Research Report

Downstream Consequences of Exercise Through the Action of BDNF

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Abstract. Physical exercise produces many beneficial responses in the brain, which affect cognitive function, blood flow, neurogenesis and resistance to injury. However, the exact mechanisms whereby exercise produces an induction in the brain are not well understood. A significant consequence is the induction of growth factors, such as Brain-derived Neurotrophic Factor (BDNF). Cognitive decline that occurs with aging, as well as progression of neurodegenerative diseases, are strongly correlated with decreases in BDNF. In this article, we discuss the properties of neurotrophins and the mechanisms that can account for the ability of exercise to promote brain plasticity through BDNF.

Keywords: Exercise, BDNF, psychiatric diseases, memory

INTRODUCTION

Exercise induces positive responses in the brain and can ameliorate the symptoms of depression [1, 2]. Many studies indicate there are pronounced structural brain changes that occur after motor training and voluntary exercise. One mechanism to account for the changes in brain morphology and plasticity engendered by exercise is through the action of growth factors [3]. Many growth factors affect the survival, growth and differentiation of the nervous system. The neurotrophins, comprising of NGF, BDNF, NT-3, NT-4, are best understood and most widely expressed in the nervous system. Other factors that have an impact include IGF-1, CNTF and TGF-β. A large focus of attention has been on BDNF, which dramatically increases with exercise and is able to improve metabolism and enhance connectivity between neurons.

While the biological roles for neurotrophins were initially characterized in the early development of the nervous system, it is now clear that they have multiple roles in the adult nervous system, such as regulating synaptic connections, synapse structure, neurotransmitter release, long-term potentiation, mechanosensation, pain and synaptic plasticity [4, 5]. Alterations in neurotrophin levels have been implicated in neurodegenerative disorders such as Alzheimer disease, and as well as psychiatric disorders such as depression and substance abuse [6].

BACKGROUND

The neurotrophins are initially synthesized as precursors or pro-neurotrophins that are cleaved to release the mature, active proteins. The mature proteins, approximately 12 to14 kDa in size, form stable, non-covalent dimers and are normally expressed at very low levels during development, that facilitates competition for trophic support. Pro-neurotrophins are cleaved

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intracellularly by furin or pro-convertases utilizing a highly conserved dibasic amino acid cleavage site to release carboxy-terminal mature proteins [7].

Neurotrophins exert their cellular effects through the actions of two different receptors, the Trk receptor tyrosine kinase and the p75 neurotrophin receptor (p75^{NTR}), a member of the tumor necrosis factor (TNF) receptor superfamily. Mature neurotrophins selectively bind to members of the tropomyosin-related kinase (Trk) family of receptor tyrosine kinases to regulate neuronal survival, differentiation and synaptic plasticity. In addition, all mature neurotrophins interact with p75^{NTR} which can modulate the affinity of Trk-neurotrophin associations [4].

NGF was the first identified neurotrophic factor, and has a restricted distribution within the neurotrophin family. In the central nervous system, NGF promotes the survival and functioning of cholinergic neurons in the basal forebrain. These neurons project to the hippocampus, and are believed to be important for memory processes, which are specifically affected in Alzheimer disease. In the peripheral nervous system, it acts on sympathetic neurons, as well as sensory neurons involved in nociception and temperature sensation. BDNF was purified from brain extracts in 1982 and subsequently cloned and shown to be closely related in structure to NGF [8, 9]. The subsequent identification of neurotrophin-3 and neurotrophin-4 (NT-3 and NT-4) established a small family of related ligands and receptors. These neurotrophins are more widely expressed in the CNS than NGF. BDNF and NT-3 are highly expressed in cortical and hippocampal structures, and have been linked to the survival and functioning of multiple neuronal populations.

