

Review

Physical Exercise Enhances Neuroplasticity and Delays Alzheimer's Disease

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Abstract. Accumulating evidence indicates that exercise can improve learning and memory as well as attenuate neurodegeneration, including Alzheimer's disease (AD). In addition to improving neuroplasticity by altering the synaptic structure and function in various brain regions, exercise also modulates systems like angiogenesis and glial activation that are known to support neuroplasticity. Moreover, exercise helps to maintain a cerebral microenvironment that facilitates synaptic plasticity by enhancing the clearance of A β , one of the main culprits of AD pathogenesis. The purpose of this review is to highlight the positive impacts of exercise on promoting neuroplasticity. Possible mechanisms involved in exercise-modulated neuroplasticity are also discussed. Undoubtedly, more studies are needed to design an optimal personalized exercise protocol for enhancing brain function.

Keywords: Exercise, neuroplasticity, dendrite, brain-derived neurotrophic factor, Alzheimer's disease

INTRODUCTION

In line with population aging, the number of people living with dementia worldwide is set to increase. According to the World Alzheimer Report 2016, there are about 47 million people worldwide living with dementia and this number may reach 74.7 million in 2030 and 131.5 million in 2050 (Alzheimer's Disease International. World Alzheimer report 2016: Improving healthcare for people living with dementia. <https://www.alz.co.uk/research/world-report-2016>). Alzheimer's disease (AD) is the most common form of dementia and possibly contributes

to 60–70% of dementia cases (WHO and Alzheimer's Disease International. Dementia: a public health priority. Geneva, Switzerland: World Health Organization, 2012). The pathological features of AD are characterized by extracellular depositions of amyloid plaques, which are primarily composed of 39–43 amino acids long A β peptides, and intracellular accumulations of neurofibrillary tangles, which are mainly composed by hyperphosphorylated tau protein [1]. Accumulations of amyloid plaques and neurofibrillary tangles in the brain have been hypothesized to cause deleterious responses in neuronal function in several brain regions related to cognition, such as the hippocampus and entorhinal cortex [1]. To date, there is no promising pharmacologic treatment (medication) that can halt AD. Therefore, nonpharmacological interventions that

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could improve or maintain cognitive function have become alternative options for the prevention and treatment of AD.

Epidemiological evidence has suggested that some lifestyle factors, such as regular exercise and cognitive activity, may delay age-related memory impairment and decrease risk of AD [2–4]. A meta-analysis examining the relationship between physical activity and the risk of neurodegenerative disease reported that engaging in physical activity reduces the risk of dementia and AD by 28% and 45%, respectively [5]. Higher levels of total daily physical exercise is associated with a lower risk of developing AD [6, 7]. Exercise can have a positive effect on multiple aspects of the brain, such as an increase in synaptic and cerebrovascular plasticity [8], a decrease in neuropathology [9], and an attenuation in neuroinflammation [10]. The wide variety of beneficial effects induced by exercise enhances overall brain health, which in turn helps to preserve neuronal function and protect against aging-associated loss of cognition. In this review, we summarize the recent advances in the beneficial effects of exercise on brain function and highlight some potential mechanisms.

BENEFICIAL EFFECTS OF EXERCISE ON BRAIN FUNCTION

Behavior level – learning and memory function

A growing number of studies support the idea that physical exercise increases brain function throughout life [11, 12]. In a meta-analysis that included a total of 59 studies (from 1947 to 2009) examining the relationship between physical activity and academic achievement in school-age children, the authors demonstrated significant and positive correlations between physical activity and cognitive outcomes [13]. In another meta-analytic review of 29 randomized controlled trials examining the association between aerobic exercise and neurocognitive performance in a group with a mean age of ≥ 18 years of age, positive association between exercise with attention, processing speed, and executive and memory function was also evident [14]. Particularly, exercise enhances pattern separation in humans, which is defined as a process to remove redundancy from similar input patterns so that events can be separated from each other and interference can be minimized [15]. An acute bout of moderate intensity aerobic exercise improves the pattern separation

in young adults [16]. This mnemonic discrimination ability is highly correlated with aerobic fitness. The higher fitness group (i.e., high endurance capacity during exercise) had better performance in the pattern separation test compared with the lower fitness group [17]. The memory-enhancing effect of exercise on young adults has also been demonstrated in a series of hippocampal-associated learning and memory tests designed for rodents. Almost all young animal studies confirmed the memory-facilitating effect (i.e., acquisition and retention) of exercise. These tests included novel object recognition [18, 19], object displacement [19], Morris water maze [18, 20–22], radial arm water maze [23], Y-maze [24], passive avoidance [25, 26] and contextual fear conditioning [27–29].

