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Mini-Review

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Oxytocin, Dopamine, and Opioid Interactions Underlying Pair Bonding: Highlighting a Potential Role for Microglia

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Abbreviations: AVP, vasopressin; BPA, bisphenol A; D1R, D1-like dopamine receptor; D2R, D2-like dopamine receptor; DA, dopamine; GPCR, G-protein coupled receptor; KOR, κ opioid receptor; LPS, lipopolysaccharide; MOR, μ opioid receptor; NAc, nucleus accumbens; OXT, oxytocin; OXTR, oxytocin receptor; V1aR/V1bR/V2R, vasopressin receptors; VTA, ventral tegmental area

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Abstract

Pair bonds represent some of the strongest attachments we form as humans. These relationships positively modulate health and well-being. Conversely, the loss of a spouse is an emotionally painful event that leads to numerous deleterious physiological effects, including increased risk for cardiac dysfunction and mental illness. Much of our understanding of the neuroendocrine basis of pair bonding has come from studies of monogamous prairie voles (*Microtus ochrogaster*), laboratory-amenable rodents that, unlike laboratory mice and rats, form lifelong pair bonds. Specifically, research using prairie voles has delineated a role for multiple neuromodulatory and neuroendocrine systems in the formation and maintenance of pair bonds, including the oxytocinergic, dopaminergic, and opioidergic systems. However, while these studies have contributed to our understanding of selective attachment, few studies have examined how interactions among these 3 systems may be essential for expression of complex social behaviors, such as pair bonding. Therefore, in this review, we focus on how the social neuropeptide, oxytocin, interacts with classical reward system modulators, including dopamine and endogenous opioids, during bond formation and maintenance. We argue that an understanding of these interactions has important clinical implications and is required to understand the evolution and encoding of complex social behaviors more generally. Finally, we provide a brief consideration of future directions, including a discussion of the possible roles that glia, specifically microglia, may have in modulating social behavior by acting as a functional regulator of these 3 neuromodulatory systems.

Key Words: pair bond, vole, oxytocin, dopamine, opioid, microglia

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Understanding the endocrine, neuromodulatory, and neurobiological basis of pair bonding has dual importance. Not only do we gain insight into what defines our humanity, but we also potentially identify ways in which we can harness the positive health consequences of social bonding and/or mitigate the deleterious effects of bond disruption and lack of attachment. A growing human research literature has begun investigating the endocrine basis of human pair bonding via multiple perspectives—for instance, by measuring peripheral hormone levels and manipulating nonapeptide systems through intranasal delivery of oxytocin (OXT) and via genetic studies linking variation in pair bond–relevant traits to allelic variation in neuroendocrine genes (1-3). In addition, neuroimaging studies have identified key neural circuits implicated in attachment and social processing (4-7). However, these studies are inherently limited in the types of manipulations and level of resolution they can attain.

To overcome these limitations, socially monogamous prairie voles (*Microtus ochrogaster*) provide an excellent and highly tractable model for studying pair bonding at multiple biological levels. These laboratory-amenable rodents form lifelong pair bonds that are characterized by a selective affiliative preference for a mating partner and aggression toward other voles. Additionally, prairie voles can be compared to closely related but promiscuous meadow voles, providing a valuable comparative model to home in on the species differences that have contributed to attachment formation exclusively in prairie voles. In this review, we focus on a subset of the neuromodulatory systems that govern attachment formation with a focus on how the social neuropeptide OXT interacts with classical reward system modulators, including dopamine (DA) and endogenous opioids during bond formation and maintenance. We highlight the role of these systems in monogamous pair bonding with brief consideration of their highly conserved role in other affiliative behaviors. Finally, in addition to considering the neural basis of social attachment, we discuss the possible roles that glia, specifically microglia, may have in modulating the communication among these 3 systems as it relates to complex social behaviors.

Sociocognitive and Reward Signaling in Attachment

Bonding is a form of complex social learning that incorporates social sensory information with reward, overlaid by experience. Decades of research on voles has elucidated a role for nonapeptidergic, dopaminergic, and opioidergic systems; here we provide a brief overview of each of these systems, which have been extensively reviewed elsewhere (8-11). Much of the work delineating a role for these systems in pair bonding has relied on the partner preference test, a social choice assay in which the focal vole can choose to spend time with either their mating partner or a novel opposite-sex vole, each tethered on opposite sides of an apparatus. Pair-bonded voles will show a robust preference to huddle with their tethered partner, while non-bonded animals will not show a social preference. Among the early observations was that mating facilitates partner preference, generating the opportunity to pursue gain- and loss-of-function experiments by facilitating bond formation in the absence of mating or blocking bond formation despite mating.

Social nonapeptides

Oxytocin (OXT) and vasopressin (AVP) are evolutionarily ancient 9-amino-acid peptides (nonapeptides) that have a strikingly conserved role in social behavior across organisms (12). In mammals, both peptides, which differ at 2 of 9 amino acid sites, are produced in the paraventricular nucleus and supraoptic nucleus of the hypothalamus, as well as in sparse cell populations in limbic structures (13-15); the functional role of the latter source of these peptides remains largely unknown. Hypothalamic AVP and OXT are the primary source of peripheral release of these peptides, where they modulate a variety of physiological functions, including osmotic balance and blood pressure, and parturition and lactation, respectively (16-19). In addition, OXT and AVP neurons project throughout the central nervous system where peptide release can modify neuronal function either through volume or synaptic transmission (20, 21).

