Review

Exercise and Dietary Factors Mediate Neural Plasticity Through Modulation of BDNF Signaling

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Abstract. The term "neural plasticity" was first used to describe non-pathological changes in neuronal structure. Today, it is generally accepted that the brain is a dynamic system whose morphology and function is influenced by a variety of factors including stress, diet, and exercise. Neural plasticity involves learning and memory, the synthesis of new neurons, the repair of damaged connections, and several other compensatory mechanisms. It is altered in neurodegenerative disorders and following damage to the central or peripheral nervous system. Understanding the mechanisms that regulate neural plasticity in both healthy and diseased states is of significant importance to promote cognition and develop rehabilitation techniques for functional recovery after injury. In this minireview, we will discuss the mechanisms by which environmental factors promote neural plasticity with a focus on exercise- and diet-induced factors. We will highlight the known circulatory factors that are released in response to exercise and discuss how all factors activate pathways that converge in part on the activation of BDNF signaling. We propose to harness the therapeutic potential of exercise by using BDNF as a biomarker to identify novel endogenous factors that promote neural plasticity. We also discuss the importance of combining exercise factors with dietary factors to develop a lifestyle pill for patients afflicted by CNS disorders.

Keywords: BDNF, diet, exercise, neural plasticity, beta-hydroxybutyrate, irisin, lactate, osteocalcin

INTRODUCTION

Neural plasticity is defined as the ability of the nervous system to perform adaptive structural and functional changes [1]. Impaired neural plasticity is observed in central nervous system (CNS) disorders [2] including psychiatric diseases such as depression [3]. Neural plasticity is influenced by environmental factors such as exercise, diet and stress [4]. Exercise promotes neural plasticity primarily by inducing the release of metabolites and proteins from the muscle, liver and bones that converge on the activation of hip-pocampal brain derived neurotrophic factor (BDNF) [5–12] signaling. The activation of BDNF signaling increases synaptogenesis, neurogenesis, angiogenesis and gliogenesis [13]. It also enhances cerebral blood flow [14], increases grey and white matter volume [15–17], and mediates neuronal activity [18–21]. As a result, exercise has been linked to improved cognitive and motor function. The composition of the human diet is also linked to changes in neural plasticity. Indeed, different dietary factors either promote or inhibit neural plasticity.

In this minireview, we will highlight the common pathways that are modulated by the liver-brain, muscle-brain, and bone-brain axes to induce neu-

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ronal plasticity. We will specifically focus on the convergence of the different circulatory factors that regulate neural plasticity on *Bdnf* expression and signaling in the brain. Our discussions will highlight the importance of using *Bdnf* expression and signaling as a biomarker to identify novel exercise and dietary factors that can be of therapeutic value. These discussions will also pave the way to completing the puzzle of how the different organ systems interact with the brain to modulate its responses.

ENVIRONMENTAL FACTORS INVOLVED IN NEURAL PLASTICITY

Two important environmental factors that modulate neural plasticity are exercise and diet. Exercise activates the liver-brain, muscle-brain and bone-brain axes to modulate neural plasticity. We will next focus on how exercise and dietary signals are integrated in the brain to promote neural plasticity.

EXERCISE-INDUCED FACTORS AND NEURAL PLASTICITY

Exercise promotes healthy brain function and improves the symptoms of a wide range of neurodegenerative diseases [22–24]. These effects are achieved by promoting neural plasticity [25, 26]. For example, mice with access to a running wheel exhibit a significant increase in hippocampal neurogenesis and enhanced spatial and temporal memory [27]. Magnetic resonance imaging (MRI) studies revealed that extended voluntary exercise increases hippocampal volume in mice [28]. Similar findings were also reported in human studies. MRI was used to show that adults who practiced moderate-intensity exercise for 12 weeks have significant increases in the volume of several brain regions, especially the hippocampus [29]. Altogether, these findings suggest that physical activity improves cognitive functions by inducing structural changes in different brain regions.

Exercise mediates its positive effects on the brain by activating several distinct pathways including neurotrophic and angiogenic pathways. One important pathway that is induced by exercise is BDNF signaling. In animal models, exercise induces BDNF expression in the hippocampus [30]. For example, middle-age rats that undergo daily treadmill exercise have increased hippocampal BDNF protein and mRNA levels as well as enhanced spatial memory and object recognition [31, 32]. BDNF production provides trophic support and increases synaptogen-

esis and dendritic and axonal branching and spine turnover. Blocking BDNF signaling inhibits the exercise-mediated improvement of spatial learning tasks [33] as well as the exercise-induced expression of synaptic proteins [34]. Moreover, mice with a single nucleotide polymorphism in the BDNF gene Val66Met (BDNF$^{Met/Met}$) have impaired exercise-induced neural plasticity [35]. BDNF promotes neural plasticity by activating tropomyosin receptor kinase B (TrkB) [36]. Exercise fails to promote neurogenesis and to enhance neural plasticity in TrkB deficient mice [37]. In humans, aerobic exercise training induces an increase in serum BDNF levels. This is associated with an increase in the volume of the hippocampus, suggesting that exercise-induced BDNF expression could reverse hippocampal volume loss and expand spatial memory [38]. Indeed, exercise induces hippocampal BDNF signaling through an elaborate coordinated response that involves several tissues and organs.

