

Effects on rat sexual behaviour of acute MDMA (ecstasy) alone or in combination with loud music

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Abstract. – The effects on sexual behaviour of acute low doses of methylenedioxymethamphetamine (MDMA) (0.3, 1, 3 mg/kg/i.p.), alone or in combination with exposure to loud music (1 h stimulation), were investigated in Wistar rats. Results indicate that acute MDMA, at dose of 3 mg/kg, notably impaired copulatory behavior of sexually experienced male rats.

In particular, MDMA-exposed animals exhibited a significant increase in intromission and ejaculation latencies as well as a significant decrease in percentage of rats displaying copulatory activity (one intromission at least). Surprisingly, one hour exposure to loud music, which per se resulted ineffective, antagonized the suppressive effect of MDMA by increasing the percent of animals displaying sexual activity. However, combined treatment of MDMA and music stimulation did not fully restore normal sexual behavior as the animals reaching ejaculation still showed a marked reduction of copulatory efficiency.

These findings demonstrate that the systemic administration of a single low dose of MDMA, alone or in combination with loud music, which is commonly present in certain environments such as rave parties, notably impairs copulatory activity of male rats.

Key Words:

MDMA, Loud music, Sexual behavior, % of ejaculating rats, Copulatory efficiency.

Introduction

The recreational use of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) has

gained increased popularity during the last decade in many countries of the world despite legislative action to limit its distribution. MDMA, structurally related to the stimulant amphetamine and the hallucinogen mescaline, is able to cause serotonergic and dopaminergic neural toxicity in every species tested and short term changes in noradrenergic system. Its acute effects appear to be mediated by the release and reuptake inhibition of brain monoamines, particularly serotonin and dopamine¹⁻³. It is well known that these biogenic amines have been implicated as facilitatory (dopamine) and inhibitory (serotonin) mediators of sexual desire, arousal and orgasm^{4,5}. Furthermore, recent findings demonstrate that serotonin is important for male reproductive development⁶. Taken together, these evidences suggest that the acute and long-term exposure to MDMA might affect sexual function and genital morphology. In fact, in spite of its mentioning as aphrodisiac, there are empirical and experimental evidence that MDMA impairs human sexual drive and behaviour. However, several methodological limitations associated with clinical studies such as the heterogeneity of human MDMA consumption, confounding variables such as doses, purity of the substance, duration and time of exposure, indicate that preclinical studies are needed in allowing a definitive account for the MDMA sexual properties. Surprisingly, to our knowledge, only one study investigated, so far, the effects of MDMA on sexual function in male rats⁷. In particular, Dornan et al. found a transient disruption of male copulatory behaviour after a

sub-chronic treatment with high doses (40 mg/kg) of the drug. Nevertheless, MDMA users typically consume much lower doses than those used in animal studies⁸⁻¹⁰. Moreover, the effect of acute low doses of MDMA on sexual behaviour remained unexplored. Therefore, further investigations on acute and chronic effects of low to moderate doses of MDMA in rodents result necessary to reach a predictive clinical value. A further source of variability in MDMA effects in humans that should be taken into account deals with the environmental conditions^{11,12}. In particular, in most cases, ecstasy is abused in organised all-night dance parties known as "raves" where techno-music is played at a high volume. It has been demonstrated that music recruits neuronal systems of rewards and emotions similar to those known to respond specifically to biologically relevant stimuli, such as food and sex and those that are activated by drugs of abuse. Techno-music is able to activate the noradrenergic system and the hypothalamic-pituitary-adrenal (HPA) axis more than slow music, producing a neuroendocrine pattern similar to that elicited by psychological stress^{13,14}.

The aim of the present study was to address both these issues, namely the acute effect of moderate MDMA doses on rat sexual function and the concomitant exposure to loud music.

Materials and Methods

Procedure

The experiments have been conducted in accordance with guidelines released by Italian Ministry of Health (D.L. 116/92 and D.L. 111/94-B), the Declaration of Helsinki, and the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health (USA). Male and female rats were housed under a reversed 12/12 light/dark cycle (light on: 20.00h-08.00 h) for two weeks before testing, with food and water ad libitum at constant room temperature (20-22°C). Ninety Wistar adult male rats weighing 300-350 g were used in the following experiments. Each male rat was given sexual screening tests during which it was placed, on alternate days, with a sexual receptive female until one ejaculation was achieved during each of the three-30 min tests. Only males reaching this criterion were subsequently used. After successful completion of the last screening

session, males with similar performance were equally distributed into eight experimental groups (10 per group).

