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Cross-talk among oxytocin and arginine-vasopressin receptors: Relevance for basic and clinical studies of the brain and periphery

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Abstract

Oxytocin (OT) and arginine-vasopressin (AVP) act in the brain to regulate social cognition/social behavior and in the periphery to influence a variety of physiological processes. Although the chemical structures of OT and AVP as well as their receptors are quite similar, OT and AVP can have distinct or even opposing actions. Here, we review the increasing body of evidence that exogenously administered and endogenously released OT and AVP can activate each other's canonical receptors (i.e., cross-talk) and examine the possibility that receptor cross-talk following the synaptic and non-synaptic release of OT and AVP contributes to their distinct roles in the brain and periphery. Understanding the consequences of cross-talk between OT and AVP receptors will be important in identifying how these peptides control social cognition and behavior and for the development of drugs to treat a variety of psychiatric disorders.

Keywords

G protein-coupled receptors; social cognition; intranasal administration; social communication; social recognition; social reward; pair bonding; prosocial behavior; social behavior; autism spectrum disorder

1. Introduction

Oxytocin (OT) and arginine-vasopressin (AVP) are important chemical signals that act in the brain to regulate a large number of adaptive social behaviors and in the periphery to coordinate a diverse group of physiological functions [1; 2]. Although the chemical structures of OT and AVP as well as their receptors are quite similar, there is substantial evidence that these nonapeptides (i.e., nine amino acid peptides) can have distinct or even opposing roles in the regulation of many behavioral and physiological functions [3; 4; 5; 6;

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7]. Recently, however, there has been increasing evidence that OT and AVP can act on each other's canonical receptors in potentially important ways. This review examines the potential interactions among OT, AVP and their receptors with an emphasis on the central role of these interactions in the regulation of social cognition and social behavior.

Much of the data discussed here has been collected in males despite the fact that there are major sex differences in OT and AVP systems [8; 9]. Indeed, the first demonstration of a sex difference in a neuropeptide system was identification of a sexually dimorphic innervation of the lateral septum by AVP fibers [10]. Subsequent work has found numerous examples of quantitative sex differences in nonapeptide-containing fibers and receptors in various brain regions. More recently, however, the existence of significant qualitative sex differences has also been identified. Activation of V1a receptors by AVP within the hypothalamus has opposite effects on the induction of aggression in males and females [11; 12; 13; 14].

OT and AVP evolved from a common precursor through gene duplication more than 600 million years ago [15]. OT and AVP share seven of nine amino acid sequences in their primary structure, differing only in the third and eighth positions (Figure 1). OT and AVP are found in extensive neural networks that innervate many regions in the mammalian brain (Figure 2). In mammals, OT is considered to have only one canonical receptor (i.e., OTR) while AVP is thought to have three: V1aR, V1bR and V2R [16; 17; 18]. These evolutionarily ancient receptors belong to the G protein-coupled receptor superfamily that have seven putative transmembrane domains and are found extensively throughout the body. Around 25% of the amino acid sequences in human OTR, V1aR, V1bR, and V2R are the same [19]. OT/AVP receptors are found in many different peripheral tissues [2; 20]. In mammalian brain OTRs and V1aRs are robustly expressed in many regions but their distributions often differ [9; 21; 22] (Figure 3). V1bRs appear to have a much more restricted distribution, although they are expressed prominently in the hippocampus and at lower levels in the hypothalamus and amygdala [23; 24]. Although V2Rs have also been reported in the mammalian brain, it seems unlikely that they play a significant role in mediating the central effects of these peptides so they will be mentioned only briefly in discussions of peripheral AVP receptors [25; 26; 27].

The selectivity of OT and AVP for OTRs, V1aRs, V1bRs, and V2Rs has been examined using a variety of *in vitro* and *in vivo* assays ranging from measurements of cellular activity to overt behavior. It is important to point out that there is no "gold standard" that necessarily applies to defining the selectivity of OT and AVP for OTRs, V1aRs, V1bRs, and V2Rs. Indeed, many factors including species differences, differences in the assays employed, and differences in the tissues examined need to be considered when drawing conclusions from data on the selectivity of these receptors. Nevertheless, it appears that there can be differences of around 10–100 fold in the selectivity of OTRs and AVP receptors for OT and AVP. AVP has a similar affinity for OTRs, V1aRs, and V1bRs while OT may have a higher affinity for OTRs than V1aRs or V1bRs [28; 29; 30; 31; 32; 33]. For example, studies employing recombinant expression systems to examine selectivity of human, rat, and mouse OT and AVP receptors have shown that only the human OTR is selective for OT using a standard criterion [34; 35] (Table 1). This overall lack of receptor selectivity is not surprising when one considers that these receptors have a high degree of structural homology (e.g.,

85% between V1aR and OTR) (Figure 4). Although their structural similarity and their lack of selectivity has been known for many years, only recently has the potential functional significance of the cross-talk between OT and AVP and their receptors been considered [36]. This emerging literature has come primarily from studies employing highly selective OT and AVP agonists and antagonists (see Table 2 for some commonly used and commercially available agonists and antagonists) as well as targeted genetic manipulations of OT and AVP as well as their receptors.

2. Cross-talk between OT and AVP administered peripherally

2.1 OT acting via V1aRs

Peripherally administered OT and AVP have a wide range of behavioral and physiological actions. Peripherally administered OT and AVP produce similar effects in reducing heart rate and body temperature, inducing contractions in ejaculatory tissues, and in promoting seizure susceptibility in male rats and rabbits [37; 38; 39]. These effects of OT and AVP can be inhibited by selective V1aR but not OTR antagonists. Other studies on pain perception also support the hypothesis that the effects of OT and AVP can be mediated by peripheral V1aRs. Peripheral administration of OT or AVP induces analgesia in OTR but not in V1aR knock-out male and female mice [40]. In addition, selective V1aR but not OTR antagonists inhibit both OT- and AVP- induced analgesia in wild-type mice. These analgesic effects of peripheral activation of V1aRs by OT and AVP may be mediated by V1aR modulation of ion channels in primary sensory neurons [41; 42]. Although both OT and AVP inhibit neuronal signaling in dorsal root ganglia, these effects can be inhibited by a selective V1aR antagonist but not by an OTR antagonist.