SYNAPTIC PLASTICITY

Many neuronal populations are not only dependent upon neurotrophins for their survival, but also for modulating neuronal activity. Neurotrophic factors play significant roles in influencing synaptic plasticity in the adult brain. Regulation of synaptic plasticity in the visual system was illustrated by the formation of ocular dominance columns in layer 4 of the cortex, which can be strongly influenced by exogenous neurotrophins such as BDNF [10]. Also, the effects upon the visual system can be observed using blocking antibodies for the neurotrophins, as well neurotrophin antagonists (TrkB-IgG fusion proteins that bind neurotrophins), indicating that an alteration in the levels of endogenous neurotrophins provided dramatic consequences.

Regulation of synaptic plasticity in the adult brain has also been demonstrated prominently in the hippocampus. BDNF promoted the induction of a prolonged strengthening of synapses, termed long term potentiation (LTP) in hippocampal slices, while blocking reagents such as the TrkB-IgG fusion protein interfered with the induction of LTP [11]. In addition, hippocampal preparations containing little or no BDNF gave rise to the same reduction in LTP, suggesting that there was a minimal quantity of BDNF required for the modulation of LTP. Subsequent addition of extra BDNF or adenoviral expression of BDNF to these preparations from mutant mice could LTP. Neurotrophins have also been shown to evoke other forms of synaptic transmission. Exogenous BDNF or NT-3 has been shown to induce enhanced evoked responses in both hippocampal preparations as well as neuromuscular junction. Thus, neurotrophins can modulate synaptic strengthening and neurotransmission, as well as promoting cell survival and axonal and dendritic growth.

A key observation that led to the consideration of neurotrophins in plasticity came from the realization that neuronal activity increased the secretion of neurotrophins, which result in the reinforcement and stabilization of synaptic connections [12]. In addition, neurotrophins can increase neurotransmitter release from neurons during activity. Other key experiments indicated that limbic seizure resulted in a dramatic increase in mRNA encoding NGF and BDNF in the hippocampus. *In situ* hybridization to BDNF mRNA indicated large increases 2–4 hours following seizure in the dentate gyrus, CA1 and CA3 regions of the hippocampus and the neocortical areas [13, 14]. These results indicate that activity-dependent regulation of neurotrophic factors occurs and suggests that other physiological stimuli, such as depolarization, neurotransmitters, light, hormones and exercise may also influence the expression and levels of neurotrophins.

RELATIONSHIP OF EXERCISE AND BDNF

Over the past two decades, many studies in humans have demonstrated the positive effects of physical exercise on function and plasticity [1, 3]. These effects have been particularly relevant in aging populations. Indeed, studies reveal that physical activity decreased the risk of cognitive impairment, dementia, and Alzheimer's disease (AD). Currently, there is a clinical trial (ADEX trial) being conducted to assess whether exercise can improve cognition and reduce

the incidence of psychiatric symptoms in patients with mild AD [15].

In animal models, exercise induces BDNF mRNA expression in the multiple brain regions, specifically in the hippocampus. On the other hand, blocking BDNF signaling attenuates the exercise-induced improvement of spatial learning tasks [16], as well as the exercise-induced expression of synaptic proteins [17]. Animal studies have also demonstrated the beneficial effect of exercise on brain function. Exercise improves cognition and hippocampal plasticity in APOE ε4 mice [18], improves cognitive performance [19] and decreases amyloid [20, 21] by altering the immune profile in Tg2576 Alzheimer mice [21]. In addition, exercise improves memory consolidation in aged animals in a time-dependent manner [22].

Exercise is also relevant to Parkinson's disease, in which BDNF has been found to be down-regulated. Activity-dependent expression of BDNF through running results in neuroprotective effects upon dopaminergic neurons [23]. A promising approach is to increase the availability of BDNF, which promotes the survival and neurite outgrowth of dopaminergic neurons by activating the TrkB receptor tyrosine kinase. BDNF is one growth factor that can alleviate the symptoms of Parkinson's disease by keeping dopaminergic neurons alive and promoting synaptic connections. Others include Glial-derived neurotrophin factor (GDNF) and related family members [24]. Another neuropsychiatric disorder, Huntington's disease, displays a considerable reduction in BDNF levels [25] may be responsive to the therapeutic effects of exercise.

