ELSEVIER

Pharmacology, Biochemistry and Behavior 69 (2001) 325–332

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

How REM sleep deprivation and amantadine affects male rat sexual behavior☆

Marcos Rochedo Ferraz*, Marcia Martins Dias Ferraz[1], Ricardo Santos

Department of Pharmacology and Psychobiology, Institute de Biology, State University of Rio de Janeiro, Av. 28 de Setembro, 87-Fundos, Rio de Janeiro 20551-030, Brazil

Received 24 April 2000; received in revised form 8 December 2000; accepted 19 January 2001

Abstract

There are conflicting findings about the sexual effects of REM sleep deprivation (REMd). Otherwise, several studies show a dopaminergic hypersensitivity after REMd. The effect of REMd and amantadine (AMA) was studied for standard measures and temporal patterning in the first experiment, in four groups: normal with vehicle, normal with AMA (5.0 and 10 mg/kg), REMd with vehicle and REMd with AMA (5.0 and 10.0 mg/kg). REMd reduced mount latency (ML), intromission latency (IL) and mount number (MN) and increased copulatory efficiency (CE) and hit rate factor. REMd also reduced the mount bout number (MBN) and increased the sexual interaction (mount bout time, MBT) among male and female during copula. AMA stimulates initiation and hit rate factors and accelerates the temporal patterning of sexual behavior, evoking fewer and quicker mount bouts. In the experiments with combination of REMd and AMA administration, AMA did not increase behavior effects evoked by REM deprivation, probably due to a top or a bottom effect, depending on the measures considered. A second experiment studied the effects of AMA (1.25 to 5.0 mg/kg) and REMd on the sexual reflexes of nonimmobilized male rats. REMd enhanced the AMA effects upon the seminal emission reflex, but inhibited the penile erection reflex elicited by 1.25 mg/kg of AMA. Curiously, our results showed that REMd, like AMA, a dopaminergic agonist, causes similar effects of sexual behavior in the male rat, particularly those related to arousal mechanism and hit rate factor. The results are discussed and the effects of REMd probably involve dopaminergic hypersensitivity and increased sexual motivational response.

Keywords: Sex; Amantadine; REM sleep deprivation; Copulatory behavior; Sexual reflexes; Dopaminergic hypersensitivity

1. Introduction

It has already been established that the direct and indirect dopaminergic stimulants affects the masculine sexual response in humans (Cummings, 1991; Uitti et al., 1989) and rats (Bitran and Hull, 1987; Bitran et al., 1988; Foreman and Hall, 1987; Hull et al., 1997; Pehek et al., 1988; Pfaus and Phillips, 1991). Amantadine (AMA), a substance described as a stimulant of dopamine release, but less specific (Bianchi and Tomasi, 1973; Buisson and Bertrand, 1998; Eisenberg and Pud, 1998; Morden et al., 1968; Stoof, 1992) than other dopaminergic agonists like apomorphine, also evokes genital reflexes (Baraldi and Bertolini, 1974; Charles and McGinnis, 1992; Maeda et al., 1990; Santos et al., 1980), and enhances sexual behavior (Ferraz and Santos, 1995; Yells et al., 1995). In a previous study, we demonstrated a typical biphasic dopaminergic effect of AMA (Ferraz and Santos, 1995) on sexual behavior of male rats. Despite its dopaminergic action, the reasons why we chose AMA in our study was because of its intense effects over sexual parameters, particularly on motivational and copulatory mechanisms (Ferraz and Santos, 1995), and as a clinical drug which induces hypersexuality in humans (Cummings, 1991; Uitti et al., 1989).

Several studies have shown that REM sleep deprivation (REMd) in rats, using the flowerpot technique (Jouvet et al., 1964; Santos and Carlini, 1987), intensified behavioral responses — such as aggressiveness and stereotypy — to

☆ This research was partially supported by grants from Brazilian National Research Council (CNPq). It is a partial fulfillment for the doctorate thesis of M.R. Ferraz to be submitted to the Universidade do Estado do Rio de Janeiro. Preliminary accounts of the results was present at the XIII Annual Meeting of FESBE, Caxambú, MG, 1997 and at XV Annual Meeting of the Brazilian Society of Etology, São Carlos, São Paulo, November 1997.

* Corresponding author. Tel.: +55-21-587-6808; fax: +55-21-587-6808.

[1] Graduate student, PIBIC-UERJ.

0091-3057/01/$ – see front matter
PII: S0091-3057(01)00508-1

dopaminergic agonists (Carlini, 1983; Hicks et al., 1979; Tufik, 1981). This behavior of REMd rats has been associated with indirect or direct evidence of a postsynaptic hypersensitivity of dopaminergic receptors (Carlini, 1983; Farooqui et al., 1996; Lara-Lemus et al., 1997; Salin-Pascual et al., 1997; Sloan, 1972; Tufik, 1981). D-amphetamine injected to REMd rats causes self-mutilation, probably by activation of D1 dopaminergic receptor (Lara-Lemus et al., 1997). REMd rats show increased dopamine metabolism in the striatum but not in the cortex (Farooqui et al., 1996). The use of sexual behavior as another approach to evaluate dopaminergic functionality after REMd has not been done until now.

