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Regular treadmill exercise prevents sleep deprivation-induced disruption of synaptic plasticity and associated signaling cascade in the dentate gyrus ☆

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ABSTRACT

Study objectives: Evidence suggests that regular exercise can protect against learning and memory impairment in the presence of insults such as sleep deprivation. The dentate gyrus (DG) area of the hippocampus is a key staging area for learning and memory processes and is particularly sensitive to sleep deprivation. The purpose of this study was to determine the effect of regular exercise on early-phase long-term potentiation (E-LTP) and its signaling cascade in the presence of sleep deprivation.
Experimental design: Rats were exposed to 4 weeks of regular treadmill exercise then subsequently sleep-deprived for 24 h using the modified multiple platform model before experimentation. We tested the effects of exercise and/or sleep deprivation using electrophysiological recording in the DG to measure synaptic plasticity; and Western blot analysis to quantify the levels of key signaling proteins related to E-LTP.
Measurements and results: Regular exercise prevented the sleep deprivation-induced impairment of E-LTP in the DG area as well as the sleep deprivation-associated decrease in basal protein levels of phosphorylated and total α calcium/calmodulin-dependent protein kinase II (P/total-CaMKII) and brain-derived neurotrophic factor (BDNF). High frequency stimulation (HFS) to the DG area was used to model learning stimuli and increased the P-CaMKII and BDNF levels in normal animals: yet failed to change these levels in sleep-deprived rats. However, HFS in control and sleep-deprived rats increased the levels of the phosphatase calcineurin. In contrast, exercise increased BDNF and P-CaMKII levels in exercised/sleep-deprived rats.
Conclusions: Regular exercise appears to exert a protective effect against sleep deprivation-induced spatial memory impairment by inducing hippocampal signaling cascades that positively modulate basal and stimulated levels of key effectors such as P-CaMKII and BDNF, while attenuating increases in the protein phosphatase calcineurin.

Introduction

Accumulating evidence has shown that physical activity in the form of aerobic exercise exerts beneficial effects on cognitive function in humans as well as in laboratory animals (Ang and Gomez-Pinilla, 2007; Berchtold et al., 2005; Cotman and Berchtold, 2002; Cotman et al., 2007). Exercise-induced adaptations in the skeletal muscle have been reported to initiate and modify various signaling mechanisms that can lead to physiologic changes in both muscle and brain neuronal networks (Lista and Sorrentino, 2009). Moreover, the structural and functional consequences of these neuronal adaptations in certain brain areas such as the hippocampus can be manipulated by the type, amount, and duration of exercise (Berchtold et al., 2010; Leasure and Jones, 2008). In animals, prior exercise protects and maintains hippocampus-dependent learning and memory (Grace et al., 2009; Khabour et al., 2009; Nichol et al., 2007), and enhances hippocampal synaptic plasticity and its signaling cascade in the hippocampal Cornu Ammonis 1 area (CA1) (Khabour et al., 2009; Kim et al., 2010; Zagaar et al., 2012). These findings suggest that exercise-induced adaptations at the neuronal level may exert protective effects on cognitive function in the case of brain injury or disease-induced impairments such as stroke and neurodegenerative disorders (Bohannon, 1993; Cotman et al., 2007; Grealy et al., 1999; Kramer et al., 1999).

The concept that exercise is beneficial in the presence of insult has recently been extended to sleep deprivation (SD). We have previously shown that prior exercise protects and maintains hippocampus-dependent learning, memory and synaptic plasticity in the CA1 after 24 h sleep deprivation (Zagaar et al., 2012). Sleep deprivation or irregular sleep patterns are disruptive as the suppression of certain sleep

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stages can negatively impact different types of memory thus resulting in profound cognitive impairment (Belenky et al., 2003; Harrison and Horne, 2000). Increasingly more studies indicate a strong correlation between SD and hippocampal memory impairment, in both animals and humans (Campbell et al., 2002; Davis et al., 2003; Ferrara et al., 2008; Guan et al., 2004; Ishikawa et al., 2006; Kopp et al., 2006; McDermott et al., 2003). These findings support the idea that sleep is important for fostering connections among neuronal networks in the hippocampus and for memory consolidation as well (Kim et al., 2005; McDermott et al., 2006). In this respect, sleep may serve as a privileged time window when the brain is not only free of interference from outside sensory inputs but characterized by distinct neurochemical and electrophysiological patterns that support consolidation of newly acquired memories (Bryson and Schacher, 1969; Diekelmann and Born, 2010).

Experimentally, long-term potentiation (LTP) is considered a substrate for synaptic plasticity and the storage of new information within hippocampal neuronal networks (Malenka and Bear, 2004). Similar to the CA1 area the DG also has two major phases of LTP that require NMDA receptor activation by glutamate, early (E-LTP) and late (L-LTP), which correlate with short- and long-term memory, respectively (Riedel et al., 2003). Like other forms of LTP, E-LTP is subserved by its own distinct kinase cascade, which begins with αCaMKII (CaMKII), an important gatekeeper for LTP induction (Giese et al., 1998; Lledo et al., 1995; Malenka et al., 1989; Pettit et al., 1994; Thomas et al., 1994). CaMKII is a key mediator of hippocampal LTP that can be constitutively activated, until protein phosphatases such as calcineurin dephosphorylate the active CaMKII (P-CaMKII). The effects of calcineurin on learning and memory are largely regulatory so as to limit the saturation of learning and its underlying synaptic processes (Groth et al., 2003). Specifically, calcineurin exerts a powerful effect on LTP by maintaining a crucial balance with P-CaMKII. However, the phosphorylation of CaMKII is of great importance in potentiated synapses because it can also lead to saturation of phosphatase activity, which ensures stable kinase:phosphatase equilibrium. Thus, newly phosphorylated CaMKII can readily enter potentiated synapses and act as a molecular switch to mediate long-term information storage despite changes in CaMKII turnover (Lisman and McIntyre, 2001). Growth factors such as BDNF are thought to enhance phosphorylation of CaMKII by initiating the release of Ca^{2+} from internal stores through the activation of tyrosine kinase B receptor/phospholipase Cγ (TrkB/PLCγ) pathway (Minichiello, 2009). Following induction, the expression phase of LTP leads to long lasting enhancements in synaptic efficacy, enhanced pre-synaptic neurotransmitter release and phosphorylation and trafficking of AMPA receptors (Barria et al., 1997; Vaynman et al., 2006).

