Effect of Physical Exercise in Alzheimer's Disease Patients

Subjects: Neurosciences
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Physical exercise (PE) can be a non-pharmacological intervention in delaying cognitive decline in patients with Alzheimer's disease (AD) not only by improving cardiovascular fitness but also by attenuating neuroinflammation. Animal studies consistently report that PE improves cardiovascular fitness and attenuates AD-promoting processing of amyloid precursor protein and neuroinflammation, facilitates brain clearance of toxic amyloid β peptides and oligomers and promotes brain connectivity and nerve cell viability. Further studies in human are necessary to develop optimal, personalised protocols to take full advantage of the beneficial effects of PE that promote cardiovascular fitness, attenuate systemic inflammation, stimulate brain amyloid β peptides brain catabolism, delay immunescence and support brain clearance of amyloid β peptides and their catabolism in peripheral organs.

Alzheimer's disease | memory impairment | ageing | neuroinflammation | physical exercise

1. Physical Exercise

Muscle activity is characterised either as physical activity (PA) or as physical exercise (PE). PA refers to any movement that is carried out by the muscles that requires energy. PE is a planned, structured, and repetitive PA with the objective to improve or maintenance of physical fitness. Physical fitness is a set of health or skill-related attributes that are evaluated by specific tests [1]. PE is preferred to PA for establishing the dose-related effects of muscle work on the human body.

The beneficial effects of regular, sustained PE (aerobic or resistance training) on the human body include:

(a) an increase in exercise tolerance (due to an increased cardiac and skeletal muscle strength, improved function and enhanced maximal oxygen consumption coupled with an increased capillary network);

(b) an increased insulin sensitivity in adipose tissue, skeletal muscle and endothelium leading to a reduced risk of systemic insulin resistance in persons type 2 diabetes;

(c) reductions in elevated body weight (due to an increased catabolism in muscles and adipose tissue) and blood pressure (due to an increased vascular density of arterioles and a reduction in systemic vascular resistance elicited by an increased release of vasodilatation promoting NO and prostacyclin from the vascular endothelium);

(d) an increase in HDL and LDL cholesterol particles size and a decrease in VLDL particles size and

(e) an improved response of the immune system with a delayed onset of immunesescence and reduced systemic inflammation (e.g., reduced numbers of exhausted/senescent T cells, an increased T-cell proliferative capacity, reduced blood levels of inflammatory cytokines, an increased neutrophil phagocytic activity, and an enhanced natural killer (NK) cell cytotoxic activity) [2][3][4].

The beneficial metabolic changes associated with regular PE are mediated by insulin-like growth factor 1 (IGF1) and insulin receptor signalling via the PI3K/AKT1/mTOR signalling that activate multiple transcriptional pathways [4].

The health effects of PE are enhanced when combined with optimal nutrition, secession of smoking and medication modification [2][3]. Sedentary persons have a considerably higher risk for cardiovascular disease than persons who engage in regular PE [4].

Not all of the beneficial health effects of sustained PE (aerobic, resistance or concurrent exercise training) can be replicated in older adults. For example, a 12-week PE intervention improved cognitive function and physical fitness (evaluated by gait speed, upper and lower limb strength, aerobic fitness, hand-grip strength, timed up-and-go and sit-to-stand) in older adults (male and female, average age 69) compared to non-exercise control [5]. However, PE may not attenuate the decline in insulin sensitivity and muscle mass, or reduce blood pressure across all age groups.

2. Alzheimer's Disease

Alzheimer's disease is the most common cause of cognitive impairment or dementia in individuals older than 65 years and rising global longevity is leading to a worldwide pandemic of mild cognitive impairment (MCI), AD, and AD-related dementia. There is no cure for AD; however non-pharmacological (e.g., exercise) and pharmacological (e.g., acetylcholinesterase inhibitors) interventions can mitigate the symptoms and attenuate the progression of the disease [6].

AD changes to conscious mental activity are not synonymous with old age changes. In AD multiple cognitive (e.g., attention, judgement, memory, intelligence, social cognition and executive function), functional and behavioural domains of conscious mental activity are impaired. In normal aging, there is a decline in fluid intelligence from early adulthood and a preservation and an increase in crystalized intelligence until late life. Also in normal aging, individuals retain at least some degree of their personality, interests, level of initiative, motivation, sociability, empathy and behaviour [7].

