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THE ROLE OF MESOCORTICOLIMBIC DOPAMINE IN REGULATING INTERACTIONS BETWEEN DRUGS OF ABUSE AND SOCIAL BEHAVIOR

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Abstract

The use of addictive drugs can have profound short- and long-term consequences on social behaviors. Similarly, social experiences and the presence or absence of social attachments during early development and throughout life can greatly influence drug intake and the susceptibility to drug abuse. The following review details this reciprocal interaction, focusing on common drugs of abuse (*e.g.*, psychostimulants, opiates, alcohol and nicotine) and social behaviors (*e.g.*, maternal, sexual, play, aggressive and bonding behaviors). The neural mechanisms underlying this interaction are discussed, with a particular emphasis on the involvement of the mesocorticolimbic dopamine system.

Keywords

Maternal behavior; social play; pair bonding; aggression; sexual behavior; drug addiction; psychostimulants; cocaine; amphetamine; opiates; morphine; alcohol; mesolimbic; dopamine; nucleus accumbens; prefrontal cortex; ventral tegmental area

Introduction

The profound consequences of substance abuse on social behaviors are readily apparent when one considers the poor parenting (Hawley et al., 1995; Johnson et al., 2002), interpersonal aggressive acts (Chermack et al., 2008; Langevin et al., 1982; Testa et al., 2003), sexual risk behaviors (Inciardi, 1994; Lejuez et al., 2005) and marital instability (Kaestner, 1995) of compulsive drug users. Equally evident is the protective nature of social bonds, including close parent-child relationships (Kendler et al., 2000), healthy family structures and nurturing peer groups (Bell et al., 2000; Ellickson et al., 1999), on the vulnerability to substance abuse. Although reciprocal interactions between drugs of abuse and social behaviors have been thoroughly documented in human and animal studies, the neural mechanisms underlying these behavioral interactions remain largely unknown.

While multiple neural systems undoubtedly underlie both social- and drug-related behaviors, the mesocorticolimbic dopamine (DA) system is in a key position to mediate interactions

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between the two. This system consists of DA producing cells that originate in the ventral tegmental area (VTA) of the midbrain and project to various forebrain regions including the nucleus accumbens (NAcc), medial prefrontal cortex (mPFC) and amygdala. This highly conserved neural circuit is thought to play a critical role in the assignment of motivational value to biologically relevant stimuli, resulting in the production of adaptive behaviors (Kelley and Berridge, 2002; Nesse and Berridge, 1997; Panksepp et al., 2002), including species-specific social behaviors (*e.g.*, pair bond formation in monogamous species and maternal motivation in mammals (Aragona et al., 2006; Curtis et al., 2006; Numan and Stolzenberg, 2009; Young et al., 2008a). Increasing experimental evidence has led to the suggestion that drugs of abuse exert their powerful control over behavior by artificially activating and ultimately altering this circuitry (Kelley and Berridge, 2002; Nesse and Berridge, 1997; Panksepp et al., 2002). Indeed, acute exposure to all known drugs of abuse directly or indirectly activates DA neurotransmission in the NAcc and repeated drug exposure results in enduring alterations in mesocorticolimbic brain regions, particularly the VTA and NAcc (Figure 1) (Berke and Hyman, 2000; Henry et al., 1989; Henry and White, 1995; Hu et al., 2002; Nestler, 2004, 2005; Pierce and Kalivas, 1997). These short- and long-term changes, in turn, modify animal behaviors (Robinson and Becker, 1986), including those of a social nature.

In the following review, we will describe the interaction that occurs between drug use/abuse and social behaviors in humans and animals alike (Table 1). We will focus on the effects of drug intake on maternal, sexual, play, aggressive and bonding behaviors. Our discussion will include the effects of psychostimulants (*e.g.*, cocaine, amphetamine (AMPH), and its derivatives methamphetamine and methlyenedioxy methamphetamine (MDMA)), opiates (*e.g.*, heroin and morphine) and other commonly abused drugs, such as alcohol and nicotine. The role of mesocorticolimbic DA in each behavior will be described as will be evidence to suggest that drug-induced alterations in this system may underlie the effects of drugs of abuse on behavior. Finally, we will discuss studies that have investigated the impact of social experiences and the presence or absence of strong social attachments on the vulnerability to drug abuse.

1. Maternal Behavior

1.1. Drug effects on maternal behavior

The display of maternal behavior after parturition is intrinsically motivated and exceptionally stable across mammalian species, yet a variety of studies have demonstrated that its integrity can be compromised by drugs of abuse. In controlled human studies, the deleterious effects of both psychostimulant and opiate addiction on maternal behaviors have been thoroughly documented. Women who abused either type of drug during pregnancy spent less time interacting with their newborns (Gottwald and Thurman, 1994), showed significantly less enthusiasm during mother-infant interactions (Burns et al., 1997), and displayed higher levels of negative parenting behaviors (Johnson et al., 2002) and less overall parental involvement (Suchman and Luthar, 2000) than non-drug abusing women. Additionally, mothers who continued drug use after parturition showed less maternal responsiveness than mothers who remained drug free (Johnson et al., 2002; Schuler et al., 2000), and demonstrated physical and emotional neglect toward their children and a loss of interest in care-giving when under the influence (Hawley et al., 1995). These and other studies indicate the profound negative consequences of drug abuse on maternal behavior. However, confounding factors within these studies—including socioeconomic status, preexisting psychopathologies and participant polydrug use—make it difficult to interpret the contribution of a specific drug or temporal pattern of drug exposure to the observed behavioral outcomes.

Nonhuman primate (Schiorring and Hecht, 1979) and rodent models have been used to examine the effects of drug exposure on maternal behavior under more controlled conditions. The vast majority of these studies have used laboratory rats to document the disruptive effects of opiate (Bridges and Grimm, 1982; Grimm and Bridges, 1983; Mayer et al., 1985; Slamberova et al., 2001), AMPH (Frankova, 1977; Piccirillo et al., 1980), methamphetamine (Slamberova et al., 2005a, 2005b), and cocaine (Febo and Ferris, 2007; Johns et al., 1994; Kinsley et al., 1994; Vernotica et al., 1996; Vernotica et al., 1999; Zimmerberg and Gray, 1992) exposure during gestation and/or after parturition on proactive, motivated maternal behaviors commonly displayed by this species, including pup retrieval, pup licking/grooming and nest building behavior (Numan and Stolzenberg, 2009). Here, we will review these studies, focusing first on the short-, and then on the long-term effects of drug exposure on these maternal behaviors in the postpartum rat (dam).

A variety of studies have indicated that drugs of abuse alter maternal behaviors in rats shortly after administration. Dams exposed to AMPH or cocaine during the postpartum period demonstrated reduced pup licking, increased latencies to contact and retrieve pups and/or reduced nest building behaviors when compared to saline-injected controls (Frankova, 1977; Piccirillo et al., 1980; Zimmerberg and Gray, 1992). Similarly, cocaine exposure throughout gestation and during the postpartum period impaired nest building behavior and decreased the percentage of females that retrieved and grouped pups (Kinsley et al., 1994; Vernotica et al., 1996). These effects may be brain region-specific, as cocaine microinfusion directly into the medial preoptic area (MPOA) and NAcc—two regions intricately involved in maternal behavior (Numan and Stolzenberg, 2009)—but not into the caudate putamen (CP) or dorsal hippocampus, impaired pup retrieval (Vernotica et al., 1999). It is important to note that in the studies described above, maternal behaviors were tested shortly after injection (*i.e.*, while drugs were still present in the bloodstream/brain). Therefore, it is possible that the drugs effects on maternal behavior were secondary to their effects on other behaviors, such as locomotor activity and stereotypy (Kunko et al., 1998). Indeed, of the studies that tested these alternate measures, almost all noted differences in locomotor activity and/or stereotypy between drug- and saline-treated groups (Frankova, 1977; Piccirillo et al., 1980; Vernotica et al., 1996; Vernotica et al., 1999). However, an argument for the direct action of drugs of abuse on maternal behavior is supported by the temporal discordance between altered locomotor behavior and impaired maternal behavior (*i.e.*, maternal behaviors remained disrupted after locomotor activity had returned to normal) (Vernotica et al., 1999).

Significant disruptions in maternal behavior persist beyond the acute phase of drug exposure. For example, pregnant rats treated with cocaine or methamphetamine throughout gestation and then withdrawn from drug treatment during the peripartum period contacted and/or groomed pups less and displayed longer latencies to build nests and/or to retrieve all pups to the nest than saline-treated females when tested at various postpartum time points (Johns et al., 1994, 1997b; Slamberova et al., 2005b). Additionally, repeated morphine administration during pregnancy increased the latency to retrieve pups and decreased licking and grooming behavior when tested on postnatal days 12 or 23, respectively (Slamberova et al., 2001). In contrast to these effects, maternal behavior was enhanced when cocaine was administered before pregnancy and in a regimen sufficient to induce behavioral sensitization (*i.e.*, exacerbation of stereotypies or general locomotion upon repeated drug exposure) (Febo and Ferris, 2007). In this study, virgin females were given daily intraperitoneal (i.p.) injections of cocaine for 14 days, a treatment paradigm that resulted in behavioral sensitization. Thereafter, the females were housed with a sexually-experienced male for 5 days and left undisturbed throughout gestation and postpartum days 1–2. Maternal behavior testing on postpartum days 3–4 revealed a shorter latency to retrieve all pups, indicating enhanced maternal behavior in cocaine-sensitized dams. It is possible that the differential

effect on motivated maternal behaviors described in these studies is due to the time of drug exposure (*i.e.*, before or during gestation). However, it is also possible that the development of sensitization to cocaine, which was only noted in the latter study, could have increased the motivation to seek a natural incentive, in this case pups (Febo and Ferris, 2007). This concept of "cross-sensitization" will be discussed in more detail later.

