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**Catecholaminergic manipulations of copulatory behaviors in
male rats**

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Iowa State University, 1991

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**Catecholaminergic manipulations of copulatory
behaviors in male Rats**

by

Mark Patrick Bowes

**A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of the
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INTRODUCTION

Systemic administration of yohimbine, an alpha-2 adrenergic antagonist, facilitates the copulatory behaviors of male rats. This facilitation has been interpreted as an increase in sexual motivation, as indexed by (a) increased mounting behavior following penile anesthetization, (b) increased copulatory performance in sexually inexperienced rats, (c) induction of copulation in sexually inactive rats, (d) enhancement of copulatory behaviors in castrated rats and (e) aged rats (Clark, Smith & Davidson, 1984, 1985a, 1985b; Smith & Davidson, 1990; see Appendix A for a discussion of pharmacological manipulations of copulatory behaviors).

Peters and associates (Koch & Peters, 1987; Peters, 1983; Peters, Blythe, Koch, & Kueker, 1989; also, see Lawrence & Kiefer, 1987) have described a copulation-illness association (C-IA) paradigm in which male rats receive lithium chloride (LiCl) after each of several copulatory opportunities. LiCl induces aversive interoceptive consequences and is commonly used to establish conditioned taste aversions in a single trial (Garcia & Koelling, 1966). The copulatory

behaviors of male rats are associatively inhibited in the C-IA paradigm, albeit at a slower rate (5-10 trials). Peters, Koch, and Blythe (1988) reported that male rats treated with yohimbine were more likely to copulate during both C-IA acquisition and extinction.

The facilitory effects of yohimbine on sexual behavior have been attributed to an increase in sexual motivation (Clark et al., 1984). The effects of yohimbine on copulatory behaviors in the C-IA paradigm are consistent with this interpretation. The inhibition of copulatory behaviors in this paradigm, however, reflects an associative process. Yohimbine's facilitation of copulatory behaviors in the C-IA paradigm could conceivably reflect an influence on associative mechanisms rather than a more direct activation of copulatory behaviors. Thus, the facilitation of copulatory behavior during C-IA acquisition may reflect yohimbine's disruption of an associative mechanism. Counter to this interpretation, however, are yohimbine's facilitory effects on copulatory behaviors during C-IA extinction (Peters et al., 1988). To the extent that both acquisition and extinction involve the formation of associative

connections (Rescorla, 1979), it is unlikely that yohimbine disrupts an associative mechanism during acquisition and facilitates an associative mechanism during extinction.

The purpose of the present experiments is to further characterize the effects of yohimbine on copulatory behaviors. Prior research (Bowes, 1990) examined the hypothesis that the effects of yohimbine on copulatory behavior may reflect an increase in activity level, making any behavior, including copulatory behavior, more likely. Yohimbine, however, significantly reduced activity suggesting that the facilitory effects of yohimbine on copulatory behavior are not mediated by an increase in general activity level.

If yohimbine's facilitation of copulatory behaviors in the C-IA paradigm reflects an increase in sexual motivation, significant differences in copulatory behaviors would be anticipated on first trial comparisons of yohimbine and control groups, prior to associative inhibition of copulation. Yohimbine's facilitation, however, is not evident until the third or fourth acquisition trial (Peters et al.,

1988; Bowes, 1990). During these trials, after C-IA suppression of copulatory behaviors, male rats treated with yohimbine had shorter intromission and ejaculation latencies, as well as a higher probability of ejaculation. If yohimbine increases sexual motivation, why is this effect not evident on the first test trial? One possibility is that during initial trials, high baseline levels of copulatory behaviors cannot be further enhanced by yohimbine. Yohimbine's facilitory effects may be observable only when copulatory behaviors occur at less than a maximal rate. These circumstances prevail following several acquisition trials in the C-IA paradigm. Similarly, the facilitory effects of yohimbine have been demonstrated when copulatory behaviors are inhibited by castration, penile anesthetization, sexual inexperience, age, and in rats that do not spontaneously initiate copulatory behaviors (sexually "sluggish" rats; Clark et al., 1984, 1985a, 1985b; Smith & Davidson, 1990).

An alternative explanation for the lack of yohimbine's facilitation of copulatory behaviors on initial trials is that habituation to the effects of yohimbine is necessary before facilitation may be

observed. On the first few trials the physiological state produced by yohimbine may interfere with the facilitory effect of the drug. After repeated exposures, animals may habituate to this initial physiological state. Consistent with this hypothesis, data from this laboratory suggest that a higher dose of yohimbine (4.0 mg/kg) significantly disrupted copulatory behavior on the first trial yet facilitated sexual behavior during later test sessions (Bowes, 1990).

Noradrenergic mechanisms have been implicated in the regulation of "vigilance", or sensitivity to environmental stimuli (Aston-Jones, 1985). Yohimbine, an alpha-2 adrenergic antagonist, increases brain norepinephrine (NE) levels, presumably by autoreceptor blockade. Neural activity of NE neurons of the locus coeruleus decreases during periods of grooming or ingestive behavior (Aston-Jones & Bloom, 1981a, 1981b). Increased NE levels may initially produce a state of heightened vigilance and decreased activity, a state inconsistent with the performance of copulatory behaviors. Habituation of this state of heightened vigilance may be prerequisite to yohimbine's facilitory

effect on copulatory behaviors. Yohimbine's reduction of locomotor activity is also consistent with this interpretation.

EXPERIMENT 1

Yohimbine (2.0 mg/kg) facilitates copulatory behavior in the C-IA paradigm (Peters et al., 1988). As noted above, this facilitory effect is not evident on initial test trials but rather, after two or more acquisition trials. This lack of facilitation of sexual behavior may reflect a ceiling effect produced by high baseline levels of copulatory behaviors (intromission latencies on these first trials are often 10 seconds or less). Alternatively, the physiological state induced by yohimbine may initially attenuate yohimbine's facilitory effect on copulatory behaviors. In this case, habituation to some of the drug's effects may be necessary before facilitation is observed.

In this experiment the effects of yohimbine on copulatory behaviors were examined using a modification of the C-IA procedure. The copulatory behaviors of all subjects were partially inhibited prior to the comparison of the effects of yohimbine and saline groups on copulatory behaviors. Male rats display a large range of intromission latencies during their first encounter with an estrous female. Upon a second encounter, this range is considerably reduced with

brief latencies (10-100 sec) observed for most animals. Post-trial LiCl administration began after the second pairing with an estrous female. Rather than initiating pre-trial administration of yohimbine on the following trial, before the third pairing with an estrous female (when intromission latencies are brief following only one copulation-illness pairing), yohimbine was not administered until the animal's intromission latency exceeded its briefest intromission latency by 100 sec. Yohimbine was then administered prior to the next pairing with an estrous female for half of the subjects; the other half received saline.

In addition, the possible effects of experience with yohimbine outside of the context of the copulation test were examined. Half of the subjects in each of the groups described above received yohimbine 24 hr following each copulation test. Thus, these animals received 2-5 intertrial yohimbine injections; the others received saline. The experimental design was thus a 2 x 2 factorial with prior drug experience (intertrial yohimbine vs. saline) and pre-trial drug groups (yohimbine vs. saline) as the two factors.

