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Amantadine Stimulates Sexual Behavior in Male Rats

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FERRAZ, M. R. AND R. SANTOS. *Amantadine stimulates sexual behavior in male rats.* PHARMACOL BIOCHEM BEHAV **51**(4) 709–714, 1995.—The effects of amantadine on sexual behavior, penile erection, and seminal emission of male rats was studied. Amantadine significantly decreased latency of mounts in all doses (1.25 to 50 mg/kg), and decreased the number of mounts and intromission latency at the highest doses used. The lowest dose of amantadine significantly increased ejaculation latency and intromission frequency, while higher doses significantly reduced it, which indicates a biphasic response of the drug. Additionally, seminal emission, erections, and genital grooming were significantly induced by amantadine. Amantadine-induced seminal emissions were impaired by spinal cord transection, which suggests the involvement of supraspinal structures in the drug action. Haloperidol and atropine sulphate significantly reduced seminal emissions and penile erections induced by amantadine. These results demonstrate that amantadine stimulates sexual behavior and genital reflexes in male rats and suggest a facilitatory effect of the drug that probably involves different mechanisms of action.

Amantadine Sexual behavior Penile erection Seminal emission Spinal transection
Atropine sulphate Haloperidol

IT HAS been shown that dopaminergic agonists induce sexual excitement in male rats (6,7,21). Apomorphine evokes penile erection, ejaculation (12,17), and stimulates sexual behavior in male rats (6,13). Sexual stimulation can also be induced by other dopaminergic agonists like L-DOPA (11) lisuride (1), quinpirolone, and quinerolane (7,10).

RDS-127, a mixed dopaminergic and 5-HT_{1a} agonist, facilitates sexual behavior (8,25) and stimulates erection and seminal emissions in the male rat. Spinal cord transection did not impair RDS-127 induced-seminal emission, and a possible spinally mediated dopaminergic mechanism has been suggested (25).

Amantadine, an indirect stimulant of dopaminergic neurons, induces penile erection and ejaculation in male rats (3,22). Penile erection induced by amantadine can be antagonized by cholinergic (3,17) and dopaminergic (17) antagonists. However, there is no information regarding the influence of amantadine on sexual behavior or the effects of cholinergic and dopaminergic antagonists and spinal cord transection on amantadine-induced ejaculation in male rats.

In the present study, we have examined the effects of amantadine on sexual behavior in male rats and the influence of spinal cord transection and pretreatment with atropine or haloperidol on the erection and ejaculation induced by this drug, to find out whether dopaminergic and cholinergic mechanisms are involved in the amantadine response.

METHOD

Animals

Adult male Wistar rats (250–350 g), 3 to 4 months old, from our own colony were used. Animals were housed in groups of three per cage, and food and water were provided ad lib. Animals were maintained on ambient temperature of 23 ± 2°C and under a 12 L : 12 D cycle. Experiments 2, 3, and 4 were conducted during the light phase of the normal cycle (0600–1800 h), and Experiment 1 was conducted during the dark phase of the inversed cycle (0600–1800 h) after an acclimatization period of the animals of at least 3 weeks.

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Drugs

Amantadine hydrochloride (De Angeli) was dissolved in distilled water immediately prior to testing. Amantadine was injected IP immediately prior to Experiments 2, 3, and 4 or 10 min before the introduction of the female rat into the mating area—Experiment 1. Doses are expressed as the salts.

Stimulus females used in mating tests were rendered receptive via SC injections of 100 μg/kg estradiol benzoate in oil 72 and 48 h before and 500 μg/kg medroxiprogesterone acetate 6 h before testing.

Atropine sulphate (Sigma) and Haloperidol (Johnson Johnson) were dissolved in distilled water immediately before use.

Spinal Transection Surgery

Midthoracic transection of the spinal cord was made as follows: rats were anesthetized with sodium thiopental (60 mg/kg), IP, shaved across the upper back, and incised to expose the thoracic vertebrae. All muscles were cut free from the spinous processes of the sixth to nineth vertebrae, and the spinal cord was exposed by drilling of the spines (16). Thus, a segment was completely removed by aspiration. Immediately after suture of the animals, rats were maintained under light to conserve body temperature. The bladders of the spinal rats were compressed manually eight times a day during 3 days following surgery and three times a day thereafter. The spinal rats received 20.000 UI/kg of penicillin benzatine (Wyeth) IM immediately prior to surgery. Postsurgical care include the administration of 6.25 mg/kg of meperidine (Sanofi Winthrop), SC, with caution to avoid respiratory depression. Experimental and surgical procedures were approved by our department.

