The neurobiology of social attachment: A comparative approach to behavioral, neuroanatomical, and neurochemical studies[*]

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Abstract

The formation and maintenance of social bonds in adulthood is an essential component of human health. However studies investigating the underlying neurobiology of such behaviors have been scarce. Microtine rodents offer a unique comparative animal model to explore the neural processes responsible for pair bonding and its associated behaviors. Studies using monogamous prairie voles and other related species have recently offered insight into the neuroanatomical, neurobiological, and neurochemical underpinnings of social attachment. In this review, we will discuss the utility of the microtine rodents in comparative studies by exploring their natural history and social behavior in the laboratory. We will then summarize the data implicating vasopressin, oxytocin, and dopamine in the regulation of pair bonding. Finally, we will discuss the ways in which these neurochemical systems may interact to mediate this complex behavior.

Keywords

Dopamine; monogamy; oxytocin; pair bonding; partner preference; selective aggression; vasopressin; voles

1. Introduction

Social behavior involves complex interactions between individuals and is displayed, in varying degrees, throughout the animal kingdom. Mating and aggression, for example, are common to species that display disparate life strategies, while the formation of strong bonds between adults and the bi-parental care of offspring are generally only displayed by species that follow monogamous life strategies, including our own. The formation of strong social bonds is essential for individual well-being, and in humans, is a critical component of mental health. As such, an inability to do so is used as a diagnostic component of various psychological disorders, including autism, social anxiety, and schizophrenia (Volkmar, 2001). Study of the neurobiology underlying social bonding may provide insight into the causes and treatment of such disorders.

Although various animal models have been developed to study social behaviors ubiquitous to mammalian species, including mating, maternal care, and aggression (Seay et al., 1962; Coe et al., 1978; Kendrick et al., 1992; Nelson et al., 2001; Weller et al., 2003; Levy et al., 2004; Moriceau et al., 2005; Hull et al., 2006; Hull et al., 2007; Nelson et al., 2007), the formation of strong bonds between mating pairs (pair bonding), and behaviors associated with these bonds, such as mate guarding (selective aggression) and paternal care, have been understudied, perhaps due to the lack of appropriate animal models. These behaviors are relatively uncommon in the animal kingdom, and in mammals are only displayed by the 3–5% of species that are monogamous (Kleiman, 1977). In recent years, rodents from the genus *Microtus* have been utilized in laboratory studies to explore these less common social behaviors and their underlying neurobiological mechanisms. Studies focusing on the monogamous prairie vole (*Microtus ochrogaster*) and other related vole species have offered insight into the hormonal, neuroanatomical, neurochemical, cellular and molecular regulation of pair bonding, selective aggression and paternal care.

In this review we will first introduce the *Microtus* rodents and discuss their potential use in comparative studies. We will then discuss the social organization of the prairie vole and how this animal model is used for the study of social behavior. Finally, we will discuss the neuroanatomical and neurochemical studies that have elucidated some important central mechanisms underlying pair bonding and its associated behaviors.

2. The *Microtus* rodents for comparative studies

The genus *Microtus* is comprised of a variety of vole species that share a close taxonomic relationship but differ quite markedly in social organization. This phylogenetic similarity, coupled with divergent life strategy, makes these rodents extremely valuable for comparative studies investigating social behavior. For example, prairie and pine voles (*M. pinetorum*) are highly affiliative (Figure 1A), monogamous rodents that form enduring bonds after mating (FitzGerald et al., 1983; Getz et al., 1986; Carter et al., 1993). In both species, pair bonded males and females share a nest and home territory and both the mother and father participate in rearing offspring (Figure 1B) (Wilson, 1982; FitzGerald et al., 1983; McGuire et al., 1984; Gruder-Adams et al., 1985; Getz et al., 1986; Oliveras et al., 1986; Carter et al., 1993). Alternatively, meadow (*M. pennsylvanicus*) and montane (*M. montanus*) voles are less social (Figure 1A), promiscuous rodents that do not form pair bonds or share a nest after mating (Getz, 1972; Madison, 1978; Jannett, 1980; Madison, 1980; Jannett, 1982; Insel et al., 1995b; Young et al., 1998). In these species, as is common for other promiscuous mammals, only the mother participates in parental care (Figure 1B) (Wilson, 1982; McGuire et al., 1984; Gruder-Adams et al., 1985; Oliveras et al., 1986). It is interesting to note that these vole species, despite their different life strategies and social behavior, display similar non-social behaviors. For example, they show similar patterns of ultradian rhythmic activity, locomotor-exploratory behavior, digging, and nest building (Tamarin, 1985). Therefore, their differences in social behavior are related to their species specific life strategies.

In addition to social behavior, vole species have also provided a comparative model for the study of other developmental and physiological processes. For example, monogamous and promiscuous voles have been found to differ in the rate of brain development (Gutierrez et al., 1989), the pattern of sexual dimorphism in particular brain areas (Shapiro et al., 1991), regional expression of neurotransmitters during development and in adulthood (Wang et al., 1996b; Wang et al., 1997b; Wang et al., 1997c; Wang et al., 1997d; Liu et al., 2001b), spatial ability (Jacobs et al., 1990), social stress response and anxiety-related behavior (Shapiro et al., 1990; Stowe et al., 2005). Together, these data demonstrate the great utility of microtine rodents for comparative studies.

3. The prairie vole and social attachment

The prairie vole is a mictrotine species, found in the grasslands of the central United States (Tamarin, 1985), that is commonly used to study social attachment. Field studies have shown that prairie voles are monogamous as males and females form long-term pair bonds after mating, share a nest and home range throughout the breeding season, and tend to travel together (Getz et al., 1981; Tamarin, 1985; Getz et al., 1986). Once bonded, an adult male and female prairie vole will usually remain together until one partner dies, and even then, will rarely form a new pair bond (Getz et al., 1996; Pizzuto et al., 1998).

It has become possible to study the social behavior of prairie voles in the laboratory as these animals adapt readily, breed well, and continue to display a monogamous life strategy in captivity (Dewsbury, 1987). One behavioral characteristic of monogamy, the bi-parental care of offspring, has been well studied in this species. Both mother and father prairie voles participate in rearing their offspring, and fathers contribute both directly and indirectly to the survival of their pups by displaying all aspects of parental behavior except nursing (see reviews Dewsbury, 1985; Wang et al., 1996a). For example, male prairie voles gather and prepare materials for nest building, participate in runway construction and food hoarding, and directly brood, groom, and retrieve pups (Thomas et al., 1979; Dewsbury, 1985; Gruder-Adams et al., 1985; Oliveras et al., 1986).

