Pharmacology Biochemistry & Behavior, Vol. 34, pp. 453–458. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

Quinelorane (LY163502), a D2 Dopamine Receptor Agonist, Facilitates Seminal Emission, but Inhibits Penile Erection in the Rat

DANIEL BITRAN,[1] JAMES T. THOMPSON,* ELAINE M. HULL* AND BENJAMIN D. SACHS

*Department of Psychology, University of Connecticut, Storrs, CT 06269-1020 and *Department of Psychology, State University of New York at Buffalo, Amherst, NY 14260*

Received 7 February 1989

BITRAN, D., J. T. THOMPSON, E. M. HULL AND B. D. SACHS. *Quinelorane (LY163502), a D2 dopamine receptor agonist, facilitates seminal emission, but inhibits penile erection in the rat.* PHARMACOL BIOCHEM BEHAV **34**(3) 453–458, 1989.—Dopaminergic compounds have been shown to facilitate male sexual responses in various contexts. We investigated the effects of a specific D2 dopamine receptor agonist, quinelorane (LY163502), on sexual responses elicited in the restrained supine male rat (i.e., ex copula reflex tests). Penile erections, evoked by retraction of the penile sheath, were inhibited by systemic administration of 10 μg/kg quinelorane; however, the occurrence of seminal emission was dramatically increased. A smaller dose of 0.25 ng/kg was without effect. In a second experiment, intracranial microinjection of quinelorane was followed by ex copula reflex tests. The medial preoptic area (MPOA) has been previously implicated in the dopaminergic regulation of male copulatory behavior (4, 18, 25). The effects of an intra-MPOA injection of quinelorane on seminal emission and erectile responses were similar to those observed following systemic administration. These results are consistent with the hypothesis that DA receptors in the MPOA are important in the regulation of male sexual behavior and suggest that D2 receptors in the MPOA may decrease ejaculatory threshold while inhibiting erectile mechanisms.

Penile erection Seminal emission Dopamine D2 receptor Quinelorane LY163502 Medial preoptic area

BASIC research on the effects of various drugs on sexual behavior has raised the possibility that sexual dysfunctions may be subject to pharmacotherapeutic approaches. Among the most studied compounds are dopaminergic agents, as they have been shown to facilitate the expression of sexual responses in various species, including human (2, 20, 21, 31) and nonhuman primates (11,26). The sexual behavior of male rats is similarly facilitated by the systemic administration of various dopaminergic compounds [reviewed in (3)]. Nonselective stimulation of D1 (positively linked to adenylate cyclase) and D2 (negatively or not linked to adenylate cyclase) dopamine receptors by apomorphine reliably reduces the number of intromissions to ejaculation (i.e., ejaculation threshold). Recent studies have demonstrated that selective activation of D2 receptors by quinelorane (LY163502) facilitated ejaculatory behavior when systemically administered in the nanogram to microgram range (14).

Studies investigating the neural substrate(s) mediating the effects of dopamine (DA) agonists on sexual behavior have shown that microinjections of apomorphine into the medial preoptic area (MPOA) facilitated sexual behavior (4, 18, 25). Moreover, intra-MPOA administration of the DA receptor antagonist, cis-flupenthixol, at a dose devoid of intrinsic activity, attenuated the facilitative effects of apomorphine and inhibited sexual behavior at higher doses (25). A microinjection of quinelorane, but not SKF-82526 (a D1 agonist), into the MPOA also reduced the number of intromissions preceding ejaculation (19), as had systemically administered quinelorane (14). These observations support the contention that the facilitative effects on ejaculatory behavior in copula result, in part, from activation of D2 DA receptors in the MPOA. Thus, the MPOA, an area that is innervated by a small dopaminergic projection from periventricular incertohypothalamic neurons (5) and known to be important for

[1]Requests for reprints should be addressed to Daniel Bitran, University of Rochester, Department of Psychology, River Campus, Rochester, NY 14627.

the mediation of male sexual behavior [reviewed in (17)], is implicated in the effects of dopaminergic agents on male copulatory behavior.

Other tests of sexual potency have been devised that eliminate the potential influence of a receptive female. In ex copula reflex tests, penile erections are evoked by retracting the preputial sheath and maintaining the sheath in a retracted position (16). Seminal emissions are infrequently observed in control conditions. The effects of dopaminergic compounds on these "reflexive" genital events have recently been described (23). The systemic administration of apomorphine increased the incidence of seminal emission and facilitated penile erections with low doses (100–300 μg/kg), but with a higher dose (500 μg/kg), apomorphine inhibited penile erections while increasing seminal emissions. These effects were blocked by cis-flupenthixol, but not by domperidone, a DA receptor antagonist that does not readily gain entry into the brain.

