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Dopaminergic Control of Male Sex Behavior in Rats: Effects of an Intracerebrally-Infused Agonist*

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Systemically-administered dopaminergic drugs have been found to facilitate sexual behavior of men and male rats. The present experiments investigated the localization within the brain of dopaminergic effects on copulation of male rats. Apomorphine, a dopamine agonist, was microinfused into the medial preoptic area, caudate-putamen, nucleus accumbens, lateral septum and lateral ventricle. The lowest dose of apomorphine (0.2 μg) infused into the ventricle reduced the number of ejaculations, slowed the rate of intromitting and decreased the percentage of mounts on which the male gained vaginal intromission. The higher two doses (0.5 and 2.0 μg) infused into the medial preoptic area and, in some cases, the ventricle, increased the number of ejaculations and the percentage of mounts with vaginal intromission, increased the rate of intromitting and decreased the latency to ejaculate and the postejaculatory interval before resuming copulation. Infusions into the caudate-putamen and lateral septum were without effect. Those into nucleus accumbens produced only a slight dose-related decrease in latency to begin copulating. The copulatory impairments associated with infusions of the lowest dose into the ventricle may have resulted from stimulation of autoreceptors, or from preferential stimulation by low doses of an undetermined area. The facilitative effects of the two higher doses into the medial preoptic area and lateral ventricle may have been due to stimulation of dopaminergic postsynaptic receptors.

INTRODUCTION

Dopaminergic drugs, administered systemically in relatively low doses, have been found to facilitate masculine sexual behavior in both men and rats. For example, L-DOPA has been found to induce hypersexuality in men with Parkinson's disease[5,10,32] and to relieve impotence associated with diabetes in some patients[29]. Following the initial reports of sexual facilitation in humans, Malmnas[24,25] found that several dopaminergic drugs also facilitated the sexual behavior of male rats. Conversely, drugs that decreased dopaminergic activity impaired masculine sexual behavior[24,25]. These effects have been confirmed and extended in several laboratories[1,6,12,14,17,26,31] (but see refs. 2, 20).

A problem with systemically-administered drugs is that they may affect numerous neural systems simultaneously. It is not clear which dopaminergic synapses mediate the drug effects. It has been suggested that the nigrostriatal tract, ascending from substantia nigra to the caudate-putamen (CP) is the most likely site of dopaminergic facilitation of male sex behavior[11,15,26]. This suggestion was based largely on the observation that chemical or electrolytic lesions of this tract impaired masculine sexual behavior, along with other active motor patterns.

Two additional sites at which dopamine might influence sexual behavior are the nucleus accumbens (NA) and the lateral septum (LS); both are major terminations of mesolimbic dopamine containing axons. Alderson and Baum[3] reported that castration of

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male rats reduced the concentrations of dopamine and its metabolites in NA and the septal area, but did not alter dopamine metabolism in the CP. This finding suggested a role for the mesolimbic tract in some aspect of testosterone-related (presumably masculine) function. Furthermore, implantation of dihydrotestosterone propionate into the LS facilitated copulation in castrated male rats given estradiol systemically[7].

A fourth potential site for dopaminergic influence is the medial preoptic area (MPOA), long recognized as critical for masculine sexual behavior[13,18,21]. A small group of dopaminergic axons of the incertohypothalamic tract terminate in the MPOA[9]. Since these neurons are small in both size and number, they are frequently overlooked in discussions of dopamine tracts; however, their location in an area important for masculine sexual behavior suggests that they may play a role in its regulation.

The experiments described here tested the relative efficacy of microinfusions of the dopamine agonist apomorphine (APO) into the MPOA, the NA, the CP and the LS. In addition, infusions were made into the lateral ventricle (LV), as a control site. In addition, these experiments investigated whether various components of masculine sexual behavior were differentially affected.

MATERIALS AND METHODS

Animals

Adult male Long–Evans rats (300–350 g), purchased from Blue Spruce Farms (Altamont, NY), were caged singly in large plastic cages in a room where lights were off between 11.00 and 21.00 h. Food and water were available ad libitum. Animals were handled daily so that intracerebral infusions could be accomplished without stress or anesthesia. Males were screened on two preoperative tests for a moderate level of sexual behavior (one or two ejaculations per test). Stimulus females of the same strain were ovariectomized under Metofane anesthesia and housed in a separate room. Forty-eight hours before a behavioral test females were injected subcutaneously with 20 μg estradiol benzoate in oil; 4 h before the test they received a subcutaneous injection of 500 μg progesterone in oil.

