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The influence of methamphetamine on maternal behavior and development of the pups during the neonatal period

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ABSTRACT

Since it enters breast milk, methamphetamine (MA) abuse during lactation can not only affect the quality of maternal behavior but also postnatal development of pups. The aim of the present study was to examine the effect of injected MA (5 mg/kg) on maternal behavior of rats and the differences in postnatal development, during postnatal days (PD) 1–11, of pups when the pups were directly exposed (i.e., injected) to MA or received MA indirectly via breast milk. Maternal behavior was examined using observation test (PD 1–22) and pup retrieval test (PD 1–12). The following developmental tests were also used: surface righting reflex (PD 1–12), negative geotaxis (PD 9), mid-air righting reflex (PD 17), and the rotarod and beam-balance test (PD 23). The weight of the pups was recorded during the entire testing period and the day of eye opening was also recorded. MA-treated mothers groomed their pups less and returned the pups to the nest slower than control dams. The weight gain of pups indirectly exposed to MA was significantly slower. In addition, pups indirectly exposed to MA were slower on the surface righting reflex (on PD 1 and PD 2) and the negative geotaxis test. In females, indirect exposure to MA led to earlier eye opening compared to controls. At the end of lactation, males who received MA indirectly via breast milk performed worse on the balance beam test compared to males who received MA directly. However, direct exposure to MA improved performance on rotarod relative to controls. Our results suggest that indirect MA exposure, via breast milk, has a greater impact than direct MA exposure.

1. Introduction

Methamphetamine (MA) is the most widely used synthetic stimulant in the world. In many countries across the globe it is reportedly the second most prevalent illicit drug after cannabis (EMCDDA, 2009). In Europe, countries with the highest production and consumption of MA are the Czech and Slovak Republic (EMCDDA, 2013).

Due to its effects, such as euphoria, increased energy, and suppressed appetite, together with its low cost and relatively easy production, MA is commonly abused among women (Smeriglio and Wilcox, 1999; Smith et al., 2008). Woman may have a greater risk of more severe MA-dependence than men. In a study by Maxwell (2014), women became dependent on MA faster than men. When abused during pregnancy, MA crosses the placental barrier (Burchfield et al., 1991; Dattel, 1990) and during lactation, MA can enter breast milk (Rambousek et al., 2014); these represent mechanisms by which MA can impair the development of the fetus both prenatally and postnatally.

Experimental studies in our laboratory have demonstrated that the administration of MA to female rats during gestation and/or lactation impairs maternal behavior. MA-exposed mothers provided less care for their pups, while showing more self-care activities (Šlamberová et al., 2005a,b). Their pups, prenatally exposed to MA, displayed delayed sensorimotor development on the surface righting reflex and on the mid-air righting reflex, beam balance, and rotarod tests (Hrubá et al., 2009; Šlamberová et al., 2006). This impairment on pup development could be modulated by postnatal fostering using control dams (Hrubá et al., 2009). In our previous study (Malinová-Ševčíková et al., 2014), pups were exposed to MA during either the first half of embryonic development (embryonic day (ED) 1–11) or the second half of embryonic development (ED 12–22); results showed accelerated eye opening and impaired surface righting reflex in pups exposed to MA during first half of prenatal development. MA exposure during the second half of prenatal development led to decreased birth weight and reduced weight gain as well as impaired performance on the beam balance test (Malinová-Ševčíková et al., 2014). The present study continues to examine the effects of MA on maternal behavior and sensorimotor development of pups during the next developmental

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stage, i.e., after parturition.

The neonatal period covered in scientific papers lies on the timeline from postnatal day (PD) 1–21, or shorter (for review see Jablonski et al., 2016). In a recent paper, we defined the neonatal period as PD 1–11 to compare our results with the result of our previous research (Malinová-Ševčíková et al., 2014).

The brain develops and matures over a longer period than most other organs. Its development begins during embryogenesis and continues through fetogenesis and the neonatal period. The normal ontogeny of neural development in rodents is different from humans because rodents undergo considerable postnatal development and humans have considerably more prenatal maturation of their nervous systems. These differences may be confounded with differences in exposure methods during critical periods of nervous system development and thus differences in vulnerability between developing animals and humans (e.g., lactation transfer during the first postnatal week in rodents and transplacental transfer during the third trimester in humans) (Benešová et al., 1984; Clancy et al., 2007; Rice and Barone 2000). Along these lines, the present study compared direct and indirect MA exposure during the neonatal period. Since drug abusing human mothers do not inject drugs into their children, children are only exposed to MA during lactation, i.e., indirectly via maternal breast milk. MA is metabolized in the body of mother (the half-life of MA in rats and humans is 70 min and 12 h, respectively) (Cho et al., 2001) therefore, pups might experience transplacental exposure to lesser amounts of the drug. There is little research reporting on the transfer of MA into human or rat breast milk. There is one clinical study that reported the presence of MA in breast milk 24 h after MA injection (Bartu et al., 2009). Another amphetamine drug class, dexamphetamine, which is common pharmacotherapy for attention deficit disorders and attention deficit hyperactivity disorder (ADHD), was confirmed to be present in maternal breast milk at 5.7% of the adjusted infant dose (Ilett et al., 2007). The presence of MA in rat breast milk, which was collected from the stomach of the pups 1 h after ingestion, was confirmed in a study by Rambousek et al. (2014). Our interest here, was to examine the effect of MA on rat pups, independent of maternal exposure.

