Do Prenatally Methamphetamine-Exposed Adult Male Rats Display General Predisposition to Drug Abuse in the Conditioned Place Preference Test?

R. ŠLAMBEROVÁ[1], M. POMETLOVÁ[1], B. SCHUTOVÁ[1], L. HRUBÁ[1], E. MACÚCHOVÁ[1], E. NOVÁ[1], R. ROKYTA[1]

[1]Department of Normal, Pathological and Clinical Physiology, Third Faculty of Medicine, Charles University in Prague, Prague, Czech Republic

Received February 28, 2012
Accepted March 26, 2012

Summary

Drug abuse of pregnant women is a growing problem. The effect of prenatal drug exposure may have devastating effect on development of the offsprings that may be long-term or even permanent. One of the most common drug abused by pregnant women is methamphetamine (MA), which is also the most frequently abused illicit drug in the Czech Republic. Our previous studies demonstrated that prenatal MA exposure alters behavior, cognition, pain and seizures in adult rats in sex-specific manner. Our most recent studies demonstrate that prenatal MA exposure makes adult rats more sensitive to acute injection of the same or related drugs than their controls. The aim of the present study was to examine the effect of prenatal MA exposure on drug-seeking behavior of adult male rats tested in the Conditioned place preference (CPP). Adult male rats were divided to: prenatally MA-exposed (5 mg/kg daily for the entire prenatal period), prenatally saline-exposed (1 ml/kg of physiological saline) and controls (without maternal injections). The following drugs were used in the CPP test in adulthood: MA (5 mg/kg), amphetamine (5 mg/kg), cocaine (5 and 10 mg/kg), morphine (5 mg/kg), MDMA (5 mg/kg) and THC (2 mg/kg). Our data demonstrated that prenatally MA-exposed rats displayed higher amphetamine-seeking behavior than both controls. MA as well as morphine induced drug-seeking behavior of adult male rats, however this effect did not differ based on the prenatal MA exposure. In contrast, prenatal MA exposure induced rather tolerance to cocaine than sensitization after the conditioning in the CPP. MDMA and THC did not induce significant effects. Even though the present data did not fully confirmed our hypotheses, future studies are planned to test the drug-seeking behavior also in self-administration test.

Key words

Prenatal methamphetamine • Drug-seeking behavior • Conditioned place preference • Psychostimulants • Opioids • Cannabinoids

Corresponding author

Romana Šlamberová, Department of Normal, Pathological and Clinical Physiology, Third Faculty of Medicine, Charles University in Prague, Ke Karlovu 4, 120 00 Praha 2, Czech Republic. Fax: +420 224902750. E-mail: rslamber@lf3.cuni.cz

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). While there are many studies showing that abuse of MA may affect maternal behavior as well as development of drug-abusing mother's offspring (Acuff-Smith *et al.* 1996, Šlamberová *et al.* 2005b, Šlamberová *et al.* 2006, Vorhees and Pu 1995), the research of the long-term effect of prenatal MA exposure is still in the beginning. Our laboratory specializes in investigation of the effects of drugs (especially MA) on rat mothers and their progeny.

Our previous studies demonstrated that prenatal MA exposure slows down the learning abilities tested in Morris water maze (Šlamberová *et al.* 2005c), alters pain sensitivity tested in Plantar test (Yamamotová *et al.* 2011), and increases seizure susceptibility in adult male

and female rats (Šlamberová 2005a). Further, 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). Only few studies (Crozatier *et al.* 2003, Stanwood and Levitt 2003), including our own (Schutová *et al.* 2009, Schutová *et al.* 2010, Šlamberová *et al.* 2008), investigated possible sensitizing effect of prenatal drug exposure. Studies of Crozatier *et al.* (2003) and Stanwood and Levitt (2003) demonstrated that prenatally cocaine-exposed rats are more sensitive to acute cocaine injection than prenatally saline-exposed rats. In addition, our results demonstrate that prenatal MA exposure makes adult rats more sensitive to acute injection of the same drug (but lower dose of 1 mg/kg) than their controls (Schutová *et al.* 2009, Schutová *et al.* 2010, Šlamberová *et al.* 2008).

Other studies showed that abuse of one drug may even increase sensitivity to abuse of another drug. This effect is called cross-sensitization (Bartoletti *et al.* 1985, Fattore *et al.* 2005). It was shown (Malanga and Kosofsky 2003) that rodents exposed to various abused drugs *in utero*, become sensitized in adulthood to the rewarding effects of drugs. For example they respond to lower doses of drug than control animals. Increased predisposition of drug abuse in adulthood has been shown in prenatally cocaine-exposed (Estelles *et al.* 2006a, Heyser *et al.* 1992a, Rocha *et al.* 2002), cannabinoid-exposed (Vela *et al.* 1998) and morphine-exposed offspring (Gagin *et al.* 1997) relative to controls. Also our most recent work demonstrated that prenatal MA exposure affects the sensitivity to cocaine and morphine in adulthood (Šlamberová *et al.* 2012). Even better how to simulate the situation in humans would however be examination of active drug-seeking behavior. There are basically only two models how to test active drug-seeking behavior: Self-administration test and Conditioned place preference test (CPP). CPP is one of the most widespread drug reward test for its availability and simplicity (for review see (Tzschentke 1998)). CPP reflects a preference for a context due to the contiguous association between the context and a drug-associated stimulus based on Pavlovian conditioning principles. 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).

