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Research Report

Aerobic exercise attenuates inhibitory avoidance memory deficit induced by paradoxical sleep deprivation in rats

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ABSTRACT

The deleterious effects of paradoxical sleep deprivation (SD) on memory processes are well documented. Physical exercise improves many aspects of brain functions and induces neuroprotection. In the present study, we investigated the influence of 4 weeks of treadmill aerobic exercise on both long-term memory and the expression of synaptic proteins (GAP-43, synapsin I, synaptophysin, and PSD-95) in normal and sleep-deprived rats. Adult Wistar rats were subjected to 4 weeks of treadmill exercise training for 35 min, five times per week. Twenty-four hours after the last exercise session, the rats were sleep-deprived for 96 h using the modified multiple platform method. To assess memory after SD, all animals underwent training for the inhibitory avoidance task and were tested 24 h later. The aerobic exercise attenuated the long-term memory deficit induced by 96 h of paradoxical SD. Western blot analysis of the hippocampus revealed increased levels of GAP-43 in exercised rats. However, the expression of synapsin I, synaptophysin, and PSD-95 was not modified by either exercise or SD. Our results suggest that an aerobic exercise program can attenuate the deleterious effects of SD on long-term memory and that this effect is not directly related to changes in the expression of the pre- and post-synaptic proteins analyzed in the study.

1. Introduction

Although the precise function of sleep is not known, it is widely accepted that sleep affects a variety of physiological functions, including those involved in learning and memory (Blissitt, 2001; Diekelmann and Born, 2010). Memory is classically defined as the ability to retain and manipulate previously acquired information by means of neuronal plasticity (Thompson et al., 2002). Indeed, sleep plays a critical role in fostering connections among neuronal networks for memory

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consolidation in the hippocampus, a critical structure for learning and memory processes (Blissitt, 2001; Diekelmann and Born, 2010; Kim et al., 2005; McDermott et al., 2006). Animal studies have demonstrated that the firing patterns of hippocampal neurons during a learning experience are replayed during the subsequent paradoxical sleep period (Louie and Wilson, 2001; Skaggs and McNaughton, 1996). Moreover, there is compelling evidence indicating that memory is impaired by SD. For example, in rodents, the memory in different hippocampus-dependent tasks, such as contextual fear conditioning, the Morris water maze (MWM), and the inhibitory avoidance task (IA), are disrupted by SD (Bueno et al., 1994; Graves et al., 2003; Smith and Rose, 1996).

The neural processing of new memories requires alterations in the protein synthesis, gene expression and structural properties of neurons and synapses (Alberini, 2009; Sultan and Day, 2011). Interestingly, some reports have provided evidence that the sleep/wake cycle may modulate the expression of certain genes implicated in synaptic plasticity and memory, such as brain derived neurotrophic factor (BDNF), synapsin I, calcium–calmodulin-dependent protein kinase II (CAMKII) and the cAMP response element binding protein (CREB) (Cirelli and Tononi, 1998, 2000; Sei et al., 2000; Taishi et al., 2001). Accordingly, in a previous study, Guzman-Marin et al. (2006) observed that the hippocampal expression of BDNF, synapsin I, CAMKII and CREB were reduced after 48 h of paradoxical SD.

Several studies have shown the ability of physical exercise, unlike SD, to ameliorate many aspects of brain function (Cotman et al., 2007; Hamer and Chida, 2009; van Praag, 2008). We recently reported that 8 weeks of endurance or resistance exercise improved the acquisition and retention in the MWM task (Cassilhas et al., 2012a). This finding corroborates previous studies conducted in aging and young rodents that showed physical exercise-induced improvements in various hippocampus-dependent memory tasks (O'Callaghan et al., 2007; Radak et al., 2006; Schweitzer et al., 2006; Vaynman et al., 2004). The mechanism underlying exercise-induced synaptic plasticity requires the involvement of a myriad of molecules implicated in the maintenance and regulation of brain function, including neurotrophic factors, signal transduction proteins, transcription factors and synaptic proteins (Cassilhas et al., 2012a; Cotman et al., 2007; Ding et al., 2004; Lista and Sorrentino, 2010).

