Molecular Neurobiology (2021) 58:5890–5906
https://doi.org/10.1007/s12035-021-02514-7

The Beneficial Role of Exercise on Treating Alzheimer's Disease by Inhibiting β-Amyloid Peptide

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Received: 10 February 2021 / Accepted: 3 August 2021 / Published online: 20 August 2021

Abstract

Alzheimer's disease (AD) is associated with a very large burden on global healthcare systems. Thus, it is imperative to find effective treatments of the disease. One feature of AD is the accumulation of neurotoxic β-amyloid peptide (Aβ). Aβ induces multiple pathological processes that are deleterious to nerve cells. Despite the development of medications that target the reduction of Aβ to treat AD, none has proven to be effective to date. Non-pharmacological interventions, such as physical exercise, are also being studied. The benefits of exercise on AD are widely recognized. Experimental and clinical studies have been performed to verify the role that exercise plays in reducing Aβ deposition to alleviate AD. This paper reviewed the various mechanisms involved in the exercise-induced reduction of Aβ, including the regulation of amyloid precursor protein cleaved proteases, the glymphatic system, brain-blood transport proteins, degrading enzymes and autophagy, which is beneficial to promote exercise therapy as a means of prevention and treatment of AD and indicates that exercise may provide new therapeutic targets for the treatment of AD.

Keywords Alzheimer's disease · Exercise · β-Amyloid peptide · Amyloid precursor protein

Introduction

Alzheimer's disease (AD) is an irreversible and progressive neurodegenerative disorder [1, 2]. It is the most common form of dementia and accounts for 60 to 70% of total dementia cases and affects about 27 million people worldwide [3, 4]. This creates a large economic burden, as the global healthcare cost for people with dementia is estimated to increase from 818 billion US dollars in 2015 to 2 trillion US dollars by 2030 [5]. The typically clinical features of AD are a gradual loss of cognitive function, episodic memory, and learning ability, followed by a decline in visuospatial skills and language [6, 7]. Patients with AD also may have behavioral problems, such as aggression, apathy, depression, and sleeping problems [8]. These symptoms adversely affect the daily life and social participation of AD patients. Currently, the pharmaceutical treatments for AD include cholinesterase inhibitors, such as galantamine, donepezil and rivastigmine, and memantine, which protects against glutamate-mediated neurotoxicity [9]. However, these medications only offer short-term remission of the development of AD rather than long-term therapeutic effects for the disease; in addition, these drugs are frequently associated with unpleasant side effects, such as weight loss, dizziness, and nausea [10]. Therefore, to clarify the mechanism of AD is a crucial issue for seeking out an effective and novel therapy for AD is urgently required.

Two typically pathophysiological changes, consisting of extracellular deposits of insoluble β-amyloid peptide (Aβ) plaque and neurofibrillary tangles (NFT) of phosphorylated tau (P-tau) within neurons, are the hallmarks of AD [11]. The accumulation of Aβ and P-tau are considered to result in atrophy and death of neurons, leading to cognitive dysfunction [12]. As one of the pathological hallmarks of AD, Aβ is a crucial target to treat AD [13]. The molecular mass

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of Aβ is 4 kDa and the amino acid sequence exhibits microheterogeneity [14]. According to a widely accepted theory, Aβ originates from the sequentially proteolytic cleavage of amyloid precursor protein (APP) [15]. The main pathways of Aβ removal include clearance by the glymphatic system, transportation across the blood–brain barrier (BBB), proteolytic degradation, and autophagy. An imbalance between the clearance and the production of Aβ causes cerebral dysfunction [16]. Aβ deposition has been proved to play a key role in AD progression, being other pathological events observed (including the NFT formation, endoplasmic reticulum stress, mitochondrial dysfunction, oxidative stress, or neuroinflammation), ultimately followed by neuronal loss [4, 17]. Decreasing the accumulation of Aβ is the main target for the treatment of AD. However, clinical trials using anti-amyloid drugs have repeatedly failed, which might be due to the presence of the blood–brain barrier or other factors. Therefore, we need to explore other types of interventions to alleviate the harmfulness of Aβ [18].

Due to the lack of a disease-modifying treatment for AD, researchers have been investigating the role that exercise, a non-pharmacological intervention, plays in alleviating AD symptoms and progression [19]. A variety of clinical studies demonstrated that aerobic exercise could promote cardiorespiratory fitness, memory, and executive function in patients with mild AD [20–24]. Fifteen weeks of physical activity was demonstrated to improve walking quality and alleviate cognitive decrease in AD patients. Another study showed that exercise can reduce the loss of global cognition in older individuals aged 70–80 with mild-to-moderate AD. The meta-analyses of randomized controlled trials indicate the slight-to-moderate effects of aerobic exercise on cognitive function across the AD spectrum [25, 26]. Due to the limitation of severe motor dysfunction in advanced AD patients, the evidence to investigate the effect of exercise on patients with advanced AD is limited. The increased physical activities caused by technology-aided program promote the positive personal involvement and independent occupation for advanced AD patients [27, 28]. Moreover, regular exercise may alleviate the progress of functional deterioration in mild AD and decrease falls in patients with advanced AD [29].``

On the other hand, exercise plays a multifactorial role in attenuating various pathophysiologic mechanisms that are associated with cognitive impairment and neurodegeneration in AD, such as the aggregation of tau and Aβ, inflammation, oxidative stress, pyroptosis, endothelial dysfunction, and so on [30–32]. Indeed, a series of studies have confirmed the effectiveness of exercise in reducing Aβ accumulation that is one of the most considerable roles in AD [16, 30, 33–39]. A study that used a mouse model of AD found evidence that voluntary running in the late stage of AD alleviated an increase in the number of Aβ plaques and improved hippocampus neurogenesis and memory [40]. However, up to now, it is still unclear how exercise reduces Aβ deposition. Hence, this review summarized the evidence of the beneficial effects of exercise on Aβ-dependent pathophysiology of AD, including Aβ generation, the glymphatic system, Aβ transport proteins across the BBB, autophagy, degrading enzymes, and other mechanisms to clarify the mechanisms involved and to explore novel and effective interventional targets for the treatment of AD (Fig. 1).

