

Review

Exercise Plays a Preventive Role Against Alzheimer's Disease

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Abstract. Alzheimer's disease (AD) is a progressive neurodegenerative disorder affecting the elderly population. It is predicted that the incidence of AD will be increased in the future making this disease one of the greatest medical, social, and economic challenges for individuals, families, and the health care system worldwide. The etiology of AD is multifactorial. It features increased oxidative state and deposition of amyloid plaques and neurofibrillary tangles of protein tau in the central cortex and limbic system of the brain. Here we provide an overview of the positive impacts of exercise on this challenging disease. Regular physical activity increases the endurance of cells and tissues to oxidative stress, vascularization, energy metabolism, and neurotrophin synthesis, all important in neurogenesis, memory improvement, and brain plasticity. Although extensive studies are required to understand the mechanism, it is clear that physical exercise is beneficial in the prevention of AD and other age-associated neurodegenerative disorders.

Keywords: Amyloid- β , amyloid- β degradation, exercise, metabolism, neurotrophins, physical inactivity, sirtuins

INTRODUCTION

There is accumulating evidence which suggests that oxygen, a key player in the evolution of life on earth, might have a crucial importance in the survival chance of a given species. It is known that regular exercise, which leads to enhanced maximal oxygen uptake, increases the mean lifespan of laboratory animals [1–3] and humans [3–6]. Booth and Lees [7] described the

importance of physical activity in the genetic adaptation of *Homo sapiens* and listed some of the striking consequences of physical inactivity on the appearance of lifestyle-related diseases. Bed rest studies used to mimic the effects of physical inactivity resulted in a massive decrease in maximal stroke volume [8], bone density, and muscle mass [9,10].

According to the Darwinian concept of evolutionary adaptation, the fittest have a higher chance for survival and reproduction. Physical inactivity has systemic effects on the body [11,12], which covers all of the organs including the central nervous system. Indeed, physical inactivity is one of the most prominent risk factors for dementia [13,14], including Parkinson's dis-

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ease [15,16] and Alzheimer's disease (AD) [17–20]. The molecular mechanisms by which regular exercise counteracts AD are not fully understood and appear to be very complex. The aim of the present review is to show these complex effects of physical activity on brain health, especially on some key factors which play an important role in the development and progression of AD. We are focusing on the neuroprotective effects of exercise including the alteration of neurotrophins, oxidative stress, inflammation, amyloid- β ($A\beta$) degrading enzymes, blood flow, and metabolism by which exercise acts against AD.

THE ROLE OF EXERCISE-INDUCED NEUROTROPHINS ON AD

The entorhinal cortex is one of the first areas to be affected in AD; hence, it is involved in the early loss of short-term memory. A recent study by Nagahara and colleagues [21] suggests that brain-derived neurotrophic factor (BDNF, a family member of the neurotrophin growth factors) administration leads to beneficial effects, including reversal of synapse deterioration, normalization of aberrant gene expression, and most importantly restoration of memory and learning in rats and primates. It was concluded that these processes are independent of the accumulation of amyloids, and BDNF administration could serve as a therapy for AD. Moreover, hippocampal neural stem cell transplantation on triple transgenic mice (3xTg-AD) improved cognitive function via BDNF [22]. Suggestively, besides artificial administration of BDNF and neuronal stem cells, natural tools which induce BDNF could counteract AD.

It is well documented that physical activity from moderate to high intensity results in increases in BDNF production [23–27]. There are several animal models available to mimic AD. Although these models are not without problems, they can serve as useful tools to study AD. When neuron-specific enolase (NSE)/Swedish mutation of amyloid- β protein precursor ($A\beta$ PP) transgenic mice were used to study the effects of exercise on AD, it was found that 16 weeks of treadmill running significantly decreased levels of the amyloid- β ($A\beta$) peptides ($A\beta_{40}$ and $A\beta_{42}$) and induced BDNF [28].

