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Haloperidol challenge during copulation prevents subsequent increase in male sexual motivation

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Abstract

Male rats manifest an increase in sexual motivation following sexual experience. The current experiment was devised to investigate the role of dopamine in this process by assessing whether sexual behavior occurring in the presence of the dopamine receptor antagonist, haloperidol, would continue to alter the subjects' subsequent sexual motivation. Four groups of male Long–Evans rats (total $N=34$) traversed an operant runway once per day for one of two goalbox targets: a nonestrous or estrous female. Following establishment of baseline run times (10 trials), all males received one ejaculation with a receptive female in a separate testing environment. Subjects were pretreated with vehicle or one of three doses of haloperidol (0.05, 0.075, 0.10 mg/kg) 45 min prior to being paired with the receptive female. All subjects successfully achieved ejaculation under these conditions. Subjects were then re-tested within the runway for their motivation to approach the two types of female targets (10 trials). Vehicle-treated subjects expressed the expected increase in sexual motivation following sexual experience, while haloperidol treatment dose-dependently attenuated this effect. Subjects that received the highest haloperidol dose subsequently manifested increased run times and intra-runway "retreat" behaviors, suggesting that female cues may have become associated with an aversive sexual experience. These results are consistent with the view that dopamine systems play a role in the rewarding or reinforcing consequences of male sexual behavior.

Keywords: Copulation; Incentive; Motivation; Dopamine; Reinforcement; Sexual experience

Compared to sexually naïve males, experienced male rats express a greater motivation to copulate with estrous females. They are more likely to initiate sexual behavior [7,18] and express shorter mount latencies [39] than naïve males when in the vicinity of a receptive female. Our own laboratory has noted that sexual experience increases subsequent sexual motivation, as measured by run time within a straight alley [27]. Specifically, male subjects that received one ejaculation with a receptive female in a separate testing environment took less time to approach both nonestrous and estrous female targets following copulation. This suggests that sexual experience enhances the incentive value of primary female cues through associative mechanisms.

This enhancement presumably depends upon the rewarding nature of male ejaculation. The efficacy of sexual reinforcement in maintaining operant responses, such as lever-pressing and runway behavior, has been well documented [3,15,16,24,25,42,43,46,47]. Similarly, repeated copulatory experiences in a bilevel chamber increase level-changing behavior, a measure of anticipatory or motivational activation [31]. In addition, sexual access to a receptive female culminating in ejaculation rapidly establishes a conditioned place preference for the environment in which copulation occurred [1,2,21,30,32].

Midbrain dopamine systems have been implicated in the processing of numerous rewarding events, including food and water, drugs of abuse, and intracranial self-stimulation (for reviews, see Refs. [8,26,37,49–51]). These conclusions are based, in part, upon the finding that systemic administration of dopaminergic antagonist drugs, such as haloperidol, effectively blocks the reinforcing consequences of such events. Thus, it seems plausible that the reward value of copulation and ejaculation is also mediated by dopaminergic transmission, and subject to alteration via dopamine receptor blockade. If this were correct, then one

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would hypothesize that haloperidol challenge during sexual experience would prevent the subsequent expected increase in sexual motivation by preventing reward-based incentive enhancement. The current experiment was devised to test this hypothesis.

1. Method

1.1. Animals

The subjects consisted of 34 male and 20 female Long–Evans rats obtained from Charles Rivers Laboratories (Wilmington, MA). Three of the females were used as runway targets, while the remaining 17 were paired with the males in order to provide them with sexual experience. The males were 70–100 days old and the females 90–180 days old at the start of testing. All animals were housed individually in hanging wire cages within a temperature-controlled 22°C vivarium environment maintained under a reverse 14:10 light–dark schedule (lights on 2300–1300 h). Food and water were provided on an ad libitum basis.

Prior to arrival at our vivarium, the males were group-housed but did not have access to females. Therefore, they were sexually naive insofar as they lacked heterosexual (but possibly not homosexual) copulatory experience.

1.2. Surgery

All females were ovariectomized (OVX) through a single lower abdominal incision 1–6 weeks prior to testing, using standard aseptic surgical techniques conducted under deep anesthesia. Each animal was pretreated with 0.3 mg/kg intraperitoneal (i.p.) atropine (Pittman-Moore, Washington Crossing, NJ) 15 min prior to the induction of anesthesia in order to reduce potential respiratory problems. Anesthesia was then induced by administration of 90 mg/kg ketamine i.p. and 2 mg/kg xylazine i.p. All females received at least 1 week post-operative care prior to use within the experiment.

