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Brain-derived neurotrophic factor mediates cognitive improvements following acute exercise

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ABSTRACT

The mechanisms causing improved cognition following acute exercise are poorly understood. This article proposes that brain-derived neurotrophic factor (BDNF) is the main factor contributing to improved cognition following exercise. Additionally, it argues that cerebral blood flow (CBF) and oxidative stress explain the release of BDNF from cerebral endothelial cells. One way to test these hypotheses is to block endothelial function and measure the effect on BDNF levels and cognitive performance. The CBF and oxidative stress can also be examined in relationship to BDNF using a multiple linear regression. If these hypotheses are true, there would be a linear relationship between CBF + oxidative stress and BDNF levels as well as between BDNF levels and cognitive performance. The novelty of these hypotheses comes from the emphasis on the cerebral endothelium and the interplay between BDNF, CBF, and oxidative stress. If found to be valid, these hypotheses would draw attention to the cerebral endothelium and provide direction for future research regarding methods to optimize BDNF release and enhance cognition. Elucidating these mechanisms would provide direction for expediting recovery in clinical populations, such as stroke, and maintaining quality of life in the elderly.

Introduction

Acute bouts of aerobic exercise have been shown to improve cognitive performance on a variety of tasks [1–3]. However, the precise mechanism(s) that mediate cognitive improvements are not well understood. Commonly studied mechanisms that may play a role in the effects of acute exercise on cognition are cerebral blood flow (CBF) and brain-derived neurotrophic factor (BDNF) [1,3–9]. Another potential factor, that is less studied in relation to cognitive improvements following acute exercise, is oxidative stress [3,4,10]. As outlined in Fig. 1A, the current article hypothesizes: (i) that BDNF released from cerebral endothelial cells mediates the effect of acute aerobic exercise on cognition: (ii) BDNF release is best explained by shear stress from cerebral blood flow and protection against oxidative stress. This article will begin with an explanation of what is known about CBF, BDNF, and oxidative stress in relation to exercise-induced improvements in cognitive performance. Then it will outline the current hypotheses, outline considerations for testing the hypothesis, and discuss the implications of the potential findings.

Cerebral blood flow (CBF)

A traditional hypothesis for exercise-induced cognitive improvements is that increased CBF makes more oxygen and glucose available for metabolic functions and improves the clearance of metabolic waste [11,12]. During aerobic exercise, CBF rises with increasing exertional intensity, but declines at very hard intensities [5,6,13–15]. There is evidence that the increase in blood flow due to exercise may be sustained for up to 30 min following termination of the activity [16,17]. It is logical that this hyper-perfusion could improve cognition, as hypoperfusion in specific regions of the brain have been associated with various forms of dementia [18]. However, there is mixed evidence as to whether increases in blood flow are actually casually linked to improved cognition [5,13,14,17,19,20].

Although CBF is vital to optimal brain health, increases in CBF do not completely explain cognitive improvements following acute exercise [5]. Blood pressure and flow to the brain are highly regulated [21]. Consequently, the mean effect sizes of cognitive improvements in studies assessing CBF are significant but small [22]. In other words, there is strong evidence that CBF increases during and following moderate-intensity aerobic exercise, but the magnitude of the difference is small. As such, these small CBF improvements do not appear to be the singular, direct cause of

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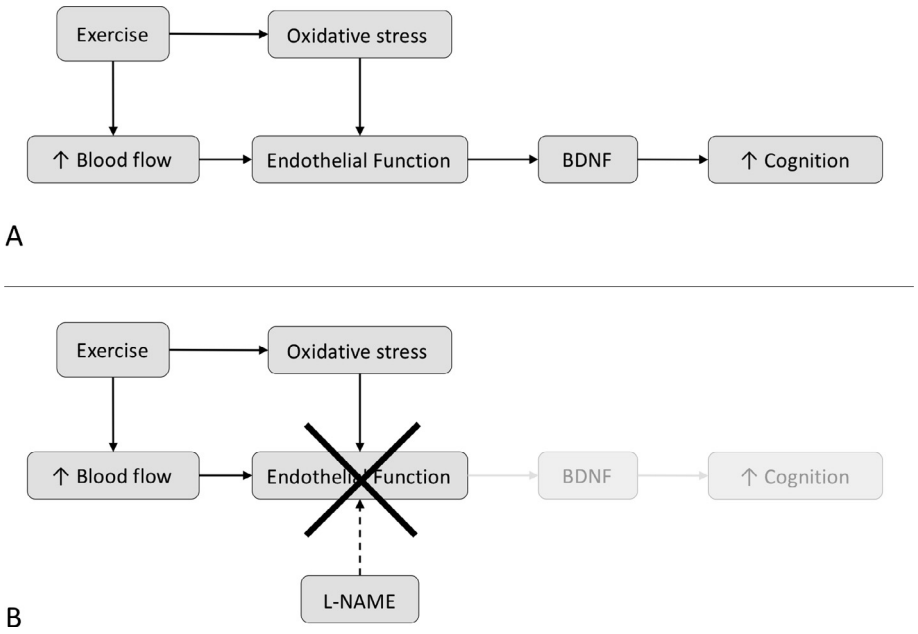