In addition to benefiting healthy young adults, physical exercise is known to delay age-related cognitive decline. A randomized, controlled trial study that evaluated the association between exercise and cognitive function in 120 healthy participants aged over 65 showed that 6 months of exercise reversed age-related loss in hippocampus volume and improved performance in a computerized spatial memory task [30]. A meta-analysis including 42 studies (from 1966 and 2010) of cognitive interventions of exercise in 3,781 healthy older adults aged 55 and older concluded that aerobic fitness training improves cognitive performance [31]. Similar findings have also been obtained in aged animals. For example, it has been shown that 6-weeks of treadmill exercise ameliorates age-induced losses in short-term (tested by step-down avoidance task) and long-term memory (tested by radial 8-arm maze) functions in 24-month-old rats [32]. Another study demonstrated that one week of mild treadmill exercise was enough to improve spatial learning and memory ability, which was tested by the Morris water maze in 23-month-old rats [33]. These results suggest that exercise not only enhances learning and memory in young adults but also protects aged individuals from age-related cognitive impairment.

Although the beneficial effects of exercise on learning and memory have been well-documented in numerous studies, some studies of rodents failed to find such an association. This discrepancy may be due to the different exercise intensities and durations employed in each study. For example, high levels of running exercise are known to impair hippocampus-dependent spatial memory [34, 35] and other types of memory [36]. It has been speculated that the exercise

intensity affects cognitive performance in a reversed U-shaped fashion. In other words, cognition improvement is most effective at moderate-intensity exercise, whereas exercise at low-intensity is less effective and at high-intensity would induce high levels of stress responses, hence impairing cognitive performance [37, 38].

Behavior level – mental function

The beneficial effects of exercise extend beyond cognitive function. A plethora of evidence supports the notion that exercise can prevent or delay the onset of various mental disorders such as anxiety, depression, and posttraumatic stress disorder [39, 40]. Several meta-analysis studies suggest that exercise could reduce depressive and anxiolytic symptoms in adolescents with clinical levels of mental illness [41, 42]. The effects of exercise on mental health are dose-dependent. In adults, a moderate amount of exercise exerts greater benefits in the mental health than low or high doses of exercise [43].

The positive effects of exercise on mood disorders have been examined in various animal models. It has been shown that a 2-week period of treadmill exercise effectively decreased anxiety-like (tested by elevated plus maze) and depressive-like (tested by sucrose preference test) behaviors in a single-prolonged stress-induced post-traumatic stress disorder rat model [44]. Besides stress, mood disorders commonly occur secondary to medical conditions such as obesity and stroke. In high-fat diet induced obesity, and middle cerebral artery occlusion-induced stroke animal models, exercise was also capable of attenuating depression- and anxiety-like behaviors in the modeled animals [45, 46].

Behavior level – motor function

Exercise has a profound effect on motor function. It has been demonstrated that a single session of exercise not only significantly improves performance in a motor learning task during the training session [47] but also leads to longer retention of said motor skills than the control group. This is especially clear when motor memory is assessed one day after practice [48]. In the animal studies, both wheel and treadmill exercise enhanced animals' motor performance in foot fault-placing and parallel bar-crossing, as well as the staircase reaching task [49], rota-rod test [50], beam walking and cylin-

der tests [51], and ladder-climbing tests [52], after ischemic or hemorrhagic stroke. Furthermore, wheel-running and treadmill exercise can also rescue motor behaviors (e.g., rotarod performance test, rotational behavior test, ladder rung walking task, and gait parameters) that are impaired by different dopamine-depletion methods such as LPS, 6-OHDA and MPTP [53–55].

Cellular level – neurons

Neuroplasticity is a continuous process that modifies existing neural networks by mediating structural and functional adaptations of synapses in response to changes in behavior. Exercise-induced structural and functional changes in the brain have been reported in both human and animal studies.

Structural changes – macroscopic levels

Using a resting MRI to evaluate human brain structure, it has been shown that aerobic exercise, from several months to a year, increased brain volume in various brain regions, such as the prefrontal and temporal cortex, [56] as well as the hippocampus [30]. Compared to healthy adults with a sedentary lifestyle, higher gray and white matter cluster concentrations (Voxel-based analysis) in the subgyrus, cuneus, and precuneus regions are found in athletes of similar ages [57]. A functional MRI study suggested that aerobic exercise at least enhanced activity in the brain areas which are involved in attentional control tasks [58]. Moreover, twelve months of chronic exercise enhanced functional connectivity in the default-mode network and the frontal executive network [59]. The increase of brain regional volume and activity may reflect an alteration in the number of neurons, synapses, and axonal and dendritic arbors.