Several studies have show conflicting findings about the sexual effects of REM deprivation. REMd stimulates testosterone action on male rat sexual behavior (Velasquez-Moctezuma et al., 1989b). On the other hand, studies using the standard method of analysis have shown that REM deprivation does not induce any change in the male rat sexual behavior (Hicks et al., 1991). But, in another study REMd induced inhibitory effects such as increased mount, intromission and ejaculation latencies and decreased ejaculation frequency and the hit rate factor (Velasquez-Moctezuma et al., 1996).

The present study, examines the effects of REMd per se on sexual behavior of male rats and the effects of AMA in previously REM sleep-deprived animals. In order to evaluate the role of AMA and REMd on male rat sexual behavior we used conventional standard measures (Beach, 1956; Ferraz and Santos, 1995) and a mount-bout analysis (Sachs and Barfield, 1970; Yells et al., 1995) which also evaluated temporal patterning of sexual behavior. Additionally, we studied the effects of AMA and REMd on the sexual reflexes of nonimmobilized male rats.

2. Method

2.1. Animals

Adult male Wistar naive rats (300–350 g) from our own colony were used for this study. They were housed, five per cage, in a room under controlled environment: inverted light/dark cycle conditions (12 h light/12 h dark; lights on at 6:00 p.m.), for an acclimatization period of at least 3 weeks. Animals had free access to water and food and ambient temperature was kept at 23 ± 1°C.

2.2. REM sleep deprivation

The REMd was brought about using the flower pot technique for 96 h. Rats were housed on a narrow circle platform (6 cm diameter) placed into a 20-l chamber surrounded by water. In a complementary experiment we tested another group, the stress control rats. Stress control rats were maintained under the same conditions, except a large platform was used (diameter of 12 cm). The uses of the wide platform allows that the "stress controlled" animals stay in similar isolation (the rat is an extremely social mammal) and humidity conditions to the REM sleep deprived group, without impeding them of presenting all the phases of the wake–sleep cycle (Carlini, 1983). The normal control rats were housed in plastic cages, as described above. Experiments were conducted in accordance with the Department Committee of Animal Care.

2.3. Drugs and procedural details

AMA, HCl (De Angeli) was dissolved in distilled water immediately prior to testing and was injected intraperitoneally (0.1 ml/100 g body weight) in male rats. Doses are expressed as salts.

Stimulus females were brought into estrous via subcutaneous injections of 100 μg/kg estradiol benzoate dissolved in corn oil 72 and 48 h before testing and 500 μg/kg medroxiprogesterone acetate 5 h before testing. The females were tested with nonexperimental sexually vigorous male rats, immediately before the experiment. Proceptivity and receptivity of female rats were evaluated using the following scale: Grade 0 — not receptive, female either does not display posture lordosis or reacts violently backwards and avoids the male; Grade 1 — slightly receptive, female displays posture lordosis sometimes when mounted, but tries to escape from the male, hiding her genitalia; Grade 2 — moderately receptive, female always displays lordosis posture when the male mounts her, but shows neither female presenting, female hopping, and female darting or posture lordosis (proceptive behavior); Grade 3 — high receptivity and proceptivity, female always displays receptive behavior when mounted, and sometimes shows a proceptive behavior; Grade 4 — very high receptivity, female frequently displays proceptive and receptive behaviors. Only those females that achieved 3 or 4 grades on our scale were used in the experiment. The present study was made with two observers evaluating the sexual behavior of each male rat. In case there was discrepancy in the observation among the two observers, with relationship to the observed pattern (mounts, intromissions, ejaculations, genital grooming, female rat pacing behavior) or at the time [mount latency (ML), onset of each mount bout, etc], the data would be eliminated.

3. Experiment 1: effects of AMA and REMd on the sexual behavior of the male rat

Sixty-three male rats were divided in six groups (10 to 12 per group), three control and three REM sleep deprived respectively treated with vehicle or AMA (5 or 10 mg/kg) immediately before the introduction on experimental cage. Ten minutes later, a female was introduced and the test started.

3.1. Standard tests

Sexual behavior observations were performed between 2:00 p.m. and 5:00 p.m. during the lights-off period of the cycle. Male rats were administered with AMA (5 and 10 mg/kg) or vehicle and subsequently placed in a standard cage. After 10 min for adaptation, a female rat was introduced into the cage and the copulatory behavior test started. The following measures were recorded: ML, latency from the introduction of the female to the first mount with or without vaginal intromission; the intromission latency (IL), latency from the introduction of the female to the first mount with vaginal intromission; the ejaculatory latency (EL), latency from the first intromission to the first ejaculation; the mount number (MN), number of mounts without vaginal insertion at the first ejaculatory series; the intromission number (IN), number of mounts with vaginal insertion to the first ejaculation; the postejaculatory interval (PEI), latency from the first ejaculation to the first intromission of the second ejaculatory series; the intercopulatory interval (ICI), the average interval between successive intromissions of an ejaculatory series (i.e., ejaculation

