

Review

The neurobiology of pair bonding: Insights from a socially monogamous rodent

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ABSTRACT

The formation of enduring relationships between adult mates (i.e., pair bonds) is an integral aspect of human social behavior and has been implicated in both physical and psychological health. However, due to the inherent complexity of these bonds and the relative rarity with which they are formed in other mammalian species, we know surprisingly little about their underlying neurobiology. Over the past few decades, the prairie vole (*Microtus ochrogaster*) has emerged as an animal model of pair bonding. Research in this socially monogamous rodent has provided valuable insight into the neurobiological mechanisms that regulate pair bonding behaviors. Here, we review these studies and discuss the neural regulation of three behaviors inherent to pair bonding: the formation of partner preferences, the subsequent development of selective aggression toward unfamiliar conspecifics, and the bi-parental care of young. We focus on the role of vasopressin, oxytocin, and dopamine in the regulation of these behaviors, but also discuss the involvement of other neuropeptides, neurotransmitters, and hormones. These studies may not only contribute to the understanding of pair bonding in our own species, but may also offer insight into the underlying causes of social deficits noted in several mental health disorders.

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1. Introduction

Intense attraction between mates, often referred to as romantic or passionate love, is one of the most powerful forces driving human social behavior, and often precedes the formation of enduring, selective attachments between sexual partners (i.e., pair bonds). Although such sociosexual attachments are most prevalent in industrialized cultures with a monogamous social organization, they occur in nearly all human societies, regardless of subsistence mode (e.g., pastoralist, agriculturalist, etc.) or mating strategy (e.g., polygamy and monogamy), and are therefore an intrinsic part of human social behavior. While the definition of a pair bond varies throughout the literature, it is typically described, across species, as an enduring preferential association formed between two sexually mature adults, and is characterized by selective contact, affiliation, and copulation with the partner over a stranger (partner preference) [105]. In addition to a preference for a partner, a variety of other behaviors are intrinsically involved in this complex social bond. For example, pair bonds in humans, as well as in other mammalian species, are regularly associated with mate-guarding (e.g., highly aggressive behavior towards sexual competitors) and the bi-parental care of young [32,86,136]. The co-occurrence of these behaviors in pair-bonded individuals makes sense when viewed through the lens of evolutionary theory, which suggests,

in part, that pair bonding became adaptive under conditions in which additional parental investment was required to ensure the successful rearing of young [45,85,89,105,208]. Indeed, the same selection pressures that necessitated the presence of both parents for offspring survival would likely facilitate the formation of a partnership between mates [86] and mechanisms through which to maintain this partnership (e.g., mate-guarding).

The functional significance of pair bonding in humans has been documented cross-culturally. Paired individuals, particularly those in stable marital relationships, live longer than their unpaired counterparts, a finding noted across demographic groups [116,144]. Additionally, high levels of intimacy between pairs has been inversely correlated with negative psychological states, such as depressed mood, and positively correlated with immune function and cardiovascular health [131,212]. Another widely acknowledged benefit of pair bonding in humans, as in other species, is the physical and psychological well-being of children, an effect likely due to the co-occurrence of pair bonding with the bi-parental care of young. Indeed, paternal involvement in childcare has become increasingly recognized as equally important as maternal influences on successful childhood development. In preindustrial societies and developing countries, for example, where food and healthcare are not readily available, children of monogamously married women have lower mortality rates than children of women who are not married or who are in a polygynous union [206]. In industrialized societies, the presence of caring fathers improves the emotional and cognitive health and development of children, as indicated by higher levels of child success on various

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indices, including academic achievement [41,71,83,88,181,191] and the prevention and treatment of anxiety problems [28], attention-deficit/hyperactivity disorder (ADHD) [75], substance use, and criminal behavior [200].

Although enduring bonds between adult mates are important for the physical and mental health of individuals and their children, and may also influence societal stability, we know surprisingly little about the neurobiology of pair bonding. This is partly due to the fact that traditional laboratory rodents used in the study of behavioral neuroendocrinology generally do not display behavioral characteristics of a pair bond, and thus cannot be used as model systems for the study of pair bonding. While a variety of nontraditional animal models have emerged to study this rare behavior, including marmoset and titi monkeys [15,197] and California mice [24–26,59,189], we will focus on one that has become increasingly popular; the prairie vole (*Microtus ochrogaster*). We will begin by describing field and laboratory studies that document prairie vole pair bonding behavior. Then we will discuss early work in the laboratory that described the neural correlates of pair bonding behavior in prairie voles. Next, we will discuss the neurobiological mechanisms involved in three separate behaviors associated with pair bonding; the formation of partner preferences, the development of selective aggression toward unfamiliar conspecifics, and the bi-parental care of young—concentrating primarily on paternal care as maternal care is common to all mammalian species and has been extensively reviewed elsewhere [31,170,171,199]. We will focus on the involvement of the neuropeptides arginine vasopressin (AVP) and oxytocin (OT) and the neurotransmitter dopamine (DA) in these behaviors, but will also review other neurochemicals that have been implicated in pair bonding. Finally, we will explore how these neurochemicals may work together to regulate the formation and maintenance of pair bonds.

2. The prairie vole model

2.1. Field studies of behavior

The prairie vole is a socially monogamous rodent species that lives primarily in the grasslands of the central United States [106]. It has been suggested that adaptation to this harsh environment, with limited food sources and scarce water supplies [27,92,159], may have contributed to the evolution of a socially monogamous life strategy in this species [38,218].¹ Early field studies using multiple-capture traps offered evidence that prairie voles form long-term bonds and travel together in the wild, as male and female pairs were repeatedly captured together [94]. Further, the use of radiotelemetry combined with repeat-trapping allowed for the observation that male and female pairs co-occupy nests and share home ranges during both breeding and nonbreeding seasons [69,94,95]. Additional studies demonstrated that such breeding pairs typically remain together until one member dies, and in many cases, the surviving partner does not pair with a new mate [38,96,97]. Further, male prairie voles contribute to nest guarding, by excluding unfamiliar males and females from the vicinity of the nest and home range, and also contribute to nest building [97,205]. Although male parental behaviors were difficult to observe in natural conditions, due to the findings described above and the high degree of paternal

investment found in other monogamous species, it was predicted that male prairie voles were highly paternal [205,230], and this prediction was confirmed in subsequent behavioral studies under laboratory conditions.

2.2. Laboratory studies of behavior

Prairie vole pair bonding behaviors have been extensively characterized in the laboratory. Sexually naïve prairie voles are highly social and display nonselective affiliative behavior toward conspecifics [194]. Following extended cohabitation and/or mating, prairie voles develop social and sexual preferences for their familiar partner [68,69,102,229]. This selective affiliation (Fig. 1A) is accompanied by selective aggression toward unfamiliar conspecifics [8,99,100,124,223,224,231]. Additionally, the mated pair shares a nest, remains together during gestation, and displays bi-parental care throughout lactation [158,174]. Below, we describe in detail these behaviors and the behavioral paradigms used to measure them.

Partner preference formation is a reliable index of pair bonding, and is characterized by selective contact, affiliation, and copulation with the partner over a stranger [105]. In a controlled environment, this behavior is studied using a three-chamber partner preference test first developed in the laboratory of Dr. Sue Carter [229] and subsequently adopted by many other laboratories. The testing apparatus consists of a central cage that is connected by hollow tubes to two identical cages, one containing a familiar animal (partner) and the other an unfamiliar animal (stranger) (Fig. 1B). These two stimulus animals are loosely tethered into their respective cages and are not allowed to interact with one another. During a 3 h partner preference test, the subject is placed into the central chamber and allowed to move freely throughout the testing apparatus. In some laboratories, a customized computer program—in conjunction with photobeam light sensors placed across the hollow tubes that connect the cages—is used to monitor the amount of time that the subject spends in each cage and the frequency of cage entries. Social behaviors, including mating and side-by-side contact, are videotaped during this test and subsequently quantified. Partner preference formation is inferred when the subject spends significantly more time in side-by-side contact with the partner than with the stranger. In both male and female prairie voles, 24 h of cohabitation with mating reliably induces partner preference formation, whereas 6 h of social cohabitation in the absence of mating does not induce this behavior [124,125,229] (Fig. 1C). This behavioral paradigm has been successfully used in neuroanatomical, neurochemical, and pharmacological studies to examine the neurobiology of partner preference formation [216,237,245].

Another behavior that emerges after mating in prairie voles is aggression toward conspecific strangers. This aggression is directed toward unfamiliar males and females, but not the familiar partner, and has therefore been termed 'selective aggression'. Selective aggression in prairie voles is assessed in the laboratory using a resident-intruder paradigm similar to that used in mice [162,231]. In this paradigm, an unfamiliar conspecific animal (intruder) is placed into the home cage of the subject (resident). Behavioral interactions between the resident and intruder are videotaped during a 6–10 min test, and the frequency and duration of a variety of aggressive behaviors are subsequently quantified. Studies using this paradigm have demonstrated that sexually naïve male prairie voles display very low levels of aggression toward intruders [124,224,231]. However, after 24 h of cohabitation with mating, aggressive behaviors toward intruders are dramatically increased [124,224,231]. While this aggression is directed at both males and females, intense offensive attack behaviors are only noted toward stranger males at this time point [224]. Selective aggression

¹ While prairie voles that originate from Illinois display behaviors indicative of a monogamous life strategy in the field, and reliably display mating-induced pair bonding behaviors under laboratory conditions, it is important to note that prairie voles from Kansas [55,186] and Tennessee [175,235] show subtle differences in some aspects of their behavior [185]. These differences support the theory that variations in ecological conditions may influence animal behavior and mating strategies between populations within the same species [73]. As a result of this variation, prairie voles from Illinois are most commonly used in laboratory studies of the neurobiology of pair bonding. Data from those studies are the focus of the current review.

