THE UNTAPPED POTENTIAL OF CONE SNAIL VENOM PEPTIDES: CONOPRESSIN'S MODULATION OF OXYTOCIN AND VASOPRESSIN HORMONE RECEPTORS

by

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The Untapped Potential of Cone Snail Venom Peptides: Conopressin's Modulation of Oxytocin and Vasopressin Hormone Receptors

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This paper provides a review of the medical and research applications of cone snail venom components. Cone snail venom contains specialized peptides called conopeptides which are estimated to number more than 800,000 in total from across all cone snail species. Depending on the needs of each cone snail species, its conopeptides can be specialized for predation or defense and can have a wide variety of effects. Despite their overall abundance and diversity of effects, however, the FDA has only approved a single conopeptide, ω-conopeptide MVIIA, which is used as a painkiller, for widespread medical use. Conopeptides, therefore, represent an underdeveloped area of research that has only just started to garner more thorough exploration in recent years. Conopressin is one such conopeptide that has received increased attention due to its capacity to bind with receptors for oxytocin and vasopressin, hormones which play critical roles in functions as diverse as social bonding, blood pressure maintenance, and kidney function. This paper will briefly outline the structure of conopressin, and highlight its ability to act as both an agonist and antagonist for specific hormone receptors throughout the body, thereby allowing for the blocking or promotion of oxytocin or vasopressin activity at desired locations to induce different desired effects. While research on conopressin is still ongoing, its versatility in modulating oxytocin and vasopressin hormonal activity positions it as a promising candidate for future therapeutic development.

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Introduction

This thesis will serve as a review of currently established and recent research on cone snail venom, with a particular emphasis on the recently discovered venom component conopressin and its ability to induce various responses from oxytocin and vasopressin hormone receptors (Turner et al., 2020). This thesis will also seek to describe the mechanisms of oxytocin and vasopressin on which conopressin acts, and to explore the current research being conducted on conopressin in regard to its potential when interacting with oxytocin and vasopressin receptors.

Overview of Cone Snails and Conopeptides

Cone snails (genus *Conus*) are a marine mollusk species, classified as gastropods of the Conidae family, which can be found among coral reefs within the Indian, Pacific, and Atlantic Oceans (Ratibou et al., 2024), and can be either vermivorous, piscivorous, or molluscivorous (Koch et al., 2024; Ratibou et al., 2024). To capture prey, cone snails employ the use of a harpoon-like tooth (Fig. 1) loaded with venom composed of specialized peptides known as conopeptides (Dutertre et al., 2014). With over 800 identified members of the *Conus* genus, each having a unique venom composed of more than

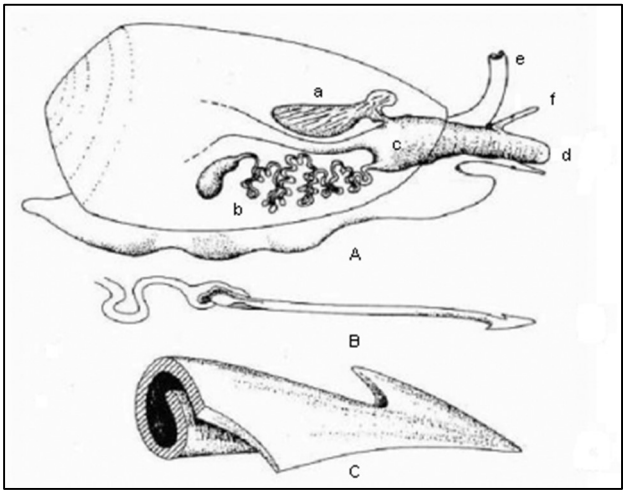

Figure 1. Cone Snail Harpoon-like Tooth Close Up.
A: Visual of cone snail organs related to venom creation and usage. a: Harpoon sac; b: Oesophageal (venom) gland; c: Pharynx; d: Proboscis; e: Sipho; f: Eye stalks. B: Harpoon-like tooth isolated from the rest of the cone snail. C: Harpoon-like tooth tip close-up.
Credit: "Cone Shells' (Conidae) Venom Apparatus."

