License to Run: Exercise Impacts Functional Plasticity in the Intact and Injured Central Nervous System by Using Neurotrophins

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Exercise has been found to impact molecular systems important for maintaining neural function and plasticity. A characteristic finding for the effects of exercise in the brain and spinal cord has been the up-regulation of brain-derived neurotrophic factor (BDNF). This review focuses on the ability of exercise to impact brain circuitry by promoting neuronal repair and enhance learning and memory by increasing neurotrophic support. A paragon for the role of activity-dependent neurotrophins in the CNS is the capacity of BDNF to facilitate synaptic function and neuronal excitability. The authors discuss the effects of exercise in the intact and injured brain and spinal cord injury and the implementation of exercise preinjury and postinjury. As the CNS displays a capacity for plasticity throughout one's lifespan, exercise may be a powerful lifestyle implementation that could be used to augment synaptic plasticity, promote behavioral rehabilitation, and counteract the deleterious effects of aging.

Key Words: *Cognition—Oxidative stress—Diet.*

The benefits of exercise on brain health have been recognized for centuries. As early as 4 B.C. to A.D. 65, Seneca, Roman philosopher and dramatist, prescribed exercise in his writings as a means to obtain a healthy mind and body.[1] Yet it has only been in the past 2 decades that scientific inquiry has stringently substantiated the effect of exercise on CNS health. Both clinical[2-4] and animal[5-7] studies have repeatedly demonstrated that exercise benefits neuronal function. Exercise improves learning and memory,[3-5] counteracts the mental decline that comes with age,[2,8] and facilitates functional recovery after brain and spinal cord injury (SCI), disease,[9-11] and depression.[12,13]

The brain and spinal cord display plasticity, a capacity that enables these systems to achieve new functions by modifying the constitutive elements of their internal milieu and/or connectivity in response to environmental constraints.[14] Both the brain and the spinal cord have a regenerative potential that constitutes part of the plastic potential of the young, adult, and senescent animal.[15] A major focus of research has been the attempt to delineate the potential therapeutic capacity of exercise in CNS injury. In fact, the major setback limiting the rehabilitative implementation of exercise can be poised in the following question: What are the molecular mechanisms and signaling pathways through which exercise promotes synaptic plasticity, functional recovery, and learning and memory? It is mainly through the use of animal studies that the underlying mechanisms subserving the ability of exercise to augment synaptic and cognitive plasticity and promote neuronal repair are beginning to be discerned.

The effects of exercise on the brain go beyond simply increasing regional blood supply,[16,17] nor are they restricted to motor-sensory regions of the brain expectant to be conjoined with a motor task. Exercise can activate specific neural circuits to modify the way that information is transmitted across cells at the synapse, possibly by impacting

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the action of specialized molecules. Characteristically, animal studies have found that exercise elevates the levels of neurotrophic factors in select regions of the adult brain and spinal cord. Neurotrophic factors have been categorically described as factors that regulate the proliferation and differentiation of cells in the developing CNS.[18] Among the trophic factors elevated by exercise are insulin-like growth factor (IGF),[19] fibroblast growth factor 2 (FGF-2),[20,21] and brain-derived neurotrophic factor (BDNF).[22] Although other trophic factors have their roles in promoting neuronal plasticity, an increase in BDNF and associated plasticity molecules has been the thematic epithet for the effects of exercise in the brain, especially in the hippocampus, an area vital for supporting learning and memory processes.[23,24]