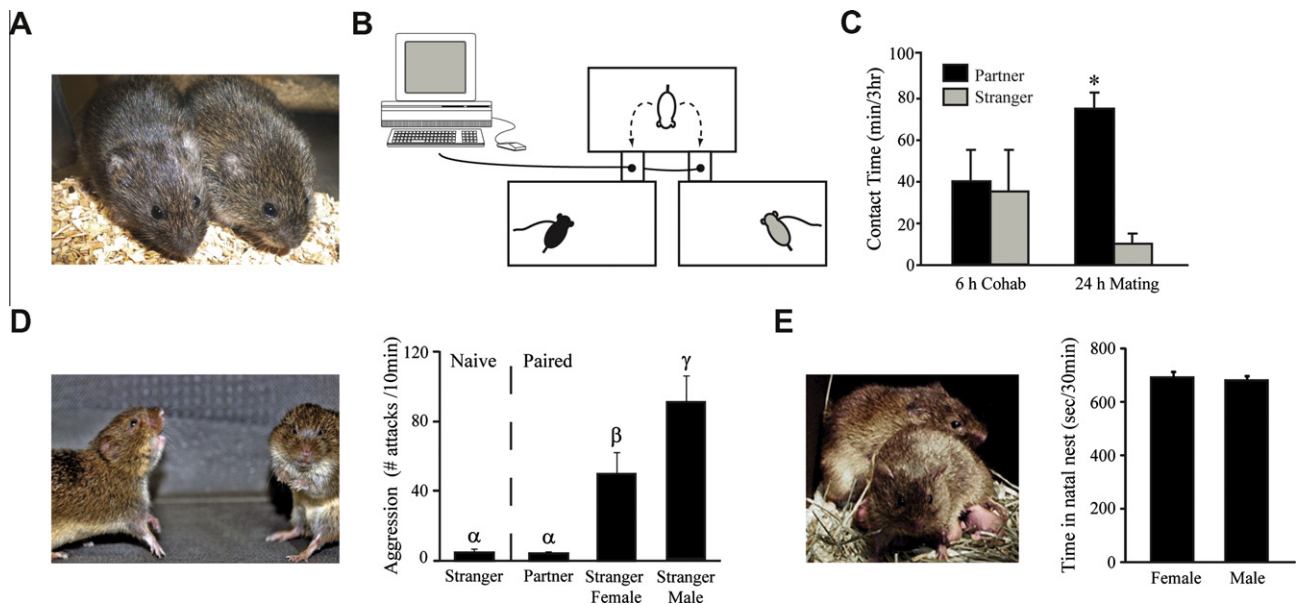


Fig. 1. Laboratory characterization of behaviors associated with pair bonding. (A) Photo illustrates a male and female prairie vole displaying side-by-side contact. (B) Three-chamber apparatus used to test for partner preferences. Three identical cages are connected by hollow tubes with light sensors allowing for automated analysis of the subject's movements throughout the apparatus. Social behaviors between the subject (white) and the partner (black) and stranger (gray) during the three hour test are recorded and subsequently scored. Duration of side-by-side contact is the primary behavior of interest. (C) In both male and female prairie voles, 6 h of cohabitation without mating does not result in partner preference formation, as the subject spends equal amounts of time in contact with the partner as with the stranger. In contrast, 24 h of cohabitation with mating leads to the formation of partner preferences, as indicated by the subject spending significantly more time in side-by-side contact with the partner than the stranger during the 3 h partner preference test. (D) Photo depicts a pair-bonded male prairie vole (left) displaying attack behavior toward an unfamiliar female. Sexually naïve (Naïve) males do not exhibit aggressive behavior toward a stranger, however males paired with a female for two weeks (Paired) demonstrate robust aggression toward stranger male and female conspecifics but not toward familiar female partners. (E) Photo shows a male and female prairie vole sharing a natal nest and contacting offspring. Male and female prairie vole parents spend equal amounts of time in the natal nest. Bars indicate means \pm standard error of the mean. Bars with different Greek letters differ significantly from each other. *: $p < 0.05$. Adapted from [10,99,222,231].

is also enduring; it lasts for at least two weeks after partner preference formation [8,99,100]. Further, males paired for this extended period of time (i.e. pair-bonded males), in contrast to those paired for only 24 h, show intense attack behaviors toward stranger females, even those that are sexually receptive, thereby rejecting potential new mates (Fig. 1D) [8,99,100]. It has therefore been suggested that selective aggression not only plays an important role to guard mate and territory [37,38], but may also function to maintain the existing pair bond [8,10] and to limit extra-pair copulations. Although selective aggression has only been systematically tested in male prairie voles, evidence exists to suggest that females may also display this behavioral pattern [94]. The reliable expression of both partner preference and selective aggression by prairie voles in carefully controlled laboratory conditions highlights the utility of this animal model in behavioral neuroendocrine studies.

Prairie voles, similar to most species that form pair bonds between adult mates [86], display bi-parental care of young (i.e., both the mother and father help to rear offspring) (Fig. 1E). As maternal care is ubiquitous across mammalian species, we will focus our discussion of bi-parental care on the role of the father (i.e., paternal care). Paternal behavior in prairie voles has been observed in the laboratory using semi-naturalistic enclosures [104,158,174]. After litter birth, fathers display all patterns of parental behaviors exhibited by females, except nursing [174,205]. These include direct parental behaviors, such as huddling over (i.e., crouching), grooming, contacting, and retrieving pups as well as indirect behaviors, such as nest building and food hoarding [104,174,205,230]. Fathers even continue to display paternal care toward their juvenile offspring after the birth of subsequent litters [218,220]. However, in the presence of juveniles, prairie vole fathers spend less time in the natal nest displaying paternal behavior and more time foraging [93,218]. The presence of juveniles may reduce the need for direct

paternal care by the father, as juveniles that remain in the natal nest beyond weaning often contribute to the care of subsequent litters—a behavior called ‘alloparenting’ [104,198,218,220,222]. Alloparental behavior in juvenile and sexually naïve adult male prairie voles qualitatively resembles paternal care in fathers [198,218,220], and these paternal behaviors are enhanced by social/sexual experience with a nonrelated female [18]. Importantly, the presence of the father and the display of paternal behavior have been shown to facilitate the physical and behavioral development of offspring [4,218,220], a finding similar to the aforementioned beneficial effects of paternal care on our own children. Thus, understanding the mechanisms regulating paternal behaviors could provide important information about optimal parental care in mammalian species that form pair bonds, including our own.

3. Neural correlates of prairie vole pair bonding

Early studies investigating the neural correlates of pair bonding compared neuropeptide and neurotransmitter systems between vole species that displayed disparate life strategies. The four species used were prairie, pine (*Microtus pinetorum*), meadow (*Microtus pennsylvanicus*) and montane (*Microtus montanus*) voles. Monogamous prairie and pine voles form pair bonds between adult mates and show bi-parental care of offspring while promiscuous meadow and montane voles do not form pair bonds and display only maternal care [37,82,91,95,104,124,126,127,154,155,158,174,230]. The close taxonomic relationship shared by these species, coupled with their differences in life strategy make these rodents ideal for comparative studies investigating social behavior (for review, see [237]).

As AVP and OT were known to regulate species-specific social behaviors, including sexual behavior (for review, see [11]), aggression [79], and maternal care [129,176,177], it was predicted that

these neuropeptide systems would differ between monogamous and promiscuous species [17,122]. To test this hypothesis, the distribution patterns of AVP and OT cells, fibers, and receptors were mapped in the vole brain. In all vole species examined, regardless of life strategy, AVP-immunoreactive (AVP-ir) neurons were found in several brain regions, including the paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus, the bed nucleus of the stria terminalis (BNST), medial amygdala (MeA), anterior hypothalamus (AH), and preoptic area (POA) [17,221,223]. AVP-ir fibers were found in the lateral septum (LS), lateral habenular nucleus (LHN), diagonal band (DB), BNST, medial preoptic area (MPOA), and MeA [17,223]. OT-immunoreactive (OT-ir) cells and fibers were located in several brain areas in each species, including the PVN, SON, MPOA, and BNST [223], and OT-ir fibers were also found in the nucleus accumbens (NAcc) [187]. Although subtle species differences were found, in general, the distribution patterns of AVP-ir and OT-ir neurons and fibers are highly conserved between monogamous and promiscuous vole species [187,221,223].

Remarkable species differences were noted, however, in the distribution patterns and regional densities of AVP and OT receptors (OTRs). Prairie voles, for example, had higher densities of AVP-V1a receptors (V1aRs) in the BNST, ventral pallidum (VP), central (CeA) and basolateral (BLA) nuclei of the amygdala, and accessory olfactory bulb (AOB), among other regions, than montane voles, whereas higher densities of V1aRs are noted in the LS and medial prefrontal cortex (mPFC) of montane voles than prairie voles [123,145,196,225,241] (Fig. 2A). Interestingly, when multiple vole species were compared, monogamous prairie and pine voles showed a similar pattern of V1aR binding, and this pattern differed

from that of promiscuous meadow and montane voles [123,145], indicating the potential involvement of region-specific V1aRs in cognitive and behavioral functions associated with different life strategies in voles [123,145,196,241]. Similarly, the distribution patterns and regional densities of OTRs also differed between monogamous and promiscuous vole species. Monogamous prairie and pine voles, for example, had higher OTR densities in the BNST, mPFC, and NAcc than promiscuous meadow and montane voles (Fig. 2D), whereas the opposite pattern was found in the levels of OTR binding in the ventromedial hypothalamus (VMH), LS, and anterior cortical amygdala (AcA) [122,196,239]. Species differences in V1aR and OTR distribution were stable across the lifespan [215,225] and were receptor-specific, as no such differences existed in benzodiazepine or opiate receptor systems [122]. Therefore, given the role of AVP and OT in social behaviors, species differences in V1aRs and OTRs are thought to be specifically related to species differences in social behaviors associated with different life strategies in voles [107].