Four groups received three MDMA dose levels (0.3, 1, 3 mg/kg) and MDMA-vehicle (control) one hour before the test session. The drug was dissolved in 0.9% saline and injected intraperitoneally (i.p.) at the volume of 1 ml/kg. Human MDMA users typically consume 1-2 tablets of MDMA in a single session giving an estimated oral dose of 1-4 mg/kg. Allowing for interspecies scaling effects and differences in route of administration, the doses of MDMA employed in the present study correspond to a low-moderate exposure to "ecstasy" in man⁸⁻¹⁰. The other four groups were treated with the same MDMA doses (0.3, 1, 3 mg/kg) and MDMA vehicle (saline) in combination with 1 h exposure to loud music (s). The acoustic stimulus (intensity = 88.2-91.8 dBA); frequency = 50 Hz-8 KHz) was delivered for one hour in a sound-attenuating cabin (3.00 x 2.00 x 2.00 m) soon after each saline or MDMA administration. At the beginning of the experiment, the sound pressure level was measured by an integrated Bruel & Kjaer phonometer placed 3 meter far from the location of the animal rack. Male rats were then tested for sexual activity in a 30 min test session.

Drugs

MDMA, (\pm)-3,4-methylenedioxyamphetamine hydrochloride, (SALARS s.p.a., Como, Italy) was dissolved in 0.9% saline and injected i.p. at a volume of 1 ml/kg. Control rats received equivalent i.p. injections of saline.

Sexual Behaviour and Ultrasonic Emission

These study procedures had been performed according with the original protocols by Cagiano et al.^{15,16}. As stimulus females we used bilaterally ovariectomized rats in which oestrus had been induced by subcutaneous injection of estradiol benzoate (8 μ g/rat) and progesterone (200 μ g/rat) dissolved in 0.2 ml of sesame oil, 52 and 4 h before the test session, respectively. Sexual behaviour was recorded by a video-tape recording unit (JVC videocamera, Videotape recorder and TV monitor). Ultrasonic calls, detected by a QMC ultrasonic microphone connected to a receiver (QMC Bat Detector S200, London, UK) which transformed, in real time, the ultrasonic calls into audible sounds, were sent to the video tape-recorder through the mi-

crophone connection terminal of the video camera. The experiments, performed in the central part of the dark period (12.00h-16.00h), were carried out in a sound-attenuating cabin (Amplifon G-type cabin) under red illumination provided by two 40 W fluorescent lamps. Each male rat was observed alone for 5 min. An oestrous female was then introduced into the centre of the arena and the behaviour of the couple was then recorded. Each test lasted a maximum of 30 minutes if no ejaculation was achieved or until one ejaculation followed by an intromission was achieved. If no intromission was displayed within the first 15 minutes, the test terminated and the male was considered a "non copulator". Video tape-recordings were later replayed and analysed (in slow motion when necessary) and the following parameters were measured: (ML) mount latency (time between the introduction of the female into the mating cage and the first mount in the first ejaculatory series); (IL) intromission latency (time between the introduction of the female into the mating cage and the first intromission in the first ejaculatory series); (M/IF) mount-intromission frequency (number of mounts or intromissions in each ejaculatory series); (EjL) ejaculation latency (time between the first intromission and ejaculation in each ejaculatory series); (EjF) ejaculation frequency (number of ejaculations in each copulatory series); (PEjI) postejaculatory interval (interval between each ejaculation and the next intromission in each copulatory series); (TM/IF) total mount/intromission frequency (total number of mount/intromission frequency (total number of mounts or intromissions during the test session); (ICI) inter copulatory interval (ejaculation latency/intromission frequency in each copulatory series); (Pseudo-ICI) pseudo intercopulatory interval (for non-ejaculating rats): time from the first intromission to the end of the 30 min session/number of the intromissions; (Copulatory Efficiency) intromission frequency/intromission + mount frequency.