The overexpression apolipoprotein E (APOE) gene is a significant genetic risk factor for AD [29]. In fact, APOE receptors, members of the low-density lipoprotein receptor family, modulate $A\beta$ production and cellular uptake by binding directly to $A\beta$. In a recent study,

APOE ϵ 3 and APOE ϵ 4 transgenic mice were used to test the role of physical exercise in this model [30]. Exercise restored the function of the BDNF receptor tyrosine kinase B (Trk B) in ϵ 4 rats, which was decreased by 50% in inactive controls. Although exercise training did not change the protein level of BDNF, the normalization of Trk B-mediated cell signaling was highly beneficial to regain cognitive functions. This is supported by the observation that neurogenesis could not be restored after Trk B ablation in hippocampal neural progenitor cells by either exercise training or antidepressants [31], which is often observed after exercise in the hippocampal region [32–34]. Besides BDNF, glial cell line-derived factor (GDNF) also plays an important role in cell survival and brain plasticity-enhancing properties of neurons, especially in the hippocampal region [35]. Although the available information on the effects of exercise on GDNF is very limited, some observations suggest that exercise induces GDNF content, which is involved in the neuroprotective effects of exercise [36,37].

AD is associated with decreased levels of nerve growth factor (NGF) and significantly increased levels of immature NGF, pro-NGF [38]. It appears that $A\beta$ -peptide accumulation curbs the maturation of NGF, which then results in increased concentrations of pro-NGF. On the other hand, exercise training has been shown to significantly induce the level of NGF [39–42]. The latter study showed that exercise training attenuated the age-associated decrease in BDNF and NGF level, which strongly affects long term potentiation (LTP).

The low circulating level of BDNF is suggested to predispose patients to AD. A recent Finnish study showed that indeed, circulating BDNF can serve as a marker of impaired memory in aging women [43]. As a result of exercise, the hippocampus and cortex release BDNF into circulation, which is due to increased BDNF mRNA and protein synthesis in these brain regions. It has been suggested that the brain contributes to about 70-80% of the circulating BDNF [44]. Exercise has the capability of significantly inducing BDNF and NGF and thereby neurogenesis in the hippocampus, resulting in enhanced cognitive function. These processes are just opposite to the deleterious effects of AD.

THE ROLE OF REACTIVE OXYGEN SPECIES IN AD AND THE NEUROPROTECTIVE ROLE OF EXERCISE

Oxidative stress mediated by reactive oxygen species (ROS) is believed to be one of the leading contributors

to age-associated diseases, such as AD. Oxidative damage occurs early in the brain of AD patients before the onset of plaque pathology and precedes A β deposition and formation of intracellular neurofibrillary tangles composed of abnormally hyperphosphorylated protein, tau. At the cellular and tissue levels, ROS also account for the neurodegenerative process and neuronal death. Indeed, the involvement of free radicals in AD has been suggested decades ago [45–49], and there are a number of suggested pathways which describe the potential source of ROS and the consequences.

It has been demonstrated that the microglial response to neuronal damage is self-perpetuating, long term, and severely toxic to neurons [50], and it is clear microglial activation takes place in association with lesions of senile, amyloid plaques and neurofibrillary tangles [51]. Microglial NADPH oxidase (NOX) is readily activated by A β [52] and A β PP [53] among others. The role of microglial NOX in ROS production was evidenced by microglial NOX knockout mice, which showed significantly reduced ROS production [54]. Besides microglia, the glutamatergic system is implicated in ROS production [55], and the excessive production of inflammatory proteins could readily result in ROS production [56]. Moreover, since local hypoxia is suggested to take place in neurodegenerative diseases, including AD, mitochondrial complex III emerged as a potential ROS generating source during AD [57]. In addition, mitochondrial dihydrolipoyl succinyltransferase, a subunit of the α -ketoglutarate dehydrogenase enzyme complex, is also involved in AD pathogenesis via ROS production [58].

