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Effect of maternal exercise on biochemical parameters in rats submitted to neonatal hypoxia-ischemia

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ABSTRACT

Pregnancy is a critical period for brain metabolic programming, being affected by individual environment, such as nutrition, stress, and physical exercise. In this context, we previously reported a cerebral antioxidant upregulation and mitochondrial biogenesis in the offspring delivered from exercised mothers, which could provide neuroprotection against neonatal insults. Hypoxia-ischemia (HI) encephalopathy is one of the most studied models of neonatal brain injury; disrupting motor, cognitive, and learning abilities. Physiopathology includes oxidative stress, allied to mitochondria energy production failure, glutamatergic excitotoxicity, and cell death. In this study we evaluated the effect of maternal swimming during pregnancy on offspring's brain oxidative status evaluated fourteen days after HI stablishment. Swimming exercise was performed by female adult rats one week before and during pregnancy, in controlled environment. Their offspring was submitted to HI on postnatal day 7, and the brain samples for biochemical assays were obtained in the weaning. Contrary to our expectations, maternal exercise did not prevent the oxidative alterations observed in brain from HI-rats. In a general way, we found a positive modulation in the activities of antioxidant enzymes, measured two weeks after HI, in hippocampus, striatum, and cerebellum of pups delivered from exercised mothers. Reactive species levels were modulated differently in each structure evaluated.

Abbreviations: CHI, control+hypoxia-ischemia; CNS, central nervous system; CS, control+sham; DCF, dichlorofluorescein; EDTA, ethylenediaminetetraacetic acid; EGTA, ethyleneglycoltetraacetic acid; EHI, maternal exercise+hypoxia-ischemia; ES, maternal exercise+sham; GPx, glutathione peroxidase; GSH, reduced glutathione; H_2DCFDA, dichlorofluorescein diacetate; H_2O_2, hydrogen peroxide; HI, hypoxia-ischemia; PBS, phosphate-buffer saline; PMSF, phenylmethylsulfonyl fluoride; PND, postnatal day; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase

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Considering the scenery presented, we concluded that HI elicited a neurometabolic adaptation in both brain hemispheres, particularly in hippocampus, parietal cortex, and cerebellum; while striatum appears to be most damaged. The protocol of aerobic maternal exercise was not enough to fully prevent HI-induced brain damages.

1. Introduction

One of the most common causes of fetal encephalopathy is the neonatal hypoxia-ischemia (HI), leading to sensory, motor, and learning disabilities; even cerebral palsy, mental retardation, and epilepsy (de Paula et al., 2009; Rivkin and Volpe, 1993). This condition could be a result of umbilical blood flow cessation, interruption of gas exchange by the placenta, premature birth, or stress during childbirth (Procianoy and Silveira, 2001). The immaturity of the central nervous system (CNS) of pups who suffer this insult is one of the most aggravating factors for the extension of injury, which may be a consequence of a "window of susceptibility" created by the synergism between excitotoxicity, oxidative stress, and inflammatory mechanisms (Ferriero, 2004). In order to study the mechanisms involved in brain injury induced by hypoxic-ischemic condition, Rice et al. (1981) developed a model, adapted from Levine (1960) using 7 days of age rats submitted to unilateral carotid occlusion with an incision at the neck, isolating and blocking the right carotid with a surgical wire, followed by a period of hypoxia (8% oxygen and 92% nitrogen), maintaining the physiological temperature. This model has been used by many authors to further elucidate the effects of perinatal asphyxia on molecular mechanisms, cognitive, morphological, biochemical, and motor changes (Arteni et al., 2003; Ikeda, 2008; Levine, 1960; Rice et al., 1981). Neonatal asphyxia can facilitate the formation of a pro-oxidative environment (Fatemi et al., 2009). Some authors show the accumulation of hydrogen peroxide (Alkan et al., 2008; Dringen et al., 2005; Lafemina et al., 2006; Sarco et al., 2000; Sheldon et al., 2007), as well as the regulation of transcription factors responsible by antioxidant enzymes expression, as a consequence of hypoxia-ischemia (Guglielmotto et al., 2009; Ishida et al., 2001).

An effective therapy to fully prevent or treat the sequelae left by HI is still far from close. Aerobic physical exercise has been recognized as an important therapeutic modality that can assist at the treatment of chronic diseases such as obesity, type 2 diabetes, heart problems, depression, and osteoporosis (Dishman et al., 2006; Powell et al., 2011; Wolff et al., 2011). In addition to promoting metabolic programming in the CNS, such as increased glucose uptake, oxidative capacity, and electron transport chain activity in some brain regions (Dishman et al., 2006; Gokbuget et al., 2011), exercise could lead to enlarged angiogenesis, cell proliferation and neurogenesis, enhanced synaptic plasticity, and modulation of inflammatory responses (Cotman et al., 2007; Itoh et al., 2011; Ratey and Loehr, 2011). The literature reports physical exercise may contribute to post-ischemic recovery in mice submitted to treadmill (Choi et al., 2013; Park et al., 2013).

Pregnancy is the most critical period for individual development when its organs and systems are growing and specializing, which makes them more vulnerable to environmental perturbations as the mother's diet, lifestyle, stress, and hormones (Desai et al., 2015; Meaney and Aitken, 1985; Pereira et al., 2014). It has been shown that moderate intensity physical exercise, performed during pregnancy, presents benefits to mother and child, such as a reduced risk of pre-eclampsia, gestational diabetes, improved pain tolerance, reduced symptoms of depression and maternal body weight gain, as well as reduced risk of premature birth (Domingues et al., 2015; Gaston and Cramp, 2011). Prenatal exercise outcomes impact in the infant birth weight, in the risk of chronic non-transmissible diseases development, improves stress tolerance and neurobehavioral maturation, with repercussion in the cognitive performance in adulthood (Melzer et al., 2010). The aquatic exercise is mostly recommended for pregnant due to the control of maternal body weight, body temperature, and the low impact on joints (Hartmann and Bung, 1999; Lynch et al., 2003). To evaluate the effects of exercise during gestational period, animal models of "involuntary" swimming have been used, demonstrating positive neural adaptations (Akhavan et al., 2008, 2012, 2013; Lee et al., 2006; Miladi-Gorji et al., 2011). Offspring born from exercised rats shows a better performance in the acquisition and retention phases in the Morris water maze task, associated to increased number of hippocampal cells, especially in CA1 and dentate gyrus regions (Akhavan et al., 2008; Lee et al., 2006). In agreement, we demonstrated a potential brain biochemical programming in pups subjected to maternal swimming, verified by mitochondrial biogenesis indicators and antioxidant upregulation, probably prompted by reactive species (Marcelino et al., 2013). Voluntary wheel running exercise appears to be effective against the hippocampal neurons loss induced by postnatal HI, in the offspring from rats trained during pregnancy, emerging a potential neuroprotective role of aerobic exercise (Akhavan et al., 2012). In addition, Mourao et al. (2014) recently demonstrated that aquatic exercise performed by rodents was able to prevent the release of glutamate in the synaptic cleft, besides decreased some pro-apoptotic factors in hippocampal slices exposed to in vitro HI. Considering the well stablished oxidative damage induced by HI model, our objective in this study was to evaluate the neuroprotective potential of maternal physical exercise on brain from offspring submitted to postnatal HI. We hypothesize that prenatal aerobic exercise induces a brain metabolic programming able to prevent the oxidative alterations elicited by neonatal HI insult.