By aetiology, AD can be classified into three groups: dominantly inherited familial AD (FAD), early onset AD (EOAD) and late onset AD (LOAD). FAD (representing less than 1% of pathologically diagnosed AD cases, average age of onset 46 years) is caused by mutations in amyloid precursor protein (APP), presenilin-1 (PS1) or

presenilin-2 (PS2) genes. EOAD (representing less than 5% of pathologically diagnosed AD cases) is present in patients with AD signs and symptoms before age 65. LOAD is the most common form of AD, where several genetic risk factors have been identified, including apolipoprotein (APO) ε gene, TREM2, ADAM10 and PLD3. Inheritance of APO ε4 also increases the risk for vascular dementia (VAD), Lewy body dementia (LBD), Down's syndrome and traumatic brain injury. In summary, AD-risk attributable to genetic factors is estimated at 70%.

Ageing is the most important of all risks for development of AD [8]. For example, in the USA, in 2021, one in nine people aged 65 and older have AD dementia and almost two-thirds of Americans with AD are women. Brain blood flow is reduced with ageing, and the reduced blood flow and hippocampal volume are associated with a reduced cognition [9]. The documented changes of PE on the human brain are: improved cerebral brain blood flow, attenuated reduction in hippocampal volume and improved cognitive ability [10][11][12]. In addition to ageing, other nonmodifiable AD risk factors are cerebral amyloidosis, Down syndrome, gender (females have a greater AD risk), family history of AD and inheritance of APO ε4 allele [7].

The key AD pathological features are the signs of a dual mixed proteinopathy, i.e., amyloid plaques and neurofibrillary tangles (NFT). Biochemical, neurophysiological, and neuroanatomical changes elicited by the AD dual mixed proteinopathy that can be measured decades before psychometrically and clinically noticeable deterioration in cognition, behaviour, and function. Therefore, AD dementia is a clinical diagnosis since, for example, 20–40% of individuals aged 70 or above do not have cognitive impairment in the presence of biomarkers for AD, or autopsy evidence of AD pathology.

3. Physical Activity Delays Ageing-Related Changes

3.1. Human Studies

Physical activity at any level contributes to healthy ageing, delays cognitive and physical decline [13]. Ageing related memory deficits are correlated with a reduced functional connectivity within the anterior and posterior default mode network in the hippocampus. In healthy, randomly recruited individuals, a higher PA score is positively correlated: (a) with a reduction in negative age-related decreases in functional connectivity of posterior default-mode network, and (b) with increases in posterior cingulate cortex (PCC) grey matter volume, PCC perfusion, and (c) improved visuospatial task performance. These positive, brain ageing reducing effects on PCC were achieved with over a decade of PA. PCC functional connectivity is also reduced in the early stages of AD [14]. Meta-analysis of randomised, controlled trials, in healthy adults aged 50 and older, reported improved memory, executive function, auditory attention, cognitive speed, visual attention motor function and cardiorespiratory fitness after aerobic PA programmes [15][16]. Guidelines for healthy ageing recommend a personalised, PA regime that enables at least 150 min of moderate-intensity aerobic activity, or 75 min of vigorous-intensity aerobic activity combined with at least two days of muscle-strengthening activities per week [17]. Physical activity also (a) reduces TNFα activity (a pro-inflammatory cytokine that attenuates apoptosis), and (b) increases brain-derived neurotrophic factor (BDNF) activity in hippocampal and cortical neurons thus contributing to improved neuronal survival, learning and memory [11][18].