The following drug effects were predicted. If yohimbine's failure to facilitate copulatory behaviors on initial C-IA trials reflects a ceiling effect due to high baseline levels of copulatory behaviors, then the yohimbine-treated animals should have significantly shorter mount and intromission latencies than the saline group on the first test trial when copulation is partially inhibited. If yohimbine produces a novel state requiring habituation before facilitation of copulatory behaviors is possible, then significantly reduced mount and intromission latencies would be expected for the subjects receiving intertrial yohimbine. Additionally, the yohimbine effects observed in the C-IA procedure may reflect only the result of repeated yohimbine exposure and may not depend on yohimbine administration at test. If yohimbine facilitates copulatory behaviors as a result of repeated exposure alone, then animals receiving intertrial yohimbine, when administered saline at test, should exhibit increased copulatory behaviors relative to the saline/saline control group. In other words, a significant intertrial by test trial interaction would indicate the possibility that the important variable in

yohimbine's facilitory effects on copulatory behavior in the C-IA paradigm is repeated exposure to yohimbine alone, independent of drug administered during the copulation test.

Method

Subjects. Male and female Sprague-Dawley albino rats were obtained at 22-25 days of age from Laboratory Animal Resources, College of Veterinary Medicine, Iowa State University. Animals were housed in groups of 5-6 until the beginning of the experiment and were individually housed thereafter. Subjects were housed in a temperature-controlled environment (22-24° C) and maintained on a reversed 12:12 hr light/dark cycle with lights off at 0800. Food (Simonsen 1526 rat/mice diet) and water were available ad lib except during testing. Behavioral testing began when the rats were 80-90 days of age.

Stimulus females. Ovariectomies were performed using ketamine (80 mg/kg) and xylazine (12 mg/kg) anesthesia, at least one week prior to test sessions. Estrus was induced with estradiol benzoate (5 ug sc, 48 and 24 hr before test sessions) in a 0.1 ml sesame oil

vehicle. Females were screened for sexual receptivity with sexually vigorous nonexperimental males prior to each behavioral test session. Only females displaying proceptive behaviors (Beach, 1976) in addition to vigorous lordosis were used in this experiment.

Apparatus. Nine test compartments were each 74 X 56 X 38 cm with inside walls painted black. Glass on the front wall allowed viewing of copulatory activity. Chambers were insulated on all sides except the viewing wall with 2.54 cm styrofoam to minimize sound transmission. Each chamber was dimly illuminated from above with a 15 W red light bulb, and ventilated with an exhaust fan.

Drugs used were yohimbine hydrochloride (Sigma Chemical Company, St. Louis) and isotonic saline. Yohimbine was dissolved in distilled water prior to each test session.

Procedure. Copulation tests were conducted at 3-4 day intervals during the middle third of the dark cycle in an observation room dimly illuminated with red light. For all copulation tests, each male was placed in the test compartment for 1-2 min prior to introduction of the female. Behavioral data collected

were the intervals between introduction of the female and the first mount (mount latency or ML), intromission (IL) and ejaculation (EL), as well as mount and intromission frequency.

Following an initial screening for copulatory activity, male rats were assigned to one of two groups. During acquisition of criterion IL (see below), half of the subjects received intertrial injections (saline 1 ml/kg ip, or yohimbine 2.0 mg/ml/kg ip) 24 hr following each acquisition session. As each animal attained the partial inhibition criterion it was randomly assigned to one of the two groups receiving yohimbine (2.0 mg/kg ip) or isotonic saline (1 ml/kg ip) 20 min prior to the next test session for that animal. There were thus four combinations (n = 8 per group) of drug condition and prior experience; saline (saline vs. yohimbine intertrial administration) and yohimbine (saline vs. yohimbine intertrial administration).

Copulatory behaviors were partially inhibited prior to the drug administration trial. Animals received a variable number of acquisition trials until the animal's IL exceeded its shortest IL by at least 100 sec; the next trial was the copulation test trial

for that animal. Thus, on any given experimental session, some animals would receive acquisition trials and some test trials. Each session was terminated with either an ejaculation, failure to intromit within 900 sec, or failure to ejaculate within 1800 sec. Each male was paired with a different female and tested in a different test compartment on each test session. Males were injected with LiCl (0.3 M, 20 ml/kg) within 1 min of termination of each acquisition trial and were returned to the home cage.

The trial following acquisition of the partial inhibition criterion was the drug trial for each subject. Twenty min prior to this test session animals received an injection of either yohimbine (2.0 mg/kg ip) or saline (1 ml/kg ip).

Results.

An average of 3.8 copulation-illness pairings preceded acquisition of criterion intromission latency. The mean number of trials required to attain the criterion intromission latency was approximately equal for the four groups.

Pretrial administration of yohimbine did not significantly affect any measure of copulatory behavior in animals with partially inhibited copulatory behaviors (see Figure 1). Intertrial exposure to yohimbine also did not increase copulatory behavior, nor was the intertrial x pretrial interaction significant for any measure of copulatory behavior (ML, IL, mount frequency, intromission frequency). A power analysis was conducted to estimate the number of subjects required to detect a difference between groups due to pretrial and intertrial yohimbine administration. Standard deviations for the pretrial and intertrial main effects were 345 and 373, respectively. With a power of .90 and an effect size of one-half standard deviation, the required number of subjects was approximately 11, in good agreement with the main-effect group sizes of 16 in this experiment. The lack of significant differences between groups does not appear to reflect merely a lack of experimental sensitivity.

A separate analysis was conducted on the data from the drug test trial and the two preceding acquisition trials to confirm that there were no group differences

prior to the drug test trial. A 3-way ANOVA with two between-subjects factors (intertrial drug and test trial drug) and one within-subjects factor (acquisition trials) was conducted. Copulatory behavior declined over the three trials, with significant increases in ML and IL (p s $< .0001$). No between-group differences were observed on the trials preceding the test trial, nor were the intertrial, test trial or acquisition trial interaction effects significant.

Discussion.

This experiment evaluated the effects of yohimbine on the copulatory behaviors of male rats when these behaviors had been partially inhibited by copulation-illness associations. Yohimbine did not significantly facilitate any measure of copulatory behavior in this experiment. This finding suggests that the failure of yohimbine to facilitate copulatory behaviors can not be attributed to high baseline levels of copulatory behaviors.

In addition to the partial inhibition procedure, the effects of intertrial yohimbine exposure were examined. Intertrial yohimbine exposure did not

facilitate copulatory behaviors in this experiment. It is possible that yohimbine exposure is effective only within the context of the copulation test. In this experiment, intertrial yohimbine exposure occurred in the home cage. A more appropriate pre-exposure procedure may involve a series of copulation tests in which yohimbine is administered, prior to C-IA acquisition. In this situation the stimulus characteristics of drug experience setting and drug test setting are more similar. Substantial evidence documents that context plays an important role in habituation to drug response and that dissimilarities between the habituation environment and test environment may attenuate habituation to drug effects (Siegel, 1988; Siegel, Hinson, Krank, & McCully, 1982).

Yohimbine failed to potentiate copulatory behaviors when first administration followed either C-IA acquisition or intertrial experience with the drug. This outcome is not consistent with an activational interpretation of yohimbine's effects in the C-IA paradigm. This also suggests that the effects of yohimbine on copulatory behaviors in this paradigm may reflect yohimbine's effects on an associative

mechanism. This possibility could be evaluated using the C-IA procedure with the modification that the test trials following partial inhibition would also serve as additional acquisition trials. These trials would be followed by LiCl administration. A gradual divergence of these groups would suggest interference with an associative mechanism. This modification was not performed in this experiment because it was felt that a large number of animals would quickly attain criterion mount and intromission latency.

