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BRAIN RESEARCH

Research Report

Exercise intensity influences the temporal profile of growth factors involved in neuronal plasticity following focal ischemia

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ABSTRACT

Exercise increases brain-derived neurotrophic factor (BDNF), phosphorylated cAMP response-element binding protein (pCREB), insulin-like growth factor (IGF-I) and synapsin-I, each of which has been implicated in neuroplastic processes underlying recovery from ischemia. In this study we examined the temporal profile (0, 30, 60 and 120 min following exercise) of these proteins in the hippocampus and sensorimotor cortex following both motorized (60 min) and voluntary (12 h) running, 2 weeks after focal ischemia. Our goal was to identify the optimal training paradigms (intensity, duration and frequency) needed to integrate endurance exercise in stroke rehabilitation. Therefore we utilized telemetry to measure changes in heart rate with both exercise methods. Our findings show that although the more intense, motorized running exercise induced a rapid increase in BDNF, the elevation was more short-lived than with voluntary running. Motorized running was also associated with higher levels of synapsin-I in several brain regions but simultaneously, a more pronounced increase in the stress hormone, corticosterone. Furthermore, both forms of exercise resulted in decreased phosphorylation of CREB and downregulation of synapsin-I in hippocampus beginning 30 to 60 min after the exercise bout. This phenomenon was more robust after motorized running, the method that generated higher heart rate and serum corticosterone levels. This immediate stress response is likely specific to acute exercise and may diminish with repeated exercise exposure. The present data illustrate a complex interaction between different forms of exercise and proteins implicated in neuroplasticity. For clinical application, frequent lower intensity exercise episodes (as in voluntary running wheels), which may be safer to provide to patients with stroke, has a delayed but sustained effect on BDNF that may support brain remodeling after stroke.

1. Introduction

The majority of individuals who survive stroke have enduring motor deficits that affect productivity and quality of life (Duncan et al., 1994; Mayo et al., 2002) and presently, rehabilitative therapy provides the only chance for stroke survivors to improve outcome. Endurance exercise enhances neurogenesis and improves memory and learning (Anderson et al., 2000; Radak et al., 2001; Van Praag et al., 1999), in part by upregulating brain-derived neurotrophic factor (BDNF) which

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in turn elevates cAMP response element binding protein (CREB) and synapsin-I (Vaynman et al., 2004). BDNF is one of a family of neurotrophins that supports neuronal survival, reduces the threshold for long term potentiation (LTP; Kiprianova et al., 1999; Zhou et al., 2000) and facilitates motor recovery after stroke (Schabitz et al., 2004). BDNF by phosphorylating its trkB receptor, activates synapsin-I, a neuron-specific protein that tethers synaptic vesicles to the actin cytoskeleton (Jovanovic et al., 2000). Synapsin-I is upregulated by exercise in normal animals and may contribute to improved performance in cognitive tasks (Vaynman et al., 2004). The transcriptional protein CREB is not only involved in learning and memory but also plays a regulatory role in dendritic spine and filopodium dynamics (Ji et al., 2005). Exercise, by elevating these critical proteins, may facilitate plastic processes that underlie recovery from brain injury. Unfortunately, stroke patients engage in endurance exercise only a few minutes each day (MacKay-Lyons and Makrides, 2002) and the optimal exercise parameters required to enhance these proteins are not known.

We previously reported that, following focal ischemia, motorized running exercise for 30 or 60 min is more effective than voluntary overnight running in the upregulation of BDNF and synapsin-I in the hippocampus and sensorimotor cortex of the intact hemisphere, measured immediately following exercise (Ploughman et al., 2005). Since these brain regions in the contralateral hemisphere contribute to stroke recovery (Biernaskie and Corbett, 2001; Biernaskie et al., 2005), we were interested in optimizing mediators of synaptic plasticity in these areas. For example, the temporal expression of BDNF in the ischemic brain within the first 1–2 h of training has not been investigated. If levels are downregulated rapidly following exercise then rehabilitative training should be scheduled repeatedly so that therapeutic levels are optimized.

