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Research Report

Long-term effects of pre and post-ischemic exercise following global cerebral ischemia on astrocyte and microglia functions in hippocampus from Wistar rats

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ABSTRACT

Persistent effects of pre- and postischemic exercise on glial cells activation after global cerebral ischemia remains poorly understood. Here, we investigated the effect of both pre and postischemic treadmill exercise protocols (20 min/day during 2 weeks) on glial cells immunostaining in the hippocampus of Wistar rats submitted to global ischemia. A synergistic effect between ischemia and postischemic exercise on the astrocytic area was demonstrated. Postischemic exercise partially reversed the ischemia-induced increase on the area occupied by microglia, without any effect of pre-ischemic protocol. In conclusion, postischemic exercise distinctly modulates astrocyte and microglia immunostaining in the hippocampal dentate gyrus following global cerebral ischemia in Wistar rats.

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1. Introduction

Epidemiological studies have shown neuroprotective effects of moderate physical activity (Yamada et al., 2012; Freiberger et al., 2012). In this context, several promising findings obtained in animal models of cerebral ischemia have been demonstrated. Pre-ischemic treadmill exercise is able to reduce infarct volume and inhibit inflammatory injury induced by the focal ischemia model (Guo et al., 2008; Ding et al., 2006; Jia et al., 2009). Indeed, pre-ischemic voluntary exercise in running wheel reduced neuronal damage induced by global cerebral ischemia (Stummer et al., 1994). It is interesting to note that postischemic treadmill exercise was able to diminish the global ischemia-induced apoptotic neuronal cell death (Sim et al., 2004; Lee et al., 2003). Besides, the traumatic brain injury-induced impairment of recognition memory, as well as the neuronal loss and activation of microglia in mice, was reversed by the postinjury exercise protocol (Chen et al., 2013). In addition, physical training improved perinatal hypoxic-ischemic encephalopathy-induced brain damage and memory impairments in Sprague-Dawley rats (Chen and Jiang, 2010). To our knowledge, there are no studies comparing the effects of pre- and postischemic exercise on cerebral ischemia outcomes.

The mechanisms by which physical activity alters brain function are not yet defined, however it has been suggested that exercise might activate cellular and molecular pathways that contribute to neuroprotection. A growing body of data demonstrates that glial cells play a multifaceted and complex role in ischemia outcomes; astrocyte and microglia can have both harmful and supportive effects on cell proliferation and survival (Ekdahl et al., 2009). Astrogliosis is recognized as a cellular response following a wide variety of insults to the CNS, such as global ischemia (Valentim et al., 1999; Petito and Halaby, 1993), however, it is important to highlight that physical exercise itself can induce this phenomenon in different brain areas, including cortex, striatum and hippocampus (Li et al., 2005; Uda et al., 2006; Saur et al., 2014). Interestingly, Lee et al. (2009) demonstrated that high intensity postischemic exercise reduced the extent of reactive astrocytosis in the peri-infarct region induced by focal ischemia, without any effect of mild and moderate intensities.

Global ischemia also triggers microglial outcomes, which was studied specifically on postischemic days 4–7 in the dentate gyrus and CA1 subfield of the hippocampus in rats submitted to global ischemia (Marioka et al., 1991; Gehrmann et al., 1992); Q2 however, to our knowledge there are no studies evaluating persistent effects of global ischemia. Besides, divergent results about the influence of exercise per se on microglia function have been found. Voluntary exercise increased microglia proliferation in mice hippocampi with access to a free running wheel (Olah et al., 2009), while Kohman et al. (2012) found that 8 weeks wheel running exercise reduces the microglia proliferation in aged. Although there are no studies, to our knowledge, reporting the exercise effect on microglia function in global ischemia.

Considering that reports describing persistent effects of exercise and/or ischemia as well as comparing pre- and postischemic exercise protocols were rarely performed. The aim of the present study was to compare the effect at long term of pre- and postischemic treadmill exercise protocols (20 min/day during 2 weeks) on glial cells immunostaining in the hippocampus of Wistar rats submitted to global ischemia.

2. Results

Persistent effects of global cerebral ischemia and exercise on astrocyte and microglia functions in the hippocampal dentate gyrus were evaluated. We evaluated the long term effects of transient global cerebral ischemia in Wistar rats using the four-vessel occlusion, besides it was compared the impact of pre- and postischemic exercise protocols (Fig. 1).

The GFAP immunostaining in the dentate gyrus is illustrated in Fig. 2. Two-way ANOVA revealed a significant effect of both factors, ischemia and exercise, on the quantification of the total percentage area (%) occupied by GFAP+ soma and astrocytic processes ($F(1,29)=297.73$; $p<0.001$; $F(2,29)=29.16$; $p<0.001$, respectively). The ischemic insult increased % of GFAP area in dentate gyrus subfield compared to sham groups. Two-way ANOVA revealed an effect of ischemia factor on GFAP+ soma and astrocytic processes in the stratum radiatum of hippocampus ($F(1,29)=39.72$; $p<0.001$; Fig. 3).

Furthermore, this exercise protocol per se increased the area occupied by GFAP+ cells in the dentate gyrus (Fig. 2), while both exercise protocols did not affect this parameter in the stratum radiatum of the hippocampus (Fig. 3). Interestingly, there was a significant interaction between ischemia

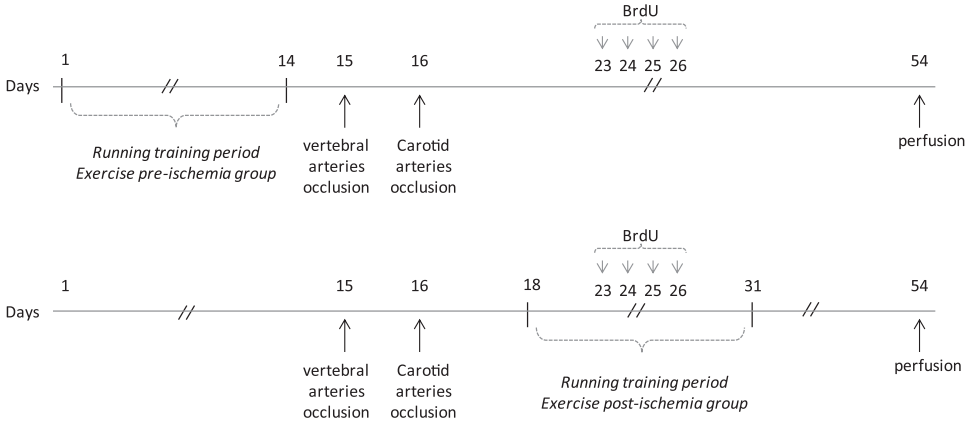

Fig. 1 – Schematic representation of the experimental design.

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