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The Neurohormonal Basis of Social Attachment: Oxytocin in Regulating Pair and Maternal Bonds

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ABSTRACT

Humans are highly social creatures that form intricate relationships, which makes studying social attachment an important part of behavioral neuroscience. These social relationships can reinforce positive well-being, but also inflict psychological damage when broken. Monogamous species form pair bonds, which are uncommon in the predominantly polygamous mammalian kingdom. Using the prairie vole (*Microtus orchogaster*), an extensively studied model organism, this review will focus on the role of oxytocin (OT) in both regulating and manipulating systems important for these bonds and discuss the possible consequences of changes to these systems. Because of the nature of these bonds, and how OT regulates the associated neural circuits, this research has important therapeutic value.

Introduction

The neurohormonal basis for feelings of love or attachment, reflected in humans as romantic or familial relationships most often, is investigated in socially monogamous species. Monogamous species display unique behaviors that are not very common in the mammalian kingdom, such as the propensity to form pair bonds. These bonds have been recently characterized as enduring bonds between two sexually mature conspecifics (Bales et al., 2021), which may involve behaviors such as biparental care of offspring, mate-guarding (aggression towards sexual competitors) (Getz et al., 1981), and mating (Kleiman, 1977).

Throughout the mammalian kingdom, however, species also form mother-infant bonds, which are the most common and enduring bonds (Numan & Young, 2016). Perhaps unsurprisingly, maternal bonds play a large role in forming the capacity to form attachments as adults and are thought to be able to manipulate neural circuits important for social behavior. Both pair and maternal bonds play an essential role in maintaining health, and bond disruption is commonly associated with deterioration in mental and physical health (Smith & Wang, 2012; Lieberwirth & Wang, 2014; Naderi et al., 2021).

Thus far, extensive research has suggested the involvement of the evolutionary ancient nine-amino-acid peptides oxytocin (OT) and arginine vasopressin (AVP) in these social bonds. This is not surprising given that OT has been shown to manipulate social stress (known as "social buffering") (Smith & Wang, 2014; Heinrichs et al., 2003), trust (Kosfeld et al., 2005) (specifically in social circumstances), as well as facial (Guastella et al., 2008) and emotional (Domes et al., 2007) recognition. OT is also implicated in aspects of maternal behavior, including parturition and lactation, and sexual behavior (Argiolas et al., 1989), an important component of the pair bond. AVP also regulates many of the aforementioned social properties, including social recognition and maternal care (Tickerhoof & Smith, 2017; Bielsky et al., 2005).

Here, I will discuss the neurobiology of pair bonding by looking at OT (and AVP, briefly) and those demonstrating the involvement of OT in maternal bonding. Further, I will briefly cover the early developmental care and changes in the OT systems that affect future affiliative behaviors, such as forming partner preference

and alloparenting. Besides overviewing relevant studies, I will also highlight the translational value of OT research, given its involvement in social behavior.

Understanding Social Attachment with Prairie Voles

As only 3-5% of mammalian species are socially monogamous (Kleiman, 1977), there are few appropriate animal models to study the underlying mechanisms. Although closely related, microtine voles display disparate social strategies, but similar non-social behaviors across species. As such, they provide a functional comparative approach to investigating the neurobiological basis of social attachment. Thus, this review will focus on the extensively studied monogamous prairie vole (*Microtus orchogaster*). In the wild, most prairie voles adopt social monogamy (Carter & Getz, 1993) and prefer pair bond establishment even when optimal conditions for promiscuity are met (Blocker & Ophir, 2016). Furthermore, prairie voles also demonstrate behaviors of great interest to pharmacological studies. That is, they mate guard, cohabitate, and usually show biparental care of offspring and alloparenting (Getz et al., 1981).

