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RESEARCH****Research Report****Dopamine and monogamy***J. Thomas Curtis**, *Yan Liu*, *Brandon J. Aragona*¹, *Zuoxin Wang**Department of Psychology and Program in Neuroscience, Florida State University, 209 Copeland Ave., Tallahassee, FL 32306, USA*

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ABSTRACT

Social attachments play a central role in human society. In fact, such attachments are so important that deficits in the ability to form meaningful social bonds are associated with a variety of psychological disorders. Although mother–infant bonding has been studied for many years, we only recently have begun to examine the processes that underlie social bonds between adults. Over the past decade, central dopamine has become a focus of such research, especially its role in pair bonding between mates in species that display monogamous life strategies. Neuroanatomical and pharmacological studies in rodents have firmly established central dopamine systems, especially the mesocorticolimbic dopamine circuitry, in the formation, expression, and maintenance of monogamous pair bonds. As this research has progressed, it has become apparent that there is considerable overlap between the processes that underlie pair bonding and those that mediate responses to abused substances. This suggests that social bonding and substance abuse each may affect the other. Herein we review the current state of knowledge of central dopamine involvement in pair bond formation, expression, and maintenance. We first describe the neuroanatomical substrate within which dopamine exerts its effects on social bonding. We then describe dopamine receptor subtype-specific influences on pair bonding and how dopamine receptor activation may interact with activation of other neurochemical systems. Finally, we describe possible interactions between social bonding and substance abuse.

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1. Introduction

Affiliative behavior is a fundamental part of the natural history for many animal species, including humans, and has been shown to have adaptive significance. Schooling by fish, flocking by birds, and other types of group living may serve to reduce predation (Hass and Valenzuela, 2002; Seghers, 1974). At the individual level, young baboons are more likely to survive if the mother has established strong social ties (Silk et al., 2003). As an extreme example, intimate contact be-

tween mother and infant can alter the rate of autonomic maturation (Feldman and Eidelman, 2003).

In some cases, natural selection may favor the formation of bonds between specific individuals. For example, there is evidence that remaining with the same partner enhances lifetime reproductive success in California mice (*Peromyscus californicus*) (Ribble, 1992). Such selective pressures may lead to the evolution of a monogamous mating strategy (Kleiman, 1977), manifested by strong affiliative bonds between members of a breeding pair. Monogamous pair bonds are relatively

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rare among mammalian species (Kleiman, 1977) and appear to have evolved independently several times (Komers and Brotherton, 1997). Only about 3% of mammalian species display such bonds, and even fewer appear to exhibit obligate monogamy (Kleiman, 1977). A number of theories have been proposed regarding the evolution of monogamy (Kleiman, 1977; Orians, 1969; Wittenberger and Tilson, 1980), however, it is unlikely that any single theory accounts for all instances of monogamy. This conclusion is supported by the observation that monogamy is not a unitary process, but rather can have species-specific manifestations (Dewsbury, 1987).

Pair bonding is part of a spectrum of individual-specific affiliative behaviors, all of which appear to share common traits such as approach and avoidance behaviors, social recognition, the formation of conditioned preferences, and motivation (Depue and Collins, 1999; Insel and Fernald, 2004; Young, 2002; Young et al., 2001). Thus, pair bonds between mates (including romantic bonds between humans), mother–infant bonds, and friendships likely all derive from the same basic mechanism (Bartels and Zeki, 2004; Depue and Morrone-Strupinsky, 2005; Fraley and Shaver, 2000; Insel, 1997; Pedersen, 2004). Although it is impossible to know exactly the evolutionary sequence that produced the neural mechanisms underlying affiliative behaviors, knowledge of current functions of neurochemical systems permits speculation as to the evolution of attachment processes.

Biogenic amine involvement in the central processes important for pair bonding appears to be phylogenetically very old (Nestler, 2002) and may predate the divergence of chordate and invertebrate taxa (Huber, 2005). These processes may originally have mediated the formation of associations between behavior and positive outcome. For example, forming an association between a particularly nutritious food source and the cues that facilitate locating that food source would likely have adaptive value. In mammals, such associations appear to be mediated via activation of central dopamine pathways (reviewed by Ikemoto and Panksepp, 1999), but in fact, monoamine systems appear to mediate the formation of conditioned preferences in taxa as diverse as planarians, crayfish, honeybees, and zebra fish (Hammer, 1997; Kusayama and Watanabe, 2000; Menzel et al., 1999; Panksepp and Huber, 2004). Such a system would be ideally suited for co-opting as a mechanism to ensure the appropriate motivations and behaviors as mating strategies became more complex, shifting from broadcast spawning to being oriented toward particular individuals (Parker, 1984). Once tied to reproduction, it is a short step to involvement in processes such as parental bonding that enhanced survival of offspring.

2. Animal models for the study of social bonding

In healthy humans, social contact can elicit a suite of physiological responses that are highly conserved and that may serve to reinforce the motivation to engage in such contact (Depue and Collins, 1999). In other words, these responses are rewarding (as defined by Ikemoto and Panksepp, 1999) in that they “elicit approach responses”. Note that this definition does not imply “subjective positive hedonic effects”. Thus, despite the

fact that humans have established emotional terms for these responses such as feelings of warmth and security, comfort, trust, and ultimately, love, these emotions represent what has been termed “autonomic–motoric–cognitive states” (Kemper, 1987). Importantly, although the cognitive, subjective components probably are unique to humans, it is likely that other mammalian species experience aspects of the emotional/physiological components of what humans term love (Porges, 1998). This likelihood is supported by the observation that activation of central pathways associated with reward processing can occur in humans despite a lack of conscious perception (Berns et al., 1997). Thus, it is possible to employ animal models to examine certain aspects of the central processes underlying the formation and maintenance of pair bonds.

Rodents from the genera *Microtus* (voles) and *Peromyscus* (deer mice) have been used extensively in the study of social behavior including social bonding, parental behavior, mating behavior, aggression, stress responses, activation of sexual receptivity, and social influences on immune function (Carter et al., 1988; Curtis et al., 2001; Cushing and Carter, 2000; de Vries and Miller, 1998; Demas et al., 1999; Dewsbury, 1995; Heise and Van Acker, 2000; Insel et al., 1995; Kirkpatrick et al., 1994; Lonstein and De Vries, 2000; Ribble, 1992; Roberts et al., 1998; Stribley and Carter, 1999; Wang et al., 1997a; Williams et al., 1992b; Winslow et al., 1993). First proposed as a model system in the 1980s (Dewsbury, 1987; Getz et al., 1981), prairie voles (*M. ochrogaster*) have been the most commonly used species in studies on the formation of monogamous pair bonds.