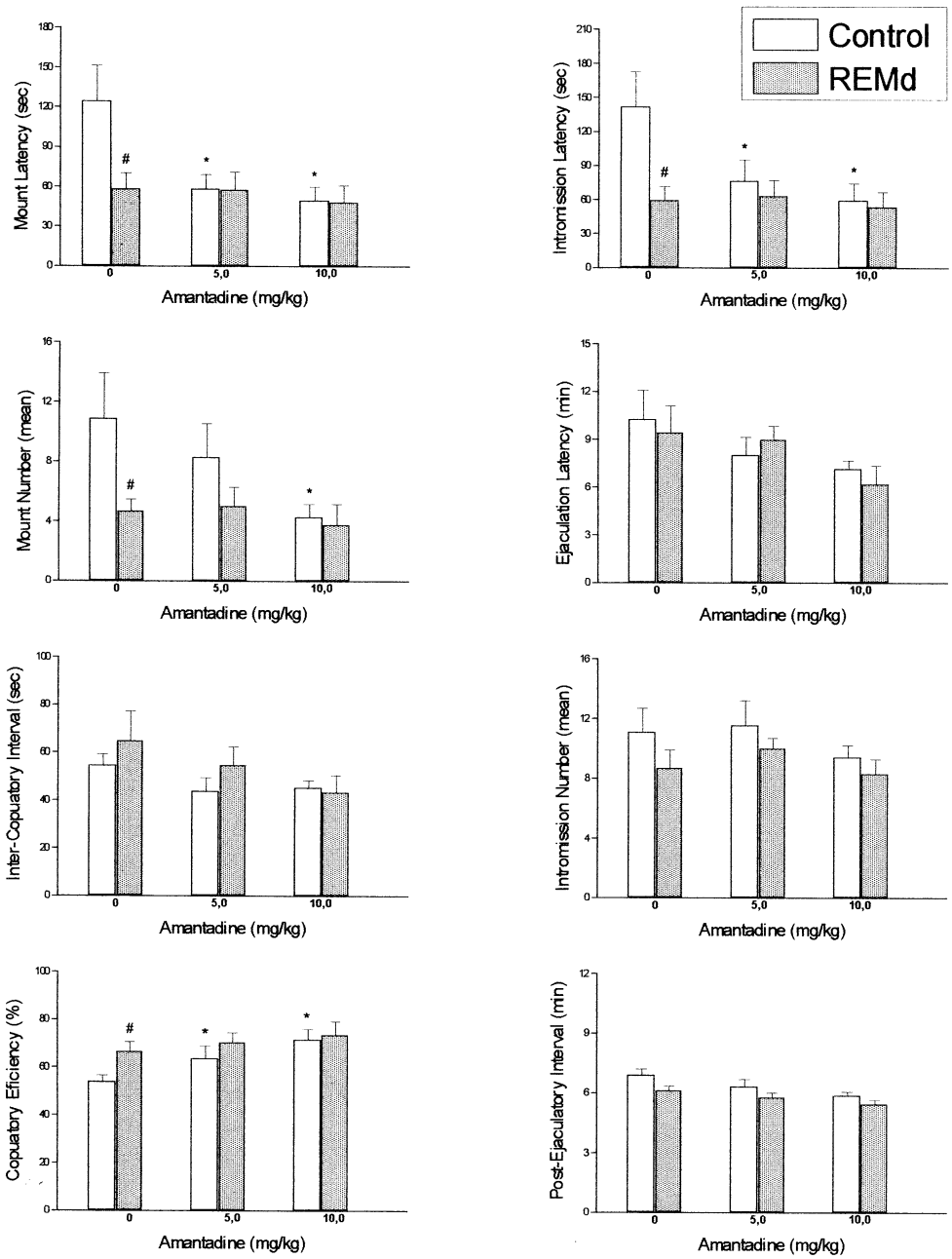

Fig. 1. Effects of AMA upon standard measures of sexual behavior. Data are reported as mean (±S.E.M.). Statistical comparisons were made between control and REMd rats (#) to each dose of the drug; between vehicle-treated control and AMA-treated control rats (*), and between vehicle-treated REMd and AMA-treated REMd rats (○). Results were statistically significant when $P \leq .05$.

latency per IN + 1); copulatory efficiency (CE), percentage of mounts in which the male gained vaginal insertion (i.e., IN per total mount with and without intromission); and copulatory rate (CR), the percentage of rats that showed ejaculation per each group.

Tests were considered negative if IL exceeded 15 min or EL exceeded 30 min. REMd rats were immediately identified by the observers by the color and humidity of their tails. This made impracticable a completely blind observation. Thus, we used two observers to evaluate sexual behavior and a third to drug administration. Data with discrepancies between the observers were discarded.

3.2. Temporal patterning analysis

Results of mount bout analysis were expressed as: mount bout number (MBN), the sequence of mounts (one or more), with or without intromission, uninterrupted by any behavior