The following ultrasonic parameters were then evaluated: (L50) latency from the introduction of the stimulus female into the mating cage and the onset of the first 50 kHz call; (L22) time from the ejaculation and the beginning of the 22 kHz vocalization in each copulatory series; (D22) duration of the 22 kHz post-ejaculatory vocalization in each copulatory series. Each group consisted of 10 animals.

Statistical Analysis

Depending on the homo or heteroschedasticity of the data, statistical analysis was based on parametric (two-way ANOVA followed by Tukey's Multiple Comparison Test) or non parametric test (Kruskal-Wallis ANOVA followed by Dunn's Multiple Comparison Test). Fisher's exact test was used where appropriate.

Results

Sexual Behaviour and Ultrasonic Emission

The results indicate that MDMA treatment notably impaired the copulatory behaviour of sexually vigorous experienced male rats only at the dose of 3 mg/kg. As far as the latency to the first intromission, Kruskal-Wallis ANOVA gave the following significant difference: $H=51.14$, $df=7$; $p<0.001$. Individual comparisons (Dunn's Multiple Comparison test) showed that, in saline-treated control rats, 1 h exposure to loud music failed to affect this end-point as compared to control rats treated with saline given alone. On the contrary, MDMA treatment significantly increased the latency to the first intromission either when given alone ($p<0.01$) or when given in combination with exposure to sound stimulation ($p<0.001$) (Figure 1).

The percentage of rats exhibiting at least one intromission during the test session was significantly lower ($p<0.005$, Fisher's exact test) in MDMA-treated rats without exposure to acoustic stimulation than in the respective vehicle group: (saline=100%; MDMA 3 mg/kg=20%). On the contrary, 1 h exposure to loud music antagonized the effect of MDMA ($p<0.05$, Fisher's exact test) restoring the number of copulating animals close to normal levels (saline + s =100%; MDMA 3 mg/kg + s=70%) (Figure 2).

As far as the ejaculation latency, two-way ANOVA showed the following results: $F_{\text{treatments}}=27.92$; $df=3/72$; $p<0.0001$; $F_{\text{music}}=12.60$; $df=1/72$, $p<0.001$; $F_{\text{treatments} \times \text{music}}=0.14$; $df=3/72$, n.s. As suggested by Wilcox (1987), in absence of significant interaction between treatments and music, selective post hoc tests (Tukey's test) provided evidence of a higher latency to the ejaculation ($p<0.01$) in both MDMA-treated groups than in the respective vehicle groups, independently by the exposure to acoustic stimulation (Figure 3).

