Neural Regulation of Pair Bond Formation in a Monogamous Rodent Species

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Abstract: The neurobiology of monogamous social organization can be studied by laboratory examination of social bonding. In this review, we discuss how the monogamous prairie vole (*Microtus ochrogaster*) has been used as a model system to provide tremendous insight into the neural regulation of pair bond formation. Neuroanatomical differences between monogamous and non-monogamous voles, as well as how neurochemical manipulations affect pair bond formation are reviewed. In addition, interactions among neurochemical systems that regulate pair bond formation and the extent of sexual dimorphism associated with pair bonding are discussed. Finally, we propose future directions for this line of research and explain why understanding the neural regulation of social bonding is important for human health.

Key words: Dopamine; Vasopressin; Oxytocin; Corticosterone; Monogamy; Vole; Pair bond

单配制啮齿动物 Pair Bond 形成的神经调节机制

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摘要: 单配制啮齿动物社会结构的神经生物学原理可以通过实验室研究 Social bonding 而获得。在本文中, 我们探讨了如何利用单配制的草原田鼠 (*Microtus ochrogaster*) 作为研究模型揭示 pair bond 形成的神经调控机制。我们进而探讨了单配制与多配制田鼠之间神经解剖学的差异以及神经化学物质的调节是怎样影响 pair bond 的。本篇综述还讨论了与 pair bond 形成有关的神经化学系统之间的相互影响以及 pair bond 形成过程中的两性差异。最后, 我们预测了这一研究领域的未来研究方向以及研究 social bonding 的神经调控对人类健康的重要性。

关键词: 多巴胺; 加压素; 催产素; 肾上腺皮质素; 单配制; 田鼠; Pair bond

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1 INTRODUCTION

Pair bonding describes an enduring attachment between members of a breeding pair that share territory and parental duties and is a fundamental characteristic of monogamy[1,2]. Unfortunately, monogamous animals are not common experimental subjects, and as a result pair bonding is understudied relative to other types of social behavior[3]. However, recent research utilizing the prairie vole (*Microtus ochrogaster*) has permitted tremendous progress toward understanding the neural mechanisms underlying pair bonding[4-8]. Here, we first provide a brief overview of prairie vole natural history and then discuss our current understanding of neural mechanisms underlying pair bonding.

2 THE PRAIRIE VOLE MODEL

Prairie voles are distributed primarily in the grasslands of the central United States[9,10]. Since the majority of studies examining neurochemical regulation of pair bonding have been performed in prairie voles originally from Illinois, these animals will be the focus of this review. However, several studies have used prairie voles from Kansas, and although these animals also are monog-

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amous, some aspects of behavior and physiology differ between Kansas voles and those from Illinois[11-13].

Prairie voles have adapted to food sources of minimal caloric value and scarce water supplies[14-17], and it has been suggested that, under conditions of limited resources, two parents may be necessary to successfully raise pups[18]. Since biparental care is a key component of a monogamous life strategy[1,2], a harsh environment may have contributed to the evolution of monogamy in prairie voles[19,20]. While males of most mammalian species provide little to no parental care, field studies have shown that male prairie voles are highly paternal, contributing significantly to nest building, nest guarding, huddling over pups, and pup retrieval[21,22]. Field studies also provided evidence suggesting that prairie voles form pair bonds. Studies of territory usage by prairie voles employing repeated trapping methods, found that male-female pairs were often trapped together, indicating that these animals traveled together and were likely pair bonded[23,24]. Additional evidence for pair bonding came from field studies showing that prairie vole nests were often occupied by a breeding pair and one or more litters of pups[24]. Such family units display high levels of social contact with minimal aggression toward one another, while unrelated intruders are aggressively repelled[14]. Perhaps the most compelling evidence for pair bonding is that the breeding pair often remains together until one dies, and in many cases, the surviving member never takes a new mate[22].

While field studies provided the initial identification of prairie voles as monogamous, investigation of the neural basis of pair bonding requires carefully controlled laboratory experiments. Fortunately, voles breed well in captivity and animal care is comparable with that of other rodents, making laboratory study of voles feasible[25,26]. Importantly, the monogamous behaviors observed in nature are also reliably expressed under laboratory conditions. For instance, prairie voles tend to copulate preferentially with a familiar mate versus a novel conspecific[2,27,28]. After mating, prairie voles remain together during gestation[21,29]. This appears to be necessary for successful pregnancy, as prairie voles show both decreased birth success if the female is alone during gestation[30], and a greater susceptibility to stranger induced pregnancy termination compared to other rodents[31,32]. Once the pups are born, males show high levels of parental care[33]. Most importantly, pair bonding can be reliably assessed in the lab by measuring behaviors associated with the formation and maintenance of the bond[4,34,35]. Prior to review of experimental manipulations of pair bonding, it is necessary to first discuss how comparative studies between vole species provided the initial evidence regarding which neurochemicals and brain regions are involved in pair bonding.