The drastic species differences in neuropeptide receptor distribution described above may be due to the subtle species differences noted in the promoter regions of the V1aR and OTR [239,240,242,243]. Although the genetic structure of the V1aR and OTR coding regions are strikingly similar across vole species [239,240,242,243], prairie and pine voles carry several repetitive microsatellite DNA sequences in the promoter region of the V1aR gene that are not found in meadow or montane voles, and these sequence changes may underlie species differences in receptor expression [107,108,242,243]. In support of this idea, mice carrying a transgene coding for the prairie vole V1aR, exhibited central

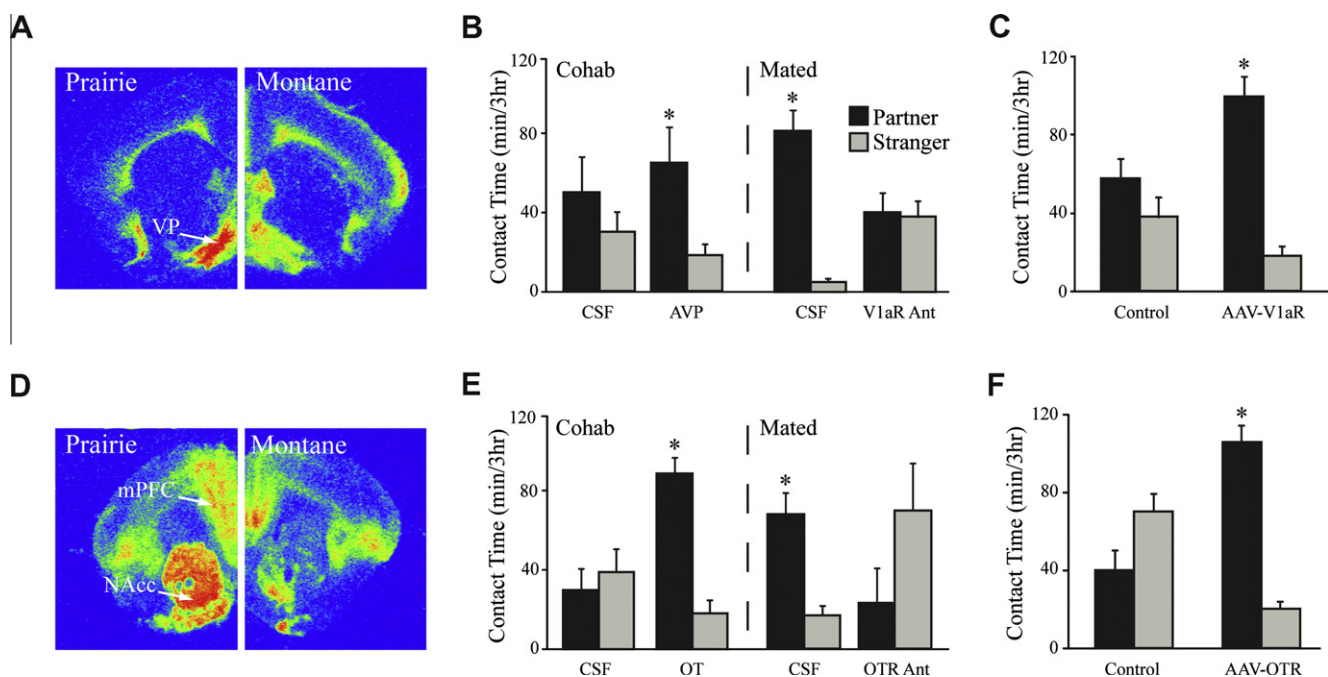


Fig. 2. Vasopressin (AVP) and oxytocin (OT) regulation of partner preference formation. (A) Species differences in vasopressin receptor (V1aR) binding in the ventral pallidum (VP) of prairie and montane voles. Higher densities of receptors are indicated by more red coloration. (B) Site-specific manipulation of AVP neurotransmission in the lateral septum (LS) of male prairie voles. Data demonstrate that after 6 h of non-sexual cohabitation with a female (Cohab), control males given LS injections of vehicle (cerebrospinalfluid; CSF) do not display partner preferences. However, AVP infusion into the LS induces partner preferences. Following 24 h of cohabitation with mating (Mated), CSF treated control males display partner preferences. However, blockade of V1aRs, via infusion of a V1aR antagonist (V1aR Ant) into the LS inhibits the formation of mating-induced partner preferences. (C) Male prairie voles overexpressing the V1aR gene (AAV-V1aR) in the ventral pallidum display partner preferences after 17 h of non-sexual cohabitation with females, whereas control males do not. (D) Species differences in oxytocin receptor (OTR) binding in the medial prefrontal cortex (mPFC) and nucleus accumbens (NAcc) of prairie and montane voles. (E) Site-specific manipulation of OT neurotransmission in the NAcc of female prairie voles. After 6 h of non-sexual cohabitation with a male (Cohab), female prairie voles infused with OT in the NAcc display partner preferences, whereas control females infused with CSF do not. After 24 h of cohabitation with mating (Mated), control females infused with CSF form partner preferences. However, intra-NAcc blockade of OTRs, via infusion of an OTR antagonist (OT Ant), inhibits the formation of mating-induced partner preferences. (F) Female prairie voles overexpressing the OTR (AAV-OTR) in the NAcc form partner preferences after less than 24 h of mating and cohabitation with a male whereas control females do not. Bars indicate means \pm standard error of the mean. *: $p < 0.05$. Adapted from [149,150,183,188].

V1aR patterns similar to prairie voles [243]. Interestingly, when injected with AVP, these transgenic mice displayed enhanced social affiliation, indicating that receptor distribution patterns may influence brain responsiveness to endogenous neuropeptides and, in this way, may modulate social behaviors [243].

More recently, comparative studies have investigated central DA systems in vole species, because DA, like AVP and OT, plays a well-known role in processes and behaviors associated with pair bonding, including learning and memory [1,23,141,234], olfaction [164], sexual behavior [22,117], and parental behavior [170,171]. These studies have noted differences in both DA cell and receptor distribution patterns, as well as differences in their regional densities, between monogamous and promiscuous voles that may be related to social behavior.

Consistent with findings in other rodent species [44,114,167,210], DA cells—those that label for tyrosine hydroxylase (TH; the rate limiting enzyme in catecholamine synthesis) in the absence of DA beta hydroxylase (the enzyme that converts DA to norepinephrine)—have been found in multiple regions in the monogamous prairie vole brain, including the principal nucleus of the BNST (pBNST), posterodorsal MeA (MeApd), and ventral tegmental area (VTA) [99,168]. Additionally, a high density of DA terminal innervation is present in the NAcc and caudate putamen (CP) [7], and recent tract tracing experiments in males have demonstrated that these terminals arise from projection neurons in the VTA [101], as has been demonstrated in other species [34,128,193]. However, promiscuous meadow voles contain very few, if any, DAergic cells in the pBNST and MeApd [168], further demonstrating neuroanatomical differences between monogamous and promiscuous vole species.

Dopamine receptor (DAR) distributions in the vole brain have also been characterized. DARs can be classified into two main families, D1-like (D1R) and D2-like (D2R) receptors, that are differentiated by their molecular structures, pharmacological affinities, and effects on intracellular signaling pathways [163,166]. In prairie voles, D1Rs are found in the NAcc, CP, and mPFC, as well as other brain regions [8,196] (B.J. Aragona, Y. Liu, and Z.X. Wang, unpublished data). D2Rs, while present in these same regions, can also be found in the VTA and substantia nigra (SN) [8,196] (B.J. Aragona, Y. Liu, and Z.X. Wang, unpublished data). Although these receptor distributions are similar to those found in other rodent species, their relative densities are species-specific and may correlate with species differences in social behavior [8,196]. For example, monogamous prairie voles have higher densities of D2Rs and lower levels of D1Rs in the mPFC than promiscuous meadow voles [196]. Further, meadow voles have a significantly higher density of D1Rs in the NAcc than prairie voles, a finding thought to be related to the relatively low degree of social affiliation noted in meadow voles [8]. Indeed, pharmacological blockade of D1Rs in the NAcc increased affiliative behaviors in meadow voles [8].

Taken together, these studies have demonstrated differences in AVP, OT, and DA systems between vole species with distinct life strategies. As a result, researchers have focused on these systems in the prairie vole brain to systematically examine the neurobiology of behaviors intrinsically associated with pair bonding, including partner preference formation, selective aggression, and paternal behavior. We will discuss the neurobiological regulation of each of these behaviors, in turn, in the following sections.

4. Neurobiology of partner preference formation

4.1. Brain activation associated with partner preference formation

One commonly used approach in the study of interactions between the brain and behavior is to map immediate early gene

expression in the brain following a behavioral test. For example, Fos is the protein product of the immediate early gene, *fos*, that is rapidly expressed in neurons following activation and can be easily visualized by immunocytochemistry. Therefore, Fos-immunoreactive (Fos-ir) staining has been used in behavioral neuroendocrine experiments to identify regional neuronal activation in the brain associated with the display of specific behaviors.

In prairie voles, heterosexual pairing, cohabitation, and/or mating induced Fos-ir staining in several brain areas including the MeA, BNST, and MPOA in both males and females [56,169]. Mating, in particular, was related to increased Fos-ir levels in the MeA, BNST, MPOA, and gracile nucleus of the medulla oblongata, implicating these brain areas as functional components of a mating circuitry that may contribute to partner preference formation [50,51,169]. A role for the MeA in prairie vole partner preference has been further implied by lesion studies, as axon-sparing lesions of the MeA in male prairie voles decreased their affiliative behavior toward a familiar female but had no effect on exploratory behavior, locomotion, or olfactory investigation [133].

4.2. Neuropeptide regulation of partner preference formation

The first evidence indicating that AVP and OT may play an important role in partner preference formation came from studies investigating the effects of social and sexual experience—prerequisites for naturally induced partner preference formation—on these neuropeptide systems in the prairie vole brain. In male prairie voles, cohabitation with mating increased the number of AVP mRNA-labeled cells in the BNST [214] and decreased the density of AVP-ir fibers in the LS [18]. As BNST-AVP neurons project to the LS [60], these data suggest that mating facilitates AVP synthesis in the BNST and AVP release in the LS of male prairie voles [216]. Since mating is essential for partner preference formation in males [124], these data offer correlative evidence of the involvement of AVP in partner preference formation. In females, instead, exposure to male chemosensory cues altered OTR density in the AOB, indicating that OT may play a role in partner preference formation in female prairie voles [233].

