# Oxytocin and Vasopressin: Powerful Regulators of Social Behavior

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## Abstract

For many, the terms oxytocin and vasopressin immediately evoke images of animals interacting with one another, as both of these neuropeptides have been implicated as being part of the neurochemical "glue" that socially binds animals. However, social environments and social interactions are complex and include behaviors that bring animals together as well as behaviors that keep animals apart. It is at the intersection of social context, social experience, and an individual's sex that oxytocin and vasopressin act to modulate social behavior and social cognition. In this review, this complexity will be explored across mammalian species, with a focus on social memory, cooperative behaviors, and competitive behaviors. Implications for humans as well as future directions will also be considered.

## Keywords

oxytocin, vasopressin, social behavior, social memory, aggression, affiliation

## Introduction

Animals live in complicated social environments. At one extreme you have individuals living in groups characterized by elaborate social structures and at the other extreme individuals living more solitary lives and only engaging in social interactions intermittently. Even with all of the variability, most social behaviors displayed across species can be broadly separated into two categories: (1) behaviors that bring animals together, such as affiliative, parental, or copulatory behaviors, and (2) behaviors that keep animals apart, such as agonistic/aggressive behaviors. Whether the behaviors are affiliative or aggressive, it is important to remember that these categories are not mutually exclusive and that, generally speaking, animals engage in behaviors that are rewarding. So, while parental or copulatory behaviors might seem obviously rewarding, aggressive behaviors (in particular, winning) can be rewarding as well. Furthermore, the social lives of animals are shaped by previous experience and often undergo dramatic changes across the lifespan. With this in mind, one of the ongoing questions in behavioral neuroscience is, "What are the neurochemical 'ties that bind' social interactions?"

Two of the neurochemicals critical for modulating social interactions are oxytocin and vasopressin. With both having highly specialized roles within species, within particular brain regions, and between sexes, oxytocin and vasopressin represent common ground for researchers interested in understanding the neural regulation of social behavior. Thus, this review will highlight what is known about these neuropeptides and areas of consensus about their roles in the neuromodulation of behaviors across species.

## The Neurochemistry of the Oxytocin and Vasopressin Systems

While originally detected by Oliver and Schäfer in 1895, oxytocin and vasopressin were not isolated and their amino acid sequences and structures determined until the 1950s by du Vigneaud (reviewed in Caldwell and Albers 2016). Since this time, interest in understanding the roles of oxytocin and vasopressin in the brain and periphery has been steadfast. However, with the development of specific agonists and antagonists in the 1990s there was a surge in studies that helped define the roles of oxytocin and vasopressin in the brain, and with the advent of transgenic mice additional insights were gained. Current technology, including optogenetics, has continued to advance the field and allowed researchers to take a true genes-to-behavior approach.

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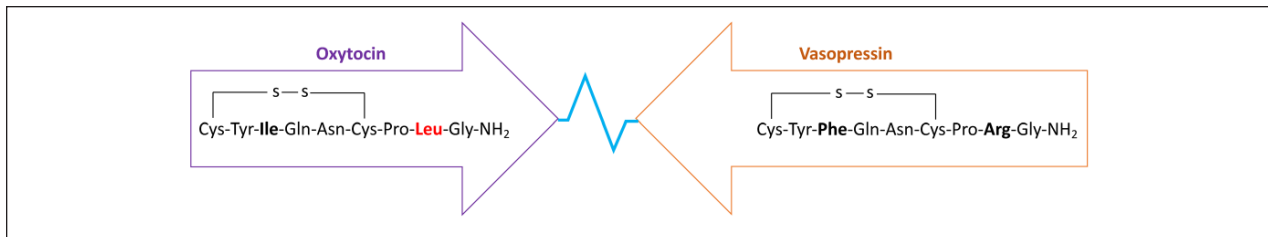Email: hcaldwel@kent.edu

**Figure 1.** Due to a gene duplication during vertebrate evolution, the genes for oxytocin and vasopressin are oriented in opposing transcriptional direction on the same chromosome. The sequence between the two genes is known as the intergenic region and contains critical enhancer elements. The bolded amino acids, those in the third and eighth positions, differ between oxytocin and vasopressin. Also, the red leucine in the eighth position is a proline in many New World primates.

## The Peptides

Mammalian oxytocin and vasopressin are evolutionarily ancient nine amino acid neuropeptides that are the result of an ancestral vasotocin gene duplication—even in an ancient organism like freshwater hydra, an oxytocin/vasopressin homologue can be found (reviewed in Caldwell and others 2008a; Lee and others 2009). Because of this duplication the genes for oxytocin and vasopressin are oriented in opposing transcription direction on the same chromosome, though the chromosome on which they are found is species-specific (reviewed in Caldwell and Young 2006) (Fig. 1). When considering the homologues for oxytocin and vasopressin, generally speaking, non-mammalian tetrapods produce mesotocin and vasotocin and bony fishes isotocin and vasotocin (Acher and others 1990). However, there are some notable exceptions to these generalities. Specifically, recent work in New World primates has found an amino acid substitution in the eighth position of the oxytocin peptide, a proline rather than a leucine (Lee and others 2011). What the functional ramifications of this amino acid change means are still being explored, but one possibility is that it may be permissive for additional cross-talk between the oxytocin and vasopressin systems. There are some other differences in these systems in other species as well, with some marsupials not having vasopressin or oxytocin, but rather lysipressin (a lysine in place of the arginine in the eighth position) and mesotocin (an isoleucine in place of the leucine in the eighth position), respectively (reviewed in Caldwell and Young 2006).