EXPERIMENT 1: EFFECTS OF AMANTADINE ON THE SEXUAL BEHAVIOR OF THE MALE RAT

Eighty-five male rats were divided into seven groups administered with either vehicle (n = 16) or amantadine at the doses of 1.25 (n = 10), 2.5 (n = 10), 5.0 (n = 19), 10 (n = 10), 25 (n = 10), or 50 mg/kg (n = 10). Immediately after injection, the animals were individually housed in an observation cage (80 × 80 × 120 cm) with a transparent front side for a 5-min adaptation period prior to the introduction of the receptive female (16). Each female was previously tested using a nonexperimental male. Experiments were performed between 1400 and 1600 h during the dark period of the light cycle. The rats were observed during 30 min and mounts, intromissions, and ejaculations were recorded. Results of the sexual behavior of rats were expressed as: mount latency (ML), the time from onset of the test to the first mount with or without penile insertion; mount frequency (MF), the number of mounts prior to ejaculatory behavior; intromission latency (IL), the time from the introduction of the female to the first intromission; intromission frequency (IF), the number of intromissions before ejaculatory behavior; ejaculation latency (EL), time from the first intromission to ejaculatory behavior; postejaculatory interval (PEI), time from ejaculatory behavior to the first intromission of the second copulatory series; intercopulatory interval (ICI), the average time between intromissions (ICI = EL/IF + 1) and copulatory eficiency (CE), the number of intromissions divided by the total number of mounts with and without penile insertion. Tests were terminated as negative if IL exceeded 15 min or EL exceeded 30 min.

EXPERIMENT 2: EFFECTS OF AMANTADINE ON GENITAL REFLEXES OF THE MALE RAT

One hundred 114 male rats were divided into five groups of 19 rats. The groups received vehicle or 1.25, 2.5, 5, 10 or 20 mg/kg of amantadine. Immediately before injections each animal had the prepuce retracted to remove eventual plug residue. After injections, each rat was placed in a wire cage (16 × 19 × 30 cm) situated upon a mirror to facilitate observation of the genital area of the animal and observed for 30 min, during which the number of seminal emissions, penile erections, and genital groomings were registered (24).

EXPERIMENT 3: EFFECTS OF ATROPINE OR HALOPERIDOL ON THE ERECTIONS AND SEMINAL EMISSION INDUCED BY AMANTADINE

Ninety-one male rats were divided into nine groups. Five groups were pretreated with atropine sulfate (1, 2, 4, 8, or 10 mg/kg) IP, three groups received haloperidol (0.5, 1.0, or 2.0 mg/kg), and one group received vehicle. Amantadine (20 mg/kg) was administered IP 1 h prior to atropine or vehicle and 2 h prior to haloperidol administration. Seminal emission and penile erections were observed as described in Experiment 2.

EXPERIMENT 4: EFFECTS OF AMANTADINE ON SPINALLY TRANSECTED RATS

Nine spinally transected and 10 normal male rats were treated with vehicle and tested for seminal emission as described in Experiment 2. The same animals were tested again after injection of 20 mg/kg of amantadine 24 h later.

Statistics

One-way analysis of variance (ANOVA) and the Student-Newman-Keuls test for further comparison between two groups (control and each experimental group) were used to analyze: in Experiment 1, all parameters; in Experiment 2, penile erections and genital grooming; in Experiment 4, number of penile erections in rats pretreated with vehicle or atropine sulphate. In Experiment 4, Student's t-test was used for comparison between vehicle and 2.0 mg/kg of haloperidol. Finally, the rate of seminal emissions (Experiments 2, 3, and 4) and rate of penile erection (Experiment 4) were analyzed using the nonparametric chi-square test.

RESULTS

Experiment 1

Administration of amantadine markedly stimulated the mating behavior of rats in comparison with vehicle controls (Fig. 1). ML was significantly reduced after administration of all doses of the drug, $F(6, 78) = 4.62, p = 0.001$. The reduction in ML values was dose dependent until 10 mg/kg and then reached a plateau (25 an 50 mg/kg). IL, $F(6, 78) = 2.67$, $p = 0.021$, and MF, $F(6, 78) = 3.68, p = 0.003$, showed significant reduction at the highest dose of the drug (50 mg/kg).