3 NEUROANATOMICAL DIFFERENCES BETWEEN MONOGAMOUS AND NON-MONOGAMOUS VOLES

In an effort to understand what neural systems may be associated with pair bonding, several studies have compared the neuroanatomy of monogamous and non-monogamous voles[36-40]. Such comparative studies allow neuroanatomical differences to be correlated with differences in mating systems and social organizations, and there is great potential for such study because the various *Microtus* species display a wide range of social behaviors. For example, while prairie voles are highly social and monogamous, other well studied vole species, such as montane (*Microtus montanus*) and meadow voles (*Microtus pennslyvanicus*), are social and non-monogamous[2]. Specifically, montane and meadow voles prefer novel mates, engage in little to no social contact, and are minimally parental, with almost no parental care from males[2,29,41,42]. Despite many differences in social behavior, these species are taxonomically close to prairie voles, and display very similar non-social behaviors, such as activity and feeding patterns[43], and therefore differences in neuroanatomy are more likely to be related to social behavior.

Interestingly, voles with different social organizations show dramatic differences in the distribution patterns of certain neurotransmitter receptors in the brain. For instance, the distributions of receptors for the neuropeptides oxytocin (OT) and vasopressin (AVP) differ significantly between monogamous and non-monogamous voles, while

distributions for other receptors, such as benzodiazepine and μ-opioid receptors, show no differences[36-40]. This information is reviewed in detail elsewhere[3,5,6]. Briefly, monogamous and non-monogamous voles show differences in OT receptor density within the nucleus accumbens (NAcc), bed nucleus of the stria terminalis (BNST), lateral septum (LS) and amygdala[36,40]. AVP receptor densities in LS, BNST, amygdala and ventral pallidum also differ between monogamous and non-monogamous voles[37,39,44]. These findings suggest that particular receptor distribution patterns may be associated with species differences in social behavior. This is further supported by a study in which normally asocial mice were genetically altered to carry the AVP receptor gene (including its promoter region) of the prairie vole. Mice expressing the vole gene showed a 'prairie vole like' distribution of AVP receptors and displayed increased affiliative social behavior in response to AVP administration[45]. Together, these studies implicate AVP and OT and specific brain regions in the neural regulation of pair bonding.

In addition to differences in receptor distribution, it is also important to note that mating differentially alters these neural systems in monogamous and non-monogamous voles. A major extrahypothalamic AVP pathway in rodents includes AVP cells in the BNST which project to the LS (Figure 1A)[46]. In male prairie voles, mating increases AVP messenger RNA in cell bodies within the BNST (Figure 1B), while decreasing AVP contents in the projections of these cells within the LS (Figure 1C)[47,48]. Based on these data, it has been suggested that AVP is released in the LS during mating[5]. OT is also released during mating in mammals[49,50]. Given that these neuropeptides are likely released during mating and that pair bonding is facilitated by mating[35,51], it has been hypothesized that release of these neuropeptides during mating is critically involved in the neural regulation of pair bonding.

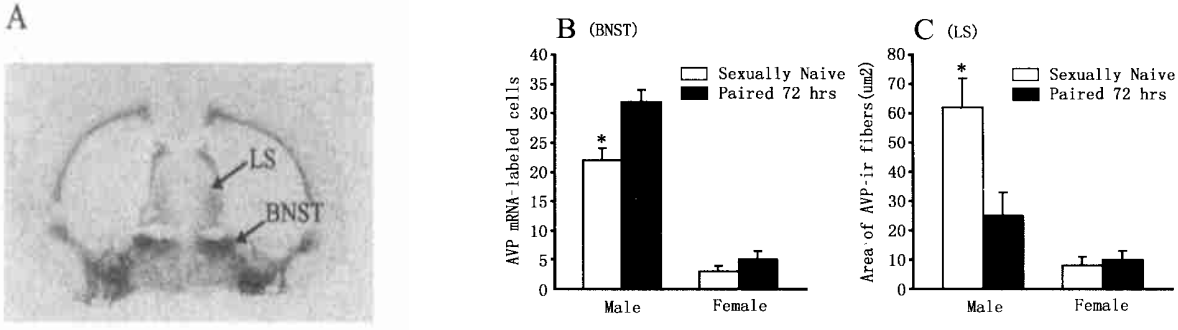

Fig. 1 Effects of mating on the AVP pathway from the BNST to the LS

(A) Receptor autoradiography shows that AVP V1a receptors are present in both the LS and BNST; (B) Mean AVP mRNA labeled cells in male and female prairie voles that are either sexually naive or have been paired with an opposite sex conspecific for 72 hrs, during which the pair mates. In males, but not females, mating induces a significant increase in AVP mRNA in the BNST; (C) Mean area of AVP immunoreactive (ir) fibers in the LS of male and female prairie voles that were sexually naive or paired with an opposite sex conspecific for 72 hrs. Mating induces a significant decrease in AVP-ir fibers in males, but not in females