In our previous study, the stress hormone corticosterone was elevated immediately following exercise. Since this hormone has been shown to attenuate BDNF expression (Smith et al., 1995; Schaaf et al., 1998; Kuipers et al., 2003), we speculated that serum corticosterone could have a delayed deleterious effect on synaptic plasticity mediators such as CREB, IGF-I and synapsin-I. IGF-I, like BDNF, is a neurotrophin that has been implicated in recovery, angiogenesis (Lopez-Lopez et al., 2004) and protection from brain injury (Carro et al., 2001). Since it is present in both the circulation and parenchyma, we examined both brain and serum levels of IGF-I.

Finally, no study has measured the physiological intensity (i.e. heart rate) of exercise required to increase growth factors and other proteins involved in neuronal plasticity. In order to utilize endurance exercise training to enhance these processes in clinical rehabilitation, the indicators of exercise intensity must be defined. The most common physiological measure of exercise intensity is heart rate, therefore we used telemetry probes to determine resting and exercise heart rate responses to different endurance training methods.

2. Results

Application of endothelin-I resulted in greater than 50% damage to the cortex and striatum. There were no differences in ischemic scores between groups in the cortex (2.77 ± 0.09) or striatum (2.2 ± 0.17). Two animals with minimal injury, scoring 1 or 0 in the cortex and striatum, were excluded from analysis, and the remaining animals' cortical infarcts scored between 2 and 4 (Fig. 1).

Animals in the voluntary running groups ran 1109.86 m ± 162.31 in 12 h while animals in the motorized wheels ran 726 m in 60 min. One animal that ran less than 500 m in 12 h in the voluntary wheel was omitted from the study. There were no differences in running distances in the voluntary running groups ($F_{3,16}=1.24$; $p=0.34$).

2.1. *Hippocampal and cortical BDNF following exercise*

Motorized and voluntary endurance training induced different temporal profiles of BDNF expression directly following exercise in the ischemic hippocampus. There was a significant treatment effect on BDNF levels in the hippocampus of the ischemic hemisphere (Fig. 2; $F_{8,62}=2.66$; $p<0.01$) but not in the intact side ($F_{8,62}=1.47$; $p=0.18$). Following motorized running, elevation of hippocampal BDNF in the ischemic hemisphere was very brief, peaking directly after the exercise challenge (141.16 ± 7.8%; $p<0.01$) but falling to sedentary levels over subsequent sample intervals. In contrast, following the 12 h voluntary run, BDNF elevation in the hippocampus of the ischemic side is sustained, remaining significantly elevated at 30 (136.68 ± 9.62%) and 120 min (140.40 ± 10.14%; $p<0.05$). Motorized exercise did not affect hippocampal BDNF in the intact hemisphere, however after completion of voluntary running, hippocampal BDNF in the intact hemisphere was elevated both immediately (120.35 ± 7.1%) and at 60 min (132.14 ± 10.8%; $p<0.05$).

In the cortex of the intact hemisphere, ANOVA showed no overall effect of group on BDNF ($F_{8,41}=1.66$; $p=0.14$) except for a brief surge at 30 min (121.28 ± 17.12%; $p<0.05$) following the motorized run (data not shown).

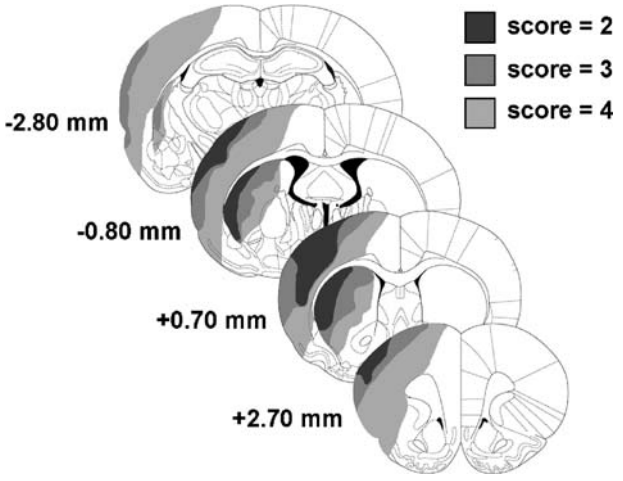

Fig. 1 – Representative sections of rat brain depicting ischemic injury of the cortex and striatum (ischemic score-2, black, ischemic score-3, medium grey, and ischemic score-4, light grey). Coordinates are with respect to bregma (Paxinos and Watson, 1997).