Exercise activates cross-talk between different tissues and the brain. It promotes the liver, muscles and bones to release factors into the circulation that reach the brain and promote learning, memory formation and neural plasticity [10, 11]. Not all the potential exercise factors have been identified or carefully studied. However, careful examination of what is currently known about exercise factors reveals that they activate converging and redundant pathways in the brain with BDNF signaling playing a pivotal role in the integrated response. Indeed, the integrated and beneficial effect of circulating exercise factors on cognitive function and neural plasticity is mediated in large part through the induction or activation of hippocampal BDNF signaling [5, 9–12, 39]. From here, hippocampal BDNF expression can be used as a biomarker to identify novel exercise factors that can become part of a comprehensive treatment for CNS disorders such as depression. Currently a limited number of exercise factors have been identified and have been shown to regulate the communication between the liver, muscle, bones and the brain. We will discuss what is known about these exercise factors below, while highlighting how they all regulate BDNF signaling supporting the usefulness of using this pathway as a biomarker to identify novel exercise factors that may have therapeutic relevance.

Liver-brain axis

Upon exercise, the liver secretes the ketone body beta-hydroxybutyrate (BHB) [9], as well as the

protein, glycosylphosphatidylinositol-specific phospholipase D1 (Gpld1) [6]. BHB is a specific inhibitor of the class I histone deacetylases [40] that increases BDNF levels in the hippocampi of mice [9, 41] and rescues neurogenesis in the dentate gyrus of adult mice [42]. Similar to BHB, Gpld1 promotes BDNF protein expression and in turn rescues impaired neurogenesis and several age-related cognitive deficits [6].

Muscle-brain axis

The muscle also secretes several factors during exercise that regulate neural plasticity by inducing BDNF expression [5, 8, 12, 43]. Such factors include the myokine FNDC5 and its cleavage product irisin [7, 12], lactate [5], cathepsin B [44] and α-ketoglutaric acid (AKG) [45].

Increases in FNDC5 levels in cortical neuronal cultures enhance BDNF levels, thereby promoting neural plasticity [12]. This increase in FNDC5 is mediated through the exercise-dependent activation of Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1a) [12]. Moreover, peripheral delivery of FNDC5 also induces hippocampal BDNF expression [12]. Indeed, exercise-induced FNDC5 and its cleavage product irisin are effective in rescuing neural plasticity deficits in AD mouse models [46] and depression models [47–49].

Lactate is also an exercise factor released by the muscle and delivered by the blood to the hippocampus where it promotes spatial learning, memory formation and rescues depression-like symptoms [5, 50]. Lactate promotes neural plasticity by inducing the expression of plasticity-related genes such as BDNF, activity-regulated cytoskeleton-associated gene (Arc), c-Fos, and the zinc finger-containing transcription factor 268 (Zif268) gene [5, 43, 51]. This induction is downstream of Sirt-1 dependent activation of the PGC1a/FNDC5 pathway [5] and can also be mediated through stimulation of N-methyl D-aspartate (NMDA) receptor activity [43, 51]. Interestingly, blocking the monocarboxylate transporter that is responsible for both lactate as well as BHB uptake into neurons abolishes exercise's ability to promote learning and memory formation [5]. This is consistent with both lactate and BHB being necessary for voluntary exercise's positive effects on learning and memory formation.

During exercise, the muscle releases Cathepsin B, which in turn induces the expression of doublecortin and BDNF in adult hippocampal progenitor cell cultures [44]. Blocking cathepsin B prevents neurite outgrowth, indicating that this exercise factor is involved in neural plasticity [8]. It is important to block BDNF signaling in order to determine whether it is indeed responsible for cathepsin B's effects.

Finally, the muscle releases multiple Kreb's cycle intermediates during exercise. For example, the muscle releases AKG during resistance exercise [45]. This metabolite extends the life span of aging mice by regulating inflammatory processes [52]. Whether this endogenous metabolite is another exercise factor that regulates neuronal plasticity and rescues cognitive deficits associated with neurodegeneration or social avoidance associated with depression and the involvement of BDNF signaling needs to be further investigated.

