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"Sex, drugs and the brain": The interaction between drugs of abuse and sexual behavior in the female rat

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ABSTRACT

Preclinical and clinical research investigating female sexual motivation has lagged behind research on male sexual function. The present review summarizes recent advances in our understanding of the specific roles of various brain areas, as well as our understanding of the role of dopaminergic neurotransmission in sexual motivation of the female rat. A number of behavioral paradigms that can be used to thoroughly evaluate sexual behavior in the female rat are first discussed. Although traditional assessment of the reflexive, lordosis posture has been useful in understanding the neuroanatomical and neurochemical systems that contribute to copulatory behavior, the additional behavioral paradigms described in this review have helped us expand our understanding of appetitive and consumatory behavioral patterns that better assess sexual motivation – the equivalent of "desire" in humans. A summary of numerous lesion studies indicates that different areas of the brain, including forebrain and midbrain structures, work together to produce the complex repertoire of female sexual behavior. In addition, by investigating the effects of commonly addictive drugs, we are beginning to elucidate the role of dopaminergic neurotransmission in female sexual motivation. Consequently, research in this area may contribute to meaningful advances in the treatment of human female sexual dysfunction.

The phrase "SEX, DRUGS and ROCK-N-ROLL" represents more than just a flashback to the attitudes of the 1960s. Instead, it epitomizes the commonly held belief that people often equate feelings elicited by sex, drugs and music. It may not be a coincidence that people often describe the experiences that they have with drugs of abuse (e.g., heroin) in sexual terms (e.g., "orgasmic"). Even dating back to Heath's famous studies of electrical brain stimulation in people with severe depression (Bishop et al., 1963), one patient who could voluntarily deliver electrical stimulation to her medial forebrain bundle was video taped calling the button that delivered stimulation – "the sexy button" (Ellis, 1999). The early studies investigating the neural mechanisms underlying the hedonia produced by drugs of abuse led people to conclude that drugs *use* or "*hijack*" the neural circuits that animals have to make the basic necessities of survival (food, water and sex) reinforcing (Kelley and Berridge, 2002). However, much of the research investigating the neural systems underlying the relationship between drugs of abuse and natural reinforcers has focused on male sexual experience.

Nevertheless, we are beginning to see advances in our understanding of female sexual motivation using a variety of different animal models. Although female rodent sexual behavior differs substantially from female human sexual behavior, the progress made has been useful in guiding clinical trials that test pharmacological treatments for sexual dysfunction (Pfaus, 2006). In addition, basic research in animal models of sexual motivation has also been useful to our study of drug addiction. The brain has evolved to respond to natural rewards, but drugs of abuse also act on these very same circuits (Kelley and Berridge, 2002). Studies of the interactions between drug rewards and natural rewards have led us to a better understanding of motivation in general. Moreover, such studies can illustrate how drugs of abuse can be disruptive to motivation for natural rewards like sex (Pfaus and Gorzalka, 1987). Because of the recent emphasis on the study of female sexual motivation, the neurochemical and neuroanatomical systems that control all aspects of female sexual behavior are beginning to be elucidated.

By using a variety of behavioral paradigms, we hope that basic research will continue to guide future clinical research on treatments for sexual dysfunction, as well as treatments for side effects produced by prescription (e.g., anti-depressants, analgesics) and illicit drug use (e.g., heroin) in women. The goal of this review is threefold: 1) to describe paradigms that are useful in assessing sexual motivation in female rats; 2) to describe the progress made in the search for the neuroanatomical systems underlying female sexual behavior; and 3) to discuss what we have learned from studying the interactions between drugs of abuse and female sexual behavior.

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Measures of female sexual behavior

Description 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, a dorsal flexion of the female rat's back in response to a mount by a male rat (Beach, 1976). Female rats also engage in proceptive or soliciting 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 naturalistic conditions and has been studied extensively in laboratory settings (for review, see Blaustein and Erskine, 2002; Erskine, 1989). When contrasted with conditions where the female ***cannot*** control the receipt of sexual stimulation from the male, paced mating behavior increases reproductive success of the female, as indicated by an increased likelihood of becoming pregnant/pseudopregnant, as well as the production of larger litters (Coopersmith and Erskine, 1994).