Almost all oxytocin and vasopressin is synthesized within the magnocellular neurons of the hypothalamic supraoptic (SON) and paraventricular (PVN) nuclei and transported to the posterior pituitary where they are stored and ultimately released into the blood stream. It is this pathway, and the subsequent physiological activities of oxytocin and vasopressin, that give them their name, with oxytocin helping regulate parturition and lactation and vasopressin salt and water balance. Within the brain, oxytocin and vasopressin that are not transported to the
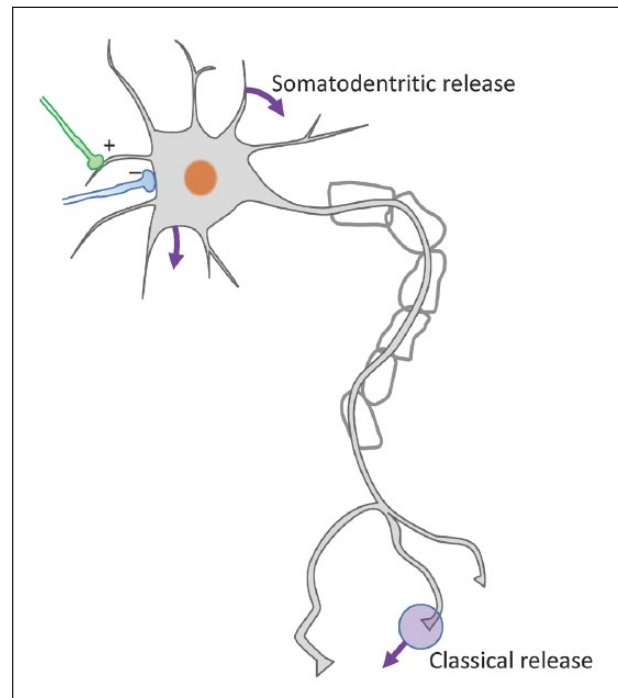


**Figure 2.** While being released as classical neurotransmitters, oxytocin and vasopressin are also released from non-synaptic regions, such as dendrites. This type of transmission, referred to as "volume transmission" results in a much more diffuse signal that can potentially impact a large number of neurons.

posterior pituitary are synthesized by and transported from smaller, parvocellular neurons located in the PVN and elsewhere. However, even the magnocellular neurons of the SON and PVN can release oxytocin and vasopressin from non-synaptic regions, such as dendrites, to produce important local effects (i.e., volume transmission) (reviewed in Ludwig and others 2016) (Fig. 2). This latter type of transmission, which results in a much more diffuse signal, can potentially affect a large number of neurons at multiple sites, likely up to 4 to 5 mm from their release site. Central oxytocin and vasopressin projections are
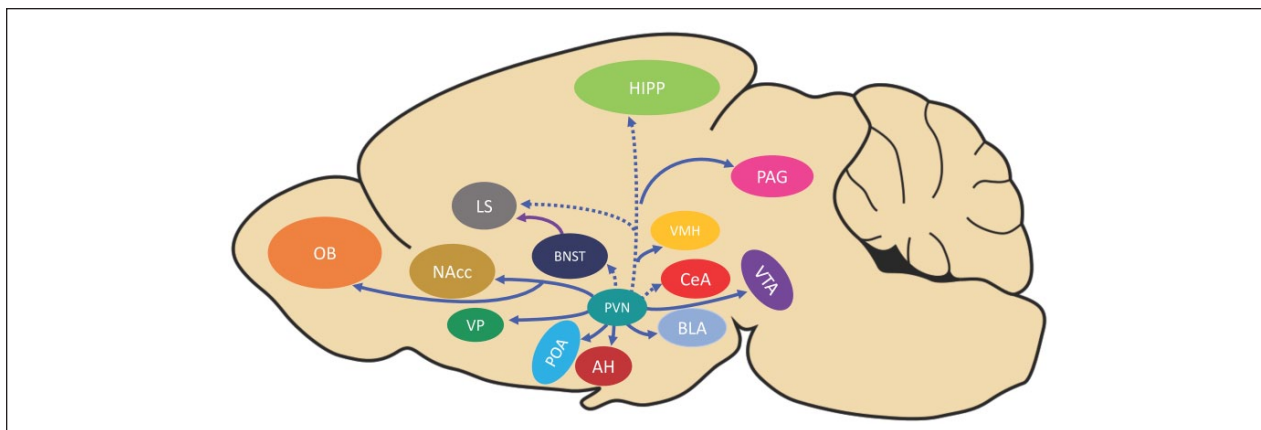
**Figure 3.** In rodents, oxytocin and vasopressin receptors are found within all of the brain regions that are a part of the social behavior neural network (SBNN), including the preoptic area (POA), the anterior hypothalamus (AH), the ventromedial hypothalamus (VMH), the periaqueductal gray (PAG), the bed nucleus of the stria terminalis (BNST), and the lateral septum (LS). The receptors are also found in other areas of the brain that interact with the SBNN, including the olfactory bulb (OB), the nucleus accumbens (NAcc), the ventral pallidum (VP), the hippocampus (HIPP), the ventral tegmental area (VTA), the basolateral amygdala (BLA), the central amygdala (CeA), and the paraventricular nucleus (PVN). Oxytocin-only projections are indicated by solid blue lines, oxytocin and vasopressin projections are indicated by dashed blue lines, and vasopressin-only projections are indicated by purple lines. Because of their extensive connectivity within the SBNN as well as to other nuclei, oxytocin and vasopressin are in a position to modulate a variety of social and reproductive behaviors.