EXPERIMENT 2

Yohimbine, an alpha-2 adrenergic antagonist, facilitates copulatory behaviors in the C-IA paradigm (Peters et al., 1988; Bowes, 1990). Naloxone, an opiate antagonist that facilitates copulatory behaviors in other test settings (Gessa, Paglietti, & Pellegrini-Quarantotti, 1979; Rhees, Badger, & Fleming, 1983) inhibits copulation in the C-IA paradigm (Peters et al., 1988). It is therefore important to determine if other pharmacological manipulations known to facilitate sexual behavior in various paradigms similarly increase copulatory behaviors in the C-IA paradigm.

The purpose of this experiment was to evaluate, using the C-IA paradigm, the effects of a pharmacological manipulation (apomorphine) known to facilitate copulatory behaviors. Dopamine agonists (e.g., apomorphine) facilitate copulatory behaviors in male rats (Argiolas, Collu, D'Aquila, Gessa, Melis & Serra, 1989; Malmnas, 1973; Paglietti, Quarantotti, Mereu, & Gessa, 1978; Pehek, Thompson & Hull, 1989; Tagliamonte, Fratta, Del Fiacco & Gessa, 1974) and Rhesus monkeys (Pomerantz, 1990; see Appendix A). Three doses of apomorphine were selected from the broad

range of dose levels that facilitate copulatory behaviors in other experimental settings.

Method.

Subjects. Forty Sprague-Dawley albino rats were housed under the conditions described in Experiment 1.

Apparatus. The apparatus was the same apparatus as used in Experiment 1. Apomorphine (Sigma chemical company) was dissolved in sterile saline containing 2 mg/ml ascorbic acid and was prepared before each test session.

Procedure. Following an initial screening trial for copulatory activity, male rats were assigned to one of four conditions. Fifteen min prior to each C-IA acquisition trial animals received an ip injection of ascorbic acid vehicle (1 ml/kg) or apomorphine (150, 300, or 450 ug/ml/kg). Each test session was terminated after either an ejaculation, a failure to intromit within 900 sec, or a failure to ejaculate within 1800 sec. Each male was paired with a different female and tested in a different test compartment on each acquisition trial. Data were collected from a total of seven sessions; one initial screening trial

for sexual activity, the initial acquisition trial, and 5 test trials. Each male was injected with LiCl (0.3 M, 20 ml/kg ip) within 1 min of termination of each acquisition session and was returned to its home cage.

Data for the first two trials (screening and initial acquisition trial) were analyzed separately. Variables of interest were the latency to first mount (ML), intromission (IL) and ejaculation (EL) as well as mount and intromission frequency. Variables were examined using one-way analysis of variance on these initial trials. On test trials EL was not analyzed due to the large number of animals failing to ejaculate during C-IA acquisition. Data from these trials were analyzed as a two-way ANOVA with repeated measures, one within-groups factor (trials) and one between groups factor (drug group).

Following C-IA acquisition, a series of four extinction trials was conducted. Only subjects attaining the 900 sec intromission latency criterion on the preceding acquisition trial were included in the extinction trial series. Twenty-three subjects were randomly assigned to vehicle or apomorphine (150 ug/kg) conditions with the constraint that the number of

subjects in each group should contain, as closely as possible, equal numbers of subjects from each of the four C-IA acquisition conditions. The apomorphine dose (150 ug/kg) was selected on the basis of the acquisition trials data. This was the only dose that provided any indication of facilitation of copulatory behaviors during C-IA acquisition. Copulation tests were conducted as described above with the exception that LiCl was not administered. Subjects were injected with either saline or apomorphine 15 min prior to copulation test.

Results.

Administration of apomorphine (150, 300, & 450 ug/ml/kg) did not significantly increase copulatory behaviors during C-IA acquisition (see Figure 2). No significant differences were observed among groups for either the screening trial or the initial acquisition trial (first exposure to apomorphine preceding LiCl exposure).

During C-IA acquisition, copulatory behaviors gradually declined following repeated pairings of LiCl with copulatory opportunities as evidenced by increased

mount latency (ML) [$F(4,140)=18.85$, $p<.0001$] and intromission latency (IL) [$F(4,140)=16.35$, $p<.0001$]. Mount and intromission frequencies significantly declined during C-IA acquisition trials ($ps <.001$). No significant drug effects were observed for any of these measures, nor were the drug x trial interactions significant.

An examination of Figure 2 indicated that the apomorphine 150 ug/kg dose was the only dose that provided any indication of facilitation of copulatory behavior. This dose was selected for extinction trials. During C-IA extinction, animals gradually resumed copulatory behaviors as evidenced by reduced MLs and ILs ($ps <.01$) as well as increased mount frequency ($ps<.001$). Apomorphine facilitated copulatory behavior during C-IA extinction as evidenced by reduced latency to mount and intromit in apomorphine-treated animals ($ps<.03$) (see Fig. 3).

Discussion.

In this experiment the effects of apomorphine, a dopamine agonist known to facilitate copulatory behaviors, were examined. Copulatory behaviors were

gradually inhibited during C-IA acquisition. Apomorphine failed to facilitate copulatory behavior during C-IA acquisition, but the 150 ug/kg dose increased copulatory behavior during C-IA extinction. This may reflect the fact that group sizes were larger in extinction than acquisition (12-13 vs. 9-10). There were, however, more trials during C-IA acquisition and therefore more statistical power using this repeated-measures design. The failure of apomorphine to facilitate copulatory behavior in C-IA acquisition contrasts with the effects of yohimbine, which has potentiated copulatory behavior in each of four experiments conducted in this laboratory. This finding may suggest that C-IA extinction is more sensitive to manipulations that increase copulatory behaviors than C-IA acquisition.

In addition to its effects on sexual behavior, apomorphine also possesses emetic properties and is capable of supporting a conditioned taste aversion, albeit at dose levels greater than those employed in this study (Parker & Brosseau, 1990). It is possible, however, that the emetic effects of apomorphine interacted with those of LiCl and the resulting illness

facilitated C-IA acquisition, which would suppress copulatory behaviors. Naloxone also failed to facilitate copulatory behavior in this paradigm. Naloxone and apomorphine may both fail to facilitate copulatory behaviors in this paradigm by increasing the perceived aversiveness of LiCl; naloxone by blocking opiate receptors and apomorphine due to its emetic properties. Dopaminergic systems also participate in the regulation of reinforcement and learning (Fouriezos & Wise, 1974; Spryaki, Fibiger & Phillips, 1982). The potential emetic, learning and copulatory effects of apomorphine may interact in this paradigm in a manner not characteristic of other procedures assessing copulatory behaviors. The result of this interaction may be a yield of no net change in copulatory behaviors.

An additional test of the utility of the C-IA paradigm as a procedure for evaluating manipulations facilitating copulation would be an examination of the effects of serotonin antagonists (e.g., p-chlorophenylalanine, PCPA). PCPA increases male copulatory behavior (Ahlenius, Eriksson, Larsson, Modigh, & Sodersten, 1971; Ahlenius, Larsson, &

Svensson, 1980). An examination of PCPA in the C-IA paradigm would provide useful information regarding the appropriateness of this testing procedure for the examination of drugs facilitating copulatory behavior.

