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Further Studies on Alterations in Male Rat Copulatory Behavior Induced by the Dopamine-Receptor Agonist RDS-127

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CLARK, J. T., M. L. STEFANICK, E. R. SMITH AND J. M. DAVIDSON. *Further studies on alterations in male rat copulatory behavior induced by the dopamine-receptor agonist RDS-127.* PHARMACOL BIOCHEM BEHAV **19**(5) 781–786, 1983.—Pharmacologic dopamine receptor stimulation by RDS-127 (2-N,N-*di-n*-propylamino-4,7-dimethoxyindane) resulted in qualitatively different changes in the mating pattern depending on the dose administered and time elapsed between treatment and behavioral observation. A low dose (0.25 mg/kg) selectively increased the latency to ejaculation whereas a high dose (3.0 mg/kg) decreased ejaculation latency and intromission frequency (both indicators of ejaculatory efficiency) when behavioral observations were begun 30 minutes after intraperitoneal administration. Intermediate doses (0.5, 1.0, and 2.0 mg/kg) did not alter the time required to achieve ejaculation but did lower the number of intromissions preceding ejaculation. These dose-dependent actions resemble the effects of dopaminomimetics (reported by others) on locomotor activity. When mating tests were conducted shortly (less than five minutes) after drug administration, the induction of ejaculation by the high dose was enhanced. At this time, as well as after a prolonged delay (two hours), signs of decreased arousal (longer intromission latencies) were also observed. However, the postejaculatory refractory period was altered in a time-dependent fashion, viz: it was shortened closest to the injection time, not altered 30 minutes after treatment, and increased two hours after RDS-127 administration. Finally, RDS-127 induced seminal emission (ex copula) in 2.9±0.9 (S.E.) minutes, and these emissions did not differ in weight from normal spontaneous (diurnal) seminal emissions. The RDS-127-induced seminal emission was not followed by a refractory period of similar magnitude to that seen after ejaculation in copula. The data are interpreted in terms of the involvement of dopamine receptor subtypes in the modulation of masculine sexual behavior.

RDS-127 Dopamine Sexual behavior Ejaculation Seminal emission

COMPOUNDS with central dopaminomimetic actions have been reported to modify the copulatory performance of male mammals ([16, 25, 26, 27] and others). In dogs, Kimura, *et al.* [24] studied penile erection and ejaculation elicited by manual stimulation and reported a suppression of ejaculation, but not erection, following (a) monoamine depletion by tetrabenazine or reserpine, and (b) dopamine receptor blockade by haloperidol. This inhibition of ejaculation was rapidly reversed by treatment with L-Dopa. Others [10] have reported suppression of male rat sexual behavior following tetrabenazine, which was antagonized by the administration of apomorphine. We have recently reported that RDS-127 (3.0 mg/kg, 30 minutes prior to mating tests) selectively lowers the ejaculatory threshold [12] inhibits the expression of penile reflexes [33] and acutely induces seminal emission without altering the pattern of spontaneous seminal emission in three day tests starting two hours after treatment [33]. A direct dopamine receptor activation is indicated for RDS-127 in view of its reported dose-dependent inhibition of DOPA accumulation in the olfactory tubercle and caudate nucleus, effects on locomotor activity, inhibition of single unit activity in the pars compacta of the substantia nigra, and production of contralateral rotational behavior in rats bearing unilateral lesions in the substantia nigra [3,4]. In addition, dopamine receptor activation is manifested in the inhibition of RDS-127 of stress-induced prolactin secretion [12].

Though these data suggest a role for dopaminergic systems in modulating ejaculation in copula and seminal emission ex copula, questions integral to this role remain unanswered. Several of these questions are addressed in this communication. First, can some insight be gained as to the types of receptors involved in modulating copulatory behavior by analyzing the dose- and time-relationships of the behavioral response? Second, does RDS-127-induced seminal emission result in a period of sexual refractoriness similar to that occurring after ejaculation during mating? The experiments reported here, then, are directed at clarifying the dose and time course of RDS-127-induced alterations in copulation and seminal emission in rats in order to further delineate the role of dopaminergic transmission in male sexual behavior.

