



Effects of Physical Activity-Induced Myocytokines on Alzheimer's Disease

He Q^{1,2*}, Wu J³, Zhu L², Wang H¹ and Han Y¹

¹Physical Education Institute, Guangxi Normal University, Guilin, China

²Department of Physical Education and Health, Guangxi University for Nationalities, China

³Department of Physical Education, Guangxi Medical University, China

*Corresponding author: Yanbai Han, Physical Education Institute, Guangxi Normal University, Yanzhong Road 1, Guilin, Guangxi, China, Tel: 86-0773-5845941; Email: yanbaih0806@163.com

Mini Review

Volume 5 Issue 1

Received Date: January 12, 2022

Published Date: February 07, 2022

DOI: 10.23880/jqhe-16000255

Abstract

This article aims to summarize the current research on the influence of physical activity-induced changes in myocytokine secreted by skeletal muscle cells on Alzheimer's disease (AD). Alzheimer's disease is the most common neurodegenerative disease leading to dementia. The limited clinical effect of current drug therapy, and there is no effective treatment strategy to treat, reverse or slow down the progression leading to an irreversible course. Physical activity (PA) is any physical exercise produced by skeletal muscles that requires energy consumption. Research shows that moderate physical activity is beneficial to health, and more evidence supports the beneficial effects of PA on neurodegenerative diseases such as AD, Mild cognitive impairment, and Dementia. This article reviewed the current research progress on the influence of changes in myocytokine expression induced by physical activity on AD, which would lay the foundation for further exploration of the mechanism of physical activity to improve cognition and prevent AD in the elderly.

Keywords: Alzheimer's Disease; Physical Activity; Myocytokines; Brain Derived Neurotrophic Factors

Abbreviations: AD: Alzheimer's Disease; PA: Physical Activity; BDNF: Brain-Derived Neurotrophic Factor; MeSH: Medical Subject Headings; BBB: Blood-Brain Barrier; TrkB: Tyrosine Kinase Receptor B; FNDC5: Fibronectin Type III Domain-Containing Protein 5; HICT: High-Intensity Circuit Training; MCT: Monocarboxylate Carrier; GPR: G Protein-Coupled Receptor.

Introduction

According to statistics, about 50 million people in the world currently suffer from dementia. It is expected that this number will increase to 152 million by 2050, leading to a trillion dollars in losses per year [1] and bringing huge

economic, living and psychological burdens to the families of patients. AD is the most common neurodegenerative disease leading to dementia with the typical pathological features including extracellular amyloid β ($A\beta$) aggregation and intracellular neurofibrillary tangles composed of excessive phosphorylation of tau protein [2]. It is accompanied by a series of neurodegenerative events in the hippocampus, including microglia and astrocyte activation, neuroinflammation, oxidative damage, energy metabolism failure, and subsequent nerve cell apoptosis [3,4]. Despite a large number of studies conducted in this field, most of them end in failed clinical trials [5]. Currently, there is no effective treatment to treat, reverse or slow down the progression of AD [6].

More evidence supports that there is an interaction between muscle tissue and other organs. The myocytokines can act on many tissues in the body and produce beneficial effects at the multi-system level. This article aims to refine the possible mechanism of myocytokine changes caused by exercise on regulating brain-derived neurotrophic factor (BDNF) expressions and provide a reference for further researches on the specific mechanism of exercise to improve AD improving AD.

The Aim

The purpose of this article is to organize and analyze the progress of the impact of physical activity on improving the cognitive functions in AD patients, explore research hotspots and future research directions in related fields, and provide references for scholars who are conducting related researches.

Methodology

The subject words, including Alzheimer's Disease, Physical Activity, Cognitive impairment, Brain-derived neurotrophic factor, and elderly/aged/Older adults/aged individuals, were selected using the Medical Subject Headings (MeSH). A comprehensive search was applied in the PubMed and Google Scholar databases. According to the search results, the research progress on the effects of physical activity on cognitive function in AD patients was organized. The changes of myocytokines expression in the peripheral blood after physical activity and their impacts on regulating the expressions of BDNF in the brain and the subsequent cognitive functions of AD patients were discussed.