Studies (Cole *et al.* 2003, Estelles *et al.* 2006b, Vela *et al.* 1998) demonstrated that prenatal drug exposure may alter active drug-seeking behavior regardless of the mechanism of action of the drug. Specifically, Vela *et al.* (1998) demonstrated that animals that were exposed to cannabinoids prenatally exhibited increase in the rate of acquisition of intravenous morphine self-administration behavior when compared to prenatally saline-exposed rats. Estelles *et al.* (2006b) found that unlike control or animals pre-treated with saline, subjects prenatally treated with cocaine did not develop conditioning with morphine. Further, Cole *et al.* (2003) showed that 3,4-methylenedioxymethamphetamine (MDMA; ecstasy) pretreatment reduced the rewarding properties of ethanol. Also our previous work (Vathy 2002) demonstrated that prenatal morphine exposure enhanced intracranial self-stimulation in the presence of a single cocaine injection in adult male rats. These studies suggest that prenatal drug exposure may induce cross-sensitization independently of the drugs that were the animals exposed prenatally and in adulthood. Thus, it seems that prenatal drug exposure induces general predisposition to drug addiction in adulthood. However, our previous study (Šlamberová *et al.* 2011) raised some doubts about this suggestion. Therefore, the present study was planned to extend our previous findings.

To prove or disprove our hypothesis that prenatal drug exposure induces predisposition to drug abuse in general, regardless of the drugs (prenatal x in adulthood), and may therefore induce cross-sensitization, three groups of drugs were tested in the present study: (1) the same drug as was used for prenatal exposure (MA), (2) drugs with similar mechanism of action (amphetamine, cocaine and MDMA) that affect dopamine, serotonin and noradrenalin systems similarly as MA, and (3) drugs with different mechanism of action (morphine and Delta9-tetrahydrocannabinol (THC)) that affect mostly opioid and cannabinoid receptors, respectively.

Methods

Prenatal and postnatal animal care

Adult female Wistar rats (250-300 g) were delivered by Anlab (Prague, the 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 0600 hr. One week after arrival females were smeared by vaginal lavage to determine the phase of the 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 a MA-treated, a saline-treated, or a control group. 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.* 2005b)). MA (Sigma Aldrich) was injected subcutaneously (s.c.) at a dose of 5 mg/kg, saline was injected s.c. at the same time in the same volume as MA, and control females were not exposed to any injections.

The day of the delivery was counted as postnatal day (PD) 0. On PD 1, pups were weighed, tattooed for further identification and cross-fostered so that each mother received the same number of pups from each of the three treatments (for detailed information see (Šlamberová *et al.* 2006)). Each mother raised 12 pups – two of each sex from each prenatal group (control, saline, MA). On PD 21, pups were weaned and group-housed by sex. Animals were left undisturbed until adulthood. Only male rats were used in the present study. Always one male rat per group was used from each litter to avoid litter effects. Females were used in other experiments that will be part of another study.

Conditioning to the drugs in adulthood

Adult male rats (PD 70-90) were used to test drug reward conditioning and how it is affected by prenatal drug exposure. The following drugs were analyzed to induce conditioning in the CPP: (1) the same drug as was used for prenatal exposure (MA), (2) drugs with similar mechanism of action as MA (amphetamine, cocaine and MDMA), and (3) drugs with different mechanism of action (morphine and THC).

MA was used at a dose of 5 mg/kg (the same dose as prenatally) during conditioning phase of the CPP test. Amphetamine was used at a dose of 5 mg/kg based on the work of Timár *et al.* (1996) showing developed positive place preference conditioning. Cocaine was used first at a dose of 5 mg/kg based on the work of Heyser *et al.* (1992b) showing developed positive place preference conditioning. However, this dose was ineffective in the CPP conditioning, so we increased the dose to 10 mg/kg. MDMA was used at a dose of 5 mg/kg based on the work of Bubeníková *et al.* (2005) showing increased acoustic startle response. Morphine was used at a dose of 5 mg/kg based on the work of Riley and Vathy (2006) showing positive place preference conditioning. THC was used at a dose of 2 mg/kg based on the work of Cheer *et al.* (2000) showing positive place preference conditioning.

There were always three groups based on the prenatal exposure used in each experiment: control without prenatal administration, prenatally saline-exposed rats and prenatally MA-exposed rats (n=8). Thus, the total number of animals tested in each of the CPP experiment was 24.

Conditioned place preference (CPP)

The CPP apparatus dimensions and general procedures were modified according to the work of Sanchez *et al.* (2003). The apparatus is made of Plexiglas, with two main compartments measuring 25x25x25 cm (l x w x h) and one central (neutral) compartment measuring 15x25x25 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) and our previous study (Šlamberová *et al.* 2011). ***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 entries and the total 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) or drug prior to being placed in the other chamber. After administration of drug or saline, animals were allowed to explore the specific chamber for 1 hour. Half of each treatment group received drug injections on the 2nd, 4th, 6th and 8th day; the remaining subjects on the 3rd, 5th, 7th, 9th day. The center chamber was never used during conditioning and was blocked by the 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 the 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

Two-Way ANOVA (factors: prenatal exposure, chamber with or without drug) with Repeated Measure (time: before vs. after conditioning) was used to analyze differences in the number of entries to chambers and the total time spent in the specific chamber. Differences were considered significant if $p<0.05$ in all statistical analyses.

