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Review

Brain-derived neurotrophic factor (BDNF) as a potential mechanism of the effects of acute exercise on cognitive performance

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Abstract

The literature shows that improvements in cognitive performance may be observed following an acute bout of exercise. However, evidence in support of the biological mechanisms of this effect is still limited. Findings from both rodent and human studies suggest brain-derived neurotrophic factor (BDNF) as a potential mechanism of the effect of acute exercise on memory. The molecular properties of BDNF allow this protein to be assessed in the periphery (pBDNF) (i.e., blood serum, blood plasma), making measurements of acute exercise-induced changes in BDNF concentration relatively accessible. Studies exploring the acute exercise–pBDNF–cognitive performance relationship have had mixed findings, but this may be more reflective of methodological differences between studies than it is a statement about the role of BDNF. For example, significant associations have been observed between acute exercise-induced changes in pBDNF concentration and cognitive performance in studies assessing memory, and non-significant associations have been found in studies assessing non-memory cognitive domains. Three suggestions are made for future research aimed at understanding the role of BDNF as a biological mechanism of this relationship: 1) Assessments of cognitive performance may benefit from a focus on various types of memory (e.g., relational, spatial, long-term); 2) More fine-grained measurements of pBDNF will allow for the assessment of concentrations of specific isoforms of the BDNF protein (i.e., immature, mature); 3) Statistical techniques designed to test the mediating role of pBDNF in the acute exercise-cognitive performance relationship should be utilized in order to make causal inferences.

Keywords: Isoforms; Mediators; Memory; Mental health; Physical activity

1. Introduction

Meta-analytic reviews support that acute exercise has beneficial effects on cognitive performance.[1,2] These effects are reasonably robust, but are generally small in magnitude (effect size (ES) = 0.11–0.20). One direction that is important for future research in this area is to further our understanding of the mechanisms underlying these cognitive benefits. The current lack of understanding concerning mechanisms has created a gap in the knowledge base that has hindered the design of efficient exercise programs intended to generate the largest possible cognitive benefits. Bridging this gap will bring about a vertical growth in knowledge that will ultimately facilitate the creation of exercise prescription strategies that are aimed at improving cognition and brain health.

In reviewing the extant literature, it is clear that there are several active lines of research designed to advance our understanding of how acute exercise may affect cognitive performance. However, much of this work has been focused on the effects of acute exercise on cognitive tasks performed during exercise. For example, Dietrich and Audiffren[3] explained how the reticular-activating hypofrontality model uses a combination of neuroscience, cognitive psychology, and functional neuroanatomy to explain the effects of acute exercise on concomitant cognitive performance and brain activation. Additionally, the relationship between catecholamines (i.e., epinephrine, norepinephrine, dopamine) and cognitive

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performance during acute exercise have been explored.[4] However, the interest of this review is on post-exercise cognitive effects and in particular on the potential role of brain-derived neurotrophic factor (BDNF) as a biological mechanism of the effects. The focus on BDNF is reflective of its demonstrated importance to cognitive performance (i.e., memory),[5,6] its unique molecular properties which allow it to be assessed in the periphery,[7,8] and evidence supporting its responsiveness to exercise.[9]

1.1. BDNF and cognitive performance

As a family of proteins, neurotrophic factors, or "growth factors", are directly involved in neuronal and synaptic growth. The BDNF protein in particular is vital for cognitive performance in the short-term and for adaptations in brain morphology (e.g., plasticity) in the long-term. Indeed, the importance of BDNF for cognitive performance is a line of research that has been given a great amount of attention.[5,6,10] Much of the focus in terms of the effects of BDNF on cognitive performance has been on memory tasks. Since the hippocampus has been identified as a major area of BDNF expression[11] and is widely accepted as being vital to the performance of memory, this is a theoretically appropriate method of cognitive assessment relative to BDNF expression.

