Can Prenatal Methamphetamine Exposure be Considered a Good Animal Model for ADHD?

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Received April 18, 2021
Accepted October 11, 2021

Summary

Attention-deficit/hyperactivity disorder (ADHD) is a mental disorder with a heterogeneous origin with a global incidence that continues to grow. Its causes and pathophysiological mechanisms are not fully understood. It includes a combination of persistent symptoms such as difficulty in concentration, hyperactivity and impulsive behavior. Maternal methamphetamine (MA) abuse is a serious problem worldwide, it can lead to behavioral changes in their offspring that have similarities with behavioral changes seen in children with ADHD. There are several types of ADHD animal models, e.g. genetic models, pharmacologically, chemically and exogenously induced models. One of the exogenously induced ADHD models is the hypoxia-induced model. Our studies, as well as those of others, have demonstrated that maternal MA exposure can lead to abnormalities in the placenta and umbilical cord that result in prenatal hypoxia as well as fetal malnutrition that can result in irreversible changes to experimental animals. Therefore, the aim the present study was to compare the cognitive impairments in MA exposure model with those in established model of ADHD – prenatal hypoxia model, to test whether MA exposure is a valid model of ADHD. Pregnant Wistar rats were divided into four groups based on their gestational exposure to MA: (1) daily subcutaneous injections of MA (5 mg/kg), (2) saline injections at the same time and volume, (3) daily 1-hr hypoxia (10 % O_2), and (4) no gestational exposure (controls). Male rat offspring were tested for short-term memory in the Novel Object Recognition Test and the Object Location Test between postnatal days 35 and 40. Also their locomotor activity in both tests was measured. Based on the present results, it seems that prenatal MA exposure is not the best animal model for ADHD since it shows corresponding symptoms only in certain measures. Given our previous results supporting our hypothesis, more experiments are needed to further test possible use of prenatal MA exposure as an animal model of the ADHD.

Key words

Methamphetamine • Hypoxia • ADHD • Prenatal exposure • Memory • OLT • NORT • Hypoxia

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Introduction

Attention deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed psychiatric disorder in children. ADHD includes a combination of persistent problems, such as difficulty maintaining attention, hyperactivity, and impulsive behavior. Children with ADHD are characterized by low self-esteem, difficult relationships, and poor performance in school (Sagvolden *et al.* 2005, Russell *et al.* 2005). The causes and pathophysiological mechanisms of ADHD are not fully understood.

There are several experimental animal models used to study ADHD. Several mouse and rat strains exhibit hyperactivity. But hyperactivity alone is insufficient to qualify rat model of ADHD. It is important to consider other behavioral characteristics (inattentiveness and hyperactivity-impulsivity) and all the complexities of the disorder under experimental conditions (Sagvolden *et al.* 2011). Genetic models are based on our understanding of the monoaminergic

systems, in particular the dopaminergic systems, which seem to be the most functionally affected in ADHD (Russell *et al.* 2007). As such, genetic animal models of ADHD use DAT (dopamine transporter) knock-out mice, SNAP-25 (synaptosomal-associated protein) mutant mice, SHR (Spontaneously hypertensive rat), or NHE (Na^+/H^+ exchanger) mutant mice. SHR appears especially useful in that it displays many of the major symptoms of ADHD (i.e. inattention, hyperactivity, and impulsivity) (Sagvolden *et al.* 2011).

Other ADHD models are based on pharmacological changes induced, for example, by prenatal ethanol exposure, which can also affect dopaminergic transmission and causes hyperactivity (Gibson *et al.* 2000, Gilbertson *et al.* 2005). Similarly, prenatal nicotine exposure can also increase dopamine reuptake in the frontal cortex and affect the fetal oxygen supply (Bush *et al.* 2000, Knopik 2009, Knopik 2010, Zhu *et al.* 2014). Both prenatal alcohol and prenatal nicotine exposure have been used as animal models for ADHD (Russel 2007, Tiesler *et al.* 2014, Atalar *et al.* 2016).

The last groups of ADHD animal models involve damage to the central nervous system during the early stages of development. Early neonatal hypoxia (postnatal day 1-3) causes ADHD-like hyperactivity in rats (Oorschot *et al.* 2007). Prenatal ischemia was also shown to induce motor hyperactivity, and short- and long-term memory impairment in adult offspring (Delcour *et al.* 2012).