1,000 conopeptides, there are estimated to be over 800,000 different conopeptides across all cone snail species (Gao et al., 2022; Puillandre et al., 2012). To help better categorize this volume of different conopeptides, they have been divided into 26 superfamilies (Robinson & Norton, 2014). These peptide superfamilies are distinguished based on characteristic arrangements of cysteine residues at their amino acid sequences of different conopeptides, with conopeptides in the same family having similar structures and functions, as well as often being derived from the same common ancestor (Koch et al., 2024; Robinson & Norton, 2014). Within these superfamilies, there are conopeptide variants which exhibit heightened effectiveness against specific cone snail prey or predator types (i.e. worms, fish, or mollusks) (Koch et al., 2024). For example, the M-superfamily contains several conopeptides that block various voltage-gated ion channels (Robinson & Norton, 2014). Within the M-superfamily, however, μ-conotoxin blocks voltage-gated sodium channels of vertebrate muscle specifically, and as such is primarily found in the venom of piscivorous cone snails (Koch et al., 2024).

Additionally, cone snails are one of very few groups that employ different venom compositions when hunting prey versus defending from predators (Dutertre et al., 2014). As a result their venom must not only be tailored to their specific prey, but also be easily swapped for a different specialized venom meant to deter and defend against specific predators (Ratibou et al., 2024). The exact mechanism by which cone snails switch between predation- and defense-evoked venoms is not fully understood, but the current theory is that the proximal portion of the venom gland contains defense-evoked venom, while the distal portion of the venom gland contains prey-evoked venom (Fig. 2). In such a case, the venom gland would utilize different excretory pathways to load the cone snail's harpoon with either type of venom, depending on what type of stimulus initiated the response in the first place, with the perception of prey leading

to the loading of the prey-evoked venom, and the perception of predators leading to the loading of the defense-evoked venom (Dutertre et al., 2014). Analysis of extracted defense- and predation-evoked venoms revealed that they shared very little overlap in conopeptide makeup, effectively meaning that each cone snail species has two separate venoms to draw potentially pharmacologically relevant conopeptides from (Dutertre et al., 2014).

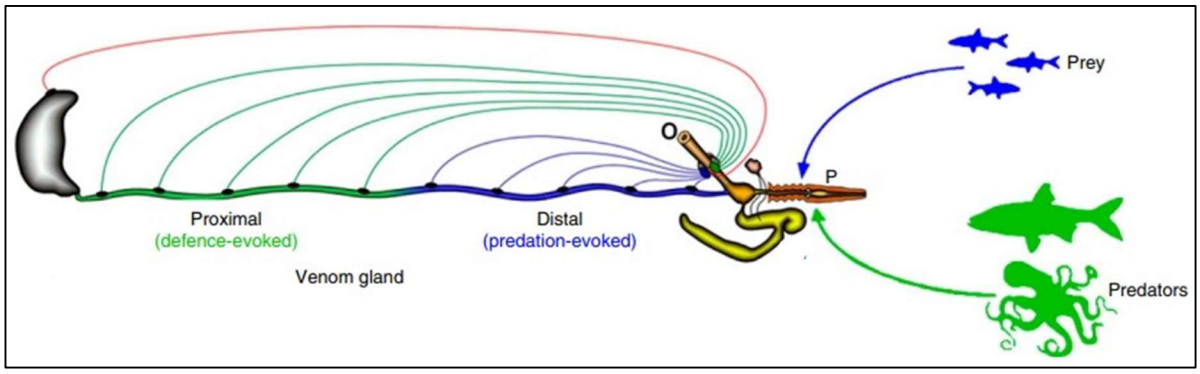

Figure 2. Simplified Diagram of Prey- and Defense-evoked Venoms in Cone Snails. When prey or predators are detected, typically via sight or olfaction, the appropriate venom gland pathway will be used to load the cone snail's harpoon-like tooth (P) with the venom that correlates with whatever instigated the response. Predators will cause the defense-evoked venom pathway (shown in green) to be used, loading venom from the proximal region of the venom gland specialized for protection. Prey will cause the predation-evoked venom pathway (shown in blue) to be used, loading venom from the distal region of the venom gland specialized for hunting.
Credit: Dutertre et al., 2014