3.2. Effects of Physical Activity and Ageing on Proteostasis

Aging is associated with a reduced proteostasis efficiency, including among others a decreased autophagy and a reduced efficiency of the ubiquitin-proteasome system (as evidenced by an intracellular accumulation of dysfunctional proteins and organelles, misfolded proteins, increased conversion of misfolded proteins into toxic peptides and protein aggregates) that contribute to neurotoxicity, neurodegeneration, accelerated ageing process and a reduced life span [19][20][21][22]. Physical activity stimulates autophagy via AMP-activated protein kinase (AMPK) activation. Increased AMPK activity inhibits the target of rapamycin complex 1, a negative regulator of autophagy and a positive regulator of cellular protein production. Thus, the combined actions of an enhanced autophagy and a reduced cell protein burden delay the development and progression of neurodegeneration [23][24][25]. Activities of the autophagy and ubiquitin-proteasome system protein degradation pathways are coordinated. It has been suggested that the early post-exercise protein degradation is mediated mainly by the UPR and the late post-exercise protein degradation by autophagy [22]. For example, in human skeletal muscle, aerobic PA stimulates autophagy in a duration and intensity dependent manner [26][27][28]. Ageing also reduces the efficiency of the UPR; both endoplasmic reticulum (ER) protein folding and UPR protein degradation are reduced [29]. In human and animal studies, regular aerobic exercise seems to attenuate ER stress in middle-aged and old subjects [29][30][31]; however, the relationship among UPR activation, exercise and aging has to be further investigated in more detail, especially in human subjects [29].

4. Physical Activity Attenuates Expression of Pro-Inflammatory Markers

During exercise, the expression of skeletal muscle mRNA PGC1α is increased via AMPK activation, and returns to baseline values after exercise [32][33]. Increased mRNA PGC1α expression is assumed to attenuate expression of pro-inflammatory cytokine TNFα and oxidative stress-mediating genes in vascular endothelial cells, and to change the balance in favour of anti-inflammatory (M2) skeletal muscle macrophages [34]. Increased levels of TNFα stimulate muscle catabolism via NFkB signalling pathway that promotes ubiquitin conjugation of muscle proteins and their proteasome degradation [34]. Depression symptoms are associated with increased levels of TNFα; in students, moderate intensity, continuous PE decreased depressive symptoms, perceived stress and TNFα levels compared to healthy students with no exercise [35]. Moderate intensity, continuous PE had a similar effect on pro-inflammatory IL1β levels that was not significant [35].

Increased PGC-1α levels in contracting muscle fibbers also stimulate the release of irisin, produced from fibronectin type III domain-containing protein 5 (FNDC5) in myocytes. Irisin crosses the BBB, attenuates brain neuroinflammation and improves hippocampal memory and learning function by increasing expression of BDNF in microglia and astrocytes. BDNF has anti-inflammatory effects by attenuating NFκB, GSK3β, p38 and JNK activity in microglia and astrocytes, thus reducing the release of pro-inflammatory cytokines of IL6 and IL1β in the brain [36]. Irisin also decreases the expression of pro-inflammatory cyclooxygenase-2 and AKT phosphorylation [36].

FNDC5 is also expressed in the hippocampus [37][38], and this brain expression could have an AD preventive effect. In vitro, FNDC5 binds to a specific domain between β- and α-secretase APP cleavage sites, thus reducing Aβ40 and Aβ42 formation [39]. In an animal model, the down regulation of brain FNDC5/irisin attenuated long-term potentiation and memory formation, while restored FNDC5/irisin brain levels improved synaptic plasticity and memory [40].

Physical exercise leads to a transient, moderate level, release of the anti-inflammatory skeletal muscle cytokine IL6; this cytokine inhibits the release of TNFα and stimulates the release of anti-inflammatory IL1 receptor antagonist in leukocytes and lymphocytes [41]. Thus, transient and moderate increases of IL6, released from myocytes, elicit in monocytes or macrophages an anti-inflammatory response, by a nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) independent signalling pathway, (i.e., with an increased production of IL10 and IL1RA). High levels and/or long term release of IL6 from macrophages elicits a pro-inflammatory response in monocytes or macrophages via the NFκB signalling pathway [42]. In summary, IL6 contribution to inflammation and muscle proteostasis is time and concentration dependent; transient and moderate increases of IL6 stimulate myogenesis and an anti-inflammatory response, chronic and large increases of IL6 promote a pro-inflammatory response in immune cells (via NFκB signalling pathway) and muscle wasting via STAT3 signalling [43].

