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Impact of Prenatal Methamphetamine Exposure on the Sensitivity to the Same Drug in Adult Male Rats

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Abstract: There are only few studies that examine the effect of prenatal methamphetamine (MA) exposure on the sensitivity to the same drug and the drug-seeking behavior in adulthood. The aim of the present study was to examine the effect of prenatal MA exposure on exploratory behavior and nociception with respect to challenge dose of the same drug. Mothers of the tested offspring received a daily injection of MA (5 mg/kg) or saline throughout the gestation period. Adult male offspring (prenatally MA- or saline-exposed) were divided to groups with challenge dose of MA (1 mg/kg) or saline. A modified Open field test (Laboras) was used to examine behavior in unknown environment. Plantar test was used to measure nociception on forelimbs, hind limbs, and the tail. Conditioned place preference (CPP) test was used to examine drug-seeking behavior. Our results in Laboras demonstrated that prenatal MA exposure sensitized the animals to the challenge dose of MA. Specifically prenatally MA-exposed animals that received the challenge MA in adulthood displayed higher locomotion and rearing activity relative to all the other groups. The Plantar test data suggest analgesic effect of MA (1 mg/kg), which however, did not differ based on the prenatal drug exposure. The results of CPP test showed that MA (5 mg/kg) conditioning resulted

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in increased drug-seeking behavior, but this effect was not affected by prenatal drug exposure. Thus, our data demonstrate that the effects of prenatal MA exposure and the challenge dose of the same drug in adulthood depend on behavioral model used.

Introduction

Methamphetamine (MA) is one of the most common "hard" drug abused by pregnant women (Marwick, 2000), which is also one of the most frequently used illicit drug in the Czech Republic (Vavřínková et al., 2001). MA is a powerfully addictive stimulant that metabolizes slowly and its high is long-lasting (8 to 24 hrs) (Marwick, 2000). This might be the reason that makes it so popular. Statistics show that only 17% of women abusers in the USA were primary MA users, but as much as 38% used it during pregnancy as some drug-abusing pregnant women replaced other drugs by MA due to its anorectic effect (Marwick, 2000). Amphetamines are able to cross both placental and blood-brain barriers (Nordahl et al., 2003; Greenhill, 2006; Sharma and Ali, 2006; Rohanová and Balíková, 2009). Experimental studies demonstrated that the level of MA in serum has peak between 30–45 minutes after administration (Acuff-Smith et al., 1996) and that MA results in increase of dopamine within 20–40 minutes, which is metabolized within 2 hours after MA administration in rats (Bubeníková-Valešová et al., 2009).

There are studies (Vorhees and Pu, 1995; Acuff-Smith et al., 1996; Smith et al., 2008) showing that prenatal MA exposure impairs postnatal development of rats with lifetime consequences. Also, our previous studies demonstrated that administration of MA during pregnancy attenuates maternal behavior of rat mothers (Šlamberová et al., 2005a) and impairs postnatal development of their pups (Šlamberová et al., 2006; Hrubá et al., 2008). Further, we found that prenatally MA-exposed adult rats are slower in learning abilities tested in Morris water maze (Šlamberová et al., 2005b) and have increased seizure susceptibility (Šlamberová, 2005; Šlamberová and Rokyta, 2005a, b).

In addition, there are studies demonstrating that repeated administration of psychostimulants such as MA enhances locomotor activities tested in the Open field in response to treatment of the same drug in rodents. This phenomenon is defined as behavioral sensitization or reverse tolerance (Suzuki et al., 2004). Once behavioral sensitization is established, it persists for several months (Cornish and Kalivas, 2001). There are however no studies, except our own, investigating possible sensitizing effect of prenatal MA exposure. Our previous studies demonstrated that prenatal MA exposure makes adult rats more sensitive to a single injection of the same drug (but lower dose of 1 mg/kg) relative to controls in models of epileptic seizures and cognition (Schutová et al., 2008; Šlamberová et al., 2008, 2009, 2010).