In the following experiments, we investigated the effects of quinelorane, a specific D2 receptor agonist (6,29), on ex copula penile responses evoked in the restrained supine rat. In Experiment 1, the effects of systemically administered quinelorane on penile responses were examined. In Experiment 2, the effects of quinelorane injected into the MPOA on ex copula penile responses were assessed. Thus, the following experiments were conducted in order to determine whether quinelorane produced analogous (i.e., biphasic dose-dependent) effects on sexual responses elicited ex copula, as had been previously reported for copulatory behavior (14), and to test the hypothesis that the effects following systemic administration of quinelorane were mediated in part, by D2 DA receptors in the MPOA.

METHOD

Animals and Housing

Male rats (Long-Evans strain) weighing 400–500 g were purchased from Blue-Spruce Farms (Altamont, NY). Each animal was housed individually during the experimental period in a temperature-controlled (23°C) colony room with a 14-hr light, 10-hr dark cycle and allowed free access to food and water.

Experimental Protocol

All animals were screened for genital responses while restrained in a supine position. Only males displaying a high level of behavioral responsiveness were chosen for study. In Experiment 1, fifteen males randomly received a subcutaneous injection of 0, 0.25 ng/kg, or 10 μg/kg of quinelorane, dissolved in 0.9% saline (0.1 ml/100 g body weight) in a counter-balanced repeated measures design. The low dose was previously shown to decrease the number of sexually active males and to increase the ejaculation latency of animals that did copulate, whereas the higher dose decreased the ejaculation threshold (14). Ten minutes following the injection, males were tested for ex copula penile responses. In Experiment 2, seventeen males bearing an unilateral cannula aimed at the medial preoptic area (MPOA) were administered a 0.5 μl injection of sterile 0.9% saline, and in a separate test, 10 μg of quinelorane in 0.5 μl saline. Immediately following intracranial injections, males were tested for ex copula penile reflexes. Intracranial cannulation procedure and coordinates were as described previously (18). At the completion of behavioral testing, cannula placement was verified histologically with cresyl violet Nissl stain.

Behavioral Test

Ex copula penile reflex tests were conducted in the dark phase of the light cycle. Animals were placed in a supine position with their upper bodies inside a cylinder and restrained with pieces of masking tape over the torso, hindlimbs, and tail. The preputial sheath was retracted and the occurrence and time of the following responses were noted (23): *seminal emission*, a discharge of seminal fluid often accompanied by several brief penile erections and rostral movement of the testes within the scrotal sac; *glans erections of varying intensities: E1*—reddening and distention of the base of the glans, *E2*—tumescence of the base and tip of the glans, and *cups*—intense erection of the glans resulting in intense flaring of the tip of the glans. From this record, other measures were derived: *latency to glans erection*, measured as time from sheath retraction to the first erection (erections that accompanied a seminal emission were not included in this measure); *number of reflex clusters*, defined as a series of erections separated by 15 sec or less. A test was terminated 20 min after the first response or 20 min after sheath retraction if no responses occurred.

Statistics

Statistical analyses of parametric data included one-way analysis of variance with repeated measures and post hoc Newman-Keuls pair-wise comparisons (Experiment 1) and paired *t*-tests (Experiment 2). Nonparametric proportional data were analyzed by Cochran Q-test (Experiment 1) followed by McNemar test (Experiments 1 and 2). Only animals that responded following vehicle injections were included in the results. Statistical significance was attributed when $p<0.05$.

RESULTS

Experiment 1

Systemic administration of quinelorane dramatically altered genital responses observed in the supine male rat (Fig. 1). Analysis of proportional data indicated that quinelorane significantly affected the number of animals displaying a seminal emission, $Q(2)=14.1$, $p<0.001$. Post hoc comparisons revealed that the 10 μg/kg dose of quinelorane increased the number of animals with a seminal emission (11/11) relative to a vehicle [2/11, $\chi^2(1)=7.1$, $p<0.01$] or a 0.25 ng/kg injection of quinelorane [4/11, $\chi^2(1)=5.1$, $p<0.05$]. As shown in Fig. 1A, quinelorane increased the mean number of seminal emissions at a dose of 10 μg/kg, $F(2,20)=29.63$, $p<0.0001$.