Surgery and cannulae

Forty-four male rats, divided into two groups of 28 (Experiment 1) and 16 (Experiment 2), received two stainless-steel cannulae, one ending 1.0 mm above the left MPOA (AP 2.4, ML 0.2, DV −6.6), the other, within the right LV (AP 0.0, ML 1.5, DV −2.8). For Experiment 3, one group of 18 animals had a single cannula ending 1.0 mm above the NA (AP 3.2, ML 1.5, DV −5.5); a second group of 17 males had a single cannula ending in the largest extent of the CP (AP −2.2, ML 3.0, DV −3.5). For Experiment 4, 14 males had a single cannula ending in the LS (AP 2.4, ML 0.2, DV −4.6). (All placements were based on coordinates of Pellegrino et al.[28].) Implantation of the outer guide cannulae was done under pentobarbital anesthesia, using a Kopf stereotaxic frame with the incisor bar 5 mm above the interaural line. After shaving, cleaning and exposing the skull, a small hole was drilled over the appropriate structure. Cannulae were lowered to the predetermined depth, using the stereotaxic drive. Four small stainless-steel screws, drilled barely through the skull, provided anchorage for the assembly. Dental cement surrounded the screws and the guide cannula.

Guide cannulae were constructed from 23-gauge thin-wall hypodermic tubing, cut to the length appropriate for each placement and sanded on a rotary sanding disk. Each guide cannula was fitted with an obturator constructed from 27-gauge hypodermic tubing. A collar of 23-gauge tubing was crimped around the top to prevent the obturator from extending more than 1.0 mm beyond the end of the guide cannula. A small length of polyethylene tubing was fitted over both the collar and the top of the guide tubing to make an airtight seal. The cannulae used for infusions were made from 28-gauge hypodermic tubing. One end of a 1-m length of polyethylene tubing was fitted over the end of the infusion cannula, thereby preventing it from extending more than 1 mm below the end of the guide cannula. At the time of drug administration the other end of the polyethylene tubing was connected to a 1-ml syringe held in a Kopf microinfusion pump.

Drugs

Apomorphine was mixed with vehicle immediately before each test. The vehicle for Experiment 1 was isotonic saline with 0.2% ascorbic acid. Since the

drug appeared to be incompletely dissolved in the saline vehicle, distilled water with 0.2% ascorbic acid was used for Experiments 2, 3 and 4. The volume of each infusion was 0.5 μl.

Procedures

At 1 and 2 weeks after surgery males were given baseline tests with a receptive female. Thereafter, animals were given weekly drug tests, with the appropriate drug dose or vehicle being infused immediately before each test. Testing occurred from 14.00 to 16.00 h. Infusion was accomplished by removing the entire obturator assembly from the guide cannula and replacing it with the infusion cannula. Infusions were administered over a 30-s interval, followed by an additional 30-s with the infusion cannula left in place. The infusion cannula was then replaced with the obturator, and the male was returned to his home cage. He was then taken to a testing room, and a stimulus female was introduced into his cage.

Each test lasted for 30 min after the male's first intromission, or for 30 min after introduction of the female if no intromission occurred. The following measures were recorded: latency to first mount, latency to first intromission, latency from first intromission to first ejaculation (ejaculation latency), postejaculatory interval before the next intromission, intromissions/mounts plus intromissions (intromission ratio), intromissions preceding each ejaculation (intromission frequency), number of ejaculations during the test (ejaculation frequency), and mean interval between intromissions (inter-intromission interval). Animals that failed to copulate were excluded from all analyses except ejaculation frequency. Intromissions were distinguished behaviorally from mounts by the presence of a rapid, springing dismount. Ejaculation patterns were characterized by longer, deeper thrusts, slow dismounts and a prolonged period of rest (postejaculatory interval) following the ejaculation.

Histology

After all behavioral tests were completed, males were anesthetized and sacrificed by decapitation. Brain slabs were removed and mounted in an American Optical cryostat. Coronal sections were cut at 40 μm, mounted on glass slides, stained with cresyl violet, and examined with a projection magnifier. Data from animals whose LV cannulae missed the ventricle were omitted from analyses of ventricular infusion effects. All MPOA, NA and CP cannulae were within approximately 0.5 mm of their intended sites; no data were excluded from these analyses. Examination of dye diffusion in other animals has suggested that diffusion of 0.5 μl within tissue is confined to a volume approximately 0.5 mm in radius.