Direct evidence of a role for AVP and OT in partner preference formation was provided by pharmacological manipulation of these systems. Intracerebroventricular (icv) administration of a V1aR antagonist blocked partner preference formation in male prairie voles, while central AVP administration induced partner preferences in the absence of mating [43,231]. Similarly, icv administration of AVP induced partner preferences in female prairie voles after just 1 h of cohabitation with a male, and this effect was blocked by concurrent administration of a V1aR antagonist, indicating that AVP regulates partner preference formation in both sexes [43]. OT treatment also influenced partner preference formation in both sexes. Specifically, icv OT administration induced partner preferences in both males and females and these effects were blocked by concurrent administration of an OTR antagonist [43]. While these data indicate that both AVP and OT regulate partner preference formation in both sexes, it is important to note that the effective doses of neuropeptides differ between males and females [43].

Site-specific manipulations have since demonstrated several brain regions important for the AVP and OT regulation of partner preference formation. In males, administration of a V1aR antagonist directly into the LS or VP, but not several other brain regions, inhibited the formation of mating-induced partner preferences, whereas administration of AVP directly into the LS induced partner preferences in the absence of mating (Fig. 2B) [146,149]. Further, administration of an OTR antagonist into the LS of male prairie voles also prevented mating-induced partner preference formation [149]. In females, instead, the prelimbic cortex (PLC; a part of the

mPFC) and the NAcc have been implicated in the neuropeptidergic regulation of partner preference formation [150,244]. OT levels increased in the NAcc during sociosexual experience with a male [187]. Additionally, OT injection directly into the NAcc induced partner preferences in the absence of mating, while blockade of OTRs in this region or the PLC prevented the formation of mating-induced partner preferences (Fig. 2E) [150,244].

Several studies utilizing viral vector-mediated gene transfer to deliver and regulate the expression of genes of interest to specific brain regions have supported the findings that AVP neurotransmission in the VP and OT neurotransmission in the NAcc regulate partner preferences in male and female prairie voles, respectively. In males, for example, an adeno-associated viral vector was used to deliver the V1aR gene into the VP [183]. As expected, this manipulation resulted in an increased density of V1aRs in this region. Interestingly, these males formed partner preferences in the absence of mating, supporting the findings that enhanced AVP neurotransmission in the VP can facilitate partner preference formation in male prairie voles [183] (Fig. 2C). Further, V1aR overexpression in the VP of male meadow voles, induced partner preference formation in this socially promiscuous species [145]. Similarly, OTR overexpression in the NAcc of sexually naïve female prairie voles accelerated partner preference formation as compared to controls (Fig. 2F), but this treatment did not alter partner preference formation in female meadow voles [188]. Taken together, these studies highlight the importance and site-specific effects of AVP and OT on partner preference formation in male and female prairie voles.

4.3. DA regulation of partner preference formation

Recent work has demonstrated that partner preference formation in prairie voles is also regulated by central DA, particularly the mesolimbic DA system—a group of DA producing cells that originate in the VTA and project to the NAcc, mPFC, and other forebrain regions. This neural circuit is thought to be integrally involved in the assignment of motivational value to environmental stimuli, resulting in the generation of adaptive goal-directed behaviors [120,232]. For example, mesolimbic DA has long been implicated in assigning salience to incentives such as food and receptive mates, thereby mediating behaviors such as feeding and reproduction that are essential for survival [120,232]. Similarly, mesolimbic DA has been proposed to facilitate mate choice, enabling mating effort to be focused on preferred conspecifics [80], a hypothesis supported by the data described below. The involvement of this system in partner preference formation makes sense in an evolutionary context, as selection pressures that necessitate the formation of a partnership between mates would likely lead to an increased motivational value assigned to one's partner, and the selective affiliation that is characteristic of a pair bond.

Early experimental evidence suggesting the involvement of DA in partner preference formation came from peripheral pharmacological manipulations. Recall that 24 h of cohabitation with mating reliably induces partner preferences in male and female prairie voles. While partner preference formation was not affected by saline injection prior to pairing, treatment with the nonselective DAR antagonist, haloperidol, blocked mating-induced partner preferences in both sexes [7,217]. Further, treatment with low doses of apomorphine, a nonselective DAR agonist, facilitated the formation of partner preferences after only 6 h of cohabitation in the absence of mating [7,217]. Taken together, these findings suggest that DAR activation is essential for partner preference formation in prairie voles.

The first functional evidence to implicate mesolimbic DA in partner preference formation was the finding that mating increases DA activity in the NAcc of both male and female prairie voles [7,98]. In females, for example, extracellular DA levels increased nearly 51% above baseline during mating [98]. Similarly, mated

males had 33% more DA turnover in this region compared to non-mated males [7]. Direct evidence for the role of NAcc DA in partner preference formation came from site-specific pharmacological manipulations of DA neurotransmission. Microinjection of haloperidol into the NAcc prevented the formation of mating-induced partner preferences, while microinjection of apomorphine into this region facilitated partner preference formation in the absence of mating [7]. These effects were site-specific, as DAR manipulation in the CP, a region adjacent to the NAcc that also receives DAergic innervation from midbrain regions, did not alter partner preference formation [7].

Additional experiments used receptor-specific agonists/antagonists to demonstrate that D1Rs and D2Rs in the NAcc differentially regulate partner preference formation (Fig. 3A and B). Specifically, NAcc D2R activation facilitated, and D2R blockade prevented, partner preference formation in both male and female prairie voles, indicating that NAcc D2R activation is both necessary and sufficient for partner preference formation [8,98]. In contrast, NAcc D1R activation prevented mating- and D2R agonist-induced partner preference formation in male prairie voles, indicating an inhibitory role of NAcc D1Rs on this behavior [8]. Importantly, these manipulations were only effective when delivered into the NAcc shell, but not the core, indicating a subregional regulation of partner preferences within the NAcc [8].

The DAR-specific regulation of partner preference formation in the NAcc has recently been examined on an intracellular level. D2Rs and D1Rs are both 7-transmembrane receptors whose intracellular effects are mediated by heterotrimeric GTP-binding proteins (G-proteins) (for reviews, see [163,166]). While D2Rs and D1Rs have similar effects on some signaling pathways, they differentially regulate the intracellular cyclic adenosine 3',5'-monophosphate (cAMP) signaling cascade through the alpha subunit of the G-proteins with which they interact [163,166] (Fig. 3C). D2Rs bind to inhibitory G-proteins ($G\alpha_i$ and $G\alpha_o$). When D2Rs are activated, the alpha subunit of $G\alpha_{i/o}$ inhibits adenylate cyclase (AC) activity, leading to the inhibition of cAMP production and a decrease in the activity of protein kinase A (PKA) [163,166]. D1Rs, instead, bind to stimulatory G-proteins ($G\alpha_s$ and $G\alpha_{olf}$). D1R activation leads to an increase in AC activity, cAMP production and PKA activation [163,166]. As D1R and D2R activation differentially affect cAMP signaling, it has been suggested that this signaling pathway may underlie the DAR-specific regulation of partner preference formation [9]. In support of this hypothesis, reduction of PKA activity within the NAcc shell, but not core, facilitated partner preference formation in male prairie voles, a result consistent with the effects of D2R activation [8,9] (Fig. 3D). Further, in two separate experiments, activation of stimulatory G-proteins and activation of PKA in the NAcc shell each prevented the formation of mating-induced partner preferences, consistent with the effects of D1R activation [8,9] (Fig. 3D). Importantly, these manipulations did not alter mating or the duration of contact during the 24 h of pairing, suggesting that increased cAMP signaling directly interferes with partner preference formation. Taken together, these experiments demonstrate that cAMP intracellular signaling in the NAcc shell regulates partner preference formation, and may underlie the DAR-specific effects on this behavior.

5. Neurobiology of selective aggression

As previously mentioned, after 24 h of mating and the formation of partner preferences, male prairie voles display high levels of aggression toward conspecific strangers, particularly male strangers, but not toward their partners [124,224,231]. Additionally, after one to two weeks of extended cohabitation and mating with their partner, pair-bonded male prairie voles display intense