In contrast to the facilitative effects on seminal emission, the total numbers of glans erections and reflex clusters were decreased by quinelorane, $F(2,20)=6.64$, $p<0.006$; $F(2,20)=10.75$, $p<0.001$, respectively (Fig. 1C and D). Pair-wise comparisons demonstrated that these measures of erectile potential were inhibited only by the 10 μg/kg dose. The inhibitory effect of quinelorane on the number of glans erections was due to a differential inhibition on the number of mild erections (i.e., E1s), $F(2,20)=7.31$, $p<0.004$. Stronger erections (i.e., E2s and cups) and the latency to the first erection were not significantly affected by the systemic administration of quinelorane (Fig. 1B and C).

Experiment 2

The effect of an intra-MPOA injection of quinelorane on genital responses is depicted in Fig. 2. As seen following systemic administration, an injection of 10 μg of quinelorane into the MPOA dramatically increased the number of animals displaying a seminal emission [vehicle = 4/16, quinelorane = 13/16; $\chi^2(1)=5.82$, $p<0.02$] and increased the mean number of seminal emissions observed, $t(15)=4.04$, $p<0.001$ (Fig. 2A). In addition, the numbers of total glans erections, $t(15)=4.7$, $p<0.0001$, and reflex clusters, $t(15)=4.49$, $p<0.0005$, were decreased by

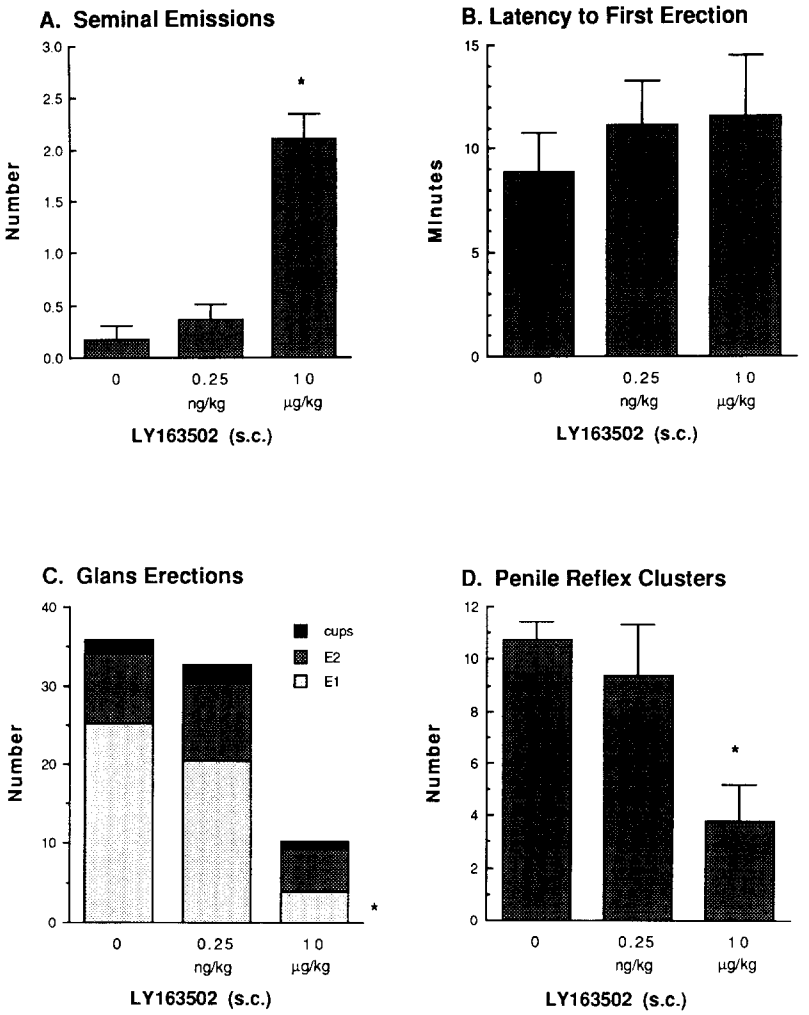

FIG. 1. (A) Number of seminal emissions, (B) latency to first erection, (C) number of glans erections, and (D) number of penile reflex clusters following the systemic administration of LY163502. Data are expressed as mean ± SEM. *Denotes a significant difference from control values; see text for p-values.

quinelorane, relative to a vehicle injection (Fig. 2C and D). Further analysis revealed that the effect of quinelorane on erectile responses was due to an inhibition of E1s, $t(15) = 3.31$, $p<0.005$, E2s, $t(15) = 4.03$, $p<0.001$, and cups, $t(15) = 2.09$, $p<0.05$ (Fig. 2C). Reflex latency was significantly decreased by an intra-MPOA injection of quinelorane, $t(15) = 2.42$, $p<0.03$ (Fig. 2B).