EXPERIMENT 1. EFFECTS ON COPULATION OF 0.2 AND 0.5 μg APO IN MPOA AND LV

Twenty-eight animals with MPOA and LV cannulae were divided into two groups; one group (n = 13)

TABLE I

Effects of apomorphine vs vehicle infusions into the medial preoptic area or lateral ventricle on masculine sexual behavior, Experiment 1

Values are the means ± S.E.M. for significantly-affected variables analyzed by *t*-test for each cannula site. EF, ejaculation frequency; IR, intromission ratio; III, inter-intromission interval.

	MPOA			*LV*		
	n	*Vehicle*	*0.2 μg APO*	*n*	*Vehicle*	*0.2 μg APO*
EF	13	2.15 ± 0.27	1.69 ± 0.29	10	2.40 ± 0.22	1.50 ± 0.27**
IR	9	66.8 ± 2.1	66.6 ± 2.8	9	79.8 ± 3.5	66.4 ± 4.9*
III	9	41.6 ± 8.1	33.9 ± 4.3	9	26.9 ± 1.7	46.2 ± 8.0*
	MPOA			*LV*		
	n	*Vehicle*	*0.5 μg APO*	*n*	*Vehicle*	*0.5 μg APO*
EF	15	1.73 ± 0.23	2.47 ± 0.17*	13	1.64 ± 0.36	1.79 ± 0.33
IR	13	66.2 ± 5.0	73.5 ± 6.7*	8	71.4 ± 4.7	84.9 ± 7.0*
III	13	51.0 ± 6.5	30.9 ± 3.3*	8	29.1 ± 3.5	24.6 ± 2.6

* $P < 0.05$; ** $P < 0.01$.

received either 0.2 μg APO or the ascorbate saline vehicle into either the MPOA or the LV cannula before each test. The other group (n = 15) received either 0.5 μg APO or vehicle into one of the two cannulae before each test. Each animal was tested 4 times, with a total of two infusions per cannula. All treatments were counterbalanced. Statistical comparisons of APO vs vehicle were based on correlated *t* tests, computed separately for each cannula site within each group of animals.

Results

Effects of APO infusions varied with both dose and site. The higher dose (0.5 μg) infused into the MPOA significantly increased both ejaculation frequency ($t = 2.65$, df = 14, $P < 0.02$) and intromission ratio ($t = 2.71$, df = 12, $P < 0.02$), and decreased inter-intromission interval (i.e. speeded the rate of intromitting) ($t = 2.69$, df = 12, $P < 0.02$). (See Table I.) The higher ejaculation frequency was in part due to an increase in number of animals achieving at least one ejaculation (87% with vehicle, 100% with 0.5 μg APO), and in part to a trend towards greater numbers of ejaculations achieved by those animals that did exhibit the behavior ($t = 1.9$, df = 12, $0.1 > P > 0.05$). When infused into the LV this dose significantly elevated only intromission ratio ($t = 2.78$, df = 7, $P < 0.05$). On the other hand, infusions of the low dose (0.2 μg) into the LV significantly decreased both ejaculation frequency ($t = 3.25$, df = 9, $P < 0.01$) and intromission ratio ($t = 2.85$, df = 8, $P < 0.05$), and increased inter-intromission interval (i.e. slowed the rate of intromitting) ($t = 2.31$, df = 8, $P < 0.05$). The decrease in numbers of ejaculations observed with MPOA infusions of this dose was not statistically significant; no other measures were affected.

EXPERIMENT 2. EFFECTS ON COPULATION OF 0.5 AND 2.0 μg APO IN MPOA AND LV

Experiment 2 was designed both to extend the dose–response curve and to confirm the previous facilitative effects of the 0.5 μg dose, using the ascorbate water vehicle. Sixteen animals with MPOA and LV cannulae were tested a total of 6 times each, with 3 infusions per cannula. Doses were 0.0 (vehicle), 0.5 and 2.0 μg APO. All animals received all treatments in counterbalanced order. One-way analyses of variance, with repeated measures on the dose factor, were computed separately for each cannula site. In addition, Cochran's Q tests for repeated observations were used to compare numbers of animals in each treatment that achieved one, two or 3 ejaculations per test. Finally, since the number of animals that consistently achieved at least two ejaculations was relatively low, data from all these animals were combined in a single two-way analysis of variance for ejaculation latency and postejaculatory interval of the second ejaculation.