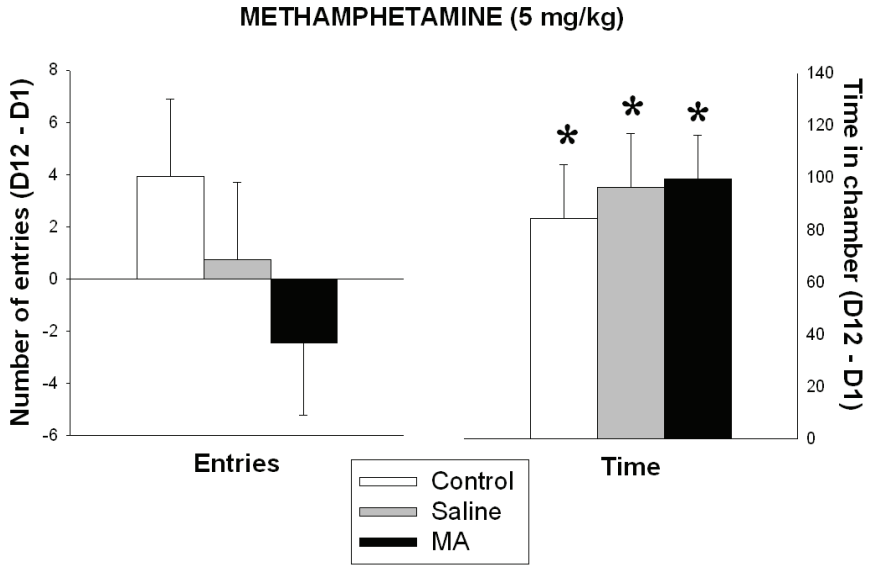

Fig. 1. Effect of MA (5 mg/kg) conditioning on drug-seeking behavior in prenatally MA-exposed, saline-exposed and control rats. **Left graph**: number of entries to the chamber associated with the drug; **Right graph**: time spent in the chamber associated with the drug. Data are presented as differences between experimental day 12 (CPP test) and experimental day 1 (pre-exposure). Values are means ± S.E.M. (n=8). * $p<0.05$ difference vs. chamber without drug (positive numbers means preference and negative numbers means avoidance of the chamber associated with the drug)

Results

MA (5 mg/kg)

MA conditioning increased number of entries [$F(2,42)=7.4$; $p<0.05$] and the time [$F(2, 42)=6.0$; $p<0.05$] spent in the chamber associated with the drug (Figure 1). Both of these effects were independent of the prenatal drug exposure.

Amphetamine (5 mg/kg)

There were no significant changes in the number of entries to the chamber associated with the drug after conditioning. The time spent in the chamber associated with the drug was higher only in prenatally MA-exposed rats, but unchanged in prenatally saline-exposed and control rats [$F(2,42)=8.80$; $p=<0.05$] (Figure 2A).

Cocaine (5 mg/kg)

Controls displayed higher number of entries [$F(2,42)=5.15$; $p<0.01$] and spent more time in the chamber [$F(2,42)=3.80$; $p<0.05$] associated with cocaine (5 mg/kg), while this increase was not apparent in rats prenatally exposed to MA or saline (Figure 2B).

Cocaine (10 mg/kg)

There was an increase in entries into the chamber associated with cocaine (10 mg/kg) that was independent of prenatal exposure [$F(2,42)=5.92$; $p<0.01$]. In addition, while prenatally saline-exposed and control rats spent more time in the chamber associated with cocaine (10 mg/kg) after conditioning, cocaine conditioning did not induce drug-seeking behavior in prenatally MA-exposed animals [$F(2,42)=5.76$; $p<0.05$] (Figure 2C).