The formation of adult attachments between male and female prairie voles has also been studied in a controlled environment. A reliable behavioral index of pair bond formation in the laboratory is the development of a preference for a familiar mate (partner preference) (Williams et al., 1992b; Winslow et al., 1993; Insel et al., 1995a). This preferential affiliation can be quantified using a partner preference test, first developed in the laboratory of Dr. Sue Carter (Williams et al., 1992b). In general, the three-chamber testing apparatus consists of a central cage connected by hollow tubes to two identical cages, each containing a stimulus animal. Each stimulus animal, one of which is the familiar partner and the other a conspecific stranger, is tethered into its respective cage and cannot interact with the other. The subject is then placed into the central cage and allowed to run freely throughout the apparatus for the duration of the three hour videotaped test. In some variations of this apparatus, including that of our own laboratory, photobeam light sensors across the connecting tubes monitor the amount of time the subject spends in each cage and frequency of cage entries. A partner preference is inferred when the subject spends significantly more time in side-by-side contact with its familiar partner than with the conspecific stranger. Partner preference formation is reliably seen in both male and female prairie voles in the laboratory after 24 hours of mating and cohabitation (Figure 1C) (Williams et al., 1992b; Winslow et al., 1993; Insel et al., 1995b). It should be noted that while mating is generally considered necessary for the development of partner preferences in prairie voles (Winslow et al., 1993; Insel et al., 1995b), one study demonstrated that ovariectomized female prairie voles were capable of forming partner preferences during an extended cohabitation with a male in the absence of mating (Williams et al., 1992b). Partner preferences, once formed, have been shown to endure for at least two weeks even in the absence of continuing exposure to the partner (Insel et al., 1995a).

Coincident with partner preference formation, aggressive behavior also develops in male prairie voles following 24 hours of mating (Winslow et al., 1993; Insel et al., 1995b; Wang et al., 1997a). While sexually naive adult males usually explore, but show little attack behavior toward an unfamiliar animal, a sexually experienced male will aggressively attack a conspecific stranger (Winslow et al., 1993; Insel et al., 1995b; Wang et al., 1997a; Aragona et al., 2006), including a sexually receptive female (Figure 1D) (Gobrogge et al., 2007). This aggression is selective, as the males remain affiliative toward their familiar mate (Winslow et al., 1993; Gobrogge et al., 2007), and is thought to function in mate guarding and in the maintenance of

the already established pair bond as it prevents the formation of future bonds with other conspecifics. Selective aggression, like pair bonding, is an enduring behavior that lasts at least two weeks following partner preference formation (Winslow et al., 1993; Aragona et al., 2006; Gobrogge et al., 2007). In the laboratory, this behavior is studied using a resident intruder test. Generally, subjects are allowed to mate and cohabitate with a female in the subject's home cage for a period of time. Then, during the resident intruder test, the familiar partner is removed and replaced by a conspecific intruder and the behavioral response of the subject toward the intruder is videotaped and quantified. Various types of behavior can be quantified, including attack bites, lateral displays, lunge threats, chasing, defensive posturing, and affiliation (Winslow et al., 1993; Aragona et al., 2006; Gobrogge et al., 2007). Studies of selective aggression have focused on male prairie voles (Winslow et al., 1993; Insel et al., 1995b; Wang et al., 1997a), however females of this species also display some mating-induced aggression (Getz et al., 1980; Getz et al., 1981).

It has been demonstrated that 24 hours of mating and cohabitation between an adult male and female prairie vole reliably results in the formation of a partner preference, as indicated by the subject's preferential affiliation with its familiar partner versus a conspecific stranger (Williams et al., 1992b; Insel et al., 1995a; Insel et al., 1995b; Aragona et al., 2003). In contrast, 1–6 hours of cohabitation without mating is insufficient to produce a partner preference in this species (Williams et al., 1992b; Insel et al., 1995a; Insel et al., 1995b; Cho et al., 1999). This paradigm has become useful in pharmacological studies investigating the neurochemical regulation of pair bonding. For example, if the blockade of a neurochemical receptor results in the inability of animals to form a partner preference following 24 hours of mating, it can be inferred that access to this receptor is necessary for pair bond formation. Alternatively, if pharmacological activation of a neurochemical receptor during the 1–6 hour social cohabitation induces partner preferences, it can be inferred that activation of this receptor is sufficient to induce pair bonding. Using this paradigm, several neurochemicals have been implicated in prairie vole social bonding including oxytocin (OT), arginine vasopressin (AVP), dopamine (DA), corticotrophin releasing factor (CRF), gamma-aminobutyric acid (GABA) and glutamate (Williams et al., 1992a; Winslow et al., 1993; Williams et al., 1994; Carter et al., 1995; Wang et al., 1998; Wang et al., 1999; Gingrich et al., 2000; Liu et al., 2001a; Aragona et al., 2003; Liu et al., 2003; Lim et al., 2004c; Curtis et al., 2005b; Aragona et al., 2006). In this review, we will focus on the involvement and interactions of the neuropeptides AVP and OT and the neurotransmitter DA in the regulation of pair bonding behavior in monogamous prairie voles.

4. Neuropeptidergic regulation of social attachment

Early studies investigating the neurobiology of prairie vole social attachment focused on the two neuropeptides AVP and OT because of their known role in key processes associated with social bonding. For example, AVP and OT had long been implicated in learning and memory (de Wied et al., 1974; Hamburger-Bar et al., 1985; Hamburger-Bar et al., 1987; Engelmann et al., 1996), two factors essential for individual recognition and ultimately pair bonding between adult prairie voles (Carter et al., 1995). Additionally, both peptides had been implicated in sexual behavior (Argiolas et al., 1988; Argiolas et al., 1989; Carter et al., 1995) and mating is important for the formation of a pair bond. Finally, OT and AVP were known to be important for the bond between mother and offspring. Indeed, central administration of OT has been found to enhance maternal behavior in sheep (Kendrick et al., 1987) and rats (Pederson et al., 1979).

Comparative studies between monogamous and promiscuous vole species have revealed the distribution patterns of central AVP and OT systems in the vole brain. Using immunocytochemistry and *in situ* hybridization, AVP positive cells have been found in several

brain regions including the hypothalamic nuclei, the bed nucleus of the stria terminalis (BNST), and the medial nucleus of the amygdala (MeA) (Bamshad et al., 1993; Wang, 1995; Wang et al., 1996b). Dense AVP-immunoreactive (AVP-ir) fibers are present in the lateral septum (LS), lateral habenular nucleus, diagonal band, BNST, medial preoptic area (MPOA), and MeA (Wang et al., 1996b). OT positive cells are found in several brain areas including the hypothalamic nuclei, MPOA, BNST, and the lateral hypothalamic area (LH) (Wang et al., 1996b). Although some subtle species differences are present (Wang, 1995; Wang et al., 1996b), in general, the distribution patterns of AVP and OT positive cells and their projections seem to be highly conserved between vole species despite their disparate life strategies. This is further supported by the fact that these neuropeptide pathways share some characteristics with those found in other species of rodents that follow non-monogamous life strategies. For example, the AVP pathway in voles, as in rats (De Vries et al., 1990; Szot et al., 1993), shows an impressive degree of sexual dimorphism in the BNST and LS. Specifically, males have more AVP positive cells and a higher density of AVP-ir projections in these regions than females (Bamshad et al., 1993; Wang, 1995; Wang et al., 1996b), and this AVP expression in males is regulated by circulating testosterone (Wang et al., 1993).

