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An acute, non-therapeutic dose of methylphenidate disrupts partner preference in female rats

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ABSTRACT

The present study was designed to test the effects of an acute, high dose of methylphenidate (MPH; trademarked as Ritalin) on sexual behavior in female Long-Evans rats. In Experiment 1, naturally cycling subjects in estrus were tested for partner preference 20 min after receiving an i.p. injection of MPH 10 mg/kg ($n = 8$) or saline ($n = 7$). During the partner-preference test, female subjects were given the choice to interact with a sexually active male stimulus or a sexually receptive female stimulus. Physical contact was limited by placing the stimulus animals behind a wire mesh during the no-contact phase of the test, whereas physical contact was not limited during the contact phase. Female subjects that received MPH spent significantly less time with the male stimulus than the saline-treated subjects during both phases (no-contact and contact) of the partner-preference test. This acute dose of MPH did not affect visits to the female stimulus; however, MPH-treated subjects made fewer visits to the male stimulus than the saline-treated subjects during the contact phase of the partner-preference test. Consistent with previous findings, MPH increased line crossings when subjects were tested in an open field immediately after the partner-preference test. In Experiment 2, female subjects were ovariectomized (OVX), primed with estradiol benzoate and progesterone, and tested for partner preference 20 min after receiving an injection of MPH 10 mg/kg ($n = 8$) or saline ($n = 8$). Similar to the results of Experiment 1, OVX hormone-primed subjects that received MPH spent significantly less time with the male stimulus than the saline-treated subjects during both phases of the partner-preference test. Although MPH-treated subjects were sexually receptive, they displayed fewer proceptive behaviors (i.e., hops and darts) than saline-treated subjects. Two-weeks later, the subjects from Experiment 2 were tested in an open field 20 min after receiving an injection of MPH 10 mg/kg or saline (counterbalancing previous MPH exposure). Once again MPH increased locomotor activity. In conclusion, the effects of MPH were equally as robust in naturally cycling subjects as in the more commonly used OVX-hormone primed subjects. The results of the present study suggest that an acute, non-therapeutic dose of MPH disrupts approach and interest in a male stimulus during a test of partner preference. This avoidance of the male stimulus may be the result of a decrease in the incentive value of a sexual partner.

1. Introduction

Methylphenidate (MPH) is one of the most common psychomotor stimulants prescribed to treat attention-deficit/hyperactivity disorder (ADHD) (Nair and Moss, 2009; Retz et al., 2011). Methylphenidate binds with high affinity to dopamine transporter proteins (Schweri et al., 1985). The increase in extracellular dopamine caused by blocking dopamine transporters likely contributes to the effectiveness of MPH to relieve ADHD symptoms (Volkow et al., 2001). It is this increase in dopamine that could also contribute to the abuse and misuse of MPH (Claussen and Dafny, 2014; Morton and Stockton, 2000).

Due to increasing production and availability of MPH since 1995 (Arria et al., 2008; Morton and Stockton, 2000), there has been a rise in the abuse of MPH, most notably among college-aged students. Sepulveda and colleagues reported that non-medical use of stimulants prescribed for ADHD, such as MPH, has reached as high as 25% among college students in the United States (Sepulveda et al., 2011). Prescription psychomotor stimulants, such as MPH, are frequently being used to enhance mood and/or cognition. For example, Maier and colleagues reported that 13.8% of the participants in their study ($n = 6275$) used prescription drugs to improve cognitive functioning (Maier et al., 2013), with MPH prescriptions being the most commonly misused (Maier et al., 2013). Of students who have been prescribed stimulant medication for ADHD, 40% reported that they misused their prescription by taking more than the dose prescribed (Sepulveda et al., 2011). The

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illicit use of MPH is most likely taken at higher doses than what is prescribed in an attempt to increase drug effects and induce euphoria (Claussen and Dafny, 2014; Morton and Stockton, 2000).

We have been investigating the effects of acute administration of psychomotor stimulants on female sexual behavior to better understand how drugs of abuse interact with natural rewards such as sex. Using a number of different paradigms, research during the past 15 years has indicated that some stimulants disrupt sexual behavior, whereas others seem to enhance sexual behavior. For example, we found that caffeine enhances sexual motivation in hormone-primed ovariectomized (OVX) rats (Guarraci and Benson, 2005). Specifically, female rats treated with caffeine (15 mg/kg i.p.) returned to a male rat faster than saline-treated females after receiving an ejaculation while pacing the receipt of sexual stimulation from the male (i.e., paced-mating behavior). When female rats were given the choice to interact with a male stimulus or a female stimulus (i.e., partner-preference test), caffeine-treated rats visited the male stimulus more frequently than saline-treated rats (Guarraci and Benson, 2005).

Recently, we reported that an acute dose of methamphetamine (METH; 1.0 mg/kg i.p.) enhanced sexual motivation, as indicated by a reduction in the "choosiness" of female rats during a mate-choice test (Winland et al., 2011). When female rats are given the choice to interact with two sexual partners, untreated females spend more time with one male rat (i.e., their preferred mate), visit their preferred mate more frequently, and return to their preferred mate faster after receiving intromissions. In contrast to untreated female rats, METH-treated females prefer the two mates equally, visiting both mates at the same rate and returning to both mates at the same rate after receiving intromissions.

