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Chronic amantadine treatment enhances the sexual behaviour of male rats☆

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Abstract

The acute administration of amantadine (AMA), a dopaminomimetic and NMDA glutamatergic receptor antagonist also used as an anti-Parkinsonian agent, stimulates male rat sexual behaviour. However it remains unclear whether long term AMA supplementation might also provoke a similar increase in male rat sexual conduct. In the present study, male rats were administered AMA (5–50 mg/kg/day) or vehicle daily for 21 days and their sexual response was monitored weekly. Chronic treatment with AMA effectively increased the sexual response of male rats, similarly to what had been observed before with acute amantadine treatment. The main effect of chronic AMA treatment occurs in arousal and in ejaculatory response, whilst the excitatory component was not affected. The 21-day treatment with AMA did not lead to tolerance, suggesting that perhaps AMA could be used in male human patients to prevent sexual inhibition caused by anti-depressant and anti-psychotic agents.

Keywords: Sex; Amantadine; Sexual behaviour; Sexual behaviour temporal patterning; Dopamine; Sexual arousal

1. Introduction

It has been demonstrated previously that dopamine agonists stimulate male sexual behaviour (Bitran and Hull, 1987; Bitran et al., 1988; Ferraz and Santos, 1995; Charles and McGinnis, 1992; Damsma et al., 1992; Du et al., 1997; Hull et al., 1997; Ferraz et al., 2001; Ferrari et al., 2002), whilst drugs used as anti-psychotics reduce sexual desire, arousal, and orgasm in human males (Petrie, 1985; Aizenberg et al., 2001; Wirshing et al., 2002) and also the initiation and rate of copulation in sexually active male rats (Pehek et al., 1988; Pfaus and Phillips, 1991; Pfaus and Phillips, 1991).

There is considerable evidence that the sexual behaviour is produced by the interaction of at least four distinct mechanisms, probably involving different neural structures, named initially by Sachs and Barfield (1970) *initiation factor* (arousal component), *intromission count factor*, *hit rate factor* and *copulatory rate factor*. Mount and intromission latencies are part of the initiation factor, the intromission count factor consists of the intromission number, and the hit rate factor involves copulatory efficiency; whilst the copulatory rate factor embraces ejaculation latency and post-ejaculatory and intercopulatory intervals (Sachs and Barfield, 1970; Sachs, 1978; Pfaus and Phillips, 1991; Ferraz et al., 2001). It has been proposed that mount and intromission latencies estimate the sexual response arousal component, whilst the intromission number and copulatory efficiency estimate the erectile response; and the ejaculatory latency and intercopulatory interval allow us to estimate the ejaculatory component of sexual behaviour (Melis and Argiolas, 1995; Ferraz et al., 2001; Ferraz et al., 2003). The temporal patterning of sexual behaviour is the most complex socio-sexual behaviour, contributing to the understanding of arousal and sexual performance (Sachs and Barfield, 1970; Pfaus and Phillips, 1991; Yells et al., 1995; Ferraz et al., 2001; Ferraz et al., 2003). Each component of male rat sexual response can be evaluated independently from the others.

Amantadine (AMA), which was originally used in the treatment and prophylaxis of influenza infection, has also proved beneficial in drug-induced Parkinsonism, Parkinson's disease, traumatic head injury, dementia, multiple sclerosis and cocaine withdrawal (Huber et al., 1999; Allers et al., 2005;

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Bibbiani et al., 2005). It has been suggested that AMA could reduce the delay in therapeutic onset effects and possibly enhance the efficacy of anti-depressants (Shrivastava et al., 1995; Aizenberg et al., 2001; Stryjer et al., 2003; Pereira da Silva-Junior et al., 2005; Owen and Whitton, 2005). AMA, initially considered solely a dopaminomimetic drug, is also a non-competitive antagonist of the *N*-methyl-D-aspartate (NMDA) receptor complex and an indirect modulator of dopamine transmission (Bianchi and Tomasi, 1973; Stoof et al., 1992; Peeters et al., 2002). AMA causes ex-copula penile erections in male rats (Baraldi and Bertolini, 1974). It has also been established that AMA stimulates all the components of male rat sexual behaviour in a dose-dependent manner (Ferraz and Santos, 1995). It has been proposed as well that AMA accelerates the temporal patterning of male rat sexual behaviour (Yells et al., 1995). Recently it has been suggested that AMA does not influence the therapeutic efficacy of anti-depressive drugs such as serotonin re-uptake inhibitors and could be used to prevent the sexual impairment associated their use (Shrivastava et al., 1995). Most recently it has been proposed that AMA could be used both with atypical anti-psychotic olanzapine to curb weight gain and with levodopa to suppress dyskinesia, common side-effects of these drugs (Graham et al., 2005; Pereira da Silva-Junior et al., 2005). However, anti-depressant or anti-psychotic therapies are usually a long term process and AMA must be used continually. The effectiveness of AMA in enhancing sexual response when administered for a prolonged period of time needs to be confirmed. The purpose of this present work is to investigate the results of the chronic treatment of male rat sexual response with AMA.

