Therapeutic exercise accompanied by neuronal modulation to enhance neurotrophic factors in the brain with central nervous system disorders

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ABSTRACT. Exercise is a primary therapeutic regimen in physical therapy to rehabilitate the motor function of patients with central nervous system (CNS) disorders such as cerebrovascular accident (CVA). Furthermore, exercise positively contributes to cognitive function related to neuroplasticity and neuroprotection in the hippocampus. Neurotrophins play a crucial role in neuroplasticity, neurogenesis, and neuroprotection in the CNS. Exercise enhances the expression of neurotrophins in the brain. Thus, novel regimens for kinesiotherapy in CNS disorders to further enhance exercise-induced expression are expected. In this review, we described three novel regimens for kinesiotherapy in CNS disorders based on the interaction between exercise and pharmacological treatment with the idea of “inhibition of inhibition” in the CNS.

Key words: exercise, neurotrophin, epigenetics, GABA, Nogo

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Neurotrophins play a crucial role in neuroplasticity, neurogenesis, and neuroprotection (neuronal maintenance and survival) in the central nervous system (CNS). Therefore, it is well recognized that the upregulation of the expression of neurotrophins positively contributes to the prevention of and recovery from CNS disorders like Alzheimer’s disease, stroke, brain injury, and Parkinson’s disease.1

The neurotrophin family includes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4/5 (NT-4). These neurotrophins have receptors called tropomyosin receptor kinases (Trks), i.e., TrkA for NGF, TrkB for BDNF and NT-4, and TrkC for NT-3. Mature neurotrophins have high affinities for Trk receptors and induce neurotrophic intracellular signals for neuroplasticity, neurogenesis, and neuroprotection.2 In addition, neurotrophins share another receptor, p75. A precursor molecule of mature neurotrophins has a higher affinity to p75, whereas mature neurotrophins have lower affinities to p75. Contrary to the beneficial roles of neurotrophins associated with Trks, the down-streams of the p75 receptor include intracellular pathways inducing apoptosis.2-4

Kinesiotherapy is a primary therapeutic regimen in physical therapy to rehabilitate the motor function of patients with CNS disorders such as cerebrovascular accident (CVA). Neurotrophins are expressed in the brain in an activity-dependent manner by the neurons. Interestingly, exercise enhances the expression of neurotrophins, specifically BDNF in the motor-related regions, including the cerebral cortex and the cerebellum.5-6 Therefore, exercise has the potential to increase the expression of BDNF and induce neuroplasticity, neurogenesis, and neuroprotection of neurons in the CNS, reconstructing motor function in patients with CNS disorders after CVA.7 Interestingly, it is known that exercise increases the expression of BDNF in the hippocampus, a crucial brain region for learning and memory.8-10 Thus, research focuses on the potential of exercise for the improvement of cognitive function and for the prevention of cognitive disorders such as in patients with Alzheimer’s disease.11-13

Considering the beneficial roles of BDNF in the brain, it is reasonable to expect novel therapeutic regimens to fur-
other increase the exercise-induced expression of BDNF in the brain. In this paper, we review the effects of exercise on cognitive function associated with epigenetic regulation, which controls hippocampal gene expressions, including BDNF. Next, we explain neuromodulation based on the inhibition of gamma aminobutyric acid (GABA)ergic neurons to enhance the expression of neurotrophins, specifically focusing on CVA rehabilitation. Then, we review the potency of the inhibition of Nogo, which regulates the myelin covering of neuronal axons. It is expected that the interactive relationship between therapeutic exercise and these novel neuromodulations could lead to further therapeutic outcomes in kinesiotherapy.

