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Gender Differences in the Effect of Prenatal Methamphetamine Exposure and Challenge Dose of Other Drugs on Behavior of Adult Rats

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Summary

The aim of the present study was to compare the response to acute application of several drugs in adult male and female rats prenatally exposed to methamphetamine (MA). Spontaneous locomotor activity and exploratory behavior of adult male and female rats prenatally exposed to MA (5 mg/kg) or saline were tested in a Laboras apparatus (Metris B.V., Netherlands) for 1 h. Challenge dose of the examined drug [amphetamine – 5 mg/kg; cocaine – 5mg/kg; MDMA (3,4-methylenedioxymethamphetamine) – 5 mg/kg; morphine – 5 mg/kg; THC (delta9-tetrahydrocannabinol) – 2 mg/kg] or saline was injected prior to testing. Our data demonstrate that prenatal MA exposure did not affect behavior in male rats with cocaine or morphine treatment, but increased locomotion and exploration in females. Application of amphetamine and MDMA in adulthood increased activity in both sexes, while cocaine and THC only in female rats. Morphine, on the other hand, decreased the activity in the Laboras test in both sexes. As far as sex and estrous cycle is concerned, the present study shows that males were generally less active than females and also females in proestrus-estrus phase of the estrous cycle were more active than females in diestrus. In conclusion, the present study shows that the prenatal MA exposure does not induce general sensitization but affects the sensitivity to drugs dependently to mechanism of drug action and with respect to gonadal hormones.

Key words

Prenatal methamphetamine • Behavior • Laboras test • Psychostimulants • Opioids • Cannabinoids

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Introduction

Methamphetamine (MA) is one of the most common drug abused by pregnant women, which is also one of the most frequently used illegal drug in the Czech Republic (Vavřínková *et al.* 2001). 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 administration of MA during pregnancy affects maternal behavior of rat mothers (Šlamberová *et al.* 2005a) and impairs postnatal development of their pups (Šlamberová *et al.* 2006). Further, we have found that prenatally MA-exposed adult rats are slower in learning skills tested in Morris water maze (Šlamberová *et al.* 2005b). Prenatal MA exposure also alters nociception in sex-specific manner (Yamamotová *et al.* 2004) and increases seizure susceptibility in adult male and female rats (Bernášková *et al.* 2011, Šlamberová 2005, Šlamberová and Rokyta 2005a, b).

There are studies demonstrating that repeated administration of psychostimulants such as MA enhances locomotor activities tested in the Open field in response

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to acute treatment of the same or structurally related drugs 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).

It was shown (Malanga and Kosofsky 2003) that rodents exposed to various drugs of abuse *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 to drug of abuse in adulthood has been shown in prenatally cocaine-exposed (Estelles *et al.* 2006a, Heyser *et al.* 1992a, b, Rocha *et al.* 2002), cannabinoid-exposed (Vela *et al.* 1998) and morphine-exposed offspring (Gagin *et al.* 1997) relatively to controls. Our previous results demonstrated that prenatal MA exposure makes adult animals more sensitive to the same drug in adulthood (Bernášková *et al.* 2011, Schutová *et al.* 2010, Šlamberová *et al.* 2008). This effect was linked to the increased dopamine levels in the nucleus accumbens (Bubeníková-Valešová *et al.* 2009, Landa *et al.* 2012).

Other studies showed that abuse of one drug may increase probability of abuse of another drug. This effect is called cross-sensitization (Arnold 2005, Bartoletti *et al.* 1985, Fattore *et al.* 2005, He and Grasing 2004, Leri *et al.* 2003, Liu *et al.* 2007, Valvassori *et al.* 2007). Cross-sensitization between amphetamine and cocaine was first demonstrated on changes of locomotor activity (Bonate *et al.* 1997, Shuster *et al.* 1977). Systematic pretreatment with amphetamine was shown to enhance the acquisition of intravenous cocaine self-administration (Horger *et al.* 1992) and escalation of cocaine self-administration (Ferrario and Robinson 2007). Microinjections of amphetamine into the ventral tegmental area were shown to increase cocaine self-administration under a progressive ratio procedure and to enhance reinstatement of cocaine seeking (Suto *et al.* 2002). Valvassori *et al.* (2007) found that rats chronically treated with methylphenidate in the adolescent period showed sensitization to D-amphetamine.