Prenatal ischemia-hypoxia or insufficient nutrients and oxygen in the developing fetus is a primary factor leading to lower birth weights (Hendriksen *et al.* 2002). It influences fetal growth and may lead to a variety of developmental, behavioral, and neurological abnormalities (Kwiatkowski *et al.* 2014). It may cause changes in the excitability of cortical neurons (Marešová *et al.* 2001). Prenatal hypoxia has been implicated in numerous neurodevelopmental disorders, including ADHD. Hypoxia, which can be caused by birth asphyxia, respiratory distress syndrome, and preeclampsia, has been independently associated with ADHD (Getahun *et al.* 2013). Prenatal hypoxia also affects the function of hippocampal neurons (Vetrovoy *et al.* 2021), which play a role in memory functions responsible for motor development (Sab *et al.* 2013). Apoptosis of hippocampal neurons, linked to hypoxia, also cause delays in the development of motor reflexes (Golan *et al.* 2006). Abnormalities in hippocampus, thalamus and striatum were observed after prenatal hypoxia exposure (Robinson *et al.* 2018). Additionally, prenatal hypoxia has been found to cause memory impairment (Sab *et al.* 2013, Wei *et al.* 2016, Zhuravin *et al.* 2019).

MA is a psychostimulant drug with hallucinogenic effect. The mechanism of action results from acute increases of serotonin and dopamine levels. MA is also described to cause neuronal damage (apoptosis in striatum and prefrontal cortex, long-term damage to dopaminergic and serotonergic axon terminals in hippocampus, striatum and prefrontal cortex) (Zhu *et al.* 2006, Wagner *et al.* 1980), excitotoxicity through excessive glutamate release or oxidative stress by increasing nitric oxide synthase activity. (Halpin *et al.* 2014). Maternal MA exposure can lead to placenta and umbilical cord abnormalities (Vavřínková *et al.* 2001) that can result in prenatal hypoxia as well as fetal malnutrition, resulting in irreversible changes. Maternal MA abuse, which is a serious problem worldwide, can lead to changes in offspring behavior very similar to that seen in children with ADHD, e.g. hyperactivity (increased locomotion on behavioral tests) linked to increased dopamine levels, and learning and memory impairment that corresponds with changes in the glutamatergic system of the hippocampus (Bubeníková-Valešová *et al.* 2009, Fujáková-Lipsky *et al.* 2017, Šlamberová *et al.* 2014, Ochozková *et al.* 2019). Prenatal MA exposure has also been shown to affect stress responses in adult animals (Holubová *et al.* 2016). Other studies have shown that prenatal MA exposure impairs postnatal development (Acuff-Smith *et al.* 1996, Šlamberová *et al.* 2006) that can lead to lower birth weight (Šlamberová 2012), which is also a risk factor of ADHD (Asherson 2012). Prenatal MA exposure has been shown to lead to morphological brain changes as well as changes in brain metabolism (Abar *et al.* 2014, Acuff-Smith *et al.* 1996).

Based on the above, the aim of the present study was to test prenatal MA exposure as a potential novel model of ADHD in comparison with prenatal hypoxia exposure. The following behavioral tests were used: The Novel Object Recognition Test (NORT), which measures the exploratory behavior in exploring two different objects-novel vs. familiar (exploratory behavior is a measure of recognition memory), and the Object Location Test (OLT), which measures the exploration of two identical objects, but one is placed to a novel location; this task mainly assesses spatial memory and discrimination (Ennaceur *et al.* 1997).

Methods

The procedures used in this study were reviewed and approved by the Institutional Animal Care and Use Committee and were conducted using the Czech Government Requirements regarding Policies for Humans Care of Laboratory Animals (No. 86/609/EEC) and in compliance with subsequent regulations from the Ministry of Agriculture of the Czech Republic.

Animal groups

Adult female (250-300 g) Albino Wistar rats were purchased from Velaz (Prague, Czech Republic, bred by Charles River Laboratories International, Inc.) and housed with 4-5 animals per cage in a temperature-controlled (22-24 °C) colony room with a standard 12 h light/dark cycle (lights on at 06.00 h). Prior to testing, animals were left undisturbed for one week with food and water *ad libitum*. After the acclimatization period, the females were weighed and smeared (vaginal lavage) to determine their phase of the estrous cycle. At the onset of the estrous phase of the estrous cycle, females were housed overnight with adult males. One female was paired with one male in a cage overnight. The following day, females were smeared again to check for the presence of sperm and were returned to their previous home cages. The day after impregnation was counted as day 1 of gestation.