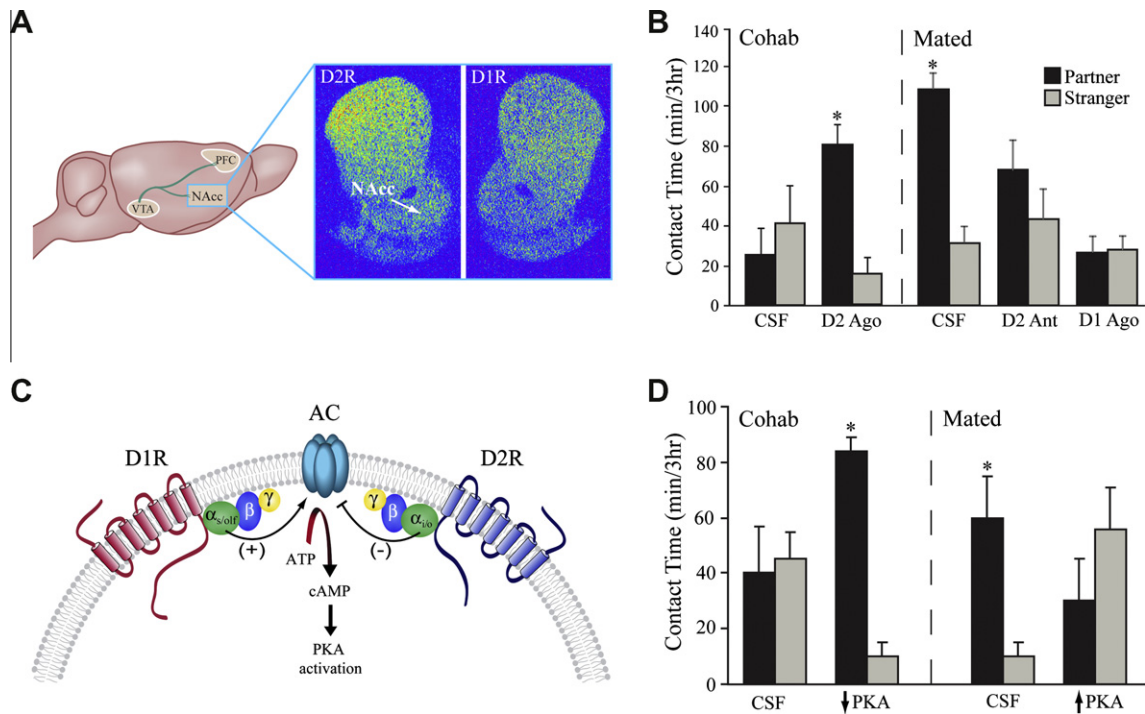


Fig. 3. Dopamine (DA) in the nucleus accumbens (NAcc) regulates partner preference formation in prairie voles. (A) Cartoon illustrates the mesolimbic DA circuit. DAergic cells in the ventral tegmental area (VTA) project to the NAcc and prefrontal cortex (PFC), as well as other forebrain regions. Released DA binds to one of two DA receptor subtypes, D1-like receptors (D1R) and D2-like receptors (D2R), which are both present in the NAcc of prairie voles, as shown in the photoimage. (B) Activation of D2Rs via injection of a D2R agonist (D2 Ago) into the NAcc of males induces partner preferences after 6 h of non-sexual cohabitation (Cohab). Twenty-four hours of mating (Mated) induces partner preferences in control males that receive intra-NAcc injection of CSF. However, mating-induced partner preference formation was inhibited by intra-NAcc blockade of D2Rs (via injection of a D2R antagonist (D2 Ant)) or activation of NAcc D1Rs (via injection of a D1R agonist (D1 Ago)). (C) Cartoon illustrating the effects of D1R and D2R activation on cAMP intracellular signaling. D1Rs are coupled to stimulatory G-proteins ($G_{\alpha_{s/olf}}$) and D2Rs are coupled to inhibitory G-proteins ($G_{\alpha_{i/o}}$). D1R activation increases adenylate cyclase (AC) activity, leading to an increase in the production of cAMP and the activation of PKA. D2R activation leads to the inhibition of AC, through the effects of the alpha subunit of $G_{\alpha_{i/o}}$, decreasing cAMP production and PKA activity. (D) Pharmacologically decreasing PKA activity (\downarrow PKA) in the NAcc induces partner preference formation in male prairie voles after 6 h of non-sexual cohabitation (Cohab). Pharmacologically increasing NAcc PKA activity (\uparrow PKA) during 24 h of mating (Mated) blocks mating-induced partner preferences. Bars indicate means \pm standard error of the mean. *: $p < 0.05$. Adapted from [7–9,238].

aggression toward both male and female intruders, including sexually receptive females, thereby rejecting potential new mates [8,99,100,231]. This selective aggression is thought to be essential for mate-guarding, nest defense, and the maintenance of the existing bond between the male and his partner [8,37,38,99,100,231]. As described below, studies have indicated multiple brain regions, and the involvement of both AVP and DA in this behavior.

5.1. Brain activation associated with selective aggression

A variety of brain regions have been implicated in selective aggression. For example, display of this behavior has been associated with elevated Fos-ir in the MeA, BNST, MPOA, LS, and AH (Fig. 4A) [99,224]. In one of these regions, the AH, differential activation was noted between exposure to the familiar partner and an unfamiliar stranger [99]. Specifically, male prairie voles that were paired with a female for two weeks (i.e., pair bonded) and were then exposed to a conspecific male or female stranger had a significantly higher density of Fos-ir cells in the AH than pair-bonded males re-exposed to their partner. Interestingly, males exposed to either male or female intruders also had a significantly higher density of cells double labeled for AVP-ir and Fos-ir in this brain region than males re-exposed to their partners, suggesting that AH AVP may regulate selective aggression [99] (Fig. 4B).

5.2. Neuropeptide regulation of selective aggression

Due to the known role of AVP in territorial displays [79], and the differences in AVP receptor distribution in forebrain regions be-

tween monogamous and polygamous voles [123,225], AVP was hypothesized to be involved in the regulation of selective aggression. In the first experiment to test this hypothesis, Winslow et al. [231] found that injection of a V1aR antagonist, but not cerebrospinal fluid (CSF), into the lateral ventricle during 24 h of mating prevented the subsequent display of mating-induced selective aggression in male prairie voles. Additionally, infusion of AVP into the lateral ventricles induced aggression toward an intruder in sexually naïve, non-female exposed males. Similar manipulations of the OT system did not alter aggressive behaviors, indicating that central AVP, but not OT, neurotransmission regulates selective aggression in male prairie voles [231].

Site-specific manipulations in the AH have further supported this hypothesis [100]. Sexually naïve males that received AVP infusion directly into the AH showed significantly higher levels of aggression toward a novel female than males treated with vehicle or with both AVP and a V1aR antagonist, indicating that AVP neurotransmission in the AH can induce aggression in prairie voles (Fig. 4E). Further, in pair-bonded male prairie voles, AVP release in the AH was significantly higher in subjects exposed to a stranger animal than those exposed to their partners (Fig. 4C). Interestingly, the magnitude of AVP release in these animals was correlated positively with their frequency of aggression and negatively with the duration of affiliation. Additionally, blockade of V1aRs in the AH, but not other brain regions, prevented the display of selective aggression in pair-bonded males, directly implicating AH AVP in this behavior (Fig. 4E). In the same study, it was found that pair-bonded males had significantly higher densities of V1aRs, but not OTRs, in the AH than sexually naïve males (Fig. 4D), suggesting that

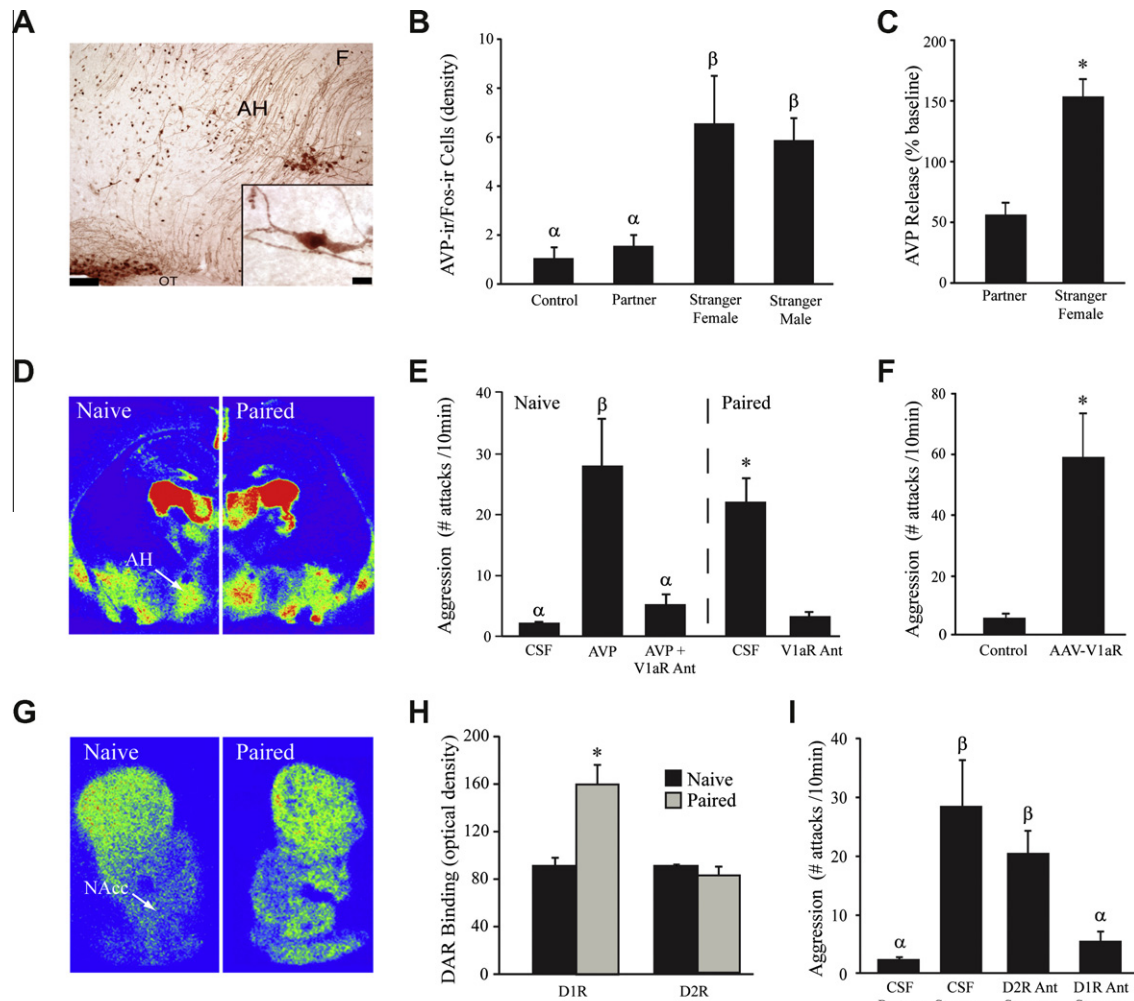


Fig. 4. Vasopressin (AVP) and dopamine (DA) involvement in selective aggression in male prairie voles. (A) Photomicrograph shows AVP-immunoreactive (AVP-ir) cell bodies and fibers (brown cytoplasmic staining), Fos-immunoreactive (Fos-ir) staining (dark nuclear staining), or both (insert) in the anterior hypothalamus (AH). (B) Males pair-bonded with a female for two weeks displaying aggression toward either male or female strangers, have a significantly higher density of AVP-ir/Fos-ir double labeled cells in the AH compared to males re-exposed to their partner or not exposed to any conspecific (control). (C) AH-AVP release is higher in pair-bonded males that are exposed to a stranger female than those that are re-exposed to their partner. (D) Males paired with a female for two weeks (Paired) have higher densities of vasopressin receptors (V1aRs) in the AH than males that are sexually naïve (Naïve). (E) Sexually naïve males (Naïve) given intra-AH injections of AVP display significantly more aggression than males treated with CSF, and this AVP-induced aggression is blocked by concurrent administration of AVP with a V1aR antagonist (V1aR Ant). Pair-bonded males (Paired) display robust aggression toward novel females and this behavior is significantly decreased by intra-AH injection of a V1aR antagonist. (F) Sexually naïve males injected in the AH with an adeno-associated virus expressing the V1aR gene (AAV-V1aR) display significantly more aggression toward stranger females than control males. (G) Pair-bonded males (Paired) have higher densities of D1Rs in the NAcc than sexually naïve males (Naïve). (H) These differences in D1R density between paired and naïve males are significant, however no group differences are found in NAcc D2R density. (I) Pair-bonded males display aggression toward a stranger female, but not their partner, and these effects are blocked by the infusion of a D1R antagonist (D1R Ant), but not D2R antagonist (D2R Ant), into the NAcc. Bars indicate means \pm standard error of the mean. Bars with different Greek letters differ significantly from each other. *: $p < 0.05$. Adapted from [8,99,100].