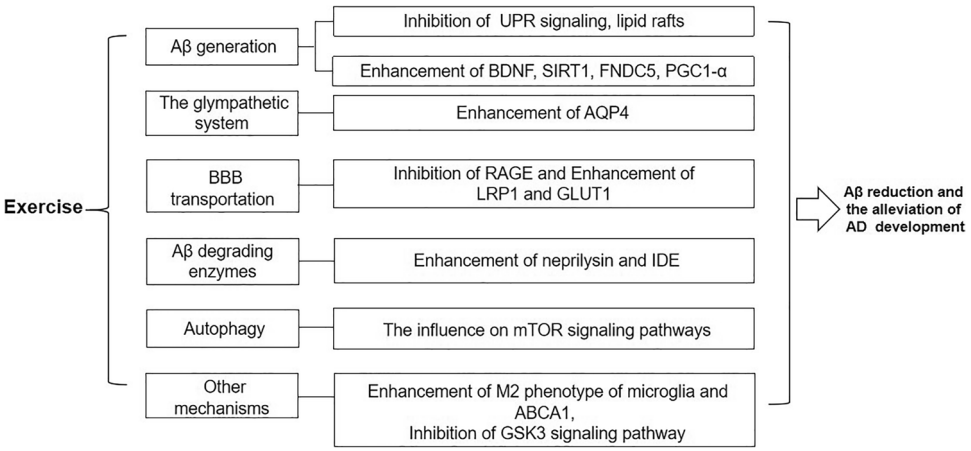

Fig. 1 Summary of mechanisms by which exercise reduces Aβ. The beneficial effect of exercise on Aβ, including APP-cleaved proteases, the glymphatic system, Aβ transport proteins across BBB, autophagy, degrading enzymes, and others. Aβ, β-amyloid peptide; ER stress, endoplasmic reticulum stress; PGC1-α, peroxisome proliferator-activated receptor-gamma coactivator 1α; FNDC5, fibronectin type III domain-containing protein 5; BDNF, brain-derived neurotrophic factor; SIRT1, sirtuin-1; AQP4, aquaporin-4: BBB, blood–brain barrier; RAGE, the receptor for advanced glycation end products; LRP1, low-density lipoprotein receptor-related protein 1; IDE, insulin-degrading enzyme; ABCA1, ATP-binding cassette transporter A1; GSK3, glycogen synthase kinase-3

The Mechanisms of the Inhibition of Aβ Deposition by Exercise Within Neurons in AD

The Effect of the Regulation of APP-Cleaved Proteases by Exercise

According to the amyloid cascade hypothesis, Aβ is generated by the protease cleavage of APP, which is predominately expressed in the central nervous system (CNS) [41, 42]. APP can undergo two alternative proteolytic processes through the non-amyloidogenic pathway and the amyloidogenic pathway. In the non-pathogenic pathway, APP is cleaved by α-secretase, such as a disintegrin and metalloprotease-10 (ADAM10), which releases an N-terminal-secreted APP (sAPPα) and C-terminal fragment of 83 amino acids (C83); sAPPα may exert a neuroprotective function [14, 43, 44]. In the amyloidogenic pathway, APP is cleaved by β-secretase, such as beta-site APP-cleaving enzyme 1 (BACE1), and γ-secretase and results in the production of Aβ [45]. Under normal physiological conditions, the two pathways coexist in equilibrium, although the non-amyloidogenic pathway is favored [46]. However, aging, genetic, and environmental factors related to AD may cause a metabolic shift that favors the amyloidogenic pathway of APP [47]. Although medications that target Aβ production to treat AD have been developed, such as γ-secretase modulators and BACE1 inhibitors, they have only recently become available [48]. Therefore, we need to explore novel methods to treat AD. Physical exercise has been proven to have the potential to reduce Aβ production by activating or inhibiting APP-cleaved proteases via multiple pathways (Fig. 2), which are summarized in the following sections.

The Brain-Derived Neurotrophic Factor

Brain-derived neurotrophic factor (BDNF) is a member of the growth factor family and plays a key role in neuronal growth, differentiation, and survival, as well as synaptic

