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OPPOSITE INFLUENCE OF MEDIAL PREOPTIC D1 AND D2 RECEPTORS ON GENITAL REFLEXES: IMPLICATIONS FOR COPULATION

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Summary

Dopamine D1 and D2 receptors may synergize with or oppose each other's effects. We suggest that stimulation of D1 and D2 receptors in the medial preoptic area (MPOA) of male rats have opposing effects on genital reflexes. In Experiment 1 a D1 agonist injected into the MPOA increased the number of ex copula erections but decreased the number of seminal emissions. In Experiment 2 a D1 antagonist had the opposite effects (decreased erections and increased seminal emissions), as had a D2 agonist previously. We also suggest that D1 and D2 mechanisms in the MPOA have different thresholds of activation. In Experiment 3 a low dose of the mixed D1/D2 agonist apomorphine increased erections and anteroflexions, an effect blocked by the D1 antagonist. In Experiments 3 and 4 a high dose of apomorphine increased seminal emissions, an effect blocked by the D2 antagonist. Thus, low levels of dopaminergic stimulation may facilitate erections and anteroflexions (controlled by the parasympathetic system and striated muscles) via D1 receptors; higher or more prolonged stimulation may shift to seminal emission (controlled by the sympathetic system) via D2 receptors. This may explain the progression from erectile to ejaculatory mechanisms during copulation.

Copulatory behavior in rats proceeds in several distinct phases. The highly variable precopulatory phase contrasts with the copulatory phase, which proceeds as a stereotyped unit (1). The male mounts at 1 - 2 min intervals; on most of these mounts his pelvic thrusting results in a vaginal intromission. After 6 - 12 intromissions, the male ejaculates. After a 6 - 10 min postejaculatory quiescent phase, the male resumes copulation, and may ejaculate up to 7 times before reaching sexual exhaustion. Several aspects of this copulatory pattern are critical for the successful impregnation of the female (reviewed in 2). At least six intromissions are required for the male to deliver the maximal number of sperm, and at least two, to trigger the progestational state in the female. However, overly prolonged copulation is energetically costly. Thus, it is important to attain an optimal number of intromissions before ejaculation.

Both the integration of locomotor and reflexive patterns within a phase and the optimal sequencing of phases are important for reproductive success. We propose that dopamine (DA) released in several brain areas during copulation (3 - 9) promotes sensorimotor processing in those sites and thereby facilitates the coordination of the functions served by those sites. In addition, rising and/or prolonged DA release may sequentially activate neural processes with different thresholds, thereby triggering the next phase of copulation.

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The MPOA is especially critical for copulation (reviewed in 10). Stimulation of DA receptors in the MPOA facilitated both copulation (11) and ex copula penile reflexes (erections and anteroflexions; 12). Blocking DA receptors in the MPOA impaired copulation (13) and decreased ex copula penile reflexes and also sexual motivation (14). These effects showed both anatomical and behavioral specificity (11, 13, 15). Therefore, one means by which DA in the MPOA may facilitate copulation is by promoting genital reflexes.

Both apomorphine and DA stimulate two classes of DA receptors. D1 receptors stimulate adenylate cyclase; D2 receptors are negatively or not linked to adenylate cyclase (16). Additional DA receptors have recently been cloned; however, they fall within the original two "families" (see 17). We refer here to any of the variants within these two families.

Stimulation of D2 receptors in the MPOA, using quinelorane (LY-163502), lowered the ejaculatory threshold in copula (18) and increased the number of seminal emissions ex copula (19). It also decreased the numbers of penile reflexes. Thus, the ejaculatory phase may be triggered by D2 receptors in the MPOA. The experiments reported here were designed to determine the role of D1 receptors in the MPOA in the control of genital reflexes and to test whether D1 and D2 mechanisms in the MPOA may have different thresholds of activation.

Methods

Subjects. Adult male Long-Evans rats (Harlan Sprague-Dawley/Blue Spruce) were housed individually in a temperature- and humidity-controlled room. Food and water were available ad lib. Lights were off from 11.00 to 21.00 hr. Animals were handled daily so that microinjections could be administered without anesthesia.

Surgical procedure. Animals were anesthetized with ketamine hydrochloride (50 mg/kg) and xylazine hydrochloride (4 mg/kg) and surgically implanted with unilateral stainless steel guide cannulae aimed at the MPOA (AP = +2.4, ML = +.2, DV = -7.0, incisor bar = +5; 20). Details of surgery are in (11).

