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Effects of Withdrawal from an Escalating Dose Schedule of *d*-Amphetamine on Sexual Behavior in the Male Rat

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BARR, A. M., D. F. FIORINO AND A. G. PHILLIPS. *Effects of withdrawal from an esclating dose schedule of* d-*amphetamine on sexual behavior in the male rat.* PHARMACOL BIOCHEM BEHAV **64**(3) 597–604, 1999.—The present study sought to determine the effect of withdrawal from an escalating dose schedule of *d*-amphetamine on sexual behavior in male rats. Tests were conducted every 5 days until stable levels of sexual behavior were obtained. With repeated testing, male rats displayed an increase in their exploration of the testing chambers prior to the introduction of an estrous female. Half of the male rats were then subjected to a 4-day escalating dose schedule of *d*-amphetamine administration (1–12 mg/kg), while half received vehicle. Twelve hours after the final drug injection, subjects were tested for sexual behavior. Withdrawal from the drug was associated with decrements in several motivational components of sexual behavior, including decreased anticipatory locomotor and increased postejaculatory intervals, while consummatory measures remained largely unaffected. This pattern of sexual deficits resembles those seen in human depressive disorders, and therefore, provides additional support for the use of psychostimulant withdrawal as a rodent model of depression. © 1999 Elsevier Science Inc.

Amphetamine Psychostimulant Withdrawal Depression Anhedonia Sexual behavior Copulation Anticipatory Preparatory Consummatory Male rat

WITHDRAWAL from binge-like doses of various psychostimulant drugs, such as cocaine and *d*-amphetamine, reliably induces a state of dysphoria in humans (10,32,49,60,67). This state is characterized by symptoms that include anhedonia, anxiety, and decreased motivation, and may last from weeks to months (20,21). The symptoms associated with psychostimulant withdrawal bear a strong resemblance to those of major depressive disorder (MDD) (10,60), to such an extent that the DSM-IV contains a specific category for the diagnosis of substance-induced mood disorders to differentiate them from isomorphic endogenous depression (3).

Administration of chronic doses of psychostimulants to animals, followed by a period of drug withdrawal, produces many of the same symptoms that are observed in humans who experience drug withdrawal (7,31,39,51,52). Extensive research has demonstrated that withdrawal from either cocaine or *d*-amphetamine in rodents generates a period of anhedonia, which is most commonly assessed by alterations in responding for reinforcing electrical brain self-stimulation (9,19,37,70). Decreased locomotor activity is another commonly observed effect of withdrawal from psychostimulants in rats (26,50,57,61), and may model psychomotor retardation, while withdrawal-induced anxiety has also been demonstrated through the use of behavioral paradigms (6,45). This combination of withdrawal-associated behavioral sequelae and their resemblance to the symptoms of MDD in humans has led to the utilization of psychostimulant withdrawal as a rodent model of depression.

Most animal paradigms of depression are developed with the intent to model accurately a specific symptom of MDD (69). One widely reported human symptom of MDD in a decrease in sexual behavior, noted as either a loss of libido or problems in sexual functioning (3,4,11,13). Despite the high incidence with which this symptom occurs in human depressives, there have been relatively few studies in which animal

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models of depression have been used to examine alterations in the sexual behavior of sexually experienced subjects. One advantage of studying male rats is that their sexual behavior is well documented (1,8,16,53), and has been demonstrated to consist of several distinct components, which represent both preparatory (motivational) and consummatory (copulatory) aspects (55). Several deficits in both the preparatory and consummatory components of sexual behavior have been reported in rats with limited or no copulatory experience using other models of depression (14,15,46,58,66), which include exposure to chronic, unpredictable stress and neonatal exposure to REM-suppressing drugs such as clomipramine.

In the present study, the psychostimulant-withdrawal model of depression was evaluated by using male rats that were well trained and exhibited high levels of sexual activity before the drug treatment conditions were implemented. In addition, all subjects were also trained in specially designed chambers that allowed the female rat to pace the level of sexual activity, by providing an opportunity to move away from the male at all times. Previous studies have employed bilevel chambers (2,42,64), which require that the male rat actively seek out and approach the female to initiate copulation. With repeated training in these chambers, male rats begin to display anticipatory searching activity prior to the entrance of the female into the chamber, and this provides a reliable measure of sexual motivation in the absence of the direct stimuli provided by the receptive female (43). Although the use of sexually naive rats is valid, the study of sexual behavior in experienced rats in this context has distinct advantages. First, it increases the face validity of a drug-induced model of depression, because many depressed patients have had sexual experience prior to the time of their sexual dysfunction: accordingly, emphasis should be placed on studying the disturbance of established sexual behavior, rather than its acquisition. Second, the activity associated with the anticipation of a receptive female in well-trained rats can provide a valuable measure of conditioned sexual motivation.