BDNF MEDIATES THE EFFECTS OF EXERCISE ON THE BRAIN

It must be emphasized that BDNF, unlike other neurotrophins, seems to be especially susceptible to regulation by activity, for both its expression and release.[25,26] This activity dependence provides a means for behavioral implementations such as exercise to easily modulate BDNF levels in the CNS. Experiments using cultured hippocampal neurons, in which the mRNAs for the precursor proteins pro-BDNF and pro–nerve growth factor (pro-NGF) were overexpressed, demonstrated that activity applied here in the form of depolarization was responsible for triggering the release of BDNF, whereas NGF secretion remained constitutive.[27] Like NGF, the expression of other neurotrophins, NT-3 and NT-4, does not seem to be as susceptible to regulation by activity.[28] In fact, this lack of activity dependence has enabled NT-3 to be used as a control to study the effects of exercise on synaptic plasticity.[29-31] The activity dependence of BDNF was especially found to be prominent in hippocampal neurons. The secretion of neurotrophins can be either regulated or constitutive. In constitutive secretion, neurotrophins are spontaneously released shortly after being synthesized, thereby enabling the neurotrophin to be continuously available to cells that need it. In contrast, in the regulated pathway, once synthesized, neurotrophins are stored in secretory granules and released in response to extracellular cues.[32] Insertion of BDNF into the hippocampus by using a vaccina virus expression system showed that BDNF is sorted into the regulated pathway, whereas other neurotrophins are mainly sorted into the constitutive pathway.[27,32] Although other neurotrophic factors, such as NGF[23] and FGF-2,[20] have been found to be induced in the hippocampus by exercise, their up-regulation was curtailed and less robust than that of BDNF. In conclusion, the activity dependence of BDNF may enable it to be particularly capable of mediating the benefits of exercise on neuronal and cognitive plasticity.

Exercise-induced increase of BDNF in the hippocampus may be archetypal for the benefits of physical activity on overall CNS health. In addition to the hippocampus, exercise induces the expression of BDNF mRNA and protein in the cerebral cortex, cerebellum, and the spinal cord.[23,33-35] As neuronal plasticity serves as the foundation for learning and the basis of recovery of function, neurotrophic factors such as BDNF, which are intrinsically involved in mediating synaptic plasticity and learning and memory mechanisms, may be especially requisite in the reorganization and regeneration of injured circuits. Exercise provides a natural and noninvasive paradigm to activate this plastic potential of the injured CNS by employing BDNF and similar trophic support factors.

EXERCISE BENEFITS COGNITIVE ABILITIES THROUGH BDNF

Learning and memory have been used as an effective paradigm to understand how the nervous system undergoes plasticity, that is, alters components of its neuronal circuitry to effectuate changes in synaptic transmission and functional outcome, in response to behaviors such as exercise. In intact animals, exercise has repeatedly been shown to improve cognitive function, in particular, to facilitate the acquisition of hippocampal-dependent learning tasks.[29,31,36,37]

The role of neurotrophic factors, especially BDNF, in mediating the effects of exercise on the brain has been explored in regard to their ability to augment cognitive function. It was first determined that animals who learned the fastest and had the best recall also had the highest levels of BDNF in their hippocampi,[17] suggesting that hippocampal BDNF levels seem to be related to learning efficiency. Recent studies indicate that the exercise-induced enhancement in learning and memory is dependent on the increase in hippocampal BDNF levels.[31] Antibodies (TrkBIgG) that quench the action of endogenous BDNF in the hippocampus during exercise training were used in those stud-

ies. Blocking the action of BDNF during exercise was found to be sufficient to abolish the exercise-induced enhancement of both learning and memory on the Morris water maze task, a hippocampal-dependent task of spatial memory.[31] Additionally, there seems to be a strong quantitative relationship between BDNF and learning and memory.[17]

Studies evaluating the importance of BDNF to cognition indicate that exercise may activate the neural circuitry necessary for the nervous system to undergo learning and memory. Reminiscent of the BDNF increases produced by physical activity, actual learning and memory tasks,[38] and long-term potentiation (LTP), the electrophysiological correlate believed to underlie learning and memory[39,40] selectively increases BDNF mRNA levels in the hippocampus. Studies have reported that BDNF mRNA levels are increased in the hippocampi of rats that have undergone 3 or 6 days of Morris water maze training.[16] Similarly, studies using alternative hippocampal-dependent learning paradigms such as contextual fear conditioning have found increases in BDNF mRNA levels in the hippocampus.[41] The demarcation that BDNF holds among its neurotrophic factors to regulation by activity may similarly be occupied in regard to memory processes. BDNF, but not NGF or NT-3, seems to play a role in consolidating short-term memories into long-term memories.[42]