OXT and AVP both play important roles in pair bonding. However, unlike OXT, the effects of AVP are sexually dimorphic, likely due to the presence of a testosterone response element in the AVP promotor that leads to elevated levels of AVP in the brains of males compared to females (8, 22-24). There are 3 receptors for AVP — V1aR, V1bR, and V2R. However, only V1aR and V1bR are located within the central nervous system, with V1aR widely expressed across limbic regions and directly implicated in pair bonding. Specifically, injections of AVP facilitate partner preference, whereas V1aR antagonists block partner preference formation (25-27). This is mediated by V1aR in the ventral pallidum—a region that reciprocally innervates the nucleus accumbens (NAc) and is a core part of the limbic loop of the basal ganglia that regulates motivational salience, behavior, and emotion (28-30). V1aR activation is necessary for bond expression in male prairie voles, even after the initial formation period (31).

OXT signaling is also necessary and sufficient for bond formation. While OXT was initially thought to play a more pronounced role in female prairie voles (25), more recent

work has solidly established a role for OXT in both male and female bonding (32). Administration of OXT facilitates partner preference formation even in the absence of mating, while blockade of oxytocin receptors (OXTR) impairs preference formation despite mating in both male and female prairie voles (25, 33). More recent work has also shown that ongoing OXT signaling is required for the continued expression of an established pair bond. However, as demonstrated in male prairie voles, continuous receptor blockade across multiple days is required to impair an existing partner preference, suggesting that the bond is not immediately erased, but rather "unlearned" though an ongoing monitoring of the attachment relationship (34).

OXT signaling localized in the NAc is particularly important for mediating bonding. Monogamous prairie voles have much higher OXTR densities in the NAc than their promiscuous cousin, the meadow vole, in both males and females (27, 35, 36), and blockade of this receptor population via local antagonist infusion is sufficient to impair partner preference formation in both male and female prairie voles (25, 32, 37). Furthermore, in female prairie voles, increasing OXTR expression in the NAc increases alloparental responsiveness and partner preference formation (38), whereas decreasing OXTR expression via RNAi in the NAc inhibits social attachment and parental care (39). In addition, OXT is released into the NAc of female prairie voles during mating, providing a potential explanation for how mating facilitates preference formation (37). Finally, individual differences in OXTR levels in the NAc are also tied to variation in bond formation within male prairie voles (40).

Dopamine and endogenous opioids

In addition to OXT, reward signaling via NAc dopamine and endogenous opioids is also required for pair bond formation in males and females (10, 41, 42). DA has been broadly implicated in mediating reward learning across species, and akin to OXT, DA is released during mating in male and female prairie voles (43, 44). Gain- and loss-of function pharmaceutical manipulations of DA signaling facilitate and impair partner preference formation, respectively. However, unlike OXTR, there are multiple dopamine receptors, and more selective pharmacological manipulations suggest that D2-like dopamine receptor (D2R) stimulation facilitates bonding while D1-like receptor (D1R) stimulation impairs preference formation in male and female prairie voles (42, 43, 45, 46). Intriguingly, the D1:D2 receptor ratio increases following bond formation, which may facilitate bond exclusivity, preventing the formation of another bond even in male voles that engage in extra-pair copulation (47, 48). However, it is important to note that D2-like receptors include D2, D3, and D4 receptors and that D1-like refers to D1 and D5 receptors (49). As the pharmacology of these receptors is relatively promiscuous, it remains to be determined exactly which of the receptors within each class are important and required in pair bond formation and maintenance.

The role of opioids in social motivation, social reward, and social attachment has also been demonstrated in several species, including rats, mice, puppies, guinea pigs, prairie voles, humans, and chicks (50-52). However, it is only within the last 2 decades that researchers have begun to study the functional role of opioids and their corresponding receptors in the context of pair bonding. The endogenous opioid system comprises 3 classes of receptors (μ, κ, δ), and their respective endogenous ligands, enkephalin, dynorphin, and endorphin (53). In 2011, Burkett et al demonstrated in female prairie voles the necessity of μ opioid receptors (MORs) in the dorsal striatum in the formation of pair bonds, mediated partially through a reduction in mating behavior (54). Resendez and colleagues were able to further expand on this finding. They confirmed that in female prairie voles, MORs in the dorsal striatum mediate partner preference by affecting mating behaviors, whereas MORs in the dorsomedial NAc shell facilitate partner preference formation through positive hedonics associated with mating (55). Additionally, Resendez and colleagues demonstrated in both male and female prairie voles that in the NAc shell, κ opioid receptors (KORs), and not MORs, mediate selective aggression, a maintenance behavior that is seen in an established pair bond (56).

Systems Communication in Social Attachment: Oxytocinergic, Dopaminergic, and Opioidergic Interactions

Each of the above-mentioned neuromodulatory systems does not act in a vacuum. In particular, OXT and AVP differ at only 2 amino acid residues and exhibit crossreactivity for their respective receptors. Evidence supporting a functional role for such crossreactivity comes from studies showing that OXT can act via V1aR in the lateral septum to impair peer affiliation in non-monogamous meadow voles (57). However, the extent to which these interactions across nonapeptide systems modulate pair bonding remains unknown, along with information about the AVP system's interactions with the DA and opioidergic systems in the prairie vole model. As such, the remainder of this review will focus on behaviorally relevant interactions between OXT, DA, and opioid systems.

The full extent and mechanisms by which OXT, DA, and opioid systems interact to mediate behavioral transitions across bond formation and maturation remains largely

unexplored. In order to successfully form and maintain a bond, an animal must integrate social sensory information, social reward, experiential factors, and internal state. One way to integrate these multiple layers of information could be through coordinated signaling. Likewise, bonding results in profound changes in behavior, which could be mediated in part by effects of one system on another. Below we outline what is currently known about interaction of these systems in social bonds, as well as unexplored interactions that may contribute to bond-related behaviors based on known interaction of these neuromodulatory systems in other contexts (Fig. 1). The majority of studies investigating these systems in the context of pair bonding studies have focused on the nucleus accumbens, driving the focus on this region in the context of this review. However, other brain regions are also likely to be involved, particularly within the context of systems communication. Specifically, the medial prefrontal cortex, the dorsal striatum, the ventral pallidum, the ventral tegmental area, bed nucleus of the stria terminalis, insular cortex, and the amygdala are involved in social decision making and reward learning, and represent intriguing targets for future study (58-68). While most of the aforementioned brain regions have studied at least 1 of the 3 systems (OXT, DA, or opioid) within the context of pair bonding, the insular cortex remains unstudied in pair bonding. The insular cortex is positioned to link integrated social sensory cues within this network to produce flexible and appropriate behavioral responses to socioemotional cues, as evidenced by work on oxytocin-dependent social approach in rats (63). Therefore, this brain region, which directly innervates the NAc, has the potential to serve a prominent role in modulating social behavior in prairie voles and represents an important target for future research.