Prairie voles (Fig. 1A) are small (~50 g) and easily bred in captivity providing an ideal animal model for examining social behavior. In addition, prairie voles are highly social and appear to seek out not just social interactions, but physical contact as well (Fig. 1B) (Shapiro and Dewsbury, 1990). Importantly, mated pairs of prairie voles are one of the few mammalian species that display pair bonding behavior. Field studies show that prairie voles display characteristics of monogamy such as biparental care of pups, sharing of a nest even beyond the breeding season, aggression toward strangers, and a tendency to travel together (Getz et al., 1981; Gruder-Adams and Getz, 1985; Hofmann et al., 1984). In the laboratory, both sexes form strong individual attachments manifested by a robust preference to associate with the familiar mate versus with a conspecific stranger. Importantly, such partner preferences can be readily quantified in an experimental setting (Fig. 1E) and provide a benchmark by which the effects of experimental manipulations can be assessed. Thus, prairie voles are an important extension of more traditional laboratory animals that do not exhibit such attachments. Furthermore, closely related vole species, such as montane (*M. montanus*) and meadow (*M. pennsylvanicus*) voles (Fig. 1D), are asocial (Fig. 1C) and differ only in their respective social structures.

3. Is dopamine involved in pair bond formation?

Activity of central dopamine systems is known to have profound effects on behavior. A variety of studies have implicated dopamine in stress responses (Abercrombie et al., 1989; Dunn, 1988), the formation of conditioned preferences (Kivastik et al.,

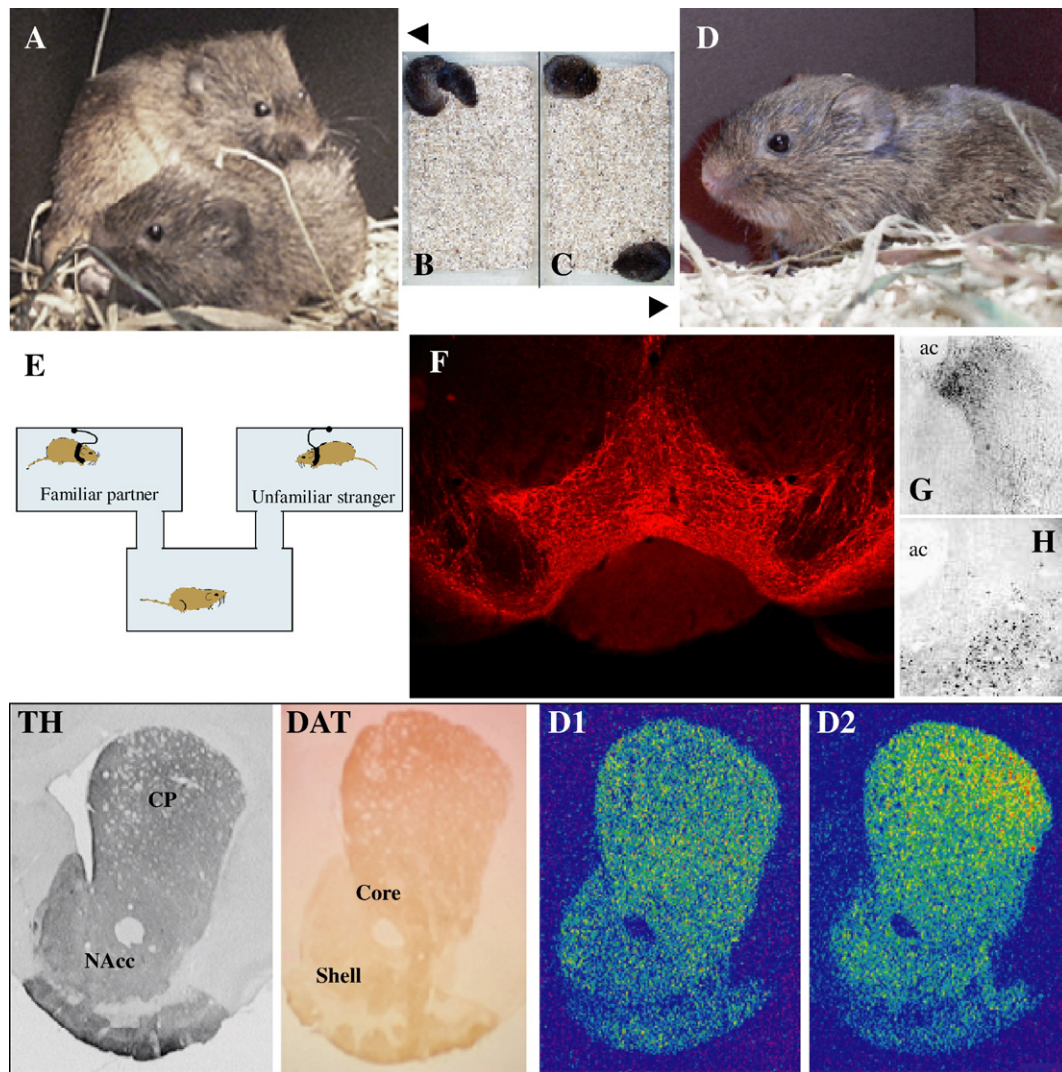


Fig. 1 – Voles provide an excellent comparative model in which to study social behavior. Monogamous prairie voles (A) are highly social and appear to seek out physical contact (B). In contrast, promiscuous meadow voles (D) are asocial and avoid contact with conspecifics (C). In a choice test (E), pair bonded prairie voles will spend the majority of their time in the cage in which their familiar partner is tethered while non-pair bonded voles may spend time with either stimulus animal. The VTA is an important catecholamine source, as evidenced by immunostaining (red fluorescence) for tyrosine hydroxylase (F). Anterograde tracers injected into the VTA identify projections to the NAcc (G), and pharmacological manipulations in the VTA alter neuronal activation in the nucleus accumbens (H) as indicated by fos immunoreactivity (ac=anterior commissure). The lower panels show extensive tyrosine hydroxylase (TH) immunostaining indicating dense catecholaminergic innervation in NAcc that is co-localized with markers for dopamine circuitry such as dopamine transporter (DAT immunostaining) and D1 and D2 dopamine receptor binding.