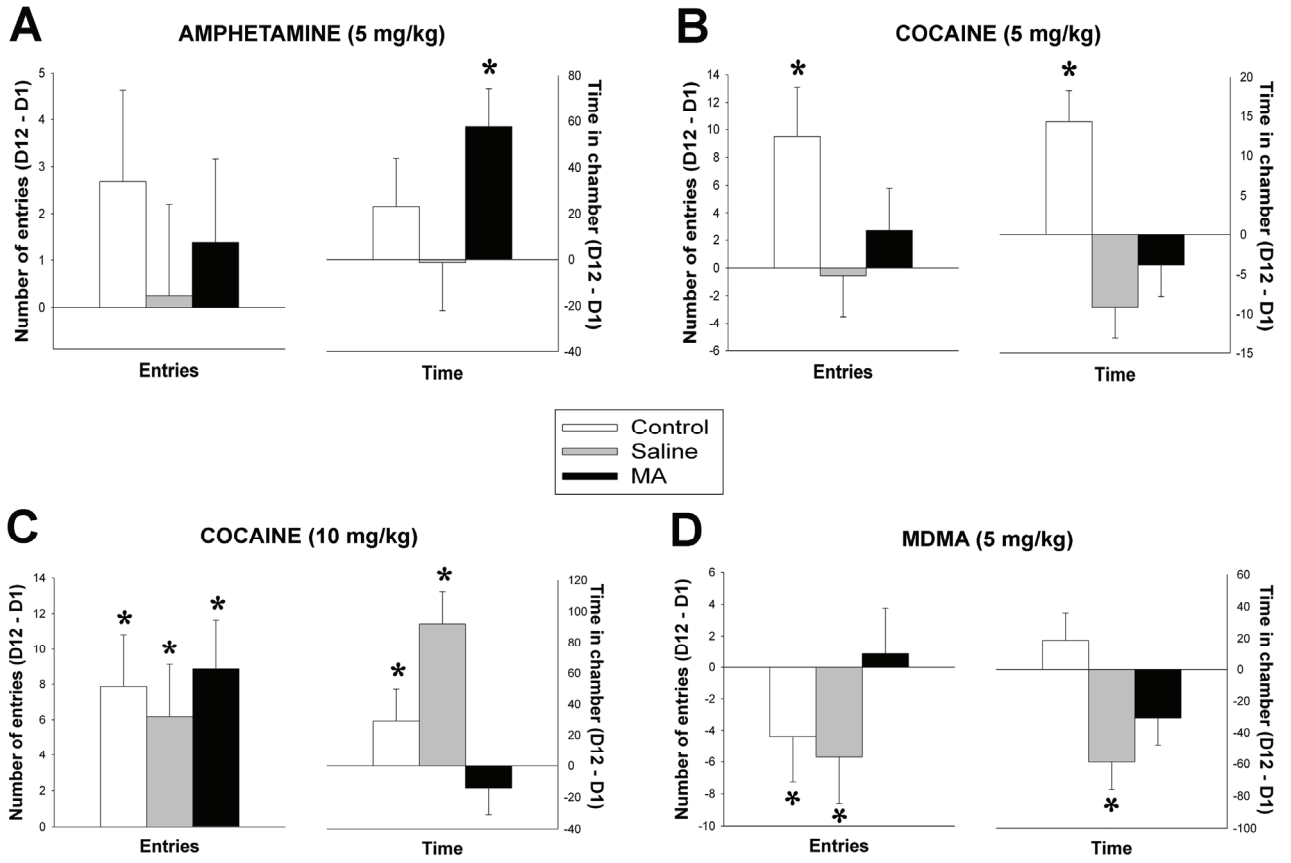

Fig. 2. Effect of (**A**) amphetamine (5 mg/kg), (**B**) cocaine (5 mg/kg), (**C**) cocaine (10 mg/kg), (**D**) MDMA (5 mg/kg) conditioning on drug-seeking behavior in prenatally MA-exposed, saline-exposed and control rats. Always, **Left graph**: number of entries to the chamber associated with the drug; **Right graph**: time spent in the chamber associated with drug. Data are presented as differences between experimental day 12 (CPP test) and experimental day 1 (pre-exposure). Values are means ± S.E.M. (n=8). * $p<0.05$ difference vs. chamber without drug (positive numbers means preference and negative numbers means avoidance of the chamber associated with the drug)

MDMA (5 mg/kg)

There was decrease in entries to the chamber associated with MDMA after conditioning in prenatally saline-exposed rats, while the MDMA did not change the number of entries to the chambers in controls or prenatally MA-exposed rats [$F(2,42)=3.67$; $p<0.05$]. Similarly, controls and prenatally saline-exposed rats spent less time in the chamber associated with MDMA, while prenatally MA-exposed rats did not prefer any chamber [$F(2,42)=3.35$; $p<0.05$] (Figure 2D).

Morphine (5 mg/kg)

All animals regardless of the prenatal drug exposure displayed higher number of entries [$F(2,42)=33.42$; $p<0.001$] and spent more time in the chamber [$F(2,42)=50.39$; $p<0.0001$] associated with morphine in the CPP test after conditioning (Figure 3A).

THC (2 mg/kg)

THC increased the number of entries to the chamber associated with the drug after conditioning only in prenatally MA-exposed rats, while did not have any effect in controls and prenatally saline-exposed rats [$F(2,42)=9.50$; $p<0.001$]. On the other hand, prenatally saline- and MA-exposed rats avoided the chamber associated with the THC after conditioning, while control rats did not display any preference [$F(2,42)=3.68$; $p<0.05$] (Figure 3B).

Discussion

Our data demonstrate that MA and morphine induced increase in drug-seeking behavior in adult male rats independently of prenatal MA exposure. The only sensitizing effect of prenatal MA exposure is shown in our results of amphetamine conditioning. Our data show that while controls and prenatally saline-exposed rats did not prefer chamber with amphetamine, there was increase in drug-seeking behavior in prenatally MA-exposed rats. Future studies are planned to test higher doses of

amphetamine that would induce drug-seeking behavior even in both control groups. Neither MDMA, nor THC was able to induce drug-seeking behavior, the effect was rather the opposite. Some animals preferred the chamber that was not associated with the drug and avoided the chamber with drug. In cocaine conditioning control animals displayed increased drug-seeking behavior, while MA-exposed animals did not. This result suggests possible effect of tolerance to cocaine induced by prenatal MA exposure.

