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Dopaminergic Influences on Male Sexual Behavior of Rhesus Monkeys: Effects of Dopamine Agonists

STEVEN M. POMERANTZ

Department of Physiology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261

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POMERANTZ, S. M. *Dopaminergic influences on male sexual behavior of rhesus monkeys: Effects of dopamine agonists.* PHARMACOL BIOCHEM BEHAV **41**(3) 511–517, 1992.—Previous research has demonstrated that the mixed D_1/D_2 dopamine receptor agonist, apomorphine, and the specific D_2 dopamine receptor agonist, quinelorane, facilitated penile erections and masturbatory behavior of male rhesus monkeys when they were tested in the presence of a female monkey that they could see, hear, and smell but not physically contact. The present study was designed to further examine dopaminergic influences on male sexual behavior of rhesus monkeys by evaluating male copulatory behavior following administration of these dopaminergic agents, as well as a D_1 agonist, CY 208-243. Apomorphine and quinelorane treatment produced dose-dependent effects on male sexual responding. Compared to vehicle-based performance, postejaculatory intervals were shortened following treatment with either 100–200 μg/kg apomorphine or 2.5–10 μg/kg quinelorane. Higher doses of apomorphine or quinelorane did not reliably influence the postejaculatory interval. Ejaculation latency, intromission frequency, and number of thrusts/intromission increased following administration of 200–400 μg/kg apomorphine and 25 μg/kg quinelorane, indicating that dopaminergic stimulation in this dose range raised the monkeys' ejaculatory threshold. No behavioral effects of the D_1 agonist, CY 208-243, were observed in this testing situation. These experiments provide further evidence that dopaminergic mechanisms may play a role in the regulation of male sexual behavior of rhesus monkeys and, in particular, demonstrate that the direction of the effect depends on the dopamine receptor subtype and dosage of the dopamine agonist being administered.

Dopamine Apomorphine Quinelorane CY 208-243 Male sexual behavior Penile erection Rhesus monkeys Primates

RESEARCH has indicated that dopaminergic mechanisms may be involved in regulating male sexual behavior. A number of studies have demonstrated that administration of pharmacological agents that stimulate dopamine synthesis or postsynaptic dopamine receptor sites facilitates both genital and copulatory events associated with male sexual behavior [reviewed in (8)]. Although most of the studies examining dopaminergic influences on male sexual behavior have been conducted on laboratory rats, the initial evidence for dopaminergic involvement in male sexual behavior came from reports that the dopamine precursor, L-DOPA, induced spontaneous penile erections in men with Parkinson's disease (4,11,18,29). More recent clinical studies reported that the dopamine agonist, apomorphine, facilitated penile erections in both normal and impotent men (22,23). Despite these indications of improved erectile potency in human clinical populations following dopaminergic stimulation, it is important to note that in most of the studies conducted to date dopamine agonists generally failed to improve other parameters of male sexual function including the ability to successfully engage in sexual intercourse and achieve ejaculation (5,34).

Studies with nonhuman primates have produced similar results to those in humans. Previous research has demonstrated that the mixed D_1/D_2 dopamine receptor agonist, apomorphine (32), and the specific D_2 dopamine receptor agonist, quinelorane (33), facilitated penile erections and masturbatory behavior of male rhesus monkeys when they were tested in the presence of a female monkey that they could see, hear, and smell but not physically contact. In contrast to these findings of improved sexual functioning following dopaminergic stimulation, other studies with rhesus monkeys failed to observe any facilitation of male copulatory performance following administration of apomorphine (14,15). Instead, apomorphine exerted a dose-dependent inhibition on the males' ability to achieve an ejaculation.

Since recent studies in rats have indicated that dopaminergic agents that differ in their selectivity for D_1 and D_2 receptors may differentially affect male sexual behavior (10,17,20, 26), it is possible that the failure of apomorphine to potentiate parameters of copulatory performance in rhesus monkeys may be due to the fact that apomorphine lacks specificity for D_1 versus D_2 receptors (3,21). In the present study, we investigated the potential of several different dopaminergic agonists that differed in their specificity for D_1 and D_2 receptors to modify male copulatory behavior of rhesus monkeys. These included the mixed D_1/D_2 agonist, apomorphine, the

D_1 agonist, CY 208-243 (24), and the D_2 agonist, quinelorane (13,16).

