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Detrimental effects of self-administered methamphetamine during pregnancy on offspring development in the rat

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ABSTRACT

Background: Methamphetamine (METH) abuse by pregnant women is a commonly observed phenomenon. While the harmful effects of METH are well described for adults, there is only limited knowledge of the effects of METH use during pregnancy on the developing child. In the present study, we investigated how intraveneous (*iv*) METH self-administration throughout pregnancy affected rat dams and their offspring through weaning, compared to controls.

Methods: Female rats (n = 16) were trained to self-administer METH *iv*; every drug infusion by a dam also resulted in a saline injection to a yoked control (n = 16). When stable levels of self-administration were reached, all females were mated. Daily, 2-h self-administration sessions continued until litters were born. General health and weight was assessed daily in dams and pups. In addition, pups were evaluated for achievement of age-appropriate developmental milestones (i.e., righting reflex, negative geotaxis, pinna detachment, fur appearance, incisor eruption and eye opening).

Results: Dams self-administered 2–3 mg/kg/day METH throughout gestation without consequence to dam health or weight gain during pregnancy. All females produced viable litters, and litter size and composition did not differ between saline and METH dams. Similarly, maternal pup-directed behavior was not affected by prior METH self-administration. However, despite a lack of weight difference in pups, METH-exposed pups were significantly delayed in reaching all assessed developmental milestones compared to controls.

Conclusion: These results indicate that in utero exposure to moderate METH doses can profoundly and adversely affect offspring development, suggesting that even recreational METH use during pregnancy has potential for harm.

1. Introduction

Illicit drug use has been increasing steadily in individuals of reproductive age (SAMHSA, 2013). This is especially true for the psychostimulant methamphetamine (METH; Zapata et al., 2008), despite efforts to curb its production and trafficking (Shukla et al., 2012). Notably, approximately 50% of the METH-abusing population are women (Anderson and Choonara, 2007). Because METH is often associated with the experience of increased pleasure during sex, risky sexual behavior, and impaired decision-making, unwanted pregnancies can be considered an expected outcome of METH use (Arria et al., 2006; Kalechstein et al., 2003; Rawson et al., 2002; Zapata et al., 2008). Even when a pregnancy is confirmed, most METH-abusing women delay seeking proper prenatal care until late in their second trimester, often due to fear of involvement from Child Protective Services (Wu et al., 2013). Although METH use tends to decline as pregnancy progresses, especially in heavy users, a significant proportion of women continue to abuse the drug throughout the nine months of gestation (Terplan et al., 2009). Because reported data only represent women that seek treatment, the actual number of pregnant, METH-abusing women is undoubtedly higher (DellaGrotta et al., 2010).

Although the adverse effects of METH are well-described in adults, there is only limited knowledge regarding the impact of METH in pregnant women. Moreover, because METH has been shown to cross the placenta (Won et al., 2001), the developing fetus presumably also is at risk. In clinical studies where METH use during pregnancy was determined via meconium screen or retrospective self-reports, neonates have been reported to be small for their gestational age, presenting with low birth weight and smaller head circumference (Zabaneh et al., 2012). They also exhibited poor movement, low arousal and increased lethargy (LaGasse et al., 2012; Minnes et al., 2011; Smith et al., 2003). Beyond the neonatal stage, METH-exposed children also were more

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likely to have increased emotional reactivity, anxiety, and diagnoses of attention deficit hyperactivity disorder (Diaz et al., 2014; Kirlic et al., 2013; LaGasse et al., 2012; Minnes et al., 2011; Shah et al., 2012; Smith et al., 2003, 2012; Van Dyk et al., 2014; Wouldes et al., 2014). While the METH exposure in utero likely plays an important role in affected development, the postnatal environment may be as important to the developing child since a negative postnatal environment characterized by as abuse or neglect has been linked to the development of psychiatric disorders in adulthood (Heim et al., 2004). This is relevant given that METH-taking mothers are more likely to have ongoing legal difficulties, experience domestic violence and experience parenthood as stressful and, thus, are more prone to inferior caregiving (Derauf et al., 2007; Good et al., 2010; Liles et al., 2012).

In recent years, a number of preclinical studies have been conducted aiming to understand the relationship between in utero METH exposure and detrimental effects on the offspring (McDonnell-Dowling and Kelly, 2015a). Exposure to repeated, high doses of METH (e.g., 10–40 mg/kg) during pregnancy has been shown to increase dam/pup mortality, significantly reduce birth weight and produce teratogenic effects (Acuff-Smith et al., 1996; White et al., 2014). Notably, repeated administration of more moderate METH doses (e.g., 2.5–5 mg/kg), before and throughout pregnancy, also has been shown to have profound effects on dams and offspring. For instance, daily, non-contingent administration of METH at moderate doses (5 mg/kg) throughout pregnancy has been shown to reduce pup-directed maternal care (Slamberova et al., 2005) and delay pup development (McDonnell-Dowling et al., 2014, 2015b). As adults, METH-exposed offspring demonstrated increased impulsivity (Lloyd et al., 2013), increased nociception (Hruba et al., 2010a), increased disposition to drug abuse (Slamberova, 2012) and disruptions in learning and memory (Hruba et al., 2010b). These findings illustrate that METH, across a range of doses, can have a multitude of detrimental effects on offspring that can persist across the lifespan.