Bone-brain axis

The bones have emerged as an endocrine organ that releases osteocalcin during exercise. A single session of a high-intensity interval exercise in sedentary males increases osteocalcin levels. Increases in osteocalcin levels are tightly associated with increases in BDNF expression and neural plasticity [53]. Osteocalcin is released by the bones into the circulation, crosses the blood brain barrier (BBB) and activates the G Protein-Coupled Receptor 158 (GPR158) receptors in the hippocampus [54]. This signaling pathway promotes hippocampal-dependent memory through the activation of the inositol 1,4,5-trisphosphate and BDNF pathways [54]. Interestingly, osteocalcin is necessary for the ability of plasma from young animals to rescue cognitive deficits in aging animals [54]. Indeed, even though osteocalcin is not expressed in the brain of mice, its genetic deletion leads to impaired cognitive behavior and increased depression and anxiety-like behavior [55]. Taken together, current evidence emphasizes the importance of this bone-derived protein for the proper function of the brain. However, it is important to determine whether osteocalcin is both necessary and sufficient to mediate the effects of exercise.

DIET AND NEURAL PLASTICITY

Another lifestyle factor that is tightly linked to exercise and that regulates neural plasticity is diet [56]. Diets rich in factors such as BHB and lactate that are released in response to exercise also mediate neural plasticity. Interestingly, like exercise, multiple

diets and dietary factors that enhance neural plasticity also converge in part on their ability to activate BDNF signaling in the brain.

Multiple studies have highlighted the importance of different dietary factors and their ability to modulate neural plasticity [57]. For example, omega-3 fatty acids have long-lasting effects that persist in adulthood. These fatty acids are structural components of the brain and are crucial for neuronal membrane synthesis [58]. Adolescents with increased levels of omega-3 fatty acids have reduced risks of developing psychotic disorders [59]. Both enhanced emotional function and memory improvement are observed in rats fed with omega-3 fatty acids [60, 61]. Three omega-3 fatty acids – α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)- increase neurogenesis, promote long-term potentiation, induce the expression of synaptic proteins and enhance cognitive function and mood [62]. Liu and colleagues (2015) demonstrated that injection of DHA in two different rodent models of spinal cord injury promotes neural plasticity by inducing anatomical sprouting [63]. DHA also normalizes BDNF levels, reduces oxidative damage, and counteracts learning disability after traumatic brain injury in rats [64]. Combined supplementation of vitamin B12 and omega-3 fatty acids increases NGF levels in the hippocampus, and BDNF in both hippocampus and cortex and decreases reference and working memory error in rats [65].

Other dietary factors that regulate the expression of genes involved in neural plasticity are ketone bodies [66]. Like exercise, intermittent metabolic switching is linked to the production of ketones such as BHB and acetoacetate (ACA) [67]. Low carbohydrate and protein diets that are enriched in fat, such as the ketogenic diet, promote the synthesis of ACA and BHB in the liver [68]. BHB in turn upregulates the expression of BDNF, promoting synaptic plasticity through the activation of tyrosine kinase receptors that stimulate synaptogenesis, neuroplasticity, and neuronal survival [9, 39]. In an uncontrolled intervention study in which sedentary obese adults followed a 12-week ketogenic diet, serum BDNF levels were significantly increased within the first 2 weeks. This increase was associated with enhanced working memory and processing speed [69].

High protein diets rich in branched chain amino acids (BCAA) rescue social deficits induced by chronic stress and increase BDNF expression in the hippocampus [48]. Inhibition of TRKB signaling abolishes the ability of BCAA to promote resilience to stress and to rescue social avoidance [48]. Interestingly, BCAA activate the exercise-regulated PGC1a/FNDC5 pathway known to induce hippocampal BDNF signaling. Although both voluntary exercise and BCAA promoted resilience to stress, combining them did not yield synergistic effects confirming that they affect similar pathways [48].

Finally, the Mediterranean diet has neuroprotective effects [70]. This diet depends on the extensive use of olive oil, as well as the consumption of fish, and meat along with the moderate intake of wine [71]. This diet is rich in olive oil constituents, omega-3 fatty acids, and polyphenols that exert antioxidant and anti-inflammatory effects, and promote the expression of BDNF, leading to increased neural plasticity and cell survival [72]. The Mediterranean diet also increases serum levels of osteocalcin which is known to increase BDNF levels in the hippocampus [73, 74].

