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The Ties That Bond: Neurochemistry of Attachment in Voles

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Abstract

In socially monogamous prairie voles (Microtus ochrogaster), mating induces three primary types of behavior; namely, partner preference, selective aggression toward conspecific strangers, and bi-parental care, making this rodent an ideal model system to study sociality and underlying neurochemical mechanisms associated with monogamous mating strategies. Here, we highlight species differences in neurochemical receptor distributions associated with mating experience leading to the establishment of stable pair-bonds. Specifically, we illustrate the role of nucleus accumbens dopamine in programming the formation and maintenance of monogamous bonds and describe the role of anterior hypothalamic vasopressin in the regulation of selective aggression. We conclude by discussing recent molecular work in voles and emphasize the importance of this rodent for future research in the behavioral neurobiology field.

Keywords

Vasopressin; oxytocin; dopamine; corticotrophin-releasing hormone; nucleus accumbens; lateral septum; anterior hypothalamus; aggression; affiliation; parental care

Introduction

Attraction and sex are hard-wired, universal, behaviors programmed in single cell organisms as well as in complex nervous systems important for sociality, competition, and reproductive success. How the brain changes after sexual experience to control social behavior is of great interest to scientists across different disciplines and to the public and society in general. Copulation comes with both benefits and costs to species survival and evolution. In the socially monogamous prairie vole (*Microtus ochrogaster*), for example, mating induces

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partner preference, aggression, and bi-parental care **[1]** - behaviors that promote fitness yet threaten survival. So, why would evolution program a socially monogamous brain when the majority of animals mate indiscriminately? Over the past few decades, a constellation of molecules, neurotransmitters, hormones, and genes have been identified that begin to unravel the complexity of prairie vole mating strategies in the context of species reproductive fitness **[2]**. In this review, we focus on recent data illustrating the critical role(s) of the neuropeptides arginine vasopressin (AVP), oxytocin (OT), corticotrophin-releasing hormone (CRH) and the neurotransmitter dopamine (DA) in the regulation of mating-induced social behavior in voles. We end by discussing recent and future work that holds great promise in elucidating the molecular neurobiology and functional significance of attachment.

The socially monogamous prairie vole

The prairie vole is a microtine rodent species that displays unique patterns of social behavior associated with a monogamous mating strategy. Sexually naïve prairie voles are gregarious and highly affiliative. After mating, they display three types of social behavior: partner preference between mates, selective aggression toward conspecific strangers but not their partner, and bi-parental care of offspring **(Figure 1)**. Extensive research has been conducted to examine the neurochemicals and neural circuitry underlying these innate behaviors **[1›2]**. There are other microtine species, such as meadow (*Microtus pennsylvanicus*) and montane (*Microtus montanus*) voles, that are taxonomically quite similar to prairie voles but socially promiscuous, do not develop mating-induced partner preference or selective aggression, and only display maternal care **[3]**. Together, these vole species provide an excellent comparative model system to study mating-induced development and/or changes in social behaviors associated with different life strategies and allow for investigation of the underlying neurobiological mechanisms.

Even though studying pair-bonding behavior in voles doesn't fully model all aspects of human attachment, this experimental approach provides a vehicle to deliver neural mechanisms programming human attraction leading to the formation of intimate partnerships. There is significant conservation between both behavioral and neurochemical mechanisms controlling prairie vole and human mating drives and interpersonal attachment behavior. Thus, the vole represents an ideal model system for translational and basic research investigating the neurobiology underlying social behavior(s) associated with various mental health deficits that are characterized by problems with attachment such as those that suffer from autism spectrum disorders.

