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Do the effects of prenatal exposure and acute treatment of methamphetamine on anxiety vary depending on the animal model used?

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HIGHLIGHTS

- Prenatal methamphetamine exposure has complex effects on development of anxiety.
- The effect of prenatal methamphetamine exposure on anxiety is modified by drug treatment in adulthood.
- The approach-avoid conflict seems to be the most prominent parameter describing fear that is affected by methamphetamine treatment.

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ABSTRACT

The aim of the present study was an evaluation of prenatal exposure to acute methamphetamine (MA) treatment on manifestations of anxiety. Anxiety was evaluated in adult animals in three different experimental models: the Elevated plus-maze (EPM), Social interaction test (SIT) and Ultrasound vocalization (USV). Female rats were administered saline (S) or MA (5 mg/kg) daily throughout their entire gestation period. The male progeny, in adulthood, were administered with challenge dose of S or MA (1 mg/kg) prior to evaluation of anxiety. The study demonstrated that prenatal MA exposure increased the anxiogenic effect on evaluated behaviour patterns in the USV model and to a lesser degree in the EPM model. In addition, the acute MA challenge in adulthood decreased the time spent during social interaction suggesting an anxiogenic effect in the SIT model as well. On the other hand, some of the evaluated parameters (e.g. the number of head-dipping in the EPM and number of dropped boluses in the SIT) also suggest MA-induced anxiolytic effects. Sensitization to a MA challenge was apparent in several parameters of the EPM (e.g. increased number of entries to the closed arms, increased stretched attend postures and increased approach-avoid conflicts) and SIT (total social interaction and following). The present data demonstrate that prenatal MA exposure and adult challenge of the same drug have diverse effects on animal behaviour that depends on the type of anxiety model used.

1. Introduction

In general, stress and drug addiction are closely connected. Either acute or chronic stress can be a reason for drug abuse and drug abuse can act as a chronic stressor [57]. Psychostimulants have been shown to affect a variety of behaviour patterns in humans [58,59] as well as in behaviour patterns in laboratory animal models of psychostimulant abuse [23,25]. Long-lasting alterations in emotional states such as fear, anxiety, social receptivity, depressive symptoms, as well as memory deficits have been demonstrated in laboratory rats repeatedly given psychostimulants [24,33,40,43,53,65,71]. These results match long-term changes reported in human studies [10].

Methamphetamine (MA) is one of the most addictive psychostimulant drugs, which is linked to a high potential for abuse. It is also one of the most frequently used "hard" drugs in the Czech Republic [68] and due to its anorectic effects, it is

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one of the most commonly abused drugs among women, even during pregnancy [32]. Previous studies [1,53,54,64,70] demonstrated that prenatal MA (5 mg/kg) exposure changes behaviour in animals and reduces adaptability to new environments in adulthood. In addition, it has been shown that prenatal MA exposure increases sensitivity to the same drug in adulthood [53,54]. Specifically, prenatally MA-exposed animals that received challenge doses of MA in adulthood displayed higher locomotion and exploratory rearing activity relative to control animals; this was found to correspond with dopamine levels in the nucleus accumbens [8]. These findings may be considered as prenatally induced long-term sensitization similar to that described in adulthood [49].

Experimental models of anxiety as well as animal models of other psychiatric disorders have been classified into five categories, by Gerlai et al. [21], based on induced changes in CNS functions: (1) models of anxiety induced by the presence of anxiogenic stimulus from the surroundings, e.g. presence of a predator (or a stimulus resembling a predator), pain stimuli or stimuli linked to an unknown environment; (2) models of anxiety induced by chemicals or hormones; (3) models created by genetic manipulations; (4) models of anxiety resulting from spontaneous mutations – inbred animals strains; and (5) models that use invasive techniques, e.g. electric stimulations of certain brain structures or other surgical techniques.

The most widely used category is the first, in which anxiety is induced by external stimuli from the surroundings. Three of the models from this category were used in the present study: (1) Geller-Seifter conflict – Elevated plus maze test (EPM) [44,50]; (2) Conditioned emotional response – Social interaction test (SIT) [19]; and (3) Fear potentiated startle reaction – Ultrasound vocalization test (USV) [20,51].

Psychostimulant drugs have been previously tested in these animal models of anxiety, with inconsistent findings. In the EPM test, acute and chronic exposure to psychostimulants has been shown to have both anxiogenic [4,15,17,24,39] as well as anxiolytic effects [13,54]. In the SIT, psychostimulant drugs usually displayed anxiogenic effect in the form of decreased social interaction (SI) indicating increased anxiety [11,19,36,66], which was also observed in our previous studies [62,63] showing that MA administration impairs SI in dose-, stress condition-, and sex-specific manners. As far as the USV test is concerned, there are number of studies showing anxiolytic effects of psychostimulants on USVs in young animals [2,3,35,41], while withdrawal from the drug intake has the opposite, anxiogenic effect [12]. Specifically, a recent study by Manduca et al. [31] demonstrated decreased social play and increased USVs in young rats, suggesting that amphetamine treatment has anxiogenic effects. In adult rats, psychostimulants have been also shown to increase vocalization, thereby to have anxiogenic effects [56]. Based on all mentioned findings, the effect of psychostimulants on anxiety is suggested to be drug-, dose-, timing of administration-, and animal model-specific.

Most of the above cited studies have demonstrated the effect of acute as well as chronic psychostimulant drugs exposure in postnatal life. To the best of our knowledge, ours is the only study examining the long-term effects of prenatal MA exposure on the manifestation of anxiety in adulthood. Therefore, the aim of this study was to investigate the effect of prenatal MA exposure on anxiety in adult offspring (following an acute MA challenge) using three different models of anxiety, the EPM, SIT, and USV. The novelty of the present study is its investigation of prenatal MA exposure on anxiety manifestations in adulthood using three different animal anxiety models.