Pregnant Wistar rats were divided into four groups. One group was given daily subcutaneous injections of MA (5 mg/kg) for their entire gestational period. The second group received daily saline injections at the same time and with the same volume. The third group was exposed to 1-hr of hypoxia (10 % O_2) daily. The fourth without any gestational interventions was used as a control.

Physiological solution (0.9 % NaCl) and d-Methamphetamine hydrochloride were purchased from Sigma-Aldrich (Czech Republic).

For hypoxia exposure, rats were placed in a normobaric chamber, which was alternately flushed with N_2 to lower the O_2 concentration to 10 % (hypoxic phase) followed by reintroduction of a normoxia gas mixture (i.e. reoxygenation phase). The hypoxic phase and the reoxygenation phase lasted 30 s. Rats were exposed to a daily 1 h reduction of oxygen concentration for three weeks of the gestation period. The chambers were made of Plexiglas (28 cm in length, 10 cm in diameter, with a volume of 2.4 l). A dampening device at the intake end of the chamber was used to dissipate the air stream so that no direct gas jets disturbed the animals.

On day 21 of gestation, females were placed individually in maternity cages (one female per cage). The days of birth were counted as postnatal day (PD) 0. Mothers and offspring were left undisturbed until the day of testing.

A total of nine litters were used in the experiment. The number of pups in each litter was adjusted to twelve. Eight or nine male and four or three female pups were kept in each litter. In total, 75 male rats were used in this study (n=9-10/group and test). We used animals from different litters to prevent the litter bias. The rest of the animals were used in different experiments that are not all a part of this paper. On PD 21, pups were moved to their own cages, where they were housed in groups of 4 until the NORT (35-38 PD) for and OLT (40-43 PD) tests could be performed.

Behavioral experiments

NORT

The Novel Object Recognition test (NORT) was conducted on PD 35-39. The same method was used as described in our previous experiments (Fialová *et al.* 2015). The NORT consists of three parts: habituation, training, and testing.

Habituation: Animals were habituated to an empty square plastic arena (45×45×50 cm) for 10 min a day for three days.

Training: On the fourth day, the animal was trained by placing two identical objects in the arena. The animals explored these objects for 5 min. After 5 min, the animals were returned to their home cages. The testing box and the objects were cleaned of potential odors (using 60 % ethanol) between single animals. Than the animals were tested in the testing phase.

Testing: on the fourth day, rats were placed individually in the plastic dark brown arena, where one of the original objects and one new object of similar size (we used glass jar and metal tin of different shape and different height) were placed in the same locations used during the training phase. The time spent exploring both objects (i.e. the familiar object and the new object) was measured automatically by Ethovision XT7 (Noldus, Netherlands). The calculation of the interest in a new object in the testing phase, which is called the Investigation Ratio (IR), was calculated as the ratio of time spent exploring the new object (T_{new}) divided by the total time spent exploring both objects (T_{total}) ($IR=T_{new}/T_{total}$).

OLT

Different group of animals was used in the Object Location Test (OLT), that was conducted on PD 40-43. The OLT works on the same rules as NORT and contains the same three parts (habituation, training, and testing); additionally, the calculations are identical ($IR=T_{new}/T_{total}$). The difference is that OLT measures the exploration time for two identical objects, but one is placed in a novel location. It assesses spatial memory and spatial discrimination (Ennaceur *et al.* 1997).

Both NORT and OLT were performed in dark room illuminated with red light.

Statistical analysis

Time spent with objects, velocity, and distance traveled were measured automatically with an Ethovision XT7 (Noldus, Netherlands). The Investigation Ratio ($IR=T_{new}/T_{total}$) of the testing phase was analyzed using a one-way ANOVA in NORT and OLT separately. Differences were considered significant if $p \leq 0.05$.

Results

As shown in Figure 1, group differences were not statistically significant.

As shown in Figure 2, there was a significant effect between groups in terms of distance traveled, NORT [$F_{(3,35)}=9.286$, $p<0.01$]. Animals prenatally exposed to hypoxia walked longer distances relative to saline and MA group. Animals prenatally exposed to saline walked longer distance relative to control group. There were also significant differences between groups [$F_{(3,35)}=7.331$, $p<0.01$] in the velocity in the NORT. Animals exposed prenatally to hypoxia walked faster in than animals from the saline as well as the MA groups. There were no differences between the investigation ratios for the group.

