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# Microinjection of *cis*-flupenthixol, a dopamine antagonist, into the medial preoptic area impairs sexual behavior of male rats

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Systemically administered dopamine agonists have been shown to facilitate copulation in male rats. Microinjection of the dopamine agonist apomorphine into the medial preoptic area has also been reported to facilitate sexual behavior. The present experiments investigated the effects of medial preoptic microinjections of the dopamine antagonist *cis*-flupenthixol on male rat copulatory behavior. Fewer males initiated copulation and fewer ejaculated following flupenthixol administration. Those males that did ejaculate following flupenthixol injections had fewer ejaculations and longer interintromission intervals. Flupenthixol also antagonized the facilitative effects of apomorphine injections into the medial preoptic area. Flupenthixol and apomorphine produced only minor alterations in non-copulatory behaviors. The results suggest that dopamine receptors within the medial preoptic area are important in the regulation of masculine sexual behavior in the rat.

## INTRODUCTION

Systemic administration of moderate doses of dopamine (DA) agonists has been reported to facilitate masculine copulatory behavior in both rats and men[1–3,7–9,11,14,15,18,20,22,23]. Conversely, peripheral administration of DA antagonists has impaired male sexual behavior[1,4,14]. Since multiple sites within the central and peripheral nervous systems may be affected by systemic injections, these studies are unable to specify the sites where dopaminergic agents may exert their effects. One potential site of dopaminergic regulation of male reproductive behavior is the medial preoptic area (MPOA). Lesions of this area abolish or severely impair male sex behavior in all species examined to date[10,12], while electrical stimulation facilitates sex behavior[16,17]. Furthermore, this area receives a small projection from the incertohypothalamic dopamine system, which originates in the A14 cell group of the hypothalamus[6].

Recently, we have shown that microinjections of moderate doses (0.5 $\mu$g and 2.0 $\mu$g) of apomorphine, a dopamine agonist, into the MPOA facilitated several measures of copulatory behavior[13]. Effects included an increase in the number of ejaculations within the test period and a decrease in several latency measures. These effects were not replicated by injections into either the caudate nucleus, the lateral septum, or the nucleus accumbens.

If DA receptors within the MPOA regulate the activity of neurons important in the facilitation of masculine copulatory behavior, then pharmacological blockade of these receptors should impair sexual behavior. The studies reported here examined the effects of microinjections of *cis*-flupenthixol (FLU), a DA antagonist, into the medial preoptic area. It was hypothesized that such injections would impair masculine copulatory behavior, as well as antagonize the facilitative effects of apomorphine on sexual behavior.

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## MATERIALS AND METHODS

Adult male Long–Evans rats, obtained from Blue Spruce Farms (Altamont, NY), and weighing 300–375 g, were used. Animals were housed singly in a temperature- and humidity-controlled environment, with food and water available ad libitum. A 14/10 light/dark cycle was in effect, with lights off at 11.00 h. Animals were handled daily so that microinjections could be accomplished without anesthesia. All behavioral testing was done during the dark period, between 13.00 and 16.00 h. Males were screened for copulatory behavior twice before receiving a preoperative baseline test. Long–Evans female rats were used as stimulus animals and were housed separately from the males. Females were ovariectomized, and brought into behavioral heat with a single s.c. injection of estradiol benzoate (20 $\mu$g in oil) administered 48 h before behavioral testing.

*Surgery and cannulae*

Implantation of cannulae was performed under Diabutal anesthesia (55 mg/kg), using a Kopf stereotaxic frame. Each animal received one guide cannula, ending 1 mm above the left MPOA, with coordinates chosen from the atlas of Pellegrino, Pellegrino and Cushman[19] (AP 2.4, ML 0.2, DV 7.0, incisor bar 5 mm above the interaural line). Briefly a small hole was drilled in the skull above the MPOA and a cannula was lowered to the appropriate depth. Four screws were inserted into the skull surrounding the cannula, which provided anchorage for an assembly constructed of dental cement that surrounded both the screws and the cannula.