2. Methods

The procedures for animal experimentation in this study were reviewed and approved by the Institutional Animal Care and Use Committee and were in agreement with the Czech Government Requirements under the Policy of Human Care of Laboratory Animals (No. 246/1992) and with subsequent regulations from the Ministry of Agriculture of the Czech Republic.

2.1. Animals and drug injections

Adult female and male albino Wistar rats (375–400 g) provided by Charles River Laboratories International, Inc. were delivered by AnLab (Prague, the Czech Republic). Animals were housed four per cage by sex and left undisturbed for a week in a temperature-controlled (22–24 °C) colony room with free access to food and water on a 12 h (light):12 h (dark) cycle with lights on at 06:00 h. Females were impregnated as described in our previous study [60]. In total, 24 dams were randomly assigned to either the MA-treated or saline-treated group. On gestational day (GD) 1 the daily injections of MA or saline started and continued until the day of delivery, which usually occurred on GD 22. D-methamphetamine HCl (Sigma–Aldrich, the Czech Republic) was diluted in distilled water in concentration of 5 mg/ml and injected subcutaneously (s.c.) in a volume of 1 ml/kg; saline was injected s.c. at the same time and volume as MA.

The day of the delivery was indexed as postnatal day (PD) 0. On PD 1, pups were weighed, tattooed for identification, and cross-fostered (for detailed information see [30,60]). The pups were cross-fostered in such a way that each of the 24 mothers received and raised 12 pups – 6 of which had been prenatally exposed to MA and 6 to saline. Whenever possible, the number of male and female pups raised by a dam was equal. On PD 21, pups were weaned and group-housed by sex (4 males per a cage and 5 females per a cage). Animals were left undisturbed until adulthood. In total 144 male rats were used in the present study (n = 8–12 per individual experiment). In order to avoid litter effects, one male rat from the MA- or saline-exposed group from each litter was used in individual experiments (EPM, SIT, and USV). The rest of the animals were used in experiments that were a part of another study.

Individual animals were subjected to only one of the three anxiety tests. Forty-five minutes prior to testing, animals were injected with either a challenge dose of MA (1 mg/ml/kg) or saline (1 ml/kg). The dose of MA was chosen based on our previous studies [55,62] because this dose does not induce stereotypical behaviours. The timing of the drug application was also chosen based on our previous study [48] that showed that peak MA level in the brain (not in the blood) occurred between the 45th and 60th minute after administration. Thus, based on prenatal drug exposure and the challenge treatment, the animals were divided to 4 experimental groups: Prenatally MA-exposed rats treated with saline (MA/S) or MA (MA/MA) in adulthood and prenatally saline-exposed rats treated with saline (S/S) or MA (S/MA) in adulthood.

2.2. Elevated plus maze (EPM)

In total, 32 adult male rats were tested in the EPM (n = 8 rats/group). The same method was used as in our previous study [46], which was a modified protocol of Fernández Espejo [16]. All animals were habituated to the laboratory environment and the experimenter during the 3 days prior to the experiment [22]. The EPM test was performed 45 min after the acute MA (1 mg/kg) or saline injection. At the beginning of the test an animal was positioned on the centre square of plus maze with the animal's nose pointing toward one of the closed arms. Animal behaviour in the EPM was video-recorded for five minutes.

Acquired video records were evaluated using the ODLog program (Macropod Software™). Animal behaviour was divided into four categories as follows.

The first category included behaviour related to anxiety. The anxiolytic effect on animal behaviour was described as activities in open arms: the number of entries to the open arms and total time spent there. Anxiogenic effect on animal behaviour involved activities in the closed arms and the centre: the number of entries to the closed arms and total time spent there, the number of protected head-dipping (pDIP) and protected stretched attend postures (pSAP) [16]. pDIP was defined as head-dipping below surface of the maze that occurred on the centre square, while the body of an animal remained in the closed arm or central platform. pSAP was defined as forward elongation of head and shoulders followed by retraction to initial position. In this study it was recorded when it occurred on the central platform, while the body and all paws of an animal remained in the closed arm.

The second category described approach-avoid conflict and also depicted types of behaviour with respect to open and closed arms, i.e. positioning of an animal with all four paws in the centre of the maze followed by retrieval (meaning moving backwards) to the closed arm.

The third behavioural category in the EPM was used to describe motor activity. Evaluated activities included the total number of entrances into all arms and sniffing in the centre of EPM (mobile or quiet olfactory exploration of the environment).

The last category included displacement behaviour as a measure of anxiety, i.e. self-grooming, etc. This category was not evaluated because at a dose of 1 mg/kg it did not occur.

Frequency of specific behaviours as well as time spent engaged in specific behaviours were used for statistical analyses.

2.3. Social interaction test (SIT)

Next group of animals ($n = 64$) was tested using the SIT ($n = 8$ pairs/group). The same method was used as described in our previous study [62]. Pairs of unfamiliar animals, of the same treatment and having similar weight, were tested for SIT in a familiar non-stressful environment of an open field [19]. Both tested animals received the same adult treatment, i.e. MA (1 mg/kg) or saline, 45 min prior to SIT testing. Their mutual behaviour was video recorded for 5 min. Video records were analysed using ODLog software (Macropod Software™).

Mutual interaction between paired animals and behaviour of individual animals were observed and divided into two categories [37] as follows: The first category depicted active SI: mutual sniffing (sniffing the other rat), genital investigation (sniffing around genitals of the other rat), following (moving in the direction of or pursuing the partner that is moving away), walking over, crawling under and allogrooming (grooming the other animal). Increases in time and frequency of SI is considered as anxiolytic signs, while decreases are considered anxiogenic signs [19]. The second category included non-social activities: locomotion (activity) and rearing (exploration). Frequency of and a time spent in specific behaviours were used for statistical analyses.