Other studies demonstrated that cross-sensitization may be induced not only between related drugs, such as cocaine and amphetamines (both of them are psychostimulants), but also between unrelated drugs, such as between opioids and cocaine or between endocannabinoids and cocaine or opioids, respectively (Arnold 2005, Fattore *et al.* 2005, He and Grasing 2004, Landa *et al.* 2006a, b, Leri *et al.* 2003). 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) pretreatment reduced the rewarding properties of ethanol. Moreover, Vathy (2002) demonstrated that prenatal morphine exposure enhanced intracranial self-stimulation in the presence of a single cocaine injection in adult male rats. The above mentioned 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 most recent studies demonstrated that prenatal MA exposure does not induce sensitization to other drugs, possibly except of amphetamine, in the test of Conditioned place preference (CPP) (Šlamberová *et al.* 2011b, 2012). In contrast, prenatal MA exposure induced rather tolerance to cocaine than sensitization after the conditioning in the CPP test (Šlamberová *et al.* 2011b, 2012). This discrepancy may be due to the difference in test conditions or due to the difference in characteristics of drug administered prenatally. It could be assumed that MA administered prenatally does not induce such marked changes in the predisposition to drug abuse in adulthood as cocaine or opioids.

To validate our hypothesis that prenatal drug exposure induces predisposition to drug abuse in general and not only to the same drug that was received prenatally, Laboras test (modified Open field) was used in the present study. Two groups of drugs were tested in the present work: (1) drugs with similar mechanism of action as MA (amphetamine, cocaine and MDMA) that affect dopamine, serotonin and noradrenalin systems, and (2) drugs with different mechanism of action than MA (morphine and Delta9-tetrahydrocannabinol (THC)) that affect mostly opioid and cannabinoid receptors, respectively.

Sexual dimorphisms have been reported in response to psychomotor drugs. Locomotor activity and stereotype (repetitive and apparently functionless) behavior are higher in female rats in comparison with male rats following acute or chronic amphetamine treatment (Bisagno *et al.* 2003, Camp and Robinson 1988a, b, Kučerová *et al.* 2009). Because our previous

data showed sex- and estrous cycle-induced differences in the effect of prenatal MA exposure on behavior of adult offspring (Hrubá *et al.* 2012, Schutová *et al.* 2013, Šlamberová *et al.* 2011a, b), we expected similar sex- and ovarian hormone-related differences in the effect of prenatal MA exposure in the planned experiments as well. There are no studies showing how ovarian hormones affect "cross-sensitization" in progeny prenatally exposed to MA available. Thus, the planned study will show novel data that would bring new insights to the research of drug abuse.

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 reversed 12 h (light) : 12 h (dark) cycle with lights on at 18:00 h. 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 MA-treated and saline-treated groups. 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 (Sigma Aldrich) 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 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.* 2005a). Each mother raised 12 pups – three of each sex from each prenatal group (saline, MA). On PD 21, pups were weaned and group-housed by sex. Animals were left undisturbed until adulthood. Both, male and female rats were used in the present study. Always one male and one female rat per group were used from each litter to avoid litter effects.

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).

Drug administration and experimental groups

Prenatal drug exposure was the same for all the experiments in this study. Females were injected with MA (5 mg/kg/day) or saline (as described above).