Cannulae were cut from 23-gauge thin-wall stainless-steel tubing, and were sanded on a rotary disk to a length of 16 mm. A 17-mm obturator, which prevented foreign material from entering the cannula, was constructed from 27-gauge stainless-steel tubing. A collar of 23-gauge tubing was crimped to the end of the obturator, to prevent descent further than 1 mm from the end of the guide gannula. A piece of polyethylene tubing (PE-50) surrounded and extended slightly from the collar and prevented loss of the obturator. An injection cannula was constructed from 27-gauge stainless-steel tubing and, during drug injections, protruded 1 mm beyond the end of the guide cannula in the brain. The other end of the injection cannula was inserted into a 1-m length of polyethylene tubing (PE-20), which was in turn connected to a 1-ml syringe. During drug administration, the syringe was held in a Harvard microinfusion pump.

*Drugs*

*cis*-Flupenthixol was kindly donated by H. Lundbeck A/S (Copenhagen, Denmark) and was dissolved in sterile water. Apomorphine (Sigma Chemicals) was dissolved in sterile water with 0.2% ascorbic acid. Both drugs were dissolved immediately before administration.

*Procedures*

All sex behavior experiments employed counterbalanced, repeated measures designs. Two weeks following surgery, males were given a single postoperative baseline test for sexual behavior. Thereafter, tests following drug or vehicle administration were given at one-week intervals. Microinjections were accomplished by removing the obturator from the guide cannula and replacing it with the injection cannula. The rate of injection was 1.0 $\mu$l/min. In order to prevent diffusion back up the guide cannula, the injection cannula was left in place for 30 s following injection. Animals were then returned to their home cage, where behavioral testing occurred upon introduction of a receptive female.

The number and time of each mount, intromission, and ejaculation were recorded during sexual behavior tests. Each test lasted for 30 min following the first intromission, or for a total of 30 min, if no intromission occurred. Measures derived from the data were: ejaculation frequency, mount frequency, intromission frequency, latency to the first mount, latency to the first intromission, ejaculation latency (time from the first intromission of an ejaculatory series to the subsequent ejaculation), postejaculatory refractory period (time from the ejaculation to the next intromission), interintromission interval (the average time between intromissions), and intromission ratio (the number of mounts plus intromissions divided by the number of intromissions).

Data from all animals in a given experiment were used in statistical analyses of ejaculation frequency. All other analyses of sexual activity utilized only the data from those rats that actually copulated. Ejaculation frequency was analyzed by a 1-way repeated-

measures ANOVA, followed by Newman–Keuls pairwise comparisons. The Cochran's Q-test was used to compare the number of animals that mounted, intromitted, or achieved one, two, or three ejaculations in each treatment. All other measures were analyzed either by an ANOVA, followed by pairwise comparisons, or via a repeated measures *t*-test. Log transforms were done on latency and interval data before parametric statistics were used.

*Histology*

Following each experiment, males were decapitated, and their brains were removed and frozen in an American Optical cryostat. Forty-$\mu$m sections were cut, mounted on glass slides, stained with Cresyl violet, and examined with a projection magnifier. Only those animals with histologically verifiable cannulae in the MPOA were included in data analyses.

*Experiment 1. Effects on copulation of 0.2, 2.0, and 10.0 $\mu$g FLU in the MPOA*

Twenty-four males were implanted with MPOA cannulae. All animals received each dose of FLU, plus a vehicle injection, for a total of 4 tests per rat. The injection volume was 1.0 $\mu$l, and testing began 5 min after drug administration.

*Experiment 2. Effects on copulation of 20.0 and 40.0 $\mu$g FLU in the MPOA*

Nineteen rats were implanted with MPOA cannulae. All rats received each dose of FLU and a vehicle injection for a total of 3 copulatory behavior tests. The injection volume was 1.0 $\mu$l and testing began 5 min after drug administration.

*Experiment 3. Effects on activity of 20.0 $\mu$g FLU and 0.5 $\mu$g apomorphine*

Following completion of copulatory behavior testing, 18 of the males from Expt. 2 were used to assess any effects of 20.0 $\mu$g FLU/1.0 $\mu$l or 0.5 $\mu$g apomorphine/0.5 $\mu$l on general activity. Males were randomly divided into two independent groups with one group receiving FLU injections while the other received vehicle. Five minutes post-injection, the animals were observed in their home cages for 30 min. Every 3 min, the presence or absence of walking, rearing, standing, sitting, lying down, anogenital grooming, non-anogenital grooming, eating and drinking was recorded. The total incidences of each behavior were then calculated for every rat, and the data were analyzed using the non-correlated *t*-test. Subsequently, these same animals were again randomly divided into two independent groups, with one group receiving apomorphine and the other vehicle. Immediately after injection, behavioral testing was conducted in the same manner as following FLU administration.