In the OLT, there were significant differences between groups [$F_{(3,32)}=4.638$, $p<0.01$] relative in distance traveled. Prenatal MA and hypoxia groups traveled longer distances than control rats. The IR differences between groups approached significance ($p=0.07$) but did not achieve it.

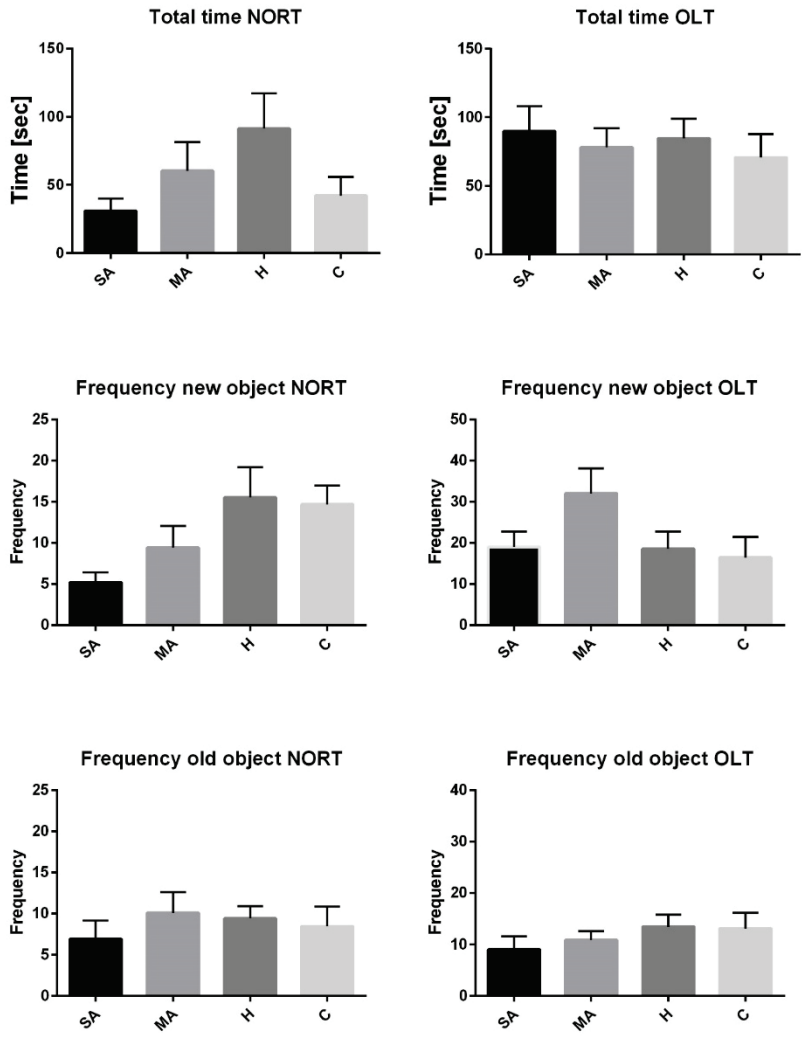

Fig. 1. The effect of prenatal MA, SA, Hypoxia, and Control on behavior in the NORT and OLT test. MA=methamphetamine; SA=saline; H=hypoxia; C=control. Values are mean ± SEM (n=9-10).