Fig. 1. A. Hypothesis regarding the mechanism of improved cognition following exercise. B. Disruption of endothelial function diminishes BDNF release and cognitive improvements following exercise. This diagrams outlines the proposed study design, in which endothelial function is inhibited by L-NAME, a nitric oxide inhibitor.

cognitive improvements [5]. However, CBF could be related to cognitive performance through an intermediary such as BDNF.

Brain-derived neurotrophic factor (BDNF)

BDNF is a protein that promotes neuroplasticity: the growth and survival of neurons, regulation of axonal and dendritic branching, and synaptic transmission [7,23–25]. More generally, neuroplasticity refers to the responsiveness of the nervous system, and elevations in BDNF have been linked to measurable improvements in cognition [7,23]. Some of the greatest benefits have been seen in executive function [4]. The most plausible mechanisms by which BDNF promotes neuroplasticity involve increasing messenger RNA levels of calcium, cyclic adenosine monophosphate response-element-binding protein (CREB), and synapsin I [22,25]. These pathways increase the rate of transmission, leading to shorter reaction times and processing speeds [22,25]. This may explain the window of opportunity following aerobic exercise when cognition is improved, as these processes happen downstream from BDNF release [7,22,25].

BDNF levels increase during and following aerobic exercise, but the precise mechanism is not well understood [7,26]. In rodent studies, high intensity exercise was the most effective means of increasing BDNF concentrations [3,26,27]. These findings were replicated in human studies that measured serum BDNF levels, and assumed that peripheral measures of BDNF correlated with cerebral concentrations [7]. CBF is known to decrease slightly during high-intensity exercise, therefore, it does not completely explain BDNF release [6,7,14]. At high intensities, oxidative stress becomes more prevalent [9]. Thus, oxidative stress is a conceivable factor contributing to BDNF release at higher intensities of exercise [9] (Fig. 1A).

Oxidative stress

Oxidative stress, which refers to an imbalance between free radicals and antioxidant defenses [28], has many deleterious effects including, protein and DNA damage, toxicity, and neuronal death [28]. The brain is highly susceptible to oxidative stress because it is a large consumer of oxygen (~20% of total body consumption) [11,12]. As an antioxidant defense, brain microvascular endothelial cells release nitric oxide following maximal exercise [29]. Brain endothelial cells are also known to release BDNF [8,9]. It is possible that BDNF is secreted during aerobic exercise to combat neuronal cell damage due to oxidative stress. This protective mechanism is the key process identified in the current hypotheses (Fig. 1A).

Hypotheses

The current hypotheses are that: (i) BDNF released from brain microvascular endothelial cells is the main factor contributing to improved cognition following aerobic exercise, and (ii) CBF and oxidative stress explain the increase in BDNF levels following exercise (Fig. 1A).

These hypotheses speculate that at lower intensities of exercise, increased CBF causes shear stress, leading to a moderate release of BDNF. At higher intensities, oxidative stress becomes more prominent, leading to a marked increase in BDNF release. If these postulations are true, BDNF release would be strongly associated with a model incorporating CBF and oxidative stress together.

The novelty of these hypotheses comes from the emphasis on the cerebral endothelium. Additionally, no previous models have examined BDNF as a function of CBF and oxidative stress combined. Prior theories have been centered around increased blood flow or BDNF in isolation, rather than exploring a relationship between CBF, BDNF, and oxidative stress.

Evaluation of hypotheses

To test the outlined hypotheses, there are a number of considerations regarding participant selection, study design, methods of measurement, and statistical analyses. Special attention must be given to the measurement of BDNF levels. Additionally, brain endothelial function and exercise intensity need to be manipulated in a way that would establish a more direct link between BDNF levels and cognitive performance. Lastly, modality and volume may also impact cognition. All of these considerations are outlined in the following sections.