1.3. Apparatus

The test apparatus was a straight-arm runway consisting of a startbox ($25 \times 25 \times 20$ cm^3), an alley ($160 \times 10 \times 20$ cm^3), and a cylindrical Plexiglas goalbox (45 cm diameter, 40 cm height). Removable doors were located between the startbox and alley, and between the alley and goalbox. Infrared photocell emitter–detector pairs were located just outside the startbox and just inside the goalbox. Interruption of the photobeam outside the startbox initiated a timer that stopped when the subject entered the goalbox. This apparatus is comparable to that used successfully by our laboratory for studying other reinforcers, including food [5,9,20], water [10,12], and drugs of abuse [11,13,28,29]. Within the goalbox, a removable Plexiglas partition divided the arena into two semi-circular halves. Sixteen 1.2 cm diameter holes drilled into the partition and spaced 8 cm apart from one another allowed air to pass between the two sides. Thus, the partition prevented even minimal tactile contact between subject and target, although visual, auditory, and olfactory cues were accessible.

1.4. Procedure

On 2 separate days, each of the male subjects was allowed to individually explore the runway apparatus for 5–7 min. The three female targets were also individually placed within the goalbox for 10 min each on 2 days. This was done to acclimate the animals to the novel runway environment. All testings took place under red light conditions during the dark portion of the rats' photoperiod.

On any given test day, all 34 male subjects ran for the same target in the goalbox; only one trial per day per subject was conducted. Before a day's trials, the designated target female was placed into the goalbox for 2–3 min. The partition was then introduced into the goalbox, with the target female placed on the side farthest from the goalbox entrance. At this point, the trials began. First, a subject male was placed into the goalbox on the opposite side of the partition from the target female for 4 min. The subject was then removed and immediately placed into the startbox. After 10 s, the goalbox door and startbox door were lifted, and the time required for the subject to traverse the alley and return to the goalbox was recorded. Once the subject had re-entered the goalbox, the door was closed, thereby restricting him to the goalbox for 1 min before he was removed and returned to his home cage. The next subject's trial was then initiated. This procedure continued, one animal at a time, until all 34 subject males were tested within the runway for their motivation to approach the female target. The order of subjects run was held constant throughout the experiment.

On different days/trials, subjects ran for one of two different targets, randomly determined: either a nonestrous female (OVX female) or an estrous female. Estrus was induced via subcutaneous (s.c.) administration of 15 μg of estradiol benzoate (in 0.1 ml sesame oil) 48 and 24 h before testing, with an additional s.c. injection of 500 μg progesterone (in 0.1 ml propylene glycol) 3–5 h before testing. Steroid hormones were purchased from Sigma (St. Louis, MO). Behavioral estrus was confirmed prior to the days' trials during a brief 1-min pretest conducted in another room, in which the target female was paired with an adult Long–Evans male (taken from another experiment). These tests confirmed that non-hormonally treated females (non-estrous condition) never displayed lordosis or any proceptive behaviors, and females given both estradiol and progesterone (estrous condition) displayed both lordosis and numerous proceptive behaviors in the space of a minute (always over five hop–darts and ear–wiggles total [4]). Each of the three target females was rotated through both hormonal conditions three to four times over the course of the experiment.

Subject males ran a total of 10 trials, one trial per day (five for a nonestrous target and five for an estrous target) before they were provided with sexual experience. These trials not only established a baseline with which to compare subsequent run times, but also permitted subjects to learn the consequences of the operant task without the introduction of copulatory experience. Following these 10 trials, each subject was assigned to one of four groups ($N=8-9$/group) such that the mean baseline run times for both nonestrous and estrous targets were approximately the same for all four groups.

Over the course of 2 days, all four groups were taken to a separate testing arena in order to provide them with sexual experience. Each subject male was tested individually under red light during the dark portion of the photoperiod. The testing arena was composed of cylindrical Plexiglas, 45 cm diameter × 60 cm height, with the floor of the arena covered with wood chips. A total of 17 OVX Long–Evans females, given estradiol and progesterone to induce robust receptivity, were used. It should be noted that while the same three females were used as targets throughout the runway portions of the experiment, none of these target females was used to provide sexual experience. Each male was individually paired with a female until he achieved one ejaculation. Males within the control group were given i.p. vehicle injections of 0.002 M lactic acid 45 min prior to testing. Subjects in the remaining three groups were given an i.p. injection of haloperidol (0.05, 0.075, or 0.10 mg/kg) dissolved in 0.002 M lactic acid 45 min prior to testing. All injections were made in a volume of 1 ml/kg. While more specific dopamine receptor antagonists are currently available, our laboratory has a long history of using this particular drug in this dosage range, allowing us to compare the effects of haloperidol on the motivational impact of a variety of rewards, including food [9,20], water [10], and numerous drugs of abuse [13,28].