2. Material and methods

2.1. Animals

Adult male Wistar naive rats (300–350 g) from our own colony were used. The animals were kept, five per cage, in temperature-controlled colony rooms (23°±1 °C) on a 12-h light/dark cycle, with lights off at 6 a.m. Food and water were available ad libitum and the ambient temperature was kept at 23±1 °C. The Ethical Committee of UERJ approved the experimental protocols.

2.2. General procedure

Amantadine was dissolved in 9% saline for the experiment and administered intraperitoneally twice a day (2.5 or 25 mg/kg/dose). The control group was treated with saline twice a day. Females were brought into estrous via subcutaneous (SC) injections of 100 μg/kg estradiol benzoate dissolved in corn oil at 48 h and 72 h and 500 μg/kg medroxiprogesterone acetate 5 h before testing. The females were tested with non-experimental sexually vigorous male rats immediately before the experiment. Proceptivity and receptivity of the female rats were evaluated using the Ferraz scale (Ferraz et al., 2001). Only those females that achieved 3 or 4 grades were used in the experiment.

2.3. Behavioural testing

Thirty-three male rats were divided into three groups treated respectively with vehicle (saline), amantadine (5 mg/kg/day) or amantadine (50 mg/kg/day) during 28 days. All the rats were tested before starting and only those that showed at least two copulatory series in 30 min were included in the testing. Mating tests were performed during the period of darkness (1 to 5 p.m.), under a red light. Subsequently, each rat was tested immediately before drug treatment (T_0) and weekly after the beginning of treatment (T_7, T_{14}, T_{21} and T_{28}).

After a 10-minute adaptation period in a rectangular wood observation cage with a transparent front (60×60×80 cm), a stimulus female rat was introduced into the cage and the copulatory behaviour test started. The following measurements were recorded or calculated: copulatory frequency, the number of complete copulatory series within 30 min; mount latency, time from the onset of the test to the first mount with or without penile insertion; intromission latency, the time from the introduction of the female to the first intromission; ejaculatory latency, time from the first intromission to ejaculation; mount frequency, the number of mounts without intromission prior to ejaculation; intromission frequency, the number of mounts with intromission before ejaculation; post-ejaculatory interval, time from ejaculation to the first intromission of the second copulatory series; intercopulatory interval, the average interval between successive intromissions (calculated as ejaculation latency divided by intromission number+1); copulatory efficiency, a measure of intromission success (calculated as percentage of mounts in which the male gained vaginal insertion). Tests were terminated if the intromission latency exceeded 15 min or if the ejaculation latency exceeded 30 min. The present study was made in the blind way as described in the literature (Ferraz et al., 2001), with two observers evaluating the sexual behaviour of each male rat in experimental or control groups. In case of a discrepancy in the conclusions of the two observers with regard to the observed pattern (mounts, intromissions, ejaculations, genital grooming, female rat pacing behaviour) or the time (mount latency, onset of each mount bout, etc.), the data were not considered.

2.4. Temporal patterning analysis

Results of the mount bout analysis were expressed as: mount bout number, sequence of mounts (one or more) with or without intromission, uninterrupted by any behaviour that is not oriented toward the female; time-out, the interval from the end of one mount bout to the start of the next mount bout; intermount bout interval, time from the onset of one mount bout to the start of the next mount bout; mount bout time, average time of mount bout preceding ejaculation; genital grooming rate, calculated as the time spent in genital autogrooming divided by the total time spent in a copulatory series; intromissions per mount bout, calculated as the intromission number divided by the mount bout number; and total mounts per mount bout, calculated as the sum of intromissions and mounts divided by the mount bout number.

2.5. Chemicals

Amantadine was purchased from the Sigma Chemical Company, USA.