4 BEHAVIORAL TESTS OF PAIR BONDING

Neurobiological investigation of pair bonding is possible because, in the lab, prairie voles reliably display behaviors that are indicative of pair bond formation. For instance, pair bonding requires that an animal recognize and choose to be with its mate over unfamiliar conspecifics. This is routinely assessed in the lab by a simple choice test, referred to as the partner preference test. The testing apparatus consists of a central cage with tubes connecting it with two identical cages (Figure 2A). The familiar partner and a novel conspecific (stranger) are tethered in separate cages and do not interact with each other, while the subject is initially placed in the neutral cage and is free to move throughout the testing apparatus during the 3-hr test. It has been demonstrated that after mating, both male and female prairie voles prefer to be with their mate, as indicated by spending significantly more time in

contact with the partner compared to time spent with the stranger[35,51]. Partner preferences are reliably produced following 24-hrs of *ad libitum* mating, whereas shorter periods of cohabitation (usually 6 hrs), in the absence of mating, do not lead to partner preferences, i.e. subjects display non-selective contact with partner or stranger (Figure 2B). While differences in experimental design exist between labs, the partner preference remains the most common behavioral index of pair bonding. In addition to partner preferences, mated prairie voles also show an increase in aggressive behavior toward unfamiliar conspecifics, which presumably allows the pair bonded animal to guard both its mate and territory (Figure 2C and D)[52]. This behavior is referred to as selective aggression and it has also been used to study the neural basis of pair bonding[51,53].

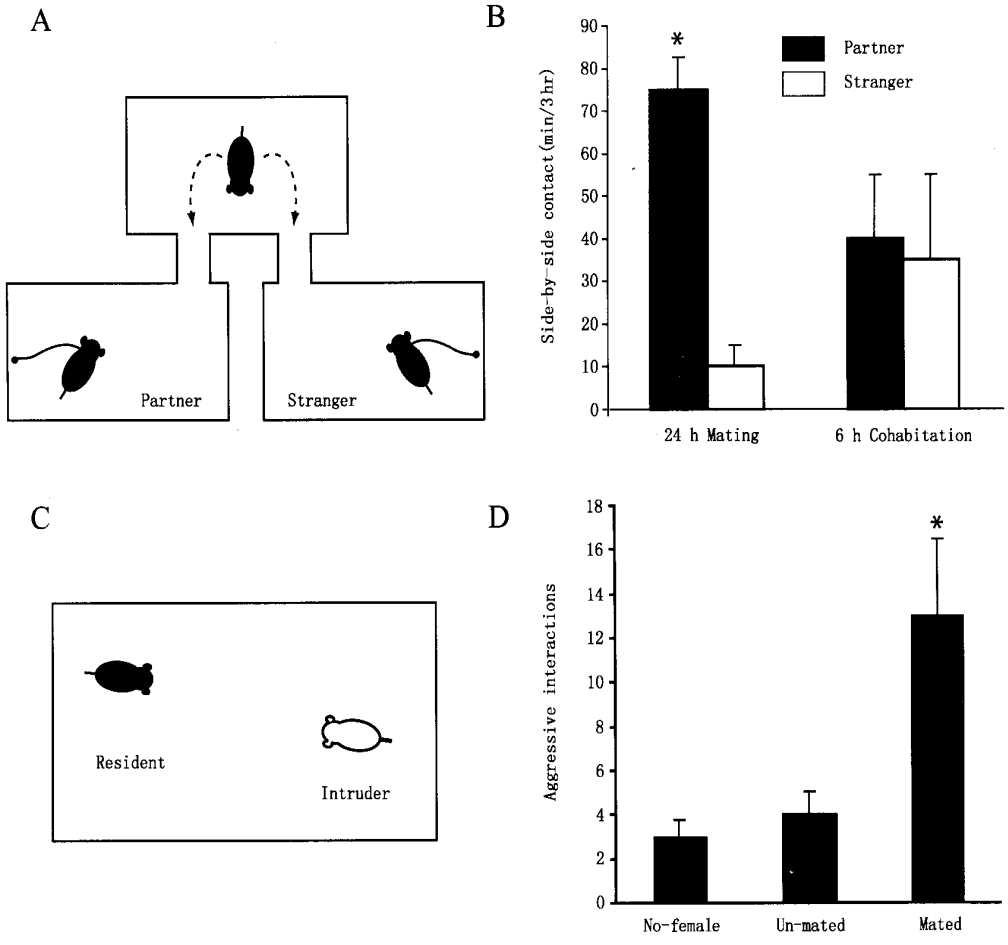

Fig. 2 Behavioral indices of pair bonding include partner preferences and selective aggression.