widely distributed throughout the brain, with fibers found from the olfactory bulbs to the spinal cord (reviewed in Caldwell and Albers 2016; Caldwell and others 2008a; Lee and others 2009). As is the focus of this review, most of the oxytocin and vasopressin found in subcortical regions are a part of the social behavioral neural network (SBNN), as well as brain areas associated with reward, and are important in the regulation of social and reproductive behaviors (Albers 2012, 2015; Newman 1999; O'Connell and Hofmann 2011) (Fig. 3).

## The Receptors

To date, only a single type of oxytocin receptor, the Oxtr, has been identified. The Oxtr is a member of the G-protein-coupled receptor family, containing seven transmembrane domains and is similar in structure to the vasopressin receptors. The Oxtr is the primary transducer of oxytocin action in both the brain and the periphery. For vasopressin, there are two main classifications of vasopressin receptors: Avpr1 and Avpr2. These also are seven-transmembrane G protein–coupled receptors, and within the Avpr1, there are two subtypes: the Avpr1a and the Avpr1b. Within the brain, the Avpr1a is found in a variety of brain nuclei and is implicated in the regulation of numerous social behaviors. The Avpr1b, on the other hand, appears to be much more discretely localized within the brain and is associated with stress adaptation, aggressive behavior, and social memory (reviewed in Roper and others 2011; Stevenson and Caldwell 2012). It should be

noted that there are a variety of peripheral actions mediated by these subtypes, but they are beyond the scope of this review.

## Cross-Talk between the Systems

As noted above, oxytocin and vasopressin are very similar in their structure; this is also the case for their receptors (Manning and others 2012; Maybauer and others 2008). The consequence of these similarities is the potential for cross-talk between the systems (Barberis and others 1992; Schorscher-Petcu and others 2010; Song and others 2014), with Oxt and Avp having similar affinities for the Oxtr, Avpr1a, and Avpr1b in rats and mice (Manning and others 2012). As would be expected, these pharmacological interactions make teasing apart the individual roles of one peptide versus the other in the neural regulation of behavior quite complicated. While this issue is not easily addressed, the next section will touch on work that has identified some of the behavioral ramifications of this cross-talk.

## Oxytocin, Vasopressin, and Social Behavior

Fundamentally, animals must evaluate and behaviorally respond to their environment, including their social environment, and remember conspecifics. This means that most animals need to be able to display behaviors that promote group cohesion, such as affiliative behaviors,

and behaviors that help them complete for resources, such as aggressive behaviors. As was noted in the introduction, cohesion and competition are not necessarily mutually exclusive. Oftentimes individuals of a species (most often males), living in a social group, may fight one another for dominance; because having a dominance hierarchy can be more stabilizing to the population than males continuing to fight. What can vary greatly between individuals of the same species are the patterns of these behaviors in terms of how they differ between sexes, how they are affected by changes in the environment, and how they may shift across the lifespan.

To begin the exploration of the behavioral roles of oxytocin and vasopressin, it is first important to think about how behavior is regulated. One could imagine that each behavior is simply regulated by a different neural circuit. Or perhaps the same circuit with more or less activation resulting in a kind of behavioral continuum from affiliation to aggression. However, the data suggest that it is neither of these, but rather, that social behaviors are regulated by a neural network. This network is made up of specific groups of neurons, referred to as nodes, that have reciprocal connectivity, express gonadal steroid receptors, and have been identified as being important to social behavior. Referred to as the SBNN, this network includes areas of the brain such as the bed nucleus of the stria terminalis, the lateral septum, the periaqueductal gray, the medial preoptic area, the ventromedial hypothalamus, the anterior hypothalamus, and the amygdala. Thus, the social behavior of an animal is thought to reflect the output of this network, being an emergent property of the activation/inhibition patterns of activity across these nodes. Given the distribution of oxytocin and vasopressin receptors throughout most of the SBNN, as well as their high level of conservation across species, the oxytocin and vasopressin systems are in a unique position to affect the output of the SBNN (reviewed in Albers 2015; Caldwell and Albers 2016; Kelly and Goodson 2014). However, to better understand the roles of oxytocin and vasopressin in the neural modulation of social behaviors, it is important to first consider their role in social recognition memory.

## Social Recognition Memory

The capacity to identify individuals and remember them is known as social recognition memory. This type of memory ultimately helps an animal determine whether to avoid or engage in an interaction, as the choice to avoid or engage is dependent on social context, with social context being the physical and social setting in which an animal finds itself. Data from numerous species suggest that oxytocin and vasopressin both play a role in the neural regulation of social recognition memory, being involved

in several aspects of the pathway from sensory input to memory consolidation.