Animal studies also support that exercise induces neuronal structural alteration in various brain regions, including the dentate gyrus (DG) and the cornu ammonis (CA) areas of the hippocampus, amygdala, cortex, striatum, and cerebellum [28, 60–63].

Structural changes – microscopic levels

The effect of exercise on neuronal morphology has also been studied in multiple brain regions. These exercise-induced neuroadaptations will be discussed separately.

In the hippocampal DG and CA regions, exercise significantly enhances dendritic length and complex-

ity as well as increases the dendritic spine density of neurons [60, 64–67]. Schaefer et al. has scored the presynaptic turnover rates by quantifying lysosomal accumulations in degrading axon terminals [68]. Their study indicates that four days of wheel-running in adulthood leads to a significant difference in the level of synaptic turnover in the stratum lacunosum-moleculare layer of the CA1 region, suggesting the effects of exercise on pre-synaptic remodeling [68]. At the post-synaptic location, exercise increased the dendritic arborization and spine density in both the CA1 and CA3 regions. The dendritic branches in the apical dendrites and the numbers of dendritic spines on both the apical and basal dendrites of CA1 pyramidal neurons also increased after treadmill and wheel-running exercise [28, 65]. In addition to normal physiological conditions, exercise can also restore impaired neuronal structure in CA regions after brain injury. For example, in the middle cerebral artery occlusion-induced ischemic rats model, the neurons in CA1 and CA3 exhibited the longer dendritic length and higher arborization after two weeks of treadmill exercise as compared to the sedentary group [69]. In the neonatal hypoxia-ischemia rat model, physical activity improved the spine density in the CA1 neurons [70].

The effect of exercise on the structure of amygdalar neurons has also been studied in rats [28] and mice [71]. By using the single neuron labeling technique, the dendritic arborization and spine density of neurons in the basolateral amygdala increased after one month of treadmill exercise [28, 71]. However, it is interesting to note that different forms of exercise induced distinct brain region-dependent neuronal adaptations. For example, 1-month treadmill running exercise, but not running wheel exercise, increased dendrite complexity and spine densities of neurons in the basolateral amygdala [28]. The differential effects between treadmill and wheel exercise may be derived from the difference in exercise intensity as skeletal muscle citrate synthase activity is only elevated in the rats trained by treadmill exercise, but not by running wheel exercise [28]. These results suggest that the influences of exercise on amygdalar neurons may depend on exercise intensity.

The cytoarchitecture of cortical neurons is also affected by exercise. It has been shown that the nitrergic neurons in the cerebral cortex exhibit larger size and extended dendritic arborization after 16-months of moderate exercise, suggesting that nitric oxide may play a role in synaptic plasticity related to exercise [61]. Higher density of dendritic spines in the medial

prefrontal cortex pyramidal neurons in rats could be identified after 2-weeks of running wheel exercise when compared to rats that didn't do the wheel exercise [62]. These results suggest that medial prefrontal cortex pyramidal neurons are much more sensitive to exercise, as such, intensity of wheel-running does not significantly affect amygdalar neurons [28]. By utilizing transcranial two-photon *in vivo* microscopy, Chen et al. investigated the turnover of dendritic spines in the barrel cortex of mice receiving exercise [72]. They demonstrated that exercise decreases the elimination but does not improve the formation of dendritic spines in the cortical neurons. The net outcome of exercise increased the percentage of mushroom-like spines and decreased the numbers of thin and filopodia spines in the barrel cortex, which represent the facilitation of maturation of dendritic spines by exercise [72].

The cerebellum and striatum are the primary structures of a distributed system for the control of motor functions [73]. Exercise has been shown to increase the density of dendrites and dendritic spines in the cerebellar Purkinje cells of animals [63, 74, 75]. Among the different types of dendritic spines, the stubby, mushroom, and wild spines are more abundant in the cerebellar Purkinje cells in exercise animals than sedentary rats [75]. The changes in morphology of dendritic spines could be related to the regulation of excitability in Purkinje cells due to motor activity [75]. Furthermore, exercise selectively increases the thickness of the molecular layer in the cerebellum [74], implying morphological adaptations in the basket and stellate cells.