(A) Apparatus used to perform partner preference tests in our laboratory. Each cage is identical (20 × 25 × 45 cm), and hollow tubes (7.5 × 16 cm) connect the neutral cage to those containing stimulus animals. The primary behavior of interest is side-by-side contact time and is recorded by an experimenter blind to treatment by reviewing time lapse video of the partner preference test. (B) Idealized data of side-by-side contact during the 3-hr partner preference test. 24 hrs of *ad libitum* mating prior to the partner preference test results in the subject spending significantly more time in contact with the partner compared to that with the stranger. In contrast, 6 hrs of cohabitation in the absence of mating results in subjects spending approximately equal time, on average, with either the partner or the stranger; (C) Selective aggression has been studied in voles by using a resident-intruder test. Subjects remain in their home cage (20 × 25 × 45 cm) and if they have a mate, the mate is removed. A novel conspecific (Intruder), usually of the same sex, is then placed in the home cage with the resident. Behavior is videotaped and an experimenter blind to treatment records the number of bites, pushes, chases, etc. during the test, which is typically 6 min. Collectively, these behaviors constitute aggressive interactions; (D) Idealized data of aggressive interactions for this resident-intruder test. Male subjects that have no experience with a female (No-female) and those that have social experience with a female, but are sexually naive (Un-mated), show very low levels of aggressive behavior. However, following 24 hrs of mating with a female (Mated), males became very aggressive toward intruders

5 NEUROPEPTIDE REGULATION OF PAIR BONDING

Initial experimental manipulations of pair bonding focused on AVP and OT systems because comparative studies indicated their potential involvement. In male prairie voles, robust partner preferences and selective aggression were displayed following 24 hrs of *ad libitum* mating[51]. It was hypothesized that mating-induced neuropeptide release was involved in the regulation of these behaviors, and this was directly tested by administration of an AVP receptor antagonist prior to mating. The drug was injected into the ventricular system (icv) which allowed it to spread throughout the brain and to bind AVP receptors, preventing their activation. In support of the hypothesis, both partner preferences and selective aggression were prevented by blockade of central AVP receptors[51]. In the same study, males paired with an ovariectomized female in the absence of mating, did not display partner preferences or selective aggression. However, these behaviors were induced with icv infusion of AVP[51], suggesting that exogenous AVP may have mimicked AVP function associated with mating. Female prairie voles also show partner preferences following 24 hrs of *ad libitum* mating, and this behavior was prevented by blocking OT receptor activation within the brain[42,54]. If females were ovariectomized and paired with a male for only 6 hrs, in the absence of mating, they did not show partner preferences, but this behavior was induced by icv infusions of OT[42,54].

Together, the above studies provide clear evidence that central AVP and OT are involved in pair bonding. However, these studies also suggested that neuropeptides regulated pair bonding in a sex specific manner. It was also reported that while AVP influenced pair bonding in males, it did not affect this behavior in females[42]. Consistent with this finding, neuroanatomical studies showed that male and female prairie voles differ in central AVP neural systems and in the activation of these systems by mating (Figure 1B and C)[5,47,48,55]. Similarly, OT manipulations that alter female pair bonding appeared to have no effects on male behavior[51]. It was therefore concluded that a sexually dimorphic mechanism was involved in pair bond regulation.

However, in a more recent study that tested wider ranges of doses of AVP and OT, icv administration of either neuropeptide induced partner preferences in both males and females, and the induction was blocked by concurrent administration of either peptide receptor antagonist[56]. These data indicate that both AVP and OT are involved in the regulation of pair bonding in both male and female prairie voles[56]. While these results differ from those of earlier studies[42,51], comparisons must be made with caution as experimental methods differed with respect to method of drug administration, doses of drug treatment, length of cohabitation prior to partner preference test, and the social experience of the subjects prior to manipulation. We have therefore performed experiments intended to replicate the methods of the earlier studies and test the role of AVP on partner preference formation in females. Central (icv) infusions of AVP at the same dose used in a previous study[42], had no effect, but when we increased the dose, AVP indeed induced partner preferences in females (Figure 3A). While it is possible that higher concentrations of AVP were effective because of activation of OT receptors[57], these data suggest that the sex differences may not be as dramatic as previously suggested.

6 BRAIN REGIONS IMPORTANT FOR PAIR BONDING

A significant limitation associated with the above studies is that drugs were administered into the ventricularsystem, allowing activation of receptors in multiple brain regions. This makes it difficult to assess the involvement of these neuropeptides in specific brain areas. Therefore more recent studies have focused on site-specific drug manipulations of partner preferences.

The brain regions primarily implicated in pair bonding were those in which monogamous and non-monogamous voles differed significantly in AVP and OT receptor densities. These brain regions include LS, BNST, amygdala, NAcc, and VP[36-39]. In addition, several other studies examined neuronal activation during behaviors associated

with pair bonding. Neuronal activation was assessed by labeling the protein product of an immediate early gene, *c-fos*. This protein is produced soon after the animal is stimulated, and it has therefore been a very useful index of where neural processing is occurring in response to particular stimuli. Forebrain *c-fos* has been measured in response to several social situations related to pair bonding, including a brief social exposure[58], a period of *ad libitum* mating conducive for partner preference formation[59], and during mating-induced selective aggression[53]. Together, the results of these studies support the involvement of LS, BNST, and the medial amygdala (MeA) in pair bonding, and these areas are therefore primary targets for site-specific manipulation of pair bonding.