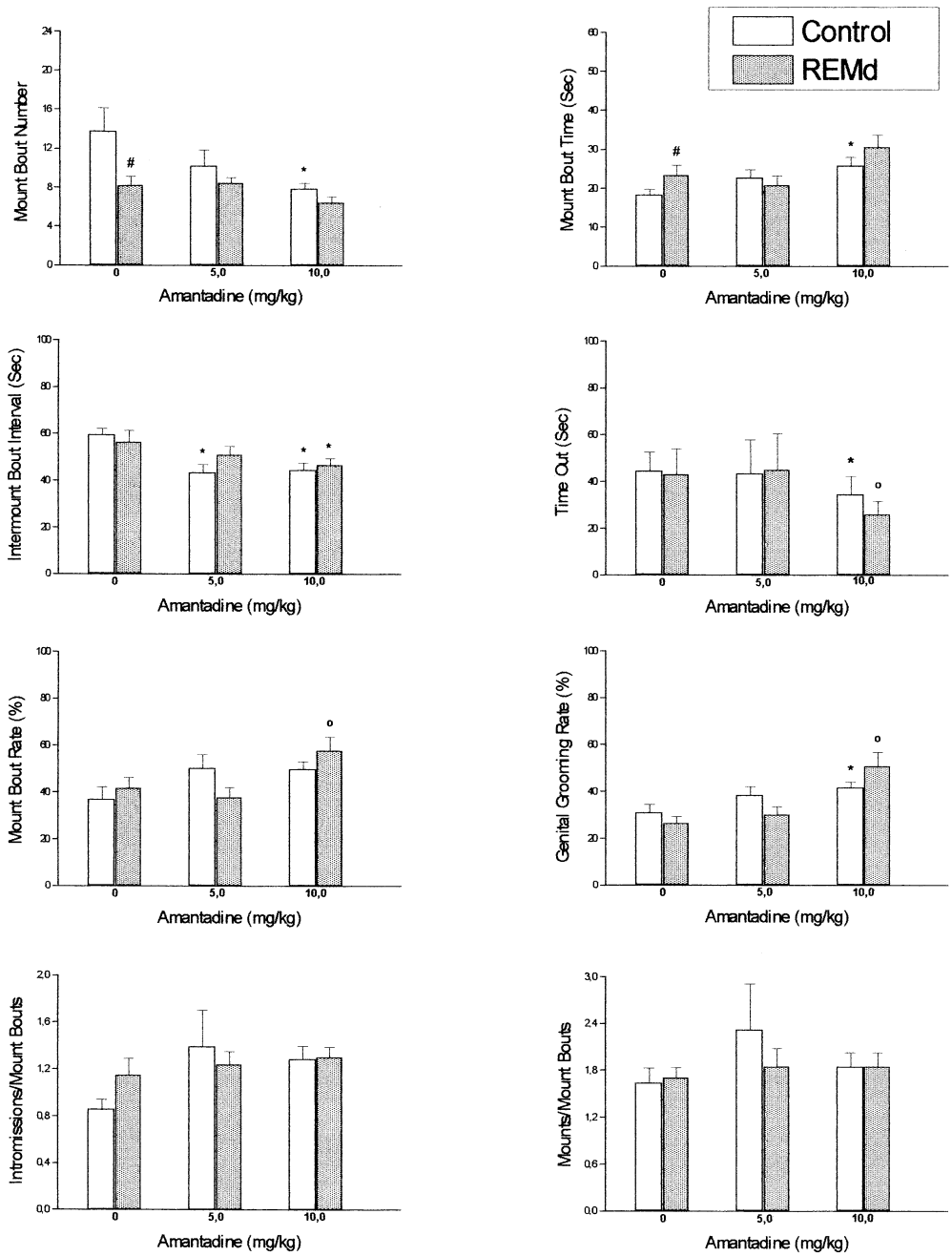

Fig. 2. Effects of AMA upon temporal patterning of sexual behavior. Data are reported as mean (± S.E.M.). Statistical comparisons were made between control and REMd rats (#) to each dose of the drug; and between vehicle-treated control and AMA-treated control rats (*), and between vehicle-treated REMd and AMA-treated REMd rats (○). Results were statistically significant when $P \leq .05$.

(other than genital grooming) that is not orientated towards the female; the time-out (TO), the interval from the last mount of one mount bout to the first mount of the next mount bout; the intermount bout interval (IMBI), the time from the first mount of one mount bout to the first mount of the next mount bout; the mount bout time (MBT), the total time of mount bout from introduction of the female to the first ejaculation (total sum); the mount bout rate (MBR), the average time of mount bout of an ejaculatory series (i.e., MBT per EL); the genital grooming time (GGT), the total time of genital autogrooming from introduction of the female to the first ejaculation; the genital grooming rate (GGR), the average time of genital autogrooming of an ejaculatory series (i.e., GGT per EL); the number of intromissions per mount bout and number of total mounts per mount bout.

In a complementary experiment, 20 normal control rats in cages and 20 stress controlled rats submitted for 4 days to the large platform were treated with vehicle or 10 mg/kg of AMA and tested for standard and mount bout measures.

4. Experiment 2: effects of AMA and REMd on genital reflexes of the male rat

One hundred and twenty naive Wistar male rats were divided in three groups: normal control, stress control and REM sleep deprived rats. Each group was treated with vehicle or AMA (1.25 to 10 mg/kg) immediately before tests.

4.1. Genital reflexes observation

Genital reflex observations were performed between 2:00 and 5:00 p.m. during the lights-on period of the cycle. Male rats were administered AMA (1.25 to 10.0 mg/kg) or vehicle and subsequently placed in a cage made of large mesh wire laid on the mirror, enabling observation of the rat genitals by means of mirror reflexes. Each rat was observed for 30 min. The following measures were recorded: latency and number of penile erections, seminal emissions and total time of genital grooming. Each rat was tested only once.

4.2. Statistics

In the mounting test, the one-way analysis of variance (ANOVA) and the Student–Newman–Keuls test for further comparison between two groups (normal control vehicle versus each experimental group) was used for: ML, IL, EL, PEI, ICI, CE, MBT, IMBI, TO, GGT, GGR and MBR; Kruskal–Wallis test, followed by the *U* Mann–Whitney test for comparison purposes between each experimental group with the normal control vehicle group was used for: NM, NI and MBN, intromissions/mount bouts and mounts/mount bouts. CRs were analyzed by use of chi-square test.