5. Physical Activity Modulates Adaptive Immunity

Regular, structured PE, provided it develops and sustains cardiorespiratory fitness, improves efficiency of adaptive immune system in human across all ages. Animal and human studies support the hypothesis that PE improves adaptive immunity by preventing the excessive accumulation of memory T lymphocytes in the body. Naïve T cells (e.g., CD4+ helper cells, CD8+ cytotoxic cells) circulate between the blood and the lymphatic system until they come into contact with antigens (on antigen presenting cells) recognised by naïve T receptors; this contact transforms naïve T cells into activated T cells that further differentiate to memory T lymphocytes. Memory T lymphocytes have a lower antigen activation threshold, a higher rate of proliferation and a better peripheral tissue and secondary lymphatic tissue penetration than naïve T cells, thus responding more quickly, in more tissues and more forcefully to a repeated antigen challenge. The process of PE promotes redistribution of CD4+ and CD8+ antigen-experienced memory T lymphocytes from the lymphatic tissue to the blood vessels, followed by migration of memory T lymphocytes to the peripheral tissue where they are eliminated by contact with pro-apoptotic molecules (ROS, cytokines and glucocorticoids). This reduction in the number of memory T lymphocytes is assumed to trigger a compensatory increase in the number of naïve T lymphocytes (T cells not yet in contact with a specific antigen) by a negative feedback loop governing the ratio of memory to naïve T lymphocytes [44].

6. Physical Activity Attenuates AD Neuroinflammation

6.1. Animal Studies

In various AD animal models, PE reduces hippocampal inflammation and the further hippocampal Aβ products deposition by: (a) an up-regulation of disintegrin and metalloproteinase 17 mRNA and down-regulation of BACE1

mRNA in ageing rats [45]; (b) an attenuation of brain GSK3α/β and/or CDK5 activity [46][47][48][49][50][51][52][53][54][55]; (c) a reduced APP phosphorylation [46]; (d) an attenuated activity of tau kinases that reduces tau phosphorylation and also reduces tau kinase mediated APP phosphorylation and γ-secretase activation [46][56]; (e) an attenuation of neuroinflammation stimulated indoleamine-2,3-dioxygenase activity by the anti-inflammatory cytokine IL10 [57][58], and (f) an attenuated phosphorylation of pro-inflammatory p38 and JNK molecules, due to a reduced MAPK and NFκB signalling [59].

6.2. Human Studies

The effect of exercise on inflammation markers in AD patients was recently evaluated in 16 weeks long, randomized controlled trial with 198 participants (average age 70 years, male and female participants), distributed among control, moderate and high exercise groups. The outcomes of PE were: (a) a small increase in plasma IL6 after PE, (b) a reduced IFNγ concentrations in APO ε4 carriers, (c) no significant effect on cerebrospinal fluid (CSF) levels of cytokines IL-10, -13, -2, -6, -8, and TNFα, and (d) the marker for myeloid cells 2 trigger receptor (measuring microglial activation) was significantly increased in CSF. The recommendations, for future evaluations of exercise-elicited effects on pro-inflammatory markers in patients with AD, were: to evaluate the duration and type of PE, to increase the number of participating patients, and to stratify the effects of exercise protocol on different stages of AD, from pre-clinical to severe AD [60].

7. Physical Activity Attenuates AD Progression

7.1. Muscle Activity Modulates Cognition via Muscle-Brain Interactions

The intensity of PE leads to a proportional increase in the release of adiponectin from adipose tissue, and IGF1 from the liver and contracting muscles. These signalling molecules cross the BBB and modulate brain activity. Adiponectin brain actions support neurogenesis, learning, memory formation and ameliorate depression-like behaviour [37]. IGF1 supports normal cognition directly by upregulating hippocampal BDNF expression and adult neurogenesis, and indirectly by increasing Aβ peptide brain clearance, stimulating Aβ peptide degradation by insulin-degrading enzyme (IDE) and increasing cellular uptake and lysosomal degradation of Aβ peptide [37][61]. Physical exercise in mammals also stimulates the release of skeletal muscle myokines cathepsin B and irisin (also discussed in Section 4.). Both of them enhance neurogenesis, learning, memory and depression-free mood by stimulating BDNF brain expression [37].

