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Dopamine antagonism attenuates the unconditioned incentive value of estrous female cues

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Abstract

The role of dopaminergic transmission in the incentive–motivational processes involved in the generation of male sexual behavior was examined. Three groups of sexually naïve Long–Evans male rats traversed a straight alley for one of three goalbox targets: an empty goalbox, a nonestrous female, or an estrous female. A Plexiglas partition within the goalbox allowed for the perception of visual, auditory, and olfactory cues, but prevented physical contact. Baseline run times revealed that subjects returned to the goalbox significantly faster for an estrous female than for a nonestrous female, replicating our earlier work on the inherent incentive value of primary female cues. When subjects were then pretreated with the dopamine receptor antagonist, haloperidol (0.0, 0.075, or 0.15 mg/kg), they expressed decreased sexual motivation as reflected by increased run times for estrous female targets. Subjects' run times for the empty goalbox condition were unaffected by haloperidol, suggesting that the drug did not reliably impair motoric capacity. Results support the contention that central dopaminergic systems are involved in the regulation of the positive, unconditioned incentive value of estrous female cues.

Keywords: Motivation; Copulation; Incentive; Dopamine; Haloperidol

1. Introduction

Substantial evidence has been accumulated documenting a crucial role for central dopamine pathways in incentive–motivational processes within a variety of behavioral domains, including aggression, eating, drinking, and the self-administration of drugs of abuse (Blackburn et al., 1987, 1989, 1992; Mogenson et al., 1980). Current theory identifies mesolimbic dopamine as a response signal triggered by the perception of potentially rewarding and/or aversive stimuli, thus leading to activation of motivational systems that mediate approach and avoidance behavior (Berridge and Robinson, 1998; Robbins and Everitt, 1996; Salamone, 1994, 1996; Schultz, 1998; Schultz et al., 1997). Research on masculine sexual behavior has generally upheld these propositions, and numerous excellent reviews have discussed the importance of dopamine systems for the generation of male sexual motivation (Agmo, 1999; Bitran and Hull, 1987; Everitt, 1990; Melis and Argiolas, 1995; Pfaus and Everitt, 1995; Stewart, 1995; Wilson, 1993). Perhaps most revealing have been the results of recent in vivo neurochemical analyses that have noted that central dopaminergic release is correlated with several aspects of male sexual behavior, including precopulatory perception of estrous female cues (for reviews, see Mitchell and Gratton, 1994; Phillips et al., 1991).

However, it remains to be determined exactly how dopamine modulates male sexual motivation. Numerous internal factors (hormonal condition, degree of sexual experience, etc.) and external inputs (female pheromones, proceptive displays, sexually conditioned contextual cues, etc.) influence the generation of the sexual motivational state. While dopamine may indeed regulate the processing of some or all of these factors, research methods employed to study male sexual motivation have often been unable to delineate and isolate the effects of these multiple variables. For example, initially, experimentation in this field adopted mount and intromission latencies, and other indices of male copulatory behavior, as measures of male sexual motivation (reviewed in Bitran and Hull, 1987; Pfaus and Phillips, 1989). However, when pharmacological manipulations are

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instituted under these conditions, it is often difficult to dissociate motivational impairments from altered motoric capacity, or deficits in the males' sexual behavior due to reduced female responsiveness to the drugged males (Agmo and Picker, 1990). As a result, within the past decade, several laboratories examining sexual motivation have adopted more innovative measures of motivation that are reflective of the animal's appetitive processes, as opposed to consummatory ability. Such measures have included operant responding (Everitt, 1990), X-maze searching (in which male subjects are offered the choice of approaching various incentives; Moses et al., 1995; Warner et al., 1991), and anticipatory level-changing (in which male subjects express sexual motivation and arousal by switching levels in a bi-level chamber prior to introduction of a female; Mendelson and Pfaus, 1989; Pfaus and Phillips, 1991).