In genital reflex tests, statistical analyses were conducted using Kruskal–Wallis test for overall analysis followed by *U* Mann–Whitney test for two comparisons (PE and GG), and chi-square test for analysis of seminal emission rate.

5. Results

5.1. Experiment 1

Fig. 1 shows that the REMd per se reduced the ML [$F(5,57) = 3.48$, $P = .036$], the IL [$F(5,57) = 3.72$, $P = .023$], the MN [KW(3) = 12.54, $P = .015$], and increased the CE [$F(5,57) = 2.62$, $P = .025$], when compared with vehicle-treated control. The PEI was small in REMd rats when compared with vehicle-control rats, but did not show significant difference [$F(2,29) = 3.19$, $P = .071$]. The administration of both doses of AMA (5 and 10 mg/kg), when compared with vehicle in control rats, decreased the ML [$F(2,29) = 5.71$, $P = .008$], the IL [$F(2,29) = 3.91$,

Table 1
Comparisons of sexual response between normal control rats and stress control rats after treatment of vehicle or 10 mg/kg body weight of AMA

	Normal control		Stress control	
Parameter	Vehicle	AMA	Vehicle	AMA
n	10	10	10	10
CR (%)	80	80	70	80
ML (s)	102.63 ± 26.67	49.38 ± 10.65*	121.71 ± 31.71	59.75 ± 14.41
IL (s)	109.50 ± 30.81	59.38 ± 15.33*	149.57 ± 43.48	79.50 ± 24.23°
EL (min)	8.27 ± 1.86	7.16 ± 0.51	14.14 ± 3.21	7.02 ± 1.86
PEI (min)	6.6 ± 0.32	5.87 ± 0.21*	6.22 ± 0.44	6.54 ± 0.24
MN (median)	9.5	5	18	7
Min–max	7–14	1–9	6–32	6–11
IN (median)	9	8.5	12	7°
Min–Max	7–12	7–17	5–21	6–11
CE (%)	49.73 ± 2.68	68.22 ± 4.31*	42.66 ± 5.18	65.97 ± 4.09°
ICI (s)	52.60 ± 4.65	45.56 ± 2.96	67.24 ± 8.19	57.90 ± 19.22

Statistical comparisons were made between AMA-treated normal control and vehicle-treated stress control group (*); and between vehicle-treated stress control and AMA-treated stress control ($\circ$). Results were statistically significant when $P \leq .05$.

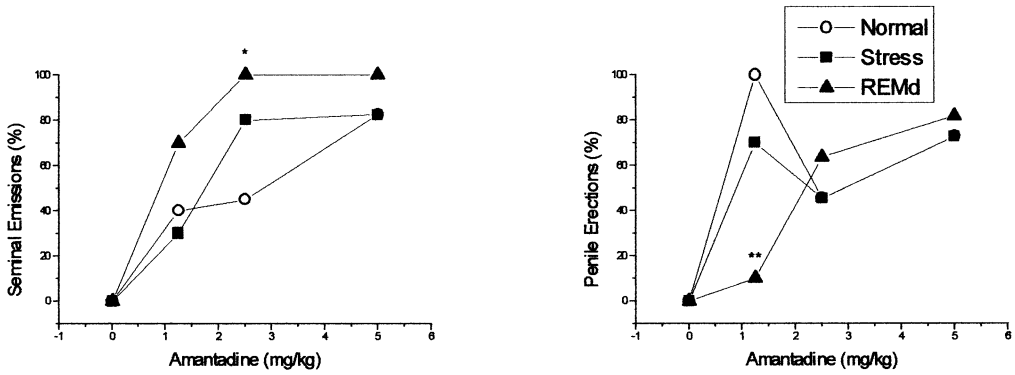

Fig. 3. Effects of AMA upon temporal sexual reflexes. Data are reported as percent of rats that achieved each reflex during 30 min after intraperitoneal injection of vehicle or drug (1.25, 2.5 and 5 mg/kg body weight). Statistical comparisons were made between normal control, stress control and REMd rats to each dose of the drug. * $P \leq .05$; ** $P \leq .01$.

$P = .031$], the MN [KW(2) = 7.46, $P = .024$; only the upper dose] and increased the CE [$F(2,29) = 4.37$, $P = .022$]. In REMd rats, the AMA, in both doses, when compared with vehicle, did not change any standard parameters of sexual behavior of animals. In addition, the effects of both doses of AMA in REMd rats when compared with control rats did not show significant differences.

Fig. 2 shows that the REMd per se when compared with vehicle-treated control also changed the temporal patterning of sexual behavior, decreasing the MBN [KW(3) = 16.39, $P = .006$] and increasing the MBT [$F(2,293) = 5.14$, $P = .049$]. In normal control rats, AMA modified the temporal pattern of sexual behavior in doses used when compared with vehicle, decreasing the MBN [KW(2) = 8.17, $P = .017$; upper dose], the IMBI [$F(2,293) = 9.67$, $P = .001$; both doses], the TO [$F(2,293) = 3.95$, $P = .049$; upper dose] and increasing the MBT [upper dose; $F(2,293) = 4.48$, $P = .012$] and the GGR [$F(5,57) = 3.39$, $P = .048$; upper dose]. In REMd rats, when compared with vehicle-treated REMd, AMA increased the MBR [$F(2,29) = 4.52$, $P = .02$], the GGR [$F(2,29) = 8.67$, $P = .001$; both doses], reduced the IMBI [$F(2,268) = 3.21$, $P = .042$; upper dose] and the TO [$F(2,268) = 3.69$, $P = .026$; upper dose]. Moreover, REMd did not change the effects of both doses of AMA when compared with control rats treated, respectively, with the same dose of the drug.