METHOD

Animals

Adult male Long-Evans rats (Simonsen Labs, Gilroy,

TABLE 1

EFFECT OF VARIOUS DOSES OF RDS-127 (IP, 30 MIN PRIOR) ON MALE COPULATORY BEHAVIOR

	0.25 mg/kg		0.50 mg/kg		1.00 mg/kg		2.00 mg/kg		3.00 mg/kg	
	RDS	VEH	RDS	VEH	RDS	VEH	RDS	VEH	RDS	VEH
Latencies (min)										
Intromission	1.75	0.25	0.30	0.22	0.25	0.48	0.35	0.20	0.28	0.25
Ejaculation	8.20	6.90*	4.35	5.35	3.00	4.30	1.85	2.70‡	2.28	6.25†
Intervals (min)										
Postejaculatory	5.95	5.60†	5.50	4.85*	7.15	5.40	4.93	5.25	3.73	4.73
Intercopulatory	1.43	0.69†	0.68	0.62	0.90	0.65	0.37	0.40	0.44	0.63
Frequencies										
Mount	8.0	9.0	4.0	7.0†	1.5	4.5†	4.0	4.5	1.0	6.0†
Intromission	6.0	10.0	6.0	9.0†	4.0	5.5‡	4.5	6.0†	4.5	7.5†
Copulatory Efficiency	0.38	0.53†	0.53	0.50	0.90	0.58‡	0.69	0.59	0.82	0.58
Number Ejaculating/N	7/7	7/7	7/7	7/7	6/6	6/6	6/6	6/6	6/7	7/7

Values presented are medians, Wilcoxan Matched-Pairs Signed Ranks test, *$p<0.02$; †$p<0.05$; ‡too few differences to test.

CA) aged 90–120 days at the beginning of experiments were used in these studies. Different groups of animals were used for each of the three studies described below. Rats were maintained three per cage under controlled light (14 hr dark; 10 hr light; lights off at 1100) and temperature (22–23°C). Food (Wayne Lab Blox) and water were available ad lib. All subjects were initially drug naive, and except for those in Experiment 1, received the drug only once.

Behavioral Screening Tests

All animals were tested for masculine sexual behavior prior to the initiation of experiments. Testing was performed in semicircular arenas during the dark phase of the light cycle (1230–1600) under dim light. The male was placed into the observation cage for a period of adaptation (two to five minutes) prior to the introduction of a female via an overhead trapdoor. Females were rendered sexually receptive by subcutaneous injection of estradiol benzoate (100 μg in 0.1 ml sesame oil) 48 hours, and progesterone (500 μg in 0.1 ml sesame oil) four to six hours before testing. Only those females exhibiting good receptive behavior with nonexperimental males were utilized. The occurrence of each mount, intromission, and ejaculation was recorded on an Esterline-Angus event recorder. Each animal was given a maximum of three tests per week, with at least three days between successive positive (those with ejaculation) tests. Only those males which achieved intromission (mounting with pelvic thrusting and penile insertion) within 15 minutes, ejaculated within one hour of the initial intromission, and again intromitted in the 15 minutes following ejaculation in at least three successive tests were used.

Definitive Behavior Tests

Behavioral observations were conducted as above and the following parameters were calculated from the record: mount latency (ML), time from introduction of female to occurrence of initial mount or intromission; intromission latency (IL), time from introduction of female to occurrence of initial intromission; ejaculation latency (EL), time between initial intromission and ejaculation; postejaculatory interval (PEI), time from ejaculation to the next intromission; mount frequency (MF), the number of mounts preceding ejaculation; and intromission frequency (IF), the number of intromissions preceding ejaculation. Additionally, intercopulatory interval (ICI), the average time between intromissions, was calculated as EL/IF, and a measure of copulatory efficiency (CE) was calculated as IF/(MF + IF) (equivalent to the hit rate of Sachs [28]). Positive tests were terminated immediately following the postejaculatory intromission. Negative tests were terminated when IL, PEI, or the time after any intromission exceeded 15 minutes, or when EL exceeded one hour. In several cases RDS-127 administration was followed by ejaculation on the initial intromission. In these cases IL was taken as time from introduction of female to ejaculation, EL as zero, IF as zero, and (if no mounts preceded ejaculation) CE was scored as 1.0.