The tasks mentioned above often require extended training periods during which subjects experience repeated sexual reinforcement. Moreover, conclusions regarding dopamine's role in regulating male sexual motivation have often been based upon the effects of dopamine antagonist drugs administered during operant responding for sexual reinforcement (e.g., Everitt, 1990; Everitt and Stacey, 1987; Everitt et al., 1987). Under such conditions, it can sometimes be unclear as to whether dopamine receptor blockade is directly affecting sexual motivation by reducing the incentive value of primary female cues and/or sexually conditioned cues, or indirectly reducing sexual motivation by attenuating the rewarding consequences of sexual reinforcement, leading to eventual extinction of the measured operant response.

The use of sexually experienced subjects is also potentially problematic in that it can confound the motivational impact of primary incentives with the effects of prior sexual experience (Lopez et al., 1999). By using experienced males, it may be difficult to determine whether experimental manipulations affect the unlearned or *unconditioned* incentive value of primary female cues. In fact, current incentive–motivation theory tends to characterize incentives as learned, by definition (Berridge and Robinson, 1998; Bolles, 1975; Dickinson and Balleine, 1994; Toates, 1986, but see Stewart, 1995), ignoring for the most part the possibility that a vast array of stimuli an organism encounters unconditionally elicit approach and/or avoidance behavior.

In order to address these issues, our laboratory has developed an operant task that allows for the analysis of sexual motivation in sexually naïve male subjects, by precluding the introduction of sexual reinforcement (Lopez et al., 1999). Subjects traverse a straight alley in order to approach and enter a goalbox containing a female target (either nonestrous or estrous). Each trial is preceded by placement of the male subject in the goalbox where the female target is located. A Plexiglas partition within the goalbox separates the male subject from the female target, preventing direct physical contact and copulation. The subject's motivation to seek the female is then measured by the time it takes the male to return to the goalbox after being placed in the startbox of the alley. Earlier work conducted by our laboratory has shown that under these circumstances, male rats will motivationally discriminate between a variety of goalbox targets, even though they do not receive sexual reinforcement for their behavior. Specifically, sexually naïve males take significantly less time to return to and enter a goalbox containing an estrous female than they do for one containing a nonestrous female, indicating that male rats are unconditionally motivated by primary female cues (Lopez et al., 1999).

In the current study, we attempted to replicate and extend these findings by examining the ability of a dopamine receptor antagonist to alter this incentive–motivational process. The hypothesis was that dopamine-antagonist haloperidol challenge would dose-dependently attenuate the motivation of sexually naïve male rats to approach estrous female targets, thus demonstrating that dopamine systems are involved in processing the unconditioned incentive value of estrous female cues.

2. Method

2.1. Animals

A total of 38 male and 3 female Long–Evans rats were obtained from Charles Rivers Laboratories (Wilmington, MA). The males were approximately 100 days old and the females were 100–150 days old at the start of testing. All animals were housed individually in hanging wire cages within a 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 in the vivarium, the males were group housed but did not have access to females. Therefore, they were sexually naïve insofar as they lacked heterosexual copulatory experience.

2.2. Surgery

All females were ovariectomized (OVX) through a single lower abdominal incision 1–6 weeks prior to testing using standard aseptic surgical techniques and under deep anesthesia. Anesthesia was induced by intraperitoneal administration of 90 mg/kg ketamine and 2 mg/kg xylazine, in a volume of 1 ml/kg. All females received at least 1 week of postoperative care prior to initiation of the experiment.

2.3. Apparatus

The test apparatus was a straight-arm runway consisting of a startbox ($25 \times 25 \times 20$ cm), an alley ($160 \times 10 \times 20$ cm), 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 within the alley 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 motivating goalbox events including food (Chausmer and Ettenberg, 1997; Ettenberg and Camp, 1986a; Horvitz and Ettenberg, 1989), water (Ettenberg and Camp, 1986b; Ettenberg and Horvitz, 1990), and drugs of abuse (Ettenberg and Geist, 1993; Ettenberg et al., 1996; McFarland and Ettenberg, 1995, 1997). Within the goalbox, a removable Plexiglas partition divided the arena into two semicircular 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.