Studies using receptor autoradiography and *in situ* hybridization have shown striking species differences in AVP and OT receptor distribution patterns and regional density in voles that follow different life strategies (Insel et al., 1992a; Insel et al., 1994; Young et al., 1996; Young et al., 1997b; Lim et al., 2004a; Smeltzer et al., 2006). For example, prairie voles have denser AVP V1a receptor (V1aR) labeling or mRNA expression than montane voles in several brain areas, including the accessory olfactory bulb, diagonal band, laterodorsal and paraventricular thalamus, and the BNST (Insel et al., 1994; Young et al., 1997b). On the other hand, montane voles have higher densities of the V1aR than prairie voles in other brain areas including the medial prefrontal cortex (mPFC) and LS (Figures 2A and B) (Insel et al., 1994; Smeltzer et al., 2006). It is interesting to note that monogamous prairie and pine voles show a similar pattern of V1aR labeling in the brain while promiscuous montane and meadow voles show another pattern, suggesting that such differences in V1aR distribution are not necessarily species specific, but instead related to social organization (Insel et al., 1994; Wang et al., 1997d; Young, 1999). Indeed, dense labeling of the V1aR was found in the ventral pallidum (VP) of monogamous prairie and pine voles (Insel et al., 1994; Lim et al., 2004a) while promiscuous meadow and montane voles show little V1aR binding in this region (Figures 2A and B) (Insel et al., 1994), indicating a relationship between the amount of V1aRs in the VP and the display of a monogamous life strategy.

Similarly, differences are also found in the distribution pattern and regional density of OT receptor (OTR) labeling and mRNA expression in vole species with different life strategies and social behavior. Monogamous voles have high densities of the OTR in the NAcc, PFC, and BNST, brain regions that show little binding in promiscuous voles (Figures 2C and D), while promiscuous species instead have a greater OTR density in the LS, ventromedial nucleus of the hypothalamus, and cortical nucleus of the amygdala (Insel et al., 1992b; Young et al., 1996; Smeltzer et al., 2006). It should be noted that these differences in V1aR and OTR distributions in the vole brain are present not only in adulthood but also during early postnatal development (Wang et al., 1997c; Wang et al., 1997d). In addition, these differences are specific to AVP and OT systems as no species differences are found for benzodiazepene or opiate receptor labeling (Insel et al., 1992a). Together, these data provide evidence to support the hypothesis that differences in the amount of receptor expression in particular brain areas determine behavioral traits (Hammock et al., 2002). In voles, these differential patterns of V1aRs and/or OTRs result in altered brain responsiveness to released neuropeptides, and may be accountable for species differences in social behavior.

Mating and social cohabitation, which induce pair bond formation, have been found to alter central AVP and/or OT activity. In male prairie voles, for example, three days of social experience and mating with a female induced an increase in the number of AVP mRNA labeled cells in the BNST (Wang et al., 1994) and a decrease in the density of AVP-ir fibers in the LS (Bamshad et al., 1994). As AVP cells in the BNST project to the LS (De Vries et al., 1983), these data suggest an enhanced AVP synthesis in the BNST associated with an increased AVP release in the LS induced by experience with a female (Wang et al., 1998). Given the sexually dimorphic nature of this AVP pathway (Bamshad et al., 1993; Wang, 1995; Wang et al., 1996b) and lack of similar changes in AVP activity in female voles (Wang et al., 1994), these data provide correlational evidence of the potential involvement of central AVP in physiological and behavioral processes associated with mating and pair bond formation in male prairie voles (Bamshad et al., 1994; Wang et al., 1994; Wang et al., 1998). In female prairie voles, exposure to male chemosensory cues induced an increase in OTR binding in the anterior olfactory nucleus (Witt et al., 1991), indicating that social behavior can also affect OTRs.

Direct evidence of AVP and OT regulation of pair bonding behavior has come from neuropharmacological studies. In male prairie voles, intracerebroventricular (icv) administration of a V1aR antagonist prevented partner preference formation following 24 hours of mating whereas administration of AVP induced partner preferences without mating, implicating central AVP in pair bonding (Figure 2E) (Winslow et al., 1993; Cho et al., 1999). This notion was further supported by data showing that icv administration of AVP facilitated, while administration of a V1aR antagonist inhibited, selective aggression in male prairie voles (Winslow et al., 1993). Further, site specific manipulation of AVP in the LS or VP, by administration of AVP or a V1aR antagonist, influenced partner preference formation, indicating the role of these brain regions in an AVP circuit important for pair bonding (Liu et al., 2001a; Lim et al., 2004c). It should be noted that central manipulations of AVP do not have similar effects on the behavior of promiscuous voles (Young et al., 1997b; Young, 1999). In female prairie voles, OT infusion into the lateral ventricle induced partner preference formation whereas infusions of an OTR antagonist blocked this behavior following mating or OT infusion (Figure 2F), indicating the necessity of central OT in pair bonding (Williams et al., 1994; Insel et al., 1995a; Cho et al., 1999). The NAcc has also been shown to be important for OT regulation of pair bonding as OT manipulation in the NAcc altered partner preference formation in female prairie voles (Liu et al., 2003).

In early studies, the effects of AVP on pair bonding were examined almost exclusively in males while those of OT were examined primarily in females. This pairing of sex with peptide was probably chosen because of the known sexual dimorphism and testosterone sensitivity of the BNST-LS AVP pathway and involvement of OT in mother-infant bonding (Pederson et al., 1979; De Vries et al., 1983; Kendrick et al., 1987; De Vries et al., 1990; Kendrick et al., 1992). Thus, AVP and OT were thought to have gender specific effects; AVP regulating pair bonding in male prairie voles and OT regulating the same behavior in female prairie voles (Winslow et al., 1993; Williams et al., 1994; Insel et al., 1995a). However, through careful pharmacological manipulation it later became evident that AVP and OT were each important for pair bonding in both sexes. For example, icv administration of either AVP or OT into male or female prairie voles induced partner preferences after only one hour of cohabitation, although the effective doses of each neuropeptide differed between sexes (Cho et al., 1999). Furthermore, administration of an OTR antagonist into the LS was effective to block partner preference formation in male prairie voles (Liu et al., 2001a). Therefore, although AVP and OT may still have gender specific roles in pair bonding (e.g., males and females are more sensitive to AVP and OT, respectively), it is likely that both neuropeptides are involved in the regulation of pair bonding in both male and female voles. Finally, it is important to note that in the abovementioned pharmacological studies, administration of AVP, OT, or their receptor

agonists/antagonists, did not generally alter subject's mating, social interactions, or locomotor activity, indicating that the effects of AVP and OT were specific for pair bonding behavior.