A recent study focused on the role of the AVP and OT systems in LS on pair bonding in males. AVP in LS was shown to be involved in this behavior as direct administration of AVP into LS induced partner preference formation in the absence of mating, whereas blockade of AVP receptors in LS prevented this behavior induced by mating or by AVP administration (Figure 3B and C)[60]. Furthermore, blockade of OT receptors within LS prevented partner preferences induced by both mating and by AVP administration (Figure 3B and C). Together, these data suggest that AVP and OT in the LS are critically involved in pair bonding[60]. Interestingly, injections of AVP directly into LS also enhanced, whereas an AVP antagonist reduced, male parental behavior, another behavioral characteristic of monogamy[61]. The MeA and BNST have received less study although lesions of the MeA in males also reduced paternal as well as other affiliative behaviors[62]. Future work is needed to define the involvement of these areas in pair bonding.

Monogamous and non-monogamous voles also show significant neuroanatomical differences in the NAcc and ventral pallidum, and recent studies have revealed that these areas also are involved in pair bonding. Prairie voles exhibit high densities of OT receptors in the NAcc compared to those seen in non-monogamous voles[4,34], and blockade of these receptors prevented mating-induced partner preferences in females[34]. Further, site specific injections of OT directly into NAcc induced this behavior in the absence of mating[63]. Prairie voles also have more AVP receptors in the ventral pallidum compared to those found in non-monogamous voles[4,34]. Administration of an AVP antagonist directly into ventral pallidum blocked mating-induced partner preferences[64], whereas increasing the number of these receptors facilitated partner preference formation[65], indicating the importance of these AVP receptors in pair bond formation.

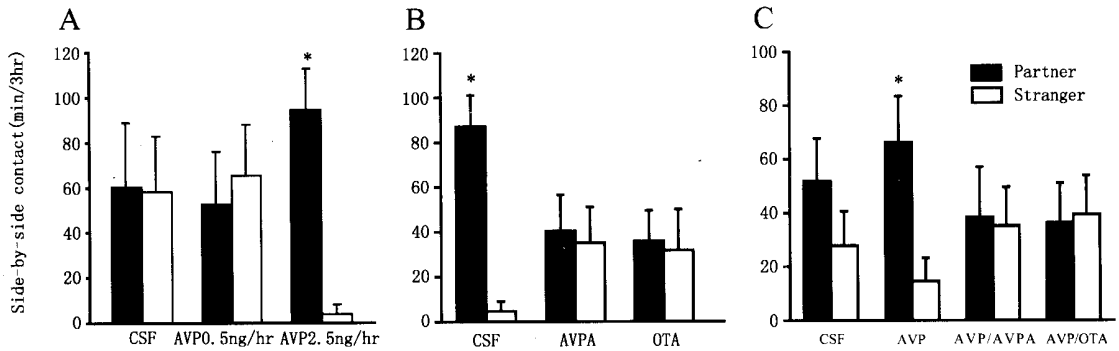

Fig. 3 AVP regulation of pair bonding

(A) Icv infusions of CSF or 0.5ng/hr AVP do not produce partner preferences in female prairie voles. However, administration of a higher dose of AVP (2.5ng/hr) produces partner preferences in females; (B) Control male subjects that were paired with a female for 24 hrs of *ad libitum* mating and that received control injections of artificial cerebrospinal fluid (CSF) into the LS showed partner preferences. However, direct injections of an AVP antagonist (AVPA) or the OT antagonist (OTA) into the LS, prior to mating, blocked partner preferences; (C) Males that cohabited with females for 6 hrs in the absence of mating did not show partner preferences; however, continuous administration of AVP into the LS induced this behavior in the absence of mating. This behavior was blocked by co-administration of either AVPA or OTA

7 DOPAMINE REGULATION OF PAIR BONDING

The formation and maintenance of a pair bond involves, at a minimum, reward processing, learning and memory, changes in motivation and attention, and the expression of appropriate behavior. Given this complexity, it has been suggested that additional neurotransmitters may be important for pair bonding. One neurotransmitter strongly implicated in the above processes is dopamine (DA). Furthermore, because mating facilitates pair bonding, it is notable that DA is released during mating in a variety of species, including prairie voles[66-70]. Therefore, DA has been strongly implicated in the regulation of pair bonding.

Similar to neuropeptide studies of pair bonding, DA involvement has also been studied by pharmacological manipulation of behavior. As DA drugs readily cross the blood brain barrier, the initial studies examining DA regulation of pair bonding used peripheral drug administration. In both males and females, 24 hrs of *ad libitum* mating produced robust partner preferences. However, peripheral injections of a DA antagonist, haloperidol, prior to copulation, prevented mating-induced partner preferences despite the fact that these subjects mated normally[71,72]. Conversely, peripheral injections of a DA agonist, apomorphine, induced partner preferences in the absence of mating[71,72]. These findings demonstrate that DA is important for pair bonding; however, understanding the nature of DA involvement requires identification of the function of specific DA receptors in the regulation of this behavior.