2.4. Procedure

All 38 male subjects were allowed to individually explore the empty runway apparatus for 5–7 min on each of two initial trials. The three female targets were also individually placed within the goalbox for 10 min on 2 days. This was done to acclimate the animals to the runway environment. All testing took place under red light conditions during the dark portion of the rats' photoperiod.

On any given test day, all 38 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 goal-door and start-door were lifted, and the time required for the subject to traverse the alley was recorded. Once the subject had entered the goalbox, the door was closed and the animal was left for 1 min before being 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 38 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. The dependent measure of interest was run time, i.e., the time elapsed between the subject's leaving the startbox and entering the goalbox. Shorter run times presumably reflect a greater motivation to approach the goalbox "target".

Over the course of repeated testing, subjects ran for three different targets: an empty goalbox, a nonestrous female (OVX female) or an estrous female. Estrous was induced via subcutaneous administration of 15 μg of estradiol benzoate (in 0.1 ml sesame oil) 48 and 24 h before testing, with an additional subcutaneous 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 estrous 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 nonhormonally treated females (nonestrous 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; Beach, 1976). Each of the three target females was rotated through each hormonal condition three to four times over the course of the experiment.

Subjects initially ran a total of nine trials (one trial per day), three for each goalbox target, in order to establish baseline run times. Following these nine trials, the subjects were divided into three groups such that the mean run times for the three baseline goalbox conditions were approximately the same for all three groups. Subjects were then retested within the runway for their motivation to approach the three goalbox targets, under differing drug conditions. Subjects within the vehicle control group ($n=12$) were given intraperitoneal injections of 0.002 M lactic acid vehicle 45 min prior to testing. Subjects in the second group ($n=13$) were pretreated with intraperitoneal injections of 0.075 mg/kg haloperidol (dissolved in lactic acid vehicle), and subjects in the third group ($n=13$) were pretreated with intraperitoneal injections of 0.15 mg/kg haloperidol. All injections were administered in a volume of 1 ml/kg. Subjects were tested under these drug conditions once for each goalbox target (yielding a total of three drug trials per subject). In between drug trials, subjects were tested under nondrug conditions for each of the three goalbox targets. Thus, the testing schedule following establishment of baseline run times was as follows: drug day, 3 nondrug days, drug day, 3 nondrug days, drug day. The order of haloperidol trials was counterbalanced between groups, as was the goalbox condition, such that one-third of the subjects within each group experienced a different order (empty/nonestrous/estrous, nonestrous/estrous/empty, estrous/empty/nonestrous).

3. Results

The baseline run times for each group of subjects were nearly equivalent, hence the data were collapsed in order to simplify statistical analysis. Baseline mean (±S.E.M.) run times for all 38 male subjects are displayed in Fig. 1, panel A. A repeated measures one-way ANOVA on the data in panel A revealed a significant effect of goalbox target on

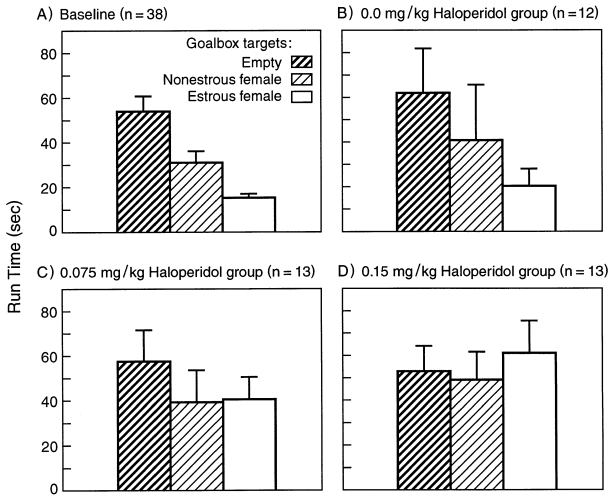

Fig. 1. Mean (±S.E.M.) run times of sexually naïve male rats running for each of three goalbox targets: an empty goalbox, a nonestrous female, and an estrous female. Panel A depicts the baseline run times for all 38 subjects for each of the three goalbox targets. Panels B–D depict run time data from three subgroups of subjects given haloperidol pretreatment (0.0, 0.075, or 0.15 mg/kg) 45 min prior to testing. Vehicle-treated controls (panel B) continued to motivationally differentiate between the goalbox targets, while drug-treated subjects (panels C and D) experienced a reduction in motivation to approach female targets.

