REVIEW

Drugs in Pregnancy: the Effects on Mother and Her Progeny

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Summary

Drug abuse during pregnancy is a growing problem in all developed countries all over the world. The drugs easily cross the placental barrier into the fetal body and are present also in the maternal milk. Therefore, it may affect the development of the child pre- as well as postnatally. The effects of prenatal drug exposure are long-lasting and persist until adulthood. The present review summarizes the clinical and experimental evidence showing how opioids and psychostimulants can affect maternal behavior of drug-abusing mother and the development of their offspring.

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Introduction

Drug addiction is a hot topic of the last few decades. However, its history is very long. Already at the time of BC, our ancestors relish various drugs. One of the oldest drugs are products of Indian hemp (*Cannabis sativa*), known for more than five millennia. Currently, this occurs mainly with the two drugs produced from the Indian hemp: marijuana and hashish. Other cultural product used for drug production for four millennia is poppy (*Papaver somniferum*). Opium contains mainly opium, which is the dried juice of unripe poppy. Only

much later it was found that opium contains 25 different alkaloids, which were isolated during the 19th century. Some of them are well known such as morphine, narcotine, papaverine and methylmorphine (codeine) (Reynolds and Randall 1957). Their discovery was an important advance in medicine, but on the other hand it increased the risk of addiction. Since it was found that morphine is dangerous for its addictive properties, search of new synthetic substances that would have the same analgesic effects but lower tendency for addiction, began. In 1875 heroin (diacethylmorphine) was discovered and in 1898 it was put into practice as a substitute for morphine and codeine. However, soon it was shown that heroin is even stronger drug of addiction than natural alkaloids. Misuse of heroin spread mainly after World War II and affected mainly the U.S., where its "popularity" has grown steadily and in 1965 90 % of all addicts was dependent on heroin.

Another of the most important substances of abuse are produced from the coca plant (*Erythroxylon coca*). The best-known drug in this group is cocaine, an alkaloid first extracted from the leaves of this plant in the second half of the 19th century. This substance has hallucinogenic effects and also causes addiction. In the late 19th century amphetamine was synthesized for use in medicine. Amphetamine is also currently part of a series of pills used in medicine. Although amphetamine itself is an addictive drug with euphoric effects, more commonly abused drug is its derivate methamphetamine (MA). These drugs, cocaine, amphetamine and MA, are representatives of the group of psychostimulants.

Opioids as well as psychostimulants and their effects on prenatal and/or perinatal development will be discussed in the present review.

Drugs in pregnancy

The abuse of drugs by women during pregnancy is growing problem in recent years. The number of infants with drug-related birth defects has increased dramatically over the past several years (Marwick 2000). Since psychoactive drugs can easily cross blood-brain barrier (one of the most impervious barriers of the body), the placental barrier is even more easily permeable. In addition, many drugs can pass into a nursing mother's breast milk and expose a developing infant to these drugs even postnatally. It is well known that women, who abuse drugs, have irregular or even missing menstrual cycle (Santen *et al.* 1975, Smith *et al.* 1982). However, when they become pregnant and do not stop using drugs, they continue to expose not only themselves but also their fetuses to the danger. Drugs during pregnancy can lead to insufficient nutrition of both mother and fetus. In addition, the risk of infection and sexually transmitted diseases increases in the case of non-sterile needle use. More frequent occurrence of anemia and hepatitis, an increased tendency to hypertension and an increased incidence of pre-eclampsia was shown in women, who abuse drugs during pregnancy (Susser 1993). Furthermore, the risk of abortion or stillborn fetuses increases (Johnson and Leff 1999). Additionally, drug-abusing pregnant women are less scrupulous in the prenatal as well as postnatal care of their children (Inaba and Cohen 1993, Vavřínková *et al.* 2001).