We hypothesized that:

1) Exposure to MA during PD 1–11 would affect neurogenesis in the neocortex, hippocampus, and cerebellum, which are still undergoing neurogenesis (Bayer, 1980; Ignacio et al., 1995; Rice and Barone, 2000); therefore, it was expected that MA exposure would affect cerebellar locomotion functions and neocortex decision making functions. In the morphological aspect of the study, defects or delays in the development of eyes were also predicted.
2) Both direct and indirect MA exposure would have adverse effects on the offspring, however, we expected direct effects of MA, after direct injection vs. indirect via maternal breast milk, based on biodegradation of MA within dam, to have the greatest effect.

2. Methods

2.1. Prenatal and postnatal animal care

Adult albino Wistar rats were purchased from Velaz (Prague, Czech Republic) raised by Charles River Laboratories International, Inc. Females (250–300 g) were housed 5 per cage and males (300–350 g) were housed 4 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 (lights on from 0600 h). After one week, 2 females were housed in a cage with 1 male, for two weeks, for mating. One day before the expected day of birth, females were housed in separate cages. The day of birth was counted as PD 0. The mothers with their pups were not disturbed on PD 0.

2.2. Organization of experimental groups

One day after parturition, females were randomly divided into the following groups:

1) Group with direct MA exposure − Mothers were left intact for the entire lactation period. In each cage, the pups were assigned to those, who were injected subcutaneously (s.c.) with MA at 5 mg/kg/day (volume 1 ml/kg/day) on PD 1–11 and the control group. The control pups received needle prick (not saline) at the same time the MA group got their s.c. injection. We used sham controls because our previous unpublished experience showed that newborn pups injected with saline died at higher rates than MA injected pups.
2) Group with indirect MA exposure − Mothers were exposed to MA or SA. MA exposed mothers were injected s.c. with MA at 5 mg/kg/day in PD 1–11, SA females received a s.c. injection of saline at the same time and same volume (1 ml/kg/day) as the MA group. All females were weighted daily (PD 1–11). The pups were exposed to the effect of SA or MA, via the maternal breast milk, depending on the mother they were assigned to.

The dose of MA at 5 mg/kg/day exposed to pregnant laboratory rats leads to such drug concentrations in the brain of fetuses that correspond to the amount of drug observed in the fetuses of drug-dependent human mothers (Acuff-Smith et al., 1996; Cho et al., 1991; Martin et al., 1976). This dose is therefore served as an experimental model for determination of potential risk related to *in utero* drug exposure in humans.

2.3. Data analyzed

2.3.1. Litter characteristics

On PD 1, the number of pups and percentage of males and females in each litter was counted. Thereafter, the number of pups in each litter was adjusted to 12. Whenever possible, the same numbers of male and female pups were kept in each litter. For identification, neonatally MA-exposed pups were injected intradermally with black India ink in the left foot and control pups in right foot.

Pups underwent the same manipulation throughout the testing period, i.e., weighing and rewriting the testing number on their backs. The day of eye opening was recorded. The eyes were considered open when both eyes of the pup were fully opened. Three-way ANOVA (*Drug x Sex x Injection period*) was used to analyze birth weight and weight gain of the pups. The Bonferroni post-hoc test was used for comparisons of ANOVA analyses. The Chi-square test was used for analysis of eye opening. Differences were considered significant, if $p < 0.05$.

2.3.2. Maternal behavior

2.3.2.1. Observational test. Maternal behavior was observed daily, PD 1–22, for 50 min in the home cage of the mother and her pups. Observations were made during the light phase of the light-dark cycle between 08:00–09:00 h (Malinová-Ševčíková et al., 2014; Šlamberová et al., 2005a,b). During each 50-min session, each mother and her pups were observed 10 times for 5 s at 5 min intervals. Eleven types of activities exhibited by mothers and three types of nursing positions (see below) were recorded during each session. Thus, each mother and her pups were observed 220 times (22 days x 10 observations per day). During each observation “1” indicated that the behavior occurred and “0” indicated that it was absent.

First, it was noted whether a mother was nursing or not. Three different positions were recognized as nursing: a) arched nursing (when the mother is arched over her pups with legs splayed), b) blanket nursing (when the mother is over her litter, but did not have her back arched, plus no obvious extension of her legs), c) passive nursing (when the mother was lying on her side or back with one or more suckling pups). The first two nursing positions were designated as active and the

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