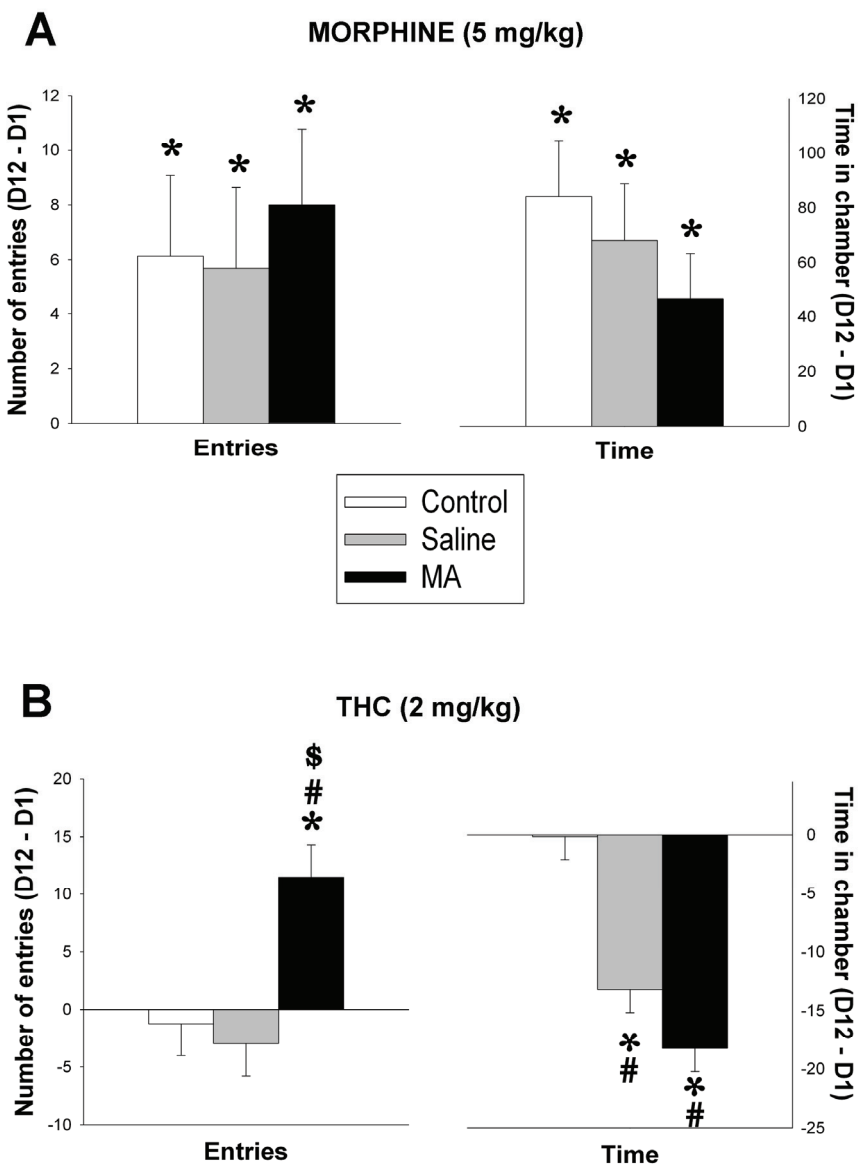

Fig. 3. Effect of (**A**) morphine (5 mg/kg), (**B**) THC (2 mg/kg) conditioning on drug-seeking behavior in prenatally MA-exposed, saline-exposed and control rats. Always, **Left graph**: number of entries to the chamber associated with the drug; **Right graph**: time spent in the chamber associated with drug. Data are presented as differences between experimental day 12 (CPP test) and experimental day 1 (pre-exposure). Values are means ± S.E.M. (n=8). * $p<0.05$ difference vs. chamber without drug (positive numbers means preference and negative numbers means avoidance of the chamber associated with the drug); # $p<0.05$ vs. prenatal controls; $ $p<0.05$ vs. prenatally saline-exposed rats

The data showing no prenatal MA exposure-induced changes in drug-seeking behavior after MA and morphine conditioning are in disagreement with studies of others showing increased drug-seeking behavior in both self-administration and CPP tests in animals exposed prenatally to cocaine (Estelles *et al.* 2006b, Heyser *et al.* 1992b, Rocha *et al.* 2002), cannabinoids (Vela *et al.* 1998) or morphine (Gagin *et al.* 1997). There are, however, no studies, instead of our own (Šlamberová *et al.* 2011), 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. In contrast, there are studies (Riley and Vathy 2006, Vathy *et al.* 2007) showing that prenatal morphine exposure does not affect self-administration of morphine or cocaine in adulthood. In addition, study of Vela *et al.* (1998) demonstrated sex differences of cross-effect between prenatal cannabinoids exposure and morphine self-administration in adulthood.

Specifically, adult female rats born from mothers that were daily treated with THC during gestation and lactation periods, exhibited a statistically significant increase in the rate of acquisition of intravenous morphine self-administration behavior when compared with females born from vehicle-exposed mothers, an effect that did not exist in THC-exposed male offspring. Thus, it seems that the possibility of increased drug-seeking of drugs in adulthood depends on the drug that was the animal exposed prenatally and also on the sex. Therefore, our future studies are planned to examine the cross-effects between prenatal MA exposure and sensitivity to other drugs in adult females.

