

Systemic or Intracranial Apomorphine Increases Copulation in Long-Term Castrated Male Rats

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SCALETTA, L. L. AND E. M. HULL. *Systemic or intracranial apomorphine increases copulation in long-term castrated male rats.* PHARMACOL BIOCHEM BEHAV 37(3) 471-475, 1990.—Testosterone or its estrogenic metabolite is thought to be necessary to activate male rat sexual behavior. However, systemic injections of dopamine agonists, alone or in combination with exogenous testosterone, can partially restore copulatory behavior during the prolonged period of its postcastration decline. The present experiments tested the ability of the dopamine agonist apomorphine, injected systemically or into the medial preoptic area (MPOA), to restore copulation in long-term castrates that had failed to copulate on two successive weekly tests. In Experiment 1, systemic injections of apomorphine increased the number of mounts and intromissions in castrated males, compared to vehicle. In castrates given subthreshold testosterone propionate (TP), apomorphine increased the number of mounts. In Experiment 2, microinjections of apomorphine into the MPOA increased the number of mounts in animals without TP. Subthreshold TP had no significant effects in either experiment, either alone or interacting with apomorphine. These results suggest that stimulation of dopamine receptors can partially restore copulation, even after its virtual elimination. Furthermore, dopamine receptors in the MPOA may contribute to sexual arousal in long-term castrates.

Apomorphine Dopamine Medial preoptic area Copulation Castration Testosterone Rats

MALE rat copulatory behavior relies heavily on the presence of testosterone. After castration, copulation ceases completely, but can be restored by hormonal replacement with either testosterone or a combination of its metabolites estradiol and dihydrotestosterone (3, 6, 11, 14, 26). However, whereas testosterone levels decline rapidly following castration, copulatory behavior declines gradually over a period of two to ten weeks (12, 19, 26). Ejaculations and intromissions disappear almost simultaneously, while mounting continues for some time. ["Ejaculation" in this context will refer to the behavioral pattern that usually accompanies the emission of seminal fluid by normal males (4).] The prolonged period of copulatory decline after castration may be related to gradual changes in cell size or number, synaptic connectivity, and/or alterations in biochemical processes [reviewed in (2)].

Dopamine agonists, administered systemically, have facilitated copulation in both intact (1, 8, 27) and castrated (17,18) male rats. Furthermore, the dopamine agonist apomorphine, injected into the medial preoptic area (MPOA) facilitated copulation in intact males (7, 16, 22). Injections into other areas produced minimal or no effects (16).

Previous studies showing pharmacological enhancement of copulation in castrated rats have tested during the prolonged phase of decline in copulation (9, 10, 18) or have given suboptimal

injections of testosterone (17,20). No study has previously attempted to restore copulation by administering a nonsteroidal drug after copulatory behavior has ceased. However, there is reason to expect greater difficulty restoring copulation after a very long postcastration interval. For example, a two-month period of hormone deprivation renders male rats refractory to the effects of testosterone; larger daily doses are required to restore behavior than if the hormone is given immediately after castration, and copulation may not return for 10 to 14 days (2,13). Thus, degeneration of various neural, muscular or other hormone-dependent mechanisms may make restoration of copulation progressively more difficult.

The present experiments tested whether the dopamine agonist apomorphine, administered either systemically or into the MPOA, could reinstate copulatory behavior in animals that had failed to mount, intromit or ejaculate on two successive weekly tests. A behavioral criterion was used, rather than a constant time after castration, because of the great variability among animals in postcastration retention of copulation. Dose-response curves were generated for both systemic and intracranial routes of administration. In addition, a subthreshold dose of testosterone was administered in the second half of each experiment in order to test whether it might enhance the effectiveness of apomorphine. Finally, behaviors were summed across treatments for each day in

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order to test whether behavioral responsiveness was progressively impaired during periods without subthreshold testosterone or was progressively enhanced during periods of hormone replacement.

METHOD

Animals

Eighteen adult male Long-Evans rats (Blue Spruce Farms, Altamont, NY) were housed singly in large plastic cages with food and water available ad lib. The light/dark cycle was 14/10, with lights off at 1100 hours. Ovariectomized Long-Evans female rats were used as stimulus animals and were housed separately from the males. Females were brought into artificial estrus with a single subcutaneous injection of estradiol benzoate (20 μg in oil) administered 48 hours before behavioral testing.

Surgery and Cannulae

Animals were anesthetized with ketamine hydrochloride (50 mg/kg) and xylazine hydrochloride (4 mg/kg) IP. A midsagittal scrotal incision was made, and the testes and surrounding fat were tied off and excised.