METHOD

Subjects

Sexually experienced adult male rhesus monkeys were used as experimental subjects. A total of 12 males were used, with 9 males being studied in each experiment. For monkeys that participated in more than one experiment, the period between experiments was always greater than 2 weeks and not more than 1 year. A pool of seven adult female rhesus monkeys served as stimulus females for the three experiments. Females were treated with estradiol cypionate (500 μg/wk, IM). This hormonal regimen maintains blood levels of estradiol around 300 pg/ml while reliably stimulating female sexual behavior (6).

Monkeys were individually housed in rooms that were temperature (18–21°C) and light controlled (12L:12D with lights on at 0700 h). They were fed Purina Monkey Chow supplemented with fresh fruit. Water was available ad lib.

Apparatus

A wire-mesh cage with a clear Lexan front and stainless steel partition dividing the cage into two identical compartments (0.9 × 0.8 × 0.85 m) was used as a testing cage. The floor of the cage was 0.75 m above the floor of the room. During the experiment, experimental males lived on one side of the cage and stimulus females lived on the other side.

Behavioral Testing Procedure

Several days before starting an experiment, the experimental male and stimulus female were moved into either side of a testing cage. Prior to experimental evaluation, experimental males were screened for sexual behavior by removing the partition separating them from the stimulus female and permitting the pair of monkeys to interact for 60 min. Following this period of interaction, the partition was put back in place, separating the two monkeys into their living compartments. Males were selected for use in experiments if they copulated to an ejaculation during this preliminary screening test. On subsequent days, the experimental male was removed briefly (<2 min) from the testing cage, weighed, transferred to a squeeze apparatus, injected with the appropriate experimental treatment, and returned to the testing cage for behavioral testing. Throughout each experiment the male was tested with the same stimulus female. The partition separating the experimental male and stimulus female was removed 10–15 min following injection and put back in place after completion of the test. Male sexual behaviors that were scored included male mount with thrusting, intromission, and ejaculation (7). Nonsexual behaviors were also scored, including grooming and yawning. Finally, instances of stereotypic behavior were noted, such as gnawing of a stainless steel clip-lock and chain attached to the cage. Mating tests lasted a minimum of 30 min and were terminated when any one of the following criteria were satisfied: 1) 30 min after the start of the test with no mount with thrusting, 2) no ejaculation within 30 min of the first mount with thrusting, 3) no mount with thrusting within 30 min of the first ejaculation, 4) no ejaculation within 10 min of reinitiating copulatory behavior after the first ejaculation, 5) second ejaculation if more than 30 min from the start of the test had elapsed. Males and females were maintained in the testing cage until the experiment was completed. Tests were conducted between 1400 and 1730 h.

During each behavior test, the following copulatory behavior measures were derived from the behavioral data: mount latency—time from start of the test to first mount with thrusting or intromission, whichever came first; intromission latency—time from start of the test to first intromission; ejaculation latency—time from first mount with thrusting to an ejaculation; intromission frequency—the number of intromissions preceding ejaculation; mean number of thrusts/intromission—the total number of intromissive thrusts divided by the number of intromissions preceding ejaculation; postejaculatory interval—time from ejaculation to the next mount with thrusting or intromission; and ejaculation frequency—number of ejaculations per test. Maximum scores of 30 min were assigned to males if they failed to exhibit a behavior relevant to a particular latency or interval measure.

Drugs

Apomorphine hydrochloride (Research Biochemicals Inc., Natick, MA) was dissolved in 10% dimethylsulfoxide (Sigma Chemical Co., St. Louis, MO). The D_2 agonist, quinelorane (LY163502, Eli Lilly and Company, Indianapolis, IN), was dissolved in sterile water. The D_1 agonist, CY 208-243 (Sandoz, Basel, Switzerland) was dissolved in 0.1 M tartaric acid. All drugs were freshly prepared immediately prior to injection.