2.6. Statistics

Two-way analysis of variance (ANOVA) and the Student–Newman–Keuls test for further multifactorial comparison

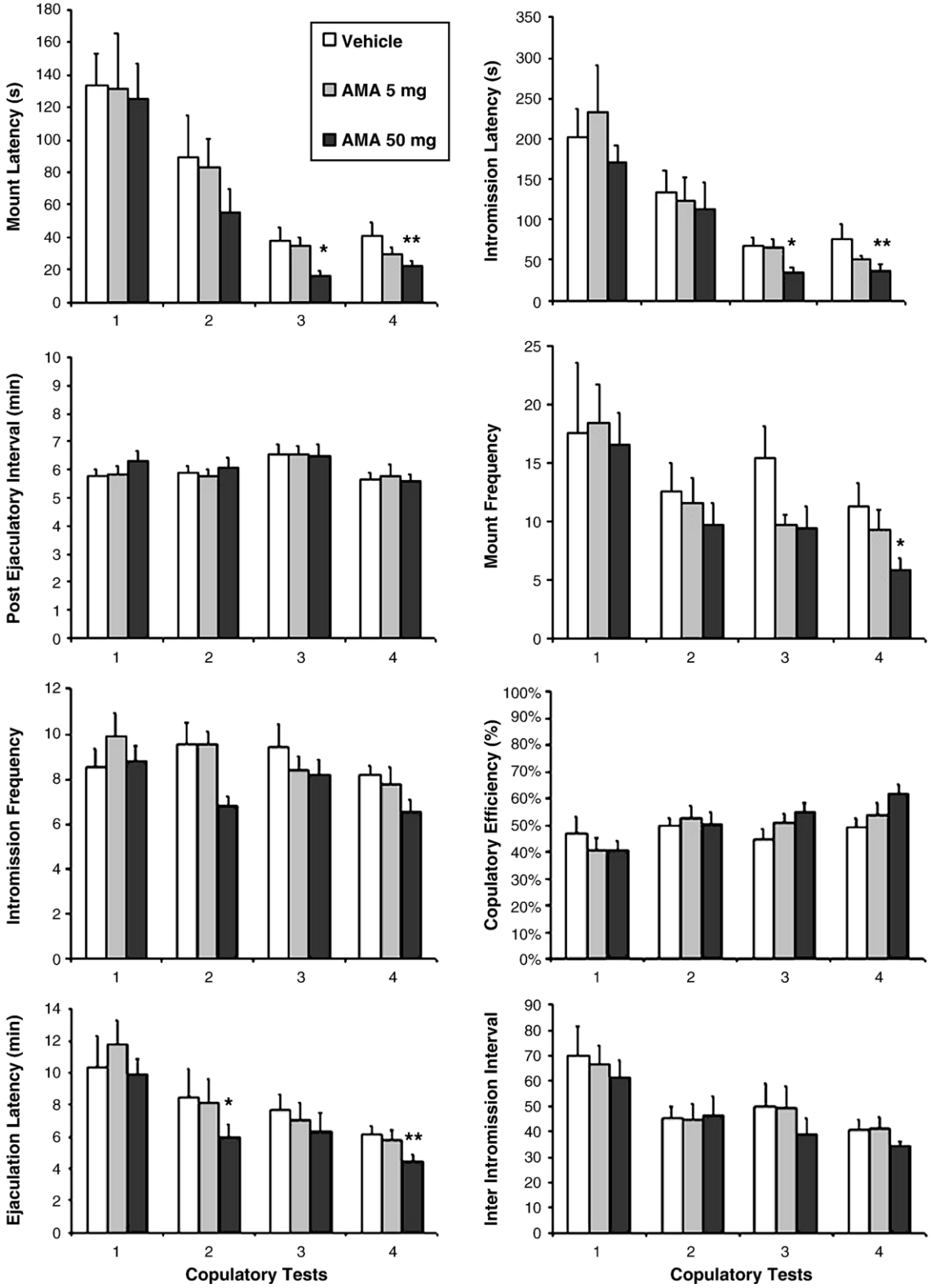

Fig. 1. Effects of chronic treatment with amantadine (5 to 50 mg/kg/day) on male rat sexual behaviour. Data expressed as mean ± SEM. Statistical analysis made by one-way ANOVA or Kruskal–Wallis test. *$p \leq 0.05$, **$p \leq 0.01$ for comparisons among control and experimental groups.

between groups were used for parametric data. All data were tested using the Bartlett method. When significant differences appeared among the SD, statistical analyses were made using a non-parametric Kruskal–Wallis test, followed by the "U" Mann–Whitney test for comparison purposes between the two groups.