Neurochemical regulation of pair-bonding behavior

Research in voles has revealed a variety of neuromodulators in the regulation of mating-induced pair-bonding and comparable work in humans has implicated several of these same neurochemical systems. For example, the nine amino-acid (nonapeptide) AVP has been implicated in human aggressive behavior, as higher levels of AVP assayed from cerebrospinal fluid taken from aggressive patients has been shown to be associated with a history of violent behavior in both men and women **[4]**. Furthermore, a structurally similar nonapeptide, OT, administered intra-nasally in human couples, significantly enhanced

several dimensions of positive communication between one-another such as agreeableness, positive regard for the self and partner, consolation, and increased eye-contact during a simulated couple's quarrel as well as significantly reduced salivary cortisol levels after a semi-naturalistic conflict **[5]**. Another important element of prosocial behavior, prerequisite for social affiliation, is trust. Trust is necessary to social, economic, and/or political success and without it these faculties quickly disintegrate. However, at the dawn of the new millennium, next to nothing was known about the biological origins of trust in humans. Thus, in a similar double-blind placebo-controlled set of experiments as outlined above, participants were intra-nasally administered OT and reported remarkable increases in their level of perceived trust during social interactions which wasn't a general effect of OT enhancing participants' readiness to bear risks. Conversely, OT specifically affected an individual's willingness to accept social risks during interpersonal interactions **[6••]**. Together, these data are in line with vole research substantiating OT as a neurobiological hallmark of prosocial approach behavior in gregarious animals and trust among humans – a necessary prerequisite to social affiliation. Finally, recent real-time functional magnetic resonance imaging research found enhanced neurotransmission in dopamine-rich brain regions, in the right ventral tegmental area (VTA) and right caudate nucleus, when participants view photographs of their life-long deeply-loving partners but not when they saw other familiar people from their life **[7]**. Furthermore, even at a relatively early stage of a pair-bond, activation in the left VTA positively correlated with facial attractiveness while activation in the right anteromedial caudate nucleus was associated with the intensity of romantic passion in individuals recently falling "in love" **[8]**. These persistent and enduring brain activation patterns suggest that DA-ergic reward circuits may encode the arousal component of the intense "high" when people are motivated to develop and maintain a life-long pair-bond, rather than representing an ephemeral emotional state of being, fleeting rationale decision, or general sex drive, *per se*. Taken together, these findings in humans suggest the possibility that similar neurochemicals and psychological facets of attachment and romance that resemble elements of pair-bonding behavior in voles may extend to people as well.

Partner Preference Formation—Evidence describing the neurobiology of human mating preferences is mixed, primarily due to the complex nature of attraction in people and the experimental limitations of cognitive neuroscience research. Therefore, investigating pair-bonding behavior in voles represents a valuable animal model system to reveal underlying neurochemical mechanisms programming social decision-making. To date, neurobiological research examining voles has implicated the neuromodulators AVP, OT, DA, and CRH in the regulation of partner preference formation.

Prior research has demonstrated that 18-24 hrs of mating, but not 6 hrs of cohabitation, reliably induces partner preference in both male and female prairie voles (**Figure 1a&b**; **[3,9••]**). Such mating also leads to changes in the activity of several neuromodulators, listed above, which have been implicated in social behavior in prairie voles. Because genetically-related vole species were originally shown to differ in their social life mating strategies, a comparative approach was initially used to investigate intra-species differences in social behavior and underlying neurobiology. Monogamous and promiscuous voles differ in the

pattern of AVP-V1a receptor (V1aR) distribution in the brain, specifically in reward-related regions such as the ventral pallidum (VP; **Figure 2**), indicating species differences in response to centrally released AVP (**Figure 2**; **[10›11]**). Intracerebroventricular (icv) infusion of a V1aR antagonist inhibits mating-induced partner preference while infusions of AVP induce this behavior in both male and female prairie voles without mating **[9••›12]**. In male prairie voles, mating enhances AVP gene expression in the bed nucleus of the stria terminalis (BNST) yet decreases AVP-immunoreactive (ir) fiber density in its projection area – the lateral septum (LS), suggesting increased AVP release in this area **[13›14]**. Indeed, intra-LS administration of AVP induces partner preference whereas a V1aR antagonist inhibits mating-induced partner preference. In the VP, V1aR antagonism impairs mating-induced partner preference whereas over-expression of V1aR by adeno-associated viral vector-mediated gene transfer (AAV-V1aR), in sexually naïve males, facilitates partner preference. Furthermore, AAV-V1aR over-expression in the VP enhances partner preference in promiscuous male meadow voles **[15••]** and facilitates social recognition in mice **[16•]**.