Furthermore, increased predisposition of drug abuse in adulthood has been shown in animals exposed to cocaine (Heyser et al., 1992; Rocha et al., 2002; Estelles et al., 2006), cannabinoids (Vela et al., 1998) or morphine (Gagin et al.,

1997) *in utero* when tested in "Self-administration test" or "Conditioned place preference test" (CPP). CPP is one of the most widespread drug reward test (for review see Tzschentke, 1998). Based on pavlovian conditioning principles, CPP reflects a preference for a context due to the contiguous association between the context and a drug-associated stimulus. It also presents important advantages, among which the possibility to reveal both reward and aversion, to test animals in a drug-free state and to allow simultaneous determination of locomotor activity (Fattore et al., 2005).

Based on the information above the present study is designed to investigate the effect of prenatal MA exposure on behavior in the Open field test and nociception in the Plantar test that both examine possible changes in the sensitivity to the same drug in adulthood. In addition, CPP test is used to examine active drug-seeking behavior of adult male rats. All experiments last for one hour which corresponds with the pharmacokinetics of MA in rat blood circulation as mentioned above (Acuff-Smith et al., 1996; Bubeníková-Valešová et al., 2009).

Methods

All experimental procedures 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).

Prenatal and postnatal animal care

Adult female Wistar rats (250–300 g) were delivered by Anlab (Prague, Czech Republic) from Charles River Laboratories International, Inc. Animals were housed 4–5 per cage 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 6:00 h. One week after arrival females were smeared by vaginal lavage to determine the phase of estrous cycle. The smear was examined by light microscopy. To ensure successful insemination, at the onset of estrous phase of the estrous cycle (Turner and Bagnara, 1976), female rats were housed with sexually mature males overnight. There were always, one female and one male in a cage. The next morning females were smeared for the presence of sperm and returned to their previous home cages. This was counted as gestational day (GD) 1.

Dams were randomly assigned to MA-treated and saline-treated. On GD 1 the daily injections started and continued to the day of delivery, which usually occurred on GD 22 (for details see Šlamberová et al., 2005a). MA (from the Faculty of Pharmacy of Charles University in Hradec Králové, Czech Republic) was injected subcutaneously (s.c.) in a dose of 5 mg/kg, saline was injected s.c. at the same time in the same volume as MA.

The day of delivery was counted as postnatal day (PD) 0. On PD 21, pups were weaned and group-housed by sex. Animals were left undisturbed until adulthood. Only male rats (PD 70–90) were used in the present study. Always one male rat per group was used in each experiment from each litter to avoid litter effects. Females were used in other experiments that will be a part of another study.

Open field test – Laboras

Laboras apparatus (Metris B.V., Netherlands) was used to test natural behavior in adult male rats. Laboras is a fully automatic system for continuous behavior recognition and tracking in small rodents. Single animal is placed to the plexiglass cage (45×30×30 cm) filled with bedding material, that is covered and equipped as normal home cage with food and water available *ad libitum*. The cage is placed on a triangular sensor platform (95×75×75 cm) which makes the basis of the system connected with a computer. The movements are analyzed by Laboras software that records different types of activities during the time of Open field testing.

To determine the effect of MA in adulthood, half of the animals from each prenatally exposed group received a low dose of MA (s.c. 1 mg/kg), and half of the animals received saline injection. The dose 1 mg/kg was used because it does not cause stereotypy, unlike the dose of 5 mg/kg used in gestation, and therefore should not affect the ability to walk. Thus, we examined 4 groups of adult male rats (n=8): prenatally saline-exposed with challenge dose of MA (S/MA) or saline (S/S) and prenatally MA-exposed with challenge dose of MA (MA/MA) or saline (MA/S). Immediately after saline or MA s.c. injection, the rat was placed to the testing Laboras cage. The behavior was monitored for 1 hour divided to six 10-minute intervals. The time spent by and frequency of each behavior was recorded for each 10-minute interval.