Drugs. The D1 agonist used in Experiment 1, dihydroxyphenyl-tetrahydrothienopyridine (THP, 21) was generously donated by Dr. David E. Nichols (Purdue University). Doses were 0, 1, or 10 μg in .5 μl sterile water vehicle. In Experiment 2, the D1 antagonist SCH-23390 (22) was a generous gift of Dr. Allen Barnett (Schering-Plough, Bloomfield, NJ). Doses were 0, 1, 3, and 10 μg in 1 μl 10% dimethyl sulfoxide (DMSO, Sigma). In Experiment 3, the mixed agonist apomorphine hydrochloride (Sigma) was administered alone (1 or 10 μg) or each dose together with 5 μg of the D1 antagonist SCH-23390 or 5 μg of the D2 antagonist raclopride (23). Raclopride was a generous gift of Dr. Sven Ahlenius (Astra Pharmaceuticals, Sodertalje, Sweden). The vehicle was .5 μl sterile water with 10% DMSO and .2% ascorbate. For Experiment 4, animals received 10 μg apomorphine, 20 μg raclopride, the combination of 10 μg apomorphine plus 20 μg raclopride, or vehicle (.5 μl of sterile water with .2% ascorbate).

Procedure. All animals received all drug doses in counterbalanced order on weekly tests. Immediately after microinjection, animals were restrained in a supine position. Their penile sheath was retracted and held in the retracted position. Typically, a series of penile erections and anteroflexions began spontaneously within 5 - 10 min after sheath retraction. Occasionally a seminal emission occurred. Details of scoring are in (12). Tests lasted 15 min from the first reflex, or 20 min total if no reflexes occurred. For Experiment 1, the penile sheath was left unretracted for 10 min after the animal was restrained. The presence of scrotal contractions together with appearance of a seminal plug was scored as a seminal emission. Seminal emissions that occurred during the 10 min with unretracted sheath were included in order to increase the baseline and prevent a "floor" effect that had been observed in pilot studies. Erections and anteroflexions were scored only after sheath retraction.

Cannula placements were verified histologically. Data from animals with cannula tips within 0.5 mm of the MPOA were analyzed, using repeated measures analyses of variance and Newman-Keuls post-hoc tests. Data from 16, 34, 20, and 20 animals were included in Experiments 1, 2, 3, and 4, respectively. Analyses of reflex latency were based on animals that

exhibited reflexes in all four treatments in Experiments 1 (N=8) and 4 (N=10). Because only 2 animals met that criterion in Experiments 2 and 3, those with reflexes on all but one test were included, with harmonic means for the missing data. Animals meeting this criterion were 12 for Experiment 2, and 8 for Experiment 4.

Results

Experiment 1. Effects of a D1 agonist on ex copula genital reflexes.
The D1 agonist THP increased the number of erections ($F(2,30)=3.35$, $p<.05$; Fig. 1A) and decreased the number of seminal emissions ($F(2,30)=3.36$, $p<.05$; Fig. 1B). Thus, stimulation of D1 receptors in the MPOA enhanced erectile processes, which are under parasympathetic and striated muscle control (reviewed in 10), and inhibited seminal emission, which is sympathetically controlled. Reflex latency was not significantly affected. These results are the opposite of those of the D2 agonist quinelorane, which had previously decreased erections and increased seminal emissions ex copula (19) and lowered ejaculatory threshold in copula (18).