However, drug-abusing pregnant women in addition to drug use often revels alcohol and smoking. More abuse of addictive substances is a common problem to monitor the effects of drugs in humans, since it is virtually impossible apart to distinguish the effects of individual drugs. Changes in the placenta, reduced placental perfusion due to vasoconstriction of blood vessels, as well as lack of appropriate oxygen and nutrients supply (Vavřínková *et al.* 2001) can also have negative effects on the newborn. Psychostimulants and opioids as representative of the "hard" drugs abused during pregnancy is a risk to the fetus in any case, although the mechanism of action of these drugs on the fetus has not been fully elucidated. It should be noted that clinical trials are usually restricted to statistical comparisons because scientific research in humans is very limited. It is not practically possible to maintain a sufficiently large study group of mothers of dependent children until their maturity period. Therefore, experimental studies using animal models are necessary.

In agreement with clinical works, the experimental studies (Bridges and Grimm 1982, Kinsley *et al.* 1994, Šlamberová *et al.* 2001b, 2005a,b, 2006, Hrubá *et al.* 2009, Pometlová *et al.* 2009) demonstrated that rat mothers, who received drugs (opioids as well as psychostimulants) during pregnancy displayed decreased maternal behavior toward their pups that may also alter healthy development of their pups. Prenatal drug exposure results in impairing effects on postnatal development of rat pups that may persist until adulthood.

Opioids
Heroin and morphine

Mothers receiving morphine can pass the drug to a child both, prenatally through the placenta and postnatally *via* mother's milk. Few minutes after its application to the mother morphine appears in the blood of the fetus or newborn and after an hour the level in a child can even exceed the level in its mother because of their worse degradation (Karch 2002). Since newborns have the ability of degradation in the liver very limited, morphine is eliminated more slowly than in adults (Lullman *et al.* 2002). Morphine can be detected in amniotic fluid, hairs and in meconium.

Research on opioids lasts for several decades. Portoghese (1965) assumed the existence of several specific receptors for opioids, which he divided based on their molecular structure and analgesic effects. The pharmacological evidence for the existence of different types of opioid receptors was first proposed by Martin *et al.* (1976). Based on different pharmacological effects of individual opioids the opioid receptors were divided into three types: μ (mu)-opioid receptors sensitive to morphine, κ (kappa) receptors sensitive to ketocyclazocin and σ (sigma) receptors sensitive to SKF 10047 (Nallylnormetazocin). These types of opioid receptors are still distinguished in these days, although some other groups were added. Description of these opioid receptor subtypes contributed to the discovery of endogenous opioid peptides such as endorphins, enkephalins and dynorphins. After the discovery of enkephalins, Hans Kosterlitz and his colleagues (Lord *et al.* 1977) posed the question whether enkephalins act on the same type of opioid receptors as opioid alkaloids. They found unknown opioid receptors that were sensitive to enkephalins and named them δ (delta) (Lord *et al.* 1977). Although later research has shown that different types of receptors are found in many places of human and animal organism, and they are far from specific only for

Table 1. Effect of drugs on maternal behavior of laboratory rats.

Activity		Opioids	Psychostimulants
Nursing	In total	↓	↓
	Active	↓	↓
	Passive	0	0
Maternal behavior	Mother in the nest	↓	↓
	In contact with pups	↓	↓
	Licking and grooming	↓	↓
	Nest manipulation	0	0
Non-maternal activities	Self-care	↑	0
	Rearing	↑	↑
	Sniffing	↑	↑
	Resting	0	0
Retrieval test	Grabbing the first pup	0	↓
	First pup in the nest	0	↓
	All the pups in the nest	↓	↓

↓ = decreased activity, ↑ = increased activity, 0 = no effect when compared to controls.

substances that were discovered, the opioid receptors μ, κ and δ are still the basic groups of opioid receptors known.

Maternal behavior and pup's development

Morphine, as the active metabolite of heroin, applied to pregnant rats adversely affects maternal behavior of these females (Šlamberová *et al.* 2001b). Female rats that were given morphine during pregnancy showed a reduced care for their offspring compared with control females, who were injected with saline (Table 1). Morphine mothers were less often present in the nest, less in contact with pups and less licking and grooming their pups than controls. Frequency and duration of breastfeeding was lowered in the morphine mothers compared with controls. During testing the females in the "Retrieval" test, in which time of the pup's return after a short separation is measured, morphine females needed more time to return all pups into the nest than control females. Deterioration of maternal behavior by morphine was replaced by other female activities, such as enjoyment of food, drink, cleansing itself and moving freely in the cage, associated with sniffing and rearing.