*Experiment 4. Effects of 10.0 $\mu$g FLU on apomorphine-induced facilitation of copulation in the MPOA*

Twenty animals were implanted with MPOA cannulae, and received 0.5 $\mu$g apomorphine, 10.0 $\mu$g FLU, FLU plus apomorphine, and vehicle injections on 4 separate tests. The injection volume was 0.5 $\mu$l and testing began immediately following drug administration.

## RESULTS

*Experiment 1*

Nineteen males had cannulae within the MPOA. There were no statistically significant effects of 0.2, 2.0 or 10.0 $\mu$g FLU on sex behavior. There was, however, a trend towards an increased interintromission interval with the 10.0-$\mu$g dose ($t = 1.74$, df = 17, $0.05 < P < 0.1$).

TABLE I

*Effects of FLU vs vehicle injections into the MPOA on masculine sexual behavior, Expt. 2*

Values are the means ± S.E.M. for significantly affected variables. EF, ejaculation frequency including all animals; $EF_e$, ejaculation frequency of those animals that ejaculated; $III_1$, interintromission interval of the first ejaculatory series; $EL_1$, ejaculation latency of the first ejaculatory series; M, number of males that mounted; I, number of males that intromitted.

| | *Vehicle* | *20.0 $\mu$g FLU* | *40.0 $\mu$g FLU* |
|---|---|---|---|
| EF | 2.58 ± 0.14 | 0.74 ± 0.23[c] | 0.74 ± 0.25[c] |
| $EF_e$ | 2.58 ± 0.14 | 1.75 ± 0.25[c] | 2.00 ± 0.31[a] |
| $III_1$ | 43.74 ± 4.06 | 89.64 ± 17.88[b] | 70.63 ± 13.21[b] |
| $EL_1$ | 397.47 ± 32.64 | 632.12 ± 106.89[b] | 532.00 ± 118.29 |
| M | 19 | 11[d] | 9[d] |
| I | 19 | 10[e] | 9[e] |
| EF ≥ 1 | 19 | 8[e] | 7[e] |
| EF ≥ 2 | 19 | 5[e] | 5[e] |
| EF ≥ 3 | 10 | 1[e] | 2[e] |

[a] $P < 0.05$, [b] $P < 0.02$, [c] $P < 0.01$, [d] $P < 0.005$, [e] $P < 0.001$.

TABLE II

*Effects of vehicle, apomorphine, FLU and FLU plus apomorphine injections into the MPOA on masculine sexual behavior, Expt. 4*

Values are the means ± S.E.M. for significantly affected variables. EF, ejaculation frequency; $III_1$, inter-intromission interval of the first ejaculatory series; APO, apomorphine.

| | *Vehicle* | *0.5 μg APO* | *10.0 μg FLU* | *FLU + APO* |
|---|---|---|---|---|
| EF | 1.86 ± 0.31 | 2.57 ± 0.14[a] | 1.79 ± 0.35 | 1.64 ± 0.36[b] |
| $III_1$ | 41.69 ± 7.62 | 37.53 ± 4.18 | 62.06 ± 11.15[a] | 83.74 ± 23.35[a,b] |
| EF ≥ 2 | 10 | 14[a] | 9 | 8 |

[a] $P < 0.05$ relative to vehicle, [b] $P < 0.05$ relative to APO.