The effects of exercise on SD-induced learning and memory impairment have not been fully investigated in the DG area. In the current study animals exercised on treadmills for 4 weeks then sleep-deprived for 24 h using the modified multiple platform method to examine the effects on short-term synaptic plasticity (E-LTP) and key signaling molecules in the DG area of the hippocampus. The current research contributes to a better understanding of the mechanism behind the neuroprotective effects of aerobic exercise in the presence of insult.

Results

Exercise enhances basal synaptic function in the DG area

Baseline fEPSP slopes of responses resulting from stimulating the perforant path-DG synapses were recorded by applying a series of increasing stimulus intensities (i.e. voltages) to construct I/O curves. There were no significant differences between control and sleep-deprived rats since both groups showed progressively increasing slopes as the stimulus intensity was increased. Interestingly the exercised/sleep-deprived group (fEPSP = 9.5 ± 0.86) showed a significantly increased ($p < 0.05$) fEPSP slope especially at maximal voltages (Fig. 1A). The exercised group (9.2 ± 1.1) showed a similar tendency of higher fEPSP slope values toward higher voltages. Moreover, the voltages required to produce the minimum, maximum and 30% maximal fEPSP responses were significantly lower ($p < 0.05$–0.01) in the exercised and exercised/sleep-deprived groups compared to the control and sleep-deprived groups (Fig. 1B).

Regular exercise prevents sleep deprivation-induced impairment of E-LTP in the DG

Application of HFS to the angular bundle area to generate E-LTP in the DG area led to sustained potentiation of the fEPSP slope and pSpike amplitude in all groups except the sleep-deprived group. In the sleep-deprived group, HFS initially generated small increases in the fEPSP slope and pSpike amplitude that gradually decreased toward the baseline 1 h after HFS (fEPSP = 103.25 ± 6.23% and pSpike = 115.8 ± 14.3% of the baseline, $F_{3,\ 15} = 5.14$, $p < 0.001$; Figs. 2A–B). In contrast, 1 h after HFS the exercised/sleep-deprived group showed a sustained increase in the fEPSP slope and the pSpike amplitude (fEPSP = 133.8 ± 8.47% and pSpike = 201.036 ± 24.8%; Figs. 2A, B) that was similar to those of control and exercised rats but significantly different compared to the sleep-deprived group ($p < 0.05$). One hour after HFS, the fEPSP slope and

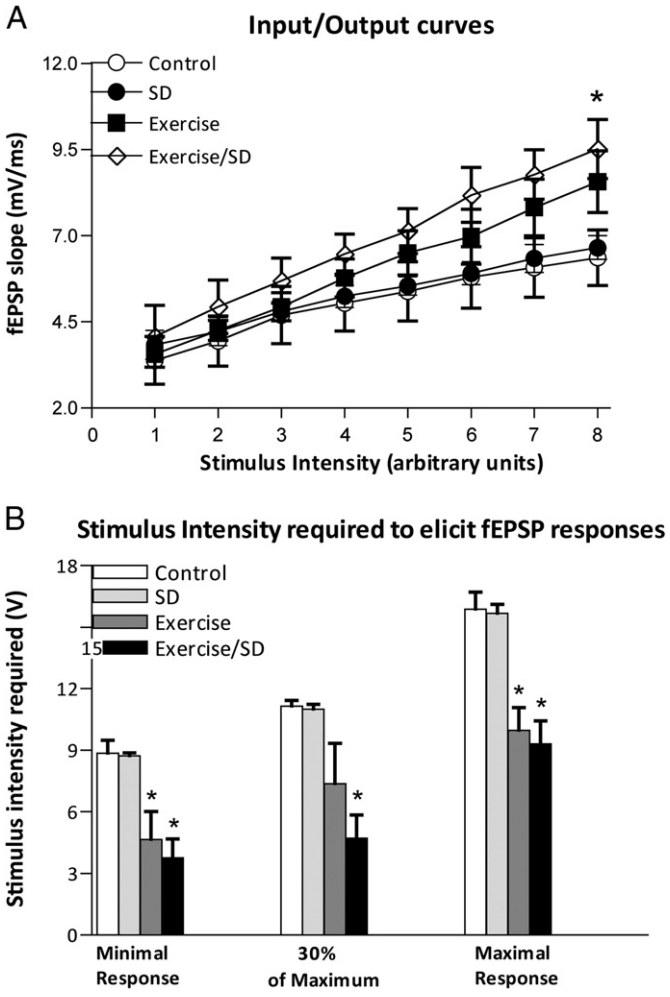

Fig. 1. Basal synaptic transmission is normal in the DG of the sleep-deprived rats and enhanced in exercised rats. (A) input/output curves were obtained from responses to different stimulus intensities in the DG. Stimulus intensity numbers are arbitrary units; where 1 is the intensity that generated minimum responses and 8 is the intensity that generated the maximum responses. (B) Stimulus intensity essential to evoke the minimum, maximum, and 30% of the maximum response. Values are mean ± SEM from 4 to 6 rats. (*) Denotes significant difference ($p < 0.05$–0.01) from control and sleep-deprived groups.