pair bonding experience may cause neuroplastic changes in the AH AVP system that underlie the emergence of selective aggression [100]. This hypothesis was supported by the finding that artificial overexpression of the V1aR by viral vector-mediated gene transfer, in sexually naïve prairie voles enhanced aggression toward novel females (Fig. 4F)[100]. Taken together, these data indicate that AVP in the AH plays an integral role in the regulation of selective aggression in male prairie voles.

5.3. DA regulation of selective aggression

Mesolimbic DA has also been implicated in selective aggression, particularly, the aggression displayed by pair-bonded males toward stranger females [8]. In two separate experiments, DAR densities in the brains of male prairie voles that were sexually naïve were compared to that of males either paired with a female for 24 h or two weeks (i.e. pair bonded) [8]. Although no differences

in DAR densities were noted between sexually naïve males and those that had mated with a female for 24 h, pair-bonded males had significantly higher levels of D1Rs, but not D2Rs, in the NAcc, but not CP, than their sexually naïve counterparts (Fig. 4G and H). As two weeks, but not 24 h, of cohabitation and mating increased NAcc D1Rs, these results indicate that this neuroplastic change is not necessary for the initial formation of partner preferences—a result that is consistent with the D2R, but not D1R, regulation of partner preference formation aforementioned—but is instead indicative of extended sociosexual experience with the partner (i.e. the full establishment of a pair bond) [8]. Interestingly, this increase in D1R levels in pair-bonded males coincides with the behavioral emergence of offensive aggression toward a stranger female (males that are paired with a female for two weeks display robust offensive aggression toward stranger females [8,99,100], whereas males that are sexually naïve or allowed to mate with a female for 24 h do not [224]). Therefore, it was hypothesized that

increased D1R levels in the NAcc of pair-bonded males may regulate selective aggression toward stranger females. Site-specific pharmacological blockade of NAcc D1Rs was used to test this hypothesis. While pair-bonded males treated with CSF displayed robust offensive aggression toward a female intruder, intra-NAcc injection of a D1R antagonist abolished this aggression (Fig. 4I). Taken together, these data suggest that NAcc D1R upregulation may underlie the important behavioral transition that occurs in male prairie voles as they progress from the state of being sexually naïve to being fully pair bonded, leading to offensive aggression toward stranger females and the maintenance of the established pair bond [8]. In an interesting parallel to this finding, repeated exposure to a common drug of abuse, amphetamine, increased aggression toward conspecifics and prevented the formation of partner preferences [100,151]. Importantly, these behavioral changes coincided with an upregulation of D1Rs in the NAcc and V1aRs in the AH, indicating that drugs of abuse can hijack natural forms of neuroplasticity that evolved to maintain pair bonds [100,151].

6. Neurobiology of paternal behavior

Paternal behavior has been reported in several nonhuman monogamous mammalian species including tamarins [246], marmosets [5], titis [160,161], hamsters [118], gerbils [182], mice [24] and voles [174,205]. Studies in nonhuman primates have focused on the characterization of paternal behaviors and the effects that manipulations of the social environment have on the display of these behaviors, and have provided important translational information for human health. Studies in rodents, instead, have focused on the central regulation of paternal behaviors and have provided valuable information concerning the neural mechanisms underlying paternal behavior. Although the California mouse has proven a useful rodent model for this purpose [24–26,59], the vole model has perhaps been used most extensively in studies of the neurobiology of paternal behavior, and data from these studies are summarized below.

6.1. Brain activation associated with paternal behavior

As in the study of partner preference formation and selective aggression, early studies examining vole paternal behavior used Fos-ir to map brain areas that are activated by pup exposure and the display of paternal behavior. After exposure to a conspecific pup, male prairie voles displayed increased Fos-ir staining in some forebrain areas including the AOB, MeA, BNST, MPOA, and LS, implicating the involvement of these regions in processing pup-associated cues and/or in the regulation of paternal behavior [134,222]. The role of the olfactory system and MeA in paternal behavior was further confirmed by lesion studies in prairie voles. Males that received bilateral bullectomy showed a significant decrease in paternal behavior along with other social behaviors, compared to males that received a sham-operation [135]. Further, axon-sparing lesions of the MeA decreased paternal behavior in male prairie voles without affecting other behaviors such as exploration, locomotion, and olfactory investigation [133]. Finally, unlike prairie voles, pup exposure did not significantly elevate Fos-ir labeling in the MeA, BNST, MPOA, or LS of male meadow voles, further suggesting the importance of these brain regions in the regulation of male parental care [222].

6.2. Neuropeptide regulation of paternal behavior

In addition to those behaviors previously mentioned, central AVP and OT have also been implicated in parental behaviors, particularly in females. Injections of AVP into the lateral ventricle of

female rats induces persistent parental behavior [177]. Further, Long-Evans rats display superior parental behavior compared to their closely related AVP-deficient mutant variants, Brattleboro rats [227]. OT, both in the periphery and brain, also plays an important role in behaviors associated with maternal care, including uterine contraction at parturition, milk ejection during lactation [87,211] and the regulation of maternal behavior in females [142,177]. As OT and AVP have therefore been implicated in parental behavior in females, and other social behaviors in both females and males, researchers began evaluating the role that these neuropeptides played in the regulation of male parental behavior.

The first evidence to suggest a role for these neuropeptides in paternal behavior was provided by studies investigating the relationship between paternal experience and AVP-ir fiber density or AVP/OT mRNA expression in the brain. Prairie voles that had been paired with a female for two weeks or were first-time fathers demonstrated significantly more paternal behaviors and had lower densities of AVP-ir fibers in the LS, but not the MPOA, than their sexually naïve counterparts [17,18]. Interestingly, this alteration in LS AVP-ir fiber density was not found in meadow vole fathers—that naturally show little to no paternal behaviors toward pups—suggesting that changes in LS AVP may indeed play a role in prairie vole paternal behavior [17]. AVP in the PVN has also been implicated in prairie vole paternal behaviors, as AVP mRNA labeling in this region was increased in male prairie voles that had recently become fathers, but did not change in naturally nonpaternal male montane vole fathers [226]. Although little is known about the role of OT in paternal behavior in prairie voles, there exists some evidence that this neuropeptide may be involved. For example, prairie vole pups reared by mothers-only received less licking/grooming and matured more slowly, compared to pups reared by both parents. In adulthood, the former showed less pup-directed parental behavior and increased OT mRNA expression in the hypothalamus than the latter, but such effects were mainly noted in females [4]. Taken together, these data indicate that AVP and OT in various brain regions may regulate paternal behavior.

Few studies have directly assessed the functional significance of central AVP and OT in paternal behavior. In one of these studies, subtle changes were noted in the paternal behaviors of sexually naïve males after icv administration of AVP or OT, whereas combined icv treatment of an OTR and V1aR antagonist affected paternal behaviors in a dose-dependent manner [13]. At low doses (1 ng each), OTR/V1aR antagonists tended to increase the latency for pup approach and huddling, while at high doses (10 ng each) paternal behavior was significantly reduced and the occurrence of pup attacks was significantly increased [13]. While this study demonstrates that central AVP and OT indeed have functional effects on paternal behavior, further experimentation is required to further understand the role of each neuropeptide on specific paternal behaviors and their sites of action within the brain. In the only study to do so to date, Wang et al. [213] examined the effects of AVP manipulation in the LS on four of the most common paternal behaviors, including licking/grooming, crouching/huddling over, contacting and retrieving pups. Sexually naïve male prairie voles injected with AVP directly into the LS spent significantly more time displaying paternal activities, specifically contacting and crouching over pups, than voles injected with saline. These effects were blocked by pre-injection of a V1aR antagonist in the LS, suggesting that LS AVP is both necessary and sufficient in the regulation of paternal behavior [213].

Although site-specific effects of OT on paternal behavior have never been tested, there is evidence to suggest that NAcc OT may be involved. This evidence stems from comparative studies demonstrating species differences in NAcc OTR densities that correlate

with species differences in paternal behavior [122], the importance of OTR activation in other behaviors associated with pair bonding in males (e.g., partner preference formation) [150,244], and various studies documenting a role of NAcc OTRs in female parental behavior. For example, NAcc OTR densities have been related to spontaneous maternal behavior in sexually naïve adult female prairie voles. Specifically, females that displayed maternal behavior had higher densities of OTRs in the NAcc than females that did not display maternal behaviors or attacked pups [173]. A similar positive correlation was noted between NAcc OTR density and alloparental care in juvenile female prairie voles [172]. Further, OTR density in the NAcc has been positively associated with other affiliative behaviors, including partner preference formation [188]. Although never directly tested in males, these data indicate the potential for NAcc OT to be involved in paternal behavior.