It is worthwhile to mention that not all dietary factors are beneficial; some may be detrimental to neural plasticity, cognitive functions and stress responses. For example, prolonged consumption of a high-fat diet exacerbates depressive-like behaviors in male adult rats, as well as decreases synaptic markers within the hippocampus. This suggests that chronic intake of this diet has detrimental effects on neural plasticity and behavioral function [75]. Interestingly, BDNF levels oscillate during the consumption of a high-fat diet; initially, levels increase, but progressively they fall below baseline levels after long-term consumption [76]. In addition, Fusco and colleagues (2019) suggested that a maternal high-fat diet could have multigenerational negative effects on synaptic plasticity through epigenetic mechanisms that inhibit BDNF expression in the hippocampus of the progeny. Epigenetic modifications that are related to gene activation, such as H3K9ac and H3K4me3, were found to be decreased in the germline and hippocampus of male descendants of mothers consuming this diet [77].

Altogether, the aforementioned studies provide strong evidence for the important roles played by dietary factors in regulating neural plasticity. Regulation of BDNF expression in response to metabolic changes and diet serves as a pivot linking peripheral factors to neural plasticity. Interestingly, diet is a key modifiable factor that regulates neural plasticity by influencing the composition of the gut microbiota and in turn the bidirectional interplay between the gut and the brain. The role of BDNF

in this interplay needs further investigation. In addition, different combinations of dietary factors and exercise factors need to be tested to identify combinations that may yield synergistic effects on neural plasticity.

CLINICAL IMPLICATIONS

The exercise and dietary factors discussed converge on regulation of BDNF signaling. Defects in BDNF signaling are observed in a number of diseases. Post-mortem studies in AD patients show significantly decreased BDNF expression in the hippocampus, and cortex [78, 79]. In addition, decreased levels of BDNF are observed in the cortex of AD mouse models [80, 81]. Conversely, BDNF gene delivery to the brain of transgenic AD mice prevents neuronal loss and synaptic degeneration and enhances neurogenesis [82]. In rats, exogenous BDNF treatment decreases the Aβ peptide in brains [83]. Neuroprotective effects were also observed in non-human primate models of AD [84]. Reduced BDNF mRNA is measured in dopaminergic neurons in Parkinson's disease (PD) [85]. In Huntington's disease (HD), the presence of mutant Huntingtin results in aberrant BDNF transport and in decreased BDNF expression [86, 87]. Indeed, symptomatic HD patients who exhibit impaired motor function have significantly lower BDNF levels [88].

Since BDNF signaling is disrupted in a wide array of CNS disorders, there have been considerable efforts to develop BDNF as a therapeutic (reviewed in [89]). Despite the encouraging preclinical data, the ability to deliver BDNF to the brain remains a challenge. This is because it is a polar protein that doesn't easily cross the BBB. This necessitates its direct delivery into the brain. Indeed, several clinical trials were conducted to assess the neuroprotective effect of exogenous BDNF administration. Clinical trials did not show any significant effects on survival following either subcutaneous/intrathecal recombinant BDNF administration. However, further analysis of these studies suggests that the trials failed because BDNF could not cross the BBB to reach the degenerating neurons [89]. Indeed, the use of the recombinant BDNF protein is hampered by protein degradation, and an inability to cross the BBB in significant quantities. The use of viral vectors may also activate the immune response, induce mutations and overload the neurons with excess BDNF, which is associated with epilepsy. As a result, harnessing the therapeutic potential of endogenous pathways that can promote BDNF signaling in the brain may serve as a strategy to overcome the difficulties associated with BDNF delivery. From here, focusing on identifying endogenous exercise factors and dietary factors that can easily cross the BBB to induce BDNF signaling at physiological levels and not pathological levels can allows us to assemble an exercise/diet pill that can be tested as a therapeutic for CNS disorders. As mentioned previously, it is important to control for age and sex differences while assembling this pill.

CONCLUSIONS

During physical activity, the liver, muscles and bones release a host of factors that include proteins and metabolites into the circulation. These circulatory exercise factors cross the BBB, and increase BDNF expression resulting in enhanced neural plasticity, spatial learning and memory formation [5, 12, 44]. It is clear that the composition of the circulatory factors following exercise dramatically changes [6]. Indeed, blood transfusion experiments revealed that these factors mediate the effects of exercise on neurogenesis and cognition [6]. It is important to systematically assess the available proteomic and metabolomic data to identify novel exercise factors that promote neural plasticity. Considering that a vast majority of the currently established exercise factors mediate their function through activation of hippocampal BDNF signaling and considering the disruptions in BDNF signaling observed in CNS diseases, rapid screens of the top identified metabolites and proteins to determine their ability to induce BDNF can help in narrowing down the search for novel components of an exercise pill. An important consideration is the need to assess the effectiveness of the exercise factors across different sexes and age groups. Most of the beneficial effects of the currently known exercise factors have been primarily identified in young males. Thus, it is important to compare the composition of the circulatory factors in males versus females as well as in younger versus older animals. Such studies will help in developing personalized exercise pills that could vary according to the age or sex of the individual requiring treatment.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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