Regular physical exercise is a well known means to reduce the rate of ROS production in different organs including the brain [59–62]. It is also well demonstrated that regular exercise increases the level/activity of antioxidant enzymes in different brain regions [62–66]. Naturally, the induction of antioxidant systems reduces the levels of ROS and the resultant oxidative stress. The other possibility by which exercise can reduce oxidative stress is the reduction of ROS production by a decrease in ROS generating sources and by the attenuation of ROS generating capacity. Indeed, regular exercise has been shown to decrease the amount of hydroxyl radical production in the brain [67]. We measured the free radical level by electron paramagnetic resonance and found that exercise training decreases the amount significantly [42,68]. In addition, in an N-methyl-D-aspartic acid lesion model, it was also shown that exercise can attenuate the DNA binding of nuclear factor κ -B, which then can result in a decreased lev-

el of inflammation [68]. Interleukin-1 (IL-1) and IL-6 have been etiologically related to early stage senile plaque formation in transgenic Tg2576 mice [69] with AD pathology. It was also observed that IL-6 secretion by peripheral blood mononuclear cells was increased in patients with AD as opposed to normal subjects or those suffering from other brain disorders such as vascular dementia. In support, overexpression of IL-6 in the brain of Tg2576 mice is associated with a variety of neuropathological findings, including tauopathy, gliosis, and disruption of cholinergic neurotransmission in the hippocampus. CXCL1 and CXCL12 expression, which affects cognition, is decreased in Tg2576 mice compared to control mice. Exercise altered increased expression of these chemokines at mRNA level both in Tg2576 and non-transgenic mice.

The level of oxidative stress is generally measured by the sum of the products of ROS-lipid, -protein, and -DNA interactions. Regular exercise decreases the level of lipid peroxidation and protein oxidation [60,61]. Interestingly, it appears that the effect of exercise training on DNA damage is not significant and the activity of 8-oxoguanine-DNA glycosylase, OGG1, is unaltered by exercise [42,62,70].

It appears that regular exercise by the induction of antioxidant systems and the down regulation of ROS producing systems significantly attenuates oxidative stress in the brain, which could be a preventive tool against AD-associated oxidative challenge.

ACCUMULATION OF A β PEPTIDES AND THE EFFECTS OF EXERCISE ON ACTIVITY/LEVELS OF DEGRADING ENZYMES

There are accumulating evidence that regular exercise, even with moderate intensity, decreases the incidence of AD [71]. The question is what could be the mechanism? Here we are suggesting that exercise has a complex effect by which the risk of AD can be reduced. Earlier the beneficial effects of exercise on neurotrophins and ROS were discussed and one can consider these effects marginal, since, according to our understanding, none of them directly caused amyloid and tangle accumulation, which are considered the hallmarks of AD.

In the transgenic mouse model TgCRND8, it has been shown that exercise training results in marked decreased in cortical accumulation of A β . The decreased concentration of the proteolytic fragments of A β PP and