Prenatally MA- and saline-exposed male and female rats were then used in five experiments by using Laboras test. The same drugs and doses were used as in our recent CPP study (Šlamberová *et al.* 2012). To determine the effect of prenatal MA exposure on the sensitivity to related drugs in adulthood the following drugs were tested:

Amphetamine: Dose of 5 mg/kg was chosen based on the work of Timár *et al.* (1996) showing developed positive place preference conditioning by using this dose of amphetamine.

Cocaine: Dose of 5 mg/kg was chosen based on the work of Heyser *et al.* (1992a) showing developed positive place preference conditioning by using this dose of cocaine.

MDMA („ecstasy"): Dose of 5 mg/kg was chosen based on the work of Bubeníková *et al.* (2005) showing increased acoustic startle response by using this low dose of MDMA.

In addition, to determine the effect of prenatal MA exposure on the sensitivity to unrelated drugs in adulthood the following drugs were tested:

Morphine: Dose of 5 mg/kg was chosen based on the work of Riley and Vathy (2006) showing developed positive place preference conditioning by using this dose of morphine.

Cannabinoids: THC in a dose of 2 mg/kg was chosen based on the work of Cheer *et al.* (2000) showing developed positive place preference conditioning by using this dose of THC.

Estrous cycle determination

As behavior in females can differ depending on the phase of the estrous cycle, gonadally intact females were smeared by vaginal lavage before testing. The smear

Table 1. Effect of drugs on behavior of adult male rats tested in the Laboras test.

	Locomotion (s)	Distance traveled (m)	Rearing (s)	Velocity (mm/s)
Amphetamine (5 mg/kg)	↑	↑	±	0
Cocaine (5 mg/kg)	0	0	0	0
MDMA (5 mg/kg)	↑	↑	↓	↑
Morphine (5 mg/kg)	↓	↓	↓	↓
THC (2 mg/kg)	0	0	0	0

↑ = increased effect; ↓ = decreased effect; 0 = no effect; ± = effect dependent of prenatal drug exposure

Table 2. Effect of drugs on behavior of adult female rats tested in the Laboras test.

	Locomotion (s)	Distance traveled (m)	Rearing (s)	Velocity (mm/s)
Amphetamine (5 mg/kg)	↑	↑	±	↓
Cocaine (5 mg/kg)	↑	↑	↑	↑
MDMA (5 mg/kg)	↑	↑	↑	±
Morphine (5 mg/kg)	↓	↓	↓	±
THC (2 mg/kg)	±	±	0	±

↑ = increased effect; ↓ = decreased effect; 0 = no effect; ± = effect dependent of prenatal drug exposure

was examined by light microscopy. Two phases of the estrous cycle were recognized in the present study: proestrus-estrus (P-E) with predominance of large nucleated and some cornified epithelial cells in the smear; diestrus (D) with predominance of leukocytes in the smear (Turner and Bagnara 1976). In a simplified way, in P-E phase females have high levels of ovarian hormones and in D phase their hormonal level is low. The level of hormones is the most important for the behavioral changes as far as sex differences are concerned (Bisagno *et al.* 2003, Camp and Robinson 1988a, b.)

Laboras test

Behavior of adult male and female rats (PD 60-90) was tested in a Laboras apparatus (Metris B.V., Netherlands) situated in a dark room. The Laboras is a fully automated system for continuous behavior recognition and tracking in small rodents. The principal of this test was in detailed described in our previous work (Schutová *et al.* 2013). Rats were injected and placed in the center of the Laboras cage for 1 h. The animals were not habituated to the apparatus, so they were exposed to a novel environment on the day of the testing. The 1 h period was divided to six 10-minute intervals, so we could see the changes in behavior in the time of habituation in the Laboras apparatus.

The following parameters were automatically evaluated in the Laboras: 1) time spent in locomotion [s]; 2) time spent rearing (exploratory behavior) [s]; 3) distance traveled (trajectory length) [m]; and 4) average velocity [mm/s].