Opioids applied to pregnant rats induce serious detrimental effects on their offspring. The percentage of stillborn pups in females, who were administered during pregnancy opioids, either morphine or heroin, is higher than in controls (Zhu and Stadlin 2000). Newborns have lower birth weight, and even body weight gain during postnatal development is lower. These experimental

findings are consistent with clinical studies showing that children of mothers, who abuse heroin or other opioids during pregnancy, are generally smaller, have smaller head circumference and lower birth weight than children of control mothers (Naeye *et al.* 1973). The functional, especially sensorimotor, development is also affected (Šlamberová *et al.* 2005c) (Table 2).

Table 2. Effect of prenatal drug exposure on sensorimotor development and behavior in adulthood.

Activity	Opioids	Psychostimulants
Sensorimotor development	→	→
Locomotion	↓	0
Learning and memory	↓	↓

↓ = decreased activity, 0 = no effect when compared to controls, → = delayed development.

Prenatal drug effects lasting to adulthood

In adulthood, the animals that were prenatally exposed to morphine show increased locomotor activity in an open-field (Šlamberová and Vathy 2002) (Table 2). Like morphine, prenatal exposure to heroin induces increased activity in both, the cage and the open arena as well as on a rotating cylinder (Lasky *et al.* 1977). It was

also found that opioids affect reproduction capacity (Vathy 1999). In adult females that were prenatally exposed to morphine the ability of lordosis, which is necessary for successful mating, is decreased. In contrast, in male rats exposed to morphine the interest in females increases, but the increased mating effort is associated with a lower effect compared with control males (Vathy 1999).

Besides the effects on reflexes, locomotion, and reproductive ability of animals, prenatally administered opioids also affect the cognitive functions (Table 2). Prenatal application of morphine in adult animals impairs learning and memory tested in the 8-arm radial maze (Šlamberová *et al.* 2001a). Learning and memory, as tested in the radial maze and in the Morris water maze, is also decreased in animals prenatally exposed to heroin (Yanai *et al.* 1992). Impaired cognitive functions in rats prenatally exposed to opioids are consistent with clinical findings. Children of mothers, who used heroin during pregnancy, have delayed mental development, decreased ability to maintain attention and impaired academic performance (Soepatmi 1994).

Prenatal application of morphine to pregnant rats also affects the susceptibility to seizures (Vathy 2001). While decreased threshold for epileptic seizures were observed in pups at postnatal day (PD) 25, at PD 38 of these pups the threshold was in contrast increased. The finding that prenatal application of morphine has proconvulsive effect in the offspring at PD 25, corresponds to the clinical findings, showing increased seizure activity, EEG changes and increased irritability in children of mothers, who abuse drugs during pregnancy (Finnegan 1985). In adult animals the predisposition to seizures is also affected by prenatal morphine exposure. However, this long-term effect is dependent on the sex of the animals and level of gonadal hormones at the time of the experiment.

Other experimental studies show that prenatal morphine application worsens the adaptability to stress in adulthood (Šlamberová *et al.* 2002b). The levels of stress hormones are also altered (Lesage *et al.* 1998). All this corresponds with clinical studies showing that children exposed prenatally to opioids adapt worse to new environments and often suffer from personality disorders whether in terms of reduced incidence of contrary emotions and frenzy. The mechanism by which prenatal heroin exposure affects animal behavior in adulthood is not yet fully understood. However, it is assumed that the opioid system of the central nervous system (CNS) plays

the most important role in these effects. It has been shown that drugs, including heroin, administered during prenatal development affect those systems that are evolving at the time of application (Kellogg 1992).