Measurement of IF, $F(6, 78) = 12.99, p = 0.001$, and EL, $F(6, 78) = 9.2, p = 0.001$, revealed a biphasic effect of amantadine (Fig. 1). While the smallest dose significantly increased ejaculation latency and intromission frequency, a marked decrease could be observed with doses above 25 mg/kg for EL and above 10 mg/kg for IF.

The smallest doses of amantadine (1.25 to 10 mg/kg) caused a progressive, but nonsignificant, reduction in PEI. No statistically significant changes were found in ICI and CE after amantadine treatment.

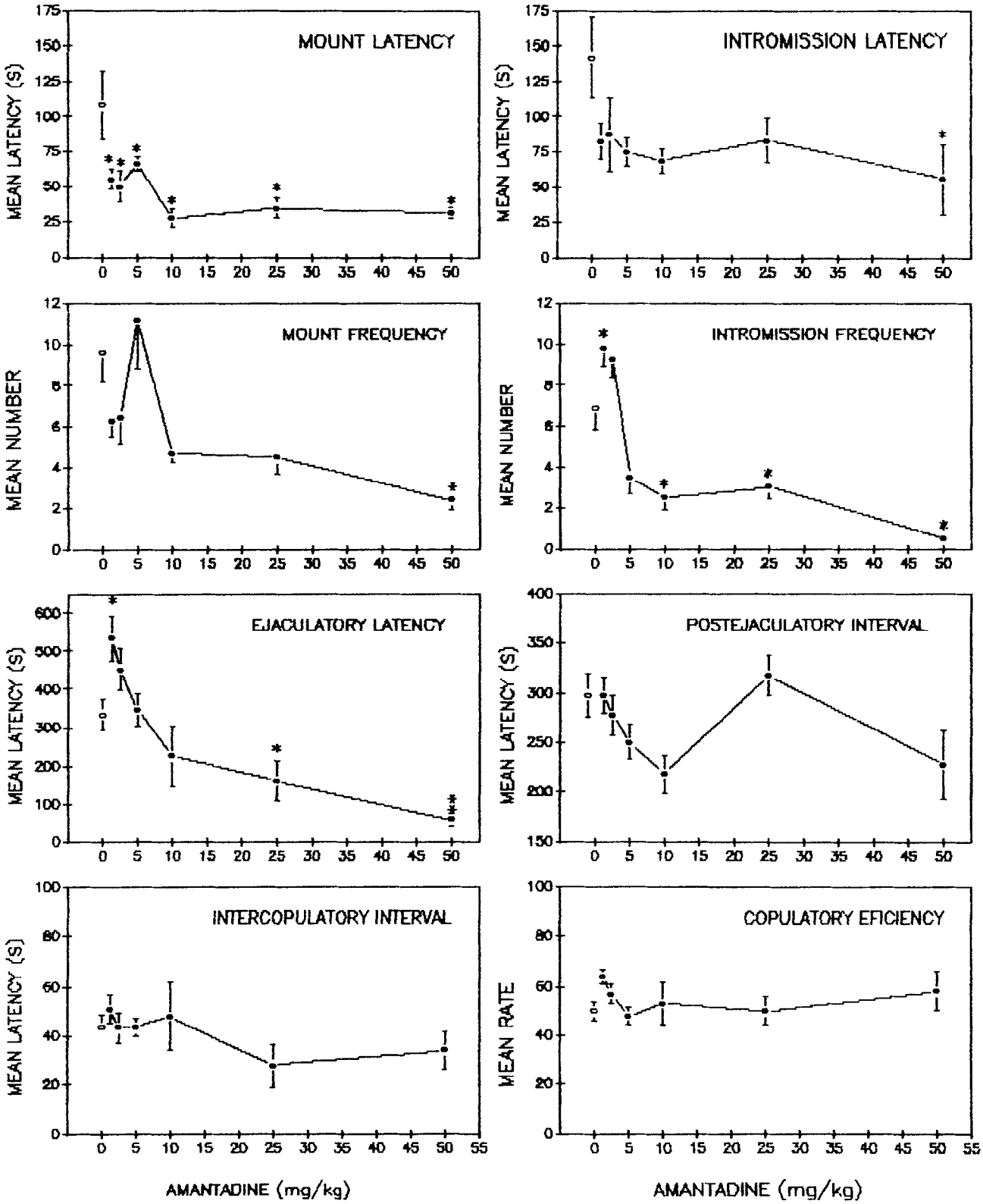

FIG. 1. Effects of amantadine administration on various parameters of male rat sexual behavior. Asterisks represent statistically significant differences between amantadine-treated rats (closed circles) and control (open circles): $*p \leq 0.05$.

