Int. J. Devl Neuroscience 33 (2014) 98–105

Contents lists available at ScienceDirect

International Journal of Developmental Neuroscience

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

Spreading depression features and Iba1 immunoreactivity in the cerebral cortex of developing rats submitted to treadmill exercise after treatment with monosodium glutamate

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ARTICLE INFO

Article history:
Received 17 July 2013
Received in revised form 9 November 2013
Accepted 18 December 2013

Keywords:
Brain development
Brain electrophysiology
Cortical spreading depression
Food flavoring agents
Rats
Treadmill exercise

ABSTRACT

Physical exercise and excessive consumption of monosodium glutamate (MSG) can affect the morphological and electrophysiological organization of the brain during development. However, the interaction of both factors remains unclear. We analyzed the effect of this interaction on the excitability-related phenomenon known as cortical spreading depression (CSD) and the microglial reaction expressed as Iba1-immunolabeled cells in the rat motor cortex. MSG (2 g/kg or 4 g/kg) was administered every other day during the first 14 postnatal days. Treadmill exercise started at 21–23 days of life and lasted 3 weeks, 5 days/week, for 30 min/day. At 45–60 days, CSD was recorded for 4 h at two cortical points and the CSD parameters (velocity, amplitude, and duration of the negative potential change) calculated. Confirming previous observations, exercised rats presented with lower CSD velocities (3.29 ± 0.18 mm/min) than the sedentary group (3.80 ± 0.18 mm/min; $P < 0.05$). MSG increased CSD velocities in the exercised rats compared to saline-treated and exercised animals in a dose-dependent manner (3.49 ± 0.19, 4.05 ± 0.18, and 3.27 ± 0.26 for 2 g/kg MSG, 4 g/kg MSG, and saline, respectively; $P < 0.05$). The amplitude (ranging from 14.3 ± 5.9 to 18.7 ± 6.2 mV) and duration (46.7 ± 11.1 to 60.5 ± 11.6 s) of the negative slow potential shift of the CSD were similar in all groups. Both exercise and MSG treatment increased Iba1 immunolabeling. The results confirm that physical exercise decelerates CSD propagation. However, it does not impede the CSD-accelerating action of MSG. These effects were accompanied by a cortical microglia reaction. Therefore, the data suggest that treadmill exercise early in life can influence the development of cortical electrical activity.

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1. Introduction

In addition to the well-known improvement in cardiovascular function (Karacabey, 2005), physical exercise seems to positively influence the nervous system, as evidenced by improved cognitive function, general arousal, and well-being (Martinsen, 2008; Anish, 2005; Hillman et al., 2004; Cotman and Berchtold, 2002; Cotman and Engesser-Cesar, 2002). In laboratory animals, exercise has been associated with improved learning and memory (Van Praag et al., 2005), neurogenesis and increased neuron survival in the hippocampus (Brown et al., 2003; Farmer et al., 2004; Van Praag et al., 2005), and capillary growth and increased vascular flow in the cerebellum and motor cortex (Black et al., 1990; Swain et al., 2003). In the hippocampus, the neural effects of exercise also include increased expression of neurotrophins (Gomez-Pinilla et al., 2002; Fang et al., 2013) and signaling molecules (Shen et al., 2001), changes in the expression of genes (Tong et al., 2001), and enhanced hippocampal excitability, as indicated by long-term potentiation (Farmer et al., 2004). Therefore, the effects of physical exercise are thought to be neuroprotective, promoting brain health, preconditioning the brain against ischemic insult, and improving long-term functioning (Zhang et al., 2013). In adult animals, these exercise-mediated alterations influence brain excitability and excitability-dependent neurological diseases (Peixinho-Pena

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http://dx.doi.org/10.1016/j.ijdevneu.2013.12.008

et al., 2012). However, little is known about the electrophysiological effects of exercise on the developing cerebral cortex.

MSG is a neuroexcitatory amino acid used primarily to reinforce the flavor of several foods. When consumed in great amounts, MSG can be harmful to the brain (Nemeroff et al., 1978). In mice and monkeys, administration of MSG results in brain lesions early in life and obesity later in life (Abraham et al., 1971). In adult Wistar rats, prolonged administration of high doses of MSG results in neurodegenerative changes in pyramidal cells (Musa and Sunday, 2013). Experimental evidence also indicates that MSG influences electrical activity in the brain, facilitating the initiation of seizures (Lopez-Perez et al., 2010).

We recently demonstrated that treadmill exercise decelerates the excitability-related brain phenomenon known as cortical spreading depression (CSD) (Batista-de-Oliveira et al., 2012), and that MSG treatment early in life increases microglial reactions in the rat cortex and accelerates CSD (Lima et al., 2013). CSD was first described as a slowly propagating wave of suppression of electrical activity in the rabbit cortex (Leão, 1944, 1947), and is characterized by a depolarization of neurons and glial cells that propagates in the gray matter of the central nervous system (Maia et al., 2009; Marrannes et al., 1988). CSD has been described electrophysiologically in laboratory animals (Gorji, 2001) and humans (Dohmen et al., 2008; Fabricius et al., 2008) as a reversible and propagating phenomenon that can be elicited by chemical, mechanical, or electrical stimulation of one point of the cortical surface. Several studies have suggested that alterations in cortical excitability are associated with changes in CSD propagation (Liebetanz et al., 2006; Fregni et al., 2007). Measuring the velocity of CSD propagation along the cortical tissue is a reasonable and simple method for estimating brain CSD susceptibility under clinically relevant conditions that influence brain excitability (Amaral et al., 2009). Conditions that modify CSD generation and propagation constitute useful opportunities for understanding the processes underlying neurological diseases that are dependent on brain excitability, such as epilepsy (Leão, 1944, 1972; Guedes and Cavalheiro, 1997; Guedes et al., 2009). In addition, the role played by microglial cells in such neurological disorders is not completely known.