Oxytocin and vasopressin alter the processing of socially salient sensory information by directly modulating olfactory input. Infusions of either oxytocin or vasopressin into the olfactory bulb facilitate social recognition memory (Dluzen and others 1998a). Conversely, disruption of catecholamine-producing cells in the olfactory bulb can block the aforementioned effect (Dluzen and others1998b), and the destruction of vasopressin neurons selectively disrupts social memory (Tobin and others 2010). Recent work suggests that oxytocin's modulation of sensory input extends beyond olfaction to somatosensory input, as social interaction-dependent somatosensory input relayed to the posterior intralaminar complex of the thalamus and then to the PVN may directly affect the activation of oxytocin neurons (Cservenak and others 2016).

Besides the modulation of sensory input, oxytocin and vasopressin also act in several brain regions to affect the formation of the memory. Specifically, oxytocin facilitates social memory when it is infused into the lateral ventricles and medial preoptic (Benelli and others 1995; Popik and Van Ree 1991). Furthermore, Oxtr knockout mice (−/−) and forebrain-specific Oxtr knockout mice (Oxtr FB/FB, where CRE recombinase is driven by a CaMKII alpha promoter; Dragatsis and Zeitlin 2000) have impaired social recognition memory (Ferguson and others 2000; Hattori and others 2015; Lee and others 2008; Macbeth and others 2009; Takayanagi and others 2005) (Fig. 4). In Oxt −/− mice this impairment appears to be due to estrogen-dependent Oxt signaling in the medial amygdala (Choleris and others 2007; Ferguson and others 2001). While social recognition memory in females is often tested differently than in males, there is evidence that oxytocin is important for them as well. Female Oxt −/− mice, when they have been mated and then re-exposed to their mate, show the Bruce Effect (Wersinger and others 2008). That is, they spontaneous abort their pregnancy when exposed to a novel male (Bruce 1959), which suggests that they have not retained the memory of their mate.

In the case of vasopressin, androgen-dependent vasopressin projections from the medial amygdala and bed nucleus of the stria terminalis to the lateral septum appear to be critical for normal social recognition memory, with microinjections of vasopressin into the lateral septum facilitating social memory in control and vasopressin-deficient (i.e., Brattleboro) rats (Bluthe and others 1990; Bluthe and others 1993; De Vries and others 1984; Mayes and others 1988). Conversely, disruption of lateral septum vasopressin signaling, either by antagonizing Avpr1a or using antisense oligonucleotides that bind to Avpr1a mRNA, disrupts social recognition memory (Engelmann and Landgraf 1994; Landgraf and others 1995). Avpr1a
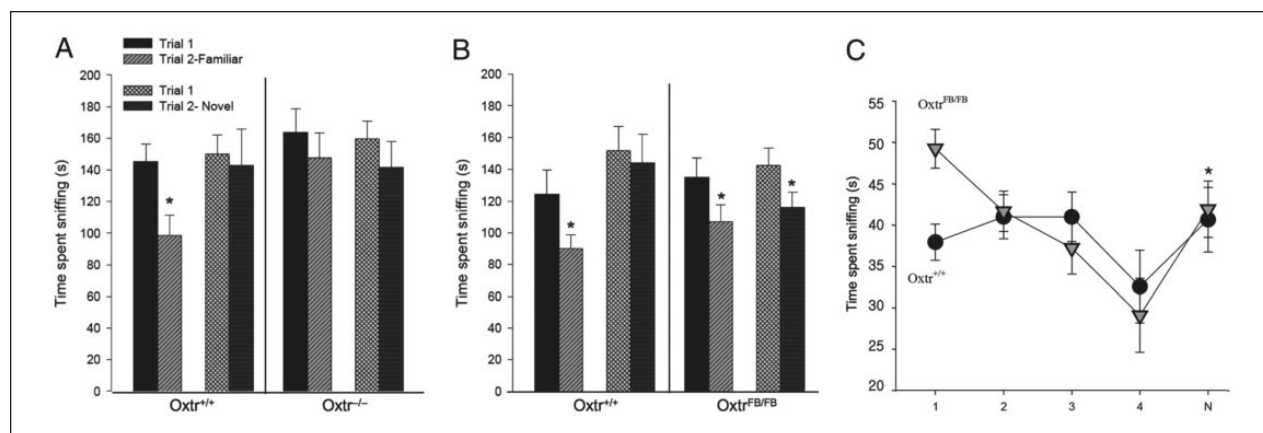
**Figure 4.** Social recognition memory tests in Oxtr knockout (−/−) and forebrain-specific knockout (FB/FB) males. In panels A and B, a two-trial test was performed. For Trial 1 males were exposed to an ovariectomized female and then 30 minutes later exposed to either a "novel" female of the same "familiar" female. In panel C, a five-trial test was performed. In this case a subject was exposed to the same female four times and on the fifth trial exposed to a novel female, there were 10 minutes between trials. An animal with normal social recognition memory will increase their investigation time with exposed to a "novel" female. In panel A, Oxtr −/− males have impaired social recognition memory compared to sibling wildtype control males. In panel B, Oxtr FB/FB males engage in less olfactory investigation during Trail 2 regardless of the stimulus. In panel C, Oxtr FB/FB males increase their investigation time when presented with a novel female on the fifth trial, which suggests that with a shorter interval to "remember" that their social recognition memory is intact. Reprinted from Lee and others (2008) by permission of Oxford University Press.

