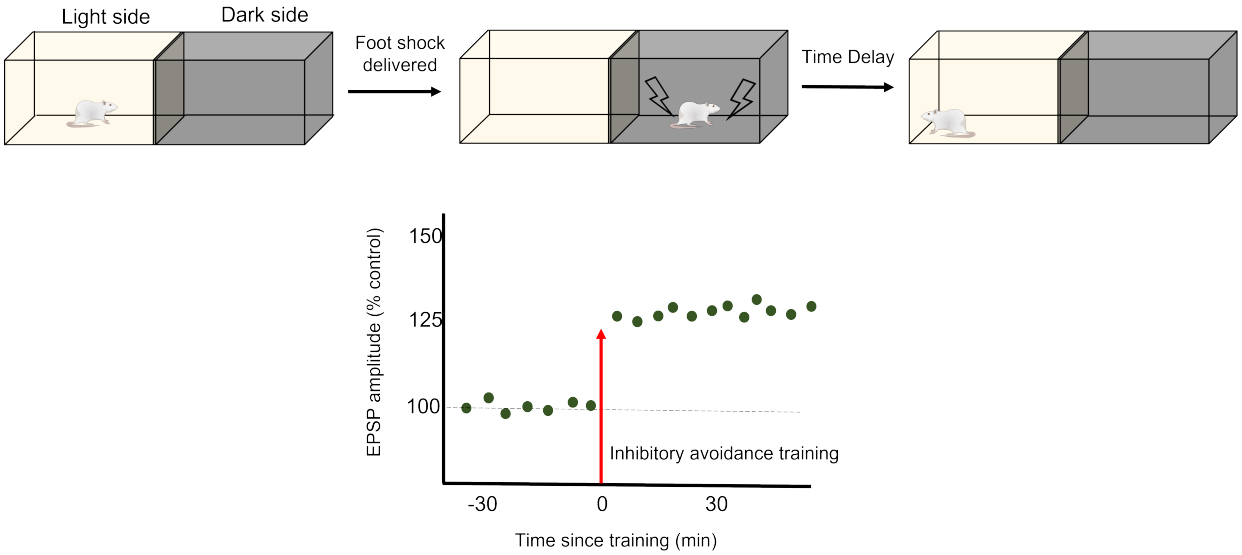


Figure 49.9. Inhibitory avoidance. In this task, rodents learn to associate an environment with an aversive experience, in this case a foot shock. In a two-chamber compartment, one side is light and one side is dark to distinguish the two compartments. When the animal is placed in the dark compartment it receives an electric foot shock. After just one trial with this protocol, the animal learns to avoid the dark chamber where it received the foot shock. One trial of inhibitory avoidance led to measurable LTP within the Schaffer collaterals, demonstrating that the behavioral learning corresponded to LTP during this task. 'Inhibitory avoidance' by Valerie Hedges is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Key Takeaways

- Plasticity in the form of LTP and LTD occurs at both inhibitory and excitatory

synapses.
- The hippocampus has a trisynaptic circuit of connections.
- Long-term potentiation (LTP) is a long-term strengthening of a synapse, whereas long-term depression (LTD) is a long-term weakening of a synapse.
- LTP is demonstrated by observing an increased EPSP amplitude following a tetanus.
- LTD is demonstrated by observing a decreased EPSP amplitude following low frequency stimulation.
- AMPA and NMDA glutamate receptors are important in LTP.
- High levels of intracellular calcium from high frequency stimulation activates protein kinases, which leads to increased conductance of AMPA receptors and insertion of AMPA receptors in the cell membrane.
- Low levels of intracellular calcium from low frequency stimulation activates protein phosphatases, which leads to decreased conductance of AMPA receptors and removal of AMPA receptors in the cell membrane.
- Inhibitory avoidance is a robust learning model in which animals only need one trial before learning occurs. It has been show to also induce LTP.

Attributions

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BIOELECTRICITY

Electricity fundamentals for BI360

Electricity is the movement of charged particles. That simple explanation applies to electricity in our daily lives, to currents that flow through wires in the wall, through devices in our hands, as well as cells in our body. The simplest charge carriers are subatomic particles, discovered toward the late 19th century. However, charge can also be carried by atoms, molecules, as well as biologically relevant macromolecules such as proteins and nucleic acids. In fact, animals and even humans can carry a charge in the form of static electricity, which is how we can shock each other, doorknobs, or other metal objects. In this chapter, we will try to understand what charge is, how subatomic particles carry charge and yet create neutrally charged atoms or elements, and finally, how charged particles can be created from neutral atoms or molecules.

Already know all about protons and electrons? Skip to '**What is Electricity**' section below!

Electrical charge

What is electrical charge? To answer that, we must travel to the golden age of physics, when the structure of matter was discovered. Physicists in the 19th century thought that matter was comprised of small particles, which couldn't be divided using the amounts of energy that was available at the time. These particles were said to be indivisible and were named ***atoms***. However, it quickly became apparent that atoms *were* in fact divisible, if enough energy was somehow applied, and two of the subatomic particles resulting from breaking up an atom carried a force that could either repel or attract. Particles of the same type repelled each other, while particles of two different types attracted each other. The property that these sub-atomic particles carried was named a '***charge***', and the two types of charge were named '*positive*' and '*negative*. It's really important to understand that the nouns 'positive' and 'negative' are only important in that they mean the two kinds of particles have opposing properties, but the 'positive' and 'negative' doesn't have an inherent physical implication: they could just as easily have been flipped around, called 'north' and 'south', or 'left' and 'right' and so on. The words positive and negative are just convention of usage, and can sometimes be confusing.

Subatomic particles that carried the positive charge were called *protons* and particles that carried a negative charge were called *electrons*. These charged particles could be separated separated by supplying enough power, for example, artificially in particle accelerators. Charged particles could were also created in nature: many radioactive materials, like uranium, were known to emit high energy charged particles without human intervention. Ernest Rutherford named the first two types of radioactive emissions as **α-rays**, which were positively charged, and **β-rays**, which were negatively charged. How the power in radioactive materials was harnessed by humans is the story of the Manhattan Project, and the subject of a recent movie (Oppenheimer). Scientists also found two other, interesting facts: the first is that the amount of charge on a proton is exactly equal but opposite to the charge on an electron! So when the number of electrons and protons is equal, as in most atoms in nature, these charges cancel out perfectly, resulting in a neutral substance. The other fact, shown in Fig E1, is that the mass of a proton is much, much more than that of an electron.

PARTICLE NAME	Proton	Neutron	Electron
CHARGE	1 Positive Charge	0 Charge (Neutral)	1 Negative Charge
Charge Representation	(+ ve)	(No Charge)	(– ve)
Mass (re Elect ron)	1836	2020	1

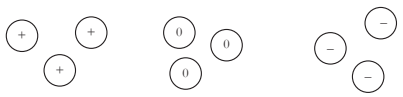


Figure E1 – Protons, Neutrons and Electrons: subatomic particles, their charges and mass.

How were these particles distributed in an atom? The popular model of the atom toward the end of the 19th century, called the **plum pudding model**, held that held that the two types of charged particles were mixed in equal proportions through the atom, sort of like plums and raisins in a pudding, as shown in Fig E1-A. Ernest Rutherford thought of an interesting experiment to test this idea: he fired high energy α-rays (positively charged) toward a thin film of gold, which is an extremely **malleable metal**. If the plum pudding model of an atom was correct, then electrons and protons would be mixed uniformly in an atom and the high energy positively charged particles in α-rays would pass right through the film of gold, since individual protons spread through the atom would not be able to repel the high energy α-particles. What did Rutherford actually find?

Rutherford found that the vast majority of α particles passed right through the gold film (Fig E2-B), as if most of the atom was empty! Some however were deflected off their path, and even fewer were reflected right back, indicating that somewhere in the atom, there was a concentrated region of positive charges. This result led to the Rutherford-Bohr model of the atom, in which all the positive charges are concentrated in a small volume of space he called the nucleus, while the rest of the atom is empty space (Fig E2-B). Where were the electrons? Orbiting the nucleus, somewhat like planets around the sun: remember, the mass of electrons is negligible compared to that of a proton. This model explained how most α particles passed through the film: an atom was in fact mostly empty space! Subsequent experiments have confirmed that all the protons and neutrons are concentrated in the small volume of the nucleus, while electrons orbit the nucleus at fixed distances, arranged in concentric spheres called 'orbitals'. Matter in general is neutrally charged, because for each atom, the number of protons is equal to the number of electrons. The simplest element, hydrogen, has one proton in its nucleus, and one orbiting electron. Adding protons and electrons to atoms leads to the

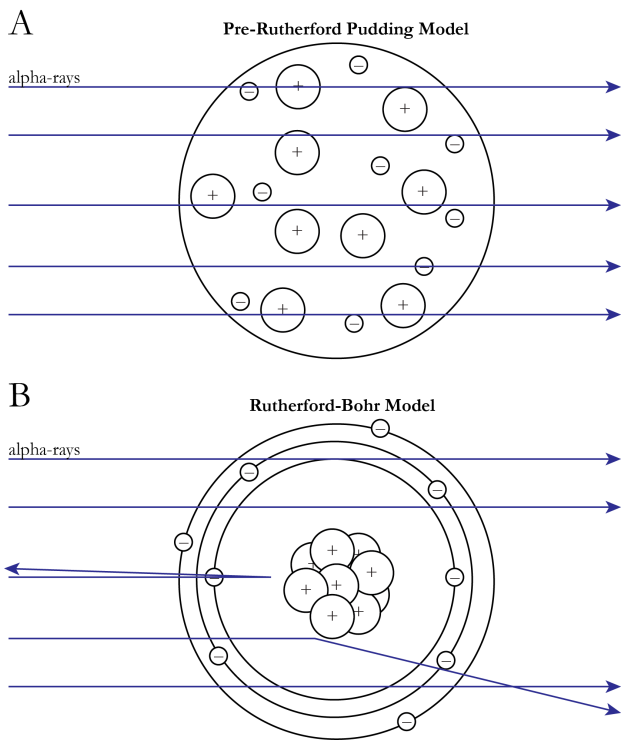


Figure E2 -The Rutherford experiment probing the structure of gold atoms. The prevailing model for atomic structure (A) would predict alpha particles go through the atom, where positive charges are distributed through the entire atom. Rutherford actually found that most alpha particles go straight through the atom, while a few are deflected or reflected, indicating the existence of a small volume where positive charges are concentrated. The resulting model of the atom, the Rutherford-Bohr model (B), has a nucleus where positive charges are concentrated, while electrons orbit around the nucleus at a large distance, such that most of the volume of the atom is empty space.

formation of new elements[1]; in all elements other than hydrogen, neutrons are also present in nuclei to ensure that the repulsion between protons doesn't rip the nucleus apart.

So: protons and electrons make up atoms (with neutrons), and in nature, elements have equal numbers of each. How do we go from neutral elements, with equal numbers of electrons and protons, to charged particles?

One way we discussed above was by splitting an atom, which released so much energy that the parts of the atom flew apart, yielding electrons as β-rays, and positively charged α-rays: alpha particles carry two positive charges, and are actually made up of two protons and two neutrons — in essence, they are helium atoms.

We can also create charged particles by **removing or adding electrons** to atoms, creating *ions*. Electrons that are furthest away from the nucleus are easiest to strip away from the atom. Metals like sodium and calcium are a good example of such elements, which become *positively charged* in water, by *losing one or more electrons*. Remember, to start with, the number of protons is equal to the number of electrons. When an atom loses an electron, it assumes an overall positive charge. Other elements form negatively charged ions. Is the negative charge a consequence of losing protons? Well, protons, since they are located in the center of the atom, are really difficult to remove – it's only in the immensely energetic nuclear reactions that protons can be removed from the nucleus. So how do we get negatively charge ions in everyday life? Some elements have the ability to *accept electrons* easily: these are said to be **electronegative**, and tend to form negatively charged ions in water – for example, chlorine. Keep in mind that losing or gaining an electron makes the ion charged, so removing an additional electron from a positively charge ion, or adding an electron to an already negative ion, is extremely energy intensive. We can also form ions from molecules: some molecules can more easily lose electrons, while others can more easily gain electrons.

Macromolecules like proteins can gain electrons in one part of their structure, and lose electrons in another part, forming negatively or positively charged domains.

So: atoms are made up of positively charged protons, and negatively charged electrons. Protons are all located at the center of the atom, and are thus really difficult to extract from an atom; electrons orbit

1. Adding subatomic particles (protons, neutrons or electrons) to atoms requires a tremendous amount of energy, and in nature, only happens in the center of stars via fusion. Every element other than hydrogen formed inside a star; so all the elements heavier than H, that make up a human like you (C, O, P, K, Na etc) were formed at the center of stars, then released into the cosmos when stars exploded. These elements in turn became parts of new stars, and fusion added more particles and created even heavier elements, and so on.

the nucleus at large distances, and thus are easier to extract from an atom. There are also a third kind of subatomic particle called neutrons, which carry no electrical charge, but lets not talk about them!

Charged particles

In the introduction above, we learned about two kinds of charged particles: **sub-atomic particles**, and **ions**. The fundamental charged particles are protons and electrons. We also learned that when in water, some atoms lose electrons to form positively *cat*ions, while others accept electrons to form negatively charged particles called *an*ions. Charge is represented by the symbol **Q**, is measured using the unit **Coulomb**: one Coulomb (1 C) of charge is created by the loss or gain of 6.25×10^{18} electrons. Or to put it differently, **1 C is equal to 6.25×10^{18} charged particles**, whether subatomic or not (Fig E.3).

Some particles can carry more than one unit of charge: alpha particles carry two positive charges. More complex ions can carry not just multiple charges of the same type, but also mixed charges – amino acids are the best example of a molecule that simultaneously carries at least a positive (amino) and a negative (acid) charge. Macromolecules like proteins and nucleic acids carry a lot of charge; overall, nucleic acids, which are huge molecules, carry negative charges, and are responsible for maintaining the charge balance across the cell membrane – we will discuss this in class, when we talk about membrane potential.

What is electricity?

Electricity is the movement of charged particles. Simple, right? Yes, and no!

In the modern world, electricity is part of our lives – electrical currents travel along metal wires, because metals, remember, have the ability to lose electrons easily. These loosely attached electrons whiz around wires, carrying current. That's why electrical cables are made of metals like copper, aluminum, and silver.

In biology, we deal with reactions involving substances dissolved in water – or as we scientists call it, aqueous solutions. Here, electricity is carried largely by ions. However there are special cases where the charges that carry electricity are subatomic particles: for example, the Electron Transport Chain in mitochondria of all living organisms involves the movement of – you guessed it right – electrons! Similarly the enormous amounts of ATP we use is generated by the movement of protons. Wait –

didn't we say that protons are really hard to extract from a nucleus? How then do we have trillions of them floating around in our bodies?

It turns out that of all the elements that can easily lose electrons – usually metals – there is a special case: hydrogen. Hydrogen is the simplest element with the simplest atom: one proton and one electron (Fig E4). That's it. So when hydrogen loses its only electron, only a proton remains!

Current, resistance, and voltage

Current

The collective movement of charged particles is called current. By convention, current moves in the direction of net movement of positive particles. In Figure E.5A, the movement of positive charges from left to right causes current to move from left to right. However, the movement of negative charges from left to right in Fig E.5B implies that by convention, current in fact moves from *right to left*! Current is measured using the unit Ampere: one **Ampere (1 A) is the movement of one Coulomb of charge** through any location. In household electrical wires, the charge carriers are electrons that separate easily from the outermost orbital of metals like copper. When an electrical appliance is required to do more work – for example, heat up food – more current is required, and more flows through electrical cables.

In the biological context, all reactions occur in an aqueous solution – here, the charge carriers are ions that are created when one atom donates electrons to another. Elements like oxygen and chlorine that can easily accept electrons are said to be *highly electronegative*. Elements like hydrogen, sodium, potassium and calcium, that easily donate electrons, are less electronegative. Dissolving NaCl in water immediately results in the creation of two sets of ions: Na cations, and Cl^- anions. These are free to move, for example. to respond to concentrations of positive or negative charges. When these ions move in water, electrical current flows.

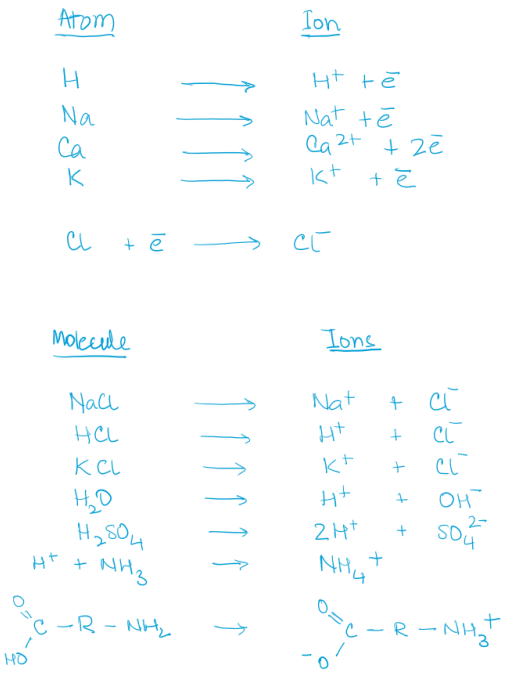


Figure E3. Formation of ions in water from (A) atoms or (B) molecules, via the loss of electrons or gain of electrons.

Voltage

What makes charges move? Or to put it differently, why does current flow? Voltage, or electrical potential, is the force that causes current to flow and is driven by a difference in charge at one location compared to another location. In biology, voltage is also referred to as the electromotive force (emf). Like gravity causes water to flow from higher to lower levels, voltage causes current to flow from a region of high potential to a region of low potential, and tends to balance out charge differences between the two locations. The SI unit for electrical potential is Volt; **one Volt (1 V) is the potential between two places, when one Joule of power is required to move 1 C of charge between the two locations**.



Figure E4. A battery stores electrical potential or voltage by separating positive and negative charges. Electrodes serve to conduct these charges through a circuit. (A) A simple circuit shown, powered by a AA battery. Such batteries typically have a potential of 1.5 V. When the switch is closed, charges will begin to move, and current will flow. As electrons travel from the negative electrode (cathode) to the positive electrode (anode), the charge difference is reduced, and the potential or voltage of the battery will decline. (B) The same circuit as in sub-figure A, but with the AA battery represented by a circuit symbol.

One can see electrical potential most easily in a battery: AA or AAA batteries have a positive end and a negative end, and if you read the description on a battery, you will see that they hold 1.5 V of electrical potential. This potential can be used for work if the two ends are connected. By adding batteries in series, we can create higher potentials (3 V, 4.5 V, 6 V etc.). A simple circuit showing a battery, a light bulb, and a switch are shown in Fig E4. A battery is depicted in FigE4 A, while the typical circuit representation of the battery is shown in FigE4 B. The battery has a positive pole or electrode called the anode, and a negative pole or electrode, called the cathode. By convention, as described above, the direction of current flow is from the positive to the negative pole of the battery (red arrow, Fig E4 B), but in reality, in metal wires, the charge carriers are electrons, which would of course flow in the opposite direction, from the cathode to the anode!

In a fully charged battery, positive charges are accumulated at the anode, and negative charge is accumulated at the cathode. Within the battery, a partition prevents charges from traveling directly to the opposite electrode, which is why we must connect the two electrodes using an external wire. Once we do that, and close the switch, charges will begin to move, causing current to flow. The current flows because the charge is different between the electrodes: this difference is called the electrical potential, or voltage! The bulb will then light up because current is flowing through it. If we keep the circuit running, what do you think will happen to the charge difference between the two electrodes? You can imagine that with every electron that reaches the anode, the two electrodes lose their charge difference. As electrons keep flowing, the battery loses potential, and the 'voltage' of the battery declines, until it has no potential left.

In biology, charge carriers are usually ions, created when atoms lose or gain electrons (Fig 3A), or when molecules lose or gain electrons (Fig 3B). Electrical potential is created in biology across semi-permeable membranes, by separating charges on one side of the membrane or another. For example, , in a neuron, there are more positive charges on the outside of the cell membrane compared to the inside. If free to move, positive charges form the outside would enter until the number of charges on

either side of the membrane were balanced. In this case, current would flow into the neuron. We will discuss this in Lecture 2, when we talk about membrane potential.

Resistance

Resistance is a measure of the difficulty with which charges can move. When charge move easily, the resistance is said to be low. When it is difficult for charges to move, the resistance is said to be high. A high resistance can occur due to various reasons: the conductive material may be reluctant to free up electrons, the material in which charges must move could be very viscous, or there may be physical barriers to the movement of particles that have very small channels, so that charges can only move through a few at a time rather than in a flood. Resistance is measured with the unit **Ohms (Ω). One Ohm (1 Ω) is the resistance between two points where 1 V of potential can move 1 A** of current between the two points.

In biology, resistance can change with changes in the size and number of pores in the membrane that allow ions to travel. If the pores are small, ions travel with difficulty, and the resistance will be high. However, if the size of the pore is increased, ions will flow more easily, and the resistance will be lower. Resistance also changes with the number of passages that allow ion movement, and with other factors like the viscosity of the fluid.

Conductance

Conductance is simply the inverse of resistance. Initially, even the units were inverted: the unit of conductance was called the Mho, represented by an upside-down sigma. However, these days, the SI unit of conductance is called the **Siemen (g), which in magnitude is still the inverse of 1 Ohm**. Conductance can be a more convenient when one is describing the ease of movement of ions, rather than resistance; when we talk about the difficulty of ions moving across membranes, we measure resistance; but when we talk about the ability of ion channels or pores to allow ions through, we often measure their conductance.

Equations Regarding Current

- $I = Q / t$ (where I = current; Q = charge; t = time)

- V = E / Q (where V = voltage; E = energy; Q = charge)
- R = V / I (where R = resistance; V = voltage; I = current)
    - Can also be expressed as:
        - V = I*R
        - I = V / R
        - I = V x g (since conductance is the inverse of resistance)

GENETICS

We have seen how neurotransmitter action can alter gene transcription and translation through binding to G-protein coupled receptors. The effectiveness of the signaling cascade on new protein synthesis does depend on some DNA-specific factors. This chapter will briefly cover how genes are transcribed and then how non-sequence, molecular changes to DNA can affect transcription rates.

Resources

- Key Takeaways
- Test Yourself
- Video Lecture

Central Dogma

DNA to RNA to protein. The central dogma of genetics. It may look simple, but many complex steps must occur for the process to be successful.

DNA

Doubled-stranded DNA (deoxyribonucleic acid) is comprised of four nucleotide bases: adenosine (A), thymine (T), guanine (G), and cytosine (C). Adenosine and thymine form base pairs whereas guanine and cytosine form pairs. The pairs cause the two strands to coil around each other and form a double helix.

RNA

The single-stranded messenger RNA (ribonucleic acid) is created from the DNA sequence via complementary base pairing. Like DNA, there are four bases, but in RNA the thymine base is replaced by uracil (U). Messenger RNA (mRNA) leaves the nucleus and interacts with ribosomes to

synthesize proteins in a process called translation. The ribosomes pair amino acids to specific three-base sequences called codons. For example, the codon sequence AUG is the start codon and it codes for methionine. The ribosomes will move down the mRNA to find the start codon of the protein and begin translation there, adding a new amino acid for each codon until a stop codon is reached.

Protein

Proteins are synthesized by the linking of amino acids together by the ribosomes. There are 20 amino acids that are each encoded by one or more mRNA codon sequences.

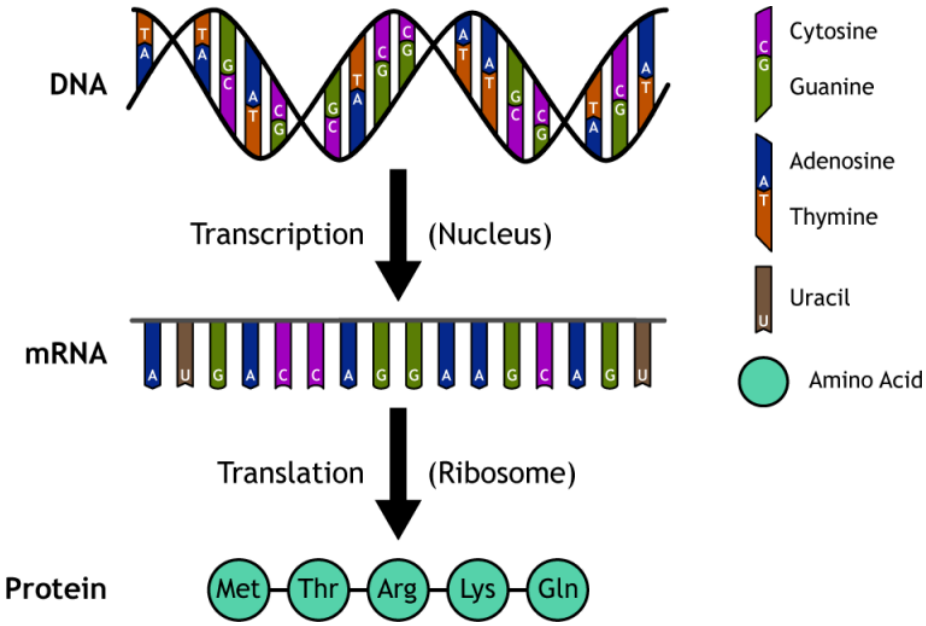


Figure G1. The central dogma of genetics. DNA is transcribed into RNA, which is translated into protein. DNA is composed of the nucleotides cytosine, guanine, adenosine, and thymine. RNA is composed of the nucleotides cytosine, guanine, adenosine, and uracil. Protein is composed of amino acids. 'Central Dogma' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Gene Transcription

In the nucleus, proteins called transcription factors and an RNA polymerase attach to the DNA. The

DNA unwinds, the proteins bind, and an mRNA strand is synthesized using the DNA as a template. The mRNA is a complementary sequence to the DNA strand being transcribed.

