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Review Article

Exercise Improves Cognitive Function in Alzheimer's Disease: The Role of Oxidative Stress Modulation

Mahnaz Talebi, Neda Ghaemian*

[a]*Neurosciences Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disease and the most common cause of dementia in the elderly. Despite the high prevalence of AD, it has no definite treatment. Therefore, many efforts are being made to find non-drug therapies along with medical treatments, particularly in mild cognitive impairment (MCI) and early Alzheimer's disease. One of the non-medical methods that have been investigated in recent years is exercise. Exercise with different mechanisms can affect the disease process and maintain nerve functions. Some of these mechanisms include regulation of neurotransmitter synthesis and increase of acetylcholine, promotion of the synthesis of neuronal growth factors, increase interconnections between synapses, increase cerebral blood flow and thereby accelerate the removal of waste, and enhance blood antioxidant enzyme. In this short study, we investigate the antioxidant aspect of exercise in improving cognitive function in Alzheimer's disease.

Keywords: *Alzheimer's disease, cognition, exercise, antioxidant, oxidative stress*

Correspondence

Mahnaz Talebi
Neurosciences Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
Tel: +98 4133340730
Email: talebi511@yahoo.com

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Introduction

Alzheimer's disease (AD) is an age-related progressive neurodegenerative disease and characterized by impairment of different aspects of cognition such as memory, executive function, language, attention, and behavior [1,2]. AD has been divided into early and late-onset forms based on the age of onset. The most common type of AD is the late-onset form. The age of onset and the familial history of dementia are the only distinguishing factors in these two forms [3].

The etiology of AD is not completely known. Only 1-2 % of the cases are due to mutations in APP, PSEN1, and PSEN2 genes [4-6]. There are various risk factors that contribute to the progression of sporadic late-onset AD such as Diabetes mellitus, head trauma, familial history, cardiovascular disease, education level, and mood disorders [7]. Although the pathogenesis of AD has not been fully understood, it is clear that the disease is related to multiple factors. The major factors are mitochondrial dysfunction, accumulation of abnormal proteins and oxidative stress [8,9]. These problems lead to synaptic dysfunction and synaptic loss. Pathophysiologically, AD is characterized by extracellular accumulation of Beta-Amyloid (Aβ) cerebral proteins which are neurotoxic and neurofibrillary tangles that prevent the axonal transport of biological elements. Moreover, cerebral amyloid angiopathy due to Aβ deposition in the cerebral vessel wall has been seen. Aβ is toxic to endothelial cells [10-12].

Although AD is the most common neurodegenerative disease affecting about 40 million people globally, no disease-modifying treatment exists yet. The main mechanism of medications is cholinesterase inhibitors which are prescribed for mild to moderate AD [13-15]. These drugs reduce some symptoms and help control some behavioral symptoms. Since there is no definite cure for AD, much research on the impact of non-pharmacological treatments is underway [16]. Exercise is one therapeutic strategy for AD that has been investigated in animal and human studies. Numerous researches have demonstrated the impact of exercise on improving cognitive functions in AD and different exercise regimes have been studied, including aerobic and resistance exercises [17-19]. Most studies have shown that both aerobic and resistance exercises are associated with neuroprotective mechanisms and contribute to the prevention of neurodegeneration and recovery of brain activities [20-23]. For example in a study on 76 patients with early AD, 150 minutes per week of aerobic exercise for 26 weeks showed improved memory performance and reduced hippocampal atrophy [20].

One cross-sectional data have demonstrated that physically active people have a lower risk of developing neurodegenerative diseases in comparison with sedentary people [24]. Larson et al have shown that resistance physical exam delays the onset of AD and dementia in very old subjects [25]. In another study on 120 older adults, the aerobic exercise training increased the size of the anterior hippocampus volume by 2%, and improved spatial memory. Or in one animal study, aerobic and resistance exercise for 8 weeks improved recognition memory in rats [26].

Antioxidative effects of exercise

Although many human and animal studies have shown the positive impact of exercise on cognitive impairments, there are not many studies on the mechanism of the effect of exercise on cognition, and it seems that exercise with different mechanisms improves cognition. Studies have shown several molecular pathways, including stimulating the release of neurotrophic factors (including brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), and VEGF) [27,28]. Neurotrophic factors especially BDNF is essential to neuronal survival, growth, and differentiation of cell, neurogenesis and myelin repair. Exercise can improve cognitive functions by increasing BDNF level [29,30]. Other mechanisms that have been proposed for exercise include anti-inflammatory and antioxidative effects, angiogenesis, regulation of neurotransmitter release, decreased deposition of Aβ and improvement of tau pathology [31-33].

