

Impact of Prenatal and Acute Methamphetamine Exposure on Behaviour of Adult Male Rats

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Abstract: Psychostimulants have been shown to alter behaviour in both rats and humans. The aim of the present study was: (1) to assess the effect of prenatal and acute methamphetamine (MA) administration on behaviour in adult male rats and (2) to find out if the prenatal exposure to MA increases sensitivity to acute MA application in adulthood. Behaviour of adult male rats prenatally exposed to MA (5 mg/kg) or no drug was tested in Open field (OF) and Elevated plus maze (EPM). Half of the animals were injected with MA (1 mg/kg) subcutaneously 30 minutes prior to testing. Locomotion, exploration, comforting behaviour and anxiety were evaluated in the OF, while anxiety and exploratory behaviour were assessed in the EPM. Our results showed that prenatal MA did not have an effect on baseline behaviour in either of the tests. By contrast, acute MA increased overall psychomotor activity by increasing locomotion and exploratory behaviour and decreasing comforting behaviour. Moreover, adult rats prenatally exposed to MA were more sensitive to the effects of acute MA on exploration. In addition, acute MA application decreased anxiety in the OF as well as in the EPM. Our present study, thus, demonstrates that acute MA increases overall psychomotor activity and decreases anxiety to novel environment. To further support our hypothesis

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that prenatal MA exposure increases sensitivity to drugs in adulthood, studies investigating the levels of dopamine in the rat brain after prenatal MA exposure are planned.

Introduction

Methamphetamine (MA) is a psychostimulant drug with high potential for abuse [1]. Moreover, intermittent administration of MA and other psychostimulants was shown to result in a progressive increase in their psychomotor activating effects, a phenomenon referred to as behavioural sensitization [2–4]. However, adult animals with mature brain structures were usually used in studies showing the sensitizing effects of psychostimulants on central nervous system [5–9]. Not only are there very few works existing on the impact of prenatal MA exposure on behavioural sensitization, but the studies that already exist are quite incoherent. While an *in vitro* study found increased susceptibility to the neurotoxic effects of MA in adult mice prenatally exposed to the same drug [10], there is another study demonstrating profound behavioural tolerance to amphetamine challenge in rabbit offspring prenatally exposed to cocaine [11]. Some other studies also did not find behavioural sensitization to MA in rats exposed to MA *in utero* [12, 13]. On the contrary, in our latest study, we showed increased sensitivity to MA in adult male rats prenatally exposed to the same drug [14]. Yet, the effect was observed in one of the performed tests only. Thus, such a result is not unequivocal and therefore we continue in studying of the problem.

Psychostimulants have been shown to affect behaviour in a serious manner; they induce aggressive behaviour and cause changes in social interactions [15, 16]. Behaviour of both, humans [17] and laboratory animals [18] was shown to be affected. As far as anxiety is concerned, most of the studies demonstrated anxiogenic effect of MA and other psychostimulants [18–20]. Acute as well as chronic cocaine administration induced an anxiogenic response in different models of anxiety in rodents [18, 21]. Similarly, our previous study showed acute MA dose in adulthood to decrease social contacts in male rats in the test of social interaction [22]. According to File [23], decreased social interactions correspond to anxiogenic behaviour.

Since MA was shown to readily cross the placenta and approximately half of MA users are women of reproductive age [24–26], there is a risk of prenatal MA exposure of their children if they become pregnant. Several studies suggest that MA can affect the development of central nervous system in a serious manner. Altered neonatal behavioural patterns characterized by abnormal sleep patterns, poor feeding, tremors, and hypertonia as well as visual and motor difficulties were demonstrated in neonates exposed to MA during prenatal period [27]. Another study showed decreased arousal, increased stress and poor quality of movement in prenatally MA-exposed neonates [25]. Our previous study demonstrated that

prenatal MA exposure impaired development of sensorimotor functions in pups during the preweaning period [28].