−/− and Avpr1b −/− mice confirm a role for vasopressin in the modulation of social memory. The data from Avpr1a −/− males have been mixed, with one group reporting impairments in social recognition that can be rescued by the overexpression of Avpr1a in the lateral septum (Bielsky and others 2003; Bielsky and others 2005) and another group reporting no deficits in social recognition, but rather in olfaction (Wersinger and others 2007b). While the reason for the discrepancy remains unknown, it is obvious from previous reports that Avpr1a in the lateral septum is important for normal social recognition memory (Bluthe and others 1990; Bluthe and others 1993; De Vries and others 1984; Mayes and others 1988).

Avpr1b −/− mice also have impairments in social recognition memory (Wersinger and others 2002), and lesions and genetic silencing of the CA2 region of the hippocampus, where the Avpr1b is prominently expressed, also results in impaired social recognition memory (Hitti and Siegelbaum 2014; Stevenson and Caldwell 2012). A recent report by W. Scott Young's group at the National Institutes of Health identified a projection from the PVN to the CA2 region of the hippocampus that is important for coding the salience of social signals. The stimulation of this projection during acquisition enhances social memory and that enhancement can be blocked by the application of an Avpr1b antagonist to the CA2 region of the hippocampus (Smith and others 2016). The authors suggest that the role of the Avpr1b in the CA2 region of the hippocampus is to increase the salience of social

signals, which represents a new and interesting role for vasopressin signaling.

## Cohesion and Cooperation

Studies of cooperative behaviors have largely focused on model systems that have long-lasting social bonds (i.e., pair bonds) as they more easily lend themselves to the studies of these types of behaviors. That said, pair bonds are somewhat unique in mammals, being observed in only 3% to 5% of the species (Kleiman 1977). So, while there is no doubt that these are valuable model systems, it does not mean that other types of behaviors associated with cohesion, such as friendships or filial bonds, are less important—they are sometimes just more difficult to study. The pair bond is operationally defined as the preference for contact with a familiar sexual partner, selective aggression toward unfamiliar conspecifics, displays of biparental care, socially regulated reproduction, and incest avoidance (Carter and others 1995). Pair bonding can be observed in species ranging from rodents to primates, including humans.

Studies in prairie voles have almost singularly defined what we know about the roles of oxytocin and vasopressin in pair bonding (Carter and others 1995). Due to the richness in social structures within the genus *Microtus*, comparative studies between vole species have been critical in providing insight into the neural regulation of social bonding. While there are some differences in oxytocin
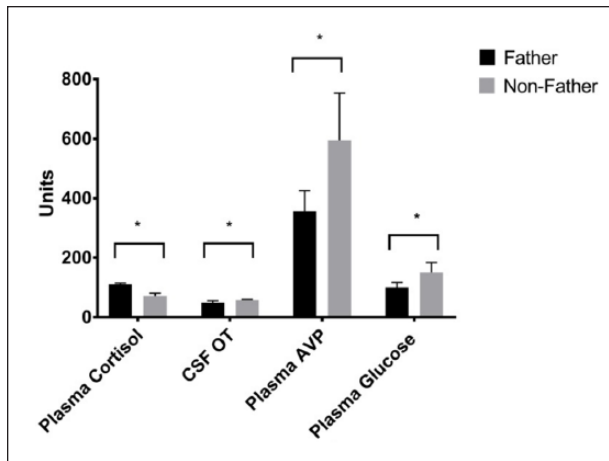
**Figure 5.** Fatherhood affects how oxytocin and vasopressin change in response to long-term separation from pair-mates in titi monkeys (*Callicebus cupreus*). Plasma vasopressin (AVP), cerebral spinal fluid oxytocin (CSF OT), and plasma glucose were all significantly lower in fathers than non-fathers during a reunion with their pair-mate. Reprinted from Hinde and others (2016), open access.

and vasopressin cell number and distribution, or their projections, between some of the vole species, it is the neuroanatomical localization of the receptors that are thought to be critical for determining whether a particular species is monogamous versus non-monogamous and having sex-specific effects within monogamous species. Based on elegant pharmacological and genetic work in several vole species these distribution differences are known to be functionally significant.

Relative to non-monogamous voles, monogamous voles have more Oxtrs in the nucleus accumbens, prefrontal cortex, and bed nucleus of the stria terminalis compared to promiscuous voles, who have higher Oxtr density in the lateral septum, ventromedial hypothalamus, and the cortical nucleus of the amygdala (Insel and Shapiro 1992; Smeltzer and others 2006; Young and others 1996). However, it is the manipulation of oxytocin signaling in the nucleus accumbens that appears to be vital in the socially monogamous prairie vole. In females, both Oxtr antagonists and RNAi knockdown of the Oxtr within the nucleus accumbens inhibit the formation of a partner preference (Keebaugh and others 2015; Liu and Wang 2003; Young and others 2001), whereas overexpression of the Oxtr in the nucleus accumbens of adult female prairie voles accelerates the formation of partner preference (Ross and others 2009). However, in non-monogamous meadow voles overexpression of the Oxtr in the nucleus accumbens is not sufficient to promote pair bond formation (Ross and others 2009), which suggests that some of the circuitry needed to support pair bonding is absent in this species.