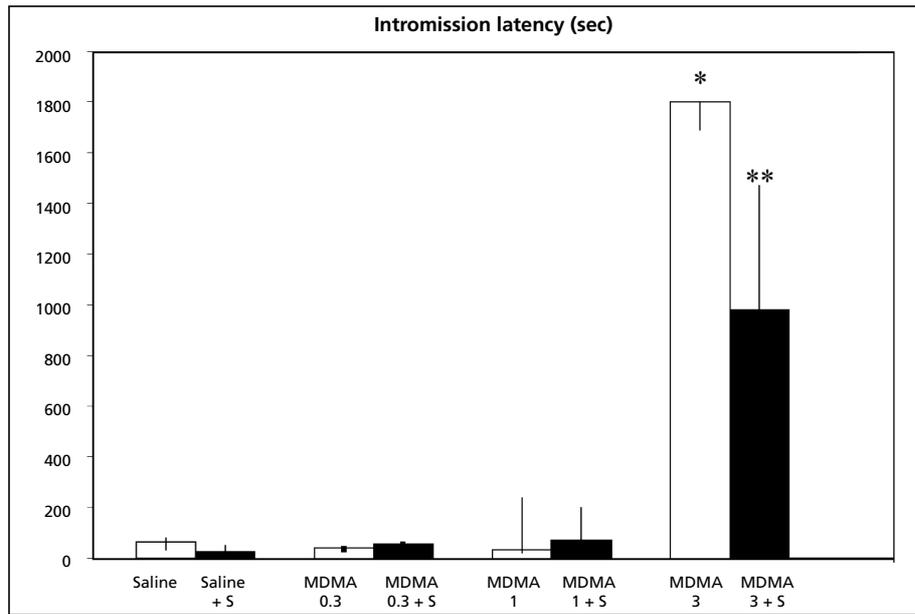


Figure 1. Effects of acute MDMA (0,3-1-3 mg/kg, i.p.) or MDMA vehicle (saline) treatment, given alone or in combination with sound stimulation (s) on Intromission Latency (I/L) of sexually experienced male rats. Data are expressed as median values and interquartiles. (____). * $p < 0.01$ vs vehicle; ** $p < 0.001$ vs vehicle + s. (Dunn's Multiple Comparison test).

The percentage of rats achieving ejaculation during the test session was totally abolished by MDMA treatment given alone with respect to the control group (saline=100%; MDMA 3 mg/kg=0%; $p < 0.0001$ Fisher's exact test). Combined treatment of MDMA and loud music significantly increase the percentage of ejaculating rats

with respect to the MDMA-alone group ($p < 0.05$ Fisher's exact test) although it remained significantly lower compared to the respective saline-control group (saline + s=100%; MDMA 3 mg/kg + s=40%; $p < 0.01$ Fisher's exact test) (Figure 4).

Furthermore, two way ANOVA for copulatory efficiency gave the following results: $F_{\text{treatments}} =$

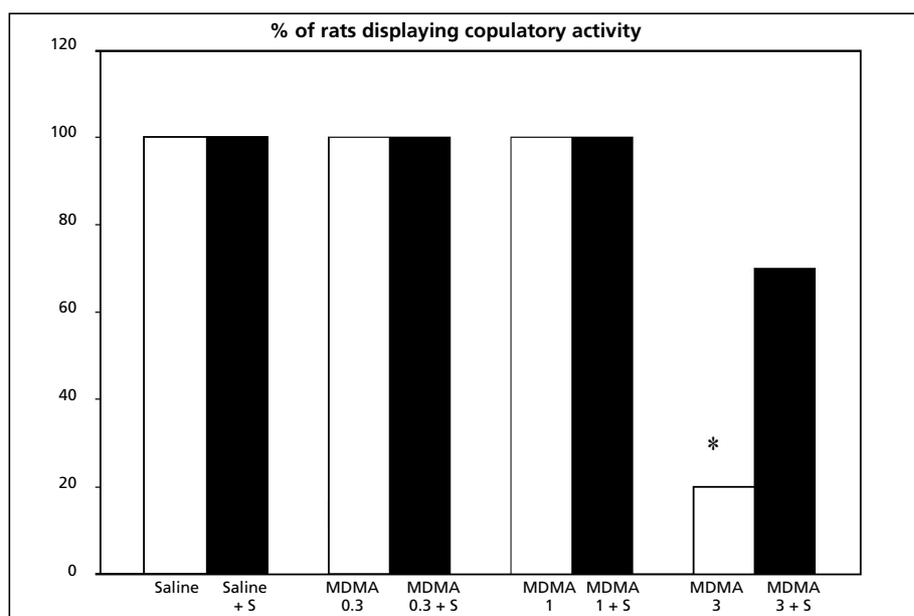
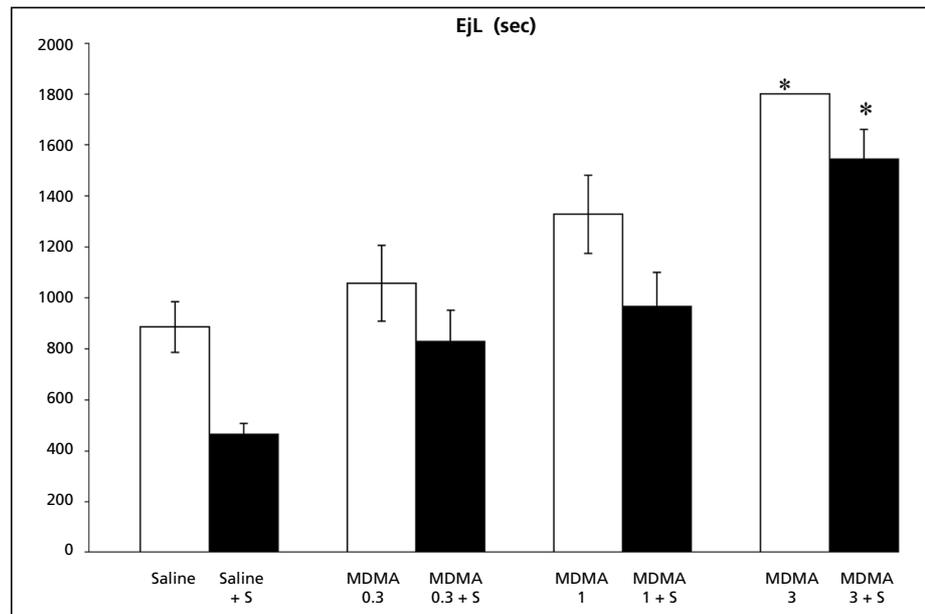