Oxytocinergic, dopaminergic, and opioidergic systems act via G-coupled protein receptors (GPCRs). GPCRs are characterized by their cell surface 7-transmembrane domain that transduces extracellular signals across the membrane in order to initiate intracellular signaling pathways through activation of a trimeric G-protein (69). GPCR signaling has been traditionally characterized through 4 different

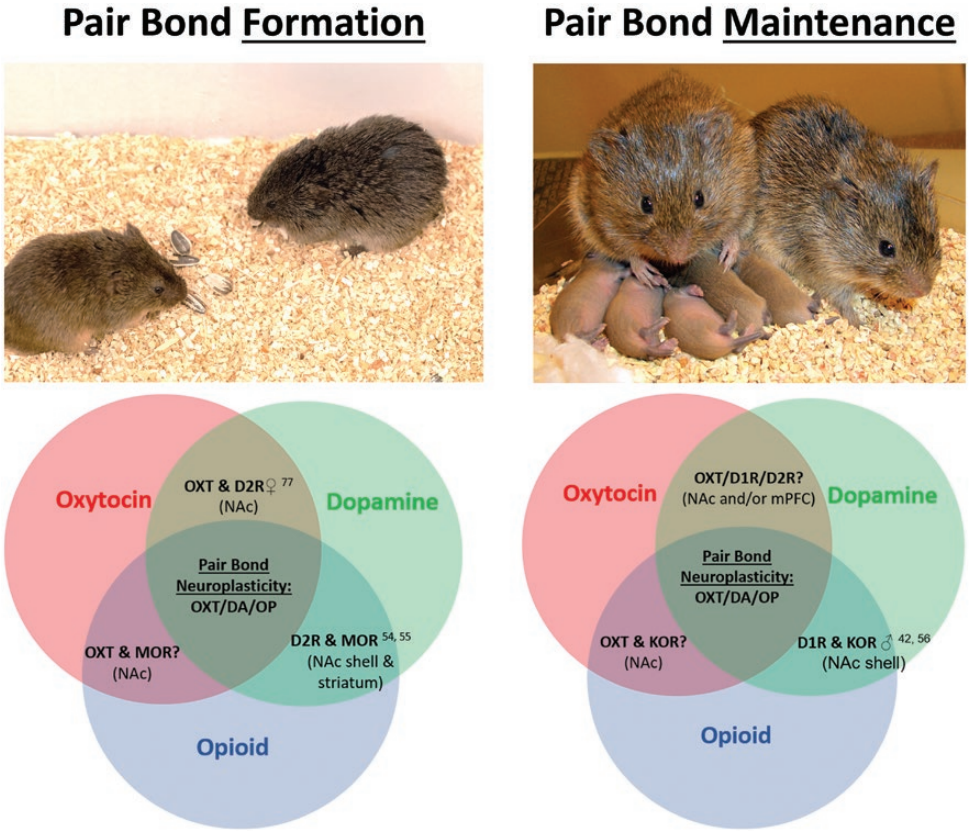

Figure 1. Known interactions among the oxytocinergic, dopaminergic, and opioidergic systems in pair bond formation and maintenance. While several neuromodulatory systems have been implicated in pair bonding, interactions of the oxytocinergic system with reward modulatory systems, such as the dopaminergic and opioidergic systems, have been the most well-studied. Known interactions are indicated in the above diagram with reference numbers. Further research is needed to address how the brain region–specific interaction(s) among these systems change depending on the stage of a pair bond and the sex of the animal. Abbreviations: D1R, dopamine 1 receptor; D2R, dopamine 2 receptor; DA, dopamine; KOR, κ opioid receptor; MOR, μ opioid receptor; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; OP, opioid; OXT, oxytocin. Photo credits Paul Muhlrad (left) and Todd Ahern (right).

G-protein classes: $G_{\alpha s}$, $G_{\alpha i/o}$, $G_{\alpha q/11}$, $G_{\alpha 12/13}$ (70). But research over the last several decades demonstrates additional models of GPCR signaling including G-protein coupled receptor kinases (GRKs) and β-arrestins (71, 72) and homo- and hetero-dimerization of monomeric GPCR molecules (73, 74). Despite the structural and general function commonality of GPCRs, individual GPCRs are extremely functionally diverse given the wide variety of ligands and stimuli they respond to, including but not limited to: biogenic amines, hormones, peptides, cations, lipids, glycoproteins, pheromones, synthetic drugs, tastes, odors, stress, and light (75, 76). Therefore, activation of GPCRs can lead to various effects on cellular function, including cell homeostasis, intra- and extracellular signaling, and physiology at a macro level; and initiation/termination of transcription, activation of ion channels and neuronal excitability, and hormone release at a micro level. As such, signaling interactions between and among the oxytocinergic, dopaminergic, and opioid systems broadly encompass multiple potential levels of biological function—from one system changing the transcriptional regulation of another to synergistic effects on neuronal activity within or between cell populations.

