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Review

"Sexy stimulants": The interaction between psychomotor stimulants and sexual behavior in the female brain

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ABSTRACT

Research indicates gender differences in sensitivity to psychomotor stimulants. Preclinical work investigating the interaction between drugs of abuse and sex-specific behaviors, such as sexual behavior, is critical to our understanding of such gender differences in humans. A number of behavioral paradigms can be used to model aspects of human sexual behavior in animal subjects. Although traditional assessment of the reflexive, lordosis posture of the female rat has been used to map the neuroanatomical and neurochemical systems that contribute to uniquely female copulatory behavior, the additional behavioral paradigms discussed in the current review have helped us expand our description of the appetitive and consummatory patterns of sexual behavior in the female rat. Measuring appetitive behavior is particularly important for assessing sexual motivation, the equivalent of "desire" in humans. By investigating the effects of commonly abused drugs on female sexual motivation, we are beginning to elucidate the role of dopaminergic neurotransmission, a neural system also known to be critical to the neurobiology of drug addiction, in female sexual motivation. A better understanding of the nexus of sex and drugs in the female brain will help advance our understanding of motivation in general and explain how psychomotor stimulants affect males and females differently.

Contents

1. Introduction

A growing body of research suggests that there are critical differences between how men and women are affected by drugs of abuse, including psychomotor stimulants (e.g., cocaine, methamphetamine, caffeine, methylphenidate, amphetamine). For example, women begin using drugs younger, enter into drug rehabilitation sooner, and experience shorter periods of drug abstinence after abuse than men (for review: Brady and Randall, 1999; Lynch et al., 2002; Walker et al., 2006). Furthermore, female injection drug users (IDU) are more likely to engage in risky behaviors (such as borrowing needles, sharing drug preparations, maintaining sexual relationships with other IDU, and failing to use a condom during vaginal/anal sex) than male IDU (Evans et al., 2003). Such gender differences may be a function of hormonal and neural differences between men and women in their response to

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drugs of abuse (reviewed in Becker, 2009). For example, women experience greater positive effects from drugs during the follicular phase of their menstrual cycle, when circulating gonadal hormones are highest (Evans et al., 2002; Justice and de Wit, 1999; Sofuoglu et al., 1999). Males have higher basal dopaminergic tone than females (Xiao and Becker, 1994, 1997), but conversely, they are less responsive to stimulation by drugs of abuse and natural reinforcers (Walker et al., 2012; Walker et al., 2006). Furthermore, the amount of dopamine released in response to drugs of abuse is modulated by estrogen in females (Becker, 2009), whereas gonadal hormones have no effect on dopamine release or drug reward in males (Castner et al., 1993; Jackson et al., 2006), suggesting a biological mechanism underlying potential differences in abuse liability between men and women, as well as differences for women across the menstrual cycle.

Not only do stimulants affect females differently than males, different stimulants also affect sex-specific behaviors, such as reproductive behavior, differently, which is consistent with the gender disparity in hormonal interactions with drug reward. It has been suggested that addictive drugs activate or "hijack" the neural circuits that are responsible for finding basic necessities of survival (i.e., food, water and sex) reinforcing Kelley and Berridge (2002). However, much of the research investigating the relationship between drugs of abuse and natural reinforcers has focused on males and specifically, male sexual behavior. Considering the pronounced gender differences in behavior and in the underlying neural circuitry described above, it is clear that a thorough investigation of how females are affected by psychomotor stimulants is necessary. In fact, considering the hormonal interactions with drugs of abuse in females that do not occur in males, we argue that the potential for interactions between drugs of abuse and sexual motivation is even greater in females than males.

We are beginning to see advances in our understanding of how drugs of abuse interact with natural rewards, such as sexual behavior, in females using a variety of different animal models. In general, research in animals is consistent with observations in women: some drugs of abuse enhance motivation for natural rewards like sex, whereas others are disruptive (Pfaus and Gorzalka, 1987). By specifically studying female models of motivated behavior, we hope that basic research can better guide our study of addiction in women and advance our understanding of potential gender differences in the neurobiology of motivation. The goal of this review is to describe paradigms that are useful in assessing sexual motivation in female rats and to summarize recent research that explores the interactions between psychomotor stimulants and female sexual behavior.

2. The female rat as a model of sexual behavior

2.1. Measures of mating behavior

Sexual behavior in the female rat is characterized by both receptive and proceptive behaviors. Receptive behavior is defined by the lordosis posture, which is the dorsal flexion of the female rat's back in response to being mounted by a male rat (Beach, 1976). The lordosis posture facilitates male penetration and reflects a female's willingness to engage in sexual behavior. Female rats also display proceptive behaviors, including hopping, darting, ear wiggling, and pacing of sexual stimulation (Erskine, 1989). These behaviors function to "solicit" the attention of potential mates. If a sexually receptive female has the opportunity, she will approach and withdraw from a sexually vigorous male, thereby controlling the timing of the receipt of sexual stimulation (i.e., mounts, intromissions, and ejaculations). This pattern is known as paced mating behavior. The pacing of sexual stimulation by the female can be observed under semi-naturalistic conditions and has been studied extensively in laboratory settings (for review see, (Blaustein and Erskine, 2002; Erskine, 1989)). Furthermore, by giving the female the opportunity to pace the receipt of sexual stimulation from more than one male simultaneously, we have been able to assess how measures of paced mating behavior reflect sexual motivation. When contrasted with conditions where the female *cannot* control the receipt of sexual stimulation from one male, paced mating behavior with multiple males is more similar to the mating conditions of rats in their natural habitat (Calhoun, 1962) and is associated with increases in the reproductive success of the female (Coopersmith and Erskine, 1994).