Each subject male was returned to his home cage following sexual experience. Two days later, subjects were re-tested within the runway for their motivation to approach either a nonestrous or an estrous female target. A total of 10 post-sexual experience trials were conducted, one trial per day, five for a nonestrous target, five for an estrous target. Thus, over the course of the entire experiment, each of the 34 subjects ran a total of 20 trials within the runway, 10 prior to sexual experience and 10 afterwards.

1.5. Dependent measures

The primary dependent measure in this experiment was run time, i.e., the time elapsed between the subject's leaving the startbox and entering the goalbox. Shorter run times reflect a greater motivation to approach the goalbox "target". Past experiments utilizing the runway apparatus have shown that under certain circumstances, subjects will stop at some point along the alley, turn around, and return to the startbox rather than continue directly to the goalbox. These "retreats" reflect an approach–avoidance conflict, insofar as they have been shown to increase in number as aspects of the goalbox experience acquire mixed positive and negative valence [11,19]. The total number of "retreats" produced by each subject on each trial was also recorded.

When the males were provided with sexual experience, two measures of copulatory performance were recorded for each subject: mount latency (ML) and ejaculation latency (EL). Mount latency is defined as the time between introduction of the receptive female and the first successful mount conducted by the male. Ejaculation latency is the time between introduction of the female and ejaculation.

2. Results

2.1. Baseline run times

Prior to receiving any sexual experience, the mean (±SEM) run time (over five trials) of all 34 male subjects was faster for the estrous female target than for the nonestrous female target: 35.8 (±5.9) and 59.4 (±6.9) s, respectively. A two-tailed paired sample *t*-test comparing these means revealed a significant difference: $t(33)=3.915$, $P<0.001$. Thus, even prior to any sexual experience, male rats are more motivated to approach an estrous female vs. a nonestrous female.

2.2. Effect of haloperidol on sexual behavior

The mean (±SEM) mount latencies for the four experimental groups (vehicle, 0.05, 0.075, and 0.10 mg/kg haloperidol) were: 39.4 (±10.5), 56.7 (±26.9), 181.1 (±110.2), and 67.5 (±24.3) s, respectively. The mean (±SEM) ejaculation latencies were: 693.8 (±117.5), 426.7 (±71.0), 544.4 (±115.7), and 531.2 (±55.3) s. A one-way ANOVA comparing the mean mount latencies between the four groups and another ANOVA comparing the mean ejaculation latencies were conducted to determine whether haloperidol had an inhibitory effect upon copulatory performance. At the doses used, there was no significant effect of haloperidol on mount latency [$f(3, 30)=1.131$, $P=0.35$] nor on ejaculation latency [$f(3,30)=1.341$, $P=0.28$]. Hence, haloperidol did not reliably alter these measures of male sexual performance.

2.3. Effect of sexual experience+haloperidol on subsequent run times

The male subjects' performance in the runway (mean +SEM run times) during pre- and post-sexual experience trials is depicted for each group in Fig. 1 (panels A–D). A mixed two-factor (Sexual experience × Target receptivity) ANOVA was conducted on the data within each group (i.e., on the data depicted in each panel of Fig. 1). For the vehicle group, there was a significant main effect of sexual