METHOD

Male Long–Evans rats (225–250 g; Charles River, Quebec) were group housed in wire cages (18 × 25 × 65 cm) and maintained on a reverse light–dark cycle (light off 0700–1900 h). One week later, they were housed individually in plastic cages with bedding (Carefresh, Absorption Corp., Bellingham, WA) for the remainder of the experiment. The colony room temperature was approximately 20°C, and rats had unlimited access to food (Purina Rat Chow) and water. Training and testing occurred during the middle third of the dark phase.

Female rats, housed in a separate colony, were anesthetized with ketamine hydrochloride (80 mg/kg, IP) and xylazine (10 mg/kg, IP), and bilaterally ovariectomized at least 4 weeks prior to testing. The use of ovariectomized rats allows the experimenter to induce receptivity in females at a predicted time (23), and also prevents the occurrence of unwanted pregnancies. Sexual receptivity in the stimulus females was induced by subcutaneous injections of estradiol benzoate (10 μg) and progesterone (500 μg), 48 and 4 h, respectively, before each test session.

Throughout the experiment, male rats were tested every 5 days for sexual behavior in Plexiglas testing chambers. The chambers (48 × 24 × 32 cm; l × w × h) were fitted with a central Plexiglas partition (32 cm in length, 20 cm high), which created a barrier that divided the chamber into two 12 cm-wide alleys along the length of the chamber, wide enough for only one rat to pass. By using a chamber of this design, in which the male was forced to approach the female from behind, the female rat could pace sexual behavior (17,18,48), and the male rat was subsequently required to cross from side to side to locate the female rat. In the absence of the female, well-trained male rats exhibited high levels of searching behavior, which, with repeated testing, was reflected as an increased number of side changes prior to the introduction of the female rat. This measure is hypothesized to represent a male rat's motivation to gain access to the female (42,43,65). Infrared photobeam emitter/detector pairs were located in the walls of the chamber, with one beam across its length on each side of the partition; three beams across its width; 12 cm apart, and were used to monitor activity. The number of side changes, defined as the complete movement from one side of the chamber to other side of the partition, were recorded automatically by a computer (2-Hz scan rate).

At the beginning of each test session, male rats were placed into the chambers and locomotor activity was recorded for 5 min. A sexually receptive female was then placed into the chamber, and copulatory behavior was monitored for 25 min. Each session was videotaped and subsequently scored for standard measures of sexual behavior using a computer and appropriate software (courtesy of Dr. Sonoko Ogawa, Rockefeller University). Testing chambers were washed thoroughly between tests to remove residual odors and pheromones (65).

Once consistent measures of preparatory and consummatory behavior were obtained (i.e., anticipatory side changes (<10% variation), intromission latencies <5 min, and ejaculation latencies <10 min for three consecutive tests), male rats were assigned to either the *d*-amphetamine (AMP; $n = 9$) or saline vehicle (SAL; $n = 9$) groups. Assignment was based upon their mean ejaculation latencies over the last four test sessions, such that there was an alternating assignment of rats into each group down a rank-ordered list of ejaculation latencies. Analysis of variance (ANOVAs) was conducted on the side changes, intromission latencies, and ejaculation latencies from the last test session to ensure there were no statistical differences between groups.

On the morning following the last baseline test session, male rats were placed on a 12-injection regimen over 4 days. Rats received three injections (1 ml/kg, IP) per day: 0900 h, 1600–1700 h, and 2300–0100 h. (i.e., 7–8 h apart) of either saline vehicle or *d*-amphetamine (Smith-Kline Beecham, Oakville, ON). The AMP group received escalating doses of drug starting at 1 mg/kg and incrementing by 1 mg/kg every injection to a final dose of 12 mg/kg. Discontinuation of this regimen has been shown to induce behavioral withdrawal in rats (12,34).