The strongest evidence for the role of BDNF in cognitive performance comes from the relatively large body of literature using rodent models to elucidate the role of BDNF on memory. As examples of this strong evidence, there are two particular studies that provide clear demonstrations of the critical role of BDNF in memory. Mu et al.[6] administered neural injections of a BDNF antibody, which effectively deprived the subjects of endogenously expressed hippocampal BDNF, to assess the impact on spatial learning and memory as assessed by the Morris water maze. Their results showed that the animals deprived of BDNF experienced declines in cognitive performance compared to controls, thus illustrating the importance of BDNF for cognitive performance. Conversely, Cirulli et al.[5] took the approach of artificially increasing BDNF to examine the effects on spatial learning and memory. In their study, which was also conducted with rodents and which used a similar form of the Morris water maze, they administered neural injections of exogenous BDNF. Results showed improvements in cognitive performance in rodents that received neural injections of exogenous BDNF compared to controls. Thus, through two different methods of inquiry, these two studies illustrated the importance of the involvement of BDNF in the cognitive processes of spatial learning and memory.

In addition to the animal literature supporting the putative role of BDNF, there is also some very limited evidence with humans. Correlational evidence with older adults has shown that peripheral measures of BDNF (pBDNF) are associated with hippocampal volume and spatial memory.[12] Erickson et al.[12] performed a cross-sectional study, utilizing MRI, enzyme-linked immunosorbent assays (ELISA's), and measures of spatial memory to assess the association between age-related decreases in brain volume, pBDNF, and memory in older adults. Results indicated that older participants had significantly lower concentrations of pBDNF, smaller hippocampal volumes, and worse performance on spatial memory tasks as compared to younger participants. Additionally, the results showed that lower levels of pBDNF were significantly associated with smaller hippocampal volumes and worse memory regardless of the age of the participant. Other studies have demonstrated that there are negative associations between measures of pBDNF and severity of cognitive decline due to Alzheimer's disease.[13,14] Laske et al.[13,14] performed cross-sectional studies to assess pBDNF concentrations between older adults with Alzheimer's disease and healthy controls. Results showed that concentrations of pBDNF were significantly lower in those with Alzheimer's disease compared to controls providing evidence in support of a link between BDNF and cognitive performance. The evidence from these studies illustrates the importance of pBDNF for cognitive performance and brain health, two related but potentially independent constructs, as well as the potential use of pBDNF concentrations as a biomarker for the form and function of the brain.

Research has identified BDNF as playing an instrumental role in the form and function of the brain. In particular, rodent studies have produced robust evidence for the role of BDNF for spatial learning and memory. Additionally, correlational studies in humans have illustrated how BDNF concentrations are not only related to spatial memory performance and the volume of brain regions important for memory in healthy older adults, but are also a potential biomarker for Alzheimer's disease.

1.2. Exercise and BDNF expression

In contrast to the limited evidence supporting a link between pBDNF, brain structure, and brain function in humans, there is a larger body of literature supporting a relationship between acute exercise and pBDNF. This line of research is critical if we are to understand the role of pBDNF as a potential mechanism of the acute exercise-cognitive performance relationship. A recent review by Knaepen et al.[9] described the positive relationship between exercise intensity and pBDNF concentrations. The evidence suggested a dose-response relationship between acute exercise and pBDNF concentrations, with high intensity and graded exercise tests eliciting the greatest exercise-induced increases in pBDNF concentration in healthy participants. Importantly, the increase in pBDNF concentrations following acute exercise has been shown to be somewhat durable following conclusion of the exercise, but to return to baseline levels after a delay of 10−60 min. In addition to the evidence supporting a dose-response effect, there is also evidence that increases in pBDNF concentrations can be observed in response to a variety of exercise protocols and modalities (e.g., step tests, VO_{2max} tests, sub-maximal endurance exercise, sub-maximal sprints).[15–20] Rasmussen et al.[17] and Tang et al.[18] observed effects that highlight the stability of this acute exercise-induced increase in pBDNF in