Unlike other brain regions, the effects of exercise on neuronal morphology of the striatum is frequently investigated after local neurons undergo pathological challenges. No apparent morphological changes in the striatal neurons are evident in healthy animals after 1-month to 1.5 years of chronic exercise [61, 76–79]. However, in MPTP- and 6-OHDA-treated Parkinson's disease animal models and in the collagenase-induced intracerebral hemorrhage model, the number of tyrosine hydroxylase-immunostaining positive fibers and dendritic spine density in the striatum are higher in the exercise group than the non-exercise group [77–79]. By using *Drd2-eGFP-BAC* transgenic (Tg) mice in conjunction with biocytin injection methods, Toy et al. showed that chronic exercise increased dendritic spine densities in the striatal medium spiny neurons in both DA-D1R-direct and DA-D2R-indirect pathways of MPTP-treated animals [77].

Functional changes

The structural changes in neurons (e.g., dendritic complexity, spine density, and newborn neuron maturation in the adult hippocampus) after exercise are highly associated with functional alterations in neurons (e.g., synaptic activity). Long-term potentiation (LTP) is a form of synaptic plasticity characterized by a prolonged increase in synaptic efficiency based on application of a patterned stimulus. Numerous studies have shown that exercise efficiently increases the LTP amplitude in the DG region [18, 21, 80–83]. It has been suggested that exercise alters the expression of LTP in the DG by reducing the threshold of LTP induction. The weak theta burst stimulation, while not reliably inducing a significant amount of LTP in the DG of sedentary animals, can trigger robust short-term potentiation and long-lasting LTP in running animals [80]. Moreover, the effectiveness of exercise on the enhancement of LTP is of a time-dependent manner (number of running days). Patten et al. examined the expression of LTP in animals that received different periods of exercise and found that LTP expression gradually increased in the DG during days 7–28 of the exercise period and reached a significant level after 56 days of running [83].

Exercise-induced improvement of LTP has also been demonstrated in other hippocampal regions. Both treadmill and wheel-running enhance the expression of a single burst of 100-Hz-induced LTP in the Schaffer collateral pathway of CA1 area [84, 85]. In addition, this exercise promotes the occurrence of a tetraethylammonium-induced potassium ion channel blockade, which in turn leads to the expression of LTP in the mossy fiber of the CA3 area [86]. A blockade of NMDA receptors, NR2A or NR2B, inhibit the effects of exercise on LTP enhancement [80, 81], suggesting that the facilitation of LTP by exercise critically relies on the functions of the NMDA and glutamate receptors [87].

Cellular level – glial cells

In parallel with the effects of exercise on neurons, exercise is also known to have multiple effects on glial cells. Astrocytes, the major glial cells in the brain, play a vital role in the regulation of brain energy transmissions from the vasculatures to the neurons [88, 89]. Because proper and efficient astrocyte function is essential for supporting neuronal function [88], it has been suggested that exercise-induced enhancement of neuronal function may occur via the adaptation of astrocyte behavior.

Exercise induces widespread plasticity in astrocytes [90]. It has been shown that one month of treadmill exercise increases GFAP-labeled cell numbers and the improvement of astrocyte plasticity in the CA1 area [91]. Furthermore, immunostaining signals of S100 β and aquaporin-4, two astrocyte-specific markers, in various brain regions related with cognitive function, such as the hippocampus, medial prefrontal cortex, and orbitofrontal cortex, increased after 12 days of wheel-running in rats [90]. In mice, 4 weeks of physical exercise (a combination of treadmill and running wheel) increased the average length and the area enclosed by each astrocytic projection in the hippocampus [92]. The exercise also changed the orientation of astrocytic projections towards DG in the hippocampus, the region with significant increase in neurogenesis following the exercise [92].

The structure and function of microglia, the major immune cells in the central nervous system, are also affected by exercise. Exercise has been reported to decrease the aging-induced activation and proliferation of microglia in the hippocampus [93, 94]. In parallel to the *in vivo* findings, microglia isolated from aged rodents that participated in chronic wheel-running exercise have a lower basal level of IL-1 β and TNF- α when compared to the microglia isolated from their sedentary littermates [95–97]. Similarly, when stimulating these microglia with LPS, the production of IL-1 β was also lower in the chronic wheel-running group. In addition to the inflammatory cytokines, neuron-microglia contact signaling, an important regulator of microglial activation, is affected by exercise. For example, CX3CL1 and CD200 are immunomodulatory factors expressed by neurons to inhibit microglial activation through binding with the CX3CL1 and CD200 receptor on microglia, respectively [98]. Chronic exercise is known to upregulate the expression of the CX3CL1 gene [99] and the CD200/CD200R proteins in the brain [100], supporting that exercise may inhibit microglial activation via the enhancement of neuron-microglia contact signaling.