Some of the behavioral actions of peripheral administration of OT also appear to be mediated by V1aRs. The ability of peripheral administration of OT to reduce locomotor activity in male rats is reduced by a selective V1aR antagonist [43]. Both OT and AVP administered peripherally increase a form of social interaction in male rats referred to as “adjacent lying” in which rats maintain passive side-by-side contact during their first interaction [44]. A selective V1aR, but not an OTR antagonist, inhibits adjacent lying following peripheral administration of OT or AVP. Peripheral administration of either OT or AVP also increases social huddling in response to threatening stimuli (i.e., cat fur) and these effects are inhibited by a selective V1aR antagonist [45]. Taken together, these data suggest that peripherally administered OT and AVP can act through V1aRs to alter physiology and behavior.

2.2 AVP acting via OTRs

There is a limited amount of evidence that peripherally administered AVP can act via OTRs. Uterine contractions induced by OT or AVP are largely mediated by OTRs [46; 47; 48]. Both OT and AVP administered peripherally also increase social investigation in male rats. Peripheral administration of a selective OTR antagonist, but not a selective V1aR antagonist, inhibits OT- and AVP-induced increases in social investigation suggesting that both peptides are acting through the OTR [49].

2.3 OT acting via V1bRs

In the pituitary gland OT induces release of adrenocorticotropin via both OTRs and V1bRs in male mice and female rats [50; 51]. There is also evidence to suggest that OT can act on V1bRs as well as OTRs and that AVP can act on OTRs as well as V1bRs to induce glucagon secretion from pancreatic islet cells in male mice [52].

3.0 Cross-talk between OT and AVP administered in the brain

3.1 OT acting via V1aRs

While there are many examples of centrally administered OT and AVP influencing behavior, emerging evidence shows that receptor cross-talk may be involved in mediating at least some of these effects. Central administration of OT or AVP induces scratching behavior in wild-type and OTR knock-out male and female mice but not in V1aR knock-out mice [40]. There are also studies that have found that OT can act via V1aRs to influence a range of social behaviors [53]. In OTR null mice social exploration and social recognition are reduced, while aggression is increased when compared to wild-type mice. While intracerebroventricular (ICV) injection of OT or AVP can restore wild-type levels of these behaviors, the effects of OT and AVP are inhibited by a selective V1aR antagonist. Another example comes from studies of peer affiliation in female meadow voles [54]. When housed in winter-like conditions female voles form partner preferences for other females. Injection of OT into the lateral septum prevents the formation of these partner preferences, an effect that is blocked by co-administration of OT with a V1aR but not an OTR antagonist.

Another social behavior that can be elicited by central administration of OT or AVP is a form of social communication in Syrian hamsters called flank marking. Injection of AVP into several brain sites including the anterior hypothalamus (AH), the lateral septum (LS), and the periaqueductal gray (PAG), induce robust bouts of flank marking [55; 56; 57; 58]. Structure-activity studies as well as the central injection of highly selective V1a agonists and antagonists indicates that AVP acts on V1aRs to stimulate flank marking [59; 60]. More recently, ICV administration of OT has also been shown to induce flank marking in male hamsters [33]. Both OT and AVP induce flank marking in a dose-dependent manner, although AVP is around 100-fold more potent than OT in inducing the behavior (Figure 5). To determine whether OT also acts on V1aRs to induce flank marking highly selective V1aR and OTR agonists and antagonists were given ICV. A highly selective OTR agonist failed to induce flank marking and a highly selective OTR antagonist failed to inhibit the induction of flank marking by OT. In contrast, not only did a selective V1aR agonist induce flank marking, a selective V1aR antagonist inhibited the ability of OT to induce flank marking.

3.2 AVP acting via OTRs

There is considerable evidence that central administration of OT and AVP significantly influences the duration of social recognition in rats and mice [61; 62]. For example, social recognition is enhanced by optogenetically-induced OT release in the brain in female rats [63], and administration of AVP into the septum improves social recognition in male Brattleboro rats, a mutant rat strain that naturally lacks AVP [64]. A majority of the studies examining the roles of OT and AVP in social recognition have used relatively short tests of

social memory, ranging from 10 min to 2 hrs, and “neutral” social stimuli such as juvenile conspecifics or ovariectomized females. Recently we used a different approach to study social recognition [65]. In these studies odors from the flank glands of adult male hamsters were used as the social stimulus. Flank gland odors are very potent social stimuli that serve to communicate a variety of different types of social information (e.g., dominance status) [66]. Indeed, flank gland odors were found to be recognized for at least 24 hrs after a brief 3 min exposure. As with other tests of social recognition, ICV injection of OT or AVP enhances social recognition; it increased social memory of flank gland odors from 24 to 48 hrs. Further, using selective OTR and V1aR agonists and antagonists these studies supported the hypothesis that OT and AVP act on OTRs to influence social recognition. ICV injection of an OTR but not a V1aR agonist increased the duration of social recognition in a manner that mimicked the effects of OT and AVP. A highly selective OTR but not a highly selective V1aR antagonist significantly reduced the duration of social recognition suggesting that OT and AVP regulate social recognition by acting on OTRs.

Several lines of evidence provide further support for the hypothesis that OTRs are essential for the expression of social recognition (for reviews see [62; 67]). For example, social recognition in OT knock-out male mice is severely impaired [68; 69]. Similarly, OTR knock-out mice also display significant deficits in social recognition [69; 70; 71; 72]. There is also evidence, however, that V1aR activation contributes to social recognition in rats and mice. Antagonism of V1aRs in several different CNS sites impairs social recognition [73; 74] and as discussed above, a V1aR antagonist inhibits the ability of OT to increase social recognition in OTR knock-out mice [53]. Conflicting results have come from studies employing the same strains of V1aR knock-out mice [75; 76; 77]. As a result, the data examining the hypothesis that OTRs and not V1aRs are essential for social recognition are not entirely consistent.

In another series of studies the roles of OTRs and V1aRs in mediating the rewarding properties of social interactions were examined [78]. Both OT and AVP injected into the ventral tegmental area (VTA), a key element in the mesolimbic reward network, enhanced social reward in male Syrian hamsters tested using the conditioned place preference (CPP) apparatus. Social reward can be measured as a preference for the chamber of the CPP apparatus where individuals are allowed to socially interact with a non-aggressive male conspecific. Hamsters injected with OT or AVP had a larger increase in the time spent in the chamber associated with social-interaction after conditioning compared to those injected with saline. A highly selective OTR but not a highly selective V1aR agonist mimicked the reward-enhancing effects of OT and AVP. Importantly, these studies also showed that an OTR, but not a V1aR antagonist injected into the VTA inhibits social reward. These data support the possibility that OT and AVP act on OTRs in the VTA, to regulate the expression of social reward.