2.4. Ultrasound vocalization (USV)

A group of adult male rats ($n = 48$) were tested using 22-kHz USV ($n = 12$ rats/group). USV was measured with a Mini-3 Bat Detector and monitored using UltraVox 2.0 software (Noldus Information Technology, The Netherlands). UltraVox software automatically monitored the number and duration of ultrasonic and audible vocalizations of each rat. An audio filter received direct output from the bat detector and forwarded it to a PC. A shock device delivered 1-mA shocks. The experimental arena consisted of a shock chamber (32.2 cm × 25.5 cm × 25.5 cm) with the floor made of stainless steel rods (4.8 mm in diameter) spaced 10.75 mm apart. The detector was set to register ultrasonic vocalizations at 22 kHz. This frequency has been found useful for differentiating fear and anxiety in rats [28,67].

The experiment was conducted on two consecutive days. On the first day USV of each animal was monitored for 10 min, as spontaneous vocalization in a novel environment. Later each animal was exposed to 10 electric inescapable foot-shocks (0.6 mA; 10 s with 50 s interval between shocks). On the second day, each animal initially was exposed to one electric foot-shock (0.6 mA; 10 s) to recall the stressful stimuli from the previous day. Immediately after the foot-shock the animal was retrieved from the chamber and an acute dose of MA or saline was administered; 45 min after the injection the USV was tested (induced vocalization). The animal was placed to the same chamber, but without any further foot-shocks.

The differences in the number and duration between induced and spontaneous USVs were recorded and compared between groups. The vocalizations that lasted less than 300 ms and 600 ms, respectively, were analysed.

2.5. Statistical analyses

The two-way ANOVA (factors: prenatal exposure, adult treatment) was used for statistical analyses of the results from individual anxiety tests. The Bonferroni test was used for post-hoc comparisons. Differences were considered significant if $p < 0.05$.

3. Results

3.1. Elevated plus maze (EPM)

3.1.1. Anxiety

The evaluation of time spent in the open and closed arms (data not shown) showed no statistically significant differences. Similarly, there were no differences in the number of entries into the open arms (Fig. 1A). On the other hand, the number of entries into the closed arms (Fig. 1B) was higher in prenatally MA-exposed rats, regardless of the adult challenge treatment [$F(1, 28) = 63.23$; $p < 0.0001$]. Moreover, prenatally MA-exposed rats treated in adulthood with MA (MA/MA) had even more entries to the closed arms than prenatally MA-exposed rats treated in adulthood with saline (MA/S) [$F(1, 28) = 5.73$; $p < 0.05$].

More detailed analysis of the anxiety behaviour in the centre area of the EPM showed that the number of pDIP was lower in prenatally MA-exposed rats, regardless of the adult challenge treatment [$F(1, 28) = 5.58$; $p < 0.05$] (Fig. 1C), while pSAP was increased in prenatally MA-exposed rats treated in adulthood with MA (MA/MA) relative to all other groups [$F(1, 28) = 7.38$; $p < 0.05$] (Fig. 1D).

3.1.2. Approach-avoid conflict

The data demonstrated that prenatally MA-exposed rats showed an increased number of returns to closed arms than prenatally saline-exposed rats, regardless of the acute treatment [$F(1, 28) = 43.35$; $p < 0.0001$]. Moreover, there was a greater number of returns to the closed arms in prenatally MA-exposed rats treated in adulthood with MA (MA/MA) relative to prenatally MA-exposed rats treated in adulthood with saline (MA/S) [$F(1, 28) = 13.99$; $p < 0.001$] (see Fig. 2).

3.1.3. Motor activity

The total number of entries into the open and closed arms (Fig. 3A) was higher in prenatally MA-exposed rats than in prenatally saline-exposed rats, regardless of the acute treatment [$F(1, 28) = 25.53$; $p < 0.0001$]. On the other hand, time spent sniffing (Fig. 3B) was reduced in prenatally MA-exposed, compared to