While studies of the interactions between these neuromodulatory systems are far from exhaustive, here we provide examples across multiple levels of biological interaction, ranging from effects on gene expression to signaling mechanisms. For the purposes of this review, we use the term "interaction" to refer to any biological effect of one system on another, as well as synergistic effects of coordinated activation. We posit that the interactions among these systems will be critical to our understanding not only of complex social behavior, but specifically for pair bonding, and that such interactions represent one mechanism for integrating multiple internal and external information sources as outlined below.

Concurrent OXT and DA signaling is required for bond formation

Pharmacological studies suggest that concurrent activation of OXTR and D2R in the NAc is required for partner preference formation in female prairie voles (77). Specifically, boosting activity in one of these systems via agonist administration is not sufficient to overcome the impairing effects of blockade in the opposite system. Thus, neither of these systems serves as an upstream regulator of the other with respect to bond formation (77). However, whether the signaling between D2R and OXTR is occurring in a cell-autonomous fashion, and/or how this combined signaling impacts circuit function remains unknown. Specifically, whether OXTR expression is biased toward D1-expressing or D2-expressing NAc medium spiny neurons has not been determined. OXTR is typically G_q coupled while D2-like receptors are typically G_i coupled. If OXTR and D2R activation are occurring within different cell populations, concurrent activation may shift the balance of activity across these populations. Alternately, if signaling is occurring in a cell-autonomous fashion, coordinated activation of different intracellular signaling pathways may be required for and result in activation of specific bond-relevant transcriptional programs.

We may be able to gain some insights into OXT/DA interactions more broadly by drawing on what is known about how systems modulate the complex relationship between social bonding and drugs of abuse (78-80). Drugs of abuse have the capacity to impair pair bonds in prairie voles, and pair bonds have been demonstrated to protect against the abusive properties of amphetamine and methamphetamine, effects that may be mediated by an interaction between oxytocinergic and dopaminergic systems. Specifically, amphetamine exposure in female prairie voles has been shown to (i) block partner preference formation; (ii) decrease OXTR in the medial prefrontal cortex (mPFC) and D2R the NAc; and (iii) increase extracellular DA in the NAc (78). However, OXT infusion into the mPFC restored partner preference in amphetamine-exposed animals and increased NAc DA levels. Relatedly, other studies have examined that pair bonds are protective against the rewarding properties of amphetamine, and that this buffering of reward is mediated through a D1-specific mechanism in male prairie voles (81). Taken together, these data indicate that the OXT and DA systems may interact not only in pair bonding, but also in mediating the relationship between drugs of abuse and social bonding, and that this is mediated through specific OXT and DA signaling pathways.

There is further evidence that OXT/DA system interactions are evident in work from other species, particularly in regard to gating reward and impacting social behavior. For example, in mice OXT gates DA release in the ventral tegmental area (VTA), another node in the mesolimbic reward circuitry (82, 83). More specifically, Xiao et al demonstrated in male and female mice that OXT enhances the activity of DA neurons in the VTA. However, this effect is region-specific, as the authors also demonstrated that OXT decreases activity of DA neurons in the substantia nigra, pars compacta (SNc) that subserve locomotion and exploratory activities (83). Furthermore, through optogenetic manipulation of OXT, Hung et al further corroborated the finding that OXT release in the VTA increased activity in DA cells, specifically on those cells that project to the nucleus accumbens and that this OXT release and increased activity of DA neurons enhanced prosocial behaviors in male mice (82). Taken together, these studies demonstrate that OXT is able to bias DA signaling toward social reward and supports the interaction of these 2 systems.

Oxytocin-opioidergic interactions are bidirectional

Oxytocinergic and opioidergic system interactions have been documented in multiple species, predominately at the level of ligand production and release. One of the first links between the OXT and opioid systems was demonstrated by Bale and Dorsa in 1997 in rats (84) and by Young et al in 2001 in prairie voles (85). Bale and Dorsa demonstrated that OXTR activation upregulated preproenkephalin gene expression (the precursor for enkephalin, the endogenous ligand for MOR) in rats, and Young et al showed that, in female prairie voles, an infusion of OXT into the NAc also increased gene expression of preproenkephalin, but did not affect the expression of preprodynorphin, the precursor for the KOR ligand, dynorphin. It is also worth noting that Resendez et al demonstrated an increase in NAc MOR mRNA during bond formation, a time associated with increased NAc OXT release, although whether this increase is OXT-dependent has not been directly tested (42, 55, 56). Thus, while preliminary evidence suggests that OXT signaling can have top-down effects on the opioid system, the specific directionality is not known, as studies similar to what has been done with OXT and DA have not been performed with OXT and opioids to determine whether signaling occurs upstream, downstream, or concurrently. However, effects of OXTR on preproenkephalin suggest that OXT is potentially upstream in some contexts.

Conversely, endogenous opioids affect OXT release in various social behaviors, although this has not been directly examined in pair bonding. The relationship between OXT and opioids has been studied within the context of pregnancy, postpartum, lactation, maternal behavior, and drug addiction (86-89). In pregnant rats, MORs are primarily involved in the inhibition of the OXT response, with no apparent involvement of KORs (90). However, other studies have reported that endogenous opioids decrease OXT release by MOR and KOR mechanisms (91, 92). In human studies, morphine inhibited the expected rise in plasma OXT seen both during the first stage of labor (93) and after delivery (94). In lactating rhesus macaques, females possessing the G allele of the MOR gene C77G SNP had higher OXT levels in their cerebrospinal fluid as compared with homozygous C females, but the 3 genotypes did not exhibit differences in quality of maternal behavior (87). Douglas and colleagues found that, in sex-steroid–treated female rats, naloxone strongly increased stress-induced OXT release, revealing strong endogenous opioid inhibition of OXT activity (88). Additionally, MOR and KOR antagonists were also able to potentiate stress-induced OXT secretion in rats. Specifically, MOR antagonists potentiated the immobilization response, and KOR antagonists potentiated a response to dehydration, demonstrating that different receptor mechanisms are associated with different functional stimuli (95).