Results

Physical activity refers to the body movement produced by skeletal muscles that requires energy consumption. Exercise is a subset of PA, which is planned, organized, and repeated PA, whose ultimate or intermediate goal is to improve or maintain physical health. It has been believed that moderate amounts of PA are beneficial to health for a long time, and much more evidence supports the beneficial effects of PA on neurodegenerative diseases such as AD, Mild cognitive impairment, and Dementia have been presented [7,8]. In the process of physical activity, the contraction and relaxation of skeletal muscle stimulate muscle cells to produce a large number of cytokines and release them into the blood, including BDNF, irisin, cathepsin B (CTSB), lactic acid, and ketone bodies, etc. These cytokines are transported throughout the body by the blood circulation and can cross the blood-brain barrier (BBB) to reach various brain regions, which further stimulates the hippocampus to increase the expression of BDNF and the subsequent neurotrophic and

neuroprotective effects.

Brain-Derived Neurotrophic Factor (BDNF)

BDNF is a basic protein isolated and purified from the pig brain in 1982, and plays a crucial role in regulating brain plasticity and memory functions [9]. The molecular weight of BDNF is 12.3 kD, and its gene is located at 11P13. The precursor of BDNF is composed of 247 amino acid residues, and it exerts the biological role by binding to the tyrosine kinase receptor B (TrkB), which can specifically binds to BDNF in the hippocampus, and then promotes the survival of nerve cells and increases synaptic plasticity and neurogenesis [10].

Exercise can increase the expression of BDNF by enhancing cytokine secretion, which is conducive to preventing cognitive damage and improving cognitive function in the elderly. The levels of BDNF in the blood and brain of AD patients are down-regulated in the early stage of AD, which is positively correlated to cognitive decline [8]. Even one-time acute physical exercise can have beneficial effects on BDNF production in healthy adults and elderly AD patients [11]. Rasmussen et al. demonstrated that aerobic exercise can increase the mRNA level of BDNF in the hippocampus and cortex of the mouse brain through a treadmill exercise test. It was also confirmed that the BDNF levels in the blood samples collected from the radial artery and internal jugular vein of subjects undergoing aerobic exercise were significantly up-regulated (3-fold) compared with the resting state, accounting for about 70-80% of circulating BDNF levels [12]. However, there is also evidence that although the mRNA and protein expressions of BDNF in human skeletal muscle is increased after exercise, myogenic BDNF is not released into the circulation, but retained in skeletal muscle and myotubes activating the phosphorylation of TrkB and ERK in an autocrine and/or paracrine manner [13]. In addition, exercise intervention contributed to the maintenance of brain homeostasis in AD transgenic model mice with invasive brain amyloidosis although the improvement of neurogenesis could not alleviate the AD symptoms [14]. Therefore, further research is needed to study the therapeutic mechanism of exercise-induced BDNF signal transduction and neurogenesis in AD patients.

Acute exercise usually increases BDNF, however, the effect of chronic exercise on blood BDNF levels is less obvious [15]. Studies have shown that BDNF level decreased after exercise training, which was closely related to metabolomic alterations. Indeed, lipid metabolites (such as ceramides and sphingolipids) regulate neurotrophin signaling in the brain [16]. However, the regulation of BDNF by metabolites in the blood under exercise conditions has not been confirmed. On the other side, there is also a report that suggested no

significant association between BDNF and the overall cognitive ability or executive functions [17], or the increased cognitive ability in patients with mild cognitive impairment was not associated with the up-regulated BDNF expression [18]. Therefore, the relationship between muscle-derived BDNF and the increase in brain-derived BDNF needs to be revealed by further studies.

Irisin

Irisin is a motion-induced myosin. Its fibronectin type 2 domain-containing protein 5 (FNDC5), which binds to the precursor protein fibronectin type III domain, and then is cleaved, secreted, modified, and released into the blood to produce a polypeptide fragment, which can promote browning of white adipose tissue and improve body energy metabolism, thereby reducing myocardial hypertrophy, myocardial fibrosis, and inhibiting oxidative stress and inflammatory responses. It is also expressed in the hippocampus, which is relieved to pass through BBB and stimulate hippocampal neurogenesis by increasing BDNF expression. During exercise, the expression of the transcription factor PPAR γ -assisted activator 1 α (PGC-1 α) in skeletal muscle cells is up-regulated, which promotes expression of the gene containing FNDC5. The extracellular segment of FNDC5 is Irisin, which falls off into the blood circulation after shearing, stimulates the expression of BDNF in the hippocampus, and improves the learning and memory function of the hippocampus. Meanwhile, the voluntary rotation exercise for 30 days enhanced the expressions of PGC-1 α and FNDC5 in the hippocampus of mice, thus increasing the expression of BDNF and other neuroprotective genes [19]. A recent study showed that irisin level was reduced in the hippocampus of AD model mice, and the memory function was impaired in brain irisin knockout mice, while memory functions in AD mouse models would facilitate along with the enhancement of the brain irisin expression [20]. In addition, the 5-week swimming exercise of A β 0-induced memory-deficient mice prevented the reduction of FNDC5/irisin mRNA and protein in their hippocampus, which were higher than those of the sedentary group, suggesting that the overexpressed peripheral irisin could reach the brain and might mediate the neuroprotective effect of exercise on AD synaptic plasticity and memory by inducing increased BDNF secretion in the hippocampus [20].