However, there are not any studies investigating the effect of prenatal MA exposure on behaviour in adulthood and thus examining the long-term effects of MA exposure in utero. There are at least studies on the effects of prenatal cocaine tested in adulthood showing hyperresponsiveness to stressors [29, 30].

The present study was therefore designed to reveal the effects of prenatal MA exposure as well as the effect of acute MA dose administered in adulthood on the behaviour of adult male rats. Additionally, possible sensitizing effect of prenatal methamphetamine exposure to acute dose of the same drug in adulthood was examined.

Material and Methods

Animals and drug administration

Adult female Wistar rats (250–300 g) from Anlab farms (Prague, Czech Republic) were randomly assigned to MA-treated or control group. They were smeared by vaginal lavage to determine the phase of estrous cycle. At the onset of the estrus phase of the estrous cycle they were housed overnight with sexually mature stimulus males. There was always one female and one male in each cage. The next morning the females were smeared again for the presence of sperm and returned to their previous home cages. The day after impregnation was counted as day 1 of gestation. MA-treated females were injected subcutaneously (s.c.) with D-methamphetamine HCl in a dose of 5 mg/kg through the entire gestation (i.e. from the first to the last day of gestation) [31]. Control females were not exposed to any injection. The day of birth was counted as postnatal day (PD) 0. On PD 1, MA-exposed pups were injected intradermally with black India ink in the left foot pad and control pups were not tattooed. A total of 20 litters were used in the experiment. The number of pups in each litter was adjusted to 12. Whenever possible, the same number of male and female pups was kept in each litter. To avoid litter bias pups were cross-fostered on PD 1, so that one mother usually raised 6 control and 6 MA pups. Four animals from each litter were used – always one control and one MA from each mother for the OF and the EPM, respectively [32]. The rest of the animals were used in other studies. On PD 21, animals were weaned and housed in groups, separated by sex. Animals were left undisturbed until adulthood.

To determine the effect of acute MA in adulthood, half of the rats from each of the prenatally treated groups were administered 1 mg/kg of MA s.c. 30 min prior to testing.

Behavioural tests

Behaviour of the adult male offspring (PD 60–90, n=80) was tested in Open field (OF) and Elevated plus maze (EPM). The OF arena (45×45×30 cm) was enclosed

by plastic walls – three of them were opaque while the front wall was made of transparent plexiglass. The floor was crisscrossed by lines and in the centre of the arena a central ring (20 cm in diameter) was drawn. The EPM consisted of four arms perpendicular to each other elevated 50 cm above the floor. Two opposite arms were enclosed by brown plastic walls (30 cm high) while the two remaining arms were open and surrounded by transparent plexiglass walls. All arms were joined in the centre of the maze so that rats could freely pass from one arm to another.

Both, the OF and the EPM were illuminated by dim lightning and rats were not habituated to either of the apparatus so that they were exposed to the unfamiliar environment during the tests. On the day of the experiment, rats were moved to the testing room, where they remained in their home cage for a 30-min acclimation period. The test started by placing a rat in the centre of the OF or the EPM. The rat's behaviour was recorded on a video camcorder – for a 10 min period in the OF and 5 min period in the EPM, respectively. After that the rat was removed and the floor and walls of the testing apparatus were cleaned by Ajatin solution and dried thoroughly before placing another rat to avoid influence of the smell traces on the behaviour.

The video recordings were evaluated manually by using ODLog software (RegSoft.com). The recorded behaviours in the OF were as follows: (a) locomotion – number of lines crossed; (b) exploratory behaviour – total time spent by sniffing and rearing; (c) comforting behaviour – total time spent by and frequency of facing and grooming; (d) anxiety – total time spent in and frequency of entering the corners and central ring; number of boluses and total time spent by freezing when animal was immobile and did not exhibit any of the aforementioned activities.