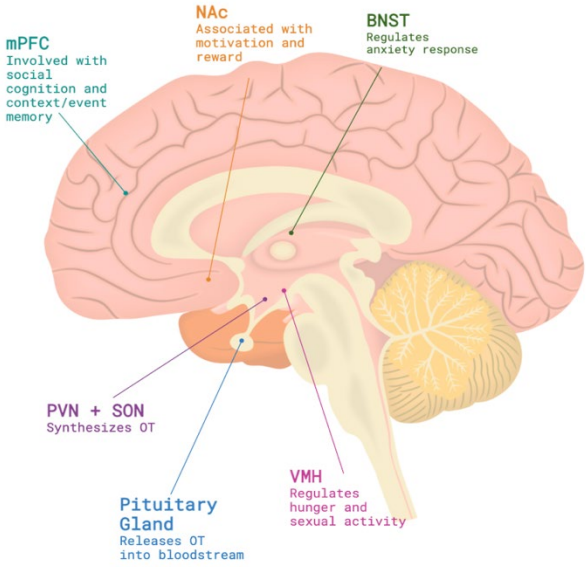

Figure 1. Regions of the brain that express OT and their functions

Neurotranscriptomics research has shown that pre-mating genome differences between monogamous and polygamous voles are associated with pair bond facilitation (Tripp et al., 2021). When comparing microtine rodents, striking OT receptor (OTR) distribution differences are apparent between species. Monogamous voles have higher densities of OTR in the bed nucleus of the stria terminalis (BNST), medial prefrontal cortex (mPFC), and nucleus accumbens (NAc) than their promiscuous counterparts. In contrast, promiscuous voles show higher binding in the ventromedial hypothalamus (VMH), lateral septum (LS), and anterior cortical amygdala, regions which show little binding in monogamous voles (Young et al., 2008). These OT and OTR-expressing regions are commonly associated with decision-making, reward, and cognitive processes, as shown by Figure 1. Interestingly, although OTR distribution is highly species-specific, OT expression is highly conserved across rats, mice, and prairie and meadow voles(Ross, Cole, et al., 2009).

The Neurobiology of Pair Bonding

Oxytocin and Vasopressin in Pair Bond Formation

In the laboratory, the pair bond is assessed with partner preference, with the traditional assessment being the 3 hr partner preference test. In this test, the focal subject is placed in a three-chambered apparatus between a tethered "partner" vole and a novel "stranger" vole tethered to the other end. Partner preference is then measured by the amount of time the subject spends with each vole, typically inferred after the subject spends more than twice the time huddling with the partner (Williams, Catania, et al., 1992; Beery, 2021). Cohabitation for 24 hr or more results in females exhibiting a strong preference for a familiar partner versus a stranger male, while females who cohabited and mated for 6 hr developed the same preferences. Together, these results show that while mating is not essential for partner preference formation, it increases the speed by which they are developed (Williams, Catania, et al., 1992).

Numerous pharmacological studies have implicated OT in the formation of pair bonds. In female prairie voles, OT infusion facilitates partner preference even without mating or estrogen priming (Williams, Carter, et al., 1992). In contrast, the administration of an OTR antagonist impairs mating-induced partner preference, indicating that central OT is critical for pair-bond formation in prairie voles (Insel & Hulihan, 1995). Moreover, the NAc has been identified as an important brain region for pair bonding. Indeed, a recent study has shown that OTR expression in the NAc is vital for female partner preference formation (Keebaugh et al., 2015); accelerated partner preference was also seen in female voles with higher OTR density in the NAc (Ross, Freeman, et al., 2009). Similarly, in the NAc, the blockade of OTR prevented partner preference, while the over-expression of OTR in adult female voles facilitated partner preference (Liu & Wang, 2003). Besides the NAc, however, the PVN plays a central role in pair bonding as well. It is one of the primary sources of OT, as stated by figure 1, and also projects OT neurons to the NAc shell and OT-immunoreactive fibers (Bosch et al., 2016).

Similar to OT, there are significant distribution differences in AVP receptors between monogamous and non-monogamous species: prairie voles have higher AVP receptor binding in the BNST, and in the central nucleus of the amygdala compared to their promiscuous counterparts, montane voles (Wang et al., 1997). Furthermore, increasing AVP receptor binding in the ventral pallidum resulted in increased affiliative behaviors in male voles; partner preference strength following cohabitation, without mating, increased as well (Pitkow et al., 2001). Interestingly, AVP manipulation, through viral vector gene transfer, was shown to essentially change the social behaviors of the polygamous meadow vole, by increasing partner preference formation (Lim et al., 2004).

However, it is worth mentioning the sex-specific effects of OT and AVP on social behavior (Lu et al., 2019), including bonding. Thus far, studies have demonstrated the role of OT in female prairie voles akin to the role of AVP in males. Indeed, peripherally injected OT induced partner preference in females, but not males (Cushing & Carter, 2000). An AVP antagonist (AVPA) failed to prevent partner preference in mated females, once again, indicating AVP may be more critical for male prairie voles (Insel & Hulihan, 1995). After cohabitation, males expressed more AVP mRNA cells in the BNST than females (Wang, Smith, et al., 1994). Nevertheless, administration of both OTA and AVPA was associated with low social behavior, regardless of sex. Therefore, it is possible that while OT and AVP are both sufficient to facilitate partner preference in females and males, respectively, access to both receptors may be required (Cho et al., 1999).