An American study of 1,740 subjects aged more than 65 years showed that the incidence of dementia in who exercise three or more times per week (≥15 min/session) is low. They showed that this neuroprotective effect is Justified by increasing the production of antioxidant enzymes (such as superoxide dismutase) and other factors such as insulin-like growth factors (IGF-1), brain-derived neurotrophic factors (BDNF), nerve growth factors (NGF), and by reducing the production of reactive oxygen species (ROS). Similarly, in recent studies, aerobic physical training in humans reduced oxidative stress [34-37]. A few research have considered the effect of resistance training on oxidative stress. Nevertheless, the studies in this area indicate the positive impact of resistance exercise on neuropsychological tests such as the Working Memory Index, the Rey Auditory Verbal Learning test and executive function tests. The most improvement was seen in executive functions [38,39]. Improvement of declarative memory in elderly women was seen after exercise [39]. Gomes and colleagues showed increased neurogenesis and decreased apoptosis signaling in the dentate gyrus of adult male rats with exercises [40].

Oxidative stress

High levels of phospholipid and unsaturated fatty acids make the brain susceptible to oxidative stress [41]. The tendency of these molecules to oxidation and on the other hand low level of brain antioxidant, facilitate the formation of ROS in the brain [42,43]. Oxidative stress is one of the most important causes of AD. A very high percentage of intracellular oxygen is consumed in the mitochondrial electron transfer chain. In the mitochondrial, the residual oxygen is converted to hydrogen peroxide and superoxide radicals. When the production of hydrogen peroxide and oxygen free radicals are excess, oxidant molecules such as highly reactive hydroxyl radicals are produced. This process causes tissue damage in the presence of metal catalysts such as iron and copper. Disturbance and disruption of equilibrium oxidant and resuscitation system lead to over production of reactive oxygen species (ROS), which mediate mitochondrial injury. The major forms of ROS involved in death of neurons are superoxide peroxide and highly active hydroxide radicals. Two major cellular sources of ROS are mitochondria and NADPH oxidase [44-46].

Reactive oxygen species (ROS) are reactive molecules derived from the reduction of molecular oxygen. This reduction is the stimulant of the production of anion superoxide (O_2^-), which is the precursor of other reactive species such as Hydrogen peroxide. Hydrogen peroxide can be converted into hydroxyl radical (OH) or water. OH Participates in the production of new radicals and ROS. The molecules of ROS are unstable and highly reactive, so they easily interfere with many cellular processes such as proteins and nucleic acids and disrupt them [37,46,47]. If the cell cannot neutralize the oxidizing agents, oxidative stress will happen. Also, evidence shows that ROS participates in synaptic plasticity processes as second messengers in the central nervous system, most of the enzymes involved in synaptic structure can be modulated by ROS levels [46].

Briefly, ROS has both physiological and pathological effects in the cell. For many physiological cellular processes, the presence of ROS is necessary, for example, ROS is involved in proliferation, differentiation, and maturation process. In the nervous system, ROS regulates neuronal development and influence signaling cascades. In the synaptic plasticity in several areas of the brain such as cortex and hippocampus, ROS is involved. Thus, although ROS is necessary for intracellular signaling and neuronal plasticity, its accumulation in the brain causes oxidative damage.

Pathological Effects of ROS

Normally due to different mechanisms against oxidative stress in the cell, oxidants are placed on a nontoxic level. If this equilibrium breaks down, the cells are exposed to destructed ROS attack [48]. Excessive production of ROS or imbalance between the production of ROS and the antioxidant cellular processes leads to oxidative stress. Accumulation of ROS causes the oxidization of cellular components such as proteins, DNA, and the lipids of membrane. In a normal situation, antioxidant enzymes such as vitamins (vitamin E, ascorbate), glutathione (mainly inside astrocytes) SOD, catalase, and peroxidases control the ROS accumulation in tissue. Because the brain has little antioxidant activity and on the other hand its oxygen demand is high, the brain is vulnerable to oxidative stress[46,49]. ROS accumulation in neurons and the resulting oxidative stress is associated with reduced several neuronal cellular functions, including synaptic plasticity, that is responsible for the loss of cognitive functions in AD. Studies have shown that large quantities of ROS have been related to the age-depended decline in cognitive functions. The level of ROS in brain tissue is high in aged animals

in comparison with young animals and administration of antioxidant supplements is effective in reducing the age-related deficits of cognitive performance in rats [50,51].

