ABSTRACT

Women, who abuse drugs during pregnancy, expose not just themselves but also their developing foetus to impairing effects, which can have potentially harmful and even long-term effects on the exposed children. For some years, methamphetamine (MA) has dominated the illicit drug market in the Czech Republic and Slovakia; additionally this drug is on the rise worldwide. It is one of the most accessible drugs, and in many cases the first choice drug for many drug-addicted pregnant women; in part due to its anorectic and stimulant effects. These women are rarely aware of the consequences of their behaviour and their pregnancy is hardly ever a good enough reason for giving up drug use.

These findings are supported by many experimental studies that show the damaging effects of maternal MA exposure on their offspring. There is growing evidence that exposure to MA *in utero* not only causes birth defects and delays in infant development, but also impairs the brain reward neural pathways of a developing offspring in such a way, that it could increase the predisposition for drug addiction later in life. Previously published animal studies have shown that offspring of mothers exposed to MA during pregnancy are more sensitive to MA when they encounter this drug later in adulthood. With respect to increased sensitivity, the term of behavioural sensitisation (BS) has been introduced. It is defined as augmented psychomotor activity, which can be observed after drug re-administration following discontinuation of repeated drug exposure, and has been demonstrated to develop not only after repeated drug administration in adulthood, but also after chronic prenatal exposure.

The aim of my PhD thesis was to determine if prenatal MA exposure can cause cross-sensitisation to different drugs administrated in adulthood.

Pregnant dams were injected daily with MA (at a dose of 5 mg/kg) or saline subcutaneously (s. c.) over the entire length of the gestation period. To test the sensitivity

after prenatal exposure, rats were administered s. c. with (a) the same drug (MA), (b) drugs with the same mechanism of action to MA (amphetamine- AMP, cocaine- COC, MDMA), or (c) drugs with different mechanisms of action (morphine- MOR, delta9-tetrahydrocannabinol- THC). The dose of the drug administered as well as the regimen of administration depended on the behavioural test used. In adulthood, males and females rats were tested using five different test situations. Conventionally, the Conditioned Place Preference (CPP) and the Laboras test are used for testing BS. Firstly, active drug-seeking behaviour tested using the CPP is thought to be a model of cue-induced craving seen in human addicts. Secondly, enhanced locomotor activity as seen in the Laboras test (after a single drug injection) models drug-induced hyperactivity and euphoria seen in drug users. Additionally, because drugs of abuse have been shown to affect various forms of behaviour as well as cognition, the following tests were also used: the Elevated Plus Maze test (EPM) for testing anxiety, the Morris Water Maze test (MWM) for testing spatial learning and memory, and the Social Interaction test (SIT) for testing social behaviour in male rats only. In adult female rats, phases of the oestrous cycle were observed and compared.

Our results showed that there was a sensitising effect that could be attributed to prenatal MA exposure to other drug treatment in adulthood, which was best demonstrated using the spontaneous locomotor activity component of the Laboras test. Specifically, increased locomotion after prenatal MA exposure was found in females and males with an adult AMP treatment, and in females with adult COC and MDMA treatment. There was no interaction between prenatal MA exposure and adult drug treatment observed using the CPP test, so that it seems that *in utero* MA exposure does not cause changes that could increase drug-seeking behaviour later in adulthood. Interestingly, prenatal MA exposure sensitised male rats to the social interaction-decreasing effect of MA, AMP, and MDMA.

As far as other tests were concerned, the study found sex differences with regard to various drugs in behaviour and cognition. It seems that in some test situations and adult drug treatment, females were more sensitive than males. Based on sex differences we observed the following: (1) In the EPM test, MA, AMP, and COC induced anxiolytic-like effect, but only in females, while MDMA induced anxiogenic-like effects. (2) In the MWM, chronic treatment with MA, AMP, COC, MDMA, MOR, and THC lowered learning abilities and memory recall in female rats. (3) Additionally, female memory recall was shown to be worse in contrast to males, regardless of the adult drug treatment; (4) moreover, females relative to males demonstrated increased locomotion and decreased anxiety, especially in the phase of proestrus/oestrus when hormone levels were high.

In conclusion, our study showed that prenatal MA exposure can influence the sensitivity to the effects of some drugs, given as a challenge, in adulthood, specifically to those with a similar action mechanism. Our findings indicate that cross-sensitisation between prenatal MA exposure and adult drug treatment cannot be simply termed as a general drug addiction, since it seems that the mechanism by which a drug impairs specific neurotransmitter systems plays an important role. The study findings show that although the offspring of MA-addicted mothers have altered sensitivity to certain drugs in adulthood, they do not display increased active drug-seeking behaviour. Therefore, if we extrapolate the results to humans, it appears that there is a relatively little risk that a person, whose mother abused MA during pregnancy, will actively seek out drugs.