Statistical analyses

Three-Way ANOVA (factors: prenatal exposure x adult drug treatment x sex/estrous cycle) with Repeated Measure (time: 10-minute intervals) was used to analyze differences. Differences were considered significant if $p<0.05$ in all statistical analyses.

Results

The effect or prenatal drug exposure

In both male and female rats, prenatal MA exposure sensitized the animals to amphetamine, which effect was most visible in the rearing activity [$F(1, 92)=5.21$; $p<0.05$]. Specifically, prenatally MA-exposed male [$F(1, 33)=5.10$; $p<0.05$] (Table 1) and female [$F(1, 59)=4.18$; $p<0.05$] (Table 2) rats that were

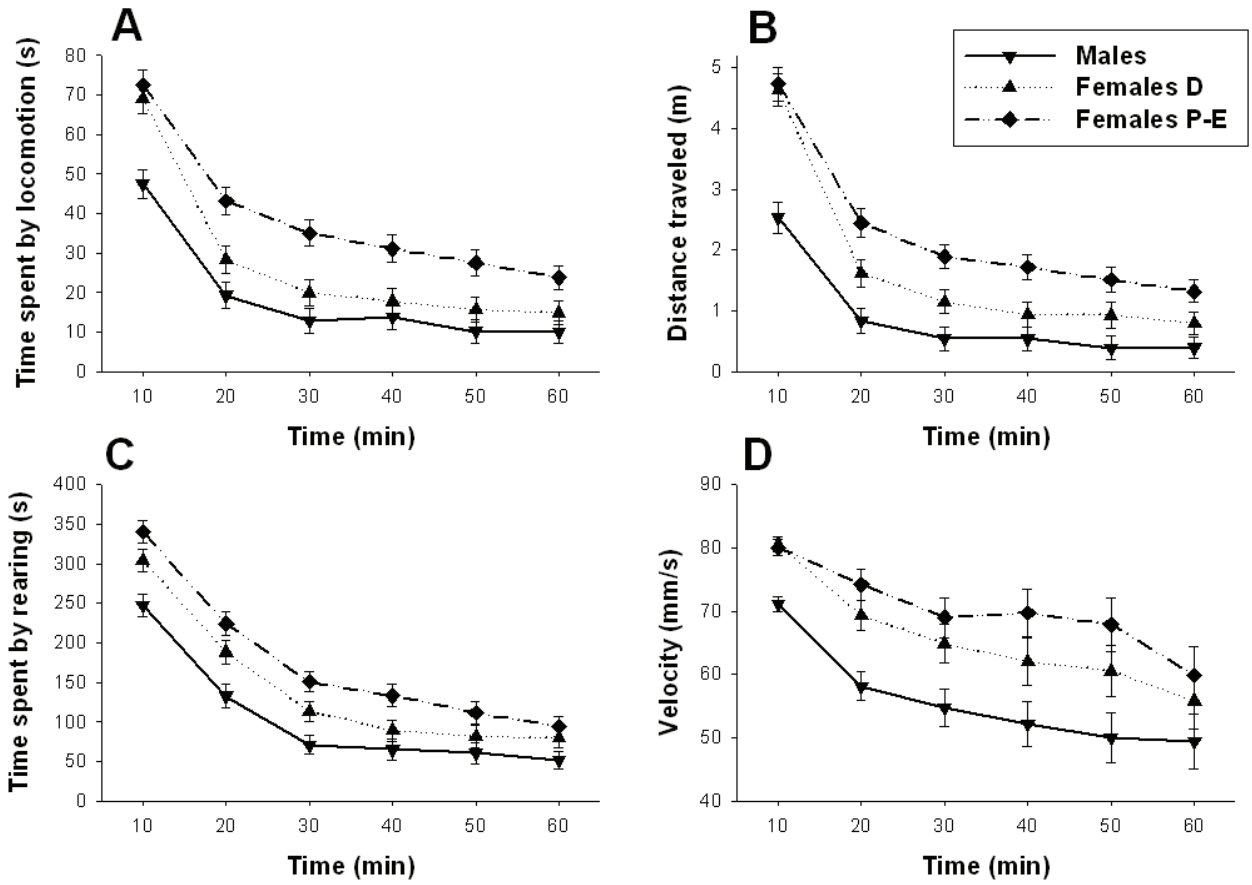

Fig. 1. The effect of sex and estrous cycle on behavior in the Laboras test. The graphs show average effect of sex and estrous cycle in the time spent by locomotion (**A**); distance traveled (**B**); time spent rearing (**C**); velocity (**D**). Values means of pairs ± SEM.

injected with amphetamine spent more time rearing than prenatally saline-exposed rats after amphetamine administration. In addition, prenatal MA exposure also sensitized animals to MDMA, but only in females, not in males. Specifically, prenatally MA-exposed female rats that were injected with MDMA spent more time rearing than prenatally saline-exposed rats after MDMA administration [$F(1, 56)=4.55$; $p<0.05$].

The main effect of prenatal MA exposure was shown in cocaine and morphine experiments, but this effect was possible to see only in female (Table 2), not in male rats (Table 1). In cocaine experiments, female rats (Table 2) prenatally exposed to MA were faster [$F(1, 55)=4.99$; $p<0.05$], spent more time in locomotion [$F(1, 55)=5.29$; $p<0.05$], traveled longer distance [$F(1, 55)=6.06$; $p<0.05$], and spent more time rearing [$F(1, 55)=7.31$; $p<0.01$] than prenatally saline-exposed female rats, regardless of the drug exposure in adulthood.