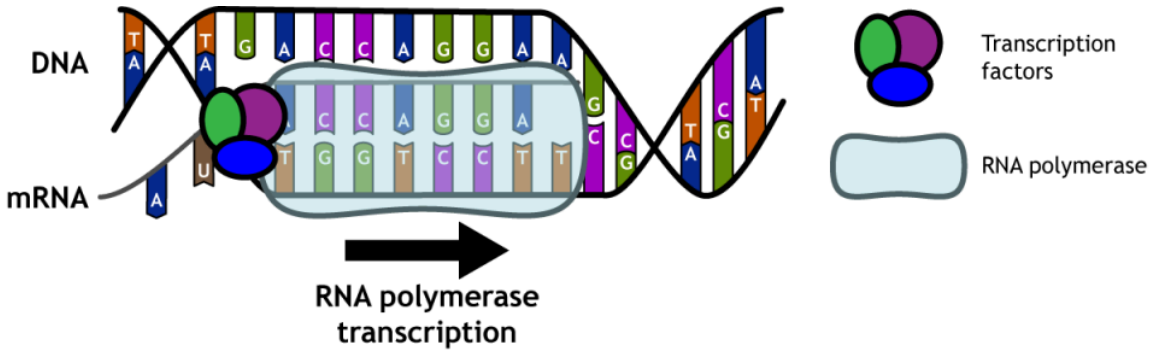


Figure G2. The double helix of the DNA unwinds, and proteins including transcription factors and RNA polymerase bind. The mRNA strand is synthesized by the proteins that use the DNA as a template for the nucleotide sequence. 'Transcription' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

DNA must be unwound from its condensed form to allow for gene transcription

---

DNA Packaging

DNA is not always accessible to those transcription proteins, though. There is so much DNA in each cell, that in order to save space, it is highly condensed in the nucleus. The double helix is wrapped around proteins called histones. The histones are then wrapped into nucleosome strands. The nucleosomes are compacted into denser structures called chromatin. Finally, the chromatin is condensed more and creates chromosomes.

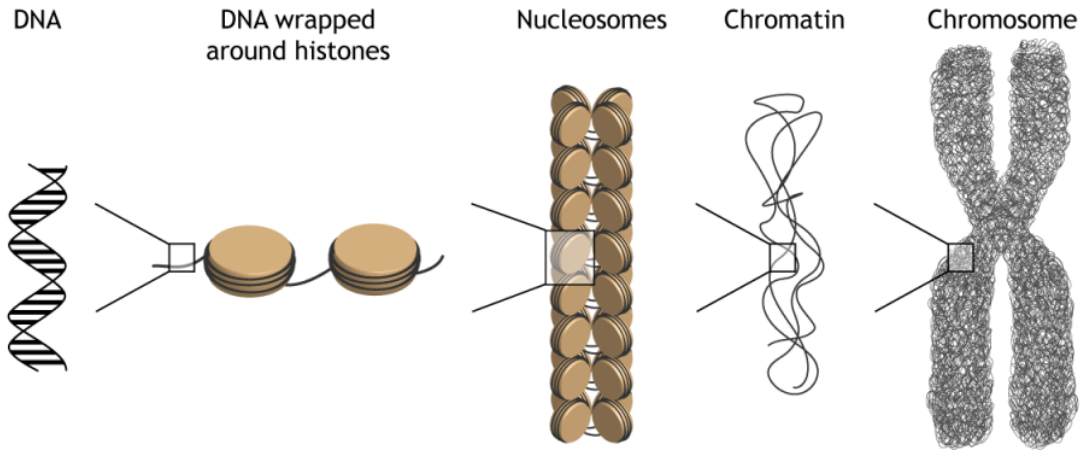


Figure G3. DNA is highly condensed within the cell. DNA is wrapped around histone proteins in a structure called nucleosomes. The nucleosomes are compacted into chromatin which is further compacted into chromosomes. 'DNA Packaging' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

In order for gene transcription to occur, the strands of DNA must uncoil from the histone bodies to become accessible to the transcriptional machinery.

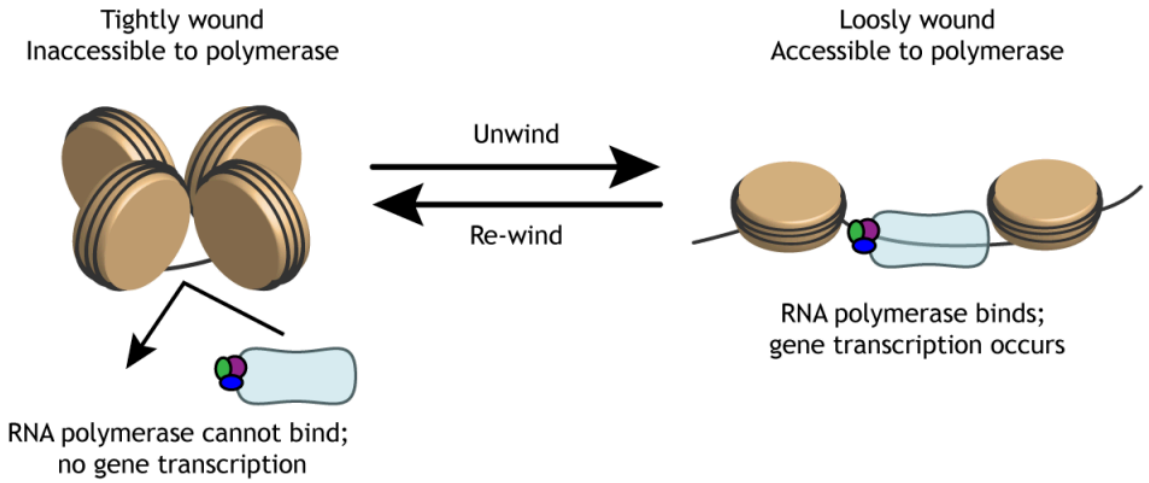


Figure G4. When the DNA is wound tightly around histones, the strands are inaccessible to the polymerase proteins and transcription factors. Since these proteins cannot bind, no gene transcription can occur. If the histones unwind, the DNA then becomes accessible to the transcription proteins. RNA polymerase can bind, and gene transcription can take place. 'RNA Polymerase Binding' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Molecular modifications to the DNA (the epigenome) can alter the ability for gene transcription

Epigenetics

Molecules such as methyl groups can be attached to DNA or on the histones. These epigenetic tags can affect how tightly the DNA is wound around the histones. Since gene expression can be altered by modifying how easily the histones unwind and how accessible DNA strands are, epigenetic tags are able to have an indirect effect on gene transcription.

Methyl groups make it more difficult for the polymerase to access the DNA by keeping the DNA coiled around the histones, reducing transcription. When the methyl groups are removed, called demethylation (not to be confused with dimethylation, the addition of two methyl groups), gene expression can increase because the DNA uncoils and is accessible to the transcriptional machinery.

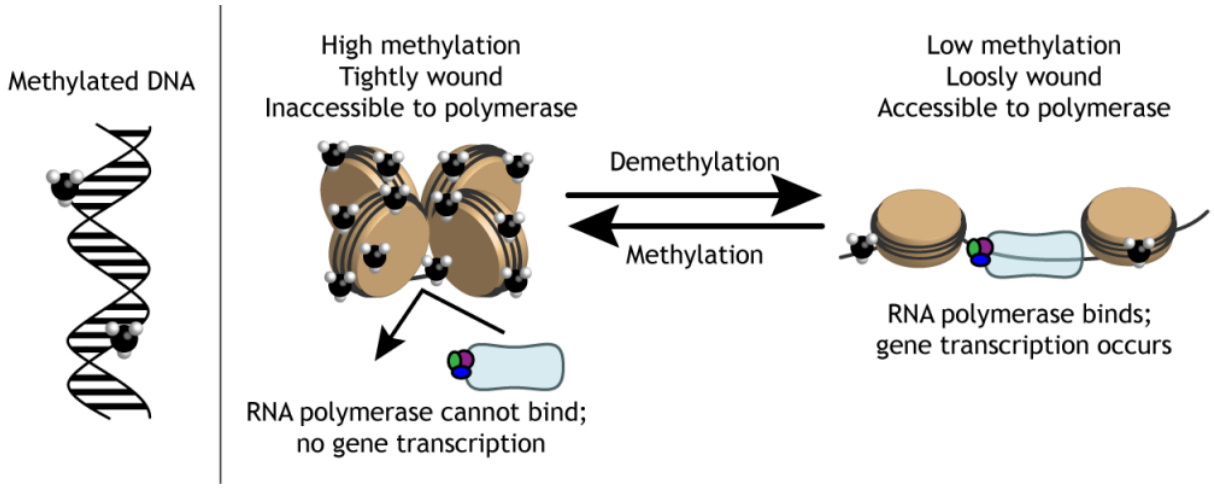


Figure G5. Methyl groups attached to DNA affect how accessible genes are to transcription proteins. Highly methylated DNA stays tightly wound around histones, preventing RNA polymerase binding and gene transcription. Low methylation loosens the coils and make the DNA accessible to RNA polymerase, allowing gene transcription. 'DNA methylation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Epigenome is Flexible

An individual's DNA sequence is fixed (excluding mutations that occur due to damage or errors in cell replication), but the epigenome is flexible and can change throughout life. An individual's life experiences, especially during development or other critical periods, are able to alter the epigenome.

Some experiences will increase methylation, sometimes for only certain genes, sometimes genome-wide, whereas other experiences will decrease it. For example, early life stress can increase the amount of methylation found on the gene that encodes for the receptor that is activated by stress hormones. Increased methylation leads to reduced transcription which has downstream effects on the negative feedback loop on the stress response. Scientists are starting to realize how important the epigenome is in regulating our brain and behavior.

Inherited Epigenome

Additionally, epigenetic modifications are heritable. Recent research is starting to show that experiences of mothers, fathers, and even grandparents can have transgenerational effects. And these effects, once thought only to be inherited from the maternal side, have now been shown to be paternally inherited as well. This means an animal that had early life stress may have increased methylation and changes in gene transcription that is then passed down for generations even if the offspring do not experience the same stressors.

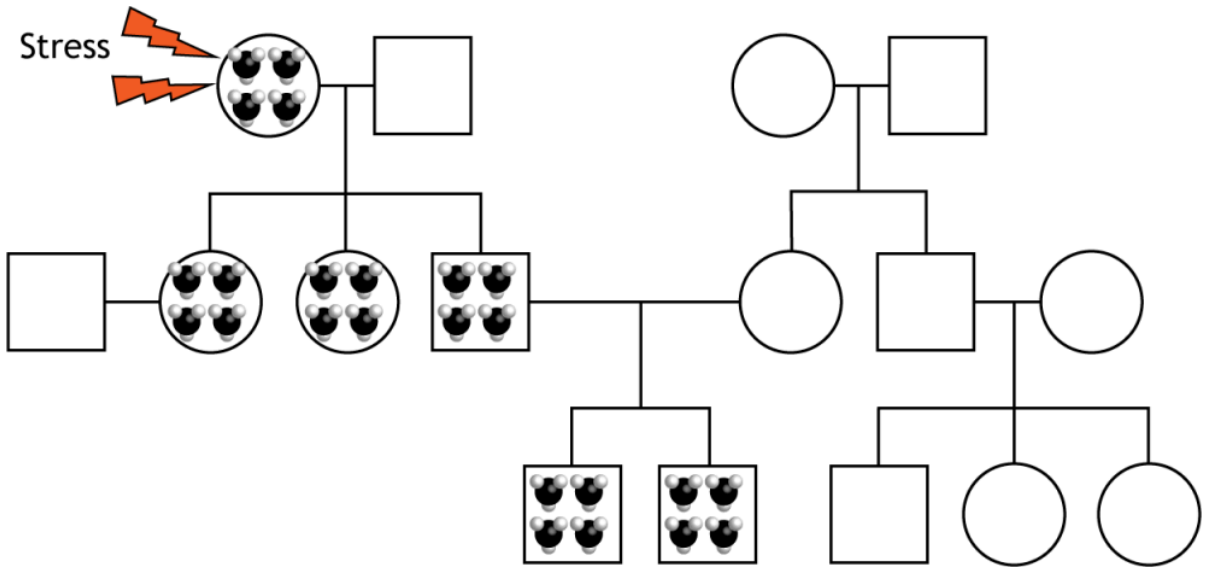


Figure G6. Epigenetic factors can be inherited. Stress experienced by a grandparent can increase DNA methylation and that effect can be found in first- and second-generation offspring. 'Transgenerational Methylation Effects' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- DNA is highly condensed in the nucleus
- The DNA must unwind for transcription to take place
- Epigenetic modifications can alter how easily the DNA can unwind
- Epigenetic modifications can be inherited

Test Yourself!

An interactive H5P element has been excluded from this version of the text. You can view it online here:
https://opentext.uoregon.edu/neurobiology/?p=1675#h5p-17

Video Lecture

One or more interactive elements has been excluded from this version of the text. You can view them online here: https://opentext.uoregon.edu/neurobiology/?p=1675#oembed-1

Attributions

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IMAGES OF ANIMATIONS

Chapter 1

Animation 1

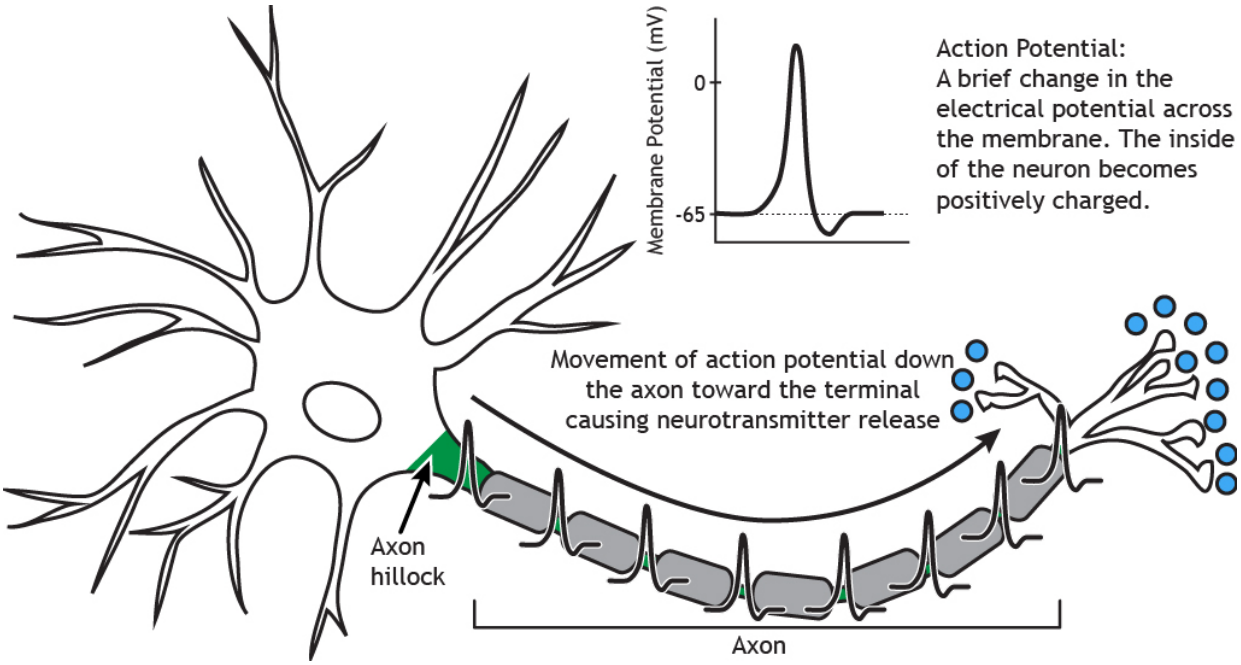


Figure 1.11. The action potential is a brief but significant change in electrical potential across the membrane. The membrane potential will move from a negative, resting membrane potential, shown here as -65 mV, and will rapidly become positive and then rapidly return to rest during an action potential. The action potential moves down the axon beginning at the axon hillock. When it reaches the synaptic terminal, it causes the release of chemical neurotransmitter. 'Action Potential Propagation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Chapter 2

Animation 1

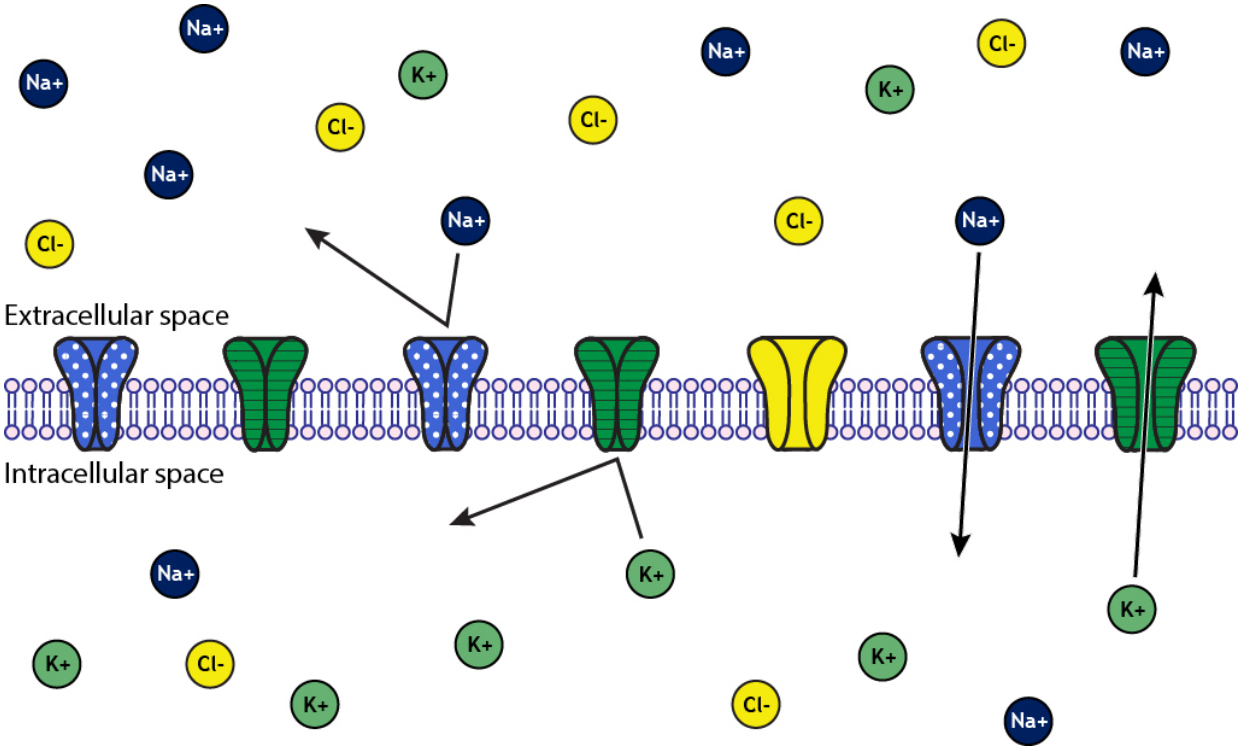


Figure 2.3. When ion channels in the membrane are closed, ions cannot move into or out of the neuron. Ions can only cross the cell membrane when the appropriate channel is open. For example, only sodium can pass through open sodium channels. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. 'Ion Movement' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial (CC-BY-NC) 4.0 International License.

Animation 2

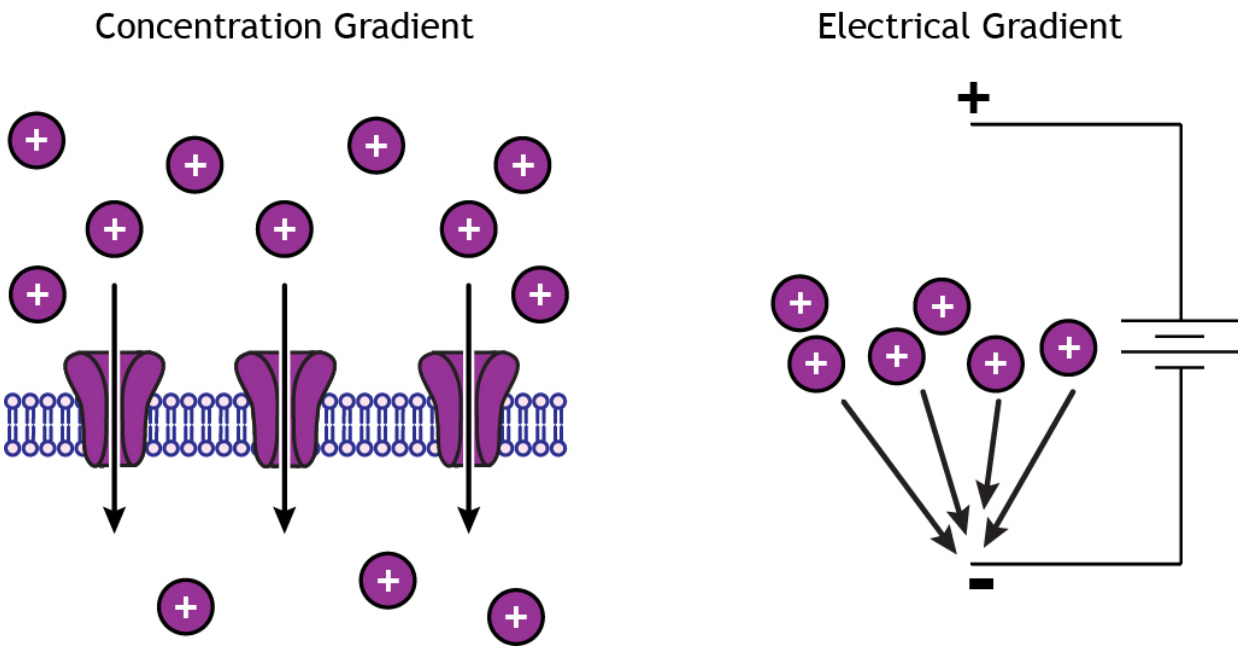


Figure 2.4. Concentration and electrical gradients drive ion movement. Ions diffuse down concentration gradients from regions of high concentration to regions of low concentration. Ions also move toward regions of opposite electrical charge. 'Gradients' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial (CC-BY-NC) 4.0 International License.

Animation 3

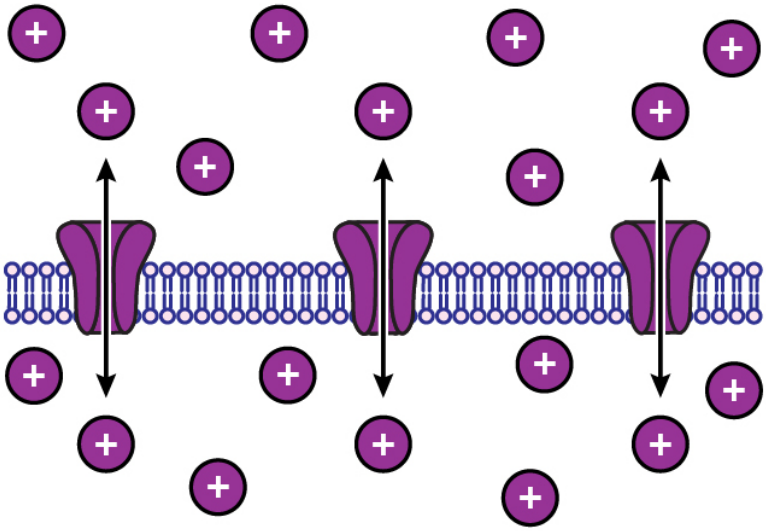


Figure 2.5. When an ion is at equilibrium, which occurs when the concentration and electrical gradients acting on the ion balance, there is no net movement of the ion. The ions continue to move across the membrane through open channels, but the ion flow into and out of the cell is equal . In this animation, the membrane starts and ends with seven positive ions on each side even though the ions move through the open channels. 'Ion Equilibrium' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial (CC-BY-NC) 4.0 International License.

