Int. J. Devl Neuroscience 47 (2015) 147–156

Contents lists available at ScienceDirect

International Journal of Developmental Neuroscience

journal homepage: www.elsevier.com/locate/ijdevneu

The consequences of prenatal and/or postnatal methamphetamine exposure on neonatal development and behaviour in rat offspring

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ARTICLE INFO

Article history:
Received 25 July 2015
Received in revised form 12 August 2015
Accepted 12 August 2015
Available online 25 September 2015

Keywords:
Methamphetamine
Pregnancy
Lactation
Oral gavage
Pharmacological dose
Neurodevelopment

ABSTRACT

Methamphetamine (MA) has become a popular drug of abuse in recent years not only in the general population but also amongst pregnant women. Although there is a growing body of preclinical investigations of MA exposure during pregnancy, there has been little investigation of the consequences of such exposure via the breast milk during the neonatal period. Therefore, the aim of this study was to determine the consequences of MA exposure during pregnancy and lactation on neurodevelopment and behaviour in the rat offspring. Pregnant Sprague–Dawley dams received MA (3.75 mg/kg) or control (distilled water) once daily via oral gavage from gestation day 7–21, postnatal day 1–21 or gestation day 7- postnatal day 21. A range of well-recognised neurodevelopmental parameters were examined in the offspring. Prenatal MA significantly reduced maternal weight gain, with a concomitant reduction in food intake. A significant increase in neonatal pup mortality was observed, being most marked in the prenatal/postnatal MA group. Significant impairments in neurodevelopmental parameters were also evident in all MA treatment groups including somatic development (e.g. pinna unfolding, fur appearance, eye opening) and behavioural development (e.g. surface righting, inclined plane test, forelimb grip). In conclusion, this study demonstrates that exposure to MA during any of these exposure periods (prenatal and/or postnatal) can have a profound effect on neonatal outcome, suggesting that regardless of the exposure period MA is associated with detrimental consequences in the offspring. These results indicate that in the clinical scenario, exposure during lactation needs to be considered when assessing the potential harmful effects of MA on offspring development.

1. Introduction

The use of methamphetamine (MA) has had a surge in popularity in recent years and MA is presently the most widely used illicit drug after cannabis (National Drug and Alcohol Research Centre, 2007; United Nations Office on Drugs and Crime, 2013). In 2012, the average age at first use of MA was 19.7 years old (Substance Abuse and Mental Health Services Administration, 2013). This age can be considered within the 'child bearing years' and consequently a time when females may become pregnant while using MA (Anderson and Choonara, 2007). Although preclinical and clinical literature exists documenting the adverse effects of this drug on offspring, there remains a significant amount of pregnant females abusing MA with one study showing a 5.2% prevalence in areas of America where MA abuse has become a problem (Arria et al., 2006).

Prenatal MA exposure has been extensively studied preclinically (Slamberova et al., 2005a; Slamberova et al., 2007a; Schutova et al., 2010; Hruba et al., 2009a; McDonnell-Dowling et al., 2014) however, the risks associated with postnatal exposure is something that has been overlooked in the preclinical literature. It has been established that MA can pass easily from the mother to infant via the breast milk (Bartu et al., 2009) and that some mothers may increase their use of amphetamines after birth and in the first few months of breastfeeding (Bartu et al., 2006). As highlighted in our recent review (McDonnell-Dowling and Kelly, 2015) there are a dearth of preclinical studies examining the effects of MA on the offspring when exposed via the breast milk of the mother. It is unknown if the effects of MA exposure during breastfeeding is comparable to the harmful effects of MA exposure during pregnancy. Recent work by Rambousek et al. (2014) demonstrated that the plasma concentrations of MA in pups at birth after exposure during gestation are greater than plasma concentrations of MA in pups at weaning after exposure during lactation. Therefore it is unknown if the risk for these offspring or the consequences on these offspring is greater if exposed to MA during gestation compared to lactation.

Abbreviations: MA, methamphetamine.

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http://dx.doi.org/10.1016/j.ijdevneu.2015.08.006
0736-5748/

Chasnoff et al. (1987) reported that following abstinence from cocaine during pregnancy one mother admitted her two week old infant to hospital with clinical manifestations of cocaine intoxication (hypertension, irritability, tachycardia and tremulousness) after she consumed cocaine during breastfeeding. If a mother remains abstinent from MA during her pregnancy but then relapses during the breastfeeding period the effects on the developing infant are largely unknown. Therefore, the aim of this study was to determine if MA exposure during pregnancy and lactation at a pharmacological dose affects neurodevelopment and behaviour in the rat offspring. The MA dose employed should represent the clinical scenario and selection was aided by our previous dose response study (McDonnell-Dowling et al., 2014). We employed a novel route of administration, as to the best of our knowledge oral gavage has never been employed in preclinical studies. The hypothesis is that both prenatal and postnatal MA exposure at a pharmacological dose when given orally will have an adverse effect on the rat offspring.

