

Role of exercise on the brain

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The functions of adult hippocampal neurogenesis have been extensively investigated during the past decade. Numerous studies have shown that adult neurogenesis may play an important role in the hippocampal-dependent learning and memory. This study evaluated the influence of exercise on hippocampal neurogenesis, neural plasticity, neurotrophic factors, and cognition. Areas of research focused on enhancing effect of exercise for adult hippocampal neurogenesis and protective role of exercise against brain diseases. The present study suggests that

exercise improves brain functions and prevents decline of cognition across the lifespan. Understanding of neurobiological mechanisms of exercise on brain functions may lead to the development of novel therapeutic strategy for neurodegenerative disorders.

Keywords: Adult hippocampal neurogenesis, Neural plasticity, Neurotrophic factors, Cognitive decline, Exercise


INTRODUCTION

Lifestyle factors such as exercise can reduce the risk of age-related cognitive decline and neurodegeneration. Exercise protects the brain function from the adverse effects of aging. This study focused on exercise as a lifestyle change for enhanced cognitive function depends on a neurobiological understanding. The neurogenesis in the brain of adult animals and humans overturned the long-held dogma that the adult brain has no capacity for generating new neurons (Altman and Das, 1965; Deng et al., 2010). In recent studies, exercise has emerged as the most effective and successful way for optimal aging. Exercise in the healthy adults brings behavioral benefits, including significant increments in memory, attention, processing speed, and executive functions (Smith et al., 2010). Regular engagement of exercise in midlife is associated with decreased risk of dementia later in life, presenting that exercise might have preventive effects on age-related cognitive decline (Hamer and Chida, 2009). Abundant evidences from animal studies have reported that an enhancement in adult hippocampal neurogenesis may underlie the beneficial effects of exercise on cognition. Indeed, exercise not only increased hippocampal neurogenesis but also improved Morris water maze performance

(Cho et al., 2013; Heo et al., 2014). Therefore, exercise can upregulate the neuronal cell proliferation process and increase the ability to maintain neuronal plasticity. Three-month regular exercise increased the volume of blood in the dentate gyrus as evaluated by functional magnetic resonance imaging and improved the cognitive scores in humans (Pereira et al., 2007). Exercise undoubtedly increased cerebral blood flow, angiogenesis, and the permeability of blood brain barrier (Black et al., 1990; Sharma et al., 1991; Yancey and Overton, 1993; Yau et al., 2014).

Positive relationship between angiogenesis and neurogenesis was presented in the animal studies. For example, the improvement of cognition through 3-month exercise is conjectured as a result of enhanced hippocampal neurogenesis via increased hippocampal angiogenesis in the human brain (Pereira et al., 2007).

These positive influences of exercise in the brain recommend that physical exercise and activity could be applied as a scheme to prevent the age-related cognitive dysfunction. Age-related decline in hippocampal neurogenesis has been associated with decrease in neurotrophins such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), and vascular endothelial growth factor (VEGF) (Lai et al., 2000; Shetty et al., 2005). BDNF, IGF-1, and VEGF have a crucial role in exercise-induced

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adult hippocampal neurogenesis. Thus, these neurotrophin factors might be worked for mediating exercise-induced adult hippocampal neurogenesis.

Here, this study was reviewed the functional and molecular role of physical exercise in cognitive function through neural plasticity, neurotrophic factors, and adult hippocampal neurogenesis. This study discussed the exercise-induced hippocampal neurogenesis and its relationship with cognitive enhancement, and concluded with a brief analysis to optimize the impact of exercise on brain function.

EXERCISE AND NEURAL PLASTICITY

Exercise-induced improvements in learning and memory have been associated with exercise-dependent neural synaptic plasticity and hippocampal neurogenesis (Baek et al., 2012; Cho et al., 2013; Heo et al., 2014). Long-term potentiation (LTP) in a neurophysiological model of learning and memory was assessed in hippocampal slices from running mice. LTP in the hippocampal CA1 area showed no differences between running and control groups. However, a significantly greater LTP was shown in the hippocampal dentate gyrus of running mice compared to the sedentary mice (van Praag et al., 1999). The enhancement in LTP following exercise is consistent with an increment of BDNF in the hippocampus, which can mediate neural plasticity (Cowansage et al., 2010).

Exercise may adjust the neural plasticity of the hippocampal dentate gyrus through the increased neurogenesis. Newborn granule cells may have a unique role in synaptic plasticity of the hippocampus, and the role of these cells can be increased with exercise (Vivar et al., 2013). The enhanced plasticity was appeared in a specific time of maturation process and was dependent on increased synaptic expression of NR2B containing *N*-methyl-D-aspartate (NMDA) receptors (Ge et al., 2007). Long-term depression (LTD) is another type of neural plasticity. LTD induced by low-frequency stimulation is relatively unaffected by exercise (Vasuta et al., 2007). However, LTD depends on the activation of NR2B containing NMDA receptors in running mice (Vasuta et al., 2007). Thus, exercise may alter the contribution of NMDA subunits to LTD.