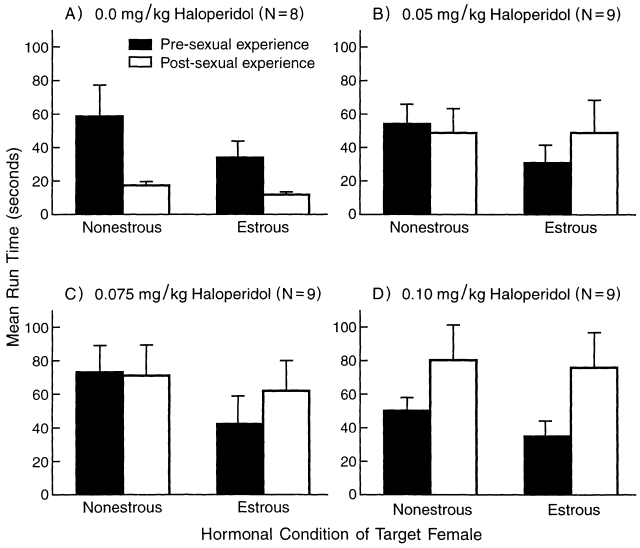

Fig. 1. Mean (+SEM) run times, pre- and post-sexual experience, for the four groups of experimental subjects. Panel A represents the vehicle controls, panels B–D depict data from subjects given haloperidol 45 min prior to sexual experience. Black bars represent mean run times prior to sexual experience, while white bars represent mean run times following sexual experience. Within each panel, the two leftmost bars are subject run times when the goalbox contained a nonestrous female target, and the two rightmost bars are subject run times for estrous female targets.

experience [$f(1,7)=5.178$, $P=0.05$] and a significant main effect of the target's sexual receptivity [$f(1,7)=9.024$, $P=0.02$], but no interaction between these two factors. Thus, subjects in this group ran reliably faster for target females following sexual experience, and faster for estrous females over nonestrous females. For the 0.05 and 0.075 mg/kg haloperidol groups, there were no significant main effects of sexual experience or receptivity, nor a reliable interaction. For the 0.10 mg/kg haloperidol group, there was a main effect of sexual experience [$f(1,7)=7.561$, $P=0.03$], but no effect of receptivity nor an interaction. However, in contrast to the vehicle group, the high-dose subjects took significantly longer to approach target females following sexual experience.

In order to better visualize the effect of sexual experience (with and without haloperidol challenge) upon sexual motivation, difference scores were calculated by subtracting the post-sexual experience run time of each subject from its pre-sexual experience run time. The means (+SEM) differences, plotted by the hormonal status of the target female, are depicted in Fig. 2 (panels A and B). Large differences (deviations from zero) indicate changes in motivation following sexual experience; positive differences reflect an increase in motivation, while negative differences reflect a decrease. A two-way (Group × Target receptivity) ANOVA comparing the difference scores across groups revealed a main effect of haloperidol dose [$f(3,30)=3.476$, $P=0.028$]. Post-hoc analyses consisted of eight pre-planned, one-sample, one-tailed *t*-tests conducted to determine whether each bar displayed in Fig. 2 was significantly different from zero (i.e., was there a reliable change in run time following sexual experience). These analyses revealed a significant decrease in run time (increase in motivation) following sexual experience for subjects within the control condition, when running for both nonestrous [$t(7)=2.221$, $P<0.05$] and estrous [$t(7)=2.256$, $P<0.05$] female targets. There were no significant pre–post differences for either the 0.05 or 0.075 mg/kg dose groups when running for either nonestrous or estrous female targets. Subjects within the 0.10 mg/kg dose group took significantly more time (expressed decreased motivation) to approach both nonestrous [$t(7)=-1.849$, $P<0.05$] and estrous [$t(7)=-2.329$, $P<0.05$] female targets following sexual experience.

2.4. Effect of sexual experience+haloperidol on subsequent runway retreat behaviors

To further examine whether haloperidol influenced the motivational impact of sexual experience, we examined the retreat behaviors of the two experimental groups that expressed a significant change in run time following sexual experience: the vehicle group and the high haloperidol dose (0.10 mg/kg) group. The mean (+SEM) numbers of retreats displayed by these two groups, pre- and post-sexual experience, are shown in Fig. 3. An overall three-way (Group × Sexual experience × Target receptivity) ANOVA on these data revealed a significant main effect of group

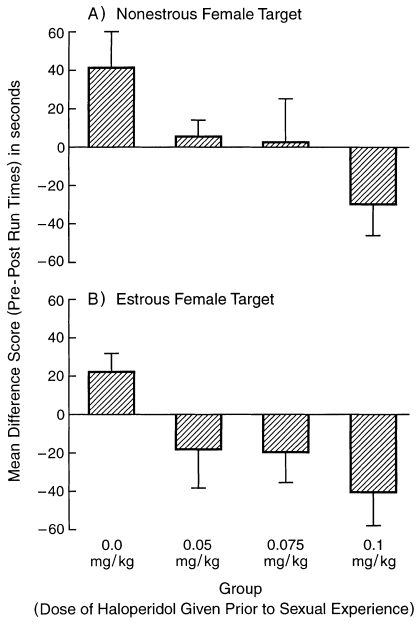

Fig. 2. Mean (+SEM) difference in run time from pre-sexual experience trials to post-sexual experience trials, for four groups of experimental subjects. Top panel A depicts difference scores when subjects were running for nonestrous female targets, and bottom panel B depicts these data when subjects were running for estrous female targets. Positive difference scores represent faster running following sexual experience (i.e., an increase in motivation), while negative difference scores indicate that subjects ran slower for the target female following sexual experience.