1996), the rewarding effects of food intake (Azzara et al., 2001) and drugs of abuse (Saal et al., 2003), parental behavior (Keer and Stern, 1999; Lonstein, 2002) and the control of sexual behavior (Becker et al., 2001; Dominguez et al., 2001; Dominguez and Hull, 2005). More recent studies also have examined the role of dopamine in mediating social behavior (Aragona et al., 2003, 2006; Curtis and Wang, 2003, 2005a,b; Curtis et al., 2001, 2003b; Gingrich et al., 2000; Keer and Stern, 1999; Lorrain et al., 1999; Mermelstein and Becker, 1995; Mitchell and Gratton, 1992; Tidey and Miczek, 1996). Much of this latter work has been directed toward the role of the mesolimbic dopamine system in social attachment, particularly in the formation and maintenance of pair bonds between male and female mates.

The observation that sexual activity both induces central dopamine release (Pfaus et al., 1990) and facilitates pair bond formation in monogamous prairie voles (Williams et al., 1992a) led to the hypothesis that dopamine might play a role in social attachment. This hypothesis was supported when it was shown that mating-induced pair bonding in prairie voles was impaired by treating them with the general dopamine receptor antagonist haloperidol, while the non-specific dopamine agonist apomorphine could induce pair bonds in the absence of mating (Aragona et al., 2003; Wang et al., 1999). Interestingly, doses of apomorphine that induced partner preferences in female voles (Wang et al., 1999) were ineffective in males (Aragona et al., 2003) suggesting sex differences in

sensitivity to dopamine manipulations. The fact that intracerebroventricular (icv) administration of dopaminergic drugs produced similar results as did peripheral treatment established central dopamine systems as being critical for pair bonding (Wang et al., 1999).

4. Neuroanatomical substrate(s)

There are three major dopaminergic pathways in the brain involved in sexual activity (Melis and Argiolas, 1995), any of which might mediate the central effects of dopamine on social attachment. The nigrostriatal pathway consists of projections from the substantia nigra (A9 cell group) to the dorsal striatum (Swanson, 1982). The incertohypothalamic pathways involve projections from the A12–A14 dopaminergic cell groups that innervate, among other areas, the medial pre-optic area (MPOA) and the paraventricular nucleus (PVN) (Cheung et al., 1998). Finally, the mesocorticolimbic pathways consist of reciprocal innervation between the ventral tegmental area (A10, VTA) and the medial pre-frontal cortex (mPFC) and projections from each to the nucleus accumbens (NAcc) (Carr and Sesack, 2000; McFarland and Kalivas, 2001; Swanson, 1982).

Which of these dopamine pathways ultimately mediates the formation and maintenance of pair bonds? To date, there have been no direct tests of incertohypothalamic involvement in pair bond formation. Nonetheless, the zona incerta, which has been implicated in sexual behavior (Edwards and Isaacs, 1991), receives input from brainstem regions (Berkley and Hand, 1978) that are activated during mating (Curtis et al., 2003a). Furthermore, it is well established that incertohypothalamic dopamine projections play critical roles in sexual behavior (Argiolas et al., 1987). Thus, this system could impact pair bonding via effects on mating. For example, in males, dopaminergic innervation of oxytocin cells in the PVN is necessary for sexual function (Andersson, 2001) and dopamine in the MPOA is involved in the regulation of sexual behavior (Dominguez and Hull, 2005; Hull et al., 1986; Triemstra et al., 2005) that in turn facilitates pair bonding. In female voles, the MPOA is activated during the early stages of pairing (Cushing et al., 2003) and by mating (Curtis and Wang, 2003). Since neurochemical responses to vaginocervical stimulation suggest that such stimulation activates dopamine receptors in the MPOA (Meredith et al., 1998), at least some portion of the neural activation in the MPOA associated with mating likely can be attributed to the effects of dopamine. Unfortunately, in most cases, the possibility that such neural activation might also be associated with the initiation of sexual receptivity in voles (Schwab et al., 2004) cannot be ruled out. The fact that MPOA activation also occurs in females during post-partum estrous (Katz et al., 1999) supports the latter interpretation. The PVN and MPOA also appear to be involved in the onset of mating-induced selective aggression (Gammie and Nelson, 2000; Wang et al., 1997a) that accompanies pair bond formation in voles (Winslow et al., 1993). As such, in addition to their roles in regulating sexual behavior, these regions may be important for the mate guarding and territorial behaviors displayed by pair bonded voles. Thus, the incertohypothalamic dopamine

system likely plays at least an important indirect role in the formation and expression of pair bonds via the regulation of sexual behavior and aggression. However, future studies may yet more directly implicate these dopamine pathways in social attachment, especially via dopamine effects on neuropeptide release.

The nigrostriatal dopamine pathway has been implicated in associative learning (Han et al., 1997) and in “habit” formation (Jog et al., 1999), both of which may play a role in pair bonding. The latter could be especially important because the dorsal striatum is involved in drug seeking after abstinence but not after extinction training (Fuchs et al., 2006), and abstinence (i.e., separation) may be a more relevant model for the natural mechanisms involved in pair bonding. In addition, dopamine release in the dorsal striatum is increased during mating both in rats (Damsma et al., 1992; Mermelstein and Becker, 1995; Pfaus et al., 1990) and in female voles (Curtis et al., 2003b). Importantly, the increases in extracellular dopamine levels in both species are independent of locomotor behaviors associated with mating (Becker et al., 2001; Curtis et al., 2003b; Mermelstein and Becker, 1995) and may be involved in mediating perception of mating stimuli (Jenkins and Becker, 2001). Finally, the nigrostriatal pathway also has been implicated in responses to stress (Abercrombie et al., 1989; Bertolucci-D’Angio et al., 1990a; Castro et al., 1996; Isovich et al., 2001; Kehoe et al., 1996) that can alter pair bonding behavior (DeVries et al., 1996). Monogamous females have elevated levels of the dopamine metabolite DOPAC in the striatum when housed alone overnight (Curtis et al., 2003b). Since elevated DOPAC may indicate stress (Bertolucci-D’Angio et al., 1990b), it is possible that monogamous females may be more motivated to engage in social contact. However, administration of dopamine receptor agonists into the dorsal striatum failed to induce partner preferences despite the fact that the same treatments were quite effective in other parts of the brain (Aragona et al., 2003; Liu and Wang, 2003). Furthermore, a comparative study found no differences in mating-induced dopamine release in the dorsal striatum between females from monogamous and non-monogamous species (Curtis et al., 2003b). Thus, the species differences in mating systems likely are not the result of species differences in striatal dopamine systems.