Neural plasticity has been associated with morphological changes that occur in response to neural activity (Nägerl et al., 2004). Some studies suggested that morphological changes in dentate gyrus of hippocampus have been observed with exercise (Eadie et al., 2005; Nägerl et al., 2004). Exercise significantly in-

creased the total length, complexity, and spine density of granule cell dendrites (Eadie et al., 2005). Also exercise enhanced dendritic complexity in all zones of the granule cell layer such as subgranular, inner and outer granule cell zones (Redila and Christie, 2006). Additionally 2-month exercise caused morphological changes not only in the dentate gyrus but also in the entorhinal cortex and CA1 pyramidal cells (Stranahan et al., 2007). There was no difference in spine density of new neurons between young and aged mice, suggesting that fewer cells proliferated in aging brain may be functionally equivalent to those generated at early period (Morgenstern et al., 2008).

Exercise modifies the morphology of dentate granule cells and other parameters related to memory function, and may also affect the rate of integration of newborn granule cells into the hippocampal circuitry (Vivar et al., 2013).

EXERCISE AND NEUROTROPHIC FACTORS

Neurotrophic factors, including BDNF, IGF-1, and VEGF are essential regulators for the effects of physical exercise on brain plasticity during development and adulthood (McAllister et al., 1999).

BDNF is a critical mediator for the beneficial effect of physical exercise on brain function because it supports neural survival, growth, and synaptic plasticity (Cowansage et al., 2010). Indeed, BDNF is considered to be the most downstream factor mediating the upregulation of hippocampal neurogenesis by exercise (Yau et al., 2014). Neeper et al. (1995) were the first reporting a positive correlation between physical exercise and BDNF mRNA levels. Both BDNF gene and protein expression are increased in the hippocampus after short- or long-period of exercise (Abel and Rissman, 2013; Marlatt et al., 2012), and remained at least 2 weeks after exercise has ended (Berchtold et al., 2010). BDNF is a neuroprotective growth factor that enhances synaptic plasticity and memory through its actions on the tyrosine receptor kinase B (TrkB) (Mattson et al., 2004). Physical exercise increases serum BDNF in humans (Tang et al., 2008) and central BDNF in rodents (Neeper et al., 1995). BDNF is apparently essential for the effects of exercise on cognition. Blocking BDNF expression prevented the enhancement of cognitive function following physical exercise (Vaynman et al., 2004). The effects of exercise on synaptic plasticity are related to BDNF (Messaoudi et al., 2002).

It has been estimated that the brain is the major source of circulating BDNF (70%–80%) both at rest and during exercise (Ras-

mussen et al., 2009). In blood, more than 90% of the BDNF is stored in platelets and is released during clotting processes. Therefore, serum is likely to reflect stored and circulating BDNF in the blood (Fujimura et al., 2002), while plasma seems to reflect only freely circulating BDNF (Lommatzsch et al., 2005). For that reason, peripheral BDNF and other factors that regulate platelet storage and release should be considered for making inferences between peripherally measured BDNF and central expression. Particularly, these factors may influence the acute changes in peripheral BDNF levels following single bout of aerobic exercise (Griffin et al., 2011).

Other neurotrophins, such as IGF-1 and VEGF have been reported as essential factors in exercise-induced adult hippocampal neurogenesis (Trejo et al., 2008). IGF-1 was shown to be involved in memory, plasticity, and neurogenic processes, especially in the aging brain (Maher et al., 2006). For instance, lack of IGF-1 results in memory loss and LTP impairment (Trejo et al., 2007). Increased IGF-1 production following exercise may interact with BDNF to modulate synaptic plasticity (Mattson et al., 2004). IGF-1 receptor activity also appears to be closely associated with the expression of BDNF following physical exercise. For example, IGF-1 signaling via the IGF-1 receptor is necessary for the exercise-induced BDNF expression. Blockade of IGF-1 prevented the exercise-induced upregulation of BDNF (Ding et al., 2006). On the other hand, blocking BDNF pathway prevented the exercise-induced upregulation of IGF-1 in the hippocampus. Based on these results, it seems that IGF-1 and BDNF interact to mediate changes in hippocampal function following exercise (Gomez-Pinilla et al., 2008).

Interestingly, it has been reported that adult hippocampal neurogenesis occurs near the local microvasculature of hippocampus (Fabel et al., 2003). Both IGF-1 and VEGF in the periphery are increased by exercise and mediate stimulation of neurogenesis and angiogenesis in the brain (Fabel et al., 2003). Peripheral IGF-1 is necessary for exercise-induced vessel remodeling in the brain (Lopez-Lopez et al., 2004). Also, VEGF level in the brain is associated with exercise-induced angiogenesis (Ding et al., 2006). The enhancement of brain VEGF has mitotic activity specific to vascular endothelial cells, affecting proliferation, survival, and migration (Ferrara and Davis-Smyth, 1997). Blockade of peripheral VEGF restricted the increment in neurogenesis by exercise (Fabel et al., 2003). In addition, exercise for 50 days increased density of blood vessels in the dentate gyrus, and enhanced spatial working memory in the water maze (Clark et al., 2009). Exercise increased cerebral blood volume with neurogenesis (Van der Borght et al., 2009)

and improved cognitive function (Pereira et al., 2007). However, van Praag et al. (2007) reported that an increment in angiogenesis is not necessarily correlated with increased neurogenesis.