Paradigms useful for measuring sexual motivation

In addition to measuring the full complement of female sexual behavior (as described above), a number of modifications have been made to traditional mating paradigms to specifically assess other aspects of 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 wire mesh such that sexual contact is limited (NO CONTACT) when compared to conditions where physical contact is unlimited and mating is possible (CONTACT). These results suggest that the distal cues of a sexual partner (e.g., auditory, visual and olfactory) 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 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 intense sexual stimulation artificially reduces the time a female rat will spend with a male rat during a partner preference test.

More recently, the **conditioned place preference (CPP) paradigm** has 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 (e.g., opiates and psychomotor stimulants; Carlezon, 2003), the CPP paradigm is now being used to identify the pattern of mating behavior that is reinforcing for female rats. Initially it was concluded that control over the timing of mating is reinforcing for female rats (Paredes and Alonso, 1997). In addition, pre-treatment with naloxone blocks the formation of a CPP paired with paced sexual stimulation, suggesting that the development of a CPP depends on opioid receptors (Paredes and Martinez, 2001). However, Meerts and Clark (2007, 2009) recently reported that vaginocervical stimulation (VCS) is reinforcing for female rats even when females have no control over the receipt of sexual stimulation (artificial VCS or non-paced mating conditions). Therefore, it is possible that a brief period of no additional sexual stimulation following intense sexual contact (e.g., an ejaculation) may be reinforcing for female rats.

Although not commonly used to study animals that are promiscuous, we have recently been able to use a **mate choice paradigm** to further our understanding of the reinforcing properties of mating behavior in female rats. We have also been able to investigate the potential benefits of sexual motivation on reproductive success (Lovell et al., 2007; Zewail-Foote et al., 2009). For example, female rats spend significantly more time with one male when they are given an opportunity to mate with multiple males simultaneously (Ferreira-Nuno et al., 2005; Lovell et al., 2007; Zewail-Foote et al., 2009). We have been able to test mate choice in the apparatus we use to measure partner preference – instead of one sexual partner and one social partner, two male rats are placed on either end of the arena. Preference for one male over another is determined by how much time a female spends with either male. In general, a female rat will spend more than twice as much time with a preferred mate than with a non-preferred mate (Fig. 1 **TOP**), as well as return quicker to a preferred mate than a non-preferred mate following sexual stimulation (Fig. 1 **MIDDLE**). Finally, female rats receive more sexual stimulations from, and make more visits to (Fig. 1 **BOTTOM**), a preferred mate than a non-preferred mate.

We have preliminary evidence that mate choice may interact with physiological characteristics of the male to produce more successful mating encounters (i.e., more offspring) when certain females and males mate, a result similar to observations made in mice (Drickamer et al., 2000). Giving a female rat an opportunity to mate with two males (differing in strain) has also been useful in determining the effect of ejaculation order on reproductive success, as well as determining sensitivity to strain preferences (Coria-Avila et al., 2006). Together, these results suggest that although rats are a polygynandrous species, female mate choice may play a critical role in the success of the species. Furthermore, some of the adaptations of mating behavior that enhance reproductive success may be reinforcing and helpful for understanding sexual motivation, thereby allowing us to use a more sophisticated and complete laboratory model of sexual motivation. For instance, our studies systematically assessing mate choice have indicated that not only is time spent in the vicinity of a stimulus animal an indication of motivation, but so too is the latency to return (i.e., contact return latency) to a mate after the receipt of sexual stimulation.

Anatomical substrates of female sexual motivation

Given the potential overlap between the neural structures that are critical for male sexual motivation and drug reward (Damsma et al., 1992; Pfaus and Phillips, 1989, 1991), our first attempt to identify the neural structures critical for female sexual motivation investigated the most obvious system: the mesolimbic dopaminergic system. For example, Pfaus and colleagues (1996) reported increased expression of Fos protein (which can be used as a marker of neuronal activity) in the ventral tegmental area (VTA) and the nucleus accumbens (NAc), which have long been associated with the rewarding effects of drugs of abuse (e.g., cocaine, amphetamine, heroin; see for review Wise, 1987; Wise and Bozarth, 1987).

Nucleus Accumbens (NAc)

Surprisingly, in our first attempt to elucidate the neural circuit critical for female sexual motivation, we came up almost completely empty-handed. Previous findings suggested that dopamine, in particular dopamine in the NAc, may be involved in paced mating behavior. Mermelstein and Becker (1995) reported that paced mating behavior is accompanied by increases in levels of extracellular dopamine in the NAc and adjacent caudate putamen. Furthermore,