In summary, endogenous opioids have the capacity to decrease or inhibit OXT secretion in both animal and human studies (92). Both MORs and KORs appear to be involved in mediating the effects of opioids on OXT, and receptor involvement depends on physiological context (eg, stress, pregnancy, etc). However, whether opioid modulation of OXT secretion occurs as a function of opioid signaling during social behavior, specifically pair bonding, remains unknown. Given the known timing of OXT release in pair bonding and the involvement of both MOR and KOR in various phases of pair bonding, there is likely to be crosstalk between the 2 systems. A study in prairie voles by Ulloa and colleagues demonstrate that the reward state induced by one ejaculation or 6 hours of mating (processes which release OXT and DA) is opioid dependent in males, but not females (89). This study indicates that there is the potential for sex differences within prairie voles in regard to opioid and OXT system interactions.

Dopamine and opioid systems interact to maintain pair bonds

Opioid and dopaminergic systems regulate reward, motivation, emotional responses, cognition, and autonomic functions. Furthermore, the organization of these 2 systems is intimately intertwined. MOR's endogenous ligand, enkephalin, is expressed in D2-like neurons (96-98) while KOR's endogenous ligand, dynorphin, is expressed in D1-like neurons (99-101). Given that D2- and D1-like receptors have been implicated in pair bond formation and maintenance, respectively, this led to specific hypotheses about the role of MOR and KOR in selective affiliation and aggression, respectively (56, 102, 103).

Within the context of pair bonds, Resendez and colleagues demonstrated that D1-like receptors act upstream of KOR in the NAc shell to mediate aggressive behavior in pair-bonded males (42). In a series of experiments using D1R agonists/antagonists and KOR agonists/antagonists, they showed that KOR-mediated decrease of stimulated DA release in the NAc shell was greater in brain slices from pair-bonded males compared with non-bonded animals. However, non-bonded and pair-bonded females showed no difference in KOR-mediated DA release. Interestingly, both males and females show an increase in D1R mRNA levels in the ventral striatum, and males show a decrease in KOR binding in the ventral NAc shell after 2 weeks of cohabitation. The evidence

for interaction of D1R and KOR was further strengthened through behavioral studies showing that attack frequency decreased when males or females received a local infusion of D1R antagonist or D1R agonist + KOR antagonist in the NAc, but returned to baseline levels when animals received a local infusion of D1R antagonist + KOR agonist. Similarly, attack latencies returned to normal levels when the antagonist for the D1R-like receptor was administered in combination with a KOR agonist, further providing support that D1R-mediated aggression occurs through downstream activation of KORs (Fig. 2). Finally, Resendez and colleagues demonstrated that male-specific alterations in the dynorphin/KOR system buffers against the rewarding properties of amphetamine, providing further support on the importance of investigating these system interactions and their possible translational importance.

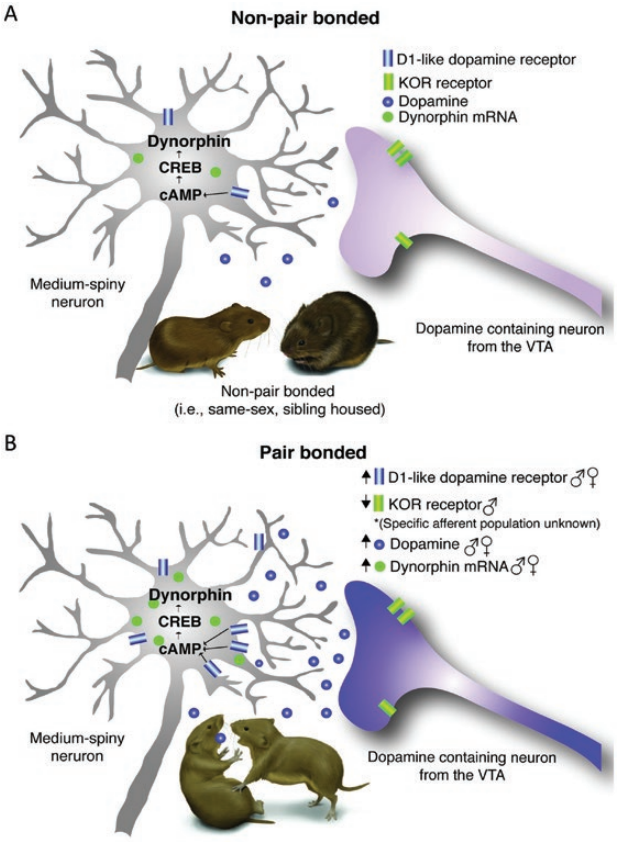

Figure 2. Proposed neural mechanism of D1R and KOR pair bond–mediated aggression. **A,** Non-pair-bonded prairie voles readily approach novel conspecifics and have lower levels of dopamine receptor 1 and prodynorphin mRNA expression within the ventral striatum and less stimulated DA release. **B,** Following the establishment of a pair bond and after 2 weeks of cohabitation with their partner, male and female prairie voles aggressively reject novel conspecifics. Pair bonding upregulates dopamine receptor 1 and prodynorphin mRNA within the ventral striatum and enhances DA release within the NAc shell of both males and females. Pair-bonded males also show a decrease in KOR binding within the NAc shell. *This figure is reprinted with permission from the authors of "Dopamine and opioid systems interact within the nucleus accumbens to maintain monogamous pair bonds," Resendez et al 2016, eLife,* (42) https://doi.org/10.7554/eLife.15325.022

Microglia as System-level Regulators of Neuromodulation of Social Behavior

As we strive to understand the neuromodulatory organization of social behavior, it is important to note that neurons are not the only cell types that play a role within behavioral circuits and systems. Microglia, the resident macrophages of the brain, sculpt and refine neural circuits, and recent work has shown that microglia help organize social circuits and shape social behavior via effects on neuromodulatory systems (104-109) (Fig. 3A). While the mechanisms surrounding social behavior are complex, and the studies examining how glia modulate social behavior are newly emerging, there is evidence that microglia work in conjunction with the oxytocinergic, dopaminergic, and potentially, opioidergic systems to shape microglia function, neural circuits, and social behaviors, including pair bonding. However, while the evidence to date suggests a hub-like position for microglia in integrating concurrent signaling information from nonapeptide and reward systems, this speculation requires additional research, which is likely to hinge on the development and implementation of microglial-specific manipulations in prairie voles.