In the EPM the anxiety was measured by using the following parameters: (a) total time spent in and frequency of entering the closed arms (all 4 paws); (b) total time spent in and frequency of entering the open arms (all 4 paws) and (c) frequency of stretched-attend postures (SAP) from closed to open arms, determined when the subject, located at the end of a closed arm, exhibited an elongated body posture stretched forward with snout entering an open arm followed by quick return into the closed arm. To differentiate the effect of MA on the anxiety from the psychomotor activating effects of this drug, locomotion and exploration were also recorded in the EPM. Locomotion was measured as the frequency of total arm entries while exploration was assessed by using total time spent by sniffing and rearing in open arms and in the centre of the maze.

The procedures for animal experimentation utilized in this report were reviewed and approved by the Institutional Animal Care and Use Committee and is in agreement with the Czech Government Requirements under the Policy of Humans Care of Laboratory Animals (No. 246/1992) and with the regulations of the Ministry of Agriculture of the Czech Republic (No. 311/1997).

Statistical analyses

As there were no differences in the animals of the same prenatal exposure that were raised by mothers of different drug treatment, the raising mother (biological vs. foster) was not taken as a factor for statistical analyses.

Two-way ANOVA (Prenatal treatment × Treatment in adulthood) was used to analyze each type of behaviour separately. Bonferroni test was used for post-hoc comparisons. Differences were considered significant if $p < 0.05$.

Statistical data will be presented as $[F (N-1, n-N) = xx.xx; p < 0.0x]$, where F = test criterion of ANOVA, $N-1$ = degrees of freedom of groups, $n-N$ = degrees of freedom of individual subjects, p = probability level.

Results

Open field

No significant effects of Prenatal treatment were found for locomotion, comforting behaviour and anxiety. In contrast, administration of MA in adulthood profoundly affected behaviour in the OF. Statistical analyses revealed significant main effect of Treatment in adulthood on locomotion $[F (1,35) = 95.70; p < 0.0001]$, such that