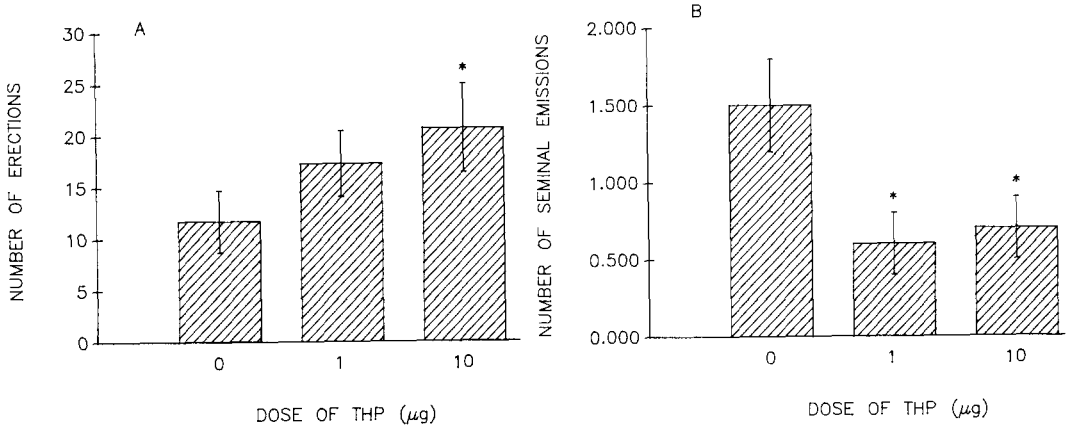

FIG. 1
Effects of a D1 agonist (THP) on ex copula reflexes. (A) THP (10 μg) increased the number of erections. (B) THP (1 and 10 μg) decreased the number of seminal emissions. THP, dihydroxyphenyl-tetrahydrothienopyridine. *$p<.05$, compared to vehicle.

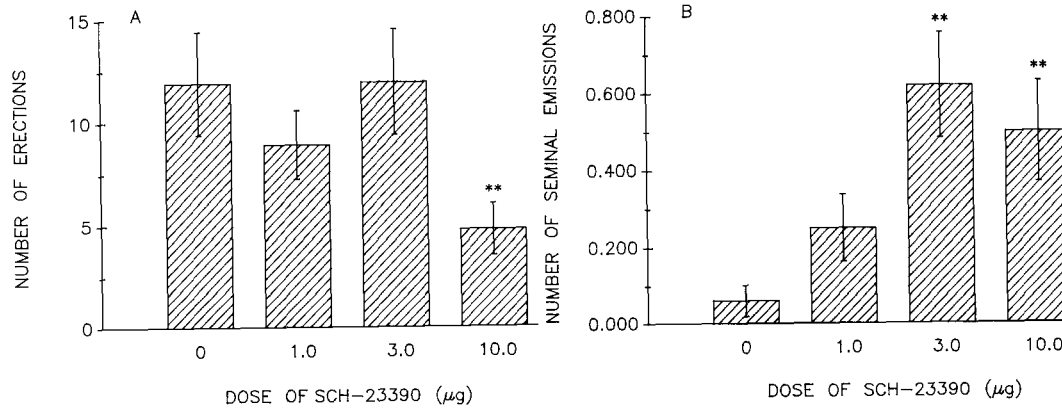

FIG. 2
Effects of a D1 antagonist (SCH-23390) on ex copula genital reflexes. (A) SCH-23390 (10 μg) decreased the number of erections. (B) SCH-23390 (3 and 10 μg) increased the number of seminal emissions. **$p<.01$, compared to vehicle.

Experiment 2. Effects of a D1 antagonist on ex copula genital reflexes.
If endogenous DA acts on D1 receptors to elicit erection and suppress ejaculation, then blocking those receptors should produce the opposite effects. As predicted, the D1 antagonist SCH-23390 decreased erections ($F(3,99)=3.15$, $p<.05$; Fig. 2A) and increased seminal emissions ($F(3,99)=5.32$, $p<.005$; Fig. 2B). Anteroflexions were also decreased (Vehicle: $2.6\pm.7$; 1 μg: $1.8\pm.5$; 3 μg: $1.7\pm.5$; 10 μg: $0.4\pm.2$; $F(3,99)=3.4$, $p<.03$). Reflex latency was not significantly affected. These data confirm the importance of endogenous DA in promoting erectile mechanisms and inhibiting ejaculatory ones. Thus, D1 and D2 receptors in the MPOA appear to exert opposing influences on genital reflexes.

Experiment 3. Effects of the mixed agonist apomorphine, alone or with a D1 or D2 antagonist.
A possible functional explanation for the opposing D1 and D2 influences may be that they have different thresholds of activation. The erectile mechanism is critical throughout the copulatory phase, whereas ejaculation is elicited later. Different levels of dopaminergic stimulation may be required to elicit these two responses. To test this hypothesis, a low (1 μg) and a high (10 μg) dose of the mixed agonist apomorphine were administered either alone or together with a D1 (5 μg SCH-23390) or a D2 (5 μg raclopride) antagonist. Vehicle injections provided a comparison.