Sexual behavior testing continued at 5-day intervals, and the first postregimen test occurred approximately 12 h after the final injection. After two more tests of sexual behavior, the identical injection regimen was repeated for a second time, and subjects were again tested 12 h after completion of the drug schedule. Subsequently, rats were tested three more times for sexual behavior. To ensure that increases in side changes observed with successive bouts of copulation reflect increases in anticipatory behavior, and not simply enhanced locomotor activity, a separate group of rats ($n = 9$) was used as a control for anticipatory activity. It was hypothesized that this group would not demonstrate a conditioned increase in side changes across the initial seven sessions. These rats were introduced into the chambers, and side changes were monitored for the first 5 min of each test. Rats were left alone in the chambers

for an additional 25 min and then returned to their home cages. They were tested every 5 days for a total of seven sessions. Earlier studies employing bilevel chambers have demonstrated that the increased locomotor activity that occurs before the presentation of the estrous female is a function of previous sexual experience (42,43).

RESULTS

Precopulatory Anticipatory Activity

Figure 1A shows the mean (±SEM) anticipatory side changes for the control, vehicle, and drug groups during the 5-min precopulatory period for the seven training sessions. An ANOVA of the data revealed a significant group effect, $F(2, 24) = 5.19$, $p < 0.05$, as well as a significant effect of training session, $F(6, 144) = 12.48$, $p < 0.001$, and an interactive effect of group × training session, $F(12, 144) = 4.12$, $p < 0.001$. Post hoc analysis of the data demonstrated that the control group, which was never exposed to the estrous females, maintained a constant number of side changes across the seven predrug sessions. In contrast, the drug and vehicle groups, which were given the opportunity to copulate for 25 min following the 5-min anticipatory period, exhibited a gradual increase in anticipatory side changes that were significantly different from both the control group and their first session by the fourth session. These results support the use of precopulatory side changes in the current chambers as an index of preparatory sexual behavior in the male rat (43).

The number of anticipatory side changes during the final predrug session and the postdrug testing sessions (i.e., following both the *d*-amphetamine drug regimens) for both the drug and vehicle groups are shown in Fig. 1B. An ANOVA revealed a significant effect of test session, $F(6, 96) = 9.81$, $p < 0.001$, as well as an interactive effect of group × test session, $F(6, 96) = 10.58$, $p < 0.001$. Further analysis of the data with the appropriate post hoc test confirmed a significant reduction in the number of anticipatory side changes by rats on sessions following both sequences of *d*-amphetamine administration. The effect of drug withdrawal was limited to the single test session immediately following each of the two series of administration of *d*-amphetamine, with a return to baseline activity levels by the next test session.

