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Research Report

Voluntary exercise regionally augments rates of cerebral protein synthesis

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ABSTRACT

Exercise is a natural form of neurophysiologic stimulation that has known benefits for mental health, maintenance of cerebral function, and stress reduction. Exercise is known to induce an upregulation of brain-derived neurotrophic factor and this is thought to be involved in associated increases in neural plasticity. Protein synthesis is also an essential component of adaptive plasticity. We hypothesized that exercise may stimulate changes in brain protein synthesis as part of its effects on plasticity. Here, we applied the quantitative autoradiographic L-[1-^{14}C]leucine method to the *in vivo* determination of regional rates of cerebral protein synthesis (rCPS) in adult rats following a seven day period of voluntary wheel-running and their sedentary counterparts. In four of 21 brain regions examined, the mean values of rCPS in the exercised rats were statistically significantly higher than in sedentary controls; regions affected were paraventricular hypothalamic nucleus, ventral hippocampus as a whole, CA1 pyramidal cell layer in ventral hippocampus, and frontal cortex. Increases in rCPS approached statistical significance in dentate gyrus of the ventral hippocampus. Our results affirm the value of exercise in encouraging hippocampal and possibly cortical neuroplasticity, and also suggest that exercise may modulate stimulation of stress-response pathways. Ultimately, our study indicates that measurement of rCPS with PET might be used as a marker of brain response to exercise in human subjects.

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1. Introduction

The positive effects of exercise on mental health and maintenance of cerebral function are well established. In addition to promoting longevity, physical exercise reduces risk of anxiety and depression, and is used clinically for their management. Physical exercise also may stave off the effects of cognitive impairments in old age (Gremeaux et al., 2012; Nelson et al., 2007). Additionally, through its relationship with brain-derived neurotrophic factor (BDNF), exercise has been implicated in stress-pathway modulation, adult neurogenesis, neuronal regeneration, and synaptic strengthening

Abbreviations: BDNF, brain-derived neurotrophic factor; LTP, long-term potentiation; rCPS, rates of cerebral protein synthesis; PVN, paraventricular hypothalamic nucleus; SON, supraoptic hypothalamic nucleus; CRH, corticotropin releasing hormone; HPA, hypothalamic–pituitary–adrenal; RM ANOVA, repeated measures analysis of variance

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(Kohman et al., 2012; Marlatt et al., 2012; van Praag et al., 1999). BDNF, a neurotrophin, is involved in various forms of neural plasticity such as axonal and dendritic extension and synaptic strengthening (Cotman et al., 2007; McAllister et al., 1999), and is an essential component of late-phase long-term potentiation (LTP) (Martinez-Moreno et al., 2011). Its expression is activity-dependent. Thus, electrical stimulation via induced seizures, direct electrical stimulation *in vitro*, and physical exercise *in vivo* produce robust increases in both BDNF mRNA expression and BDNF protein concentration in the hippocampus and cortex, suggesting a role in higher-level cognitive functioning such as learning and memory (Cotman and Berchtold, 2002; Cotman et al., 2007; Kornblum et al., 1997; Nawa et al., 1995; Neeper et al., 1996).

It is well documented that protein synthesis plays an essential role in adaptive neural plasticity throughout the brain. Activity-dependent upregulation of mRNA expression (Frey et al., 1996) and protein synthesis (Frey et al., 1988) are necessary features of late-phase LTP, and accordingly, protein synthesis inhibition prevents long-term memory storage (Agranoff, 1981). Consequently, how exercise alters overall brain protein synthesis is of significance, since exercise may serve as a natural and readily accessible means to encourage neural plasticity and stave off cognitive decline due to aging (Nagamatsu et al., 2013).