GENERAL DISCUSSION

The purpose of the present experiments was to further characterize the effects of catecholaminergic manipulations on copulatory behaviors in the C-IA paradigm. Yohimbine did not facilitate copulatory behaviors on initial C-IA acquisition trials, even when copulatory behaviors had been previously partially inhibited, and the animals had prior experience with the drug. Apomorphine, a dopamine agonist known to facilitate copulatory behaviors, did not facilitate these behaviors during C-IA acquisition, although copulatory behaviors were significantly facilitated during C-IA extinction. It is possible that other effects of apomorphine (e.g., reinforcement and emetic) and yohimbine (e.g., vigilance) interact in this paradigm to prevent facilitation of copulation.

In some respects, the C-IA procedure resembles the conditioned emotional response (CER) paradigm (Brush, 1971). Briefly, this procedure involves pairing an electric shock with some stimulus, such as a light or tone presentation. Following several signal-shock pairings, barpressing in the presence of the signal is decreased. The CER procedure contrasts with punishment

procedures in that the shock is not preventable and is not contingent on any particular behavior. In the C-IA procedure, animals are given LiCl regardless of whether they copulate. The presence of the female may serve as a signal. Following several pairings of the aversive contingency with the signal, a suppression of behavior results.

Naloxone potentiates sexual behavior in some paradigms (Gessa et al., 1979; Rhees et al., 1983) but interferes with copulatory behaviors in the C-IA paradigm (Peters et al., 1988). Opiate antagonists such as naloxone potentiate CER acquisition (Gallagher, Kapp, McNall, & Pescoe, 1981), but do not increase sensitivity to pain when administered alone (Goldstein, Pryor, Otis, & Larsen, 1976; Rodgers, 1978). Thus, naloxone effects in the C-IA procedure paralleled those of the CER paradigm. It is possible that this paradigm is an extension of the CER paradigm, and that similar pharmacological manipulations of the two procedures may provide similar results. Thus, the effects of naloxone in the C-IA paradigm are consistent with the effects of naloxone in the CER paradigm, but not with its facilitation of copulatory behaviors.

In addition to its prosexual effects, yohimbine has been described as an anxiogenic substance (Huang, Messing & Sparber, 1987). Anxiolytics antagonize the suppression of behavior induced by CER training (Rawlins, Feldon, Salmon & Gray, 1980). Consequently, it would be anticipated that the anxiogenic properties of yohimbine would suppress copulatory behaviors in the C-IA paradigm. In actuality, yohimbine potentiates behavior in this paradigm. Thus, the effects of yohimbine more closely resemble those of an anxiolytic than an anxiogenic.

Additional research is necessary in order to characterize the effects of catecholaminergic manipulations on copulatory behaviors. Yohimbine did not facilitate copulatory behavior despite prior experience with the drug. It is possible that the stimulus characteristics of the experience setting and drug test setting were too dissimilar. Thus, a better procedure may be to give subjects access to a receptive female following yohimbine administration for a few trials before C-IA acquisition begins. Additionally, other pharmacological manipulations expected to facilitate copulatory behavior should be examined. A

large number of substances facilitate sexual behaviors of male rats (see Appendix A). Additionally, the apomorphine doses presented may have been too high; a lower apomorphine dose may have facilitated copulatory behaviors.

The C-IA paradigm demonstrates the importance of the interaction between a pharmacological manipulation and environmental contingencies in producing a behavioral response. Naloxone and apomorphine, known to facilitate sexual behavior in other paradigms, were ineffective in C-IA acquisition, demonstrating differential behavioral responding in test situations which do and do not contain aversive elements. Additionally, the lack of facilitation of copulatory behavior by yohimbine on initial test trials apparently does not reflect a ceiling effect due to high baseline levels of responding.