Table 1 shows the effects of AMA (10 mg/kg) or vehicle in stress control rats. After both treatments, the sexual response of stress control rats were not different to normal control rats. In normal control rats, AMA decreased the mount [$F(3,27) = 5.53$, $P = .004$] and intromission latencies [$F(3,27) = 3.17$, $P = .04$], the MN [KW(3) = 14.83, $P = .002$] and increased the CE [$F(3,27) = 9.02$, $P = .0003$]. In the stress control group, AMA also decreased the IL [$F(3,27) = 5.53$, $P = .04$] and the MN [KW(3) = 14.83, $P = .004$] and increased the CE [$F(3,27) = 9.02$, $P = .0034$] when compared with vehicle-treated stressed rats. The temporal patterning of sexual behavior (data not shown in Table 1) also were modified by stress in vehicle-treated rats because the MBN were significantly higher [KW(3) = 17.19, $P = .002$] than normal control response. The other temporal patterning measures did not change by stress.

5.2. Experiment 2

AMA elicited penile erections and seminal emissions in rats in a dose–effect curve (Fig. 3). The REMd highlights the seminal emissions induced by 5 mg/kg of AMA when compared with normal control rats, $\chi^2(2) = 8.13$, $P = .05$. In rats treated with the smaller dose of AMA, the REMd decreased drastically the penile erection number, $\chi^2(2) = 16.92$, $P = .001$.

6. Discussion

It has been reported that the male rat sexual response has at least four different factors, respectively: initiation factor, the CR factor, the intromission count factor and the hit rate (intromission ratio) factor (Sachs, 1978; Sachs and Barfield, 1970). Contributing to the initiation factor are the mount and intromission latencies; contributing to CR factor are the EL, PEI and ICI. The number of intromissions contributing to the intromission count factor and the CE are termed intromission ratio (hit rate) factor. Several works suggest that each factor could be activated by different neural mechanisms, and appears be controlled by dopaminergic neurons (Bitran and Hull, 1987; Ferraz and Santos, 1995; Velasquez-Moctezuma et al., 1989b).

At least two more recent studies have described that REMd does not increase the sexual behavior of male and female rats (Hicks et al., 1991); and short- and long-term REMd in male rats induced: increase in mount, intromission and ejaculation latencies; mount frequency, decrease ejaculation frequency and of the hit rate factor (Velasquez-Moctezuma et al., 1996). The authors recognized that this is a matter of controversy since opposite effects of REM deprivation (Canchola et al., 1986; Velasquez-Moctezuma et al., 1989a; Verma et al., 1989) have been described. Otherwise, some studies that show facilitation of sexual behavior

in REMd rats, used castrated animals with reposition of testosterone, and REMd altered the sexual responses induced by testosterone (Velasquez-Moctezuma et al., 1989b). In the present study, REMd reduced mount and intromission latencies, reduced MN, increased CE and hit rate factors. These data are in contradiction with previous described works (Hicks et al., 1991; Velasquez-Moctezuma et al., 1996) and in agreement with the others (Velasquez-Moctezuma et al., 1989a; Verma et al., 1989). Our study introduced originally the mount bout analysis to investigate the effects of REMd, never studied before in REMd rats. In this work, we introduced new measures to evaluate the sexual behavior temporal patterning, the GGR and the MBR. An analysis of GGT and MBT is not easy because these measures are dependent on total time of the copulatory series. Sometimes when the rat was treated with a stimulant drug the EL is very short and the respective time of genital grooming and mount bout are consequently short too, inducing false positive results. Therefore, the analysis of genital grooming and MBRs can provide more information about this behavior than a single measure of grooming and MBTs. REMd also reduced the MBN and increased the MBT among male and female rats. The REMd modified the temporal pattern of sexual behavior, increasing the male and female sexual contact but without changing the start of each mount bout.

Our data shows clearly that REMd facilitates the sexual behavior of male rats. The present results suggest that the arousal mechanism (the initiation factor) and the hit rate factor are more sensitive to modification by the REMd and favor a motivational response induced by the sleep deprivation procedure. The PEI only shows a marginal decrease after REMd. The REMd decreased the MN, but not the IN. The significance of this result is unclear, but suggests that the intromission count factor is less sensitive to environmental alterations.

On the other hand, the stress with large platforms does not affect sexual response; using the two approaches confirm that the stimulant effects of REMd cannot be associated to stress by the flower pot technique.

Curiously, the effects of AMA on sexual behavior in these conditions were very similar to that induced by REMd. The drug also stimulates principally the initiation and hit rate factor measures, confirming previous works (Ferraz and Santos, 1995; Yells et al., 1995).