2.2. Beyond the lordosis reflex

In addition to measuring a full range of female sexual behaviors (as described above), a number of paradigms can specifically assess sexual motivation. For example, the partner preference paradigm is used commonly to evaluate the appetitive aspects of sexual behavior (Avitsur and Yirmiya, 1999; Bakker, 2003; Paredes and Alonso, 1997; Paredes and Vazquez, 1999). Partner preference tests typically allow an experimental animal to make a choice between two stimulus animals; one that is a sexual partner (e.g., sexually vigorous male) and one that is not (e.g., female). In female rats, preference for a male rat is most robust when the male is placed behind a wire mesh such that sexual contact is limited (NO CONTACT; Fig. 1, TOP), when compared to conditions where physical contact is not limited and mating is possible (CONTACT; Fig. 1, MIDDLE). These results suggest that the distal cues (i.e., auditory, visual and olfactory) of a sexual partner are sufficient for the display of partner preference in females (Clark et al., 2004). Because female rats spend less time with a male partner when mating is possible than when mating is prohibited, it is possible that some aspects of physical contact during a sexual encounter are aversive for female rats. It is also possible that pacing the receipt of sexual stimulation by the female, when there is an opportunity to mate, can interfere with the expression of a preference for a male partner. Specifically, withdrawing from the male and remaining away after sexual stimulation artificially reduce the time a female rat will spend with a male rat during a partner preference test.

The conditioned place preference (CPP) paradigm has also been used to assess the reinforcing aspects of a sexual encounter for female rats. Long used to assess the reinforcing properties of drugs of abuse

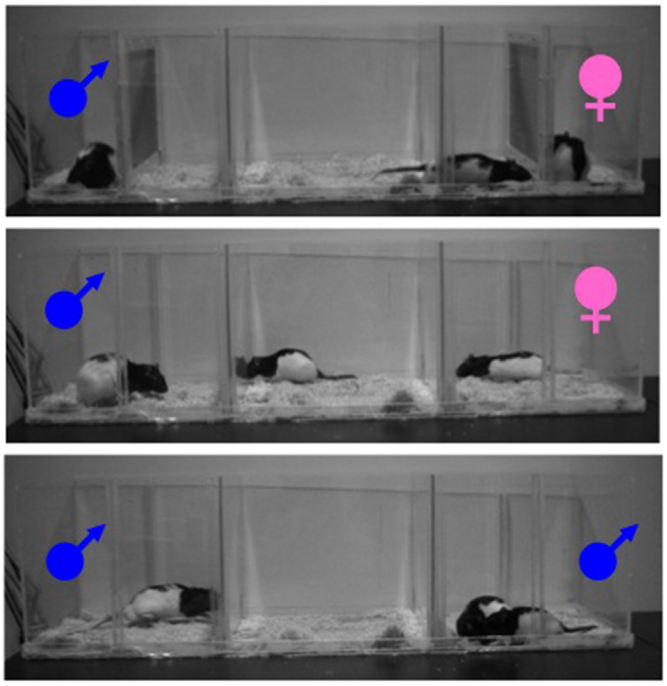

Fig. 1. Photographs of a female rat during a test of partner preference, where stimulus rats (male in LEFT compartment and female in RIGHT compartment) were placed behind wire mesh (TOP; NO CONTACT) or where a female rat could interact freely with stimulus rats (MIDDLE; CONTACT). Photograph of a female rat during a test of mate choice, where experimental female rat could interact freely with two male stimulus rats (BOTTOM).

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(e.g., opiates and psychomotor stimulants; (Carlezon, 2003)), the CPP paradigm has been used to identify the aspects of a mating encounter that are reinforcing for female rats. Initially it was concluded that control over the timing of mating is reinforcing for female rats (Paredes and Alonso, 1997). Because pre-treatment with naloxone blocks the formation of a CPP paired with the receipt of paced sexual stimulation, it was concluded that the reinforcing value of paced mating behavior depends on opioid receptors (Paredes and Martinez, 2001). However, Meerts and Clark (2007, 2009) have since reported that vaginocervical stimulation (VCS) is reinforcing even when females have no control over the receipt of sexual stimulation (i.e., artificial VCS or non-paced mating conditions), as long as females are given a brief period of no additional sexual stimulation following the most intense sexual contact (i.e., an ejaculation). In support of the importance of the timing of sexual stimulation, Becker and colleagues demonstrated that dopamine release increases in the mesencephalic dopaminergic system (i.e., striatum, nucleus accumbens) in response to copulation if the female experiences her "preferred pacing interval" between stimulations, independent of her active control of this interval (Jenkins and Becker, 2001, 2003a, 2003b).

Although not commonly used to study animals that are promiscuous, we have used the mate choice paradigm to advance our understanding of the reinforcing properties of mating behavior in female rats. For example, female rats spend significantly more time with one male when they are given an opportunity to mate with multiple males simultaneously (Ferreira-Nuño et al., 2005; Lovell et al., 2007; Zewail-Foote et al., 2009). In the mate choice paradigm, preference for one male over another is typically determined by how much time a female spends with a particular male (Fig. 1, BOTTOM). In general, a female rat will spend more than twice as much time with her preferred mate than with her non-preferred mate (Fig. 2, TOP), as well as return faster to her preferred mate than to her non-preferred mate following sexual stimulation (Fig. 2, MIDDLE). Finally, female rats receive more sexual stimulations from, make more visits to, and display more proceptive behaviors to (Fig. 2, BOTTOM) their preferred mate than their non-preferred mate. We have also investigated the potential benefits of sexual motivation on reproductive success (Lovell et al., 2007; Zewail-Foote et al., 2009). Our studies systematically assessing mate choice have indicated that females are more likely to prefer males who have a reproductive disadvantage (Winland et al., 2012). From these studies, we have found that not only is time spent in the vicinity of a stimulus animal an indication of sexual motivation, but so too are other measures, including the likelihood of leaving a mate after the receipt of sexual stimulation (i.e., percentage of exits) and the latency to return to a mate after the receipt of sexual stimulation (i.e., contact return latency).

