

The Effects of Different Exercise Modalities in Alzheimer's Disease

Farklı Egzersiz Yöntemlerinin Alzheimer Hastalığındaki Etkileri

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disease and the most common cause of dementia. Increased oxidative stress, abnormal amyloid β ($A\beta$) accumulation, tau aggregation, neuroinflammation, neuronal plasticity failure, and neuronal loss are the main factors related to the pathophysiology of AD. Increasing evidence suggests that physical activity has a positive effect on both cognitive function and cellular pathologies of AD. It has been demonstrated that aerobic exercise (AE) increases the activity of antioxidant enzymes and synthesis of neurotrophic factors, decreases the levels of neuroinflammatory markers, and enhances the functions of learning and memory. It is also beneficial for the improvement of cell survival and upregulation of $A\beta$ clearance. AE has been shown to reduce the levels of soluble $A\beta_{1-42}$ via an increase in enzyme activity, which is responsible for the upregulation of $A\beta$ clearance in brain tissues. It also represses apoptotic cascades such as the caspase-9, cytochrome c, Bax, and caspase-3 cascades. Although there are no clear data on the effects of resistance exercise (RE) on AD, only a small number of articles have studied the effects of RE on models of aging. In these studies, RE increased the serum concentrations of insulin-like growth factor-1 and brain-derived neurotrophic factor (BDNF), reduced oxidative stress in humans, and up-regulated the hippocampal expression of BDNF mRNA in animals. In addition, RE and AE therapies may help progress in daily activities and enhance physical ability in AD patients. Eventually, exercise therapy regimens may lead to more effective treatment options and slow the progression of AD without any side effects.

Keywords: Alzheimer's disease, exercise therapy, antioxidant enzymes, neuronal plasticity

Öz

Alzheimer hastalığı (AH) ilerleyici nörodejeneratif bir hastalık olup demansın en sık görülen nedenidir. Artmış oksidatif stres, anormal amiloid β ($A\beta$) ve tau proteinlerinin birikimi, nöroinflamasyon, nöronal plastisite yetmezliği ve nöronal kayıp AH'nin patofizyolojisi ile ilişkilendirilen ana faktörlerdir. Artan kanıtlar fiziksel aktivitenin, hem kognitif fonksiyona hem de AH'de gözlenen hücre patolojilere iyileştirici etkileri olduğunu göstermektedir. Aerobik egzersizin (AE) antioksidan enzim aktivitesini, nörotrofik faktörlerin sentezini arttırdığı, nöroinflamatuvar belirteçleri azalttığı, öğrenmeyi ve bellek fonksiyonlarını iyileştirdiği gösterilmiştir. Ayrıca hücre yaşayabilirliği ve $A\beta$ klirensi üzerine yararlıdır. AE, beyin dokusundaki çözülebilir $A\beta_{1-42}$ düzeylerini klirensen sorumlu enzimlerin aktivitelerini artırarak düşürür. Aynı zamanda kaspaz-9, sitokrom c, Bax ve kaspaz-3 gibi apoptotik enzimleri baskılar. Direnç egzersizlerinin (DE) AH'deki etkileri hakkında açık bir bilgi bulunmamakla birlikte az sayıda çalışmada daha çok yaşlanma modellerinde etkilerine bakılmıştır. Bu çalışmalarda DE'nin insülin benzeri büyüme faktörü-1 ve beyin kaynaklı nörotrofik faktörün (BDNF) serum konsantrasyonlarını artırdığı, oksidatif stresi azalttığı insanlarda gösterilmiş olup, hayvanlarda hipokampal BDNF mRNA düzeyinde artış yaptığı bildirilmiştir. Ek olarak DE ve AE, Alzheimer hastalarında günlük aktivitelerin gelişimine ve fiziksel becerilerin artırılmasına yardımcı olabilir. Sonuç olarak egzersiz terapisi uygulamaları daha etkili tedavi seçenekleri geliştirilmesine ve AH'nin ilerlemesinin yavaşlatılmasına, herhangi bir yan etki yapmaksızın yardımcı olabilir.

Anahtar Kelimeler: Alzheimer hastalığı, egzersiz terapisi, antioksidan enzimler, nöronal plastisite

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by vascular and neuronal dysfunction and cognitive regression (1, 2). The pathophysiology of AD is associated with different mechanisms such as genetic mutations, amyloid β ($A\beta$) burden, tau hyperphosphorylation, increased oxidative stress, neuroinflammation, neuroplasticity failure, neuronal loss, and synaptic degeneration (1-4) (Figure 1). Oxidative stress is an important underlying mechanism of neuronal loss that leads to a reduction in brain metabolism and an increase in mitochondrial damage (Figure 2).