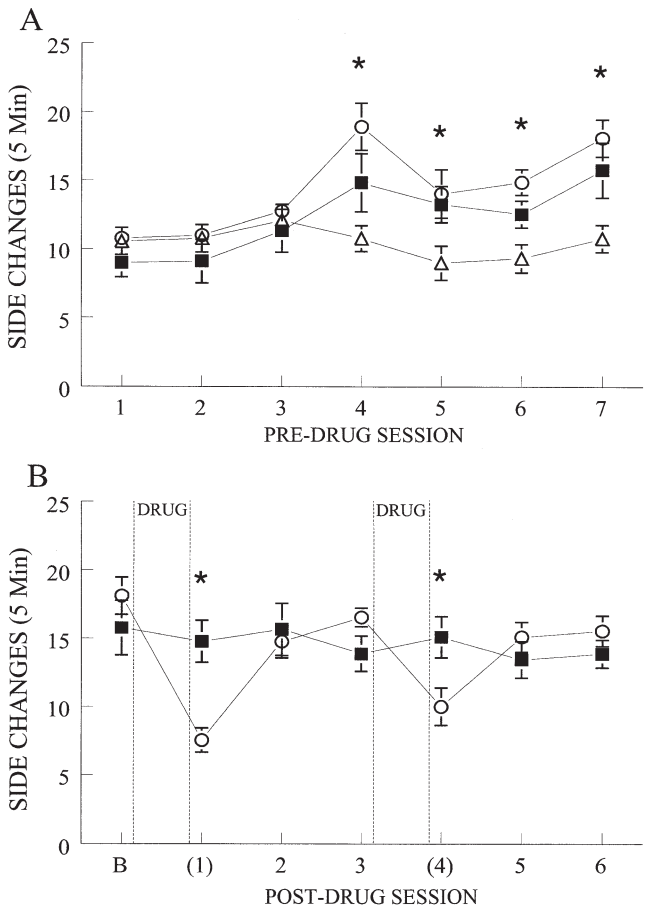

FIG. 1. The effect of withdrawal from an escalating dose schedule of *d*-amphetamine on anticipatory locomotor activity. (A) Values represent anticipatory side changes (±SEM) after repeated training sessions in which both drug (○) and vehicle (■) groups are allowed to copulate for 25 min after the 5-min anticipatory period, while the control (△) group is not provided with access to estrous females. Stars indicate significantly different from control group: $*p < 0.05$, $**p < 0.01$. (B) Effect of withdrawal from *d*-amphetamine on anticipatory side changes (parentheses indicate test 12 h after withdrawal from drug regimen). Tests occur every 5 days. Stars indicate a significant difference between groups, $*p < 0.05$.

Sexual Behavior

Withdrawal from *d*-amphetamine produced no significant effect on mount latencies (Fig. 2A), defined as the latency to the animal's first mount or intromission. Latencies in both drug and vehicle groups were short (averaging 5–30 s), reflecting the sexual experience of the subjects. An ANOVA on postejaculatory interval data, another preparatory measure of sexual behavior, revealed a significant group effect, $F(1, 13) = 4.39$, $p < 0.05$, an effect of test-session, $F(6, 78) = 3.79$, $p < 0.005$, and also an interaction of group × test session, $F(6, 78) = 3.06$, $p < 0.01$. Post hoc analysis of these results showed that there was a significant increase in the postejaculatory intervals on each test session following withdrawal from *d*-amphetamine, and that latencies returned to normal by the next test session + 5 days later (Fig. 2D).

No significant effect of drug withdrawal was found on either the ejaculation latencies (Fig. 2C), or the number of ejaculations, although a significant effect of test session was observed on the number of ejaculations, $F(6, 96) = 3.51$, $p < 0.005$ (Fig. 3C). In contrast with the absence of any effect of withdrawal from *d*-amphetamine on ejaculation frequencies, a significant group effect was found for intromission frequencies (defined as the total number of intromissions during the 25-min test) throughout the entire session (Fig. 3B), $F(1, 16) = 6.86$, $p < 0.05$, and also an effect of test session, $F(6, 96) = 2.92$, $p < 0.05$, although the interaction did not reach significance, $F(6, 96) = 1.67$, $p = 0.14$. Similarly, a large group effect was noted for mount frequencies (which were defined as the total number of mounts in the 25-min test), $F(1, 16) = 10.35$, $p < 0.005$, as well as an effect of test session, $F(6, 96) = 1.85$, $p < 0.10$, but with a nonsignificant interaction (Fig. 3A). Withdrawal from *d*-amphetamine was associated with fewer intromissions throughout the postdrug session, while the ejaculation frequency remained constant, indicating a possible facilitation of this copulatory measure.

Other measures of copulatory ability were unaffected by drug withdrawal. No effect was seen on either the interintromission interval, $F(1, 16) < 1$, NS (Fig. 2B) or the intromis-