EXERCISE AND ADULT HIPPOCAMPAL NEUROGENESIS

New neuron production can be regulated by many different extrinsic and intrinsic factors. In the healthy brain, at least two constitutive neurogenic regions exist (Ortega-Perez et al., 2007): the subventricular zone (SVZ) of olfactory bulb and the subgranular zone (SGZ) of hippocampal dentate gyrus. Neurons born in the SGZ differentiate and integrate into the local neural network as granule cells of the dentate gyrus. In the dentate gyrus of the hippocampus, newborn neurons migrate from the SGZ to the granule cell layer. The origin of adult hippocampal neurogenesis is adult neural stem cells, which can grow into functionally matured neurons through a development process that is divided into three main stages—cell proliferation, differentiation, and functional maturity—over 4 to 6 weeks (Duan et al., 2008). About 9,000 new cells are generated each day in the rodent hippocampus of which about 80%–90% differentiated into neurons (Cameron and McKay, 2001). In humans, approximately 700 new neurons are added to the adult hippocampus each day from a study reporting the presence of positive staining for 5-bromo-2'-deoxyuridine (a thymidine analog) in the SVZ and the dentate gyrus region of postmortem brain sections (Eriksson et al., 1998). However, adult neurogenesis is dependent on the production of new neurons and declines with aging (Yau et al., 2014).

Enhanced hippocampal neurogenesis is one of the most notable effects of exercise in the brain (Clark et al., 2009), and might be a key mechanism intermediating exercise-related improvement in the brain functions. Adult hippocampal neurogenesis is doubled by exercise (van Praag et al., 1999). Exercise influences on all aspects of new neuronal maturation, including cell proliferation, survival, and differentiation in the dentate gyrus (Speisman et al., 2013). Furthermore, exercise-enhanced adult hippocampal neurogenesis plays an important role in learning, memory, and neural plasticity (van Praag et al., 1999). In rodents, voluntary running increased the proliferation of cells in the SGZ of both young and aged animals (van Praag et al., 1999). Moreover, voluntary running for three weeks enhanced the survival of adult-born neurons in the hippocampus (Muotri et al., 2009). In addition, voluntary running increased the amplitude of LTP in the dentate gyrus and improved the hippocampus-dependent task in the Morris water

maze (van Praag et al., 2005), indicating that increased neurogenesis correlates with improved cognition. Mild exercise, but not of intense exercise, is effective for the enhancing adult hippocampal neurogenesis, especially the number of mature neurons that improve the spatial memory (Inoue et al., 2015).

Hippocampal neurogenesis is affected by aging (Speisman et al., 2013) and several neurological disorders causing cognitive decline (Zhao et al., 2008). Neurogenesis declines as early as middle-age, and may refer the age-related decline of cognitive function (Erickson and Barnes, 2003). However, the effect of exercise on neurogenesis is retained over the lifespan. Neuroimaging studies indicated that elderly humans with higher aerobic fitness have larger hippocampal volumes and better scores in cognition tasks (Erickson et al., 2009). Young and aged rodents performed running wheel exercise showed enhanced plasticity and better performances on hippocampus-dependent tasks (van Praag et al., 2005).

Short- and long-term exercise improved memory function and prevented hippocampal impairments in Alzheimer disease (AD) model (Parachikova et al., 2008). Also, physical exercise is beneficial for ameliorating some of the neuropathological and behavioral deficits in Parkinson disease animal models (Yau et al., 2014). Exercise promoted the preservation of tyrosine hydroxylase (TH; the rate-limiting enzyme during the synthesis of dopamine)-positive fibers in the striatum and TH-positive neurons in the substantia nigra (Tajiri et al., 2010). Several clinical studies reported that physical exercise can improve motor function and cognitive performance in Parkinson disease patients (Petzinger et al., 2013). These findings suggest that exercise may represent a noninvasive therapeutic intervention to attenuate cognitive decline in neurodegenerative diseases.

CONCLUSIONS

The present study presented evidences suggesting that exercise-induced improvements in cognitive functions are correlated with neurogenesis, synaptic plasticity, and neurotrophins in the hippocampus. Exercise has a positive impact on the aged brain with neurodegenerative disorders that are associated with cognitive decline. Within the hippocampus, the most noticeable changes with exercise are increased production of new neurons and neurotrophic factors. Understanding of neurobiological mechanisms of exercise on brain functions and behaviors may lead to the development of novel therapeutic strategy for neurodegenerative disorders.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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