Microglial Mechanisms Regulate Social Behavior

Depletion of microglia leads to persistent changes in social behavior

While the role of microglia in cellular brain development is relatively well-studied, less is known about the microglial role in behavioral development. A handful of studies have sought to determine how temporary depletion of microglia in early life contributes to programming of normal adult social behaviors (105, 128). Nelson and Lenz found that neonatal chemical depletion of microglia via an infusion of liposomal clodronate affected several adult social behaviors in male and female rats including: increased social avoidance behavior, decreased passive interaction time, decreased behavioral despair as measured by the forced swim test, and a blunted corticosterone response in females to acute stress in adulthood. VanRyzin and colleagues found that postnatal depletion of microglia using liposomal clodronate also affected several adult behaviors including deficits in male sexual behaviors, increased body weight in adult females, and decreased body weight in adult males. Taken together,

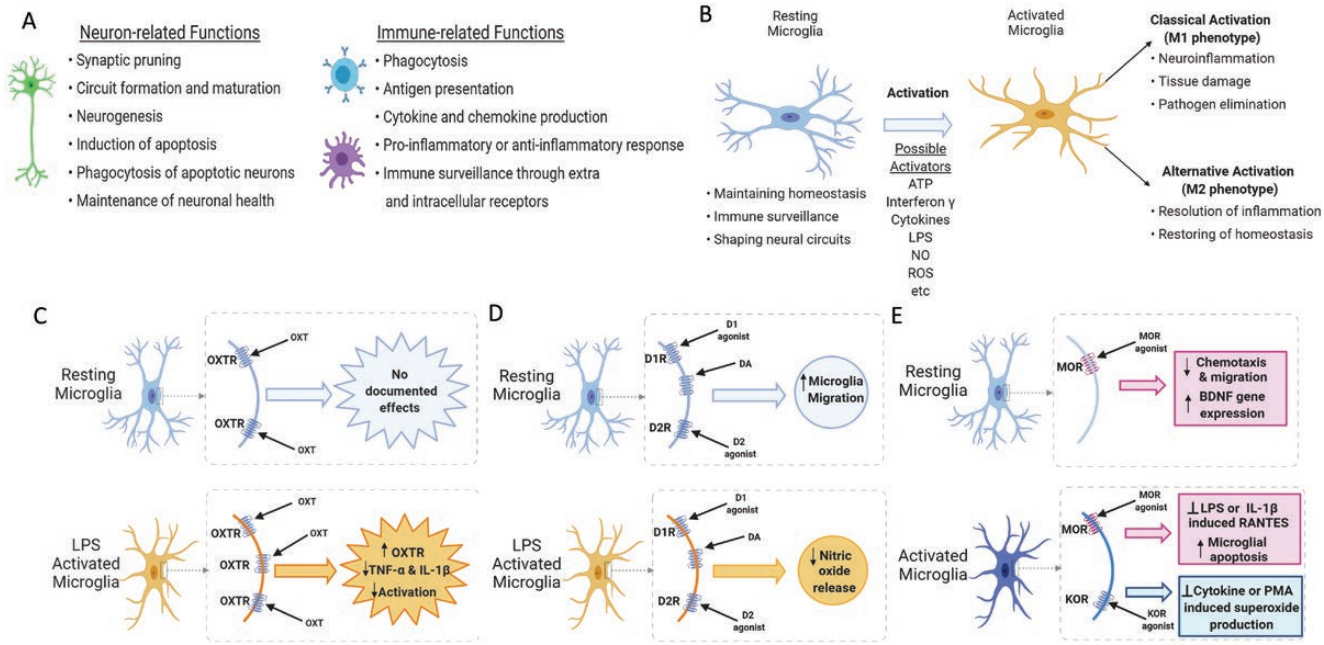

Figure 3. Oxytocin-, dopamine-, and opioid-mediated microglial function. **A,** Summary of microglia functions related to neurons and the immune system. **B,** A simplified schematic demonstrating microglia functions while in the surveilling/resting state and while in the activated state. While 2 activated state phenotypes are demonstrated here, there is evidence that there are more activation phenotypes and that they exist amongst a spectrum (110) **C-E,** Microglia work in conjunction with the oxytocinergic, dopaminergic, and potentially, opioidergic systems to shape microglia function, neural circuits, and social behaviors. Here is a summary of oxytocin- **(C**; (111-116), dopamine- **(D** (117, 118), and opioid- **(E** (117, 119-127) mediated microglial function.

these studies support a role for microglia in the normal development of motivated behaviors.

Similarly, Zhan and colleagues demonstrated that mice deficient in Cx3cr1, a chemokine fractalkine receptor, demonstrate a reduced number of microglia, and ultimately show decreased functional connectivity between the prefrontal cortex and hippocampus (104). Furthermore, altered social and repetitive behaviors were observed, such as reduced social exploration, decreased social interaction, and increased repetitive self-grooming behaviors under stressful conditions (104). These data imply a critical role for microglia in sculpting neural social circuit function and give insight into a potential mechanism that can contribute to aberrant social behaviors.