The mesolimbic dopamine system has been implicated in mediating motivated behaviors and in reward processing and is critical for the processes underlying addiction, which in turn appears to share a number of common features with pair bonding. As with the dorsal striatum, dopamine release is enhanced by sexual activity in a variety of species including rats, voles, and hamsters (Becker et al., 2001; Gingrich et al., 2000; Kohlert and Meisel, 1999; Pfaus et al., 1990). Furthermore, the fact that mating can induce a conditioned place preference (Martinez and Paredes, 2001) suggests that this dopamine release is associated with positive reinforcement that, in turn, may contribute to pair bond formation. In contrast to the minimal involvement of other dopamine systems in social attachment, the mesocorticolimbic dopamine pathway has been found to be of critical importance in the formation and maintenance of pair bonds in both sexes of prairie voles (Aragona et al., 2003, 2006; Gingrich et al., 2000). Furthermore, mesocorticolimbic areas are activated in humans when

subjects view images of their respective love interests (Aron et al., 2005; Bartels and Zeki, 2000, 2004).

As noted earlier, mating induces changes in dopamine metabolism (Aragona et al., 2003) and in extracellular levels of dopamine within NAcc (Gingrich et al., 2000). Furthermore, site-specific manipulations of the NAcc dopamine system can fundamentally alter pair bonding behavior. It should be noted that the NAcc is not a homogeneous nucleus but rather is comprised of functionally distinct sub-regions (Zahm, 1999), most notably the core and shell sub-regions (Fig. 1, lower panel). Moreover, there also appears to be functional segregation along an anterior–posterior gradient within each of these sub-regions (reviewed by Zahm, 2000) (Reynolds and Berridge, 2002). This functional segregation is reflected in the effects of dopamine manipulations within NAcc on pair bonding. Administration of a dopamine receptor agonist into the rostral

shell effectively induced pair bonds in the absence of mating, while administration into the rostral core or into the caudal shell was ineffective (Aragona et al., 2006) (Fig. 2A).

The dopaminergic innervation of the NAcc originates primarily from within the VTA in the ventral mid-brain (Figs. 1F, G, H) (Hasue and Shammah-Lagnado, 2002; Swanson, 1982). In addition, the VTA also projects to other brain regions (Swanson, 1982) that in turn can modulate NAcc activity. Thus, the VTA may affect NAcc function indirectly as well as directly. Modulation of dopaminergic output from the VTA appears to involve a complex interplay between excitatory and inhibitory inputs, as well as inhibitory interneurons within the VTA itself. First, the activity of VTA dopamine cells is influenced by afferent inputs to the VTA. For example, the burst pattern of firing is missing in slice preparations in which afferent connections are absent (Grace and Onn, 1989). GABAergic

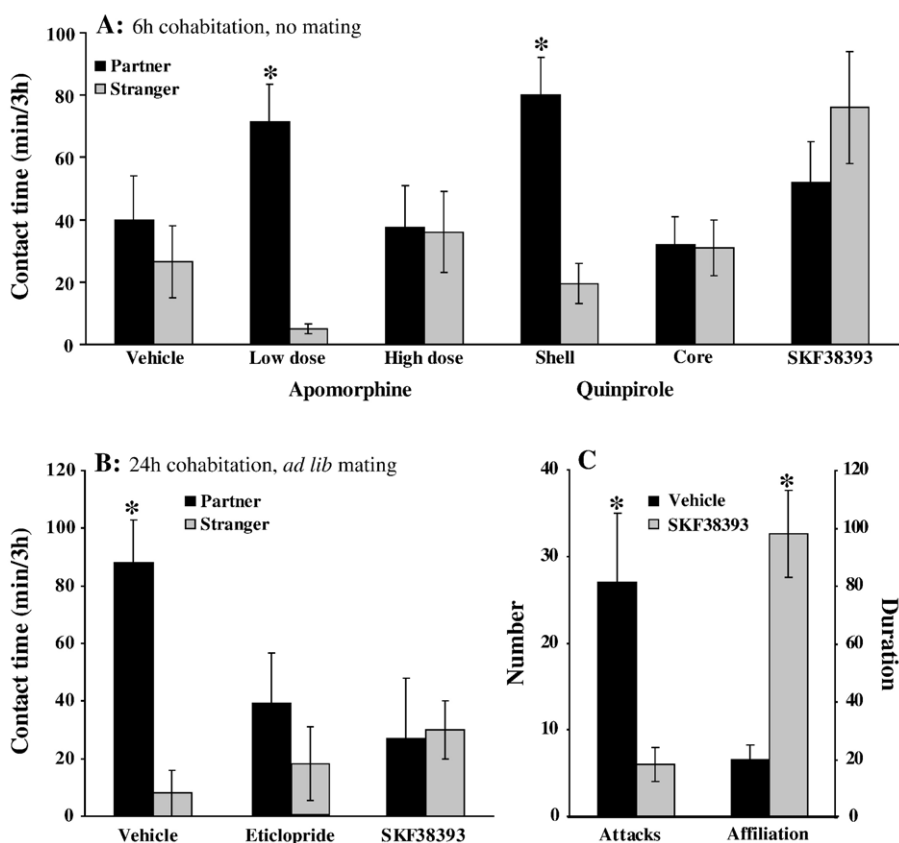


Fig. 2 – Dopamine receptor pharmacology and pair bonding. Prairie voles that have cohabited for 6 h without mating display non-specific affiliation. This paradigm is useful for testing the effects of manipulations designed to induce pair bonds.

Under these conditions (A), vehicle treated males show no preference for the partner vs. the stranger. Low doses, but not high doses, of a non-specific dopamine receptor agonist (apomorphine) into the NAcc induce partner preferences. Similarly, activation of D2 receptors (quinpirole) induces partner preferences, but only when injected into the NAcc shell. Neither D2 activation in the NAcc core nor D1 activation (SKF38393) in the shell altered affiliative behavior. Voles paired for 24 h with ad libitum mating reliably display a preference for their familiar partner. This paradigm is useful for testing the effects of manipulations designed to inhibit pair bonds. Under these conditions (B), vehicle treated males display a robust partner preference, behavior not seen in males in which D2 receptors are blocked (eticlopride) or D1 receptors (SKF38393) are activated. Males that are pair bonded for 2 weeks display high levels of antagonist behavior and low levels of affiliative behavior when confronted with a stranger. This pattern is reversed when D1 receptors in NAcc are blocked (C). * Indicates significantly more contact with the partner (panels A and B) or a significant increase in attack or affiliative behaviors (panel C). Figures are redrawn using data from several sources (Aragona et al., 2003; Aragona et al., 2006; Gingrich et al., 2000), and thus are representative of typical results.