Exercise is not only protective in neurodegenerative disease animal models, but also against acute insults to the central nervous system (CNS), such as spinal cord injury [26, 27]. This protective effect was associated with changes in gene expression in the spinal cord [28]. Indeed, combining exercise with a diet rich in antioxidants results in decreased levels of activated caspase-3 and this reduction in caspase-3 correlated with enhanced frontal cortex function [29].

Increases of neurotrophins from physical exercise can influence common physiological processes in the central nervous system ranging from spatial learning and cognition to stress and depression [30]. Interestingly, hallmarks of stress and depression are hypersecretion of glucocorticoids, decreased brain BDNF levels and TrkB signaling and hippocampal degeneration. One hypothesis to account for glucocorticoid resistance is that additional stress-sensitive pathways influence GR function. For example, BDNF is essential for the enhancement of contextual fear memories by glucocorticoids [31]. In contrast, BDNF deficiency diminished the complexity of hippocampal dendritic territories with no further atrophy by stress [32]. Insights into how glucocorticoids and BDNF influence adaptive and maladaptive actions that are relevant to memory formation, stress response and depression [33].

MECHANISM OF ACTION

Many hypotheses have been proposed to explain the positive effects of exercise on brain function. The benefits of exercise in the brain are mediated through many growth factors, among which BDNF is the most prominent. Early studies in rodents demonstrated that several days of voluntary wheel running increased BDNF mRNA and protein in the hippocampus [34]. These changes were specific to the neurons of the dentate gyrus, the hilus and the CA3 region [35]. The increase in BDNF mRNA was observed within days of voluntary running in both females and male rats and was sustained even after several weeks. Increases in BDNF mRNA were also detected in the lumbar spinal cord [36], the cerebellum and the cortex, but was not in the striatum [37]. Voluntary exercise also enhances the process of learning. Indeed, running enhances LTP in the DG and improves spatial learning in the Morris water-maze assay [38]. Considering that increases in BDNF facilitate learning, the role of BDNF signaling was tested in exercise-induced learning processes [39]. Inhibiting BDNF-TrkB receptor signaling led to decreases in both exercise-induced spatial memory acquisition and maintenance [39]. Moreover, inhibition of BDNF/TrkB signaling attenuated the exercise-mediated induction in CREB mRNA expression and CREB protein phosphorylation.

Taken together, these results implicated BDNF signaling in mediating the positive effects of exercise on the brain and memory formation through a CREB-mediated mechanism. Moreover, the combination of exercise and the antidepressant imipramine treatment leads to an additive induction of BDNF levels within the hippocampus suggesting that exercise may be a potential enhancer to antidepressant treatment through BDNF induction [40]. Even though these results demonstrated an important role for BDNF signaling in mediating exercise-induced effects on the brain, the mechanism by which exercise induces BDNF expression have remained elusive.

A recent study has implicated two muscle-specific proteins, Errα and PGC1α in the induction of the

expression of the myokine Fndc5, which in turn was shown to induce BDNF expression [41]. Even though this study has advanced our understanding of the molecular mechanism underlying the exercise-mediated induction of BDNF, several questions remain. For example, even though peripheral injection of Fndc5 led to increases in BDNF expression in the hippocampus, the cleavage product of Fndc5, irisin, did not. These observations raised the possibility that though an exercise factor may be derived from Fndc5 to augment BDNF expression, there may be other factors aside from irisin [54, 55]. Another caveat was that a loss in BDNF induction in response to exercise was not observed in the absence of Fndc5. The results were also confounded by the observation that exercise induces the expression of Fndc5 both in the periphery and in hippocampal neurons. The precise role of exercise-induced Fndc5 in mediating BDNF expression therefore remains unclear. As a result, it remains uncertain whether Fndc5 production is responsible for the induction of BDNF expression. Another question that was raised by the study concerns the factors that interconnect the periphery and the CNS during exercise and that result in the induction of PGC1α and Errα expression in the hippocampus.