3. Psychomotor stimulants interact with female sexual behavior

In an attempt to map the neural circuit underlying female sexual motivation, we looked to the neural circuit underlying drug reward for insight. Because the rewarding effects of most psychomotor stimulants are related to increases in dopamine release in the forebrain (Wise, 1987; Wise and Bozarth, 1987) and because female sexual behavior also increases dopamine release in the forebrain (Pfaus et al., 1995), we focused on assessing the effects of psychomotor stimulants on female sexual motivation in order to better characterize their point of intersection in the brain. Most of our studies were conducted in ovariectomized (OVX), hormone-primed rats tested for mating behavior following systemic administration of a psychomotor stimulant. However, a few studies are described that involved localizing drug effects to specific brain areas (e.g., nucleus accumbens, medial preoptic nucleus or medial amygdala) known to be involved in mediating the rewarding effects of natural reinforcers (e.g., sexual motivation) and/or drugs of abuse.

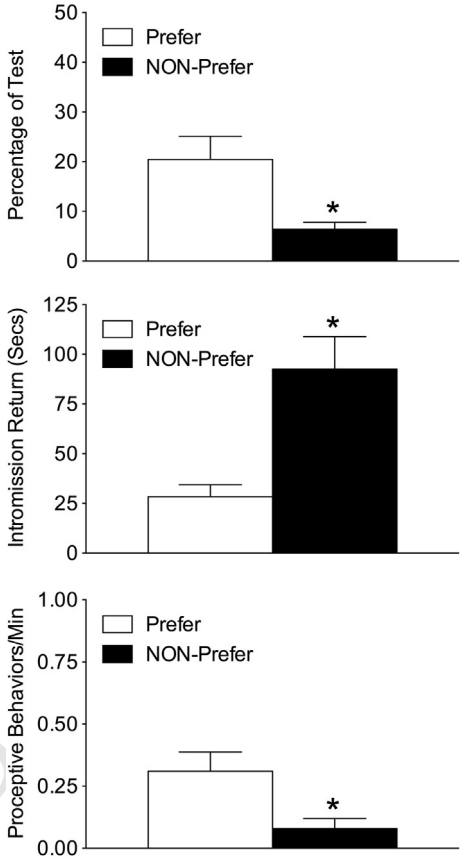

Fig. 2. Female rats spent more time with their preferred mate than their non-preferred mate during a test of mate choice (TOP; n = 18). Female rats returned to their preferred mate faster than to their non-preferred mate following intromissions (MIDDLE). In addition, female rats displayed more proceptive behaviors per minute when in the vicinity of their preferred mate than when in the vicinity of their non-preferred mate (BOTTOM). Data are expressed as means ± S.E.M. Note: n's = number of rats in each group. *Significant effect of mate choice (i.e., Prefer vs. NON-Prefer mate; within subject comparisons), $p < .05$.

3.1. Amphetamine

Early studies investigating the effects of *d*-amphetamine on sexual behavior in habitual drug users reported variable and inconsistent results. Some users reported disruptions of sexual behavior, whereas others reported increases in libido/desire (Bell and Trethowan, 1961). Subjects were more often male than female; however, one study, in which chronic drug users were given a large dose of *d*-amphetamine, included one female subject (Angrist and Gershon, 1976). The authors reported that this one female subject "…became seductive and propositioned the investigator during the study". Since the early observations that humans readily become addicted to *d*-amphetamine, a great deal of research has accumulated investigating *d*-amphetamine. Amphetamine acts as a positive reinforcer (Bevins et al. 1997; Piazza et al., 1990; Pierre and Vezina, 1997), and has been shown to enhance the reinforcing properties of other drug- (Horger et al., 1992; Piazza et al., 1990; Pierre and Vezina, 1997; Valadez and Schenk, 1994) and natural-rewards (e.g., food, sex; (Fiorino and Phillips, 1999; Nocjar and Panksepp, 2002)). Previous experience with *d*-amphetamine has been shown to facilitate: 1) the acquisition and rate of sexual behavior in sexually naïve male rats (Fiorino and Phillips, 1999; Fiorino and Phillips, 1999), 2) the acquisition of drug self-administration (Mendrek et al., 1998; Piazza et al., 1990) and 3) the development of a CPP associated with other drugs of abuse (Lett 1989). This facilitation is called behavioral sensitization or cross-sensitization and is characterized by an enhanced behavioral response to other similar drugs (e.g., cocaine) or natural rewards