1. Exercise Increases the Expression of BDNF in the Hippocampus Associated with the Modification of Epigenetic Regulation

Several studies have shown that exercise acutely and chronically increases the expression of BDNF in the hippocampus and improves cognitive function in animal models for aging and CNS disorders like Alzheimer’s disease and post-stroke dementia\(^1\). Literature has shown that the upregulation of BDNF expression is affected by the intensity, duration, and frequency of exercise. However, there is no consensus on the recommended exercise regimen. Some literature recommends moderate aerobic exercise with lower intensity rather than high-intensity exercise\(^6\). Some studies recommend voluntary exercise without stress rather than forced exercise\(^7\). One paper found that involuntary and forced exercise equally attenuated cognitive deficit by the activation of the BDNF-mediated pathway\(^8\). Some papers showed that the exercise-induced expression of BDNF reached a maximum level two to three hours after the exercise and gradually decreased\(^9\), whereas other papers showed chronic upregulation of BDNF following long-term exercise\(^10\). Literature has shown that aging and neurodegenerative diseases such as Alzheimer’s decrease the expression of BDNF and are associated with the decay in cognitive function. Thus, researchers appreciate that exercise prevents the decrease of BDNF expression, attenuating the deficit of cognitive function in animal models\(^11\). Human studies have shown that the serum BDNF level increases following exercise\(^12,13\). Literature has shown that aging and neurodegenerative diseases like Alzheimer’s disease decrease the expression of BDNF, and are associated with the decay in cognitive function. Thus, researchers appreciate that exercise prevents the decrease of BDNF expression, attenuating the deficit of cognitive function in animal models\(^14,15\). Human studies have shown that the serum BDNF level increases following exercise\(^16\). Furthermore, one human study showed that the increased serum BDNF was actually associated with increased expression of BDNF in the brain\(^17\). Altogether, exercise is recommended to prevent the development of dementia in older adults and to treat patients with CNS disorders.

Our previous study also showed that exercise improved cognitive function with the increase of hippocampal BDNF in a senescence-accelerated mouse model. Interestingly, exercise not only increased the expression of BDNF but also modified the expression of BDNF receptors. Specifically, exercise decreased the expression of p75, which is related to neuronal death, and it decreased the expression ratio of p75 to TrkB (p75/TrkB\(^20\)). ProBDNF, a precursor molecule of mature BDNF, has a high affinity to p75. ProBDNF activates mitogen-activated protein kinase signaling pathways, including c-Jun N-terminal kinase, and induces apoptosis, long-term depression, and neuronal death\(^21\). Thus, there is a need to focus not only on the expression of neurotrophins but also on the balance between the contribution of Trk-pathways and that of p75-pathways. Furthermore, our previous studies demonstrated that exercise activated histone acetyltransferase (HAT), an enzyme for epigenetic regulation that acetylates histones and potentiates gene transcription\(^12,24\).

Acetylation and methylation of DNA promoter regions or that of histones in the chromatin have crucial roles in modifying gene transcriptions in epigenetic regulation. Epigenetic regulation could mediate crucial factors of aging and degenerative diseases like Alzheimer’s disease. Studies have shown that exercise modifies the epigenetic mechanism in the hippocampus\(^22,23\) and may prevent epigenetic changes due to aging or CNS disorders\(^24,25\). Specifically, acetylation of histones (histone 3 and histone 4) enhances gene expression, including hippocampal BDNF. The acetylation level of histones is regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs), i.e., HATs acylate histones, and HDACs deacetylate histones. Activated HATs or inhibited HDACs increase acetylated histones and enhance total gene transcriptions. Previous literature has shown that exercise increases histone acetylation associated with the increase of beneficial proteins for learning and memory, including hippocampal BDNF\(^26,27,28\). In addition, exercise reduces the expression\(^29,30\) and activity level of HDACs\(^31\) and increases the activity level of HATs in the hippocampus\(^32,33\).

Pharmacological treatment with HDAC inhibitors enhances histone acetylation and gene expression. Recently, HDAC inhibitors like sodium butyrate (NaB), suberoylanilide hydroxamic acid (SAHA), and valproic acid (VAP) have been used clinically to target the down-regulated HDACs to treat cognitive disorders\(^34,35\). In addition, administration of an HDAC inhibitor increased the down-regulated expression of hippocampal BDNF in a mouse model of depression\(^36\). One study showed that BDNF production was required for cognitive enhancement from exercise and HDAC inhibitors, suggesting that exercise positively contributed to epigenetic regulation of hippocampal neurons like administration of HDAC inhibitors\(^37\). Considering the beneficial effects shared by exercise and HDAC inhibitors, it is reasonable to expect a novel regimen for kinesiotherapy with HDAC inhibition to enhance hippocampal BDNF and improve cognitive function in patients with CNS disorders.
2. Pharmacological Neuromodulation Targeting the Inhibition of GABAergic Neurons for Patients with CNS Disorders

Neuromodulation is defined by the International Neuromodulation Society as “the alteration of neural activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body.”