At the end of the first experiment, animals were again anesthetized and received a unilateral stainless steel guide cannula ending 1 mm above the MPOA (AP: 2.4, ML: 0.2, DV: -7.1, incisor bar: +5 mm) (23). An obturator, cut to the same length as the guide cannula, prevented foreign material from entering the brain and maintained the patency of the guide cannula [see (16) for details of surgery and cannula construction].

Drugs

Apomorphine hydrochloride (Sigma) was mixed with vehicle immediately before behavioral testing. The vehicle for both experiments was distilled water with 0.2% ascorbic acid. Testosterone propionate (TP) was dissolved in olive oil and administered subcutaneously.

Procedures

Males were given two preoperative tests to screen for copulatory behavior before receiving a preoperative baseline test. They were then castrated and given 2 weeks to recover. Thereafter, males received a copulatory test once a week with a receptive female until they failed to copulate on two successive weekly tests. Three castrates were eliminated from the first experiment because they continued to copulate after all others had ceased. The average postcastration interval before the first drug test was 80 days, with a range of 54 to 116 days.

Fifteen males were tested for sexual behavior once a week following systemic injections of 50, 100, or 200 $\mu\text{g}/\text{kg}$ of apomorphine or vehicle; all treatments were counterbalanced. Ten min after injection, the males were taken to the testing room, where a receptive female was introduced into the male's home cage. Each behavioral test lasted for 30 min after the male's first intromission or 30 min after the introduction of the female if no intromission occurred. Each mount, intromission, and ejaculation was recorded by a program for the IBM XT microcomputer (15). An intromission was distinguished behaviorally from a mount by the occurrence of a deeper thrust and a rapid, springing dismount. An ejaculatory pattern was characterized by a longer, deeper thrust followed by a slow dismount and a period of inactivity. Too few copulatory acts occurred under vehicle conditions to permit comparisons of copulatory rate and efficiency.

One week after the fourth drug test the animals received a

single subthreshold dose of TP (20 $\mu\text{g}/\text{kg}$) but were not tested for sexual behavior. Thereafter, the animals received four weekly injections of subthreshold TP three days preceding behavioral tests. The testosterone replacement regimen was adapted from that of Malmnas (17), using a dose that produced noticeable, but not statistically significant, enhancement of behavior in preliminary pilot tests. As before, 50, 100, or 200 $\mu\text{g}/\text{kg}$ of apomorphine or vehicle was injected 10 min before each test. The average postcastration interval for the first drug plus TP test was 115 days. Once an animal had completed the first experiment, he remained in the colony room until all males completed the systemic treatments.

All animals then received guide cannulae aimed at the MPOA and were given 2 weeks to recover. The three animals that were not included in the first experiment were also fitted with guide cannulae. One male died during the second experiment, leaving 17. Immediately before each weekly test, animals received microinjections of 2 or 5 μg of apomorphine or 0.5 μl vehicle. Microinjections were administered over a 30-sec interval, during which the animals could move freely. After an additional 30-sec period to allow for drug diffusion into brain tissue, the injection cannula was removed and replaced with the obturator. After the first three counterbalanced tests, the same subthreshold TP regimen as in Experiment 1 was begun, with behavioral tests three days after TP injections (20 $\mu\text{g}/\text{kg}$). Drug tests without TP began 193 days after castration; drug tests with TP began 214 days after castration.

Statistical Analyses

Because of the large number and unequal distribution of zero scores, data were analyzed by the Page Test for Ordered Alternatives, followed by the post hoc Comparison of Groups with a Control (25). Data are presented as mean \pm standard errors. In addition, the number of animals exhibiting a given behavior under various drug treatments was analyzed by Cochran's Q, followed by post hoc McNemar's tests.

Histology

At the conclusion of the second experiment, the animals were anesthetized with ether and decapitated. Brains were removed and frozen in an American Optical cryostat. Coronal sections were sliced at 40 μm and mounted on glass slides. The slides were stained with Cresyl violet and examined under a projection magnifier. All animals had correct placements.

RESULTS

Experiment 1

Apomorphine (without TP) significantly increased the number of mounts, $L(3) = 323$, $p < 0.02$, and intromissions, $L(3) = 317$, $p < 0.05$, compared to vehicle (see Table 1). Also, the number of animals that mounted was increased by the highest dose, $Q(3) = 9.18$, $p < 0.05$; $\chi^2(1) = 5.14$, $p < 0.05$. In addition, a few castrates were able to exhibit the ejaculatory pattern after apomorphine injections, although the increase was not statistically significant. No animal intromitted or ejaculated after vehicle injections.