Following parameters were analyzed in all animals during the 1-hour period of testing: the duration spent by locomotion, immobility, rearing (exploratory behavior).

Plantar test

Another group of animals were used to test nociception. Plantar test (Plantar test; Ugo Basile, Comerio, Italy) was used to measure pain threshold. A beam generator, which is controlled by the experimenter under the floor of the plexiglass box (size 27×17×14 cm) allows to stimulate the sole (planta) of the paw in a freely moving rat. The latency of paw withdrawal on painful heat stimulus was measured for each of the 4 paws. Latency to withdrawal of the tail was measured as a modified method of the Tail-flick test. The maximal intensity was set to 90 and cut-off time was 22 s to prevent tissue damage.

Four measures were done in 15-minute intervals. First measure was used as a control without MA challenge. When the first measure was finished, MA (1 mg/kg)

was injected. Next measures were performed 15, 30, and 45 minutes after the drug administration. Thus, the effect of challenge dose of MA between prenatally MA- and saline-exposed male rats (n=8) was compared during time period of 45 minutes.

Conditioned place preference (CPP)

Other groups of adult male rats were used to test drug reward conditioning and how it is affected by prenatal drug exposure. Because our preliminary results (data not shown) showed that the dose 1 mg/kg was ineffective in inducing drug-seeking behavior, the dose of 5 mg/kg (the same dose as in prenatal period) was used for conditioning in the CPP apparatus to examine our hypotheses.

The CPP apparatus dimensions and general procedures were modified from the work of Sanchez et al. (2003). The apparatus is made of Plexiglas, with two main compartments measuring 25×25×25 cm (l×w×h) and one central (neutral) compartment measuring 15×25×25 cm. Central and main chambers are divided by removable doors. Walls of one of the main compartments are painted with 2.5-cm-wide alternating black and white horizontal lines, walls of the other main compartment are painted with 2.5-cm-wide alternating black and white vertical lines. The neutral compartment is made of gray opaque Plexiglas. The floor of both main compartments is made from wire mesh with different size of the meshes, while the central compartment has smooth plexiglass floor.

The place conditioning procedure consisted of three phases: pre-exposure, conditioning, and the CPP test as in work of Mueller and Stewart (2000). *Pre-exposure:* On the Day 1, animals received a single pre-exposure test in which they were placed in the center choice chamber with the doors open to allow access to the entire apparatus for 15 min. The amount of time spent in each chamber was monitored and used to assess unconditioned preferences. *Conditioning:* During the following conditioning phase (8 days), rats were assigned to receive drug pairings with one of the two chambers in a counterbalanced fashion (the "unbiased" procedure). Half of each group started the experiment on the drug-paired side and half on the saline-paired side. On alternate days, rats received saline injections (1.0 ml/kg) prior to being placed in the other chamber. After administration of drug or saline, animal were allowed to explore the specific chamber for 1 hour. Half of each treatment group received drug injections on the 2^{nd}, 4^{th}, 6^{th} and 8^{th} day; the remaining subjects on the 3^{rd}, 5^{th}, 7^{th}, 9^{th} day. The center chamber was never used during conditioning and was blocked by doors. *CPP test:* Two days after the last conditioning trial (Day 12), a test for CPP was given. Animals were placed in the center choice chamber with the doors opened and allowed free access to the entire apparatus for 15 min. The time spent in each chamber and number of entries was recorded to assess individual preferences. No injections were given during the CPP test, maintaining the same procedure as that used during the pre-exposure test.

Statistical analyses

Laboras. All behavioral activities were evaluated separately. Three-way ANOVA (between factors: prenatal drug, challenge dose; within factors: 10-minute intervals) was used.

Plantar test. Average of measurements of both forelimbs (left and right), both hind limbs and all tail measurements, respectively, were used for statistical analyses. Two-way ANOVA (between factor: prenatal drug exposure; within factor: 15-minute intervals) was used.