Prenatal morphine exposure increases the amount of μ-opioid receptors in the nucleus accumbens and in some nuclei of the amygdala (Vathy *et al.* 2003), which are structures of the CNS associated with drug reward system. In addition to these brain structures prenatal exposure to morphine increases μ-opioid receptors in structures associated with the initiation, spread and termination of epileptic seizures such as the substantia nigra, subthalamic nucleus and hippocampus (Šlamberová *et al.* 2002a, 2003a). The effect of prenatal morphine exposure do not affect only μ-opioid receptors to which morphine binds the most, but also δ- and κ-opioid receptors (Vathy *et al.* 2000, Rimanóczy *et al.* 2001). Moreover, it appears that long-term effects of morphine are also dependent on the immediate level of gonadal hormones in adult animals tested (Vathy *et al.* 2000, 2003, Rimanóczy *et al.* 2001, Šlamberová *et al.* 2002a, 2003a,b, 2005d). Based on the above changes in the CNS opioid system, we can assume that at least some changes in behavior induced by prenatal opioid exposure can be explained by the direct effect of opioids on opioid receptors.

Psychostimulants

Cocaine

Laboratory experiments in animals have shown that prenatal cocaine exposure has long-term effects on functional rather than morphological development of the organism. While prenatal cocaine exposure has no effect on calf birth weight, its length, eye opening and sexual maturation are impaired. The functional development is also affected, e.g. slower righting reflexes, motor failure, protective reflexes and sensitivity to pain (Smith *et al.* 1989, Henderson and McMillen 1990, Sobrian *et al.* 1990). Prenatal cocaine exposure further results in decreased ability to learn and retain memory traces (Sobrian *et al.* 1990, Heyser *et al.* 1992a, Levin and Seidler 1993, Salas-Ramirez *et al.* 2012) and also affects sexual behavior and reproductive ability of adult rats (Vathy 1993).

Although the mechanism of action of prenatal cocaine exposure on the body and CNS is not yet fully elucidated, there are many studies showing that cocaine administered during pregnancy influences some

neurotransmitter systems of the mother's CNS. One of the systems that is influenced by prenatal cocaine application is the catecholaminergic system (Seidler and Slotkin 1992). They demonstrated that adult rats, which were exposed prenatally to cocaine, have more α-adrenergic receptors and increased activity of noradrenergic receptors. Similarly, dopamine receptors (the quantity and sensitivity) are altered in animals after prenatal cocaine exposure: increased D_1 receptor and reduced D_2 receptors (Dow-Edwards *et al.* 1990, Henderson *et al.* 1991). Even though all the psychostimulants, cocaine as well as amphetamines, are known to affect all the noradrenergic, dopaminergic and serotoninergic systems, the ratio of involvement of these neurotrasmitter systems differs between these psychostimulant drugs. While MA and amphetamine seem to affect noradrenergic system the most, a little bit less the dopaminergic system, and at minimum the serotoninergic system, cocaine seems to affect the most the serotoninergic system (Fleckenstein *et al.* 2000, Rothman *et al.* 2001, Shoblock *et al.* 2003). Thus, it is possible that the rate of involvement of these neurotransmitter systems in prenatal life with respect of the involvement of the other system(s) in adulthood may play a role in the impairing effects of cocaine and amphetamines.

Methamphetamine and amphetamine

Statistical survey studies from last few years (Polanecký *et al.* 1996, Šejda *et al.* 1998) have demonstrated that MA is the most frequently abused illicit drug in the Czech Republic. Approximately 66 % of registered drug-abusing men and women use MA as primary drug in our country (Vavřínková *et al.* 2001). In recent years, MA is becoming more and more "popular street drug" also in other countries because of it's relatively uncomplicated production and low price compared to cocaine or heroin (Marwick 2000). MA is a powerfully addictive psychostimulant with a high potential for addiction. Because it metabolizes slowly, the MA high lasts for a long period (for 8 to 24 hours). Women, especially during pregnancy, take MA because it decreases appetite and therefore, helps them to control weight, while increasing energy. Statistics show that only 17 % women abusers in the USA were primary MA users, but 38 % had used it during pregnancy (Marwick 2000). Therefore, National Institute of Drug Abuse (NIDA) in the USA decided to increase substantially financing of studies testing the effects of MA

administration during pregnancy. However, the findings of this research is still inconclusive.

