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Are changes in excitability in the hippocampus of adult male rats induced by prenatal methamphetamine exposure or stress?

Klara Bernaskova, Simona Tomkova, Romana Slamberova*

Charles University, Third Faculty of Medicine, Department of Normal, Pathological and Clinical Physiology, Prague, Czech Republic

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ABSTRACT

Prenatal stress and drug exposure induce permanent alterations of the brain. Even though different brain structures are involved, alterations almost always refer to the hippocampus. The aim of this study was to investigate the excitability of hippocampal slices in low-magnesium epilepsy model of prenatally methamphetamine (MA, 5 mg/kg sc.) or saline (sc., stress model) exposed animals in adult male rats. The second aim was to investigate, if a low dose of MA (1 ml/kg s.c.) administered in adulthood changes the hippocampal activity of these animals. Adult Wistar male rats were divided into groups according to their prenatal treatment (C − naïve control; Sa − saline; MA − MA administration). One half of the animals was treated with a challenge dose of MA (1 mg/kg sc.) 45 min before hippocampal slices were cut. The activity of 350 μ thick transversal slices of CA1 hippocampi was recorded (latencies of the first epileptiform discharge and the regular epileptiform activity) and evaluated in ACSF with low-magnesium concentration. Effects of prenatal exposure: The highest excitability was found in the Sa (prenatally stressed) group in respect to C and MA groups. This group developed also the highest number of seizure-like events. In addition, the prenatally MA treated group had also higher excitability than C group. Effects of the MA challenge dose: The challenge dose decreased the excitability of prenatally SA- exposed group. To conclude, even a mild prenatal stress significantly increases hippocampal excitability in adulthood and a challenge dose of MA is able to dampen it.

1. Introduction

Over the past decades, intensive scientific activities have been devoted to deciphering the obvious link between states of maternal stress and drug exposure on the behavioral, cognitive, emotional and physiological reactivity of the progeny. It was found that prenatal stress and prenatal drug exposure have detrimental effects on the newborn and its brain development (Van den Bergh et al., 2005; Thompson et al., 2009) and that the consequences might be seen also later in adulthood (Weinstock, 2005; Maccari et al., 2014).

In our previous studies (Slamberova and Rokyta, 2005; Slamberova et al., 2008) we have found, that prenatal methamphetamine (MA) exposure has proconvulsant effect in seizure models in adult rats induced by convulsant drugs as flurothyl, bicuculline, N-Methyl-D-Aspartate (NMDA) and kainic acid. On the other hand, prenatal and adult challenge MA dose exposure has decreased the epileptiform activity (seizure threshold, incidence and length of seizures) of sensorimotor cortex elicited in adulthood by electrical stimulation (Bernaskova et al., 2011). Both these experiments were performed in animals where one of the control groups (exposed to saline prenatally) had changed the adult rat brain excitability in another manner than drug-exposed or naïve control group. According to some studies (Peters, 1982; Day et al., 1998) prenatal saline exposure has been used as a model of mild prenatal stress. It has been shown that both, prenatal stress and prenatal MA exposure change the development, morphology and activity of the hippocampus of the offspring (Lemaire et al., 2000; Harris and Seckl, 2011). We therefore decided to explore the changes in hippocampal excitability in rats exposed to prenatal stress (saline administration to rat mothers) and prenatal MA exposure.

Epileptiform activity is identified with spontaneously occurring synchronized discharges of neuronal populations (Schwartzkroin, 1994). Such activity is often induced using experimental models of epilepsy. Hence we have studied the electrophysiological activity of brain slices of differently prenatally prepared animals in low-magnesium epilepsy model. In addition we have also studied the effects of acute challenge MA dose in adulthood.

Abbreviations: 5-HT, serotonin; ACSF, artificial cerebrospinal fluid; aMA, acute (challenge) dose of methamphetamine; C, naïve control; DA, dopamine; GABA, gamma amino butyric acid; GD, gestational day; GR, glucocorticoid receptors; MA, methamphetamine; MR, mineralocorticoid receptors; NE, norepinephrine; NMDA, NMethyl-D-Aspartate; PND, postnatal day; s.c., subcutaneously; Sa, saline

* Corresponding author.
E-mail address: romana.slamberova@lf3.cuni.cz (R. Slamberova).

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2. Methods

2.1. Animals

Female Wistar rats (Charles River Laboratories International, Inc.) were supplied by Anlab (Prague, Czech Republic). They were housed in groups of 4–5 per cage with a free access to water and food and left undisturbed for a week after transportation. There was controlled temperature (22–24 °C), humidity 50–60% and maintained dark–light cycle (12h–12 h) with the light on at 6 o'clock in the room.

