Abstract  There is a developing consensus that physical exercise is useful as a preventive strategy for cognitive impairment found in patients with dementia, particularly those affected by Alzheimer’s disease. Many reports state that the exercise-induced improvement of cognitive performance is an enhanced expression of a brain-derived neurotrophic factor and adult neurogenesis in the hippocampus, which is an area of the brain that is important for learning and memory. The process of adult hippocampal neurogenesis consists of the proliferation of neural progenitor cells (NPCs) and neural differentiation and maturation involving the neurite (axons and dendrites) extension of NPCs. Exercise training is well known as a promoter of cell proliferation and survival in the hippocampus; however, little is known about the effects of exercise training on neurite outgrowth in the hippocampus. This review presents the effect of exercise training on neurogenesis and neurite outgrowth in the hippocampus.

Keywords: Exercise training, Cognitive impairment, Hippocampus, Neurogenesis, Neurite outgrowth

Introduction

Sharp increases in the number of patients with dementia, involving Alzheimer’s disease (AD), are considered a grave public health problem. Worldwide, 35.6 million people live with dementia; the number has doubled every 20 years and is expected to reach an estimated 65.7 million by 2030, and 115.4 million by 20501. In Japan, the number of patients with dementia involving AD has also increased2. Therefore, finding strategies for the prevention and improvement of dementia and AD is extremely important.

Many epidemiological studies, intervention trials, and animal experiments have demonstrated that cognitive impairment, which is the predominant symptom of dementia and AD, can be prevented and reduced in aged subjects through physical exercise3-5. People who engage in regular exercise or in higher physical activity can lower their risk for dementia and AD6,7. In another study, a 10-week intervention of pool-based aerobic exercise brought about improvements in dual-task performance9. Similar results were observed in studies using an AD model with amyloid precursor protein transgenic (APP-Tg) mice3,10. Cognitive performance of Tg2576 mice, which is one strain of APPTg mice, was improved by self-propelled running exercise in a rotating cage over a period of 5-weeks11. Furthermore, Nichol et al.12 reported that 3-weeks of voluntary wheel running provided improvement in declined spatial learning and memory in aged Tg2576 mice. From these results, physical exercise is strongly suggested to be an effective preventive strategy for dementia and AD.

One of the major reasons for the exercise-induced improvement of cognitive performance is suggested to be enhanced expression of brain derived neurotrophic factor (BDNF) in the hippocampus, which is crucial for the formation of certain types of memory such as episodic and spatial3,10,13,14. BDNF plays an important role in synaptic plasticity, neural cell differentiation, and survival15. In fact, mice deficient in BDNF show learning deficiencies and impaired long-term potentiation15. Moreover, there are many reports that exercise training can induce neurogenesis (the generation of new neurons) in the dentate cognition over an 18-month follow-up period. In another study, a 24-week intervention program of physical activity provided a modest improvement in cognition over an 18-month follow-up period. In another study, a 10-week intervention of pool-based aerobic exercise brought about improvements in dual-task performance9. Similar results were observed in studies using an AD model with amyloid precursor protein transgenic (APP-Tg) mice3,10. Cognitive performance of Tg2576 mice, which is one strain of APPTg mice, was improved by self-propelled running exercise in a rotating cage over a period of 5-weeks11. Furthermore, Nichol et al.12 reported that 3-weeks of voluntary wheel running provided improvement in declined spatial learning and memory in aged Tg2576 mice. From these results, physical exercise is strongly suggested to be an effective preventive strategy for dementia and AD.

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*Correspondence: sakutaku@ks.kyorin-u.ac.jp
gyrus (DG) area of the hippocampus\textsuperscript{16-19}. Neurogenesis involves both proliferation and differentiation involving neurite (axons and dendrites) outgrowth of neural progenitor cells (NPCs) derived from neural stem cells (NSCs)\textsuperscript{20}. Exercise training can enhance cell proliferation in the DG area of the hippocampus; however, little is known about whether exercise training can enhance neurite outgrowth in the hippocampus\textsuperscript{19}. This article reviews the effect of exercise training on neurogenesis, and, in particular, neurite outgrowth in the hippocampus.

**Neurogenesis and neurite outgrowth in the hippocampus**

Neurogenesis, a process of generating functionally-integrated neurons from progenitor cells, was traditionally believed to occur only during embryonic and perinatal stages in the mammalian central nervous system (CNS)\textsuperscript{21}. In 1965, however, Altman and Das\textsuperscript{22} discovered the existence of newly generated dentate granule cells (DGCs) in a postnatal rat hippocampus; and subsequent studies have shown new neurons in the adult CNS and NSCs existing in the adult mammalian brain\textsuperscript{21,23}. Adult neurogenesis occurs throughout life in local microenvironments, or neurogenic niches in the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampal DG subregion, which is a substrate for both cognition and mood regulation\textsuperscript{21,23-25}. The process of adult hippocampal neurogenesis begins with the proliferation of NSC-derived NPCs in the SGZ of the DG\textsuperscript{21,23-25}. Most progeny of NPCs migrate a short distance to the granular cell layer of the DG where they differentiate into DGCs\textsuperscript{23,24} (Fig. 1). Then, DGCs undergo a process of neural morphological and physiological maturation involving neurite outgrowth\textsuperscript{23,24} (Fig. 1). During the process of adult neurogenesis in the SGZ of the DG, a substantial fraction of new-born cells undergo BAX-dependent programmed cell death; that is, only surviving new-born cells can become mature neural cells\textsuperscript{27}.