Chapter 3

Animation 1

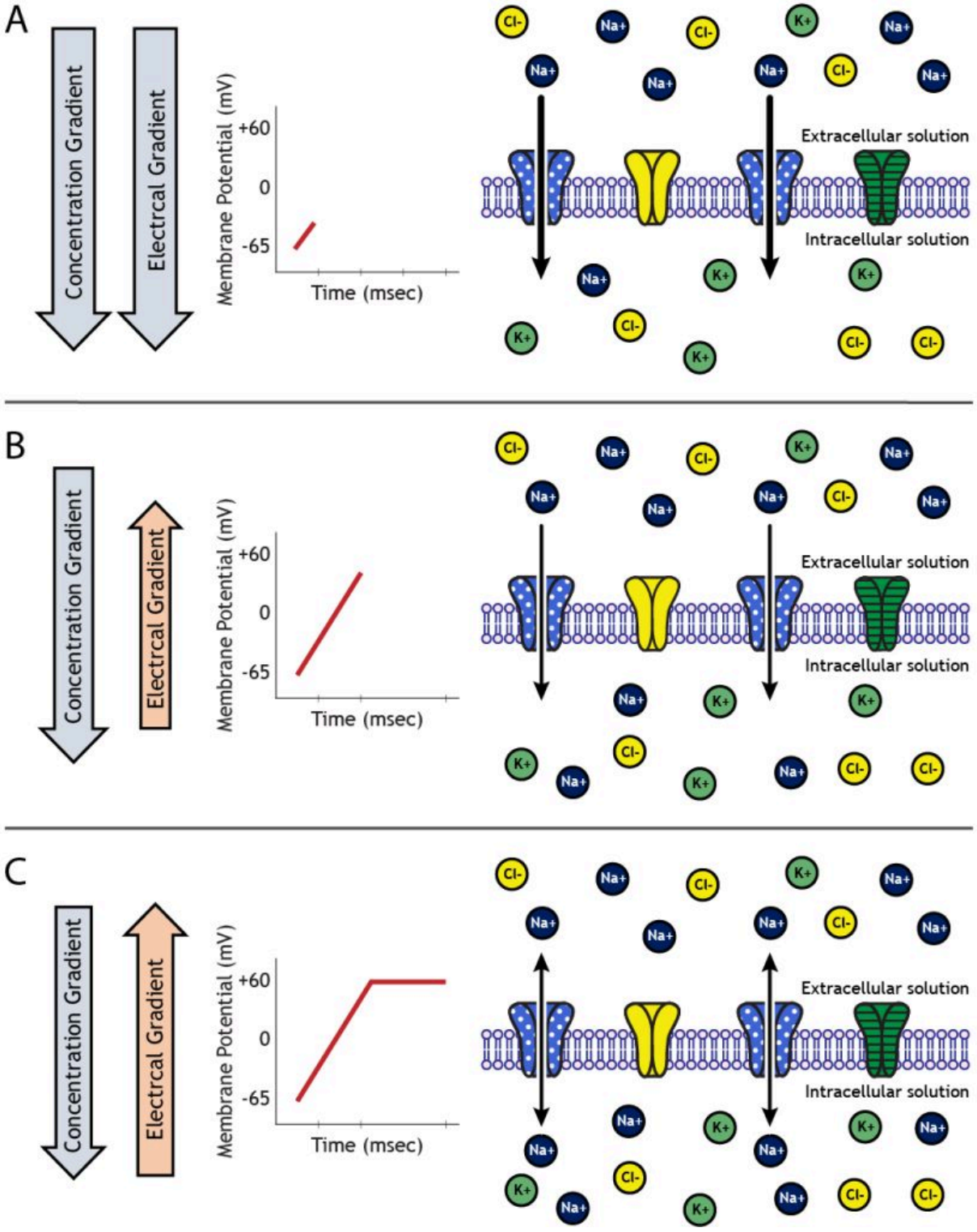


Figure 3.7. A) At rest, both the concentration and electrical gradients for sodium point into the cell.

As a result, sodium flows in. As sodium enters, the membrane potential of the cell decreases and becomes more positive. B) As the membrane potential changes, the electrical gradient decreases in strength, and after the membrane potential passes 0 mV, the electrical gradient will point outward, since the inside of the cell is more positively charged than the outside. C) The ions will continue to flow into the cell until equilibrium is reached. An ion will be at equilibrium when its concentration and electrical gradients are equal in strength and opposite in direction. The membrane potential of the neuron at which this occurs is the equilibrium potential for that ion. Sodium's equilibrium potential is approximately +60 mV. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels.' Sodium Gradients' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Chapter 4

Animation 1

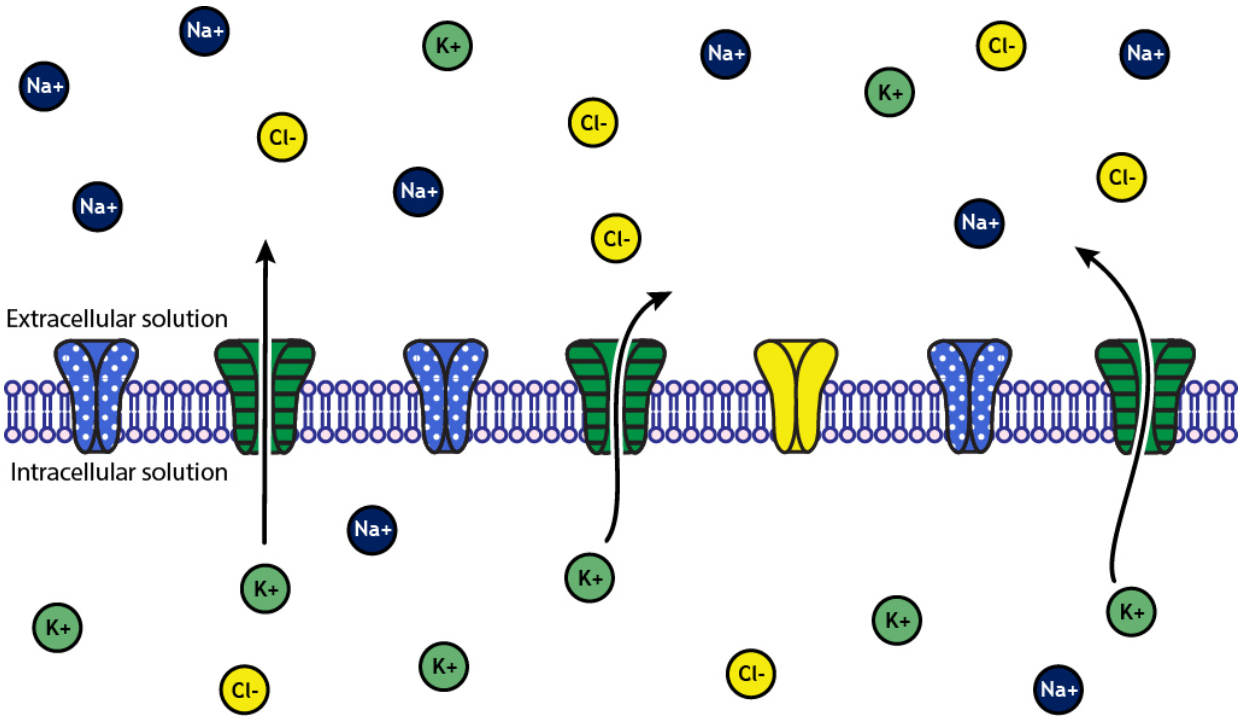


Figure 4.3. Electrochemical gradients drive potassium out of the cell, removing positive charge, making the cell's membrane potential more negative, in the direction of potassium's equilibrium potential. The dotted, blue channels represent sodium leak channels; the striped, green channels represent potassium leak channels; the solid yellow channels represent chloride leak channels. 'Potassium at Rest' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 2

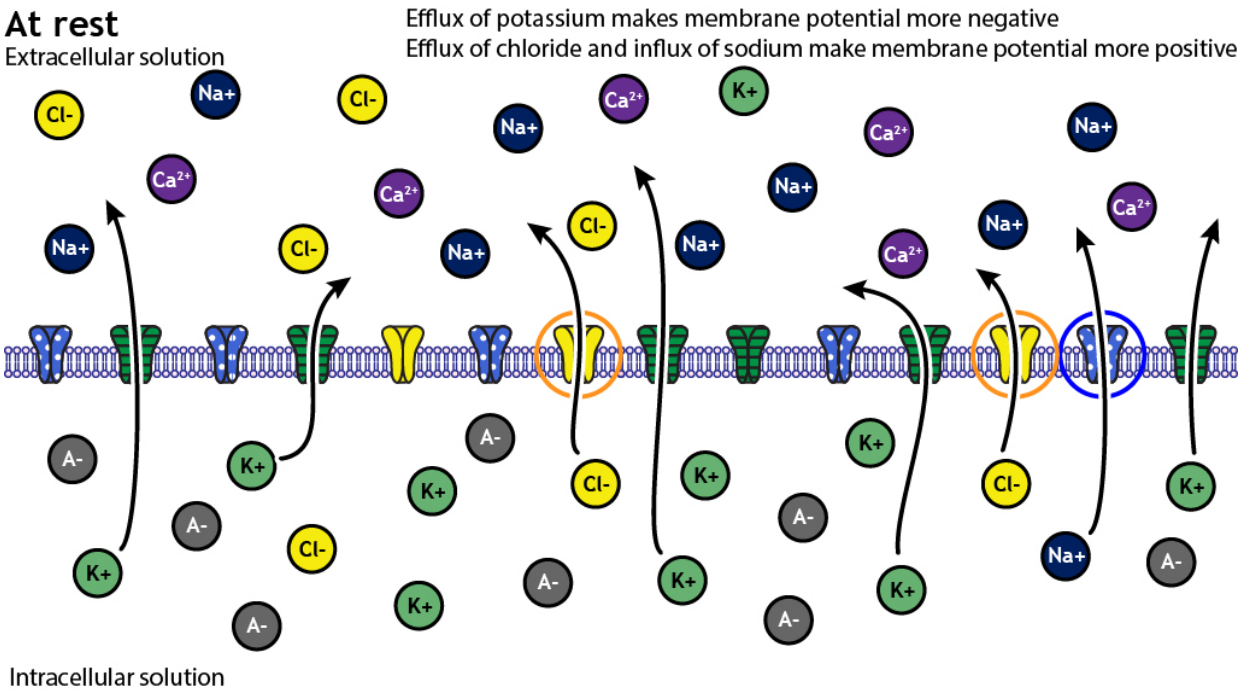


Figure 4.4. The membrane is most permeable to potassium at rest, and this leads to potassium efflux. However, the membrane is also permeable to chloride and sodium, and the flow of these ions keep the resting membrane potential more positive than potassium's equilibrium potential. The dotted, blue channels represent sodium leak channels; the striped, green channels represent potassium leak channels; the solid yellow channels represent chloride leak channels. 'Ion Flow at Rest' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 3

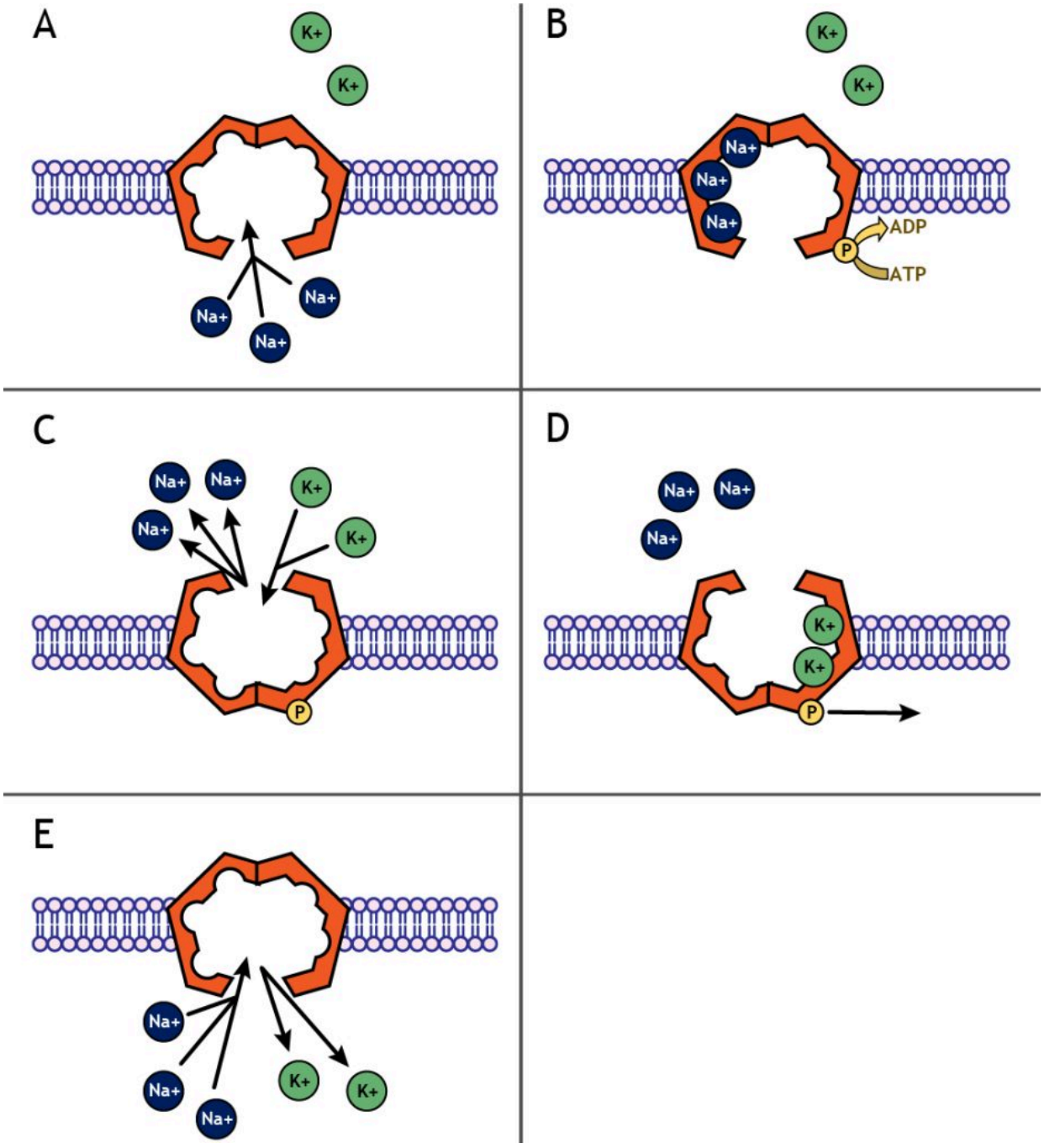


Figure 4.5. The sodium-potassium pump is embedded in the cell membrane and uses ATP to move sodium out of the cell and potassium into the cell, maintaining the electrochemical gradients necessary for proper neuron functioning. A) Three intracellular sodium ions enter the pump. B) ATP is converted to ADP, which leads to a conformational change of the protein, closing the intracellular side and opening the extracellular side. C) The sodium ions leave the pump while two extracellular potassium ions enter. D) The attached phosphate molecule then leaves, causing the pump to again

open toward the inside of the neuron. E) The potassium ions leave, and the cycle begins again. ‘Sodium-Potassium Pump’ by by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Chapter 5

Animation 1

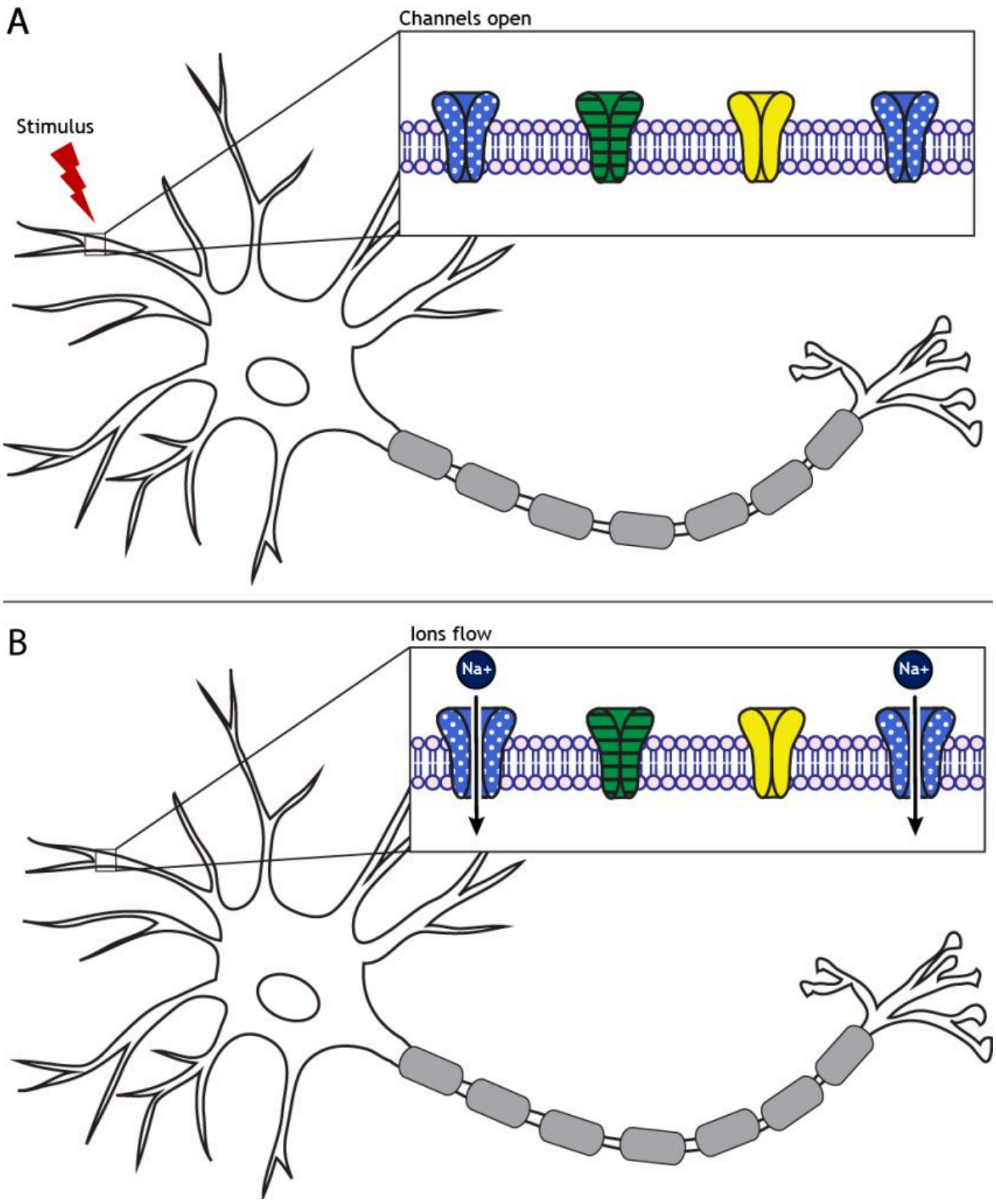


Figure 5.3. Top panel: A stimulus can cause ion channels in the membrane of the cell body or dendrites to open. Bottom panel: The open ion channels allow ion flow across the membrane. The

dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. 'Postsynaptic Ion Flow' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 2

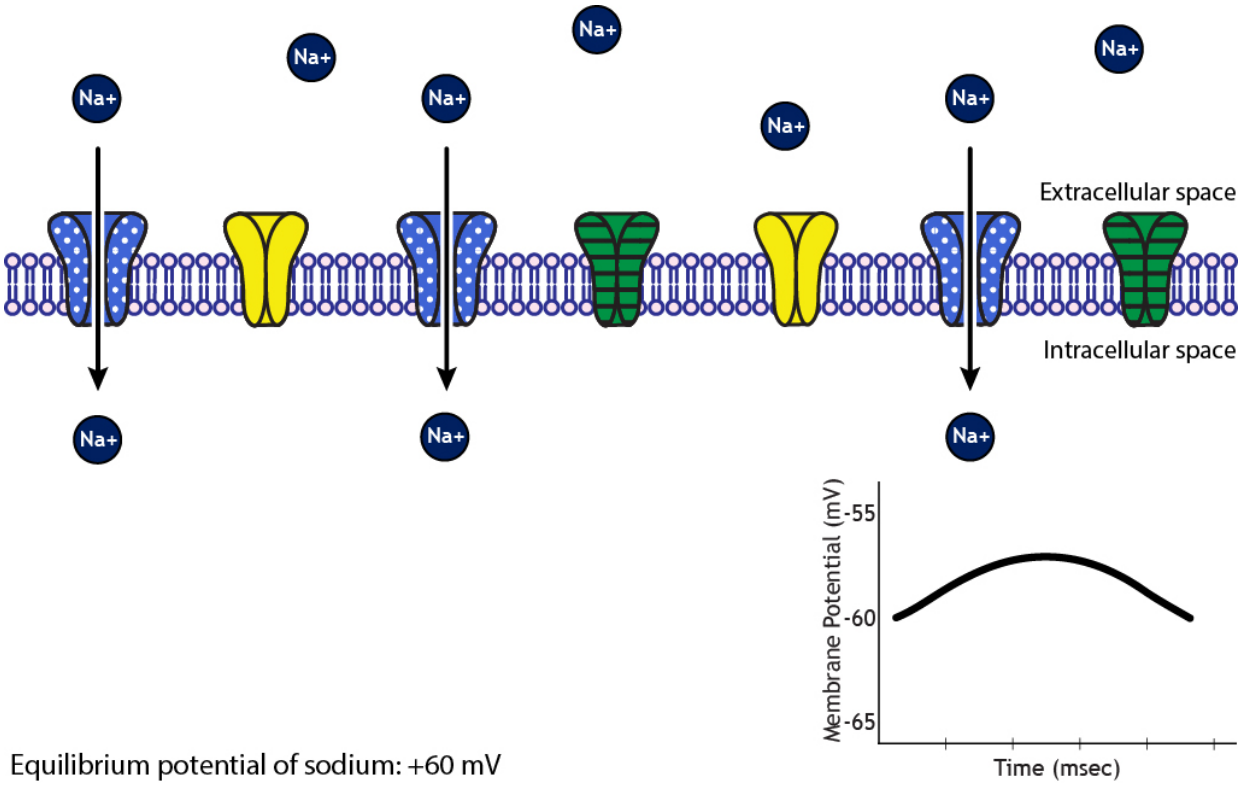


Figure 5.4. When a stimulus opens sodium channels, sodium rushes into the cell because the equilibrium potential of sodium is +60 mV. This causes an excitatory depolarization called an excitatory postsynaptic potential (EPSP). After the stimulus, the ion channels close, and the membrane potential returns to rest. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. 'EPSP' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 3

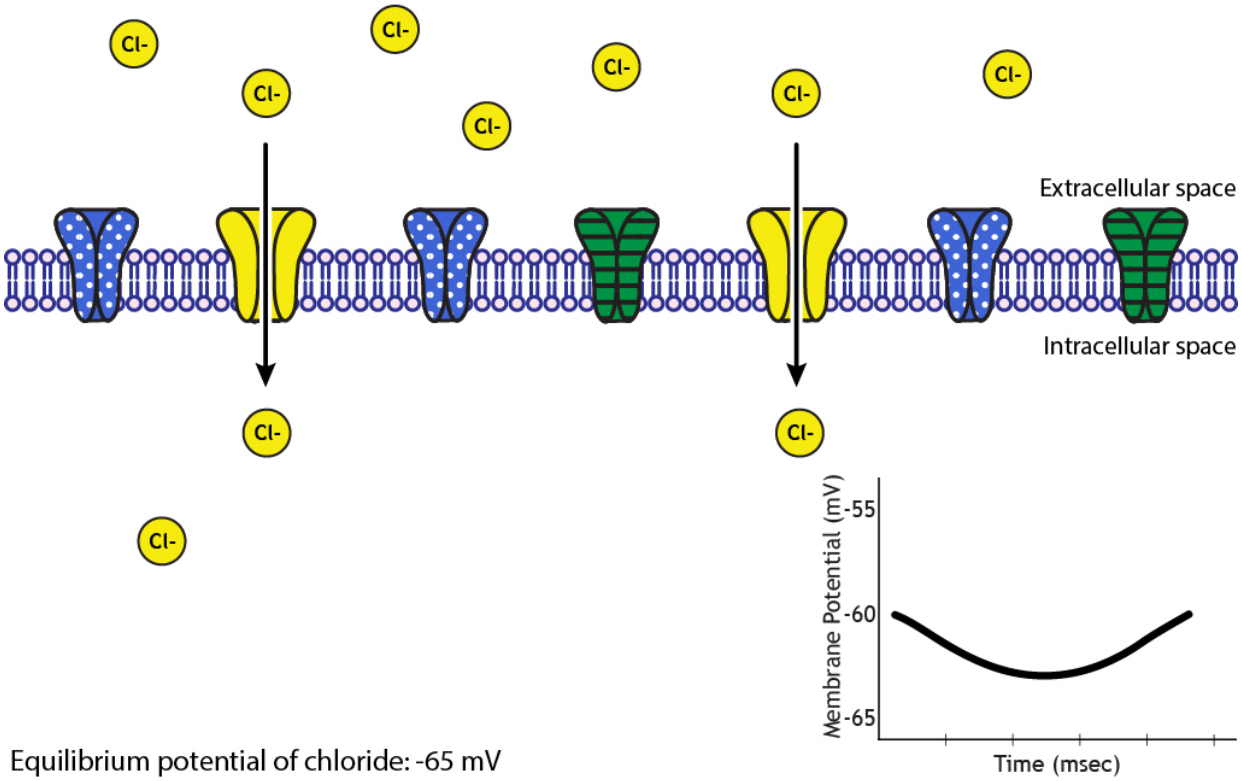


Figure 5.5. When a stimulus opens chloride channels, and the resting membrane potential is more positive than chloride's equilibrium potential of -65 mV, chloride rushes into the cell. This causes an inhibitory hyperpolarization called an inhibitory postsynaptic potential (IPSP). After the stimulus, the ion channels close, and the membrane potential returns to rest. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. 'IPSP' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 4