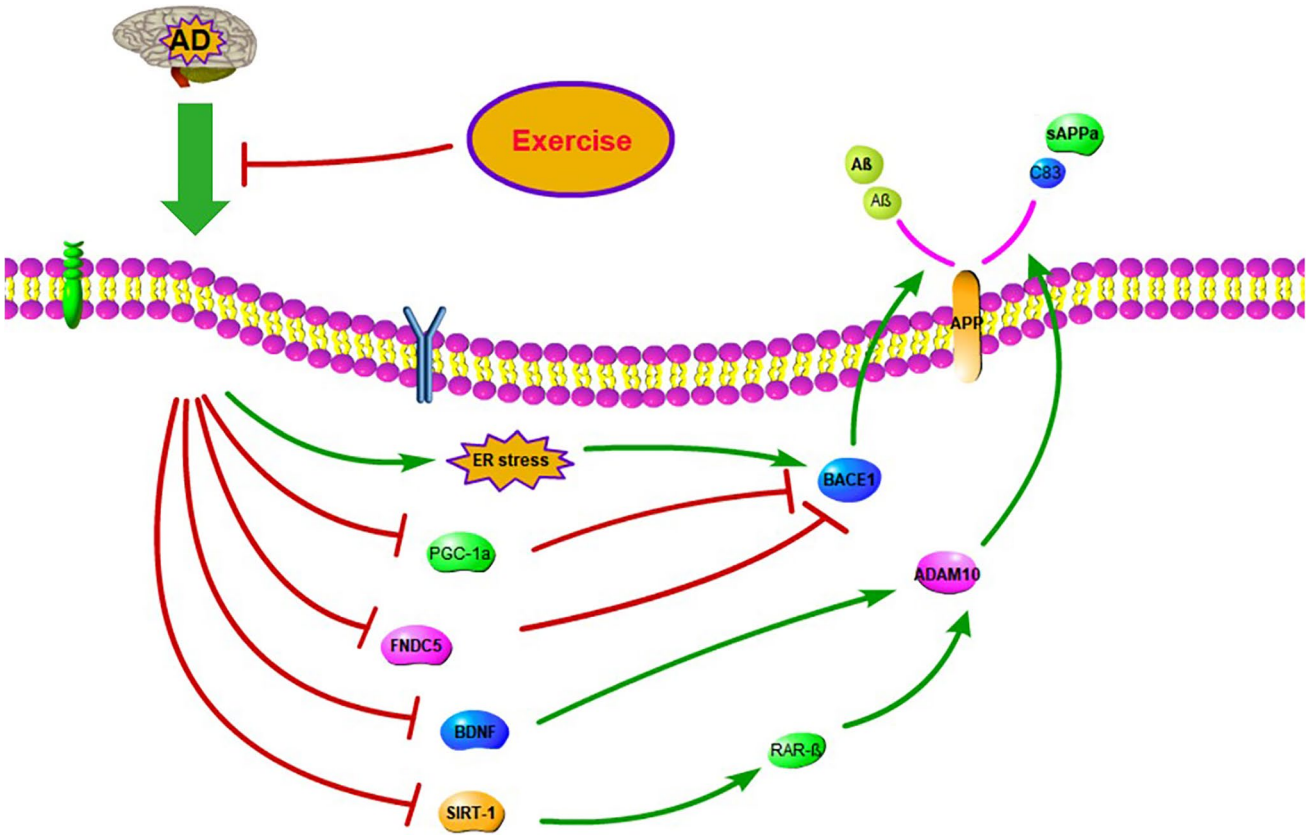

Fig. 2 Molecular mechanisms of the reduction of APP-cleaved proteases by exercise. ADAM10, BACE1, and γ-secretase are the main proteases for APP metabolism. SIRT1, PGC-1α, FNDC5, BDNF, and the ER stress are all involved in the regulation of APP-cleaved proteases by exercise. Green arrows represent promotion; red lines represent inhibition; pink lines represent production. ER stress, endoplasmic reticulum stress; PGC1-α, peroxisome proliferator-activated receptor-gamma coactivator 1α; FNDC5, fibronectin type III domain-containing protein 5; BDNF, brain-derived neurotrophic factor; SIRT1, sirtuin-1; RAR-β, retinoic acid receptor-β; BACE1, beta-site APP-cleaving enzyme 1; ADAM10, a disintegrin and metalloproteinase-10; APP, amyloid precursor protein; Aβ, β-amyloid peptide

plasticity [49, 50]. Converging studies have suggested that impaired BDNF signalling contributes to the pathological mechanisms of several main disorders and diseases, including AD, Huntington's disease (HD), and depression. BDNF is one of the elements responsible for synaptic integrity and cognitive function. Patients with AD have decreased expression of BDNF in the brain, and the infusion of BDNF can lessen cognitive dysfunction in elderly primates [51]. Moreover, high levels of peripheral BDNF may provide protection against the occurrence of AD [51, 52]. Importantly, BDNF can reduce Aβ deposition by activating α-secretase, which results in the increased levels of sAPPα, which has neuroprotective effects [53]. Several studies have shown that physical exercise in rats with AD obviously promotes the levels of BDNF and decreases the levels of Aβ [53–55]. Lin et al. also reported that 10-week treadmill training of APP/presenilin 1 (PS1) double transgenic (TG) mice elevated the expression of the phosphorylated protein kinase B, tyrosine kinase B receptor, and protein kinase C, which were the BDNF signalling pathway molecules, and prevented AD-related degeneration in the hippocampus and amygdala [56]. Therefore, we can infer that exercise partly reduces Aβ production through the BDNF pathway.

Sirtuin-1 Signalling Pathway

Sirtuin-1 (SIRT1), as an important member of the sirtuin family, plays a crucial role in maintaining cellular homeostasis via influencing insulin sensitivity, mitochondrial biogenesis, glucose metabolism, and neuronal survival [57–60]. SIRT1 has been verified to be related to numerous neurodegenerative pathophysiological process, such as AD and Parkinson's disease. Especially, SIRT1 can exert a neuroprotective effect against AD [61, 62]. Downregulation of SIRT1 has been found in AD, causing increased Aβ production, while overexpression of SIRT1 can reverse this pathology, suggesting the profound effect of SIRT1 on Aβ production [63]. Porquet et al. also showed that SIRT1 activation by resveratrol improved neurodegeneration by decreasing oxidative stress and neuroinflammation induced by amyloid accumulation in AD [64]. Revilla et al. have reported that the downregulation of SIRT1 in 3xTG (triple-transgenic) AD mice can be recovered by exercise treatment. Moreover, Koo et al. used a mouse model to show that treadmill exercise promoted the expression level of SIRT1, which subsequently caused the activation of ADAM10 by increasing the retinoic acid receptor-β and inhibiting Rho-associated kinase 1; the SIRT1 signalling pathway eventually activated the non-amyloidogenic pathway. The promotion of SIRT1 also increased the levels of peroxisome proliferator-activated receptor-gamma coactivator 1α (PGC-1α) and decreased the levels of BACE1, which suppressed the amyloidogenic pathway [58].

Fibronectin Type III Domain-Containing Protein 5 and PGC-1α

Fibronectin type III domain-containing protein 5 (FNDC5), which is the precursor protein of irisin, has been categorized as a PGC-1α-dependent myokine [65]. FNDC5 is proteolytically cleaved to myokine irisin, which regulates the beneficial role of exercise on human metabolism [66]. In recent years, studies have focused on the role of FNDC5 as a mediator of AD. For instance, one study found that increased levels of FNDC5/irisin in the brains of mice with AD improved impaired memory and synaptic plasticity [67]. Another cell study reported that FNDC5 regulated the β-cleavage of APP through intercommunications with APP, which reduced the levels of Aβ [68]. Choi et al. reported that running exercise enhanced the expression of FNDC5 in the hippocampus of 5xFAD TG mice that coinherited and co-overexpressed familial AD mutant forms of human PS1 and APP transgenes, and their results suggested that exercise attenuated the action of β-secretase through FDNC5 [69].