Results

In this group of MPOA/LV animals, the facilitation by the 0.5 μg dose of APO was confirmed, and was observed with the 2.0 μg dose as well. (See Table

TABLE II

Effects of apomorphine vs vehicle infusions into the medial preoptic area or lateral ventricles on masculine sexual behavior, Experiment 2

Values are the means ± S.E.M. for significantly-affected variables. EF, ejaculation frequency; PEI1, postejaculatory interval following the first ejaculation (s); EL2, ejaculation latency to the second ejaculation (s); PEI2, postejaculatory interval following the second ejaculation (s).

	MPOA				*LV*			
	n	*Vehicle*	*0.5 μg APO*	*2.0 μg APO*	*n*	*Vehicle*	*0.5 μg APO*	*2.0 μg APO*
EF	16	1.94 ± 0.23	2.69 ± 0.15**	2.63 ± 0.13**	10	1.20 ± 0.33	2.30 ± 0.37*	2.40 ± 0.22*
PEI1	14	469.0 ± 34.6	382.6 ± 26.6*	399.0 ± 17.0	5	494.2 ± 37.4	428.4 ± 73.8	422.0 ± 26.4
EL2	13	248.2 ± 34.1	166.2 ± 13.3*	237.9 ± 32.7	4	301.8 ± 61.8	136.0 ± 13.6*	159.8 ± 23.8*
PEI2	13	590.0 ± 40.2	506.9 ± 45.8	491.7 ± 16.2*	4	630.5 ± 34.8	441.5 ± 27.7*	488.3 ± 40.5*
EF ≥ 2	16	13	16*	16*	10	6	8	9
EF ≥ 3	16	4	10*	10*	10	0	5*	5*

* $P < 0.05$; ** $P < 0.01$.

II.) Ejaculation frequency was increased by both doses infused into both sites (MPOA, $F = 7.05$, df = 2,30, $P < 0.01$; LV, $F = 5.05$, df = 2,18, $P < 0.05$). The increased ejaculation frequency observed with MPOA infusions was statistically significant even when only data from animals that did ejaculate were analyzed ($F = 4.28$, df = 2,26, $P < 0.05$). A similar trend for LV infusions failed to reach significance, using only data from animals that did ejaculate. Cochran's Q comparisons showed that significantly more animals achieved at least two ejaculations (Q = 6, df = 2, $P < 0.05$) and more achieved at least 3 ejaculations (Q = 6, df = 2, $P < 0.05$) after MPOA infusions of APO than after vehicle infusions. Similarly, more animals ejaculated at least 3 times with LV infusions of APO than with vehicle infusions (Q = 7.4, df = 2, $P < 0.05$). In addition, the postejaculatory interval after both the first (MPOA, $F = 3.47$, df = 2,26, $P < 0.05$; LV, $F = 1.11$, n.s.) and second ($F = 6.07$, df = 2,62, $P < 0.01$) ejaculations was shortened, and latency to the second ejaculation ($F = 3.21$, df = 2,62, $P < 0.05$) was also shortened. (Only the significant main effect for dose is presented; neither the main effect for cannula site nor the interaction was significant.)

EXPERIMENT 3. EFFECTS OF APO INFUSIONS INTO CP AND NA

Since LV infusions in the preceding experiments affected several copulatory measures, Experiment 3 was conducted to ascertain whether those effects were mediated by either the NA or the CP. The 17 animals with single CP cannulae and the 18 animals with single NA cannulae were tested a total of 3 times each, after infusions of 0.0 (ascorbate water vehicle), 0.5 and 2.0 μg APO, in counterbalanced order. One-way analyses of variance, with repeated measures on the dose factor, were used for each group of animals.

Results

Infusions of APO into the CP had no effect on masculine sexual behavior; nor did they produce any obvious effects on motor behavior. Infusions into the NA produced a dose-related decrease in intromission latency; however this effect was of borderline statistical significance (vehicle, 407.2 s; 0.2 μg, 261.7 s; 0.5 μg, 152.5 s; 2.0 μg, 127.1 s; $F = 2.66$, df = 3,56, $P = 0.058$). No other measures were affected.

EXPERIMENT 4. EFFECTS OF APO INFUSIONS INTO LS

Since the effects of ventricular infusions appeared not to be mediated by either the CP or the NA, a fourth experiment was conducted to test the effects of septal infusions. The coordinates for these cannulae were almost identical to those used by Baum et al.[7] to demonstrate facilitation of masculine sexual behavior by septal implants of dihydrotestosterone. Furthermore, they were the same as those used for the MPOA cannulae in Experiments 1 and 2, except that septal cannulae ended 2 mm more dorsal. Thus, Experiment 4 was designed to answer two questions: (1) whether infusions of APO into the LS affected copulation; and (2) whether the effects of MPOA infusions in previous experiments might have been mediated by drug diffusing up the cannula track.