2. Materials and methods

2.1. Animal housing

Adult male (275–325 g, approx. 4 months old) and female (275–325 g, approx. 4 months old) Sprague–Dawley rats were used for this study. All females were bred in house, all males were obtained from Charles River (Kent, U.K.) and animals were habituated for one week from arrival. After mating, all female rats were housed singly in plastic bottom cages with additional nesting materials. All animals were maintained under standard laboratory conditions under artificial 12-h light/dark cycle (lights on from 08:00 h) and temperature was maintained at 20–24 °C with relative humidity at 35–60%. Food and water were provided ab libitum. Following littering, the rat pups remained with their biological dams until postnatal day (PND) 21, at which point the pups were weaned. Cross-fostering was not employed in this study in order to mimic the clinical scenario but also to ensure that active drugs present in the MA mother are not passed onto the control pups via breastmilk or urinary and faecal excretions (McDonnell-Dowling and Kelly, 2015). All experiments were approved by the Animal Care and Research Ethics Committee, National University of Ireland, Galway (12/NOV/07) and in compliance with the European Communities Council directive 86/609.

2.2. Mating

For this study, 52 female rats and 12 male rats were used. A male:female ratio of 1:3 for mating was used. Each cage of female rats (three) was housed overnight with one sexually mature male rat. At the beginning of the light phase the following morning, vaginal smears were obtained from all females to check for the presence of sperm. All smears were examined under a light microscope. Gestation Day (GD) 0 was deemed the day that sperm was present in the smear. Of the 52 females that were mated with males, 37 females became pregnant (71% success rate).

2.3. Gestation period and deliveries

The pregnant females were checked daily and the expected day of delivery (birth) in rats is GD 21–22 (Daston et al., 2004). Offspring in each litter were checked and counted daily in the week after delivery to monitor for pup mortalities. The pups were randomly culled (using a random number generator) to 10 per litter on PND 1 with a litter ratio of 50:50 ratio of males:females whenever possible. One male and one female were selected for testing from each litter in order to avoid litter effects and these same pups continued through all neonatal testing. These two pups were selected as they represented the average weight of the litter. Each of these pups was injected intradermally with black, India ink in the footpad for unique identification purposes in a litter.

2.4. Drug treatment

Methamphetamine HCl was purchased from Sigma–Aldrich (Wicklow, Ireland; M8750). Rats were assigned randomly to control or MA treated groups based on body weight and likelihood of pregnancy. The dose of MA given was 3.75 mg/kg at a volume of 1 ml/kg and controls received the vehicle alone (VEH), i.e. 1 ml/kg distilled water. Our previous dose response study (McDonnell-Dowling et al., 2014) aided in deciding this dose as it relates to a clinically relevant dose in the human scenario and the use of an allometric scale takes into account the body weight and body surface area of a pregnant human versus a pregnant rat (Reagan-Shaw et al., 2008) therefore maintaining the viability of the project and its comparison to clinical situations. For MA or control treatments, the dams were dosed via oral gavage once daily at 14.00 h from GD 7 until PND 21 (time of weaning). Oral gavage was used as this represents the most common route of MA administration in humans (Department of Health and Human Services, 2006), but has heretofore been disregarded in preclinical investigations. During the gestation period two groups of dams received VEH and two groups received MA. During the postnatal period, one group of dams receiving VEH continued to take VEH and the other was switched to MA, one group of dams receiving MA continued to take MA and the other was switched to VEH. This gave four treatment groups.

2.5. Maternal daily measurements

Maternal body weight was recorded daily from GD 0 to PND 21 prior to dosing of each rat (between 14.00 and 16.00 h). Maternal food and water consumption were also recorded daily from GD 0. Although maternal behaviours were not examined in this study, previous work in our lab has shown that when given orally at a dose of 3.75 mg/kg MA does not impair maternal behaviour in the observation or retrieval test (unpublished data). On PND 21 (day of weaning), all dams were sacrificed by decapitation.

2.6. Development of offspring

The development of the offspring involved examining somatic development and behavioural testing. The day on which each test was performed related to the time at which its development milestone normally occurs in rats and each test has a specific PND. Both dam and pups remained in the home cage room while testing occurred. At the time of testing, the dams were removed from the home cage and placed in a separate cage. The pups were taken directly from the home cage and placed back into the home cage after testing was completed.

2.6.1. Somatic development

Somatic parameters included pinna (ear) unfolding, fur apperance, eye opening, ano-genital distance, body lengths and body weights. Pinna unfolding was recorded from PND 3, eye opening was recorded from PND 14 and fur appearance was recorded from PND 3 for males and females. The time of first appearance of fur was considered the first day of occurrence, whilst in the cases of pinna unfolding and eye opening, where both pinna or eyes must unfold or open respectively to denote the first day of appearance. Record-