In morphine experiment, prenatally MA-exposed female rats (Table 2) spent more time in locomotion [$F(1, 56)=4.78$; $p<0.05$], traveled longer distance [$F(1, 56)=4.65$; $p<0.05$], and spent more time rearing [$F(1, 56)=4.19$; $p<0.05$] than prenatally saline-exposed female rats, regardless of the drug exposure in adulthood. However, their velocity was not affected by prenatal drug exposure [$F(1, 56)=0.89$; $p=0.35$].

The effect of adult drug treatment

Amphetamine: In both males (Table 1) and females (Table 2), amphetamine (5 mg/kg) increased the distance traveled {males: [$F(1, 33)=20.06$; $p<0.0001$]; females: [$F(1, 59)=5.66$; $p<0.05$]} and the time spent by locomotion {males: [$F(1, 33)=15.24$; $p<0.0001$]; females: [$F(1, 59)=4.64$; $p<0.05$]}. Surprisingly, amphetamine decreased the velocity in female rats [$F(1, 59)=5.36$; $p<0.05$], while it does not change it in males [$F(1, 33)=0.00003$; $p=0.99$].

Cocaine: Cocaine (5 mg/kg) did not affect behavior in the Laboras test in adult male rats (Table 1). In female rats (Table 2), cocaine increased the distance traveled [$F(1, 55)=6.97$; $p<0.05$], velocity [$F(1, 55)=15.62$; $p<0.001$], time spent by locomotion [$F(1, 55)=9.29$; $p<0.01$] and time spent rearing [$F(1, 55)=14.66$; $p<0.001$].

MDMA („ecstasy"): MDMA (5 mg/kg) increased the distance traveled {males: [$F(1, 33)=81.97$; $p<0.0001$]; females [$F(1, 56)=96.55$; $p<0.0001$]} and time spent by locomotion {males: [$F(1, 33)=198.15$; $p<0.0001$]; females [$F(1, 56)=181.70$; $p<0.0001$]} in both sexes (Table 1 and 2). Rearing was decreased by MDMA in males [$F(1, 33)=4.85$; $p<0.05$], while increased in females [$F(1, 56)=4.56$; $p<0.05$] (especially in P-E). The velocity was increased in males [$F(1, 33)=29.36$; $p<0.0001$] and in prenatally saline-, but not MA-exposed females [$F(1, 56)=4.55$; $p<0.05$].