Conopeptide Current Uses in Medicine and Research

Research on conopeptides has been primarily focused on their use as potential painkillers (Turner et al., 2020). One particular group, ω-conopeptides, are among the most heavily researched due to exhibiting a high affinity for mammalian neuronal voltage-gated calcium ion channels responsible for pain perception (Safavi-Hemami et al., 2019). The specific ω-conopeptide, ω-conopeptide MVIIA (M referring to the conopeptide originating from the venom of the *Conus magus*, VII referring to its C-C-CC-C-C cysteine residue arrangement, and A used to identify its status as the first of the MVII conopeptides to be discovered) is particularly notable

for being the first conopeptide to enter clinical trials, as well as the first to eventually receive FDA approval (Schroeder & Lewis, 2006). Referred to as Ziconotide when synthesized, ω-conopeptide MVIIA has recently been used as a substitute for morphine due to patients not developing a tolerance to it, and it not inducing withdrawals (Safavi-Hemami et al., 2019). The implementation of ω-conopeptide MVIIA in clinical settings has been limited, however, as it is more difficult to administer than morphine, requiring injection into the spinal cord (Robinson et al., 2017). Still, ω-conopeptide MVIIA represents only a single conopeptide from among the estimated 800,000, and other conopeptides have demonstrated just as much pharmacological potential. One such conopeptide that has received increased attention in recent years is conopressin. Conopressin is capable of interacting with the receptors for oxytocin and vasopressin, hormones involved in social interactions, reproductive functions, blood pressure maintenance, kidney function, and more (Carter, 2022; Cuzzo et al., 2025; Ito et al., 2019; Turner et al., 2020). Conopressin, therefore, represents new avenues of research into conopeptide uses that have previously gone unexplored.

Oxytocin and Vasopressin Overview

What is Oxytocin and How Do its Receptors Work?

Oxytocin is a small peptide hormone composed of nine amino acids in the sequence Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2. The molecule features a disulfide bridge between the cysteine residues at positions 1 and 6, forming a cyclic structure characteristic of this and similar hormones (Fig. 3A). Oxytocin is primarily synthesized in the hypothalamus at the supraoptic nucleus (SON) and paraventricular nucleus (PVN) and expressed through the posterior pituitary, though synthesis has also been observed in peripheral tissues such as the uterus, placenta, amnion, corpus luteum, testis, and heart (Gimpl & Fahrenholz, 2001). Oxytocin is released into the bloodstream in response to stimuli such as social bonding, physical contact, and childbirth, and binds with oxytocin receptors (OTR) located throughout both the central and peripheral nervous systems, with a particular abundance of the receptors present at several brain regions like the hypothalamus, the olfactory nucleus, and the amygdala (Ito et al., 2019). The binding of oxytocin to different receptors is responsible for a variety of biological functions such as regulation of inflammation, initiation of uterine contractions during labor, milk ejection during lactation, and activity in sexual organs, such as promoting spermatogenesis (Gimpl & Fahrenholz, 2001; Ito et al., 2019). Oxytocin can also modulate emotional and social behaviors such as trust, empathy, and pair bonding (Gimpl & Fahrenholz, 2001; Meyer-Lindenberg et al., 2011).

Upon the binding of oxytocin, OTRs carry out their functions through a signal transduction pathway. OTRs are G protein-coupled receptors (GPCRs) which, when bound with oxytocin, become functionally coupled to $G_{q/11}\alpha$ class GTP binding proteins that stimulate the activity of phospholipase C, leading to the generation of inositol trisphosphate. Inositol

trisphosphate is then responsible for the triggering of Ca^{2+} release from existing intracellular stores, which can then induce several of the previously mentioned effects. For example, an increase in intracellular Ca^{2+} is capable of forming Ca^{2+}-calmodulin complexes which in smooth muscle cells can trigger activity in light-chain kinase, initiating smooth muscle contraction as seen during uterine contractions and when inducing lactation in mammary glands (Gimpl & Fahrenholz, 2001). The heightened Ca^{2+} levels also play a role in emotional and social behavioral modulation, as Ca^{2+} levels can influence cellular excitability and transmitter release in neurosecretory cells (Gimpl & Fahrenholz, 2001).

What is Vasopressin and How Do its Receptors Work?