Examples of studies on exercise and antioxidants

During the past two decades, a number of studies have been conducted to determine the effect of exercise on the prevention of dementia. Various human and animal studies have shown that exercise improves the cognitive process. Researches show that exercise increases cellular aerobic metabolism and thereby decreases oxidative stress by reducing basal production of oxidants and enhance antioxidant defense [52]. Regular physical activity increases the vascularization and neurotrophin synthesis that are important in neurogenesis and improvement of memory [18]. In an experimental study, swimming training (ST) for 8 weeks performed on male AD mice and behavioral as well as oxidative stress in the hippocampus and prefrontal cortex were assessed. Results showed that exercise was effective in preventing memory impairment. In addition, ST was effective in superoxide dismutase (SOD) and glutathione peroxidase activity in the hippocampus and prefrontal cortex [53]. In a cohort study of 347 elderly men, the mini-mental status examination (MMSE) score was lower for individuals who exercised less than 1 h of weekly in comparison to those who were more active [54]. In another study on 929 subjects above 76 years old, 30 min of aerobic exercise, three times a week during a period of 2 years, reduced cognitive decline by half in comparison with those who were not physically active [55]. In another study on 1,740 subjects above 65years old, the incidence of dementia in elderlies who exercised three or more times per week was 13per 1,000 person-years, but the incidence of dementia was 19.7 per 1,000 person-years for those who exercised less [56]. A meta-analysis has shown that there is an inversely relationship between the regular physical exam and the risk of developing AD. Thierry Paillard reported that the mechanism of regular physical exercise in cognition improvement applies with increase angiogenesis, synaptogenesis, the synthesis of neurotransmitters and the production of enzymatic antioxidants [57].

Some studies show that exercise acts with antioxidant mechanisms include: In a study by Freitas et al on Wistar rats, they concluded that high-intensity interval training by increasing concentration of non-enzymatic antioxidant capacity (FRAP) improve cerebellar tissue [58]. Zhang, in a study on methamphetamine-dependent patients, showed that 12-week moderate-intensity aerobic exercise has beneficial effects on serum oxidative stress markers, including total anti-oxidation capability, SOD and catalase (CAT) [59]. In another study, Vanzella et al researched the effects of treadmill running in young (3month-old) and aged (22month-old) male Wistar rats and assessed oxidative stress parameters and the expression of neurotrophic factors BDNF, NT-3, IGF-1 and VEGF in the hippocampus. Results demonstrate that the moderate treadmill running exercise had a positive effect on memory performance in aged rats. They suggested that this effect is done with the increase of reactive oxygen species levels and lipid peroxidation in the hippocampus [60]. Cui et al in another study showed that regular treadmill exercise had a protective effect on spatial memory impairment through inhibition of oxidative stress [61]. Kwon et al concluded that chronic exercise can improve stress-induced cognitive impairment by detoxifying ROS in the hippocampus and activating BDNF signaling [62].

Conclusion

In AD as noted above there is a close relationship between disease progression and oxidative damage. Studies show that the oxidative damage of the brain occurs prior to brain inflammation and synaptic loss. Different preventive and therapeutic techniques are used to stop the progression of the disease and prevent the conversion of mild forms to severe stages of the disease. Oxidative stress is the most important factor in disease progression, so blocking the production of ROS is an effective prophylactic and therapeutic strategy in AD. Studies show that regular exercise can reduce the production of toxic radicals, improve mitochondrial function, optimize brain function and improve cognition, this can also prevent or slow down the progression of dementia and reduce the risk of cognitive decline and AD in elders. Researches indicate the effect of regular exercise on cognition improvement and oxidative stress markers. Physical activity acts as a regulator of oxidative stress. Therefore, it is recommended that exercise be considered in the treatment plan of AD patients.

Conflict of interest

None

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None

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