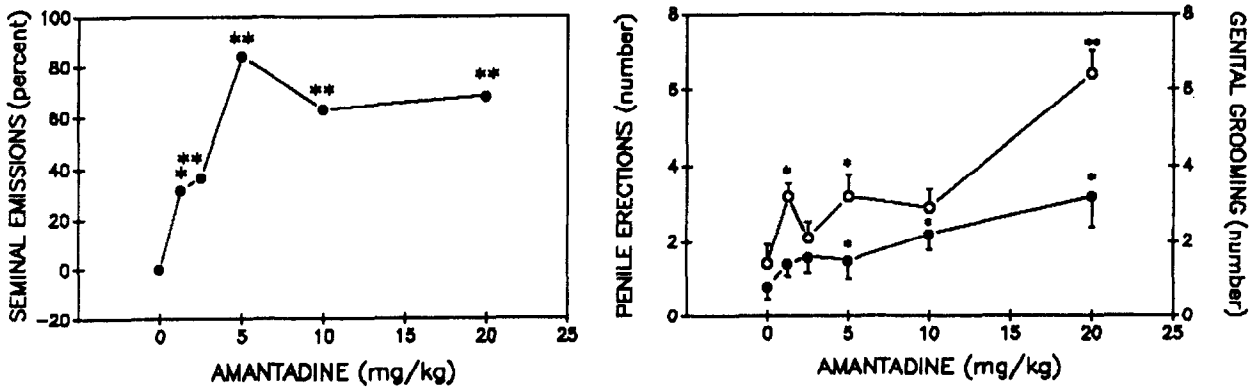

FIG. 2. Effects of amantadine administration on seminal emission (2A), penile erection, and genitalia grooming (2B) in the male rat. Asterisks denote significant differences from vehicle controls: $*p \leq 0.05$; $**p \leq 0.001$.

Experiment 2

Figure 2A shows that amantadine significantly elicited seminal emissions in rats in comparison with control animals. The effect of the drug appears dose dependent until 5.0 mg/kg and then reached a plateau. The figure 2B demonstrated a significantly elevated number of erections, $F(5, 54) = 2.65$, $p = 0.032$, in rats treated with 20 mg/kg of amantadine, which was accompanied by a significant elevation in genital grooming behavior, $F(5, 54) = 11.95$, $p = 0.001$.

Experiment 3

Spinally transected rats showed (Fig. 3) a significant decrease in seminal emission induced by amantadine (20 mg/kg) when compared with normal animals under the same conditions. Vehicle-treated groups, spinally transected, and normal rats were not significantly different regarding the observed reflex.

Experiment 4

Seminal emissions induced by 20 mg/kg of amantadine (Table 1) were significantly decreased in rats pretreated with atropine sulphate (8 or 10 mg/kg) or haloperidol (2.0 mg/kg), and amantadine-induced penile erection was significantly reduced in rats pretreated with atropine sulphate (1 or 10 mg/kg), $F(2, 27) = 8.2$, $p = 0.002$, or haloperidol (2.0 mg/kg).

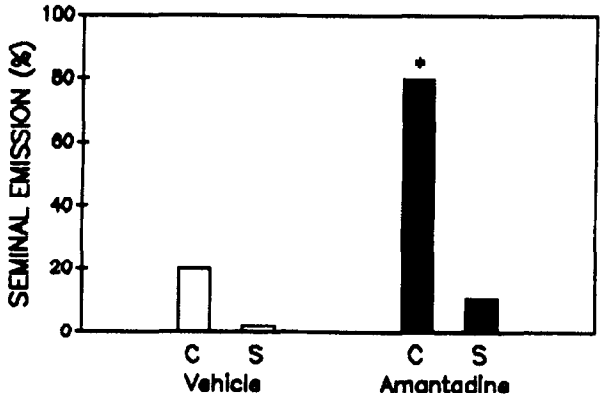

FIG. 3. Seminal emission induced by vehicle (open columns) and amantadine (closed columns) in spinally transected (S) and normal (C) rats. Asterisks denote significant differences from normal rats: $*p \leq 0.001$.