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(e.g., sex) as a consequence of repeated exposure to a psychomotor stimulant (e.g., *d*-amphetamine), especially when tested long after the initial drug exposure had been discontinued. Adaptation of the mesocorticolimbic dopaminergic system during repeated drug exposure underlies behavioral sensitization (Vezina, 2004) and is responsible for *d*-amphetamine facilitation of other motivated behaviors. Based on previous studies in male rats, we hypothesized that *d*-amphetamine would enhance sexual motivation in female rats. In particular, we predicted that *d*-amphetamine would cross-sensitize with the rewarding aspects of sexual behavior as Phillips and colleagues observed in males rats (Fiorino and Phillips, 1999). Therefore, we tested the effects of acute and chronic *d*-amphetamine administrations on female sexual behavior. Following chronic exposure (3 weeks of injections) and a period of abstinence (1–4 weeks), we found that *d*-amphetamine enhanced the rewarding effects of sexual stimulation received from males (Guarraci and Clark, 2003). In particular, we found that female rats displayed shorter latencies to return to the male following the receipt of mounts if they were sensitized to *d*-amphetamine (Fig. 3, TOP). However, the cross-sensitization was not as robust as what had been observed in males. Afonso and colleagues also found enhanced sexual behavior (i.e., more solicitation behaviors) in female rats tested 21 days after their last of three injections of *d*-amphetamine (1.0 mg/kg every other day) (Afonso et al., 2009). In contrast to the effects of chronic administration, we found that an acute dose of *d*-amphetamine failed to enhance female mating behavior (Guarraci and Clark, 2003); if anything, acute *d*-amphetamine administration disrupted sexual behaviors. Specifically, female rats given *d*-amphetamine (1.0 mg/kg i.p.) were more likely to leave the male after receiving sexual stimulation than saline-treated rats (Fig. 3, MIDDLE) during a test of paced mating behavior. In addition, *d*-amphetamine decreased time spent with stimulus rats (i.e., male and female partners) during a NO CONTACT test of partner preference (Guarraci and Clark, 2003). Furthermore, moderate to high acute doses of *d*-amphetamine (>2.0 mg/kg) have been shown to reduce sexual receptivity (Guarraci and Clark, 2003; Michanek and Meyerson, 1977). It is unlikely that the effects of either acute or chronic *d*-amphetamine administration were merely a consequence of changes in locomotor activity, because the effects of *d*-amphetamine on sexual behavior were 1) limited to responsiveness to one type of stimulation (i.e., mounts but not intromissions or ejaculations) or 2) observed when locomotor-stimulating effects had dissipated (i.e., during a drug-free period following chronic exposure).

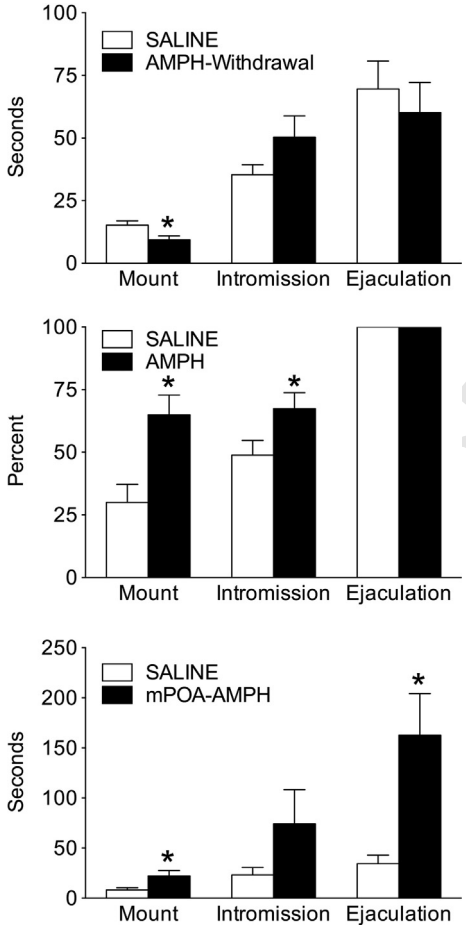

Fig. 3. Female rats treated chronically with *d*-amphetamine (1.0 mg/kg, i.p. daily for 3 weeks) returned to the male rat faster following mounts than saline-treated females, when tested 1 week after their final injection during a test of paced mating behavior (TOP; SALINE n = 11; AMPH-Withdrawal n = 13). However, female rats treated with an acute dose of *d*-amphetamine (1.0 mg/kg, i.p.) were more likely to leave the male rat following mounts and intromissions during a test of paced mating behavior (MIDDLE: SALINE, n = 24; AMPH, n = 23). Finally, when *d*-amphetamine was infused directly into the mPOA, female rats took longer to return to the male rat following mounts and ejaculations during a test of paced mating behavior (MIDDLE: SALINE n = 15; AMPH 10 μg/0.5 μl/side n = 11). *Significant effect of treatment (i.e., AMPH vs. SALINE for that sexual stimulus; between subject comparisons), $p < .05$.

To localize the effects of acute *d*-amphetamine, we infused *d*-amphetamine directly into specific areas of the brain (Guarraci et al., 2008). Surprisingly, infusions of *d*-amphetamine (40 μg/0.5 μl/hemisphere) directly into the main projection area of the mesolimbic dopaminergic system (i.e., NAc core or shell) had no effect on female sexual behavior, even though locomotor behavior was significantly increased. These results indicate that even when general locomotor behavior is increased, paced mating behavior can remain undisrupted — an important observation given that all psychomotor stimulants have the confound of increasing general locomotor behavior. In contrast, *d*-amphetamine infusions into the mPOA (10 μg/0.5 μl/hemisphere) disrupted female sexual behavior in a test of paced mating behavior, producing behavioral effects very similar to the effects produced by acute systemic *d*-amphetamine administration, as well as lesions of the mPOA, an area critical for the display of female sexual behavior (Guarraci and Clark, 2006; Guarraci et al., 2004). Specifically, female rats that received intra-mPOA *d*-amphetamine spent very little time with the male during a test of paced mating behavior and delayed their return to the male rat after receiving sexual stimulation (Fig. 3, BOTTOM). Importantly, general locomotion, as measured in a test for open field activity, was not affected by intra-mPOA infusions of *d*-amphetamine. Care was taken to ensure that no damage to cells in the mPOA occurred during cannula implantation or injector insertion. Therefore, we interpreted these findings to indicate that excessive dopaminergic neurotransmission within the mPOA is inhibitory to the functional output of the mPOA. Future studies are necessary to determine if *d*-amphetamine disrupts sexual motivation by altering the aversive and/or rewarding aspects of mating or if the anxiogenic effects of *d*-amphetamine (Dringenberg et al., 2000; Goudie, 1979; Goudie and Thornton, 1975; Kunin et al., 2001) disrupt the expression of appropriate sexual/social interactions.