Apomorphine plus subthreshold TP significantly increased the number of mounts, $L(3) = 317$, $p < 0.05$, compared to vehicle plus hormone (see Table 1). Several castrates were able to intromit and ejaculate after apomorphine; the increase in intromissions approached statistical significance ($0.05 < p < 0.1$). No animal ejaculated after vehicle injections, and only two intromitted. Testosterone had no significant effect on its own and did not signif-

TABLE 1

EFFECTS OF SYSTEMIC APOMORPHINE ON COPULATORY BEHAVIOR OF LONG-TERM CASTRATES

	Vehicle	50 µg/kg APO	100 µg/kg APO	200 µg/kg APO
No TP				
Mean No. of mounts	1.6 ± 1.3	5.7 ± 2.4	9.7 ± 4.3*	7.9 ± 2.9*
% mounting	20	53	47	67*
Mean No. of intromissions	0.0	0.9 ± 0.5	0.8 ± 0.4	3.0 ± 1.4*
% intromitting	0	20	33	33
Mean No. of ejaculations	0.0	0.1 ± 0.1	0.0	0.1 ± 0.1
% ejaculating	0	7	0	13
TP				
Mean No. of mounts	2.4 ± 1.1	4.9 ± 2.4	4.1 ± 2.2	11.2 ± 3.3*
% mounting	40	47	67	73
Mean No. of intromissions	0.3 ± 0.2	2.6 ± 1.4	1.0 ± 0.9	3.8 ± 1.6
% intromitting	13	20	13	40
Mean No. of ejaculations	0.0	0.4 ± 0.2	0.1 ± 0.1	0.4 ± 0.2
% ejaculating	0	20	7	27

**p*<0.05, compared to appropriate vehicle.
APO = Apomorphine hydrochloride.
TP = Testosterone propionate.

icantly enhance apomorphine's ability to restore copulation. There were no other significant differences on any measure.

In order to test whether animals became less responsive to drug treatments across the four weeks without testosterone, and whether progressive exposure to testosterone throughout tests 5–8 may have increased responsiveness to apomorphine, we compared total numbers of mounts and intromissions on each day, across drug treatments. There was considerable variability from day to day, but no steady decline in scores during weeks without testosterone replacement, nor a steady increase during weeks with replacement. Analysis of variance revealed no significant differences across days with or without TP.

Experiment 2

Apomorphine alone significantly increased the total number of mounts compared to vehicle, *L*(2) = 130.5, *p*<0.05, and also the number of animals mounting, *Q*(2) = 6.25, *p*<0.05 (see Table 2). One animal intromitted after apomorphine, but none ejaculated. Only 2 animals mounted after vehicle injections, and none intromitted or ejaculated.

Apomorphine plus subthreshold TP had no significant effect on copulatory behavior (see Table 2). However, there was a non-significant increase (0.05 < *p* < 0.1) in mounting behavior with apomorphine plus TP compared to vehicle plus hormone. Two animals intromitted after apomorphine, but none ejaculated. No animal intromitted or ejaculated after vehicle injections.

TABLE 2

EFFECTS OF APOMORPHINE IN THE MPOA ON COPULATORY BEHAVIOR OF LONG-TERM CASTRATES

	Vehicle	2 µg APO	5 µg APO
No TP			
Mean No. of mounts	0.3 ± 0.2	2.2 ± 0.9*	3.1 ± 1.5*
% mounting	12	41	41
Mean No. of intromissions	0.0	0.0	0.0
% intromitting	0	0	0
TP			
Mean No. of mounts	0.7 ± 0.4	2.5 ± 1.0	2.3 ± 1.1
% mounting	18	41	47
Mean No. of intromissions	0.0	0.1 ± 0.2	0.1 ± 0.6
% intromitting	0	6	6

**p*<0.05.
APO = Apomorphine hydrochloride.
TP = Testosterone propionate.

The numbers of mounts plus intromissions on each test day were compared, as in Experiment 1. As before, there was no progressive decline across test days without TP, and no steady increase across days with TP.

DISCUSSION

The present results demonstrate that apomorphine, with or without subthreshold testosterone replacement, can partially restore the sexual behavior of male rats castrated 3 to 8 months previously. Systemic injections of apomorphine alone facilitated mounts and intromissions, and apomorphine plus subthreshold testosterone increased the number of mounts. Apomorphine injections into the MPOA also increased the number of mounts.

Apomorphine was previously shown to facilitate copulation in castrates with (17) or without (18) testosterone replacement during the prolonged period of copulatory decline. The present study tested whether apomorphine could restore copulation after it had completely ceased. A behavioral criterion of two weekly tests without copulation was imposed before drug testing began. The average postcastration interval before the first test was 80 days, and the postcastration interval for the last intracranial injection test was 228 days. Comparisons of behavior after vehicle injections (without testosterone) in Experiments 1 and 2 showed similar copulatory abilities: 3 animals mounted in Experiment 1, and 2 mounted in Experiment 2; none intromitted or ejaculated. Therefore, copulation had almost completely ceased in vehicle-treated animals. By comparison, Malmnas tested his animals 56 days after castration, at which time 37% mounted, 25% intromitted, and 7% ejaculated after vehicle injections (18). Thus, even in long-term castrates, which had lost virtually all copulatory ability, stimulation of dopamine receptors could partially restore copulation.

