Role of physical exercise in Alzheimer's disease (Review)

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Abstract. The benefits of physical exercise on the brain and general wellness are well recognised, but not particularly well known to the general public. Understanding the importance of integrating active behavior for overall health is crucial at any age and particularly for the elderly who are at risk of developing Alzheimer's disease (AD), a disease mainly affecting individuals aged >65 years. AD is a neurodegenerative disease characterized by extracellular senile plaques of amyloid-β, intracellular neurofibrillary tangles of the protein tau, brain atrophy and dementia. The beneficial effects of physical exercise have been observed on the maintenance of brain size and efficiency for the prevention of AD risks, such as obesity, hypertension and stroke. These effects are extended to individuals with, or at risk of dementia and other age-related neurodegenerative disorders. Accordingly, although extensive studies are required to fully understand the mechanisms by which physical exercise procures beneficial effects, data suggest the relevance of integrating physical exercise in the prevention and/or cure of AD, disease whose incidence is predicted to increase in the future. Such an increase, may pose medical, social and economical challenges for populations and the health care system worldwide. In the present review we assess the positive aspects of physical exercise with regard to prevention and cure of AD.

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1. Introduction

Regular exercise including jogging, walking, biking, stretching, swimming and skipping may prevent and/or retard the progression of brain disorder and metabolic diseases such as obesity, diabetes and hypertension, which are risk factors of diseases affecting the brain (1). Regular physical exercise enhances the endurance of cells, tissues and organs to oxidative stress (2), increase energy metabolism (3), vascularization (4) as well as neurotrophin synthesis (5), all of which constitute important inducers of neurogenesis, muscle development, memory improvement and brain plasticity. These benefits are important in the prevention of Alzheimer's disease (AD) and provide treatment options for age-associated neurodegenerative disorders such as AD (6).

High-intensity training is more effective in women than in men after six months of training (7) and is associated with an increase in functional cognitive faculties, glucose metabolism, cardiorespiratory fitness and body composition (7). Furthermore, when the regular or high-intensity trainings are reinforced or replaced by resistance training or strength training (8), such as walking and moving around the house, climbing stairs, getting up from the floor and putting on socks daily or ≥2 days per week at a moderate intensity of ≥50% of one's maximum, there are long-term effects on brain health. For other causes of dementia, previous studies have reported an almost 37% reduction of the risk (9). These types of training particularly increase muscle mass in the human body and have beneficial effects on metabolic ageing (10). Loss of muscle mass has been identified in individuals at risk or diagnosed with AD (11,12). In concordance with the abovementioned data, a strong correlation between greater muscle strength and a low risk of developing dementia or AD in healthy individuals has been identified (13). Additionally, the abovementioned data suggest that practicing physical activity routinely throughout a subject's lifetime, at any age and especially for older adults, constitutes a strategy for increasing overall health and risks involved in the development of dementia and AD (9). Thus, engaging in such activity may reduce the wide range of individuals with neurological conditions. However, the benefits of exercise on brain health and wellness are poorly studied and the general public is unfamiliar with these benefits.

In this review, we evaluated aspects by which physical activity procures beneficial preventive or curative effects on AD and other age-associated neurogenerative diseases.

2. Alzheimer's disease

Ageing is a risk factor of cognitive function impairment and dementia including AD, which is characterized by the

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extracellular deposition of senile plaques of amyloid-β (Aβ), intracellular neurofibrillary tangles of protein tau, brain atrophy and dementia (14). Aβ-induced mitochondrial dysfunction has been associated with inhibition of the production of ATP (15-18) and the reduction of the activities of key enzymes of oxidative stress metabolism such as α-ketoglutarate dehydrogenase complex, pyruvate dehydrogenase complex and cytochrome oxidase. In addition, Aβ-induced reduced complex IV activity in mitochondria of the hippocampus and platelets (19) and the dysfunction of calcium homeostasis thereby increasing the accumulation of mitochondrial calcium that contribute to the decreased reuptake of calcium (20), leading to the translocation of pro-apoptotic molecules from mitochondria to cytosol and apoptosis, which results in increased activity of calmodulin-dependent kinase and calpain (17,21). Aβ-induced also increased the mutations of mitochondrial DNA (18,22). Together with Aβ, intracellular neurofibrillary tangles favour the excessive accumulation of reactive oxygen species (ROS) due to mitochondrial dysfunction which increases oxidative stress (19) leading to increased levels of lipid peroxidation, protein oxidation and DNA/RNA oxidation (23) thereby causing neurodegeneration and cerebral amyloid angiopathy (CAA). ROS can also aggravate the production and aggregation of Aβ and promote the phosphorylation of tau, thus establishing a vicious cycle of pathogenesis in AD (15).

Another risk factor associated with ageing is the increase of small vascular diseases (SVD) (24), a set of pathophysiology involving subcortical lesions, microinfarction, lacunas and intracerebral small vessels including arteries, arterioles, capillaries and small veins (25). Specifiallcy, unrelated to CAA, SVD is the most frequent vascular pathology in ageing in a healthy manner and AD brain. However, SVD alone or associated with AD has been considered as the major etiologic cause of morbidity, disability, and cognitive dysfunctions leading to dementia and mortality (26,27). Accordingly, several SVD, unrelated to atherosclerotic disease, are associated with inherited mutations (28) that result in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) (29,30). CARASIL is a single-gene encoding cell-signaling receptors instigating the degeneration of vascular smooth muscle in small arteries and arterioles, caused by mutations in the *HTRA1* gene encoding HtrA serine peptidase/protease 1 (29). Aberrant HTRA1 activity, results in increased transforming growth factor (TGF)-β1 signaling provoking multiple actions including vascular fibrosis and extracellular matrix (ECM) synthesis (29,30). TGF-β1 is increased in AD and is associated with the release of pro-inflammatory cytokines interleukin-1β and tumor necrosis factor-α, and results in the initiation and/or the propagation of a destructive inflammatory cycle in astroglial cells and neuronal apoptosis together with the development of vascular hypertrophy, fibrosis, and the accumulation of ECM components (31-35), which result in the decrease of brain perfusion and cerebral glucose metabolism. These reductions are also associated with the decrease in the neuronal expression of genes encoding subunits of the mitochondrial electron transporter chain (36).