The low dose of apomorphine increased the total number of erections plus anteroflexions ($F(6,114)=3.875$, $p<.002$; Fig. 3A). This increase was completely blocked by the D1 antagonist, suggesting that it was mediated largely by D1 receptors. The high dose of apomorphine alone did not significantly increase erections and anteroflexions; however, when it was administered together with the D2 antagonist (removing D2 inhibition), the number of erections and anteroflexions increased dramatically. Therefore, the ineffectiveness of the high dose of apomorphine alone resulted from its simultaneous stimulation of D1 receptors, which facilitated erections and anteroflexions, and of D2 receptors, which opposed that facilitation. A similar pattern of effects was seen when erections and anteroflexions were analyzed separately (Erections: $F(6,114)=3.881$, $p<.002$; Anteroflexions: $F(6,114)=2.431$, $p<.05$).

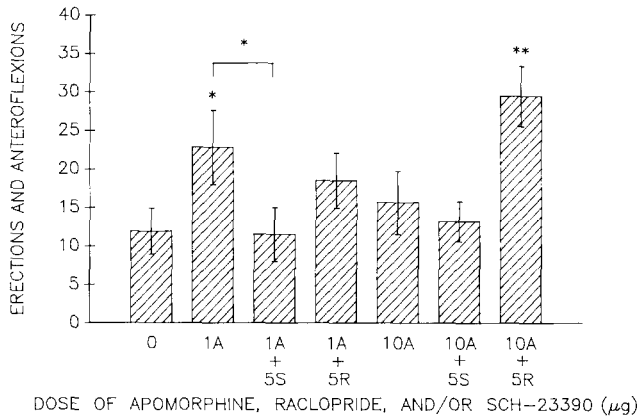

FIG. 3A
Effects of low and high doses of apomorphine, alone or with a D1 or D2 antagonist, on erections and anteroflexions. The low dose (1 μg) of apomorphine (1A) increased total erections plus anteroflexions. Addition of 5 μg of the D1 antagonist SCH-23390 (1A+5S) blocked this effect. The high dose (10 μg) of apomorphine alone (10A) did not facilitate this measure; addition of 5 μg of the D2 antagonist raclopride to apomorphine (10A+5R) significantly increased erections plus anteroflexions. A, apomorphine; S, SCH-23390; R, raclopride. *$p<.05$, **$p<.01$, compared to vehicle, except for bracketed comparison.

The high, but not the low, dose of apomorphine increased the number of seminal emissions ($F(6,114)=3.330$, $p<.005$; Fig. 3B). The addition of the D1 antagonist to the high dose of apomorphine tended to increase seminal emissions even more than did apomorphine alone (see also Fig. 2B). Addition of the D2 antagonist partially inhibited apomorphine's effect (10 μg apomorphine + 5 μg raclopride was not significantly different from vehicle or from 10 μg apomorphine alone). Thus, seminal emission is elicited by D2, and opposed by D1, receptors.

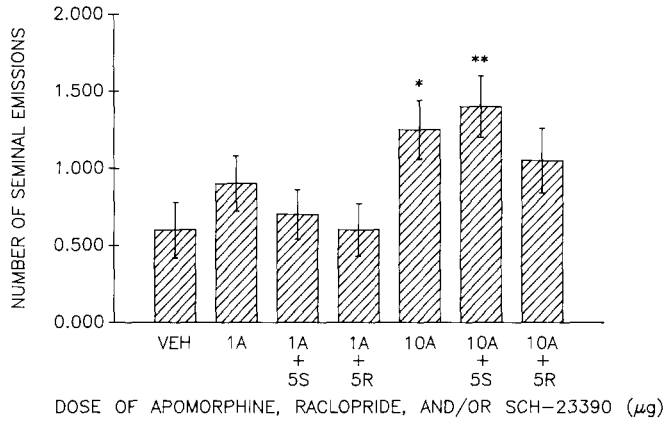

FIG. 3B

Effects of low and high doses of apomorphine, alone or with a D1 or D2 antagonist, on seminal emissions. The high dose (10 μg) of apomorphine increased the number of seminal emissions. Addition of 5 μg of the D1 antagonist SCH-23390 resulted in slightly more seminal emissions than with apomorphine alone. Addition of 5 μg of the D2 antagonist raclopride (10A+5R) reduced the effectiveness of apomorphine. A, apomorphine; S, SCH-23390; R, raclopride. *$p<.05$, **$p<.01$, compared to vehicle.