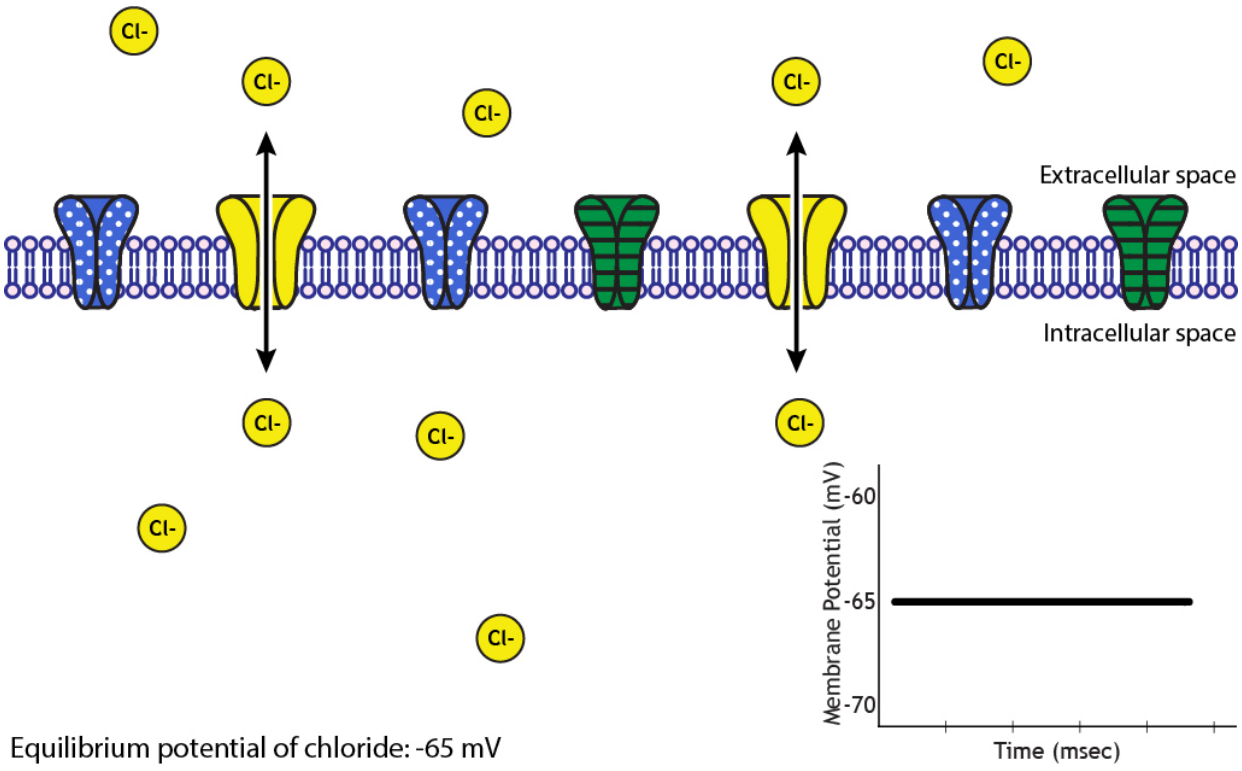


Figure 5.6. If the cell is at rest at chloride's equilibrium potential, when a stimulus opens the chloride channels, there will be no net movement of chloride in either direction because chloride will be at equilibrium. Since there is no net movement, there will also be no change in membrane potential because there is an equal amount of ion flow into and out of the cell. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. 'IPSP at Equilibrium' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 5

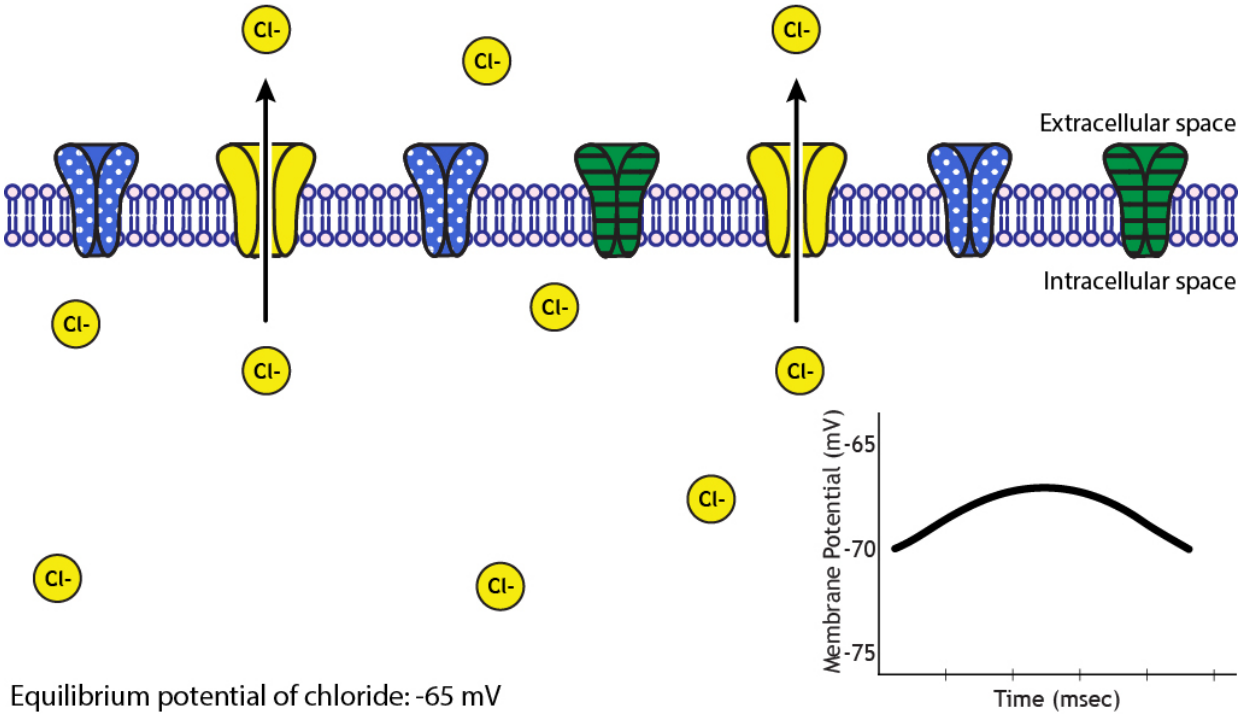


Figure 5.7. If the cell is at rest at chloride's equilibrium potential, when a stimulus opens the chloride channels, chloride will leave the cell, removing its negative charge. This causes a depolarization in the membrane potential, but it is still inhibitory since chloride movement will try to keep the cell near -65 mV. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels.'Inhibitory Depolarization' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 6

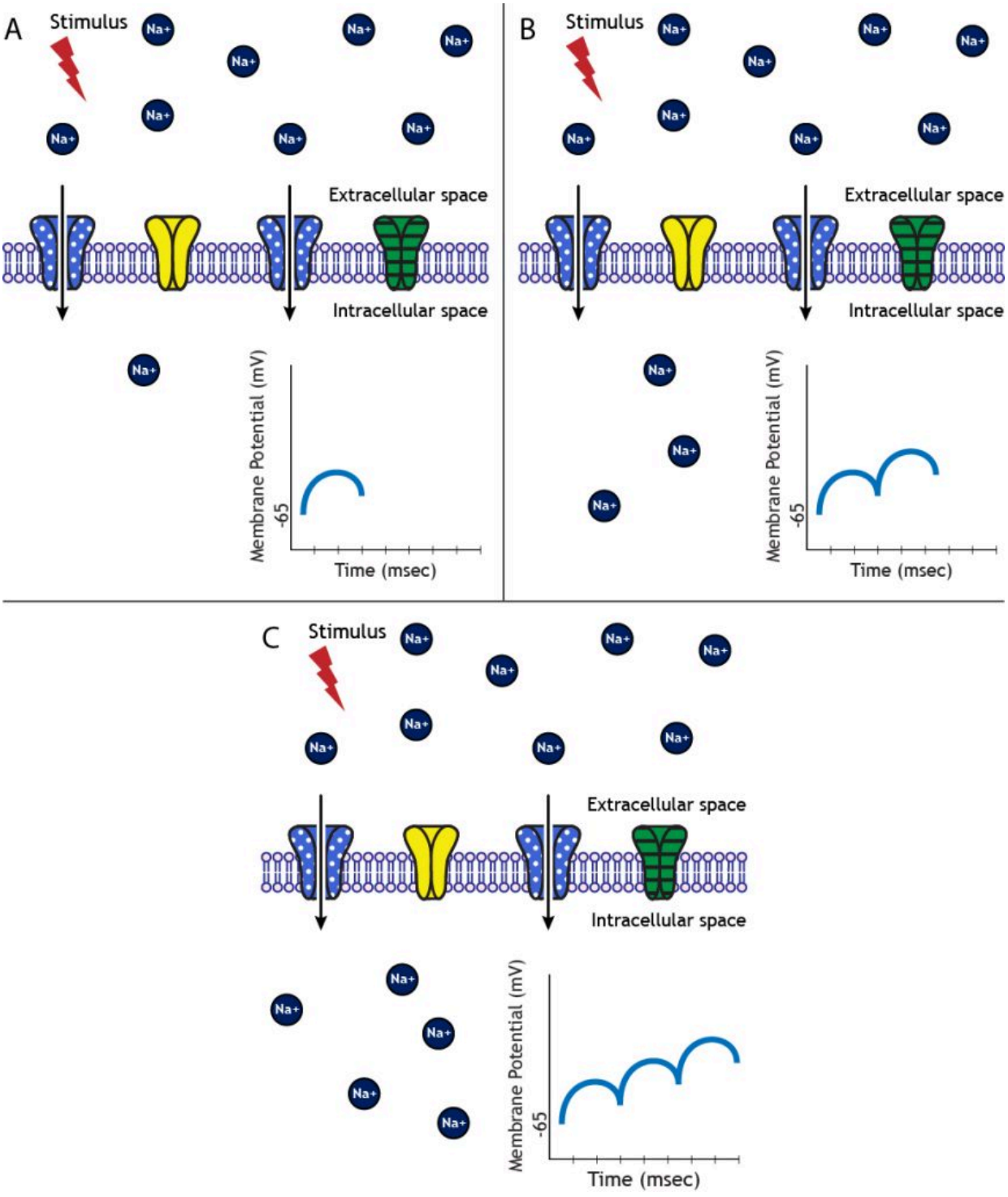


Figure 5.8. Excitatory stimuli that occur quickly in succession lead to summation of EPSPs. This leads to increased depolarization of the membrane potential compared to a single EPSP. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the

solid yellow channels represent chloride channels. 'Summated EPSPs' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 7

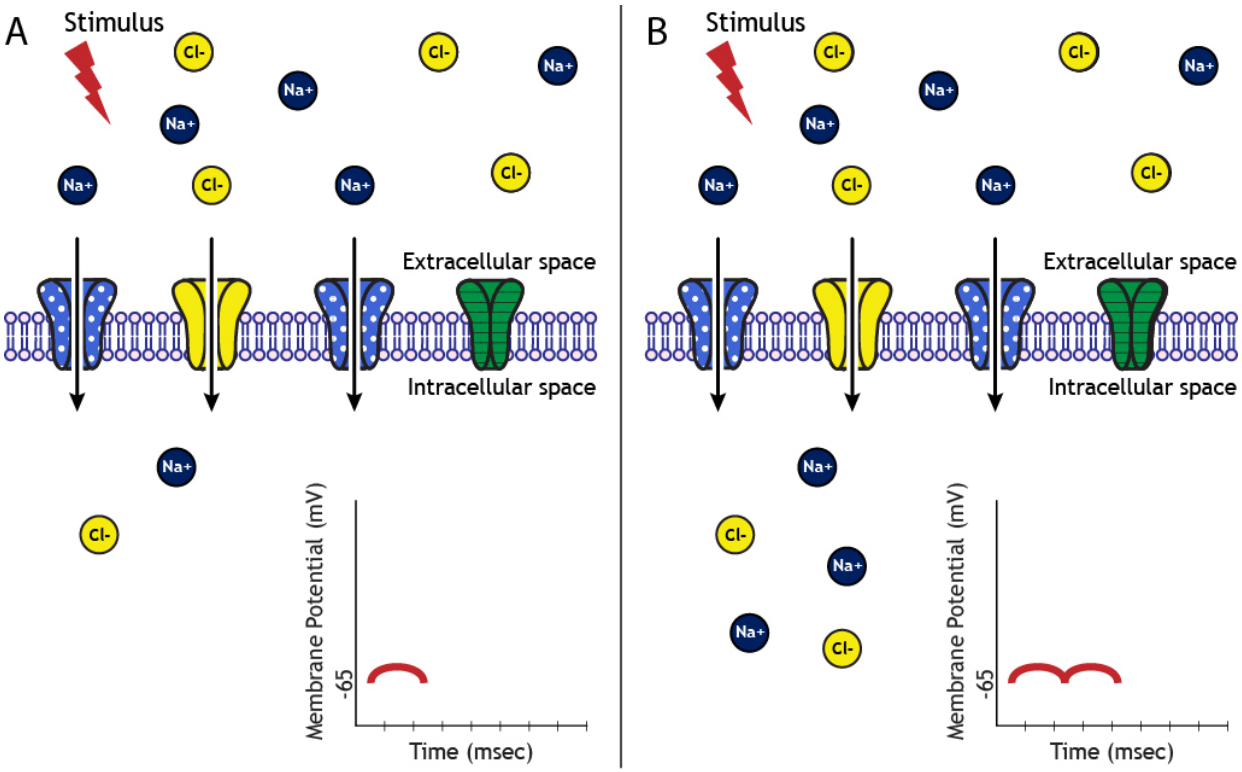
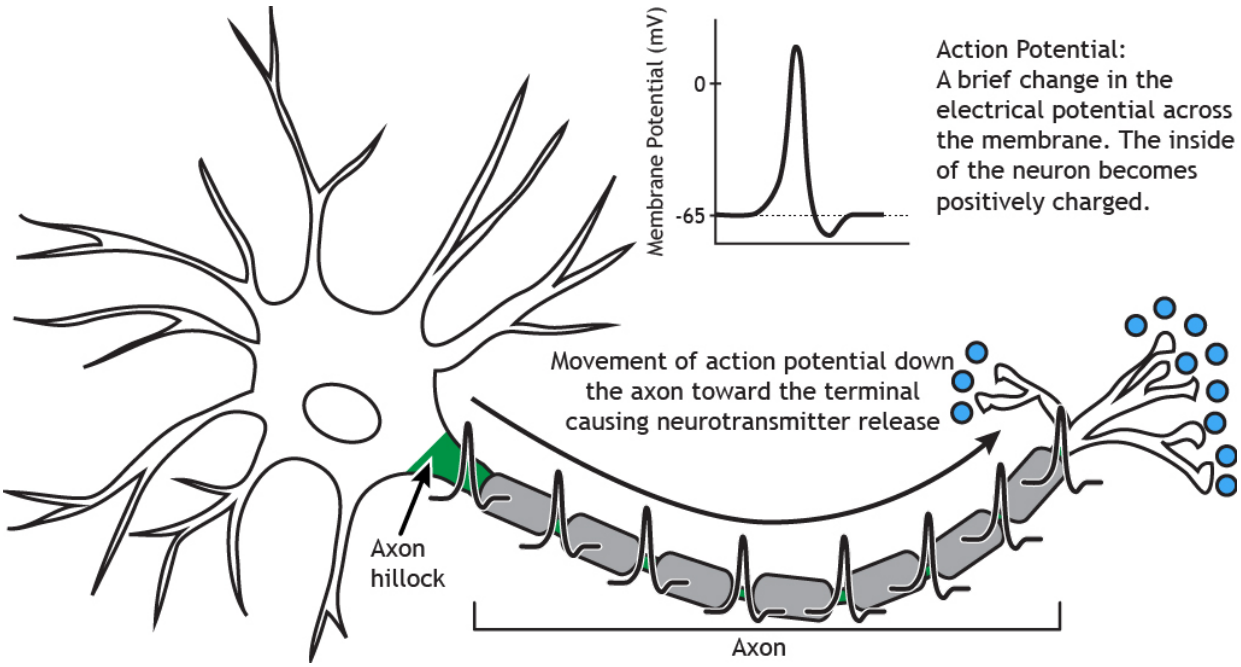


Figure 5.9. When an inhibitory input and an excitatory input stimulate a postsynaptic neuron at the same time, chloride and sodium channels open. Due to the equilibrium potentials of the two ions, both will flow into the cell. Sodium tries to depolarize the cell, whereas chloride tries to keep the cell near rest. The dotted, blue channels represent sodium channels; the striped, green channels represent potassium channels; the solid yellow channels represent chloride channels. 'EPSP and IPSP Ion Flow' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Chapter 6

Animation 1



Animation 6.9. The action potential moves down the axon beginning at the axon hillock. The action potential moving down a myelinated axon will jump from one Node of Ranvier to the next. This saltatory conduction leads to faster propagation speeds than when no myelin in present. When the action potential reaches the synaptic terminal, it causes the release of chemical neurotransmitter. 'Action Potential Propagation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 2

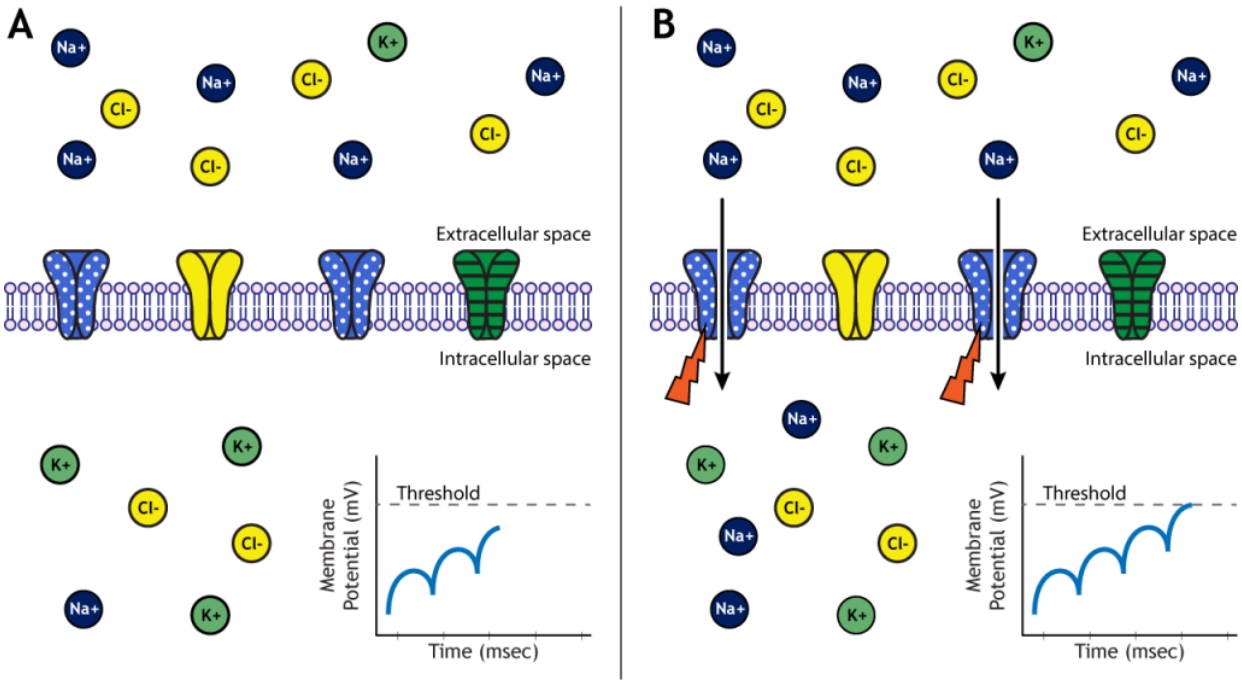


Figure 6.10. A. As EPSPs summate, a result of ion movement not shown in the figure, the cell's membrane potential will depolarize. B. Reaching threshold causes voltage-gated ion channels to open. Once the channels are open, ions will move toward equilibrium. In the figure, sodium ions flow inward. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels; the solid yellow channels represent chloride channels. 'Voltage-Gated Channel' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 3

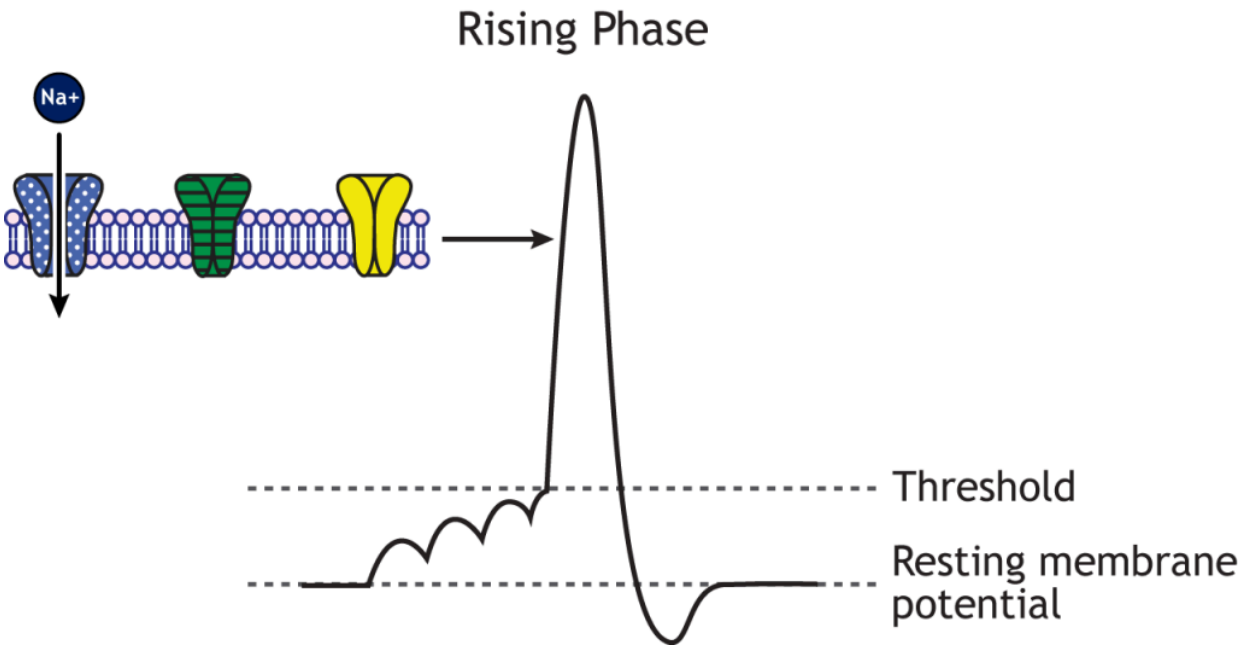


Figure 6.11. Voltage-gated sodium channels open once the cell's membrane potential reaches threshold. The rapid influx of sodium results in a large depolarization called the rising phase. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels; the solid yellow channels represent chloride channels. 'Rising Phase' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 4