The use of conditioned place preference paradigms may allow for a more lucid interpretation of the effects of drugs of abuse on maternal motivation. Based upon classical conditioning, a conditioned place preference reflects a preference for an environmental context (conditioned stimulus) that has been paired with a primary reinforcer (unconditioned stimulus), such as a drug (Bardo and Bevins, 2000). Using this paradigm, cocaine has been shown to be a potent reinforcer for postpartum female rats. When tested during early or late postpartum phases, female rats readily form conditioned place preferences to cocaine- but not saline-paired environments (Seip et al., 2008). Importantly, pups are also powerful reinforcers. Maternal females readily form conditioned place preferences to pup-associated chambers (Wansaw et al., 2008) and will bar-press multiple times or even cross an electrical grid to gain access to pups (Lee et al., 1999). The reinforcing properties of pups and cocaine have recently been exploited to gain insight into the effects of cocaine on maternal motivation. Using a dual-choice conditioned place preference paradigm to simultaneously assess pup- and cocaine-motivated behaviors, it has been shown that cocaine may impair maternal motivation and that this impairment varies across the postpartum period (Mattson et al., 2001; Seip and Morrell, 2007). Specifically, early postpartum dams preferred a pup-associated chamber over a cocaine-associated chamber, while mid to late postpartum dams preferred the cocaine-associated chamber. These results indicate that dams in the early postpartum period have a high level of maternal motivation, as demonstrated elsewhere (Wansaw et al., 2008), while mid to late postpartum dams may be more susceptible to the reinforcing properties of cocaine.

1.2. Role of mesocorticolimbic DA

Direct investigation into the mechanisms underlying drug impairment of maternal behavior has been scarce. However, a variety of indirect evidence suggests that alterations in the mesocorticolimbic DA system may be involved. This evidence stems from multiple studies detailing the involvement of mesocorticolimbic DA in maternal behaviors and a vast body of literature describing the short- and long-term alterations induced in this circuitry by drugs of abuse. As the latter topic is beyond the scope of this review and has been summarized extensively elsewhere (Di Chiara, 1995; Di Chiara et al., 2004; Hyman et al., 2006; Koob and Nestler, 1997; Kuhar et al., 1991; Nestler, 2005; Pierce and Kalivas, 1997; Thomas et al., 2008; White and Kalivas, 1998), we will focus first on evidence suggesting the involvement of mesocorticolimbic DA in maternal behavior. Then, we will review recent studies that have begun to investigate drug-induced alterations in this DAergic circuitry, specifically in maternal dams, which may interfere with maternal behavior.

The mesocorticolimbic DA system is thought to be intricately involved in a neural circuit that regulates motivated maternal behaviors (for a detailed review see (Numan and Stolzenberg, 2009)). DA is released into the NAcc (Hansen et al., 1993) and mPFC (Febo and Ferris, 2007) when maternal rats interact with or lick/groom pups (Champagne et al., 2004), and blockade of NAcc DA receptors (Keer and Stern, 1999) or lesion of the mPFC (Afonso et al., 2007) disrupts licking/grooming behavior. Nest building is likely mediated by VTA activation, as lesion of the VTA results in the construction of inferior nests by postpartum dams (Gaffori and Le Moal, 1979). Further, a variety of studies have indicated that the VTA, NAcc and mPFC are all important for the expression of normal pup retrieval. For example, using an electroencephalogram (EEG) to measure real-time electrical activity during maternal behavior, it has been shown that activity is increased in the VTA and mPFC

during pup retrieval (Hernandez-Gonzalez et al., 2005). Consequently, both VTA inactivation (Numan and Stolzenberg, 2009) and mPFC lesion (Afonso et al., 2007) disturb pup retrieval in postpartum rats. This effect is likely mediated by dopaminergic activity in these regions, as similar disruptive effects on pup retrieval were noted after dopamine depletion in the VTA or NAcc (Hansen, 1994; Hansen et al., 1991). Taken together, these studies indicate that the mesocorticolimbic DA system plays an important role in the display of maternal behavior.

While it is well-accepted that DA receptor activation, particularly in the NAcc, is essential for the display of maternal behaviors (Keer and Stern, 1999), the contribution of specific receptor subtypes remains controversial. There are two main families of DA receptors, D1-like receptors (D1R) and D2-like receptors (D2R), that differ in their effects on certain behaviors, their anatomical distribution within the NAcc, and their effects on intracellular signaling pathways (Box 1; Figure 2) (Missale et al., 1998; Neve et al., 2004; Sibley and Monsma, 1992). Recent investigation into the relative importance of these receptor subtypes for maternal behavior has yielded conflicting results. In one study, NAcc injection of SCH23390, a D1R antagonist, but not eticlopride, a D2R antagonist, at various postpartum time points disrupted normal pup retrieval (Numan et al., 2005), suggesting a role for D1R, but not D2R, activation in this behavior. However, in another study, NAcc D2R blockade disrupted pup retrieval, suggesting a role for D2R activation in maternal behavior as well (Silva et al., 2003).

Box 1

The complexity of DA neurotransmission within the NAcc

Five main subtypes of DA receptors have been classified to date, D1-, D2-, D3-, D4- and D5-receptors, and these subtypes are often grouped into two main families, D1-like receptors (D1R), which include both the D1- and D5-receptor subtypes, and D2-like receptors (D2R), which include the D2-, D3-, and D4-receptor subtypes (Missale et al., 1998; Neve et al., 2004). DA released in the NAcc may bind to either D1Rs or D2Rs, as both receptor families are present in this brain region (Cooper et al., 2003), and a variety of studies have demonstrated the importance of NAcc D1R activation, D2R activation, or concurrent activation of both receptor types in specific behaviors. In many cases, D1R and D2R activation within the NAcc have opposite effects on behavior. This phenomenon has been observed for both social (Aragona et al., 2003; Aragona et al., 2006) and drug-related (Self et al., 1996) behaviors. DA receptor-specific effects on behavior may be related to differences in the distribution of D1Rs and D2Rs within the NAcc and/or differences in the effects of D1R and D2R activation on intracellular signaling pathways and cellular activation, as described below.

The vast majority of neurons in the NAcc are GABA-producing medium spiny neurons (MSNs) (Meredith, 1999). These neurons can be divided into subpopulations that differ in their projection fields, their neurochemical phenotypes, and the type of DA receptor that they express (Gerfen et al., 1990; Surmeier et al., 2007). D1Rs are primarily expressed on MSNs that project to midbrain regions, such as the VTA, and produce the endogenous opioid dynorphin. D2Rs, instead, are primarily expressed on MSNs that project to the ventral pallidum and subthalamic nucleus and produce the endogenous opioid enkephalin. However, it should be noted that some MSNs co-express both receptor types (Lee et al., 2004). Additionally, D2Rs that function as autoreceptors are also present within the NAcc and are located on DAergic terminals themselves (Khan et al., 1998). Due to the different projection fields of MSNs expressing D1Rs and D2Rs, and the different roles of DA receptors within the NAcc (post-synaptic receptor vs.

autoreceptor), activation of DA receptors in this region lead to changes in distinct regions of the brain that may mediate different aspects of behavior.

Although activation of D1Rs and D2Rs lead to similar effects on some intracellular signaling pathways, it leads to differential regulation of the cyclic adenosine 3′, 5′-monophosphate (cAMP) intracellular signaling pathway (Missale et al., 1998; Neve et al., 2004), a pathway that is of particular interest to the current topic as it has been implicated in both social (Aragona and Wang, 2007) and drug-related (Lynch and Taylor, 2005; Self et al., 1998) behaviors. D1Rs and D2Rs oppositely regulate the cAMP signaling cascade through the alpha subunits of the G-proteins with which they interact (Figure 2) (Missale et al., 1998; Neve et al., 2004). Briefly, activation of D1Rs—which are coupled to stimulatory G-proteins ($G\alpha_s$ and $G\alpha_{olf}$)—leads to the activation of adenylyl cyclase (AC), an increase in the production of the second messenger cAMP, and an increase in protein kinase A (PKA) activation. Active PKA phosphorylates transcription factors and depolarizing ion channels, leading to gene transcription and increased cellular activity, respectively. Instead, activation of D2Rs—which are coupled to inhibitory G-proteins ($G\alpha_i$ and $G\alpha_o$)—inhibits AC activation, cAMP production, PKA activity and its downstream effects. Further, although D1Rs and D2Rs are traditionally thought to have independent effects on intracellular signaling pathways, as described above, new evidence suggests that these receptors may interact with one another to mediate intracellular signaling. In cells in which both D1Rs and D2Rs are expressed, these receptors can form heteromeric D1–D2 dopamine receptor signaling complexes that have unique effects on intracellular signaling (Rashid et al., 2007). Taken together, the existence of multiple DA receptor subtypes, coupled with their differential neuroanatomical location within the NAcc, and their differential effects on intracellular signaling highlight the complexity of DA neurotransmission within the NAcc.

The significant involvement of mesocorticolimbic DA in maternal behavior led researchers to hypothesize that the effects of drugs of abuse on maternal behavior may be a consequence of drug-induced alterations in DA neurotransmission (Vernotica et al., 1996; Vernotica et al., 1999). Indeed, all known drugs of abuse directly or indirectly activate mesocorticolimbic DAergic neurotransmission and chronic drug use results in lasting adaptations in the VTA, NAcc and mPFC (Koob, 1992; Nestler, 2005)—brain regions whose normal function, as described above, is essential for maternal behavior. However, research directly investigating the neural substrates that may underlie the drug-induced impairment of maternal behavior has only just begun and to our knowledge, has focused almost exclusively on cocaine.

Using functional magnetic resonance imaging (fMRI), a recent study revealed that acute i.p. cocaine administration induced differential patterns of brain activation between virgin females and maternal lactating dams (Ferris et al., 2005). In virgins, cocaine treatment activated mesocorticolimbic brain regions, inducing a positive blood-oxygenation-level-dependent (BOLD) signal in the NAcc and mPFC. This pattern of activation is very similar to that noted in male rats (Luo et al., 2003) and other species (Breiter et al., 1997) after cocaine administration, and to the pattern induced by pups in lactating dams. In contrast, i.p. cocaine treatment in lactating dams resulted in a noticeable absence of mPFC activation, an anatomically altered activation within the NAcc, and a robust negative BOLD signal change throughout the mesocorticolimbic DA system (Ferris et al., 2005), indicating that exposure to cocaine may interfere with the DAergic substrates in lactating dams that are essential for maternal behavior. In another study, the effect of previous cocaine experience on patterns of pup-induced activation within the mesocorticolimbic DA system of lactating dams was examined. Females sensitized to cocaine before pregnancy showed significantly less BOLD activation in the mPFC during pup interaction than saline-treated dams (Febo and Ferris, 2007). Further, baseline levels of DA in the mPFC—as measured by *in vivo* brain

microdialysis—were lower in cocaine-sensitized dams than saline-treated subjects, however pup-induced DA release in this region was similar between groups (Febo and Ferris, 2007). Importantly, these differences in pup-induced neuronal activation and baseline DA levels were present nearly 30 days after the final cocaine injection, suggesting that repeated drug exposure can result in enduring changes within mesocorticolimbic brain regions implicated in maternal behavior. While this evidence indicates that alterations in mesocorticolimbic DA may indeed be involved, further investigation is needed to understand specific mechanisms by which drugs of abuse alter maternal behaviors.