There are also differences in the vasopressin system in vole species, specifically with the distribution of the Avpr1a. Prairie voles have a higher density of Avpr1a within the medial amygdala, accessory olfactory bulb, diagonal band, thalamus, ventral pallidum, and bed nucleus of the stria terminalis compared to montane voles (Insel and others 1994; Young and others 1997). Montane voles, in contrast, have a higher density of Avpr1a in the medial prefrontal cortex and the lateral septum (Insel and others 1994; Smeltzer and others 2006). These differences in Avpr1a distribution are thought to contribute to differences in social organization between monogamous and non-monogamous vole species. Pharmacological and genetic manipulations of the Avpr1a in prairie voles have shed light on vasopressin's effects via this receptor in males. When an Avpr1a antagonist is injected centrally prior to mating, the formation of a partner preference is inhibited. Conversely, vasopressin centrally infused facilitates the formation of the partner preference (Cho and others 1999; Winslow and others 1993). The importance of the distribution of the Avpr1a is best illustrated with a study in which the prairie vole Avpr1a gene was overexpressed in the ventral forebrain of meadow voles, resulting in increases in the amount of time meadow voles spent huddled with their partners compared to controls (Lim and others 2004).

In primates, oxytocin's and vasopressin's story regarding the modulation of social bonds is still being written. Evidence from Titi monkeys (*Callicebus cupreus*), a socially monogamous New World monkey species that forms adult pair bonds, suggests that there are marked neural changes in response to separation and reunion that may be mediated by oxytocin and vasopressin. The authors of this work suggest that the same regions of the brain needed to facilitate social memory in rodents, such as the amygdala, are also important in primates (Hinde and others 2016) (Fig. 5). Recent work in marmosets suggests a role for oxytocin in infant-care behavior, with higher levels in urine being correlated with increased infant care in parents as well as alloparents (Finkenwirth and others 2016). Even in humans there evidence that oxytocin and vasopressin may be important in the pair bond, as plasma oxytocin and vasopressin change in sex-specific ways in response to the loss of a loved one (Taylor and others 2010). These findings, however, may be limited in terms of what they can tell us about neuropeptide release in the brain, as plasma oxytocin and vasopressin are not necessarily associated with elevated concentrations of the neuropeptides in cerebral spinal fluid (Freeman and others 2016; Landgraf and Neumann 2004).

## Competition

Competition for resources is the hallmark of most social groups, being played out through agonistic interactions,

that is, the interplay of aggressive and submissive behaviors, which ultimately determine which individuals will have better access to resources such as mates, food, and/or territory. Key to competition is aggression, however, less overt forms of dominance are conveyed and/or maintained through different forms of social communication (e.g., scent marking, vocalization, etc.), which serve to reduce risks associated with fighting (Albers and others 2002; Fernald 2014). Oxytocin and vasopressin have both been implicated the modulation of competitive behaviors, specifically those known to be mediated by gonadal steroids, such as intermale aggression and maternal aggression.

*Male Aggression.* To set the stage, it is important to note that an animal's social experience is critical, as it shapes the way that the brain responds to oxytocin and vasopressin. For example, oxytocin stimulates scent marking in subordinate male squirrel monkeys but has no effect in dominant males (Winslow and Insel 1991). While there has been little to no data supporting a role for oxytocin in the regulation of intermale aggression in laboratory species of rodents, some recent work suggests that pharmacological treatment with oxytocin may have anti-aggressive effects within the central amygdala of adult male rats (Calcagnoli and others 2015). However, whether or not these findings extend to the endogenous oxytocin system remains unknown. Other work in Oxt −/−, Oxtr −/−, and Oxtr FB/FB mice suggests that oxytocin plays a role in early development to set the trajectory for displays of intermale aggressive behavior in adulthood (Dhakar and others 2012; Takayanagi and others 2005; Winslow and others 2000). Essentially, male mice that have an absence of oxytocin signaling in fetal development go on to display heightened aggressive behaviors in adulthood. It is hypothesized that this is due to disruption of normal organizational effects of oxytocin on key brain structures important to the neural regulation of social behavior (Dhakar and others 2012; Miller and Caldwell 2015; Takayanagi and others 2005; Tamborski and others 2016). While this work is still in its early stages, it is consistent with some very elegant work in voles and mice in which postnatal oxytocin manipulation has been found to alter social behavior in adulthood (Bales and Carter 2003; Mogi and others 2014).

Early work linking vasopressin and aggression comes from experiments in Syrian hamsters, where vasopressin signaling via the Avpr1a in the anterior hypothalamus could facilitate offensive aggression (Caldwell and Albers 2004; Ferris and others 1997). As mentioned above, an individual's prior social experience is an important factor, as vasopressin's effects are limited to those individuals predisposed to aggression (i.e., trained fighters or socially isolated for a long time). In this case, the responsiveness of the anterior hypothalamus to oxytocin and vasopressin is shaped by experience-dependent increases in Avpr1a expression (Albers and others 2006). These findings are not limited to Syrian hamsters as something similar is observed in prairie voles (Gobrogge and others 2009; Winslow and others 1993). Aside from the anterior hypothalamus, vasopressin can also modulate aggressive behaviors through its actions in the ventrolateral hypothalamus (Delville and others 1996), the lateral septum (Compaan and others 1993; Everts and others 1997), and the bed nucleus of the stria terminalis (Bester-Meredith and Marler 2001).

