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Research Report

# Exercise differentially regulates synaptic proteins associated to the function of BDNF

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ABSTRACT

We explored the capacity of exercise to impact select events comprising synaptic transmission under the direction of brain-derived neurotrophic factor (BDNF), which may be central to the events by which exercise potentiates synaptic function. We used a specific immunoadhesin chimera (TrkB-IgG) that mimics the BDNF receptor, TrkB, to selectively block BDNF in the hippocampus during 3 days of voluntary wheel running. We measured resultant synapsin I, synaptophysin, and syntaxin levels involved in vesicular pool formation, endocytosis, and exocytosis, respectively. Synapsin I is involved in vesicle pool formation and neurotransmitter release, synaptophysin, in the biogenesis of synaptic vesicles and budding, and syntaxin, in vesicle docking and fusion. Exercise preferentially increased synapsin I and synaptophysin levels, without affecting syntaxin. There was a positive correlation between synapsin I and synaptophysin in exercising rats and synapsin I with the amount of exercise. Blocking BDNF abrogated the exercise-induced increases in synapsin I and synatophysin, revealing that exercise regulates select properties of synaptic transmission under the direction of BDNF.



## 1. Introduction

Exercise has the capacity to induce hippocampal synaptic plasticity, prominently enhancing synaptic efficacy (Farmer et al., 2004; Vaynman et al., 2003) and the expression of molecules implicated in learning and memory (Farmer et al., 2004; Vaynman et al., 2003, 2004). These molecular changes may comprise the ability of exercise to impact behavioral plasticity, i.e. to improve learning and memory (Fordyce and Wehner, 1994; Kramer et al., 1999) and reduce the mental decline associated with aging (Laurin et al., 2001). Specifically, exercise-induced synaptic plasticity in the hippocampus, a site critical for learning and memory, may sub-serve the ability of exercise to enhance hippocampal-dependent cognitive function.

Exercise alters molecules implicated in learning and memory functions, distinctly increasing hippocampal brain derived neurotrophic factor (BDNF; Molteni et al., 2004; Neeper et al., 1995; 1996; Vaynman et al., 2004). BDNF modulates synaptic-plasticity in the adult brain (Lo, 1995), and has the capacity to modify synaptic function in the hippocampus by modulating the efficacy of neurotransmitter release (Kang and Schuman, 1995). However, it remains to be determined if exercise impacts events constructing

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vesicular release properties and the role of BDNF in these events.

In the present study, we selected a group of molecules involved in synaptic transmission, i.e., synapsin I, synaptophysin, and syntaxin, which have distinct actions on vesicle clustering, endocytosis, and exocytosis, respectively, and which may comprise main events characterizing synaptic function during exercise. Synapsin I is a member of a family of terminal specific phosphoproteins involved in synaptic vesicle clustering and release, which mediates synaptic transmission (Jovanovic et al., 1996). Synaptophysin is a specific component of the membrane of presynaptic vesicles, and possibly important for the biogenesis of synaptic vesicles, vesicle budding, and endocytosis (Daly et al., 2000; Tartaglia et al., 2001). Syntaxin, localized to the presynaptic plasma membrane, plays a crucial role in the docking and fusion of vesicles during neurotransmitter release (McMahon and Sudhof, 1995). We used a specific immunoadhesin chimera (TrkB-IgG) that mimics the BDNF receptor TrkB to selectively block the function of BDNF and measured the protein levels of synapsin I, synaptophysin, and syntaxin in the hippocampus following 3 days of exercise. Our results demonstrate that exercise uses BDNF to selectively modulate the levels of synapsin I, and synaptophysin but not that of syntaxin in the hippocampus.

## 2. Results

### 2.1. *Effect of blocking BDNF action during exercise on vesicle associated proteins*

Quantitative analysis of Western blot assay revealed that 3 days of exercise significantly ($P < 0.05$) increased synapsin I levels in the hippocampus (133 ± 12%) compared to sedentary/cytC controls (Fig. 1A). Fig. 1A shows a significant difference between the Exc and Sed group, Exc and Exc/IgG group, and Exc and the sed/IgG group ($P < 0.05$). Exercise significantly ($P < 0.05$) increased synaptophysin in the hippocampus (202 ± 25%) above sedentary/cytC controls (Fig. 1B), but did not significantly alter syntaxin levels (106 ± 14%) from sedentary/cytC controls (Fig. 1C). Fig. 1B shows significant changes between the Exc and sed control, Exc and Exc/IgG, and Exc and Sed/IgG ($P < 0.05$). Blocking the action of BDNF effectively prevented the exercise-induced increases in synaptic plasticity markers, by reducing synapsin I (133 ± 12% to 58 ± 4%), below sedentary control levels (Fig. 1A) and synaptophysin by (202 ± 25% to 119 ± 21%) to approach control levels (Fig. 1B). Blocking BDNF action during the sedentary condition significantly ($P < 0.05$)