The ability of exercise to induce BDNF takes on an even greater significance when presented with studies that illustrate that BDNF may be constitutive for proper cognitive function. For example, depleting the hippocampus of BDNF, by using transgenic animals quenching endogenous BDNF with function-blocking anti-BDNF antibodies, has been demonstrated to impair spatial learning and memory in rats on both the water maze and an inhibitory avoidance task[43-45] and reduce LTP.[44,46] Exogenously reinstating BDNF into the depleted hippocampus seems to ameliorate these deficits. Exogenous BDNF application[46] or transfection of hippo- campal slices with a BDNF-expressing adenovirus[47] has been shown to restore the ability to induce LTP. Clinical studies support the importance of BDNF in learning and memory in humans.[48,49] A study conducted by Egan and colleagues found that individuals expressing a specific polymorphism in the BDNF gene exhibit learning impairments.[48] The possibility of using chronic delivery of BDNF in human patients for nervous system repair is problematic, in that it is unable to cross the blood-brain barrier[50] and directly infusing it into the brain would be too invasive. Therefore, using exercise as a physiological means to increase BDNF levels makes it a suitable candidate to be instated as a component of neurorehabilitative therapy.

EXERCISE ACTIVATES SIGNAL TRANSDUCTION MECHANISMS

The ability of physical activity to activate elements of neuronal gene expression is fundamental to the proficiency of exercise in inducing long-lasting and/or permanent changes in the morphology and function of the nervous system. Exercise impacts downstream effectors of BDNF action on gene expression by increasing the transcriptional regulator cAMP response element binding protein (CREB).[30] CREB activation rapidly actuates de novo transcription and translation of inducible transcription factors, such as cFos and Jun, whose transient expression leads to the more persistent expression of their target genes. It is the expression of these target genes that results in changes in structural proteins, enzymes, ion channels, and neurotransmitters that eventuate changes in the structure and function of neuronal circuitry.[51] The functional outcome of CREB induction has been applied to the field of learning and memory. CREB has been found to be an evolutionarily conserved molecule requisite for the formation of long-term memory (LTM).[52-54] CREB has been described as a molecular switch for the activation of transcription necessary for LTM.[54] Disrupting CREB function with a dominant negative CREB protein impairs odor memory in *Drosophila*[55] and an LTM deficiency in mice.[53]

CREB seems to be an important link in the BDNF-mediated machinery responsible for advancing the effects of exercise on learning and memory. Blocking BDNF action during exercise was sufficient to abrogate the exercise-induced enhancement in learning and memory and prevent exercise-induced increase in CREB mRNA levels and the active form of CREB (p-CREB).[31] With exercise, BDNF and CREB mRNA levels were significantly and positively associated with each other as well as with performance on the probe trial, illustrating that animals with the highest BDNF expression also had the highest CREB expression and the best memory recall. Moreover, the effect of exercise may be potentiated through CREB as it may provide a self-perpetuating loop for BDNF action during exercise, in that it regulates BDNF transcription[56] and in turn is regulated by BDNF.[57,58]

EXERCISE USES BDNF TO FACILITATE THE SYNAPSE

Exercise may benefit brain function by facilitating transmission of nerve impulses at the synapse. The most chronicled synaptic protein found to be regulated by exercise under the action of BDNF is synapsin I.[17,30,31] Synapsin I tethers synaptic vesicles to the actin cytoskeleton,[59] thus providing for a substantial and localized vesicular pool of vesicles remote from the active zone that serves as a reserve pool and proper neurotransmitter release; inhibiting synapsin I reduces both the synaptic vesicle reserve pool and neurotransmitter release.[60] The presence of an adequate vesicular pool becomes apparent during high-frequency stimulation, as without it vesicular rundown occurs.[61] The ability of BDNF to regulate synaptic release proteins such as synapsin I may explain why BDNF gene deletion in mice results in a reduction in synaptic proteins, sparsely docked vesicles, and impaired neurotransmitter release.[62] In fact, blocking the action of BDNF produces synaptic fatigue and decreases synapsin I levels.[62] An adequate vesicular release pool and adequate and sustainable transmitter release provided by functional levels of synapsin I may afford the level of synaptic communication necessary for learning. A recent clinical study conducted on familial epileptics showed that a genetic mutation in the synapsin I gene may be associated with learning difficulties.[63]

The action of exercise on presynaptic membrane molecules such as synapsin I may contribute to the observation that physical activity induces perforated synapses, which characteristically have multiple dendritic contacts.[64,65] Synapsin I also regulates neurite development,[66,67] the formation and maintenance of the presynaptic structure,[68] axonal elongation,[69] and new synaptic formation.[70] Synapses with multiple dendritic contacts may not only contribute to the efficacy of synaptic transmission but may also represent newly formed conduits for communication.