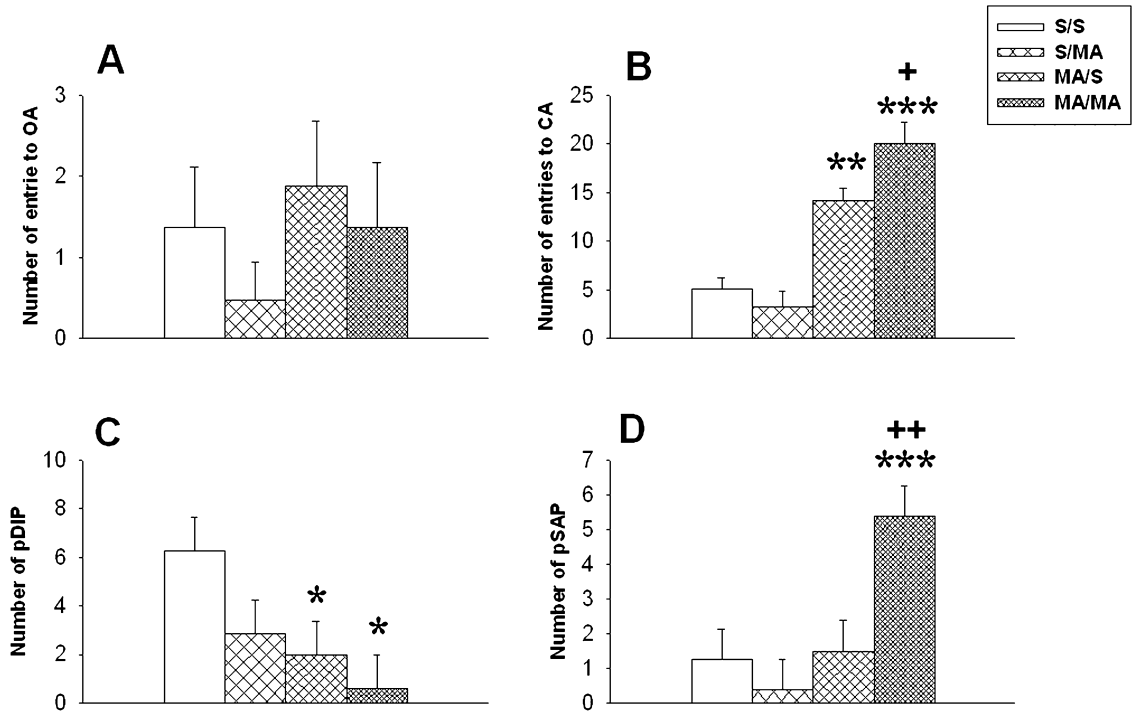

Fig. 1. The effect of prenatal MA exposure and MA challenge dose in adulthood on anxiolytic (A) and anxiogenic (B–D) effects on a given behaviour in the EPM. Graphs are presented as (A) Number of entries into open arms; (B) Number of entries into closed arms; (C) Number of pDIP and (D) Number of pSAP. Values are mean ± SEM ($n = 8$); $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.0001$ vs prenatally saline exposed animals of the same adult treatment; $+p < 0.05$, $++p < 0.001$ MA/MA > all other groups.

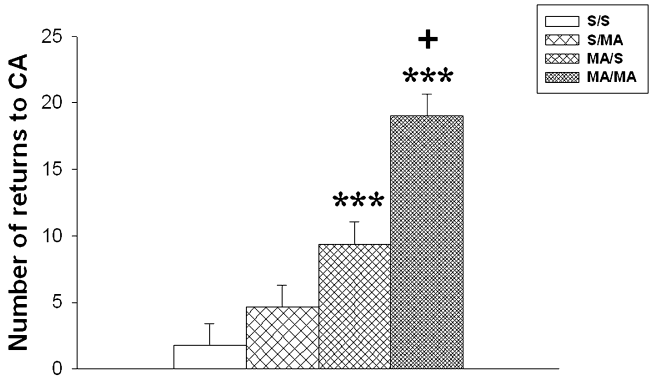

Fig. 2. The effect of prenatal MA exposure and MA challenge dose in adulthood on approach-avoid conflict. Graph is presented as the number of returns to closed arms. Values are mean ± SEM ($n = 8$); $^{***}p < 0.0001$ = main effect of prenatal MA exposure; $+p < 0.01$ MA/MA > all other groups.

prenatally saline-exposed rats, regardless of the acute treatment [$F(1, 28) = 29.29$; $p < 0.0001$]. Regarding sniffing (Fig. 3C), prenatally saline-exposed animals treated in adulthood with MA (S/MA) displayed a higher frequency of sniffing than all other groups [$F(1, 28) = 4.88$; $p < 0.05$].

3.2. Social interaction test (SIT)

Social activities are presented in Table 1 and non-social activities in Fig. 4.

3.2.1. Social interactions in total

Statistical analysis showed that challenge dose of MA decreased overall time spent in SI [$F(1, 28) = 8.05$; $p < 0.01$], regardless of prenatal drug exposure. In addition, there was a relationship between prenatal drug exposure and the adulthood challenge dose, relative to the frequency of overall SI [$F(1, 28) = 5.15$; $p < 0.05$]. Specifically, MA treatment in adulthood decreased time spent in overall SI ($p <$ S/S > S/MA); however, in prenatally saline-exposed rats there was an increase in the frequency of SI ($p < 0.05$; S/S < S/MA). On the other hand, both, duration as well as frequency of SI was decreased by acute MA treatment in adulthood in prenatally MA-exposed rats ($p < 0.05$; MA/S > MA/MA). Moreover, when compared to prenatal saline-exposed controls, prenatally MA-exposed rats treated in adulthood with saline displayed a higher frequency of SI ($p < 0.05$; MA/S > S/S), while prenatally MA-exposed rats treated in adulthood with MA had a lower frequency of SI (MA/MA < S/MA).

3.2.2. Specific patterns in the SI repertoire.

Focused on specific patterns in the SI repertoire, the data demonstrated that a challenge dose of MA decreased time spent in mutual sniffing [$F(1, 28) = 17.26$; $p < 0.001$], but not the frequency of mutual sniffing in both, prenatally saline- and MA-exposed rats. Regarding genital investigation, prenatally MA exposed rats with adult MA treatment (MA/MA) spent the shortest time [$F(1, 28) = 11.61$; $p < 0.05$] and displayed the lowest frequency [$F(1, 28) = 4.86$; $p < 0.05$]. There was relationship between prenatal drug exposure and adult challenge treatment with regard to the frequency of the following [$F(1, 28) = 12.23$; $p < 0.01$]: While acute MA treatment increased the frequency in prenatally saline-exposed rats ($p < 0.01$), in prenatally MA-exposed rats the effect of the MA challenge dose was opposite ($p < 0.05$). Moreover, the frequency was increased by prenatal MA exposure in rats treated in adulthood with saline (MA/S > S/S), while it declined in prenatal MA exposed rats treated in adulthood with MA (S/MA > MA/MA). The frequency of other SI patterns, such as crawling over, crawling under and allogrooming, were very low (zero incidence in most of the animals), therefore, it was not possible to calculate the statistical differences and this data was not included in the analysis.