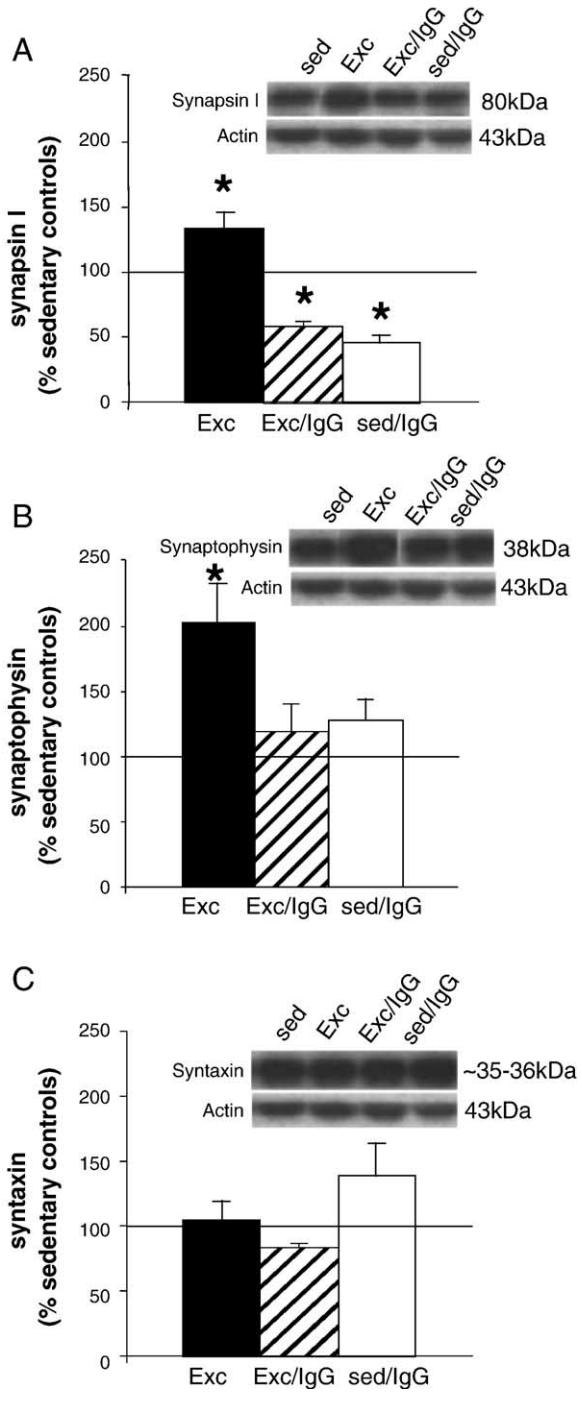


**Fig. 1 – Effect of exercise and blocking BDNF action on (A) synapsin I, (B) synaptophysin, and (C) syntaxin proteins in the hippocampus. Exercise significantly increased the expression of synapsin I and synaptophysin (without affecting the expression of syntaxin). Blocking BDNF action inhibited the upregulation of synapsin I and synaptophysin proteins induced by exercise in the hippocampus. Blocking BDNF action during the sedentary condition reduced synapsin I levels below sedentary/cytC controls but did not significantly alter synaptophysin and syntaxin levels. Representative immunoblots for synapsin I, synaptophysin, and syntaxin of each group are shown to the right of the graph, with actin as an internal standard control. Each value represents the mean ± standard error of the mean (SEM) (*$P < 0.05$; ANOVA). Exc ($n = 5$) = exercise/cytC, Exc/IgG ($n = 6$) = exercise/TrkB-IgG, Sed/IgG ($n = 6$) = sedentary/TrkB-IgG. Sedentary/cytC ($n = 5$) controls are represented by the 100% horizontal line, such that the statistical significance of protein levels for exercise animals is represented compared to this line.**