EXERCISE, NEUROTROPHINS, AND THE INJURED BRAIN

Similar to the developing nervous system, which is structurally and functionally dynamic, the injured CNS is undergoing processes of reorganization and regeneration that may make it especially responsive to being primed by external cues such as physical activity. Exercise may potentiate the intrinsic plasticity of the injured brain by increasing expression of trophic support systems.

Animal studies have determined that exercise may be therapeutic in the management of CNS injury, by reducing the degree of initiatory damage, limiting the amount of secondary neuronal death, and supporting neural repair and behavioral rehabilitation. These above-mentioned effects of exercise have been accredited in part to neurotrophic factors, such as BDNF. BDNF gene deletion in mice increases the incidence of apoptosis,[45] whereas the addition of BDNF in cultured rat hippocampal neurons protects neurons against excitotoxicity.[71] Studies have shown that the powerful role of BDNF in promoting neuronal survival in the developing nervous system[72] seems to extend to injuries suffered by the adult brain. For instance, BDNF is associated with improving cognitive function and ameliorating neurological deficits caused by ischemia.[73-77]

EXERCISE BEFORE OR AFTER BRAIN INJURY

A pressing concern in need of being answered about the implementation of exercise as a rehabilitative intervention is what time period should physical activity be applied to produce its ameliorative effects on structural and functional CNS damage. In animal studies, performing exercise prior to brain trauma has been found to produce prophylactic effects on attendant brain damage, such as limiting the infarct size following forebrain ischemia.[78,79] Moreover, preinjury exercise has been shown to have transoperative benefits in animal models of stroke and Parkinson disease.[78,80] Obviously a preinjury exercise regimen for humans may not be the most effective treatment because the time of injury cannot be predicted. However, exercise therapy may be beneficial for certain patient populations such as those who have sustained a transient ischemic attack and therefore have a high disposition to experience a secondary insult.[81]

The implementation of exercise during the postinjury phase requires paying attention to specific protocols to be beneficial. In slow-degeneration, nonsevere models of Parkinson disease, the application of exercise during the incipient phase of neuronal degeneration is neuroprotective, functioning to attenuate neurochemical deficits and provide a measure of behavioral recovery.[82] These effects of exercise have been reproduced in

human subjects. Physical therapy is effective in increasing motor ability when implemented extant to the diagnosis of Parkinson disease.[83-86] In contradiction to these findings, animal studies exploring the use of exercise immediately following traumatic brain injury (TBI) found that exercise can exaggerate the extent of ischemic or TBI.[87,88]

The above-mentioned diametric findings bring up the question of when postinjury physical activity should be implemented to be beneficial. Post-TBI, an energy crisis prevailing among surviving cells may make them more vulnerable to secondary activation.[89-91] Studies suggest that postinjury, there is less cellular ATP availability[89,90,92] as an immediate source of energy for cellular processes. As exercise has been shown to increase the energy demand in various parts of the brain such as the hippocampus, motor cortex, and striatum,[93] it is possible that implementing physical activity during this energetically compromised time may further accelerate cellular dysfunction. In a TBI animal model, premature exercise blocked the activity-dependent BDNF up-regulation and even impaired the recovery of cognitive function.[94] Moreover, the immediate implementation of exercise following TBI precluded the normal up-regulation of plasticity molecules regulated by BDNF action, such as CREB and synapsin I seen with exercise.[94,95] However, when exercise is delayed 14 days postinjury, it increases BDNF and enhances cognitive function.[95]

In conclusion, exercise provides a therapeutic tool for TBI by managing its time of application.[10,96,97] Especially because the traumatically injured brain has not been responsive to exogenously administered BDNF,[98] it seems that exercise, by activating the intrinsic milieu for the action of trophic support, may be more propitious at bequeathing the beneficial effects of BDNF on restoring brain function. This understanding tempered with the knowledge that the injured brain is metabolically distressed should accede that there exists a critical time window post–CNS injury in which the application of exercise may be therapeutically implemented.