6.3. DA regulation of paternal behavior

While a great deal of research has documented the importance of central DA in maternal behaviors (see [171] for review), fewer studies have investigated a role for central DA in paternal behavior. Although limited in number, these studies have provided compelling preliminary evidence that DA is also involved in male parental care.

In the only pharmacological experiment to examine the DAergic regulation of paternal behavior in prairie voles, Lonstein [153] illustrated that DAR blockade has differential effects on distinct aspects of paternal behavior (e.g. contacting, licking, and huddling over pups). Specifically, blockade of DARs with the nonselective DAR antagonist, haloperidol, impaired some paternal behaviors—including contacting and licking pups—yet enhanced others, such as huddling over pups. Although haloperidol disrupts general motor activity at some doses [195], the effects of haloperidol on some paternal behaviors, specifically pup licking, were noted at doses that did not alter total activity scores, indicating that DAR activation has primary effects on paternal behavior. Therefore, these data not only demonstrate a role for DA in paternal behavior but also illustrate that the DAergic regulation of paternal behavior is behavior-specific [153]. No site-specific manipulations have yet been used to reveal brain regions involved in the DAergic regulation of paternal behavior. However, an experiment mapping neuronal activation in response to pups has offered some insight into this matter. Recall that the prairie vole brain contains a group of DAergic cells in the pBNST and MeApd that is sexually dimorphic—males have more DAergic cells in these areas than females [168]—and these cells are potentially sensitive to androgens and estrogens [40]. Interestingly, these cell populations are activated (indicated by Fos/TH double-labeling) in the male prairie vole brain after interactions with conspecific pups [168], and may therefore be involved in paternal behavior.

Although no studies have yet been conducted to this end, it is suggested that NAcc DA may also play a role in paternal behavior. As described previously, the vole NAcc contains dense DA terminals and receptors and NAcc DA plays an important role in the regulation of other social behaviors associated with pair bonding, including partner preference formation and selective aggression in male prairie voles [7,8]. Additionally, NAcc DA plays a well-known role in maternal behavior in other rodent species. In rats, for example, DA is released in the NAcc in response to pup stimuli [109] and alterations in NAcc DA activity across postpartum periods are correlated with changes in a variety of parental behaviors ranging from pup retrieval, nursing, licking/grooming, and maternal memory [3]. It may therefore be worthwhile for future investigations of male parental behavior to examine the possibility that NAcc DA plays an important role.

7. Other neurochemicals/hormones implicated in pair bonding

In addition to AVP, OT and DA, several other neurotransmitters and hormones have been implicated in social behaviors associated with pair bonding in prairie voles. One interesting example involves neurochemicals associated with the hypothalamic–pituitary–adrenal (HPA) axis, the system that mediates stress responses. Briefly, during a stressor, corticotrophin-releasing factor (CRF) released from the hypothalamus binds to CRF receptors in the anterior pituitary leading to the synthesis of adrenocorticotrophic hormone (ACTH) [143]. ACTH is then released into the bloodstream and acts on the adrenal cortex to produce glucocorticoids, such as corticosterone (CORT), which can then act on glucocorticoid receptors (GR) in the brain to mediate responses to stress [143]. Prairie voles are considered to be glucocorticoid resistant rodents as they have about 5- to 10-fold greater basal plasma CORT and 3-fold greater basal levels of ACTH, along with 10-fold lower affinity GRs, especially the type-I GR, that are expressed in lower densities in the brain, compared to rats and promiscuous voles [110,204].

Data from behavioral experiments indicate that the effect of CORT on pair bonding is sexually dimorphic. In female prairie voles, cohabitation with a male, which led to partner preference formation, significantly decreased serum CORT levels [63]. Further, reduction in GR activity, either by decreasing circulating CORT through adrenalectomy [63] or by treating animals with a GR antagonist [52], facilitated partner preference formation. In contrast, CORT injections or a stressful swim test, which increased circulating CORT [66], prevented the development of partner preference formation [63]. Together, these data suggest that a decrease in HPA axis activity facilitates partner preference formation in female prairie voles. In males, on the other hand, adrenalectomy inhibited partner preference formation and this effect was reversed by CORT replacement [64], indicating that CORT is necessary for partner preference formation in males. Additionally, in a more recent study, loss of a bonded partner significantly increased circulating CORT levels and adrenal gland weight in male prairie voles, suggesting that HPA axis activity may mediate the aversive effects of partner separation and thus, play a role in the preservation and maintenance of existing pair bonds [29]. The HPA axis has also been implicated in paternal behavior. Males exposed to a swimming stress spent significantly more time huddling over pups and a trend toward more time licking and grooming pups than unstressed controls [14]. These behavioral effects were not found in female prairie voles, indicating that the effects of stress on parental behavior—like partner preference formation—may be sexually dimorphic [14].

CRF has also been implicated in pair bonding behaviors. Male prairie voles that received CRF injections displayed partner preferences in the absence of mating, and this induced behavior was blocked by co-administration of a CRF receptor antagonist [67]. Brain areas involved in the CRF mediation of partner preferences have also been identified. Local CRF injections into the NAcc facilitated, whereas CRF receptor antagonists inhibited, partner preference formation in male prairie voles [148]. Further, pairing with a female elicited an increase in CRF mRNA in the BNST of male prairie voles [29]. Finally, icv administration of urocortin-II, a member of the CRF peptide family, increased passive parental behavior in both male and female prairie voles, but this treatment had no effects on anxiety or locomotor behaviors [190].

Several other neurochemicals are also involved in social bonding in prairie voles. For example, in male prairie voles, intra-VTA administration of NBQX, an AMPA receptor antagonist, or bicuculline, a GABA receptor antagonist, induced partner preference formation, implicating these amino acids in selective affiliation [53]. Administration of the selective serotonin reuptake inhibitor,

fluoxetine, increased the latency to engage in parental behavior in both male and female prairie voles, decreased aggression in males, and had no effects on nonsocial behaviors [209], indicating that serotonin may also mediate social behaviors associated with pair bonding. Gonadal steroids can also be added to this list. Manipulation of testosterone or estrogen during the first or second week of life significantly altered subsequent affiliative and/or alloparental behaviors in juvenile prairie voles [138,184]. Estrogen receptor alpha ($ER\alpha$) may mediate some of the effects of gonadal steroids on pair bonding behaviors in prairie voles. Studies have demonstrated that females have more $ER\alpha$ -ir cells in several brain areas including the MeA, BNST, MPOA, and VMH than males, and a decrease in $ER\alpha$ -ir staining in the BNST, MPOA, and VMH of females was associated with induction of sexual receptivity [113]. In males, enhanced $ER\alpha$ expression in the MeA, by transfection of an adeno-associated viral vector, disrupted the display of alloparental behavior and impaired partner preference formation [58]. Similarly, males with enhanced $ER\alpha$ expression in the BNST displayed decreased social affiliation [140]. These data indicate an inverse relationship between regional $ER\alpha$ expression and social behavior in prairie voles. Taken together, the studies described above highlight the involvement of multiple neurochemicals and hormones in the regulation of pair bonding behaviors in both male and female prairie voles.

8. Neurochemical/hormone interactions

As reviewed above, a variety of neurochemical, neurotransmitter, and hormone systems have been implicated in pair bonding. However, it is unlikely that these systems act independently to regulate this complex social behavior. In the following section, we will review studies documenting known interactions between some of these systems, including CRF, OT, AVP, DA, glutamate (GLU), gamma-aminobutyric acid (GABA), and gonadal steroid hormones, in the regulation of pair bonding behaviors, primarily partner preference formation.

Two of the first neurochemicals suggested to interact with one another in the regulation of partner preference formation in prairie voles were CORT and OT. Recall that in sexually-naïve females, exposure to an unfamiliar male significantly increased central OT release [187] and decreased serum CORT levels [63], effects thought to facilitate partner preference formation. Interestingly, icv injections of OT produced a comparable decrease in serum CORT levels, suggesting that OT may interact with the HPA axis to regulate partner preference formation [65] – an idea that may warrant future investigation given the suggested interaction between OT and CORT in other social behaviors [6,39,42,132].

OT has also been shown to interact with AVP in the regulation of partner preferences, a finding that is not surprising given that these two neuropeptides are closely related to one another and not only share similar chemical structures—differing by only two amino acids—but can also interact with each other's receptors [19]. As previously described, icv injection of AVP or OT can induce partner preferences in both male and female prairie voles after as little as 1 h of cohabitation with an opposite sex conspecific animal. Interestingly, the effects of AVP on partner preference formation are abolished in the presence of an OTR antagonist, and the effects of OT are abolished in the presence of a V1aR antagonist, indicating that AVP and OT can interact to mediate partner preferences [43]. Further, these results indicate that the facilitation of partner preference formation may require simultaneous activation of both V1aR and OTRs [43]. Site-specific manipulation in the LS of male prairie voles has since supported this hypothesis. Partner preference formation induced by AVP microinjection into the LS was blocked by simultaneous administration of an OT receptor antagonist [149]. Taken together, these studies suggest that central

OT and AVP systems may work in concert with one another to mediate partner preference formation.

OT and AVP have also been shown to interact with other neurotransmitter systems, such as DA, to mediate partner preferences. In female prairie voles, for example, partner preferences induced by NAcc D2R activation were prevented by concurrent administration of an OTR antagonist [150]. Conversely, partner preferences induced by central OT administration were blocked by concurrent administration of a D2R antagonist in the NAcc [150]. These results suggest that simultaneous activation of both D2Rs and OTRs in the NAcc are required for the facilitation of partner preferences in female prairie voles. AVP-DA interactions have also been implicated in partner preference formation. In a recent study, naturally promiscuous male meadow voles—that would not otherwise form partner preferences with a mate—received viral vector-mediated transfer of the prairie vole V1aR gene into the VP, resulting in upregulation of the V1aR in this region and the formation of partner preferences after 24 h of mating [145]. In a second experiment, these viral vector-induced preferences were blocked by administration of a D2R antagonist prior to mating, suggesting that AVP and DA may interact to mediate pair bond formation [145]. This hypothesis is supported by the well-known neuroanatomical connection between these two regions, as D2R expressing medium spiny neurons in the NAcc project directly to the VP [90].