PGC-1α, an upstream activator of FNDC5, can be stimulated during exercise. In addition, PGC-1α plays a regulatory role in energy metabolism during the early stages of neurological diseases [70]. For instance, the increase of PGC-1α could alleviate the damaged cognition and neuronal injury in TG mice with AD by improving mitochondrial dysfunction and alleviating oxidative stress and insulin resistance [71]. Interestingly, low levels of PGC-1α result in Aβ aggregation in the brains of patients with AD [72]. The reason for this may be that the decreased levels of PGC-1α fail to block the action of BACE1, which increases the production of Aβ [73]. In this regard, both FNDC5 and PGC-1α are involved in the mediation of exercise to Aβ pathology.

Furthermore, FNDC5 can also regulate the levels of BDNF in hippocampus of mice [74]. One study demonstrated that treadmill exercise potentially reduced Aβ aggregation and improved impaired cognition through the PGC-1α/FNDC5/BDNF pathways in a rat model of AD [75]. Meanwhile, PGC-1α is a substrate of SIRT-1. Thus, it is logical to conclude that the interactions between SIRT1, PGC-1α, FNDC5, and BDNF are related to the exercise-regulated reduction of Aβ production. However, these interactions require further research.

The Unfolded Protein Response Signalling Pathway

The endoplasmic reticulum (ER) is responsible for protein quality control and folding. Multiple environmental and genetic insults can destroy the function of the ER and induce ER stress [76]. The unfolded protein response (UPR) is a complicated adaptive cellular mechanism that is related to ER stress [77]. There are three main signalling branches of the UPR: activating transcription factor 6 (ATF6),

inositol-requiring enzyme 1α (IRE1α), and protein kinase RNA-like endoplasmic reticulum kinase (PERK) [78]. The UPR is triggered in multiple neurodegenerative diseases, including AD and Parkinson's disease, due to the aggregation of misfolded proteins [79]. The accumulation of Aβ disrupted several cellular processes, caused ER stress, and activated the UPR, which aggravated the process of inflammation and apoptosis [80, 81]. Conversely, the overactivated UPR contributes to β-amyloidogenesis. In 5xFAD TG mice that coexpress human APP and PS1 with five familial AD mutations, the activation of PERK in response to ER stress results in elevated eukaryotic initiation factor-2α (eIF2α, the downstream substrate of PERK) phosphorylation, which increases BACE1 translation and Aβ accumulation [82]. In addition, prolonged and excessive ER stress could enhance the expression of PS1 through activating transcription factor 4 (ATF4), which could lead to an increase in Aβ secretion by activating γ-secretase activity [83]. Xia et al. showed that treadmill exercise inhibited the expression of glucose-regulated protein 78 (GRP78) and suppressed activation of ATF4, eIF2α, and PERK, along with the downregulation of the BACE1 in APP/PS1 mice. Therefore, exercise-induced inhibition of ER stress may regulate the amyloidogenic pathway. However, further research is needed to determine if exercise influences the activity of γ-secretase by inhibiting ATF4 [84].

Lipid Rafts

Lipid rafts are special cholesterol-rich membrane microdomains that play a vital role in cell survival and signal transduction [85]. In AD, lipid rafts are closely associated with Aβ deposition. Lipid rafts may obstruct autophagic-lysosomal system, a degenerative pathway of Aβ, thus accelerating AD development. In addition, previous studies indicated that Aβ production was dependent on lipid rafts [86]. The amyloidogenic pathway of APP cleavage primarily occurs in lipid rafts where BACE1 and γ-secretases show their optimum activities [87]. Zhang et al. reported that 12 weeks of treadmill exercise inhibited the formation of lipid rafts in the hippocampus of APP/PS1 TG mice, which hindered the function of BACE1 [88].

Thus, exercise exerts a beneficial role in reducing Aβ levels by mediating ADAM10 and BACE1 through the pathways of BDNF, SIRT-1, PGC-1α, and FNDC5, activating the UPR and decreasing lipid rafts. Besides, these pathways may alleviate cognitive impairment and pathophysiology of AD through an Aβ-independent manner, including increased synaptic plasticity and decreased inflammation and oxidative stress. Relatively little is known about the underlying mechanisms of the association between physical exercise and γ-secretase, which requires further investigation.

The Effect of the Regulation of Autophagy by Exercise

Autophagy is a key cellular pathway that is responsible for the disposal of waste components, which allows for cell renewal and ensures cellular bioenergetic homeostasis. As a conservative self-degrading process, autophagy can remove useless and toxic proteins or damaged cytoplasmic constituents and organelles through a lysosomal degradation system [5, 89]. Disorders in the autophagy process accelerate the aggravation of various neurodegenerative diseases that are associated with the aggregation of pathological proteins, such as PD, HD, and AD [90]. Bordi et al. investigated the relationship between autophagy and the pathogenesis of AD and found that lysosomal biogenesis and autophagosome formation were activated by various forms of cellular stress, such as damaged organelles Aβ aggregates, reactive oxygen species, and so on, as an early disease response, and in the late stages of AD, autophagy flux was increasingly hindered due to the inefficient substrate clearance by the lysosomes [91]. Under normal circumstances, Aβ degradation is implemented through the autophagy-lysosomal pathway, which is involved in protein quality control and the clearance of abnormal forms of proteins [92]. In contrast, impaired autophagy results in Aβ deposition. For instance, one study found that the genetic deletion of beclin 1, which was an essential autophagy gene, disrupted autophagy and elevated Aβ accumulation in cultured neurons from APP TG mice; the effect could be reversed by the administration of a beclin 1 viral gene delivery vector [93].