Cathepsin B (CTSB)

CTSB, an important member of the papain family located in lysosomes, is expressed intracellularly in various animal tissues [21]. Current studies have found that CTSB mediates different effector mechanisms in different tissues and cells, including the degradation of extracellular matrix proteins, the induction of apoptosis, and the activation of inflammasomes,

which play a critical role in neurodegenerative diseases and brain injury and are related to the mechanism of neurodegenerative diseases such as inflammatory molecule activation, neuroimmune responses, energy metabolism disorders, cell signaling and neuronal apoptosis [22,23].

It was reported that exercise promoted the expression of plasma CTSB in mice, which further elevated the expression of BDNF in the hippocampus through the BBB, thereby enhancing neurogenesis and memory function in wild-type mice [24]. A recent study of adult sedentary women showed that after 5 weeks of high-intensity circuit training (HICT), the CTSB and BDNF concentrations in plasma were increased. Their quality of life and cognitive functions were improved [25]. These results suggest that plasma CTSB can be upregulated by aerobic exercise training, which may be associated with cognitive performance in young adults.

The results of a study observing the effect of long-term exercise on the memory of men aged 17-68 [26] show that long-term exercise training was related to higher memory functions of middle-aged subjects. Although there was a temporary increase in the levels of serum BDNF with CTSB in the subjects immediately after exercise, they returned to resting levels or even lower in 1 hour after exercise. Compared with the sedentary group, the levels of serum BDNF and CTSB in the long-term exercise group were lower in the resting state. Moreover, there was no significant correlation between CTSB and score in the memory test. The researchers also found that middle-aged subjects had significantly higher resting serum BDNF levels and lower serum CTSB levels than young adults, both in the sedentary and trained groups, and that peripheral blood levels of CTSB and BDNF did not follow the same pattern in terms of age.

Therefore, although most current studies suggest that the improved cognitive function with exercise is generated following strenuous exercise and/or chronic aerobic exercise, there is disagreement about the mechanism by which exercise improves AD because of the different research protocols. The mechanism of action of CTSB in muscle-brain interaction needs to be further investigated.

Lactate (LA)

During strenuous exercise, muscle cells mainly use blood glucose and muscle glucose to synthesize ATP to provide fuel for glycolysis [27]. Pyruvate produced in the process is reduced to LA by lactate dehydrogenase under anaerobic (hypoxic) conditions. Most of the LA is released and absorbed by skeletal muscle, heart, and brain through the lactate shuttle process, and oxidized and energized again as an energy substance, or transported to the liver to synthesize glucose through gluconeogenesis, while part of them is

released into the blood circulation and passes through the BBB under the mediation of monocarboxylate carrier (MCT) acting as substrates to provide energy for the maintenance of normal physiological functions of brain cells [28]. Moreover, it was reported that the elevation of LA level in peripheral blood was related to the upregulation of circulating BDNF, the increase of hippocampus volume, and the improvement of cognitive functions [29]. A recent study in mice indicated that voluntary aerobic exercise (30-day round running) led to the accumulation of LA in the hippocampus, which improved cognitive functions (learning and memory) by increasing BDNF expression. Meanwhile, the inhibition of LA transport in the brain decreased the BDNF expression after exercise. After intraperitoneal injection of LA, the expression of BDNF was up-regulated and the related signal transduction in the hippocampus was enhanced, which improved the cognitive functions of mice [30]. LA induces neurogenesis in the rat brain by activating nuclear factor κ B (NF- κ B). The connection between LA and BDNF in humans has also been reported [31] and intravenous infusion of LA would increase the level of circulated BDNF [32]. Consistently, acute high-intensity exercise (90% of the maximum work rate) resulted in higher blood LA values and plasma BDNF concentrations than moderate-intensity exercise (70% of the maximum work rate) [33].