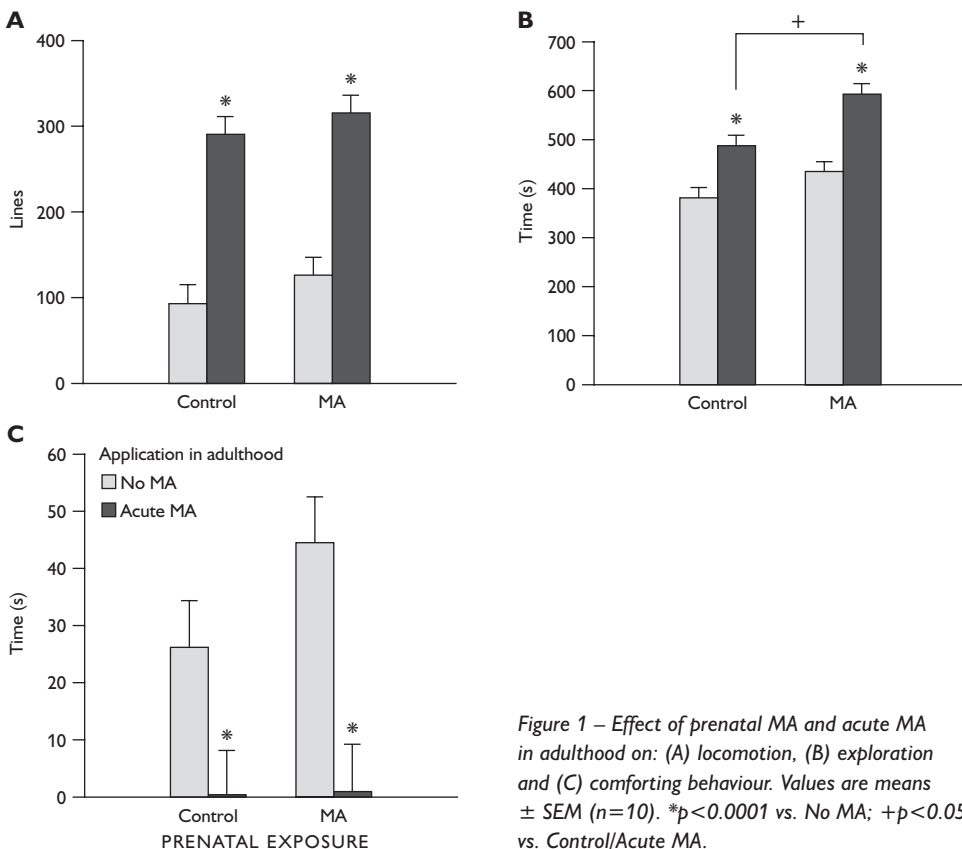


Figure 1 – Effect of prenatal MA and acute MA in adulthood on: (A) locomotion, (B) exploration and (C) comforting behaviour. Values are means ± SEM (n=10). * $p < 0.0001$ vs. No MA; + $p < 0.05$ vs. Control/Acute MA.

rats after acute MA dose in adulthood crossed more lines than the rats without any exposure before testing as shown in Figure 1A, regardless of prenatal treatment.

For exploration significant main effect of Treatment in adulthood was found [$F(1,35) = 25.22$; $p < 0.0001$], rats with MA pre-treatment exhibited increased exploratory activity when compared to rats with no MA challenge in adulthood (Figure 1B). Prenatally MA exposed rats explored the OF more than the controls, regardless of MA challenge in adulthood [$F(1,35) = 9.15$; $p < 0.01$]. In addition, significant interaction (Prenatal treatment \times Treatment in adulthood) [$F(1,35) = 5.12$; $p < 0.05$] was demonstrated. The post-hoc test showed no difference in time spent by exploration between the controls and prenatally MA-exposed group without MA challenge in adulthood, while acute dose of MA administered in adulthood increased the rate of exploration more in prenatally MA-exposed rats than in control rats (Figure 1B).