Similarly, species differences are found in the patterns of OT receptor (OTR) distribution in the vole brain – in regions critical in the regulation of social behavior and motivation like the medial prefrontal cortex (mPFC), nucleus accumbens (NAcc), and BNST (**Figure 2**; **[17•]**). ICV OT injection induces partner preference in both male and female prairie voles, and this effect is blocked by infusion of an OTR antagonist **[12]**. In female prairie voles, OT release is increased in the NAcc during mating **[18•],** pharmacological blockade of OTRs in the NAcc (or the prelimbic cortex (PLC)) prevents mating-induced partner preference, and intra-NAcc OT infusion induces this behavior without mating **[19›20]**. Furthermore, AAV-OTR over-expression in the NAcc facilitates partner preference formation in sexually naïve female prairie voles, but not in female meadow voles (**Figure 3**; **[21•]**). Finally, blocking OTRs in the LS of male prairie voles also prevents mating-induced partner preference **[22]**.

The mesocorticolimbic DA circuit underlies emotional valence to control intrinsically-motivated behavioral drives like hunger and mating **[23›24]**. Not surprisingly, this system has also been identified as being important in the regulation of social memory encoding partner preference and attachment. The first series of experiments that examined the central role of DA and partner preference formation employed a behavioral pharmacological approach. Peripheral (intraperitoneal (ip)) treatment of a non-selective DA receptor (DAR) antagonist was sufficient to block mating-induced partner preference whereas treatment of a DAR agonist facilitated partner preference without mating **[25].** Similar effects were found by treating prairie voles with a D2R-, but not D1R-, specific antagonist/agonist, indicating that D2R activation is critical for partner preference formation **[25]**. In the NAcc of both male and female prairie voles, mating was found to induce DA release **[26›27]** and administration of a non-selective DAR or D2R-specific antagonist impaired mating-induced partner preference whereas treatment of a non-selective DAR or D2R-specific agonist facilitated partner preference formation in the absence of mating experience **[27›28••]**. Conversely, intra-NAcc D1R activation prevented partner preference induced by mating or by D2R activation **[28••]**. This receptor-specific DA-ergic regulation of partner preference was found to be due to the opposing effects of D1R/D2R, via the activity of the intra-cellular

cyclic adenosine monophosphate (cAMP) signaling cascade and its conjugated G-proteins, site-specifically, within the rostral NAcc shell **[29•]**.

In addition to AVP, OT, and DA, the stress neuropeptide, CRH, also plays a significant role in the regulation of pair-bonding behavior. Male prairie voles treated with exogenous CRH display partner preference, without mating, which can be blocked with co-administration of a CRH receptor antagonist. Site-specific micro-infusion of CRH in the NAcc facilitates, while CRH receptor antagonist treatment inhibits, partner preference formation in male prairie voles. Pair-bonding with a female also significantly increases CRH mRNA in the BNST of males.

CRH is secreted from the paraventricular nucleus of the anterior hypothalamus (PVN) and binds to CRH receptors in the anterior pituitary which synthesizes adrenocorticotrophic hormone (ACTH). ACTH is then released into the bloodstream and acts on receptors expressed on the adrenal cortex which produces glucocorticoids, like corticosterone (CORT), that then bind to glucocorticoid receptors (GRs) in the brain during stress. The prairie vole is glucocorticoid resistant and has approximately 5-to 10-times greater basal plasma CORT, 3-times higher basal levels of ACTH, and 10-times lower affinity for the GR-type-1 receptor relative to non-monogamous rodents. In female prairie voles, cohabitation with a male significantly reduces serum CORT levels. Furthermore, adrenalectomy or GR antagonist treatment in females is sufficient to facilitate while CORT injections, or exposure to swim stress, prevents partner preference formation. In short, these results suggest that decreases in hypothalamic pituitary adrenal (HPA) axis activity facilitate the formation of partner preference in female prairie voles. In males, the story is completely the opposite. Adrenalectomy inhibits partner preference formation and this effect can be reversed with CORT replacement. Furthermore, males experiencing the loss of a bonded partner exhibit significantly higher levels of circulating CORT and adrenal gland weight, implicating the HPA axis in partner separation.