Molecular level – brain-derived neurotrophic factor (BDNF)

The mechanisms underlying exercise-induced neuroplasticity involve, at least in part, several neurotrophic and growth factors. Among them, BDNF is a well-characterized mediator of neuronal growth [101], plasticity [102, 103], and survival [99]. Human

and animal studies collectively suggest that exercise is an active strategy to upregulate the expression of BDNF, which plays an essential role in exercise-induced neuroplasticity [104, 105]. Different types of exercise (i.e., voluntary wheel-running and mandatory treadmill running) all seem to be capable of enhancing the production of BDNF in the hippocampus of young and aged animals [22, 28, 106–108]. It is believed that BDNF binds to its receptor, tropomyosin receptor kinase B (TrkB), which increases the phosphorylation levels of cAMP response-element-binding (CREB) and the translation of synaptic-plasticity related proteins [22, 28, 103, 109, 110], and finally enhances neuroplasticity. It has been demonstrated that animals with higher levels of BDNF and TrkB receptor in the hippocampus exhibit better performance in radial water mazes [23] and passive avoidance tasks [26]. On the contrary, blocking the TrkB receptor with a TrkB receptor-IgG chimera or antagonist inhibits the efficacy of exercise-induced upregulation of synaptic plasticity-related proteins significantly [103, 109], resulting in a disruption of benefits on cognitive function. Behavior tests in the Morris water maze, passive avoidance, and contextual fear condition also suggest that the learning and memory abilities enhanced by exercise are reduced to sedentary levels after treating the animals with TrkB receptor blockers [26, 28, 111].

Molecular level – insulin-like growth factor 1 (IGF-1)

IGF-1 is also a key modulator of neuronal functions in the central nervous system, including synaptic plasticity, synapse density, neurotransmission, neurogenesis and neuron differentiation [112–114]. Chronic exercise-enhanced adult hippocampal neurogenesis, learning, and memory performance have been attributed to IGF-1 signaling in the hippocampus [115–117]. The levels of IGF-1 in the blood positively correlated with the time animals spent in the target quadrant during the probe trial of the Morris water maze [115]. The levels of IGF-1 in the brain are also increased after exercise, which is a result of uptake in circulating IGF-1 [118]. Infusion of anti-IGF-I antiserum or neutralization of hippocampal IGF-1 receptor inhibits the exercise-induced brain uptake of circulating IGF-I, disrupts neurogenesis, and lessens the effects of exercise on memory retention [116, 117, 119]. Exercise-induced upregulation of BDNF may be partially affected by the IGF-1 pathway. Blockade of the IGF-I receptor during exercise

inhibits the ability of exercise to enhance the expressions of pro-BDNF and BDNF in the hippocampus [119].

Molecular level – vascular endothelial growth factor (VEGF)

VEGF, an angiogenic protein, is known to have neuroprotective and neurotrophic functions [120]. VEGF can be synthesized and released by peripheral vascular endothelial cells and brain cells, including astrocytes, ependymal cells, and neuronal stem cells [121]. Intracerebroventricular injection of VEGF or gene transfer of VEGF in the hippocampus increases the number of BrdU labeling cells in the subventricular zone and the subgranular zone of the DG, suggesting an intimate association between angiogenesis and neurogenesis [122, 123]. The changes in the vascular niche promotes local signaling that directly regulates or indirectly activates other regulatory factors to stimulate the proliferation, differentiation, and survival of newborn neurons [124]. Voluntary exercise is known to increase the expressions of VEGF receptors, fms-like tyrosine kinase (Flt-1/VEGF1), and fetal liver kinase (Flk-1 or VEGFR2) in the hippocampus [125]. The activation of the intracellular tyrosine kinase domains of the VEGF receptors induces the activation of several downstream signaling pathways which in turn enhances the proliferation of neuron precursors [126, 127]. Peripheral VEGF seems to play an essential role in exercise-induced adult hippocampal neurogenesis [128, 129]. Blockade of VEGF signaling by intravenous injection of adenoviruses carrying the chimeric VEGFR1 receptor or conditionally knocking down skeletal myofiber-specific VEGF gene nullifies running-induced adult hippocampal neurogenesis [128, 129].