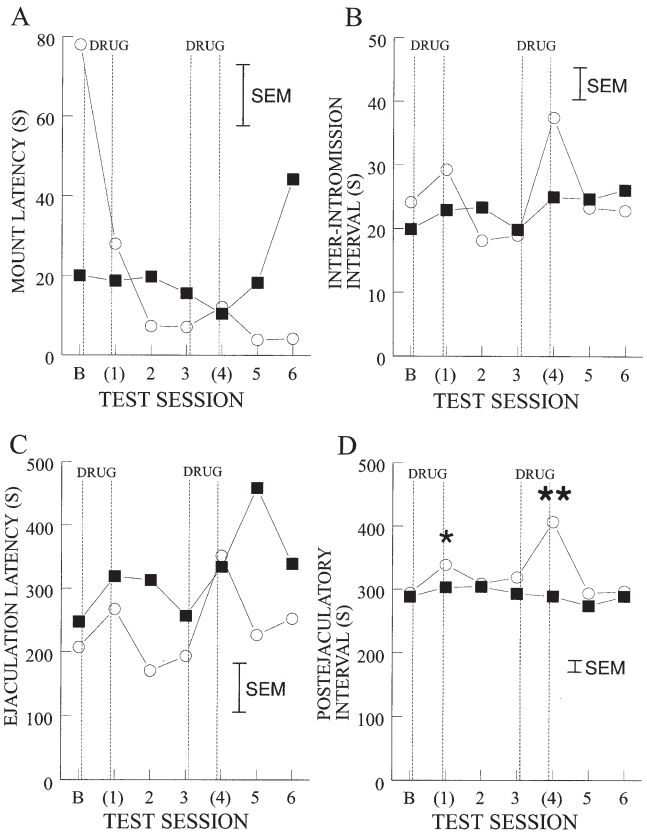

FIG. 2. The effects of withdrawal from an escalating dose schedule of *d*-amphetamine on different appetitive measures of sexual behavior in male rats. (B) represents predrug values corresponding to final training session values. Test sessions in parentheses indicate tests occuring 12 h after withdrawal from drug regimen. Tests occur every 5 days. Stars indicate a significant difference between drug (○) and vehicle (■) groups, $*p < 0.05$, $**p < 0.01$. (A) Effect of withdrawal from drug on latency to first mount or intromission. (B) Effect of withdrawal from drug on interintromission interval. (C) Effect of withdrawal from drug on ejaculation latency. (D) Effect of withdrawal from drug on postejaculatory interval.

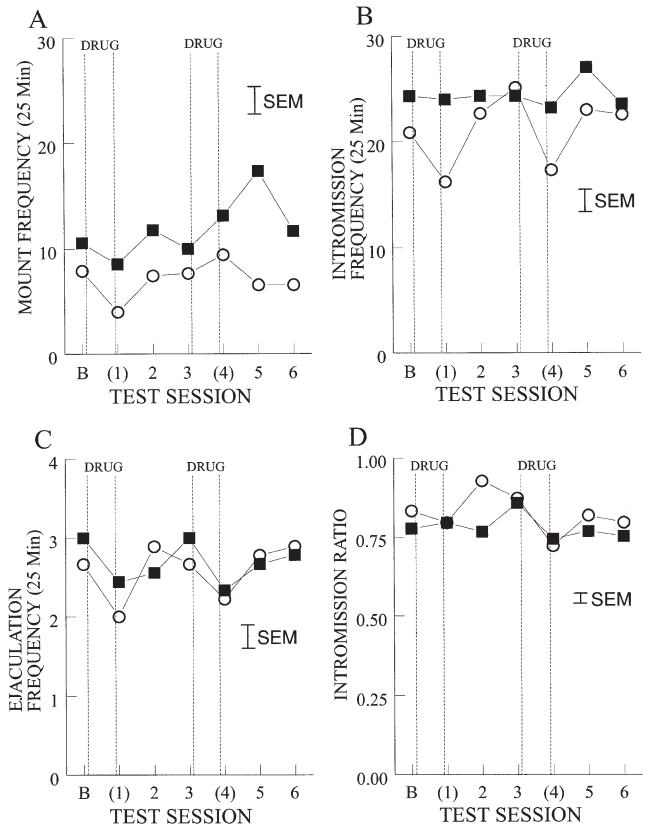

FIG. 3. The effects of withdrawal from an escalating dose schedule of *d*-amphetamine on different copulatory measures in male rats. (B) represents predrug latencies corresponding to final training session values. Test sessions in parentheses indicate tests occuring 12 h after withdrawal from drug regimen. Tests occur every 5 days. No significant differences were observed between drug (○) and vehicle (■) groups. (A) Effect of withdrawal from drug on total number of mounts. (B) Effect of withdrawal from drug on total number of intromissions. (C) Effect of withdrawal from drug on total number of ejaculations. (D) Effect of withdrawal from drug on "hit rate," i.e., total number of intromissions/total number of mounts + total number of intromissions.

sion ratio (i.e., "hit rate") $F(1, 15) = 1.58$, NS (Fig. 3D). Interestingly, results from both withdrawal sessions were similar in that the same two measures of sexual motivation (side changes and the postejaculatory interval) were affected each time. However, the size of the effect of drug withdrawal upon anticipatory side changes decreased slightly during the second test, but remained statistically significant. In contrast, there was a "sensitized" response to the effect of withdrawal on the postejaculatory interval, as a greater significant difference was observed between the groups during the second test.