Both 1 and 10 μg apomorphine decreased reflex latency ($F(6,42)=2.34$, $p<.05$; Fig. 3C). Both the D1 and D2 antagonists partially blocked this decrease (i.e., neither 1 μg apomorphine + 5 μg SCH-23390 nor 1 μg apomorphine + 5 μg racloparide differed significantly from vehicle or from 1 μg apomorphine alone). Thus, both D1 and D2 receptors may contribute to the dopaminergic reduction of reflex latency. Neither antagonist blocked the effects of the high dose of apomorphine, possibly because of the relatively low dose of the antagonists.

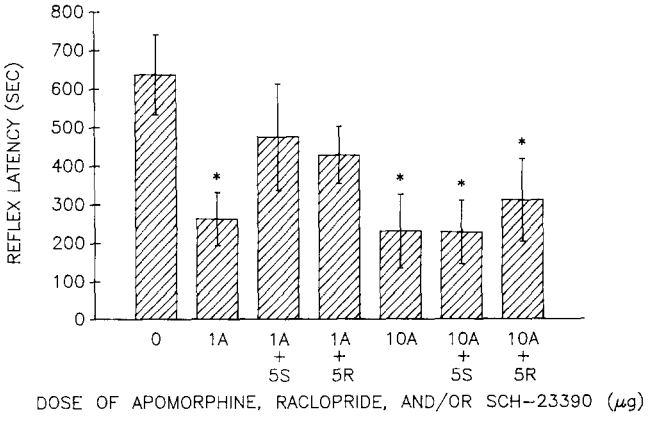

FIG. 3C

Effects of low and high doses of apomorphine, alone or with a D1 or D2 antagonist, on reflex latency. Both 1 and 10 μg apomorphine decreased reflex latency. Both antagonists partially blocked the effects of the low dose, but not of the high dose. *$p<.05$ compared to vehicle.

Experiment 4. Effects of apomorphine and a higher dose of the D2 antagonist.
The failure of the D2 antagonist to block completely the effects of 10 μg apomorphine on seminal emissions may have been due to the relatively low dose (5 μg) of the antagonist. Therefore, additional animals received 10 μg apomorphine, 20 μg raclopride, apomorphine plus raclopride, or vehicle. Neither apomorphine nor raclopride alone affected erections and anteroflexions. As before, addition of raclopride to apomorphine significantly increased performance on this measure, so that this group exhibited significantly more erections and anteroflexions than when they received vehicle alone ($F(3,57)=3.83$, $p<.02$; Fig. 4A). As before, 10 μg apomorphine increased seminal emissions; this effect was completely blocked by the higher dose of raclopride ($F(3,57)=25.16$, $p<.000001$; Fig. 4B). These data confirm the positive influence of D2 receptors in the MPOA on seminal emission.