Animal care and use was in accordance with the Ethical Guidelines of the Third Faculty of Medicine, Charles University in Prague, with the Czech Government Requirements under the Policy of Humans Care of Laboratory Animals (No. 246/1992) and with the regulations of the Ministry of Agriculture of the Czech Republic (No.311/1997). The experiment was approved by the Institutional Care and Use Committee and carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments.

2.1.1. Prenatal exposure

At the onset of the estrus of the estrous cycle females were housed with adult male (always one male and female per cage) overnight as described in the study of Slamberova et al. (2005). The next day after impregnation (Turner and Bagnara, 1976), the females were smeared to check the sperm presence and then they were returned to their group home cages. The animals were weighted, marked and randomly assigned to following groups: control animals (C, n = 16), saline (Sa, n = 12) and MA (n = 12) treated. From this day (the gestational day 1–GD 1; Fig. 1) the pregnant animals were daily injected until the day of delivery (usually GD 22) according to the group assignment (Slamberova and Rokyta, 2005). MA-injected group received chloride salt of D-methamphetamine (5 mg/kg; Sigma Aldrich, Czech Republic) subcutaneously (s.c.) and the saline group received saline s.c. in the same volume as MA (1 ml/kg). Control group was left untreated. All the animals were daily handled and weighed.

The day of delivery was counted as postnatal day 0 (PND 0). On PND 1 the pups were weighed, identified and cross-fostered. Each litter was adjusted to ten pups. The pups were weaned and housed in groups by sex on PND 21. The animals were then left undisturbed until adulthood (PND 60). Only male rats (60–85 days old) were used in this study, the females underwent other experiments. To avoid litter effects only one male per group of each litter was used.

2.1.2. Experimental groups

There were following groups of adult animals (Table 1): C (naïve control animals, only handled prenatally), Sa (prenatal saline exposure, 1 ml/kg, s.c.) and MA (prenatal MA exposure, 5 mg/kg, s.c.). Further, one half of the animals from each group was injected with MA challenge dose of 1 mg/kg s.c., just before the experiment (45 min). This time period was chosen based on the finding of Rambousek et al. (2014) showing that the highest level of the drug in the brain after MA s.c. injection is after 45 min. Thus three more experimental groups were obtained: C + aMA (naïve control with challenge (acute) dose of MA), SA + aMA (prenatal saline + acute MA) and MA + aMA (Prenatal MA + acute MA) (Fig. 1).

Table 1
Experimental group assignment: their prenatal and adulthood treatment.

Group	Manipulations	
	Prenatal	In adulthood
C, n = 8	Handling	–
C + aMA, n = 8	Handling	MA challenge dose
Sa, n = 6	Saline exposure	–
Sa + aMA, n = 6	Saline exposure	MA challenge dose
MA, n = 6	MA exposure	–
MA + aMA, n = 6	MA exposure	MA challenge dose

2.1.3. Brain slices preparation

One animal was used per day. The animal was briefly anesthetized by light ether anesthesia and immediately decapitated. The brain was removed and quickly placed into ice cold bathing medium. After two mins it was quickly truncated on a plate to a cube containing intact hippocampus. Transversal hippocampal slices were then cut (350 μm thick) with a vibratome (MA752, Campden Instruments). All these procedures were done in an ice cold artificial cerebrospinal fluid (ACSF − containing NaCl 124 mmol/l, KCl 2.5 mmol/l, NaH_2PO_4 1 mmol/l, $NaHCO_3$ 26 mmol/l $CaCl_2$ 2 mmol/l, $MgSO_4$ 1.3 mmol/l, glucose 20 mmol/l). The solution was saturated with carbogene (95% O_2 and 5% CO_2). The slices were then placed into interface chambers with carbogene aerated ACSF and incubated during one hour until reaching 25–27 °C maintaining pH of 7.4. After one hour incubation the slices were one by one transferred to a nylon mesh of an interface-style recording chamber (Velisek et al., 2003). The chamber was permanently perfused with 32–34 °C carbonated ACSF at a rate of 3–4 ml/min.

Recording electrode (a glass micropipette with resistance of 0.8–3 MΩ and filled with 2 M NaCl solution) was placed extracellularly to the central part of CA1 hippocampal region into stratum pyramidale. Viability of the CA1 region was tested by stimulating the Schaffer collaterals. A single biphasic stimulus by a wire microelectrode (World Precision Instruments, Inc.) with intensity range of 35 − 350 μA was used. Only slices with response by a single population spike of minimally 1 mV in amplitude were accepted. Since accepted, the physiological electrical activity in normal ACSF was recorded for control for ten mins. (The signal was amplified thousand times by BVC-700 amplifier.) The slice was then perfused with the ACSF without magnesium [low-magnesium epilepsy model (Lewis et al., 1989)] to induce epileptiform discharges. No more than two slices were used from each animal. A total of 73 slices derived from 40 animals were examined.

Fig. 1. Scheme of the experiment time schedule.

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