Behavioural Brain Research 279 (2015) 87–99

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Review

Sources of variation in the design of preclinical studies assessing the effects of amphetamine-type stimulants in pregnancy and lactation

Kate McDonnell-Dowling[a,b,*], John P. Kelly[a,b]

[a] Discipline of Pharmacology and Therapeutics, School of Medicine, National University of Ireland, Galway, Ireland
[b] Galway Neuroscience Centre, National University of Ireland, Galway, Ireland

HIGHLIGHTS

- This review illustrates the variation in the design of preclinical studies.
- Focus on amphetamine-type stimulants taken during pregnancy in animal models.
- There is large diversity and little consistency among these studies.
- The interpretation of these results may not be as relevant as previously thought.

ARTICLE INFO

Article history:
Received 8 September 2014
Received in revised form 3 November 2014
Accepted 8 November 2014
Available online 15 November 2014

Keywords:
Amphetamine
Methylendioxymethamphetamine
Methamphetamine
Pregnancy
Animal model
Neurodevelopment

ABSTRACT

The prevalence of drug use during pregnancy has increased in recent years and the amount of drug-exposed babies has therefore increased. In order to assess the risk associated with this there has been an increase in the amount of preclinical studies investigating the effects of prenatal and postnatal drug exposure on the offspring. There are many challenges associated with investigating the developmental and behavioural effects of drugs of abuse in animal models and ensuring that such models are appropriate and clinically relevant. The purpose of this review is to illustrate the variation in the design of preclinical studies investigating the effects of the amphetamine-type stimulants taken during pregnancy and/or lactation in animal models. Methamphetamine, methylendioxymethamphetamine and amphetamine were included in this review. The protocols used for exploring the effects of these drugs when taking during pregnancy and/or lactation were investigated and summarised into maternal experimental variables and offspring experimental variables. Maternal experimental variables include animals used, mating procedures and drug treatment and offspring experimental variables include litter standardisation, cross fostering, weaning and behaviours and parameters assessed. The findings in this paper suggest that there is a large diversity and little consistency among these studies and so the interpretation of these results may not be as clinically relevant as previously thought. For this reason, the importance of steering the preclinical studies in a direction that is most clinically relevant will be an important future recommendation. This will also allow us to be more confident in the results obtained and confident that the human situation is being replicated as closely as possible.

Contents

Abbreviations: MA, methamphetamine; AMP, amphetamine; MDMA, methylendioxymethamphetamine.

* Corresponding author at: Discipline of Pharmacology and Therapeutics, School of Medicine, National University of Ireland, Galway, Galway, Ireland. Tel.: +353 91495246.
E-mail address: k.mcdonnelldowling1@nuigalway.ie (K. McDonnell-Dowling).

http://dx.doi.org/10.1016/j.bbr.2014.11.021
0166-4328/

1. Introduction

1.1. Drug abuse during pregnancy

Substance abuse in women typically occurs during the childbearing age [1] and reports have shown that over 90% of women that abuse drugs are aged between 15 and 39 years of age [1]. It has been shown that out of all substances taken during pregnancy, tobacco and alcohol are the most commonly used [2]. However, the prevalence of other drug use during pregnancy is increasing and so the amount of drug-exposed babies is also increasing. Ostrea et al. [3] performed drug screening of new-borns in a high-risk urban population by meconium analysis and showed that over 40% of babies tested positive for drugs such as cocaine and morphine but that only 11% of the mothers had admitted to using such drugs during pregnancy. More recently, results from the U.S. national survey on drug use and health showed that 4% of pregnant women admitted to using drugs during pregnancy but again this figure is probably an underestimate of the actual prevalence of use [4].

1.2. Amphetamine-type stimulants (ATS)

According to the World Health Organization, the ATS drugs are primarily made up of methamphetamine (MA) and amphetamine (AMP) but they also include methylendioxymethamphetamine (MDMA), methylphenidate, methcathinone, ephedrine, fenetylline and pseudoephedrine [122]. ATS use has become the most significant drug problem worldwide since the 1990s replacing that of cannabis, heroin and opium which had dominated the illicit drug market up until a decade ago [5]. When looking at the effects of prenatal ATS exposure in humans it is difficult, as it is for all drugs of abuse, as sample sizes are small, subjects can differ greatly with regard to dose and frequency of drug exposure and confounding variables such as other drug use are also common [2]. Therefore, in order to assess risk, there has been an increase in the amount of preclinical studies investigating the effects of prenatal and postnatal ATS exposure on the offspring (Fig. A.1). This review is confined to MA, AMP and MDMA use in a rat model due to the predominant use of these three ATS drugs.

1.2.1. Methamphetamine

The U.S. National Survey on Drug Use and Health in 2012 showed that 12 million people (over 5% of population) aged 12 or more had used MA in their lifetime [4]. MA can easily cross the placental barrier during pregnancy [1] and therefore may put the offspring at risk. Early human studies found that children prenatally exposed to MA had increased stress, decreased arousal, movement disturbances and decreased school achievements [6,7]. Similar studies also showed that children had lower verbal and long-term spatial memory and lower visual motor integration [8].

Many animal studies have aimed to elucidate the short and long-term effects of prenatal MA exposure. Behavioural consequences seen in rats include decreased pre-pulse inhibition and increased startle reflexes [9]. Adverse effects that have been reported include cleft palate, retinal eye defects, delayed motor development and physical growth [10–14]. One study using a rat model interestingly found that the adverse effects found after prenatal MA exposure were even passed to the next generation of offspring such as poorer performance in righting reflex and bar-holding tests [15].

1.2.2. Amphetamine

In a similar fashion to MA, AMP can cross the blood–brain barrier easily and stimulates the CNS by acting as a sympathomimetic drug, as does MA [16]. Early human studies by Larsson [17] showed that women who had taken AMP throughout their pregnancy had complications such as preeclampsia and higher incidences of preterm births with a quarter of these mothers delivering preterm. Congenital malformations include uro-genital anomalies, pilonidal sinus, limb deformity and ear abnormalities [18,19]. These malformations were seen after various AMP exposures including the whole pregnancy, the first trimester and even after the first 14 days of pregnancy.

Malformations that have been observed in rat embryos after AMP exposure include neural tube defects, microcephaly and incomplete rotation of the body axis and tortuous spinal cord [20]. Behavioural alterations have also been reported after in utero AMP exposure. Tan [21] showed that AMP exposure from gestation day (GD) 8 until birth, increased startle amplitude in the offspring and showed less inhibition for the prepulse startle trials after an AMP challenge. This indicates a different profile of behavioural reactivity in adulthood after this psychopharmacological challenge.

1.2.3. Methylendioxymethamphetamine

MDMA acts as both a stimulant and a hallucinogenic drug and it is usually ingested in pill or tablet form [5]. It is commonly sold as 'ecstasy' in pill form which contains other psychoactive substances [5]. Infants who are exposed to MDMA during pregnancy show poor motor quality and lower milestone attainment at four months of age [22]. These retardations have also been reported after MDMA exposure during just the first trimester of pregnancy and a recent drugs and infancy study showed that the degree of psychomotor deficit was directly correlated to the dose of MDMA used [23].