Vasopressin is a small peptide hormone, like oxytocin, and is composed of nine amino acids in the sequence Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH_2. Like oxytocin, the molecular structure of vasopressin contains a disulfide bridge between cysteine residues at positions 1 and 6, forming the same characteristic cyclic structure (Fig. 3B). Vasopressin is primarily synthesized in the hypothalamus at the SON, though a lower level of production does also take place at the PVN. It is released from the posterior pituitary gland into the bloodstream in response to stimuli such as increased plasma osmolality and decreased blood volume (Cuzzo et al., 2025).

Upon release into the bloodstream, vasopressin binds to specific GPCRs located throughout the body, which are classified into three types: $V1_A$, $V1_B$, and V2 receptors. $V1_A$ receptors are responsible for causing vasoconstriction and are primarily expressed in vascular smooth muscle cells. $V1_B$ receptors are expressed in cells of the anterior pituitary and aid in regulating the release of adrenocorticotropic hormone (ACTH), which is involved in the

stimulation of stress responses like the release of cortisol, as well as regulating physiological functions like metabolism and blood pressure (Koshimizu et al., 2012). V2 receptors are predominantly expressed in the kidneys and contribute to maintaining the kidneys' ability to retain water by limiting the excretion of sodium (Stockand, 2010). V2 receptors are also expressed at lower levels throughout the vascular endothelial cells, and as such, high levels of V2 receptor activation can lead to vasoconstriction (Cuzzo et al., 2025).

The mechanism of action followed by the $V1_A$ and $V1_B$ receptors greatly resembles what was seen with OTRs. The $V1_A$ and $V1_B$ receptors, once bound with vasopressin, become functionally coupled to $G_{q/11}\alpha$ class GTP binding proteins. This leads to the stimulation of phospholipase C, which in turn leads to the generation of inositol trisphosphate and the triggering of Ca^{2+} release from existing intracellular stores (Koshimizu et al., 2012). At sites of $V1_A$ receptors, such as vascular smooth muscle cells, the increased Ca^{2+} release is responsible for smooth muscle contraction, leading to vasoconstriction, and at sites of $V1_B$ receptors, the increased Ca^{2+} release can influence the release rate of hormones such as ACTH (Koshimizu et al., 2012). Compared to the V1 receptors, however, the V2 receptor follows a different mechanism of activation. Within the hypothalamus there are neurons which express osmoreceptors which are sensitive to blood osmolarity. These osmoreceptors are capable of detecting when blood osmolarity increases, or when blood volume decreases, and can trigger an increased production and excretion of vasopressin as a result. The vasopressin then binds to V2 receptors, triggering the activation of adenylate cyclase, which causes a subsequent increase in the second messenger cyclic AMP (cAMP). cAMP activates a phosphorylating enzyme called protein kinase A (PKA), which then phosphorylates aquaporin-2 (AQP2), a channel that allows for the intracellular flow of water across an osmotic gradient. Within the kidneys, a higher

concentration of NaCl should be present, resulting in the osmotic gradient leading water to be drawn across the AQP2 and into the kidney for reabsorption (Cuzzo et al., 2025; Stockand, 2010). In cases where the osmoreceptors are activated due to a low volume of blood, activation of V2 receptors along the vascular endothelial cells can result in direct vasoconstriction to increase the proportionate volume of blood within the constricted area, thereby aiding in blood pressure regulation while the rest of the body works to restore normal blood volume levels

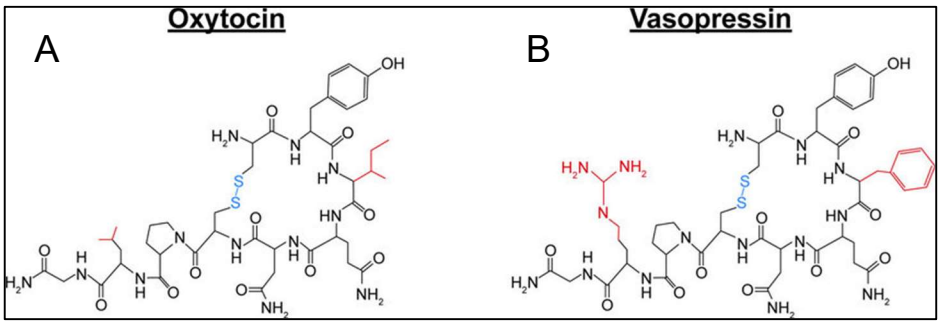

Figure 3. Oxytocin and vasopressin structures. Molecular structures of oxytocin and vasopressin. Blue shows a disulfide bond present in both structures. Red shows two amino acids each that differentiate oxytocin and vasopressin. Credit: Bordt et al., 2018

(Cuzzo et al., 2025).