The exposure to amphetamines has been shown to induce birth defects (malformations) such as cleft lip, heart defects and biliary atresia with hyperbilirubinemia, low birth weight and low body fat, small head circumference, stillbirth, cerebral hemorrhage, and undescended testicles (Oro and Dixon 1987, Little *et al.* 1988). The vasoactive action of amphetamines limits supply of the developing fetus with nutrients and they have a direct effect of anorectic amphetamine appetite suppressant. The systemic effects observed in neonates increased muscle tone, tremor, irritability, irregular sleep and impaired adaptability to stress (Wouldes *et al.* 2004). Variation in heart rate is caused by a change in the metabolism, which returns to normal after the drug effect wears off (Oro and Dixon 1987). Hansen *et al.* (1993) found that the drug causes developmental delays and even alteration of the memory and the signals processed by the cortex.

A study in Sweden (Cernerud *et al.* 1996, Eriksson *et al.* 1978) demonstrated the effect of the prenatal drug exposure on functional development in adolescence. Adolescent boys prenatally exposed to amphetamines were taller and heavier than the norm. On the contrary, it was not truth for girls. These results can be interpreted as a possible consequence of the influence of amphetamine at a faster onset of puberty in boys than in girls. Amphetamines can interfere with normal CNS development when the exposed persons lagged behind in language, mathematics and physical education and the development of anterior pituitary. Chang *et al.* (2004) found that prenatal exposure to MA in children leads to a reduction in the volume of subcortical structures in the brain (caudate nucleus, putamen, globus pallidus, hippocampus) and the associated neuro-cognitive deficit compared with controls. Reduction in these brain structures correlated with poorer performance in sustained attention and delayed verbal memory. In contrast, there was no difference between the groups in motor skills, spatial memory and nonverbal intelligence parameters. However, the effects on behavior and cognitive functions appear to be permanent (Hansen *et al.* 1993).

Maternal behavior and pup's development

Administration of MA to pregnant laboratory mice or rats (5, 10, 15, or 20 mg/kg) leads to such drug concentrations in the brain that correspond to the values

observed in the fetuses of the drug-dependent mothers (Martin *et al.* 1976, Cho *et al.* 1991, Acuff-Smith *et al.* 1996). These doses therefore serve as an experimental model to determine the potential risk exposure *in utero* effects of drugs in humans. Repeated subcutaneous administration of a high dose of MA (50 mg/kg) to pregnant rats leads to increased likelihood of abortion and maternal death (Acuff-Smith *et al.* 1992). Rat mothers, which were administered MA, have shorter gestation period, their weight gain during pregnancy is lower and there have fewer pups in the litters than control mothers (Martin 1975, Martin *et al.* 1976).

There are studies, including our own, demonstrating the detrimental effects of amphetamines on maternal behavior (Fraňková 1977, Piccirillo *et al.* 1980, Šlamberová *et al.* 2005a,b) (Table 1). Piccirillo *et al.* (1980) found that repeated administration of amphetamine injections during lactation have disruptive effects on mother-pup intercontact interval, retrieval latency, inter-retrieval interval, number of pup retrieved and number of corners to which they were retrieved, time nest building, number of paper strips used, nursing time, time in motion, and number of squares entered. Similarly Fraňková (1977) showed that mothers, which received amphetamine during the first 10 days of lactation period, have increases latencies in the Retrieval test, and decreased maternal activities such as caring for the pups and building the nest.

Also our results demonstrated that the application of MA during pregnancy, or pregnancy and lactation, negatively affects maternal behavior (Šlamberová *et al.* 2005a,b). Specifically, we found that mothers receiving MA display less nursing and care for their offspring than the control mothers. Instead, they take care more of themselves (drinking, eating, self-grooming) or relax outside the nest. In addition, the time to return the pups into the nest is prolonged in the Retrieval test.