Our data demonstrating rather decreased than increased preference of the cocaine-associated chamber in prenatally MA-exposed rats, thereby inducing rather tolerance to cocaine conditioning than sensitization, are surprising. To the best of our knowledge, there are only two studies supporting our finding demonstrating tolerance to cocaine induced by MA. Peltier *et al.* (1996) demonstrated that chronic treatment with psychostimulants, such as amphetamine and MA, produces cross-tolerance to both the discriminative and reinforcing effects of cocaine. In addition, study of Gygi *et al.* (1996) suggesting that MA causes tolerance to serotonergic effects of psychostimulants might also support our results. Because, it was repeatedly shown that cocaine affects serotoninergic system the most, while MA and amphetamine influence more the noradrenergic and dopaminergic systems than serotoninergic (Fleckenstein *et al.* 2000, Rothman *et al.* 2001, Shoblock *et al.* 2003), study of Gygi *et al.* (1996) is also in agreement with the present data.

Our findings that neither MDMA, nor THC, was able to induce drug-seeking behavior in control rats are in disagreement with some studies of others. These inconsistencies may be due to different doses of the drug used in the experiments. For example, Vela *et al.* (1998) used 5 mg/kg of THC, while we used 2 mg/kg. On the other hand, our results showing no THC-seeking behavior and furthermore demonstrating aversion of prenatally saline- and MA-exposed rats to THC in the measure of time spent in the drug-associated chamber are in agreement with the study of Cheer *et al.* (2000). Cheer *et al.* (2000) found also aversion to the chamber associated to the THC at such a low dose as 1.5 mg/kg. In addition, the available MDMA studies showing results of CPP are even more inconsistent. Most of them show mice data (Daza-Losada *et al.* 2009, Do Couto *et al.* 2011, Ribeiro Do Couto *et al.* 2011) that are hard to compare to rats because of the dosage. Some of them tested effect of MDMA together with ethanol (Do Couto *et al.* 2011, Ribeiro Do Couto *et al.* 2011). Only studies of Diller *et al.* (2007) and Jones *et al.* (2010) tested the effect of MDMA conditioning in rats. Results of Jones *et al.* (2010), who used MDMA at a dose of 6.6 mg/kg and showed no conditioning are in agreement with the present study. On the other hand, Diller *et al.* (2007) showed that the conditioning was induced with a dose of 5 mg/kg, while the 10 mg/kg dose returned the performance to the baseline (control) level. These findings are very surprising and in disagreement with all other studies. Future studies are planned to test also higher doses of THC and MDMA in the CPP test to try to solve these inconsistencies of the available studies.

In conclusion, our expectation that animals prenatally exposed to MA would have increased active drug-seeking behavior in adulthood was not confirmed (possibly with exception of amphetamine conditioning). Moreover, the opposite (tolerance) was shown in cocaine conditioning. Question remains, if other method examining drug-seeking behavior, such as self-administration test, would show the same results. However, many studies repeatedly demonstrated that both models are equivalent and show similar results of drug-seeking behavior (Tzschentke 1998). Future studies are planned to compare the present results to drug-seeking behavior in self-administration test.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

This study was supported by grant GA 305/09/0126 from Grant Agency of the Czech Republic, grant # NS10509-3/2009 from the Internal Agency of the Ministry of Health of the Czech, project CSM 110 from Ministry of Education, Youth and Sports and project 264706/SVV/2012 from Charles University in Prague. The procedures for animal experimentation utilized in this report was 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).

References

ACUFF-SMITH KD, SCHILLING MA, FISHER JE, VORHEES CV: Stage-specific effects of prenatal d-methamphetamine exposure on behavioral and eye development in rats. *Neurotoxicol Teratol* **18**: 199-215, 1996.

BARTOLETTI M, GAIARDI M, GUBELLINI C, BACCHI A, BABBINI M: Cross-sensitization to the excitatory effect of morphine in post-dependent rats. *Neuropharmacology* **24**: 889-893, 1985.

BUBENÍKOVÁ V, VOTAVA M, HORÁČEK J, PALENÍČEK T: Relation of sex and estrous phase to deficits in prepulse inhibition of the startle response induced by ecstasy (MDMA). *Behav Pharmacol* **16**: 127-130, 2005.

CHEER JF, KENDALL DA, MARSDEN CA: Cannabinoid receptors and reward in the rat: a conditioned place preference study. *Psychopharmacology (Berl)* **151**: 25-30, 2000.

COLE JC, SUMNALL HR, O'SHEA E, MARSDEN CA: Effects of MDMA exposure on the conditioned place preference produced by other drugs of abuse. *Psychopharmacology (Berl)* **166**: 383-390, 2003.

CORNISH JL, KALIVAS PW: Cocaine sensitization and craving: differing roles for dopamine and glutamate in the nucleus accumbens. *J Addict Dis* **20**: 43-54, 2001.

CROZATIER C, GUERRIERO RM, MATHIEU F, GIROS B, NOSTEN-BERTRAND M, KOSOFSKY BE: Altered cocaine-induced behavioral sensitization in adult mice exposed to cocaine in utero. *Brain Res Dev Brain Res* **147**: 97-105, 2003.

DAZA-LOSADA M, RODRIGUEZ-ARIAS M, AGUILAR MA, MINARRO J: Acquisition and reinstatement of MDMA-induced conditioned place preference in mice pre-treated with MDMA or cocaine during adolescence. *Addict Biol* **14**: 447-456, 2009.