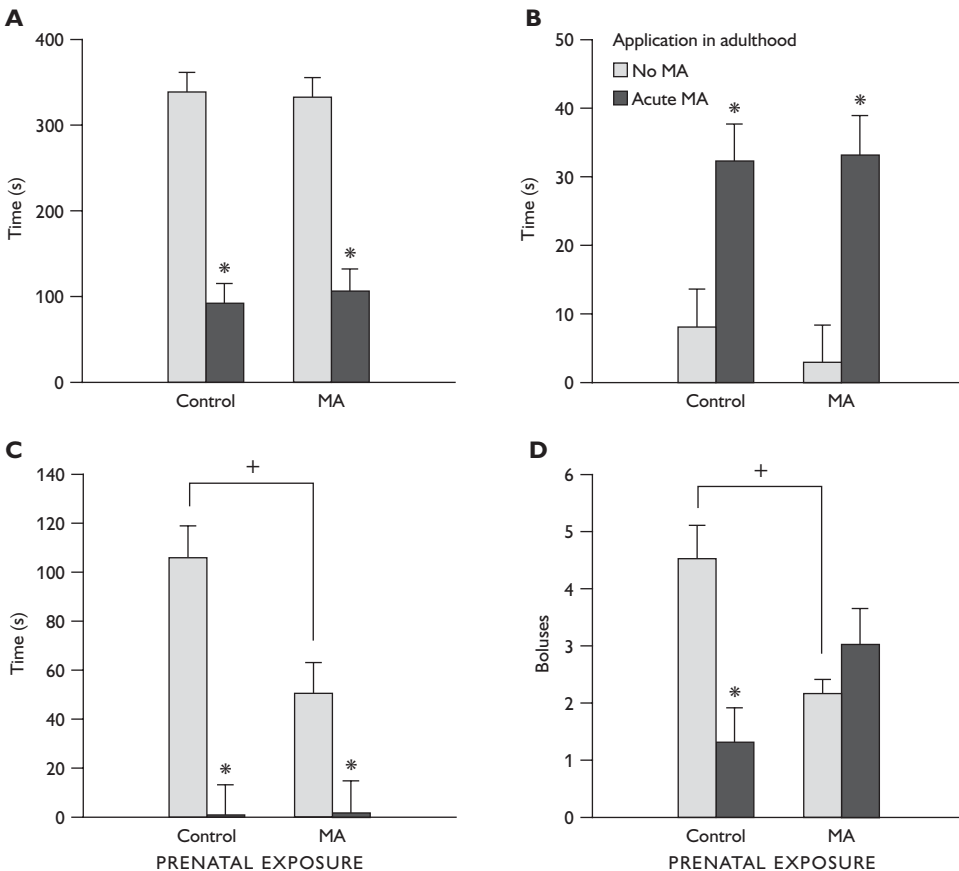


Figure 2 – Effect of prenatal MA and acute MA in adulthood on: (A) time spent in corners, (B) time spent in central ring, (C) freezing and (D) boluses. Values are means \pm SEM ($n=10$). * $p < 0.0001$ vs. No MA; + $p < 0.05$ vs. Control/No MA.

For comforting behaviour there was a main effect of Treatment in adulthood [$F(1,35) = 32.27$; $p < 0.0001$], such that rats with MA challenge in adulthood exhibited less facing and grooming activities when compared to rats without acute MA dose in adulthood as shown in Figure 1C, regardless of prenatal exposure. Further, MA administration in adulthood decreased the time spent in corners [main effect of Treatment in adulthood, $F(1,35) = 94.29$; $p < 0.0001$] while increased the time spent in the central ring [main effect of Treatment in adulthood, $F(1,35) = 17.87$; $p < 0.001$] as shown in Figure 2A and 2B, respectively.

For freezing there was main effect of Prenatal treatment [$F(1,35) = 5.01$; $p < 0.05$], Treatment in adulthood [$F(1,35) = 40.06$; $p < 0.0001$] and significant interaction of the two factors [$F(1,35) = 5.43$; $p < 0.05$] (Figure 2C). Prenatal MA exposure as well as MA administration in adulthood decreased amount of time being immobile relative to control group and group without MA challenge in