DISCUSSION

The results of the present study indicate that withdrawal from an escalating dose schedule of *d*-amphetamine decreases certain preparatory components of sexual behavior in sexually experienced male rats, but leaves their copulatory behaviors fundamentally unaltered. Twelve hours after the administration of a 4-day escalating-dose schedule of *d*-amphetamine, anticipatory locomotor activity (measured as the side changes in a modified single-level chamber) in the 5-min period prior to the presentation of an estrous female was reduced, reflecting a decrease in anticipatory search behaviors. Furthermore, postejaculatory intervals were significantly longer in *d*-amphetamine-treated rats, demonstrating a reduction in an additional component of motivated sexual behavior. These effects were replicated within the experiment after the animals were exposed to the same drug schedule a second time, and similar results were obtained. There was also a strong trend towards fewer mounts and intromissions in *d*-amphetamine–treated rats during the period of drug withdrawal, although these effects were not statistically significant.

In the present experiment, control rats that were never exposed to a receptive female failed to show augmented locomotor activity over trials. These data are in agreement with a previous study that reported that male rats presented with anestrous females failed to show an increase in level changes after repeated testing in bilevel chambers (43). The use of partitioned testing chambers, such as bilevel chambers or the design used in this study, in which the female rat paces sexual activity, allows the experimenter to gain additional informa-

tion about the conditioned sexual motivation of male rats in the absence of the female. With repeated exposure to a receptive female, male rats in bilevel chambers typically engage in increased searching behavior, in "anticipation" of the female, which is reflected as more numerous level changes (42) (or side changes, with the present chambers). Consistent with the hypothesis that level changes are representative of sexual motivation, van Furth and van Ree (65) have demonstrated that a reduction in sexual motivation, which was achieved by testing rats during the refractory period, decreased the number of anticipatory level changes prior to the presentation of an estrous female. Additionally, Mendelson and Pfaus (43) observed that level-searching activity extinguishes in experienced male rats when the receptive female is repeatedly withheld. These results re consistent with the assumption that precopulatory activity serves as a sensitive measure of preparatory sexual behavior in male rats. Postejaculatory intervals represent an additional measure of preparatory behavior, and provide a further index of sexual motivation. The increase in postejaculatory intervals observed in rats that were withdrawn from the *d*-amphetamine regimen is consistent with a decrease in motivation to reinitiate copulatory activity, postcoitus. It is unclear why this particular measure of sexual latency was affected so noticeably but other latency measures were not. This may reflect the suggestion that the postejaculatory interval is unique, in that it represents a time of active inhibition of preparatory mechanisms, possibly through the suppression of the mesolimbic dopamine system (40,41), hence making it more susceptible to the effects of withdrawal from a psychostimulant drug.

Although the present experiment was not designed to determine the neurochemical correlates of the observed changes in sexual behavior in drug-treated rats, a body of evidence implicates the mesolimbic dopamine system. Through the use of in vivo monitoring techniques, research from our laboratory has found that extracellular dopamine concentrations in the nucleus accumbens (NAcc) remain significantly lowered for up to 48 h following the administration of the identical drug regimen that was used in this study (63). A role for mesoaccumbens dopamine in sexual motivation is supported by in vivo microdialysis studies, which have demonstrated that dopamine levels in the NAcc rise significantly above baseline in sexually experienced male rats when they are exposed to a receptive yet inaccessible female during a 5-min anticipatory period (17,18). The critical importance of mesoaccumbens dopamine in sexual motivation is supported by the research of Everitt and his colleagues (16,54,59), in which selective neurotoxic lesions of dopamine terminals in the NAcc caused impairments in rats' motivation to approach and mount nonproceptive females, but had no effect on copulatory abilities (16). These effects on sexual motivation are consistent with our previous behavioral observations. Bilateral infusions of low concentrations of the D_2 antagonist haloperidol into the NAcc produced behavioral effects similar to those observed in the present study. Anticipatory locomotor activity (measured as level changes in bilevel chambers) was significantly decreased, and there were no other significant effects on other measures of preparatory or consummatory sexual behavior (56). Copulatory behavior has been more closely linked to dopaminergic activity in the medial preoptic area of the hypothalamus (28,29), and this may partially explain the dissociation between the effects of psychostimulant withdrawal on preparatory and consummatory behaviors. In synthesis, the specific deficits in sexual behavior observed in the current experiment suggest that withdrawal from an escalating dose schedule of *d*-amphetamine preferentially disrupts preparatory behaviors over consummatory behaviors, and hence, causes a reduction in subjects' sexual motivation rather than in their physical capacity to engage in copulatory behavior.