Recently, Li et al. reported that swimming exercise for 12 weeks could promote the autophagy and alleviate the formation of atherosclerosis in the aorta of apolipoprotein E knockout mice [94]. Zhao et al. showed that 12 weeks of treadmill exercise in an APP/PS1 TG mouse model elevated autophagy-lysosomal activity, as evidenced by a reduction in the levels of lysosome-associated membrane protein 1, a lysosomal marker, and p62, an autophagy marker, as well as a decreased Aβ burden [95]. Improvement of abnormal autophagy that is induced by exercise might be achieved by regulating the mTOR signalling pathway, which is a repressor of autophagy; however, the excessive activation of the mTOR signalling pathway could inhibit autophagy and result in the malfunction of Aβ clearance [92, 96, 97]. Thus, exercise has a positive effect on autophagy, which plays an important role in the regulation of Aβ clearance within neurons.

The Mechanisms of Aβ Clearance by Exercise Outside Neurons in AD

The Regulation of Aβ Clearance from the Glymphatic System by Exercise

Recently, a cerebral lymphatic system, known as the glymphatic system, was determined to be responsible for the

removal of neuronal extracellular waste protein through a paravascular pathway [98]. In the glymphatic system, the CSF accesses the brain through the periarterial spaces, crosses the interstitium through the astrocytic aquaporin-4 (AQP4) water channels located on the perivascular cells, and drains the interstitial fluid and its solute into the perivenous zones and the deep cervical lymph nodes [99]. The subsequent influx of the CSF into the dense brain parenchyma is implemented by the expression of the AQP4 water channels in significantly polarized astrocytic endfeet that ensheath the cerebral vasculature [100, 101]. The glymphatic system can clear a major percentage of Aβ, tau protein, and other metabolites in the brain parenchyma [99]. However, a damaged glymphatic system is commonly found with senile and neurodegenerative diseases, such as AD [102–104]. Moreover, Aβ accumulation in the periarterial space can block perivascular pathway, consequently decreasing glymphatic clearance [105]. As the most affluent water channel in the CNS, AQP4 plays a key role in maintaining brain-water homeostasis and modulating the glymphatic system to accelerate Aβ clearance [106, 107]. Altered localization and expression of AQP4 are related to AD pathology and status [108]. When the glymphatic system is damaged, interstitial clearance decreases by approximately 70%, which leads to a 55–65% inhibition of Aβ clearance in AQP4 knockout mice [100, 101]. Xu et al. demonstrated that AQP4 knockout mice with AD showed more evident spatial memory and learning dysfunction, as well as enhanced amyloid angiopathy, Aβ deposition, atrophy of astrocytes, and synaptic protein loss in both the cortex and hippocampus compared with untreated AD mice [109].

Interestingly, one study showed that after 5 weeks of running on a wheel, the perivascular CSF influx was enhanced in young, awake, and freely behaving mice, which indicated that exercise increased the glymphatic activity and had beneficial effects on brain health through the increased clearance of neurotoxic products from the brain [110]. Moreover, 5 weeks of wheel exercise was shown to improve glymphatic activity, reduce the aggregation of Aβ plaques and neuroinflammation, enhance the level of AQP4, and ultimately prevent spatial cognitive decline and synaptic impairment [111]. Therefore, we propose that exercise may contribute to the clearing function of the glymphatic system via regulating AQP4 expression, which could alleviate the symptoms of AD.

Studies have found that the glymphatic system is suggested to function almost completely during sleep [112]. In addition, a genetic variation in AQP4 may impair the clearance mechanism and impact the relationship between sleep and the brain Aβ-amyloid burden [113]. These evidences suggest that Aβ removal by the glymphatic system is closely linked to sleep. Unfortunately, sleep disorders occur frequently with AD and affect nearly 45% of patients with AD [114]. Enhanced sleep latency is related to higher brain Aβ burden in older adults with normal cognition [115]. Several clinical trials have suggested that exercise could exert a positive influence on improving sleep quality in patients with AD [116, 117]. Therefore, exercise may be an auxiliary treatment choice for sleep dysfunction in patients with AD because it plays a crucial role in the clearance of Aβ via the glymphatic system, which can delay the progress of AD [118].

The Effect of the Regulation of Neuroinflammation by Exercise

Neuroinflammation is considered as a main feature of AD, which contributes to the pathogenesis of AD [119, 120]. In physiological conditions, astrocytes, microglia, and the other types of innate immune cells in the CNS can deal directly with multiple pathogens, toxins, and tissue damage [21]. As for astrocytes, AD-related neuroinflammation is generally along with reactive astrogliosis and significant changes of morphology and function following CNS damage [121]. Reactive astrocytes can seek, absorb, and degrade Aβ, potentially through its high binding ability to the nicotinic acetylcholine receptors of astrocytes [122]. However, astrocytes may become overloaded with Aβ, resulting in consequent lysis, which in turn contributes to forming Aβ plaque deposition [123]. With respect to microglia, AD-induced polarization of microglia to M1 phenotype causes the release of various pro-inflammatory factors and the failure of removing pathological protein accumulation, thus facilitating Aβ deposition and APP expression [124, 125]. In contrast, the shift of activated microglia from the M1 phenotype to the M2 phenotype inhibits inflammation by expressing various cytokines, thus alleviating the toxic effect of Aβ deposition[126, 127]. Thus, neuroinflammation promotes amyloid pathology, whereas anti-inflammatory strategies potentially hold promise for alleviating AD.