Figure 2. Effects of acute MDMA (0,3-1-3 mg/kg; i.p.) or MDMA vehicle (saline) treatment, given alone or in combination with sound stimulation (s) on percentage of sexually experienced male rats displaying copulatory activity. * $p < 0.005$ vs vehicle (Fisher's exact test).

Figure 3. Effects of acute MDMA (0,3-1-3 mg/kg; i.p.) or MDMA vehicle (saline) treatment, given alone or in combination with sound stimulation (s) on Ejaculation Latency (EjL) of sexually experienced male rats. Data are expressed as mean values \pm S.E.M. * p < 0.001 vs vehicle and vehicle + s groups (Tukey's Multiple Comparison Test).

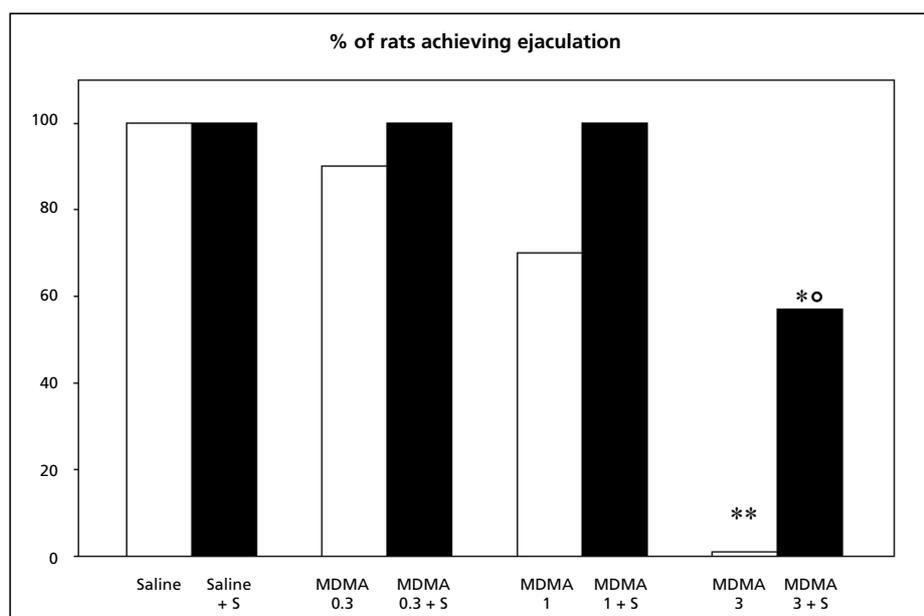


40.41 $df=3/72$; $p < 0.001$; $F_{music}=11.34$; $df=1/72$, $p < 0.0025$; $F_{treatments \times F_{music}}=5.25$; $df=3/72$, $p < 0.005$.

Individual comparisons (Tukey's test) showed that MDMA treatment markedly decreases the copulatory efficiency in both groups (< 0.001 Fisher's exact test) as compared to the respective vehicle groups.

As far as the ultrasonic emission during sexual encounters, the co-administration of MDMA and loud music significantly reduces the percentage of ejaculating animals showing 22 kHz PEj ultrasonic emission as compared to the respective vehicle group ($p < 0.025$ Fisher's exact test). Statistical analysis for all other sexual and ultrasonic parameters did not show any significant difference.