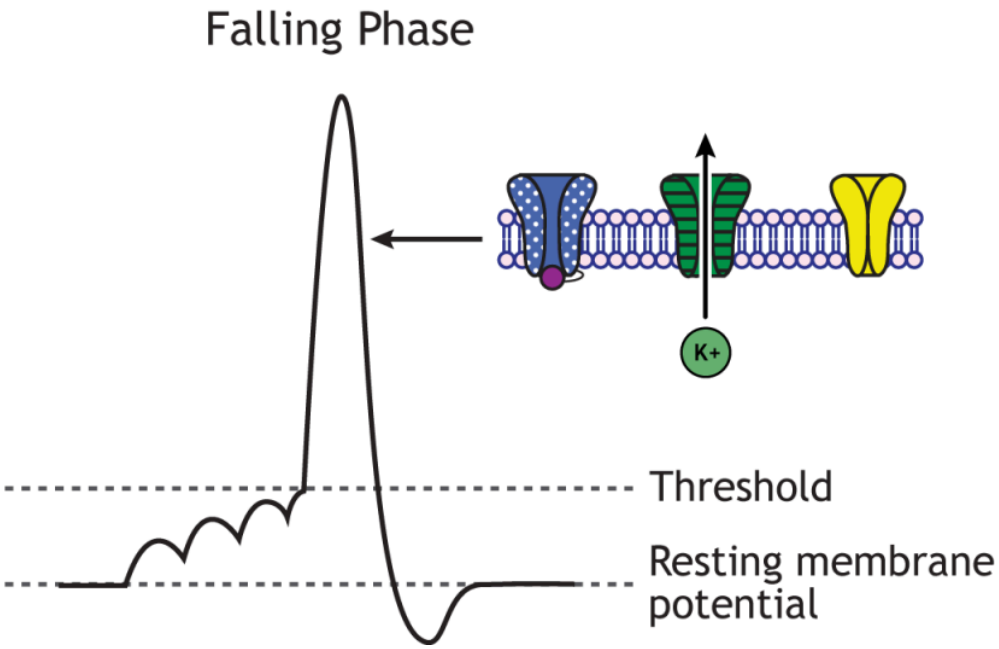


Figure 6.12. After approximately 1 msec, the voltage-gated sodium channels inactivate, which prevents any further ion flow into the cell. Although the voltage-gated potassium channels are activated in response to the cell reaching threshold, their opening is delayed and occurs alone with the sodium channel inactivation. This allows an efflux of potassium ions, which causes the repolarization of the falling phase. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels; the solid yellow channels represent chloride channels. 'Falling Phase" by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 5

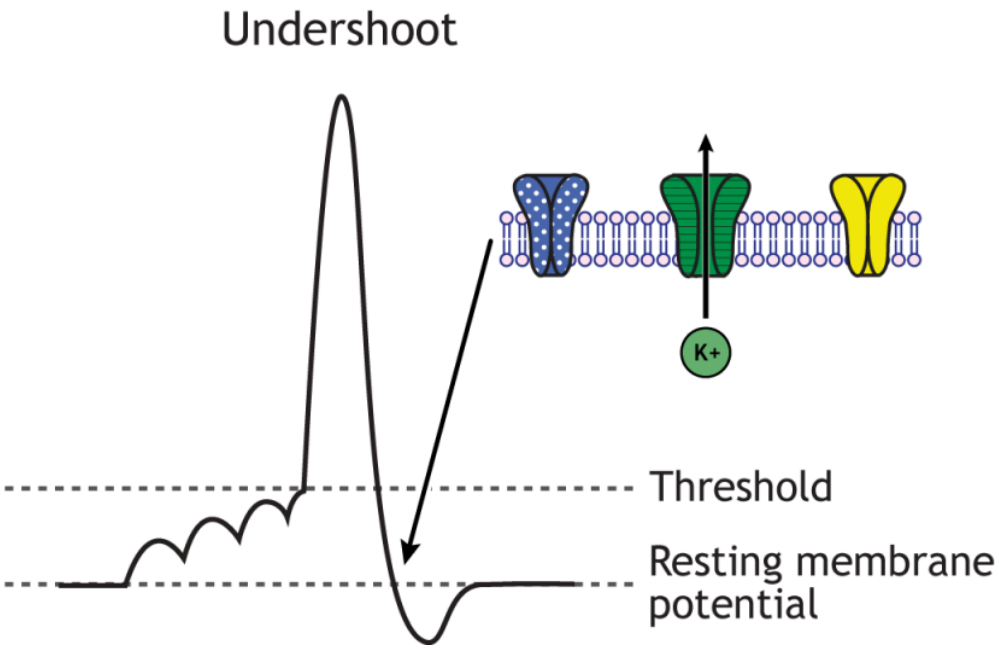


Figure 6.13. Once the cell's membrane potential repolarizes, the voltage-gated sodium channels de-inactivate and return to their closed state. The voltage-gated potassium channels remain open long enough for the undershoot to occur as potassium continues to flow out of the cell. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels; the solid yellow channels represent chloride channels. 'Undershoot' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 6

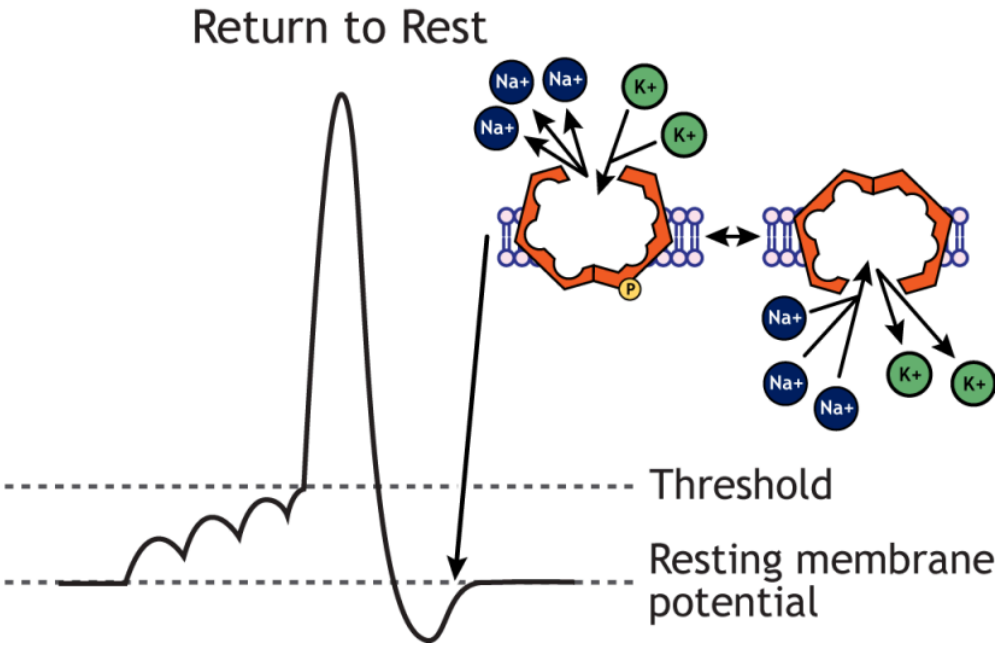


Figure 6.14. Once the voltage-gated potassium channels close, the sodium-potassium pump will work to re-establish the electrochemical gradients and return the cell to its resting membrane potential. 'Return to Rest' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 7

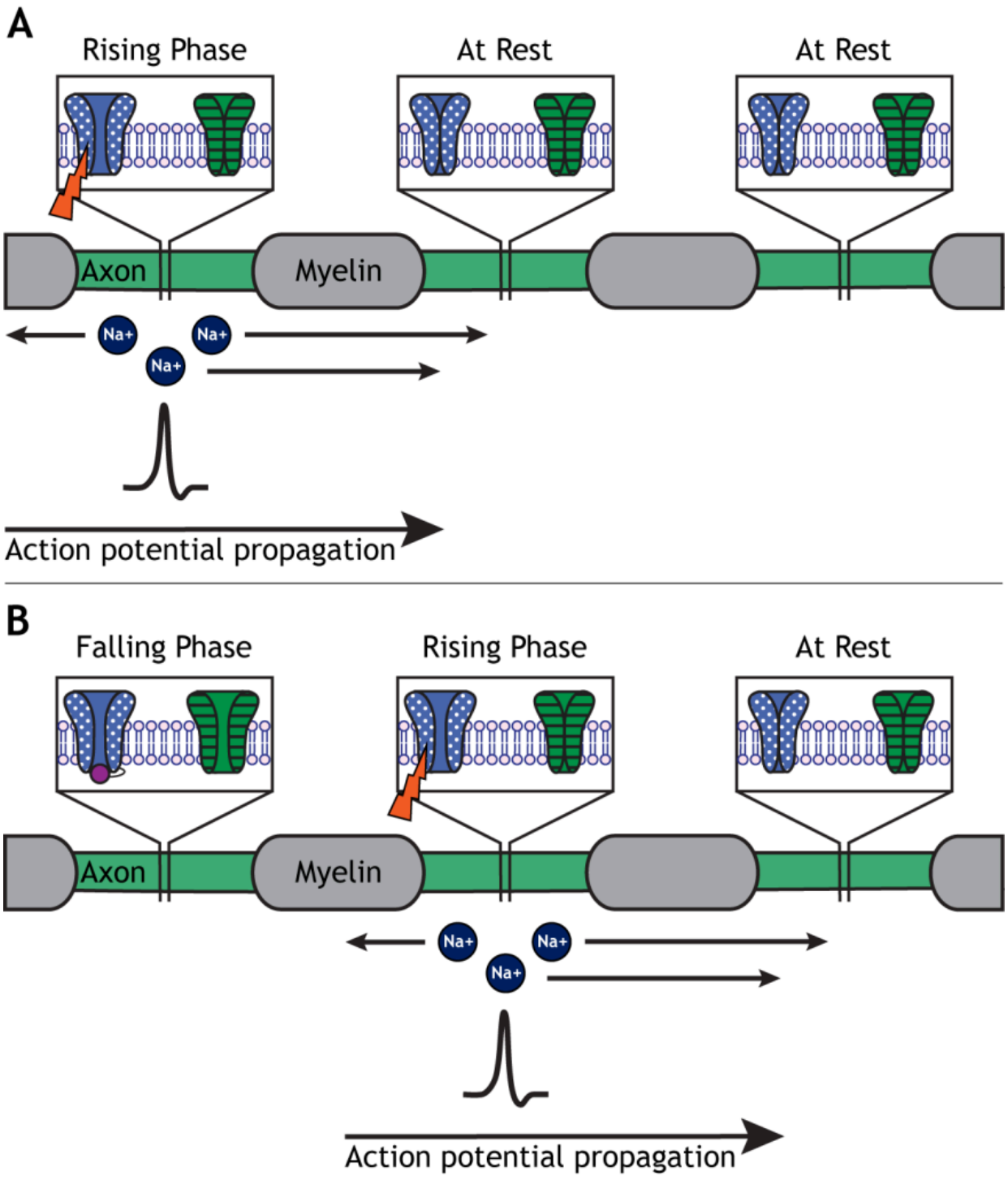


Figure 6.15. A) A voltage change that reaches threshold will cause voltage-gated sodium channels to open in the axonal membrane. The influx of sodium causes the rising phase of the action potential, but the ion flow also depolarizes nearby axon regions. B) As the depolarization reaches threshold,

the action potential moves down the axon. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels. 'Action Potential Movement' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 8

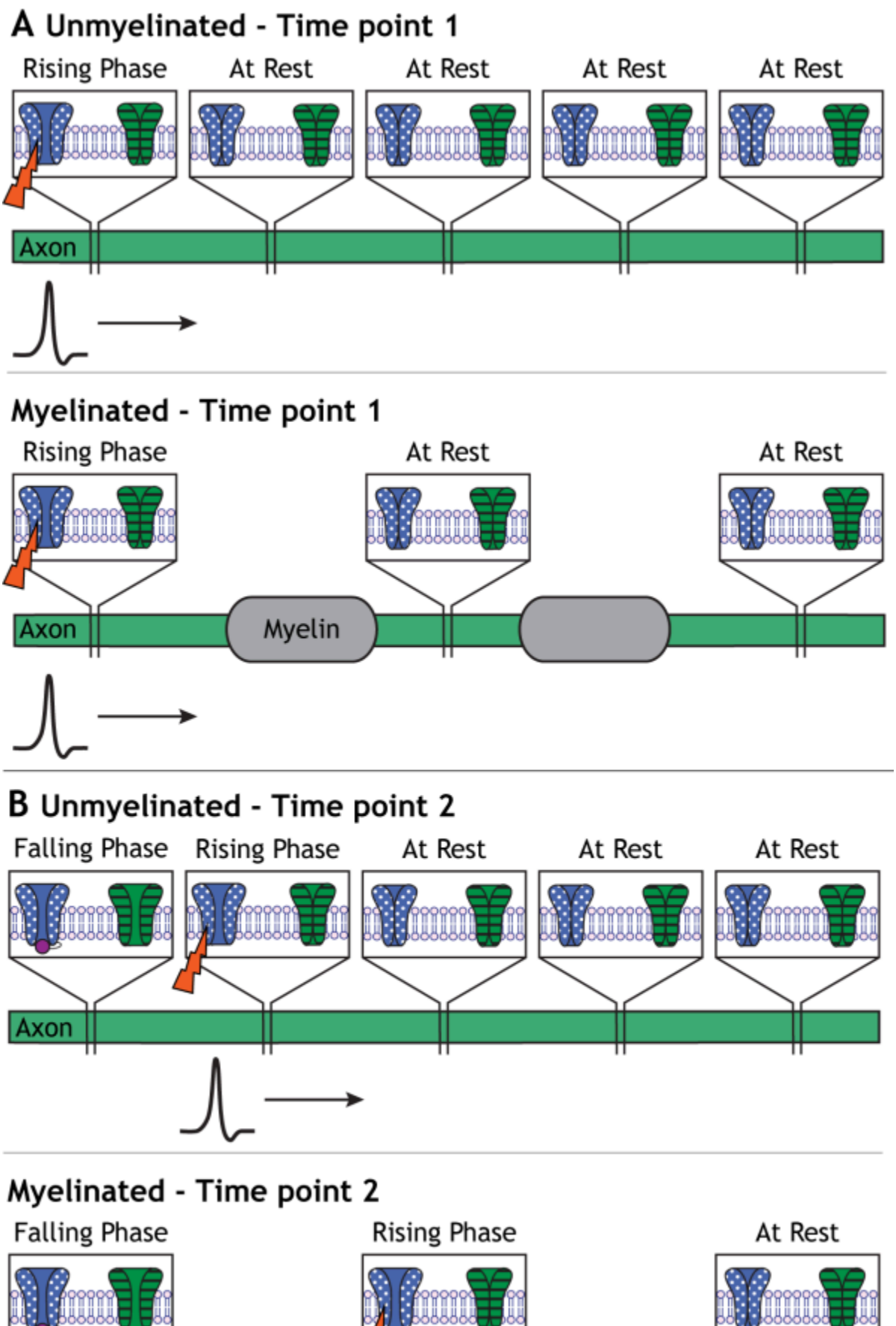

A Unmyelinated - Time point 1
Rising Phase
At Rest
At Rest
At Rest
At Rest
Axon
Myelinated - Time point 1
Rising Phase
At Rest
At Rest
Axon
Myelin
B Unmyelinated - Time point 2
Falling Phase
Rising Phase
At Rest
At Rest
At Rest
Axon
Myelinated - Time point 2
Falling Phase
Rising Phase
At Rest

Figure 6.16. The action potential moves down an unmyelinated axon like a wave, opening voltage-gated channels along the length of the axon. In a myelinated axon, though, the action potential is able to skip portions of the axon that are covered by the myelin; the action potential jumps from node to node and travels further down the axon in the same amount of time. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels. 'Action Potential Speed' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Chapter 7

Animation 1

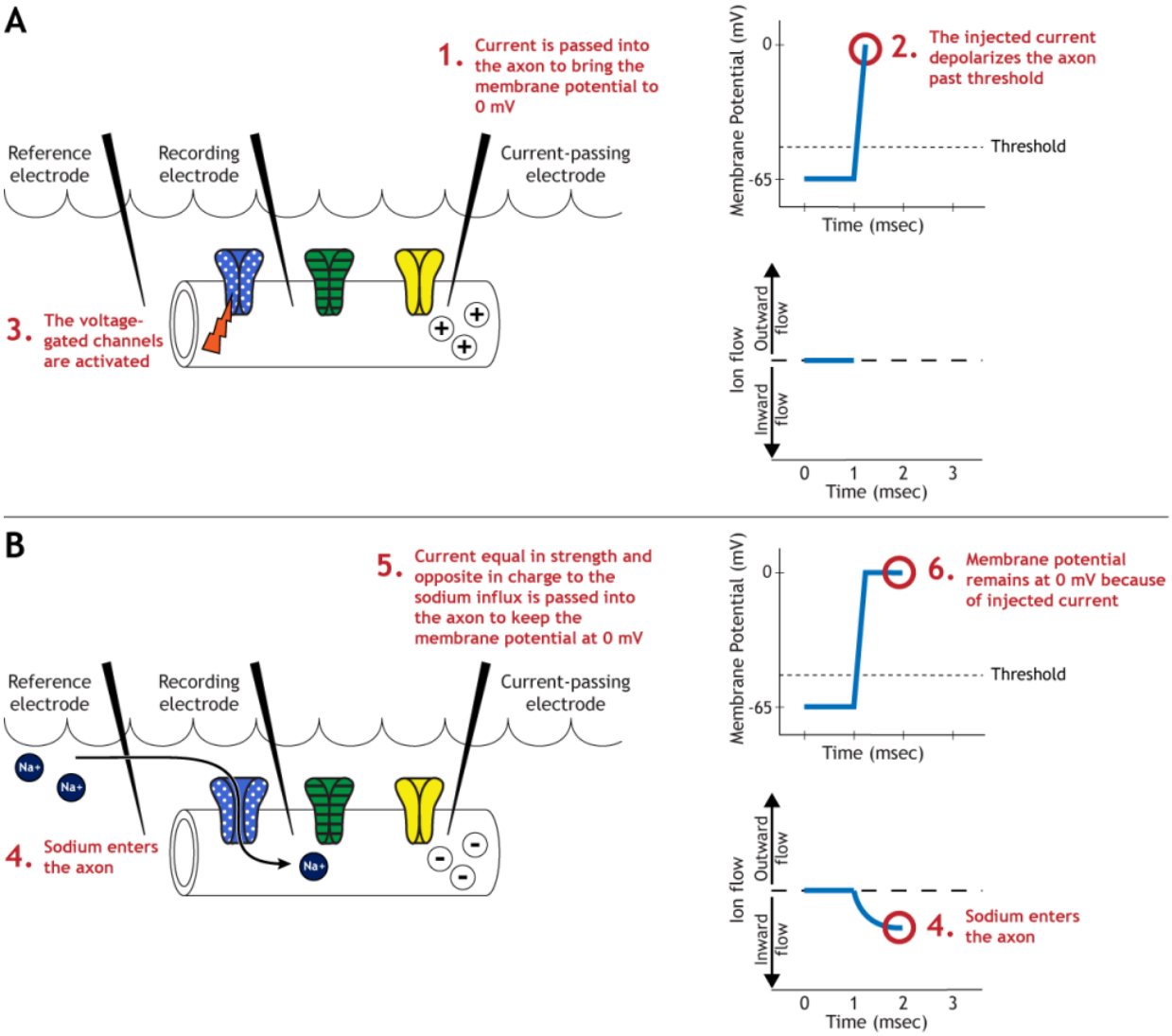


Figure 7.9. A) Clamping the cell at 0 mV will result in current being passed into the axon to depolarize the membrane potential. This depolarization is above threshold, so the voltage-gated ion channels in the membrane will be activated. B) Sodium will enter the axon through the open sodium channels. The voltage clamp equipment will inject current equal in strength and opposite in charge to the sodium influx in order to keep the membrane potential of the axon at 0 mV. The membrane potential will remain at 0 mV because the injected current offsets any change that would normally occur due to ion flow. 'Voltage Clamp Sodium Flow' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 2

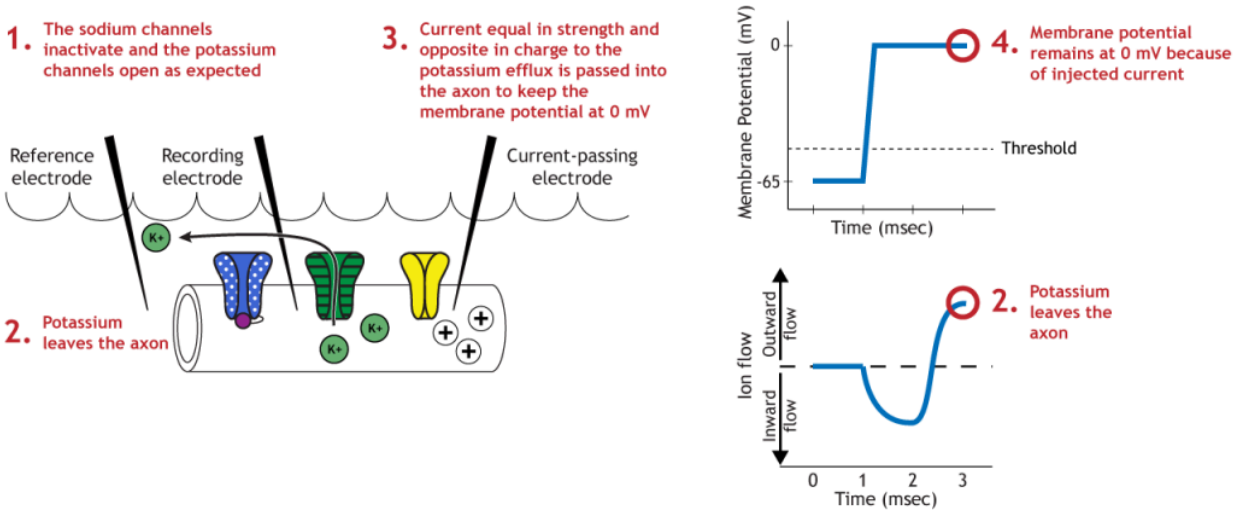


Figure 7.10. The voltage-gated sodium channels will inactivate, and the potassium channels will open. Potassium will then flow out of the axon. Similar to the sodium influx, the voltage clamp equipment will inject current equal in strength and opposite in charge to the potassium efflux in order to keep the membrane potential of the axon at 0 mV. 'Voltage Clamp Potassium Flow' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Chapter 8

Animation 1

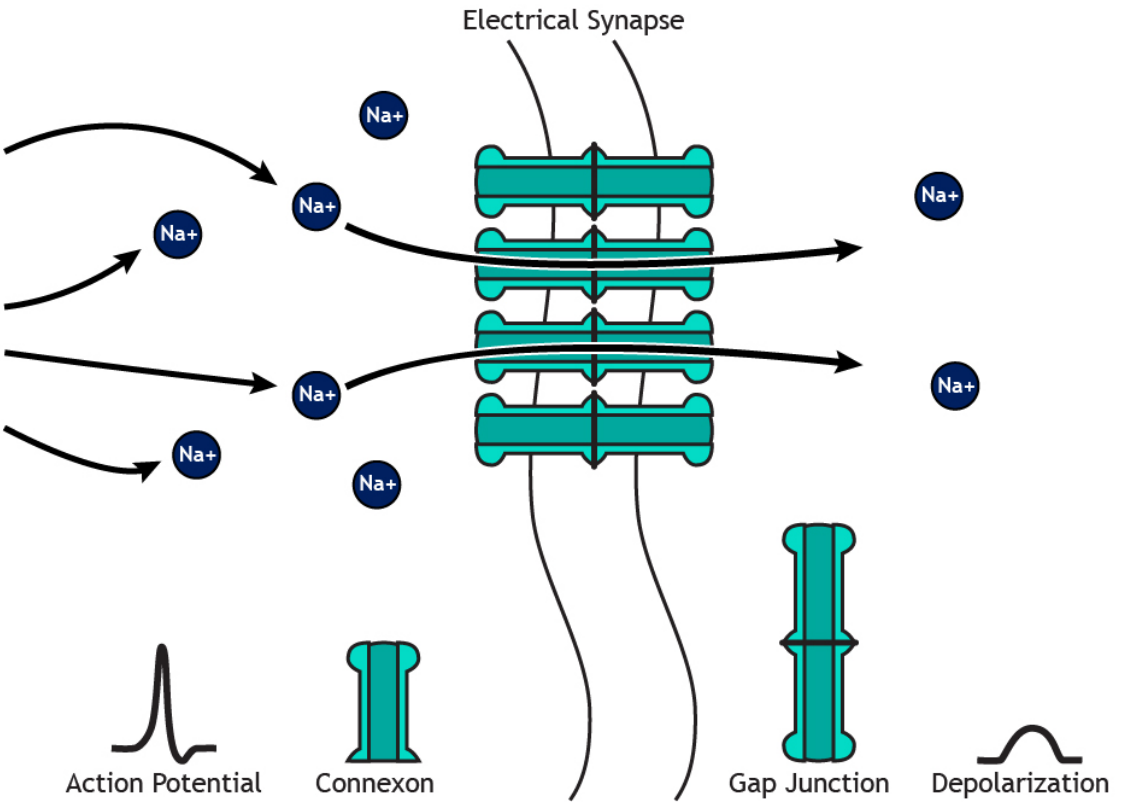


Figure 8.4. Membrane-bound proteins called connexons form gap junctions between presynaptic and postsynaptic neurons. This allows for direct exchange of ions between neurons. An action potential in the presynaptic neuron will cause an immediate depolarization of the postsynaptic membrane because the sodium ions will cross the membrane through the gap junctions. 'Electrical Synapse – Ion Flow' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 2