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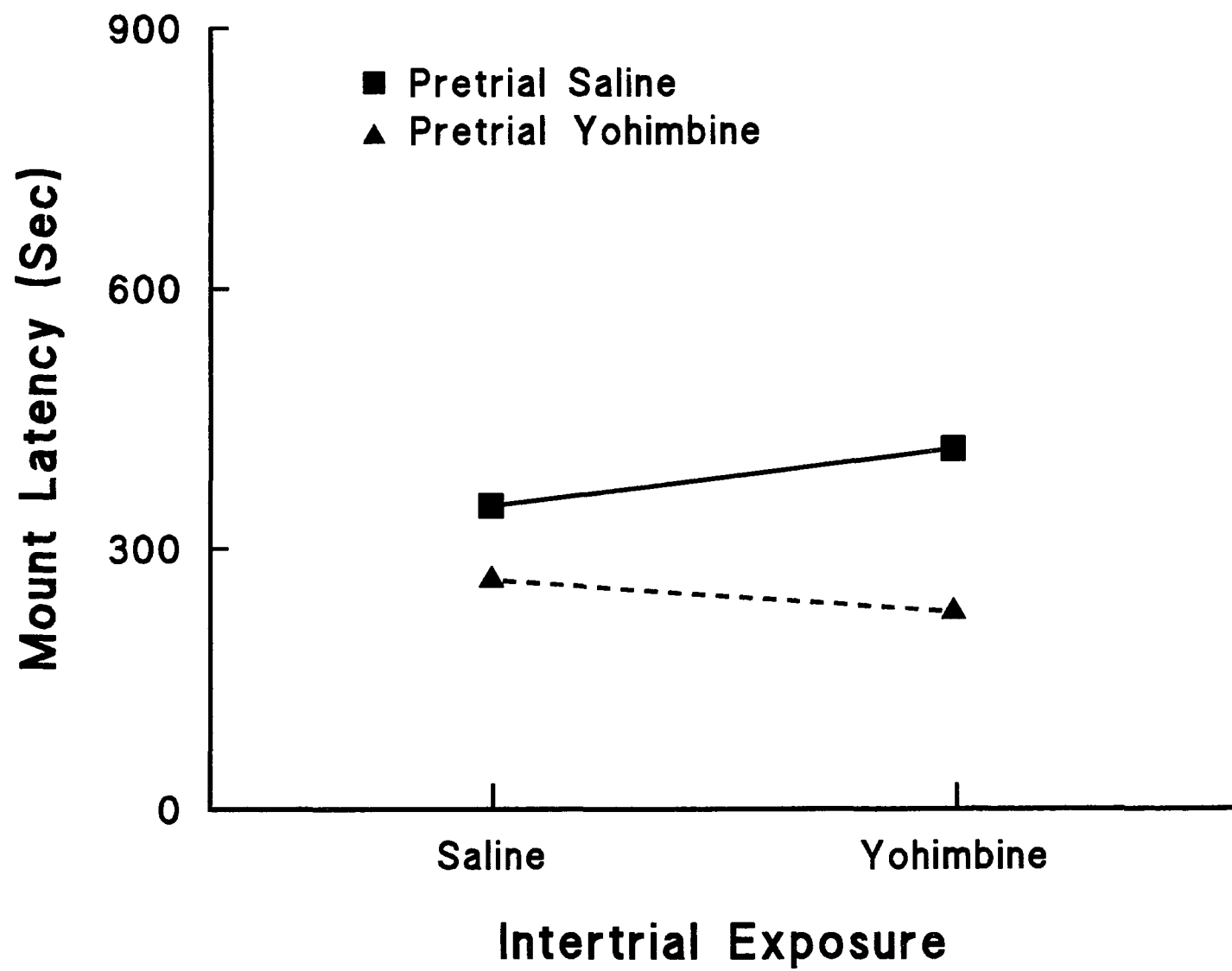
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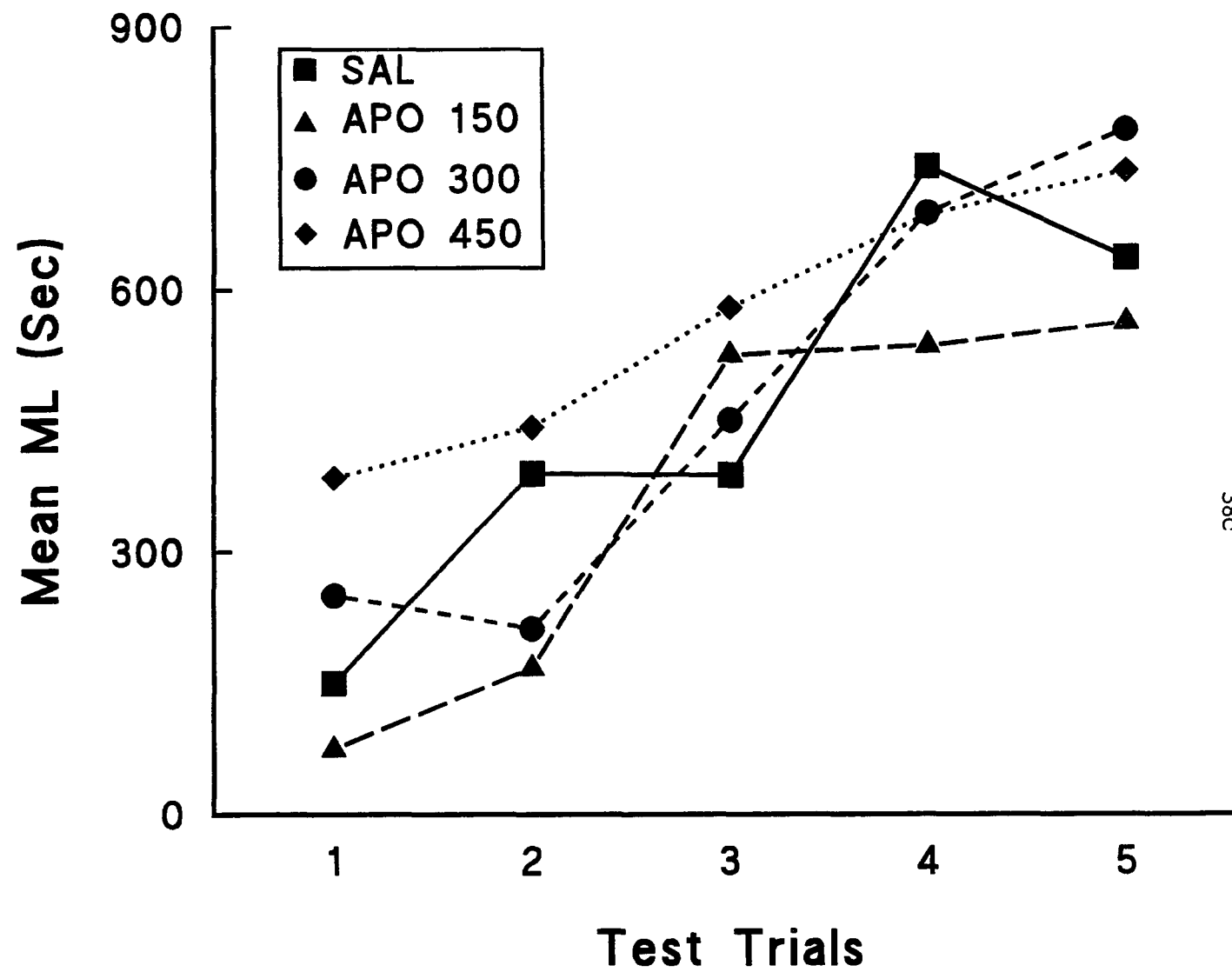
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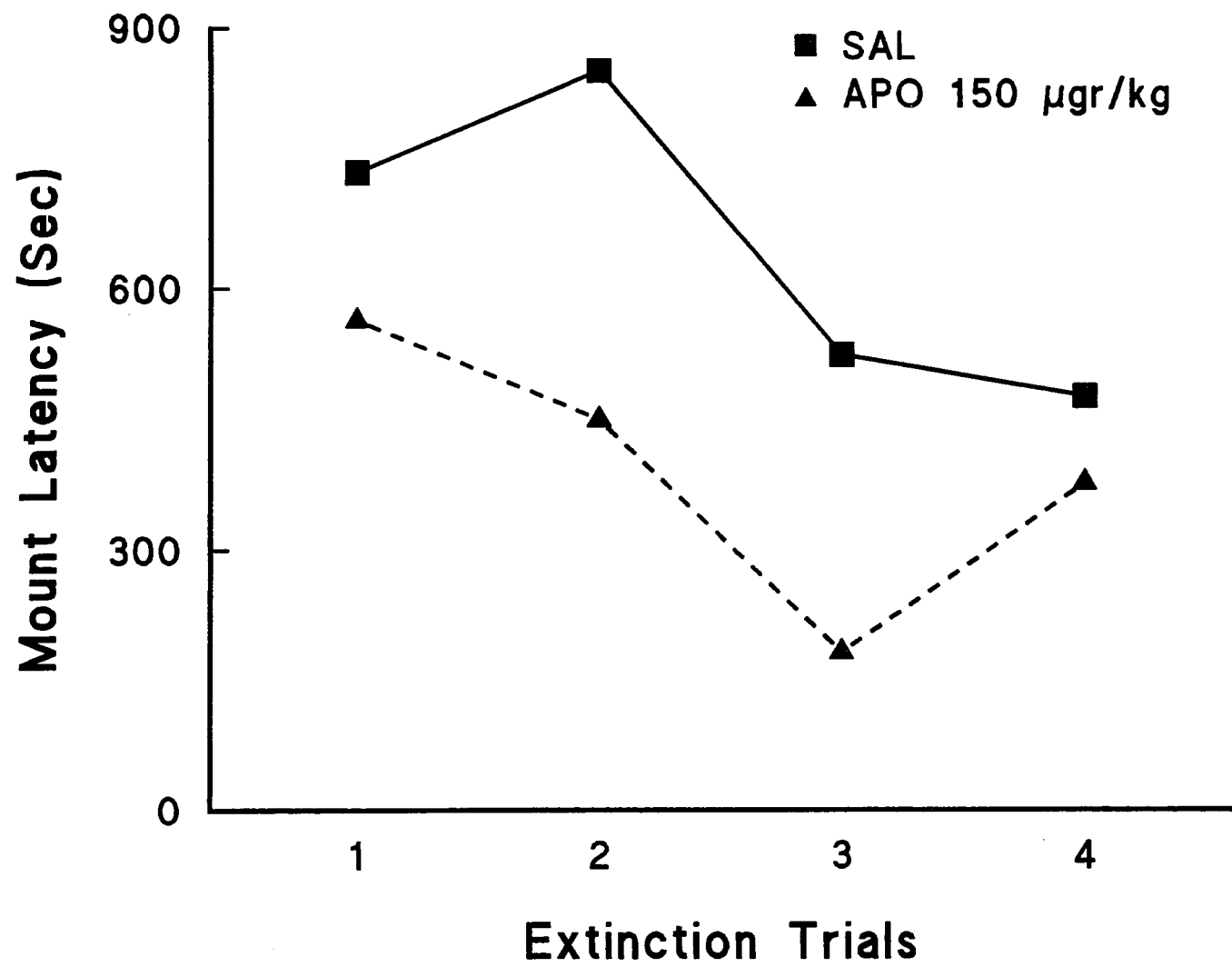
FIGURE 1. Effects of test trial treatment condition as a function of intertrial exposure.