Experimental Protocol

RDS-127 was dissolved in distilled water and diluted to the appropriate concentration. The compound was administered by IP injection in a volume of 0.1 ml per 100 g body weight. Control injections were equal volumes of the distilled water vehicle.

Experiment 1

To determine the effect of various doses of RDS-127 on male copulatory behavior, 0.25, 0.5, 1.0, 2.0, or 3.0 mg/kg were administered 30 minutes prior to initiation of behavioral observation. Two groups of animals were used such that one group received the two lower doses and the highest dose (n=7), and the other group received the two other doses (n=6). Each individual served as his own control in vehicle injection tests three days after the RDS-127 injection test. Statistical comparisons were made utilizing the Wilcoxon Matched Pairs-Signed Ranks test.

Experiment 2

To ascertain the time course and nature of seminal emission induced by RDS-127, and the effect of this emission on

subsequent copulation, male rats (n=13) were injected with 3.0 mg/kg RDS-127 and immediately introduced into the behavioral observation cages. These animals were closely observed until evidence of seminal emission was seen. As reported for parachloroamphetamine [22] seminal emission was not always accompanied by stereotyped ejaculatory behavior. Thus, to ascertain seminal emission, male rats were examined at one to two minute intervals to check for the presence of coagulated seminal material (plugs). This procedure included manual retraction of the penile sheath and removal of any plugs. Plugs were allowed to air dry for at least seven days and weighed. Immediately upon seminal emission the receptive female was introduced, and behavioral observation began. This copulatory behavior was compared to that recorded from these same individuals three days earlier, when vehicle injections were administered, and as none of the animals seminally emitted behavior tests were initiated six minutes after injection. Several of the RDS-127 treated rats ejaculated extravaginally during copulatory tests, and in these cases the copulatory plug was retrieved and treated as above.

Experiment 3

To determine the effect of a longer latency between drug treatment and behavioral observation, male rats were injected with 3.0 mg/kg RDS-127 (n=13) or water (n=13) observed for penile reflexes (results reported in 33) and introduced into the behavioral arenas for testing two hours after injection. In other studies [30,32] it has been reported that although copulation enhances the display of penile reflexes, no converse relationship exists. The parameters of copulatory behavior were analyzed using the Mann-Whitney U-test, two-tailed.

RESULTS

Experiment 1

Treatment of male Long-Evans rats with 0.25–3.0 mg/kg RDS-127 30 minutes prior to the onset of behavioral observations resulted in dose related changes in the mating pattern (Table 1, Fig. 1). EL was affected in a dose-dependent fashion: it was increased at 0.25 mg/kg ($p<0.02$), not significantly altered at 0.5, 1.0, or 2.0 mg/kg, and markedly reduced at 3.0 ($p<0.05$) mg/kg (Fig. 1). Decreases in IF were seen after 0.5, 1.0 ($p<0.05$), 2.0 ($p<0.05$) and 3.0 ($p<0.05$) mg/kg. Changes in MF typically followed IF, and a reduction in CE ($p<0.05$) was seen at the lowest administered dose. PEI was increased at 0.25 ($p<0.05$) and 0.5 ($p<0.02$) mg/kg, and ICI was increased at the lowest dose ($p<0.05$; Table 1).