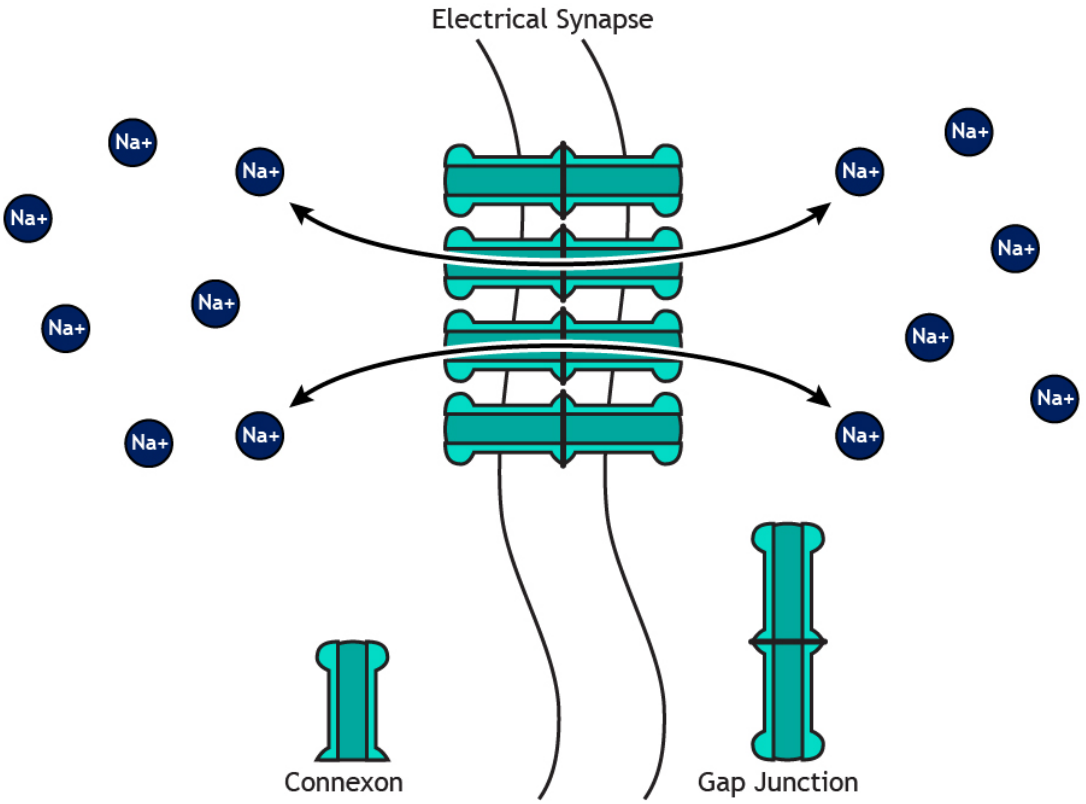


Figure 8.5. Since an electrical synapse is a direct, physical connection between two neurons, ions are able to flow either direction across the gap junction. 'Bidirectional Electrical Synapse' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 3

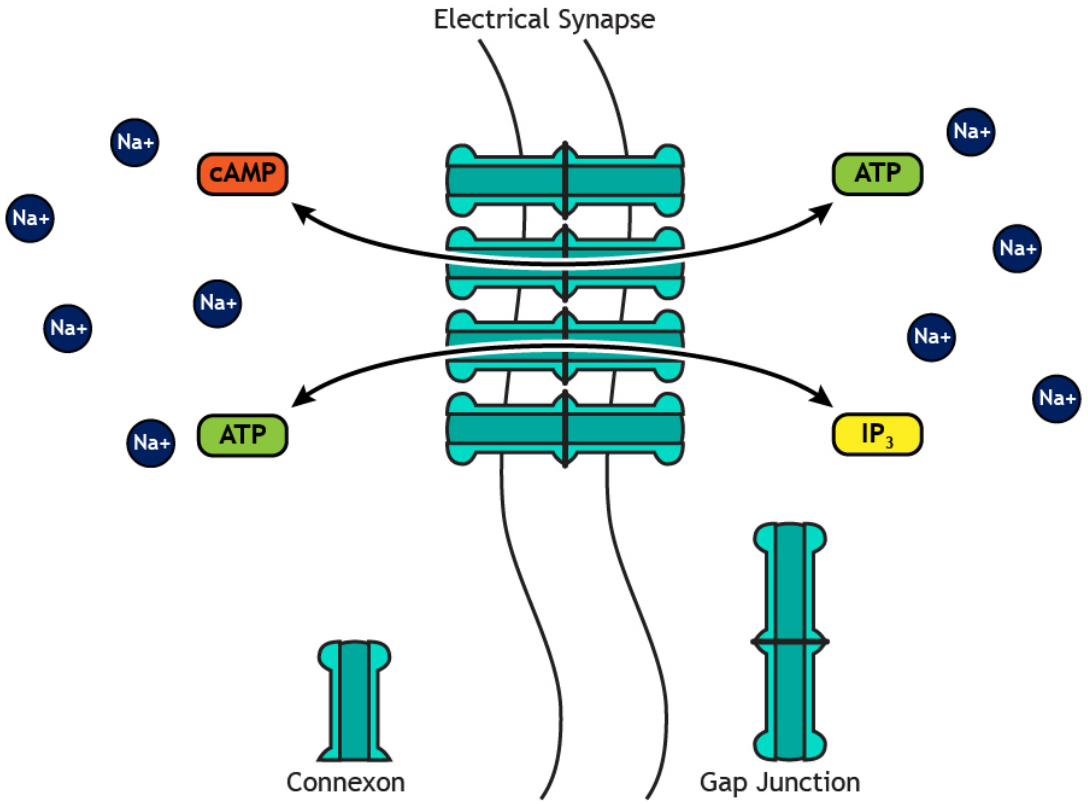


Figure 8.6. Gap junctions are large enough to allow the flow of small cellular molecules like ATP or second messengers. 'Electrical Synapse – Small Molecules' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 4

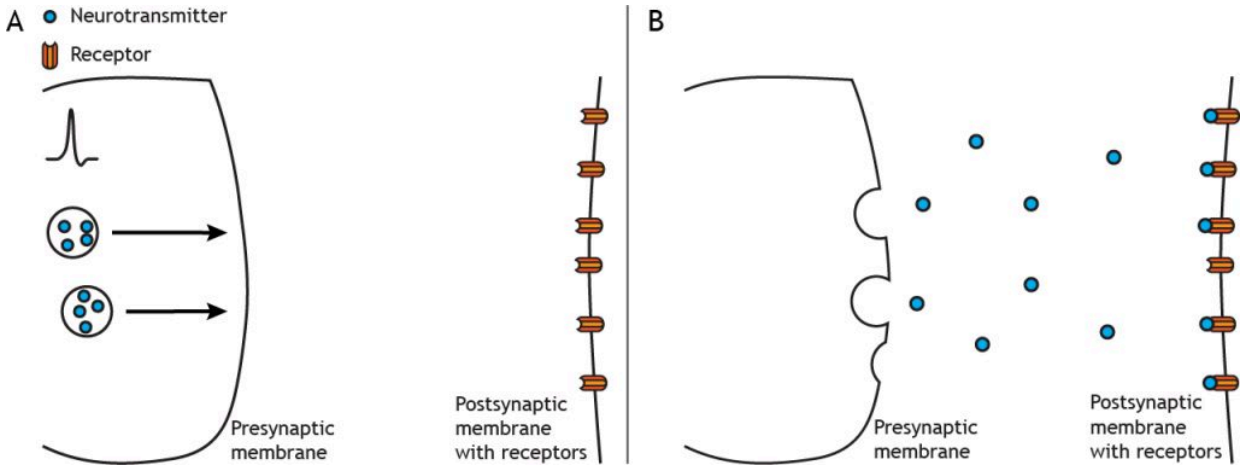
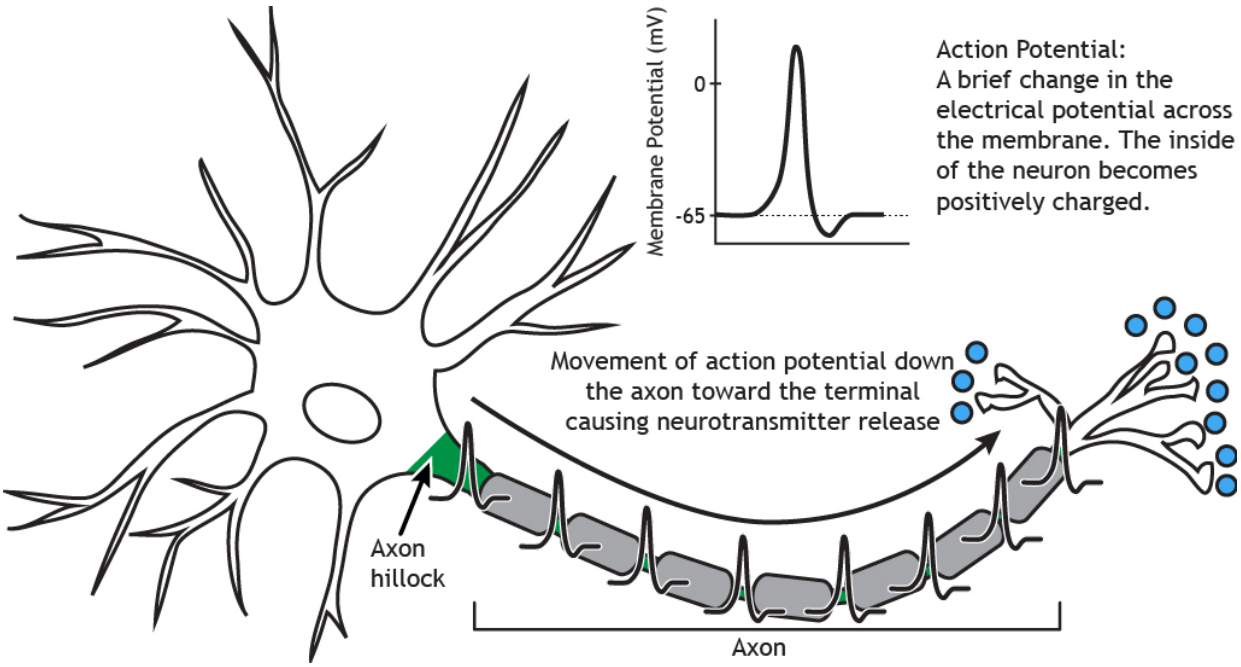


Figure 8.7 When an action potential arrives in the presynaptic terminal, neurotransmitters are released into the synaptic cleft where they can act on neurotransmitter receptors in the postsynaptic membrane. 'Chemical Synapse – Neurotransmitter Release' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Chapter 10

Animation 1



Animation 10.5. The action potential is a brief but significant change in electrical potential across the membrane. The membrane potential will move from a negative, resting membrane potential, shown here as -65 mV, and will rapidly become positive and then rapidly return to rest during an action potential. The action potential moves down the axon beginning at the axon hillock. When it reaches the synaptic terminal, it causes the release of chemical neurotransmitter. 'Action Potential Propagation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 2

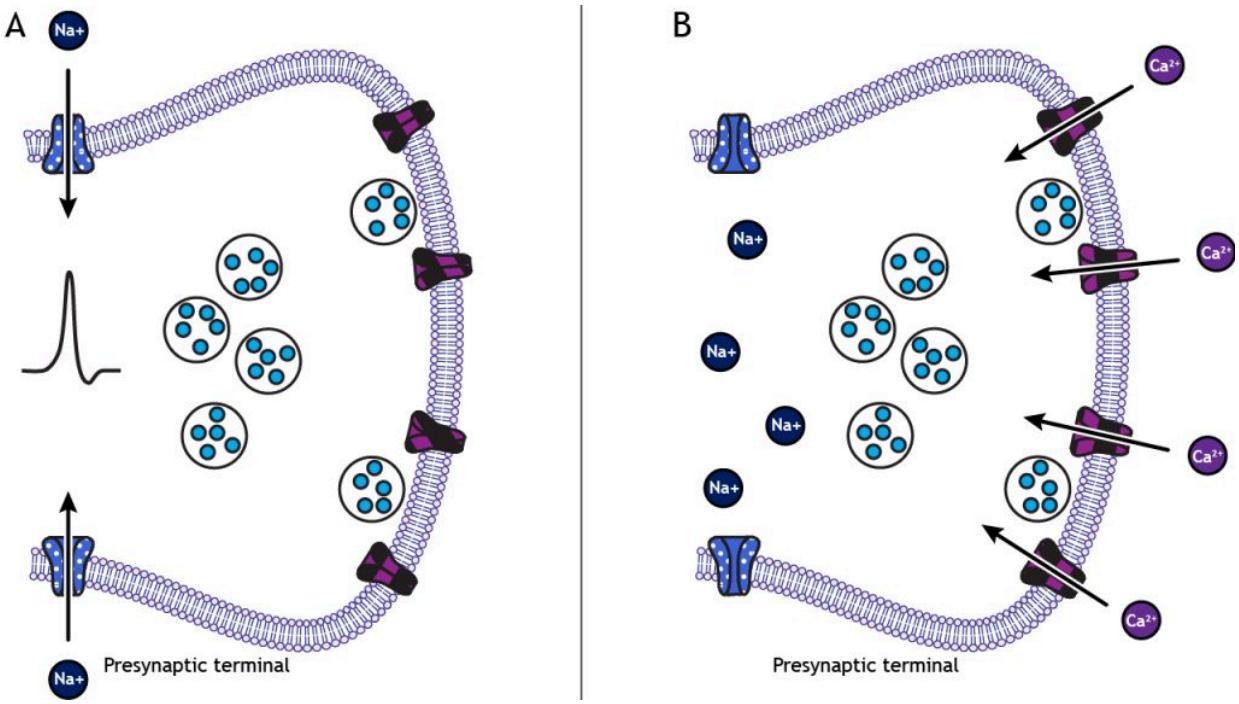


Figure 10.6. A) An action potential causes an influx of sodium in the terminal. B) The depolarization opens voltage-gated calcium channels, and calcium ions flow into the terminal down their electrochemical gradient. The blue, dotted channels represent voltage-gated sodium channels, and the purple, striped channels represent voltage-gated calcium channels. 'Terminal Calcium Influx' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 3

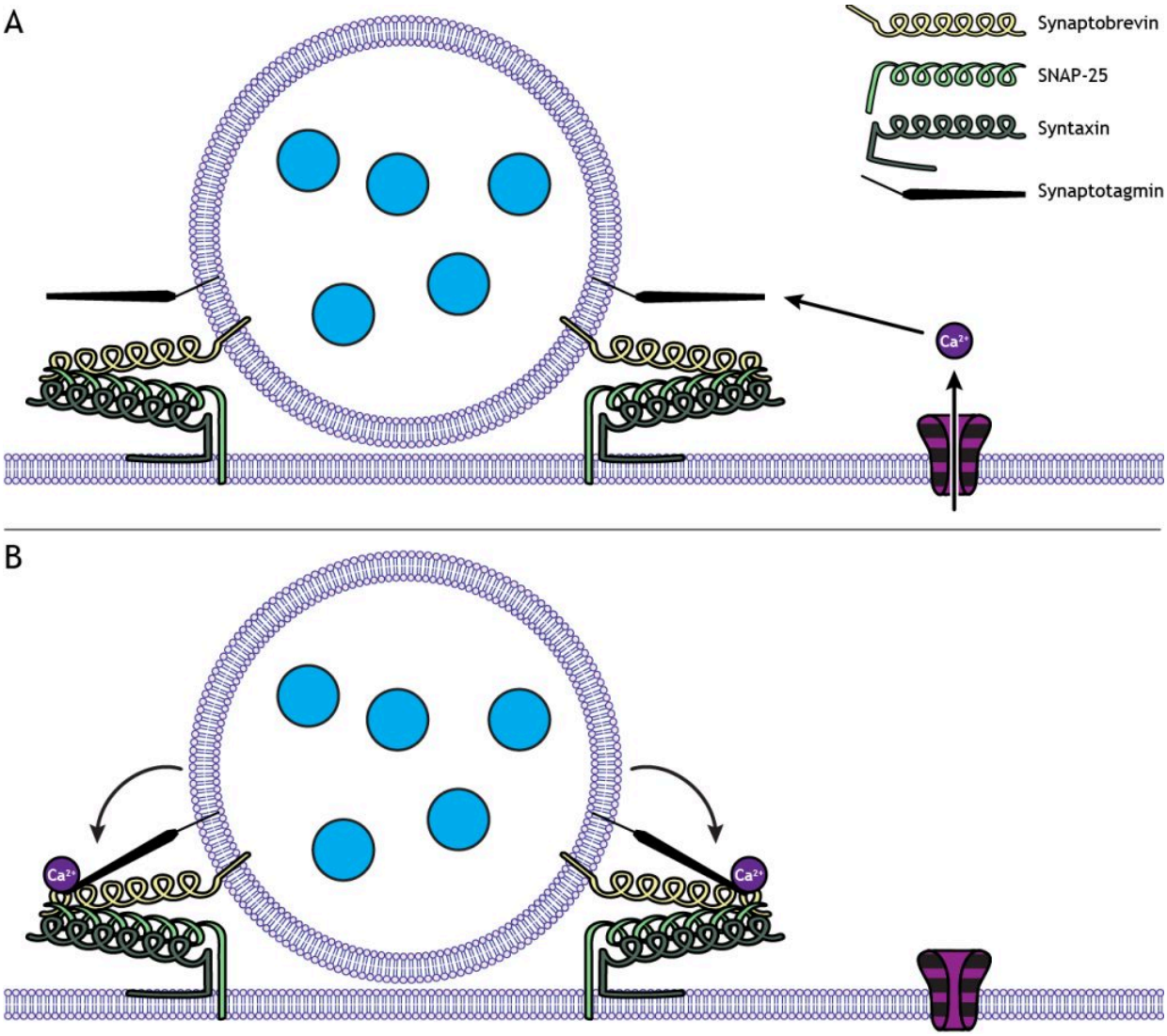


Figure 10.7. A) Calcium enters the cell when the voltage-gated channels open. B) In the presence of calcium, synaptotagmin, a protein bound to the vesicular membrane interacts with the SNARE proteins. The purple, striped channels represent voltage-gated calcium channels. 'Synaptotagmin' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 4

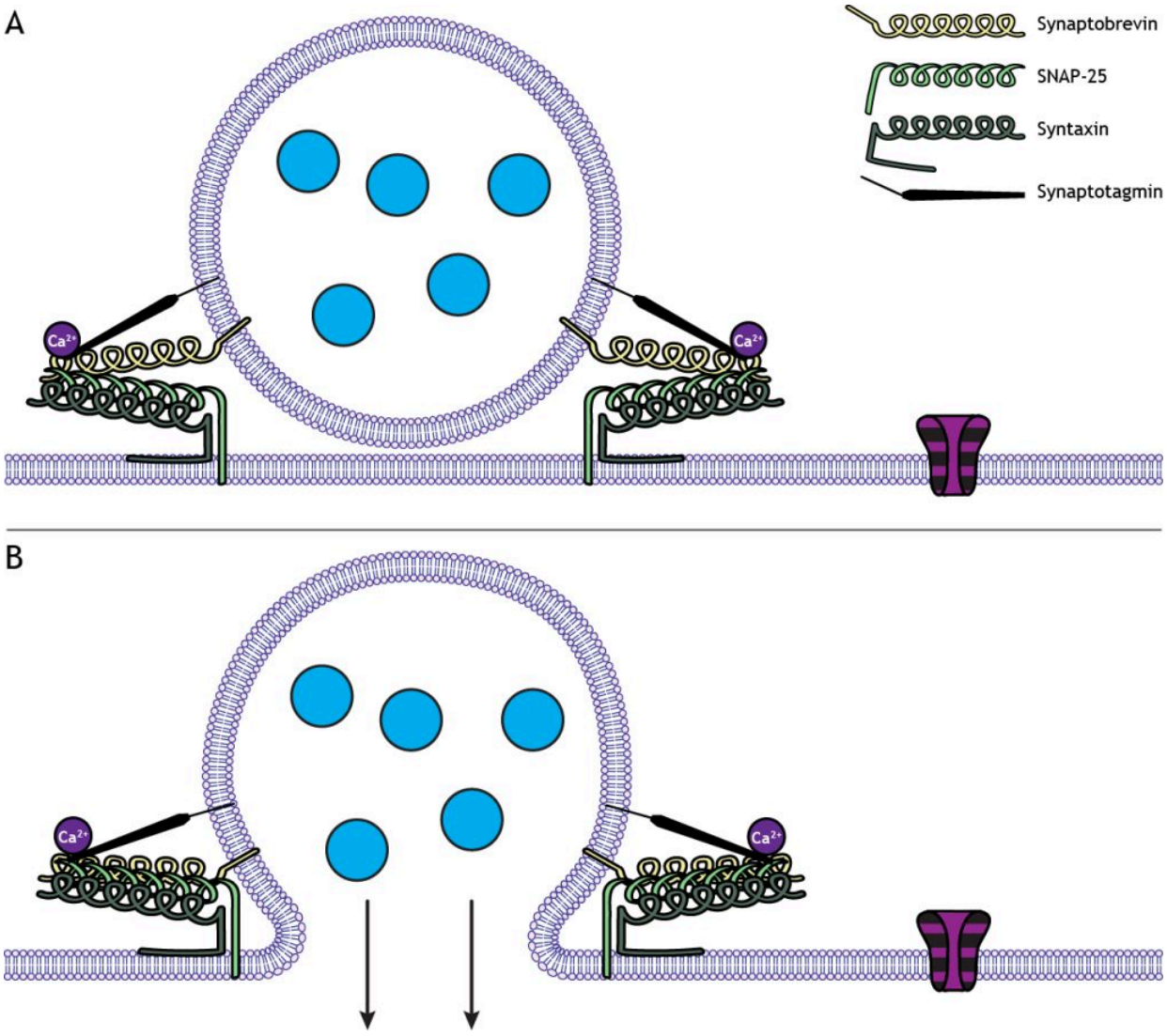


Figure 10.8. Once the synaptotagmin-SNARE protein complex forms, the synaptic vesicle membrane fuses with the terminal membrane, and the neurotransmitters are released into the synaptic cleft through exocytosis. The purple, striped channels represent voltage-gated calcium channels. 'Transmitter Exocytosis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Chapter 11

Animation 1

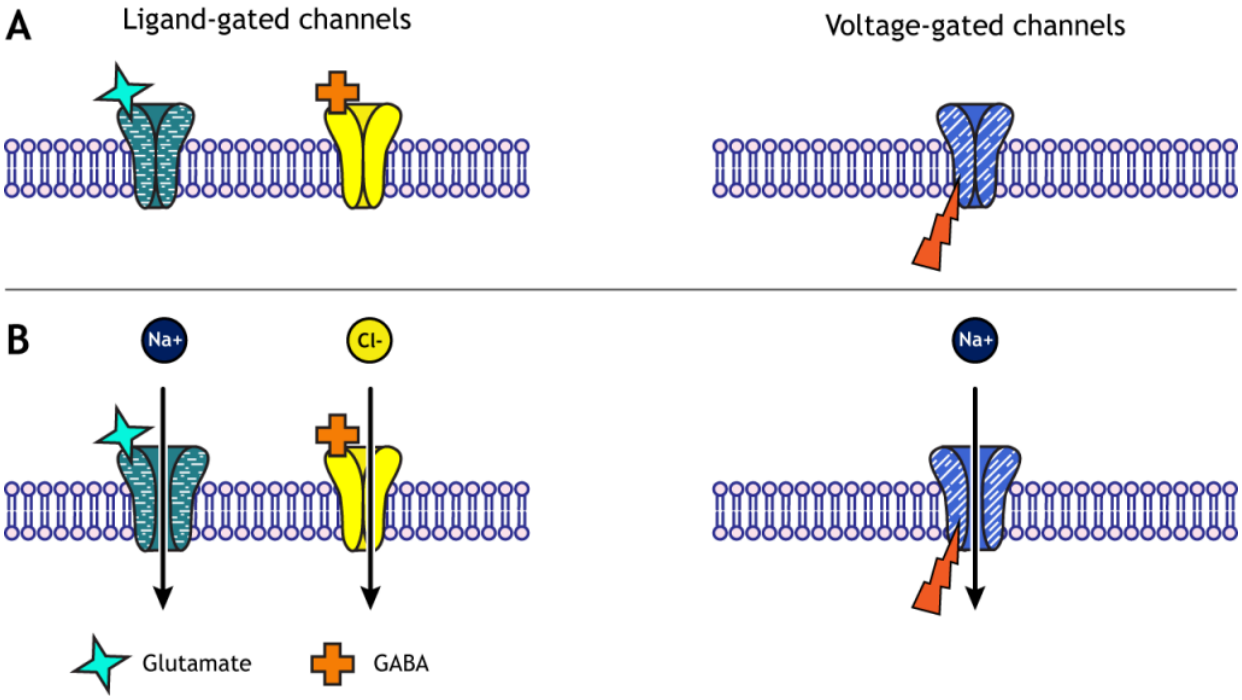


Figure 11.2. A) Ionotropic receptors, also called ligand-gated channels, are ion channels that are opened by the binding of neurotransmitters. Voltage-gated channels are opened by the membrane potential of the cell reaching threshold. B) Both types of channels allow ions to diffuse down their electrochemical gradient. The lined, teal channels represent glutamate receptors; the solid yellow channels represent GABA receptors; the dotted, blue channels represent voltage-gated sodium channels. 'Ion Channel Gating' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 2