Changes to the Oxytocin System Following Pair Bond Disruption

In male titi monkeys, both short (48h) and long (2-3 weeks) term separation with their mate resulted in elevated cerebrospinal fluid (CSF) OT concentrations, and males who had previously mated with their partner had lower

CSF OT concentrations than those who did not (Hinde et al., 2016). Furthermore, increased plasma OT is seen with repeated isolation throughout 4 weeks in females only, while chronic isolation leads to higher OTR expression in the PVN (Pournajafi-Nazarloo et al., 2013). Similarly, increased OTR expression is also seen in males following bond disruption. After the loss of a female partner, male voles have reduced OT synthesis in the PVN as well, and OTR binding is reduced in the NAc (Bosch et al., 2016). A possible explanation is that OT is released as a way to alleviate stress following partner loss, or to encourage finding a new mate, which postulates the involvement of OT in bond disruption-related behaviors. Indeed, as mentioned before, OT has protective effects against negative behaviors induced by separation. Thus, because the OT system is closely affiliated with social behavior, and bond disruption leads to changes in the OT system, it is reasonable that separation is followed by psychological damage and psychiatric disorders.

Following partner loss, only 19% of prairie voles will repair in the wild (Sue Carter & Getz, 1993). In contrast, in the laboratory, monogamous voles will readily form new bonds (Renfro et al., 2009), even after repeated dissolution, with ensuing bond strength depending on separation and mating time. Voles choose their second partner over their first only after 4 weeks, with partner preference decreasing before this time requirement (Harbert et al., 2020; Sun et al., 2014). This suggests that the behaviors of laboratory voles may not entirely reflect those out in the wild. Interestingly, mating, following the first bond, becomes increasingly important, suggesting that these male prairie voles recognize the importance of mating from past partnerships (Harbert et al., 2020). Further, it was shown that pair bond disruption in males is also related to their female partner's reproductive status (Curtis, 2010). In a study conducted with stud males repeatedly forming new bonds, males who only formed one bond had the highest OTR density, with OTR density in the BNST decreasing with repeated pairings (Kenkel et al., 2019). Together, these results once again highlight the involvement of OTR in these bonds, particularly the first, and that although repeated bonds are feasible, they are most likely formed for reproductive reasons.

The Role of Oxytocin in Regulating Maternal Behavior

OT plays a fundamental role in establishing and regulating mother-infant bonds. Vaginocervical stimulation during mating releases OT (Ross, Cole, et al., 2009), as shown by an increase in central extracellular OT following copulation, which induces the formation of the pair bond in prairie voles. On the other hand, during parturition, this stimulation forms a maternal bond instead. After birth, behaviors such as the suckling of the nipple in infants are induced by pheromonal signals regulated by OT. Infant suckling then stimulates OT release, peripherally but also in the brain, which causes milk ejection in lactating females (Nagasawa et al., 2012). Central OT is also crucial for enabling and enhancing olfactory (Kojima & Alberts, 2011) and auditory (Marlin et al., 2015; Carcea et al., 2021) cues important for mother-infant recognition. These stimuli help reinforce maternal bonds and behavior, as shown by how maternal responsiveness declined after the separation between mother and pups occurred (Orpen & Fleming, 1987). Consequently, it is reasonable that OT also regulates mother-infant interactions (Kojima & Alberts, 2011; Kohlhoff et al., 2022).

Furthermore, OT administration to female rats during parturition increases maternal responsiveness (Pedersen & Prange, 1979). In pups, OTR and V1aR binding in brain regions associated with stress and maternal responsiveness is correlated with levels of maternal licking and grooming (Champagne et al., 2001; Francis et al., 2000; Francis et al., 2002). In contrast, an OTA administered on postnatal day 3 eliminated differences between high-licking and grooming dams and low-licking and grooming dams (Champagne et al., 2001). Similarly, NAc OTR facilitated, whereas an OTA blocked, spontaneous maternal behavior (Olazábal & Young, 2006).

Because of the nature of maternal bonds, maternal care during adolescence may influence social and affiliative behavior, or the related neuropeptide systems, later in life (Bales & Saltzman, 2016). Therefore, changes to the mother and child relationship (i.e. separation) early in the postnatal period can have injurious

consequences. Besides altering typical maternal behaviors (Baracz et al., 2020), the OT system experiences change after mother-infant separation. Unpredictable maternal separation results in stress susceptibility, regulated by the mPFC OT pathway in rats; however, predictable separation increases resilience (Shi et al., 2021). Similarly, OT reduces stress-induced anxiety in adult females who were separated from their mothers postnatally (He et al., 2018).

Moreover, parental care and contact (i.e. licking and grooming) in offspring are positively correlated with their alloparenting and affiliative behavior as adults (Perkeybile et al., 2013; Arias Del Razo et al., 2016). Single mother (SM)-reared females exhibited less licking and grooming (Ahern et al., 2011), and huddling, and spent less time with stimulus pups. They are also classified as less spontaneously maternal than biparental (BP)-reared females. Contrastingly, male prairie voles showed no significant difference between SM or BP units. Moreover, SM-reared females had substantially more OT mRNA clusters; however, SM-reared offspring had less OTR binding than their BP-reared counterparts. Interestingly, a positive correlation was seen between PVN OT mRNA clusters and corticotrophin-releasing factor receptor 2 (CRF2), a regulator of the stress response, in the caudal dorsal raphe (Ahern & Young, 2009). It was also postulated that OT release is stimulated by parental licking and grooming, and thus in neonates, these behaviors help reinforce the ability for forming future attachments. It is clear the changes to the OT system reflect maternal behavior and care and thus, the social and affiliative behaviors of adults strongly depend on the relationship between a mother and her young.