Recently, transcranial direct current stimulation (tDCS) has attracted increased attention as a tool for clinical neuromodulation. tDCS can modulate cortical excitability by applying a weak transcranial electric current. Interestingly, DCS promoted BDNF-dependent synaptic plasticity for motor learning. Cortical excitability is modulated by a balance between excitatory and inhibitory neuronal transmission, specifically excitatory-glutamatergic and inhibitory-GABAergic synapses in the mammalian cortex. Human studies have shown that the application of tDCS to the primary motor cortex (M1) can enhance cortical excitability and decrease GABA concentration in M1, improving motor learning and motor function in patients after stroke. Furthermore, Stagg et al. reported a positive correlation between the magnitude of tDCS-induced GABA decrease in M1 and the degree of motor learning. Therefore, it is reasonable to expect that GABA could potentially have a crucial role in cortical excitability and motor learning.

Stroke, a CNS disorder causing physical disability, affects GABA-mediated tonic inhibitory function. Clarkson et al. showed that extrasynaptic GABAergic tonic inhibition in the peri-infarct cortical neurons was enhanced after stroke, resulting in neuronal hypoxic excitability. This enhanced tonic inhibition was mediated by an extrasynaptic GABA receptor because of a dysfunction in the GABA transporter (GAT-3/GAT-4). In addition, Clarkson et al. also showed that enhanced tonic inhibition impaired functional recovery because mice after stroke showed improved sensorimotor function with the administration of L655,708, a benzodiazepine inverse agonist specific for α5-subunit-containing extrasynaptic GABA receptors that reduces the contribution of those receptors. Indeed, following this study by Clarkson et al., several studies indicated that reducing extrasynaptic GABAergic inhibition enhanced functional recovery after stroke. Lake et al. showed beneficial effects of L655,708 in the chronic stage of stroke recovery. Interestingly, Orfila et al. showed that extrasynaptic GABAergic tonic inhibition caused impairment of both cognitive function and synaptic plasticity in the hippocampus after stroke, and pharmacological treatment with L655,708 improved these impairments. In addition, Kim et al. showed that increased neural activity by a GABA receptor antagonist improved learning and memory and upregulated BDNF expression in the hippocampus of normal mice. This suggested the beneficial effects of pharmacological neuromodulation by the inhibition of GABA receptors in stroke as well as other CNS disorders such as Alzheimer’s disease. Altogether, these studies have provided the rationale for the neuromodulation strategy based on the pharmacological inhibition of GABAergic neurons for CNS disorders.

It is well known that neurotrophins also play a crucial role in post-stroke neuroplasticity. In particular, it is recognized that the expression of BDNF contributes to functional recovery after stroke because attenuating BDNF prevents motor recovery after stroke. The modification of BDNF expression after stroke depends on the timeframe of the recovery of each hemisphere. Thus, it is expected that exercise combined with pharmacological neuromodulation based on GABA receptor inhibition could enhance the exercise-induced expression of neurotrophin in an activity-dependent manner by cortical neurons.

In our previous study using bicuculline, a GABA receptor antagonist, we examined the interactive effect of exercise and low-level bicuculline administration on the expression of neurotrophins in the motor cortex of mice. The study showed that two weeks of exercise combined with low-level GABA receptor inhibition upregulated the expression of BDNF in the motor cortex, whereas exercise without low-level GABA receptor inhibition had a marginal effect on motor function and the expression of neurotrophins. This indicated a benefit of low-level GABA receptor inhibition for enhancing exercise-induced neuroplasticity. Furthermore, to investigate the appropriate intervention duration, we examined the effect of long-term exercise and the inhibition of GABA receptors for four weeks. Results showed that the inhibition of GABA receptors did not affect BDNF protein expression in the motor cortex despite the increase in the expression of BDNF mRNA and protein in the cerebellum. However, we also presented the possibility that long-term inhibition of GABA receptors could decrease the mRNA expression of cortical BDNF and induce cumulative side effects on muscle coordination. This suggested that the combined effect of low-level inhibition of the GABA receptor could be more beneficial for short-term administration.