CPP test. Three-way ANOVA (between factors: prenatal exposure, chamber with or without drug; within factor: time – before vs. after conditioning) was used to analyze differences in number of entries to chambers and total time spent in the specific chamber.

Bonferroni post-hoc test was used when appropriate. Differences were considered significant if $p<0.05$.

All 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 test – Laboras

Locomotion (Figure 1A). There was a main effect of prenatal drug exposure [$F(1, 28) = 4.80$; $p<0.05$], challenge dose [$F(1, 28) = 18.29$; $p<0.001$] and interaction between prenatal drug exposure and challenge dose [$F(1, 28) = 5.32$; $p<0.05$]. Specifically, administration of MA challenge increased locomotion in prenatally MA-exposed rats (MA/S < MA/MA; $p<0.0001$), while did not affect it in prenatally saline-exposed rats (S/S vs. S/MA; P=0.17). Moreover, prenatally MA-exposed rats administered with MA challenge in adulthood spent more time with locomotion relative to prenatally saline-exposed rats with challenge dose of MA (MA/MA > S/MA; $p<0.05$). In addition, all animals, regardless of prenatal drug exposure or the challenge dose in adulthood displayed decreased locomotion during the 1-hour testing period [$F(5, 140) = 48.83$; $p<0.0001$].

Immobility (Figure 1B). There was a main effect of prenatal drug exposure [$F(1, 28) = 9.10$; $p<0.01$], challenge dose [$F(1, 28) = 73.20$; $p<0.0001$] and an interaction between prenatal drug exposure and challenge dose [$F(1, 28) = 7.98$; $p<0.01$]. Specifically, administration of MA challenge decreased the immobility in prenatally saline or MA-exposed rats (S/S > S/MA; $p<0.01$ and MA/S > vs. MA/MA; $p<0.001$). The immobility did not differ between prenatally saline- and MA-exposed rats treated with MA challenge (MA/MA vs. S/MA; P=0.89), but the immobility was lower in prenatally MA-exposed rats treated in adulthood with saline relative to prenatally saline-exposed rats (MA/S < S/S; $p<0.001$). In addition, there was a main effect of time [$F(5, 140) = 37.10$; $p<0.0001$] and an interaction between

time, prenatal drug exposure and challenge dose [F(5, 140) = 7.85; p<0.0001]. As expected, there was an increase in immobility within the time period in control animals (S/S), the increase was lower in animals prenatally MA-exposed without MA challenge (MA/S) and there was no increase in animals with adult MA challenge regardless of the prenatal MA exposure (S/MA and MA/MA).

Rearing (Figure 1C). The prenatal drug exposure did not show any significant differences in rearing behavior [F(1, 28) = 4.02; p=0.055], however, there was a main effect of challenge dose [F(1, 28) = 9.11; p<0.01] and an interaction between prenatal drug exposure and challenge dose [F(1, 28) = 7.09; p<0.05]. Specifically, administration of MA challenge increased rearing only in prenatally MA-exposed