Furthermore, LA may be a molecule with important effects on cerebral metabolism. For instance, LA plays a regulatory role in cerebral blood flow control and maintenance of synaptic function through binding to the receptor GPR81, which is a G protein-coupled receptor (GPR) localized in the hippocampus, neocortex, and cerebellum [34].

Limitations

In addition to the above-mentioned cytokines, the balance between exercise-mediated interleukin and cytokines plays a key role in the progression of neuroinflammation. Prolonged aerobic exercise can induce an increase in the expression of ketone bodies, which can also cross the BBB to stimulate the production of BDNF after being released into the blood, there by presenting a neuroprotective effect on synaptic plasticity and memory in AD. The related information is not detailed in this paper.

Conclusion

In summary, physical exercise can affect AD through multiple pathways. Based on the existing evidence, it is conceivable that physical exercise-based interventions may help prevent AD or delay (at least partially delay) the process of neurological damage in patients. Although many hypotheses and mechanisms for the benefit of exercise in AD

prevention have been proposed in preclinical studies, the exact biological basis underpinning the benefits of exercise remains to be elucidated. Further research is needed to confirm whether these benefits apply to all populations (particularly older adults with AD).

Funding: NSSFC: 21XTY018.

References

1. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, et al. (2020) Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* 396(10248): 413-446.
2. Spiers Jones TL, Hyman BT (2014) The intersection of amyloid beta and tau at synapses in Alzheimer's disease. *Neuron* 82(4): 756-771.
3. Grimaldi A, Pediconi N, Oien F, Pizzarelli R, Rosito M, et al. (2019) Neuroinflammatory processes, A1 astrocyte activation and protein aggregation in the retina of Alzheimer's disease patients, possible biomarkers for early diagnosis. *Front Neurosci* 13: 925.
4. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, et al. (2017) Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* 541(7638): 481-487.
5. Golde TE, DeKosky ST, Galasko D (2018) Alzheimer's disease: The right drug, the right time. *Science* 362(6420): 1250-1251.
6. Long JM, Holtzman DM (2019) Alzheimer disease: an update on pathobiology and treatment strategies. *Cell* 179(2): 312-339.
7. Pedersen BK, Saltin B (2015) Exercise as medicine - Evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand J Med Sci Sport* 3: 1-72.
8. Qin XY, Cao C, Cawley NX, Liu T-T, Yuan J, et al. (2017) Decreased peripheral brain-derived neurotrophic factor levels in Alzheimer's disease: a meta-analysis study (N=7277). *Mol Psychiatry* 22(2): 312-320.
9. Barde YA, Edgar D, Thoenen H (1982) Purification of a new neurotrophic factor from mammalian brain. *EMBO J* 1(5): 549-553.
10. Wetmore C, Olson L, Bean AJ (1994) Regulation of brain-derived neurotrophic factor (BDNF) expression and release from hippocampal neurons is mediated by non-NMDA type glutamate receptors. *J Neurosci* 14(3Pt2): 1688-1700.