DISCUSSION

The present data have demonstrated that amantadine stimulates sexual behavior and sexual reflexes in male rats.

Amantadine facilitation of sexual behavior in male rats was demonstrated by: a) a significant reduction of mount (all doses, Fig. 1) and intromission latencies (50 mg/kg), which suggests an increase in arousal (4) or motivational mechanisms (22); b) a significant reduction of mount and intromission frequencies at higher doses of the drug (50 mg/kg for MF and 10 to 50 mg/kg for IF), which indicates that less copulatory stimulation was needed to achieve ejaculation; and finally, c) a significantly decreased ejaculation latency at the highest doses, which shows a reduction of ejaculatory threshold.

In contrast to the highest doses of amantadine, the lowest dose caused a significant increase in ejaculation latency (Fig. 1) and in intromission frequency, which indicates a biphasic effect of the drug also observed with other dopaminergic agonists (6,10,13). Amantadine caused a nonsignificant reduction in postejaculatory interval and did not change intercopulatory intervals and copulatory efficiency.

The facilitatory effects of amantadine on sexual behavior were substantiated by the observation that a significant increase in erection, seminal emission, and genital grooming were induced by the drug in male rats (Fig. 2A and B) without the presence of an estrous female or any kind of stimulation except drug administration. Results for seminal emission appear dose dependent until 10 mg/kg, with the dose of 20 mg/kg of amantadine apparently reaching a plateau at 80% of the maximum response. Spontaneous seminal emission occurring before the experiment may explain the absence of this amantadine-induced effect in some animals and, consequently, the lack of a 100% maximal response. Erections and genital grooming were significantly increased after injection of 20 mg/kg of amantadine (Fig. 2B). Our data shows that we can examine and quantify separately the two genital reflexes, confirming and amplifying previous studies with nonimmobilized male rats (3,17). In another study (24), amantadine induced a dose-dependent increase of all genital reflexes evoked in the immobilized male rat, as partial and total erections, quick and long flips and ejaculation, which are spinally mediated reflexes (16).

TABLE 1

EFFECTS OF ATROPINE OR HALOPERIDOL ON AMANTADINE (20 mg/kg)-INDUCED PENILE ERECTION AND SEMINAL EMISSION IN MALE RATS

Pretreatment	Dose (mg/kg)	n	Penile Erection %	Penile Erection n	Seminal Emission %
Vehicle	0	10	80	3.1 ± 0.86	80
Atropine	1	10	40	1.0 ± 0.42*	50
	2	10	–	–	50
	4	10	–	–	50
	8	11	–	–	27*
	10	10	0*	0 ± 0*	0*
Haloperidol	0.5	10	–	–	50
	1.0	10	–	–	30
	2.0	10	30	0.5 ± 0.31*	20

Values are mean number ± SE. *n* indicate the number of rats. All animals were treated with 20 mg/kg of amantadine after the pretreatment specified in the table. Dashes indicate not measured. Asterisks indicate statistically significant differences from control: $*p \leq 0.05$.

Spinal cord transection impaired the patterns of seminal emission induced by amantadine (Fig. 3), which indicates that the site of action of the drug is more central than the level of spinal reflexes. Our data differ from the observed stimulating effect of RDS-127 in spinally transected rats (25) and, thus, are not in accord with the hypothesis that a spinal dopaminergic mechanism is responsible for the stimulation of ejaculation in the male rat.

In fact, erections and seminal emissions induced by amantadine were antagonized by atropine-sulphate and haloperidol (Table 1), which suggests that centrally mediated mechanisms are involved in erection and seminal emission, including cholinergic and dopaminergic pathways, previously proposed for erection (17). A nonsignificant reduction of seminal emission response with 0.5 or 1.0 mg/kg of haloperidol may be explained by the high dose of amantadine administered. The maximum seminal emission effect observed was induced with 5 mg/kg of amantadine. Otherwise, 10 mg/kg of amantadine antagonized the cataleptic effect of 1 mg/kg of haloperidol (18,19), probably by competitive action at postsynaptic dopaminergic receptors. Possible peripheral cholinergic actions of the drug may also be excluded because atropine methyl bromide (3) and methylscopolamine (17) failed to antagonize the stimulant effect of amantadine on penile erection.