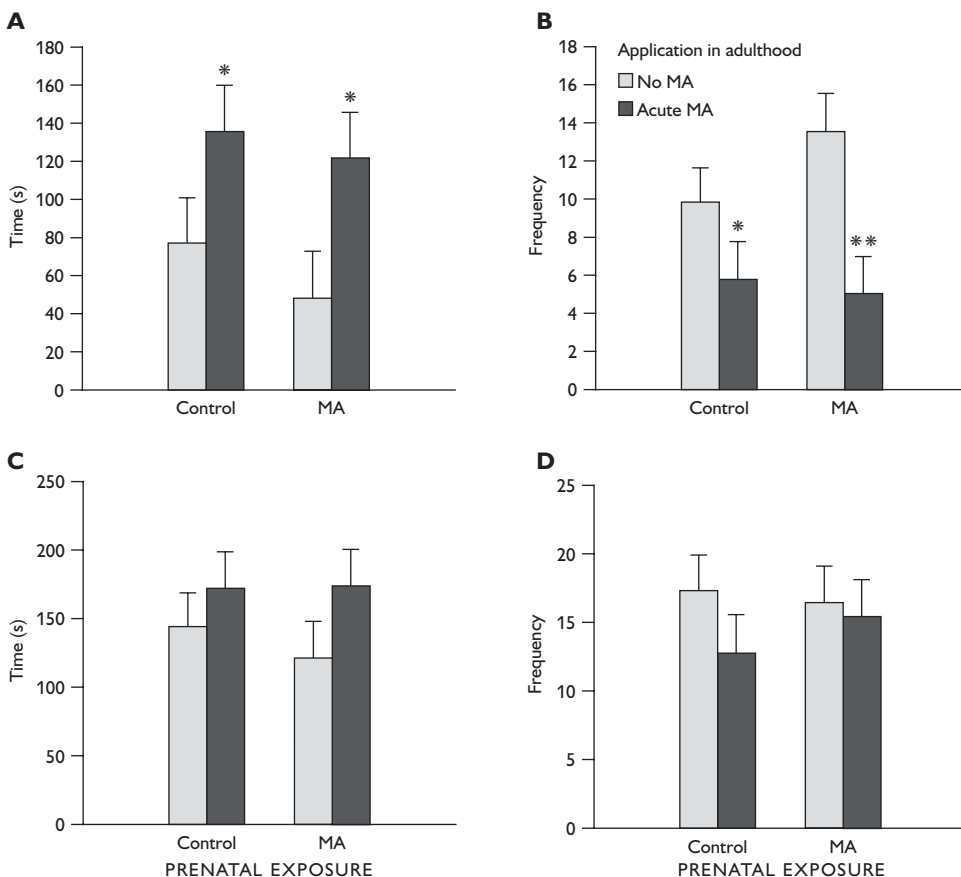


Figure 3 – Effect of prenatal MA and acute MA in adulthood on: (A) time spent in open arms, (B) SAP, (C) exploration and (D) locomotion (total arm entries). Values are means \pm SEM ($n=10$). ** $p < 0.01$ vs. No MA; * $p < 0.05$ vs. No MA.

adulthood, respectively. Moreover, MA administration in adulthood decreased the immobility to zero in both prenatal groups (i.e. control, MA).

No main effects for number of boluses were observed although the interaction (Prenatal treatment \times Treatment in adulthood) was present [$F(1,35) = 12.86$; $p < 0.01$] (Figure 2D). Post-hoc test showed that acute dose of MA in adulthood lowered the number of boluses in control rats while this effect was absent in rats prenatally exposed to MA. Further, in groups without MA challenge in adulthood, rats prenatally exposed to MA had lower number of boluses than the controls.

Elevated plus maze

Data analysis did not reveal any main effects of Prenatal treatment for neither of the behavioural parameters in the EPM. However, there were main effects of Treatment in adulthood for time spent in open arms [$F(1,37) = 6.28$; $p < 0.05$] and for the frequency of SAP [$F(1,37) = 8.97$; $p < 0.01$] as shown in Figure 3A and 3B, respectively. Rats administered MA in adulthood spent more time in open arms and displayed decreased frequency of SAP when compared to rats without MA challenge in adulthood. In addition, no main effects for time spent by exploration or locomotion were found (Figure 3C and 3D, respectively).

Discussion

Our results showed that prenatal MA exposure did not influence either behaviour in the OF and the EPM. Although there are studies on rats exposed to MA in utero demonstrating neurobehavioural alterations in early postnatal period, such as impaired development of sensorimotor functions [33] or decreased total motor activity [13], our study indicates that changes in normal behavioural activities after MA exposure in utero probably do not persist until adulthood.

To the best of our knowledge, there are no studies examining the effect of prenatal MA on anxiety in rats. The existing studies on prenatal cocaine exposure showed increased behavioural responsiveness to stress in adult rats [29, 30]. Similarly in humans, newborns exposed to MA in utero exhibited an increase in physiological stress [25]. In the present study we found in groups without MA challenge in adulthood that rats prenatally exposed to MA spent less time by freezing and had less boluses than control rats. This tendency was not present in prenatal groups administered acute MA dose in adulthood probably because of the different effect of acute MA on each of the prenatally treated groups. However, the rest and most of the anxiety parameters (time spent in the centre and corners of OF, time spent in open arms of EPM, SAP) were not affected by prenatal MA exposure; therefore, the prenatal MA exposure did not affect anxiety in adult male rats. This finding is in agreement with the study of Acevedo et al. [34], who found no effect of neonatal (a period corresponding to the third trimester of pregnancy in humans) MA 5 mg/kg on anxiety in adult mice.