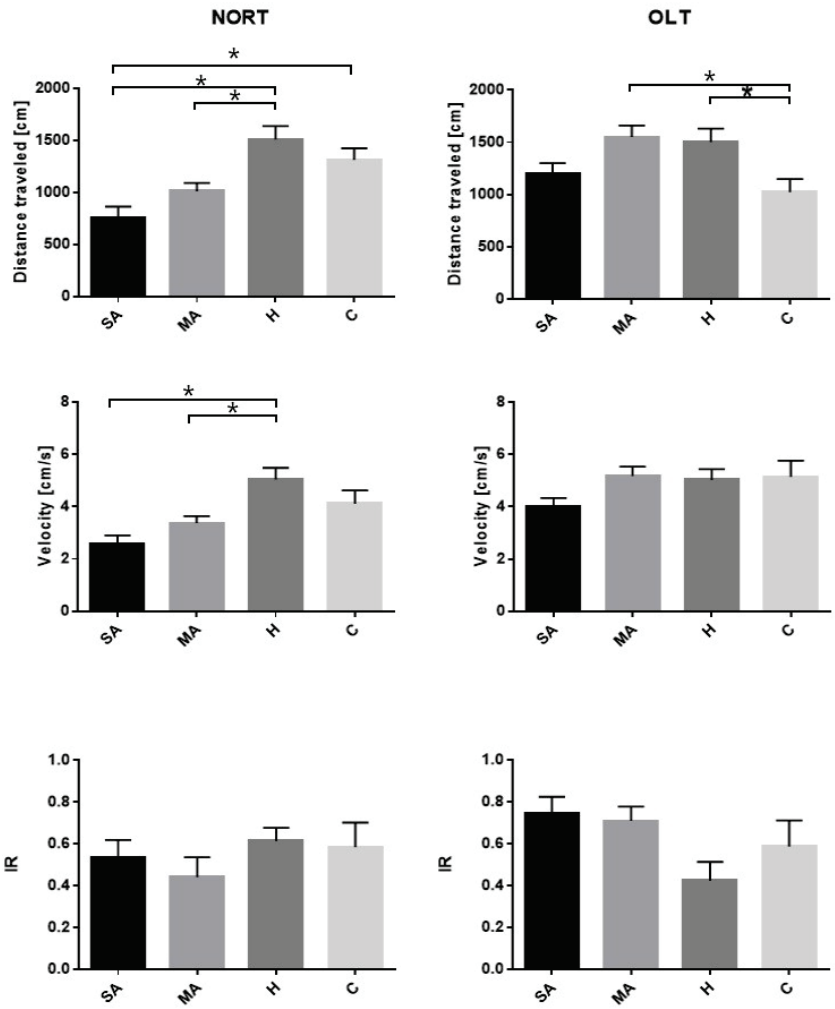

Fig. 2. The effect of prenatal MA, SA, Hypoxia, and Control on behavior in the NORT and OLT test. MA=methamphetamine; SA=saline; H=hypoxia; C=control. Values are mean ± SEM (n=9-10), * p<0.01.

Discussion

The goal of the present study was to find a novel animal experimental model for ADHD since our previous studies have shown memory recognition impairment in adults after prenatal MA exposure (Fialová *et al.* 2015) and increased locomotor activity in adolescents and adults (Ochozková *et al.* 2019). We used NORT to test working and OLT to test spatial memory. Both tests are commonly used in Wistar rats strain (Swartzwelder *et al.* 2012, Moreton *et al.* 2019).

Surprisingly, the data from this study did not find any significant differences in the investigation ratios between groups relative to NORT and OLT, which means no memory impairment, was detected in adolescents after prenatal MA exposure or after prenatal hypoxia on these types of cognition tests. In summary, (1) hypoxia-induced significant differences in distance traveled and velocity on the NORT compared to controls, as well as the saline- and MA-exposed groups, and (2) greater distance traveled was observe on the OLT in the hypoxia and MA exposed groups relative to controls.

These findings support those seen in previous studies. Rats exposed to prenatal hypoxia showed behavior changes during the open-field test (Hermans *et al.* 1992, Sab *et al.* 2013). Different types of hyperactivity were described; rats had spontaneous exploratory and motor hyperactivity during the open field test and short-term memory deficits relative to object recognition in adulthood after prenatal hypoxia on day GD 17. In the same study, they also found that prenatal hypoxia caused white matter damage to the corpus callosum and brainstem, but not in the motor cortex (Delcour *et al.* 2012). Hyperactivity during the open field test was also observed in newborn (P15) rats exposed to prenatal hypoxia (Cai *et al.* 1999). Interestingly, another study showed that prenatal hypoxia leads to hyperactivity during the open field test during postnatal development. However, in adulthood, rats had a greater tendency to "freeze", and overall locomotor activity was reduced (Dubrovický *et al.* 2014). Rats exposed to prenatal hypoxia had delayed nerve cell maturation and increased

neurodegeneration in the cortex and striatum, although these structural changes were no longer apparent in adulthood (Dubrovskaya and Zhuravin 2010). In humans, prenatal hypoxia may result in disturbances in central dopaminergic systems that persist in adulthood (Plomp *et al.* 2009). It was also found that prenatal hypoxia may cause selective vulnerability of mesencephalic dopaminergic neurons and affect noradrenergic neurons in the locus coeruleus *via* immunoreactivity of tyrosine hydroxylase, an enzyme that limits catecholamine synthesis. Both these effects are likely to predispose survivors of prenatal hypoxia to psychiatric or neurological disorders in adulthood (Pagida *et al.* 2016). Dysregulation of dopaminergic neurotransmission plays a significant role in the pathophysiology of several neurological disorders, including ADHD (Pagida *et al.* 2013).