Therefore, we decided to investigate in 45–60-day-old rats whether physical (treadmill) exercise (performed from 21–23 to 42–44 days of life) interacts with MSG in regards to the effects on CSD and microglial reaction. We characterized CSD parameters (propagation velocity and the amplitude and duration of the negative slow potential shift) and the Iba1-immunolabeled microglial reaction in exercised rats, comparing them to those of sedentary animals. Furthermore, we compared MSG- and saline-treated groups of exercised rats. We hypothesized that treadmill exercise attenuates the effects of previous MSG treatment on the brain's ability to propagate CSD and microglia reaction.

2. Materials and methods

2.1. Animals

The animals were handled in accordance with the norms (Approval Protocol no. 23076.002006/2009-80) of the Ethics Committee for Animal Research of the Universidade Federal de Pernambuco, Brazil, which complies with the "Principles of Laboratory Animal Care" (National Institutes of Health, Bethesda, USA). The rats were housed in polypropylene cages (51 cm × 35.5 cm × 18.5 cm) in a room maintained at 22 ± 1 °C with a 12:12 h light–dark cycle (lights on at 7:00 a.m.) and fed a 23% protein lab chow diet (Purina do Brazil Ltd., São Paulo, Brazil).

2.2. Treatment with MSG

Male Wistar rat pups ($n = 28$) were treated with MSG as previously described (Lima et al., 2013). Briefly, the animals received subcutaneous injections of 2 g/kg ($n = 13$; MSG-2) or 4 g/kg MSG ($n = 15$; MSG-4) administered every other day during the first 14 days of life. Two control groups were used for comparison: one injected with saline ($n = 12$) and the other not injected at all (naïve; $n = 6$).

2.3. Treadmill exercise

After weaning, from postnatal days 21–23 to 42–44, the animals were submitted to daily sessions of running on a treadmill (Insight EP-131, 0° inclination; 30 min/day, 5 days/week, total time 3 weeks). As control group, sedentary rats ($n = 15$) were placed in the treadmill apparatus daily for a time-period similar to that of the exercised group, but the treadmill apparatus remained off.

2.4. Body weights

The rats were weighed at postnatal days 2, 10, and 45–50.

2.5. CSD recording

When the animals were 45–60 days old they were submitted to CSD recording for 4 h as described previously (Accioly et al., 2012). Under anesthesia (1 g/kg urethane plus 40 mg/kg chloralose, ip), the rat's head was secured in a stereotaxic apparatus (Kopf, USA) and three trephine holes (2–3 mm in diameter) drilled in the right side of the skull: two holes in the parietal bone and one in the frontal bone, aligned in the anteroposterior direction and parallel to the midline. CSD was elicited at 20-min intervals by applying a cotton ball (1–2 mm diameter) soaked in 2% KCl solution (approximately 0.27 M) to the anterior (frontal) hole for 1 min. The electrocorticogram (ECoG) and slow direct current (DC) potential change accompanying CSD were recorded simultaneously at the two parietal points on the cortical surface via a pair of Ag-AgCl agar-Ringer electrodes. These electrodes consisted of plastic conic pipettes (5 cm length, 0.5 mm tip inner diameter) filled with Ringer solution solidified by adding 0.5% agar and into which a chlorided silver wire was inserted. The pipettes were fixed in pairs with cyanoacrylate glue, maintaining a constant interelectrode distance for each pair (range: 4–5.5 mm). The electrode pair was fixed to the electrode holder of the stereotaxic apparatus in a manner that allowed the electrodes to be gently placed on the intact dura-mater under the control of a low-power microscope without any excessive pressure on the cortical surface. A common reference electrode of the same type was placed on the nasal bones. The velocity of CSD propagation was calculated based on the time required for a CSD wave to cross the interelectrode distance. When measuring CSD velocities, the initial point of each DC negative rising phase was used as the reference point. We also calculated the amplitude and duration of the CSD negative slow potential shifts. During the recording session, rectal temperature was maintained at 37 ± 1 °C using a heating blanket. At the end of the recording session, the animal was euthanized by an overdose of anesthetic.

2.6. Iba1 immunolabeling of microglial cells

Thirteen rats treated with saline ($n = 4$), MSG-2 ($n = 4$), or MSG-4 ($n = 5$) were perfused with 0.9% saline solution followed by 4% paraformaldehyde diluted in 0.1 M phosphate-buffered saline (pH 7.4). After being immersed in the fixative for 4 h, the brains were transferred to a 30% (w/v) sucrose solution for cryoprotection. Longitudinal serial sections (40-μm thickness) were obtained at −20 °C

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