Acuff-Smith *et al.* (1996) further studied the effect of MA on the weight of mothers and pups and found lower weight compared with both the controls fed *ad libitum* and a group with the same food intake as drug exposed individuals. Thus, the lower body weight was caused not only by lower nutritional intake and decreased appetite. One of these mechanisms may be a vasoconstrictor effect on the utero-placental blood supply, which further reduces the supply of nutrients to the fetus. The critical phase for the uptake of nutrients appears to be later embryonic stages. To eliminate the

effects of vasoconstriction and mother´s malnutrition or hypoxia on the developing fetus, Yamamoto *et al.* (1992) isolated 10.5 days old rat embryos and cultivated them in the presence of different concentrations of MA. They found that the drug has a dose-related effect on the yolk sac diameter, the incidence of malformations and growth disorders. High doses (50 mg/kg) of prenatally applied MA lead to eye disorders such as anophthalmia, microphthalmia and retinal detachment (Vorhees and Acuff-Smith 1990, Acuff-Smith *et al.* 1992, 1996). These findings suggest that repeated administration of MA during pregnancy can have serious long-term effects on the offspring. MA administered prenatally increases pup mortality, reduces their weight gain, delays development and slows their reflexes (Martin *et al.* 1976, Cho *et al.* 1991, Acuff-Smith *et al.* 1996).

In agreement with the above mentioned studies, our results also showed that prenatal exposure negatively affects postnatal development of pups, especially the sensorimotor functions, (Table 2) and that the impairing effect of MA may also influence the development of future generations (Šlamberová *et al.* 2006, 2007). This is a very serious findings indicating the potential effect of MA and influencing a generation that has not been exposed to the drug at all. Question remains if the effect of drug that affects second generation is genetic or epigenetic.

Prenatal drug effects lasting to adulthood

There are still not many studies available that would address the effects of prenatal psychostimulants exposure in adults (Table 2). Acuff-Smith *et al.* (1996) found that adult animals exposed prenatally to the effect of MA show a reduced ability to keep learning and memory traces. Prenatal MA exposure also causes a reduction in adaptability to new environments in adulthood (Weissman and Caldecott-Hazard 1995). The mechanism of action, however, has not yet been fully elucidated. It is assumed that MA acts on serotonergic and dopaminergic neurotransmitter systems and thus produces not only long but also permanent changes in the CNS (Ramamoorthy *et al.* 1995, Weissman and Caldecott-Hazard 1995). It has been shown that MA administered prenatally at a dose of 10 mg/kg increases the concentration of binding sites for the uptake of monoamines, suggesting a stimulating effect on the growth of parts of the axon terminal (containing the binding sites) in different parts of the brain (Weissman and Caldecott-Hazard 1995). Prenatal exposure to MA

also affects the neurological development of young animals and causes persistent behavioral modifications such as the deterioration of learning and memory. Latency to find the hidden platform in the Morris water maze is longer (Cho *et al.* 1991). Data inconsistency can be explained by differences in exposure time of the drug, its dose and age of pups tested (Middaugh 1989). Similarly, our studies also show that prenatal exposure to MA affects the behavior of adult male and female rats, their learning and memory, nociceptive sensitivity and susceptibility to epileptic seizures (Šlamberová 2005, Schutová *et al.* 2009, Yamamotová *et al.* 2011).

Long-term (cross)-sensitization

There are studies demonstrating that repeated administration of psychostimulants enhances locomotor activities tested in the Open field in response to treatment with the same or 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). Only few studies investigating possible sensitizing effect of prenatal drug exposure are available. There are studies (Crozatier *et al.* 2003, Stanwood and Levitt 2003) showing that prenatally cocaine-exposed rats are more sensitive to acute cocaine injection than prenatally saline-exposed rats. Furthermore, 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, e.g. they respond to lower doses of drug than control animals. Increased predisposition to drug abuse in adulthood has been shown in prenatally cocaine-exposed (Heyser *et al.* 1992b, Rocha *et al.* 2002, Estelles *et al.* 2006a), cannabinoid-exposed (Vela *et al.* 1998) and morphine-exposed offspring (Gagin *et al.* 1997) relative to controls. Our results in modified Open-field test (Laboras) (Schutová *et al.* 2012) demonstrated that prenatal MA (5 mg/kg) exposure sensitized the animals to the challenge dose of MA (1 mg/kg). Specifically prenatally MA-exposed animals that received the challenge dose of MA in adulthood displayed higher locomotion and rearing activity relative to all the other groups. These results correspond with the dopamine levels in the nucleus accumbens (Bubeníková-Valešová *et al.* 2009).