2. Sexual Behavior

2.1. Drug effects on sexual behavior

Controlled studies detailing the effects of drugs of abuse on human sexual behavior are rare. However, self-report studies note that drugs of abuse profoundly impact the sexual behavior of men and women. Prosexual effects, including increased sexual arousal and desire, enhanced performance and pleasure, and intensified orgasms have been reported by AMPH, MDMA, cocaine and heroin users alike (El-Bassel et al., 2003; Kall, 1992; McElrath, 2005; Rawson et al., 2002). Intriguingly, negative effects of these drugs are also commonly reported, including sexual dysfunction and a loss of sexuality during periods of addiction (De Leon and Wexler, 1973; El-Bassel et al., 2003; Mintz et al., 1974; Weatherby et al., 1992). The directionality of this impact seems to depend on many factors including drug type, dose, gender, and intake history, baseline levels of sexual activity and expectations of drug effects.

To systematically gain insight into the effects of specific drugs of abuse on sexual behaviors, laboratory studies have employed the rat as an animal model. As noted above, drugs of abuse alter both appetitive (*e.g.*, sexual arousal and desire), and consummatory (*e.g.*, copulation proper), aspects of sexual behavior, and do so through combined actions on central and peripheral systems. Here, we will focus on drug-induced alterations in the appetitive (*i.e.*, motivated) aspects of sexual behavior, as a role for mesocorticolimbic DA in sexual motivation has been well established (the reader is referred elsewhere for a discussion of drug effects on consummatory sexual behaviors (Pfaus et al., 2009)). In the male rat, female-directed investigative behaviors (*e.g.*, sniffing and grooming), latencies to mount and intromit, postejaculatory intervals, proportion of males to copulate and conditioned level changes made in search of a female in a bi-level apparatus are often used as indices of sexual motivation (Everitt, 1990; Mendelson and Pfaus, 1989). In female rats instead, sexual motivation can be quantified by the occurrence of proceptive or soliciting behaviors, including hopping, darting, ear-wiggling and pacing of sexual stimulation (Erskine, 1989).

Studies in both male and female rats have indicated that sexual motivation may be altered by drugs of abuse when delivered immediately prior to behavioral testing. Psychostimulants, including AMPH, MDMA and cocaine, produce dose-dependent decreases in sexual motivation in sexually-experienced males. This decrease is evidenced by a reduction of anticipatory level changes and proportion of copulating males, as well as by an increase in postejaculatory intervals following drug treatment (Bignami, 1966; Cagiano et al., 2008; Dornan et al., 1991; Pfaus et al., 2009). However, as described in each study, these effects are largely due to competing locomotor activation and stereotypies induced by drug treatment. In contrast, psychostimulant exposure enhances sexual motivation in sexually-naïve males. Indeed, AMPH treatment reduced mount and intromission latencies in virgin males (Agmo and Picker, 1990). In females, the effects of acute psychostimulant exposure are equally complicated, as both increases and decreases in proceptive and soliciting behaviors have been found depending on the drug used and hormonal status of the animals (Guarraci and Clark, 2003; Guarraci et al., 2008; Holder et al., 2010; Pfaus et al., 2009).

Inconsistencies have been reported concerning the acute effects of depressants on sexual motivation in male rats. For example, while increases in anticipatory level changes have been noted after acute administration of alcohol (Ferraro and Kiefer, 2004), suggesting a facilitation of sexual motivation, similar doses delayed operant responding to gain access to a sexually receptive female (Scott et al., 1994), indicating a decrease in sexual motivation. Further, acute morphine injection significantly increased female-directed behaviors, including sniffing, grooming, pursuing and mounting in one study (Mitchell and Stewart, 1990), but had no effect on these or other appetitive behaviors in another (Pfaus et al., 2009).

Consistency has been achieved, however, in the examination of the effects of repeated psychostimulant exposure—particularly treatment paradigms that result in behavioral sensitization—on sexual motivation in both male and female rats (Afonso et al., 2009; Fiorino and Phillips, 1999a, 1999b; Guarraci and Clark, 2003; Nocjar and Panksepp, 2002). Collectively, these studies have indicated an enduring enhancement of sexual motivation following the cessation of drug treatment. For example, in one study, male rats were given a sensitizing regimen of AMPH injections (i.p.) and were tested for sexual behavior three weeks following the final AMPH administration (Fiorino and Phillips, 1999b). On the first test day, AMPH-treated virgin males displayed significantly shorter latencies to mount and intromit, yet displayed no changes in locomotor activity, indicating that AMPH treatment enhanced sexual motivation *per se*. Accordingly, AMPH-treated rats also made significantly more level changes in anticipation of a sexually receptive female than saline-treated rats on the final test day (Fiorino and Phillips, 1999b). Similar findings have been documented in females, as repeated intermittent AMPH exposure increased the number of solicitations, hops and darts displayed in the presence of a male (Afonso et al., 2009) and decreased the latency to return to a male during paced mating behaviors (Guarraci and Clark, 2003) for up to three weeks following the cessation of drug treatment. Taken together, these studies indicate that a sensitizing regimen of AMPH exposure may result in an enduring “cross-sensitization” to sexual incentives.

2.2. Role of mesocorticolimbic DA

We will focus on the concept of “cross-sensitization” to discuss how alterations in mesocorticolimbic DA may underlie the reliable enhancement of sexual motivation induced by repeated exposure to psychostimulant drugs of abuse. The incentive sensitization theory of addiction (Robinson and Berridge, 1993, 2008) postulates that repeated exposure to drugs of abuse (under certain conditions) persistently alters the neural circuitry responsible for assigning salience to stimuli. These neuroadaptations result in the sensitization of salience attributed to drug incentives, and thus a pathological motivation to seek drugs. Importantly, drug-induced neuroadaptations may also alter the incentive properties of natural stimuli, increasing the motivation for natural reinforcers, such as sucrose (Avena and Hoebel, 2003), food (Bakshi and Kelley, 1994), or in this case, a sexually receptive partner (Fiorino and Phillips, 1999b; Guarraci and Clark, 2003).

Studies on the neurobiology of sensitization have indicated that mesocorticolimbic DAergic neurons undergo both pre- and post-synaptic alterations following chronic drug exposure, as reviewed in detail elsewhere (Pierce and Kalivas, 1997; White and Kalivas, 1998). For example, while acute exposure to psychostimulant drugs of abuse increased extracellular DA levels in the NAcc (Di Chiara et al., 1993; Hurd and Ungerstedt, 1989), this DA increase was significantly enhanced after repeated treatment with psychostimulants, a result due to both increased activity of DA neurons and alterations in DA axon terminals (for review, see (Pierce and Kalivas, 1997)). Additionally, changes in DA receptor activity have been noted following repeated psychostimulant administration, including a persistent enhancement of NAcc D1R sensitivity (Henry et al., 1989; Henry and White, 1991, 1995;

Simpson et al., 1995). Finally, enduring structural modifications in NAcc and PFC neurons also occur, including increased dendritic length, branching and density of dendritic spines (Robinson et al., 2001; Robinson and Kolb, 1997).

Such psychostimulant-induced changes are of interest to this discussion because the mesocorticolimbic DA system plays an integral role in sexual motivation. DA is released into the NAcc of male and female rats upon the presentation of a sexually receptive partner, prior to copulation (Becker et al., 2001a; Pfaus et al., 1990; Pfaus et al., 1995). Furthermore, in females, DA release is enhanced during the pacing of sexual stimulation (Becker et al., 2001a; Mermelstein and Becker, 1995). In males, NAcc DA depletion increased, while the stimulation of NAcc DA release reduced, the latency to mount and intromit, yet had no effect on the number of mounts and intromissions (Everitt, 1990), indicating a direct action of NAcc DA neurotransmission on sexual motivation. Multiple studies have indicated the importance of DA receptor activation for sexual motivation. The blockade of NAcc DA receptors via haloperidol reduced the number of anticipatory level changes before introduction of a female to a bi-level testing apparatus, indicating that activation of DA receptors in the NAcc is involved in sexual motivation (Pfaus and Phillips, 1991). Activation of D2Rs in the NAcc may be of particular importance, as D2R blockade increased mount and intromission latencies (Everitt, 1990), however additional receptor specific manipulations in the NAcc are needed to verify a role for a particular family of DA receptors in the appetitive aspects of sexual behavior. Mesocorticolimbic DA has been further implicated in sexual motivation as electrical stimulation of the VTA decreased mount, intromission and ejaculation latencies in male rats (Eibergen and Caggiula, 1973; Markowski and Hull, 1995), while VTA lesions increased postejaculatory intervals (Brackett et al., 1986).

Given the critical role of mesocorticolimbic DA in appetitive sexual responses (Everitt, 1990; Melis and Argiolas, 1995), psychostimulant-induced changes associated with drug sensitization could underlie the enhancement of sexual motivation. To our knowledge however, only one study has directly investigated this possibility (Fiorino and Phillips, 1999a). In this study, male rats were given a sensitizing regimen of AMPH injections (i.p.) and were tested three weeks later for sexual behavior. During behavioral testing, microdialysis was performed in the NAcc to measure DA efflux. No differences in basal extracellular levels of NAcc DA between AMPH- and saline-treated rats were found. However, DA release was significantly higher in AMPH-sensitized rats when placed in proximity to a sexually receptive female. Additionally, when allowed to interact with the female, AMPH-sensitized rats had a greater increase in DA efflux during the first 10 min copulatory sample than saline-treated rats, and displayed significantly shorter latencies to mount. These results indicate that enhanced NAcc DA release in response to a sexual incentive may underlie increased sexual motivation in AMPH-sensitized rats (Fiorino and Phillips, 1999a). Therefore, just as a priming drug injection elicits elevated DA efflux in psychostimulant-sensitized animals (Pierce and Kalivas, 1997), so does exposure to a sexually receptive female, supporting the notion that a sensitizing regimen of drug exposure may result in an enduring “cross-sensitization” to sexual incentives. Future investigations of mechanisms that may underlie this phenomenon are needed and could provide useful insight into treatments for sexual desire disorders in humans (Fiorino and Phillips, 1999b).