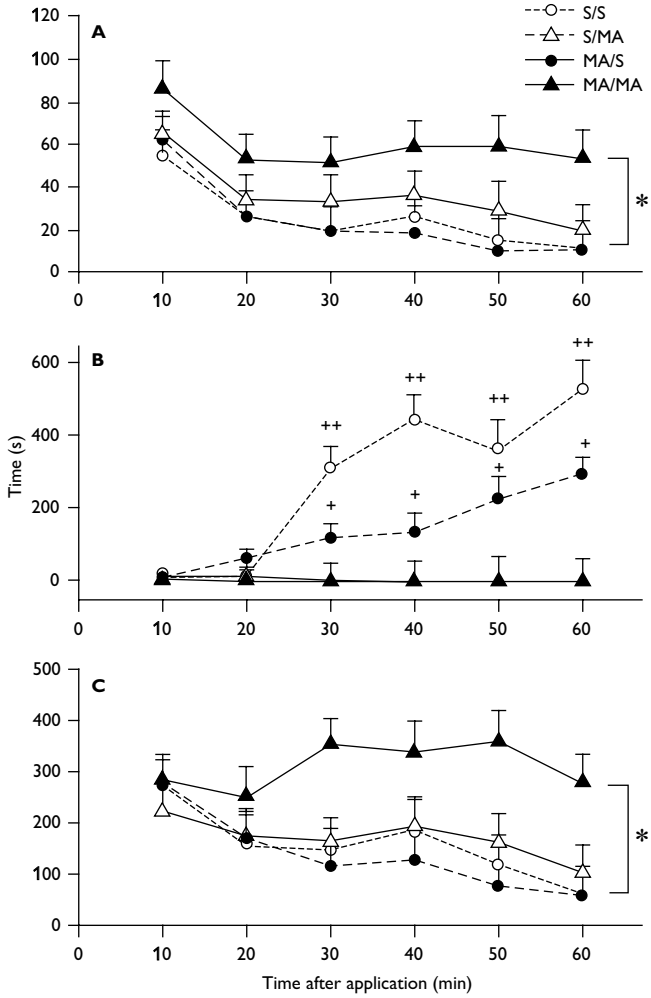

*Figure 1 – The effect of prenatal MA exposure (5 mg/kg) and challenge dose of MA in adulthood (1 mg/kg) on locomotion (A), immobility (B) and rearing (C) in Laboras test. Values are means ± SEM (n=8). *p<0.05; MA/MA > S/S; S/MA; MA/S regardless of the time +p<0.01; ++p<0.001; S/S and MA/S > S/MA and MA/MA*

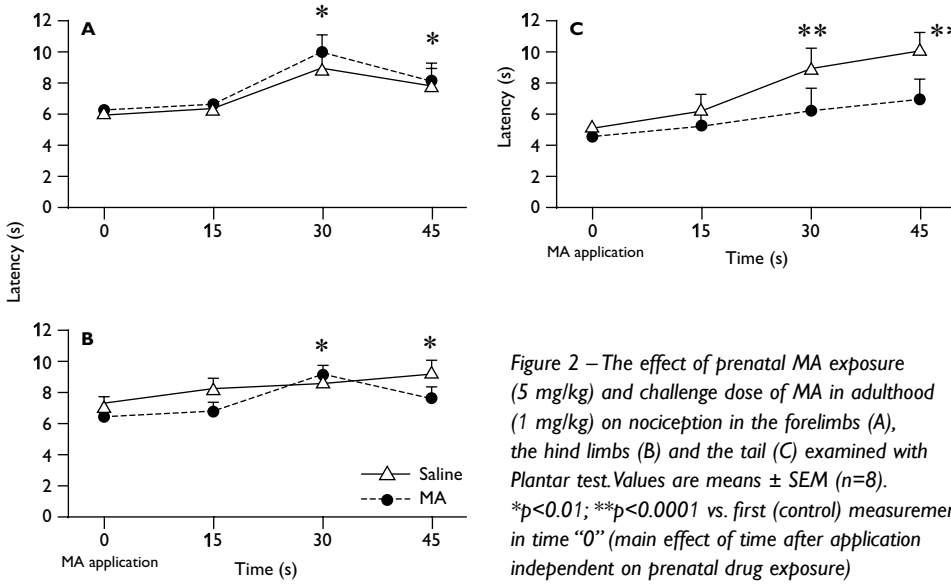

*Figure 2 – The effect of prenatal MA exposure (5 mg/kg) and challenge dose of MA in adulthood (1 mg/kg) on nociception in the forelimbs (A), the hind limbs (B) and the tail (C) examined with Plantar test. Values are means ± SEM (n=8). *p<0.01; **p<0.0001 vs. first (control) measurement in time "0" (main effect of time after application independent on prenatal drug exposure)*