3.2. Methamphetamine

Unlike other psychomotor stimulants such as *d*-amphetamine, methamphetamine (MA) is purported to have distinct and robust effects on sexual behavior among human drug users, especially women (Leavitt, 1969; Rawson et al., 2002). When compared to reports of cocaine and *d*-amphetamine use in humans, MA use is more often associated with enhanced positive experiences during sex and enhanced libido/desire (Rawson et al., 2002; Sherman et al., 2008). In addition, a number of correlational studies indicate that women who use MA are more likely to engage in risky sexual behaviors (e.g., sex for drugs, sex for money, unprotected sex, anal sex, and sex with multiple partners) than women who inject other drugs of abuse (e.g., heroine, cocaine; (Lorvick et al., 2006; Molitor et al., 1999; Semple et al., 2004a; Semple et al., 2004b)). In order to more fully characterize the causal link

between MA use and enhanced sexual activity, we investigated the effects of MA on sexual motivation in female rats. Based on the reports from female drug users, we predicted that MA would enhance sexual motivation in rats. As hypothesized, we found that an acute dose of MA (1.0 mg/kg i.p.) enhanced sexual motivation, as indicated by a reduction in the "choosiness" of female rats administered MA (Ford et al., 2009; Winland et al., 2011). Unlike saline-treated females (who spent more time with one male, returned to their preferred mate faster following sexual stimulation and visited their preferred mate more frequently), MA-treated females visited their preferred mate at the same rate as their non-preferred mate and returned to their non-preferred mate faster following intromissions than saline-treated rats during a mate choice test (Fig. 4, TOP). Furthermore, MA-treated females did not spend significantly less time with their non-preferred mate. These results indicate that MA may reduce the impact of a preference for one male when mating with multiple males simultaneously. Interestingly, the effects of MA on mate choice were not the result of increased general locomotion or failure to discriminate between stimulus animals, because when we tested MA-treated rats in the NO CONTACT partner preference paradigm, MA-treated females made significantly more visits per minute only to the male stimulus partner, and spent significantly less time with the female stimulus partner than saline-treated rats (Fig. 4, MIDDLE; (Winland et al., 2011)), suggesting enhanced interest in a sexual partner over a non-sexual partner. Furthermore, three injections of MA (5.0 mg/kg/day) increased the lordosis response as well as the frequency of solicitation behaviors (e.g., hops, darts, ear wiggling, presenting) in female rats tested 4 h after their last MA injection (Holder et al., 2010). Female rats treated with repeated MA were also less likely to leave the male rat after receiving sexual stimulation than the female rats treated with saline during a test of paced mating behavior. However, if MA-treated females did leave the male, they returned to him faster than the saline-treated females (Holder and Mong, 2010). Because mating behavior in both of these studies (Holder et al., 2010; Holder and Mong, 2010) was observed after the locomotor stimulatory effects of MA had dissipated, the effects of MA on sexual motivation are independent from MA effects on general locomotion.

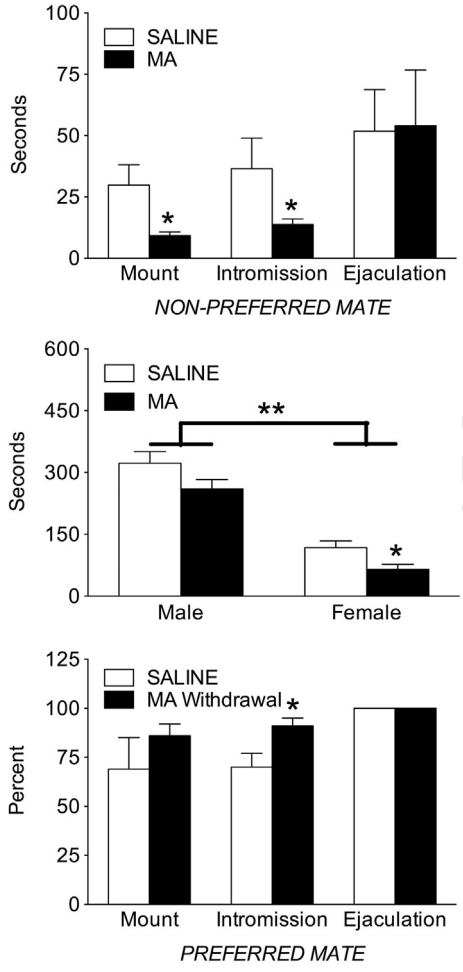

Fig. 4. Female rats treated with an acute dose of methamphetamine (MA; 1.0 mg/kg i.p.) returned to their non-preferred mate faster following mounts and intromissions than saline-treated females during a test of mate choice (TOP; SALINE n = 8; MA n = 12). During a test of partner preference with stimulus rats were placed behind a wire mesh (NO CONTACT); MA-treated females spent less time with the female stimulus than saline-treated females (MIDDLE; SALINE n = 8; MA n = 12). However, female rats treated daily with MA for 12 days were more likely to leave their preferred mate following intromissions than saline-treated subjects, when tested 24 h after their last injection during a test of mate choice (BOTTOM; SALINE: n = 9; MA: n = 10). *Significant effect of treatment (i.e., MA vs. SALINE for that sexual stimulus; between subject comparisons). **Significant effect of partner preference (Male vs. Female partner; within subject comparisons), $p < .05$.

Unexpectedly, when we tested for cross-sensitization between MA and sexual behavior, we found that exposure to MA (3 or 12 injections) did not appear to cross-sensitize with sexual behavior after a short (1 week) or long (3 weeks) period of drug abstinence (Thibodeau et al., 2013). However, we did find that sexual behavior was impaired in female rats exposed chronically to MA (1.0 mg/kg i.p. daily for 12 days), when tested during acute withdrawal. Specifically, when tested 24 h after their last injection, sexually naïve female rats were more likely than saline-treated females to leave their preferred mate after sexual stimulation (Fig. 4, BOTTOM) and less likely to solicit the attention of their preferred mate (Thibodeau et al., 2013). These results are consistent with findings from studies investigating the acute phase of withdrawal from psychomotor stimulants. During the hours immediately following withdrawal from psychomotor stimulants like MA or *d*-amphetamine, animals and humans experience a depressive state (McGregor et al., 2005; Newton et al., 2004), which is characterized by psychomotor retardation, lethargy, dysphoria and decreased motivation for natural rewards. In summary, MA enhances copulatory behavior and interest in sexual contact when compared to controls, as well as reduces pickiness in potential mates. As a consequence of long-term, chronic exposure to MA, the effects of MA may actually become disruptive to sexual behavior during any initial attempts to discontinue drug use.