EXERCISE, NEUROTROPHINS, AND THE INJURED SPINAL CORD

It is time to realize that the spinal cord, like the brain, is capable of using experience to modify its existing circuitry to affect behavior, in effect exhibiting the essentials of what we call learning. Although our conception of the spinal cord has substantially matured beyond the Galenic view of the spinal cord as a mantled bundle of nerves connecting the brain to the body,[99] it is in need of reorganization.

The ability of exercise to enhance SCI recovery may be extensively due to its adeptness at enhancing sensory function,[100,101] which seems to be mediated by molecular systems dependent on neurotrophic action.[102] Voluntary wheel running and forced treadmill exercise elevate the expression of BDNF and molecules important for synaptic function and neurite outgrowth in the spinal cord and innervated skeletal muscle.[34]

The results of several studies in which BDNF has been added to the neural milieu support the possibility that these factors promote survival and growth of brain and spinal cord neurons affected by several types of insults.[103,104] It has been shown that BDNF administration after midthoracic complete spinal cord transection improves the functional recovery of hind limb stepping and that these changes appear to be associated with neuronal sprouting at the injury site.[105,106]

BDNF and NT-3 mRNA levels have been found to be increased in the lumbar region of the spinal cord and in the soleus muscle, whose innervating motorneurons are located in the lumbar region. The findings that 1) the soleus muscle contained significant increase in BDNF mRNA levels without concurrent increases in protein and 2) the spinal cord protein levels far exceeded the small increases in spinal BDNF mRNA levels have lead to the suggestion that neuromuscular activity might increase retrograde transport of BDNF from the muscle.[33] It is likely that peripheral sources of neurotrophins are transported retrogradely from the muscle via motorneuron axons to serve as trophic sources for neurons in the spinal cord and dorsal root ganglia.[33] Using spinal cord isolation to eliminate supraspinal and peripheral monosynaptic input to the lumbar regions of the spinal cord while retaining motorneuron-muscle connectivity decreased the levels of BDNF and NT-3 mRNA and protein levels in the isolated regions.[107] Paralyzing the soleus muscle with intramuscular botulin toxin type A injection, thereby reducing activity of this normally animated muscle, decreased BDNF and synapsin I expression but increased NT-3 in the lumbar spinal cord.[107] Although classic treadmill training has been shown to increase the production of BDNF and NT-3 in the spinal cord and skeletal muscle,[34] this paradigm showed that there is a differential effect of activity provided by exercise on these 2 neurotrophins.

DO ALL FORMS OF EXERCISE LEAD TO THE SAME DESTINATION?

Functional recovery seems to be highly task specific. Possibly the most lucid representation of this in action can be found in the study performed by Nudo and colleagues.[108] Squirrel monkeys who had undergone unilateral microlesions to the hand representation area of the cortex showed behaviorally dependent changes in the damaged hemisphere. Spontaneous recovery consisted of the animal relying on the unimpaired limb and resulted in a decrease of the hand representation area.[109] When the animals were forced to use the impaired limb in a set of training tasks by restraining the unimpaired limb, they showed a sparing of the hand representation area of the cortex.[108] Forced limb motor activity also adheres to the laws of postinjury CNS vulnerability. When animals were forced to rely on the unimpaired forelimb immediately following the cortical injury for 14 days, neuroanatomical and functional losses were exacerbated.[110]