4. Receptor cross-talk in response to exogenously administered peptides

Because OT and AVP as well as their canonical receptors display strikingly similar chemical structures, it is not surprising that there can be substantial cross-talk between these peptides and OTRs and V1aRs [79]. Crosstalk may also occur among *all* OT/AVP receptors

particularly when these peptides are administered at high concentrations. Existing data suggest that there are 10–100 fold differences in the selectivity of OT and AVP for OTRs, V1aRs, and V1bRs, and that AVP has similar affinities for OT and AVP receptors while OT has a higher affinity for OT receptors than AVP receptors. As a result, very high levels of OT and AVP would likely result in the activation of all OT/AVP receptors. It must be remembered, however, that these estimates of receptor selectivity come from studies using different *in vitro* and *in vivo* assays in a limited number of tissues taken from only a very few species. As a result, our understanding of the selectivity of OT/AVP receptors may change as additional data become available.

There is considerable evidence that exogenously administered OT can act on V1aRs in the periphery and several examples that exogenously administered AVP can act on peripheral OTRs to influence both physiological and behavioral endpoints. There is also some evidence to suggest that OT can act on V1bRs to influence endocrine activity. In the brain, there is strong support for the hypothesis that OT can act on V1aRs and that AVP can act on OTRs to influence several different behaviors. There is also some evidence to suggest that OT and AVP act exclusively on V1aRs to influence some behaviors (e.g., social communication) and that OT and AVP act exclusively on OTRs to influence other behaviors (e.g., social reward). As a result, it is clear that the actions of exogenously administered OT and AVP in both the periphery and the brain cannot be assumed to be the sole result of activation of their canonical receptors. These and other studies illustrate the importance of employing selective OT and AVP receptor agonists and antagonists [80].

The potential for cross-talk between OT and AVP receptors should be a consideration in all situations where these peptides are exogenously administered, particularly when given in high concentrations. Studies in humans have employed intranasal administration to investigate the role of OT and AVP in both basic mechanisms of social cognition as well as in treatment for various psychiatric disorders including autism, anxiety and schizophrenia [81; 82; 83]. The commonly used intranasal concentrations of OT and AVP (i.e., 20 IU to 40 IU) produce high, supraphysiological levels of peptide in the periphery, and these concentrations are likely high enough to also produce biologically active levels in the brain [2]. The high levels of peptide produced within the periphery by intranasal administration likely results in activation of peripheral OTRs, V1aRs, V1bRs, and V2Rs. Because OTRs, V1aRs, V1bRs, and V2Rs are found on peripheral tissues of virtually every major physiological system of the body, the impact of these peptides is likely to be very widespread [2; 20]. The potential consequences of the simultaneous activation of OTRs, V1aRs, V1bRs and V2Rs are not understood. Although these receptors are contained on systems that have the potential to impact cognitive functioning indirectly (e.g., adrenal gland), it does not appear that they alter body temperature, heart rate or blood pressure [84]. It is clear, however, that peptides administered via the intranasal route produce significant alterations in cognition and neuronal activity whether they are acting peripherally and/or centrally.

Because the brain levels of peptide produced by intranasal administration are not well understood [2; 85], it is not clear if the central levels of these peptides induced by this form of administration could be sufficiently high to produce cross-talk across OT/AVP receptors

in the brain. Cross-talk between OT and AVP receptors may be more limited in humans when the peptides are given at more physiological levels because in humans, OT appears to have a higher affinity for its receptors than for AVP receptors. The few studies that have compared the effects of intranasally administered OT and AVP in humans have reported that these peptides do not have opposing roles. These data have, however, found OT and AVP can have differential effects on neural activity (i.e., BOLD fMRI responses) and cognition, at least in some cases although the effects of OT are more robust [84; 86; 87; 88; 89; 90]. It is not possible to compare the effects of OT and AVP in these studies because the peptides are consistently administered in different doses. Thus, differences in the effects of OT and AVP could simply be the result of different doses and/or differences in the selectivity of OTRs for OT in humans. As such, it is important to consider the possibility that intranasal administration of OT or AVP produces a global activation of both OT and AVP receptors. Therefore, the use of intranasal administration in studies of the specific roles of OTRs, V1aRs or V1bRs in social cognition or for therapeutic purposes will require the administration of selective OT or AVP receptor agonists and antagonists, many of which are currently under development [80; 91; 92].

5. Is there cross-talk in response to endogenously released OT and AVP?

The endogenous release of OT and AVP in the brain may be the result of neuropeptide release from synaptic and/or non-synaptic regions of neurons, although the relative roles of these forms of release in different populations of OT and AVP-containing cells are controversial [93; 94; 95; 96]. Several lines of evidence support the possibility of synaptic release of OT and AVP (for a review see [97]). For example, electron microscopic analysis has revealed dense core vesicles containing AVP- and OT-ir in terminals located in synaptic regions of brain areas such as the habenula, lateral septum, amygdala, supraoptic nuclei, ventromedial hypothalamus and the nucleus of the solitary tract [98; 99; 100; 101; 102; 103; 104]. In addition, depolarizing stimuli can induce OT and AVP release in a calcium-dependent manner in brain regions where AVP and OT fibers terminate synaptically [105; 106; 107]. OT or AVP release from synaptic terminals or release from axons in passage could therefore produce a focal activation of local receptors (Figure 6). The potential for receptor cross-talk would likely be reduced by local synaptic release of neuropeptide and the anatomical segregation of OT and AVP receptors. That being said, however, comparatively little is known about the fate of endogenously released neuropeptides because the dynamics of peptide degradation in the brain are not well understood. Therefore, the possibility that synaptically released neuropeptides could spread beyond the synaptic space (e.g., synaptic spillover) cannot be excluded (Figure 6).

