Serotonin and exercise-induced brain plasticity

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Exercise/physical activity causes a lot of influences on the central nervous system of animals in terms of structure and function. Many studies have reported morphological and behavioral changes that are induced by exercise. For instance, previous studies have shown that exercise augments neurogenesis and synaptogenesis in the hippocampus. Exercise also induces antidepressant effects, and enhances learning and memory. As it is known that exercise induces an increase in serotonin (5-hydroxytryptamine, 5-HT) levels in the animal brain, the serotonin system has been suggested to play a significant role in the neuronal effects induced by exercise. In this review, we discuss the action of serotonin in the brain plasticity, such as enhanced neurogenesis in the hippocampus and antidepressant effects, which are induced by exercise.

Keywords: Serotonin; Exercise; 5-HT receptor; hippocampal neurogenesis; antidepressant effects

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Introduction

It is well known that the risk for cardiovascular and metabolic diseases can be reduced by exercise/physical activity [1,2]. Recently, a lot of evidence has accumulated that exercise causes dramatic influences on the central nervous system [1,2]. Actually, previous studies have shown that exercise has various effects on animal brains at a lot of levels, from the cellular level to the behavioral level. For instance, exercise induces augmentation of neurogenesis [3,4] and synaptogenesis [5,6] in the hippocampus. As for behavioral effects, exercise has antidepressant effects [7,8,9,10], and enhances learning and memory [4,12,13]. Furthermore, exercise has beneficial effects on brain diseases [1,2]. In humans and rodents, exercise delays age-related memory decline [14], reduces risk of neurodegenerative diseases [15,16,17,18], and promotes recovery from brain injury [19]. Many studies have been suggested that neurotransmitters and neurotrophins, such as serotonin (5-hydroxytryptamine, 5-HT) [20,21], BDNF (brain-derived neurotrophic factor) [22,23], IGF-1 (insulin like growth factor-1) [24,25] and VEGF (vascular endothelial-derived growth factor) [26,27], mediate these exercise-induced morphological and functional changes in the animal brain [1,2].

Serotonin is known to play a central role in the regulation of adult hippocampal neurogenesis, and the potential functional relationship between major depression and adult neurogenesis in the hippocampus has been a matter of broad interest [28,29]. In the mammal brains, serotonin is produced in neurons that are located mainly in the brainstem raphe nuclei [30]. The hippocampal dentate gyrus has a very dense plexus of serotonergic fibers [31,32,33]. Previous studies have shown that the increase in neurogenesis in the hippocampal dentate gyrus is necessary for antidepressant effects of serotonin-based antidepressant drugs, such as the selective serotonin reuptake inhibitor (SSRI) [34,35,36]. Both serotonin and exercise augment adult hippocampal neurogenesis [3,4,7,8,9,10], and have antidepressant effects [1,7,8,9,30,11,40]. Moreover, exercise results in elevated levels of serotonin in the hippocampus, which could affect cognitive and emotional behavior [41,42,43,44]. Interestingly, it has recently been
demonstrated that the brain serotonin is an essential positive regulator of exercise-induced hippocampal neurogenesis by using the Tph2-deficient mice, which are selectively depleted in serotonin in the brain [21]. Then, how does serotonin act in the neurogenic response in the dentate gyrus of the hippocampus and antidepressant-like behavior that are induced by exercise? In this review, we discuss the action of serotonin in the brain plasticity, such as enhanced hippocampal neurogenesis and antidepressant effects that are induced by exercise.