DA receptors fall into one of two distinct classes, referred to as D1-type and D2-type receptors, and the experiments described above used drugs that act on both types of receptors[73]. As these distinct subtypes of receptors serve different functions, it is necessary to identify the specific type of DA receptor mediating pair bonding. Receptor specificity was addressed by administration of drugs that act on the specific DA receptor subtypes. In females, mating-induced partner preferences were prevented by blockade of D2-type receptors using peripheral administration of the D2-type antagonist, eticlopride. However, this behavior was unaffected by peripheral administration of the D1-type antagonist, SCH 23390[71]. Furthermore, partner preferences were induced, in the absence of mating, by activation of D2-type receptors with the D2-type agonist, quinpirole. Administration of the D1-type agonist, SKF 38393, did not produce partner preferences. Therefore DA appears to regulate pair bonding through specific activation of D2-type receptors[71].

Since the above studies utilized peripheral administration of DA drugs, the brain region where DA is influencing pair bonding could not be determined. Mating-induced DA release occurs primarily within NAcc[66,74,75], and this is also true for prairie voles[69,72]. Furthermore, prairie vole NAcc appears similar to that in other rodents with respect to density of DA terminals and receptors (Figure 4A)[72]. Based on these observations, the role of DA processing within NAcc in pair bonding has been carefully examined.

Blockade of DA receptors within NAcc via site specific administration of a DA antagonist (Figure 4B), prevents partner preferences in males (Figure 4C)[72]. Furthermore, studies using female prairie voles confirmed that DA within NAcc acts on D2-type, but not D1-type, receptors in the formation of pair bonds. Site specific administration of the D2-type, but not the D1-type antagonist, directly into NAcc blocked mating-induced partner preferences[69]. Additionally, NAcc injections of the D2-type agonist, but not the D1-type agonist, induced partner preferences in the absence of mating[69]. Similar manipulations in another highly DAergic brain region, the caudate-putamen (CP), did not alter pair bonding, suggesting that the D2-type activation important for pair bonding occurs specifically within NAcc. Additional studies in males have further defined the site-specific regulation of D2-type activation within NAcc. Administration of the D2-type agonist induced partner preferences if injected into the shell subregion of NAcc, but had no effect if delivered into NAcc core[76].

While these experiments show that D2-type receptors within the NAcc are critical for pair bonding, recent studies have demonstrated that DA regulation of this behavior is more complex. Specifically, D1-type activation is not

simply uninvolved, but activation of these receptors actually prevents pair bond formation. The first evidence that D1-type receptor activation may antagonize pair bonding came from studies using the non-selective DA agonist, apomorphine. In males, either peripheral or NAcc administration of apomorphine induced partner preferences only at low doses; higher doses of apomorphine did not produce this behavior (Figure 4D)[72]. While apomorphine binds both D1- and D2-type receptors, it has stronger affinity for D2-type receptors[73]. Therefore, one possibility is that low doses of apomorphine bind primarily D2-type receptors, facilitating partner preferences, but high doses also activate D1-type receptors, which prevents the formation of the bond. This was directly tested in male prairie