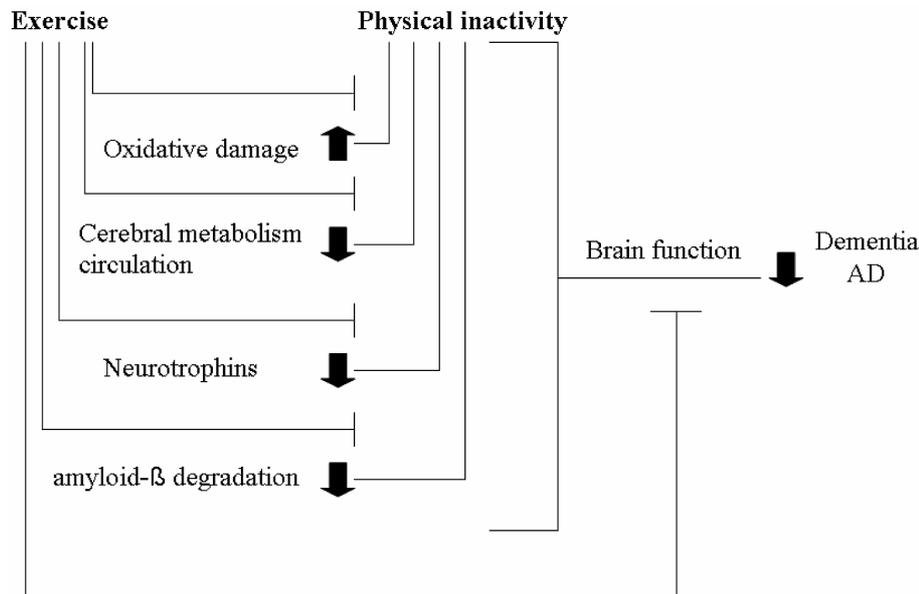


Fig. 1. Figure shows the hypothetical model of the effect of exercise and physical inactivity on dementia and AD.

the unaltered levels of neprilysin, an $A\beta$ -degrading enzyme, and insulin degrading enzyme (IDE) suggest that the beneficial effects of exercise are mediated by $A\beta$ PP degradation [72]. Interestingly, it has been shown that in transgenic mice, accumulation of $A\beta$ curbs the activity of proteasome, hence impairs the degradation of $A\beta$ PP [73]. Moreover, postmortem measurement of the proteolytic activity of the proteasome complex decreased by nearly 50% in the samples from AD patients [74]. Inhibition of $A\beta$ production by a γ -secretase restores proteasome activity to levels of wild-type neurons [73], which indeed suggests the involvement of the proteasome in the pathology of AD. The age-associated decrease in activity, on the other hand, has been shown to be prevented by exercise training in Wistar rats [61]. The question arises whether this induction of proteasome could contribute to the beneficial effects of exercise, which results in a decreased level of $A\beta$. At the moment, there is no significant evidence that the activity of neprilysin and IDE could be significantly induced by exercise in the brain. On the other hand, it is known that environmental enrichment, which includes physical activity, results in increased neprilysin activity and massive decrease in $A\beta$ concentration [75].

BLOOD FLOW AND METABOLISM

There is a debate on whether AD-associated decrease in cerebral blood flow precedes the decline in cerebral

metabolism or is the consequence; nevertheless, both are decreased with AD [76,77]. The decrease in cerebral metabolism includes different brain regions [78]. On the other hand, physical exercise significantly increases both the cerebral blood flow, if the intensity of exercise exceeds 60% of the maximum [79,80], and cerebral metabolism [81–83]. There is accumulating evidence that regular exercise induces the vascular endothelial growth factor (VEGF) content not only in skeletal muscle but in the brain as well [84]. This is just opposite to the effect of aging, which results in decreases in density of nigral microvessels and VEGF mRNA expression, which could be attenuated by exercise training [85]. Moreover, it appears that regular exercise at a young age has a massive effect on VEGF expression, which is associated with the intensity of exercise [86]. These events strongly indicate that exercise complexly modulates brain function.

This complexity could even include the alteration of acetylation/deacetylation levels of certain proteins in the brain. NAD^+ / $NADH$ levels might reflect not only the metabolic and redox status of the cells, but NAD^+ serves as fuel for sirtuins which are potential lysine deacetylases. Acetylation/deacetylations are powerful posttranslational modifications by which the function of proteins can turn on or off. A recent study indicates that SIRT1 and resveratrol could attenuate of the acetylation of number of proteins involved in AD [87]. Our observations suggest that regular exercise increases the activity of SIRT1 in the cerebellum [88] and maybe in

other brain regions as well, which might indicate another pathway by which exercise could facilitate brain health.

CONCLUSION

Physical inactivity is a major risk factor of a number of conditions, including senescence and AD. Regular physical activity promotes brain function in a variety of mechanisms, including enhanced antioxidant and oxidative damage repairing systems. Exercise-induced upregulation of neurotrophins involved in neurogenesis improved memory and brain plasticity, increased resistance to stress and relieved depression. Exercise could even curb the generation of A β and enhance its degradation. Moreover, exercise improves the healthy vascularization and energy metabolism of different brain regions, which could be an important mean to reduce the incidence of AD and ameliorate cognitive dysfunction in AD patients. Taken together, regular exercise acts upon a variety of factors to improve and keep our brain healthy and productive.

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