inputs can alter dopamine release directly via GABA receptors on dopamine cells or indirectly via GABA receptors on secondary cells that ultimately modulate dopamine release (Kalivas, 1993; Xi and Stein, 1998). Second, GABAergic interneurons within the VTA can exert a significant inhibitory influence on dopamine release in VTA terminal fields (Johnson and North, 1992). Third, autoreceptors have been found to regulate VTA dopamine cells, and these receptors may respond primarily to local somatodendritic release of dopamine (Adell and Artigas, 2004). Fourth, there appear to be connections via gap junctions (Bayer and Pickel, 1990) that may serve to coordinate cell firing (Grace and Bunney, 1983). Finally, the timing or intensity of synaptic input can dictate whether that input will produce excitatory or inhibitory responses (Chen and Rice, 2002). Given the complexity of the control of VTA dopamine cells, it is perhaps not surprising that experimental manipulations produce mixed results depending on the type of manipulation and on the terminal region examined. For example, in one study, blockade of AMPA-type glutamate receptors resulted in increased dopamine release in NAcc, while reducing dopamine release in the mPFC (Takahata and Moghaddam, 2000). Such results likely reflect findings that excitatory inputs to VTA synapse on two separate populations of projection neurons: non-TH immunopositive cells that project to NAcc and non-GABA immunopositive cells that project to the mPFC (Carr and Sesack, 2000).

Mice will self-administer glutamate receptor antagonists into the VTA, suggesting that blockade of those receptors is positively reinforcing (David et al., 1998). These results, in conjunction with the suggestion that glutamate receptor blockade can increase dopamine release in NAcc (Takahata and Moghaddam, 2000), raise the possibility that blockade of excitatory input to the VTA might facilitate pair bonding. Indeed, this appears to be the case: administration of the AMPA-type glutamate receptor antagonist NBQX in the VTA can induce pair bonds in the absence of mating (Curtis and Wang, 2005b). On the surface, this observation seems counter-intuitive. We are suggesting that increased NAcc dopamine in response to NBQX is responsible for the pair bond induction, yet NBQX treatment reduces excitatory influence. The resolution to this paradox may be found in the suggestion that the excitatory receptors being blocked are not on dopamine cells. Wang and French (1995) established the presence of glutamate receptors on non-dopaminergic cells within the VTA and showed that glutamate responses by these cells were blocked by NBQX. Since a significant portion of non-dopamine cells within the VTA are GABAergic, it is possible that NBQX blocks receptors on GABAergic interneurons that ultimately modulate dopamine release (David et al., 1998). Thus, blockade of glutamate receptors reduces an inhibitory influence on dopamine cells that project to NAcc, resulting in increased NAcc dopamine release and the induction of a pair bond. The fact that the GABA receptor antagonist bicuculline also induces pair bonds when injected into the VTA is further evidence for such a circuit.

Differential staining for vesicular glutamate transporters suggests that the VTA receives excitatory input from a variety of sources (Balfour et al., 2006). Indeed, there are reports that the mPFC, laterodorsal tegmentum, and pedunculopontine nucleus all may influence VTA dopamine cells (Forster and

Blaha, 2000; Pan and Hyland, 2005). Of these, only the mPFC has been examined for a role in pair bond formation. Dopaminergic projections from the VTA innervate the mPFC (Carr and Sesack, 2000) and can influence mPFC function (Brady and O'Donnell, 2004). In turn, excitatory projections from the mPFC are associated with VTA cells that are activated during mating (Balfour et al., 2006). In addition, projections from the mPFC exert a strong influence on NAcc function (King et al., 1997; You et al., 1998), either directly (Carr et al., 1999) or indirectly via connections with VTA cells that project to NAcc (Carr and Sesack, 2000). These data suggest that the mPFC could play a role in pair bonding. Indeed, this appears to be the case. In fact, the effects of dopamine manipulations in the mPFC appear to mirror those in the NAcc. In contrast to its effects in the NAcc, dopamine receptor blockade in the mPFC does not impair mating-induced pair bond formation (Gingrich et al., 2000). Instead, when injected into the rostral portion of the mPFC dopamine receptor antagonists facilitated pair bond formation, even in the absence of mating (Smeltzer et al., 2005).

5. Dopamine receptor subtypes in pair bonding

Dopamine exerts its effects via interaction with membrane-bound receptors coupled to G-protein mediated second messenger systems (Missale et al., 1998). An extensive review of the pharmacology and physiology of dopamine receptors is beyond the scope of the present paper, thus the reader is referred to one of several reviews addressing this subject in detail (cf. Missale et al., 1998). For the purposes of the current discussion, it is important to note that dopamine receptors are classified based on their interactions with second messenger cascades (Missale et al., 1998). The D1 family of dopamine receptors (D1 and D5 receptors) activates adenylyl cyclase (AC) increasing intracellular levels of cAMP. On the other hand, the D2 family of dopamine receptors (D2, D3, and D4 receptors) inhibits AC. Thus, activation of D1- and D2-type dopamine receptors may produce opposite effects on neuronal function (West and Grace, 2002).

Comparative studies using monogamous and promiscuous sister species have revealed differences in receptor binding for several neurotransmitters/neuromodulators (Insel and Shapiro, 1992; Insel et al., 1991; Lim et al., 2005; Wang and Young, 1997; Wang et al., 1997b, 1998; Young et al., 1996). Similar species differences have been found for dopamine receptors as well, although such differences are less extreme than was seen for other receptor systems. In the mPFC, promiscuous meadow voles have higher D1 receptor binding, but lower D2 binding than do monogamous prairie voles (Smeltzer et al., 2006). In the NAcc, the reverse is found for D2 receptors with promiscuous voles displaying greater D2 binding than do monogamous voles (Aragona et al., 2004a). The situation for D1 receptors in NAcc is a bit more complicated. While no differences in D1 binding are seen among females displaying differing mating systems, males from the promiscuous species have greater D1 binding than do males of monogamous species (Aragona et al., 2004a). These results suggest that species-specific patterns in the

distributions of dopamine receptors may contribute to species-typical mating systems.

Social functioning in humans is known to involve dopamine receptor activation (Lawford et al., 2003). For example, people expressing a D2 receptor genotype associated with reduced post-synaptic D2 activity have negative parenting perceptions (Lucht et al., 2006). Similarly, when compared to healthy subjects, patients with social phobias have lower D2 binding (Schneier et al., 2000). Finally, other members of the D2 family of receptors also can impact human social bonding. For example, disorganized mother–infant attachment is associated with a polymorphism of the gene for the D4 dopamine receptor (Gervai et al., 2005).