3. Social Play

3.1. Drug effects on social play

Social play (also called rough and tumble play) between juvenile mammals is thought to be fundamentally involved in the development, practice and refinement of skills necessary for the normal display of social behaviors in adulthood (Panksepp et al., 1984). Consequently,

the deprivation of play during juvenile development results in salient behavioral consequences, including altered affiliative, aggressive and sexual behaviors later in life (for review, see (Vanderschuren et al., 1997)). In the following section, we will discuss how exposure to drugs of abuse, either acute exposure in juveniles or repeated exposure during prenatal development, can severely alter social play behaviors.

Social play in rats is characterized by a number of behavioral acts including pinning, pouncing, nape attacks, boxing, wrestling and social grooming (Panksepp et al., 1984; Vanderschuren et al., 1997), all of which are severely disrupted following acute exposure to a wide variety of drugs of abuse (with the notable exceptions of morphine and ethanol). For example, peripheral injection of methylphenidate (MP), a psychostimulant drug that, like cocaine, blocks DA reuptake and elevates extracellular DA levels (Ferris and Tang, 1979), virtually eliminated play behaviors in young rats (Beatty et al., 1982; Vanderschuren et al., 2008). In experiments where MP was given to just one member of a play dyad, MP-treated animals did not pounce upon the saline-treated partner although this partner attempted to solicit play, indicating that MP suppressed both the initiation of play and the responsiveness to play initiation (Vanderschuren et al., 2008). Importantly, no alterations in locomotor activity were evident during this social encounter. Peripheral injection of AMPH significantly decreased the duration of social play and the number of pins displayed during play, yet increased social investigation in multiple studies (Beatty et al., 1984; Beatty et al., 1982; Sutton and Raskin, 1986). Additionally, caffeine and nicotine also disrupted play behaviors (Holloway and Thor, 1985; Thiel et al., 2009). However, the acute effects of nicotine may be temporally mediated as nicotine decreased social play when given subcutaneously within 5min of behavioral testing, and increased social interactions 10 and 30min after injection (Irvine et al., 1999; Thiel et al., 2009; Trezza et al., 2009). In addition to nicotine, exposure to morphine (Normansell and Panksepp, 1990; Vanderschuren et al., 1995a; Vanderschuren et al., 1995b) and ethanol (Trezza et al., 2009) also enhanced play between partners without altering anxiety-related, social exploratory or locomotor behaviors.

Repeated exposure, particularly prenatal exposure, to drugs of abuse also results in alterations of juvenile social play behavior. In humans, children who were prenatally exposed to either cocaine or heroin demonstrated fewer spontaneous play events than non drug-exposed controls and these play events were disorganized and non-thematic (Rodning et al., 1989). In rats, cocaine-exposed offspring pinned play partners less (Wood et al., 1994) and elicited less play solicitation from conspecifics (Wood et al., 1995). Importantly, the effects of gestational cocaine exposure may persist into adulthood. Rats prenatally-exposed to cocaine exhibited less social interaction, including sniffing, following, grooming, boxing and wrestling with a partner, than saline-exposed rats when tested as adults at 120 days of age (Overstreet et al., 2000). Opposite effects on social play have been noted after prenatal exposure to morphine. Specifically, rats prenatally-exposed to morphine pinned play partners significantly more at 3 and 4 weeks of age and exhibited more social approach and less social avoidance in adulthood (Niesink et al., 1996).

3.2. Role of mesocorticolimbic DA

Like other naturally motivated behaviors, social play is reinforcing (*e.g.*, animals will negotiate complex mazes in order to engage in brief periods of social play with a play partner) (Normansell and Panksepp, 1990), and is mediated, in part, by mesocorticolimbic DA (Panksepp et al., 1984; Vanderschuren et al., 1997). Social play increased DA levels and DA turnover in the forebrain of juvenile rats (Panksepp, 1993). The frequency and/or duration of pinning behavior and/or social grooming was significantly decreased by haloperidol, a general DA receptor antagonist (Beatty et al., 1984; Holloway and Thor, 1985; Niesink and Van Ree, 1989). Additionally, low doses of apomorphine, which are thought to preferentially activate presynaptic DA receptors (*i.e.*, autoreceptors), and thereby

inhibit DA release, decreased the frequency and duration of pinning and grooming behavior (Niesink and Van Ree, 1989). In contrast, higher doses of apomorphine, which likely activate both pre- and postsynaptic DA receptors, stimulated pinning behavior (Beatty et al., 1984). Taken together, these studies suggest the involvement of DA neurotransmission in social play. Further, neonatal rats given intraventricular injections of 6-hydroxydopamine (6-OHDA), had significantly depleted DA levels in the dorsal striatum and NAcc and showed altered offensive and defensive play behaviors as juveniles that led to the truncation of playful sequences and the transition to other, non-play behaviors, such as allogrooming (Pellis et al., 1993). While mesocorticolimbic DA may therefore be important for social play, the involvement of specific brain regions and DA receptor families is still largely unknown.

The mechanisms by which acute drug exposure may alter play behavior are unclear. As psychostimulants directly increase DA levels in the NAcc, the behavioral effects of these drugs are often attributed to their impact on DA neurotransmission. However, pretreatment with DA receptor antagonists did not influence the MP- or AMPH-induced disruption of play behaviors (Beatty et al., 1984; Vanderschuren et al., 2008), indicating that altered DA neurotransmission may not be responsible for the effects of these drugs on social play. As these pharmacological manipulations were systemic, further central manipulations may be required to more definitively evaluate the involvement of central DA in the effects of MP and AMPH on social play. DA receptor activation, however, is clearly important for the positive acute effects of nicotine and ethanol on social play, as the behavioral effects of these drugs were blocked by pretreatment with the DA receptor antagonist a-flupenthixol (Trezza et al., 2009).

Although few studies have directly examined the neural mechanisms underlying the alteration of social play in subjects prenatally exposed to drugs of abuse, it has been suggested that prenatal exposure to drugs of abuse, particularly cocaine, results in lasting alterations in central DA systems, and that these alterations may underlie impaired behavior later in life (Spear et al., 1989). Given that monoamines play an important role in neural development (for review see (Levitt et al., 1997)) and DAergic afferents and receptors are notably present in limbic regions during brain development (Schambra et al., 1994; Tennyson et al., 1973), these regions are likely vulnerable to the effects of drugs of abuse during this time period. Indeed, subjects prenatally exposed to cocaine have pronounced anatomical changes and altered D1R-G protein coupling in DA-rich areas of the cerebral cortex (Levitt et al., 1997). Densities of DA receptors are also altered in both mesocorticolimbic and nigrostriatal DAergic brain regions as a consequence of prenatal cocaine exposure, and these alterations seem to be moderated by both age and sex of offspring (Dow-Edwards et al., 1990; Ferris et al., 2007; Glatt et al., 2000; Leslie et al., 1994; Scalzo et al., 1990). Further, many of these regions, including the NAcc, VTA, amygdala, MPOA, substantia nigra and CP exhibit significantly reduced metabolic activity as a consequence of prenatal cocaine exposure (Dow-Edwards et al., 1990). Psychopharmacological experiments have also supported the suggestion that *in utero* cocaine exposure may result in lasting alterations in DA systems, as cocaine-exposed juveniles have altered sensitivities to DAergic manipulations (Spear et al., 1989). Moreover, meta-analysis of the existing literature has indicated that age moderates the effects of prenatal cocaine on DA levels specifically within the striatum, such that DA levels tend to be decreased in adolescents prenatally exposed to cocaine and marginally increased in adults (Glatt et al., 2000). While these studies provide important information about the effects of prenatal cocaine exposure on DAergic neural substrates, future studies will need to examine whether these or other alterations are responsible for the drug-induced impairment of social play.

4. Aggressive Behavior

4.1. Drug effects on aggressive behavior

Another prominent effect of drug abuse on human social behavior is the augmentation of aggression. When tested in placebo-controlled laboratory settings, men and women that consumed alcohol displayed significantly higher levels of aggression toward others (Chermack and Taylor, 1995; Giancola et al., 2009). Further, substance abuse has been strongly associated with weapon-related violence and homicide (Hagelstam and Hakkanen, 2006; Madan et al., 2001; Spunt et al., 1998), intimate partner aggression, including partner-directed physical and psychological aggression (Chermack et al., 2008; O'Farrell and Fals-Stewart, 2000), sexual abuse (El-Bassel et al., 2001) and child abuse (Haapasalo and Hamalainen, 1996; Mokuau, 2002; Walsh et al., 2003). Collectively, drug related violence leads to family system dysfunction and incarceration (Krug et al., 2002), creating significant societal concerns.

While aggression research in humans has provided valuable information regarding the relationship between drug abuse and violence, non-human primate and rodent models have been employed to systematically examine the effects of drug exposure on aggression. In rodents, aggressive behavior is typically classified into two distinct categories: offensive and defensive. Examples of offensive aggression include threats, attacks, bites, and chases whereas defensive aggression often includes upright posturing and retaliatory attacks (Blanchard and Blanchard, 1977; Blanchard et al., 1977). While these aggressive behaviors are most often tested in males, during intermale encounters, they are also commonly measured in females after parturition, and under these conditions, are collectively referred to as 'maternal aggression' (Gammie and Stevenson, 2006; Johns et al., 1998a; Johns et al., 1994; Numan, 1994; Siegel et al., 1983). We will focus on research examining these behaviors to describe the effects of acute and repeated drug exposure on aggression in males and females.

Multiple studies have demonstrated that aggressive behaviors may be altered shortly after drug exposure, and that the directionality of these effects depends on the drug and dose administered, as well as individual differences between subjects. For example, while some resident male mice displayed heightened offensive and defensive aggression toward an intruder after low-dose administration of alcohol, aggression in other residents was unaffected or even decreased (Berry, 1993; Miczek et al., 1998), a finding thought to depend on individual differences between subjects. Gamma-hydroxybutyrate (GHB), a relatively new drug with addictive properties, significantly increased offensive aggression (threats and attacks) in male mice at low doses, but decreased attack behavior at high doses (Navarro et al., 2007). Further, low-dose administration of cocaine in males had no effect on offensive aggression, whereas higher doses of either cocaine or AMPH decreased offensive aggression (Darmani et al., 1990; Tidey and Miczek, 1992a), highlighting the importance of drug dose on behavioral outcome. Similar to the effects of cocaine in males, high-dose cocaine treatment decreased offensive maternal aggression in females (Vernotica et al., 1996). The administration of opiate drugs of abuse, such as morphine, has also been shown to alter patterns of aggression, particularly offensive aggression (Ferrari and Baggio, 1982; Gianutsos et al., 1976; Gianutsos et al., 1974; Puri and Lal, 1973; Rodriguez-Arias et al., 1999; Tidey and Miczek, 1992b). For example, male mice injected with morphine displayed enhanced offensive aggression toward other male conspecifics (Rodriguez-Arias et al., 1997). In contrast, morphine injections in lactating female rats decreased offensive maternal aggression toward conspecific males (Kinsley and Bridges, 1986).