3. Results

Chronic administration of Amantadine (AMA) was followed by an increase in copulatory frequency (Table 1). The number of complete copulatory series increased significantly after 21 days of chronic treatment with AMA (50 mg/kg), Chi-square = 4.444, $p = 0.035$, but not in rats treated with 5 mg/kg/day. Chronic treatment with 5 mg/kg/day of AMA did not change the sexual response in relation to controls, Fig. 1. After 14 days, the rats treated with 50 mg/kg/day exhibited a decrease in mount latency, $F(2,51) = 3.15$, $p \leq 0.05$, and in intromission latency, $F(2,51) = 3.02$, $p \leq 0.05$, but not in the post-ejaculatory interval, $F(2,48) = 0.116$, $p = 0.89$. After 21 days, the effects of the drug on the same parameters were enhanced. The mount frequency, KW = 6.32, $p = 0.042$, was reduced only after 21 days of chronic treatment with the maximum dose of amantadine (50 mg/kg/day), but copulatory efficiency was not affected by chronic treatment with AMA, $F(2,49) = 2.86$, $p = 0.067$. After 7 days of chronic treatment with AMA (50 mg/kg/day), ejaculation latency was reduced, $F(2,39) = 3.53$, $p = 0.039$, compared with controls. Also after 21 days of chronic treatment with AMA, the reduction in ejaculation latency was enhanced when compared with controls ($F(4,36) = 4.357$, $p = 0.018$). The interintromission interval was also not modified by the treatment with AMA ($F(2,49) = 1.8$, $p = 0.177$) as compared with controls.

Chronic treatment with 5 mg/kg/day of AMA also did not modify any measures of the sexual behaviour temporal patterning. After 7 days, treatment with AMA in higher doses decreased the mount bout frequency, KW = 10.31, $p = 0.006$, in relation to controls, but did not modify any other measure related to sexual behaviour temporal patterning. After 21 days, chronic treatment with AMA reduced mount bout frequency, KW = 6.31, $p = 0.043$; increased intromission per mount bout, $F(2,49) = 4.45$, $p = 0.017$; increased the mount bout rate, $F(2,33) = 4.256$, $p = 0.0227$; and increased mount bout time, $F(2,321) = 3.325$, $p = 0.0372$. The total mounts per mount bout, however, were not modified by chronic treatment with AMA, $F(2,49) = 1.154$, $p = 0.324$. Chronic AMA treatment also did not modify the other measures related to sexual behaviour temporal patterning, such as the intermount bout interval, $F(2,285) = 2.88$, $p = 0.058$; time out, $F(2,285) = 1.601$, $p = 0.223$; or genital grooming rate, $F(2,33) = 0.817$, $p = 0.451$ (Table 2).

Table 1
Percentage of male rats that achieved complete copulatory series within 30 min after chronic oral treatment with amantadine (5–50 mg/kg/day)

Groups (treatment)	T (days)	*n*	One series (%)	Two series (%)	Three series (%)	Four series (%)
Vehicle	0	12	100	41.7	8.3	0
AMA 5 mg		12	100	50.0	8.3	0
AMA 50 mg		12	100	41.7	0	0
Vehicle	7	12	100	50.0	25.0	0
AMA 5 mg		12	100	66.7	33.3	0
AMA 50 mg		12	100	83.3	58.3	16.7
Vehicle	14	12	100	91.7	41.7	8.3
AMA 5 mg		12	100	83.3	41.7	8.3
AMA 50 mg		12	100	100	66.7	25
Vehicle	21	12	100	100	41.7	8.3
AMA 5 mg		12	100	100	50.0	16.7
AMA 50 mg		12	100	100	83.3 *	41.7*

Statistical analysis made by Chi-square.
* $p \leq 0.05$ compared to vehicle vehicle-treated rats.

Table 2
Temporal patterning of male rat sexual behaviour after 21 days of chronic oral treatment with amantadine (5–50 mg/kg/day)

Measures (mean ± S.E.P.)	Vehicle	Amantadine 5 mg/kg/day	Amantadine 50 mg/kg/day
Mount bout frequency	9.63 ± 0.77	7.0 ± 0.58	5.8 ± 077 *
Intromission/mount bout	1.04 ± 0.1	1.33 ± 0.12	1.73 ± 0.22*
Mounts/mount bout	2.21 ± 0.2	2.57 ± 0.18	2.8 ± 0.34*
Intermount bout interval	38.89 ± 4.92	32.86 ± 2.39	52.6 ± 9.02
Time out	20.33 ± 3.72	19.71 ± 2.15	13.0 ± 1.82
Mount bout time	17.0 ± 3.12	13.13 ± 1.99	29.17 ± 7.67*
Mount bout rate	48.16 ± 8.18	39.75 ± 5.96	78.33 ± 13.7*
Genital grooming rate	29.04 ± 6.95	24.94 ± 5.17	38.81 ± 10.56

Statistical analysis made by one-way ANOVA or Kruskal–Wallis test.
* $p \leq 0.05$.