FIGURE 2. Mean mount latency for apomorphine- (150, 300 and 450 ug/kg) and vehicle-treated rats during C-IA acquisition.

Figure 3. Mean mount latency for apomorphine- and vehicle-treated rats during C-IA extinction.







APPENDIX

PHARMACOLOGICAL MANIPULATIONS OF MALE SEXUAL BEHAVIORS

The purpose of this appendix is to provide a summary of pharmacological manipulations of male sexual behavior. A goal of this research has been to identify neurotransmitter systems that participate in the regulation of these behaviors. Male copulatory behaviors are regulated by complex interactions among the monoamine neurotransmitters, neuroactive peptides, and steroid hormones. This review will focus on neural modulation of copulatory behavior, specifically, the results of pharmacological manipulations of a number of neurochemical systems including dopamine, serotonin, norepinephrine, GABA, and neuroactive peptides.

Dopaminergic modulation of sexual behavior.

Considerable evidence suggests that increased activity within dopaminergic systems facilitates copulatory behaviors. Tagliamonte, Fratta, del Fiacco, and Gessa (1974) reported that the dopamine synthesis precursor L-DOPA increased copulation in sexually sluggish rats (rats that do not initiate a copulatory sequence when

paired with a receptive female). L-DOPA increased the proportion of male rats copulating after castration and administration of subthreshold testosterone replacement (Malmnas, 1973; 1976). Paglietti, Pellegrini-Quarantotti, Mereu, and Gessa (1978) reported that L-DOPA decreased ejaculation latencies in sexually active male rats. L-DOPA also increased the percentage of males that ejaculated. Clinical data also suggest a facilitory role for dopamine in human sexual behavior. Male patients receiving L-DOPA for Parkinson's disease have reported increased sex drive and erectile ability (Barbeau, 1969; Benkert, Crombach, & Kockott, 1972; Bowers, van Woert, & Davis, 1971).

Although suggestive, reports of copulatory facilitation by L-DOPA cannot be considered conclusive because high doses of L-DOPA interfere with male sexual behavior (Gray, Davis, & Dewsbury, 1974). It is possible, however, that this effect is mediated by an indirect effect on serotonin turnover. High levels of L-DOPA decrease brain serotonin and increase levels of 5-HIAA, a serotonin metabolite (Bartholini, de Prada, & Pletscher, 1986; Hyppa, Lehtinen, & Rinne, 1971). Another possibility is that high levels of dopamine act

in the spinal cord to inhibit sexual behavior. Pehek, Thompson, and Hull (1989) reported that intrathecal administration of apomorphine (a dopamine agonist) inhibited penile reflexes. Effects of L-DOPA administration are also difficult to interpret because L-DOPA is the precursor for both norepinephrine and dopamine. Thus, the observed effects on sexual behavior could conceivably reflect increased norepinephrine synthesis, rather than an effect on dopamine neurotransmission.

Additional evidence of dopaminergic regulation of male sexual behavior comes from an examination of the effects of dopamine receptor agonists and antagonists. Although the specificity of any substance for a certain population of receptors is only relative, evidence suggests that activation of central dopaminergic systems increases copulatory behavior.

A number of studies have examined the effects of the dopamine receptor agonist apomorphine on measures of copulatory behavior. Tagliamonte et al., (1974) reported that apomorphine increased copulatory behavior of male rats with low baseline rates of sexual activity. The effect was prevented by haloperidol, a

dopamine receptor antagonist, suggesting that the effect of apomorphine was not the result of secondary modulation of another neurotransmitter system. The authors also reported, however, that apomorphine decreased copulatory behaviors in male rats with high baseline rates of sexual activity. Apomorphine reduced the number of penile intromissions preceding ejaculation in male rats (Paglietti et al., 1978). This facilitation was prevented by the dopamine receptor antagonist pimozide. Malmnas (1973) reported that apomorphine both increased the proportion of male rats displaying copulatory behaviors and decreased mount and intromission latency. Pomerantz (1990) described a facilitory effect of apomorphine on the copulatory behaviors of male Rhesus monkeys. In contrast, Chambers and Phoenix (1989) reported no significant facilitation of copulatory behavior in Rhesus monkeys, although the dose of apomorphine used in their study was considerably higher than that used by Pomerantz (1990; 150 vs. 50 ug/kg).

Falaschi, Rocco, DeGiorgio, Frajese, Fratta, and Gessa (1981) evaluated the relative contributions of central versus peripheral dopamine receptors in the

modulation of copulatory behavior. Domperidone is a dopamine antagonist that does not cross the blood-brain barrier. The facilitory effect of apomorphine on sexual behavior was prevented by haloperidol, but not by domperidone, suggesting that the effects of apomorphine on copulatory behaviors depend on activation of central, rather than peripheral, dopamine receptors.

Anatomical studies also support the hypothesis that dopaminergic systems participate in activation of copulatory behaviors. Substantial evidence documents the importance of the nucleus accumbens in reinforcement (Guerin, Goeders, Dworkin, & Smith, 1984; Stellar, Kelley, & Corbett, 1983). Pleim, Matochik, Barfield and Auerbach (1990) reported elevated dopamine and DOPAC (a dopamine metabolite) in the nucleus accumbens during sexual behavior. Pehek, Warner, Bazzet, Bitran, Band, Eaton and Hull (1988) found that cis-flupenthixol, a dopamine antagonist, impaired copulation when injected into the medial preoptic area of male rats, a brain region implicated in regulation of male sexual behaviors (Hart & Leedy, 1985).

Although evidence suggests that dopaminergic systems participate in regulation of male sexual behavior, the specific mechanisms remain unclear. Apomorphine commonly facilitates copulatory behaviors at dose levels lower than those that produce hyperactivity, suggesting that apomorphine facilitates copulatory behavior by the selective activation of presynaptic autoreceptors (Bitran & Hull, 1987). The implication of this suggestion is that apomorphine's facilitation of copulatory behaviors is mediated by a reduction in dopamine activity. Additionally, drugs described as dopamine autoreceptor agonists (e.g., RDS-127; but note that RDS-127 is also a 5-HT_{1A} agonist) reduce ejaculatory thresholds in sexually active male rats (Clark, Smith, Stefanick, Arneric, Long, & Davidson, 1982; Clark, Stefanick, Smith, & Davidson, 1983). Conversely, studies of the drug 3-PPP have not supported the autoreceptor stimulation hypothesis. (-)3-PPP is an autoreceptor agonist and postsynaptic receptor antagonist whereas (+)3-PPP stimulates pre- and post-synaptic dopamine receptors (Hjorth, Carlsson, Clark, Svensson, Lindberg, Wikstrom, Sanchez, Lindberg, Hacksell, Arvidsson, Johansson, & Nilsson, 1983). If

dopamine's facilitation of copulatory behaviors results from decreased dopamine activity via autoreceptor stimulation, then (-)3-PPP should be more effective than (+)3-PPP at increasing copulatory behaviors. In fact, the opposite is true. Ahlenius and Larsson (1984) reported that (+)3-PPP stimulated copulatory behavior, whereas (-)3-PPP was without effect. Thus, it is unclear at present to what extent the observed effects of dopaminergic manipulations on copulatory behaviors reflect the relative activation or blockade of pre- and post-synaptic dopamine receptors.