A study conducted using 3 different exercise paradigms, treadmill training, swim training, and stand training, found that treadmill exercise was the most propitious among the 3 for improving sensory recovery after spinal cord contusion in rats.[102] Thus, it seems that rehabilitative strategies that simulate walking are distinctively effective at reclaiming locomotion. The beneficial effects of exercise paradigms, such as running or walking, on SCI may be attributed to the phasic sensory input produced by repetitive foot contact with the ground to result in the induction of activity-dependent events such as increased neurotrophin levels in selective circuitry. As for the case of the brain, BDNF is a prized candidate for use in spinal cord therapies. BDNF localizes to synaptic vesicles in the dorsal horn[111] and modulates sensory input within the spinal cord.[112,113] BDNF acts to confer tactile sensitivity to the spinal cord by transducing tactile stimuli from slow-adapting mechanoreceptors innervating Merkel cells within touch dome complexes of the skin to the spinal cord.[114] This may explain why repetitive loading of the hind limb provided during running but not standing or swimming exercise paradigms produces increases in BDNF levels.[102] In fact, the recent findings from Hutchinson and colleagues[102] suggest that the best predictor of tactile sensory recovery after SCI seems to be spinal and peripheral expression of BDNF.

THE SPINAL CORD CAN ALSO BENEFIT FROM LEARNING AND MEMORY MECHANISMS

Recent experiments have found that the up-regulation of BDNF by exercise in the spinal cord may activate the select machinery employed by BDNF to promote synaptic plasticity in brain regions central to learning and memory. Hemisectioned rats conditioned by 28 days of exercise, initiated 1 week postinjury, showed significant increase in BDNF levels in the lumbar region of the hemicord ipsilateral to the lesion. Moreover, exercise also augmented the consummate end products of BDNF action on synaptic transmission and gene transcription, that is, synapsin I and CREB.[115] Like BDNF, these factors have been found to be fundamental to promoting synaptic plasticity underlying learning and memory.[53,54,64] These findings advocate for the existence of spinal cord learning mechanisms that may be harnessed to promote neuronal repair and functional recovery. In conclusion, the use of exercise training may activate mechanisms of motor skill learning in patients with a moderate to profound loss of ascending and descending spinal pathways by using activity-dependent plasticity to increase rehabilitative gains.

Particularly, our understanding of spinal cord competence has been broadened by the finding of a spinal central pattern generator (CPG) constituted from interconnected spinal neurons. The CPG is stimulated by supraspinal tracts that descend from the locomotor regions in the brainstem and the thalamus, but it relies on proprioceptive and cutaneous inputs from the periphery to continually adjust its activity.[116] Studies conducted in cats have found that when supraspinal control is removed, by transecting the thoracic spinal cord, the CPG in the lumbosacral spinal cord is still capable of producing well-planned and coordinated treadmill locomotion.[117] Studies in humans confirm animal studies, showing the presence of the CPG in the lubrosacral spinal cord.[118,119] Advantageously, the existence of a CPG allows for the possibility that exercise training can be used to guide the performance of the CPG and result in restoring some aspects of locomotion. A robust body of data indicates that repetitive locomotor activity can improve functional recovery following different types of injuries to the spinal cord in humans and animals.[120-125]

RUNNING OUT OF TIME: EXERCISE, NEUROTROPHINS, AND AGING

The aging brain is beset by ever-accumulating challenges to the neuronal milieu such as those generated by oxidative damage and metabolic changes.[126,127] It is believed that these processes contribute to the cellular and molecular abnormalities that impose the dysfunction and eventual death of neuronal populations in age-related neurodegenerative diseases. Among these, oxidative stress and lack of trophic support may engender the pathology of various neurodegenerative diseases. Aging is also accompanied by decreased BDNF signaling in the brain. Studies conducted in monkeys have shown that BDNF levels are decreased during aging, especially in hippocampal pyramidal and dentate granule cells.[128] Conspicuously, age-related decreases in hippocampal BDNF levels consort with age-related impairments in learning and memory in rats.[129]

Reigning supreme among the neurodegenerative diseases afflicting the aging brain are Alzheimer disease (AD), Parkinson disease (PD), and stroke. The preclusion of normal BDNF expression is a repeated characteristic in many disorders of cognitive function that occur later in life, such as schizophrenia,[48] PD,[130] dementia,[131] and AD.[132] For example, AD brains exhibit region-specific decreases of BDNF in the hippocampus,[133,134] which are also accompanied by decreases in the expression of BDNF's cognate TrkB receptor.[135]