Microglia as master regulators of transitions in social play behavior

Juvenile male rats exhibit high levels of social play that wane as they transition to adulthood; females also play but at reduced levels (129). Microglia have been implicated in mediating both the onset and eventual curbing of this behavior (106, 108). In particular, sexual dimorphism in testosterone-mediated endocannabinoid tone sculpts sex differences in juvenile rat social play via microglial phagocytosis (108). The neonatal testosterone surge increases endocannabinoid tone, and thereby increases microglial phagocytosis of newborn astrocytes in the medial amygdala of male rats. This leads to increased social play in exclusively male, and not female, juvenile rats.

Microglia have also been implicated in closing the developmental social play window in rats through NAc D1R downregulation during adolescence (106, 130). This mechanism of patterning also occurs in a sexually dimorphic manner. More specifically, in males, D1Rs tagged by Complement Receptor 3 (C3) are phagocytosed by microglia, resulting in decreased social play. Conversely, D1R downregulation in female rat adolescence is not associated with microglia and C3 immune signaling, and the authors speculate that this process is regulated by some other unknown protein. Taken together, the above-cited studies (106, 108) indicate that microglia modulate social play behavior in sex-specific manners, and that these mechanisms vary depending on the brain region examined.

Interestingly, the 2 studies above (106, 108) that determined how microglia modulate social play behavior were done in 2 brain regions well-studied within the context of prairie voles and social behavior, the amygdala, and the NAc. Specifically, the amygdala is known to regulate various aspects of prairie vole social behavior (131, 132) although the role of microglia in mediating these behaviors has not been explored. In a model of social defeat, male and female prairie voles display social avoidance, in addition to increased D1R protein levels (132). Relatedly, increasing

D1R signaling pharmacologically was sufficient to induce a socially avoidant state. And finally, microglia number and colonization increase in the medial amygdala in male prairie voles when exposed to low doses of the endocrine disruptor bisphenol A (BPA) and in female prairie voles at high doses of BPA (133). Interestingly, these doses of BPA have been demonstrated to abrogate partner preference in female prairie voles when assessed after 3 hours of pairing without mating (134). The effect of BPA on partner preference in male prairie voles is not known as the untreated/control male prairie voles did not form a partner preference under these pairing conditions.

Furthermore, as previously discussed in this review, many studies surrounding pair bonding have focused on the NAc and the DA system. Of relevance to microglia pruning D1R synapses in the NAc study, the ratio of D1R to D2R has been documented to change in the NAc as prairie voles transition from pair bond formation to maintenance. Therefore, these developmental reductions in social play behavior found in the NAc of rats mirror the reduction in general prairie vole affiliative behavior following bond formation. While the specific molecular mechanisms remain unknown, glial-mediated regulation of DA receptors may contribute to bond-associated behavioral transitions. Moving forward, it would be interesting to examine if microglia have a role in modulating well-known changes in DA receptor levels in the NAc during the transition from pair bond formation to pair bond maintenance, and if sex differences exist in the molecular mechanism of the development of a pair bond.

Lipopolysaccharide, a known microglia activator, induces partner preference in female prairie voles

While the above outlines the general role of microglia in affiliative social behavior, a role for microglia in pair bonding is further supported by the finding that lipopolysaccharide (LPS), which activates microglia, induces partner preference (135). Broadly, LPS administration has been used to examine the mechanism underlying alterations in sexual, parental, and other social interaction behaviors associated with sickness behavior (135). Sickness behavior is a response to infection characterized by anorexia, depressed activity, loss of interest in usual activities, and disappearance of body-care activities (136). LPS is a known endotoxin that induces a proinflammatory cascade by binding to Toll-like receptor 4 (TLR4), predominantly expressed in microglia in the central nervous system (137). LPS has been used in several models to induce an acute immune response within an animal (135) and to activate microglia in cell culture studies (111, 138, 139) (Fig. 3B). Importantly, LPS has been shown to cross the blood-brain barrier (140) and systemic injections have been demonstrated to cause microglial activation and neuroinflammation (141, 142). In prairie voles, a single LPS injection facilitated partner preference formation at 6 hours in female prairie voles, but not male prairie voles (135). These results were somewhat surprising as other stress-inducing manipulations, including manipulations of the hypothalamic-pituitary-adrenal axis, typically reduce bonding in female prairie voles (143, 144). However, the authors note that the "involvement of LPS with central hormonal and neurotransmitter systems are proximate mechanisms through which LPS may facilitate pair bonding."

Although the neural circuitry involved in processing signals from the immune system is not yet fully understood, there are several areas of overlap in the systems known to be implicated in LPS exposure and pair bonding—including DA release and OXT release. First, LPS administration increases DA release in the nucleus accumbens (145) and locus coeruleus (146) in rats. As stated previously, DA release, in the NAc specifically is a requirement for pair bonding. Second, LPS also increases OXT release in the posterior pituitary gland in rats (147, 148). However, it has not been documented if LPS increases OXT release in other brain regions. Therefore, given that LPS facilitates partner preference formation in female prairie voles, activates microglia, and that LPS has known effects on DA and OXT release in other species, it is plausible that microglia may play a role within pair bonding, particularly within a pathological inflammatory context.

However, relatedly, the effect of a single LPS challenge during the postnatal period has been examined in mice, and differential effects have been found in males in females regarding effects on adult social behavior (149). More specifically, neonatal LPS treatment decreased sociability in adult female, but not male mice. LPS-treated females also displayed reduced social interaction and social memory in a social discrimination task as compared to saline-treated females. The authors stated that these effects appear to be independent of microglia inflammatory signaling given that *MyD88* knockdown (which prevents LPS-induced release of the proinflammatory cytokines TNFα and IL-1β) did not prevent LPS-induced changes. These data highlight the importance performing studies at different periods of development in both sexes in a species-specific manner. Smith et al found that a single neonatal LPS injection results in reduced sociability in adult female mice and not male mice, whereas Bilbo et al found that a single LPS injection in adult prairie voles increases partner preference in female prairie voles and not male prairie voles. Importantly, sociability tests were done with animals of the same sex, so direct relevance to pair bonding remains a topic of future research.