A more global form of OT and AVP release can occur when these neuropeptides are released from non-synaptic regions of neurons (e.g., dendrites) (Figure 6) [108; 109; 110]. Non-synaptic neuropeptide release is stimulated by Ca^{2+} coming from intracellular stores (e.g., endoplasmic reticulum) as opposed to synaptic release that is mediated by the influx of extracellular Ca^{2+} through voltage-gated channels [105]. Because non-synaptic release does not require a change in membrane voltage, synaptic release and non-synaptic release can occur independently of each other. A major source of non-synaptically released OT and AVP is the magnocellular neurons in the hypothalamus, although there is also evidence that

hypothalamic parvocellular neurons can also release neuropeptides from dense core vesicles non-synaptically [111]. The distance that non-synaptically released neuropeptides travel is uncertain, but is the subject of active investigation [96; 109]. The further that non-synaptically released neuropeptides spread at high concentrations the greater potential for receptor cross-talk despite the anatomical segregation of OT and AVP receptors.

There are anatomical regions where OT or AVP have not been detected and yet their receptors are present at high levels. For example, in hamsters the lateral septum contains large numbers of V1aRs but few, if any, AVP containing fibers or cell bodies have been identified with immunohistochemistry [112; 113; 114; 115]. Although “isolated” receptors appear to be a common phenomenon in the brain [116], the number of mismatches between the presence of neuropeptides and their receptors may be at least partially the result of a lack of sensitivity of the techniques used to localize neuropeptides [98; 117]. Nevertheless, when isolated receptors do occur more global forms of neuropeptide release, such as non-synaptic release, would be required for their activation. In any case, non-synaptic release of OT and AVP has the potential to result in substantial cross-talk among OT and AVP receptors across many brain regions.

There is only a limited amount of evidence that *endogenously* released OT or AVP can produce functionally significant responses by acting on each other’s receptors. One approach has been to stimulate the endogenous release of OT by the central administration of melanocyte stimulating hormone (α-MSH) and to determine whether the effects of the endogenously released OT are mediated by V1aRs. α-MSH acts on melanocortin 4 receptors to induce non-synaptic release of OT but not AVP from hypothalamic neurons [118; 119]. Studies in hamsters have found that ICV or hypothalamic injection of α-MSH induces flank marking behavior and that α-MSH-induced flank marking is blocked by central administration of a selective V1a antagonist [33]. These data provide support for the possibility that endogenously released OT can act on V1aRs to induce social behavior.

6. Conclusions

Untangling which receptors mediate the actions of exogenously administered and endogenously released OT and AVP is critically important for understanding the central and peripheral actions of these peptides. It is clear, however, that the actions of OT and AVP cannot be assumed to be the sole result of activation of their canonical receptors. Rather, OT and AVP can activate each other’s receptors, particularly when present at high levels, resulting in the potential for substantial cross-talk between the OT and AVP systems. Of course, cross-talk comes into play only when OT interacts with AVP receptors and vice versa. When they do it is likely that OT and AVP will produce similar effects. Therefore, a simple notion that OT and AVP always have diametrically opposed actions is incorrect. When considering the evidence that OT and AVP can produce distinct and in some cases opposite effects it is important to consider the effects of these peptides in the context of their ability to activate each other’s receptors. OT and AVP receptors are imbedded in neural circuits that are frequently anatomically separate so it is likely that the opposite effects of these peptides are more the result of which receptor is activated rather than which peptide was responsible for the activation.

Unfortunately, little is known about how frequently synapses containing OT or AVP also contain OT receptors or AVP receptors because it has not been possible to identify OT or AVP receptors with immunohistochemistry. Based on approaches with less anatomical resolution (i.e., receptor autoradiography) OT and AVP receptors appear to be anatomically segregated in many areas of the brain (e.g., Figure 3). If the presence of both OT and AVP receptors in the same synaptic regions is rare then the possibility of cross-talk following synaptic release of these neuropeptides would seem unlikely, with the exception of when these neuropeptides spillover beyond synaptic regions (i.e., synaptic spillover).

Cross-talk is likely to occur when neuropeptides are released non-synaptically and spread more globally due to volume transmission. Substantial non-synaptic release of either OT or AVP could activate a large number of OT and AVP receptors indiscriminately, thereby overriding the “wiring” diagrams of OT and AVP networks. Therefore, OT and AVP receptors within these networks could be activated in very different patterns as the result of different combinations of synaptic and non-synaptic release. Different patterns of OT and AVP receptor activation across structures within these networks could contribute to the regulation of the complex behaviors and physiological processes under their control (see [8] for a review). As discussed above, however, it remains important to confirm that cross-talk can occur in response to endogenously released OT and AVP and to have a better understanding of the dynamics of non-synaptic release of these neuropeptides. It is clear that dose-response studies and the use of selective OTR, V1aR, and V1bR agonists and antagonists as well as animal studies employing gene targeting techniques will be important for understanding the ligand/receptor interactions of OT and AVP.

Several different social behaviors can be influenced by both OT and AVP, but this influence appears to be mediated by only one of their receptors. For example, although OT and AVP increase social communication, social recognition, and social reward, the effects of these neuropeptides on social communication are mediated by V1aRs and their effects on social recognition and social reward are mediated by OTRs. Although much more work needs to be done, these data suggest that certain classes of social behavior are mediated by OTRs while other classes of social behavior are mediated by V1aRs. Exogenous administration of OT, AVP and selective agonists and antagonists of their receptors have considerable potential as new drugs to treat a number of different psychiatric disorders. Understanding cross-talk has the potential for substantial translational relevance that could lead to important clinical breakthroughs. Dysfunctions in the actions of OT and AVP have been linked to psychiatric disorders such as autism, anxiety and schizophrenia. As such, a better understanding of how these signals exert their effects could potentially lead to important new treatments of these disorders. For example, perhaps deficits in social communication would be most effectively treated with drugs that target V1aRs, while deficits in social recognition and social reward would be most effectively treated with drugs targeting OTRs. These data are also potentially important for the understanding of the actions of intranasally administered OT and AVP in humans. Intranasal OT and AVP administration, which is currently in use in clinical trials, produces supraphysiological levels of these peptides in peripheral tissues. These high levels of peptide have the potential to result in significant amounts of receptor cross-talk in the periphery as well as in the brain resulting in the activation of large numbers of OT and AVP receptors. Therefore, the use of intranasal administration in studies of the specific roles of

OT and AVP receptors in social cognition/social behavior or in studies of the efficacy of these peptides for therapeutic purposes likely require the administration of selective OT or AVP receptor agonists and antagonists. As such, the development of highly selective agonists and antagonists will be particularly important for future clinical applications targeting OT or AVP receptors.