A comparative approach has also been used to examine the molecular basis of social behavior and life strategy. Studies focusing on the gene structures of the V1aR and OTR in microtine rodent species have found that receptor coding regions are highly conserved between monogamous and promiscuous voles (Young et al., 1996; Young et al., 1997a; Young et al., 1999). However, analysis of the 5' flanking region of the V1aR and OTR gene revealed some species differences in potential regulatory elements (Young et al., 1996; Young et al., 1997a; Young et al., 1999). Specifically, monogamous prairie and pine voles have a sequence of repetitive microsatellite DNA in the promoter region of the V1aR gene that is not present in promiscuous meadow and montane voles (Young et al., 1999; Hammock et al., 2002; Hammock et al., 2004).

It has been hypothesized that species differences in the structure of the V1aR promoter region are responsible for species specific gene expression and related social behavior (Hammock et al., 2004). This idea is supported by data from several transgenic studies (Pitkow et al., 2001; Landgraf et al., 2003; Lim et al., 2004b). For example, transgenic mice that received the prairie vole V1aR gene had a distribution pattern of V1aRs in the brain similar to that of prairie voles but different from that of nontransgenic mice. Further, these V1aR transgenic mice responded to AVP injection with an increase in affiliative behavior in comparison to their wild-type littermates (Young et al., 1999). Additionally, increased V1aR expression, by viral vector gene transfer, in the VP of male prairie voles enhanced affiliative behavior and facilitated partner preference formation (Pitkow et al., 2001). In a more recent study, a viral vector was used to transfer the prairie vole V1aR to the VP of male meadow voles (Lim et al., 2004b). Interestingly these transgenic meadow voles not only showed prairie vole-like V1aR densities in the VP (Figures 3A–C), but also displayed enhanced partner preference formation (Figure 3D), a trait characteristic of a monogamous life strategy (Lim et al., 2004b). It is important to note, however, that variation in the V1aR gene alone is not sufficient to determine social organization. In fact, a recent study found that various rodent species, including other nonmonogamous vole species, also feature V1aR promoter regions with repetitive microsatellite sequences similar to that of monogamous prairie and pine voles (Fink et al., 2006). This recent finding highlights the complexity of pair bonding and the likelihood that multiple neurochemical systems contribute to this behavior. Indeed, the transgenic meadow voles described above did not form partner preferences in the presence of a dopamine receptor antagonist (Lim et al., 2004b), further indicating that the behavioral effects of V1aR gene transfer may rely on the interaction of this gene with other neurochemical systems, such as the mesolimbic dopamine system.

5. Dopaminergic regulation of social attachment indeed

Central dopamine (DA) plays an important role in most, if not all, of the key cognitive and behavioral processes associated with pair bonding including olfaction, sexual behavior, learning, memory, and conditioning (Mitchell et al., 1992; Cheng et al., 2003; Hull et al., 2004; Hull et al., 2006; Lemon et al., 2006; Tillerson et al., 2006; El-Ghundi et al., 2007). DA, particularly in mesolimbic brain regions, has also been implicated in the mediation of a variety of natural rewards (Wise et al., 1989; Bozarth, 1991) including mating (Everitt, 1990) which facilitates pair bonding (Carter et al., 1990; Williams et al., 1992b; Insel et al., 1995b; Curtis et al., 2003a; Wang et al., 2004). For these reasons, DA was hypothesized to play a role in pair bonding and the DAergic regulation of social attachment has since become an important focus of the field.

The distribution of DA cells and projections in the prairie vole brain has been mapped by various immunocytochemical studies. A cell can be determined to be DAergic if it labels for tyrosine hydroxylase (TH), the rate limiting enzyme in catecholamine synthesis, in the absence of labeling for dopamine beta hydroxylase (DBH), the enzyme that converts DA to norepinephrine. Using this method, studies have shown that DAergic cells are present in several brain regions relevant to pair bonding including the BNST, MPOA, ventral tegmental area (VTA), MeA, and LH (Aragona, 2004; Gobrogge et al., 2007; Northcutt et al., 2007). Additionally, the NAcc, caudate putamen (CP) and olfactory tubercle show intense staining for both TH and the dopamine transporter (DAT), indicating the presence of dense DA terminals in these regions (Aragona et al., 2003).

Comparative studies have shown that although presynaptic DA distribution patterns are generally similar between monogamous and promiscuous voles (Liu et al., in prep), some species differences in cell density exist. For example, prairie voles were found to have qualitatively denser labeling of TH-immunoreactive (TH-ir) cells in the BNST and the MeA than meadow voles (Northcutt et al., 2007). These same cells did not express DBH labeling indicating that they were DAergic. As the BNST and MeA function in processing chemosensory cues and in mediating behaviors associated with pair bonding in prairie voles (Kirkpatrick et al., 1994; Wang et al., 1994; Wang, 1995; Curtis et al., 2003b), these data indicate important species specific differences in DAergic brain regions associated with social organization.

Additionally, differences have been found in DA receptor density between meadow and prairie voles. DA receptors can be categorized into two main families, D1-like receptors (D1Rs) and D2-like receptors (D2Rs). In both meadow and prairie voles, D1Rs and D2Rs are present in the NAcc, CP, mPFC and amygdala and D2Rs are also present in the substantia nigra and VTA (Aragona et al., 2003; Liu et al., in prep). While this pattern of receptor distribution is similar between meadow and prairie voles, species differences in receptor density exist. Male meadow voles have significantly more D1R binding within the NAcc and mPFC than do male prairie voles, while prairie voles have more D2R binding in the mPFC (Aragona et al., 2006; Smeltzer et al., 2006). These differences in density of specific DA receptor subtypes could have profound effects on brain responsiveness to released DA and corresponding effects on behavior. Indeed, the high level of D1Rs in the NAcc of male meadow voles has been found to be responsible for their decreased social behavior relative to prairie voles (see below) (Aragona et al., 2003; Aragona et al., 2006).