Although the short-term effects of drug exposure on aggression seem to depend on many factors, as noted above, repeated exposure to drugs of abuse consistently enhances agonistic

behaviors—specifically those associated with offensive aggression—and these effects are enduring. For example, treatment of male Syrian (*i.e.*, golden) hamsters (*Mesocricetus auratus*) during adolescence with cocaine (DeLeon et al., 2002a; Harrison et al., 2000a; Jackson et al., 2005; Knyshevski et al., 2005a; Knyshevski et al., 2005b; Melloni et al., 2001) significantly increased offensive/escalated aggression in adulthood. Exposure to anabolic steroids—substances which are also commonly abused—during adolescence has also been found to enhance offensive aggression in adulthood (DeLeon et al., 2002b; Harrison et al., 2000b; Melloni et al., 1997; Melloni and Ferris, 1996). Further, repeated drug exposure during gestation elevated subsequent maternal aggression in lactating dams. Specifically, pregnant rats that received daily cocaine injections from gestation day 1–20 displayed increased threats and attacks toward an intruder one to two weeks after parturition (Johns et al., 1997b; Johns et al., 1998b). Interestingly, prenatal drug exposure may affect aggressive behaviors later in life. Adult female dams prenatally exposed to cocaine displayed elevated levels of offensive maternal aggression toward an intruder (McMurray et al., 2008). Further, male mice exposed prenatally to alcohol displayed enhanced offensive aggression in adulthood relative to control males (Krsiak et al., 1977). Withdrawal from repeated drug exposure, particularly from central nervous system depressants, has also been associated with the induction or enhancement of aggression. For example, male mice treated with a daily peripheral injection of morphine for 14 days - which reliably induces morphine dependence, displayed higher levels of offensive aggression during a 48-hour withdrawal period than vehicle-treated littermates (Rodriguez-Arias et al., 1999). Other studies have also documented this withdrawal-induced aggression after repeated treatment with morphine (Ferrari and Baggio, 1982; Gianutsos et al., 1976; Gianutsos et al., 1974; Puri and Lal, 1973; Rodriguez-Arias et al., 1999; Tidey and Miczek, 1992b), and various other drugs including methadone (Singh, 1975), benzodiazepines (Nath et al., 2000) and ethanol (File et al., 1991).

Drug-induced aggression has also recently been examined in the prairie vole (*Microtus ochrogaster*), a socially monogamous rodent species that forms pair bonds after mating. Although sexually naïve male prairie voles are highly affiliative toward unfamiliar conspecific animals, mated males are highly aggressive (as characterized by both offensive and defensive aggressive behaviors) toward unfamiliar strangers (Aragona et al., 2006; Gobrogge et al., 2007; Gobrogge et al., 2009; Insel et al., 1995a; Wang et al., 1997; Winslow et al., 1993). This mating-induced aggression has been termed ‘selective aggression’ because it is directed toward unfamiliar male and female strangers, but not toward the familiar female mate (Insel et al., 1995a; Wang et al., 1997; Winslow et al., 1993). Interestingly, repeated AMPH exposure (1.0 mg/kg i.p. injection per day for 3 days) induced aggression (a combined score of both offensive and defensive behaviors) toward unfamiliar conspecific animals in sexually naïve male prairie voles (Gobrogge et al., 2009). Further, this AMPH treatment not only enhanced aggression toward unfamiliar strangers, but also toward familiar female conspecifics (Gobrogge et al., 2009). These results suggest that the prairie vole could be used in future studies to test interactions between drug exposure and partner-directed aggression, one of the most common forms of drug-induced aggression noted in humans (Chermack et al., 2008; O’Farrell and Fals-Stewart, 2000). Results from these types of studies have the potential to reveal neuromechanisms underlying this behavioral interaction and may allow for the development of novel therapeutics for drug addiction and/or pathological aggression in humans.

4.2. Role of mesocorticolimbic DA

Although many non-DAergic systems have been implicated in aggression (Adams, 2006; Kavoussi et al., 1997; Miczek et al., 2002; Nelson and Trainor, 2007; Siever, 2008), mesocorticolimbic DA may also play an important role. Early research into this matter demonstrated that low frequency electrical stimulation of the VTA and NAcc suppressed

attack behavior induced by hypothalamic electrical stimulation in felines (Goldstein and Siegel, 1980) and neurochemical lesions of the NAcc facilitated apomorphine-induced aggression in rats (Pucilowski and Valzelli, 1986). More recently it was demonstrated that DA release increased in the NAcc of rats during the anticipation and display of an aggressive episode (Ferrari et al., 2003). Further, blockade of NAcc D1Rs decreased aggression toward unfamiliar male conspecifics in pair bonded male prairie voles, indicating that NAcc D1R activation may be important for aggressive behavior (Aragona et al., 2006).

Indirect and direct evidence for a role of mesocorticolimbic DA in drug-induced alterations in aggressive behaviors exists. For example, cocaine-induced maternal aggression has been associated with increased DA content in various mesocorticolimbic brain regions including the VTA and amygdala (Lubin et al., 2003). Further, vervet monkeys chronically treated with methamphetamine had substantially decreased striatal DA content and DA transporter binding levels than saline-injected controls (Melega et al., 2008), however it should be noted that these changes were associated with decreased levels of aggression throughout drug treatment. There are a limited number of studies that have directly assessed the role of mesocorticolimbic DA in drug-induced aggression. Of these studies, many have been performed within a few days of the cessation of repeated drug treatment (*e.g.*, during drug withdrawal). Systemic blockade of DA receptors in general, D1Rs alone, or D2Rs alone, significantly decreased morphine withdrawal-induced aggression (Rodriguez-Arias et al., 1999). However site-specific manipulations have shown the opposite effect. General blockade of NAcc DA receptors or D2Rs alone enhanced morphine withdrawal-induced aggression in rats (Harris and Aston-Jones, 1994), while activation of D1Rs decreased the display of aggressive behavior during morphine withdrawal without changing locomotive behavior (Tidey and Miczek, 1992b). While these studies certainly indicate a role for DA neurotransmission in drug-induced aggression, future studies are needed to clarify the role of mesocorticolimbic DA in this behavior.

5. Pair Bonding

5.1. Drug effects on pair bonding

The formation of enduring social attachments, or pair bonds, between sexual partners occurs in nearly all human societies and is common among the 3–5% of mammalian species that follow a monogamous life strategy (Kleiman, 1977). Despite its highly reinforcing nature, pair bonding can be compromised by drugs of abuse, as evidenced by the disruptive effects of illicit drug use on marital stability (Kaestner, 1995). Recently, we have developed the prairie vole model for the investigation of the neurobiological mechanisms underlying the complex relationship between drugs of abuse and pair bonding. As previously mentioned, prairie voles are highly social, monogamous rodents that form long term pair bonds after mating (Aragona and Wang, 2004; Carter et al., 1995; Insel and Young, 2001; Young et al., 2008a). 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 and Carter, 1996; Pizzuto and Getz, 1998). A reliable behavioral index of pair bond formation in the prairie vole is the development of a preference for a familiar mate over a conspecific stranger, referred to as a partner preference (Insel and Hulihan, 1995b; Williams et al., 1992; Winslow et al., 1993). In the laboratory, partner preference formation is reliably seen after 24 hrs of cohabitation with mating, and endures for at least 2 weeks thereafter (Insel and Hulihan, 1995b).

Recently, we have demonstrated that repeated AMPH exposure inhibits the formation of partner preferences in male prairie voles (Liu et al., 2010). In this study, male prairie voles were divided into four groups that received no injection (intact), a saline injection, or an injection of 1.0 or 5.0 mg/kg AMPH (i.p.) once per day for 3 consecutive days. On the day

immediately following the final injection, subjects were paired with a female for 24hrs of mating and then tested for the formation of partner preferences. Consistent with previous studies, intact and saline-treated prairie voles spent significantly more time with their familiar mate than the stranger (*i.e.*, formed mating-induced partner preferences) (Aragona et al., 2003; Aragona et al., 2006; Winslow et al., 1993). However, males pretreated with AMPH spent equal amounts of time with both animals, indicating that repeated exposure to AMPH prevented partner preference formation (Figure 3A). It is important to note that the effects of AMPH on partner preference formation were not secondary to effects on other behavioral measures, as no differences in mating frequency during the cohabitation period or locomotor activity during the partner preference test were noted between saline- and AMPH-treated animals.

The data described above highlight the deleterious effects of repeated AMPH exposure on social bonding in male prairie voles, however, repeated drug exposure may also negatively affect social bonding in females. Indeed, recent experimental evidence from our laboratory has demonstrated that repeated exposure to AMPH inhibits the formation of mating-induced partner preferences in female prairie voles (Young et al., 2008b). Interestingly, lower doses of AMPH were effective to inhibit this social preference in females than males, indicating that females may be more sensitive to the effects of AMPH than males. This hypothesis has been supported by previous studies in prairie voles—demonstrating a leftward shift in the dose response curve of females in the development of AMPH-induced conditioned place preferences (Aragona et al., 2007)—and has also been supported by studies in other rodent species documenting sexual dimorphisms in the behavioral and neural responses to psychostimulant drugs of abuse (Becker, 1999; Becker et al., 2001b; Roth et al., 2004).