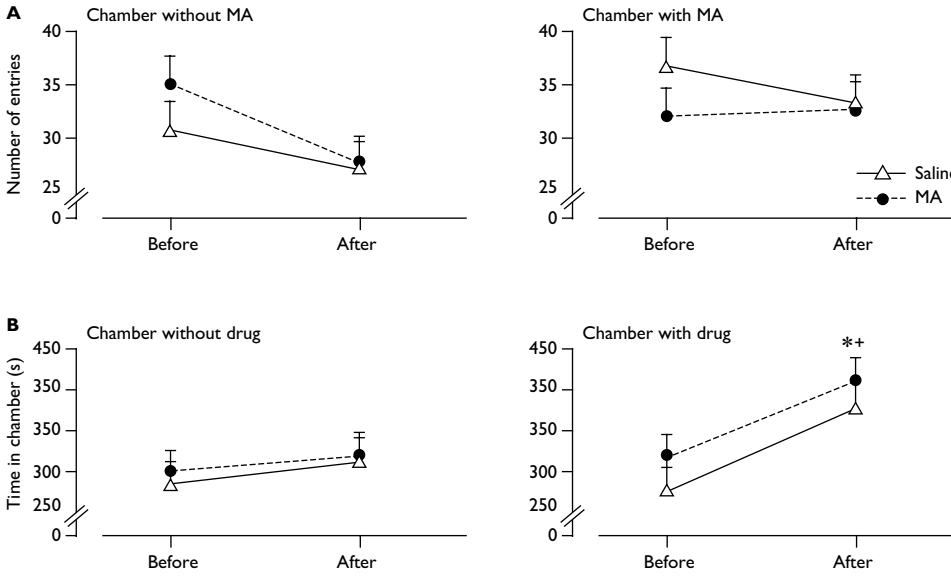

Figure 3 – The effect of prenatal MA exposure (5 mg/kg) and MA (5 mg/kg) conditioning on drug-seeking behavior in the CPP test. (A) Number of entries to the chamber with and without drug. (B) Time spent in the chamber with and without drug. Values are means ± SEM (n=8).
**p<0.05; after conditioning > before conditioning in the chamber with drug*
+p<0.05; chamber with drug > chamber without drug in the session after conditioning

rats (MA/S < MA/MA; $p<0.01$), but not in prenatally saline-exposed rats (S/S vs. S/MA; $p=0.80$). There was an increase in rearing in prenatally MA-exposed rats after the injection of MA challenge compared to prenatally saline-exposed rats with a challenge dose of MA (MA/MA > S/MA; $p<0.01$). In addition, there was a main effect of time [$F(5, 140) = 26.59$; $p<0.0001$] and an interaction between time, prenatal drug exposure and challenge dose [$F(5, 140) = 4.81$; $p<0.001$]. These results show that there was a decrease in rearing activity as the time of experiment progressed in groups without MA challenge (S/S and MA/S) and group of animals prenatally exposed to saline with adult MA challenge (S/MA), while the rearing activity did not change with the time in animals prenatally exposed to MA, with adult MA challenge (MA/MA).

Plantar test

MA in a dose of 1 mg/kg showed analgesic effect at all parts of the body; the forelimbs [$F(3, 12) = 6.38$; $p<0.01$] (Figure 2A), the hind limbs [$F(3, 36) = 6.41$; $p<0.01$] (Figure 2B) and the tail [$F(3, 36) = 10.51$; $p<0.0001$] (Figure 2C). However, this analgesic effect did not differ based on the prenatal drug exposure; forelimbs [$F(3, 12) = 0.08$; $p=0.972$], hind limbs [$F(3, 36) = 1.49$; $p=0.23$], tail [$F(3, 36) = 0.97$; $p=0.42$].

Conditioned place preference (CPP)

As shown in Figure 3A, there were no significant differences in the number of entries to the chambers with or without the drug before and after conditioning in respect of prenatal drug exposure [$F(1, 28) = 0.29$; $p=0.60$]. Figure 3B demonstrates that while the conditioning increased the time spent in the chamber where animals received drug relative to the chamber without drug [$F(1, 28) = 5.03$; $p<0.05$], this effect was not influenced by prenatal MA exposure [$F(1, 28) = 0.11$; $p=0.74$].