Fourteen males received unilateral cannulae aimed at the anterior end of the LS. Data from 3 animals were later discarded because of inaccurate cannula placement. Each animal was tested 5 times, after infusions of 0.0, 0.2, 0.5, 2.0 or 4.0 μg APO, in counterbalanced order. Data were analyzed with a one-way analysis of variance with repeated measures.

Results

Infusions of APO into the LS had no effect on any parameter of sexual behavior.

DISCUSSION

In Experiments 1 and 2, several copulatory measures were affected by infusions of APO. These included ejaculation frequency, intromission ratio, inter-intromission interval, ejaculation latency, and postejaculatory interval. The complexity of masculine sexual behavior contributes to the difficulty of studying the mechanisms that regulate it. Beach[8] argued that male sexual behavior should not be considered a unitary construct, but rather that it is composed of at least two separate mechanisms. The sexual arousal mechanism was hypothesized to control the male's initiation of copulation as well as his resumption of it following an ejaculation. The copula-

tory mechanism was assumed to summate the excitatory effects of repeated intromissions and to maintain the series of intromissions until they culminated in ejaculation. Additional complexity was noted by Sachs[30], who further analyzed the copulatory mechanism into several components: a copulatory rate factor (inter-intromission interval, ejaculation latency, and postejaculatory interval), a hit rate factor (percentage of attempts on which the male gained intromission), and an intromission count factor (number of intromissions per ejaculation). He also suggested that the neural mechanisms regulating these various factors may be differentially localized within the brain. The present experiments were designed to assess the possibility of such differential localization.

The major site-dependent effect in these experiments was the impairment of copulation by the lowest dose of APO only when it was infused into the LV. This impairment was manifested as a decline in ejaculation frequency and in intromission ratio, and a lengthening of inter-intromission interval; all are measures of a copulatory mechanism (or, in Sachs' terms, a copulatory rate factor and a hit rate, or intromission ratio, factor; Sachs did not discuss ejaculation frequency[30]). One possible explanation for these results is that a site other than the MPOA or the LS, presumably in close contact with the ventricular circulation, mediates the inhibitory effects of low doses of APO on a copulatory mechanism. (The lowest dose was not tested in the CP or the NA.) A second possible explanation will be discussed below.

On the other hand, the facilitative effects of the two higher doses were in most cases similar for MPOA and LV infusions. There are at least 3 possible explanations for this similarity. First, APO infused into the MPOA may have leaked into the ventricular circulation and produced its effects on the same structure(s) as did LV infusions. Alternatively, APO infused into the ventricles may have acted on the MPOA. The third possibility is that several structures may act in concert in dopaminergic regulation of sexual behavior, and were affected similarly by the drug. In an attempt to resolve these conflicting interpretations, we tested the effectiveness of APO infusions into 3 major dopamine-containing areas, the CP, the NA and the LS, in Experiments 3 and 4. However, infusions into these sites failed to reproduce the effects of infusions into the MPOA or the LV. Infusions into the CP and LS failed to affect any aspect of behavior. Infusions into the NA did decrease intromission latency in a dose-dependent fashion; however, the effect was of only borderline statistical significance and no other measures were affected. Therefore, the structure(s) mediating the effects of ventricular infusions is (are) not known. The MPOA may be important for at least the facilitative effects, but the CP, the NA and the LS appear not to play a major role.

The effects of APO infusions into the MPOA and LV were dose-dependent. On several measures one or both of the two higher doses facilitated a copulatory mechanism, while the lower dose in the LV impaired its function. Specifically, the 0.5 and 2.0 μg doses increased ejaculation frequency in Experiments 1 and 2, and the 0.5 μg dose increased intromission ratio and decreased inter-intromission interval in Experiment 1; both doses decreased ejaculation latency and postejaculatory interval in Experiment 2.