5.2. Role of mesocorticolimbic DA

Previous work from our laboratory and others has demonstrated that mesocorticolimbic DA—particularly DA neurotransmission in the NAcc—is essential for the formation of partner preferences (Aragona et al., 2003; Aragona et al., 2006; Curtis et al., 2003; Curtis and Wang, 2005; Gingrich et al., 2000; Liu and Wang, 2003; Wang et al., 1999). Mating—which facilitates partner preference formation—increases DA activity in the NAcc of both male and female prairie voles (Aragona et al., 2003; Gingrich et al., 2000). Pharmacological blockade of NAcc DA receptors via haloperidol blocks partner preference formation induced by mating while activation of NAcc DA receptors via apomorphine dose-dependently induces partner preference formation in the absence of mating (Aragona et al., 2003). These results indicate that DA neurotransmission in the NAcc plays a critical role in the formation of a pair bond. Additional pharmacological manipulations have demonstrated that the dopaminergic regulation of partner preference formation is receptor specific, such that D1R activation inhibits, and D2R activation facilitates partner preferences. Indeed, activation of D2Rs, but not D1Rs, in the NAcc facilitated the formation of partner preferences in female and male prairie voles, whereas blockade of NAcc D2Rs inhibited partner preference formation (Aragona et al., 2003; Aragona et al., 2006; Gingrich et al., 2000). Additionally, administration of a D1R agonist into the NAcc blocked partner preference formation induced by mating or D2R activation (Aragona et al., 2006). The DA receptor-specific regulation of partner preference formation has been further supported by the manipulation of the cAMP intracellular signaling pathway within the NAcc (Aragona and Wang, 2007). Recall that activation of D1Rs and D2Rs, through the alpha subunits of the G-proteins with which they interact, have opposing effects on cAMP intracellular signaling (Box 1; Figure 2). In a recent study, intra-NAcc injection of a pharmacological agent that inhibits the activation of PKA facilitated partner preference formation (an effect consistent with D2R activation) (Aragona and Wang, 2007). Additionally, intra-NAcc injection of a pharmacological agent that increases PKA activity prevented the formation of mating-

induced partner preference formation (an effect consistent with D1R activation) (Aragona and Wang, 2007). Interestingly, all of the pharmacological manipulations described above affected pair bonding only if performed in the NAcc shell, as opposed to the NAcc core or CP, indicating that the DAergic regulation of pair bonding is also brain region- and subregion-specific (Aragona et al., 2006; Aragona and Wang, 2007).

As mesocorticolimbic DA plays a critical role in partner preference formation and is altered by repeated exposure to drugs of abuse, we hypothesized that alterations in this system may underlie the AMPH-induced impairment of partner preference formation. To investigate this possibility, levels of DA receptor gene and protein expression in mesocorticolimbic brain regions were compared between male prairie voles treated with saline and AMPH (one 1.0 mg/kg i.p. injection per day for 3 consecutive days—the same dosing regimen that inhibited partner preference formation). Males treated with AMPH showed significantly higher levels of D1R, but not D2R, mRNA and protein labeling in the NAcc than males treated with saline, indicating that AMPH exposure increased D1R expression in the NAcc (Figure 3B) (Liu et al., 2010). As changes in the density of only one DA receptor type were noted, these results suggest that AMPH administration may alter the balance between DA receptor subtypes in the NAcc, leading to the inhibition of mating-induced partner preferences through an increased ratio of D1Rs to D2Rs in this region. In an additional experiment, pharmacological blockade of D1Rs before daily AMPH injections dose-dependently eliminated the AMPH-induced impairment of partner preference formation (Liu et al., 2010). Taken together, these data indicate that AMPH exposure may inhibit partner preference formation through a D1R mediated mechanism. This notion is supported by our previous work in prairie voles, which demonstrated that D1R activation not only inhibits the formation of mating-induced partner preferences but also likely plays a role in preventing the formation of additional pair bonds, once one has already been formed (Aragona et al., 2003; Aragona et al., 2006). For example, pair bonded male prairie voles have significantly higher levels of D1R binding in the NAcc than sexually-naïve males (Figure 3C). This elevated level of D1R density is thought to underlie, in part, the display of aggression toward conspecific stranger females (Aragona et al., 2006), including sexually receptive females (Gobrogge et al., 2007; Gobrogge et al., 2009), as NAcc D1R blockade in pair bonded males inhibits selective aggression toward stranger females (Aragona et al., 2006) (Figure 3D). As such, it is thought that this natural form of neuroplasticity (*i.e.*, increased NAcc D1Rs in pair bonded males) functions to maintain established pair bonds by preventing the formation of new ones. As AMPH exposure increases NAcc D1R expression, it is possible that AMPH artificially triggers this neuroplasticity, resulting in the drug-induced impairment of partner preference formation. Indeed, after repeated exposure to AMPH, sexually-naïve male prairie voles display enhanced aggression toward both familiar and unfamiliar females (Figure 3E) (Gobrogge et al., 2009), which could lead to the impairment of pair bonding. Ongoing experiments in our lab are aimed at further investigation of the mechanisms by which AMPH impairs pair bonding in male and female prairie voles with a focus on interactions between mesocorticolimbic DA and neuropeptide systems essential for social behavior.

6. Effects of Social Experience on the Vulnerability to Drug Abuse

6.1. Effects of social experience on drug abuse

While it is clear from the studies described above that drug abuse can profoundly alter social behaviors, there is an increasing amount of evidence to suggest that this relationship is reciprocal. Social experiences and the presence/absence of social attachments and interactions during early development and throughout life can greatly influence drug intake and the susceptibility to drug abuse. Indeed, perturbations in the social environment, particularly during early development, can increase the vulnerability to drug abuse later in

life, while the development of strong social attachments, including parent-offspring and adult pair bonds may protect against substance abuse. This notion has been supported by several studies described below.

Disruptions in the social environment during early development and throughout life may increase the propensity for substance abuse. Indeed, childhood neglect in humans has been associated with an increased risk of alcohol-related problems later in life, an effect most prominent in women (Widom et al., 1995). In rhesus monkeys, alcohol consumption was compared in 4 year olds that had been reared during the first six months of life either by their peers without any access to adults or by their mothers (Higley et al., 1991). When given free access to both an ethanol/sucrose solution and a sucrose control solution, peer-reared subjects consumed significantly more ethanol than mother-reared subjects, indicating that disrupted mother-infant bonds may play a role in later alcohol abuse. Further, in the same study, when 4 year old subjects were separated for multiple days from their cage mates, mother-reared subjects increased their ethanol consumption, indicating that social interactions later in life could also have a profound impact on drug use (Higley et al., 1991).

Maternal separation/deprivation studies in rodents have further demonstrated the importance of early social experiences on responses to drugs later in life. In these studies, maternal separation was defined as the separation of an entire intact litter from the dam for 1 or more hours each day over multiple days within the first few postnatal weeks. Maternal deprivation was similar to maternal separation, except that individual pups were isolated from each other during daily separations. In accordance with the study in rhesus monkeys aforementioned, maternally-separated rats drank significantly more ethanol than normally-reared controls (Huot et al., 2001; Ploj et al., 2003). Importantly, in these studies, no differences in total fluid intake were noted, indicating that early maternal separation directly altered alcohol intake. Similarly, maternally-deprived rats showed significantly increased morphine and AMPH intake and enhanced acquisition of cocaine self-administration as compared to normally-reared controls (Kosten et al., 2000; Vazquez et al., 2006). Importantly, in the self-administration study, no differences in the acquisition of operant responding for food or locomotor activity were noted (Kosten et al., 2000). Taken together, these studies highlight the effects of early disruptions in the social environment on the vulnerability to substance abuse later in life. However it should be noted that genetic factors and the specific time course of social disruptions also play a role (Matthews et al., 1999; van der Veen et al., 2008). Further, in addition to altering drug-associated behaviors, early environmental perturbations can also have a profound effect on social behaviors later in life (Cushing and Kramer, 2005; Lee and Hoaken, 2007; Veenema, 2009). Therefore, it is intriguing to consider the relationship between altered social behavior and the higher vulnerability to drug abuse displayed by adults exposed to negative early life events.

The quality of early life social interactions may also impact later drug use. In humans, for example, the quality of parent-child relationship has been found to influence the likelihood of alcohol and drug dependence later in life (Kendler et al., 2000). Similarly, levels of maternal care in rats, characterized by licking and grooming of pups, have also been correlated with the self-administration of both cocaine and ethanol. Specifically, low levels of licking and grooming were correlated with higher levels of pup drug intake and higher levels of licking and grooming were associated with lower levels of pup drug intake (Francis and Kuhar, 2008). This raises the important point that maternal drug exposure, which disrupts the display of licking and grooming as well as other maternal behaviors, may directly influence drug abuse vulnerability in offspring.

Just as disturbed social interactions may increase the vulnerability to drug abuse, strong social attachments between individuals may protect against substance abuse. In humans,

having an intact nuclear family has been negatively associated with substance abuse problems in general, and the use of “hard” drugs such as AMPH and cocaine (Bell et al., 2000; Ellickson et al., 1999). Further, stable, intimate relationships between adult pairs have been associated with decreased rates of relapse to drug use (Kosten et al., 1987). This notion is further supported by our recent study in which pair-bonded male prairie voles required a higher dose of AMPH to express conditioned place preferences than sexually-naïve males, suggesting that pair bonding experience may decrease AMPH-associated motivation (Liu et al., 2007).

6.2. Role of Mesocorticolimbic DA

Although little is known about the mechanisms underlying the behavioral interactions noted above, childhood neglect in humans and maternal deprivation in non-human primates and rodent species have been associated with altered activity of DA systems. For example, children subjected to maltreatment, of which child neglect is the most prevalent form (National Research Council, 1993), within the first 6 years of life had significantly lower DA beta hydroxylase (the enzyme that converts DA to norepinephrine in neurons) activity than children that had not been maltreated (Galvin et al., 1995). Elevated baseline urinary DA levels have also been associated with childhood maltreatment (De Bellis et al., 1999). Although the functional significance of these alterations is not yet known, it has been suggested that neurophysiological alterations induced by social disruptions early in life may underlie later vulnerability to drug abuse (De Bellis, 2002; Gordon, 2002). Support for this idea comes from studies in rodent models. For example, maternal deprivation, which enhanced the self-administration of various drugs of abuse (as described above) resulted in enhanced NAcc DA transmission in response to AMPH and cocaine, suggesting an increased sensitivity of mesocorticolimbic DA to drugs of abuse. Further, this enhanced sensitivity was noted in infant, juvenile and adult rats, indicating an enduring effect of maternal deprivation on the mesocorticolimbic DA system (Kehoe et al., 1998; Kehoe et al., 1996; Kosten et al., 2003, 2005). Drug intake may also differentially affect mesocorticolimbic DA receptor levels depending on social experience, as maternally-separated rats had significantly lower D1R binding levels in multiple brain regions, including the NAcc core, after ethanol consumption compared to non-treated rats (Ploj et al., 2003).