Overall, the patterns of behavior associated with MA exposure in animals are consistent with the enhanced sexual motivation and increased risky sexual behaviors observed in human MA users. Methamphetamine enhances dopamine availability in the synaptic cleft by reversing catecholamine transporter proteins (Fleckenstein et al., 2000; Fukui et al., 2003). Interestingly, the increase in dopamine availability caused by exposure to MA is similar to the effects of *d*-amphetamine; however, the effects of MA on female sexual behavior in humans and animals are different than the effects of other stimulants. Given that we found a decrease in sensitivity to mate choosiness following neurotoxic lesions of the medial amygdala (including the medial posterior dorsal amygdala; MePD) (Siciliano et al., 2008), it is possible that the different effects of *d*-amphetamine and MA are related to differences in the ability of these two drugs to alter dopamine neurotransmission in different areas of the brain (MePD vs. mPOA). Specifically, we found that similar to MA-treated females, female rats with lesions targeted at the MePD returned to their non-preferred mate faster than female rats with sham lesions (Siciliano et al., 2008). There is also evidence to support a specific action of MA in the MePD, which could underlie the differences between *d*-amphetamine and MA. For example, the ability of MA to interact with gonadal hormones to enhance sexual behavior (i.e., increase proceptive behaviors and enhance lordosis) has been localized to increases in spinophilin expression, a marker of structural neuronal plasticity, in the MePD, but not in the ventromedial nucleus of the hypothalamus, when female rats were exposed to MA in the presence of mating-inducing gonadal hormones (Holder and Mong, 2010). Future studies investigating the neural adaptations to chronic MA exposure in other areas of the brain (e.g., mPOA), especially after prolonged

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periods of drug abstinence, are necessary to fully explain the differences observed in the effects of MA vs. other stimulants.

3.3. Caffeine

Although caffeine is the most commonly used psychomotor stimulant in the world, it is rarely considered a drug of abuse. Nevertheless, studying the effects of caffeine can be useful for elucidating the neurobiology of drug abuse (Holtzman, 1990). Similar to illicit drugs of abuse, the reinforcing properties of caffeine have been demonstrated in the laboratory. For example, caffeine is self-administered by animals (Griffiths and Woodson, 1988a, 1988b), albeit less reliably than other stimulants (e.g., cocaine or *d*-amphetamine), and only under specific circumstances. Furthermore, animals will readily prefer places associated (CPP) with caffeine administration (Bedingfield et al., 1998; Tuazon et al., 1992). Similar to other psychomotor stimulants (Wise, 1987; Wise et al., 1992; Wise and Bozarth, 1987), an alteration in dopamine neurotransmission in the forebrain is a likely mechanism underlying the reinforcing effects, as well as the stimulant properties of caffeine (Anden and Jackson, 1975; Cauli and Morelli, 2005; Estler, 1979; Hadfield and Milio, 1989; Solinas et al., 2002; Watanabe and Uramoto, 1986).

The main pharmacological action of caffeine, however, is the blockade of adenosine receptors (Cauli and Morelli, 2005; Fredholm et al., 1999). Although there are 4 types of adenosine receptors (A_1, A_{2A}, A_{2B} and A_3), the stimulant properties of caffeine are mediated through blockade of A_1 and A_{2A} receptors (Cauli and Morelli, 2005; Fredholm et al., 1999; Halldner et al., 2004). A_1 receptors are found throughout the cerebral cortex, the hippocampus, and the basal ganglia (Fastbom et al., 1987; Goodman and Synder, 1982), whereas A_{2A} receptors are found specifically in dopaminergic areas of the brain (Fredholm, 1977; Fredholm et al., 1999; Parkinson and Fredholm, 1990; Premont et al., 1979). Similar to the effects of *d*-amphetamine (Mendrek et al., 1998; Piazza et al., 1990), acute pretreatment with caffeine enhances self-administration of other drugs of abuse, such as cocaine (Comer and Carroll, 1996; Schenk et al., 1994). Pretreatment with caffeine also facilitates the development of a CPP associated with the administration of other drugs of abuse (Bedingfield et al., 1998; Tuazon et al., 1992). Furthermore, previous experience with caffeine has been shown to facilitate sexual behavior in male rats as measured by shorter latencies to engage in sexual behavior (Soulairac and Soulairac, 1978; Zimbardo and Barry, 1958). Interestingly, we have found that the effects of an acute dose of caffeine on female sexual behavior are more similar to the effects of MA than *d*-amphetamine. We reported that caffeine enhanced sexual motivation (Guarraci and Benson, 2005), as indicated by our observations that female rats treated with caffeine (15 mg/kg i.p.) returned to a male rat faster than females treated with saline during a test of paced mating behavior (Fig. 5, TOP). Because shorter latencies were only observed following ejaculations, it is unlikely that the effects of caffeine on sexual behavior only reflect a general increase in locomotion.