On the other hand, the lowest dose of APO (0.2 μg) decreased both ejaculation frequency and intromission ratio when infused into the LV in Experiment 1, and also significantly slowed the rate of intromitting. All of these effects may be interpreted as an impairment of a copulatory mechanism. As noted above, one possible explanation of this pattern of effects is that one or more structures in contact with the ventricles are very sensitive to low doses of APO and interfered with a copulatory mechanism. The MPOA, according to this hypothesis may be less sensitive to low doses, but higher doses activate its facilitative effects. A second possible explanation suggests that both inhibitory and facilitative effects may be exerted by the same structure(s); however, the lowest dose of APO may have activated, primarily, the more sensitive autoreceptors, thereby decreasing the output of endogenous dopamine and impairing copulation. The higher doses may have been sufficient to activate postsynaptic receptors, thereby facilitating the behavior. The lack of impairment produced by infusions into the MPOA may have resulted from an inappropriate choice of dose. Thus, 0.2 μg infused into the LV would have been diluted by cerebrospinal fluid and therefore would have been less concentrated at the active structure(s). The same dose infused directly into the MPOA, then, might have been

sufficiently concentrated to stimulate at least some postsynaptic receptors, thereby cancelling the inhibitory effects of autoreceptor stimulation. The observation that in Experiment 1 the same copulatory measures were affected in opposite directions by the two doses is compatible with this hypothesis. More direct tests of the hypothesis are planned.

The opposite hypothesis has been previously proposed, namely that facilitative effects of dopaminergic agonists on sex behavior are exerted via autoreceptor activation[16,27], while stimulation of postsynaptic receptors impairs copulation[16]. Both reports suggesting that autoreceptor activation reduced ejaculatory threshold rested on assumptions that their low doses of dopamine agonists stimulated only autoreceptors[16,27]. However, convincing evidence that the drug doses they used did indeed stimulate only autoreceptors in the relevant systems was not presented. Their assumption that only autoreceptors were stimulated was based on the fact that their doses were lower than those needed to induce stereotypy and hyperactivity, and may even have been capable of inducing sedation (an effect thought to be mediated by stimulation of autoreceptors), although neither paper presented data on this measure. However, the use of sedation as a general indicator of autoreceptor stimulation has recently been questioned[4]. Furthermore, the dopaminergic systems regulating masculine sexual behavior may be affected by a lower range of doses than those capable of inducing abnormal motor patterns. In the present study the doses of APO were one to two orders of magnitude lower than those that have been infused into the CP or olfactory tubercles to induce contralateral rotation or stereotypy, respectively[19]. Additional evidence consistent with our interpretation is the finding that at the lowest doses administered (systemically), the specific dopamine (D-2) agonist LY163502 inhibited the sexual behavior of male rats, while higher doses facilitated their behavior[17] (Foreman, personal communication). Furthermore, the doses that affected sexual behavior were several orders of magnitude lower than those that induced hypoactivity; and those doses, in turn, were much lower than those that induced hyperactivity or stereotypy. Thus, both masculine sexual behavior and locomotor activity may be characterized by biphasic dose–response curves, with lower doses of dopamine agonists inhibiting the behavior and higher doses increasing it. However, the whole dose–response curve for sex behavior may be displaced towards the low end of the dose range.

Additional evidence against the interpretation that dopamine autoreceptor stimulation facilitates sexual behavior was presented by Ahlenius and Larsson[1]. They administered the enantiomers of 3-PPP (initially thought to be a specific autoreceptor agonist) separately, and found that only the unselective dopamine agonist (+)-3-PPP decreased both ejaculation latency and intromissions per ejaculation. These effects were interpreted as a facilitation of sexual behavior, i.e. increased efficiency of a copulatory mechanism. The (−) enantiomer, which is thought to stimulate dopamine autoreceptors (and block postsynaptic receptors) failed to affect sexual behavior. The lack of an inhibitory effect by the (−) enantiomer appears inconsistent with our interpretation of autoreceptor-induced impairment of a copulatory mechanism. However, the 3 measures on which we observed impairment by our lowest dose (ejaculation frequency, intromission ratio and inter-intromission interval) were not recorded by Ahlenius and Larsson.

The proposal[16] that postsynaptic dopamine receptor stimulation impairs masculine sexual behavior was based largely on the observation that relatively large doses of systemically-administered apomorphine suppressed copulation in sexually vigorous rats. However, large doses of dopamine agonists elicit hyperactivity and stereotyped movements that interfere with sexual behavior[1,24].

Finally, some of the apparent discrepancies concerning doses that facilitate, versus those that impair, sexual behavior may be resolved by noting the particular behavioral measures affected. Perhaps the most commonly reported effect is a decrease in intromission frequency, observed both with dopamine agonists and antagonists, frequently accompanied by a decrease in ejaculation latency, and usually interpreted as a facilitation of sexual behavior[1,14,27,31]. However, none of our intracerebral APO infusions affected intromission frequency. The dopaminergic neurons regulating intromission frequency may be located outside the areas reached by our infusions. Sachs[30] suggested that the corticomedial amygdala and the bed nucleus of stria terminalis may be especially important for control of intromission frequency. Indeed, we have observed decreases in intromission