Although cocaine is another highly addictive psychomotor stimulant, its effects on sexual behavior are mixed and depend on dose and hormonal status of female subjects. For example, Kohtz and colleagues found that cocaine (5, 10 or 20 mg/kg) attenuated the lordosis response when female rats were tested for paced-mating behavior during behavioral estrus (Kohtz et al., 2010). Paradoxically, a moderate dose of cocaine (10 mg/kg) increased lordosis in female rats tested during diestrus (Kohtz et al., 2010), when gonadal hormones are low and sexual receptivity (i.e., lordosis) is all but absent. Similarly, Pfaus and colleagues reported that cocaine (10, 20 or 40 mg/kg) dose dependently decreased receptive and proceptive (e.g., hops and darts, ear wigginling, solicitations) behaviors in OVX rats primed with estradiol benzoate (EB) alone (Pfaus et al., 2010). In contrast, administration of cocaine to OVX rats primed with EB and progesterone (P) produced a slightly different pattern of results. Although cocaine dose dependently impaired lordosis in OVX-EB + P rats, the lower doses of cocaine (10 mg/kg and 20 mg/kg) paradoxically increased proceptive behaviors.

Unlike METH, but similar to cocaine, acute administration of D-amphetamine (AMPH) disrupts sexual behavior. It has long been known that administration of an acute, high dose of AMPH (>2.0 mg/kg) reduces sexual receptivity (Michanek and Meyerson, 1977a, 1977b). Furthermore, even a low dose of AMPH is disruptive. Specifically, female rats treated with AMPH (1.0 mg/kg i.p.) were more likely than controls to leave the male after receiving mounts or intromissions during a test for paced-mating behavior (Guarraci and Clark, 2003).

The results from such studies testing the effects of psychomotor stimulants on female sexual behavior could have been confounded by the stimulant properties of these drugs. Alterations in approach or choice behavior could merely reflect the inability to suppress or control behavior when general locomotor activity is increased. However, in the studies discussed above, alterations in behavior tended to be directed specifically towards one of the stimulus animals (e.g., male, not female) or in response to the receipt of one type of sexual stimulation from the male (e.g., intromissions, not ejaculations). Therefore, it is unlikely that the effects of psychomotor stimulants on female sexual behavior only reflect a general increase in locomotion.

The present study was designed to test the effects of administering a high, non-therapeutic dose of MPH (10 mg/kg i.p.) on female sexual behavior during a test for partner preference. This dose of MPH is significantly more than a prescription dose (~1.0 mg/kg/day) for an adult diagnosed with ADHD (Morton and Stockton, 2000). More specifically, a therapeutic dose of MPH for an adult with ADHD ranges from 20–30 mg/day (not exceeding 60 mg/day), with 1.0 mg/kg/day representing an efficacious dose for adults (Morton and Stockton, 2000). Although more difficult to estimate, some reports indicate that people take between 40 and 1000 mg (~0.5–12.5 mg/kg) intravenously and up to 200 mg (2.5 mg/kg) intranasally for recreational purposes (Morton and Stockton, 2000). Therefore, the current dose is within the range of doses people take for the cognitive and/or euphoric effects of MPH (Arria et al., 2008; Morton and Stockton, 2000). During a partner-preference test, a female rat is given the choice to interact with a sexually active male rat or a sexually receptive female rat when physical contact is limited by placing the stimulus animals behind a wire mesh (i.e., no-contact phase) and when physical contact is not limited by removing the wire mesh (i.e., contact phase). The no-contact phase of the partner-preference test allows females to make choices based on the distal cues (e.g., auditory, olfactory, and visual) of the stimulus animals in the absence of bodily contact. The contact phase of the partner-preference test allows females to make a choice based on the distal and proximal cues of the stimulus animals when bodily contact is inevitable (i.e., when no wire mesh separates the subject from the stimulus animals). During the contact phase of the partner-preference test, female rats can pace the receipt of sexual stimulation from the male, display lordosis in response to sexual stimulation, and demonstrate proceptive behaviors (e.g., hops and darts, ear wiggling) near the stimulus animals. The use of the partner-preference test allows us to assess attraction to a sexual partner with and without the receipt of sexual stimulation from the male. When taken together, changes in these behaviors can reflect changes in the level of motivation in sexually receptive female rats.

Because most research investigating female sexual behavior uses OVX rats primed with hormones, the present study assessed the effects of MPH in OVX hormone-primed rats. Although time consuming and more complicated, it is ideal to measure sexual behaviors in naturally cycling female rats on the day of behavioral estrus, especially given that some drug effects interact with gonadal hormones (Pfaus et al., 2010). Therefore, the effects of MPH on partner preference were tested in naturally cycling female rats on the day of behavioral estrus in Experiment 1, as well as in OVX rats primed with gonadal hormones (EB + P) in Experiment 2.

2. Materials and methods

2.1. Subjects

Thirty-two adult female Long-Evans rats (200–300 g) were purchased from Envigo (Indianapolis, IN) and used as experimental subjects ($n = 16$/experiment). Additional male and female Long-Evans rats were purchased from Envigo and used as stimulus animals. Rats were group housed with same-sex cage mates in hanging polycarbonate cages that included aspen wood shavings for bedding and a red plastic tube for enrichment. Food and water were available ad libitum. Temperature and humidity in the animal colony were controlled and monitored daily. The lights in the colony were maintained on a reversed 12:12 hour light-dark cycle (with lights off at 10:00 a.m.). Behavioral testing occurred during the dark phase of the cycle under dim red light.

2.2. Acclimation

Female subjects were acclimated to the mating chambers on two separate occasions for 15 min each prior to any partner-preference tests. Each mating chamber consisted of a Plexiglas arena (101.0 cm long × 32.0 cm high × 37.0 cm wide) divided into three equal compartments using two clear Plexiglas dividers, each of which had a 5.0 cm hole in both bottom corners. Aspen wood shavings covered the floor