The REMd did not change the effects of AMA on standard measures of sexual behavior, probably by a top or bottom effect. As AMA has a biphasic effect, low doses have inhibitory effect on sexual behavior, when we observed male and female behavior and not genital reflexes, without the presence of a female. High doses of AMA (until 50 mg/kg) increased the sexual responses with the female in normal rats(Ferraz and Santos, 1995) and not justifying an increase of the range of the doses. The REMd did not evoke the sexual reflexes, but enhanced the AMA effects in seminal emission, increasing the percent of rats that display seminal emission and the number of seminal emissions per rat too. These findings suggest that the REMd can decrease the threshold of seminal emission reflex center, probably by evoking D_2 receptor supersensitivity in the medial preoptic area (MPOA). The penile erection also was elicited by AMA, but it was not enhanced by REMd. Indeed, the small dose of AMA produced a considerably decreased percentage of REMd rats that achieved penile erections. In a former report (Ferraz and Santos, 1995), we showed a biphasic effect of AMA on EL and IN: AMA increased both parameters in a dose of 1.25 mg/kg. The seminal emission does not agree with these results, but penile erection reflex appears to be inhibited in REMd rats treated with 1.25 mg/kg of AMA, suggesting an inhibitory influence of REMd on this reflex at low doses of AMA. This phenomenon, apparently contradictory, may have an explanation: REMd could modify the D_1/D_2 balance, shifting to favor seminal emission reflex and initiation and hit rate factors of sexual behavior.

In general, the effects of AMA probably involve the dopaminergic action of the drug, although we do not discard the hypothesis of involvement of other systems. The role of dopamine, released on MPOA by incertohypothalamic neurons, facilitating both anticipatory and consummatory components of sexual response, has been known (Bitran et al., 1988; Charles and McGinnis., 1992; Ferraz and Santos, 1995; Foreman and Hall, 1987; Pehek et al., 1988; Pfaus and Phillips, 1991). In a recent report, Hull et al. (1997) suggested that activation of the D_1 family of DA receptors in the MPOA, elicited by small concentrations of DA, facilitate penile erections by stimulation of the parasympathetic pathway to the genital area, while the activation of D_2 receptors in the MPOA, by great concentrations of DA, is involved with sympathetically mediated ejaculation. The present results of AMA support this suggestion because only the arousal parameters were changed by drug with the doses used, suggesting an action on first mechanism.

The stimulant action of REMd (Canchola et al., 1986; Velasquez-Moctezuma et al., 1989a) upon sexual response is widely confirmed by our research in support of solving the controversy. However, we do not know the specific role of REMd upon the arousal or consummatory mechanisms. The REMd facilitates the effects of dopaminergic drug, increasing the motor activity, aggressive and stereotypic behavior, by inducing central dopaminergic hypersensitivity (Carlini, 1983; Salin-Pascual et al., 1997; Tufik, 1981). Since the effects of REMd on sexual response are very similar to AMA effects, the present results suggest that the facilitatory effects of REMd on sexual response probably involve an increase on dopaminergic transmission, supporting the hypothesis of dopaminergic hypersensitivity (Carlini, 1983; Salin-Pascual et al., 1997; Tufik, 1981).

The effects of AMA on seminal emission in nonimmobilized rats agree with other reports (Baraldi and Bertolini, 1974; Ferraz and Santos, 1995; Maeda et al., 1990). Further research is needed to check the specific relationship between

each component of sexual response and genital reflex and the respective type of dopaminergic receptors.

Finally, we suggest that REMd facilitates the initiation factor (arousal component) and hit rate factor, accelerating the temporal patterning of male rat sexual behavior. These effects, particularly the increase of motivational responses, probably involve the different hypersensitivity of D_1/D_2 receptors, but we do not discard the hypothesis of other mechanisms being implicated in this phenomenon.

Acknowledgments

The authors wish to thank Dr. Paulo R. Brasil Fernandes and Professor Paul Dykstra for their comments and corrections of the manuscript. We are grateful to Elaine C.A. Kaehler for her technical participation in this work and also to those who, although not taking direct part in our scientific research, worked hard and solved many problems for us.

References

Baraldi M, Bertolini A. Penile erection induced by amantadine in male rats. Life Sci 1974;14:1231–5.

Beach FA. Characteristics of masculine "sex drive". In: Jones MR, editor. The Nebraska symposium on motivation. Lincoln, NE: Univ. of Nebraska Press, 1956. pp. 1–32.

Bianchi C, Tomasi L. Central nervous system and autonomic nervous system effects of amantadine and some standard anti-Parkinson drugs. Pharmacology 1973;10:226–37.

Bitran D, Hull EM. Pharmacological analysis of male rat sexual behavior. Neurosci Biobehav Rev 1987;11:365–89.

Bitran D, Hull EM, Holmes GM, Lookingland KJ. Regulation of male rat copulatory behavior by preoptic incertohypothalamic dopamine neurons. Brain Res Bull 1988;20:323–31.

Buisson B, Bertrand D. Open-channel blockers at the human alpha-4, beta-2 neuronal nicotinic acetylcholine receptor. Mol Pharmacol 1998; 53(3):555–63.

Canchola E, Monroy E, Velazquez-Moctezuma J. REM sleep deprivation facilitates the estrogen effects on heterotypical sexual behavior in male rats. Physiol Behav 1986;37:33–7.

Carlini EA. REM sleep deprivation and dopamine in the central nervous system. Rev Pure Appl Pharmacol Sci 1983;4:1–25.

Charles MA, McGinnis MY. Effects of LY 163502, a D_2 dopaminergic agonist, on the sexual behavior of male rats. Pharmacol, Biochem Behav 1992;43:1087–92.