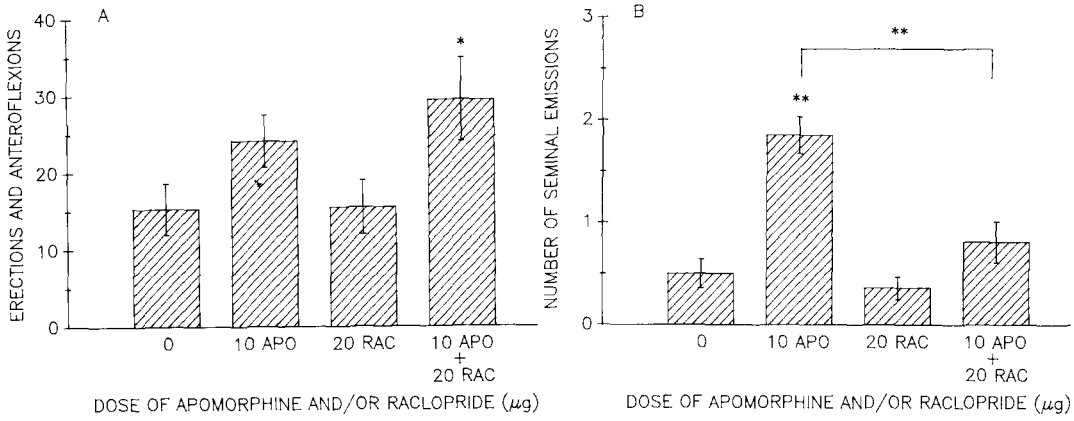

FIG. 4A and 4B

Effects of the high dose of apomorphine, the D2 antagonist raclopride, and their combination on genital reflexes. (A) The combination of apomorphine (10 μg) and raclopride (20 μg) increased the number of erections plus anteroflexions. Neither apomorphine nor raclopride alone was effective. (B) Apomorphine alone increased the number of seminal emissions. This increase was blocked by raclopride. 0, Vehicle; APO, apomorphine; RAC, raclopride. *$p<.05$, **$p<.01$, compared to vehicle, except for bracketed comparison.

As in Experiment 3, 10 μg apomorphine decreased reflex latency ($F(3,27)=4.95$; Fig. 4C). However, 20 μg raclopride failed to block this effect.

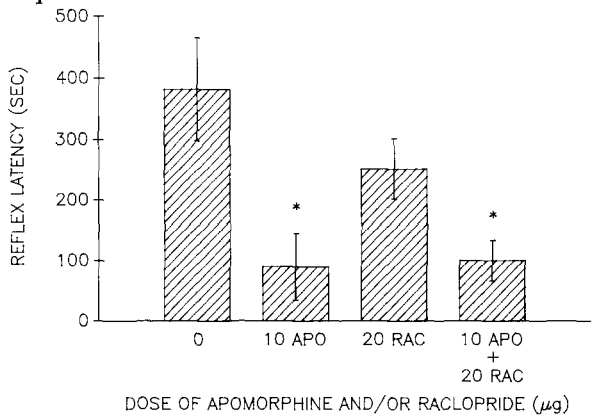

FIG. 4C

Effects of the high dose of apomorphine, the D2 antagonist raclopride, and their combination on reflex latency. Apomorphine alone decreased latency; raclopride failed to block this effect. *$p<.05$ compared to vehicle.

Discussion

These data indicate that D1 receptors in the MPOA facilitate the occurrence of erections and anteroflexions and inhibit seminal emission. We previously reported that D2 receptors in the MPOA have the opposite effects, namely decreased erections and anteroflexions and increased seminal emissions (19). Furthermore, D1 mediated erection and anteroflexion and D2 mediated seminal emission appear to have different thresholds of activation.

Although the timing and effective stimuli for ex copula genital reflexes differ from those of reflexes in copula (24), there are notable similarities in their neural control (reviewed in 10). The relevance for copulation of the D1 and D2 mediated effects reported here is suggested by our previous demonstration that the D2 agonist quinelorane (LY-163502) and the D1 antagonist SCH-23390 delayed and slowed copulation, and also lowered the threshold for ejaculation (18). The delay and slowing of copulation may have resulted from inhibition of erectile potential by the D2 agonist (19) and the D1 antagonist (Experiment 2). Thus, either stimulating D2 receptors or blocking D1 receptors may delay and slow copulation by inhibiting erectile potential. The lowering of ejaculatory threshold (decreased intromissions preceding ejaculation) may have been related to D2 mediated facilitation of seminal emission (19) or the removal of D1 mediated inhibition by the D1 antagonist (Experiment 2). We have recently observed a speeding of copulatory rate by the D1 agonist THP (in preparation), which may be related to an increase in erectile potential (Experiment 1). Therefore, while some parameters of ex copula genital reflexes differ from those of in copula reflexes, the biochemical factors that influence their ease of elicitation may be common to the two situations.