Experiment 2

Seminal emission was seen in all 13 animals after injection of RDS-127 (3.0 mg/kg). None of these individuals had shown evidence of seminal emission on a previous trial after vehicle injection. Mean latency to seminal emission was 2.9±0.9 minutes (±SE). The mean weight of the 13 RDS-127-induced plugs was 13.6±3.3 mg. The copulatory plug was retrieved from five of the 13 rats as they exhibited extravaginal ejaculatory patterns during mating tests. Mean weight of these five copulatory plugs was 53.2±12.5 mg. The drug-induced plugs for these five indivduals weighed 20.3±7.6 mg.

The copulatory patterns of the 13 animals observed immediately after seminal emission are shown in Fig. 2. The IL was approximately twice that seen following vehicle injection ($p<0.01$) but was still considerably shorter than the duration of the refractory period normally seen after ejaculation in copula (Fig. 2). EL and IF were dramatically reduced, to about 25% of their control values ($p<0.01$). PEI was also significantly reduced ($p<0.01$), as was ICI ($p<0.05$). Two of the RDS-127 treated animals ejaculated on the initial intromission, and four ejaculated on the initial intromission of the second copulatory series.

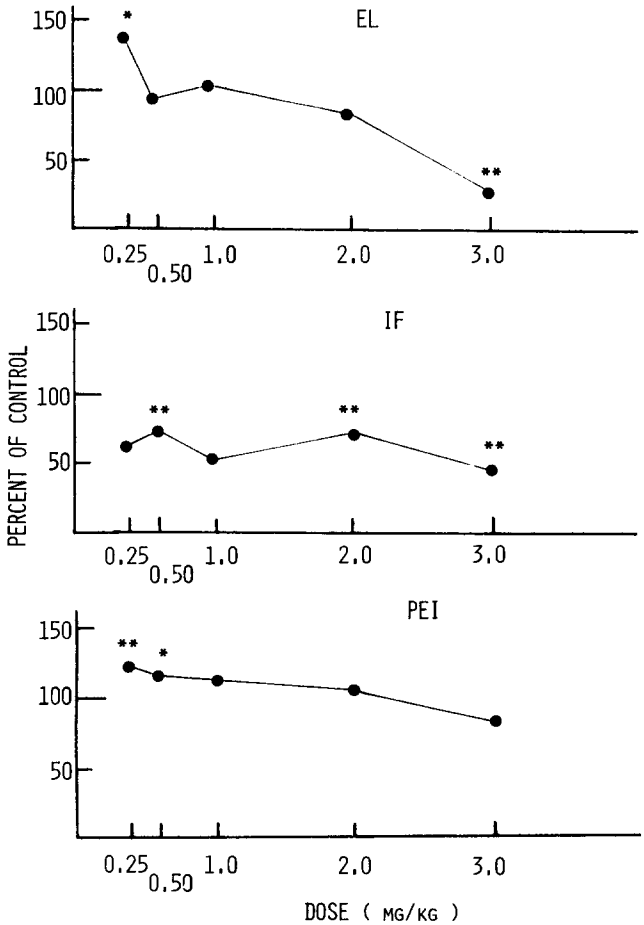

FIG. 1. Effect of RDS-127 injection 30 minutes prior to mating tests on ejaculation latency (EL), intromission frequency (IF), and postejaculatory interval (PEI) in male rats. Values are "percent of control" calculated as RDS-127 test value ÷ vehicle test value × 100. (*=$p<0.02$; **=$p<0.05$, Wilcoxon matched pairs-signed ranks test; n=6 for 1.0 and 2.0 mg/kg; n=7 for 0.25, 0.5, and 3.0 mg/kg).

Experiment 3

In tests conducted two hours after administration of 3.0 mg/kg RDS-127 several changes in the copulatory pattern were seen (Fig. 3), viz: increased mount (data not shown) and intromission latencies ($p<0.05$), decreased EL ($p<0.05$), decreased MF and IF ($p<0.02$), and an increased PEI ($p<0.05$).