Mating facilitates pair bonding (Carter et al., 1990; Williams et al., 1992b; Insel et al., 1995b; Wang et al., 2004) and increases DA activity in the NAcc of both male and female prairie voles (Gingrich et al., 2000; Aragona et al., 2003; Curtis et al., 2003a). It has therefore been suggested that DA plays an important role in pair bonding behavior. Pharmacological manipulations in the prairie vole have provided direct evidence to support this hypothesis. For example, peripheral injection of a nonspecific DA receptor agonist induced partner preference formation in the absence of mating, while injection of a nonspecific DA receptor antagonist blocked mating-induced partner preferences (Figure 4A) (Wang et al., 1999; Aragona et al., 2003). These findings indicate that DA is necessary for partner preference formation (Wang et al., 1999; Aragona et al., 2003). Studies in both male and female prairie voles indicate that the DA regulation of pair bonding is both receptor- and site specific. For example, activation of D2Rs, but not D1Rs, in the NAcc, but not CP, facilitated partner preference formation in female and male prairie voles, whereas blockade of D2Rs in the NAcc inhibited the formation of partner preferences (Figure 4B) (Gingrich et al., 2000; Aragona et al., 2003; Aragona et al., 2006). Additionally, administration of a D1R agonist into the NAcc blocked partner preference formation induced either by mating (Figure 4C) or by D2R activation (Aragona et al., 2006). These data suggest an opposing effect of NAcc DA receptors on pair bonding such that D2R

activation facilitates and D1R activation inhibits partner preference formation. Further, the DA regulation of pair bonding is sub-region specific within the NAcc, as activation of D2Rs in the NAcc shell, but not the core, induces partner preference formation (Aragona et al., 2006). Interestingly, this receptor- and region specific DA regulation has also been known to mediate other behaviors, such as copulation and drug-seeking behavior (Hull et al., 1992; Self et al., 1996; Graham et al., 2007).

The receptor specific DA regulation of pair bonding is further supported by recent data from a pharmacological study involving manipulations of a DA receptor signaling pathway. D1Rs and D2Rs are G-protein coupled receptors that oppositely modulate cyclic adenosine 3', 5'-monophosphate (cAMP) intracellular signaling through their alpha G-protein subunits (Missale et al., 1998; Neve et al., 2004). D1Rs are coupled to G-proteins with stimulatory alpha subunits that increase adenylate cyclase (AC) activity when activated, yielding an increase in cAMP formation, cAMP-dependant protein kinase (PKA) phosphorylation and subsequent cell activation. Alternatively, D2Rs are coupled to G-proteins with inhibitory alpha subunits. When activated by D2Rs, these subunits decrease AC activity, cAMP levels, PKA activation, and ultimately post-synaptic cell activity. In a recent study, activation of stimulatory G-proteins or PKA activity in the NAcc shell prevented partner preference formation (Aragona et al., 2007), the same behavioral result observed when D1Rs themselves were activated (Aragona et al., 2006). In contrast, decreasing cAMP signaling in the NAcc shell, thereby mimicking the molecular effects of D2R activation, induced partner preference formation (Aragona et al., 2007). These data have provided the first intracellular evidence that D1Rs and D2Rs oppositely regulate pair bonding.

Finally, DA is not only critical for partner preference formation, but also plays a role in pair bond maintenance (Aragona et al., 2006; Gobrogge et al., 2007). As discussed earlier, pair bonded prairie voles aggressively attack unfamiliar intruders and reject potential mates even when their partner is removed (Winslow et al., 1993; Pizzuto et al., 1998; Aragona et al., 2006; Gobrogge et al., 2007). This selective aggression prevents the formation of a second pair bond, thereby maintaining the initial one. It is known that AVP is important for this behavior (Winslow et al., 1993). However, recent evidence has also implicated the involvement of DA (Aragona et al., 2006; Gobrogge et al., 2007). Specifically, pair bonded male prairie voles show substantially more D1R binding in the NAcc than sexually naive prairie voles (Figures 4D and E). This accumbal reorganization is not due to female exposure or mating, but instead is specific to pair bonding (Aragona et al., 2006). D1Rs in the NAcc have been found to mediate selective aggression in pair bonded animals as intra-NAcc blockade of D1Rs, but not D2Rs, abolishes the behavior (Figure 4F) (Aragona et al., 2006). Therefore, an increase in the number of NAcc D1Rs in pair bonded animals may be directly responsible for pair bond maintenance. Comparative studies have supported this hypothesis as, in comparison to prairie voles, promiscuous male meadow voles have a higher basal level of D1Rs in the NAcc, and blockade of these receptors results in increased affiliative behavior (Aragona et al., 2006).

6. Neurochemical interactions in the regulation of pair bonding

Complex social behaviors, such as pair bonding, require many aspects of physiological, cognitive, and behavioral functions. Therefore, it is not surprising that multiple neurotransmitter systems are involved in the regulation of social behavior. The data presented above have implicated three separate neurochemical systems, AVP, OT and DA, in pair bonding. Not surprisingly, these systems interact in the regulation of pair bonding. Furthermore, other neurochemicals including corticotropin release factor, GABA and glutamate are also involved in the regulation of pair bonding.

One of the first neurochemical interactions noted in the regulation of pair bonding involved AVP and OT. While central administration of either AVP or OT facilitated partner preference formation, blockade of either neuropeptide receptor was effective to inhibit partner preferences induced by either AVP or OT (Cho et al., 1999). These data suggest that AVP and OT can interact to mediate pair bonding. AVP and OT cells and their receptors overlap in many vole brain regions including the LS (Insel et al., 1992a; Insel et al., 1994; Wang et al., 1996b). In fact, site specific administration of AVP directly into the LS induced partner preferences, and this behavior was inhibited by concurrent administration of AVP with a V1aR antagonist or OTR antagonist (Liu et al., 2001a). This finding suggests that access to both AVP and OT receptors in the LS is important for pair bonding and that these two neuropeptides may cooperate in the mediation of this social behavior.

AVP and OT have also been found to interact with DA in the regulation of pair bonding. Intra-NAcc administration of an OTR antagonist in female prairie voles blocked partner preferences induced by D2R activation (Liu et al., 2003). In the same study, blockade of D2Rs in the NAcc prevented partner preferences induced by OT administration (Liu et al., 2003). These data indicate that concurrent activation of OT and D2Rs in this region is necessary for pair bonding. In support of this hypothesis, it was found that intra-NAcc administration of a D1R antagonist did not block OT induced partner preferences (Liu et al., 2003), a result consistent with the mediation of partner preference formation by D2R, but not D1R activation in the NAcc (Aragona et al., 2003; Aragona et al., 2006). Studies have also shown that AVP and DA interact to mediate pair bonding. Male meadow voles that received viral vector transfer of the prairie vole V1aR gene into the VP showed an increased region specific V1aR expression accompanied by mating induced partner preference formation (which would not naturally occur in meadow voles) (Lim et al., 2004b). Interestingly, administration of a D2R antagonist abolished this partner preference formation, indicating that DA and AVP interact to mediate pair bonding behavior (Lim et al., 2004b). The idea that DA and AVP interact in the VP is consistent with the current literature. Indeed, this region is enriched with V1aRs (Insel et al., 1994), implicated in the AVP mediation of partner preferences (Pitkow et al., 2001; Lim et al., 2004b), and receives the majority of accumbal output (Heimer et al., 1991).