The effects on pair bonding of dopamine manipulations within the NAcc also appear to be mediated primarily via D2-type receptor activation. Site-specific administration of the general dopamine receptor antagonist haloperidol into NAcc of male prairie voles inhibits mating-induced pair bond formation, while apomorphine, a non-specific dopamine agonist, induces pair bonds in the absence of mating (Aragona et al., 2003). Similar studies employing more specific dopamine agonists and antagonists established that these effects are mediated primarily via D2-type receptors in both sexes. Administration of the D2 antagonist eticlopride inhibits pair bond formation (Fig. 2B) (Gingrich et al., 2000), while administration of quinpirole, a D2 agonist, induces partner preferences in the absence of mating (Fig. 2A) (Aragona et al., 2006; Gingrich et al., 2000). Interestingly, eticlopride administration produces the opposite effect when injected into the mPFC (Smeltzer et al., 2005). This difference may reflect the earlier observation that monogamous and promiscuous species display opposite relationships between D2 receptor density and mating system (Aragona et al., 2004a; Smeltzer et al., 2006).

The D1 dopamine receptor subtype was originally described as playing no role in pair bonding (Fig. 2A) (Wang et al., 1999). This is probably true in terms of pair bond formation, but increasing evidence suggests that D1 dopamine receptors may be critical for pair bond maintenance. In male prairie voles, only very low doses of apomorphine induce partner preferences, whereas higher doses are ineffective (Fig. 2A) (Aragona et al., 2003). This apparently paradoxical result may reflect the opposing effects of D1- and D2-type dopamine receptor activation. Apomorphine has a greater affinity for D2-type receptors (Missale et al., 1998). Thus, at low doses, apomorphine binds preferentially to these receptors, eliciting the D2 facilitation of pair bonding. However, at higher doses, apomorphine begins to recruit D1 receptors, which appears to counteract the effects of D2 activation. In fact, concurrent activation of both D1 and D2 receptors in NAcc eliminates partner preferences induced by D2 activation alone (Aragona et al., 2006). Importantly, D1 activation also blocks the effects of mating on pair bond formation (Fig. 2B) (Aragona et al., 2006). This being the case, it might be expected that D1 blockade would facilitate pair bonding. However, D1 receptor blockade, in the absence of D2 activation, is not sufficient to induce pair bonds in sexually naive male prairie voles (Curtis and Wang, in preparation). So what role does D1 activation play in pair bonding? The answer resides in the observation that there is a significant reorganization in the NAcc of pair bonded voles.

Sexual experience has been shown to alter locomotor responses after amphetamine treatment (Bradley and Meisel, 2001) in rats possibly as a result of increased D1 receptor sensitivity (Bradley et al., 2004) after mating. These results provide ample precedent for changes in central dopamine systems after sexual contact. Pair bonded prairie voles of both sexes display a robust selective aggression toward unfamiliar conspecifics of either sex, behavior not seen in sexually naive, unpaired voles (Aragona et al., 2006; Thomas and Wolff, 2004; Wang et al., 1997a; Winslow et al., 1993). Male prairie voles that have lived with their mate for 2 weeks display significantly higher D1 receptor binding than do sexually naive males or sexually experienced males with only short-term exposure to a mate. In contrast to non-pair bonded individuals, in a resident–intruder test, pair bonded males are highly aggressive toward unfamiliar females but not toward their respective mates. Why is there such a robust difference in the response toward a stranger vs. that toward the partner? It appears that the increase in D1 may mediate the transition from highly social to highly aggressive. When treated with vehicle prior to aggression testing, pair bonded males are highly aggressive toward unfamiliar females. However, pair bonded males that receive intra-NAcc administration of a D1 antagonist prior to aggression testing display the high levels of affiliative behavior and low levels of aggression (Fig. 2C) typical of sexually naive, unpaired male prairie voles (Fig. 2C) (Aragona et al., 2006; Getz, 1962).

Since mate guarding and rejecting potential new mates are critical aspects of monogamy, increased D1 receptor activation in pair bonded animals in response to strangers may serve to maintain an established monogamous relationship. How might such a change be manifested under natural circumstances? It is well established that NAcc dopamine is elevated in response to novelty including exposure to another individual (Damsma et al., 1992; Noguchi et al., 2001). However, when a familiar stimulus is encountered, dopamine release in NAcc, especially in the shell portion, is attenuated relative to that in earlier encounters (Bassareo et al., 2002). Even in monogamous species members of a pair occasionally are separated, as evidenced by sex-specific predation risk (Sommer, 2000). Upon reuniting, familiarity may preclude dopamine release in NAcc, thereby avoiding initiation of the D1 receptor-mediated aggression and thus preserving the pair bond. Strangers, on the other hand, may cause novelty-induced elevation of NAcc dopamine that in turn activates the increased D1 receptors, eliciting an aversive response to unfamiliar individuals.

It should be noted that the change in D1 receptor binding does not appear to be universal among monogamous voles (Aragona et al., 2006). A small percentage of prairie voles fail to display an increase in D1 receptor density after long-term cohabitation and mating. This individual variation may account for the small percentage of monogamous voles that form new pair bonds after losing a mate (Getz et al., 1993; Pizzuto and Getz, 1998). It is tempting to speculate that the increase in D1 receptors seen in pair bonded prairie voles may cause them to behave more like the closely related but non-monogamous meadow vole when confronted with a stranger. Sexually naive male meadow voles have a higher density of D1 receptors in NAcc than do male prairie voles (Aragona et al.,

2006) and tend to be much more aggressive during intraspecific encounters (Getz, 1962). Notably, blockade of D1 receptors in normally solitary meadow voles significantly increases social contact (Aragona et al., 2006).

To date, the extent to which female prairie voles also may display a similar increase in D1 receptors has not been examined. It is known that sexually experienced female prairie voles are quite aggressive toward strangers (Villalba et al., 1997) and that “widowed” females will aggressively reject males (Thomas and Wolff, 2004), both of which suggest that D1 receptor density/function also is increased in females during pair bonding. Although aggression has been linked to mating in male voles, the onset of aggression by females does not appear to require mating. Ovariectomized (and thus unmated) females that have lived with a male for at least 12 days also display increased aggression (Bowler et al., 2002). Note that these non-mated females began to decrease affiliative behavior several days before the emergence of aggression (Bowler et al., 2002), suggesting the possibility that a gradual increase in D1 receptor density may accompany pair bond formation in females. If this is the case, affiliative behavior in voles may be more sensitive than is aggression to an increase in D1 activation.