In contrast to prenatal MA exposure, acute MA pre-treatment in adulthood affected behaviour significantly in both tests. In accordance with other works on behavioural effects of acute MA and other psychostimulants [35, 36], our dose of MA 1 mg/kg increased overall psychomotor activity in both prenatally treated groups (i.e. control, MA) as was shown by increased locomotion, exploration and decreased comforting behaviour. While locomotion was increased after acute MA dose to the same extent in both prenatal groups, acute MA application in adulthood increased exploration more in rats prenatally exposed to MA than in control rats. Consequently, the rats exposed to MA in utero exhibited increased sensitivity to the effects of acute MA in adulthood, which increased the rewarding value of exploration in the OF. Although prenatal MA exposure did not affect baseline behavioural activity, it altered the response to acute MA challenge in adulthood. This finding is in agreement with our previous study [14] but in disagreement with some other studies [11–13]. As MA increases the dopamine release in nucleus accumbens and the meso-accumbens dopamine system is assumed to mediate the effects of behavioural sensitization [37, 38], we plan to test the effect of prenatal MA exposure on basal and challenged levels of dopamine and its metabolites in nucleus accumbens in rats to better demonstrate the effect of prenatal MA exposure on dopamine transmission and behavioural sensitization.

Acute MA in adulthood also influenced the anxiety parameters in both the OF and the EPM. It decreased time spent in corners, time spent by freezing and increased time spent in the central ring of the OF, regardless of prenatal treatment. The OF exposure paradigm is a generally accepted animal model for measurement of anxiety-related behaviour [39]. It is based on a conflict between the internal drive to explore a novel environment (based on the potential for rewarding outcomes) versus the internal drive to avoid a novel environment (based on the potential for aversive outcomes) [40]. However, it can be difficult to distinguish between these two factors influencing the behaviour in the OF when testing the effects of psychostimulant drugs, since they were shown to act as “false positives”: they increase anxiolytic-like behaviour by making exploration more rewarding, i.e. through a mechanism unrelated to anxiety [41]. Therefore, we tested rats also in the EPM, which is more specific for testing anxiety because except for unfamiliarity, the environment of this apparatus is divided into two parts: non-aversive (closed arms) and aversive (open arms). Anxiolytic drugs were shown to increase time spent in more aversive open arms while anxiogenic drugs reduce open arm exploration [42–44]. In the present study we showed that acute MA application in adulthood increased the time spent in open arms, regardless of prenatal exposure. To further dissociate the effect of acute MA on anxiety from its effect on locomotor activity, exploration in open arms and the centre of the EPM, locomotion (total arm entries) and frequency of SAP, – a “risk assessment” parameter closely related to anxiety [45, 46] were measured. We found that rats after acute dose of MA in adulthood exhibited decreased frequency of SAP while time spent by exploration

or total arm entries were not influenced by acute MA. The findings indicate that acute MA 1 mg/kg in adulthood increased exploration of aversive arms by affecting anxiety rather than by increasing drive to explore. These results are, however, incongruent with studies demonstrating anxiogenic effect of MA and other psychostimulants [18–20]. Thus, the effect of MA on anxiety is probably dependent on the dose and duration of its administration as those studies used either higher doses of MA or administered MA chronically. Moreover, it appears that the effect of MA on anxiety is dependent also on stressful factors, since in our previous study we tested the anxiety of rats in social interaction test and found that acute MA 1 mg/kg had an anxiogenic effect by decreasing time spent by social interaction [22]. Therefore, we conclude that acute dose of MA 1 mg/kg increased anxiety to foreign animal, while decreased anxiety to novel environment.

Conclusion

Our present study demonstrates that acute MA increases overall psychomotor activity, as was shown by increased locomotion and exploration. In addition, unlike the previous study which showed increased anxiety to foreign animal after acute MA application this study shows that the same dose of acute MA decreases anxiety to novel environment. Finally, to further support our hypothesis that prenatal MA exposure increases sensitivity to drugs in adulthood, we plan studies investigating the levels of dopamine in the brain in rats after prenatal MA exposure.

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