3. Beneficial effects of physical exercise on Alzheimer's disease

Although there is a lack of consensus regarding optimal physical activities associated with AD prevention or improvement, aerobic activities (37-41) and balanced training of moderate-to-severe intensities are considered optimal (42). A meta-analysis suggested that although exercise has a positive effect on cognitive performance, cardiovascular fitness alone (VO2 Max) does not explain these benefits (43). However, the regular practice of walking improves cognition in AD (44,45), while strength training is particularly more effective for improving postural and motor function, and reducing the risk of developing AD (46), since it improves muscle mass and strength, shown to be affected in AD patients (10). In addition, environmental conditions such as bright light exposure and good nutrition may play an important role in improving training results (47,48). Accordingly, the meta-analysis identified the preventive effects of physical activities against AD.

The majority of longitudinal epidemiological studies have clearly shown associations between physical activities and the risk of cognitive decline in a dose-response manner (49,50), suggesting that physical activities may delay the onset of AD as well as the risk of cognitive decline (51-58) and mortality (59). The reduction of depression symptomatology (60-62), improvements in postural, motor functions (63,64) and the reduction of Aβ plaques as shown in a mouse model in which mice were required to run in the wheel have also been identified (65,66). The reduction of Aβ referred to neuroprotective mechanisms. Specifically, 40 min of physical activities such as the ergocycle, treadmill and stair-climbing activities over a period of 12 consecutive weeks, has been associated with an increase of cerebral blood flow that improves neurogenesis (67) in brain areas, including dentate gyrus of the hippocampus. The beneficial effects on cerebral blood flow have been associated with the reduction of cerebrovascular and endothelial dysfunction pathophysiology by improvement through the activation of nitric oxide (NO)/endothelial NO synthase (eNOS), resulting in the building of vascular reserve and the maintenance of neuronal plasticity (68). In addition, an aerobic program session lasting 3 weeks for 1 h for a period of 6 months increased the volume of gray and white matters in the cortical regions of subjects >60 years (69). Similar data however, were not identified in anaerobic conditions (69).

In concordance with those data, physical activity has been found to counteract the noxious effects of oxidative stress in animal models in which the reduction of oxidative stress was also associated with the reduction of cholesterol and insulin resistance, resulting in increasing vascularization and improving energy metabolism such as glucose metabolism (40,68,70-72) and facilitating neurogenesis and synaptogenesis, which improve memory and cognitive functions (40,55,67,68,70,72). Accordingly, in old mouse models of AD trained with sedentary control mice, the hippocampal neurogenesis was associated with synaptogenesis and spatial memory improvements (71,73). Similarly, increases of the volume of hippocampus of >2% together with plasma concentration of brain-derived neurotrophic factor (BDNF) were also observed in older healthy subjects (74) and in individuals with AD (75) following one year of moderately intense

aerobic exercise (3 days per week, 40 min per session). The increase in BDNF can be enhanced by the environmental condition. In mice trained in an enriched environment, cognitive improvements related to benefits from environmental enrichment were higher in BDNF, hippocampal neurotrophin and activation of hippocampal neurogenesis than those of mice in the same training program in poor environmental enrichment (66). Additionally, physical training was associated with the decrease of neurofibrillary degeneration and neuroinflammation as well as in the prevention against loss of the expression of choline acetyltransferase which is affected in mouse models of AD after 9 months of training (76,77). Of note, neurotrophins are proteins classically identified as mediators of neuronal survival and differentiation during development. They also maintain viability of neurons in adulthood, protecting, restoring neurons in response to injury and ageing. The efficacy of synaptic transmission is adaptable and neurotrophins serve as activity-dependent modulators of synaptic plasticity (78) in which BDNF has emerged as a key mediator in the memory centers of the brain (79). Notably, neurotrophins regulate target genes encoding structural proteins, enzymes or neurotransmitters resulting in the modification of neuronal morphology and function. These data are appropriate for prescription of physical activity for brain health although further investigations are required to identify reasonable standards and universal preventives and/or curative protocols for AD and related dementia.

4. Conclusion

Aerobic multicomponent training involving power and balance exercises induces important beneficial effects on health thereby improving the executive function, attentional capacity, processing speed, episodic memory and procedural memory (80-82). Moderate and high intensities have demonstrated a neuroprotective effect through the production of antioxidant enzymes and growth factors such as superoxide dismutase, eNOS, BDNF, nerve growth factors, insulin-like growth factors and vascular endothelial growth factor and by reducing the production of ROS, neuroinflammation, the concentration of Aβ plaques in cognitive regions and tau pathology, leading to the improvement of cerebral blood flow, hyperemia, cerebrovascular reactivity and memory (68,70,83). Although extensive studies are required to understand mechanisms by which physical exercise procures beneficial effects to establish standard protocols, the practice of physical activity may be disregarded by a large number of people, particularly those at risk or suffering AD, or taking medication.

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