subjects' run time, $F(2,37) = 30.177$, $P < .001$. Post-hoc comparisons using two-tailed paired sample t tests revealed significant differences between subject run times for the empty goalbox and nonestrous female target, $t(37) = 3.835$, $P < .001$, between the empty goalbox and estrous female target, $t(37) = 5.493$, $P < .001$, and between the nonestrous and estrous female targets, $t(37) = 3.362$, $P = .002$.

The mean (±S.E.M.) run times for the three experimental groups while under drug treatment are displayed in Fig. 1, panels B–D. A repeated measures one-way ANOVA comparing run times for the three goalbox targets was conducted on the data depicted in each of these panels. The vehicle group (panel B) behaved comparably to baseline, with the ANOVA confirming a significant main effect of goalbox target, $F(2,11) = 5.986$, $P = .03$, and the pattern of results similar to that in Fig. 1, panel A. For both the 0.075 and 0.15 mg/kg haloperidol groups, there was no significant effect of goalbox target on subject run time, $F(2,12) = 1.454$, $P = .251$, and $F(2,12) = 0.207$, $P = .657$, respectively.

Fig. 1 seems to indicate that the primary effect of haloperidol was to decrease the subjects' motivation to approach estrous female targets. Three one-way ANOVAs, testing the main effect of drug dose on run time for each goalbox target, were conducted to test this possibility. There was no significant effect of haloperidol dose on subjects' run times for either the empty goalbox, $F(2,35) = 0.089$, $P = .91$, or the nonestrous female target, $F(2,35) = 0.092$, $P = .91$. However, there was a main effect of drug dose on mean run time for the estrous female target, $F(2,35) = 3.204$, $P = .05$, indicating that haloperidol reduced the incentive value of estrous female cues. The fact that subjects' run times for the empty goalbox were unaffected by haloperidol pretreatment implies that the drug did not significantly reduce the motoric capacity of the subjects.

4. Discussion

Sexually naïve male rats expressed an increased motivation to approach estrous females over nonestrous females, and an increased motivation to approach a female target over an empty goalbox, as reflected by run times in an operant runway. These data replicate prior work done in our laboratory demonstrating an inherent male tendency to be motivated by primary female cues (Lopez et al., 1999). Our results also reveal that male rats are less motivated to approach female targets when pretreated with the dopamine receptor antagonist, haloperidol. Furthermore, the slowed approach behavior during haloperidol challenge was restricted to the estrous female target condition — there were no changes in the subjects' response to the empty goalbox or nonestrous female.

The fact that subject run times for the empty goalbox were unaffected by haloperidol treatment reduces the likelihood that the observed changes in runway behavior were a consequence of the potential motor-debilitating effects of haloperidol. However, it is possible that haloperidol differentially impaired faster running (for the estrous target) vs. slower running (for the empty goalbox). There are several reasons to suspect that this is not the case. First, a number of studies (see Wise, 1982, for a review) have dissociated the performance-debilitating effects of neuroleptics from their motivational or reward actions. For example, the administration of such drugs does not influence the response-initiation latencies nor running speeds of subjects working in an operant runway for access to self-stimulation or food reward on the first few days of training (Franklin, 1978; Horvitz and Ettenberg, 1989; Wise, 1978). Slowed running only appears once subjects have had repeated experience with the goalbox reward while drugged, suggesting an extinction-like effect. Indeed, this work was crucial in demonstrating the role of dopamine in reward processes (Wise, 1982). Second, prior work in our laboratory has shown that at the doses used in the current study, haloperidol does not compromise a rat's ability to respond normally in the alley on a single trial (McFarland and Ettenberg, 1995, 1998, 1999). Lastly, during pilot studies aimed at determining an appropriate dosage regiment for this research, we found that higher doses of haloperidol (i.e., 0.30 mg/kg) dramatically retarded operant running, even for an empty goalbox. Thus, the reported baseline run times for an empty goalbox in the current study do not represent a ''ceiling'' that prevents the detection of motor impairment. Collectively, these considerations increase our confidence that the effect of haloperidol on the subjects' run times for the nonestrous and