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Highlights

- The chemical structures of oxytocin and arginine-vasopressin are similar, and the structures of their receptors are also similar
- Exogenously administered oxytocin and arginine-vasopressin can activate each other's canonical receptors (i.e., cross-talk)
- Receptor cross-talk can occur in the brain and the periphery
- Understanding oxytocin and arginine-vasopressin receptor cross-talk will be an important consideration in drug development

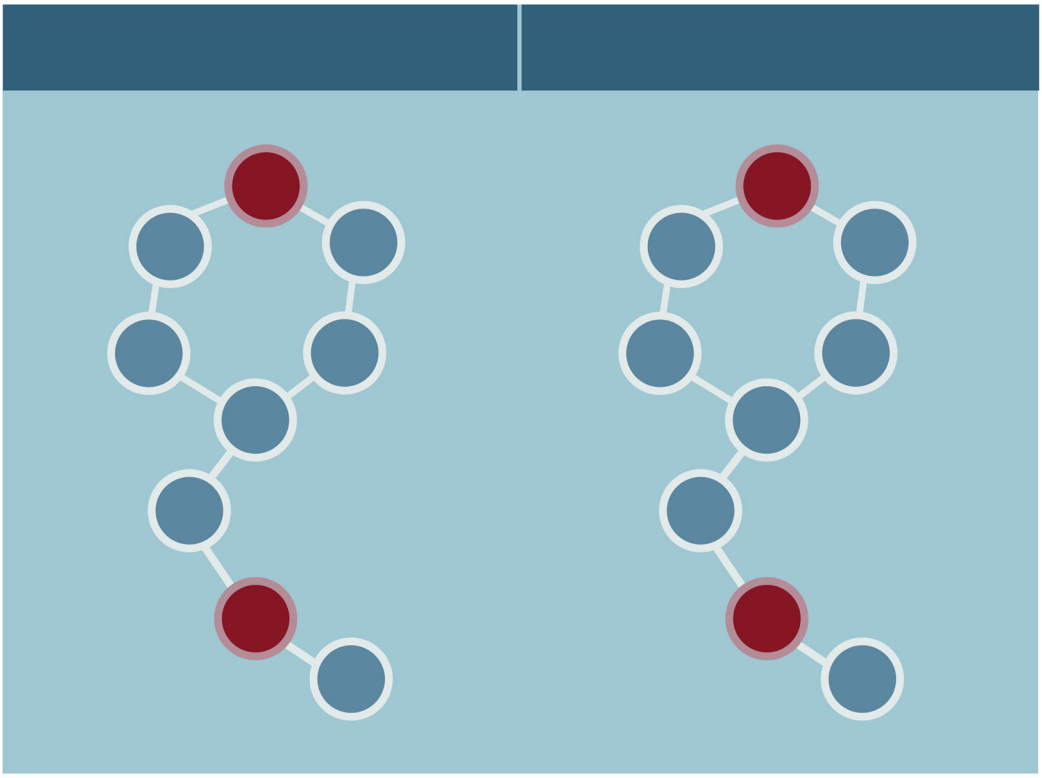

Figure 1.

Schematic diagram of the primary structure of oxytocin and arginine-vasopressin. Seven of the nine amino acid sequences of these peptides are identical. Amino acids in the third and eighth positions differ (in red). Both peptides contain disulphide bridges between Cysteine (Cys) residues at positions one and six.

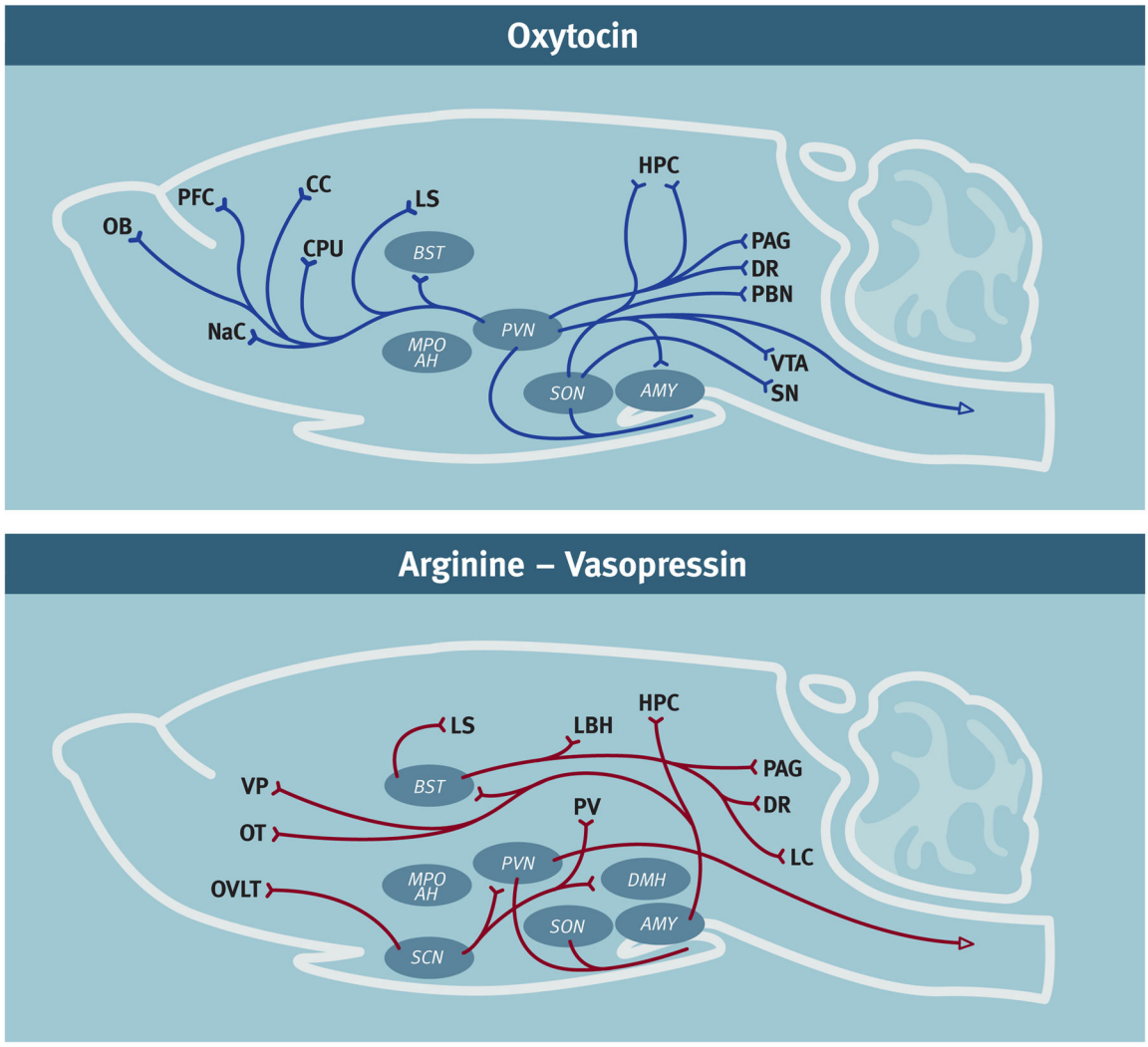

Figure 2.