Current Research on Oxytocin and Vasopressin Based Medication

There are several pharmacological agents currently approved by the FDA that interact with oxytocin and vasopressin receptors. *Pitocin*, which is a brand name for synthetic oxytocin, is used to induce labor and control postpartum bleeding through regulation of uterine contractions ("Pitocin Induction During Labor," n.d.). The medication atosiban, on the other hand, is intended to prevent premature labor by inhibiting oxytocin and vasopressin receptors ("Atosiban," n.d.). Desmopressin, a synthetic version of vasopressin, is capable of selectively

activating V2 receptors to aid in water reabsorption, effectively acting as an antidiuretic ("Desmopressin," n.d.). Terlipressin, another form of synthetic vasopressin, is used to manage complications due to vasodilation, such as excessive bleeding or esophageal rupture. It acts by inducing vasoconstriction through heightened selectivity for $V1_A$ receptors ("Terlipressin," n.d.). Conversely, conivaptan and tolvaptan can be used to treat hyponatremia by inhibiting V2 receptor-mediated water reabsorption. They are particularly effective compared to other hyponatremia treatments, as conivaptan and tolvaptan can demonstrate meaningful improvement to blood sodium levels within 24 hours, and last for up to 96 hours, whereas other treatments like fludrocortisone may take days before it reaches peak effectiveness (Der-Nigoghossian et al., 2017).

Though still undergoing active research and not yet approved by the FDA, intranasal oxytocin and vasopressin are being explored as methods for direct application of oxytocin or vasopressin to the brain. Intranasal oxytocin and vasopressin have undergone decades of preclinical and clinical trials to observe their effects on patients with autism, anxiety, depression, and schizophrenia, but as of current it is unclear whether the treatment is able to bypass the blood-brain barrier (Yao & Kendrick, 2022). The treatments are intended to utilize receptors for advanced glycation end products (RAGE), which are capable of crossing the blood-brain barrier. The intention is for oxytocin or vasopressin to bind with RAGE, thereby granting them access to the brain. At current, however, it is still unclear if oxytocin or vasopressin are actually crossing the blood-brain barrier, or if any results may simply stem from the induction of oxytocin or vasopressin into peripheral systems, rather than the brain (Yao & Kendrick, 2022).

Conopressin Structure and Potential Uses

Conopressin has been shown to exhibit effects on oxytocin receptors and the three vasopressin receptor types, $V1_A$, $V1_B$, and V2 (Turner et al., 2020). To explain these different effects, however, we first need to cover the structure of conopressin, and how that structure plays a role in its ability to interact with different hormone receptors. Conopressin is, like oxytocin and vasopressin, a small peptide composed of nine amino acids that form a disulfide bridge between cysteine residues at positions 1 and 6, forming the same characteristic cyclic structure seen in oxytocin and vasopressin (Fig. 4). Different conopressin subtypes can be derived from different cone snail species, and each subtype has its own unique amino acid sequence. For example, conopressin-G, which originates from *Conus geographus*, has the amino acid sequence Cys-Phe-Ile-Arg-Asn-Cys-Pro-Arg-Gly-NH_2, whereas conopressin-T from *Conus tulipa* has the amino acid sequence Cys-Tyr-Ile-Gln-Asn-Cys-Leu-Arg-Val-NH_2. In addition to the amino acid sequence for all conopressin subtypes retaining the cystines at positions 1 and 6, nearly all conopressin subtypes retain proline and glycine at positions 7 and 9. A notable exception to this is Conopressin-T, which is the only conopressin to have a different amino acid at position 7 (Dutertre et al., 2008). Conopressin-M1/M2 are also exceptions as they, along with conopressin-T, have a different amino acid at position 9, with serine instead being present for M1 and M2, and valine for T (Giribaldi et al., 2020). The differences in amino acid sequences is likely what confers varying affinities for different receptors of oxytocin and vasopressin across the different conopressin subtypes, such as conopressin-T exhibiting high affinity for the OTR and $V1_A$ receptors, but no detectable interactions were observed with the $V1_B$ or V2 receptors (Dutertre et al., 2008). Changes to the amino acid sequence of conopressin has been shown to alter its affinity for receptors, such as with the L7P-conopressin-T mutant, which displays an increased affinity