frequency with cholinergic agonists infused somewhat more laterally in the preoptic area, near the bed nucleus of stria terminalis[22,23]. The reason for the lack of effect on this measure in the present experiments is not clear. Ejaculation frequency, on the other hand, was consistently affected by APO infusions into both the MPOA and LV, being decreased by the lowest dose (in the LV) and increased by the two higher ones. Our observation that the two higher doses of APO decreased ejaculation latency, postejaculatory interval, and (in Experiment 3) intromission latency, is, as expected, the inverse of others' findings that drugs or lesions that decreased dopaminergic activity increased these measures[6,12,26]. Similarly, our interpretation that the slower rate of intromitting observed with our lowest dose resulted from reduced dopaminergic activity is consistent with observations that dopamine antagonists also slowed the rate of intromitting[6,12].

The results reported here suggest that small increases in dopaminergic activity facilitate several measures of a copulatory mechanism. Both decreases in dopaminergic activity (via autoreceptor activation or postsynaptic blockade) and large increases that activate competing behavior patterns may impair this mechanism. Furthermore, the MPOA, and perhaps other structures with direct access to ventricular circulation, may be important in dopaminergic regulation of sexual behavior. However, at the doses tested here, there is no evidence that dopaminergic synapses in the CP and the LS regulate copulation specifically. The importance of the NA in this respect is still uncertain. Multiple sites in the brain, spinal cord and periphery, may interact in dopaminergic regulation of masculine sexual behavior; the dose–response curves, receptor mechanisms and copulatory parameters affected, may be different in these various sites.

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REFERENCES

1 Ahlenius, S. and Larsson, K., Apomorphine and haloperidol-induced effects on male rat sexual behavior: no evidence for actions due to stimulation of central dopamine autoreceptors, *Physiol. Biochem. Behav.*, 21 (1984) 463–466.
2 Ahlenius, S. and Larsson, K., Lisuride, LY-141865, and 8-OH-DPAT facilitate male rat sexual behavior via a non-dopaminergic mechanism, *Psychopharmacology*, 83 (1984) 330–334.
3 Alderson, L.M. and Baum, M.J., Differential effects of gonadal steroids on dopamine metabolism in mesolimbic and nigro-striatal pathways of male rat brain, *Brain Research*, 218 (1981) 189–206.
4 Argiolas, A., Nereu, G., Serra, G., Melis, M.R., Fadda, F. and Gessa, G.L., N-n-propyl-norapomorphine: an extremely potent stimulant of dopamine autoreceptors, *Brain Research*, 231 (1982) 109–116.
5 Barbeau, A., L-DOPA therapy in Parkinson's disease, a critical review of nine years' experience, *Can. Med. Assoc. J.*, 101 (1969) 791–800.
6 Baum, M.J. and Starr, M.S., Inhibition of sexual behavior by dopamine antagonist or serotonin agonist drugs in castrated male rats given estradiol or dihydrotestosterone, *Pharmacol. Biochem. Behav.*, 13 (1980) 57–67.
7 Baum, M.J., Tobet, S.A., Starr, M.S. and Bradshaw, W.G., Implantation of dihydrotestosterone propionate into the lateral septum or medial amygdala facilitates copulation in castrated male rats given estradiol systemically, *Horm. Behav.*, 16 (1982) 208–223.
8 Beach, F.A., Characteristics of masculine 'sex drive'. In M.R. Jones (Ed.), *Nebraska Symposium on Motivation, Vol. 4*, Univ. Nebr. Press, Lincoln, NE, 1956, pp. 1–32.
9 Bjorklund, A., Lindvall, O. and Nobin, A., Evidence of an incertohypothalamic dopamine neurone system in the rat, *Brain Research*, 89 (1975) 29–42.
10 Bowers, M.B., van Woert, M. and Davis, L., Sexual behavior during L-DOPA treatment for Parkinsonism, *Am. J. Psychiat.*, 127 (1971) 1691.
11 Caggiula, A.R., Antelman, S.M., Chiodo, L.A. and Lineberry, C.G., Brain dopamine and sexual behavior: psychopharmacological and electrophysiological evidence for an antagonism between active and passive components. In Usdin, Kopin and Barchas (Eds.), *Catecholamines: Basic and Clinical Frontiers, Vol. 2*, Pergamon Press, New York, 1978, pp. 1765–1767.
12 Caggiula, A.R., Shaw, D.H., Antelman, S.M. and Edwards, D.J., Interactive effects of brain catecholamines and variations in sexual and non-sexual arousal on copulatory behavior of male rats, *Brain Research*, 111 (1976) 321–336.
13 Caggiula, A.R. and Szechtman, H., Hypothalamic stimulation: a biphasic influence on copulation of the male rat, *Behav. Biol.*, 7 (1972) 591–598.
14 Clark, J.T., Stefanick, M.L., Smith, E.R. and Davidson, J.M., Further studies on alterations in male rat copulatory