The most widely accepted mechanism of action of amantadine is an indirect dopamine releasing action (2,5,9,23). However, other possible mechanisms of action have been proposed for amantadine including a direct stimulation of dopamine receptors (2,18), blocking of catecholamine reuptake (2), enhancement of synthesis, and release of dopamine (2), and, more recently, an inhibitory action on the MK-801 binding site *N*-methyl-D-aspartic-acid glutamate receptor evoked release of acetylcholine (14,26).

Amantadine (10–40 mg/kg) increases dopamine levels in the corpus striatum and may accelerate dopaminergic neurotransmission by increasing dopamine release from the frontal cortex (27). Chronic administration of amantadine (5 mg/kg) in male rats induces a decrease in the density of dopamine D_2 binding sites (15). Therefore, it appears likely that a central dopaminergic action is involved in the action of amantadine. Some reports have shown that the amphetamine-like release of dopamine occurs at high doses of amantadine (14,26); at lower doses, amantadine action appears to involve the activation of dopaminergic receptors (2,18), or the NMDA glutamatergic receptor blockade (14,26). In our study, some effects are induced by low doses of amantadine and others by the highest dose used. Thus, decreased mount latency was observed after administration of lower doses of amantadine. In contrast, decreased intromission latency and mount frequency were induced only by the highest dose of amantadine. Otherwise, intromission frequency and ejaculation latency showed a typical biphasic effect: low doses increased and higher doses decreased IF and EL. Amantadine in lower doses undeniably elicited seminal emissions. Penile erections and genital grooming were only observed, in our experimental conditions, with the dose of 20 mg/kg. The apparent dichotomy in amantadine activity may be related to direct action on dopaminergic receptors at low doses and a amphetamine-like activity at the highest doses of the drug.

A dose-dependent biphasic response on sexual behavior parameters was also observed after administration of other dopaminergic agonists such as apomorphine (13,20), quinerolane (7,10), and RDS-127 (8). The inhibitory component of the biphasic effect may be explained by a dopaminergic autoreceptor activation at the lowest doses of the drug (12,13), while the sexual facilitatory effects of high doses were related with dopamine postsynaptic receptor activation (6,8,10,13). The biphasic response induced by amantadine on ejaculation latency and intromission frequency may represent activation of dopaminergic presynaptic and postsynaptic receptors, respectively, by low and high doses of the drug.

Several studies have demonstrated that dopaminergic agonists such as lisuride (1), apomorphine (6), RDS-127 (8), and quinerolane (7) cause facilitation of sexual behavior. Conversely, dopaminergic antagonists such as cis-flupenthixol, SCH 23390, haloperidol, pimozide, and sulpiride (20,21) have been shown to disrupt anticipatory and consummatory measures of sexual behavior.

Some dopaminergic agonists such as apomorphine and RDS-127 induced erection and seminal emission in male rats (12,17,25). Haloperidol, sulpiride, and pimozide antagonized erection induced by dopaminergic agonists (17,20), but seminal emissions elicited by RDS-127 were not antagonized by haloperidol pretreatment (25). Activation of D_2 receptors by

quinerolone, injected into the medial preoptic area, inhibited penile erection, while apomorphine facilitated it (7). These effects suggest that activation of different subtypes of postsynaptic dopamine receptors in the incertohypothalamic pathways elicits stimulation or inhibition of penile erection.

The fact that amantadine-induced erection and seminal emission could be antagonized by anticholinergic drugs discards any possibility that this facilitatory effect of amantadine on sexual reflexes involves inhibition of acetylcholine release by *N*-methyl-D-aspartic-acid receptors.

In conclusion, our data are in accordance with a central dopaminergic action of amantadine to explain its stimulatory effects on sexual behavior and genital reflexes, that possibly involves autoreceptor or postsynaptic receptor attivation or amphetamine-like action at the different doses used. Amantadine-induced erection and seminal emission appears to involve an indirect activation of a cholinergic pathway. Nevertheless, we cannot discard the possibility that other neurotransmitters may be involved in the amantadine-induced stimulatory effects upon male rat sexual behavior.

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