Serotonergic modulation of sexual behavior.

Whereas increased dopaminergic activity is generally considered to increase sexual behavior, substantial evidence suggests that increased serotonin activity inhibits copulatory behavior. Tagliamonte, Tagliamonte, and Gessa (1971) reported that p-chlorophenylalanine (PCPA), a serotonin synthesis inhibitor, increased sexual behavior previously inhibited by pargyline, a monoamine oxidase inhibitor. Additionally, pargyline increased brain serotonin levels to a greater extent than catecholamine levels,

suggesting that the increase in serotonin, rather than other monoamines, inhibited male sexual behavior. Tagliamonte, Tagliamonte, Gessa, and Brodie (1969) reported that PCPA increased male-to-male mounting behavior in rats. This increase was greatest at the time of maximal brain serotonin depletion. Other reports have described decreases in ejaculation latency (Malmnas, 1973), and postejaculatory interval (Mitler, Morden, Levine & Dement, 1972), as well as increased number of males mounting (Malmnas & Meyerson, 1971) following PCPA administration. Similarly, serotonin depletion by the neurotoxin 5,7-DHT decreased ejaculation latency, postejaculatory interval, and number of intromissions preceding ejaculation in male rats (Larsson, Fuxe, Everitt, Holmgren, & Sodersten, 1978).

Disruption of serotonin synthesis facilitates copulatory behavior. Conversely, elevation of serotonin suppresses male sexual behavior. Malmnas (1973) reported that administration of 5-HTP, the synthesis precursor of serotonin, decreased copulation as indexed by a decreased percentage of animals mounting and intromitting, as well as an increase in

the latency to intromission for animals that did copulate. Ahlenius, Larsson, & Svensson (1980) administered a subthreshold dose of 5-HTP in combination with a serotonin reuptake blocker (zimelidine). This drug combination decreased the number of animals mounting and increased intromission latencies.

The effects of direct stimulation or blockade of serotonin receptors are less consistent and more difficult to interpret, probably as a consequence of the large number of receptor subtypes and few substances that activate or block only a specific population of receptors. The serotonin agonist 8-OH-DPAT facilitates copulatory behaviors as evidenced by a decrease in both ejaculation latency and postejaculatory refractory period (Ahlenius, Larsson, Svensson, Hjorth, Carlsson, Lindberg, Wikstrom, Sanchez, Arvidsson, Hacksell, & Nilsson, 1981). As a serotonin agonist, 8-OH-DPAT would be expected to inhibit male copulatory behavior. Clark, Smith, Stefanick, Arneric, Long, and Davidson (1982) reported that another serotonin agonist also facilitated copulatory behaviors. RDS-127 decreased both

ejaculation latency and the number of intromissions preceeding ejaculation.

Serotonin receptors have been classified into two major types, designated 5-HT₁ and 5-HT₂ receptors (see Bradley, Engel, Feniuk, Fozard, Humphrey, Middlemiss, Mylecharane, Richardson, & Saxena, 1986, for a discussion of receptor classification). 5-HT₁ receptors have been further classified as either 5-HT_{1A} or 5-HT_{1B} receptors. Accumulating evidence suggests that activation of 5-HT_{1A} facilitates sexual behavior in male rats.

A variety of 5-HT_{1A} receptor agonists facilitate copulatory behavior. Fernandez-Guasti, Escalante, Hong, and Agmo (1990) reported that the 5-HT_{1A} receptor agonist indorenate reduced the number of intromissions preceding ejaculation in male rats, although a higher dose completely inhibited sexual behavior. Similarly, RDS-127 and 8-OH-DPAT, selective 5-HT_{1A} agonists, facilitated copulatory behavior, possibly by blockade of presynaptic autoreceptors (Ahlenius et al., 1981; Clark et al., 1982; 1983). At present, studies of serotonin agonists and antagonists are inconclusive and difficult to interpret. Most serotonergic agents

affect multiple receptor populations and have mixed agonist and antagonist properties. In addition, serotonin manipulations may interact with central noradrenergic systems. Fernandez-Guasti, Hansen, Archer and Jonsson (1986) reported that the serotonin agonists lisuride and 5-MeODMT (a selective 5-HT_{1A} agonist) reduced the number of intromissions preceding ejaculation, and that this copulatory facilitation was blocked by administration of the noradrenergic neurotoxin DSP-4. Present evidence suggests that stimulation of 5-HT_{1A} receptors (autoreceptors) may facilitate male sexual behavior. In general, manipulations increasing serotonin activity tend to decrease copulatory behavior, and those that decrease serotonin activity facilitate copulation. Thus, it is likely that the facilitation of sexual behavior by 5-HT_{1A} receptors reflects a decrease in serotonin synthesis or release, rather than a more specific regulation of copulatory behavior by these receptors.

Noradrenergic modulation of sexual behavior.

Although norepinephrine (NE) has traditionally been considered relatively unimportant in the

regulation of male sexual behavior (Crowley & Zemlan, 1981), more recent research has demonstrated that manipulations that decrease noradrenergic neurotransmission disrupt copulation. Inhibition of NE synthesis with dithiocarbamate or electrolytic lesions of the locus coeruleus increased mount, intromission, and ejaculation latencies, as well as the duration of the postejaculatory refractory period (McIntosh & Barfield, 1984). DSP4, an NE neurotoxin, increased the postejaculatory refractory period (Hansen, Kohler, & Ross, 1982). Drugs acting at NE receptors may similarly decrease sexual behavior. Activation of alpha-2 adrenergic receptors (presynaptic autoreceptors) decreases central NE activity (Kwong, Smith, Davidson & Peroutka, 1986). Clark Smith and Davidson (1985a) reported that clonidine, an alpha-2 adrenergic agonist, decreased the number of male rats ejaculating, whereas the alpha-1 antagonist prazosin increased intromission and ejaculation latencies. Thus, decreasing NE activity by stimulating presynaptic receptors or blocking postsynaptic receptors disrupted copulatory behaviors.

Whereas decreased NE activity is associated with a suppression of copulatory behaviors, manipulations that increase NE activity facilitate sexual behaviors. Substantial evidence indicates that yohimbine, an alpha-2 adrenergic antagonist, facilitates copulatory behaviors. Yohimbine stimulates NE release by blockade of presynaptic autoreceptors (Goldberg & Robertson, 1983). Clark, Smith, and Davidson (1984; 1985a; 1985b; also, see Smith & Davidson, 1990) reported that yohimbine facilitated copulatory behaviors in male rats following penile anesthetization and castration. Additionally, yohimbine increased the copulatory performance of sexually inexperienced rats and induced copulation in sexually inactive rats. Yohimbine also facilitated sexual behavior in male rats in which sexual behavior had declined due to age.