Exercise is a non-pharmacological form of treatment for the prevention of AD and for slowing the progression of its symptoms (5-9). Recent studies have shown the beneficial effects of physical exercise on behavioral and psychological symptoms such as depressed mood and agitation, which are prevalent in AD. Not only the type of exercise but also its duration and frequency are unclear for the efficient prescription of exercise for AD. Although some studies have proposed that aerobic exercise for at least 30 min a few times a week has a beneficial role, the probable effects of resistance exercise and combined exercise are not yet known (10, 11).

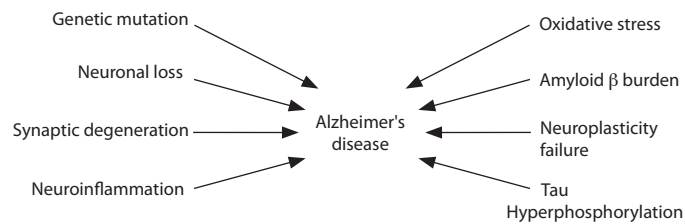


Figure 1. Mechanisms involved in the pathogenesis of Alzheimer's disease

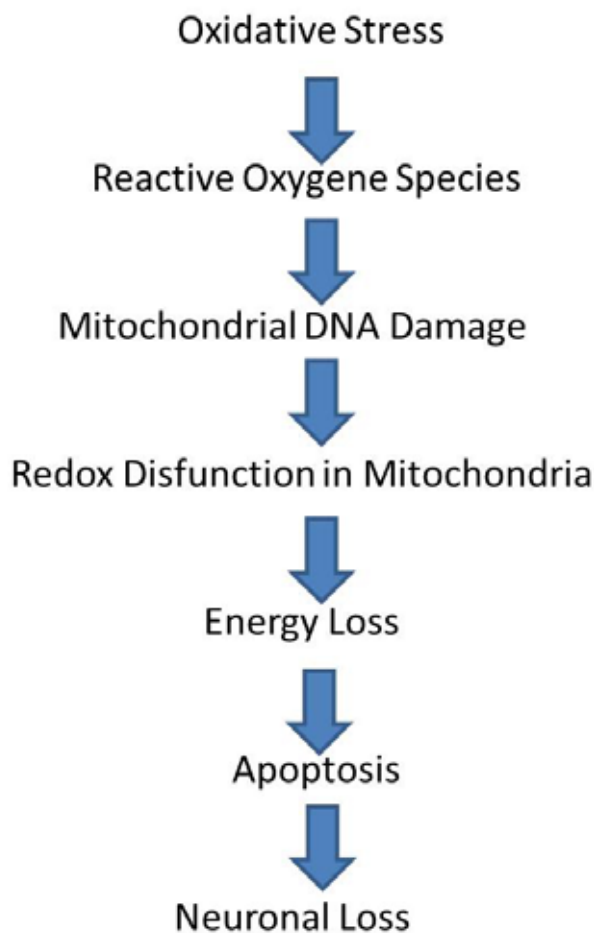


Figure 2. Mechanism of neuronal loss via oxidative stress

Exercise Modalities

The term "physical activity" refers to actions that are produced via the consumption of energy by the striated muscles of the body. Physical activities are generally categorized into three types: flexibility (stretching) exercises, anaerobic (resistance/strengthening) exercises, and aerobic (cardiovascular) exercises (12-14) (Table 1). Flexibility exercises, such as dynamic and static stretching, improve the motion of muscles and joints. Aerobic exercises, such as swimming, running, walking, and cycling, are performed by larger muscle groups in the form of dynamic physical actions that require free oxygen and focus on increasing cardiovascular endurance (12, 14). It has been reported that regular aerobic exercise may lead to increases in the activity of

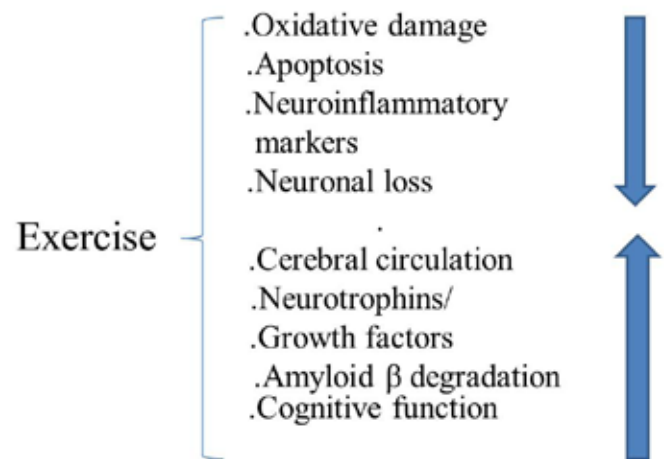


Figure 3. Underlying mechanisms of the beneficial effect of exercise on Alzheimer's disease