Gross behavioral observation revealed changes in locomotor activity after RDS-127 administration. These included slight to marked ataxia and some verticalization (rearing, standing on hindlimbs) behavior. Ataxia was most marked

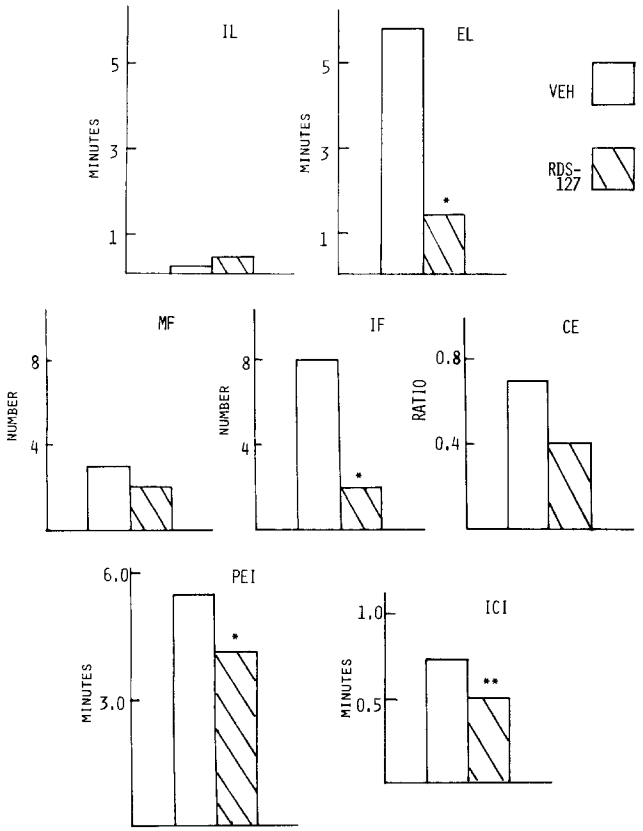

FIG. 2. Effects of 3.0 mg/kg RDS-127-induced seminal emission on copulatory behavior observed immediately after emission. (Median values; *=$p<0.01$, **=$p<0.05$, Wilcoxon matched pairs-signed ranks tests; n=13).

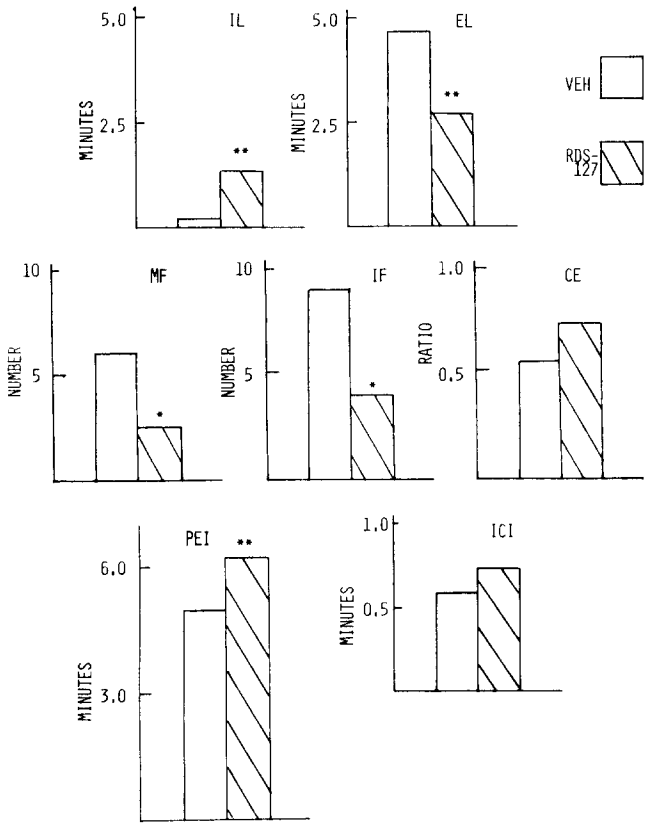

FIG. 3. Effect of 3.0 mg/kg RDS-127 administered two hours prior to mating tests on male rat copulatory behavior (Median values; *=$p<0.01$, **=$p<0.05$, Mann-Whitney U-Tests; n=13 per group).

immediately following treatment but some degree was evident in individual animals at each time point. It should be noted that even those animals exhibiting marked ataxia vigorously attempted to copulate. In addition, females appeared more antagonistic (e.g., less proceptive, more kicking, biting, and evading) towards males treated with the higher doses of RDS-127.