for the $V1_A$ receptors (Giribaldi et al., 2020). Importantly, the change from leucine to proline in the L7P-conopressin-T mutant demonstrated no changes to its affinity for $V1_B$ or V2 receptors, indicating the potential for conopressins to be modified to exhibit only a desired level of affinity for specific target receptors (Dutertre et al., 2008; Giribaldi et al., 2020).

Conopressin-M1 shows agonist activity at both the $V1_A$ and $V1_B$ receptors, meaning it is capable of binding to, and subsequently eliciting reactions from, vasopressin receptors, initiating the same transduction pathways and subsequent reactions as if vasopressin were bound to the receptor (Giribaldi et al., 2020). Like conopressin-M1, conopressin-M2 also acts as an agonist, but rather than acting on the $V1_A$ and $V1_B$ receptors, M2 acts only on the V2 receptor (Giribaldi et al., 2020). In addition to the capacity for conopressin to elicit reactions from receptors similar to what would be seen from the binding of oxytocin or vasopressin, as was the case with conopressin-M1/M2, sone subtypes have exhibited the ability to act as antagonists, effectively decreasing or outright blocking the ability for oxytocin or vasopressin to bind with their receptors, and thereby preventing oxytocin or vasopressin from carrying out any of their functions (Dutertre et al., 2008; Giribaldi et al., 2020; Turner et al., 2020). This antagonistic activity has been seen in conopressin-T, which is significant due to its similarity to antagonistic oxytocin and vasopressin

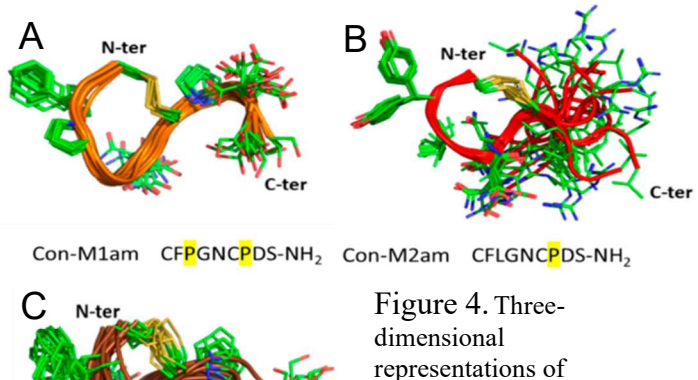

Figure 4. Three-dimensional representations of different conopressin types. Conopressin-M1 (A), Conopressin-M2 (B) and Conopressin-T (C). Chemical formulas for the different conopressin subtypes are shown to the right of the subtype names. Proline, which constrains the structure of M1 and M2 is highlighted in yellow.
Credit: Giribaldi et al., 2020

mutants. As in conopressin-T, valine, rather than glycine, is found at position 9 of the amino acid sequence for these oxytocin and vasopressin mutants. Given that the oxytocin and vasopressin mutants had no other meaningful differences from normal oxytocin and vasopressin, it is believed that a change in the amino acid sequence of glycine to valine at position 9 acts as a switch from agonistic to antagonistic activity (Giribaldi et al., 2020). Conopressin-T reinforces this idea as the only antagonistic conopressin and the only conopressin subtype with valine at its 9th amino acid position. It therefore represents how this idea of valine serving as an agonist/antagonist switch is applicable for conopressin as well. This is further supported by the fact that conopressin-M1/M2 also lack glycine at their 9th amino acid position, having serine instead, but they retain their agonist activity, indicating that it is valine specifically that causes the antagonistic activity (Giribaldi et al., 2020).

The L7P-conopressin-T mutant demonstrated that alterations to the affinity of conopressin to target receptors can be accomplished through alterations in its amino acid sequence. It also demonstrated that this can be accomplished without altering its affinity for other receptors. These facts, combined with the knowledge of valine's capacity as an agonist/antagonist switch, indicate the potential for conopressin to be modified to accomplish deliberate and measured activation or blocking of specific receptors.