Experiment 1

In a counterbalanced fashion, monkeys were injected (IM) daily with either apomorphine or 10% dimethylsulfoxide vehicle and tested for copulatory behavior 10–15 min later. Each monkey was tested once with a range of apomorphine doses in random order that included 50, 100, 200, and 400 μg/kg apomorphine.

Experiment 2

Monkeys were injected (IM) daily with quinelorane or sterile water vehicle and tested for copulatory behavior 10–15 min later. Each monkey was tested once with a range of quinelorane doses in random order that included 1, 2.5, 5, 10, and 25 μg/kg quinelorane.

Experiment 3

Monkeys were injected (IM) daily with either CY 208-243 or 0.1 M tartaric acid vehicle and tested for copulatory behavior 10–15 min later. Each monkey was tested once with a range of CY 208-243 doses in random order that included 50, 100, 200, and 400 μg/kg CY 208-243.

Data Analysis

In each experiment, one-way analysis of variance (ANOVA) tests were conducted to determine whether repeated testing of the monkeys influenced their behavior in vehicle tests. Since no effects of repeated testing were found for any of the measures of copulatory behavior being assessed, for each measure the males' mean score in vehicle tests was used in subsequent analyses aimed at evaluating the effects of the different drug treatments. For these analyses, repeated measures one-way ANOVA tests were conducted. Analyses yielding significant overall effects were followed by posthoc comparisons using the Duncan multiple range test (36).

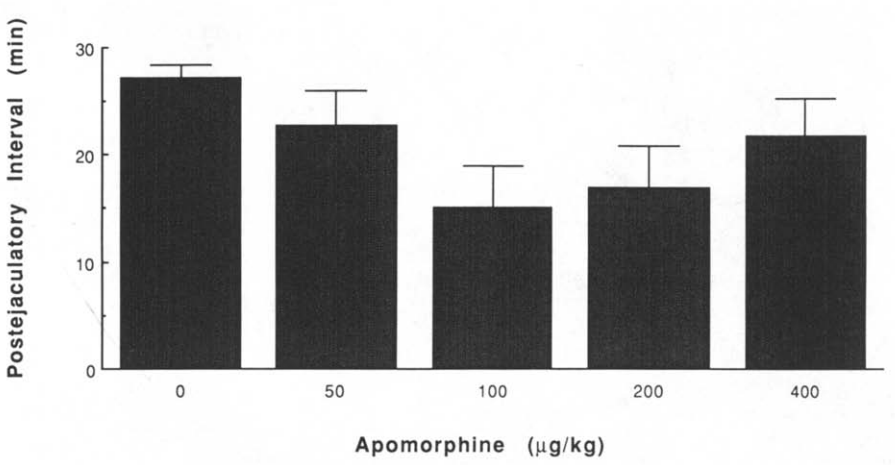

FIG. 1. Mean ± SEM postejaculatory intervals of male rhesus monkeys (n = 9) following administration of varying doses of apomorphine (50–400 μg/kg) or 10% DMSO vehicle.

RESULTS

Experiment 1

As shown in Fig. 1, apomorphine treatment significantly influenced the postejaculatory interval of the monkeys, $F(4,32) = 3.96$, $p < 0.01$. Further analysis revealed that compared to vehicle-based performance monkeys reinitiated copulation significantly sooner after ejaculation when they received 100 or 200 μg/kg apomorphine ($p < 0.01$). The number of monkeys reinitiating copulation following ejaculation varied with the different treatments. Following vehicle administration, five of nine monkeys reinitiated copulation within 30 min of ejaculation, whereas following 50, 100, 200, and 400 μg/kg apomorphine administration the number of monkeys reinitiating copulation within the 30-min postejaculatory period was four, seven, six, and four, respectively.