Smith, Lee, Schnur and Davidson (1987) examined the effects of yohimbine and two other alpha-2 adrenergic antagonists (idazoxan and imoloxan) on copulatory behavior. Yohimbine and idazoxan increased the percentage of animals that copulated, and all three substances reduced ejaculation latency and postejaculatory interval. Sala, Braida, Leone,

Calcaterra, Monti, and Gori (1990) reported that yohimbine facilitated copulatory behaviors, whether administered systemically or intraventricularly. Peters, Koch, and Blythe (1988) demonstrated that yohimbine facilitated copulatory behaviors in male rats in which copulation had been associatively inhibited. Thus, considerable evidence documents the facilitory effects of alpha-2 adrenergic antagonists on copulatory behaviors.

Cholinergic and GABAergic modulation of sexual behavior.

In contrast to the transmitter substances previously described, little evidence documents modulation of male sexual behaviors by cholinergic neurotransmission. Soulairac and Soulairac (1975) reported decreased intromission frequency, ejaculation latency, and postejaculatory refractory period following nicotine administration, although motor behavior and brain serotonin levels were also affected. More recently, it has been reported that the muscarinic agonist oxotremorine reduced ejaculation latency and number of intromissions preceding ejaculation, at doses

lower than those producing locomotor impairment (Ahlenius & Larsson, 1985). This copulatory facilitation was reversed by scopolamine but not methylscopolamine, suggesting that the effects of oxotremorine on sexual behavior are mediated by central muscarinic receptors.

Activation of GABA receptors has been associated with a decrease in copulatory behavior. Agmo and Paredes (1985) reported that systemic administration of baclofen (a GABA_B agonist) or THIP (a GABA_A agonist) decreased the number of male rats that mounted or intromitted. Whereas stimulation of GABA receptors decreased male sexual behavior, GABA antagonists facilitated male sexual behaviors. Injections of the specific GABA_A antagonist (+)bicuculine into the medial preoptic area decreased the postejaculatory refractory period and increased sexual behavior in castrated rats given sub-optimal doses of testosterone (Fernandez-Guasti, Larsson, & Vega-Sanabria, 1986). Bitran, Miller, McQuade, Leipheimer, and Sachs (1988) reported that intrathecal administration of both GABA_A and GABA_B agonists (baclofen and THIP, respectively) interfered with male penile reflexes. Thus, stimulation of either

GABA_A or GABA_B receptors disrupts male copulatory behaviors, whereas blockade of GABA_A receptors facilitates male sexual behaviors.

Peptidergic modulation of sexual behavior.

A large volume of recent research has examined the role of neuropeptides in the regulation of male sexual behavior. Peptides examined include gonadotrophin releasing hormone (GnRH), endogenous opiate-like substances, oxytocin, neuropeptide Y, substance P, cholecystokinin, and others. As with the neurotransmitter substances described previously, male sexual behaviors may be either facilitated or disrupted by a wide range of pharmacological manipulations of these substances.

Gonadotrophin releasing hormone (GnRH), released by the hypothalamus, stimulates the release of luteinizing hormone and follicle-stimulating hormone from the pituitary. In view of its obvious significance in reproductive physiology, the role of GnRH in the modulation of copulatory behaviors has been examined. Moss, Dudley, Foresman, and McCann (1975) reported that GnRH reduced intromission and ejaculation

latencies in sexually experienced male rats. Similarly, Myers and Baum (1980) found that GnRH reduced ejaculation latency in castrated male rats receiving testosterone replacement. Dorsa and Smith (1980) examined the effects of intracranial administration of GnRH and found increased mounting following penile anesthetization. Thus, GnRh appears to have some facilitory effect on male sexual behavior.

Another peptide with obvious reproductive relevance is oxytocin, which stimulates uterine contraction and milk production. Administration of oxytocin into the internal carotid artery reduced the number of intromissions preceding ejaculation (Stoneham, Everitt, Hansen, Lightman, & Todd, 1985). Arletti, Bazzani, Castelli, and Bertolini (1985) reported that a smaller dose, administered intraventricularly, reduced ejaculation latency and postejaculatory interval. Additionally, copulatory behavior was disrupted by administration of the oxytocin antagonist $d(CH_2)_5Tyr(Me)-Orn^8$ -Vasotocin (Argiolas, Collu, D'Aquila, Gessa, Melis & Serra, 1989). Some evidence suggests that oxytocin may participate in human male sexual behavior: Tindal

(1975) found that plasma oxytocin increased in human males following exposure to erotic stimuli.

Corticotropin releasing factor (CRF) is a hypothalamic peptide which regulates the pituitary-adrenal stress response (Britton & Koob, 1988). CRF acts to decrease GnRH secretion in response to stress. Sirinathsinghji (1987) reported that CRF administration disrupted male copulatory behavior. Intraventricular administration of CRF increased mount, intromission and ejaculation latencies as well as the number of mounts preceding ejaculation.

Disruption of copulatory behavior by CRF was antagonized by naloxone, suggesting an interaction with central opioid systems. The inhibitory effects of opiates on copulatory behaviors are well known (see Pfaus & Gorzalka, 1987, for a review). For example, Hughes, Everitt, and Herbert (1990) found that intracranial microinjections of beta endorphin increased mount, intromission, and ejaculation latencies but did not affect appetitive or reward-related aspects of sexual behavior (e.g., place preference or partner preference). Meyerson and Terenius (1977) reported a decrease in copulatory

behavior, as evidenced by fewer males mounting, following administration of beta-endorphin. Conversely, administration of the opiate antagonist naloxone induced copulatory behaviors in sexually inactive rats (Gessa, Paglietti & Pellegrini-Quarantotti, 1979). Administration of opiates, however, does not universally decrease copulatory behavior. Band and Hull (1990) recently reported that microinjections of small quantities of morphine or dynorphin into the medial preoptic area decreased both ejaculation latency and number of intromissions preceding ejaculation. The precise role of opiate peptides in the regulation of copulatory behaviors remains in question.

A large body of evidence now documents regulation of male sexual behavior by a number of neuropeptides. In addition to the results described above, disruption of copulatory behavior has been observed for neuropeptide Y (Clark, Kalra, & Kalra, 1985) and angiotensin II (Clark, 1989). Facilitation of copulatory behavior has been observed for substance P (Dornan & Malsbury, 1989) and cholecystokinin (Dornan & Malsbury, 1989; Pfaus & Phillips, 1987).

Summary

Male copulatory behaviors are regulated by complex interactions involving, to some extent, all of the classical neurotransmitters (dopamine, serotonin, acetylcholine, norepinephrine) as well as GABA and a number of neuropeptides. No reports exist at present of the effects of excitatory amino acids (e.g., glutamate) on copulation. That a large number of neurochemical systems regulate male sexual behavior should not be surprising, considering the biological and adaptive significance of these behaviors. It is clear, however, that attempts to characterize the effects of a given pharmacological manipulation on sexual behavior are complicated by the complexity of interactions among neurotransmitter systems and receptor subpopulations existing within any one neurotransmitter system. The development of compounds possessing greater selectivity for a particular population of receptors may eventually enable the assessment of possible unique contributions of specific receptor populations in the control of male sexual behaviors.

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