Abstract

Introduction: Methamphetamine (MA) belongs to the psychostimulants with a central stimulating and anorectic effect. It has been found that MA is the most frequently abused drug of drug-addicted pregnant women. Drug abuse of mother can cause worsening maternal behavior and delayed offspring development. Prenatal application of MA can also lead to long-term changes in behavior, cognition and social interaction. It was also shown that maternal injections induce long-lasting effects on stress responsiveness in adult progeny. Stress and drug addiction are therefore closely connected. In children, perinatal stress is associated with cognitive, behavioral, physical and emotional problems as well as with autism. In adults, it is linked to depression and schizophrenia. In animals, perinatal stress reduces social play and social behavior, increases anxiety and impairs cognitive functions.

Aim: The aim of this thesis was to determine the effect of perinatal factors such as prenatal MA/stress and/or early postnatal stress on sensorimotor development of pups and their mothers' behavior during lactation period, social behavior and oxytocin levels in juvenile age and subsequently on cognitive functions and behavior of exposed offspring in adulthood. For all behavioral tests of offspring, we monitor the possible sensitization of the same drug (MA) on the day of the test.

Methods: Female Wistar rats were divided into three groups of those, who received: MA (s.c., 5 mg/kg), SA (s.c., 1 ml/kg), or no injections (C, controls), during the entire period of gravidity. Litters were then divided into four groups relative to exposure to postnatal stress: maternal separation (S), maternal cold-water stress (W), maternal separation plus maternal cold-water stress (SW), and controls (N). The early postnatal stress was applied daily on postnatal days (PD) of pups PD 1-21. During the experiments, 8-10 individuals from each group were tested. In all behavioral tests, the offspring received an acute administration of MA at a lower dose of 1 mg/kg 45 minutes before the test. The sensorimotor development of pups and maternal behavior was tested during lactation period. Social play test and peripheral plasma oxytocin levels was determined in juvenile age of rats. In the adulthood, the anxiety-like behavior was tested in the Open field arena (OF) and the Elevated plus maze (EPM) and cognition functions in the Morris water maze (MWM).

Results: Our results suggest that the combination of prenatal MA/stress and maternal postnatal stressors has detrimental effects on maternal behavior and early sensorimotor development of pups. However, the decisive factor in this case seems to be MA exposure during pregnancy.

Prenatal exposure to MA/stress did not affect the social play behavior or social exploration of two unknown rats at a juvenile age. Postnatal stress, regardless of the type of stressor, also did not show a significant effect on the social play of juvenile rats. However, the acute MA before the test significantly attenuated social behavior of a pair of animals. Juvenile females also significantly increase their activity in social play compared to males. Early postnatal stress can reduce oxytocin secretion, but mild prenatal stress can prevent this effect. In prenatal controls, acute MA stimulated basal plasma oxytocin levels. Our results further show that early postnatal stress, as well as acute use of MA in adulthood, can reduce anxiety-like behavior in adult male rats in the OF and the EPM regardless of prenatal effects. In terms of cognitive functions, prenatal exposure to MA or stress may not significantly affect the animal's learning and memory, as shown in the MWM test. However, the early postnatal social stressor (S) has significantly impaired cognitive function. Our results further suggest that MA application improves learning and memory performance during testing regarding to the postnatal stressors.

Conclusion: Based on the results of our work, we concluded that the observed perinatal factors affecting the individual's functions in different ways. The use of MA in utero has the greatest effect on the sensorimotor development of pups, the behavior of their mothers during lactation and leads to an increase in oxytocin levels. Our data further point to the modular role of mild stress in the oxytocin response to postnatal stress and acute drug in adulthood. Even early postnatal stress can disrupt pup development and further reduce oxytocin levels in the juvenile age of animals. However, its effect on adult behavior and cognitive functions is more significant than the effect of prenatal factors. Acute MA administered on the day of the test suppresses social play and social exploration of a pair of animals regardless of perinatal factors and increases oxytocin levels depending on prenatal drug/stress exposure. Acute MA also reduces anxiety-like behavior and improves some cognitive functions depending on the type of postnatal stress.