·Minireview·

Beneficial effects of moderate voluntary physical exercise and its biological mechanisms on brain health

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Abstract: This article reviewed the beneficial effects of moderate voluntary physical exercise on brain health according to the studies on humans and animals, which includes improving psychological status and cognitive function, enhancing psychological well-being, decreasing the risks of Alzheimer's disease (AD) and dementia, and promoting the effects of antidepressant and anxiolytic. The possible underlying neurobiological mechanisms are involved up-active and down-active pathways. The up-active pathway is associated with enhancements of several neurotransmitters systems afferent to hippocampus, including norepinephrine (NE), serotonin (5-Hydroxytryptamine, 5-HT), acetylcholine (ACh) and γ-aminobutyric acid (GABA). The down-active pathway is mainly concerned with up-regulation of the brain-derived neurotrophic factor (BDNF) and neurogenesis. It is suggested that NE activation via β-adrenergic receptors may be essential for exercise-induced BDNF up-regulation. The possible intracellular signaling pathways of NE-mediated BDNF up-expression may be involved in GPCR-MAPK-PI-3K crosstalk and positive feedback.

Keywords: exercise; brain; cognition; norepinephrine; serotonin; brain-derived neurotrophic factor

1 Introduction

Benefits of moderate physical exercise are well established in the cardiovascular system and are becoming clear in a range of physical disorders including diabetes, renal disease, and osteoporosis. Although physical exercise has long been equated with better physical health, there is now extensive research showing that it has substantial benefits for the psychological health as well. One of the most important effects of exercise is the effect on cognition. Exercise not only improves cognitive function in normal individuals, but also is associated with a lower risk for depression, AD and other types of neurodegenerative diseases[1]. Studies on humans and animal models also suggest that moderate voluntary physical exercise might attenuate some of the cognitive symptoms and mitigate the psychological disorders. Recent research has attempted to identify molecular and cellular changes in the central nervous system elicited by physical activity. Studies in animal models have identified several key responses, including activation of neurotransmitter systems, up-regulation of neurotrophic factors, increase of neurogenesis, and improvement of learning and memory, which might be keys to improve brain health in response to exercise.

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2 Data from studies on humans

Apart from physiological benefits associated with moderate physical exercise regularly performed, a number of psychological benefits have also been reported in the literatures. Exercise not only improves cognitive function in normal individuals, but also is associated with a lower risk for depression, AD, and other types of neurodegenerative diseases and cognitive decline related to aging.

2.1 Exercise induces psychological and cognitive improvements Regular moderate physical exercise has beneficial short-term and long-term effects on psychological improvements. DiLorenzo TM *et al*. ever reported that adult

exercisers experienced a positive fitness change and psychological improvement over the initial 12-week aerobic fitness program compared with the control group. At one year follow-up, physiological and psychological condition remained to be improved *vs* baseline significantly. The researcher reported that participants in the exercise group did not increase the amount of weekly exercise they performed over the 12-month follow-up period and thus the maintenance of psychological improvements occurred concurrent with equal or lesser amounts of exercise[2]. These results indicate that exercise-induced aerobic fitness have beneficial short-term and long-term effects on psychological outcomes.

Regular moderate physical exercise enhances psychological well-being. Hassmén P *et al*. indicated the consistent connection between enhanced psychological well-being and regular physical exercise from an investigation of a total of 3403 adult participants (1856 women and 1547 men). The results of the cross-sectional study suggested that individuals who exercised at least two to three times a week experienced significantly less depression, anger, cynical distrust, and stress than those exercising less frequently or not at all. Furthermore, regular exercisers also perceived their health and fitness to be better, while less frequent exercisers did not. Finally, those who exercised at least twice a week reported higher levels of coherence sense and a stronger feeling of social integration than their less frequently exercising counterparts[3]. These results indicate that regular exercise has beneficial effect on psychological well-being enhancement.