Summary and Future Directions

The evidence reviewed here suggests a significant interaction between drugs of abuse and social behavior. Acute exposure to both psychostimulants and central nervous system depressants transiently alters social behaviors, and repeated use may lead to enduring deficits in adaptive behaviors such as maternal care and pair bonding, and the compulsive display of sexual behaviors and aggression. Interestingly, while drug exposure reduces the display of some social behaviors, it facilitates the display of others. The mechanisms underlying these differential effects on behavior are unclear. However, social behaviors are complex and are regulated by multiple neural circuits. While some circuits are likely involved in all social behaviors, others may be recruited during specific social interactions. Differences in the neural circuitry that mediate each behavior may explain why drugs of abuse increase the display of some behaviors, but decrease the display of others. Further, as described above, drug type may differentially mediate social behaviors (*e.g.,* morphine and ethanol increase, while psychostimulants decrease, social play). Drug-specific effects on multiple neurotransmitter (e.g., DA, serotonin, norepinephrine) and neuropeptide (e.g., oxytocin, arginine vasopressin, opioid, dynorphin) systems may explain these drug-specific effects on social behaviors. Finally, just as drugs of abuse may alter social behaviors, social interactions and the existence of strong social bonds during early development and

throughout life may protect against future vulnerability to substance abuse and relapse to drug seeking in addicted individuals.

As discussed above, the mesocorticolimbic DA system is in a key position to mediate the interaction between drugs of abuse and social behavior. This system is not only intrinsically involved in social behavior—due to its role in the assignment of motivational value to biologically relevant social stimuli—but also undergoes well-characterized alterations following acute and repeated exposure to drugs of abuse (Nestler, 2005). DA neurotransmission in the NAcc may play a particularly important role, as it has been implicated in all of the social behaviors discussed above. However, as NAcc DA is involved in a variety of processes associated with social behaviors, including locomotion, reward, and motivation, its specific role—and whether it contributes in a similar way to all of these behaviors and their interactions with drugs of abuse—is unclear. One possibility is that NAcc DA mediates the reinforcing aspects of social interactions, and that disruption of this process underlies drug-induced alterations in social behavior. For example, it has been suggested that reduced activation of NAcc neurons, a consequence of D2R activation, is critical for reward-related processes (Carlezon and Thomas, 2009). In line with this hypothesis, NAcc D2R activation mediates many of the social behaviors discussed above, including maternal, sexual, and pair bonding behaviors (Aragona et al., 2003; Aragona et al., 2006; Gingrich et al., 2000; Everitt, 1990; Silva et al., 2003). Drug-induced alterations that increase NAcc activity, such as the psychostimulant-induced enhancement of NAcc D1R sensitivity and expression (Henry et al., 1989; Henry and White, 1991, 1995; Liu et al., 2010; Simpson et al., 1995), may therefore alter the rewarding properties of social interactions, leading to the impairment of social behavior. Such alterations in the balance of NAcc DA receptor activity may play a key role in the effects of drugs of abuse on social behaviors—through their effects on reinforcement as well as other processes related to social behavior—and may explain how drugs of abuse can affect such a diverse range of behaviors.

Although this review has focused almost exclusively on mesocorticolimbic DA, many other neural systems are also likely involved in the interaction between drugs of abuse and social behavior. For example, neuropeptide systems, such as arginine vasopressin and oxytocin, regulate a variety of social behaviors and are significantly altered by acute and chronic exposure to drugs of abuse (Butovsky et al., 2006; Johns et al., 1997a). Additionally, sensitivity to these neuropeptide systems—as well as steroid hormones—is thought to be altered by early social experiences, and these alterations likely underlie the effects of early social experience on adult behavior (Cushing and Kramer, 2005). Further, these systems interact with mesocorticolimbic DA to mediate social (Liu and Wang, 2003) and drug-related behaviors (Sarnyai, 1998; Sarnyai and Kovacs, 1994). Therefore, although this idea has been relatively unexplored, these systems (McGregor et al., 2008), and their interactions with mesocorticolimbic DA, may play an important role in the reciprocal relationship between substance abuse and social behaviors. Future investigation into the neural substrates and neurotransmitter systems that mediate interactions between drug use and social behavior could provide information essential for the prevention and treatment of drug addiction and social disorders in humans.

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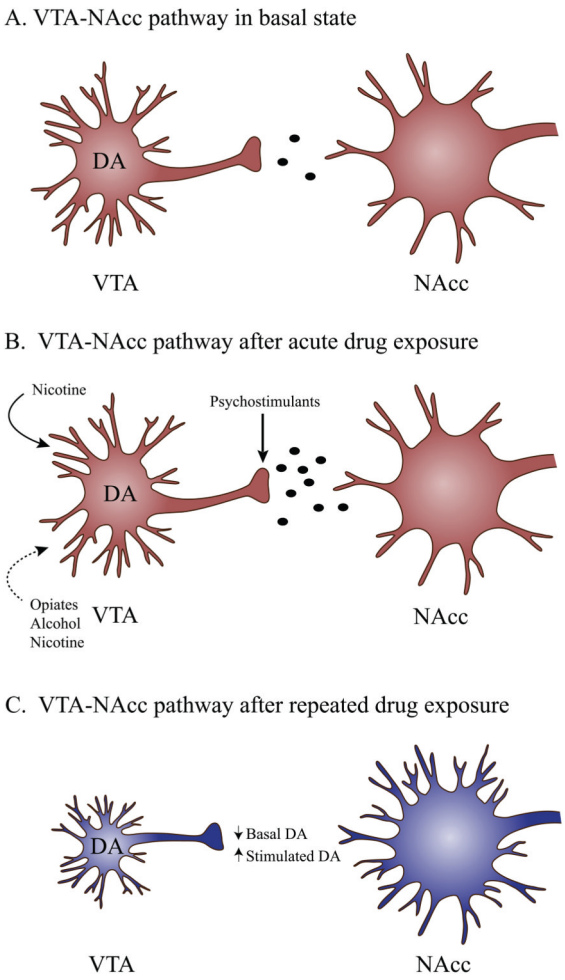

Figure 1.

Simplified cartoon illustrating the common effects of drugs of abuse on the mesocorticolimbic dopamine (DA) system. A) The mesocorticolimbic DA system consists of DAergic cells in the ventral tegmental area (VTA) that project to various forebrain regions including the nucleus accumbens (NAcc). In the basal state, a baseline level of DA (black circles) is present in the synapse. B) Though achieved through diverse mechanisms, acute exposure to all known drugs of abuse increases DAergic transmission in the NAcc (Di Chiara et al., 2004). Psychostimulants do so directly by acting on DAergic terminals located in the NAcc (Amara and Kuhar, 1993; Floor and Meng, 1996; Jones et al., 1998; Khoshbouei et al., 2003). Opiates do so indirectly by inhibiting GABAergic interneurons in the VTA, resulting in the disinhibition of VTA DA neurons (Devine et al., 1993; Gysling and Wang, 1983; Johnson and North, 1992; Kalivas et al., 1990; Matthews and German, 1984). Many mechanisms have been proposed for alcohol, including the disinhibition of VTA DA neurons (Herz, 1997). Nicotine is thought to increase NAcc DA both directly and indirectly, through stimulation of nicotinic cholinergic receptors on mesocorticolimbic DA neurons or glutamatergic terminals that innervate mesocorticolimbic DA neurons, respectively (Balfour, 2009; Wonnacott et al., 2005). Direct/indirect effects are symbolized by solid/dotted lines. C) After repeated exposure to most drugs of abuse, VTA neurons decrease in size (Nestler, 2005; Sklair-Tavron et al., 1996). Repeated psychostimulant or nicotine exposure induces dendritic outgrowth in NAcc neurons (Brown and Kolb, 2001; McDonald et al., 2005; Robinson et al., 2001; Robinson and Kolb, 1997), as pictured.

However, repeated opiate exposure has the opposite effect (Robinson et al., 2002; Robinson and Kolb, 1999). Several other effects have been noted after repeated psychostimulant exposure, including decreased basal DA levels in the NAcc and enhanced DA release induced by a stimulus (*e.g.,* drug exposure or stressor) (Pierce and Kalivas, 1997).

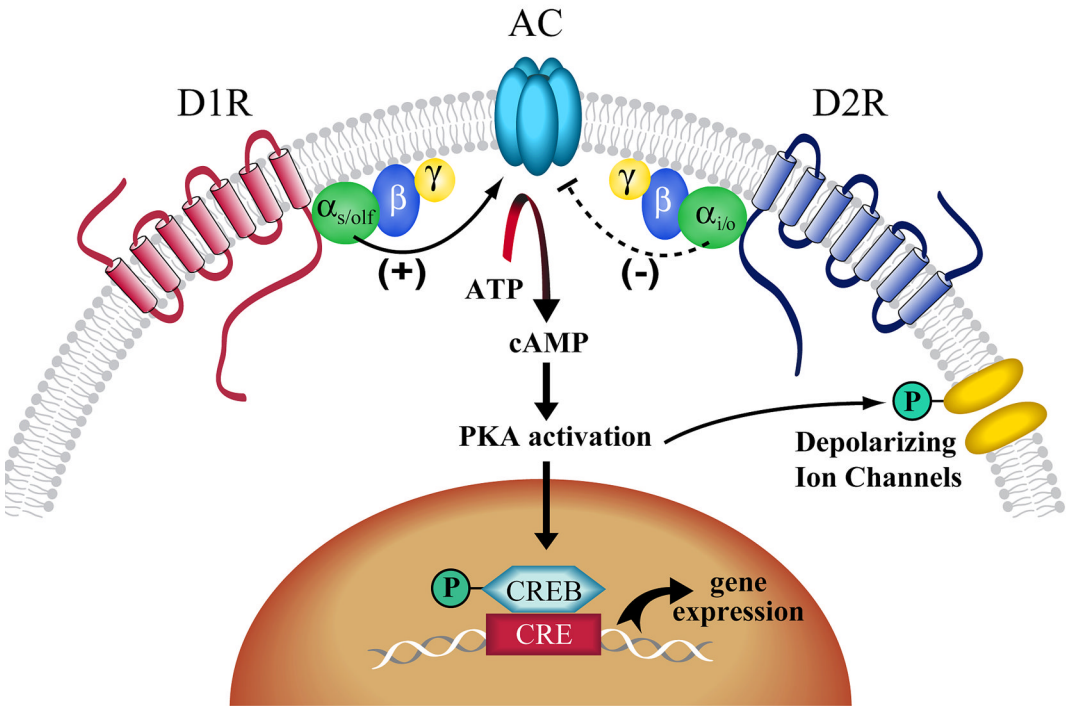

Figure 2.