Discussion

The present study demonstrates that prenatally MA-exposed animals had increased locomotion and rearing activity in the Laboras test when compared to all the other groups. The finding that challenge dose of MA increases locomotion and rearing only in prenatally MA-exposed rats, but not in prenatally saline-exposed rats, suggests that prenatally MA-exposed animals are sensitized to the effect of the same drug in adulthood. This finding is in agreement with our previous studies showing increased sensitivity to single injection of MA in rats exposed with MA *in utero* when using several seizure models (Šlamberová et al., 2008, 2009, 2010) or examining learning and memory in Morris water maze (Schutová et al., 2008). These data are further in agreement with studies (Crozatier et al., 2003; Stanwood and Levitt, 2003) investigating the sensitizing effect of prenatal exposure to cocaine (other stimulant drug), which demonstrated

that prenatally cocaine-exposed rats are more sensitive to acute cocaine injection than prenatally saline-exposed rats. Surprisingly, the present study did not find sensitizing effect of prenatal MA exposure to the same drug in the test of nociception. Because there are no studies investigating the effect of psychostimulant's maternal administration and its sensitizing effect on nociception in adult offspring, we do not have any data to compare our results with. Anyhow, our results demonstrating that prenatal MA exposure does not influence sensitivity to pain in adult male rats is in agreement with our previous study (Yamamotová et al., 2004) showing no differences in males, but increased sensitivity to pain in female rats prenatally exposed to MA. Thus, the future study may examine the effect of prenatal MA exposure and challenge MA dose on nociception in adult females with respect to the estrous cycle. The present data, however, show interesting analgesic effect of challenge dose of MA in both prenatal groups. This effect was the highest 30 minutes after MA administration. This time interval corresponds with the peak of extracellular dopamine in the striatum, as measured by microdialysis in freely moving rats (Pereira et al., 2006; Bubeníková-Valešová et al., 2009). Besides dopamine, acute MA also increases brain serotonin and noradrenalin levels (Rothman et al., 2001). Thus, we suppose that MA may have had a sensitizing effect especially on the dopaminergic brain reward system, which can also represent a common-final pathway of both opioid and non-opioid analgesia (Altier and Stewart, 1999; Borsook, 2007). The difference in analgesia observed at different body sites further indicates the possible existence of a somatotopic organization of pain inhibition, which is under control of spinal or supraspinal mechanisms on tail or paws, respectively (Fang and Proudfit, 1996).

Our results showing no prenatal MA exposure-induced changes in drug-seeking behavior are in disagreement with studies of others showing increased drug-seeking behavior in both "Self-administration test" or CPP test in animals exposed to cocaine (Heyser et al., 1992; Rocha et al., 2002; Estelles et al., 2006), cannabinoids (Vela et al., 1998) or morphine (Gagin et al., 1997) *in utero*. There are, however, no studies investigating the long-term effect of prenatal MA exposure on drug-seeking behavior. It is therefore possible that MA (5 mg/kg) administered prenatally does not induce such serious changes in the predisposition to drug abuse as cocaine or opioids. Possible mechanism of such long-term changes induced with prenatal drug exposure that result or do not result in the increase of drug-seeking behavior might be in the mesolimbic (cortico-striatal) reward circuit that is responsible for development of drug abuse (Everitt and Robbins, 2005).

In conclusion, the present study demonstrates increased sensitivity to the same drug that was induced by prenatal MA exposure in Laboras test that examined locomotion and exploratory behavior, while it does not show change in the sensitivity to the same drug in Plantar test examining nociception. In addition, our expectation that animals that are exposed to MA *in utero* would have increased active drug-seeking behavior in adulthood was not confirmed. Question remains,

if other method examining drug-seeking behavior, such as self-administration model, would not show different results. However, many studies repeatedly demonstrated that both models are equivalent and show similar results of drug-seeking behavior (Tzschentke, 1998).

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