Accumulating evidence from animal experiments and clinical trials proves the general anti-inflammatory effect of exercise on AD. In AD rats, treadmill exercise improved spatial learning memory function by inhibiting neuronal apoptosis and suppressing pro-inflammatory cytokines via inhibiting NF-κB/MAPK signalling pathway [128]. Moreover, resistance exercise alleviated the locomotor hyperactivity associated with AD behavior and elevated microglia recruitment, which might further contribute to the reduction in the volume of Aβ deposition, and reduced the overexpression of cytokines in APP/PS1 TG mice [129]. Furthermore, 12 weeks of treadmill exercise obviously suppressed oxidative stress, elevated the shift of M1 to M2 microglia polarization, and inhibited neuroinflammation in the hippocampus of APP/PS1 TG mice, which were related to significant

improvement of cognition ability and decrease of Aβ deposition [130]. In clinical research, the quality of life and psychological states of AD patients were improved following aerobic exercise training, along with inhibition of systemic inflammation, including the decreased levels of interleukin (IL)-6 and tumor necrosis factor (TNF)-α in serum [131]. Moreover, physical training evidently improved the problem-solving ability and judgment function, and reduced the level of reactive oxygen species, catalase activity, and neuron-specific enolase (a sign of neuronal injury) in AD patients [132]. However, Camilla et al. found that physical exercise exerted a mild inflammatory systematic effect on AD patients, which is inconsistent with abovementioned results [133]. Therefore, the further research is required to confirm the effect of exercise on AD and explore detailed molecular mechanisms of exercise in AD-associated inflammation.

The Effect of the Regulation BBB Transport Proteins by Exercise on AD

The BBB is a dynamically protective boundary between the CNS and the peripheral circulation. The BBB is a highly specific chemical barrier with a semipermeable structure that isolates the brain from circulating blood and extracellular fluids [134, 135]. It provides an extremely stable intracerebral environment and prevents foreign materials, such as toxins or microorganisms, from disrupting the brain homeostasis [136].

The Receptor for Advanced Glycation End Products and Low-Density Lipoprotein Receptor-Related Protein 1

There is a tight balance between Aβ influx and efflux across the BBB, which is disturbed in AD and results in aggregation of toxic protein. This balance partly depends on the BBB receptors; receptor for advanced glycation end products (RAGE) and low-density lipoprotein receptor-related protein 1 (LRP1) control the transport of Aβ into and out of the brain, respectively [137]. RAGE, a multiligand receptor, belongs to the immunoglobulin superfamily. Its ligands consist of Aβ, advanced glycation end products, amphoterin, and S100/calgranulin family members [138]. The increased expression of RAGE in the astroglial and neural cells was reported in animal models of AD and closely related to cognitive impairment and AD pathogenesis [139, 140]. LRP-1 is a lipoprotein receptor in the cytomembrane that induces endocytosis or the cellular internalization of diverse ligands; the ligands for LRP1, which include secreted APP, α2-macroglobulin (α2M), apolipoprotein E, and Aβ, are involved in the pathogenesis of AD [138, 141]. Various studies have reported that LRP1 plays an essential role in the three-step mechanism that regulates Aβ clearance from the brain and body [142]. A recent study showed that the upregulation of LRP1 by vitamin D was responsible for the Aβ clearance in models of AD [143].

Studies have confirmed that physical exercise improves several pathological mechanisms of AD, such as neurovascular unit dysfunction or cognitive deficits, through differential modulation of RAGE and LRP1 to reduce the amyloid plaque load in the brain [144–146]. However, in 2018, Zhang et al. found no obvious alteration in LRP1, although they did find a decrease in RAGE in the hippocampus after long-term treadmill exercise, which resulted in the reduction of Aβ deposition mainly through the suppression of the amyloidogenic pathway of APP cleavage [146].

LRP1 in the liver induces rapid peripheral Aβ clearance [147]. In healthy human or mice, plasma soluble LRP1 (sLRP1) binds more than 70% of circulating Aβ in order to prevent it from accessing the brain; it also takes part in maintaining brain Aβ homeostasis [148, 149]. In rats treated with $Aβ_{1–42}$, researchers found that 4 weeks of treadmill exercise elevated the sLRP1 levels in plasma and the LRP1 protein and mRNA levels in the liver and reduced the levels of circulating $sAβ_{1–42}$ [145]. Other studies found that soluble RAGE (sRAGE) could restrict the binding of RAGE to its ligands as a decoy in plasma, thus inhibiting a variety of pathological processes of AD, such as oxidative stress and inflammation [150–153]. One study reported that physical activity for 8 months caused a significant elevation in plasma sRAGE levels in 98 participants [154]. These results highlighted the protective effect of exercise on cardiovascular disease or other diseases, such as AD, that were partially mediated by an increase in inflammatory conditions. In conclusion, RAGE and LRP1 have beneficial effects on Aβ clearance in the brain and in the blood. Exercise training can regulate these two factors and remove generated Aβ to alleviate AD.

The Glucose Transporter 1

Glucose transporter 1 (GLUT1), which is mainly expressed at the BBB, is the major transporter of glucose to mediate glucose enter into the brain [155]. The supply of glucose is vital for maintaining brain energy metabolism homeostasis and supporting the activated nerve cells to function properly [156]. Early decrease in glucose transport related to reduced levels of GLUT1 at the BBB is one of the characterized features of AD [157]. Diminished expression of GLUT1 and GLUT3 (the glucose transporter 3) caused the impairment of brain glucose uptake process in the cerebral cortex of AD patients, resulting in hyperphosphorylation of tau protein [158]. The reduction of GLUT1 at BBB aggravated cognitive dysfunction, cerebrovascular degenerative changes, and neuropathology of AD [159]. In addition, GLUT1 deficiency resulted in decrease of Aβ clearance and facilitated

Aβ pathology by decreasing the expression of LRP-1, indicating that GLUT1 reduction could promote the disease process via amplifying vascular injury and Aβ deposition [159]. The regular exercise training increased GLUT1 and GLUT3 expression levels in the central nervous system (CNS) of AD model mice, playing an important role in the process of energy metabolic adaptation [156]. In summary, exercise can reduce Aβ by elevating GLUT1/LRP1 expression levels at BBB in AD. However, the exact mechanism among exercise, GLUT1, LRP1 still needs further exploration.