Selective Aggression—Among the neurochemicals implicated in maladaptive forms of escalated aggression and violence in humans and laboratory animals **[30]**, AVP and DA have been shown to be important in the regulation of adaptive forms of agonistic behavior such as selective aggression in prairie voles. Following mating and extended cohabitation, males that are pair-bonded with a female exhibit aggression toward conspecific male and female strangers but not toward their familiar female partner (selective aggression; **Figure 1c&d**), and this behavior is important in maintaining established pair-bonds **[31]**. Selective aggression is associated with increased neuronal activation, measured by Fos-ir labeling, in several brain areas including the anterior hypothalamus (AH), LS, medial preoptic area (MPOA), BNST, and posterior dorsal medial amygdala (MeAPD; **[32•,33])**. In the AH, selective aggression is accompanied by activation of AVP expressing neurons and increased AVP release **[32•,34••]**. Administration of the V1aR antagonist, icv or site-specifically into the AH, diminishes selective aggression **[9••,34••]**. Conversely, administration of AVP enhances selective aggression in sexually naïve males, and this AVP-facilitated aggression can be blocked by concurrent administration of a V1aR antagonist **[9••,34••]**. Furthermore, pair-bonded males exhibit an increased density in V1aR binding in the AH compared to their sexually naïve counterparts (**Figure 3**), and over-expression of V1aR in the AH, by AAV-

V1aR, facilitates selective aggression in sexually naïve males **[34••]**. These data demonstrate that AH-AVP is involved in the regulation of selective aggression in male prairie voles. AH-AVP has also been shown to regulate aggression in Syrian hamsters **[35]**. In human clinical studies, CSF levels of AVP are associated with a lifetime history of physical violence and assault in individuals with borderline personality disorder **[4]** and may control the perception of social cues conveying anger in research participants **[36]**.

The frequency and intensity of physical aggression is typically observed more in males than in females across many species. Because of these sex differences, previous research examined the potential role of steroid hormones, like androgens, in the development of aggressive behavior. However, castration in male prairie voles and male rats has no effect on aggression. Therefore, circulating testosterone cannot be the sole contributor of aggressive behavior. For example, AVP infused directly into the MeAPD facilitates territorial aggression in castrated male rats. Because the act of aggression relies heavily on motivation and emotional valence, these affective states are encoded via central DA.

The mesocorticolimbic DA system has been implicated in prairie vole aggression **[28••]**. Two weeks of pair-bonding lead to enhanced expression of D1Rs, but not D2Rs, in the rostral NAcc shell in the male prairie vole brain (**Figure 3**). Furthermore, male meadow voles exhibit significantly more D1-like DA receptors in the NAcc than do male prairie voles (**Figure 2**), providing evidence to potentially explain why non-monogamous animals display general levels of aggression while socially monogamous species exhibit “jealousy”-like behavior including patterns of mating-induced selective aggression directed toward other conspecifics except toward their familiar partner (**Figure 1c&d**). Pharmacological blockade of D1Rs in the NAcc reduces selective aggression in pair-bonded males. In parallel drug experiments, repeated treatment of the commonly abused psychostimulant, amphetamine (*d*-AMPH), enhanced aggression toward conspecific females as well as toward a female partner which prevented partner preference formation **[34••,37••]**. Pharmacologically, these drug-addled pair-bonding deficits can be reversed via micro-infusion of OT in the mPFC **[38•]**. Finally, these alterations in social behavior overlap with an increase in NAcc-D1R and AH-V1aR, indicating that drugs of abuse can hijack neuroplasticity evolved to retain social fidelity **[34••,37••]**.