It is well documented that systemic injections of testosterone can restore the copulatory behavior of castrates [e.g., (6, 17, 26)]. However, we wished to use a dose of TP that would be ineffec-

tive on its own but that might enhance the facilitative properties of apomorphine. In comparisons of vehicle injections, with vs. without hormonal replacement, testosterone by itself was not effective in facilitating sexual behavior. Similarly, comparisons of apomorphine injections, with vs. without testosterone, revealed no effect of testosterone. Thus, the testosterone replacement regimen used here was ineffective on its own, and it did not significantly enhance the facilitative properties of apomorphine. Indeed, more measures were facilitated by apomorphine without testosterone than with it. However, there were trends ($0.05 < p < 0.1$) toward increases in each of the measures that failed to attain statistical significance in the TP condition. Examination of the data suggests that one reason for the loss of statistical significance in those measures was a slight facilitation of behavior by TP in both vehicle and apomorphine conditions; this slight overall facilitation may have obscured the differences between vehicle and drug.

Other drugs, administered systemically, have been reported to facilitate copulatory behavior of castrates. A single dose of the alpha-2 receptor agonist yohimbine significantly increased mounting and intromitting in nonhormone-treated males 35, 56, and 91 days after castration (9). Yohimbine slightly increased the number of ejaculations on day 56 only. Systemically injected RDS-127, a dopamine and serotonin (5-HT_{1A}) agonist, also increased mounting 35 days postcastration, but not at 56 days (10). Neither intromissions nor ejaculations were significantly increased by RDS-127 on either day. Apomorphine in the present experiment was as effective as either of the other treatments, even though it was administered much longer after castration, when copulatory behavior had virtually ceased.

In the present study, apomorphine microinjected into the MPOA increased the number of mounts. However, very few animals intromitted and none ejaculated. The inability of apomorphine in the MPOA to restore intromissions may be related to either of two factors. First, there was a substantial lapse of time between castration and the intracerebral injections. Animals had been castrated 193 days before the beginning of the second experiment. Not only had the animals been deprived of endogenous testosterone for a number of months, they had experienced many weekly tests on which they were unable to copulate. The length of deprivation and number of preceding tests was greater for the second experiment than the first. It is possible that in long-term castrates the loss of neuronal, muscular, or other hormone-dependent mechanisms precludes intromission and/or ejaculation. Although several studies have shown restoration of the full copulatory sequence by intracranial hormone implants, in spite of peripheral atrophy [reviewed in (24)], these studies used shorter postcastration intervals than in the present experiments. Additional structures may have atrophied or become nonfunctional during the lengthy hormone deprivation of this study. However, there was not a signif-

icant difference in behavioral scores across days within each experiment.

Second, castrated males may need dopaminergic stimulation of multiple areas in order to restore sexual behavior more completely. Activation of the mesolimbic dopamine tract, in particular, may be important for the restoration of copulation in castrates. The opiate agonists morphine or dynorphin, microinjected into the ventral tegmental area (the site of cell bodies of the A10 mesolimbic dopamine tract), increased mounting in castrates maintained on suboptimal testosterone (21). Furthermore, the morphine, though not dynorphin, microinjections increased the turnover of dopamine in the nucleus accumbens (a terminal field of the mesolimbic tract). Finally, castration-induced decreases in sexual arousal coincided with decreases in dopamine levels and turnover in the nucleus accumbens (20). Mitchell and Stewart (20) suggested that the mesolimbic dopamine tract is involved in mediating sexual arousability.

Beach (5) suggested that male copulatory behavior can be divided into at least two factors, sexual arousal and an intromission and ejaculation mechanism. Earlier studies in our lab indicated that apomorphine in the MPOA facilitated the intromission and ejaculation mechanism (increased copulatory rate and efficiency), rather than sexual arousal (7, 16, 22). Therefore, it is especially interesting that in long-term castrates apomorphine in the MPOA increased only mounting, and not intromissions or ejaculations. In this respect, its effects were similar to those of morphine and dynorphin in the ventral tegmental area (21). We have very recently found that blocking dopamine receptors in the MPOA with cis-flupenthixol impaired sexual motivation as well as genital reflexes (28). Thus, the MPOA may contribute to both sexual arousal and the intromission and ejaculation mechanism.

In conclusion, apomorphine, with or without hormonal replacement, was able partially to restore sexual behavior in previously noncopulating castrated males. Systemic injections of this dopamine agonist increased both mounts and intromissions. Apomorphine microinjected into the MPOA increased mounting behavior. These data suggest that one means by which testosterone activates copulation is through increased synthesis and/or release of dopamine in one or more brain areas.

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