Regular exercise retards the accumulation of cell damage and physiological dysfunction characteristic of the aging process,[136,137] especially attenuating the oxidative stress and consort cognitive decline in the brain. Rats that exercised regularly during a 9-week period exhibited improved performance on a learning and memory task accompanied by reduced brain levels of membrane lipid peroxidation and oxidative damage to DNA.[36] This result is especially prominent in older rats.[138]

The ability of exercise to improve cognitive function, especially in age-compromised neural integrity, may lie in its ability to interface metabolic process altering oxidative stress by-products with BDNF pathways. BDNF may be part of a system that enhances neuronal plasticity and the resistance to oxidative and metabolic insults. The ability of BDNF to promote the survival of various cell types throughout the CNS and PNS has been recurrently reported in both the in vitro and in vivo literature.[103,139-141] Particularly, BDNF can protect CNS neurons from oxidative stress[142,143] such that BDNF addition impacts mitochondrial activity.[144] Other neurotrophins such as NT-3 and NGF have been shown to have antioxidant effects.[143,145] However, the benefits gained from NGF induction may be limited given that there are few types of neurons in the CNS that can maintain their survival in response to NGF.[146,147] In contrast, the cognate TrkB receptor to BDNF is expressed abundantly throughout the CNS,[148] especially the hippocampus, which exhibits a bountiful constitution of both BDNF and the TrkB receptor.[149,150] Considering the evidence that other neurotrophins are less susceptible to regulation by activity and those that are, such as NGF, show transient and less robust responses to activity than BDNF suggests that BDNF may be the predominant neurotrophin employed by exercise to perpetuate its effects on the synaptic and cognitive plasticity of an animal experienced over time.

LIFESTYLE CHOICES: A LACK OF EXERCISE, A LACK OF BDNF

The issue of aging has particular relevance to our present-day society. Our lifestyle of consummatory overindulgence and sedentary adherence has created an authentic version of "Logan's Run," a society that precludes us from successful aging and where the only way out is to start "running." The current trend to supersize meals and minimize exercise has grown into an obesity epidemic. The number of obese individuals has been increasing in the past 40-year period. Between the 1960–1962 and the 1988–1994 period, the amount of U.S. adults fit into class I obesity (BMI, 30–34.9 kg/m^2) increased to 66% (2.2% increase per year).[151] This rate seems to only be increasing, as reported between 1991 and 1998, the proportion of U.S. adults with a BMI > 30 kg/m^2 rose 49% (7% increase per year).[152] Unfortunately, the younger generation is not immune. The number of overweight children and adolescents has likewise increased between the 1960–1962 and the 1988–1994 periods.[151] Alarmingly, there was a greater than 70% increase in the proportion of obese individuals in the 18- to 29-year-old age range between 1991 and 1998.[152] The estimated 280,000 to 325,000 deaths accounted for by obesity in 1991 is escalating.[153] Moreover, obesity is a comorbidity factor for the most prevalent of diseases in our society, such as coronary heart disease and diabetes.[154,155] Coronary heart disease accounts

for the vast majority of deaths in the United States in the 20th century,[156] whereas diabetes has been estimated to kill 193,000 Americans per year.[157] A sobering wakeup call should be the fact that the increase in child obesity seems to coincide with the increase in type II diabetes in youngsters, a disease that has historically been relegated to the adult and aging population.[158] Between 1982 and 1994, there was an estimated 10-fold increase in type II diabetes in adolescents, whereas in 1994 alone, 33% of all newly diagnosed cases occurred in patients 10 to 19 years of age.[159]

Besides an improper diet, the lack of exercise seems to be a leading culprit in sustaining this epidemic.[96] Accordingly, physical inactivity seems to be the primary causal factor responsible for about one third of deaths due to coronary heart disease, colon cancer, and type II diabetes.[160] If these statistics are not sobering enough, it should be reiterated that the effects of physical inactivity go beyond affecting the body, but also are a cost to the preservation of our cognitive faculties during our aging process.