Complicated brain function, involving learning and memory, is thought to be provided by advanced neural circuits that are formed due to the extension of neurites that can connect via synapses to other neurons and cells. Neurite outgrowth is a complex differentiation process stimulated by many neuronal growth factors, intracellular signal transducers and neurotransmitters, as well as by electrical activity\textsuperscript{26}. For example, fundamental to neurite initiation, elongation and branching are the dynamics of the intracellular cytoskeletons; and the Rho GTPase family of intracellular regulators plays an important role in regulating the cytoskeletal dynamics involved in the processes of axon initiation, elongation, and guidance\textsuperscript{27,28}. Rho GTPases regulate both actin cytoskeletal reorganization and microtubule orientation and stabilization\textsuperscript{27,28}. Furthermore, the serine/threonine kinase Akt, also known as protein kinase B, has a positive influence on neurite outgrowth through its downstream factors, such as cAMP response element binding protein (CREB) and glycogen synthase kinase 3b\textsuperscript{29}. Extracellular agents, such as Wnt signaling, also play a role in the axonal induction and remodeling of the growth cone, which is a structure at the tip of a neurite, via the activation of Rho and c-Jun N-terminal kinases\textsuperscript{30}.

![Schematic model for adult neurogenesis in the dentate gyrus area of the hippocampus (modified from Ref. 16)](image)

**Fig. 1** Schematic model for adult neurogenesis in the dentate gyrus area of the hippocampus (modified from Ref. 16)

Adult neurogenesis begins with the proliferation of neural progenitor cells (NPCs) in the subgranular zone (SGZ) of the hippocampal dentate gyrus subregion, and most progeny of NPCs differentiate into dentate granule cells (DGCs). Then, DGCs undergo a process of neural differentiation and maturation. MOL: molecular layer, GCL: granule cell layer.
Neurogenesis and memory function

A decline in neurogenesis in the hippocampus has been observed in aged rodents and common marmosets, and is thought to be associated with ordinary age-associated cognitive deficits; however, in neurodegenerative diseases accompanied by cognitive impairment such as AD, elucidation of the relationship between cognitive impairment and neurogenesis in the hippocampus remains elusive. For example, regarding neurogenesis in APP mutant mice, both reductions and increases in hippocampal neurogenesis have been observed.

A number of investigations concerning the roles of hippocampal neurogenesis for learning and memory have been performed using a rodent model. In some studies, hippocampal neurogenesis was found to be crucial for certain types of hippocampus-dependent memory, spatial learning, novel object recognition, and pattern separation tasks; although other studies have not indicated a significant relationship between hippocampal neurogenesis and memory function. Dupret et al. used a Morris water maze to evaluate a complex form of spatial memory and found that impairment due to the ablation of hippocampal adult neurogenesis in mice was induced by the death of Bax-dependent hippocampal neural precursor cells. Furthermore, the ablation of hippocampal neurogenesis in adult rats by methylazoxymethanol acetate (MAM) treatment resulted in a deficiency in hippocampus-dependent trace conditioning tasks, but not in hippocampus-independent delay conditioning tasks.

Effects of exercise training on neurogenesis and neurite outgrowth in the hippocampus

An increase in cell proliferation and survival in the DG of the hippocampus is one of the most consistently observed effects of exercise training. In fact, a mere 10 days of wheel running increased cell genesis, evaluated by the labeling of proliferating cells with 5-bromo-2'-deoxyuridine in individually housed rodents. Moreover, exercise training-induced hippocampal cell proliferation and survival occurs at different stages of development, including young adulthood and old age. As a result, exercise training can bring about increases in the quantity of newborn neurons in the DG area of the hippocampus. However, it has remained unclear whether exercise training-induced increases in the quantity of newborn neurons in the DG contribute to improvements in learning and memory. Quite recently, Sahay et al. reported that mice with increased adult hippocampal neurogenesis showed normal spatial learning and contextual fear conditioning, but were more efficient in differentiating between overlapping contextual representations. Since exercise training is able to enhance spatial memory and contextual fear memory, not only an increase in the quantity of newborn neurons, but also an enhancement in the quality of newborn neurons - such as enhanced neurite outgrowth - might be necessary for exercise training-induced prevention and improvement of cognitive deficits.

Several studies have focused on the effects of exercise training and on the elongation of neurite outgrowth in the hippocampus. Wu et al. subjected middle-aged mice to treadmill training and reported that not only neurogenesis, but also the maturation of NPCs and neurite outgrowth of immature neurons located in the area of the DG were promoted by exercise training. Furthermore, the total dendritic length of DG granule cells was significantly increased due to running training.

The authors recently conducted voluntary exercise training that consisted of running on a wheel for 4 months using 2 month-old senescence-accelerated mouse prone 8 (SAMP8) mice, which are considered a model mouse for AD research. The procedure included a conditioned fear memory test. Hippocampus- and amygdala-dependent contextual fear memory in the SAMP8 mice was significantly impaired when compared with that of non-senescent (SAMR1) mice. Exercise training definitely attenuated such cognitive impairment in SAMP8 mice. Moreover, the results of real-time PCR and Western blot analyses following a DNA array analysis in the hippocampus.
Conclusions and future perspectives

As indicated above, compared with hippocampal cell proliferation and survival, there has been little information available about the effects of exercise training on the promotion of neurite outgrowth in the hippocampus. More examination into the effects of exercise training on not only hippocampal cell proliferation and survival, but also neurite outgrowth in the hippocampus, appears to be providing very important information about the mechanisms of the exercise-induced improvement of brain function. Because exercise training, as a preventive and improvement tool for dementia and AD, will probably grow in importance, further studies are required.

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