The escalating 12-dose schedule of *d*-amphetamine utilized in the current experiment has been used previously to demonstrate that withdrawal from a psychostimulant can generate anhedonia and a consequent reduction in the motivation of male rats. Two previous studies have shown that withdrawal from a drug schedule identical to that employed in the present experiment reduces intracranial self stimulation (ICSS) of the lateral hypothalamus in rats (12,34). This is consistent with a subsensitivity of the neural systems involved in behavioral reinforcement. Additionally, recent research in our laboratory has found that withdrawal from a similar drug schedule of *d*-amphetamine decreases rats' motivation to obtain a rewarding sucrose solution, as measured by decreased breakpoints on a progressive ratio schedule of reinforcement, without affecting their free consumption of the same solution (5). The results of the present study are, therefore, consistent with those of previous studies, and imply in turn that the reductions in sexual behavior in the current experiment reflect a drug withdrawal-induced state of anhedonia and a consequent decrease in motivation. To our knowledge, this is the first experiment that has specifically examined the effects of psychostimulant withdrawal and its associated anhedonia on sexual behavior, in either rats or humans.

The similarity between the effects of cocaine and amphetamine withdrawal and the features of human depression has led to the proposition that psychostimulant withdrawal in rats is a valid animal model of depression (22,35,38,62). Anhedonia, one of the two core symptoms of depression, is widely noted in rodent paradigms of drug withdrawal, and many of the deficits observed in ICSS responding during early psychostimulant withdrawal can be alleviated by administration of a tricyclic antidepressant (30,36). Symptoms other than anhedonia are also frequently modeled in animal paradigms of depression, and the high incidence of sexual dysfunction associated with MDD has led to the testing of sexual behavior of rodents with alternate animal models of depression. Exposure of rats to continuous low-intensity stress in the Chronic Mild Stress model of depression reduced dramatically the number of mounts during the testing session (14), while the removal of the olfactory bulbs in rats reduced mounting activity to a similar extent and also disrupted ejaculatory capacity (15,24). Pharmacological models of depression, for example, the administration of clomipramine to rat neonates, result in comprehensive deficits in nearly all aspects of sexual activity, including both motivational and copulatory components of sexual behavior (46,66).

The results from the present study thus appear to be milder than those from other animal models of depression, as rats in the present study did not exhibit significant alterations in either mounting activity or ejaculatory ability. These differences may be attributed to the side effects produced by alternate techniques used to induce a "depressive"-like state in animals. For example, the olfactory bulbectomy model removes the olfactory sensory systems critical for rodent stimulus-bound sexual behavior (65,71), and the administration of REM-suppressing serotonergic drugs, such as clomipramine, to rat neonates may have unknown effects upon the sexual development of the maturing brain (33,68). Administration of the current escalating-dose schedule of *d*-amphetamine and its subsequent withdrawal does not create general sensorimo-

tor deficits, and the behavioral effects are reversible with time, thus providing a potential model of the natural remission to normal activity that is commonly seen in most patients with MDD (3).

It is generally acknowledged that MDD is associated with a range of deficits in sexual functioning in humans (4,25). Two recent studies have shown that depressed men, who maintained daily diaries of their sexual activity, reported decreases in both sexual interest and satisfaction (i.e., reduced libido) yet showed deficiencies in neither sexual capacity nor activity (27,47). These studies indicate that the sexual problems facing male depressives are primarily motivational and emotional, rather than of a physical nature. Therefore, the absence of an effect of withdrawal from *d*-amphetamine on any of the copulatory behaviors in rats in the present study provides additional support for the use of psychostimulant withdrawal as a valid model of depression. As a caveat, it should be noted that relatively short-lasting motivational deficits were observed with rats in this study, following two exposures to the drug regimen. Long-term dysphoria and anhedonia have been reported by human substance abusers, based upon numerous "binges" and lengthy exposure to psychostimulant drugs (20). The duration and magnitude of the behavioral effects that were observed in this animal model of depression might feasibly be increased by exposing subjects to multiple drug regimens, hence improving the utility of this model.

In conclusion, the present study found that withdrawal from an escalating-dose schedule of *d*-amphetamine in male rats was associated with significant decreases in several motivational components of sexual behavior, although most copulatory components were resistant to the effects of the drug withdrawal. The pattern of behavioral changes resembles the types of sexual deficits seen in humans diagnosed with MDD (27,47), and therefore, supports the development of psychostimulant withdrawal in rats as a rodent model of depression. Further studies, with the use of in vivo monitoring techniques, are required to elucidate the neurochemical nature of psychostimulant withdrawal-associated deficits in sexual behavior.

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