Diagrammatic representations of the oxytocin- (OT) and arginine-vasopressin- containing (AVP) neural network in rodents. It is noteworthy that OT and AVP immunoreactivity can vary by species, sex, age and social experience [8; 127]. These diagrams represent a compilation of the major OT and AVP projections from several rodent species. In addition to the cell bodies indicated in the diagram there are also accessory nuclei that likely also play an important role. A. OT network: [97; 128; 129; 130; 131; 132]. B. AVP network: [97; 114; 131; 133; 134; 135; 136] Abbreviations: Amygdala (AMY), Bed nucleus of the stria terminalis (BST), Caudate-putamen (CPU), Cingulate cortex (CC), Dorsal raphe (DR), Hippocampus (HPC), Lateral septum (LS), Locus coeruleus (LC), Medial preoptic area – anterior hypothalamus (MPO AH), Nucleus Accumbens (NaC), Olfactory bulb (OB), Olfactory tubercle (OT), Organum vasculosum laminae teriminalis (OVLT), Parabrachial nucleus (PBN), Paraventricular nucleus (PVN), Periaqueductal grey (PAG), Periventricular nucleus hypothalamus (PV), Prefrontal cortex (PFC), Substantia nigra (SN), Suprachiasmatic nucleus (SCN), Supraoptic nucleus (SON), Ventral pallidum (VP), Ventral tegmental area (VTA)

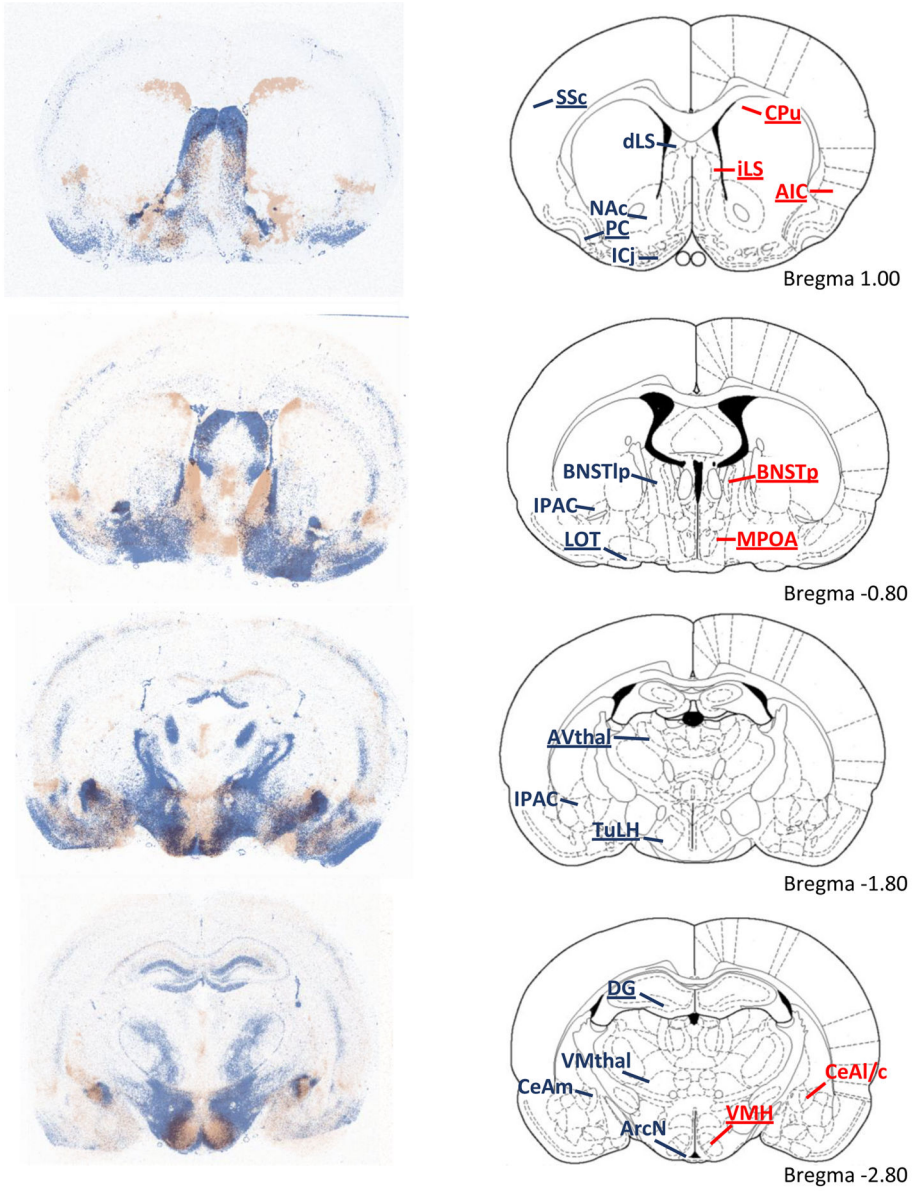

Figure 3.

The distribution of V1aR (blue) and OTR (red) binding in male rats. Overall, there is little overlap between the patterns of V1aR and OTR binding. The right column illustrates rat brain images adapted from The Rat Brain Atlas [137]. Dense V1aR binding was found in somatosensory cortex (SSc), piriform cortex (PC), Islands of Calleja (ICj), nucleus accumbens (NAc), lateral septum (LS), lateral posterior bed nucleus of the stria terminalis (BNST) (BNSTlp), nucleus of the lateral olfactory tract (LOT), dentate gyrus (DG), tuberal lateral hypothalamus (TuLH), anteroventral thalamus (AVthal), interstitial nucleus of the posterior limb of the anterior commissure (IPAC), arcuate nucleus of the hypothalamus (ArcN), ventromedial thalamus (VMthal), and medial central amygdala (CeAm). Dense OTR binding was found in the dorsal caudate putamen (CPu), agranular insular cortex (AIP), posterior BNST (BNSTp), medial preoptic area (MOPA), ventromedial hypothalamus

(VMH), and later and capsular central amygdala (CeAl/c). Regions where sex differences were identified are underlined. Taken from Dumais and Veenema (2016) with permission.