Irisin inhibits the binding between Aβ oligomers and neurons, thus preventing eIF2α phosphorylation (the phosphorylated form acts as an inhibitor of its own guanine nucleotide exchange factor) and inhibition of protein synthesis [62]. In non-demented humans, the levels of CSF irisin increase with ageing. Patients with AD have normal irisin plasma levels, concomitant with reduced CSF irisin levels. Hippocampal FNDC5/irisin is reduced in moderate-to-late AD, but not in MCI [62]. A recent study reported that CSF irisin levels were positively correlated with CSF BDNF and Aβ42 CSF levels, and with MMSE scores, but not with CSF total tau. Therefore, decreased CSF irisin and BDNF levels do not seem to be associated with total tau but with brain amyloid pathology.

Compared to non-demented controls, patients with AD had reduced CSF levels of BDNF and Aβ42, increased levels of CSF total tau, and lower cognitive scores [63].

Increased BDNF brain expression is also elicited by an increased sympathetic nervous system activity and elevated blood concentration levels of ketone bodies during PE [37]. BDNF attenuates Aβ peptide toxicity on neurons, promotes synaptic plasticity by increasing the strength of synaptic connections, promotes LTP and by extension memory formation, learning and cognition, therefore is essential for normal hippocampal neurogenesis and development of hippocampal neural circuits [64]. Interventions to increase brain BDNF in human could improve learning and memory, ameliorate AD pathology and mood disorders [65][66][67][68][69][70].

7.2. Human Studies on Old Age Health Subjects

Changes in hippocampal volume, in response to different levels of PA, can occur within weeks. In young to middle-aged adults, a six-week aerobic training exercise intervention transiently increased the hippocampal volume (due to an increase in hippocampal myelination). This observed increase was reversed after six weeks without aerobic exercise [71].

Memory function and plasma values of factors BDNF, IGF1, VEGF or platelet-derived growth factor C were measured before and after a 3-month aerobic exercise regime in 40 humans, age 60–77 years. Although the aerobic exercise regime improved memory function, there were no concomitant changes in the measured plasma values. Explanations given for the observed discrepancy were: a high intra-individual variability of base plasma values, a low number of participants, diurnal variation of measured factors due to sex and/or other interfering metabolic processes (e.g., food intake) [72].

56 healthy elderly participants, male and female, (average age 68) were involved in 12 weeks randomised physical training study (high resistance training only (80% of one repetition maximum (1RM), low resistance training only (20% 1RM), or mixed low resistance training (20% and 40% 1RM)). BDNF levels were increased in males only of the mixed low resistance training group [73].

There is a lack of controlled, randomised studies that evaluate the effect of PE on systemic and brain pro-inflammatory markers in patients with AD. A two-months aerobic exercise regime improved quality of life and psychological wellbeing parameters, and reduced systemic pro-inflammatory markers (e.g., TNFα) in patients with AD (age 67 to 75 years, male and female participants) [74]. The effect of exercise on inflammation markers in AD patients was recently evaluated in 16 weeks long, randomized controlled trial with 198 participants (average age 70 years, male and female participants), distributed among control, moderate and high exercise groups. The outcomes of PE were: (a) a small increase in plasma IL6 after PE, (b) a reduced IFNγ concentrations in APO ε4 carriers, (c) no significant effect on cerebrospinal fluid (CSF) levels of cytokines IL-10, -13, -2, -6, -8, and TNFα, and (d) the marker for myeloid cells 2 trigger receptor (measuring microglial activation) was significantly increased in CSF. The recommendations, for future evaluations of exercise-elicited effects on pro-inflammatory markers in

patients with AD, were: to evaluate the duration and type of PE, to increase the number of participating patients, and to stratify the effects of exercise protocol on different stages of AD, from pre-clinical to severe AD [60].

7.3. Human Studies on Persons with AD

Cognition and molecular biomarkers were evaluated in two subgroups of nondemented persons with a family history of Alzheimer's disease; subgroup + APO ε4 (with APO ε4 genotype) and subgroup—APO ε4 (without the APO ε4 genotype allele), and compared to their senior functional physical fitness test values. The + APO ε4 subgroup had a lower cognitive score, when performing cognitive tasks with a higher visuospatial working memory load, compared to the—APO ε4 subgroup. There were no significant changes in the levels of molecular markers IL1β, BDNF, Aβ40 and Aβ42 between the two subgroups. Compared to the + APO ε4 subgroup, the—APO ε4 subgroup had a better cardiorespiratory fitness score, and this difference was positively correlated with the higher cognitive fitness in the—APO ε4 subgroup [38].

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