Although caffeine-treated rats spent approximately the same amount of time with a male and a female partner during a CONTACT partner preference test (Fig. 5, MIDDLE), they visited the male stimulus rat more frequently than saline-treated rats (Fig. 5, BOTTOM). Because the increase in locomotor activity was directed specifically towards the male partner, it is again unlikely that effects of caffeine on sexual behavior only reflect a general increase in locomotion. Furthermore, caffeine-treated females *can* display a robust preference for the male partner when tested in a NO CONTACT partner preference test (Guarraci and Benson, 2005), which suggests that even when locomotion is stimulated, a partner preference can still be observed. Future studies are needed to localize the effects of caffeine to specific areas of the brain, as well as describe the pattern of responses to chronic exposure of caffeine to determine if caffeine cross-sensitizes with sexual behavior or disrupts sexual behavior during acute/long-term withdrawal.

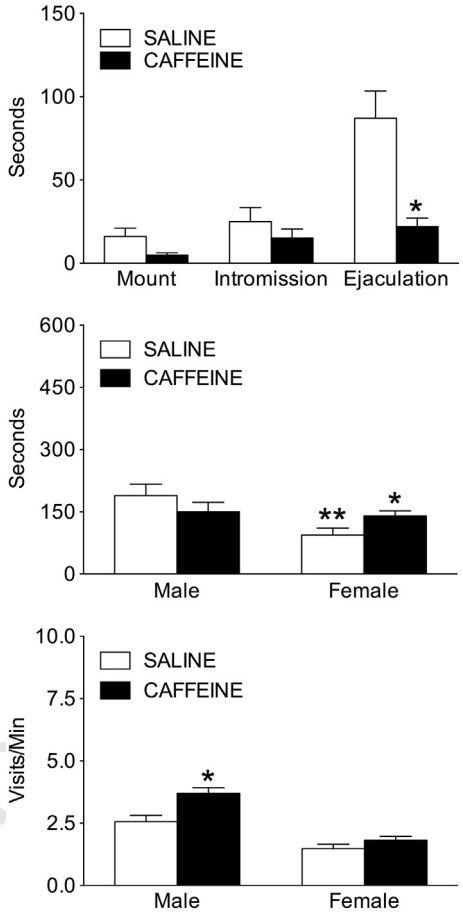

Fig. 5. Female rats treated with an acute dose of caffeine (15 mg/kg i.p.) returned to the male rat faster following ejaculations during a test of paced mating behavior (TOP; SALINE n = 7; CAFFEINE n = 7). During a CONTACT partner preference test, caffeine-treated females spent a similar amount of time with the male and the female partners (MIDDLE); however, caffeine-treated females made more visits to the male partner than saline-treated females (BOTTOM; SALINE n = 13; CAFFEINE 15 mg/kg n = 14). *Significant effect of treatment (i.e., CAFFEINE vs. SALINE for that sexual stimulus; between subject comparisons). **Significant effect of partner preference (i.e., Male vs. Female partner; within subject comparisons), $p < .05$.

3.4. Cocaine

Cocaine is one of the most highly abused psychomotor stimulants; however, its effects on sexual behavior are somewhat contradictory and not well characterized. Acute cocaine use is thought to intensify normal pleasures, including emotions and sexual arousal (reviewed in (Gawin and Ellinwood, 1989)). Similar to MA, correlational studies in humans have shown that smokers of crack cocaine are more likely to practice high-risk sex behaviors, including having a greater number of sex partners, exchanging sex for drugs or money, and having unprotected sex, than non-users (Edlin et al., 1992). Crack cocaine smokers are also more likely to use a variety of drugs before and/or during sex (Booth et al., 1993), suggesting that crack cocaine either acutely enhances sexual experiences, or that chronic crack cocaine use impairs sexual ability, such that other drugs are needed to compensate. Self-reports from cocaine users reveal that 65% of men believe that cocaine enhances orgasm, whereas only 20% of women report that cocaine increases sexual desire and ability to achieve orgasm, suggesting that the impact of chronic cocaine use on sexual function may be sexually dimorphic (Smith et al., 1984). Indeed, women tend to report less euphoria and more anxiety following cocaine use than men (Kosten et al., 1993; Lynch et al., 2002). Thus, unlike MA, cocaine may increase high-risk sexual behavior without enhancing female sexual pleasure.

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Unfortunately, our understanding of the interaction between cocaine and sexual motivation using animal models remains extremely limited at this point. To our knowledge, there are only two published studies that have examined the effects of cocaine on sexual behavior in female rats (Kohtz et al., 2010; Pfaus et al., 2010). Kohtz and colleagues used a paced mating paradigm, but only measured male sexual performance and female sexual receptivity (i.e., measuring only lordosis and no other components of sexual behavior, such as proceptive behavior) 30 min following a low (5 mg/kg), intermediate (10 mg/kg), or high (20 mg/kg) dose of cocaine (Kohtz et al., 2010). These acute doses of cocaine caused sexual dysfunction in both sexes (although to a greater extent at low and intermediate vs. high doses), decreasing the number of mounts and intromissions performed by male rats and attenuating the lordosis response of female rats in estrus. However, paradoxically, the high dose of cocaine increased slightly the receptivity of female rats in diestrus, who would otherwise have been completely non-receptive, suggesting that cocaine, like MA, may interact with gonadal hormones to influence sexual behavior. Indeed, Kohtz and colleagues measured the levels of progesterone and its metabolite, 5α-pregnan-3α-ol-20-one (3α,5α-THP), in the brain after the mating test and found that the low and intermediate doses of cocaine decreased progesterone and 3α,5α-THP in the brains of estrus females, but the high dose increased progesterone in the brains of diestrus females (Kohtz et al., 2010). Both progesterone and 3α,5α-THP are known to facilitate lordosis behavior (Frye et al., 2009), so it is likely that the described changes in neuronal progesterone and 3α,5α-THP contributed to the cocaine-induced decrease in receptivity in estrus females and increase in receptivity in diestrus females, respectively. However, the high dose of cocaine also increased progesterone in the brains of estrus females, and paradoxically, resulted in a slight decrease in lordosis behavior, suggesting that other factors may be involved at this high dose to induce disruptions in sexual behavior. The authors concluded that cocaine-induced changes in progesterone levels may partly explain the observed changes in female sexual behavior, but additional research is required to verify the causal nature of this interaction.