Figure 4. Effects of acute MDMA (0,3-1-3 mg/kg/i.p.) or MDMA vehicle (saline) treatment, given alone or in combination with sound stimulation (s) on the % of sexually experienced male rats displaying ejaculation * p < 0.01 vs vehicle + s; ** p < 0.001 vs vehicle; $^{\circ}p$ < 0.05 vs MDMA (Fisher exact test).



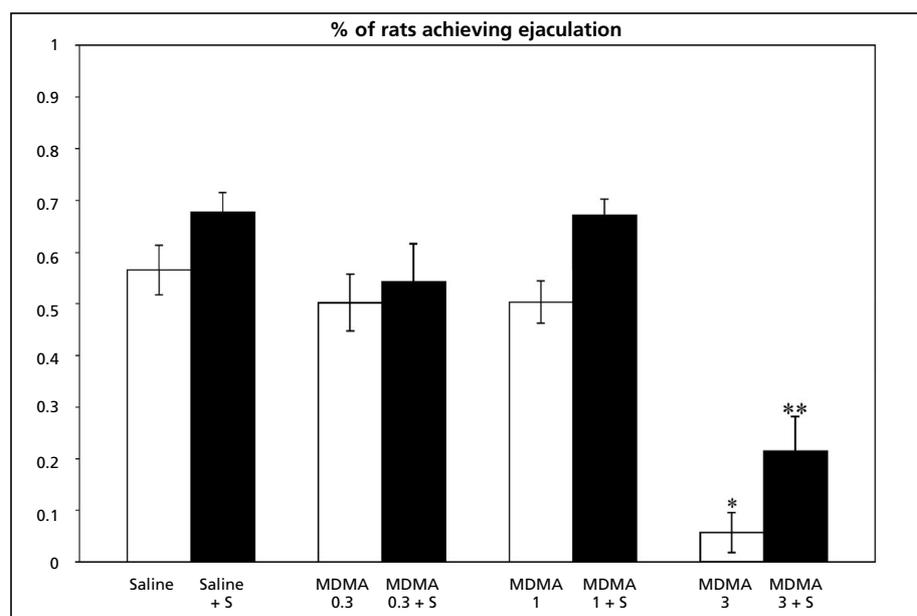


Figure 5. Effects of acute MDMA (0,3-1-3 mg/kg; i.p.) or MDMA vehicle (saline) treatment, given alone or in combination with sound stimulation (s) on copulatory efficiency. Data are expressed as mean values \pm S.E.M. * p < 0.001 vs vehicle and vehicle + s groups (Tukey's Multiple Comparison Test).

Discussion

The most relevant finding in these experiments is that the higher dose of MDMA used in this study (3 mg/kg) induced a significant impairment of sexual performance in male rats only in absence of music stimulation. On the contrary, the exposure to an acoustic stimulation (95 Db), which per se did not modify the evaluated sexual parameters, produced a reduced improvement of copulatory activity with respect to animals treated with the same dose of the drug, but in absence of music stimulation. However, combined treatment of MDMA and music was not able to fully restore normal sexual behaviour since copulating rats still showed a marked reduction of copulatory efficiency. The behavioural alterations exhibited by MDMA male treated rats (increase in intromission and ejaculation latencies, decrease in the percentage of rats exhibiting at least one intromission or achieving ejaculation during the test session) are consistent with the results of few clinical and experimental findings showing an impairment of sexual performance after MDMA ingestion^{7,17,18}. However, it should be pointed out that experimental data available in literature are mainly related to tests on animals, in which the short and long-term neurotoxic effects are evaluated following sub-chronic administration of high repeated doses (40 mg/kg) of MDMA⁷. Furthermore, it is well known that several methodological limitations are associated with clinical

studies (see introduction). Conversely, the behavioural changes observed in this study, occurred at MDMA dose levels equivalent to an acute low-exposure to "ecstasy" in man, reproduce the environmental conditions occurring in human life within the social gatherings of young people (rave or techno type). Indeed, dance parties, rave parties and after-hour dancing with techno-music are frequently characterized by the recreational use of amphetamine-type stimulants, in the attempt to decrease perception of fatigue and to increase endurance.