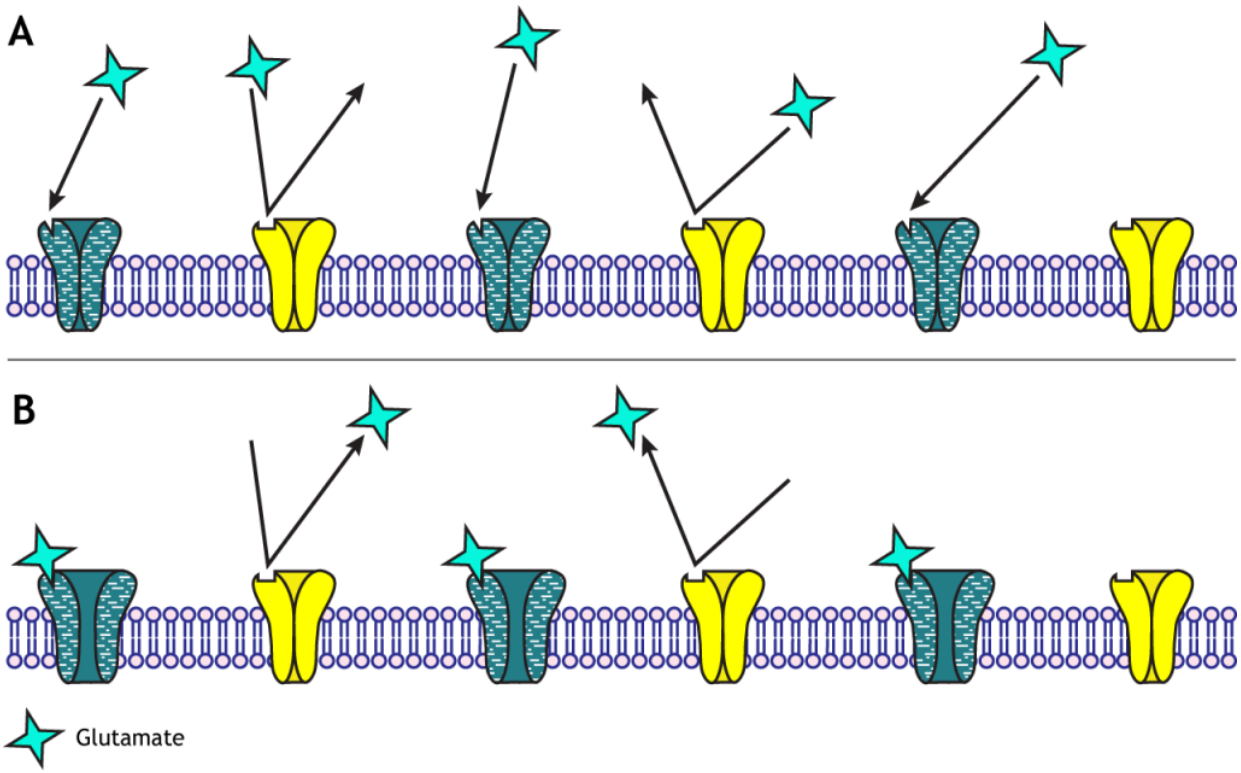


Figure 11.3. Since neurotransmitter receptors can only bind specific neurotransmitters. glutamate binds to (A) and opens (B) glutamate receptors but has no effect on GABA receptors. The lined, teal channels represent glutamate receptors; the solid yellow channels represent GABA receptors. 'Ligand and Receptor' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 3

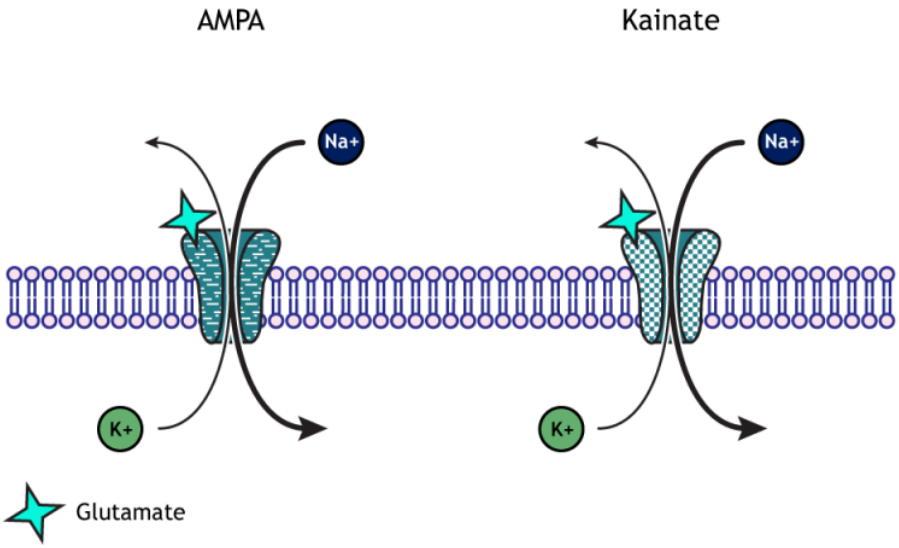


Figure 11.4. AMPA and kainate glutamate receptors are non-selective ion channels that allow both sodium and potassium to flow across the membrane. When glutamate binds, sodium flows in and potassium flows out. The lined, teal channel represents AMPA receptors; the checkered, teal channel represents kainate receptors. 'AMPA and Kainate' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 4

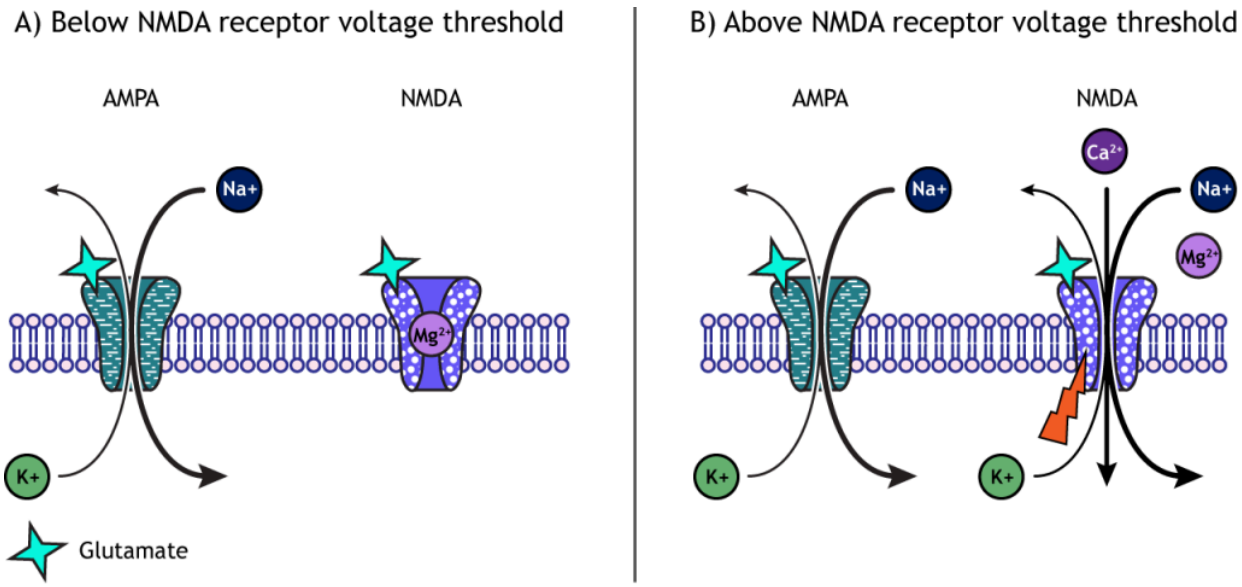


Figure 11.5. NMDA receptors are opened by a combination of glutamate binding and a voltage trigger. A) At low levels of stimulation when the the membrane potential is near rest and below the NMDA receptor voltage threshold, a magnesium ion blocks the open NMDA receptor channel preventing ion flow. Ions can flow through open AMPA receptors, which begins to depolarize the membrane. B) Once the NMDA receptor voltage threshold has been reached, the magnesium ion is expelled from the channel, allowing sodium, potassium, and calcium to cross the membrane. The lined, teal channels represent AMPA receptors; the dotted, violet channels represent NMDA receptors. 'AMPA and NMDA' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 5

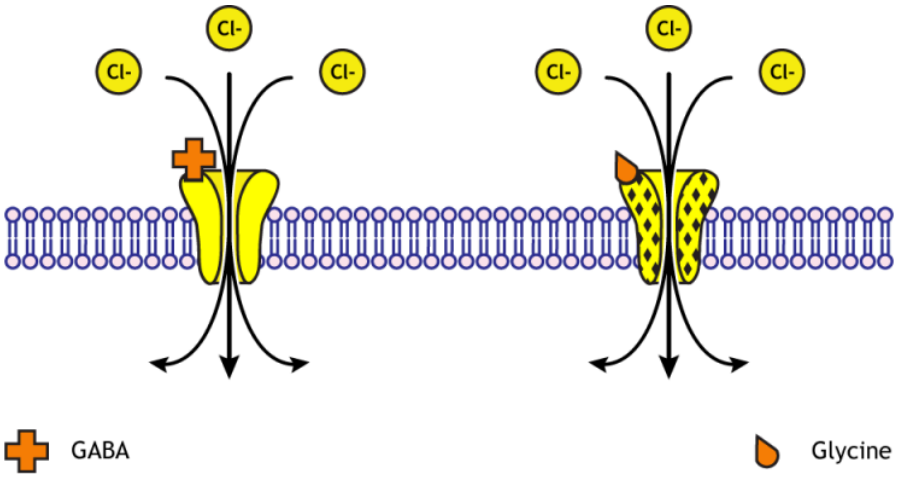


Figure 11.6. GABA and glycine are inhibitory receptors that are selective to chloride. The solid yellow channel represents a GABA receptor; the patterned, yellow channel represents a glycine receptor. 'GABA and Glycine' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 6

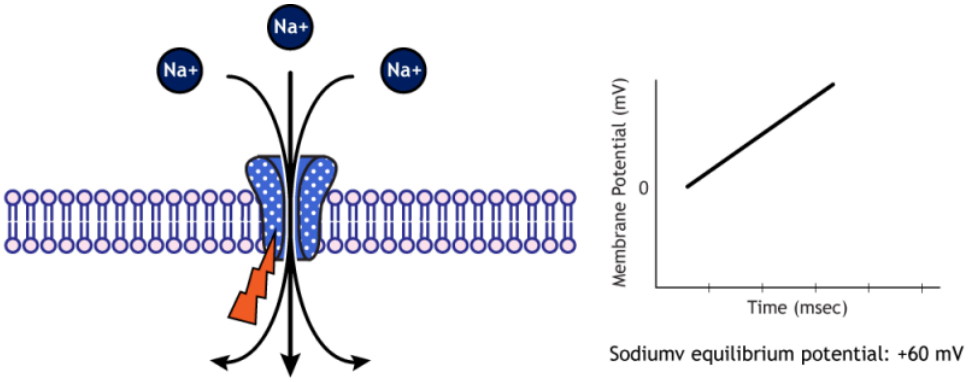


Figure 11.7. Ions move through open voltage-gated channels trying to reach equilibrium. As the ions cross the membrane, the neuron's membrane potential moves closer to the ion's equilibrium potential. In the figure, a voltage-gated sodium channel opens, and sodium flows in until the membrane potential equals approximately +60 mV, sodium's equilibrium potential. The blue, dotted channel represents a voltage-gated sodium channel. 'Equilibrium Potential' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 7

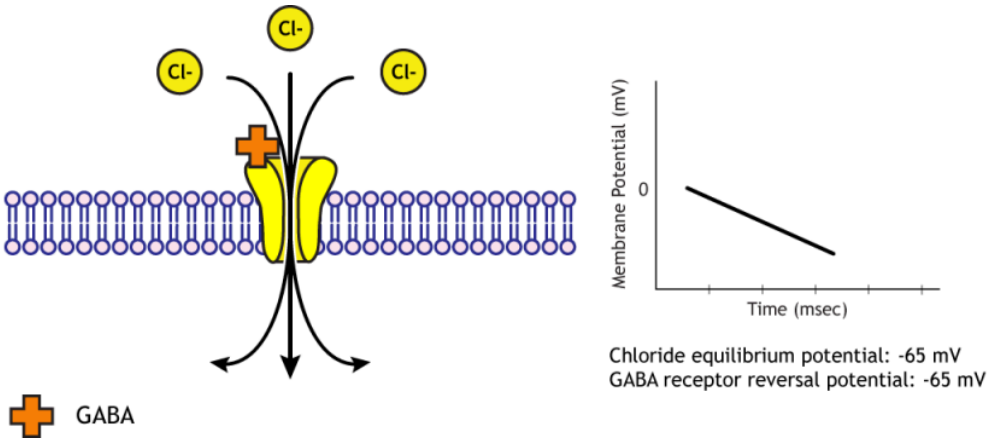


Figure 11.8. Ions move through open ligand-gated channels trying to reach equilibrium. As the ions cross the membrane, the neuron's membrane potential moves closer to the receptor's reversal potential. When the ionotropic receptor only increases permeability for one ion, the receptor's reversal potential is the same as the ion's equilibrium potential. In the animation, a GABA receptor open, and chloride flows in until the membrane potential equals approximately -65 mV, GABA's reversal potential and chloride's equilibrium potential. The yellow, checkered channel represents a GABA receptor. 'GABA Reversal Potential' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 8

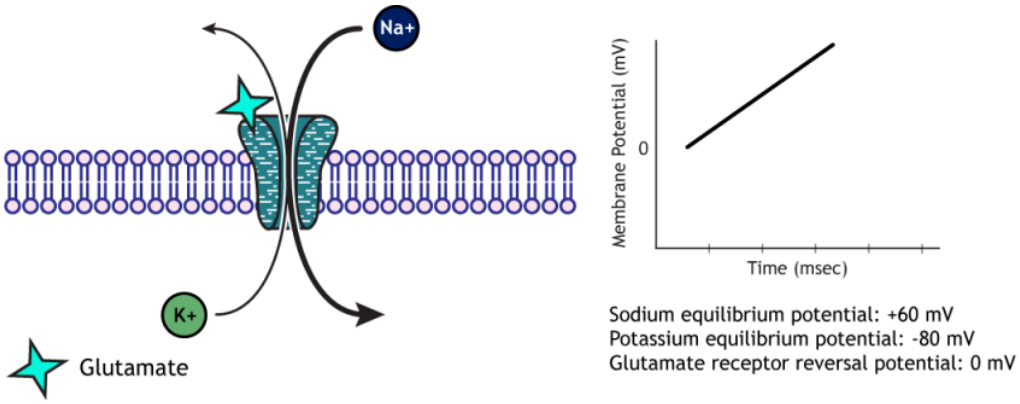


Figure 11.9. The reversal potential of an ionotropic receptor that is not selective to one ion will fall between the equilibrium potentials of the permeable ions. Glutamate receptors allow the flow of both sodium and potassium ions, so the reversal potential for the receptor is approximately 0 mV. More sodium will flow into the cell than potassium flows out, resulting in a depolarization of the membrane. The line, teal channel represents a glutamate receptor. 'Glutamate Reversal Potential – Rest' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Animation 9

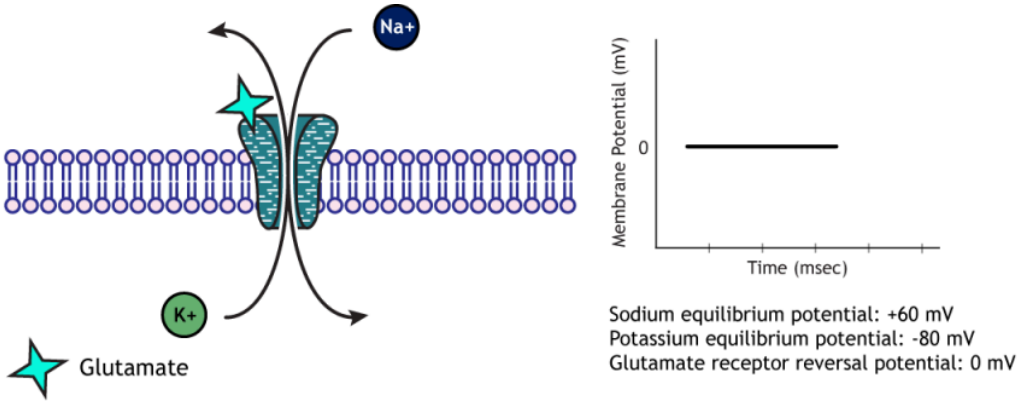


Figure 11.10. At the reversal potential, there is no net ion flow in either direction. An equal number of sodium ions enter the cell as potassium ions leave. Since there is no change in voltage at the reversal potential, if the receptor remained open, the membrane potential would stay at 0 mV. 'Glutamate Reversal Potential – 0 mV' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC-BY-NC-SA) 4.0 International License.

Chapter 12

Animation 1

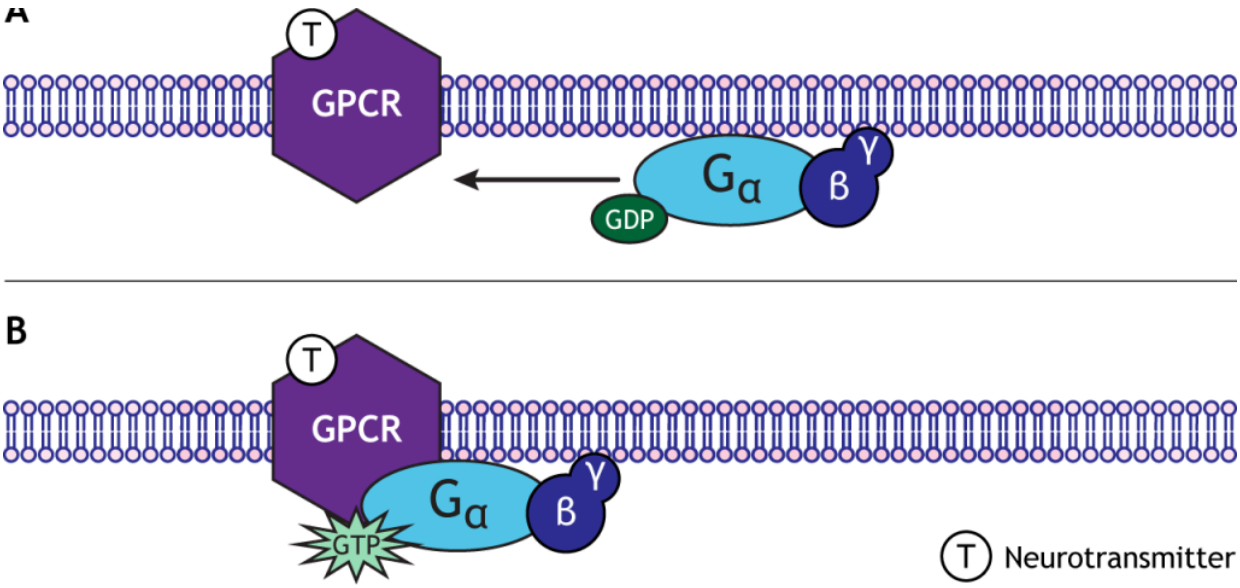


Figure 12.5. A) Neurotransmitter binding to a G-protein-coupled receptor causes the inactivated G-protein complex to interact with the receptor. B) The GDP molecule is then exchanged for a GTP molecule, which activates the G-protein complex. 'G-protein Binding' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 2

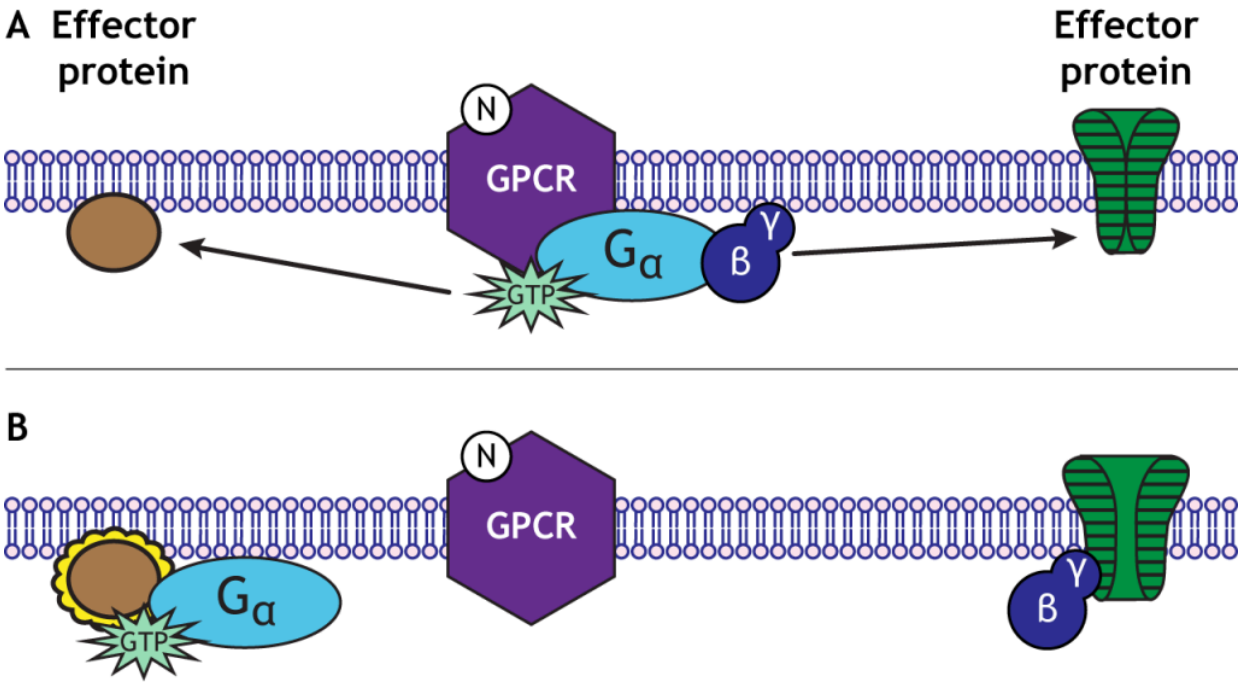


Figure 12.6. A) Once activated, the G-protein complex will separate into the alpha-GTP subunit and the beta-gamma subunit. B) These subunits can stimulate or inhibit effector proteins within the cell. 'G-protein Effects' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 3

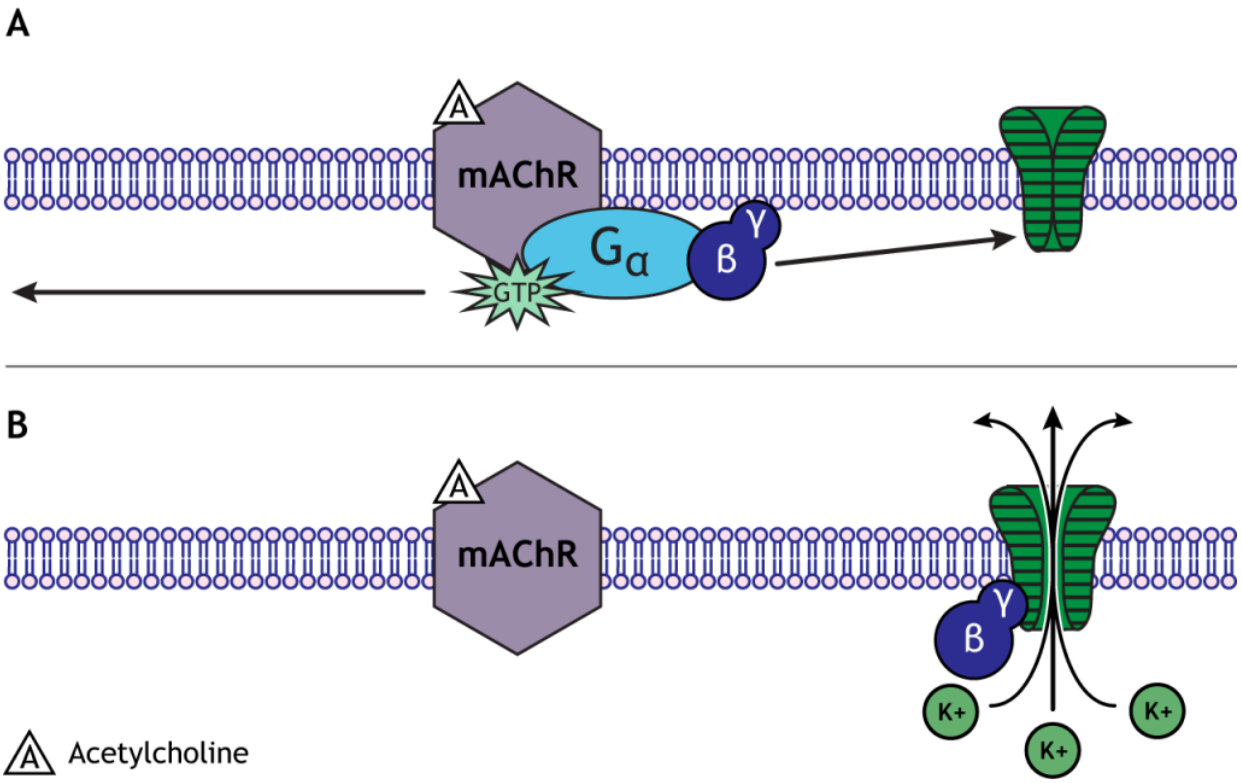


Figure 12.7. Some GPCRs, like the muscarinic acetylcholine receptors in the heart, alter cellular permeability by opening ion channels. The activated beta-gamma subunit of the muscarinic receptor (A) opens GIRK potassium channels and allows the efflux of potassium (B). 'Beta-Gamma Ion Channels' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 4