DISCUSSION

Similar results were produced by quinelorane when injected systemically or directly into the MPOA. Seminal emission was facilitated, while the numbers of erections and of penile reflex clusters were decreased. The only measure that was not similarly affected with the two routes of administration was latency to the first penile response, which was unaffected by systemic injections and paradoxically shortened by MPOA injections. The explanation for the shortened latency, suggestive of a facilitation of penile reflexes, coupled with a reduction in the number of erections, an inhibition, is not clear. It is possible that the decrease in latency may have been due at least partially to a facilitation by a preceding seminal emission. A preceding ejaculation in copula has been shown to facilitate the onset of subsequent ex copula erections (27). There was a trend for the latency to the first reflex to be shorter after a seminal emission in these experiments; however, this trend was not statistically reliable.

The higher systemic dose of quinelorane (10 µg/kg, SC) was chosen because it was in the range of doses previously shown to decrease the number of mounts and intromissions preceding ejaculation, as well as to decrease the latency to ejaculation (14). The intracranial dose (10 µg/0.5 µl) was chosen because it too was previously found to decrease the number of intromissions preceding ejaculation after intra-MPOA injections (19). Surprisingly, however, intracranial administration of quinelorane resulted in an increased latency to the first intromission (19). The lower systemically administered dose (0.25 ng/kg, SC) was chosen because it had been shown to raise ejaculatory threshold in copula, perhaps by preferentially stimulating inhibitory autoreceptors (14). However, this dose was without effect in the present tests of ex copula penile responses.

Our results are remarkably similar to previously published reports on the effects of RDS-127, a mixed dopamine/serotonin (5-HT_{1A}) receptor agonist (8), on ex copula penile responses.

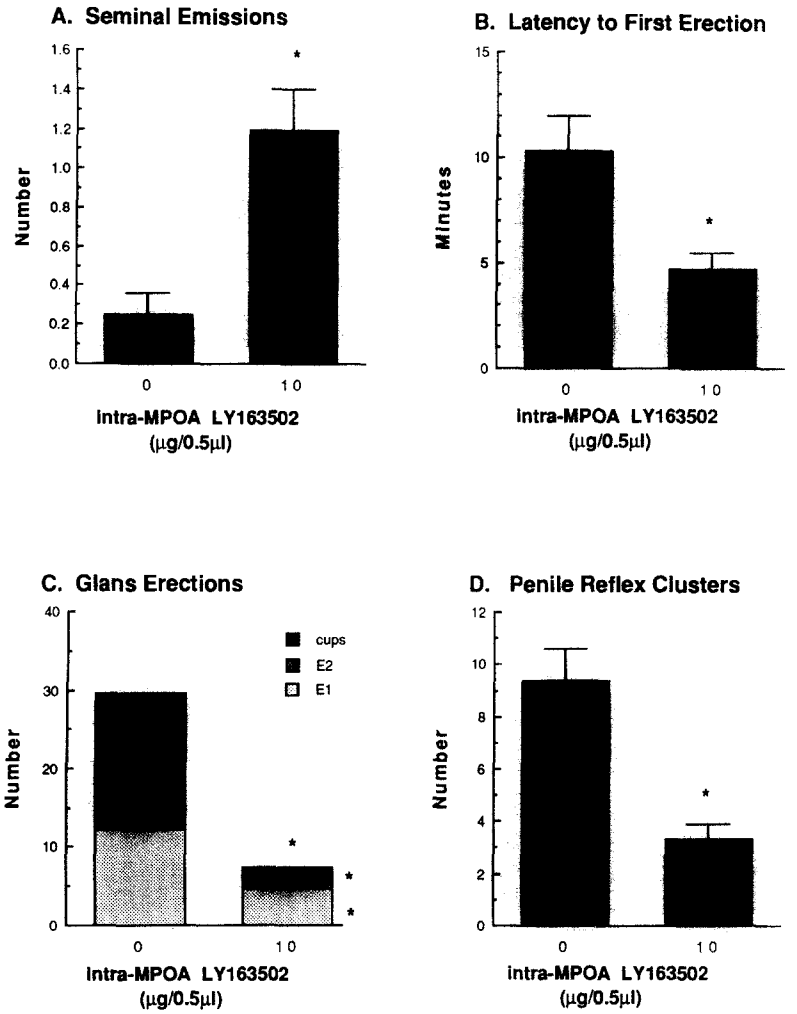

FIG. 2. (A) Number of seminal emissions, (B) latency to first erection, (C) number of glans erections, and (D) number of penile reflex clusters following a microinjection of LY163502 into the medial preoptic area (MPOA). Data are expressed as mean ± SEM. *Denotes a significant difference from control values; see text for *p*-values.