The second study (Pfaus et al., 2010) also evaluated male sexual performance and female sexual receptivity 30 min following an acute dose of cocaine (10 mg/kg, 20 mg/kg, or 40 mg/kg). However, this study also assessed female proceptive behaviors (e.g., hops and darts). In male rats, acute administration of cocaine at the two highest doses increased the latency to mount and intromit, which agrees with the sexual dysfunction reported by Kohtz and colleagues. However, additional testing revealed that this effect disappears after a week of cocaine dosing at 4-day intervals, and that chronic cocaine actually facilitates ejaculation in male rats. Similar to the female sexual dysfunction described by Kohtz and colleagues, OVX female rats primed with estradiol alone displayed a dose-dependent decrease in both receptive and proceptive behaviors, with the highest dose (40 mg/kg) causing the greatest disruption of sexual behavior. In contrast, OVX female rats primed with estradiol and progesterone showed a slightly different pattern, in that lordosis was still impaired in a dose-dependent fashion, but proceptive behaviors were actually enhanced at the two lower doses (10 mg/kg and 20 mg/kg). Pfaus and colleagues concluded that these differences may be attributable to the interaction of cocaine-stimulated dopamine release with progesterone signaling, which agrees with the findings of Kohtz et al. Unfortunately, no studies to our knowledge have confirmed this conclusion. Nevertheless, the sex differences observed thus far are consistent with human drug users reporting enhancement of orgasm in men and impairment of orgasm in women (Smith et al., 1984). Interestingly, the increase in proceptive behaviors in female rats after acute cocaine administration, despite a decrease in receptivity, may offer insight into the phenomenon that cocaine can increase high-risk sexual behaviors in women despite its negative effects on sexual pleasure.

It is apparent that additional testing using the paradigms described in this review is needed in order to separate positive effects from negative effects in evaluating cocaine's effects on female sexual motivation. In addition, the interpretation of the changes in sexual behavior is complicated by the fact that acute cocaine also increased locomotor behavior at the time point used by both studies to assess mating behavior (Kohtz et al., 2010). Future studies should be conducted using the partner preference paradigm in order to determine if the effects of cocaine are due to an increase in locomotor activity directed towards or away from a sexual stimulus (i.e., the male) or merely reflect an artifact of a general increase in locomotion. Furthermore, the use of a greater variety of behavioral measures of sexual motivation could reveal if proestrus females given cocaine actually find sex more aversive (e.g., as indicated by an increase in the likelihood of leaving the male after sexual stimulation and longer intervals between sexual contact with the male), as we observed with acute *d*-amphetamine. Like *d*-amphetamine, it is possible that cocaine would induce an aversion to all social contact (e.g., if the female rat spends less time with both the male and female stimulus animals) during a test of partner preference. In support of this possibility, a recent study with female mandarin voles demonstrated that chronic cocaine treatment leads to an increase in locomotor behavior but a decrease in social investigation and body contact with other female voles (Wang et al., 2012). Nevertheless, unlike *d*-amphetamine, which appears to be anxiogenic, acute cocaine actually decreases the display of anxiety-like behaviors (Kohtz et al., 2010), suggesting that the disruption of sexual motivation or social behavior by cocaine is due to a mechanism other than generalized anxiety.

In conclusion, future studies should characterize the neuroanatomical site of cocaine's interaction with sexual motivation via targeted intracerebral infusions (e.g., mPOA, MePD). As Holder and Mong localized the facilitative effects of MA and gonadal hormones on female sexual behavior to plasticity in the medial amygdala (Holder and Mong, 2010), it is possible that cocaine acts through a related mechanism in its interaction with progesterone, but in the opposite direction. Finally, future studies should also compare the effects of acute vs. chronic administration of cocaine, as we have demonstrated that *d*-amphetamine and MA show divergent effects depending on the extent of previous drug exposure.

In summary, acute low doses of caffeine and MA enhance sexual motivation, independent of increases in general locomotor activity, by increasing reward and/or decreasing aversion. On the other hand, acute administrations of *d*-amphetamine and cocaine interfere with sexual motivation, likely via distinct mechanisms. By investigating the effects of drugs infused directly into different brain areas, together with assessing drug effects in a multitude of tests for sexual motivation, we might be able to address the many unresolved issues.

4. Implications

Although we continue to identify the neuroanatomical and neurochemical systems that control female sexual motivation and how drugs of abuse interact with these neurobiological systems, we should be cautious when making the leap from the lab to the clinic. Animal models cannot replace studies of human–drug interactions. When considering the results from studies in animals to understand the effects of drugs on human behavior, we must be careful to consider the methodological issues that influence drug effects on sexual motivation. A few issues to consider are: 1) previous drug exposure, 2) route of administration, 3) dose, and 4) timing. Given that these issues affect the results from animal studies, it is likely that these issues affect the translation of research from animal models to human application.

Research investigating the use of other licit (i.e., methylphenidate) and illicit drugs (i.e., cannabinoids, MDMA) will also advance our understanding of the nexus of drug abuse and sexual behavior in females. Future evaluation of the effects of prescription drugs like methylphenidate in females is important, especially as the number of young girls prescribed methylphenidate before/during puberty, as well as into adulthood, grows. An understanding of the relationship between gonadal hormones, psychomotor stimulants and sexual behavior throughout

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the life cycle, including reproductive senescence, is important, especially as men extend their sexual vitality with the help of pharmacotherapy (i.e., sildenafil). The hope is that by understanding the motivational system that draws us to sex and drugs, we can develop treatments for those who "abuse the system".

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