In contrast, an additional measure of anxiety, number of dropped boluses, which is a particular reaction to acute stress conditions, showed that prenatally saline-exposed rats with acute

Table 1
The effect of prenatal MA exposure and challenge dose in adulthood on social activity tested in SIT.

Social interaction pattern		Prenatal saline				Prenatal MA			
		Adult saline		Adult MA		Adult saline		Adult MA	
Total SI	Duration (s)	48.38 ± 8.3		35.50 ± 7.9	+	55.75 ± 8.4		21.00 ± 8.1	+
	Number	42.88 ± 5.4		55.38 ± 5.6	+	54.63 ± 5.3	*	41.75 ± 4.5	*+
Mutual sniffing	Duration (s)	26.12 ± 4.3		15.50 ± 4.1	++	37.25 ± 4.7		9.13 ± 2.4	++
	Number	29.13 ± 3.1		28.25 ± 2.5		30.75 ± 3.1		26.75 ± 2.8	
Genital investigation	Duration (s)	9.63 ± 2.1		5.25 ± 1.5		14.00 ± 2.7		0.25 ± 0.1	#
	Number	8.5 ± 1.2		9.00 ± 1.5		9.88 ± 1.9		3.00 ± 0.8	#
Following	Duration (s)	22.00 ± 5.2		19.75 ± 4.8		17.50 ± 4.5		11.88 ± 4.2	
	Number	11.50 ± 2.3		25.88 ± 3.2	++	21.38 ± 2.9	*	13.25 ± 2.1	*+
Boluses	Number	3.38 ± 0.7	#	1.13 ± 0.5		0.50 ± 0.3		0.50 ± 0.3	

Values are mean ± SEM ($n = 8$ pairs). *$p < 0.05$ vs prenatally saline-exposed rats of the same adult treatment; +$p < 0.05$, ++$p < 0.001$ vs rats of the same prenatal exposure treated in adulthood with saline; #$p < 0.05$ vs all the other groups.

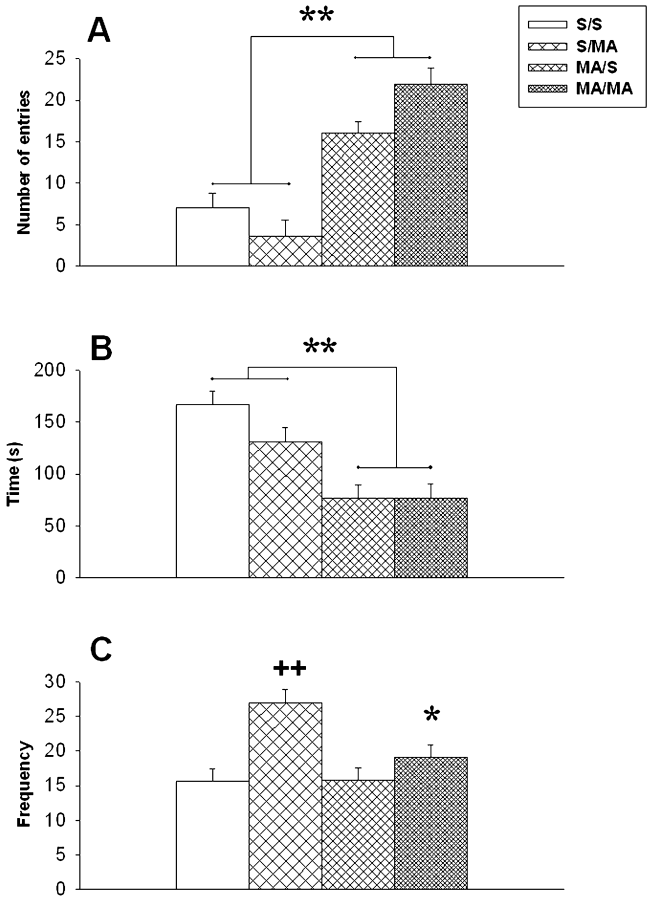

Fig. 3. The effect of prenatal MA exposure and MA challenge dose in adulthood on activity tested in the EPM. Graphs are presented as (A) Number of entries into all arms; (B) Time spent sniffing in the central arena; (C) Frequency of sniffing episodes in the central arena. Values are mean ± SEM; (A) **$p < 0.0001$ main effect of prenatal drug exposure (prenatal S < prenatal MA); (B) **$p < 0.0001$ main effect of prenatal drug exposure (prenatal S > prenatal MA); (C) *$p < 0.01$ vs prenatally saline-exposed rats treated in adulthood with the same adult treatment; ++$p < 0.001$ vs prenatally saline- and MA-exposed rats with adult saline treatment.