Molecular level – nerve growth factor (NGF)

NGF also plays a role in promoting neuronal function, especially the survival of neural progenitors [130]. Results gathered from microarray and nuclease protection assays indicate that the expression of hippocampal NGF is increased after wheel-running, with a peak at 2 to 3 days after exercise [87, 131]. The expressions of hippocampal NGF and one of its receptors, tropomyosin receptor kinase A (TrkA), are increased after 8-weeks of treadmill running in rodents. Similar to BDNF/TrkB signaling, the binding of NGF to TrkA stimulates the downstream

transcription factor, CREB, and induces various gene transcriptions related to cell survival and neuroplasticity [132].

PHYSICAL ACTIVITY, AGING, AND AD

Physical activity and aging

Aging is an irreversible and inescapable process. Age alone increases the risk of dementia and AD [133]. Even in the absence of overt disease symptom, increasing age is associated with decreasing cognitive function of varying severity in human beings. The hippocampus is considerably vulnerable to aging and is involved in the development of aging-related deficits of neuroplasticity and memory functions [134]. Aging-associated memory deficits are accompanied by abnormal structural and functional changes in the hippocampus. Aging also reduces hippocampus size, induces hippocampal neuron loss [135, 136], suppresses dendritic arbors and spine density of the hippocampal neurons [137–139], decreases the degrees of DG neurogenesis [140, 141], and represses the field excitatory postsynaptic potentials [142, 143] and LTP induction [144] in the hippocampus.

Several lines of evidence indicate that exercise can ameliorate the structural and functional changes in the brain during aging. In the pioneer study, Samorajski et al. showed that exercise (spontaneously wheel-running) significantly increased recent memory in the passive avoidance test in adults (10–14 month), middle-aged (20–24 month), and old (28–30 month) C57BL/6J male mice [145]. Later studies also demonstrated that physical activity increases the cognitive reserve and prevents aging-related memory decline [108, 146, 147]. Regular aerobic exercise increases the hippocampal volume by 2%, effectively countering age-related loss in volume in older adults (55–80 years old) without dementia [30]. Six-weeks of moderate treadmill training reverses the age-related declines in the complexity of dendritic arbors and the density of the dendritic spines of hippocampal CA1 pyramidal neurons in mice [139]. Furthermore, six-weeks of moderate-intensity running enhanced the LTP induced by high-frequency stimulation in the CA1 regions and hippocampal memory in mice of different ages, even when the memory impairment had progressed to an advanced stage [139]. It is widely accepted that exercise enhances the adult hippocampal neurogenesis that is critical for hippocampal memory functions [21, 148–150]. The

decline in neurogenesis in aged (19 months of age) mice is reversed to 50% of young (3 months of age) control levels by 45-days of voluntary wheel-running [141]. Yang et al. demonstrated that the hippocampal neurogenesis dramatically decreased by the time mice reached nine months of age and 5-weeks of treadmill running attenuated the decrease of the number of neural stem/progenitor cells during aging and enhanced the maturation of newborn neurons [66].

Physical activity and AD – neuroprotection

It is well known that neurotrophic and growth factors (BDNF, IGF-1, VEGF, NGF) are attenuated in AD [151–154]. Therefore, one of the potential mechanisms for exercise to protect the brain against AD may be via the upregulations of neurotrophic and growth factors. In the following section, we will discuss exercise-induced neuroprotection against AD with focuses on the four trophic factors.

Both clinical and basic research documents that BDNF mRNA and proteins, including proBDNF, are severely decreased in AD, especially in the hippocampus [155–157]. Several lines of evidence have suggested that decreases in brain BDNF and NGF levels contribute to AD pathology [158, 159]. On the contrary, administration of lentiviral vectors to constitutively express BDNF in the hippocampus can prevent cell death, reverse neuronal atrophy, and ameliorate behavioral deficits, hence delaying the development of AD [160]. As a physiological approach to increase the production of neurotrophic factors, exercise has been reported to alleviate hippocampal functional impairment in AD through the induction of BDNF expression in the hippocampus [71, 105]. Exercise-induced BDNF signaling activation has been applied to a variety of AD models, including the A β injection-induced non-Tg AD model [161], APP/PS1 [71, 162], APOE4 [163], NSE/APPsw [164] and NSE/PS2m [165, 166] Tg animal models. Increased BDNF signaling due to exercise is suggested to protect against AD-induced learning and memory deficits through enhancing neurogenesis [167] and LTP expression [161, 162], modulating dendritic morphology [71], and reversing A β -induced neurotoxicity [168].