behavior induced by the dopamine-receptor agonist RDS-127, *Pharmacol. Biochem. Behav.*, 19 (1983) 781–786.
15 Crowley, W.R. and Zemlan, F.P., The neurochemical control of mating behavior. In N.T. Adler (Ed.), *Neuroendocrinology and Reproduction,* Plenum Press, New York, 1981, pp. 451–484.
16 Davidson, J.M., Clark, J.T., Mas, M., Martino, V. and Smith, E.R., Neurotransmitters in the modulation of male rat sexual behavior, *Conference on Reproductive Behavior,* Pittsburgh, PA, 1984, p. 6A.
17 Foreman, M.M. and Hall, J.L., Effects of LY163502, a selective D-2-dopaminergic receptor agonist, on copulatory behavior of male and female rats, *Conference on Reproductive Behavior,* Pittsburgh, PA, 1984, p. 47A.
18 Giantonio, G.W., Lund, N.L. and Gerall, A.A., Effect of diencephalic and rhinencephalic lesions on the male rat's sexual behavior, *J. Comp. Physiol. Psychol.*, 73 (1970) 38–46.
19 Gower, A.J. and Marriott, A.S., Pharmacological evidence for the subclassification of central dopamine receptors in the rat, *Br. J. Pharmacol.*, 77 (1982) 185–194.
20 Gray, G.D., Davis, H.N. and Dewsbury, D.A., Effects of L-DOPA on the heterosexual behavior of male rats, *Eur. J. Pharmacol.*, 27 (1975) 367–370.
21 Heimer, L. and Larsson, K., Impairment of mating behavior in male rats following lesions in the preoptic-anterior hypothalamic continuum, *Brain Research,* 3 (1966/1967) 248–263.
22 Hull, E.M., Bitran, D., Pehek, E.A. and Clemens, L.G., Intracerebral infusions of carbachol affect male sex behavior, *Soc. Neurosci. Abstr.*, 9 (1983) 136.
23 Hull, E.M., Bitran, D., Pehek, E.A., Warner, R.K. and Band, L.C., Intracerebral infusions of oxotremorine affect male sex behavior, *Soc. Neurosci. Abstr.*, 10 (1984) 822.
24 Malmnas, C.O., Monoaminergic influence on testosterone-activated copulatory behavior in the castrated male rat, *Acta. Physiol. Scand.*, Suppl., 395 (1973) 1–128.
25 Malmnas, C.O., Dopaminergic reversal of the decline after castration of rat copulatory behaviour, *J. Endocr.*, 73 (1977) 187–188.
26 McIntosh, T.K. and Barfield, R.J., Brain monoaminergic control of male reproductive behavior. II. Dopamine and the post-ejaculatory refractory period, *Behav. Brain Res.*, 12 (1984) 267–273.
27 Napoli-Farris, L., Fratta, W. and Gessa, G.L., Stimulation of dopamine autoreceptors elicits 'premature ejaculation' in rats, *Pharmacol. Biochem. Behav.*, 20 (1984) 69–72.
28 Pellegrino, L.J., Pellegrino, A.S. and Cushman, A.J., *A Stereotaxic Atlas of the Rat Brain,* 2nd edn., Plenum Press, New York, 1979.
29 Pierini, A.A. and Nusimovich, B., Male diabetic impotence: effects of dopaminergic agents, *Arch. Androl.*, 6 (1981) 347–350.
30 Sachs, B.D., Conceptual and neural mechanisms of masculine copulatory behavior. In T.E. McGill, D.A. Dewsbury and B.D. Sachs (Eds.), *Sex and Behavior: Status and Prospectus,* Plenum Press, New York, 1978, pp. 267–296.
31 Tagliamonte, A., Fratta, W., del Fiacco, M. and Gessa, G.L., Possible stimulatory role of brain dopamine in the copulatory behavior of male rats, *Pharmacol. Biochem. Behav.*, 2 (1974) 257–260.
32 Vogel, H.P. and Schiffter, R., Hypersexuality — a complication of dopaminergic therapy in Parkinson's disease, *Pharmacopsychiatry,* 16 (1983) 107–110.