estrous female targets in the current study was primarily due to a motivational and not motoric impairment.

This study supports prior conclusions on dopamine's role in the generation of male sexual motivation (Agmo, 1999; Bitran and Hull, 1987; Everitt, 1990; Melis and Argiolas, 1995; Pfaus and Everitt, 1995; Stewart, 1995; Van Furth et al., 1995; Wilson, 1993). However, since our male subjects did not receive sexual experience within the test apparatus, we were able to dissociate dopamine's role in regulating the incentive value of primary female cues from that of secondary conditioned incentives (e.g., environmental stimuli) established via sexual reinforcement. Similarly, we were not faced with the need to control for the effects of sexual experience upon sexual motivation, which we have previously shown to dramatically alter male motivation to seek female targets (Lopez et al., 1999). Thus, by keeping subjects sexually naïve throughout the experiment, and by adopting an operant paradigm that allows for the examination of motivational processes without the introduction of reinforcement, we can safely conclude that haloperidol reduces male sexual motivation by decreasing the unconditioned incentive value of female cues.

This conclusion is supported by recent in vivo analyses, utilizing both microdialysis and voltammetry, showing an increase in dopamine levels within the nucleus accumbens during a naïve male rat's *first* exposure to a sexually receptive female (Louilot et al., 1991; Wenkstern et al., 1993). This response occurs even if the male remains behind a wire-mesh screen and is not allowed to initiate copulation (Louilot et al., 1991). Such data strongly suggest that enhanced dopaminergic activity within the nucleus accumbens prior to copulation is an innate, unconditioned neurochemical event (Wenkstern et al., 1993). However, in vivo observations do not explicitly identify a functional role for this dopaminergic response. Our experiment is the first to illustrate that blocking the postsynaptic effect of dopamine in response to the perception of primary female cues reduces sexual motivation in naïve males, as measured by approach behavior within a runway.

As stated in the Introduction, the concept of an "unconditioned incentive" is generally ignored in the current literature on motivation (e.g., Berridge and Robinson, 1998; Dickinson and Balleine, 1994; Schultz, 1998). It is assumed that incentive-learning develops in response to an initial random consummatory encounter with a rewarding stimulus, such as food, water, or a receptive female (Agmo, 1999; Dickinson and Balleine, 1994). Environmental stimuli associated with that goal gain positive valence, presumably through dopaminergic mediation of an associative process (Berridge and Robinson, 1998). This description of the evolution of goal-directed behavior is inadequate, as it does not explain why or how organisms come to approach or avoid meaningful stimuli in the first place. Indeed, there are strong theoretical reasons to believe that natural selection has "built in" a variety of motivational predispositions that encourage adaptive, goal-directed behavior in the appropriate context (e.g., Daly and Wilson, 1984). One means of accomplishing this is to grant particularly relevant (in terms of survival and reproductive success) stimuli "privileged status," or in other words, unconditioned incentive value. The present data suggest that one neurochemical effect of perceiving such privileged stimuli is the activation of central dopamine circuits, which in turn mediate the initiation of appropriate behavioral sequences.

It seems likely that multiple factors, including but not limited to general feminine cues, estrous female cues, conditioned incentives, and sexual experience, influence male sexual motivation. Elucidation of the precise role of dopamine pathways in the generation of this motivational state will require careful independent examination of each of these contributing factors. The current study represents a step in that direction by providing evidence for dopaminergic modulation of primary female incentives independent of sexual experience or reinforcement.

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