The effects of apomorphine on other measures of behavior are shown in Table 1. Apomorphine produced dose-dependent increases in mount latency, $F(4,32) = 3.40$, $p < 0.05$, ejaculation latency, $F(4,32) = 23.49$, $p < 0.001$, intromission frequency, $F(4,28) = 5.30$, $p < 0.01$, and number of thrusts/intromission, $F(4,28) = 6.78$, $p < 0.001$. Compared to vehicle treatment, the increases in ejaculation latency, intromission frequency, and number of thrusts/intromission were statistically significant ($p < 0.01$) at 200 and 400 μg/kg apomorphine and the increase in mount latency was statistically significant ($p < 0.01$) at 400 μg/kg apomorphine. One monkey failed to exhibit copulatory behavior following treatment with 200 and 400 μg/kg apomorphine and another monkey copulated but failed to ejaculate following administration of 400 μg/kg apomorphine. In all other tests, monkeys copulated to at least one ejaculation.

Apomorphine also produced a dose-dependent stimulation of stereotypic gnawing behavior, $F(4,32) = 13.49$, $p < 0.001$. This type of oral hyperkinesia was not seen in vehicle tests but was observed in one, two, three, and eight monkeys following treatment with 50, 100, 200, and 400 μg/kg apomorphine, respectively.

Experiment 2

As shown in Fig. 2, quinelorane treatment significantly influenced the postejaculatory interval of the monkeys, $F(5,40) = 4.37$, $p < 0.01$. Further analysis revealed that compared to vehicle-based performance monkeys took significantly less time to reinitiate copulation following an ejaculation when they received 2.5, 5, or 10 μg/kg quinelorane ($p < 0.01$). During vehicle tests, seven of nine monkeys reinitiated copulation within the 30 min allotted following ejaculation. The number of monkeys reinitiating copulation within this time period was six, nine, nine, seven, and four for the different groups receiving 1, 2.5, 5, 10, and 25 μg/kg quinelorane, respectively.

The effects of quinelorane on other measures of behavior are shown in Table 2. Quinelorane treatment had a dose-

TABLE 1

EFFECTS OF APOMORPHINE ON BEHAVIOR OF RHESUS MONKEYS IN COPULATORY BEHAVIOR TESTS

Apomorphine (μg/kg)	Mount Latency (min)	Ejaculation Latency (min)	Intromission Frequency	Thrusts/ Intromission	Stereotypy (min)
0	0.4 (0.1)	5.1 (1.1)	6.4 (1.3)	7.6 (0.9)	0.4 (0.4)
50	1.6 (1.1)	5.1 (1.5)	7.3 (2.0)	7.7 (0.6)	2.7 (2.7)
100	2.4 (1.5)	7.0 (1.9)	9.4 (1.8)	9.0 (1.0)	2.7 (1.8)
200	3.5 (1.0)	11.9 (3.1)*	12.0 (2.6)*	10.2 (1.6)*	11.6 (3.3)
400	8.7 (3.5)*	21.2 (2.6)*	16.8 (3.7)*	12.0 (1.6)*	19.9 (3.8)

Values represent mean (± SEM).
*$p < 0.01$ relative to vehicle-treated monkeys.

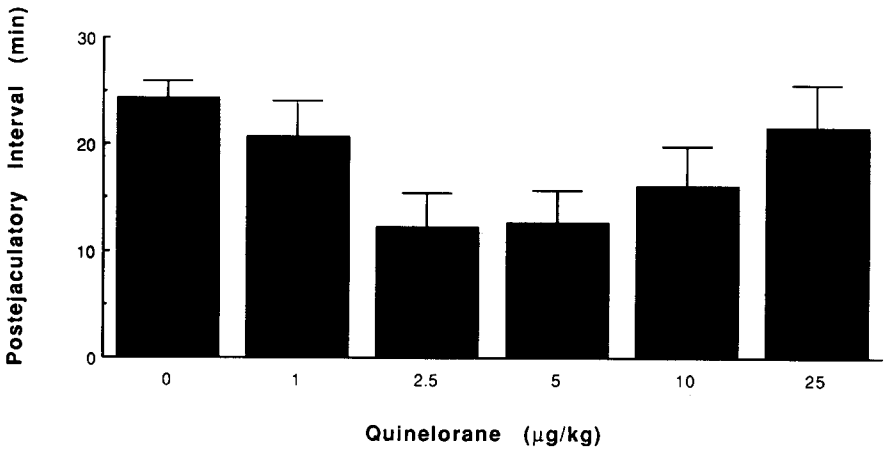

FIG. 2. Mean ± SEM postejaculatory intervals of male rhesus monkeys (n = 9) following administration of varying doses of quinelorane (1-25 μg/kg) or sterile water vehicle.