Future Directions for Conopressin Research

While ω-conopeptide MVIIA is the only clinically approved conopeptide at the current time, research on potential medical applications of other conopeptides, including conopressin, are ongoing (Gao et al., 2022; Turner et al., 2020). Despite active research, however, information on conopressin's medical applications is surprisingly sparse, as the capacity of conopeptides to

act as painkillers has drawn the attention of most conopeptide-based research up to this point (Turner et al., 2020). Still, conopressin has shown a few promising avenues of research.

Given the disproportionate attention conopeptides have received for their painkiller properties thus far, that may be a strong starting point to garner increasing interest in conopressin. Existing pain treatments using ω-conopeptide MVIIA involve the blocking of voltage-gated calcium channels related to pain perception, but the treatment is only effective for acute pain and is not feasible to administer without specialized care due to its administration requiring a spinal cord injection (Safavi-Hemami et al., 2019). Unlike acute pain, however, chronic pain currently has no established treatments using conopeptides, though conopressin may be able to change that. Oxytocin is currently being researched as a potential treatment for chronic pain, but the exact mechanisms by which this is accomplished are not yet fully understood (Mekhael et al., 2023). Research suggests that in response to chronic pain oxytocin is projected into the dorsal horn, where most nociceptive neurons terminate, at which point the oxytocin is capable of inhibiting pain transmission (Jo et al., 1998). Oxytocin may also be released into the peripheral nervous system from the SUN of the hypothalamus, where it exhibits indirect antinociceptive effects (Eliava et al., 2016). Despite an incomplete understanding of the exact mechanisms by which it alleviates chronic pain, the use of oxytocin as a treatment method has seen success, though results have been inconsistent due to varying levels of oxytocin among different patients (Mekhael et al., 2023). These mixed results indicate the need for precise control over the amount of oxytocin used in treatments, which is where conopressin-T becomes a promising alternative to oxytocin moving forward. Conopressin-T is the only conopressin naturally capable of binding to OTRs, and the ability to be modified for desired levels of affinity means it may be more suited for treatments that require precise control over dosages compared to

unmodified oxytocin (Dutertre et al., 2008; Mekhael et al., 2023). Additionally, the versatility of conopressin-T could help to better identify the mechanisms by which oxytocin, and by extension conopressin-T, are capable of treating chronic pain. By using the antagonistic activity of conopressin-T to selectively block oxytocin reception by OTRs in different potential pathways, it could be deduced, through process of elimination, which pathways are responsible for the alleviation of chronic pain by determining which pathways were not blocked when alleviation occurred (Eliava et al., 2016; Jo et al., 1998; Mekhael et al., 2023). Conopressin-T therefore represents not only a more precise pharmacological agent for the treatment of chronic pain compared to oxytocin, but also a useful tool for better deciphering the mechanisms by which chronic pain may be treated.

Conopressin-T may also be useful for treating psychiatric disorders such as major depressive disorder (MDD). Some current treatments for MDD utilize oxytocin, as patients with MDD often have below-average oxytocin levels. Specific variations of MDD such as postpartum depression have seen treatment success by taking low doses of oxytocin for the duration of one week, or a high dose only a single time, either of which has been shown to raise activity in the limbic region of the brain, which can alleviate the patients' depressive symptoms (Kagizman & Hocaogu, 2023). This treatment has faced complications, however, as doses at higher volumes or for more prolonged periods have led to worsening of symptoms rather than alleviation (Kagizman & Hocaogu, 2023). In this way, conopressin-T is uniquely suited to be a more effective alternative to the existing treatment method. The L7P-conopressin-T mutant has shown conopressin-T's capacity for heightened, yet still selective, receptor affinity through modification, and a change of conopressin-T from an antagonist to an agonist is possible by changing the identity of valine to glycine at the 9th position in its amino acid sequence.

Modifications to conopressin-T for heightened OTR affinity may therefore be capable of more precise agonistic activity compared to current treatment methods using oxytocin, and as such, may be more effective for avoiding overdosing and the subsequent worsening of symptoms (Kagizman & Hocaogu, 2023; Turner et al., 2020).