11. Dinoff A, Herrmann N, Swardfager W, Lanctôt KL (2017) The effect of acute exercise on blood concentrations of brain-derived neurotrophic factor in healthy adults: a meta-analysis. *Eur J Neurosci* 46(1): 1635-1646.
12. Rasmussen P, Brassard P, Adser H, Pedersen MV, Leick L (2009) Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. *Exp Physiol* 94(10): 1062-1069.
13. Matthews VB, Astrom MB, Chan MHS, Bruce CR, Krabbe KS, et al. (2009) Brain-derived neurotrophic factor is produced by skeletal muscle cells in response to contraction and enhances fat oxidation via activation of AMP-activated protein kinase. *Diabetologia* 52(7): 1409-1418.
14. Choi SH, Bylykbashi E, Chatila ZK, Lee SW, Pulli B, et al. (2018) Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model. *Science* 361(6406): eaan8821.
15. Nicolini C, Michalski B, Toepp SL, Turco CV, Hoine TD, et al. (2020) A Single Bout of High-Intensity Interval Exercise Increases Corticospinal Excitability, Brain-Derived Neurotrophic Factor, and Uncarboxylated Osteocalcin in Sedentary, Healthy Males. *Neuroscience* 437(2020): 242-255.
16. Crivelli SM, Giovagnoni C, Visseren L, Scheithauer AL, de Wit N, et al. (2020) Sphingolipids in Alzheimer's disease, how can we target them?. *Adv Drug Deliv Rev* 159: 214-231.
17. Rezola Pardo C, Hervas G, Arrieta H, Hernández de Diego A, Ruiz Litago F, et al. (2020) Physical Exercise Interventions Have No Effect on Serum BDNF Concentration in Older Adults Living in Long-Term Nursing Homes. *Exp Gerontol* 139: 111024.
18. Nascimento CM, Pereira JR, Pires de Andrade L, Garuffi M, Ayan C, et al. (2015) Physical Exercise Improves Peripheral BDNF Levels and Cognitive Functions in Mild Cognitive Impairment Elderly With Different Bdnf Val66Met Genotypes. *J Alzheimers Dis* 43(1): 81-91.
19. Williams CJ, Gurd BJ, Bonafiglia JT, Voisin S, Li Z, et al. (2019) A multi-center comparison of VO₂peak trainability between interval training and moderate intensity continuous training. *Front Physiol* 10: 19.
20. Lourenco MV, Frozza RL, de Freitas GB, Zhang H, Kincheski GC, et al. (2019) Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. *Nat Med* 25(1): 165-175.
21. Liu CL, Guo JL, Zhang X, Sukhova GK, Libby P, et al. (2018) Cysteine protease cathepsins in cardiovascular disease: from basic research to clinical trials. *Nat Rev Cardiol* 15(6): 351-370.
22. Liu C, Cai Z, Hu T, Yao Q, Zhang L, et al. (2020) Cathepsin B aggravated doxorubicin-induced myocardial injury via NF- κ B signalling. *Mol Med Rep* 22(6): 4848-4856.
23. Abdulla MH, Valli Mohammed MA, Al Khayal K, Shkieh AA, Zubaidi A, et al. (2017) Cathepsin B expression in colorectal cancer in a Middle East population: potential value as a tumor biomarker for late disease stages. *Oncol Rep* 37(6): 3175-3180.
24. Moon HY, Becke A, Berron D, Becker B, Sah N, et al. (2016) Running-induced systemic cathepsin B secretion is associated with memory function. *Cell Metab* 24(2): 332-340.
25. Micielska K, Kortas JK, Gmiat A, Jaworska J, Kozłowska M, et al. (2021) Habitually inactive physically-a proposed procedure of counteracting cognitive decline in women with diminished insulin sensitivity through a high-intensity circuit training program. *Physiol Behav* 229: 113235.
26. De la Rosa A, Solana E, Corpas R, Bartrés Faz D, Pallas M, et al. (2019) Long-term exercise training improves memory in middle-aged men and modulates peripheral levels of BDNF and Cathepsin B. *Sci Rep* 9(1): 3337.
27. Chatham JC (2002) The forgotten fuel!. *J Physiol* 542(Pt2): 333.
28. Van Hall G, Stromstad M, Rasmussen P, Jans O, Zaar M, et al. (2009) Blood lactate is an important energy source for the human brain. *J Cereb Blood Flow Metab* 29(6): 1121-1129.
29. Schiffer T, Schulte S, Sperlich B, Achtzehn S, Fricke H, et al. (2011) Lactate infusion at rest increases BDNF blood concentration in humans. *Neurosci Lett* 488(3): 234-237.
30. El Hayek L, Khalifeh M, Zibara V, Assaad RA, Emmanuel N, et al. (2019) Lactate mediates the effects of exercise on learning and memory through SIRT1-dependent activation of hippocampal brain-derived neurotrophic factor (BDNF). *J Neurosci* 39(13): 2369-2382.
31. Zhou J, Liu T, Guo H, Cui H, Li P, et al. (2018) Lactate potentiates angiogenesis and neurogenesis in experimental intracerebral hemorrhage. *Exp Mol Med* 50(7): 1-12.
32. Schiffer T, Schulte S, Sperlich B, Achtzehn S, Fricke H, et al.

- al. (2011) Lactate infusion at rest increases BDNF blood concentration in humans. *Neurosci Lett* 488(3): 234-237.
33. Saucedo Marquez CM, Vanaudenaerde B, Troosters T, Wenderoth N (2015) High-intensity interval training evokes larger serum BDNF levels compared with intense continuous exercise. *J Appl Physiol* 119(12): 1363-1373.
34. Lauritzen KH, Morland C, Puchades M, Signe Holm-Hansen S, Hagelin EM, et al. (2014) Lactate receptor sites link neurotransmission, neurovascular coupling, and brain energy metabolism. *Cereb Cortex* 24(10): 2784-2795.