Bi-parental Care—Although the neurobiology of maternal behavior has been extensively studied, we know virtually nothing about the neurobiology of paternal behavior, mainly due to the lack of appropriate animal models that display bi-parental care. Thus, prairie voles provide a unique opportunity to study the neurochemical regulation of paternal behavior. Both female as well as male prairie voles spend equal amounts of time in their natal nest providing parental care for their offspring (**Figure 1e&f**). Pup exposure induces an increase in Fos-ir in the accessory olfactory bulb (AOB), MPOA, BNST, MeAPD, and LS in male prairie, but not meadow, voles, suggesting increased, regional neuronal activation associated with the display of paternal behavior in prairie voles **[39,40]**. When this socioemotional circuit is impaired via bulbectomy or MeAPD lesioning, paternal behavior is dramatically decreased in male prairie voles **[41,42]**. After pairing with a female for two weeks or becoming fathers, male prairie voles display higher levels of paternal behavior

associated with altered AVP activity in the brain including increased AVP mRNA expression in the BNST and PVN **[13,14]** and decreased AVP-ir fiber density in the LS **[43,44].** Infusion of AVP or OT in the brain (icv) enhances paternal behavior in sexually naïve male prairie voles whereas V1aR or OTR blockade decreases pup retrieval and huddling and increases pup attacks **[45]**. The LS has also been identified as a target brain area in which infusions of AVP enhance and a V1aR antagonist impairs paternal behavior in male prairie voles **[46]**. In other laboratory rodents, AVP in the LV increases maternal behavior in female rats **[47]** and in new father marmosets, whom also display paternal behavior, the density of V1aRs and dendritic spines in the mPFC is significantly increased, compared to non-fathers **[48]**.

Because good parenting represents a critical social behavior necessary for healthy development of offspring and species survival, it's not surprising to also learn that central DA plays a critical role in the regulation of parental behavior. Like its role in maternal behavior **[49]**, central DA has also been implicated in paternal behavior. In male prairie voles, neurons that express tyrosine hydroxylase (TH; rate limiting enzyme for DA biosynthesis) in the BNST and MeAPD are activated by pup interaction **[50].** Peripheral administration (ip) of a DAR antagonist reduces pup licking and contact yet increases pup huddling without affecting locomotor activity in both male and female prairie voles **[51•]**. DA is released in the NAcc of female rats exposed to pup stimuli **[52]** and released DA regulates maternal behavior in a DAR-specific manner **[53]**.

The HPA axis has also been described in parental behavior of voles. For example, swim stress experience significantly enhances time spent huddling over and licking and grooming, pups but isn't observed in unstressed male father controls. Importantly, these effects on paternal behavior are not observed in female prairie voles which suggest that, like the sexually dimorphic effects of CRH on partner preference formation, CRH may exert sex-specific effects on parental behavior as well. Finally, icv micro-infusion of urocortin-II, a closely related member of the CRH neuropeptide family, significantly increased passive parental behavior in both male and female prairie voles, without affecting locomotor or anxiety-like behaviors.

Conclusions and future directions

In humans, AVP, OT, DA, and CRH underlie many social behaviors including bonding, aggression, and parental care. These systems work in concert with one another to control levels of sociality. Mating in the socially monogamous prairie vole induces long-lasting neuroplasticity in circuits that regulate an enduring suite of pair-bonding, mate guarding, and parental behavior. In the prairie vole, the same neuromodulators interact to produce these robust behavioral patterns after copulation. Emerging research using the prairie vole has begun to investigate the neurobiology of pair-bond functions such as the role of OT on partner's stress-buffering **[54–56•]** and consolation **[57••]**. Furthermore, exciting molecular work demonstrates epigenetic regulation of AVP and OT neuropeptidergic systems underlying mating-induced pair-bonding **[58••]**. Novel semi-naturalistic field studies in prairie voles has found that DNA variation in the V1aR gene includes polymorphisms that predict the epigenetic status and neuronal expression of V1aR in a spatial memory circuit

and this genomic diversity in V1aR is favored by selection **[59••]**. Finally, our most recent data reveal neurochemical interactions between AVP, serotonin (5-HT), and CRH, in a neuronal microcircuit, encoding a male prairie vole's decision to affiliate or fight his female partner or a stranger female **[60••]**. Together with previous studies, the prairie vole field is ripe for incorporating contemporary molecular genetic tools like genomic tract-tracing, opto/chemo-genetic approaches, and gene editing via CRISPR technology. By adding these techniques to the vole toolbox, the field will be able to molecularly target and genetically manipulate neurotransmitter systems underlying the neuroplasticity accompanied by sexual experience and the resulting innate social drives that ensue.