The Effect of the Regulation of Aβ-Degrading Enzymes by Exercise on AD

In the brain, Aβ clearance can also be enzymic [160]. For example, neprilysin (CD10) and insulin-degrading enzyme (IDE) are two key enzymes that are involved in the clearance of Aβ, especially the proteolytic degradation to monomeric Aβ. These enzymes are expressed in multiple cellular constituents of the brain, including the BBB endothelium [161]. Studies have shown that CD10 and IDE are upregulated in mice with AD after a period of exercise [18, 145]. However, other studies have yielded different results. For instance, Adlard et al. found that exercise induced a reduction in the extracellular Aβ plaques that was independent of CD10 and IDE [162]. The researchers concluded that the reduction in Aβ might be related to neuronal metabolic alterations that were known to be modulated by exercise and to influence APP processing [162]. Zhang et al. discovered that APP/PS1 TG mice that were subjected to 5 months of treadmill exercise had decreased CD10 and IDE expressions, which indicated an inhibited degradation pathway [40]. One possible explanation for these discrepancies is that these studies involved different types and durations of exercises or animal models [138].

Other Mechanisms Involved in the Therapeutic Effect of Exercise on AD

It has been well established that tau phosphorylation is a key pathophysiological change in AD patients. The resistance training inhibited tau pathology and neuroinflammation, and improved synaptic plasticity in the hippocampus and frontal cortex of AD mice [163]. The treadmill exercise exerted inhibitory effects on tau phosphorylation, neuronal apoptosis, and mitochondrial dysfunction, as well as improved hippocampal-dependent cognitive function in the streptozotocin-induced rat model of AD after 4 weeks of treadmill exercise [30]. In addition, voluntary running exercise diminished the loss of neurons and spatial memory, reduced the levels of tau phosphorylation and Aβ accumulation, and increased hippocampal neurogenesis in TG mice of AD [164].

Glycogen synthase kinase-3 (GSK3) that is a main kinase in AD, which can inhibit hippocampal neurogenesis and stimulate neuroinflammation, is a regulator of tau hyperphosphorylation [165, 166]. Its role in APP phosphorylation may be involved in aberrant APP processing and the pathological aggregation of Aβ. A previous study reported that 5 months of treadmill exercise led to a strong reduction in Aβ accumulation and tau phosphorylation, along with a significantly decreased PS1 expression and APP phosphorylation by inhibiting the GSK3-dependent signalling pathway in APP/PS1 mice [167]. Moreover, exercise training could promote the phosphorylation of PI3K/AKT, the upstream precursors of GSK-3, and then suppress the kinase activity of GSK-3 via phosphorylation, thus mitigating the pathological changes of AD [168].

ATP-binding cassette transporter A1 (ABCA1) is a key transmembrane protein that promotes the extracellular transport of cholesterol; it is mainly regulated by retinoid X receptor (RXR) and liver X receptor (LXR) [169]. It has been shown that LXR and RXR accelerate the intracellular cholesterol efflux by modulating ABCA1, which participates in the deposition and transport of Aβ. However, the exact mechanism by which ABCA1 affects APP processing is not clear. One study found that long-term exercise changed cholesterol transportation and reduced soluble Aβ by increasing ABCA1 expression and influencing the levels of RXR and LXR [146].

Developmental Origins of Health and Disease (DOHaD) is a rising field that aims to delay the rapid growth of noncommunicable chronic diseases [170]. The environmental exposures during important periods of development may result in subtle alternations in certain biological functions, although almost invisible, and can raise the risk of dysfunction and disease later in life [129]. DOHaD research lays emphasis on how environmental conditions sustained by the developing fetus affect the subsequent development of health or disease in adulthood. Consistently, there is evidence for beneficial effects of physical or cognitive activity at early stage of ontogenesis [171]. Clinical trials showed that maternal exercise during pregnancy positively affected the fetal health and the cognitive functioning of offspring until childhood [172, 173]. Additionally, Herring et al. studied female transgenic (TG) CRND8 mice with the human APP 695 transgene and reported that wheel running during pregnancy alleviated amyloidogenic APP processing and provided long-lasting protection from neurodegeneration in their unstimulated progeny, indicating that maternal exercise interferes with the AD-like pathology of offspring [174]. Therefore, we can conclude that intrauterine milieu mediated by exercise in the period of pregnancy can provide long-lasting benefits to the health of offspring and some resistance

Table 1 The age of animals, duration and intensity of exercise, AD models, Aβ changes, and associated mechanisms in the referenced studies. *m*, months; *w*, week; *Aβ*, β-amyloid peptide; *APP*, amyloid precursor protein; *PS1*, presenilin 1; *3xTG AD mice*, triple-transgenic AD mice; *NSE/APPsw*, neuron-specific enolase (NSE)-controlled APPsw