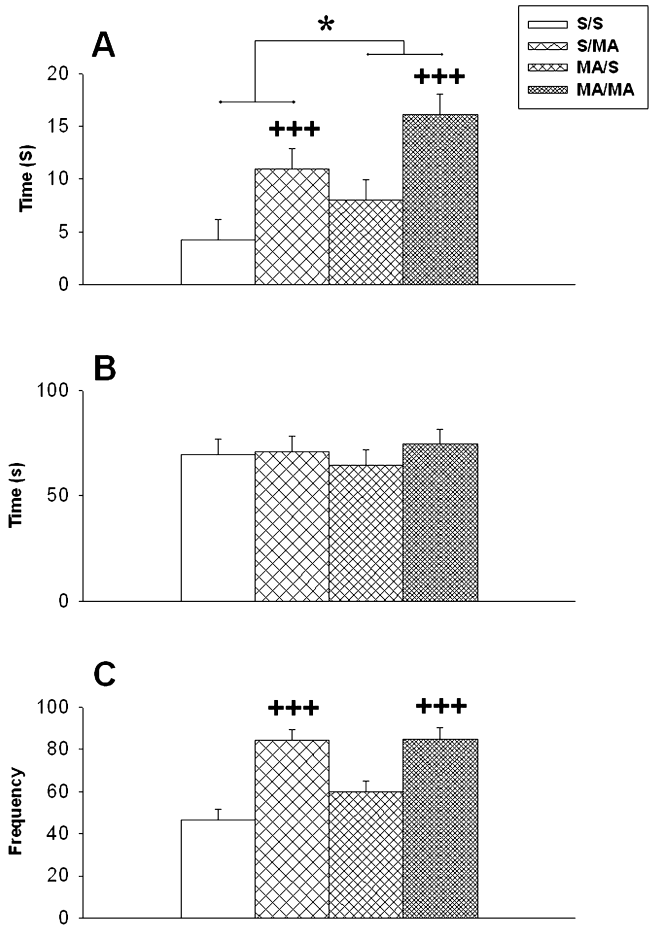

Fig. 4. The effect of prenatal MA exposure and MA challenge dose in adulthood on non-social activity tested using the SIT. Graphs are presented as (A) Time spent in locomotion; (B) Time spent rearing; (C) Frequency of rearing. Values are mean ± SEM; *$p < 0.05$ = main effect of prenatal drug exposure; +++$p < 0.0001$ = main effect of adult drug treatment.

saline treatment (S/S) defecated more than all groups [$F(1, 28) = 5.59$; $p < 0.05$] as shown in Table 1.

3.2.3. Non-social activities

As shown in Fig. 4A, both prenatal MA exposure [$F(1, 28) = 5.32$; $p < 0.05$] and MA challenge dose [$F(1, 28) = 14.96$; $p < 0.001$] increased locomotion time in the SIT. In addition, adult MA treatment increased the frequency of locomotion episodes [$F(1, 28) = 5.78$; $p < 0.05$] (data not shown). Regarding exploratory behaviour, there were no significant differences in time spent rearing (Fig. 4B). The frequency of rearing was increased in rats treated in adulthood with MA [$F(1, 28) = 36.89$; $p < 0.0001$], regardless of the prenatal exposure (Fig. 4C).

3.3. Ultrasound vocalization (USV)

As shown in Fig. 5, prenatally MA-exposed rats vocalized more often {300 ms [$F(1, 45) = 11.5$; $p < 0.01$]; 600 ms [$F(1, 45) = 12.3$; $p < 0.01$]} and had longer durations of their emitted sounds {300 ms [$F(1, 45) = 7.47$; $p < 0.01$]; 600 ms [$F(1, 45) = 8.65$; $p < 0.01$]} than pre-

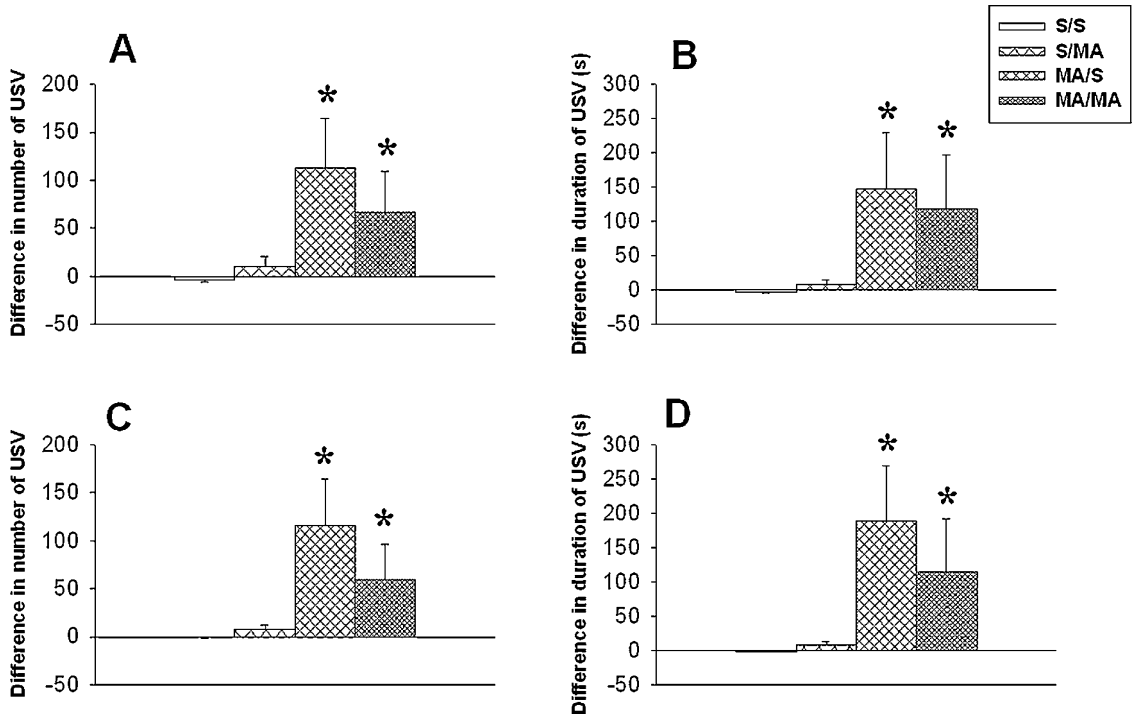

Fig. 5. The effect of prenatal MA exposure and MA challenge dose in adulthood on anxiety tested using USV. Graphs are presented as differences between induced and spontaneous USV. (A) difference in the number of USV emitted sounds lasting less than 300 ms; (B) difference in the average duration of USVs lasting less than 300 ms; (C) difference in number of USVs lasting less than 600 ms; (D) difference in the average duration of USVs lasting less than 600 ms. Values are mean ± SEM ($n = 12$), $^{*}p < 0.01$ = main effect of prenatal drug exposure.

natally saline-exposed rats. This effect was independent of adult drug treatment.