Neurotrophic signaling not only directly enhances neuronal function but also decreases AD pathological burden. An *in-vitro* study suggests that APP processing shifts towards the non-amyloidogenic α -secretase pathway in response to BDNF treatment

[169], which is known to reduce the production of A β ₁₋₄₀ and A β ₁₋₄₂. Beyond amyloid pathology, BDNF also affects the tau pathology through mediating tau phosphorylation. In P19 neurons, BDNF stimulation induces a rapid decrease in tau phosphorylation [170]. The effects of BDNF on tau dephosphorylation is known to be TrkB dependent. TrkB activation induces AKT-dependent phosphorylation of GSK-3 β at the Ser9 site, resulting in the inhibition of tau phosphorylation [171]. The K252a treatment, a Trk receptor inhibitor, attenuates the effect of BDNF stimulation on tau dephosphorylation [170].

The reduction of the cerebrospinal fluid/plasma IGF-I ratio has been found in AD patients and AD model mice [172, 173], reflecting an impaired uptake of IGF-I from the serum to the CSF. Exercise is known to increase the uptake of IGF-1 in the central nervous system [118]. Elevated IGF-1 not only benefits neuronal functions but also influences the production of A β and the formation of neurofibrillary tangles [174]. IGF-1 also affects brain amyloidosis [175, 176]. Crossing APP^{swe}/PS1^{dE9} Tg mice with serum IGF-I deficient LID mice accelerates brain amyloidosis significantly [175]. Conversely, increases of serum IGF-1 levels decrease the A β load in the brain of aged APP/PS2 Tg mice [176]. IGF-1-induced inhibition of amyloidosis could be due to, at least in part, an increase of A β clearance. This is because IGF-1 increases the levels of A β carrying proteins, such as apolipoprotein J, transthyretin, and albumin, which are all known to facilitate A β clearance via blood-brain barrier (BBB) transportation [176, 177]. Antagonization of IGF-1 by TNF- α reduces IGF-I signaling at the BBB, resulting in a decrease of the expression of A β -carrying proteins and an increase of A β levels in the brain [177]. Furthermore, *in vitro* cell culture studies (i.e., NT2N cells and rat primary cortical neurons) reveal that IGF-1 induces the phosphorylation of GSK3 α (ser21)/ β (ser9) and attenuates tau phosphorylation through activating IRS1/PI3K/AKT/mTOR pathway [178, 179]. It has been reported that exercise increases the activity in the IRS/PI3/AKT pathway to dephosphorylate GSK-3 α / β [180] and inhibit tau phosphorylation in APP/PS1 [181] and NSE/htau23 Tg mice [182] as well as in the ICV-STZ non-Tg AD model [183]. This supports the assertion that exercise-induced IGF-1 signaling plays an important role in preventing pathologies associated with AD.

Exercise elevates VEGF transcription, mRNA, and protein in the brain [184]. In addition to sup-

porting neurogenesis, VEGF could protect neurons against AD via the following potential mechanisms. Firstly, VEGF increases angiogenesis to help the maintenance of BBB integrity [185, 186], which is essential in preventing the entry of systemic A β [187]. Secondly, VEGF regulates the expression of A β transporters on the BBB [188]. It has been shown that an implant of VEGF-secreting fibroblast microcapsules into the brain of APP/PS1 mice not only enhances brain vessel density but also increases the level of LRP-1 expression, which is an A β efflux transporter on the BBB, accompanied by a reduction of A β deposition in the brain [189]. Thirdly, VEGF directly affects APP processing by decreasing β -secretase activity [190, 191]. Applying VEGF to Tg2576 mouse brain slices decreases β -secretase activity and production of both soluble A β ₁₋₄₀ and A β ₁₋₄₂ [190]. Finally, VEGF directly binds to A β and eliminates A β toxicity. VEGF contains a heparin-binding domain that can be recognized by A β [192]; therefore, it is capable of binding to A β (at around the 26–35 amino acid region), hence inhibiting A β aggregation and A β neurotoxicity [192].

Decreases in mature NGF expression as well as increases in Pro-NGF expression have been found in postmortem AD brains [152, 193, 194], suggesting that diminished conversion of pro-NGF to mature NGF and increased degradation in the activity of mature NGF in AD brains [152]. It is known that proNGF preferentially binds to p75^{NTR} and initiates the activation of apoptotic pathways, which may contribute to AD neurodegeneration [195, 196]. Increased mature NGF due to exercise could protect neurons against AD pathologies through acting on the trkA receptor to promote neurite generation, neuronal survival, and synapse formation [197, 198]. It has been reported that exercise-induced increases of mature NGF expression and decreases of Bax expression, the downstream molecule of p75^{NTR}, are involved in the inhibition of neuronal death during AD development [165]. An *in-vivo* study of Tg mice expressing a neutralizing antibody directed against NGF showed a progressive development of amyloid deposition and neurofibrillary pathology in the brain [199, 200]. An *in-vitro* study using PC12 differentiated cells revealed that withdrawal of NGF caused the overproduction of A β peptides, increasing tau phosphorylation and neurite degeneration [201, 202]. Similar to BDNF, mature NGF increases the metabolism of APP from amyloidogenic towards non-amyloidogenic processing through binding to the TrkA receptor [203, 204]. Mature NGF is also

able to decrease the hyperphosphorylation of tau via increasing the phosphorylation of GSK3 β at the Ser 9 site [204].