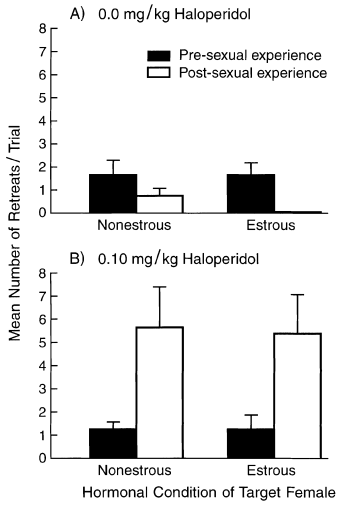

Fig. 3. Mean (+SEM) retreats per trial, pre- and post-sexual experience, for two groups of experimental subjects. Panel A depicts the retreat behavior of the vehicle controls, and panel B displays the retreat data of the 0.10 mg/kg haloperidol-treated subjects. Black bars represent mean number of retreats prior to sexual experience, while white bars are mean retreats following sexual experience. Within each panel, the two leftmost bars are group retreats when the goalbox contained a nonestrous female target, and the two rightmost bars are retreats during trials when an estrous female target was in the goalbox.

[$f(1,14)=5.932$, $P=0.029$] and a significant interaction between group and sexual experience [$f(1,14)=13.498$, $P=0.003$]. This suggests that those subjects given the 0.10 mg/kg dose of haloperidol prior to sexual experience associated both positive and negative experiences with the female, later expressed as approach–avoidance conflict behavior (i.e., retreats) within the runway.

3. Discussion

This experiment successfully replicated work conducted within our laboratory on the sexual motivation of male rats [27]. First, prior to receiving any sexual experience, the male subjects were more motivated to approach estrous females over nonestrous females, reflecting an inherent motivational bias toward the former. Second, in our previous paper, we reported that males given one ejaculation subsequently decreased their run times for both nonestrous and estrous female targets. In the current experiment, male subjects within the control group that received vehicle injections prior to sexual experience expressed a similar increase in motivation. Thus, sexual experience consisting of one ejaculation is sufficient to enhance the incentive value of primary female cues.

Haloperidol challenge during copulation dose-dependently attenuated this effect. In particular, subjects within the 0.05 and 0.075 mg/kg groups did not experience an increase in sexual motivation following sexual experience. Their pattern of pre-to-post sexual experience run times mirrors that of subjects not given any sexual experience at all or merely one intromission without ejaculation (see Ref. [27]). Based upon these results, we suggest that the positive, rewarding properties of sexual behavior and ejaculation enhance the incentive value of female cues associated with copulatory experience through central dopaminergic release.

Subjects within the high haloperidol dose group (0.10 mg/kg) expressed a decreased motivation to approach female targets following their sexual experience. There are at least three possible explanations for this. First, the haloperidol itself might have been punishing, causing the subjects to associate a negative drug experience with female cues. However, similar doses of haloperidol do not produce place aversions when paired alone with one side of a preference chamber, indicating that environmental cues associated with a haloperidol experience do not acquire negative valance [44,45]. A second possibility is that the haloperidol compromised the sexual performance of the treated males, such that they were not able to engage in a similar degree of sexual behavior as control subjects. The data collected on mount and ejaculation latencies do not support this interpretation; there were no significant group differences on these measures, and all drug-treated males successfully achieved ejaculation following repeated mounting and intromission.

Although speculative, a third hypothesis is that the highest dose of haloperidol not only negated the positively reinforcing properties of sexual activity, but also caused the subjects to experience copulation as an aversive form of physical stimulation. This was not a consequence of either the haloperidol or the sexual behavior per se, but rather a negative result of the interaction or combination of the two (at least at the highest haloperidol dose). If this were true, then one might expect subjects, on subsequent trials, to approach the female targets because of their aforementioned inherent sexual attractiveness, but also avoid the targets because of the associated negative sexual experience. This approach–avoidance conflict would account for the increased frequency of post-experience runway retreats observed in the high-dose group (see Fig. 3), particularly in view of the fact that such "retreat" behaviors have been shown to reflect motivational conflict under other circumstances [11,19].