4. Discussion

The results from this study offers insight into the effects of MA-induced anxiety from two perspectives. The first was evaluation of prenatal MA exposure relative to changes in behaviour in adulthood. The second was a comparison of the effects of such exposure in combination with reactions to an acute challenge with the same drug in adulthood using three experimental models of anxiety. Therefore, the results can be divided as follows: (1) the effect of prenatal and acute MA treatment on anxiety in different animal anxiety models; (2) the effect of prenatal and acute MA treatment on locomotor and exploratory behaviour; (3) the effect of sensitization induced by prenatal MA exposure; and (4) a comparison and validation of the three anxiety models used in our study.

First, with regard to prenatal and acute MA treatment on anxiety, our results show that both, prenatal and acute MA treatments have mostly anxiogenic effects. However, the extent of the impact of prenatal and acute MA treatment differed depending on the test used to assess anxiety behaviour. Moreover, some results, such as the number of dropped boluses in the SIT and the number of pDIP in the EPM might be interpreted as anxiolytic and should be therefore, discussed in regard to their specific aspects.

In the EPM, our results demonstrate that prenatal MA exposure increases anxiety. This conclusion was based on the increased number of entries to the closed arms of the EPM regardless of the acute treatment (saline or MA) and an increased in pSAP in prenatally MA-exposed rats with the acute MA challenge (MA/MA). Similar results were shown in the study of Hayase et al. [24] i.e. why acute and chronic exposure to MA having anxiogenic effects in the EPM. Additionally, other drugs, such as MDMA and amphetamine, which have similar mechanisms of actions as MA, were also shown to have anxiogenic effect on specific behaviours in the EPM [4,39].

On the other hand, these results contradict those of Schutová et al. [54], who showed that acute MA treatment has anxiolytic effects in rats prenatally exposed to MA; however this effect was diminished in rats prenatally exposed to saline. Such a discrepancy with present study might be explained by the 3 days habituation to the experimenter, used to reduce stress from an unknown environment, which we incorporated into our study. A second reason might be the scheduling of the challenge dose of MA (1 mg/kg). In the study by Schutová et al. [54], MA was administered 30 min prior to EPM testing and in the present study it was 45 min prior to the test. The choice of the time of injection was based on our recent results showing that MA levels in the brain of an adult male rat peaks from 45 min to 1 h after MA administration [48]. One might therefore, speculate that there was some crucial period between the 30th and 45th minute after MA administration that changed the effect of MA from anxiolytic to anxiogenic. This speculation, however, would need to be further verified in future studies.

More detailed analyses of behaviour in the central open area of the EPM, which included parameters pDIP, pSAP and returns to the closed arms of the EPM, suggest that MA has dual effects on behaviour and also increases approach-avoid conflict in prenatally MA exposed animals. Because our study showed that the pDIP, as a parameter of anxiogenic effect on behaviour [16], is decreased in prenatally MA-exposed animals, this would suggest an anxiolytic effect of prenatal MA exposure. This is however in disagreement with the other anxiogenic effects seen in specific measurements. This contradiction was further emphasized by the increased frequency of entries (especially into the closed arms) without changing the time spent there.

In the SIT, our results demonstrated that a single adult MA dose decreases overall SI as well as mutual sniffing, which suggests increased anxiety in the animals (see [19]). Moreover, another paradigm of SI, genital investigation, was decreased in prenatally MA-exposed rats treated with a challenge dose of MA in adulthood (MA/MA) relative to all other tested groups. These results are in

agreement with our previous studies [11,36,62,63] that showed decreased social behaviour after MA treatment, which is associated with dopamine depletion. Interestingly, the effect of prenatal MA exposure on the SIT differed based on the acute treatment. While prenatal MA exposure decreased the overall number of SIs and the number of "followings" in animals treated in adulthood with MA (suggesting increased anxiety), these measures were increased by prenatal MA exposure in animals treated in adulthood with saline, i.e. decreased anxiety (see Table 1 for details). Moreover, the number of boluses was decreased in prenatally MA-exposed animals regardless of adult treatment. Decreased defecation suggests decreased stress, which does not necessarily have to correspond to decreased anxiety. It seems that prenatal MA exposure makes the animals more resistant to acute stress in adulthood relative to prenatal saline exposure, which could be thought of as chronic prenatal stress. This finding corresponds with the decreased corticosterone levels seen in prenatally MA-exposed male rats in one of our recent studies [61].

The results of the USV confirmed increased anxiety induced by prenatal MA exposure similar to that seen in the EPM and SIT. To the best of our knowledge, there are no studies that analyze the effect of prenatal MA exposure using the USV model of anxiety. However, our results correspond with findings showing that acute amphetamine treatment increase USV, which seems to be associated with dopaminergic transmission [52,72]. It should be noted that rodents use vocalizations to communicate information regarding mother-offspring interactions as well as information about mood state (fear, anxiety, pain, distress, aggression, joy etc.). Adult rats primarily emit two types of USVs that can be distinguished on the basis of their frequency. Vocalizations typically, referred to as "22-kHz vocalizations," have frequencies between 18 and 32 kHz. Animals emit 22-kHz vocalizations during a number of aversive behavioural situations when distressing events occur. It is assumed that these sounds reflect a negative affective state. The anxiety model based on induced vocalization does not depend on motor activity in comparison to the EPM model of anxiety. A USV anxiety model based on foot-shocks can be designed with different protocols. The procedures, which were used in our study, were adapted from previous USV studies [29,38,47].