GLU, GABA, and CRF have also been suggested to interact with DA in the regulation of partner preferences [52,53]. Blockade of AMPA GLU or GABA receptors, via injection of NBQX or bicuculline, respectively, into the VTA induced partner preferences in the absence of mating. As the VTA provides the major source of DAergic afferents to mesolimbic brain regions, including the NAcc, it has been suggested that the effects of these antagonists on partner preference formation may have been mediated by their effects on NAcc DAergic neurotransmission [53]. In a separate study, peripheral administration of RU-486, a GR antagonist, induced partner preferences in female prairie voles in the absence of mating [52]. These effects were blocked by co-administration of either a D1R or D2R antagonist into the lateral ventricle, suggesting that the effects of GR antagonism on partner preference formation may be mediated through an interaction with central DA systems [52]. Further experimentation is needed to detail the nature of interactions between GLU, GABA, CRF, and DA in partner preference formation.

Finally, gonadal steroids play an important role in pair bonding and are thought to interact with a variety of neuropeptide and neurochemical systems implicated in this behavior. For example, extended exposure to a male (or male chemosensory signals) increases circulating estradiol levels and subsequently, behavioral estrus, or sexual receptivity in female prairie voles [35,36,47,203]. Sexual receptivity can also be induced in ovariectomized females through estrogen administration alone [35]. Interestingly, increased serum estrogen levels, induced by exposure to male chemosensory signals or by exogenous estrogen administration, significantly increased OTR binding in the prairie vole brain [233], indicating that estrogen and OT may interact to regulate mating—which facilitates partner preference formation in females [228]. In males, testosterone has been found to influence the effects of AVP on partner preference formation. Recall, that icv administration of AVP facilitates the formation of partner preferences in male prairie voles following only 1 h of cohabitation [43]. Interestingly, AVP administration does not induce partner preferences in adult male prairie voles that were castrated on the day of their birth, suggesting that the organizational effects of testosterone are required for the effects of AVP on partner preference formation [57]. Testosterone and AVP may interact in the regulation of paternal behavior as well, as male prairie voles that were castrated in adulthood had a reduced density of AVP-ir fibers in

the LS and displayed less paternal behavior than controls with intact gonads [219] (cf. [152,153]).

9. Summary and additional considerations

Pair bonding in prairie voles is a complex social behavior that involves the coordination of several distinct behaviors, including selective affiliation, selective aggression, and parental care. The appropriate expression of these behaviors requires a variety of cognitive functions, including sensory processing, memory formation, and individual recognition, as well as motor output. Multiple brain regions, such as the MeA, BNST, LS, NAcc, PFC, and AH, known to mediate these processes, have been implicated in pair bonding behaviors in prairie voles, as described above. Further, many of the neurochemicals that have been implicated in pair bonding behaviors, including AVP, OT, DA, CRF, and GLU are known to act in these brain regions to mediate processes essential for pair bonding. For example, AVP in the LS [78] and OT in the MeA [77] mediate social recognition in other species, a process inherent to the formation and display of partner preferences in prairie voles. As another example, DA in the NAcc plays an important role in conditioned reward learning [23,119], a process that likely contributes to partner preference formation by mediating a learned association between the reinforcing properties of mating and the specific olfactory signature of the mate [8,10,245].

Although careful experimentation has revealed the importance of each of these separate brain regions and neurochemicals for pair bonding behaviors, each behavior tested is undoubtedly regulated by a larger circuitry involving multiple brain regions and neurochemicals. While not yet fully examined in voles, data from other rodent species have demonstrated clear anatomical connections between the brain regions noted above, and these connections form neural circuits with discrete functions relevant to pair bonding [245]. For example, connections between the vomeronasal organ (VNO), AOB, and MeA play an important role in processing chemosensory cues [30,72,121,130,192], and not surprisingly, activation of both the VNO and MeA during social and sexual experience (when discrete conspecific olfactory cues are present) are essential for the formation of partner preferences [49,133]. Connections between the MeA and AH regulate aggression [33,202], and activation of this pathway likely regulates selective aggression in prairie voles [99,224]. Additionally, the well-characterized mesolimbic DA system, which consists of DAergic cells in the VTA that project to the NAcc and mPFC, is regulated by reciprocal GLUergic projections from the mPFC to the NAcc and VTA [34,193]. This neural circuit assigns motivational salience to environmentally relevant stimuli [120,232], facilitating adaptive goal-directed behaviors, such as copulation with a receptive mate [22,74,179,180] and the retrieval of pups [2,112,171]. It is important to note that just as the same system can mediate more than one behavior, as evidenced by the latter example, the same neurochemical can regulate more than one behavior. For instance, AVP neurotransmission, in the LS, VP, and/or AH plays an important role in partner preference formation, selective aggression, and paternal behavior. Further, one behavioral event can be mediated by more than one neural circuit. For example, sociosexual experience – a prerequisite for partner preference formation – induces both DA and OT release in the NAcc [98,187], AVP release in both the LS [216] and VP [245], and has also been suggested to release OT in the PFC [245]. Thus, multiple neural circuits and neurochemicals work in concert with one another to regulate behaviors associated with pair bonding.

Finally, in the discussion of pair bonding in the prairie vole, sex differences should not be overlooked. As discussed above, the neural regulation of pair bonding behaviors is in some cases sexually dimorphic (e.g., CORT regulation of partner preference formation

[63,64]). Further, some neuropeptides, such as AVP and OT, may have gender specific roles in certain behaviors related to pair bonding: AVP regulates selective aggression [99,100,201] and paternal behavior [149,213] in males, while OT regulates maternal care in females [16,76,165,173,178]. Additionally, males and females seem to differ in their sensitivities to AVP and OT. Although both neuropeptides have been implicated in partner preference formation in both sexes [43], lower doses of AVP were sufficient to induce partner preferences in males than females and peripheral OT administration was effective to induce partner preference formation only in female, but not male, prairie voles [54]. Sexual dimorphisms in physiology and neural substrates may underlie these differences in behavior. For example, as found in other rodent species [48,61,207], male voles have more AVP mRNA-labeled cells in the BNST and MeA and a higher density of AVP-ir fibers in the LS (most likely projections from AVP producing cells in the BNST and MeA) than female voles [17,221]. Interestingly, 3 days of cohabitation with an opposite sex conspecific induces an increase in the number of AVP mRNA-labeled cells in BNST and a decrease in the density of AVP-ir staining in the LS in male, but not female, prairie voles, indicating a sexually-dimorphic effect of sociosexual experience on AVP activity, which, in turn, may play a role in the regulation of pair bonding behavior in male prairie voles. Sex differences have also been found in a population of TH synthesizing cells in the anteroventral periventricular preoptic area [139] and the extended amygdala [168] in the prairie vole brain, however the functional role of these cells in pair bonding still needs to be examined. It is well recognized that sexual dimorphisms in physiology and neural substrates may underlie sex differences in behavior. In addition, sex differences in the brain may allow for the display of similar behaviors between males and females despite their different physiologies [62]. In other words, sexually dimorphic neurochemical systems may allow males and females to have compensatory mechanisms that work in concert with their physiologies to produce similar behavioral outcomes. This suggestion is consistent with studies in the prairie vole demonstrating that sexually dimorphic systems, such as the AVP pathways from the MeA and BNST to the LS [17], enable the display of parental behaviors in males [216] while OT systems enable the same behaviors in females [16,173].

10. Conclusions and future directions

Although study of the bonds formed between prairie vole pairs cannot possibly allow us to fully understand the intricacies of human relationships, they can certainly offer insights into the basic neural mechanisms underlying adult attraction and attachment. The literature reviewed above has implicated a variety of neuropeptide, neurotransmitter, and hormonal systems in the regulation of pair bonding in prairie voles. Accordingly, preliminary work in humans has implicated many of these same systems in human social behaviors. For example, recent research utilizing functional magnetic resonance imaging to measure real-time brain activation in humans has suggested that DA neurotransmission may underlie human mate choice and attachment [81]. These studies found that DA-rich areas, such as the VTA, were activated when participants in either early stages of intense romantic relationships or in long-term deeply-loving relationships viewed a photograph of their beloved but not when they viewed pictures of other familiar individuals [12,20,21]. Recent studies have also implicated the OT system in human couple interactions. In a placebo controlled experiment, for example, intranasal administration of OT—a method of delivery that readily allows the neuropeptide access to the brain—significantly increased positive communication between couples, as indexed by eye-contact, curiosity/care, and agreement scores [70]. Additionally, OT has been found to increase trust

among humans—a prerequisite to social affiliation [137]. Further, AVP has been implicated in human aggressive behavior, as levels of AVP in the cerebrospinal fluid of men and women were positively correlated with a life history of aggressive behaviors [46]. Taken together, these studies highlight the possibility that similar neural mechanisms may mediate social behaviors in humans and nonhuman mammals.

A relatively high degree of conservation between the behavioral and neurobiological aspects of prairie vole and human social behaviors suggests that the prairie vole model may be ideal for basic and translational research investigating the neurobiology of social behavior. Accordingly, research in prairie voles may not only allow us to learn more about the factors that underlie normal social behaviors, but may also enable us to explore the underlying causes of social deficits noted in several mental health disorders. A noteworthy example involves the use of the prairie vole model for the study of autism spectrum disorders [147,157], in which AVP, OT, and DA have already been implicated [111,115,156,236]. Additionally, the prairie vole has recently been established as an animal model for depression, specifically depression induced by social loss in adulthood [29,103]. Finally, prairie voles have most recently been utilized to study the effects of drugs of abuse on pair bonding, and these studies have demonstrated that dysregulation of the mesolimbic DA system may be involved in the drug-induced impairment of social behavior [151,238]. These and other studies [84] demonstrate the utility of this animal model for the investigation of neural mechanisms underlying normal and abnormal social behaviors, and their related processes.

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