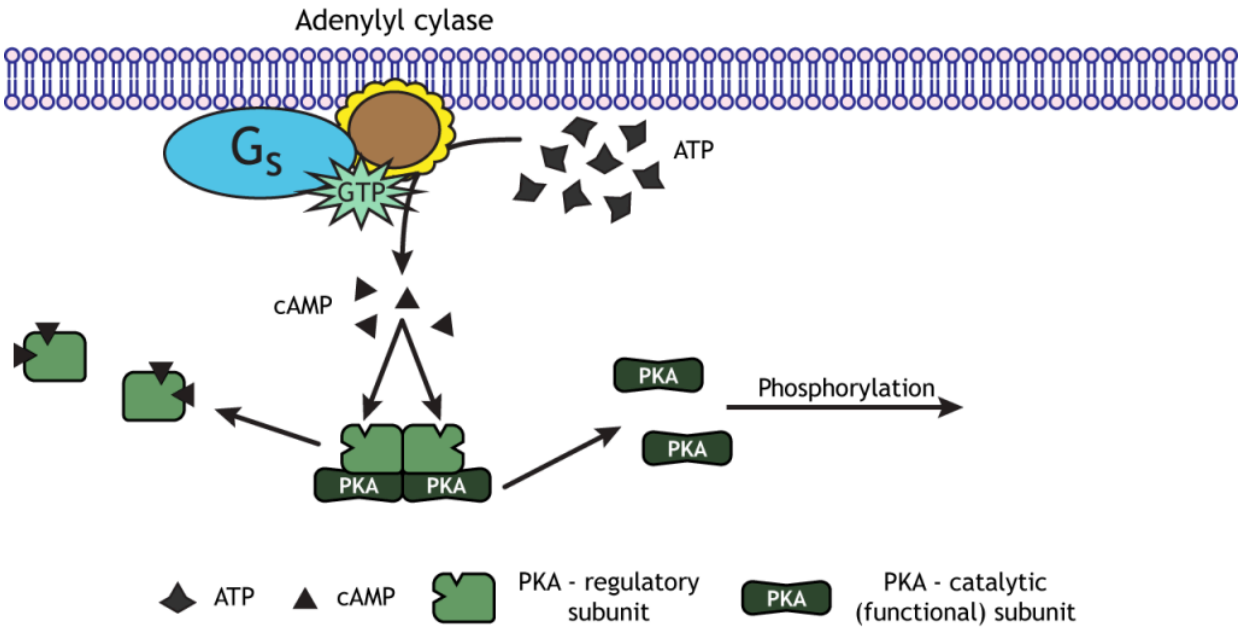


Figure 12.8. GPCRs that couple to the Gs alpha subunit initiate the adenylyl cyclase / cAMP pathway. The Gs subunit activates adenylyl cyclase, which then converts ATP to cAMP. cAMP binds to and activates protein kinase A (PKA), which phosphorylates proteins in the cell. 'Adenylyl Cyclase Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 5

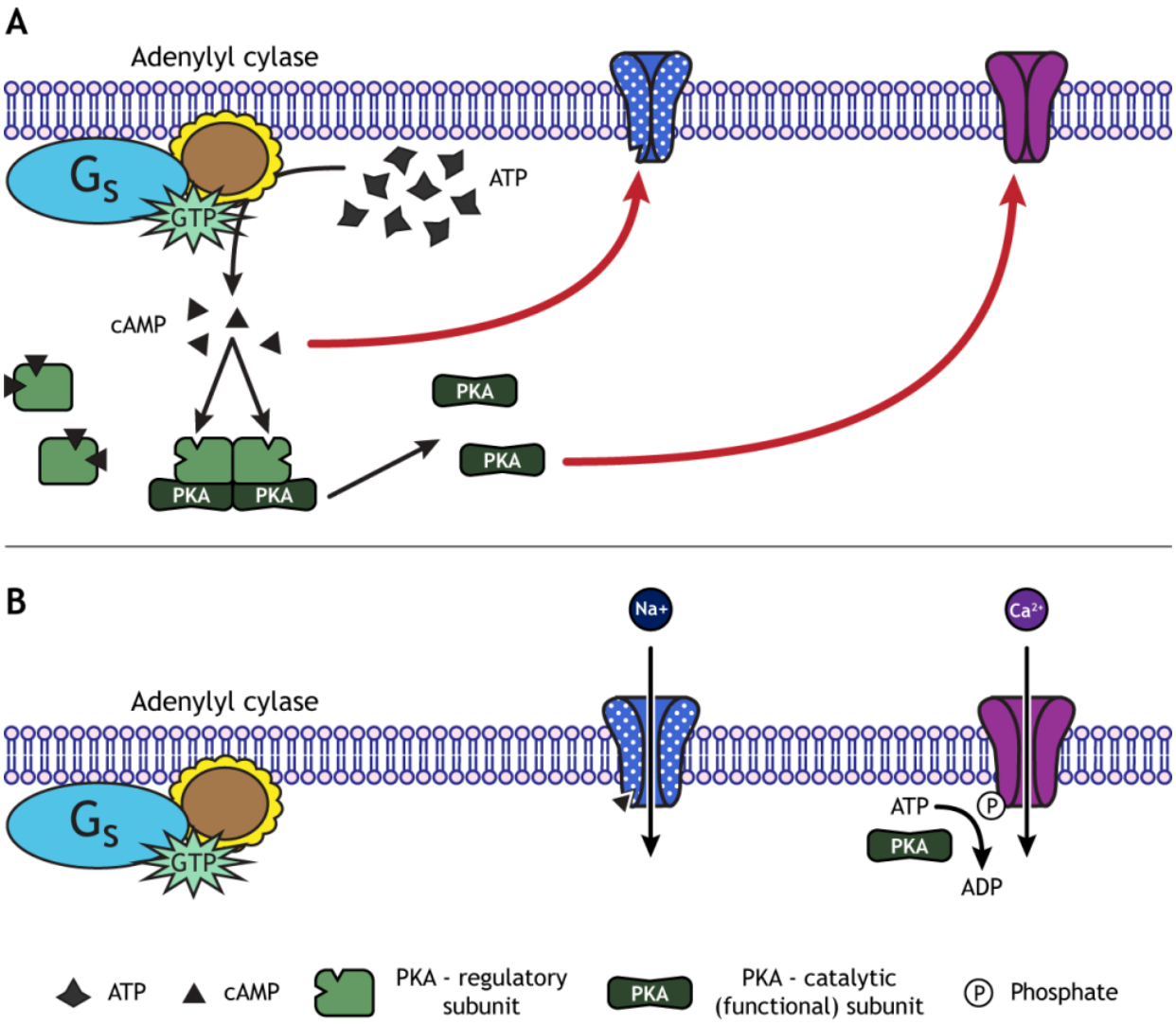


Figure 12.9. A) The adenylyl cyclase / cAMP pathway can alter many cellular functions. One example is that both cAMP and PKA can open ion channels. B) Like ligand-gated channels, there are also cAMP-gated channels, which open after cAMP binding. PKA is able to phosphorylate and modulate ion channel function by converting ATP to ADP. 'Second Messenger Ion Channel Action' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 6

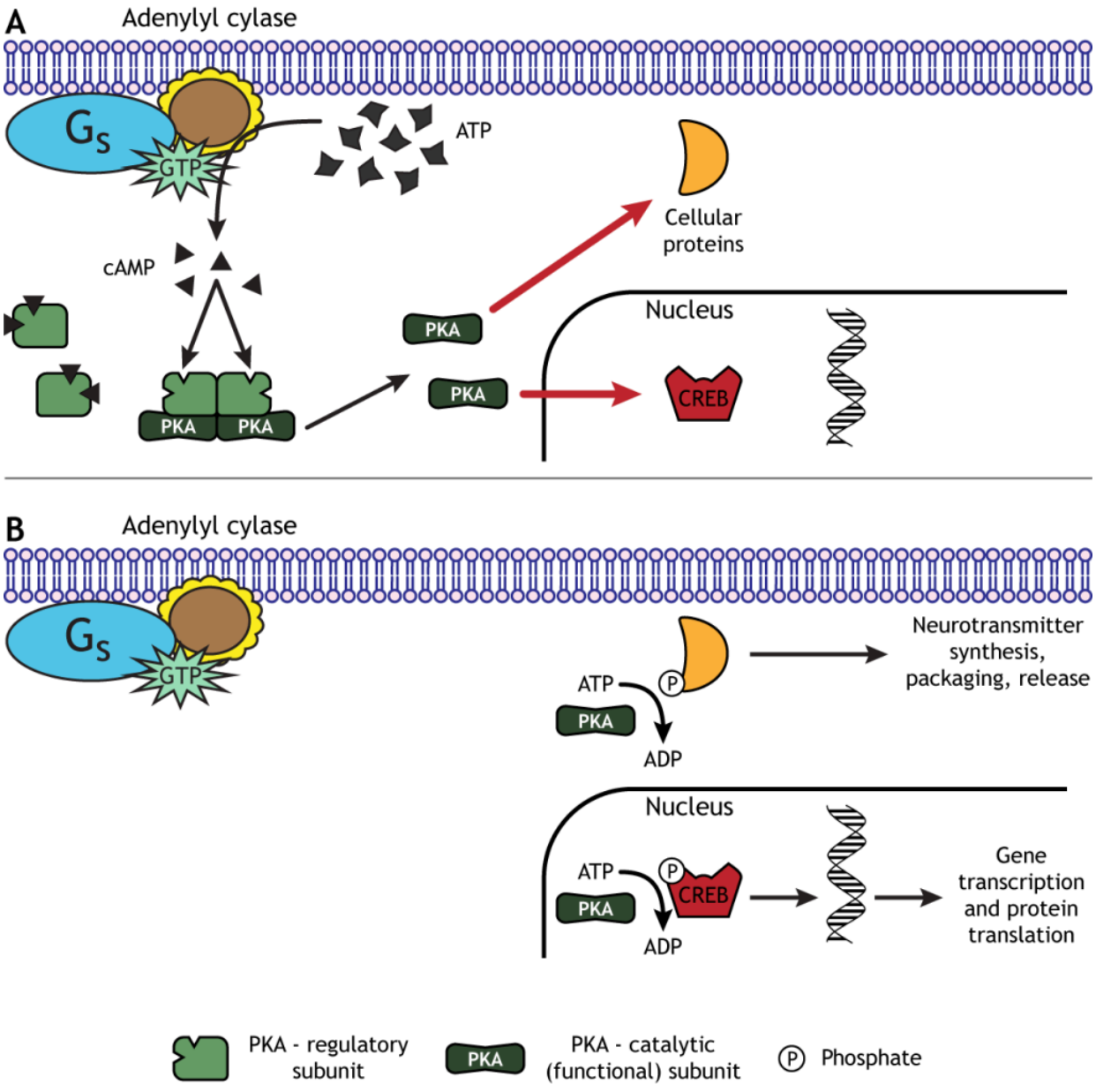


Figure 12.10. A) PKA can phosphorylate a number of proteins involved with neuron function. B) It can target proteins involved with neurotransmitter synthesis, packing, and release, or it can enter the nucleus and phosphorylate CREB, a transcription factor that can initiate gene transcription and protein synthesis. 'PKA Targets' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animation 7

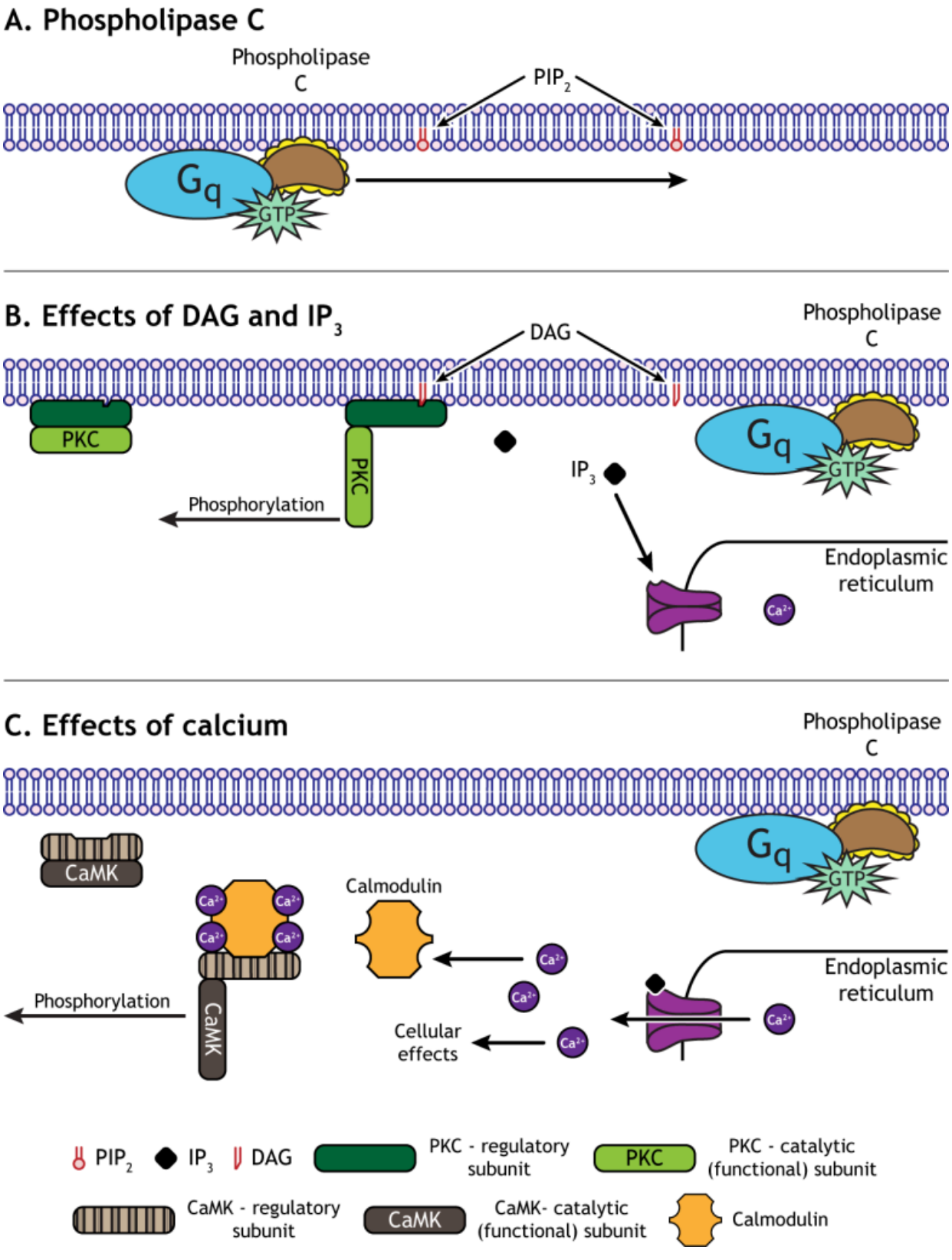

A. Phospholipase C
Phospholipase C
PIP2
Gq
GTP
B. Effects of DAG and IP3
DAG
Phospholipase C
PKC
PKC
Phosphorylation
IP3
Gq
GTP
Endoplasmic reticulum
Ca2+
C. Effects of calcium
Phospholipase C
CaMK
Ca2+
Calmodulin
Gq
GTP
Endoplasmic reticulum
Phosphorylation
CaMK
Cellular effects
PIP2
IP3
DAG
PKC - regulatory subunit
PKC
PKC - catalytic (functional) subunit
CaMK - regulatory subunit
CaMK
CaMK- catalytic (functional) subunit
Calmodulin

Figure 12.11. A) The Gq G-protein subunit activates phospholipase C, which converts the phospholipid PIP2 in the cell membrane into DAG, another membrane-bound molecule, and IP3, a cytoplasmic molecule. B) DAG can interact with PKA, initiating phosphorylation of cellular proteins. IP3 opens calcium channels in the endoplasmic reticulum, allowing calcium to flow into the cytoplasm. C) Calcium, another second messenger can have many cellular effects. It can bind to calmodulin, which then activates CaMK, causing phosphorylation of more protein targets. 'IP3-DAG Pathway' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Chapter 19

Animation 1

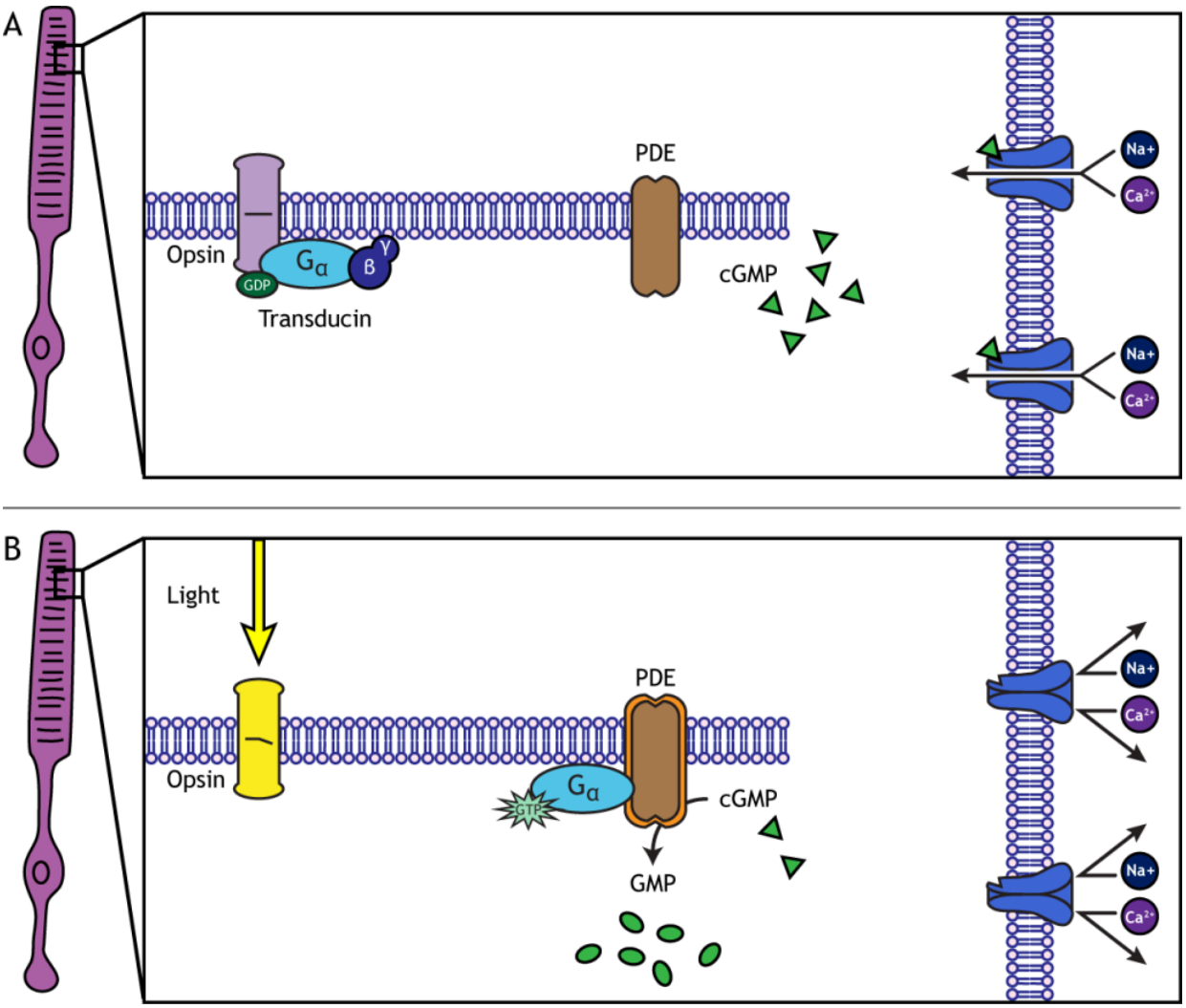


Figure 19.16. A) In the dark, the photoreceptor is depolarized due to an influx of sodium and calcium through open ion channels that are gated by cGMP. The photoreceptor has high levels of cGMP when it is in the dark. Additionally, the opsin proteins, the G-protein transducin, and phosphodiesterase (PDE) are all inactivated. B) Light reaching the photoreceptor causes a conformational change in the opsin protein, which activates the G-protein transducing. Transducin activates phosphodiesterase (PDE), which converts cGMP to GMP. Without cGMP, the cation channels close, stopping the influx of positive ions. This results in a hyperpolarization of the cell. 'Phototransduction' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

GLOSSARY

5-α reductase

enzyme that converts testosterone into DHT

ablation

A procedure that removes a structure and/or its function

absolute refractory period

occurs during the rising and falling phase of the action potential. Another action potential cannot be fired under any circumstance during this time.

acetylcholinesterase

enzyme that breaks down acetylcholine

Alpha (α) rays

Alpha (α) rays are high energy rays emitted by radioactive particles. α-rays are comprised of alpha (α) particles, each of which carries two positive charges. Based on its mass, it was apparent that each α-particle is equivalent to a Helium (He) nucleus, with two protons and two neutrons.

Axon

The long process that extends from the cell body; transmits the action potential from the cell body to the axon terminal.

Beta (β) rays

Beta (β) rays are emitted by radioactive materials. β-rays were found to be made up of high

energy electrons; so each β-particle is an electron, moving at a high speed because breakdown of radioactive atoms results in emission of electrons which are accelerated to a high speed..

cleavage

Cell division in the early embryo, following fertilization. Initial cell divisions are synchronized, since expression is controlled by translation of maternally contributed mRNA and enzymes. After a few cycles of cell division, embryonic transcription starts, at which point each cell starts to develop differently.

Current

Current flow is essentially any movement of ions; conversely, ion flow is assessed as current

Dendrites

Processes that branch out in a tree-like fashion from the neuronal cell body and are the main target for incoming signals received from other neurons.

electronegative

More electronegative elements have atoms that easily attract or accept electrons. Oxygen is an important biologically relevant electronegative element; in fact, oxygen is the most electronegative biologically relevant element.

epiblast

Stage in development where all the precursor (stem) cells are arranged in a single layer, ready for gastrulation.

gastrulation

Stage in development where the zygote transforms into a 3-layered structure, with defined ectoderm, mesoderm and endoderm. In most animals, this involves folding in which one group of cells passes under or below other cells to create multiple layers.

graded

Vary in magnitude, depending on input. Graded potentials thus differ from action potentials, which are all or none (binary).

Ion

An atom or molecule that carries a net positive or negative charge (See Fig E3, chapter Bioelectricity). Net charge is changed by the loss or gain of electrons.

Charged particles are generally hydrophilic, since they can assimilate within the fluid structure of polarized water molecules.

malleable metal

Malleability is the property of a metal that allows it to be beaten (hammered) into extremely thin sheets. Gold can be made into sheets that are only a couple of atoms thick! These sheets are so thin, that some are used as decoration in very expensive sweets in South Asia, especially during weddings and festivals.

Neuron

The basic cellular unit of the brain that is electrically excitable and can transmit information to other cells through synapses.

notochord

Mesodermal cylinder formed during gastrulation. It serves as a signaling center, and specifies ventral cells of the neural tube as motor neurons, while dorsal cells develop into sensory interneurons under the influence of epidermal signaling.

plum pudding model

The model of an atom where all subatomic particles are distributed evenly within the atom, like plums, raisins, and nuts in a pudding. Note that by this time, scientists already knew that atoms were made up of subatomic particles, named neutrons, protons and electrons.

Soma

The cell body, which houses the nucleus and other organelles necessary for cellular functioning.