As noted, at the doses administered, haloperidol had no significant effect upon either the mount or ejaculation latencies of the subject males. This finding is partly in contrast with earlier work demonstrating an inhibitory effect of dopamine antagonists on mount latency [14,35,36]. However, in these earlier studies, decrements in sexual performance generally occurred following administration of higher doses of haloperidol (0.1, 0.2, 0.5 mg/kg). The fact that haloperidol did not affect the sexual performance of our subjects diminishes the possibility that the subsequent differences in sexual motivation resulted from differences in the quantity of sexual experience received, rather than differences in the reinforcing quality of the act. Nevertheless, only two measures of sexual performance (mount

and ejaculation latency) were examined. Hence, a more detailed observational analysis of the copulatory sessions, involving alternate behavioral measures such as copulatory hit rate, might have revealed subtle decrements in sexual function during dopamine antagonist challenge.

Surprisingly, alternate evidence supporting a dopaminergic basis to sexual reward has been sparse. If true, one would expect that dopamine receptor antagonists would be capable of extinguishing operant responses maintained via sexual reinforcement, and prevent sexually conditioned place preferences. While it has been reported that the mixed D_1/D_2 antagonist, alpha-flupenthixol, dose-dependently decreased responding for access to a receptive female under a second-order schedule [14], Agmo and Berenfeld [1] failed to block a sexually conditioned place preference with a 1 mg/kg systemic dose of the dopamine antagonist, pimozide. However, their experiment more specifically focused upon the rewarding properties of the post-ejaculatory interval: males were placed in the preference chamber following copulation. Thus, pimozide did not challenge the reinforcing consequences of sexual behavior and ejaculation per se.

In contrast, numerous studies utilizing in vivo neurochemical techniques, such as microdialysis and voltammetry, have documented a significant correlation between sexual activity and central dopamine release. Dopamine concentrations within the nucleus accumbens (NA [34,38]) and the medial preoptic area of the hypothalamus (MPOA [22,23,40]) rise prior to (following exposure to estrous female cues) and during copulation. Moreover, repeated exposure to estrus female bedding leads to an increased, or sensitized, dopaminergic response within the NA [33]. It seems plausible then that dopaminergic activity during sexual behavior modulates the incentive value of primary female cues through this process of sensitization [48]. Increased mesolimbic dopamine transmission during copulation could serve both to reward ongoing sexual activity and to facilitate subsequent preparatory behaviors elicited by primary female incentives. The relative contribution of the MPOA and NA to reward-mediated incentive enhancement could be examined by directly comparing the intensity of the dopaminergic response to estrous cues in sexually naïve and experienced males. We would hypothesize that males with prior sexual experience would exhibit a stronger dopaminergic response within one or both of these regions, in comparison to their naïve counterparts, indicative of a more potent motivational state.

These considerations attest to the difficulty in identifying the exact mechanism by which dopamine mediates changes in incentive value. While it is clear that dopaminergic activity during copulation induces learning, there are several potential explanations for this process. One possibility is that dopamine regulates the ability of animals to attend to biologically significant stimuli and events [6]. Under this conception, reward acts as a signal to activate non-dopaminergic learning mechanisms, which permit the association of the positive mental state with relevant environmental stimuli (including female cues). Consequently, haloperidol challenge during copulation would prevent incentive enhancement by attenuating feelings of reward, even though the necessary learning mechanisms remain intact. In support of this possibility, Fleming and Kucera [18] have noted that administration of the protein synthesis inhibitor, cycloheximide, or the noncompetitive NMDA antagonist, MK-801, during sexual behavior blocks the subsequent facilitation of male mounting behavior following sexual experience. Perhaps, these drug treatments prevented the expected motivational increase by directly interfering with the development of stimulus–reward associations mediated by glutamatergic learning mechanisms (e.g., Ref. [17]).

Yet another possibility is that dopamine mediates both the reward value of sexual experience and association formation itself. For example, recent work by Schultz [41] suggests that dopamine neurons activated by rewarding events are also implicated in modifying synaptic transmission. Thus, sexual activity may increase the future response properties of neurons that signal the presence of sexually relevant female cues. Dopamine receptor antagonism during sexual activity would interfere with the modulation of female incentive value by preventing synaptic change. Clearly, more detailed experimentation will be necessary to dissociate these various hypotheses regarding dopamine's role in sexually mediated learning.

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