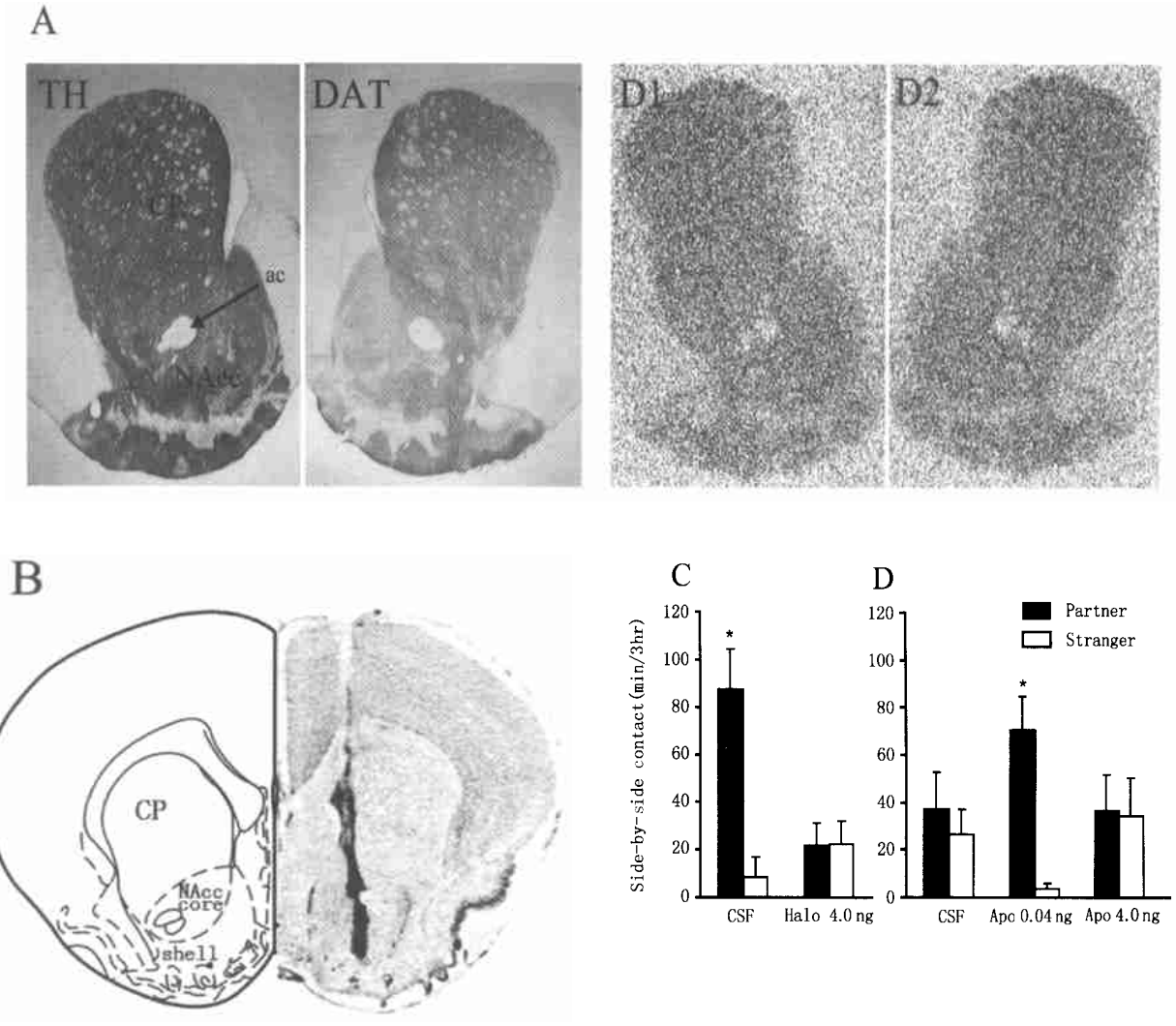

Fig. 4 DA anatomy and DAergic regulation of pair bonding in male prairie voles

(A) Immunocytochemical labeling of tyrosine hydroxylase (TH), the rate limiting enzyme in DA synthesis, reveals that the NAcc and the CP are heavily innervated by DAergic fibers. Similar staining is found for a more specific marker, the DA transporter (DAT), which is responsible for DA reuptake. The final two photos show receptor autogradiographic labeling of D1- and D2-type DA receptors, and demonstrate that these brain regions have high levels of both DA receptor subtypes; (B) Cannula tract and injection site of a typical subject receiving direct pharmacological manipulation of the NAcc. On the left is a schematic drawing, and on the right is stained vole tissue; (C) Control subjects that received CSF injections and mated *ad libitum* for 24 hrs showed partner preferences, whereas subjects that received intra-NAcc administration of the DA receptors antagonist, haloperidol, do not show this behavior; (D) Control subjects paired with a female for only 6 hrs in the absence of mating show non-selective side-by-side contact. However, low, but not high, dose administration of the DA agonist, apomorphine, directly into NAcc induced partner preferences

voles. Intra-NAcc administration of the D2-type agonist, induced partner preferences in the absence of mating[76], as it did in females[69]. However, when the D1- and D2-type receptor agonists were co-administered into NAcc, no partner preference was formed[76]. These data suggest that D1-type receptor activation can prevent pharmacologically induced pair bonding. Even more striking, administration of the D1-type agonist alone prevented partner preference formation induced by 24 hrs of *ad libitum* mating. Together, these findings strongly suggest that D1- and D2-type receptor activation in NAcc exert opposing modulation over pair bond formation[76].

The above studies demonstrate that both DA receptor subtypes are important for the neural regulation of pair bonding. Given that pair bonding is an enduring behavioral change, it was hypothesized that it may be modulated by stable changes in the brain. Based on this idea, a recent study compared DA receptor densities between sexually naive male prairie voles and those that had been paired with a female for two weeks. This two-week cohabitation resulted in pregnancies, and thus it was likely that these animals were pair bonded. Pair bonded males showed a substantial increase in D1-type, but not D2-type, receptor density in the NAcc[76]. This increase was not seen in the CP, which suggests that the change in receptors is not generalized to all DAergic brain regions. Furthermore, an additional group of males that mated *ad libitum* for 24 hrs did not show this increase. This suggests that the increase in D1-type receptors seen in pair bonded males was not due solely to cohabitation or mating. It is therefore possible that this increase in D1-type receptors in the NAcc is fundamental to neural mechanisms associated with pair bonding. Since D1-type receptor activation prevents pair bond formation, this increase may antagonize the formation of new bonds. Such a neural modification could explain why prairie voles rarely form a second bond, and therefore is a potential mechanism for the maintenance of monogamous behavior.