dependent effect on ejaculation latency, $F(5,40) = 5.32$, $p < 0.001$, intromission frequency, $F(5,30) = 4.207$, $p < 0.001$, and number of thrusts/intromission, $F(5,40) = 5.83$, $p < 0.001$. Compared to vehicle-based performance, monkeys receiving 25 μg/kg quinelorane took longer to ejaculate, had more intromissions prior to ejaculation, and had more thrusts/intromission ($p < 0.01$). Treatment of the monkeys with quinelorane did not alter mount latency, $F(5,40) = 1.14$, ns. Copulatory behavior was observed in every test; however, two males failed to ejaculate when they received 10 and 25 μg/kg quinelorane. In the dose range being employed, quinelorane treatment did not reliably lead to the induction of stereotypic behavior, $F(5,40) = 1.65$, ns. However, some signs of stereotypic behavior were observed in two monkeys following 5 μg/kg quinelorane and four monkeys following 10 and 25 μg/kg quinelorane. In two of the monkeys, the stereotypic behavior involved gnawing, but in the other two monkeys different behaviors were involved, with one monkey walking backward frequently and the other monkey exhibiting continuous side-to-side feinting movements.

Experiment 3

In contrast to apomorphine and quinelorane, the D_1 agonist, CY 208-243, did not affect the length of the monkeys' postejaculatory interval (Fig. 3). Regarding other measures of copulatory performance (see Table 3), monkeys receiving 400 μg/kg CY 208-243 exhibited a marginally significant increase in intromission frequency, $F(4,32) = 2.36$, $p < 0.10$. However, ejaculation latency and the number of thrusts/intromission were not reliably affected by CY 208-243 treatment. No effects of CY 208-243 on nonsexual measures of behavior were observed in this testing situation.

DISCUSSION

In the present study, administration of selected low to moderate doses of either the mixed D_1/D_2 agonist, apomorphine, or the D_2 agonist, quinelorane, markedly reduced the length of time it took male rhesus monkeys to reinitiate copulation following ejaculation (postejaculatory interval). By contrast, no effect of the D_1 agonist, CY 208-243 on postejaculatory interval was observed. These data indicate that the rearousal of sexual behavior following ejaculation is more strongly influenced by D_2 as opposed to D_1 receptor mechanisms. Although previous studies with rhesus monkeys did not find any facilitation of male sexual behavior following administration of apomorphine (14,15), these studies were not designed to examine the postejaculatory behavior of the animals since their total test durations were not long enough, 10 (14) and 30 min (15), respectively, to adequately examine the monkeys' behavior during this period.

In earlier research using a different experimental paradigm, both apomorphine and quinelorane facilitated penile erections

TABLE 2

EFFECTS OF QUINELORANE ON BEHAVIOR OF RHESUS MONKEYS IN COPULATORY BEHAVIOR TESTS

Quinelorane (μg/kg)	Mount Latency (min)	Ejaculation Latency (min)	Intromission Frequency	Thrusts/ Intromission	Steroetypy (min)
0	0.5 (0.2)	5.3 (1.0)	7.5 (1.6)	7.6 (1.1)	0.0 (0.0)
1.0	0.3 (0.1)	5.0 (1.1)	8.6 (2.7)	8.0 (0.9)	0.0 (0.0)
2.5	0.6 (0.4)	3.4 (0.9)	4.9 (1.3)	8.4 (0.8)	0.0 (0.0)
5.0	0.2 (0.1)	4.6 (1.3)	7.2 (3.0)	9.4 (0.7)	1.8 (1.3)
10	1.4 (1.0)	9.2 (4.0)	6.4 (1.5)	10.4 (1.3)*	4.5 (3.0)
25	2.6 (1.9)	13.6 (3.8)*	17.5 (6.1)*	11.9 (1.6)*	2.5 (1.0)

Values represent mean (± SEM).
*$p < 0.01$ relative to vehicle-treated monkeys.