The benefits of exercise also have an effect on older persons. A meta-analysis examined data from 36 studies linking physical activity with well-being in older adults without clinical disorders. The result showed that aerobic training was most beneficial for several types of well-being, and moderate intensity activity was the most beneficial activity level[4]. Moreover, Colcombe S *et al*. also provided convincing evidence that aerobic fitness training in older persons improved cognitive function, especially executive-control processes. Although the magnitude of the effects varied, a beneficial impact of aerobic exercise training was found in general, independent of type, duration, or intensity of physical activity[5]. All these results indicate that exercise can benefit and improve cognitive function to older persons especially.

In addition, exercise also has antidepressant and anxiolytic effects. Salmon P demonstrated from reviewing results of cross-sectional and longitudinal studies that aerobic exercise training has antidepressant and anxiolytic effects and protects against harmful consequences of stress[6].

2.2 Exercise decreases risks of Alzheimer's disease (AD) and dementia AD is a progressive neurodegenerative disease for which there are few therapeutics that affect the underlying disease mechanism. Recent epidemiological studies, however, suggested that lifestyle changes may slow the onset or progression of AD, which revealed that physical activity is associated with lower risks of cognitive impairment, AD and dementia in general.

A retrospective case control study reported that patients with AD were less active (both intellectually and physically) in midlife and that inactivity was associated with a 250% increased risk of developing AD[7]. Similarly, a prospective study also demonstrated that physical activity was protective against the development of cognitive impairment, AD, and any types of dementia, and that the highest activity group showed a 60% decrease in the incidence of AD[8].

An animal study with transgenic model of AD showed that voluntary physical exercise can decrease significantly amyloid-β protein (Aβ) loaded in brain regions. Whereas pharmacological interventions have sought to reduce Aβ to constrain the AD cascade, Paul AA *et al*. demonstrated here that exercise represents a simple behavioral strategy that may promote a resistance to the development of the neuropathology of AD[9].

3 Data from studies on animals

Extensive research on humans suggests that physical exercise could benefit to cognitive function. Studies using animal models have been directed towards understanding the neurobiological bases of these benefits. It is now clear that physical exercise produces beneficial effects on neuronal functions, including hippocampal dependent learning and neuroprotection. The mechanisms underlying these effects are mediated in part by increased expression of neurotrophic factors, and most work has focused on the brain-derived neurotrophic factor (BDNF). In addition, exercise also increases neurogenesis in the granule cell layer of the adult hippocampus, and neurotransmission as well.

3.1 Exercise increases BDNF BDNF, as a member of the structurally and functionally homologous neurotrophins family, is the most widely distributed trophic factor in brain,

and acts as a key mediator to regulate neuronal survival, growth, maintenance, neurogenesis and synaptic plasticity, such as long-term potentiation (LTP)—a biological model of learning and memory. Furthermore, BDNF is present in the hippocampus with highest concentrations, a brain area with vital functions in learning and memory as well as behavioral.

Neeper SA *et al*. first reported in 1995 that voluntary physical exercise increased hippocampal BDNF mRNA levels in adult rats[10]. Now, much evidence proves that exercise increases BDNF expression in many brain regions. Notably, the voluntary wheel running activity, the most common physical exercise model in the research area, increased BDNF mRNA levels in the rat hippocampus in as little as 6 h[11]. It is reported that several days (2-20 d) of voluntary wheel running increased levels of BDNF mRNA in the hippocampus and that the changes in mRNA levels were also found in several hippocampal regions, most notably in the dentate gyrus (DG), CA3 and CA4. Moreover, the exercise-induced incensement (120 - 300 pg mL^{-1}) of BDNF mRNA levels were also correlated with running distance (1-5 km per night) and sustained even after several weeks of exercise, and were also paralleled with the increased amounts of BDNF protein[12]. In addition to in the hippocampus, the running activity also increased levels of BDNF mRNA in the lumbar spinal cord, cerebellum and cortex as well, but not in the striatum. Although other trophic factors, including nerve growth factor (NGF) and fibroblast growth factor 2 (FGF-2) , were also induced to increase in the hippocampus in response to exercise, their up-regulation was transient and less robust than that of BDNF, suggesting that BDNF is a better candidate for mediating the long-term benefits of exercise on the brain[13].