DISCUSSION

It is generally accepted that several mechanisms underlie the expression of male copulatory behavior. Initially, an arousal mechanism is responsible for the initiation of the copulatory sequence. Once copulation has started, a consummatory mechanism regulates the amount of stimulation required to reach ejaculation (ejaculatory threshold). Following ejaculation, a refractory mechanism determines the duration of a sexually quiescent period. Individual parameters of the copulatory pattern are often associated with each of the mechanisms as follows: arousal—ML and IL [7], and occasionally ICI [29], and performance on a specialized test in which intromission is prevented by anesthetization of the penis [20]; consummatory—EL and IF [7], CE [28], and the ex copula display of penile reflexes or seminal emission; and refractory—PEI. This operational dissemination of the male copulatory pattern allows the formation of hypotheses on the neurochemical substrates underlying each mechanism.

It has been suggested that dopamine is "stimulatory" to male sexual behavior (e.g., [25,35]). This terminology is too vague to adequately describe dopaminergic modulation of copulation in the normal, sexually vigorous male. The data from experiments with dopamine agonists almost universally show decreased EL or IF, or both. Thus moderate doses of apomorphine lowered the ejaculatory threshold [16, 27, 35, 36], various doses of lisuride [2] and pergolide [1] selectively reduced EL and IF, and N-*n*-norpropylapomorphine induced premature ejaculation [16,17] in male rats. In our laboratory, the dopamine agonist RDS-127 selectively lowered the ejaculatory threshold in copulatory tests, did not alter performance on genital anesthetization mounting tests, acutely induced seminal emission, and inhibited the display of penile reflexes in male rats [12,33]. The present studies extend these findings and indicate a dose-relationship, with a low dose causing an increase and a moderate dose causing a decrease in ejaculatory threshold. Additionally, analysis of data collected at three time points after drug administration reveals that the most potent effects are seen shortly after treatment, but that the major effects (reduced EL and IF) are still evident two hours after treatment. Also, a time-dependent change in PEI was noticed; viz: it was decreased immediately after treatment, not changed 30 minutes after treatment, and increased in mating tests conducted two hours after drug administration. These data indicate separate neurochemical substrates for consummatory and arousal mechanisms and suggest that dopaminergic transmission plays a major role in the regulation of ejaculation in and ex copula.

Dopamine agonists exhibit a biphasic effect upon locomotor activity in rodents [34]. Low doses typically inhibit whereas high doses excite activity. The dopamine agonists apomorphine and RDS-127 fit this model precisely [4,6]. However, the dose-dependent effects on male copulatory behavior are dissimilar for these two agents. In moderate doses, apomorphine reduced IF and EL [16,27] EL alone [10] whereas high doses suppressed the occurrence of copulation ([36] Clark and Smith, unpublished observation). Conversely, RDS-127 increased EL at low doses and decreased the ejaculatory threshold at high doses. The differences between RDS-127 and apomorphine effects on male rat copulatory behavior suggest that different types of receptors may be involved in the differential modulation of copulation by dopaminergic systems. In particular the short time course of RDS-127-induced seminal emission, the longer duration of the lowered ejaculatory threshold, and the time-dependent changes in PEI deserve attention.