Morphine: In both males (Table 1) and females (Table 2), morphine (5 mg/kg) decreased the distance traveled {males: [$F(1, 28)=15.44$; $p<0.001$]; females [$F(1, 56)=27.99$; $p<0.0001$]}, the time spent by locomotion {males: [$F(1, 28)=20.29$; $p<0.001$]; females [$F(1, 56)=36.21$; $p<0.0001$]}, and the time rearing {males: [$F(1, 28)=41.63$; $p<0.0001$]; females [$F(1, 56)=76.93$; $p<0.0001$]}. While the velocity was slowed down in both, prenatally saline- and MA-exposed male rats [$F(1, 28)=28.26$; $p<0.0001$], in females morphine slowed down their walking only in the group of prenatal saline exposure [$F(1, 56)=22.28$; $p<0.05$].

Cannabinoids (THC): THC (2 mg/kg) did not affect behavior in the Laboras test in male rats (Table 1). In female rats (Table 2), THC increased the distance traveled [$F(1, 58)=3.49$; $p<0.05$], increased the time spent by locomotion [$F(1, 58)=3.87$; $p<0.05$], and increased the velocity [$F(1, 58)=3.48$; $p<0.05$] in prenatally saline-exposed, but not in prenatally MA-exposed animals.

The effect of gonadal hormones

Generally, our results (Fig. 1) demonstrated that males were less active than females {were slower in walking [$F(2, 87)=13.29$; $p<0.0001$], spent less time in locomotion [$F(2, 87)=12.93$; $p<0.0001$], traveled shorter distance [$F(2, 87)=15.26$; $p<0.0001$], and spent less time rearing [$F(2, 87)=12.63$; $p<0.0001$]}. In females the phase of estrous cycle played a role (Fig. 1). The results could be simplified that females in P-E were more active such than D females {were faster in walking [$F(1, 55)=3.84$; $p<0.05$], spent more time in locomotion [$F(1, 55)=6.07$; $p<0.05$], traveled longer distance [$F(1, 55)=3.75$; $p<0.05$], and spent more time rearing [$F(1, 55)=5.66$; $p<0.05$]}.

Discussion

Our data demonstrate that prenatal MA exposure (5 mg/kg daily) did not affect behavior in males after cocaine and morphine injection, while it increased locomotion and rearing (exploration) in females after the same treatment in the Laboras test. The data showing no effect of prenatal MA exposure on behavior in males is in agreement with our previous study examining adult male rats prenatally exposed to MA in the Open-field test (Schutová *et al.* 2010). To the best of our knowledge there is no literature available showing effect of prenatal MA exposure on behavior in the Open-field in adult female rats instead of our own (Hrubá *et al.* 2012). The only available study of Peris *et al.* (1992) showing increased locomotion induced by prenatal cocaine exposure in females, but not in males, is in agreement with our present data.

In addition, prenatal MA exposure in males induced sensitization only to amphetamine, but not to the other drugs. This is in agreement with our recent CPP study (Šlamberová *et al.* 2012). Females (especially in P-E) displayed sensitization induced by prenatal MA exposure to amphetamine as well as MDMA. On the other hand, prenatal MA exposure induced something like tolerance to THC in females; i.e. prenatally saline-exposed females displayed increased locomotion, velocity and distance traveled, but this increase was not apparent in prenatally MA-exposed females. Unlike other studies (Estelles *et al.* 2006a, Gagin *et al.* 1997, Heyser *et al.* 1992b, Rocha *et al.* 2002) we did not show general predisposition of drug abuse induced by prenatal MA exposure. The reason may be that MA is not as potent drug to have such serious long-lasting effect of cross-sensitization as cocaine or morphine. Moreover, our data showing sex differences in sensitization are in agreement with studies of Melnick and Dow-Edwards (2001) and Peris *et al.* (1992) suggesting that these sex differences correspond with dopamine activity. Because our previous study (Bubeníková-Valešová *et al.* 2009) showed sensitization induced by prenatal MA exposure to MA challenge in adult male rats corresponding with dopamine levels in the nucleus accumbens, our future studies are planned to see whether there are also sex differences in the dopamine concentration that would support our finding showing sex differences in the sensitization.

