Therapeutic physical exercise in neural injury: friend or foe?

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Abstract. [Purpose] The intensity of therapeutic physical exercise is complex and sometimes controversial in patients with neural injuries. This review assessed whether therapeutic physical exercise is beneficial according to the intensity of the physical exercise. [Methods] The authors identified clinically or scientifically relevant articles from PubMed that met the inclusion criteria. [Results] Exercise training can improve body strength and lead to the physiological adaptation of skeletal muscles and the nervous system after neural injuries. Furthermore, neurophysiological and neuropathological studies show differences in the beneficial effects of forced therapeutic exercise in patients with severe or mild neural injuries. Forced exercise alters the distribution of muscle fiber types in patients with neural injuries. Based on several animal studies, forced exercise may promote functional recovery following cerebral ischemia via signaling molecules in ischemic brain regions. [Conclusions] This review describes several types of therapeutic forced exercise and the controversy regarding the therapeutic effects in experimental animals versus humans with neural injuries. This review also provides a therapeutic strategy for physical therapists that grades the intensity of forced exercise according to the level of neural injury.

Key words: Neurological injury, Neuroprotective effect, Physical exercise

INTRODUCTION

Among the many therapeutic strategies used following neurological injuries, physical exercise aids in functional recovery by increasing resistance to nerve injury, enhancing neuron survival, stimulating neurogenesis, increasing learning ability, and improving recognition and memory function. A dominant theory regarding the central nervous system (CNS) following neurological injury posited that no reassortment of any type occurs in neuronal populations. Since the 1990s, however, various studies have identified precursor neural stem cells (NSCs) and demonstrated that neurons are generated continuously within the CNS. It is now widely accepted that neurogenesis in adults occurs in the subventricular zone of the forebrain and subgranular zone of the hippocampus, particularly via the proliferation, differentiation, and migration of precursor NSCs. These processes are regulated by neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), and basic fibroblast growth factor (FGF-2), which are increased in the brain by physical exercise and sensory stimulation and, in turn, increase the number of surviving new neurons. This suggests that neurological disorders, such as stroke, spinal cord injury (SCI), and Alzheimer’s disease (AD), are treatable.
DIFFERENT EFFECTS OF MILD AND FORCED EXERCISE IN PHYSIOLOGICAL AND NEURAL THERAPY

In animal models, forced exercise, such as treadmill running, and voluntary exercise, like wheel running, are interventions that are used widely to study the effects of physical exercise on the recovery of physiological function in neurological injury. The application of these exercises following neurological injury results in increased angiogenesis in the cerebral cortex and enhanced neurogenesis and positively affects neuroplasticity, recognition, and memory function via neuroprotective actions against the structural injury of nerve cells and the increased expression of neurotrophic factors and memory function. Rehabilitation therapies following neurological injury vary based on the ethological aspects of forced and voluntary exercise, including timing, period, and intensity in terms of the recovery of nerve cells. The intensity of the exercise is an important factor.

Mild exercise is effective for neurological recovery. Exercise intensity influences cell proliferation and neurogenesis in the adult dentate gyrus, and mild exercise is more effective for cell proliferation than high-intensity exercise. Mild treadmill exercise increases cell proliferation via the enhancement of insulin-like growth factor (IGF)-1 and FGF-2 levels in the brain. Moreover, Lee et al. found that the application of mild exercise in ischemic animal models resulted in a lower infarct volume and greater numbers of astrocytes than high-intensity exercise, indicating that mild exercise is more effective for neurological and functional recovery. Astrocytes are glial cells in the brain and spinal cord that are more active in proximate injury regions and act in the repair and scarring process following neuronal injury. These glial cells contribute to functional recovery through the activation of angiogenesis, neurogenesis, and the secretion of neurotrophic factors. Accordingly, mild exercise is effective for neurological recovery via the induction of astrocyte proliferation. By contrast, forced exercise inhibits the degree of cell proliferation in the adult dentate gyrus, and it also reduces cell proliferation by decreasing the amount of BDNF in the dentate gyrus. Additionally, forced exercise induces stress, which enhances the secretion of glucocorticoids and may initiate increased corticosterone synthesis. Otherwise, long-term voluntary exercise has a considerable impact on hypothalamic-pituitary-adrenal (HPA) axis regulation; thus, clarification of the association between exercise intensity and the HPA axis is needed.

However, some studies have found that high-intensity exercise has more positive effects on neurological recovery and neuroprotection. Hayes et al. reported that forced exercise, with a stressful component, was neuroprotective after nerve injury via upregulation of the expression of the stress-induced heat shock protein (Hsp)27 and Hsp70 genes. Hsp27 and Hsp70 have been identified in many areas of the brain and skeletal muscle. In addition, these genes exhibit altered expression following exposure to different environmental stresses, such as heat, exercise, infection, inflammation, ischemia, and oxidative stress. Hsp27 and Hsp70 act as intracellular chaperones for other proteins with physiologically neuroprotective activities. In particular, Hsp70 regulates apoptotic cell death by interfering with apoptosis-inducing factors and increasing the expression of anti-apoptotic proteins via the inhibition of caspase and cytochrome c (Cyt c) release. The expression of the Hsp27 and Hsp70 genes increased significantly following forced exercise, compared with voluntary exercise, and their expression could play an important role in neuroprotection. Kinni et al. investigated cerebral metabolism using the expression of glucose transporter (GLUT)-1 and GLUT-3, phosphofructokinase (PFK), lactate dehydrogenase (LDH), and adenosine monophosphate kinase (AMPK) mRNA and protein and found significantly greater increases following forced exercise versus mild exercise. These authors suggested that forced exercise was more effective for neuroprotection.

Physical exercise facilitates functional recognition and memory recovery after nerve injury and improves short-term and spatial memory by repressing apoptotic neuronal cell death and enhancing newborn cell survival in the hippocampal dentate gyrus. Shimada et al. investigated the recovery of memory function following different levels of exercise intensity and found that mild exercise resulted in greater improvements in memory function than high-intensity exercise by increasing the number of neurons in the hippocampal dentate gyrus and enhancing microtubule-associated protein (MAP) expression. Similarly, low-intensity exercise enhanced neurogenesis and significantly increased the expression of neurotrophic factors, such as BDNF, N-methyl-d-aspartate receptor type 1 (NMDAR1), and vascular endothelial growth factor (VEGF), in the dentate gyrus of the hippocampus, compared with high-intensity exercise. Increased BDNF gene expression effectively increases neurogenesis and neuroplasticity, which may have a positive effect on the structural and functional recovery of neurons. By contrast, although the method of exercise was different, Ogonovszky et al. found that overtraining of swimming exercise in rat with neurological disturbance improved memory and increased BDNF expression.

Although these studies showed some discrepancies regarding the physiological and ethological effects of voluntary versus forced exercise during neurological treatment, exercise intensities should be compared very carefully. They are similar, have been applied in a variety of ways by different studies, and are associated with many other factors that are not yet understood. Determining an appropriate exercise strategy to aid recovery following neurological injury also depends not only on the exercise intensity but also on the timing and period.

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