On the other hand, there are also a growing body of evidence demonstrating that a lack of neurotrophic support contributes to the pathology of those principal mental disorders, such as AD, depression, and other chronic stress-induced metal disorders[12,14]. Many researchers have theorized that neuronal atrophy and death in neurodegenerative disorders result from, in part, a lack of neurotrophic support. In fact, it is possible that physical exercise might protect against those mental disorders and exert beneficial effects by counteracting the decrease in neurotrophin levels caused by these disorders. Consequently and rationally, up-regulation of neurotrophic factors, such as BDNF, is thought to be the main opposite-effect induced by exercise[15].

3.2 Exercise increases neurogenesis Neurogenic activity has been observed in the DG of adult animals in a number of species, including mice, rats, birds, primates and humans[16]. van Praag H *et al*. reported that voluntary physical activity in running wheel enhanced the number of hippocampal DG cells in mice. Concurrently, the exercise also improved of the performance in Morris water maze and increased the DG LTP selectively[17], which suggested a close relationship between neurogenesis and the hippocampal function involved in the behavioral performance on spatial memory task.

Further studies confirmed that the enhancements in neurogenesis and LTP induction/expression are accompanied by concurrent increases in the expression of BDNF, NR2B (subtype of NMDA receptor) and glutamate receptor 5 (GluR5) mRNA[16]. As these increases are confined to the DG, it strongly indicated that these alterations may be involved in regulating the enhanced functional and structural plasticity.

3.3 Exercise increases neurotransmission Chronically physical exercised animals have shown increased levels of norepinephrine (NE) and serotonin (5-HT) in most brain areas, compared to sedentary controls. Chronic voluntary wheel running increases NE in several brain regions and spinal cord[18]. Dramatic increases in NE can also be observed with treadmill running in brain regions such as hippocampus, locus coeruleus, and central and medial amygdala[19]. Evidence also proves that exercise increases 5-HT release and metabolism[25]. In addition, the effects of exercise on the 5-HT system appear to be highly dependent upon the receptor subtypes and brain areas examined, and may not be as immediate as NE system[20].

Studies demonstrated that NE and 5-HT, known to be monoamines and two of classical central neurotransmitters, can regulate synaptic plasticity, enhance neuronal survival, promote neural repair and improve mood, respectively[20-22]. Therefore, it is hypothesized reasonably that NE and/or 5-HT may be important in the exercise-induced protective effects on brain, and may participate in the up-regulation of BDNF in response to exercise.

Moreover, other studies ever reported that exercise activates cholinergic and GABAergic afferents to the hippocampus, and suggested ACh-mediated and/or GABA-mediated activation might also underlie the regulation of BDNF by exercise[12].

4 Possible relationships between exercise-induced BDNF expression and neurotransmission

Evidence from both human and animal studies has implicated monoaminergic hypofunction as a treatable component of depression. Antidepressant medications are therefore designed to enhance serotonergic (5-HT) or noradrenergic (NE) neurotransmission to counteract the effects of depression. Recent studies demonstrated that down-regulations of neurotrophic factors levels and neurogenesis could contribute to the risk of depressed subjects, leading to a neurotrophic hypothesis of depression[23]. Therefore, up-regulation of neurotrophic factors, especially BDNF, can block or reverse the depression effects, which highlight the mechanism underlying the action of antidepressants treatment[14]. In fact, those studies provide strong evidence that increased expression of BDNF is a downstream effect of increased 5-HT/NE neurotransmission, and that may be responsible for the therapeutic effect of antidepressants.

Conceivably, physical exercise has the same effects of antidepressants to increase hippocampal BDNF expression and NE/5-HT levels, which leads to the hypothesis that the pathway of increased BDNF mRNA expression occurring with exercise may be initiated by monoaminergic activation (the same mechanism proposed for antidepressant action)[12]. In addition, further studies suggested that noradrenalin-mediated signaling might be particularly important in the modulation of BDNF gene expression by exercise. These results confirmed that NE stimulation is an important initial event in the cellular mechanisms leading to enhanced BDNF transcription following physical exercise. It is suggested that NE activation via β-adrenergic receptors may be essential for exercise- and antidepressant-induced BDNF regulation[23]. 5-HT_{1A} and $5\text{-HT}_{2A/C}$ receptors activation, on the other hand, appear to be most important for antidepressant-induced BDNF regulation[20].