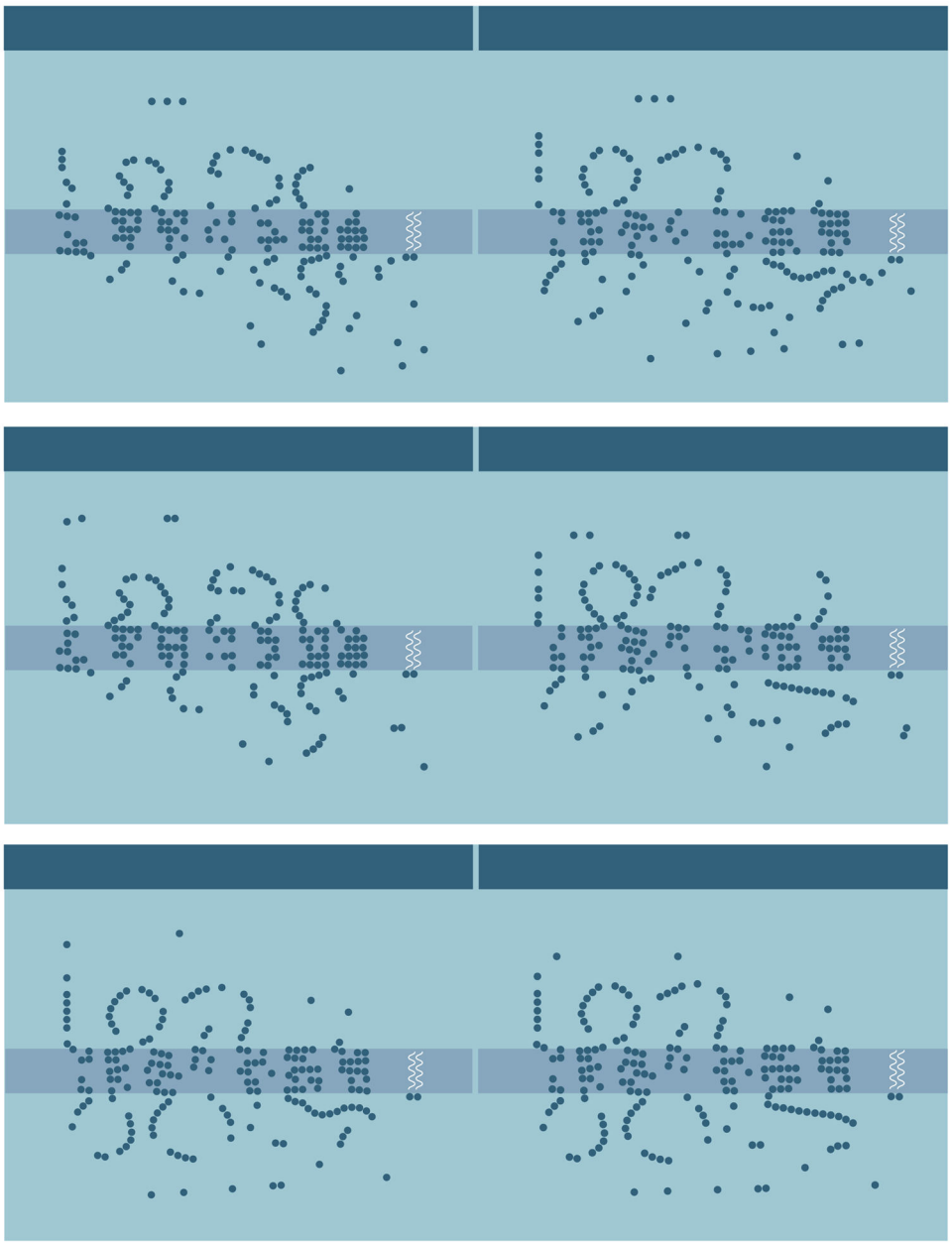

Figure 4.

Diagrammatic representations comparing the primary structures of human OTRs, V1aRs and V1bRs. Amino acid residues conserved between receptors are indicated by dark circles: (A) OTRs and V1aRs, (B) V1aRs and V1bRs, and (C) V1aRs and V1bRs. See [19; 20]

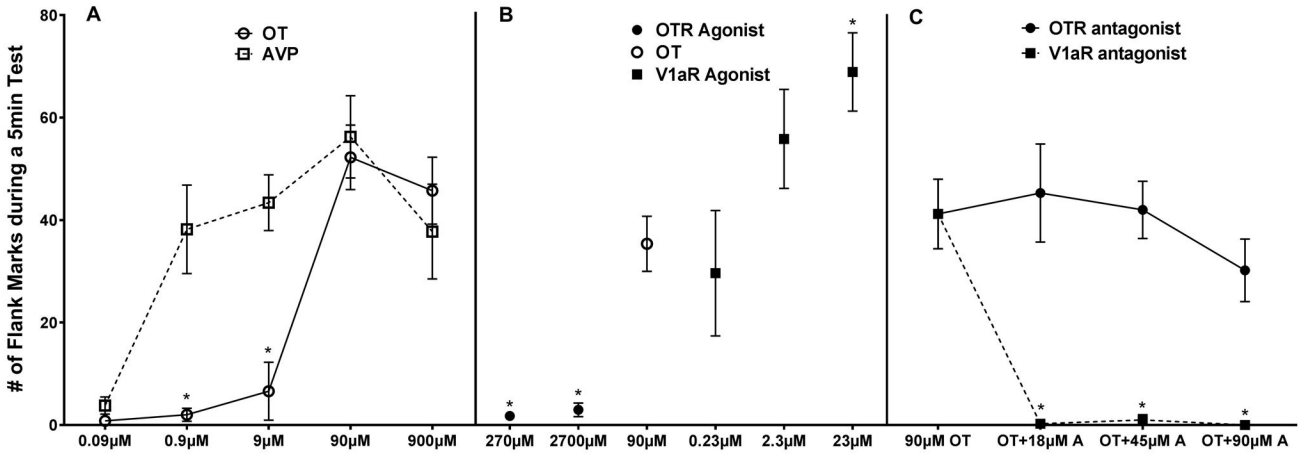

Figure 5.