Age of animals	Duration of exercise	Exercise protocol	Models	Effects on Aβ	Mechanism associated with Aβ changes	Reference
24 m	12w	30 min/day, 5 days/w	3xTG AD mice	Aβ↓, soluble Aβ↓	The suppression of the amyloidogenic pathway	[24]
7w	4w	5 days/w	Rats with Aβ infusion	Aβ↓	Increased BDNF caused the suppression of the amyloidogenic pathway	[23]
5 m	5 m	30 min/day, 6 days/w	APP/PS1 transgenic mice	Aβ↓	The suppression of the amyloidogenic pathway	[25]
7–9 m	3w	Voluntary training	APP/PS1 transgenic mice	Aβ 40, 42↓	Increased BDNF caused the suppression of the amyloidogenic pathway	[43]
6w	10w	60 min/day, 5 days/w	APP/PS1 transgenic mice	Soluble Aβ↓	Activated BDNF/TrKB signalling pathway suppressed the amyloidogenic pathway and increased Aβ clearance	[145]
12 m	5w	30, 50, 60 min/day, 5 days/w	NSE/APPsw transgenic mice	Aβ↓	Increased SIRT1 level	[48]
3 m	3 m	45 min/day, 5 days/w	APP/PS1 transgenic mice	Aβ↓, soluble Aβ↓	Suppressed the overactivation of the UPR signalling	[74]
3 m	12w	45 min/day, 5 days/w	APP/PS1 transgenic mice	Aβ↓	Reduced lipid rafts	[78]
3 m	5 m	30 min/day, 5 days/w	APP/PS1 transgenic mice	Soluble Aβ↓	The alterations of the lipoprotein content increased lipid metabolism and cholesterol transportation	[112]
9w	5w	Voluntary training	C57BL/6 J young mice	–	Increased glymphatic function	[91]
14–16 m	6w	Voluntary training	C57BL/6 J old mice	Aβ↓	Increased glymphatic function	[92]
3 m	12w	45 min/day, 5 days/w	APP/PS1 transgenic mice	Aβ↓, soluble Aβ↓	Increased autophagy activity	[132]
1 m	4 m	Voluntary training	TgCRND8	No change	The increased transportation across BBB	[110]
8w	4w	–	Rats with Aβ infusion	Aβ↓, soluble Aβ↓	The increased Aβ outflow and free Aβ clearance in plasma	[111]
5 m	7 m	Voluntary training	APP/PS1 transgenic mice	Soluble and insoluble Aβ40 and Aβ42↓	The suppression of the amyloidogenic pathway	[26]
2 m	8w	30, 40, 50, 60 min/day respectively in every 2 weeks	D-Galactose induced aging rats	Aβ 42↓	The suppression of the amyloidogenic pathway and the activation of non-amyloidogenic pathway	[27]
3/12 m	5 m	–	APP/PS1 transgenic mice	Soluble Aβ↓, no changed in Aβ plaque	Changes in soluble Aβ levels rather than Aβ plaque deposition may be conducive to exercise-induced benefits	[28]

Table 1 (continued)

Age of animals	Duration of exercise	Exercise protocol	Models	Effects on Aβ	Mechanism associated with Aβ changes	Reference
Not mentioned	4 weeks	30 min/day, 5 days/w	Streptozotocin-induced rat model	Aβ↓	–	[21]
2 m	8 weeks	Progressive increase in intensity and duration	Injection of Aβ 1–40 peptide	Aβ↓	–	[29]

against chronic diseases in adult stage. In summary, exercise could exert neuroprotective effects on AD via different types of mechanisms.

The Related Mechanisms of Exercise on Other Neurodegenerative Diseases

Except for AD, exercise also could exert benefits on various neurodegenerative diseases, such as Parkinson's disease (PD) and Huntington's disease (HD). PD is characterized by the deficiency of dopaminergic neurons and the existence of Lewy bodies within the substantia nigra [175, 176]. Exercise could markedly improve motor dysfunctions, such as gait and balance, and non-motor disorders, such as cognitive function and quality of life, in PD patient [177]. Moreover, aerobic exercise can exert neuroprotective and neurorestorative effects in PD via modulating neurotrophic factors to promote angiogenesis and synapse formation, enhancing mitochondrial function and suppressing oxidative stress and apoptosis [178]. HD is an autosomal dominant neurodegenerative disease, resulting from polyglutamine expansion in the Huntingtin gene [179]. In HD patients, neuropathology leads to progressive motor dysfunction, cognitive impairment, psychiatric symptom, and peripheral organ disturbances [180]. Exercise training can exert a beneficial role in motor behavior by reducing deficits in mitochondrial function in a HD rodent model [181]. Moreover, a series of studies with physical activity have displayed an improvement in motor function and specific tasks, suggesting that exercise is safe and feasible treatment for HD patients [182]. To sum up, exercise is an effective treatment for various neurodegenerative diseases. More research is required to solve the detailed problems, including the exercise type, appropriate intensity, duration, and so on.

Conclusion

As the elderly population gradually increases and no disease-modifying treatments are available, AD has been one of the central global medical issues in the twenty-first century. AD proceeding is closely related to extracellular accumulation of Aβ in the brain. Exercise provides a cost-effective and non-invasive way to influence many of the mechanisms that have been displayed to reduce Aβ levels and alter AD progression, which can serve as the basis for non-pharmacological means to combat neurodegeneration in AD.

In Table 1, we have summarized some details in the above-mentioned literatures on the mechanisms of exercise on Aβ, including models, AD ages/stages (no matter animals or humans), and exercise time and strength in the referenced studies. In addition, most longitudinal prospective studies have confirmed that higher levels of physical exercise are

protective against AD dementia and, conversely, lower levels of physical activity are relevant to higher risks of AD development [183–185]. Of note, at very high intensity, exercise may become a stressor that has negative effects on human because of the diminished protective response to oxidative stress in brain [187]. Therefore, a medium amount of physical exercise seems to be beneficial for AD patients. Although exercise has multiple positive effects on regulating Aβ and AD, a few studies reported no changes of Aβ after exercise. Such discrepancies are probably explained by the age of mice, the phase of AD progression and different exercise protocols, and environment. Moreover, vigorous exercise might do more harm than good for the elderly. Exercise strategies should be recommended by experts to avoid excessive intensity.

In summary, this review summarized the related mechanisms that are involved in the effect of exercise on AD. However, it remains unclear whether the intensity or duration of the exercise affects Aβ clearance, degradation, and APP processing; it is also unknown how exercise initiates the changes to remove Aβ. Moreover, it needs to be stated that the aggregation of all these mechanisms might be important and acting on a single target might not be sufficient, and exercise might be of interest in that it may act on multiple targets concurrently. The application of exercise to alleviate AD abnormalities still needs further and more detailed research in the future.

Author Contribution ZXT, FD, and FZ had the idea for the article. YSF, ZXT, LYW, and FD performed the literature search and data analysis. ZXT and FZ drafted and critically revised the work.

Funding The present study was supported by the National Natural Science Foundation of China (no. 82072531; the recipient is Feng Zhang).

Data Availability Not applicable.

Code Availability Not applicable.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest The authors declare no competing interests.

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