Cummings JL. Behavioral complications of the drug treatment of Parkinson's disease. J Am Geriatr Soc 1991;39(7):708–16.

Eisenberg E, Pud D. Can patients with chronic neuropathic pain be cured by acute administration of NMDA receptors antagonists amantadine? Pain 1998;74(2–3):337–9.

Farooqui SM, Brock JW, Zhou J. Changes in monoamines and their metabolite concentrations in REM sleep deprived rat forebrain nuclei. Pharmacol, Biochem Behav 1996;54(2):385–91.

Ferraz MR, Santos R. Amantadine stimulates sexual behavior in male rats. Pharmacol, Biochem Behav 1995;51:709–14.

Foreman MM, Hall JL. Effects of D_2-dopaminergic receptor stimulation on male rat sexual behavior. J Neural Transm 1987;68:153–70.

Hicks RA, Moore JD, Hayes C, Phillips N, Hawkins J. REM sleep deprivations increase aggressiveness in male rats. Physiol Behav 1979;22:1097–100.

Hicks RA, Bautista J, Phillips N. REM sleep deprivation does not increase the sexual behaviors of male rats. Percept Mot Skills 1991;73(1):127–30.

Hull EM, Du J, Lorrais DS, Matuszewich L. Testosterone, preoptic dopamine, and copulation in male rats. Brain Res Bull 1997;44(4):327–33.

Jouvet M, Vimont P, Delorme F, Jouvet M. Étude de la privation selective de le phase paradoxale de sommeil chez le chat. C-R Soc Biol 1964;158:756–9.

Lara-Lemus A, Perez dela Mora M, Mendez-Franco J, Palomero-Rivero M, Drucker-Colin R. Effects of REM sleep deprivation on the D-amphetamine-induced self-mutilating behavior. Brain Res 1997;770(1–2):60–4.

Maeda N, Matsuoka N, Yamaguchi I. Septohippocampal cholinergic pathway and penile erections induced by dopaminergic and cholinergic stimulants. Brain Res 1990;537:163–8.

Morden B, Conner R, Mitchell G, Dement W, Levine S. Effects of rapid eye movement (REM) sleep deprivation on shock-induced fighting. Physiol Behav 1968;3:425–32.

Pehek EA, Warner RK, Bazzett TJ, Bitran D, Band LC, Eaton RC, Hull EM. Microinjection of *cis* flupenthixol, a dopamine antagonist, into the medial preoptic area impairs sexual behavior of the male rat. Brain Res 1988;443:70–6.

Pfaus JG, Phillips AG. Role of dopamine in anticipatory and consummatory aspects of sexual behavior in the male rat. Behav Biosci 1991;105: 727–43.

Sachs BD. Conceptual and neural mechanisms of masculine copulatory behavior. In: McGill TE, Dewsbury DA, Sachs BD, editors. Sex and behavior: status and prospectus. New York: Plenum, 1978. pp. 267–95.

Sachs BD, Barfield RT. Temporal patterning of sexual behavior in the male rat. J Comp Physiol Psychol 1970;73:359–64.

Salin-Pascual RJ, Garcia-Ferreiro R, Moro-Lopez ML, Blanco-Centurion C, Drucker-Colin R. Repeated REM sleep deprivation after chronic haloperidol administration in the rat. Psychopharmacology 1997;131(3):216–9.

Santos R, Carlini EA. Central response to cholinergic drugs of REM sleep deprived rats. Pharmacol, Biochem Behav 1987;29:217–21.

Santos R, Paungartten FJR, Silva VA, Lindsey CJ. Estudo da influência da amantadina sobre os reflexos genitais do rato. Resumos 32[a] Reun Anu Soc Bras Prog Ciênc. 1980;32:924.

Sloan MA. The effect of deprivation of rapid eye movement (REM) sleep on maze learning and aggression in the albino rat. J Psychiatr Res 1972;9:101–11.

Stoof JC. Amantadine as NMDA receptor antagonist: new possibilities for therapeutic applications? Clin Neurol Neurosurg 1992;213:439–43.

Tufik S. Changes of response to dopaminergic drugs in rats submitted to REM-sleep deprivation. Psychopharmacology 1981;72:257–60.

Uitti RJ, Tanner CM, Rajput AH, Goetz CG, Klawans HL, Thiessen B. Hypersexuality with antiparkinsonian therapy. Clin Neuropharmacol 1989;12(5):375–83.

Velazquez-Moctezuma J, Monroy E, Cruz ML. Facilitation of the effect of paradoxical sleep deprivation on two-way avoidance acquisition. Physiol Behav 1989a;29:581–7.

Velazquez-Moctezuma J, Monroy E, Cruz ML. Facilitation of the effect testosterone on male sexual behavior in rats deprived of REM sleep. Behav Neural Biol 1989b;51(1):46–53.

Velazquez-Moctezuma J, Salazar ED, Retana-Marquez S. Effects of short- and long-term REM sleep deprivation on sexual behavior in male rats. Physiol Behav 1996;59(2):277–81.

Verma S, Chhina GS, Kumar VM, Singh B. Effect of rapid eye movement sleep deprivation on sexual behaviour of male rats. Indian J Exp Biol 1989;27(10):892–4.

Yells DP, Prendergast MA, Hendricks SE, Miller ME. Monoaminergic influences on temporal patterning of sexual behavior in male rats. Physiol Behav 1995;58:847–52.