8 NEUROCHEMICAL INTERACTIONS

While it is clear that DA plays a critical role in pair bond formation, DA is also released in NAcc during mating in rodent species that do not form pair bonds[74,75]. Therefore, mating-induced DA release is unlikely to fully account for the neural control of pair bonding. Instead, the NAcc DA system may interact with other neurochemrcial systems that differ between monogamous and non-monogamous voles. As noted above, prairie voles have more OT receptors in NAcc compared with non-monogamous voles, and these receptors are involved in pair bonding[34,36,63]. Therefore, it was hypothesized that DA and OT systems within NAcc interact to regulate pair bonding, and data from a recent study indeed supported this hypothesis. Blockade of OT receptors in NAcc not only prevented partner preferences induced by OT, but also prevented partner preferences induced by administration of the D2-type agonist[63]. Further, blockade of D2-type receptors actually prevented partner preferences induced by OT administration in NAcc, whereas OT induced partner preferences were not prevented by D1-type blockade[63]. This study suggests that activation of both OT and D2-type DA receptors in NAcc are necessary for pair bonding. Given the complex nature of this behavior, it is not surprising that different neurochemical systems interact to achieve its regulation. Indeed, there is also evidence that OT and AVP interact to regulate pair bonding[56,60]. Clearly, future studies of pair bonding should continue to address such interactions.

9 NON-SEXUAL REGULATION OF PAIR BONDING

Although a pair bond is a state that exists between members of a breeder pair, non-sexual experience can also influence this behavior. Female prairie voles show partner preferences and selective aggression in the absence of mating if the period of cohabitation is long enough[35,77]. Such changes in behavior may be associated with the fact that female voles do not have an estrous cycle, and estrous is induced by the extended presence of a novel male[78,79]. Several physiological events are associated with the initial encounter with a male. For instance, male exposure increases estrogen and lutenizing hormone in females[80,81], and these hormonal changes lead to sexual receptivity[82,83]. Furthermore, these changes in repro-

ductive status are mediated by olfactory and pheromonal stimuli[84]. Importantly, olfactory/pheromonal processing is critical for pair bonding as lesions of the olfactory bulb or the vomeronasal organ abolish partner preferences[85,86].

In prairie voles, non-sexual conspecific interactions also alter stress hormones, such as corticosterone (CORT). Prairie voles have an atypical CORT physiology with unusually high levels of serum CORT, and a corresponding decrease in receptor responsiveness[87,88]. Prairie voles also show unique changes in serum CORT in response to various social situations. For example, social isolation increases CORT in prairie vole pups, but not in non-monogamous vole pups[89]. Social isolation also increases CORT in adult female prairie voles, suggesting that isolation is stressful; however, exposure to a novel male decreases CORT levels[90,91]. Therefore, a decrease in CORT was hypothesized to be involved in pair bonding. This hypothesis was supported by an experiment showing that females with reduced CORT, via adrenalectomy, form partner preferences after only 1 hr of cohabitation with a male in the absence of mating. Further, induction of partner preferences was prevented by peripheral injections of CORT, and similar CORT treatment of intact females led to avoidance of the partners[90]. While decreases in CORT lead to partner preference formation in females, peripheral injections of CORT, or a stressor known to increase CORT release (forced swimming), induced partner preferences in males[92]. Central administration of corticotropin-releasing factor also induced partner preferences in the absence of mating in males[93]. Together, these studies show that CORT is critically involved in pair bonding, and its regulation of this behavior appears to be sexually dimorphic: decreased CORT facilitates partner preference formation in females, but CORT promotes pair bonding in males.

10 CONCLUSION AND FUTURE DIRECTION

In summary, pair bonding is an extremely complex behavior, which makes investigation of its neural regulation difficult. This difficulty is largely overcome with utilization of an appropriate animal model, and tremendous insights have been gained from studies of pair bonding in prairie voles. These studies have identified specific neurochemicals, interactions of neurochemical systems, and specific brain regions involved in the regulation of pair bonding. Future research will continue to focus on the neural circuitry involved in pair bonding as well as additional aspects of neural processing of social information. For instance, prairie voles are currently being used to examine intracellular regulation of pair bonding (Aragona and Wang, unpublished observations), individual differences in affiliation[94], and the role in social behavior on newly born neurons in the adult[95].

Apart from the inherent interest of pair bonding as a phenomenon, it must be emphasized that understanding the neurobiology of this behavior is relevant for human health issues. Similar social bonds are formed by humans, and the inability to form such bonds is associated with certain psychological disorders. It is believed that a better understanding of the neural processing of social information will improve treatments for such disorders, and advances toward achieving this goal are being made by investigations of the neural regulation of pair bonding.

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