As mentioned earlier, the effects of dopamine receptor activation are manifested via G-protein mediated second messenger cascades. Activation of D1 receptors ultimately increases cAMP, while D2 activation reduces cAMP levels. Thus, treatments that increase cAMP should prevent the formation of partner preferences that arise after mating, while decreases in cAMP levels should promote pair bonding in the absence of mating. Indeed, this appears to be the case. Treatments, such as pertussis toxin, that artificially enhance cAMP levels in the NAcc inhibit mating-induced pair bonding (Aragona et al., 2004b). Conversely, treatment with Rp-cAMPS, which mimics the effects of decreased cAMP, induces pair bonding in the absence of mating (Aragona et al., 2004b). These results not only provide important verification of dopamine receptor involvement in pair bonding by showing that manipulation of processes downstream from the receptor in question produces the same result as manipulation of the receptor itself, but also further establish the role of opposite modulation of neuronal activity by D1- and D2-type dopamine receptors.

6. Dopamine interactions with other neurotransmitter systems

Mesolimbic dopamine release associated with mating appears to play an important role in pair bond formation (Aragona et al., 2003; Gingrich et al., 2000; Wang et al., 1999). However, mating induces the same response in species that do not form pair bonds (Mermelstein and Becker, 1995; Pfau et al., 1990). Why then does mating induce pair bonds in prairie voles, but not in meadow voles or rats? The answer appears to lie in dopamine interactions with other neurochemical systems. Non-pair bonded male prairie voles groom more frequently than do pair bonded males (Wolff et al., 2002). Since grooming behavior is mediated in part by an interaction of dopamine and the neuropeptide oxytocin

in the NAcc (Drago et al., 1986), this observation suggests that dopamine may interact with oxytocin in pair bond formation. It is well-established that oxytocin plays a critical role in the formation of bonds between adults (Insel and Hulihan, 1995; Williams et al., 1994), just as it does in the formation of maternal bonds (Carter, 1998). Like D2 dopamine receptors, oxytocin receptors may be coupled to G_i proteins (Burns et al., 2001; Strakova and Soloff, 1997). This convergence suggests the possibility of a synergistic interaction of oxytocin effects with those of dopamine. In both *Microtus* and *Peromyscus*, monogamous and promiscuous species differ in the distributions of central oxytocin receptors (Insel and Shapiro, 1992; Insel et al., 1991), especially within the NAcc where monogamous prairie voles display a much higher density of oxytocin receptors than do promiscuous montane voles (Insel and Shapiro, 1992). The observation that OT receptors in the NAcc are located post-synaptically relative to dopamine inputs (Lim et al., 2004a) suggests that activation of these receptors does not modulate dopamine release and, in fact, may be co-localized with dopamine receptors on the same cells. Furthermore, it has been shown that these receptors play a role in pair bond formation since blockade of OT receptors in the NAcc impairs partner preference formation (Young et al., 2001). More recent work has shown that concurrent activation of both dopamine and oxytocin receptors is necessary for pair bond formation (Fig. 3A). Blockade of either type of receptor inhibits pair bonds induced by activation of the other (Liu and Wang, 2003). Similarly, there is considerable overlap between the distributions of oxytocin and dopamine receptors in the mPFC (Smeltzer et al., 2006). While it is known that manipulation of either system can impact pair bonding (Smeltzer et al., 2005; Young et al., 2001), interaction between the two systems has not yet been examined. Nonetheless, these observations suggest that species-specific patterns of oxytocin activation, in combination with mating-induced dopamine release, may partially explain the variety of rodent mating systems.

We recently have shown that glucocorticoid receptor antagonists facilitate the formation of pair bonds in female prairie voles and that this effect was reversed by central administration of either D1 or D2 antagonists (Fig. 3B) (Curtis and Wang, 2005a). These findings suggest the possibility that dopamine also may interact with stress hormones during pair bond formation. Monogamous prairie voles display basal circulating levels of corticosterone about tenfold higher than those found in non-monogamous species such as meadow voles and rats (Hastings et al., 1999). Nonetheless, prairie voles still experience stress-induced increases in corticosterone (Taymans et al., 1997), which in turn can significantly affect pair bond formation. Interestingly, the effects of stress on pair bonding are sexually dimorphic in monogamous voles (DeVries et al., 1996). In females, reducing circulating corticosterone via adrenalectomy enhances pair bonding, whereas stress inhibits pair bond formation (DeVries et al., 1995, 1996). In males, the opposite pattern is found; the effects of stress, presumably including increased circulating corticosterone, enhance the formation of pair bonds, while adrenalectomy inhibits pair bond formation (DeVries et al., 1996).

How might dopamine and corticosterone interact to affect pair bond formation? Stress can alter excitatory glutamate