Finally, the NAcc receives DAergic projections from the VTA (Swanson, 1982). Glutamate and GABA in the VTA, therefore, can alter the activity of DAergic cells and thus influence DA release in the NAcc (Xi et al., 1998; Takahata et al., 2000). Interestingly, blockade of either AMPA-type glutamate receptors or GABAA receptors in the VTA induces partner preference formation without mating in male prairie voles (Curtis et al., 2005a), suggesting an interaction between GABA, glutamate, and DA in the regulation of pair bonding behavior. Further studies are needed to determine the specific nature of these interactions.

7. Conclusion

In summary, comparative studies using microtine rodents offer a unique opportunity to explore the neurobiology of complex social behaviors. The prairie vole model, in particular, has been extremely useful in the study of adult social attachments. Information acquired from these studies has the potential to greatly enhance our understanding of the mechanisms underlying human disorders that have previously been difficult to study due to a lack of appropriate animal models such as autism, social anxiety and schizophrenia. Indeed, the inability to form social bonds is a major diagnostic component of these disorders (Volkmar, 2001). Furthermore, recent data from our laboratory has shown that social bonding and drug reward in the prairie vole may interact, indicating an innovative use for the prairie vole model in the study of drug addiction. It is hoped that continued research using microtine rodents will further enhance our understanding of normal and abnormal behaviors in humans.

Acknowledgements

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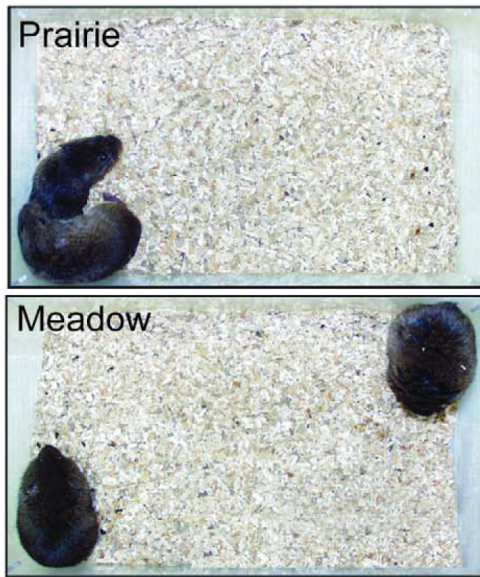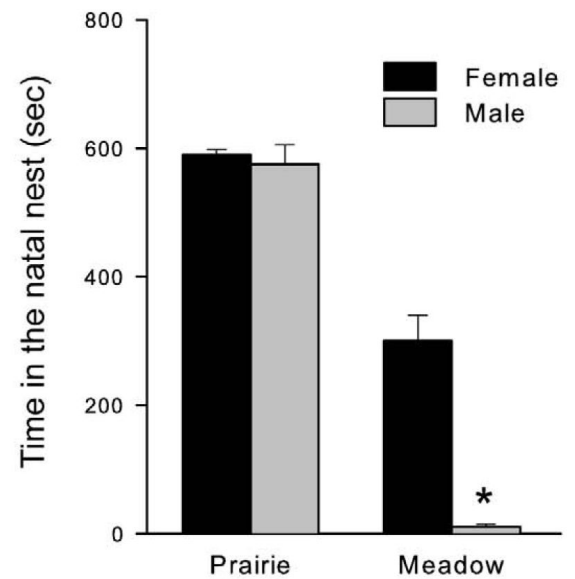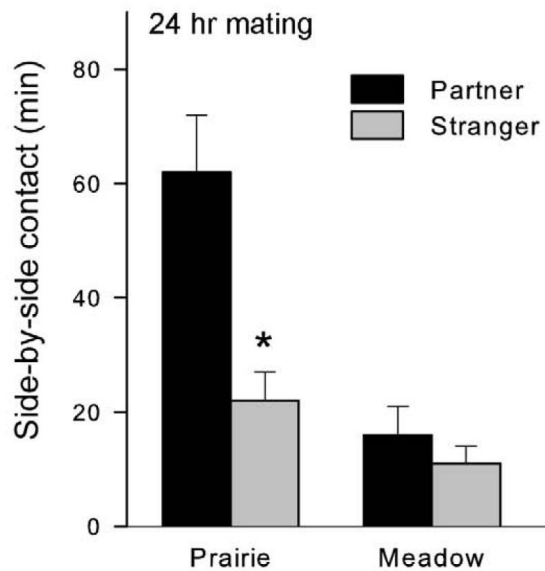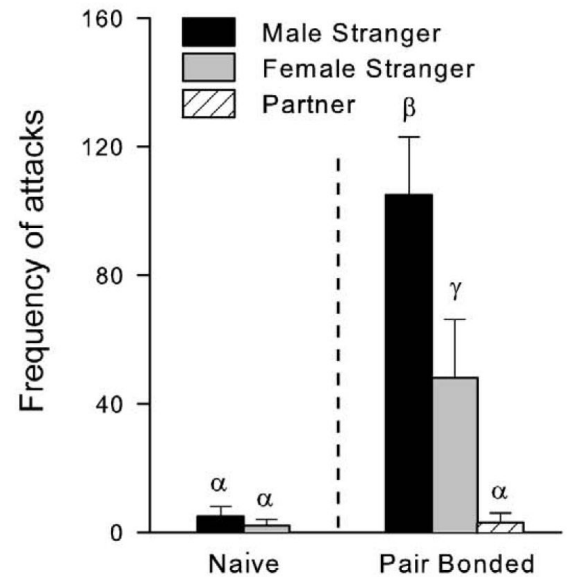
Figure 1. Comparison of prairie and meadow vole social behavior
(A) Photos showing species differences in affiliative behavior of conspecific sexually naive prairie (top) and meadow (bottom) voles. (B) Prairie voles show bi-parental care of offspring whereas meadow voles show maternal care. (C) After 24 hours of mating, prairie, but not meadow, voles develop a partner preference and spend significantly more time in side-by-side contact with their partner than a conspecific stranger during a three hour choice test. (D) Sexually naive male prairie voles (Naive) show little aggression, whereas pair bonded males display intense aggression toward conspecific male and female strangers, but not toward their partner (selective aggression). (Adapted from McGuire et al., 1984; McGuire et al., 1986;