Table 1. Types of exercise

Types of Physical Exercise		
Flexibility	Anaerobic	Aerobic
Ballistic stretching	Lifting weights (resistance)	Walking
Dynamic stretching	Sprinting	Jogging
Proprioceptive neuromuscular facilitation	Rowing	Swimming
Static stretching	Sprinting activities	Hiking
Yoga	Tug of war	Playing tennis
	Jumping rope	Cycling
	Climbing	
	Sit-ups	
	Chin-ups	
	Isometrics	

antioxidant enzymes, improvements in angiogenesis, and upregulation in the synthesis of neurotrophic factors (7). Resistance exercises, such as weightlifting and jumping, which are also referred to as anaerobic exercises, are characterized by dynamic or static muscular contractions and are organized against manual or mechanical forces. Resistance exercises that use free weights increase muscle strength (12, 15). Regular resistance exercise is correlated with several positive adaptations such as increases in protein levels, enlarged cross-sectional areas of muscles, and elevated levels of insulin-like growth factor-1 (IGF-1) (16).

Underlying Mechanisms of the Effects of Different Exercise Modalities

There is no consensus about the best type of exercise for the amelioration of clinical outcomes in AD. A large number of studies have focused on the effect of aerobic exercise. Different mechanisms are known to mediate its beneficial effects (Figure 3). Aerobic exercise initially contributes to an increase in the levels of growth factors such as vascular endothelial growth factor, brain-derived neurotroph-

ic factor (BDNF), IGF-1, glial-derived neurotrophic factor, neuronal growth factor (NGF), and neurotrophin-3, all of which act in a synergistic manner to induce neuroplasticity and neurogenesis (7, 17-19). The growth factors then improve memory and cognitive functions via the stimulation of neurogenesis, synaptogenesis, neuroplasticity, and angiogenesis (7, 20, 21). Moreover, aerobic exercise increases cerebral blood flow and the levels of endothelial nitric oxide synthase and additionally decreases the levels of reactive oxygen species (ROS) in brain tissues, particularly in the hippocampus (7, 9, 21). Exercise-induced elevations in hippocampal cerebral blood volume were found to be associated with enhanced neurogenesis (22). Furthermore, in animal studies, improvements in cognitive functions after exercise have been shown in spatial learning memory, recognition memory, and contextual memory (23, 24). Aerobic exercise also increases cell survival and proliferation, upregulates A β clearance, decreases apoptotic cascades, and reduces A β_{1-42} peptide levels in the rodent brain (25-27). Moreover, oxidative damage takes place initially in the brain of AD patients prior to the onset of A β deposition and plaque and neurofibrillary tangle formation (21). It is well known that regular swimming and running exercise reduce the production of ROS and upregulate antioxidant enzymes in different brain regions in rats (27, 28). Although an ameliorative effect of resistance exercise on any of the behavioral or biological signs of AD has not yet been reported, there is evidence that the prevalence of this disease is associated with a decline in muscle mass and muscle strength (28, 29). With reference to these data, it has been reported that resistance exercise may slow down the impairment of mobility and enhance balance in AD patients (30). In a similar way to the effect of aerobic exercise, levels of IGF-1 and BDNF have been shown to increase via resistance exercise (31, 32). In addition, there are numerous studies that reveal probable enhancements of cognitive functions after resistance exercise in elderly people (16, 31). Although the effect of a multicomponent exercise regimen that includes aerobic, balance, and strength training on AD is not known, it is shown to be particularly effective for improving motor and postural functioning and mitigating the risk of falling in AD patients (7, 33).

CLINICAL and RESEARCH CONSEQUENCES

Human and Animal Research Outcomes

Most of the present information about the mechanisms involved in the effects of exercise training has been obtained by animal studies of AD. It has been reported that regular swimming training, which is a well-known model of aerobic exercise, was able to protect against A β_{1-40} -induced neurotoxicity by decreasing short- and long-term impairments in object recognition memory by means of increasing the activity of antioxidant enzymes via decreasing the levels of neuroinflammatory markers in mouse models of AD (34). In addition, in a model of A β -induced AD, a decline in spatial memory and suppression of early long-term potentiation (E-LTP) and E-LTP-related signaling molecules such as phosphorylated Ca²⁺/calmodulin-dependent protein kinase II (p-CaMKII), calcineurin (PP2B), and BDNF were observed in the hippocampus, and treadmill exercise, which is another model of aerobic exercise, had beneficial effects on E-LTP and memory performance by increasing levels of p-CaMKII, PP2B, and BDNF (35). Furthermore, it has been reported that even a light running exercise protocol increased cell survival and proliferation in transgenic mice and rat brain tissues (36). Related to this concern, it has also been reported that treadmill exercise inhibited apoptotic cascades, such as the caspase-9, cytochrome c, Bax, and caspase-3 cascades, in the brain tissues of