Physical activity and AD – glia cells regulations

Accumulated evidence suggests a strong association between risk factors of cerebrovascular disorders, such as hypertension, diabetes, hypercholesterolaemia, hyperhomocysteinaemia, and APOE4, with AD [205]. Astrocytes play an important role in maintaining neurovascular function [205]. The prodromal stage of AD has been linked to dysregulated astrocytes in the neurovascular unit, which may then cause disruptions of neuronal metabolic support, impairment of synaptic functions, onset of neuronal death, and decreases of degradation and clearance of A β [206–208]. One of the exercise-induced neuroprotective pathways is mediated by astrocytes. For example, S100B, a calcium-binding protein, is predominantly secreted by astrocytes and acts as a neurotrophic factor to support neuronal survival. In the sporadic AD animal model, five weeks of treadmill exercise could reverse the reduced extracellular levels of S100B [209], suggesting that exercise can alleviate neuronal dysfunction via controlling astrocyte signaling. Furthermore, exercise increases the A β clearance abilities of astrocytes in the AD brain. The recently identified glymphatic pathway, which critically relies on AQP4 in astrocytes, contributes to A β clearance. Mice lacking the AQP4 in astrocytes exhibit slower paravascular cerebrospinal fluid-interstitial fluid exchange and lower A β 1-40 clearance rate than those of intact mice [210, 211]. Chronic exercise can increase A β clearance through the glymphatic pathway [212]. Two-photon imaging reveals that six weeks of wheel-running increases AQP4 expression in the perivascular region and increases the rate of paravascular cerebrospinal fluid-interstitial fluid exchange in the brain of aged mice; this is accompanied by a decrease of A β accumulation in the cortex and hippocampus [212].

In addition to amyloid plaque and neurofibrillary tangle deposition, neuroinflammation is considered a key feature of AD pathology. AD inflammation is characterized by the presence of reactive astrocytes and activated microglia surrounding amyloid plaques. Chronic exercise has been reported to decrease neuroinflammation in AD. In the Tg animal models, wheel-running and treadmill exercise decreased the levels of hippocampal pro-inflammatory cytokines (i.e., IL-1 β and TNF- α) of

Tg2576 AD mice and NSE/htau23 Tg mice to levels indistinguishable from wild-type mice [213, 214].

Physical activity and AD – A β transportation and degradation

LRP-1 and RAGE are major A β carrier proteins that regulate A β efflux and influx, respectively, in transportation across the BBB [215, 216]. The expression of LRP-1 and RAGE can be detected in both neurons and glial cells [215, 216]. It has been demonstrated that exercise increases LRP-1 and decreases RAGE expression in the hippocampus of Tg2576 [217] and APP/PS1 [71, 181] mice, suggesting enhanced brain-to-blood A β transportation after exercise. Also, exercise can increase the activity of A β degradation enzymes that prevent the aggregation of A β . Tg2576 mice given a 12-week period of exercise significantly increased hippocampal levels of neprilysin, insulin-degrading enzyme, and matrix metalloproteinase 9; all of which are A β proteolytic enzymes [217]. Interestingly, exercise-induced changes in the expression levels of A β transport proteins and proteolytic degrading enzymes depend on the intensity of exercise training [217].

CONCLUSION

Although much progress has been made in AD studies, effective pharmacological treatments remain evasive. Alternatively, non-pharmacological strategies to delay AD have become a major health issue. There is no doubt that brain health can be improved through physical exercise. Exercise benefits neuroplasticity in health and disease stages by targeting different aspects of brain function. Firstly, increases of trophic factors exert net effects on enhancing neuroplasticity, and cognitive and behavioral function. Secondly, exercise synchronously changes cerebrovascular function and glial cells to support enhanced neuroplasticity. Finally, lowering of toxic A β and tau by exercise decreases neuronal vulnerability, which may help the maintenance of synaptic function. Overall, exercise enhances neuronal plasticity (brain reservoir) and could be a strategy to delay the onset of AD.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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