*Experiment 2*

All animals had cannulae within the MPOA. Both the 20.0- and 40.0-μg doses of FLU dramatically reduced ejaculation frequency ($F = 36.81$, df = 2.36, $P < 0.001$) (see Table I). Fewer males mounted ($Q = 12.0$, df = 2, $P < 0.005$), intromitted ($Q = 14.0$, df = 2, $P < 0.001$), and achieved one ($Q = 16.63$, df = 2, $P < 0.001$), two ($Q = 24.5$, df = 2, $P < 0.001$), or 3 ejaculations ($Q = 16.22$, df = 2, $P < 0.001$) following FLU injections. Among those males that did ejaculate following FLU administration, ejaculation frequency was reduced (20.0 μg FLU, $t = 3.74$, df = 7, $P < 0.01$; 40.0 μg FLU, $t = 2.5$, df = 6, $P < 0.05$). In addition, the interintromission interval of the first ejaculatory series was lengthened by FLU in those animals that ejaculated (20.0 μg FLU, $t = 3.01$, df = 7, $P < 0.02$; 40.0 μg FLU, $t = 3.18$, df = 6, $P < 0.02$). The 20.0-μg dose also significantly lengthened the latency to the first ejaculation ($t = 3.49$, df = 7, $P < 0.02$).

*Experiment 3*

The only difference found in general activity following FLU injections was that the FLU animals were observed to sit more than controls ($t = 4.0$, df = 16, $P < 0.005$). Apomorphine administration increased the incidence of standing ($t = 2.4$, df = 16, $P < 0.05$) and decreased the incidence of lying down ($t = 2.34$, df = 16, $P < 0.05$), but did not affect any other behaviors.

*Experiment 4*

Fourteen animals had cannulae in the MPOA. Apomorphine increased ejaculation frequency and FLU blocked this effect, while FLU had no effect of its own on this measure ($F = 2.86$, df = 3.39, $P < 0.05$) (see Table II). Apomorphine increased the number of rats ejaculating two or more times and FLU antagonized this effect ($Q = 9.22$, df = 3, $P < 0.05$). FLU increased the interintromission interval of the first ejaculatory series, but 0.5 μg apomorphine did not block this effect ($F = 5.6$, df = 3.21, $P < 0.01$).

## DISCUSSION

The present results demonstrate that administration of the dopamine antagonist FLU directly into the MPOA impairs masculine copulatory behavior. In Expt. 2, fewer males copulated following FLU microinjections, and those that did copulate achieved fewer ejaculations and had a slower rate of intromitting. These effects were dose-dependent, requiring a dose of 20.0 μg FLU to decrease ejaculation frequency, whereas lengthening of the interintromission interval was seen with 10.0 μg FLU. Furthermore, although a 10.0-μg dose of FLU did not impair ejaculation, this dose was sufficient to block the facilitative effect of 0.5 μg apomorphine on ejaculation.

The present data show that the effects of dopaminergic agents injected into the MPOA are pharmacologically specific to the dopamine receptor. Previous studies in our laboratory have shown that stimulation of dopamine receptors (probably postsynaptic) within the MPOA facilitates copulation[13]. We have now shown that blockade of MPOA dopamine receptors produces the opposite effect, namely an impairment of copulation. Evidence that these effects are mediated by actions on the same population of dopamine receptors is given by the observation that FLU antagonized the action of apomorphine on male sexual behavior. The finding that 0.5 μg of apomorphine did not diminish the lenghtening of the interintromission interval by 10.0 μg FLU, may be due to an insuf-

ficient dose of agonist in relation to antagonist (a 1:20 ratio). Possibly a higher dose of apomorphine would antagonize this effect of FLU.

The third experiment addressed the behavioral specificity of MPOA injections of FLU and apomorphine. Although both agents produced significant, and, in the case of 20.0 $\mu$g FLU, profound, effects on copulation, neither agent produced global effects on general activity. The only alteration in non-copulatory behaviors seen after FLU injections was an increase in the incidence of sitting in the home cage. The finding that other behaviors such as walking and rearing were unaffected suggests that a general alteration in overall activity cannot account for the present results. Likewise, the finding that MPOA apomorphine injections increased the incidence of standing and decreased the incidence of lying down, but did not alter other non-copulatory behaviors such as walking and rearing, suggests that apomorphine-induced facilitation of copulation cannot be explained by an increase in general activity levels. Furthermore, the lack of effects of either FLU or apomorphine injections on eating or drinking, suggests that alteration of a general motivational state does not mediate the effects of these agents on copulation.