Previous studies have extensively demonstrated the deleterious effects of SD on memory and the contrasting beneficial effects of physical exercise on this behavior. However, only one study was conducted to investigate the interaction of the two at the molecular level. Zagaar et al. (2012) observed that 4 weeks of aerobic exercise was able to attenuate the short-term memory loss induced by 24 h of paradoxical SD in rats. Additionally, physical exercise abrogated the detrimental effects of SD on early phase of long-term potentiation (LTP) and rescued hippocampal levels of BDNF and CAMKII. However, given the positive effects of exercise on neurobiology, the molecular mechanisms through which exercise prevents the SD-induced cognitive decline still remain to be explored. Considering that no study, to date, has investigated the effects of physical exercise on long-term memory after prolonged SD periods, the present study aimed to verify the influence of 4 weeks of aerobic treadmill exercise on long-term memory in normal and sleep-deprived rats subjected to an inhibitory avoidance task and to analyze the expression of synaptic proteins (GAP-43, synapsin I, synaptophysin, and PSD-95) with critical roles for synaptic plasticity and memory process.

2. Results

2.1. Inhibitory avoidance

No significant differences were observed in the latency to cross the aversive compartment between groups [$F(3, 31)=1.653$; $p=0.200$] during the training session for the IA task (Fig. 1). However, the latency in the test session was reduced in the SSD group compared with that of the SC group (221.5±40.69 s vs. 514±26.00 s; $p<0.001$, respectively) and between the ExSD and Ex groups (405.5±48.24 s vs. 540.0±0.00 s; $p=0.044$, respectively). Additionally, the ExSD group showed a higher latency to cross the aversive compartment than shown by the SSD group (405.5±48.24 s vs. 221.5±40.69 s; $p=0.004$, respectively). No significant differences were observed in the SC group relative to the Ex and ExSD groups.

2.2. Synaptic protein expression

To verify the underlying mechanisms of the beneficial effects of aerobic exercise on the memory deficits induced by 96 h of paradoxical SD, we conducted western blot analysis of pre- and post-synaptic proteins. Significant differences were observed in the hippocampal levels of GAP-43 [Fig. 2a; $F(3, 19)=4.789$; $p=0.014$]. These increases were observed in the Ex (167±15%; $p=0.015$) and ExSD (156±15%; $p=0.047$) groups relative to the SC group. In contrast, no significant differences were found in the hippocampal expression of the other analyzed proteins: synapsin I (Fig. 2b; $F(3, 19)=0.55$; $p=0.65$); synaptophysin (Fig. 2c; $F(3, 19)=1.241$; $p=0.328$) and PSD-95 (Fig. 2d; $F(3, 19)=2.754$; $p=0.077$).

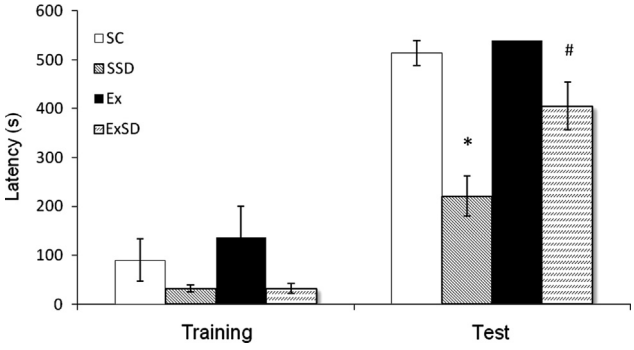

Fig. 1 – Effects of aerobic exercise and paradoxical sleep deprivation on the mean latency to cross to black compartment during training and test session of the inhibitory avoidance task. Sedentary control group (SC, $n=8$), sedentary sleep-deprived group (SSC, $n=8$), exercise group (Ex, $n=8$) and exercise sleep-deprived group (ExSD, $n=8$). Values are expressed as mean±SEM. *Indicates significant difference from SC group and # indicates significant difference from Ex group. One-way ANOVA followed by the Tukey's post hoc test ($P<0.05$).