Microglia express OXTR, D1R, D2R, MOR, and KOR

The functional properties of microglia also suggest that they are responsive to OXT (111-116), DA (117, 118), and opioid signaling (117, 119-127) (Fig. 3C-3E). Of these, the most intriguing role for modulation of microglia as potentially important mediators of bonding comes from studies of DA and microglial function. Specifically, studies suggest microglia respond to D1R and D2R-specific ligands through increased microglial migration, and chronic DA stimulation decreased LPS-induced microglial nitric oxide production. Thus, DA release may function to attract microglia with DA receptors to areas with dopaminergic transmission (118). This could be relevant not only in development, but also when DA is released during mating and pair bond formation, and it provides further support for the hypothesis that DA is a potential mediator of neuroimmune mechanisms regulating social behavior (130). However, it remains to be determined if microglia expression and behavior change throughout pair bond formation, maintenance, or dissolution.

Regarding microglia and OXTR functional studies, LPS upregulates OXTRs in microglia and macrophages (111, 142, 150). OXT dampens proinflammatory pathways in these cell types, but through separate mechanisms. Microglia work via a decrease in ERK and p38 phosphorylation mechanism (142), and peripheral macrophages act through a decrease in p65 subunit of NF-kB phosphorylation mechanism (111, 150) to reduce proinflammatory pathways. Relatedly, pretreating LPS-exposed mice with OXT decreases microglial activation as determined by Iba-1 expression and decreases proinflammatory factor levels of TNF-α and IL-1β in the prefrontal cortex of animals, with the same effects being replicated in microglia studies in vitro (142). The authors concluded, as several others have (111-116, 150), that OXT may have anti-neuroinflammatory properties, in which case it would be highly probable that microglia would be involved in mediating the anti-inflammatory properties of OXT in the brain. Intriguingly, the release of OXT during pair bond formation and OXT's putative role in decreasing the proinflammatory responses of microglia could serve as a potential mechanism underlying the stress-protective effects of pair bonds (151, 152).

In regard to the opioid system, both MORs and KORs (but not DORs) appear to be present in microglia, according to descriptive and/or functional studies (117, 119-126), where they both appear to have anti-inflammatory properties. MOR studies demonstrate inhibition of chemotaxis and microglial migration, as well as increased *BDNF* gene expression (121, 122, 124, 153) in several systems including rat, cat, and human fetal microglia. Additionally, morphine inhibits RANTES (regulated upon activation, normal T-cell expressed and secreted chemokine) production in activated microglia (124) and triggers microglial apoptosis (127). KOR studies demonstrate that KOR agonists mitigate cytokine or PMA-induced superoxide production (124, 126, 154, 155) and that KOR agonists also attenuate HIV-related toxicity and quinolinate release from human fetal microglia (126, 155). Thus, while signaling via these receptors in microglia is generally classified as anti-inflammatory, their potential role in social behavior remains largely unexplored. Notably, MORs and KORs are both implicated in juvenile rat social play (156) and, as previously mentioned, pair bonding.

A recent paper by Rivera and colleagues has provided some evidence that microglial *MyD88* signaling is protective in reward learning and maintenance and that impairing this neuroimmune signaling pathway enhances opioid drug seeking and reward memories in male mice (157). More specifically, the authors demonstrated that in animals that had morphine (a known MOR agonist) conditioned place preference, *MyD88* depletion in microglia resulted in increased numbers of immature neurons in the dentate gyrus. Furthermore, this lack of *MyD88*-signaling-induced increase in immature neurons was associated with prolonged extinction and enhanced reinstatement of a reward memory (157). Thus, given that microglia signaling via these opioid receptors is generally classified as anti-inflammatory and that microglia have been documented to respond directly to morphine, among other opioid agonists, it is possible that microglia may play a physiological role in modulating adult hippocampal neurogenesis through the phagocytosis of newborn neural precursor cells. This would enable microglia to mediate not only drug/context associations, but also other forms of learning and memory involving reward, such as pair bonding.

Why Is it Important to Examine These System Interactions?

The molecular toolkit hypothesis posits that a handful of neuromodulatory systems underlie social behavior across species (67, 158-161). To date, explanations for how these systems mediate species differences in social behavior have investigated differences in receptor patterning or ligand production/release. We posit that interactions across relevant neuromodulatory systems may also have contributed to the elaboration of social behaviors in certain species. In particular, such interactions may be critical for the evolution of more complex forms of social behavior, such as pair bonding. For instance, the coordinated signaling of OXT

and DA as outlined above may provide a mechanism by which social information conveyed by OXT is integrated with DA reward signaling to produce a partner-reward association underlying a pair bond. As such, a further understanding of interactions between neuromodulatory systems in the context of pair bonding may elucidate the evolution of more complex, human-relevant social behaviors.

In addition, neuromodulatory systems represent common clinical targets. For instance, DA systems are targeted by pharmacotherapies for mental illness and neurodegenerative diseases (162-166) and opioids are routinely used for pain management and have great potential for abuse (167, 168). While less developed, OXT systems have recently become the focus of potential treatments for addiction, schizophrenia, and autism (169-172). A better understanding of interactions among these systems may aid in the prediction of side-effects, the identification of new druggable targets, and the use of precision-based medicine to incorporate data on potential sex differences, as well as individual genetic variability.

Finally, as we look to expand our viewpoint and determine how systems within the brain are interacting with one another, it is important we also consider all pieces of the system and/or circuit that could contribute to communication, such as cell types in addition to neurons, including microglia, astrocytes, oligodendrocytes, and others. As briefly outlined here, microglia have the capacity to be system-level regulators of neuromodulation of social behavior, and as such, it would behoove us all to take their role into account when attempting to identify new clinical targets.

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