4. Discussion

In rats and humans, direct and indirect dopaminergic stimulants affect masculine sexual response (Hull et al., 1997). Amantadine, a stimulant of dopamine release, also evokes genital reflexes and enhances sexual responses acutely in rats (Ferraz and Santos, 1995). The present results show for the first time that similarly to acute treatment, chronic administration of AMA stimulates sexual response in the male rat. Our data also suggest that the enhanced sexual response observed in chronic treatment with amantadine does not produce pharmacological tolerance in rats. It is interesting to note that chronic treatment with 5 mg/kg/day of AMA (2.5 mg/kg twice a day) does not influence sexual response in rats, whilst the same amount is effective in acute treatment (Ferraz and Santos, 1995; Ferraz et al., 2001). Another intriguing result of the present work is that acute treatment with 50 mg/kg/day (25 mg/kg twice a day) of AMA stimulates all sexual behaviour components as well as accelerating sexual behaviour temporal patterning (Ferraz and Santos, 1995; Yells et al., 1995; Ferraz et al., 2001). These previous findings contrast with our results, showing that the chronic treatment of rats with 50 mg/kg/day of AMA enhances arousal measures and facilitates the ejaculatory mechanisms, but is ineffective in changing either the excitatory component or sexual behaviour temporal patterning.

In our present study, the copulatory frequency of all the rats increased from beginning to end, probably because training enhances sexual response. However, in the last test performed, the AMA-treated rats showed an increased sexual drive in relation to controls, strongly suggesting that AMA increments

sexual behaviour. These data are in agreement with the reduction in mount, intromission and ejaculation latencies. We can conclude that AMA treatment is associated with an activation of the arousal and ejaculatory components of sexual response. These stimulant effects could have masked improvement on excitatory component, because we observed a lack of significant effect on the copulatory efficiency in the last test.

At the 7th day of treatment, the AMA-treated rats showed a decrease in ejaculation latency, intromission frequency and mount bout frequency, whilst the arousal measures were not changed. On the other hand, the control rats showed improved sexual response from the first to the second copulatory tests. These results indicate that the ejaculatory component is more sensitive to AMA than the sexual training effect, whilst the opposite effect occurs with the arousal measures, suggesting that 7 days is a relatively short time period. The intercopulatory interval now called the interintromission interval is related to the ejaculatory mechanism (Sachs and Barfield, 1970; Melis and Argiolas, 1995). Chronic AMA treatment has not significantly modified this parameter. The lack of effects in the interintromission interval could be explained by the fact that the ejaculation latency reduced by AMA is not accompanied by a reduction in intromission frequency. After 14 days of chronic treatment with AMA, arousal was increased, but other measures were not affected. At 21 days, conversely, chronic treatment with AMA was effective in facilitating both the arousal and consummatory measures of sexual behaviour, probably due to the fact that the control group response reached a training plateau.

The effects of chronic AMA treatment upon the excitatory component and temporal patterning were less consistent, most likely because the AMA-treated rat's copulatory efficiency was not different from that of controls. Therefore, we suggest that the reduction in intromission frequency is not related to the penile erectile mechanism, but reflects improvement in the ejaculation component. Sachs (1978) has proposed that the reduction of the ejaculation threshold is triggered by successive mounts with and without intromissions. We believe that the main measure related to the excitatory component is copulatory efficiency, more than the analysis of intromission or mount frequencies. We can conclude that AMA treatment is associated with an activation of the arousal and ejaculatory components of sexual response. These stimulant effects could have masked improvement on excitatory component, because we observed a lack of significant effect on the copulatory efficiency in the last test.

The modifications in the sexual behaviour temporal patterning of the male rats brought about by chronic treatment with AMA were: a decrease in frequency but an increase in both the interval and time spent in mount bout, intensification in the number of intromissions per mount bout, and an increase in both mount bout time and mount bout rate. These data are consistent with an improvement in the social–sexual behaviour of the animals. We propose that the reduction in mount bout frequency and the increase in mount bout time and rate were probably related to the properties of the drug in enhancing the sexual drive of the male rats.

In conclusion, the main findings of our present work may be summarized as follows: a) chronic treatment with AMA effectively stimulates sexual response in male rats, similarly to the effect observed after acute treatment; b) the stimulating effects on the arousal measures of sexual behaviour are observable after 7 days of chronic treatment, increasing considerably after 28 days of the administration of AMA; c). The main result of chronic AMA treatment occurs in the arousal and ejaculatory components, whilst its effects on the excitatory component are less consistent; d) chronic treatment with AMA does not lead to tolerance.

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