Otherwise, some studies showed that the medial septum, being a source of cholinergic and GABAergic afferents to the hippocampus, might also participate in the up-regulation of BDNF in response to exercise. However, although septal ACh-mediated input provides tonic regulation of baseline hippocampal BDNF gene expression, it is not a key regulator in the activity-dependent state. By contrast, when partial loss of septal cholinergic afferents was combined with loss of medial septal GABAergic neurons, exercise-dependent BDNF regulation was disrupted, notably in the DG and hilus. Thus the medial septum may be involved in activity-dependent regulation of BDNF expression[13].

5 Possible NE-mediated pathways of exercise-induced BDNF expression

Previous studies indicate that stimulation with NE may be essential for the increases in hippocampal BDNF mRNA expression in rats following voluntary physical exercise in rats. Furthermore, Chen's study determines which are the key signaling cascades taking part in the intracellular events of enhanced BDNF expression following NE stimulation in these neurons, using isolated embryonic hippocampal neurons and immunoblotting. Results of this study provide an *in vitro* model of the intracellular signaling mechanisms activated by NE, via ligand-G-protein-coupled receptor (GPCR)-to-BDNF-RTK transactivation. It is demonstrated that NE-induced BDNF signaling takes effect via GPCR-MAPK-PI-3K crosstalk and positive feedback. This mechanism may partly explain the rapid and robust enhancement in BDNF expression observed with physical exercise *in vivo*[22].

6 Conclusions

Studies on humans demonstrate that regular moderate physical exercise has beneficial effects on brain health. Exercise improves psychological status and cognitive function, enhances psychological well-being, promotes the effects antidepressant and anxiolytic and decreases the risks of AD and dementia. Studies on animals with voluntary physical exercise partly reveal the neurobiological mechanisms underlying these effects, mostly involved in the hippocampus. The possible exercise-induced up-active pathway may be associated with enhancement of several neurotransmitters systems afferent to hippocampus, including NE, 5-HT, ACh and GABA. The possible down-active pathway may mainly be the up-regulation of BDNF and the neurogenesis increase, which are the key outcomes in response to exercise. Moreover, exercise-induced NE activation could be important in up-regulation of BDNF. It is suggested that NE activation via β-adrenergic receptors may be essential for exercise -induced BDNF regulation. The possible intracellular signaling pathways of NE-mediated BDNF up-expression is involved in GPCR-MAPK-PI-3K crosstalk and positive feedback.

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References:

[1] Dishman RK, Berthoud HR, Booth FW, Cotman CW, Edgerton VR, Fleshner MR, *et al*. Neurobiology of Exercise. Obesity (Silver Spring) 2006, 14: 345-356.

[2] DiLorenzo TM, Bargman EP, Stucky-Ropp R, Brassington GS, Frensch PA, LaFontaine T. Long-term effects of aerobic exercise on psychological outcomes. Prev Med 1999, 28: 75-85.

[3] Hassmén P, Koivula N, Uutela A. Physical exercise and psychological well-being: a population study in Finland. Prev Med 2000, 30: 17-25.

[4] Netz Y, Wu MJ, Becker BJ, Tenenbaum G. Physical activity and psychological well-being in advanced age: a meta-analysis of intervention studies. Psychol Aging 2005, 20: 272-284.

[5] Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci 2003, 14: 125-130.

[6] Salmon P. Effects of physical exercise on anxiety, depression and sensitivity to stress: a unifying theory. Clin Psychol Rev 2001, 21: 33-61.

[7] Friedland RP, Fritsch T, Smyth KA, Koss E, Lerner AJ, Chen CH, *et al*. Patients with Alzheimer's disease has reduced activities in midlife compared with healthy control-group members. Proc Natl Acad Sci USA 2001, 98: 3440-3445.

[8] Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol 2001, 58: 498-504.

[9] Paul AA, Victoria MP, Viorela P. Voluntary Exercise decreases amyloid load in a transgenic model of Alzheimer's disease. J Neurosci 2005, 25: 4217-4221.

[10] Neeper SA, Gómez-Pinilla F, Choi J, Cotman C. Exercise and brain neurotrophins. Nature 1995, 373: 109.