While studies using non-contingent drug administration are important for pinpointing the effects of prenatal METH exposure and also allow for precise control over dosage, it is well-documented that passive drug administration elicits markedly different effects on neuroadaptation, toxicity, stress hormone levels and behavior when compared to active self-administration (e.g., Dworkin et al., 1995; Fouquet et al., 2001; Galici et al., 2000; Jacobs et al., 2003). In addition, the fixed dose scenario of prior studies does not recapitulate the human reality of variable intakes across time and individuals. Thus, the aim of the present study was to use a model of METH self-administration during pregnancy to study the effects of in utero METH exposure on offspring development. While it is true that under a self-administration procedure, intake is likely to vary across animals, we believe that this potential disadvantage is outweighed by the increased translational relevance. In addition, it also was aimed to elucidate possible changes of METH self-administration across gestation and its effects on dam health, behavior and pregnancy outcome.

2. Material and methods

2.1. Subjects and surgery

All experiments were conducted in accordance with the NIH Guide for Care and Use of Laboratory Animals and the University of Mississippi Medical Center Animal Care and Use Committee. Adult male and female Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA), approx. 65 days of age, weighing 300–350 g or 200–250 g respectively at arrival were housed in single-sex pairs in standard shoebox cages in a temperature and humidity controlled vivarium with a reverse 12-h light/dark cycle (lights on at 20:00 h). Food and water were available *ad libitum*. Behavioral testing occurred during the dark phase.

Female rats were implanted with indwelling jugular vein catheters (3 Fr medical grade polyurethane, Instech Laboratories, Plymouth Meeting, PA) under isoflurane anesthesia. The distal end of the catheter was routed subcutaneously *(sc)* and connected to a vascular access button (Instech Laboratories) implanted in the mid-scapular region, permitting access to the catheter without exposing it to air. Catheters were flushed daily with heparinized saline (30 IU/ml) to maintain patency. Animals were allowed to recover from surgery for 7 days before starting METH self-administration.

2.2. Apparatus and drugs

Experimental sessions were conducted in operant chambers (Med Associates, Georgia, VT) equipped with an infusion pump, two levers, a white stimulus light above each lever and a house light on the opposite wall. An infusion line was connected to a rotating swivel and routed through a spring tether that was attached to the skin button. Recording of responses and activation of lights and infusion pump were computer-controlled (MED-PC IV, Med Associates, Georgia, VT).

Methamphetamine hydrochloride was purchased from Sigma Aldrich (St. Louis, MO) and prepared in sterile saline for self-administration.

2.3. METH self-administration and mating

Half of the females (one female/cage, randomly chosen) were trained to self-administer METH (0.08 mg/kg/infusion) under a fixed-ratio (FR) schedule, for daily 2-h sessions. Females were weighed prior to each session and the infusion duration was adjusted via the computer program (maximum of ± 0.5 s) to ensure accuracy of the infusion dose. Completion of the FR on the active lever led to a 4-s drug infusion concomitant with the illumination of the stimulus light above the lever, followed by a 6-s time-out during which the light remained illuminated. Lever presses on the inactive lever were recorded, but had no programmed consequences. Initially, rats were trained under a FR1 schedule until they reached the criteria of a minimum of 3 days with at least 2 days with over 15 infusions/session earned; after which, the FR requirement was increased to 2. The remainder of the females served as yoked saline controls (i.e., they received a saline infusion and light stimuli whenever a METH infusion was delivered).

Once stable levels of self-administration were reached (at least 20 infusions/session with no upward or downward trends in number of infusions over a 3-day period, with the number of infusions within ± 20% of the last 3-day mean), a male was introduced to the home cage of a METH-saline yoked female pair and allowed to mate. Males remained with the females until the females were close to delivering their litters, as estimated by time elapsed since first signs of pregnancy (e.g., obvious weight gain, rounded abdomen). METH self-administration was continued daily throughout the mating and gestational periods and ceased the day a litter was born.

2.4. Pup-development and maternal pup-directed behavior

On the day litters were born (designated postnatal day 0, PND0), all pups were sexed, weighed and inspected for anomalies. Litters were culled to four males and four females where possible, keeping the most viable pups. Starting on PND1, pups and dams were weighed daily and their overall health was assessed (i.e., fur appearance of dam, lack of chromodacryorrhea in dam, milk visible in pup's stomach, pups age-appropriately active and warm to the touch). Daily, each pup was assessed for achievement of species-specific developmental milestones as described in Table 1 (adapted from McDonnell-Dowling et al., 2014). Maternal pup-directed and self-directed behavior (see Table 2) was assessed from PND1-14 for one hour, twice daily – immediately before the transition to the light portion of the cycle (7:00–8:00 h) and at the usual start time of the self-administration session (12:00–13:00 h) – using the scan sampling method described in Rüedi-Bettschen et al. (2004). Specifically, behavior of each dam was recorded by observers