Another consideration is whether our effects are anatomically specific. The present studies employed microinjections into the MPOA. Since this structure surrounds the third ventricle, the question arises as to whether our effects are due to diffusion into the ventricular circulation, which would affect multiple central nervous system (CNS) sites. We do not believe that ventricular diffusion can account for our results, since 10.0 $\mu$g FLU microinjected into the right lateral ventricle produced no effects on copulatory behavior (unpublished observations). Furthermore, we have been unable to reproduce the facilitative effect of MPOA apomorphine injections with injections into any other CNS structure examined to date. As previously reported[13], these structures included the caudate nucleus, the nucleus accumbens, and the lateral septum. We have recently found that apomorphine injections into either the paraventricular nucleus or the ventral tegmental area also fail to mimic the effects produced by MPOA administration of apomorphine (unpublished observations). Thus, the evidence suggests an important role for dopamine receptors within the MPOA in the regulation of masculine sexual behavior. However, since multiple CNS sites interact in the regulation of male sexual behavior, dopamine receptors in other areas may also contribute to the control of copulation.

Our past and present results are in agreement with previous studies showing a dopaminergic facilitation of copulation. However, there has been debate about whether these effects are mediated by actions on presynaptic autoreceptors or on postsynaptic receptors[1,2,8,9,13,18]. Utilizing systemic injections of relatively low doses of dopamine agonists, some investigators have suggested that the resultant enhancement of sexual behavior is due to stimulation of dopamine autoreceptors, which would decrease the release of endogenous dopamine[2,8,18]. Thus, these authors argue that the role of endogenous dopamine in copulation is one of inhibition. These conclusions are based on the assumption that the doses of dopamine agonists employed preferentially stimulated the more sensitive autoreceptors. However, while the doses utilized may have preferentially stimulated autoreceptors in some brain areas (e.g. caudate), there is no evidence to suggest that such preferential stimulation occurred in CNS areas regulating male copulatory behavior. In fact, we have previously shown that injections of low doses of apomorphine (possibly autoreceptor-selective) into the lateral ventricle[13] or MPOA[5] impaired copulation, whereas higher doses (presumably able to stimulate postsynaptic receptors) facilitated copulation[5,13]. Recent studies in our laboratory utilizing the neurotoxin 6-hydroxydopamine also support the contention that the facilitative effects of dopamine agonists on copulation are mediated via binding to postsynaptic receptors[5]. Furthermore, the present results demonstrating an inhibition of sexual behavior following blockade of MPOA postsynaptic receptors, suggest that the role of endogenous dopamine within the MPOA is one of facilitation of copulation.

Copulation is a complex behavior, consisting of both motivational and performance aspects. Using the technique of factor analysis of normative data, Sachs[21] has suggested that a minimum of 4 conceptual factors are needed to explain copulatory behavior in the male rat. These factors may be regulated by different neural mechanisms that normally interact to produce the fully integrated behavior pattern. Sachs has termed these 4 components: the initiation factor,

the copulatory rate factor, the intromission count factor, and the hit rate (intromission ratio) factor. Contributing to the initiation factor were the latencies to the first mount and to the first intromission, following exposure to a female. The ejaculation latency, postejaculatory interval, and interintromission interval all contributed to the copulatory rate factor. The number of intromissions preceding an ejaculation comprised the third component, the intromission count factor. Finally, the percentage of mounts in which vaginal penetration occurred, out of the total number of mounts, was termed the hit rate (intromission ratio) factor. Our previous results have shown that the most consistent effects of apomorphine injections into the MPOA are on Sachs' copulatory rate factor, as well as on the total number of ejaculations per test[13]. These findings support the notion that the various factors comprising male sexual behavior may be regulated by different neural substrates. In the present experiments, FLU also altered measures contributing to copulatory rate, namely the interintromission interval and ejaculation latency. FLU had the additional effect of decreasing the number of males that mounted and intromitted, suggesting an additional role for MPOA dopamine receptors in the initiation of copulation (sexual arousal).

In conclusion, the present results suggest that postsynaptic dopamine receptors within the MPOA are involved in the promotion of copulatory behavior in the male rat. These receptors appear to regulate copulatory rate and may contribute to sexual arousal as well.

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