[11] Oliff HS, Berchtold NC, Isackson P, Cotman CW. Exercise-induced regulation of brain-derived neurotrophic factor (BDNF) transcripts in the rat hippocampus. Brain Res Mol Brain Res 1998, 61: 147-53.

[12] Antonio AG, Tony GH, Celithelma G, Chen MJ, Russo-Neustadt AA. Exercise antidepressant treatment and BDNF mRNA expression in the aging brain. Pharmacol Biochem Behav 2004, 77: 209-220.

[13] Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci 2002, 25: 295-301.

[14] Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. Biol Psychiatry 2006, 59: 1116-1127.

[15] Duman RS. Neurotrophic factors and regulation of mood: role of exercise, diet and metabolism. Neurobiol Aging 2005, 26 Suppl 1: 88-93.

[16] Farmer J, Zhao X, Van PH, Wodtke K, Gage FH, Christie BR. Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-dawley rats *in vivo*. Neuroscience 2004, 124: 71-79.

[17] van Praag H, Shubert T, Zhao C, Gage FH. Exercise enhances learning and hippocampal neurogenesis in aged mice. J Neurosci 2005, 25: 8680-8685.

[18] Dunn AL, Reigle TG, Youngstedt SD, Armstrong RB, Dishman RK. Brain norepinephrine and metabolites after treadmill training and wheel running in rats. Med Sci Sports Exerc 1996, 28: 204-209.

[19] Sarbadhikari SN, Saha AK. Moderate exercise and chronic stress produce counteractive effects on different areas of the brain by acting through various neurotransmitter receptor subtypes: a hypothesis. Theor Biol Med Model 2006, 23: 33-43.

[20] Garcia C, Chen MJ, Garza AA, Cotman CW, Russo-Neustadt AA. The influence of specific noradrenergic and serotonergic lesions on the expression of hippocampal BDNF transcripts following voluntary physical activity. Neuroscience 2003, 119: 721-732.

[21] Mark PM, Atuart M, Bronwen M. BDNF and 5-HT: a dynamic duo in age-related neuronal plasticity and neurodegenerative disorders. Trends Neurosci 2004, 27: 589-594.

[22] Chen MJ, Nguyen TV, Pike CJ, Russo-Neustadt AA. Norepinephrine induces BDNF and activates the PI-3K and MAPK cascades in embryonic hippocampal neurons. Cell Signal 2007, 19: 114-128.

[23] Gobbi G, Blier P. Effect of neurokinin-1 receptor antagonists on serotoninergic, noradrenergic and hippocampal neurons: Comparison with antidepressant drugs. Peptides 2005, 26: 1383-1393.

[24] Ivy AS, Rodriguez G, Garcia C, Chen MJ, Russo-Neustadt AA. Noradrenergic and serotonergic blockade inhibits BDNF mRNA activation following exercise and antidepressant. Pharmacol Biochem Behav 2003, 75: 81-88.

[25] Xu CX, Liu HT, Wang J. Changes of 5-hydroxytryptamine and tryptophan hydroxylase expression in the ventral horn of spinal cord. Neurosci Bull 2008, 24: 29-32.

自愿适量运动对脑的有益作用及其生物学机制

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摘要：本文综述了在人和动物方面有关自愿适量运动有益于脑作用的研究，包括改善心理状态和认知功能、增强心理幸福感、降低老年痴呆症发生危险度和发挥抗抑郁及抗焦虑药的作用等。运动对脑的作用机制包含上游和下游两方面：上游途径主要涉及投射到海马的几种神经递质系统的功能增强，其中包括去甲肾上腺素、5-羟色胺、乙酰胆碱和γ-氨基丁酸；下游途径主要涉及脑源性神经营养因子的表达提高和神经元发生的增强；其中，激活β受体介导的去甲肾上腺素能神经的传递被认为是运动导致脑源性神经营养因子表达增强的前提，上述过程在细胞内的可能信号转导机制主要涉及G-蛋白偶联受体-促分裂原活化蛋白激酶-磷脂酰肌醇(-3)激酶等细胞信号转导通路的交互及正反馈调控。

关键词：运动；脑；认知；去甲肾上腺素；5-羟色胺；脑源性神经营养因子