Given the important role of protein synthesis for memory and neural plasticity, we asked if voluntary exercise in adult rats produces an increase in *in vivo* regional rates of cerebral protein synthesis (rCPS). We used the quantitative autoradiographic L-[1-^{14}C]leucine method (Smith et al., 1988) to evaluate *in vivo* changes in rCPS in young adult rats selected for a voluntary seven day exercise regimen. We chose to study animals after seven days of exercise because of the known changes in BDNF mRNA that take place in the brain following two to seven days of exercise (Neeper et al., 1996). We focused our analysis on 21 brain regions including some regions in which changes in BDNF and other mRNAs are known to occur (*e.g.*, hippocampus and cortex), some regions involved in stress and emotional responses (*e.g.*, amygdala, cingulate cortex, and hypothalamus), and some regions in which we did not expect to find a change (*e.g.*, corpus callosum and caudate nucleus). We report statistically significant increases in rCPS in the ventral hippocampus as a whole, the CA1 pyramidal cell layer of the ventral hippocampus, frontal cortex, and paraventricular hypothalamic nucleus (PVN). Our results affirm the value of exercise to encourage neuroplasticity, modulate stress pathways, and maintain proper cerebral function.

2. Results

2.1. Running behavior

Rats that underwent voluntary exercise were permitted to exercise *ad libitum*. In the 11 exercised rats, we found that running behavior mirrored their natural circadian cycle (Fig. 1), *i.e.*, all rats were more active during the dark phase of the circadian cycle and tended to be quiescent during the light phase. Running distances, however, varied widely among the animals. Animals that ran more did so over the entire duration of the study, and rats that ran less did so consistently. Consequently, the total distance run over the 7-day exercise period varied among the 11 rats. Some weight loss (14.9±11.6 g, mean±SD) was observed during the first three days of exercise in ten of the eleven exercised rats. As the exercise period progressed, all exercised rats gained weight, and at the time of rCPS determination, the weight of exercised rats did not differ significantly from that of sedentary rats (Table 1).

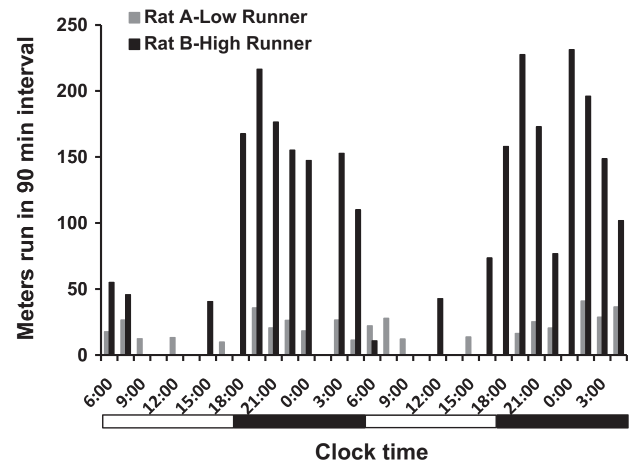

Fig. 1 – Distance run in meters in 90 min intervals by two representative rats over a 48 h period. During their 7 day exercise period, Rat A ran 2,022 m and Rat B ran 8,735 m. The bar below the graph indicates the light-dark cycle for all rats. The blackened portion of the bar indicates lights out time, and the white portion of the bar indicates lights on time in the facility.

2.2. Effects of exercise on cerebral protein synthesis

At the time of rCPS determination, the exercised and sedentary groups were well-matched with respect to the physiological variables measured (Table 1). The effects of exercise on rCPS were determined in 21 regions of the brain (Table 2), and results were analyzed by means of repeated measure analysis of variance (RM ANOVA) with condition (sedentary, exercised) as the between subjects factor and regions as the within subjects factor. The region x condition interaction was statistically significant ($F_{(4.20,\ 54.56)}=2.60$; $p<0.05$), so we proceeded with pairwise comparisons. We found statistically significant ($p<0.05$) increases in rCPS in the exercised rats in four regions: ventral hippocampus as a whole (11.1% effect), CA1 pyramidal cell layer of the ventral hippocampus (9.5% effect), frontal cortex (8.4% effect), PVN (29.8% effect) (Fig. 2). Increases approached statistical significance ($0.05\leq p\leq 0.11$) in the dentate gyrus of the ventral hippocampus (6.5% effect).

Among the exercised rats, rCPS did not appear to vary with distance run. Pearson's correlations were computed between total distance run and rCPS in all 21 regions analyzed. Results revealed no significant relationship between the distance run in the 7-day exercise period and rCPS ($0.26\leq p\leq 0.95$). An additional analysis was conducted in which rats that