Changes in the OT System Influence Adult Alloparenting and Partner Preference Formation

OT is also implicated in alloparenting behavior in prairie voles. Regarding microtine species differences, alloparental care in prairie voles is higher than in meadow voles, as shown by OTR density differences in the striatum and LS (Olazábal & Young, 2005). In a recent study, OT was observed to help induce alloparenting behavior in virgins, with the authors positing that OT neurons are required to enable parental behavior through social stimuli (Carcea et al., 2021). Moreover, even though earlier studies have shown that OTR density has no short-term effect on alloparental care (Ross, Freeman, et al., 2009), it was shown with viral vector gene transfer that female prairie vole alloparenting behavior is modulated through long-term OTR activation through development; that is, the overexpression of OTR in prepubertal voles increased their alloparental behavior as adults (Keebaugh & Young, 2011). OT treatment in female neonates also manipulates parental behavior (i.e. retrievals) (Bales et al., 2007).

Moreover, partner preference formation is also sensitive to manipulations of the OT system during development and the neonatal period. Female prepubertal voles with over-expressed OTR in the NAc displayed increased partner preference formation as adults (Keebaugh & Young, 2011), and developmental exposure to exogenous OT significantly facilitated partner preference formation in female voles (Bales et al., 2007). Family structure also contributes to adult sociality: SM-reared males and females displayed delayed partner preference formation compared to their BP-reared counterparts (Ahern & Young, 2009). Nevertheless, the effects of OT administration are still dose dependent. For example, in male voles, acute administration of any dosage of OT increased mate contact, while OT had varying effects on social approach. Intranasal treatment of low and medium dosages decreased partner preference formation in males, but not in females, demonstrating the sex-specificity of partner preference. Together, the aforementioned studies point to the importance of the OT in adult social behavior, as changes to the OT system in development can have strong consequences on the sociality of adults.

Discussion

Table 1. How OT contributes to pair bonding, maternal bonding, and the related social behaviors

	Pair bonds	Maternal bonds	Social behaviors
OT administration	Facilitates formation even in the absence of mating	Increases maternal responsiveness	Developmental exposure increases partner preference in female adult voles
OTA administration	Impairs mating induced partner preference	Blocks spontaneous maternal behavior and licking/grooming	Associated with low social behavior across male and female voles
OTR expression	Required in NAc for female bond formation	Facilitates spontaneous maternal behavior in NAc	Long term modulation in prepubertal voles affects adult alloparenting and partner preference formation

Together, the data presented in this review primarily demonstrates the role of the neuropeptide OT in regulating social attachment, in the form of pair and maternal bonds (Figure 2). Changes to these neuropeptide systems, particularly OT, as focused on in this review, have strong effects on the prosocial abilities of monogamous species. Moreover, the evidence has highlighted the utility of the prairie vole model, as well as other monogamous species in investigating affiliative behaviors.

In humans, there are obvious limitations as to how neuropeptides can be manipulated, whereas in animals multiple methods are available. However, with the advancement of intranasal OT, a non-invasive delivery method, these studies investigating this peptide prove to be more important than ever. Given the role of OT in prosocial behavior and changes to the OT system that occur following negative events (i.e. bond dissolution), it is suggested that it has therapeutic applications. In humans, clinical studies involving administered OT highlight the use of OT in psychobiological therapy (Meyer-Lindenberg et al., 2011; Heinrichs et al., 2009). Moreover, studies on developmental critical periods, such as the period in which the PVN rapidly synthesizes OT and AVP in prairie voles (Kelly et al., 2018), can bring insight into when they are most sensitive to changes in social environment, and when treatment is most effective. For example, a recent study has demonstrated the involvement of OT in reopening a social reward learning pathway, through a dose of MDMA (Nardou et al., 2019). Thus, more light can be shed on possible therapies for social disorders, such as autism spectrum disorder and social anxiety disorder. Nevertheless, while these studies appear to be promising, there are incongruences in how decreased OT is associated with psychiatric disorders (Rutigliano et al., 2016), and currently, no empirical evidence supports intranasal OT therapy (Meyer-Lindenberg et al., 2011; Yamasue et al., 2018; Guastella et al., 2015; Sikich et al., 2021), or even that OT is able to pass the blood-brain barrier. However, future studies targeting the OT system could potentially lead to new insights into the neurobiology of social attachment, and thereby its translational benefits.

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