Systemic administration of RDS-127 was found to induce seminal emission and inhibit penile erections (30), at a dose that decreased ejaculation latency in copula (10). Facilitative effects on seminal emission and inhibitory effects on erectile responses were successfully blocked by pimozide (9), supporting the contention that RDS-127-induced effects were mediated by stimulation of DA receptors.

In contrast to the inhibitory effects of intra-MPOA quinelorane on penile erections are the findings that an injection of the mixed D1/D2 agonist, apomorphine, into the MPOA facilitated erectile responses and had no effect on seminal emission in the restrained supine rat (24). Microinjection of cis-flupenthixol (a D1/D2 antagonist) into the MPOA decreased penile erection, again without effect on seminal emission (Thompson, Markowski and Hull, unpublished observations). The differences between quinelorane's and apomorphine's effects may be related to preferential versus combined stimulation of DA receptor subtypes. Thus, erectile potential may be facilitated by combined stimulation of D1 and D2 receptors in the MPOA, and inhibited by simultaneous blockade of both types. On the other hand, selective stimulation of D2 receptors in the MPOA appears to facilitate seminal emission and inhibit penile erection. Since erection is mediated primarily by the parasympathetic nervous system, and seminal emission, by the sympathetic nervous system [reviewed in (28)], we suggest that selective stimulation of D2 receptors may shift the balance of autonomic influence in favor of the sympathetic system.

That apomorphine and quinelorane may elicit different effects on sexual responses is not without precedent. Microinjection of apomorphine into the MPOA facilitated copulatory behavior by decreasing the interval between successive intromissions, thereby increasing the number of ejaculations within the test period (4,18), whereas quinelorane decreased the number of intromissions required to trigger ejaculation, but did not increase the number of ejaculations (19).

The systemic administration of dopamine agonists to unrestrained, freely-moving male rats in the absence of a female conspecific results in a constellation of behavioral responses collectively termed "penile erection/stretching and yawning syndrome" (PE/SYS) (1, 13, 15). However, since genital grooming occurs concomitantly with PE/SYS, it is not known whether penile erections are also accompanied by emission of seminal fluid. Intracranial microinjection studies have found that PE/SYS occurs

following the administration of apomorphine or a D2 agonist (LY171555) into the paraventricular nucleus of the hypothalamus (PVN) (22), an area also innervated by incertohypothalamic dopamine projections (5,12). Recent studies using the ex copula reflex paradigm in restrained rats, which allows observation of penile erections and seminal emission, have found that intra-PVN administration of apomorphine increased the incidence of seminal emission, as well as the number of penile erections (24). The ability of apomorphine in the PVN, but not in the MPOA, to increase seminal emission, raises the possibility that our current finding of increased seminal emission by intra-MPOA quinelorane may have resulted from spread of the drug to the PVN. However, this seems unlikely, since our microinjection procedures were identical to those that demonstrated differential effects on seminal emission of apomorphine injections into the MPOA and PVN (24).

The generalizability of our results to nonhuman primate species is questioned by the recent finding that systemic administration of quinelorane induced penile erection in rhesus monkeys that were allowed visual exposure, but not physical contact with a female conspecific (11). A notable difference between these studies and those reported here was that the effects of quinelorane on sexual responsiveness were dependent on the presence of a female, a condition not necessary for the effects we observed in the rat. Another difference was that erectile responses were facilitated. However, the effects of quinelorane on ejaculatory behavior per se were not noted. Since penile erections may be elicited reflexively by fluid in the urethra (7), as occurs during seminal emission, it is not clear whether the reported effects on 'erection' in freely moving animals are due to a direct facilitation of erection, or to an indirect effect due to seminal emission.

In conclusion, our studies have shown that the systemic and intracranial administration of a specific D2 DA receptor agonist facilitates seminal emission, but also inhibits reflexive erections. It is important to note that in the rat, unlike the human male, ejaculation facilitates subsequent erectile responses ex copula (27). Thus, the inhibitory effects on penile erection cannot be viewed as secondary to the facilitative effects on seminal emission. Findings from Experiment 2 confirm the importance of the MPOA in mediating effects of DA agonists on male sexual responses.

ACKNOWLEDGEMENTS

We wish to thank Vincent Markowski, Peter McAllister and Denise McQuade for their technical assistance, and Dr. Mark Foreman and Eli Lilly Co. for their generous donation of quinelorane. These studies were funded by grants MH40826 to E.M.H. and HD08933 to B.D.S.

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