In addition, there are studies showing that the abuse of one drug may increase sensitivity to the abuse of another drug. This effect is called cross-sensitization (Bartoletti *et al.* 1985, Leri *et al.* 2003, He and Grasing 2004, Arnold 2005, Fattore *et al.* 2005, Liu *et al.* 2007, Valvassori *et al.* 2007). Cross-sensitization between amphetamine and cocaine was first demonstrated with locomotor activity (Shuster *et al.* 1977, Bonate *et al.* 1997). Systematic pretreatment with amphetamine was shown to enhance the acquisition (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 augmented locomotor sensitization to D-amphetamine. Other studies demonstrated that cross-sensitization may be induced not only between related drugs, such as cocaine and amphetamines, but also between unreleated drugs, such as between opioids and cocaine (Leri *et al.* 2003, He and Grasing 2004) or between endocannabinoids and cocaine (Arnold 2005) or opioids (Fattore *et al.* 2005), respectively.

Some studies (Vela *et al.* 1998, Cole *et al.* 2003, Estelles *et al.* 2006b) demonstrated that prenatal drug exposure may alter the predisposition to abuse drugs with different mechanisms of action in adulthood. 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 when compared to prenatally saline-exposed rats. Estelles *et al.* (2006b) showed that unlike control or animals pretreated with saline, subjects prenatally treated with cocaine did not develop conditioning with morphine. Furthermore, Cole *et al.* (2003) showed that 3,4-methylenedioxy-methamphetamine (MDMA) pretreatment reduced the rewarding properties of ethanol. Our previous work (Vathy 2002) also demonstrated that prenatal morphine exposure enhanced intracranial self-stimulation in the presence of a single cocaine injection in adult male rats.

Our most recent data (Šlamberová *et al.* 2011, 2012) demonstrate that cocaine increases the exploratory activity of prenatal controls in Laboras test, but decreases it in prenatally MA-exposed rats. In contrast to cocaine effects, morphine decreases rearing activity in both, prenatally MA-exposed rats and controls, and locomotion only in prenatally MA-exposed rats in the Laboras test. In

the plantar test, the results show that morphine has an analgesic effect in controls but this effect is suppressed in prenatally MA-exposed rats. Thus, our data suggest that there is a cross-effect between prenatal MA exposure and the challenge dose of other drug in adulthood. These studies suggest that prenatal drug exposure may induce "cross-sensitization" independently on the drugs that are the animals exposed prenatally and in adulthood. Thus, it seems that prenatal drug exposure induces a general predisposition to drug addiction in adulthood.

Conclusion

Drug abusing in women during pregnancy is a very serious problem because the drugs do not only threaten their health, but also the healthy development of their children. Proportionally with increasing number of people abusing drugs and reducing their age, the number of children prenatally exposed to the effects of drugs increases. Yet unsolved problem is how to prevent the impairing effects of drugs on child development and to avoid the above-mentioned long-term neurobehavioral changes discussed in the present manuscript. Our experimental studies (Hrubá *et al.* 2009, 2010, 2011) suggested that the adverse effects of prenatal drug exposure are at least partially reversible by postnatal care. This positive effect of fostering may persist until adulthood in rats. Therefore, question arises of whether early adoption into functional families with additional support from the child's functional stimulation would help to alleviate the delayed development of children prenatally exposed to drugs.

Because it is always better to prevent negative consequences than to retrieve them, the best "therapy" is therefore the prevention. However, the conviction of mothers to give up drugs at the beginning of the pregnancy does not resolve the problem with negative social influences during postnatal development of the child, despite the fact that a woman would go through phases of abstinence during pregnancy, which may also have impairing effects on fetal development (Zagon and McLaughlin 1992). Another option seems to be a treatment by methadone or other substances that prevent craving and abstinence. However, there are studies showing (Darmani *et al.* 1992, Zagon and McLaughlin 1992) that methadone has similar impairing effects on fetal development as heroin and morphine. Thus it seems that general prevention of drug addiction, especially in women in childbearing age, is still the best way how to deal with the impairing effects of prenatal drug exposure.

Conflict of Interest
There is no conflict of interest.

Acknowledgements

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