Even though the signaling pathways between the muscle and CNS during exercise are being clarified, not all the mechanisms responsible for BDNF induction from physical exercise have been identified. One mechanism that may link peripheral tissues, such as muscle and liver, to CNS are molecules produced through increased metabolism during exercise that may function to regulate epigenetic modulators. Epigenetics lies at the intersection of the environment and changes in gene expression. One can speculate that molecules produced by the higher metabolic rate achieved during exercise can serve as signaling molecules linking metabolism to changes in gene expression. Indeed it was recently shown that combining exercise with the histone deacetylase inhibitor sodium butyrate can transform a sub-threshold learning event into long-term memory via a BDNF dependent mechanism [42]. Considering that exercise increases the levels of ketone bodies such as beta-hydroxybutyrate and affects citric acid intermediates such as α-ketoglutarate. Both are known to regulate histone deacetylases and histone/DNA demethylases respectively, suggesting there are several ways that these molecules may be involved in exercise-induced BDNF expression.

One hypothesis is that epigenetic regulation of gene expression is downstream of physical exercise [43]. Exercise may induce BDNF levels in the hippocampus by altering the epigenetic landmarks of the BDNF promoters. Because histone acetylation changes are observed at the BDNF promoters [44], deacetylation of chromatin associated with the hippocampus could in turn induce BDNF expression through a process involving HDAC inhibition.

PERSPECTIVES

Neurotrophic factors have been proposed as a treatment for Alzheimer's disease, amyotrophic lateral sclerosis and peripheral neuropathy. However, many clinical trials have met with disappointing results, in part due to difficulties of delivery and unanticipated side effects [45]. Several acute side reactions such as pronounced pain, weight loss, diarrhea, hyperplasia, increased epileptic and motor activity, have been documented when high levels of neurotrophins are administered in animal models or in human trials of amyotrophic lateral sclerosis. The problems in managing the dose and pharmacokinetics of these proteins have hindered the application of neurotrophic factors as therapeutic intervention for neurodegenerative diseases.

One clinical symptom associated with psychiatric disorders is impairment of higher cognitive abilities. BDNF regulates the formation and maintenance of neuronal networks and changes in BDNF signaling have been linked to psychiatric [6] and neurodegenerative disorders [25]. Levels of BDNF are reduced in patients with depression. Indeed, a human BDNF polymorphism, Val66Met, causes a 30% reduction in BDNF levels and has been associated with increased susceptibility to learning and memory disorders, hippocampal deficits and an anxiety phenotype in humans and mice models [46]. Antidepressant treatment both in human and animals lead to increases in BDNF in the hippocampus and their therapeutic effect is lost in the BDNF knockout. Interestingly, environmental factors significantly contribute to depression and robustly regulate BDNF expression. For example, BDNF levels are dramatically decreased in the adult brain in response to stress and in the hippocampus of mice with social defeat, and are elevated by changes in activity or increased exercise.

Numerous studies have validated the effects of physical exercise upon the expression of BDNF [47] and improvements in cognitive function [48]. These effects are the result of metabolic changes, increased neurogenesis and effects upon the vascular system [34]. Indeed, a remarkable impact of exercise has been noted in models

of Parkinsons disease [49, 50], in which there is reduced expression of BDNF. These findings have that treadmill training provides a strong neuroprotective effect upon dopaminergic neurons in the basal ganglia.

Therefore, a practical way of increasing neurotrophic factors in the nervous system is through physical exercise, which has been shown to increase the transcription of the BDNF gene in the cortex and hippocampus [51]. Exercise also stimulates dendritic growth and spine formation that has been shown to be BDNF-dependent [52]. This strategy can benefit many neurodegenerative disorders, which are characterized by a deficit of BDNF and other trophic factors [52]. Further understanding of the mechanisms that lead from physical exercise to the activation of the BDNF gene in the brain promises to be a fruitful path to the repair and restoration of the nervous system.

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