Winslow et al., 1993; Aragona et al., 2003; Lim et al., 2004b; Aragona et al., 2006; Gobrogge et al., 2007).
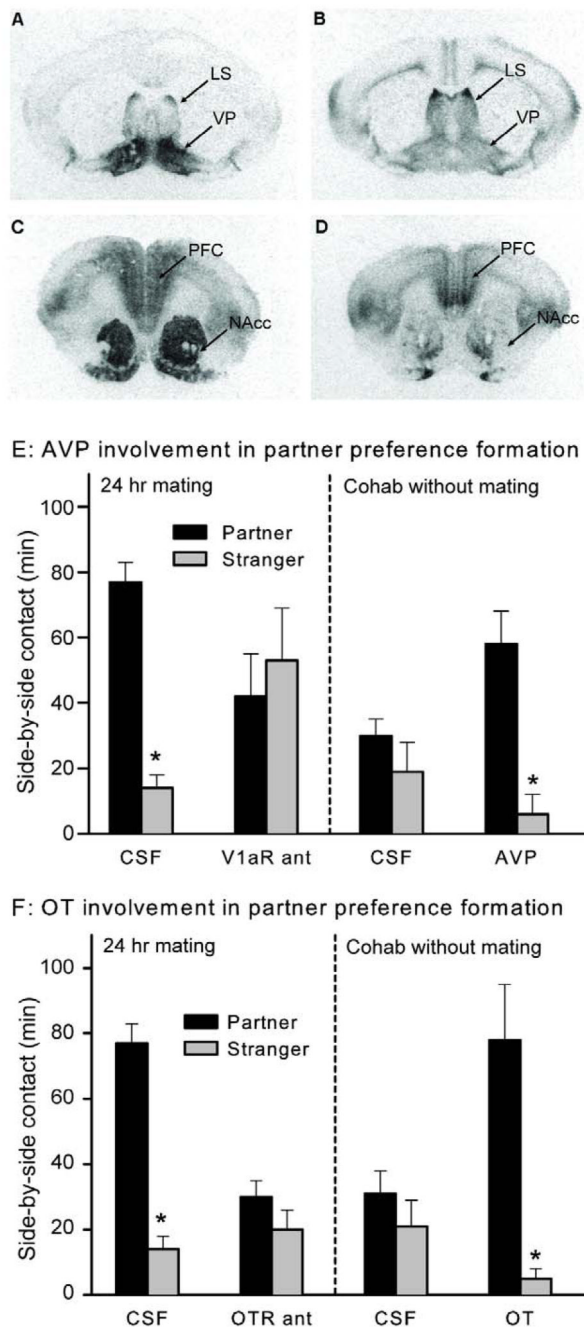
Figure 2. AVP and OT involvement in pair bonding in prairie voles
(A) Photomicrographs showing that monogamous prairie voles have higher V1aR labeling densities in the ventral palladium (VP) and lower densities in the lateral septum (LS) than (B) promiscuous montane voles. (C) Prairie voles have higher densities of OTR labeling in the nucleus accumbens (NAcc) and prefrontal cortex (PFC) than (D) montane voles. (E) Mating induced partner preferences in male prairie voles that received injections of cerebrospinal fluid (CSF) into the lateral ventricle but not in males that received injections of a V1aR antagonist (V1aR ant). Infusion of AVP into the lateral ventricle induced partner preferences without mating. (F) Similarly, central administration of an OTR antagonist (OTR ant) blocked mating induced partner preferences in female prairie voles, whereas OT infusion into the lateral