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Highlights

- Mating induces partner preference, aggression, and bi-parental care in prairie voles.
- Species differences in mating strategies are explained by neurogenetic variation.
- Vasopressin, oxytocin, dopamine, and stress peptide signaling facilitate attachment.
- Nucleus accumbens dopamine programs formation and maintenance of pair-bonds.
- Anterior hypothalamic vasopressin regulates selective aggression.

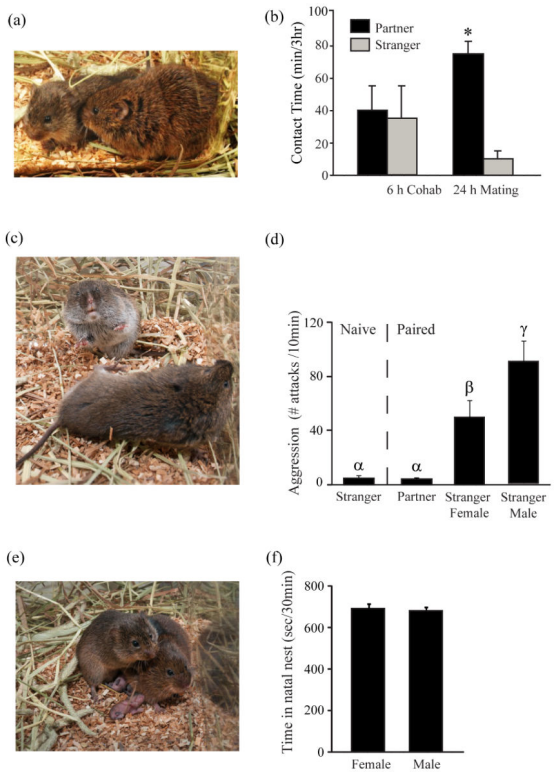

Figure 1. Laboratory characterization of mating-induced pair-bonding behavior

(a) Photo depicts a pair-bonded male and female prairie vole displaying side-by-side (cuddling) contact (Photo by C. Badland & A. Smith). (b) In male and female prairie voles, 6 hrs of social cohabitation, without mating, is not sufficient to induce partner preference, as voles spend approximately an equal amount of contact time with their partner or with a stranger. Conversely, 24 hrs of cohabitation with successful copulation promotes partner preference formation, as voles spend significantly more time in side-by-side contact with their partner than with an unfamiliar stranger during a 3 hr partner preference assay. (c) Photo shows a pair-bonded male prairie vole (top) preparing to attack an unfamiliar stranger male prairie vole (bottom; Photo by C. Badland & A. Smith). (d) Sexually inexperienced (Naïve) male prairie voles do not display aggressive behavior toward a stranger, although successful mating and two weeks of social cohabitation engenders escalated selective aggression toward stranger male and female conspecifics but not toward familiar female partners. (e) Photo illustrates a pair-bonded male and female prairie vole huddling over and protecting their newly born pups (Photo by C. Badland & A. Smith). (f) Male and female prairie vole parents spend equivalent time in their natal nest huddling, contacting, and licking/grooming their offspring. Bars indicate means ± standard error of the mean. Bars with different Greek letters differ significantly from each other. *: $p < 0.05$. Adapted from **[2,32•,40,61]**.