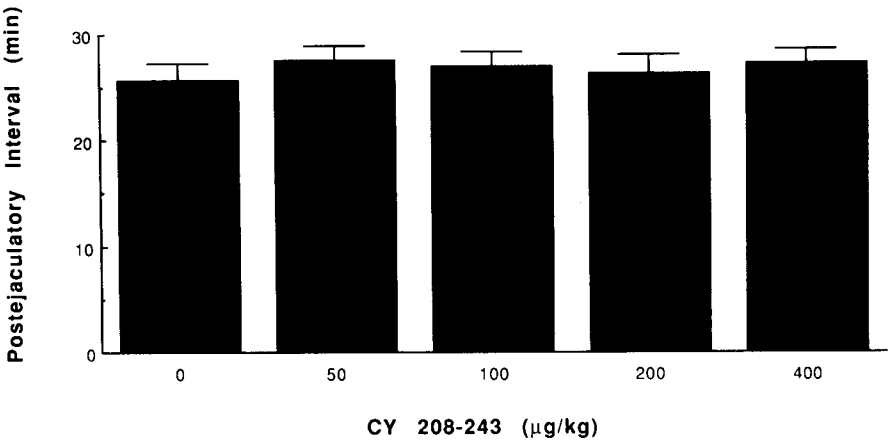

FIG. 3. Mean ± SEM postejaculatory intervals of male rhesus monkeys (n = 9) following administration of varying doses of CY 208-243 (50–400 μg/kg) or 0.1 M tartaric acid vehicle.

and masturbation (32,33). Despite the fact that penile erections could not be reliably recorded and masturbation was rarely observed in the present study, it is still interesting to note that the reduction of the monkeys' postejaculatory refractory period in the present study occurred at the same doses of these compounds that had previously been found in a different experimental context to facilitate penile erections and masturbation. Although these findings point to a potential role for D_2 receptors in mediating penile erection, masturbation, and reinitiation of copulatory behavior following ejaculation, additional studies administering dopamine antagonists will need to be conducted to determine the degree to which the expression of these sexual behaviors depends upon D_2 receptor stimulation. Furthermore, based on our nonhuman primate studies one might predict that erectile potency and male sexual arousal in humans could be potentiated by selected doses of dopamine agonists that possess D_2 receptor activity. However, since the present study dealt only with evaluating sexual behavior in normal sexual functioning male rhesus monkeys it is not clear whether a similar facilitation in sexual behavior could be anticipated following the administration of these agents in sexually dysfunctional populations. Nevertheless, it is important to note in this regard that apomorphine stimulated penile erections in both normal (22) and impotent men (23). Thus, at least in this instance, the effect of apomorphine in individuals exhibiting normal sexual behavior was a valid predictor of its beneficial effect in sexually dysfunctional individuals.

In the present study, high doses of both apomorphine and quinelorane failed to further facilitate copulatory performance. Instead, they appeared to raise the ejaculatory threshold of the monkeys with increases in ejaculation latency, intromission frequency, and number of thrusts/intromission being noted. Previously, apomorphine was found to reduce the percentage of monkeys achieving ejaculation (14). Although such an effect was not observed in the present study, monkeys in the previous study were only allotted 10 min in which to initiate copulation and achieve an ejaculation. If a similar time constraint were applied to the present study, then a dose-dependent reduction in the percent of monkeys achieving an ejaculation would also have been observed with 89, 78, 67, 44, and 0% of the monkeys achieving ejaculation following 0, 50, 100, 200, and 400 μg/kg apomorphine, respectively.