ventricle induced partner preferences without mating. (Adapted from Winslow et al., 1993; Insel et al., 1995a; Cho et al., 1999).
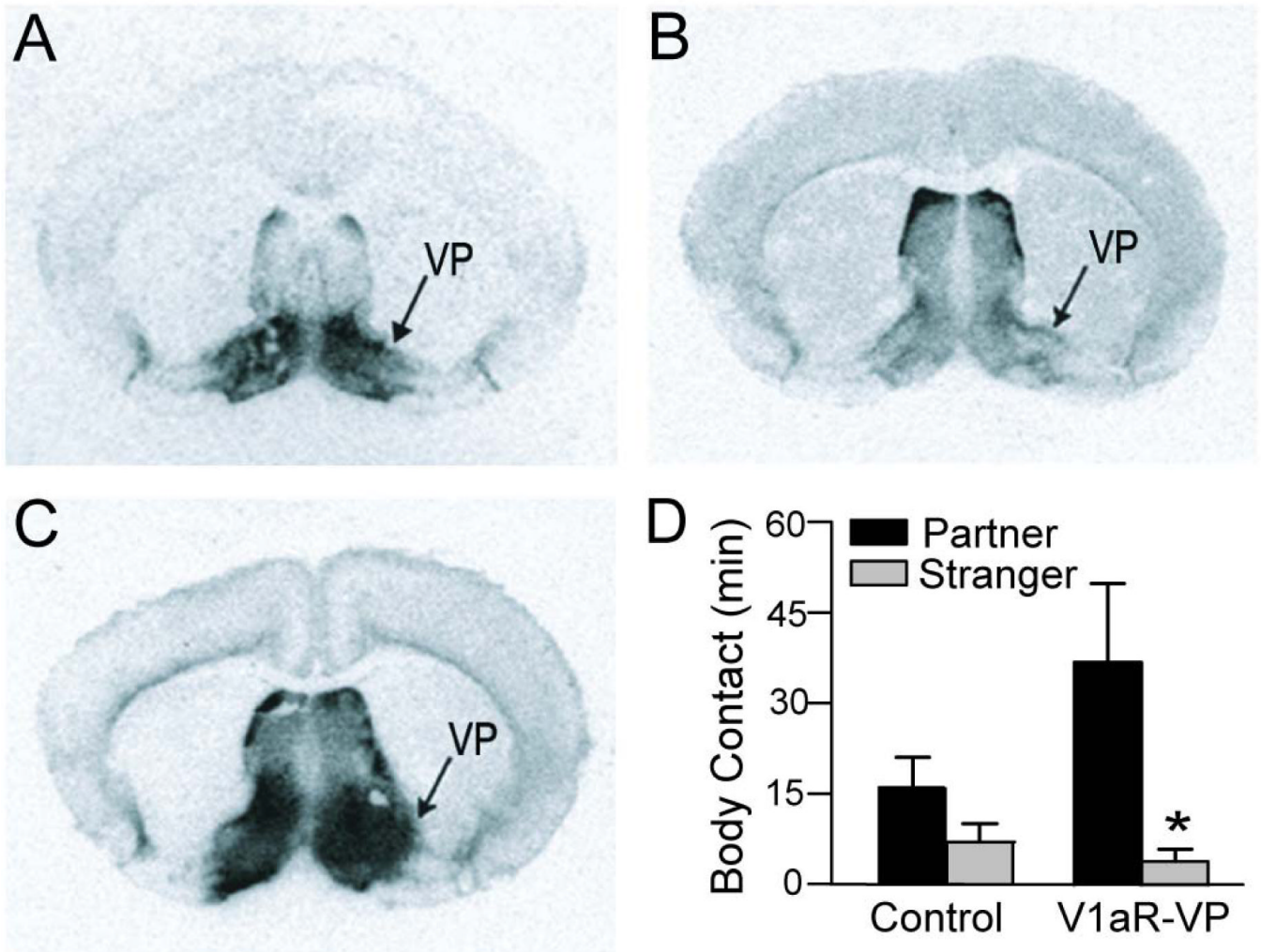
Figure 3. V1aR distribution may contribute to social organization
Photomicrographs showing V1aR labeling in the ventral pallidum (VP) of prairie (A) and
meadow (B) voles. (C) Meadow voles transgenic for the prairie vole V1aR gene (V1aR-VP)
showed an increased density of V1aR labeling in the VP. (D) Twenty-four hours of mating
induced partner preferences in the V1aR-VP transgenic, but not control, meadow voles.
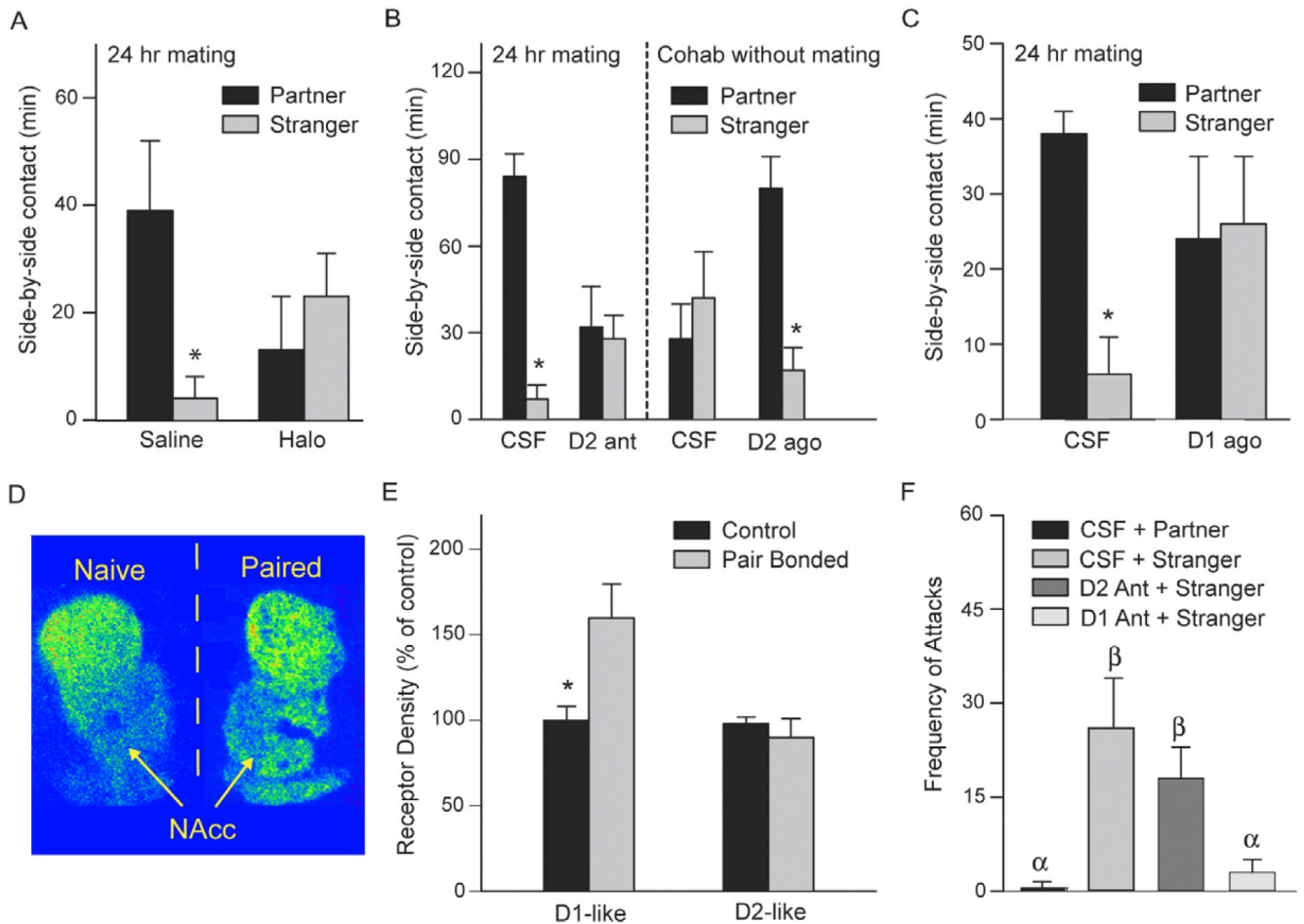(Adapted from Lim et al., 2004b).

Figure 4. DA regulation of pair bonding in male prairie voles
(A) Peripheral injection of haloperidol (Halo), a nonspecific DA receptor antagonist, blocked partner preference formation following 24 hours of mating. (B) Pharmacological blockade of D2Rs (D2 ant) in the nucleus accumbens (NAcc) prevented mating induced partner preferences, whereas administration of a D2R agonist (D2 ago) induced partner preferences without mating, indicating the importance of D2R activation in partner preference formation. (C) Intra-NAcc injection of a D1R agonist (D1 ago) blocked partner preference formation following 24 hours of mating. (D) Photomicrographs showing increased D1-like receptor binding in the NAcc of male prairie voles that were pair bonded for two weeks (Paired) in comparison to sexually naive males (Naive). (E) Two weeks of pair bonding induced a significant increase in the density of D1-like, but not D2-like, receptors in the NAcc of male prairie voles. (F) Pair bonded male prairie voles displayed a high level of aggression toward a stranger female (CSF + Stranger), but not toward their own familiar partner (CSF + Partner). Intra-NAcc blockade of D1-like receptors (D1 Ant + Stranger), but not D2-like receptors (D2 Ant + Stranger) abolished selective aggression toward a stranger female. (Adapted from Wang et al., 1999; Aragona et al., 2003; Young et al., 2004; Aragona et al., 2006).