While the Avpr1a is certainly the most heavily studied of the central vasopressin receptors, in part because it was the first one identified, there is a clear role for the Avpr1b as well. Avpr1b is essential for displays of aggressive behavior directed toward a conspecific (reviewed in Caldwell and others 2008b; Stevenson and Caldwell 2012). Avpr1b −/− mice have reduced levels of aggressive behaviors and altered dominance behaviors compared to controls (as measured by attack frequency and latency to attack) (Caldwell and others 2010; Caldwell and Young 2009; Wersinger and others 2002; Wersinger and others 2007a). Pharmacological studies support the assertion that the Avpr1b is important to the modulation of aggressive behavior, with the Avpr1b antagonist SSR149415 decreasing species-specific aggressive behaviors in mice (Griebel and others 2002) and hamsters (Blanchard and others 2005). Recent work suggests that Avpr1b expression in the CA2 region of the hippocampus is critical for the aforementioned effects. Virus-mediated overexpression of the Avpr1b in the dorsal CA2 region of Avpr1b −/− mice restores socially mediated attack behaviors (Pagani and others 2015) (Fig. 6). Based on the genetic and pharmacological data, it has been hypothesized that the disruption of the *Avpr1b* does not specifically disrupt aggressive behavior, but rather the ability to display the appropriate behavioral response within a given social context—specifically aiding in the formation and/or recall of accessory olfactory-based memories and as mentioned previously, increasing the salience of social stimuli (Caldwell and others 2008b; Smith and others 2016; Young and others 2006).

*Female Aggression.* The role of oxytocin in the neural regulation of female offensive aggression appears to be fairly limited. One possible reason for this may simply be due to researchers not studying female aggression as intensely as male aggression, mostly because females often do not display aggressive behaviors outside of the peripartum period. One notable exception to this is female Syrian hamsters, who tend to be larger and more aggressive than males. In this species, injections of oxytocin into the medial preoptic-anterior hypothalamic area reduces offensive aggression (Harmon and others 2002).
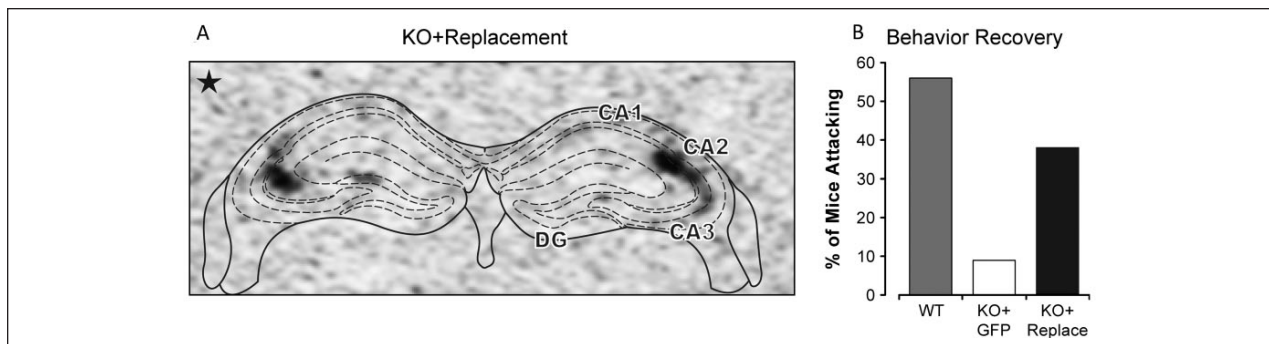
**Figure 6.** When a lentivirus expressing the vasopressin 1b receptor (Avpr1b) is overexpressed in the hippocampal CA2 region of Avpr1b knockout (−/−) males (panel A) aggressive behavior is rescued (panel B). Modified and reprinted with permission from Macmillan Publishers Ltd: Mol Psychiatry, Pagani and Colleagues, 2015.

More commonly though, the role of oxytocin in the context of female aggression has focused on maternal aggression, as this is a unique physiological time characterized by high levels of nurturing behaviors directed toward pups and aggressive behaviors directed toward intruders. In this context the effects of oxytocin appear to be brain region- and context-specific (reviewed in Bosch 2013). Generally, though, oxytocin injected into the amygdala of female hamsters (Ferris and others 1992) or the paraventricular nucleus of the hypothalamus of low-anxiety rats facilitates maternal aggression (Bosch and others 2005). However, in Wistar rats, oxytocin injected into the bed nucleus of the stria terminalis decreases maternal aggression (Consiglio and others 2005). With the data from different species focusing on different brain areas, identifying the points of consensus for the role of oxytocin in the neural modulation of maternal aggression remains a challenge.

With respect to vasopressin, these effects too are sex specific. In female hamsters, vasopressin in the anterior hypothalamus inhibits, rather than stimulates, aggression (Gutzler and others 2010). Studies examining female Avpr1a −/− mice, however, have not reported any genotypic differences in maternal aggression (Wersinger and others 2007b); this finding is inconsistent with studies in rats demonstrating that vasopressin administered centrally to lactating females reduces maternal aggression (Nephew and Bridges 2008; Nephew and others 2010). Similar to what is observed in males, life history is important, with the effects of central administration of vasopressin and an Avpr1a antagonist on maternal aggression dependent on whether a rat has been bred for high or low anxiety (Bosch and Neumann 2010). In those characterized as "high anxiety," vasopressin in the central nucleus of the amygdala is positively correlated with maternal aggression. Similar effects have also been reported in Sprague-Dawley rats (Meddle and Bosch, unpublished; cited in Bosch 2011). In the case of the Avpr1b there has been only one study in postpartum Avpr1b −/− females,

but like male Avpr1b −/− mice, they too have decreases in aggression behavior (Wersinger and others 2007a).