In contrast to the opposing effects of D1 and D2 stimulation on numbers of genital reflexes, stimulation of these subtypes may produce synergistic effects on reflex latency. Both D1 and D2 antagonists partially blocked the reduction in reflex latency by the low dose of apomorphine in Experiment 3. On the other hand neither antagonist blocked the effects of the high dose of apomorphine on reflex latency. The partial inhibition of the effects of the low dose of apomorphine was observed with a 5-fold higher concentration of antagonist than of agonist. A similar ratio was not used for the high dose of apomorphine because of the absolute concentration that would have been required. However, a 2-fold excess of antagonist in Experiment 4 was sufficient to block the increase in seminal emissions. Sachs and Bitran (25) proposed that two separate spinal mechanisms regulate penile reflexes. A "starter" mechanism governs the onset of erections, whereas a "generator" mechanism increases their number. Furthermore, separate supraspinal mechanisms provide tonic inhibition of the "starter" and facilitation of the "generator." We previously observed that MPOA injections of the D2 agonist quinelorane decreased both the latency and the number of erections and anteroflexions (19). Furthermore, quinelorane's reduction of reflex latency was observed at a lower dose than its facilitation of seminal emission or its inhibition of erections and anteroflexions. The greater sensitivity of D2 effects on latency than on numbers of reflexes is consistent with the relative ineffectiveness of the antagonists to block the decrease in reflex latency by the high dose of apomorphine in Experiments 3 and 4; it would be more difficult to block the effect of an agonist if only a small amount of the agonist were sufficient to produce the full effect. We suggest that D2 receptors in the MPOA, perhaps with permissive or enabling contributions of D1 receptors, remove the tonic supraspinal inhibition of the "starter" mechanism of Sachs and Bitran (1990). However, maximum activation of erections and anteroflexions (Sachs and Bitran's proposed "generator") may require D1 mediated facilitation of parasympathetic and striated muscle mechanisms.

The differential effects of low and high doses of apomorphine in the MPOA may reflect similar functions of endogenous DA during copulation. Catecholamine release in the MPOA, measured voltammetrically, increased as soon as a male rat confronted a receptive female (26). The signal remained elevated until the first ejaculation, after which it fell sharply. During the postejaculatory period the signal increased gradually, and the male resumed copulation when it reached a certain level. The catecholamine signal probably reflected increased DA, rather than norepinephrine (NE), since others have observed copulation-induced increases in DA and/or its metabolites, but not NE, using high performance liquid

chromatography (HPLC) analyses of MPOA tissue punches (5, 6) or microdialysis (4). Early DA release may enhance erections and anteroflexions via D1 receptors and suppress seminal emission, thereby preventing "premature ejaculation." Continued or increased DA release (or perhaps co-release of a neuromodulator that increases the effectiveness of DA) may shift from parasympathetically elicited erection to sympathetically induced ejaculation.

Both low and high doses of apomorphine probably acted postsynaptically. We have previously shown that very low doses of apomorphine (.1 and .2 μg) inhibited copulation, whereas higher doses (.5 to 10 μg) facilitated copulation (11, 27). The inhibitory effects of the very low doses were blocked by 6-hydroxydopamine (6-OHDA) lesions of DA terminals in the MPOA (27). However, the facilitative effects of the higher doses were not affected by these lesions. This suggests that the inhibitory effects of the low doses, which were abolished by 6-OHDA lesions, resulted from a decrease in DA release, in turn caused by stimulation of the more sensitive presynaptic autoreceptors. On the other hand, the facilitation by the higher doses was mediated by postsynaptic receptors. All doses used in the current experiments were within the range that we previously suggested act on postsynaptic receptors.

Most behavioral effects of DA stimulation require concurrent stimulation of D1 and D2 receptors for maximal effects (reviewed in 28, 29). Exceptions are vacuous chewing and grooming, both of which were elicited by D1, and opposed by D2, receptors (30, 31). However, D1 and D2 receptors in the MPOA are not only not coupled, they actually produce opposite effects on genital reflexes.

We believe this to be the first report of opposing effects of the two receptor subtypes on separate but related normal behavioral functions. One hypothesis may explain the functional significance of synergistic and opposing D1 and D2 functions. Different thresholds of activation would allow for the expression of first one effect, and then either a more intense or an opposite effect, elicited by the other subtype (32, 33). Factors that may affect the threshold of activation include the relative numbers, affinity states, and/or efficacy of D1 and D2 receptors. In any case, low levels of DA may be sufficient to stimulate one mechanism, and higher levels or prolonged release of DA, or co-release of a neuromodulator, might then stimulate the other mechanism, which could either summate with or oppose the effects of the first. Thus, variations in DA release could provide a "switch" that activates a new phase of behavior. We suggest that this is an important means of controlling the balance of autonomic influence on the genitals and of shifting from the copulatory phase to the ejaculatory/postejaculatory phase.

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