Effects of OT, AVP and highly selective OTR and V1aR agonists and antagonists on a form social communication called flank marking in hamsters. (A) introcerebroventricular injections of both OT and AVP induced flank marking, but AVP is about 100 times more potent than OT (* indicates a significant difference between OT and AVP). (B) Effects of OTR and V1aR agonists on flank marking. The V1aR agonist but not the OTR agonist induced high levels of flank marking (* indicates a signficant difference compared to OT). (C) Effects of OTR and V1aR antagonists on OT-induced flank marking. All three concentrations of the V1aR antagonist completely blocked OT-induced flank marking while the OTR antagonist did not significantly affect flank marking (* indicates a significant difference compared to OT).

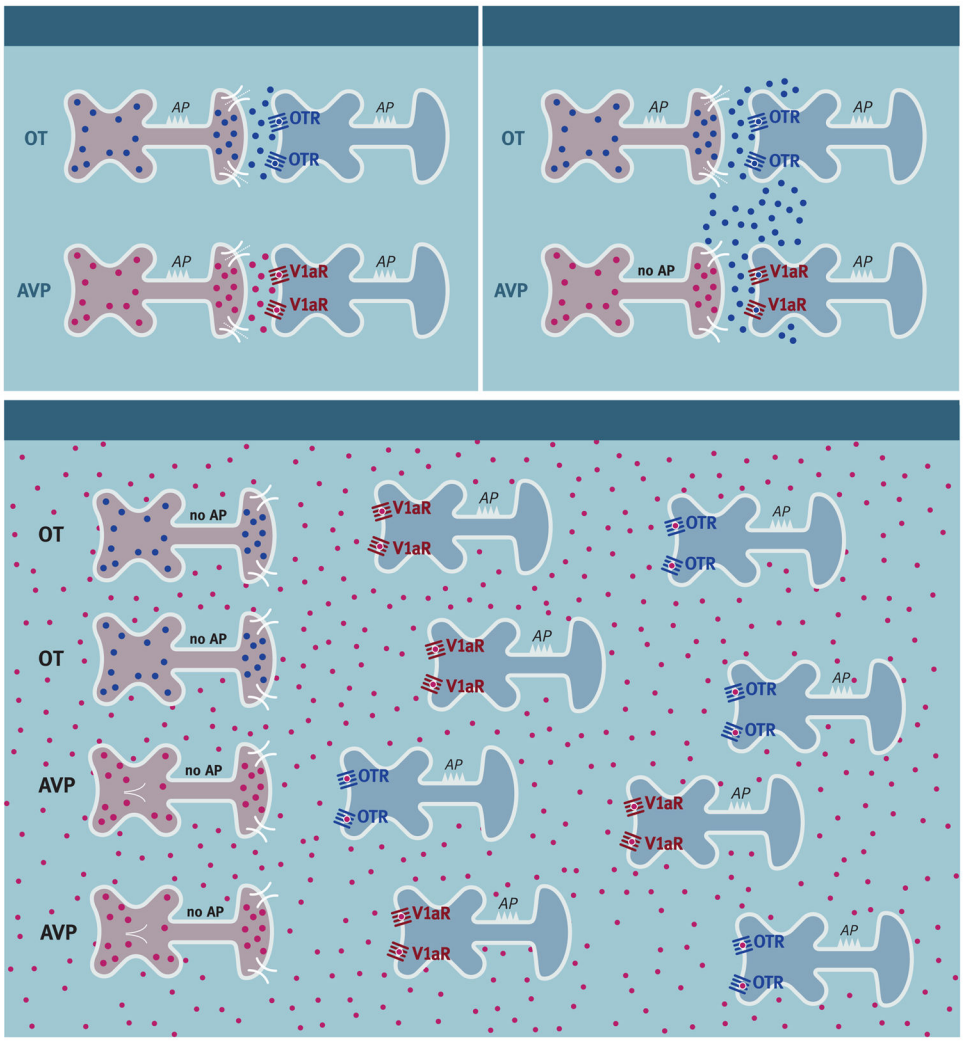

Figure 6.

Diagrammatic representation of synaptic release with no cross-talk, synaptic release with cross-talk, and non-synaptic release with volume transmission and cross-talk in neurons that produce oxytocin (OT) or arginine-vasopressin (AVP). Synaptic release of OT or AVP is produced by action potentials (AP) that activate an influx of extracellular calcium (Ca^{2+}) through voltage sensitive Ca^{2+} channels. Non-synaptic release of OT or AVP is produced by the release of Ca^{2+} from endogenous stores (e.g., endoplasmic reticulum (ER)).

Table 1

Selectivity of arginine-vasopressin (AVP) V1aR, AVP V1bR and oxytocin receptors (OTR) to AVP and OT.

	AVP			OT		
Receptor	**V1aR**	**V1bR**	**OTR**	**V1aR**	**V1bR**	**OTR**
Humans	1.1	0.7	1.7	120	>1000	0.8*
Rats	2.6	0.3	1.7	71	294	1.0
Mice	1.3	0.3	1.8	46.1	494	0.6

Affinity values in K_i (nM);

* defined as selective as compared with the two other receptors of that species by the selectivity criteria of having a two orders of magnitude lower K_i; Modified from[35].

References: [28; 120; 121; 122; 123; 124; 125]

Table 2

Commonly used commercially available oxytocin (OT) and arginine-vasopressin (AVP) receptor agonists and antagonists.

Category	Compound	Name/acronym	Supplier
OTR agonist	[Thr4, Gly7]-OT	TGOT	Abgent; Bachem
	WAY267, 464 *#	N/A	Tocris
OTR antagonist	d(CH2)5-Tyr(Me)-[Orn8]-vasotocin	N/A	Bachem
V1aR antagonist	d(CH2)5[Try(Me)2]AVP	Manning Compound	Sigma-Aldrich
	SR49059 *	N/A	Tocris; Sigma-Aldrich
V1bR antagonist	SSR149415 *	Nelivaptan	Sigma-Aldrich

* indicates non-peptide agonists/antagonists.

is also a V1aR antagonist [126].