Dopamine receptors differentially regulate cAMP intracellular signaling and cellular activity (Missale et al., 1998; Neve et al., 2004). D1-like receptors (D1R) are associated with stimulatory G-proteins ($G\alpha_s$ and $G\alpha_{olf}$) that when activated, increase the activity of the membrane bound enzyme adenylyl cyclase (AC). Active AC catalyzes the conversion of ATP to cAMP, which leads to the activation of protein kinase A (PKA) and subsequent increases in gene expression (through the phosphorylation of transcription factors, such as cyclic AMP response element binding protein (CREB)) and cellular activity (through the phosphorylation of membrane bound depolarizing ion channels). D2-like receptors (D2R), instead, are coupled to inhibitory G-proteins ($G\alpha_i$ and $G\alpha_o$). When D2Rs are activated, the alpha subunit of these G-proteins inhibits the activity of AC, leading to decreased cAMP production, PKA activity, gene expression, and cellular activity. Solid lines ending in an arrowhead indicate stimulatory effects, while dotted lines ending in a bar indicate inhibitory effects.

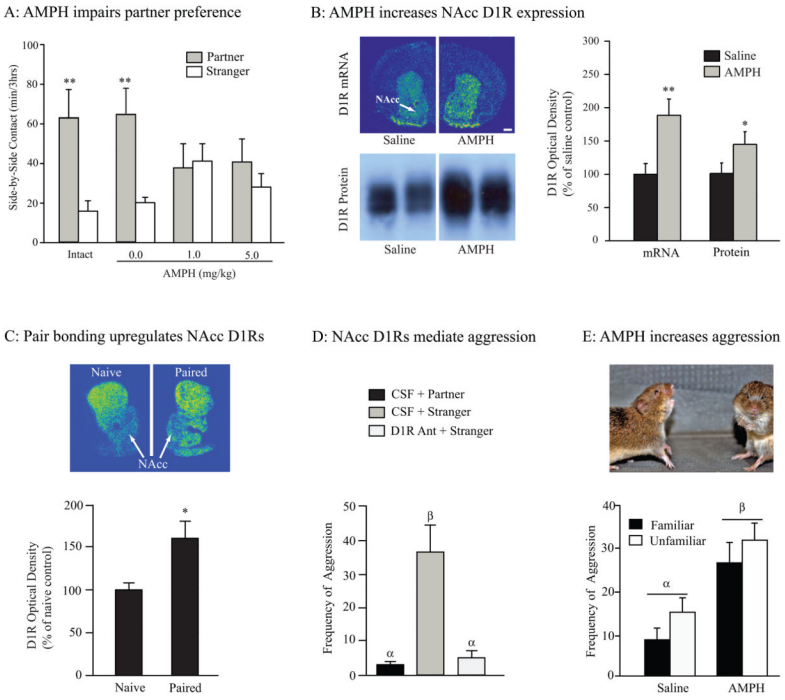

Figure 3.

Dopamine (DA) in the nucleus accumbens (NAcc) is involved in the amphetamine (AMPH)-induced impairment of pair bonding. A) After 24hrs of mating, intact and saline-treated (0.0; 1 injection/day/3 days) male prairie voles spent significantly more time in side-by-side contact with their familiar partner than a stranger (*i.e.*, formed partner preferences). However, males treated with 1.0 or 5.0 mg/kg AMPH (1 injection/day/3 days) spent an equal amount of time in contact with the partner as with the stranger. These results demonstrate that repeated AMPH exposure inhibits mating-induced partner preference formation in male prairie voles. B) Male prairie voles treated with AMPH (1.0mg/kg/day/3 days) had higher levels of DA D1 receptor (D1R) mRNA (top image) and protein expression (bottom image) in the NAcc than saline-treated controls. Quantitative analysis demonstrated that these differences were statistically significant (graph on the right). C) Pair bonded (Paired) male prairie voles have significantly higher levels of D1R binding in the NAcc than sexually-naïve (Naive) males. D) Pair bonded male prairie voles that received intra-NAcc injections of cerebral spinal fluid (CSF) showed low levels of aggression (data includes the frequency of both offensive and defensive aggression) toward their partner, but high levels of aggression toward a stranger (*i.e.*, selective aggression). Pharmacological blockade of NAcc D1Rs (D1R Ant) in pair bonded males abolished aggression toward a stranger, indicating that NAcc D1R activation mediates selective aggression in pair bonded voles. E) AMPH-treated sexually-naïve male prairie voles display significantly more aggression (data includes the frequency of both offensive and defensive aggression) toward both familiar and unfamiliar conspecific females than saline-treated controls. Picture illustrates a male prairie vole (left) displaying aggression toward an unfamiliar female prairie vole (right). Bars with different Greek letters differ significantly from each other. *: $p<0.05$; **: $p<0.01$. Adapted from (Aragona et al., 2006; Gobrogge et al., 2009; Liu et al., 2010).

Table 1

Short- and long-term effects of drugs of abuse on social behaviors.

Behavior	Drug Type	Short-term Effects [a]	Short-term Refs	Long-term effects [b]	Long-term Refs
Maternal Behavior	Psychostimulants	↓[c]	(Frankova, 1977; Johns et al., 1994; Kinsley et al., 1994; Piccirillo et al., 1980; Schiorring and Hecht, 1979; Vernotica et al., 1996; Zimmerberg and Gray, 1992)	↓	(Burns et al., 1997; Gottwald and Thurman, 1994; Hawley et al., 1995; Johns et al., 1994, , 1997; Johnson et al., 2002; Schuler et al., 2000; Slamberova et al., 2005b, , 2005a)
				↑[d]	(Febo and Ferris, 2007; Slamberova et al., 2005a)
				--[e]	(Vernotica et al., 1996)
	Opiates	↓	(Bridges and Grimm, 1982; Grimm and Bridges, 1983; Mayer et al., 1985)	↓	(Bauman and Dougherty, 1983; Schuler et al., 2000; Slamberova et al., 2001; Suchman and Luthar, 2000)
Sexual Behavior	Psychostimulants	↓	(Bignami, 1966; Cagiano et al., 2008; Dornan et al., 1991; El-Bassel et al., 2003; Guarraci and Clark, 2003; Guarraci et al., 2008; Pfaus et al., 2009; Weatherby et al., 1992)		
		↑	(Agmo and Picker, 1990; El-Bassel et al., 2003; Holder et al., in press; Kall, 1992; McElrath, 2005; Pfaus et al., 2009)	↑	(Afonso et al., 2009; Fiorino and Phillips, 1999a, , 1999b; Guarraci and Clark, 2003; Nocjar and Panksepp, 2002)
	Opiates	↓	(De Leon and Wexler, 1973; El-Bassel et al., 2003; Mintz et al., 1974)	↓	(Mintz et al., 1974)
		↑	(El-Bassel et al., 2003; Mitchell and Stewart, 1990)	↑	(De Leon and Wexler, 1973)
		--	(Pfaus et al., 2009)		
	Alcohol	↓	(Scott et al., 1994)		
		↑	(Ferraro and Kiefer, 2004)		
Social Play	Psychostimulants	↓	(Beatty et al., 1984; Beatty et al., 1982; Holloway and Thor, 1985; Sutton and Raskin, 1986; Vanderschuren et al., 2008)	↓	(Overstreet et al., 2000; Rodning et al., 1989; Wood et al., 1994; Wood et al., 1995)
	Opiates			↓	(Rodning et al., 1989)
		↑	(Normansell and Panksepp, 1990; Vanderschuren et al., 1995)	↑	(Hol et al., 1996; Niesink et al., 1996)
	Alcohol	↑	(Trezza et al., 2009)		
	Nicotine	↓	(Irvine et al., 1999; Thiel et al., 2009)		
		↑	(Irvine et al., 1999; Trezza et al., 2009)		
Aggressive Behavior	Psychostimulants	↓	(Darmani et al., 1990; Tidey and Miczek, 1992a)	↓	(Darmani et al., 1990; McMurray et al., 2008; Melega et al., 2008)
		↑	(Tidey and Miczek, 1992a)	↑	(Chermack et al., 2008; Darmani et al., 1990; DeLeon et al., 2002a; Gobrogge et al., 2009; Harrison et al., 2000a;

Behavior	Drug Type	Short-term Effects [a]	Short-term Refs	Long-term effects [b]	Long-term Refs
					Jackson et al., 2005; Johns et al., 1994, , 1997; Knyshevski et al., 2005a; Knyshevski et al., 2005b; Lubin et al., 2003; McMurray et al., 2008; Melloni et al., 2001)
		--	(Darmani et al., 1990; Johns et al., 1994)	--	(McMurray et al., 2008)
	Opiates	↓	(Kinsley and Bridges, 1986)		
		↑	(Rodriguez-Arias et al., 1997)	↑	(Ferrari and Baggio, 1982; Gianutsos et al., 1976; Gianutsos et al., 1974; Harris and Aston-Jones, 1994; Nath et al., 2000; Puri and Lal, 1973; Rodriguez-Arias et al., 1999; Singh, 1975; Tidey and Miczek, 1992b)
	Alcohol	↓	(Berry, 1993; Miczek et al., 1998)		
		↑	(Berry, 1993; Chermack and Taylor, 1995; Godlaski and Giancola, 2009; Hagelstam and Hakkanen, 2006; Madan et al., 2001; Miczek et al., 1998; Spunt et al., 1998)	↑	(Chermack et al., 2008; Krsiak et al., 1977; Mokuau, 2002; Walsh et al., 2003)
		--	(Berry, 1993; Miczek et al., 1998)	--	(Haapasalo and Hamalainen, 1996)
	Anabolic Steroids			↑	(DeLeon et al., 2002b; Harrison et al., 2000b; Melloni et al., 1997; Melloni and Ferris, 1996)
	Gamma- hydroxybutyrate	↑	(Navarro et al., 2007)		
		↓	(Navarro et al., 2007)		
Pair Bonding	Psychostimulants			↑	(Gobrogge et al., 2009; Liu et al., 2010)

[a] Short-term effects refer to studies that conducted behavioral tests within 5 hours of drug administration. These studies may have tested behaviors after single or repeated drug administration.

[b] Long-term effects refer to studies that conducted behavioral tests at least 5 hours after drug injection. Most of these studies were conducted after repeated drug administration.

[c] ↓ Decrease

[d] ↑ Increase

[e] -- no effect

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