Exercise and serotonin

Fourteen distinct 5-HT receptor subtypes have been identified by cloning technique and pharmacological analyses, and these are classified into seven receptor families, from 5-HT1 to 5-HT7, on the basis of the structural, functional and pharmacological properties [45]. Most members of the 5-HT receptor family are G protein-coupled metabotropic receptors which activate an intracellular second messenger cascade [45], but one member of the family, the 5-HT3 receptor, is a ligand-gated ion channel [46,47]. The 5-HT receptors show regional distribution in brain areas that are involved in cognitive and emotional function, such as hippocampus, amygdala, and prefrontal cortex [45,48]. It has been shown that exercise increases the levels of serotonin in the animal brain [41,42,43,44]. Actually, it has been reported that exercise increases tryptophan hydroxylase, which is the rate-limiting enzyme of serotonin biosynthesis in brainstem raphe neurons [2,49]. The raphe nucleus is densely populated with serotonergic neurons, and sends projections to the hippocampus, especially to the dentate gyrus [31,32]. Therefore, the serotonin system can control neural plasticity in the hippocampal dentate gyrus [33]. Furthermore, the hippocampal dentate gyrus is involved in the affective processes, and is an important brain region associated with mood disorders, such as major depression [50]. These findings have been suggested that serotonin is one of the most important factors which mediate exercise-induced neuronal effects on the brain. From the next part, we review the 5-HT receptors and neuronal plasticity, such as enhanced hippocampal neurogenesis and antidepressant effects, which are induced by exercise.

Serotonin and hippocampal neurogenesis

Neurogenesis continues postnatally and into adulthood in some regions of the animal brain [8,28]. Adult neurogenesis occurs prominently in the dentate gyrus of the hippocampus [8,28]. The hippocampal dentate gyrus is composed of round granule cells. New neurons are derived from progenitor cells that reside in the subgranular zone just below the granule cell layer. Progenitor cells migrate into the granule cell layer and differentiate into mature neurons [50]. Thus, newly generated granule cells in the dentate gyrus are integrated into the neural network functionally, and increase the neuronal capacity of the brain function [51,52].

Serotonin is known to be a mitogenic factor in non-neuronal systems [53,54]. In addition, serotonin has been shown to cause a neurogenic effect in the hippocampus. The depletion of serotonin in the brains of adult rodents decreases neurogenesis in the hippocampal dentate gyrus [55]. Furthermore, many studies demonstrate that chronic administration of an antidepressant, such as SSRIs, increases generation of new granule cells in the adult hippocampal dentate gyrus [34,36,39,56]. Recent findings suggest that an increase in hippocampal neurogenesis could be a causal factor in the effects of serotonin-based antidepressant drugs [34,35,36]. Research using genetically 5-HT receptor-deficient mice and pharmacological analyses revealed that several 5-HT receptors are involved in the regulation of adult hippocampal neurogenesis [57]. Treatment with the selective 5-HT1A receptor agonist 8-OH DPAT produces an increase in cell proliferation in the dentate gyrus [39,58]. Meanwhile, the 5-HT1A receptor antagonist administration decreases cell proliferation [39,59]. The 5-HT1A receptor-deficient mice show no changes in baseline cell proliferation but exhibit a decreased cell survival in the hippocampal dentate gyrus [34,60]. In addition, the 5-HT1A receptor has been shown to be required for the cell proliferation by fluoxetine, which is one of SSRIs [34]. The 5-HT2 receptor antagonist Cinanserin induces an increase in cell proliferation [39]. In contrast, administration of the 5-HT2 receptor agonist α-methyl-5-HT decreases hippocampal cell proliferation [39]. Treatment with the selective 5-HT2C receptor agonist WAY161503 decreases cell proliferation moderately [39]. The 5-HT2C receptor antagonists, SB 243213 and S 3206, induce an increase in cell proliferation in the dentate gyrus [61]. Acute treatment with the selective 5-HT3 receptor agonist SR 57227A promotes hippocampal neurogenesis [62,63]. The 5-HT3A receptor subunit-deficient mice show normal basal cell proliferation and cell survival in the hippocampal dentate gyrus [62,63]. Intriguingly, it has recently been revealed that the 5-HT3 receptor is necessary for the exercise-induced neurogenic response in the hippocampal dentate gyrus [62,63]. Three day treatment of the 5-HT4 receptor agonist RS 67333 increases cell proliferation [65]. Treatment with the 5-HT7 antagonist SB 269970 for seven days causes an increase in cell proliferation [66]. Different 5-HT receptor subtypes can be involved in the neurogenic response in the hippocampal dentate gyrus [57]. Molecular mechanisms of the 5-HT receptor-mediated effects on adult hippocampal neurogenesis are not fully known. Detail studies of the molecular mechanism will contribute to understanding of the regulation of hippocampal neurogenesis.