Second, our results showed changes in locomotor and exploratory behaviours induced by MA exposure. Amphetamine derivatives have been repeatedly shown to increase locomotor activity of experimental animals [6,34,54]. It is worth noting that the extent of the effect of prenatal MA exposure and adult MA treatment in our study differed between the EPM and SIT anxiety models. While only prenatal MA exposure, regardless of acute treatment, increased locomotion in the EPM, locomotor activity in the SIT was increased by both prenatal MA exposure and acute MA treatment. The differences may be due to the different setups for the two tests. The EPM test evaluated behaviour in the narrow arms of the maze, which were elevated 50 cm above the floor. This environment might have been more stressful for animals than the SIT environment, and as a result the effect of the acute MA treatment was not evident. SIT, on the other hand, was tested after habituation and therefore, in a relatively safe and known open field. Even in the presence of an unknown animal, which was not aggressive, increased locomotion resulting from acute MA application was observed. As a matter of exploration, prenatal MA exposure decreased exploration in the EPM, while acute MA exposure increased exploration in the SIT. This is in agreement with previous studies [5,8,40] and may be associated with changes in dopamine release [7]. It should be pointed out, that exploration in the EPM was measured as time and frequency of sniffing, which is horizontal exploratory behaviour, while exploration in the SIT was measured as time and frequency of rearing, which is vertical exploratory behaviour.

Third, regarding the sensitizing effect of prenatal MA exposure, our data showed increased sensitivity to the acute challenge dose of the same drug in adulthood in the EPM. Regarding the number of entries into the closed arms (see Fig. 1B), in pSAP (see Fig. 1D) and in approach-avoid conflict (see Fig. 2), prenatally MA-exposed rats had a more pronounced reaction to the acute dose of MA (MA/MA) than prenatally saline-exposed rats (S/MA). Similar effects of increased anxiety in MA/MA relative to S/MA animals were also observed in the SIT, specifically in regard to genital investigation and following behaviour (see Table 1). USV showed changes associated with prenatal MA exposure, but there were no changes associated with the challenge dose in adulthood. Thus, USV appears unsuitable for evaluating the effect of sensitization to acute treatment in adulthood induced by prenatal MA exposure.

Fourth, if we compare our results from the three anxiety models (EPM, SIT, USV) used in the present study we observe different results. These differences can be explained the following way.

Test EPM in its basis is ethological model for unconditioned aversion [9], which measures the basal level of anxiety [14]. That is why it might be influenced by many variables. They include (1) the organismic (species, strain, gender, age) variables and (2) procedural ones, such as pre-test manipulations, condition and construction of the EPM and eventually scoring of behaviour [9,26,69]. Those factors most probably affect the reliability and variability of our results [45].

Different results as a matter of the effect of MA in the EPM and SIT raises question about the validity of the SIT as anxiety test. Based on the study of File and Hyde [19] decrease of active SI tested under different environmental stress condition is considered as anxiogenic behaviour, while increase of active SI as anxiolytic behaviour. The same conclusion was made in our previous study [62] showing that MA administration impairs SI in dose- and stress condition-specific manner suggesting anxiogenic effect of MA. However, because other our results (previous as well as present) indicate that acute administration of MA in adulthood has anxiolytic effect when tested in the EPM [54], we suggest being more careful with such a conclusions. Moreover, number of studies showed contradictory findings when examining anxiety: from anxiolytic action, through no effect, to anxiogenic action [24,36,40,42]. Such results suggest that SIT and non-social tests of anxiety probably measure different states of fear [18,27].

As a third model of anxiety, the USV test was used in the present study. This test is based on painful stimulation (direct electrical shocks to the paws) and subsequent observation of animal's behaviour relative to expectations of further stimulus (anticipatory stress). Thus, conditioning plays role in the rat response in the test of USV. On the other hand, in the EPM and SIT no pain stimuli were present and the type of stress was situational.

Even though all the models were previously repeatedly used as valid models for testing anxiety-like behaviour in animals [19,20,44,50,51], nowadays questions about the validity rise in some cases. As part of the evaluation of our results we took the following items into account with regard to the specificities associated with each of the individual models of anxiety. (A) Animals were habituated and handled prior to the EPM and SIT in an effort to reduce the effect of acute stress while testing anxiety [26]. (B) The animals had to walk on the narrow arms of the EPM apparatus, which was raised 50 cm above the floor, which induced a stress condition different from the presence of an unknown animal in the open field of the SIT [45,50]. (C) Even though the SIT has been shown to be a valid test of anxiety [19] it seems that the effect of MA was more prominent with regard to decreased sociability per se than the presence of an anxiety-like behaviour. (D) Changes in USV observed in our study involved a fear conditioning component and therefore, cognition could have potentially influenced the results.

In conclusion, prenatal MA exposure has complex effects on development of anxiety that is further modified by drug treatment in adulthood. Although these differences are not robust and they are not recognizable at first sight, a detailed analysis reveals increased fear of unknown environments or unknown individuals. The approach-avoid conflict seems to be the most prominent parameter describing fear that is affected by MA treatment. The sensitizing effect of prenatal MA exposure took the form of increased sensitivity to an acute challenge dose of the same drug. This study highlights the influence of prenatal MA exposure on stress- and anxiety-related behaviour in various, unique and specific, animal anxiety models. Thus, our study shows that the effect of the drug depends on many factors and that each method of anxiety has its pros and cons. In humans, confirmation MA prenatal exposure with regard to vulnerability or susceptibility to psychiatric disorders in adulthood will need confirmation with clinical studies.

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