## Cooperativity and Competition in Humans

Do the roles for vasopressin and oxytocin that are described above have implications for humans? Physiological, pharmacological, and genetic studies suggest that the answer is "yes". There have been numerous studies to suggest that intranasal treatment with vasopressin and oxytocin can affect aspects of social cognition. For instance, males treated with intranasal vasopressin prior to an economic-based social test show an increase in their willingness to cooperate, as well as changes in activation in brain areas associated with vasopressin-associated social reward processing (Brunnlieb and others 2016). Intranasal oxytocin has also been shown to promote prosocial behaviors, though there is nuance to its effects. Essentially, depending on an individual's cognitive style, the social context, and their sex, intranasal oxytocin can have differing effects on social cognition (reviewed in Caldwell and Albers 2016). There are also studies that suggest that oxytocin and vasopressin may be dysregulated in some individuals with neuropsychiatric disorders characterized by impaired social cognition, such as autism spectrum disorder, personality disorders, schizophrenia, and posttraumatic stress disorder. So, too, is there evidence that the manipulation of these systems may have some therapeutic benefit (for reviews of this topic, see Caldwell and Albers 2016; Kirsch 2015; Rich and Caldwell 2015; Zhang and others 2017).

## Conclusion

Oxytocin and vasopressin are powerful regulators of social behavior across species and across the lifespan (Fig. 7). However, they do not simply promote prosocial behaviors, rather their individual effects vary greatly, not
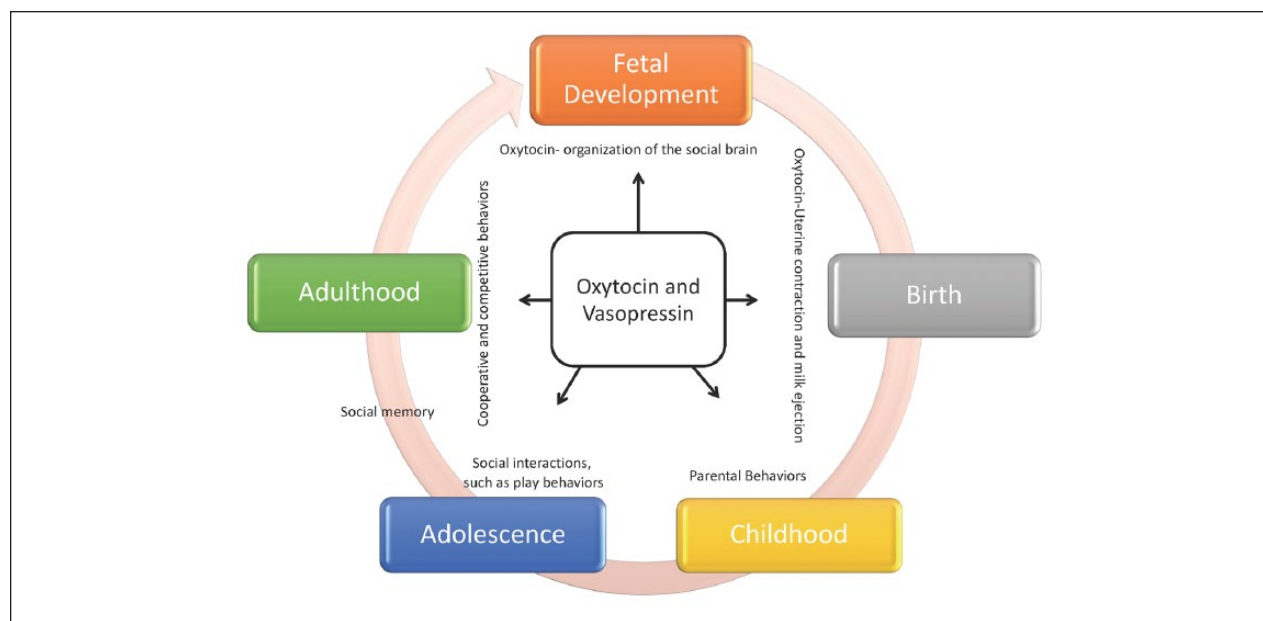
**Figure 7.** Oxytocin and/or vasopressin have important roles in physiology and behavior across the lifespan for many mammalian species.

just between species, but also within a species, between the sexes, and within specific brain regions. Furthermore, an animal's life history and the social context shape the way the brain responds to these neuromodulators. Therefore, it is often at the individual level that the elegance of these systems can be fully appreciated. Looking forward, a better understanding of how these neurohormones differentially affect behaviors between/within individuals will continue to be a key area of scientific inquiry. Likewise, studies focused on how these systems may interact with one another as well as other neurotransmitter systems will be important to understanding the SBNN. Given the complexities of social behavior, perhaps it is not surprising that even after over 70 years of research on the oxytocin and vasopressin systems that there is still much to discover about how they function.

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