The damage imposed by diseases of metabolic function characteristic of today's American society may be especially conspicuous in the brain. As BDNF is intimately connected with energy metabolism, these metabolic disorders can affect BDNF levels in the brain. Molecular systems related to energy metabolism seem to interface with BDNF-mediated synaptic plasticity mechanisms subserving cognition.[161] Thus, the connection between cognitive function and metabolism may be intimately related, suggesting that behaviors such as eating and physical activity, which modulate our energy metabolism, may affect our ability to learn. In fact, the mitochondrial powerhouse of the cell driving the cellular energy production also encodes 11 human mental retardation genes.[162] Hypoglycemia and intermittent fasting both increase BDNF levels, whereas hyperphagia and high oxidative stress levels decrease BDNF levels.[163-165] In studies conducted with BDNF knockout mice, BDNF has been shown to be important for controlling glucose and insulin levels and body weight,[166] such that low levels of BDNF produce hyperglycemia and obesity.[167] Mice with reduced BDNF levels are obese.[168] Peripheral BDNF administration can reduce body weight and normalize glucose levels in diabetic rodents.[169] Likewise, BDNF administration into the brain has been shown to reduce body weight and increase insulin sensitivity.[170,171] Importantly, the role that BDNF holds in both metabolism and synaptic plasticity of the CNS especially as related to learning and memory processes underlines the importance of implementing lifestyle changes such as exercise. Given the ability of exercise to augment BDNF levels, it is possible that exercise may be an effective lifestyle implementation to abate if not combat the effects of stress-related lifestyle choices. In particular, it has been found that exercise can counteract the decrease in hippocampal BDNF levels due to the consumption of a high-fat diet.[29] It should be emphasized that other complementary lifestyle changes such as dietary restriction[172] and cognitive stimulation[173] can also be implemented to counteract the stress-induced decrease in BDNF expression and contribute to successful aging.

THERAPEUTIC CHALLENGES: COMBINING EXERCISE WITH OTHER INTERVENTIONS

The future of using exercise as an intervention for the treatment of CNS trauma may be combined with other protocols such as stem cells and pharmacological manipulations. In addition to increasing the regenerative processes, a prominent goal in spinal cord repair has been to neutralize the inhibitory CNS environment. Identified inhibitory molecules are NogoA, Mag, tenascin-R, and veriscan. The inhibitory action of NogoA has been found to be suppressed by the IN-1 antibody.[174] Since then, it has been demonstrated that the IN-1 antibody has cooperative effects when applied with NT-3 or BDNF. Rats receiving the combination treatment had a larger number of axons regenerated for a great distance than those in rats who received either treatment alone.[175] Thus, in the human patient, it is possible that the future may combine physical training with pharmacological interventions that down-regulate the inhibitory cues of the CNS to optimize functional recovery from brain and spinal cord trauma.

Exercise may be combined with stem cell grafts to treat neurological disorders and SCI. Olfactory ensheathing cells and embryonic stem cells have been successfully used to promote the recovery of the spinal tract in rats.[176,177] Using the endogenous ability of exercise to promote factors such as BDNF, which have trophic, survival, and growth-stimulating properties, may help cell grafts survive and integrate into existing circuitry. In fact, the incorporation of motor training has been found to enhance the survival and function of grafts of

transplanted tissue in stroke and Parkinsonian models.[178,179]

CONCLUSIONS

It is becoming recognized that exercise has the capacity to promote synaptic and functional plasticity in the brain and spinal cord. In the intact brain, exercise can enhance synaptic and cognitive plasticity by using the aptitude of neurotrophic factors such as BDNF. In the injured CNS, exercise can facilitate functional recovery by harnessing the intrinsic capacity of the intact nervous system that uses BDNF-dependent synaptic plasticity. Especially in the hippocampus, exercise has been shown to effectuate synaptic plasticity and to enhance learning through the action of BDNF. Recent findings support the contention that the spinal cord, like the hippocampus, uses a BDNF-mediated mechanism to facilitate learning. Although the underlying mechanisms responsible for the effects of exercise on synaptic plasticity, functional recovery, and learning and memory are still waiting to be delineated, the current findings promote exercise as a potential rehabilitative therapy for the injured CNS. In conclusion, exercise should be considered as an important tool capable of improving overall neural health and cognitive ability and particularly as a regimen that can sustain cognitive function throughout one's lifetime.

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