A system for classifying central dopamine receptors has been proposed based on in vitro data on competition between ^{3}H-dopamine agonists and antagonists in brain membrane preparations (for review see [31]). This system involves four subtypes of dopamine receptors: D1—those linked to adenylate cyclase; D2—those sensitive to dopamine at 5000 nM and to neuroleptics at 1 nM; D3—those sensitive to dopamine at 3 nM and neuroleptics at 1500 nM; and D4—those sensitive to dopamine at 3 nM and neuroleptics at 1 nM. RDS-127 effectively displaces ^{3}H-apomorphine from striatal membrane preparations [4] suggesting good D3 activity. Also, RDS-127 did not alter dopamine sensitive adenylate cyclase in carp retinal preparations [3,4] indicating a lack of D1 activity, and only weakly displaced ^{3}H-spiroperidol from striatal membranes (Clark, Tan and Ciaranello, unpublished observations) indicating only weak D2 activity. These results suggest that RDS-127 may exert its primary effect of a decreased ejaculatory threshold by interacting with the D3 class of dopamine receptors. Recent evidence [9] has led to the suggestion that RDS-127 preferentially activates presynaptic dopamine receptors (autoreceptors), which most closely resemble the D3 receptor [38].

An alternative, less quantitative, classification system for multiple types of dopamine receptors has been proposed by Cools and van Rossum [13,14]. They have suggested that at least two distinct types of dopamine receptors exist, DA-e and DA-i, whose stimulation results in physiologically different, often opposite, responses. They have classified DA-e and DA-i receptors according to many criteria, including neuronal cells of origin, histochemistry, metabolic rates, and pharmacologic agents which preferentially interact with one type. They also suggested that DA-e receptors are involved with fast onset, short duration actions whereas DA-i receptors mediate slower onset, longer duration actions in behavioral models. Several agents classified as effective at the DA-i, but not the DA-e, receptor show effects on male copulatory behavior parallel to those seen after treatment with RDS-127. Most notable among these is the ergoline lisuride, which shares many pharmacological and behavioral properties with RDS-127. Lisuride produces a potent anorectic-like effect in rats [11], an effect also reported for RDS-127 [6]. Both agents also antagonize the actions of serotonin in the periphery [5,37] and alter the accumulation of DOPA in the caudate nucleus and olfactory tubercle [3, 4, 21, 23]. In contrast, lisuride [21], but not RDS-127 [4], antagonizes the accumulation of 5-hydroxytryptophan in rat brain. The reductions in ejaculatory threshold seen after RDS-127 ([12] this paper) and lisuride [2] are strikingly similar. In addition, Ahlenius *et al.* [1], have observed similar alterations of the mating pattern after administration of the ergot derivative pergolide, which has no appreciable serotonergic activity in rat brain [18,19]. N-*n*-norpropylapomorphine has also been suggested to interact preferentially with the DA-i receptor [14]. This agent has also been reported to affect copulation in a manner similar to RDS-127 and lisuride [16,17]. These data provide evidence (although circumstantial) suggesting that the DA-i receptor may be the one involved in regulating the amount of stimulation required to elicit ejaculatory behavior in the male rat.

Thus, the data presented herein, when coupled with other reported data, suggest that D3, or alternatively DA-i, receptors may be the main substrate on which RDS-127 (and other dopaminergic agonists) acts in order to affect a reduction in the ejaculatory threshold in the male rat.

Finally, the induction of seminal emission by RDS-127 does not induce a refractory period equivalent to that seen after ejaculation during mating. Additionally, it does not alter the weight of the copulatory plug produced with ejaculation in copula [32]. This finding does not support (for the rat) the suggestion (for the human) that the process of seminal emission is responsible for the induction of the refractory period following ejaculation [15]. Moreover, the PEI seen in the copulatory series immediately following seminal emission was reduced, whereas the PEI of the second copulatory series is almost universally increased [8]. The lack of a normal refractory period (e.g., a PEI) following seminal emission suggests that the mechanisms involved in emission and ejaculation are separable. On the other hand, the consistent induction of seminal emission by the dose (3.0 mg/kg) of RDS-127 which lowers the ejaculatory threshold in mating tests suggests a participation of the mechanism underlying seminal emission in the establishment of the ejaculatory threshold in copula. Thus, as the threshold for emission ex copula is reached, less stimulation is necessary to initiate ejaculation in copula, which, in turn is accompanied by the characteristic display of non-genital behavioral events and the subsequent period of sexual refractoriness.

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