It is not clear whether apomorphine acted in a direct or indirect manner to raise the ejaculatory threshold of the monkeys. At high doses, apomorphine produced a delay in the monkeys' initiation of copulation. This effect coincided with its induction of high levels of stereotypic gnawing behavior. Thus, elicitation of oral hyperkinesia by apomorphine may have interfered with the monkeys' ability to initiate copulation. However, once the monkeys began copulating their ability to continue copulating was not impaired by apomorphine treatment. In fact, monkeys receiving 200 or 400 μg/kg apomorphine exhibited significantly more intromissions before ejaculating. In addition, apomorphine did not affect the rate of copulation (data not shown). These data indicate that apo-

TABLE 3

EFFECTS OF CY 208-243 ON BEHAVIOR OF RHESUS MONKEYS IN COPULATORY BEHAVIOR TESTS

CY 208-243 (μg/kg)	Mount Latency (min)	Ejaculation Latency (min)	Intromission Frequency	Thrusts/ Intromission
0	1.6 (0.4)	5.6 (1.1)	7.6 (1.4)	8.4 (1.0)
50	1.6 (1.0)	6.2 (1.0)	9.5 (2.8)	6.3 (0.6)
100	2.3 (1.4)	6.8 (1.3)	7.1 (0.9)	8.8 (1.5)
200	1.9 (0.8)	6.8 (0.9)	8.1 (1.8)	8.7 (1.3)
400	1.3 (0.4)	9.7 (2.4)	10.9 (2.1)	6.7 (0.9)

Values represent mean (± SEM).

morphine may have acted directly to raise the monkeys' ejaculatory threshold. Evidence with the D_2 agonist, quinelorane, further support the notion that excessive D_2 stimulation may act directly to raise the monkeys' ejaculatory threshold since, in most monkeys, administration of 25 μg/kg quinelorane increased ejaculation latency, intromission frequency, and thrusts/intromission without significantly influencing other competing behaviors that might interfere with the monkeys' ability to copulate and ejaculate.

It is interesting to compare the present results detailing the effects of dopamine agonists on male sexual behavior of rhesus monkeys with similar studies conducted on laboratory rats. In general, administration of apomorphine and quinelorane to rats resulted in the animals achieving ejaculation more rapidly and after fewer intromissions (2,16,28,30), indicating that these agents lower rather than raise the rats' ejaculatory threshold. These findings, as well as the results of other studies in which a similar lowering of the ejaculatory threshold followed central administration of apomorphine (9,19) and quinelorane (20), have led to the suggestion that selective stimulation of D_2 receptors may lower the ejaculatory threshold. Although this hypothesis appears to be well substantiated in rats, D_2 receptor stimulation in rhesus monkeys appears to inhibit rather than facilitate the occurrence of ejaculation. With regard to dopaminergic regulation of the postejaculatory refractory period, although a few studies in rats have reported a lengthening of the postejaculatory period following dopamine antagonist administration (2,25,31) or lesions that disrupted central dopaminergic pathways (12,25), most studies have failed to find any beneficial effects of dopamine agonist administration (2,17,28,30). By contrast, in rhesus monkeys the postejaculatory period was markedly reduced following administration of dopamine agonists that possess D_2 receptor activity.

Despite the fact that CY 208-243 exhibits only a slightly higher binding affinity in vitro for D_1 versus D_2 receptors (24, 27), previous studies have indicated that the behavioral properties of this compound are most closely related to its activity at D_1 receptor sites (1,24,27,35). A similar conclusion can be reached from the present study, in which except for a modest increase in intromission frequency following administration of 400 μg/kg CY 208-243 this compound did not share apomorphine's and quinelorane's ability to alter a number of different measures of copulatory performance. Although the results of the present study do not support a role for D_1 receptor stimulation in regulating male sexual behavior of rhesus monkeys, it should be noted that the lack of effect of CY 208-243 on male rhesus sexual behavior may be due to its inability to further stimulate D_1 receptor populations beyond their endogenous level of activation. In previous studies with primates, CY 208-243 elicited behavioral effects only when it was administered to animals that had received prior treatment with dopamine-depleting agents such as MPTP (24,35). No effect of CY 208-243 was observed in animals receiving this agent alone (35). Thus, to more fully evaluate whether D_1 receptor stimulation plays a role in regulating primate male sexual behavior it may be necessary to administer D_1 agonists after first reducing endogenous levels of dopamine stimulation with agents such as MPTP or specifically reducing endogenous levels of D_1 receptor stimulation with D_1 antagonists.

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