DILLER AJ, ROCHA A, CARDON AL, VALLES R, WELLMAN PJ, NATION JR: The effects of concurrent administration of +/-3,4-methylenedioxymethamphetamine and cocaine on conditioned place preference in the adult male rat. *Pharmacol Biochem Behav* **88**: 165-170, 2007.

DO COUTO BR, RODRIGUEZ-ARIAS M, FUENTES S, GAGLIANO H, ARMARIO A, MINARRO J, AGUILAR MA: Adolescent pre-exposure to ethanol or MDMA prolongs the conditioned rewarding effects of MDMA. *Physiol Behav* **103**: 585-593, 2011.

ESTELLES J, RODRIGUEZ-ARIAS M, MALDONADO C, AGUILAR MA, MINARRO J: Gestational exposure to cocaine alters cocaine reward. *Behav Pharmacol* **17**: 509-515, 2006a.

ESTELLES J, RODRIGUEZ-ARIAS M, MALDONADO C, MANZANEDO C, AGUILAR MA, MINARRO J: Prenatal cocaine alters later responses to morphine in adult male mice. *Prog Neuropsychopharmacol Biol Psychiatry* **30**: 1073-1082, 2006b.

FATTORE L, DEIANA S, SPANO SM, COSSU G, FADDA P, SCHERMA M, FRATTA W: Endocannabinoid system and opioid addiction: behavioural aspects. *Pharmacol Biochem Behav* **81**: 343-359, 2005.

FLECKENSTEIN AE, GIBB JW, HANSON GR: Differential effects of stimulants on monoaminergic transporters: pharmacological consequences and implications for neurotoxicity. *Eur J Pharmacol* **406**: 1-13, 2000.

GAGIN R, KOOK N, COHEN E, SHAVIT Y: Prenatal morphine enhances morphine-conditioned place preference in adult rats. *Pharmacol Biochem Behav* **58**: 525-528, 1997.

GYGI MP, GYGI SP, JOHNSON M, WILKINS DG, GIBB JW, HANSON GR: Mechanisms for tolerance to methamphetamine effects. *Neuropharmacology* **35**: 751-757, 1996.

HEYSER CJ, GOODWIN GA, MOODY CA, SPEAR LP: Prenatal cocaine exposure attenuates cocaine-induced odor preference in infant rats. *Pharmacol Biochem Behav* **42**: 169-173, 1992a.

HEYSER CJ, MILLER JS, SPEAR NE, SPEAR LP: Prenatal exposure to cocaine disrupts cocaine-induced conditioned place preference in rats. *Neurotoxicol Teratol* **14**: 57-64, 1992b.

JONES BC, BEN-HAMIDA S, DE VASCONCELOS AP, KELCHE C, LAZARUS C, JACKISCH R, CASSEL JC: Effects of ethanol and ecstasy on conditioned place preference in the rat. *J Psychopharmacol* **24**: 275-279, 2010.

MALANGA CJ, KOSOFSKY BE: Does drug abuse beget drug abuse? Behavioral analysis of addiction liability in animal models of prenatal drug exposure. *Brain Res Dev Brain Res* **147**: 47-57, 2003.

MARWICK C: NIDA seeking data on effect of fetal exposure to methamphetamine. *JAMA* **283**: 2225-2226, 2000.

MUELLER D, STEWART J: Cocaine-induced conditioned place preference: reinstatement by priming injections of cocaine after extinction. *Behav Brain Res* **115**: 39-47, 2000.

PELTIER RL, LI DH, LYTLE D, TAYLOR CM, EMMETT-OGLESBY MW: Chronic d-amphetamine or methamphetamine produces cross-tolerance to the discriminative and reinforcing stimulus effects of cocaine. *J Pharmacol Exp Ther* **277**: 212-218, 1996.

RIBEIRO DO COUTO B, DAZA-LOSADA M, RODRIGUEZ-ARIAS M, NADAL R, GUERRI C, SUMMAVIELLE T, MINARRO J, AGUILAR MA: Adolescent pre-exposure to ethanol and 3,4-methylenedioxymethylamphetamine (MDMA) increases conditioned rewarding effects of MDMA and drug-induced reinstatement. *Addict Biol* **17**: 588-600, 2012.

RILEY MA, VATHY I: Mid- to late gestational morphine exposure does not alter the rewarding properties of morphine in adult male rats. *Neuropharmacology* **51**: 295-304, 2006.

ROCHA BA, MEAD AN, KOSOFSKY BE: Increased vulnerability to self-administer cocaine in mice prenatally exposed to cocaine. *Psychopharmacology (Berl)* **163**: 221-229, 2002.

ROTHMAN RB, BAUMANN MH, DERSCH CM, ROMERO DV, RICE KC, CARROLL FI, PARTILLA JS: Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse* **39**: 32-41, 2001.

SANCHEZ CJ, BAILIE TM, WU WR, LI N, SORG BA: Manipulation of dopamine d1-like receptor activation in the rat medial prefrontal cortex alters stress- and cocaine-induced reinstatement of conditioned place preference behavior. *Neuroscience* **119**: 497-505, 2003.

SCHUTOVÁ B, HRUBÁ L, POMETLOVÁ M, DEYKUN K, ŠLAMBEROVÁ R: Cognitive functions and drug sensitivity in adult male rats prenatally exposed to methamphetamine. *Physiol Res* **58**: 741-750, 2009.