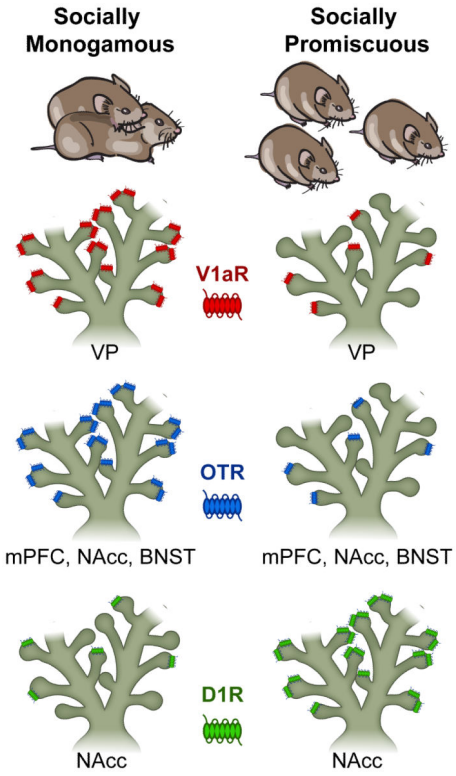

Figure 2. Microtine species differences in neurotransmitter receptor distribution and social behavior

Prairie voles display a socially monogamous life strategy after mating and pair-bonding (Left Image) while Meadow and Montane voles' exhibit socially promiscuous behavior (Right Image). Vasopressin V1a-type receptor (V1aR) expression in the ventral pallidum (VP) and oxytocin receptor (OTR) density in the medial prefrontal cortex (mPFC), nucleus accumbens (NAcc), and bed nucleus of the stria terminalis (BNST) are both higher in sexually naïve prairie voles (Left) while promiscuous voles have fewer endogenous V1a/OT receptors available in these brain regions (Right). Species differences in neuropeptide receptor density have been shown to explain why these systems may be involved in the evolution of divergent mating strategies in across rodent species. Conversely, dopamine D1 receptor (D1R) expression is higher in the NAcc of non-monogamous voles (Right) and lower in prairie voles (Left). Species differences in dopamine neurotransmitter receptor density have been shown to explain why prairie voles display mating-induced selective aggression while meadow voles exhibit general levels of aggressive behavior toward conspecific animals. (Illustration by C. Badland). Adapted from **[19,21•,22,26,28••,29•,62-64]**.

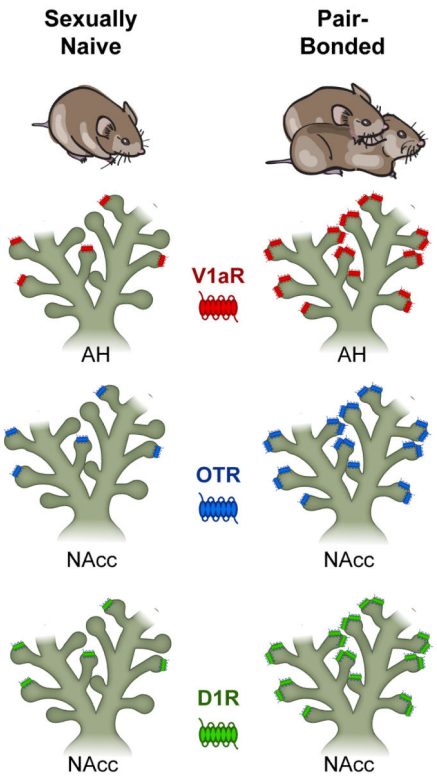

Figure 3. Pair-bonding-induced neuromodulator receptor plasticity and sociality in the prairie vole

Sexually naïve male prairie voles (Left) and pair-bonded male prairie voles (Right) exhibit experience-dependent changes in neurotransmitter receptor density in select brain regions including the anterior hypothalamus (AH) and nucleus accumbens (NAcc). Specifically, successful mating and pair-bonding site-specifically enhances the density of vasopressin V1a-type receptor (V1aR) expression in the AH and oxytocin receptor (OTR) and dopamine D1-type receptor (D1R) density in the NAcc. These mating-induced neuroplastic changes in receptor densities explain the behavioral switch from general patterns of social affiliation and aggression to robust social memory and selective aggression in pair-bonded male prairie voles. (Illustration by C. Badland). Adapted from **[28••,32•,34••,64]**.