Because no memory impairment was detected, our present study is at odds with our previous findings (Fialová *et al.* 2015). Adolescent rats were used in the present study, while adult animals were used in the earlier study (Fialová *et al.* 2015); the maturation of the hippocampus may explain some or all of the discrepancies. On the other hand, the greater motor activity (distance traveled) observed in the OLT experiment involving MA exposed animals was consistent with that seen in our previous studies and the studies of others (Diaz *et al.* 2014). Prenatal MA exposure resulted in increased locomotor activity (i.e. voluntary movement) and also increased locomotor activity in a novel environment (Ochozková *et al.* 2019).

The question of whether prenatal MA exposure can be considered a good animal model for ADHD remains unanswered. ADHD is a heterogeneous disorder with different behavioral symptoms that probably result from different combinations of genetic and environmental factors. The heterogeneity is often divided into hyperactivity and inattention. Animal models are characterized by a list of criteria, which include behavioral characteristics (e.g. impulsivity, hyperactivity, altered reinforcement of novel behavior and deficient extinction of previously reinforced behavior, and impaired learning and memory) together with neurobiological characteristics (Sagvolden *et al.* 2011). Interestingly, according to recent findings, hyperactivity may be a compensatory mechanism to produce more lactate in muscles and thereby supply the brain with energy (Medin *et al.* 2019).

The most relevant animal model of ADHD is spontaneously hypertensive rats (SHR), which exhibits all the behavioral and most of the neurobiological criteria. SHR have higher extracellular dopamine in the nucleus accumbens shell, and juvenile SHR have increased levels of dopamine in the striatum and prefrontal cortex, with upregulation of D1 receptors (DRD1) in the prefrontal cortex and hypofunction of D2 receptors or hyperexpression of the integral plasmalemmal protein of the dopamine transporter responsible for dopamine clearance (Viggiano *et al.* 2004, Russell 2007).

Our previous study found that prenatal MA exposure increased basal levels of dopamine in the nucleus accumbens in rats (Bubeníková-Valešová *et al.* 2009). A major function of dopaminergic transmission is to modulate fast, ionotropic synaptic transmission mediated by the neurotransmitter glutamate. SHR have decreased activation of DRD1 in the striatum, which leads to decreased facilitation of N-methyl-D-aspartate (NMDA) receptor function (Papa *et al.* 1998). We found that prenatal MA exposure leads to changes in the NMDA NR1 receptor subunits in the hippocampus (Šlamberová *et al.* 2014). We previously found that prenatal MA exposure impairs recognition memory in adult rats and impairs their ability to concentrate (Fialová *et al.* 2015). A study from 2009 found that no significant effects of prenatal MA exposure were detected regarding open field test behaviors (Schutová *et al.* 2009). Collectively, our previous findings show that prenatal MA exposure has similar neurobiological characteristics to those seen in SHR. Hyperactivity alone is insufficient for the animal to qualify as ADHD model. Other characteristics have to be considered (Sagvolden *et al.* 2011).

In conclusion, our data showed no memory impairment after prenatal MA exposure or prenatal hypoxia; while prenatal hypoxia led to greater motor activity and velocity in rats on the NORT and OLT, while prenatal MA exposure only led to greater motor activity and velocity on the OLT.

This present study was conducted to better understand the effects of prenatal MA exposure on spatial and recognition memory of rats relative to prenatal hypoxia exposure and determine if prenatal MA exposure could be used as a valid model of ADHD. We are aware of the fact, that this current data are not sufficient to confirm or refute our hypothesis. Because our previous results (Ochozková *et al.* 2019) demonstrated that prenatal MA exposure induces hyperactivity, another symptom of the ADHD, more studies are necessary to

test possible use of prenatal MA exposure as an animal model of the ADHD.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

This work was supported by research program Progres Q 35, GAUK 1520218, GACR 18-03806S, and 260533/SVV/2021. This work was further supported by the ERDF/ESF project "PharmaBrain" CZ.02.1.01/0.0/0.0/16_025/0007444 funded from OP VVV. The authors express their appreciation to Thomas Secrest, for editing of the manuscript.

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