SCHUTOVÁ B, HRUBÁ L, POMETLOVÁ M, ROKYTA R, ŠLAMBEROVÁ R: Responsiveness to methamphetamine in adulthood is altered by prenatal exposure in rats. *Physiol Behav* **99**: 381-387, 2010.

SHOBLOCK JR, SULLIVAN EB, MAISONNEUVE IM, GLICK SD: Neurochemical and behavioral differences between d-methamphetamine and d-amphetamine in rats. *Psychopharmacology (Berl)* **165**: 359-369, 2003.

ŠLAMBEROVÁ R: Flurothyl seizures susceptibility is increased in prenatally methamphetamine-exposed adult male and female rats. *Epilepsy Res* **65**: 121-124, 2005a.

ŠLAMBEROVÁ R, CHAROUSOVÁ P, POMETLOVÁ M: Methamphetamine administration during gestation impairs maternal behavior. *Dev Psychobiol* **46**: 57-65, 2005b.

ŠLAMBEROVÁ R, POMETLOVÁ M, SYLLABOVÁ L, MANČUŠKOVÁ M: Learning in the Place navigation task, not the New-learning task, is altered by prenatal methamphetamine exposure. *Brain Res Dev Brain Res* **157**: 217-219, 2005c.

ŠLAMBEROVÁ R, POMETLOVÁ M, CHAROUSOVÁ P: Postnatal development of rat pups is altered by prenatal methamphetamine exposure. *Prog Neuropsychopharmacol Biol Psychiatry* **30**: 82-88, 2006.

ŠLAMBEROVÁ R, BERNÁŠKOVÁ K, MATĚJOVSKÁ I, SCHUTOVÁ B: Does prenatal methamphetamine exposure affect seizure susceptibility in adult rats with acute administration of the same drug? *Epilepsy Res* **78**: 33-39, 2008.

ŠLAMBEROVÁ R, SCHUTOVÁ B, HRUBÁ L, POMETLOVÁ M: Does prenatal methamphetamine exposure affect the drug-seeking behavior of adult male rats? *Behav Brain Res* **224**: 50-86, 2011.

ŠLAMBEROVÁ R, YAMAMOTOVÁ A, POMETLOVÁ M, SCHUTOVÁ B, HRUBÁ L, NOHEJLOVÁ-DEYKUN K, NOVÁ E, MACÚCHOVÁ E: Does prenatal methamphetamine exposure induce cross-sensitization to cocaine and morphine in adult male rats? *Prague Med Rep* **113**: 189-205, 2012.

STANWOOD GD, LEVITT P: Repeated i.v. cocaine exposure produces long-lasting behavioral sensitization in pregnant adults, but behavioral tolerance in their offspring. *Neuroscience* **122**: 579-583, 2003.

SUZUKI T, FUKUOKA Y, MORI T, MIYATAKE M, NARITA M: Behavioral sensitization to the discriminative stimulus effects of methamphetamine in rats. *Eur J Pharmacol* **498**: 157-161, 2004.

TIMÁR J, GYARMATI Z, BARNA L, KNOLL B: Differences in some behavioural effects of deprenyl and amphetamine enantiomers in rats. *Physiol Behav* **60**: 581-587, 1996.

TURNER CD, BAGNARA JT: Endocrinology of the ovary. In: *General Endocrinology*. CD TURNER, JT BAGNARA (eds), W. B. Saunders Company, Philadelphia, 1976, pp 450-495.

TZSCHENTKE TM: Measuring reward with the conditioned place preference paradigm: a comprehensive review of drug effects, recent progress and new issues. *Prog Neurobiol* **56**: 613-672, 1998.

VATHY I: Maternal opiate exposure: long-term CNS consequences in the stress system of the offspring. *Psychoneuroendocrinology* **27**: 273-283, 2002.

VATHY I, ŠLAMBEROVÁ R, LIU X: Foster mother care but not prenatal morphine exposure enhances cocaine self-administration in young adult male and female rats. *Dev Psychobiol* **49**: 463-473, 2007.

VAVŘÍNKOVÁ B, BINDER T, ŽIVNÝ J: Characteristics of a population of drug dependent pregnant women in the Czech Republic. *Ceska Gynekol* **66**: 285-291, 2001.

VELA G, MARTIN S, GARCIA-GIL L, CRESPO JA, RUIZ-GAYO M, JAVIER FERNANDEZ-RUIZ J, GARCIA-LECUMBERRI C, PELAPRAT D, FUENTES JA, RAMOS JA, AMBROSIO E: Maternal exposure to delta9-tetrahydrocannabinol facilitates morphine self-administration behavior and changes regional binding to central mu opioid receptors in adult offspring female rats. *Brain Res* **807**: 101-109, 1998.

VORHEES CV, PU C: Ontogeny of methamphetamine-induced neurotoxicity in the rat model. *NIDA Res Monogr* **158**: 149-171, 1995.

YAMAMOTOVÁ A, HRUBÁ L, SCHUTOVÁ B, ROKYTA R, ŠLAMBEROVÁ R: Perinatal effect of methamphetamine on nociception in adult Wistar rats. *Int J Dev Neurosci* **29**: 85-92, 2011.