Like oxytocin, there are several vasopressin-related treatments for which conopressin may serve as a promising alternative, most notable of which being the treatment of a certain type of cancer. One such cancer, small-cell carcinoma of the lung (SCCL), undergoes rapid proliferation in the presence of high concentrations of intracellular free Ca^{2+}. $V1_A$ receptors are expressed by all SCCL tumors, and are largely responsible for their proliferation due to the binding of vasopressin to $V1_A$ receptors leading to an increased release of Ca^{2+} from intracellular stores (Koshimizu et al., 2012; North et al., 1997). Some variants of SCCL are resistant to chemotherapy (North et al., 1997), leaving treatment alternatives all the more desirable. Current treatment methods involve using V2 receptors, capable of regulating blood osmolarity, and therefore capable of reducing the concentration of Ca^{2+} at sites of SCCL tumors (Cuzzo et al., 2025; Pifano et al., 2017). Conopressin-M2 would make for a potential treatment option, as it has an inherent selectivity for V2 receptors and has the capacity for further modulation of V2 receptor affinity via alteration of its amino acid sequence (Giribaldi et al., 2020). It would, however, have to compete with the synthetic alternative to vasopressin, desmopressin, which exhibits an even greater affinity for the V2 receptor than conopressin-M2 does. In fact, administration of desmopressin to tumor sites is the current treatment method for SCCL (Pifano et al., 2017). Conopressin distinguishes itself not as a replacement for desmopressin, but instead as a complementary treatment. While conopressin-M2 would have to compete with desmopressin for the role of most effective V2 receptor-based treatment, conopressin-M1, selective for the $V1_A$

receptor, faces no such competition. While the current method of treatment for SCCL involves reducing the concentration of Ca^{2+} at tumor sites, research has found that limiting the ability for the $V1_A$ receptors to bind with vasopressin, and subsequently preventing the release of Ca^{2+} before it even begins, is another effective method of treatment (Zhao et al., 2019). Research on limiting $V1_A$ activity has been primarily based on $V1_A$ deficient mutants up until this point, however, but the ability to modulate the agonistic/antagonistic activity of conopressin through the valine switch at position 9 in the amino acid sequence allows for conopressin-M1, which normally exhibits agonistic activity at the $V1_A$ receptor, to serve as an antagonist to block any vasopressin binding, thereby preventing any release of Ca^{2+} (Giribaldi et al., 2020; Zhao et al., 2019). Conopressin-M1, is therefore a novel treatment method for SCCL, utilizing a method not currently employed by blocking $V1_A$ receptors, rather than activating V2 receptors as is the case with the current desmopressin-based treatment.

Conclusion

Conopeptides are abundant and varied in their pharmacological applications, yet they remain underexplored in the fields of research and medicine (Turner et al., 2020). While ω-conopeptide MVIIA has seen success in achieving FDA approval and reaching more widespread applications, it is but one from among more than 800,000 different conopeptides, representing a small fraction of the potential they hold. Conopressin is a prime example of the untapped potential of conopeptides due to its versatility. Different conopressin types have shown to be either agonists capable of activating OTRs and the $V1_A$, $V1_B$, and V2 receptors, or antagonists capable of blocking those receptors from binding with oxytocin or vasopressin (Dutertre et al., 2008). Additionally, conopressin subtypes have exhibited selectivity for different receptors, and their affinity for those different receptors can be modified (Dutertre et al., 2008; Giribaldi et al., 2020). Taken together, these factors indicate the potential for conopressin to be effective when used for precise and targeted treatments that would otherwise have to rely on the less versatile oxytocin or vasopressin. Research into utilizing conopressin is still in the early stages, however, and more work is required to understand how to best utilize it for specific treatments before it can see the same level of usage as ω-conopeptide MVIIA (Turner et al., 2020). The versatility of conopressin may help advance treatments for ailments such as chronic pain and MMD (Kagizman & Hocaogu, 2023; Mekhael et al., 2023), and open up new treatment options for things like SCCL (Zhao et al., 2019). Despite the nascency of conopressin's applications in medicine and research, it holds much promise and is indicative of just how much potential there may still be lying in wait among the other 800,000 conopeptides yet to be fully understood.

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