The effect of adult drug treatment was also sex-specific. While amphetamine and MDMA increased behavioral activities in both, male and female rats, cocaine and THC increased the activity only in females, but not in males. Moreover, morphine as expected had the opposite effect; i.e. it decreased all of the measures, and

this effect was independent on sex. Our amphetamine and MDMA data are in agreement with studies of others (Bisagno *et al.* 2003, Melnick and Dow-Edwards 2001, Páleníček *et al.* 2005). Amphetamine was repeatedly shown to increase locomotor activity (Bisagno *et al.* 2003, Melnick and Dow-Edwards 2001) similarly to MA (Schutová *et al.* 2010). The present study demonstrates that the locomotion and distance traveled was increased by amphetamine at the beginning of the Laboras test, while the differences between amphetamine and saline were not further significant after 40th minute of the testing. In contrast to our amphetamine results, the present study show that MDMA increased all the activities in the Laboras during the entire hour of testing. Because MDMA effect on locomotion was shown to be dose specific (Páleníček *et al.* 2005), it is possible that the dose of 5 mg/kg was too high to return the increased locomotion to the level of controls within one hour. Therefore, future studies are planned to test the effect of MDMA in more doses to better demonstrate its effect on behavior.

Our finding showing no significant increase in locomotion of male rats after cocaine administration is surprising. There are many studies showing increased behavioral activities after cocaine administration (Broderick *et al.* 2003, De La Garza and Cunningham 2000, Tzschentke and Schmidt 1998). However, after detailed analysis of our results we could see that in females there was slow increase in the activity induced by cocaine from the 30th minute further, but not at the beginning of testing as after amphetamine exposure. There was however no increase within the 1-h interval in males. It is therefore possible that the cocaine effect arises in males later than in females and thereby females are more sensitive than males to cocaine administration. Based on the studies of others (Broderick *et al.* 2003, De La Garza and Cunningham 2000, Tzschentke and Schmidt 1998) it seems that either higher doses or longer duration of the experiment would be necessary to see the increased locomotion in males also.

As far as the gonadal hormone differences are concerned, the present study demonstrates that males were generally less active than females and females in P-E cycle were more active than females in D. These data are in agreement with our previous Open-field study (Hrubá *et al.* 2012). Similarly, other studies showing sex differences in locomotion or other behavioral activities (Bisagno *et al.* 2003, Melnick and Dow-Edwards 2001, Páleníček *et al.* 2005), and studies showing behavioral changes that are dependent on female estrous cycle (Morgan and Pfaff 2002, Peris *et al.* 1991), also support our present results. Specifically, there are studies (Becker 1999) showing that estrogen and progesterone affect striatal dopamine function. Females rats show a greater behavioral response when the striatal dopaminergic system is stimulated in estrus than in diestrus (Becker *et al.* 1982). Thus, it seems, that locomotor and exploratory behaviors, that are suggested to be mediated *via* the dopaminergic system (Glatt *et al.* 2000), are increased by ovarian hormones (estrogen and progesterone).

In conclusion, the present study demonstrates that prenatal MA exposure and adult drug administration affects behavior of adult rats dependently on sex and estrous cycle. As a matter of sensitization or tolerance, the present data demonstrate that prenatal MA exposure induces sensitization to amphetamine in both sexes and to MDMA in female rats. On the other hand, prenatally MA-exposed females are less sensitive to THC than controls suggesting rather tolerance to THC than sensitization.

Conflict of Interest

There is no conflict of interest.

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