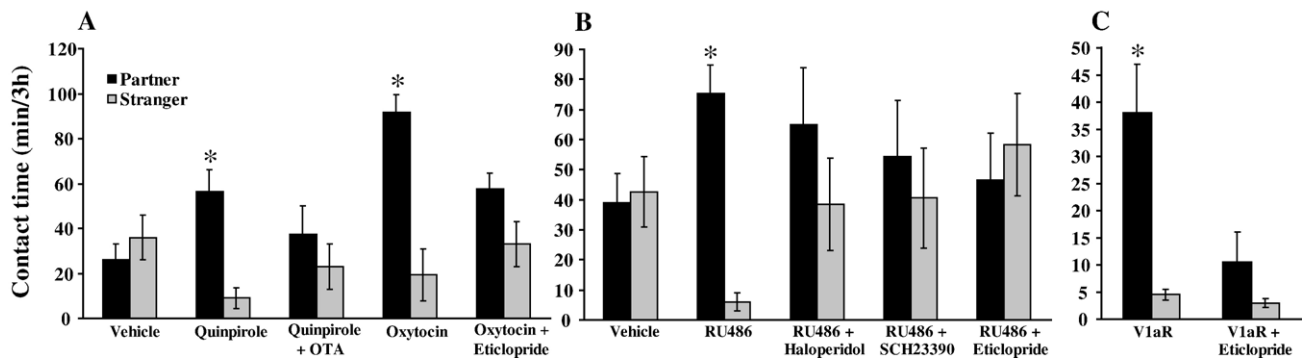


Fig. 3 – Dopamine interaction with other neurotransmitter systems in pair bonding. Vehicle treated males display non-selective affiliation after 6 h of non-sexual cohabitation (A), however, males treated with either oxytocin or a D2 receptor antagonist (eticlopride) display significant preferences for contact with the familiar partner. Access to both OT and dopamine receptors appears to be necessary since blockade of either type of receptor reverses the pair bond-inducing effects of the other agonist. Under similar conditions, blockade of glucocorticoid receptors (RU486) induces pair bonds (B) while vehicle treatment has no effect. Central (icv) administration of dopamine receptor antagonists (haloperidol, SCH23390, eticlopride) reverses the effects of glucocorticoid receptor blockade. Normally solitary meadow voles display partner preferences after being treated so they display increased expression of the vasopressin V1a receptor in the VP (C). Like prairie voles, partner preference formation in V1aR meadow voles is inhibited by D2 receptor blockade (eticlopride). * Indicates significantly more contact with the partner. OTA = $[d(\text{Ch}_2)_5, \text{Tyr}(\text{Me})^2, \text{Thr}^4, \text{Tyr-NH}_2^2]$ -OVT. Figures are redrawn using data from several sources (Curtis and Wang, 2005a; Lim et al., 2004b; Liu et al., 1995).

receptors on dopaminergic cells in the VTA, likely via activation of glucocorticoid receptors (Saal et al., 2003). Since the VTA is the primary source of dopamine input to the NAcc (Schoffelmeer et al., 1995), glucocorticoid receptor activation in the VTA may alter dopamine release in NAcc. There also may be direct effects of glucocorticoid receptor activation within NAcc. For example, there is a correlation between dopamine transporter (DAT) activity and corticosterone levels in the shell portion of NAcc (Sarnyai et al., 1998). Circulating corticosterone levels are lower in voles that are paired (DeVries et al., 1995, 1997); thus, it is possible that DAT activity also is decreased. Such a change could result in reduced clearance of dopamine from the synapse, potentiating the effects of released dopamine and altering the reinforcing aspects of contact with the partner.

The ventral pallidum (VP) plays an important role in mediating the behavioral output associated with dopamine activation in NAcc (McBride et al., 1999) and is known to be involved in pair bonding through the actions of the neuropeptide arginine vasopressin (Pitkow et al., 2001). The fact that the VP also receives dopaminergic input from the VTA suggests the possibility for interaction between these two neurochemical systems (McBride et al., 1999). As was seen for oxytocin receptors in NAcc, monogamous species display higher vasopressin receptor densities in the VP than do promiscuous species (Young et al., 1997). Since vasopressin exerts its effects through second messengers (Sugimoto et al., 1994), this neuropeptide could interact directly with dopamine via convergent effects on second messenger systems. Although the specific role that VP dopamine may play in pair bonding has not yet been assessed, it is important to note that a systemically administered D2 antagonist impaired the formation of the pair bonds after vasopressin receptor expression was artificially enhanced in this area in voles (Lim et al., 2004b) (Fig. 3C).

7. Interactions between pair bonding and substance abuse

We have alluded to roles for dopamine in a variety of behaviors that might be related to the formation and expression of social attachments. However, as knowledge of pair bonding mechanisms has expanded, it has become apparent that these mechanisms may overlap with those underlying non-social behaviors. Although one might quibble with the suggestion that social attachment might be termed a “disorder” (Insel, 2003), the idea that social bonding shares a common basis with addiction has certain logic to it. In both cases, an external force (drug or mate) takes on special importance, resulting in robust goal-directed behavior. Whether this reflects an intense liking or a strong desire (wanting) (Berridge, 1996) for the drug or mate is subject to debate. Nonetheless, it seems clear that there may be a connection between the need for social contact and pathological activation of central dopamine reward systems. For example, isolated rhesus monkeys will consume alcohol (Kraemer and McKinney, 1985), which activates central dopamine systems in several species (Piepponen et al., 2002) including humans (Boileau et al., 2003). On the other hand, rats that displayed higher levels of social behavior such as play were less likely to later become addicted to amphetamine (Galli and Wolffgramm, 2004). Among humans, cohabitation and especially marriage are associated with decreased substance abuse (Duncan et al., 2003) and social ties impact treatment outcomes of former substance abusers (Havassy et al., 1995; Moos et al., 2002).

How might social bonding and substance abuse interact? As mentioned earlier, it is possible that mechanisms originally evolved for cementing relationships between environmental cues and food sources may have been adapted to cement relationships between individuals. Similarly, it has been

suggested that the mechanisms underlying social attachment have themselves been co-opted a “second” time and underlie the responses to drugs of abuse (Insel, 2003; Lende and Smith, 2002; Panksepp et al., 2002). If this is the case, central changes associated with the formation of social bonds have the potential to impact subsequent responses to addictive substances. For example, activation of cocaine seeking behavior is inhibited by D1 dopamine receptor activation (Self et al., 1996). Since pair bonding increases D1 receptor density, it is possible that pair bonded animals may be less susceptible to the addictive properties of drugs of abuse. In fact, preliminary studies from our laboratory suggest that pair bonded male voles are less susceptible to the reinforcing effects of amphetamine (Aragona et al., 2004a). Such a result could account for the suggestion that strong social attachments may be “protective” against substance abuse (Ellickson et al., 1999; Recio Adrados, 1995).

The converse also is possible; previous substance abuse may alter the brain in such a way that it becomes difficult for a person to form and maintain meaningful social attachments. Such an outcome could have serious consequences in the form of such societal ills as divorce and child abuse. Given all of the social, cultural, and economic variables that influence human behavior, it is not possible to ascribe absolute causal relationships. Nonetheless, there is some indication that substance abuse may negatively impact pair bonding in humans. For example, substance abuse has been found to affect patterns of marriage and divorce (Kaestner, 1995; Kandel et al., 1994; Yamaguchi and Kandel, 1985).

8. Conclusions

It is well established that strong social bonds offer tremendous benefits in terms of human health and well-being (Seeman and McEwen, 1996). Conversely, the inability to form lasting social bonds is associated with autism and schizophrenia while deficits in social bonding have been implicated in the etiology of eating disorders such as anorexia and bulimia (Chassler, 1997; Ericsson et al., 1996). The work outlined above establishes central dopamine-mediated processes as playing an important role in the formation, expression, and maintenance of social bonds. Understanding the role of central dopamine systems in social bonding not only illuminates an important aspect of human biology, but may also provide insights into human ailments that either affect or are affected by social bonding.

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