It has been well demonstrated that acoustic stimulation, combined with "ecstasy", produced a selective enhancement of cardio and neurotoxicity^{11,12}. However, despite the increasing number of evidence demonstrating the synergism between noise and MDMA in inducing toxic effects, the underlying mechanisms remained unknown. Also for our findings, the mechanisms underlying the difference in the copulatory effects of similar treatments (MDMA 3 mg/kg + music vs non music) remain unexplained. However, one might speculate that, since fast music is a powerful stimulus for the activation of the noradrenergic system and the hypothalamic-pituitary-adrenal axis (HPA), when combined with amphetamine-type stimulants may produce a synergistic effect on the monoaminergic pathways. Indeed, it has been demonstrated that music is able to produce intense pleasure responses which are correlated with brain regions activities

implicated in reward and emotion. The activation of the reward system by music may maximize pleasure, not only by activating the reward system, but also simultaneously decreasing activity in brain structures associated with negative emotions and could explain the improvement of sexual activity in presence of music stimulation, as obtained in our experiments. The main limitation of the present study is clearly the lack of neurochemical analysis of the brain of rats treated with both low MDMA doses and music stimulation. The hypothesis that the observed effects on sexual performance are related to the action of MDMA on brain 5HT and DA systems, needs further scientific demonstration. The neurobiological substrate of human sexuality is, up to now, still poorly understood. Current hypothesis suggest that dopaminergic activity in nucleus accumbens (NAc) is associated with sexual desire and erectile response while central serotonergic activity is inhibitory to erectile and orgasmic function⁵. The stimulant and rewarding properties of MDMA are in part thought to arise from the activation of mesolimbic dopaminergic neurons in the Ventral Tegmental Area (VTA) which project to NAc. MDMA causes simultaneous release of 5-HT and both transporter-mediated and impulse-mediated DA release, this latter depending on 5-HT transmission and may be explained by the stimulatory effect of 5-HT_{1B/2A} and inhibitory effect of 5-HT_{2C} receptors. Recent findings suggest that MDMA-mediated dopamine (DA) increases, within the NAC shell, are dampened by the increases in VTA GABA levels subsequent to activation of 5-HT_{2B/2C} receptors¹⁹. Furthermore, pharmacological studies demonstrated that drugs which enhance serotonergic activity elevate serum corticosterone and/or prolactin (PRL) concentrations making these as sensitive indicators of 5HT receptor stimulation. Serum level of PRL were significantly increased by MDMA at doses ranging from 1 to 20 mg up to 4 h after ingestion of the drug. Recent neuroendocrine studies, examining the effects of sexual arousal and orgasm in humans, demonstrated a marked elevation of plasma prolactin in both males and females immediately after orgasm. As prolactin was shown to be a robust marker of orgasm, it may act as peripheral neuroendocrine reproductive reflex (improving fertility and conception) and/or as a feedback signal to neuronal systems that may mediate sexual arousability and satiation following orgasm. Prolactin may be able to down regulate the dopaminergic activity in certain areas,

modulating sexual arousability and satiation. Interestingly, clinical studies have shown an impairment of sexual drive and performance after MDMA-ingestion, which may be caused by the MDMA-induced secretion of prolactin leading to a psychophysical equivalents state of sexual satiation compared to the post-orgasmic period²⁰. Therefore, the results of our study, showing a marked impairment of sexual performance in experienced MDMA treated rats, which is in line with clinical data, could explain the frequent observations of 22 kHz calls in non-copulating MDMA-treated animals, mainly in the absence of music stimulation (data not shown). These post-orgasmic vocalizations (22 kHz) occur concurrently with the absolute refractory period during which the male is incapable of renewed sexual activity. Even if their communicative function is not yet established, it has been suggested that 22 kHz calls serve to discourage other males from mating with the same female or to keep the female at a distance during the total postejaculatory refractory period²¹.

In conclusion, these data demonstrate that MDMA, even in low doses, can disrupt sexual performance of experienced male rats and that this effect is blunted by strong sensorial stimulation. Our results, therefore, further confirm the role of environmental factors in modulating the central effects of MDMA, even if the underlying mechanisms remain to be elucidated.

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