transgenic mice (25, 27). Only a small number of articles concerning the effects of exercise on AD have demonstrated controversial results. Within the context of a meta-analysis, it has been shown that both combined (aerobic and non-aerobic) and aerobic exercise training, at both low and high intensities, had ameliorative effects on cognitive function. On the other hand, the same type of relationship between non-aerobic exercise training and cognitive functions was not found (37). Likewise, an 8-week program of resistance exercise training was found to be ineffective on cognitive functions (38). On the other hand, there is evidence that resistance exercise may be beneficial in AD. After resistance exercise, the serum concentrations of IGF-1 and BDNF were found to increase. Therefore, oxidative stress was demonstrated to be reduced and cognitive performance was shown to be improved in humans; further, the hippocampal expression of BDNF mRNA has been reported to be upregulated in rats (31, 32). Resistance exercise at moderate and high intensities for 24 weeks had advantageous effects on cognitive functions in elderly people (16). Resistance training significantly improved global cognitive scores, executive functions, and attention time in adults (39). It has been reported that resistance exercise has beneficial effects in older adults, increases the uptake of IGF-1 in the brain, insulin sensitivity, and cerebral blood flow, and decreases stress and depression (40). In addition to IGF-1, it is suggested that resistance training inhibits cognitive decline among elderly people via an increase in homocysteine levels (41). Moreover, strength or aerobic exercises may help increase independence in daily life activities and improve the physical ability of AD patients (33). These results have revealed that aerobic and resistance exercise therapies increase neurogenesis and neuroplasticity, act against brain alterations that occur during aging, and help to enhance cognitive functions and improve the quality of life of patients.

In animal studies, the A β load, which is a major sign of AD, has been reduced by exercise (26, 27). The main type of amyloid that accumulated in brain tissues has been reported to be A β_{1-42} monomers. These monomers were formed by the clipping of amyloid precursor proteins (APPs) by beta and gamma secretases. When neuronal and astrocytic lysosomal and proteolytic degradation mechanisms are inadequate, A β_{1-42} monomers become soluble and accumulate as oligomers of 2 to 6 peptides, which cause synaptic dysfunction (42). These soluble A β oligomers are regarded as major toxic species because their abundance is correlated with the intensity of synaptic dysfunction and neurodegeneration in AD (43). Studies based on describing the relationship between exercise and A β load mostly indicate aerobic exercise. In this context, A β load has been shown to be reduced by wheel running in transgenic mice (44). Furthermore, levels of soluble A β_{1-42} in the hippocampus and cortex have been reduced by treadmill exercise in a dose-dependent manner. Moreover, the levels of A β -degrading proteins, such as matrix metalloproteinase-9, insulin-degrading enzyme, neprilysin, heat shock protein-70, and lipoprotein receptor-related protein-1, increased by treadmill exercise and have been revealed to be responsible for the upregulation of A β clearance (26). Besides, treadmill exercise for 5 weeks reduced the hippocampal microglial activity and A β levels but did not reduce plaque formation, and wheel running for 10 days reduced the expression of APP mRNA and A β levels but did not reduce plaque load in transgenic mice (45, 46). On the other hand, another study has shown that wheel running reduced the number of A β plaques and memory decline in transgenic mice (47). It has also been demonstrated in humans that physical activity has led to lower levels of A β in plasma and brain tissues (48, 49).

In our study group, different types of exercise, which were performed 3 days a week, had beneficial effects on the function of object recognition memory in an experimental rat model of AD, which was induced by D-galactose and ovariectomy. All types of exercise reduced oxidative stress by decreasing lipid peroxidation and increasing antioxidant status in rat brain tissues. Combined exercise has a stimulatory effect on NGF levels in the cortical part of the brain, which shows an improvement in neuroplasticity. The serum levels of IGF-1 increased by all exercise modalities. Elevated hippocampal levels of APP in the experimental model decreased with combined exercise, and the burden of A β was alleviated with all types of exercise in rat brain tissues. Consequently, our results suggest that different types of exercise attenuate the severity of AD (50).

CONCLUSION

Exercise leads to a significant improvement in cognitive functions and neuropathological markers related to AD. Because a large number of mechanisms of the pathogenesis of AD have been identified, it is clear that pharmacological treatment together with exercise therapies as a non-pharmacological form of treatment can succeed in inhibiting most mechanisms, in contrast to a treatment that targets only one mechanism. Adding exercise regimens to current treatments may lead to more effective treatment options and have benefits without any side effects.

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