Overall, the interactive effect of exercise and GABA receptor inhibition could be influenced by various factors such as the intervention duration, drug concentration, and timing. Thus, it is important to consider the appropriate regimen for therapeutic exercise combined with neuromodulation targeting the inhibition of GABAergic synapses in CNS disorders.
3. Control of Nogo Expression and Exercise in Stroke Rehabilitation

Neuronal plasticity is necessary for motor function recovery after CNS injury such as stroke. The upregulation of neurotrophic factors represented by BDNF promotes neuronal plasticity and provides functional recovery after CNS injury, and these are called growth-promoting factors. BDNF binds to the Trk and induces the upregulation of polyamines, which perform protein synthesis via cyclic adenosine monophosphate (cAMP), protein kinase A (PKA), and the cAMP response element binding protein pathways. However, negative factors inhibiting neuronal plastic changes, such as cytoskeletal remodeling of axons and dendrites, are also upregulated after CNS injury. Nogo, chondroitin sulfate proteoglycan, and semaphorin 3A are included in these negative factors, which are called growth-inhibiting factors. Nogo-A, a main isoform of the Nogo family expressed in oligodendrocyte or neurons of the CNS, binds to Nogo receptor 1 (NgR1) together with Leucine-rich repeat and Immunoglobulin-like-domain-containing protein 1 (LINGO-1) and p75 or tumor necrosis factor-α receptor superfamily member 19 (TROY). It inhibits neurite growth via the Rho-associated, coiled-coil containing protein kinase (ROCK) pathway. It has been reported that growth-promoting factors (e.g., BDNF) and growth-inhibiting factors (e.g., Nogo-A) were antagonistic in relation to cytoskeletal regulation. Therefore, it is important to enhance the upregulation of growth-promoting factors and to suppress that of growth-inhibiting factors to enhance beneficial neuronal plasticity after CNS injury.

Nogo-A expression is upregulated after CNS injury. However, the administration of Nogo-A antagonist (anti-Nogo-A therapy) improves motor function and enhances the neuronal plasticity in rats after stroke. Furthermore, it is also reported that anti-Nogo-A therapy improves cognitive function in aged rats after stroke. Therefore, the inhibition of Nogo-A function may provide beneficial effects for motor/cognitive functional recovery and neuronal plasticity after stroke.

Running exercise could increase expression of BDNF and inhibit that of Nogo-A after stroke or traumatic brain injury. Constant-induced movement therapy, which is a rehabilitative approach used with patients after stroke, inhibits the expression of Nogo-A and its related factors. Furthermore, the corticospinal tract (CST) fibers projecting beyond the midline to the opposite side of the spinal cord increase with the improvement of motor function. These studies suggest that some exercises for rehabilitation after stroke could inhibit Nogo-A expression and provide similar effects as anti-Nogo-A therapy on motor functional recovery and neuronal plasticity.

There is an interesting report on a combination of drugs and rehabilitation in a rat model of stroke. When rats received physical training at the same time as anti-Nogo-A therapy for two weeks after stroke, the functional recovery four weeks later was minimal. However, drug treatment for two weeks after stroke, followed by physical training for two weeks, resulted in remarkable motor function recovery at four weeks after stroke. It was also shown that behavioral recovery was associated with an increased amount of CST fibers crossing the midline of the spinal cord. Furthermore, the termination pattern of CST sprouting showed aberrant growth when there was early intensive training after stroke. Altogether, the inhibition of Nogo-A function induces positive effects on functional and cognitive recovery after stroke. Therefore, it is important to carefully consider the timing of drug administration and therapeutic exercise.

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