The differences have been demonstrated between the dorsal and ventral hippocampus in the connectivity and function [29,67,68]. In addition, it has been suggested that adult neurogenesis in the dorsal and ventral hippocampal dentate
gyrus plays distinct roles in regulation of cognitive and emotional function \cite{29,69,70}. It has been reported that serotonergic fibers supply dense input to the ventral part of the hippocampus \cite{71,22}. Further analyses of the relationship of serotonin to adult hippocampal neurogenesis in terms of the dorsoventral/septotemporal axis are necessary in future studies.

**Serotonin and antidepressant effects**

Major depression is one of the most common mental disorders. The serotonin system is involved in the pathophysiology and treatment of major depression \cite{73}. Actually, serotonergic antidepressant drugs, such as SSRIs, are the first-line drug treatments for depression \cite{73}. The preclinical and clinical studies have shown the involvement of distinct 5-HT receptors in the therapeutic effects of antidepressant drugs \cite{73}. Activation of the presynaptic 5-HT1A and 5-HT1B receptors reduces terminal serotonin release, which leads to negative effects of antidepressant treatments \cite{74,75}. In contrast, stimulation of the postsynaptic 5-HT1A receptor causes positive effects on the antidepressant action. Previously, clinical effects of the 5-HT1A receptor partial agonists on depression were reported \cite{76}. Further, deletion of the 5-HT1A receptor results in loss of the behavioral effects of SSRIs \cite{34}. Previous studies have shown that the blockade of the 5-HT2C receptor potentiates the effects of SSRIs on neurochemical and behavioral properties \cite{77,78}. Although some studies have shown that the 5-HT3 receptor antagonist produces antidepressant-like effects \cite{79} and the agonist attenuates the action of antidepressants \cite{80}, others have reported antidepressant-like effects of the selective 5-HT3 receptor agonist SR 57227A on its own \cite{81}. Treatment of the 5-HT4 receptor agonist produces antidepressant effects \cite{65}. The 5-HT6 receptor antagonist exerts antidepressant effects in rodents \cite{82}. In addition, the 5-HT7 receptor antagonist causes antidepressant-like effects in preclinical studies \cite{83}. The precise mechanism of serotonin action in exercise-induced antidepressant effects was unknown; however, a recent study has shown that the 5-HT3 receptor plays an indispensable role in antidepressant-like behavior induced by exercise \cite{62,63}.

**Discussion**

There is a lot of evidence that exercise can be an effective treatment for major depression \cite{7,8,9}. In addition, exercise causes an increase in adult neurogenesis in the hippocampal dentate gyrus \cite{3,4}. Many studies have shown that adult hippocampal neurogenesis is enhanced by interventions which are involved in positive effects on mood and cognition, such as exercise \cite{3,21} and antidepressants treatment \cite{34,36}. These findings have suggested that enhanced neurogenesis in the hippocampal dentate gyrus could be a cellular basis for beneficial behavioral responses, such as antidepressant effects \cite{34,35,36}. However, it has been suggested that behavioral effects induced by exercise \cite{62} and antidepressants \cite{84} are mediated by two types of mechanisms: one is neurogenesis-dependent and the other is neurogenesis-independent. Considering previous findings in the studies of behavioral effects caused by SSRIs \cite{84}, serotonin is involved in both mechanisms. Therefore, the signaling pathway could be different; however, this possibility should be carefully examined in the future research.

**Conflict of interest**

The authors declare no conflict of interest.

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**References**


68. Fanselow MS, Dong HW. Are the dorsal and ventral hippocampus functionally distinct structures? Neuron 2010; 65: 7-19.


