

Molecular mechanisms of glial cells in brain disorders following physical exercise

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ARTICLE INFO

Received: 28 November 2023

Revised: 15 December 2023

Accepted: 15 December 2023

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KEYWORDS

Exercise, glial cells, neural network

ABSTRACT

Physical exercise generally improves health in humans and animals and may enhance cognitive function and neural function in the brain, especially in the prefrontal cortex and hippocampus. It is also a promising intervention for brain disorders such as psychiatric conditions and neurodegenerative diseases. The neuroprotective mechanisms of exercise are related to synaptic plasticity, neurogenesis, and autophagy. Moreover, the therapeutic effects of exercise are associated with glial cell function in the brain. In this review, we examine the relationship between glial cell function and brain disorders. We also consider the role of glial cells in modulating the effects of exercise on the molecular mechanisms and neural circuits involved in central and peripheral brain function. This review demonstrates that glial cells may play an important role in the effects of physical exercise interventions on the brain, particularly in those with neurological disorders.

1 Introduction

Physical exercise has therapeutic potential as a nonpharmacological intervention able to maintain health and slow the progression of neurodegenerative and psychiatric diseases [1, 2]. Exercise may enhance brain functions, improve spatial learning and memory, recover impaired motor functions, and promote mental health [3]. The benefits of exercise extend to patients with brain disorders. This appears to be achieved through the reduction of neuroinflammation,

the stimulation of neurotrophic factors, the enhancement of neurogenesis and synaptogenesis, and the regulation of epigenetics and neuroplasticity [3–5]. For example, a clinical trial found exercise to reduce neuropsychiatric symptoms in patients with mild Alzheimer's disease (AD) [6]. In AD transgenic mice, long-term exercise has been found to improve cognitive function by promoting microglial glucose metabolism and morphological plasticity and reducing soluble TREM2 levels [7]. Exercise also provides cognitive benefits to AD mice

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by inducing hippocampal neurogenesis and elevating levels of brain-derived neurotrophic factor (BDNF) [8]. Exercise improves gait speed, muscle strength, and fitness in patients with Parkinson's disease (PD) [9]. Treadmill exercise has been shown to decrease α -synuclein spreading and accumulation, which was dependent on the activation of peroxisome proliferator-activated receptor- α (PPAR α) in the brains of mice, the prion-like spreading of α -synuclein would exacerbate the pathology of PD, and PPAR α activation would consequently up-regulate lysosomal biogenesis [10]. In addition, aerobic exercise training improves the gut microbiota of PD mice [11]. For patients with major depression, exercise can significantly improve mood and psychomotor retardation [12]. Exercise has also been found to exert anxiolytic effects on both people with anxiety disorders and nonclinical populations [13]. In ovariectomized rats, exercise reduced depression-like behavior and levels of interleukin (IL)-1 β and IL-18 in the hippocampus [14]. Aerobic exercise also reduces chronic stress-induced depression-like behavior in rodents, which may be related to the AMP-activated protein kinase (AMPK)/PGC-1 α pathway [15]. Overall, physical exercise appears to protect the brain's health, prevent neurological dysfunction, and alleviate the symptoms of various neurological diseases.

Recent evidence has shown that physical exercise may affect glial cells by inducing the production of neurogenetic factors that activate downstream signaling pathways [16]. Exercise affects microglial activity by regulating inflammatory factors, such as IL-6, IL-10, and IL-1 β [17]. Animal research indicates that exercise can reduce the activation of glial cells [18] such as attenuating astrocyte glia [19], affect glial fibrillary acidic protein (GFAP) expression, and induce morphological changes in hippocampal astrocytes [20]. In exercised AD transgenic mice,

astrocytes in hippocampus displayed increases in the numbers of primary branches and in the soma area, and most were beta-amyloid (A β) plaque-associated [21–23]. In both AD and PD, microglial activation and inflammation were inhibited through exercise interventions [17, 24, 25]. It is apparent that glial cells play an important role in the effects of physical exercise on the brain. Therefore, in this review, we present recent research findings that demonstrate the beneficial effects of physical exercise in patients with brain disorders. More importantly, we also summarize the effects of exercise on glial cells and the underlying molecular mechanisms.

2 Glial cells in brain disorders

The human central nervous system has evolved with two essential cellular networks in the brain: neuronal networks and nonexcitable glial cells [26]. Neuronal networks are neural circuits of biological neurons. There are several subtypes of non-excitable glial cells, including astrocytes, microglia, and oligodendrocytes. Astrocytes serve metabolic, structural, homeostatic, and neuroprotective functions such as clearing excess neurotransmitters, stabilizing the blood–brain barrier, and facilitating synapse formation [27]. Microglia are the key cells in brain maintenance. They are responsible for the elimination of plaque, damaged or unnecessary neurons, and redundant synapses. They also release inflammatory cytokines to modulate a broad spectrum of cellular responses [28]. Oligodendrocytes are myelinating cells that provide axons with support, insulation, and faster transmission between cells [29]. The coordinated actions of the two networks regulate the functions and basic activity of the central nervous system, culminating in the execution and maintenance of autonomic functions, perception, cognition, emotion, and behavior. Although most previous

models of brain disorders have focused on neurons, mounting evidence indicates that glial cells are also involved. Dysfunction of both astrocytes and microglia can lead to severe pathology and cognitive decline in AD. In a human pluripotent stem cell-derived microglia and triculture system AD model, an increase in C3 production was found due to microglia initiating reciprocal signaling with astrocytes [30]. Astrocyte-derived IL-3 promotes microglial phagocytosis of A β plaques, thereby decreasing cognitive impairments [31]. Furthermore, it has been shown that proinflammatory microglia contribute to the development of depression by releasing proinflammatory cytokines, such as TNF- α and IL-6 [32, 33]. Proinflammatory microglia can release inflammatory cytokines to induce neurotoxic reactive A1 astrocytes, the A1 astrocytes would lose the ability to promote neuronal survival, outgrowth, synaptogenesis and phagocytosis, leading to the death of neurons and oligodendrocytes, and A1 astrocytes may be abundant in various brain disorders, including AD, PD, Huntington's disease, and amyotrophic lateral sclerosis (ALS) [34]. In major depression, changes in astrocytes reduce glutamate uptake, impair neurotrophic support, and disrupt glucose metabolism [35]. Recent findings have revealed that oligodendrocytes may be involved in the pathogenesis of depression and neurodegenerative diseases [36]. Significant alterations have been found in the *MOBP* and *MAG* genes exclusively expressed in oligodendrocytes, of women with depression [37]. In ALS, oligodendrocytes contribute to motor neuron death via a SOD1-dependent mechanism [38].

3 Exercise-induced functional recovery and neuroprotection

Physical exercise has long been known to be good for health in general, yet it is also beneficial

to the cellular system of the brain. Clinical studies indicate that exercise has potential benefits in the treatment of stroke, diabetes, heart failure, depression, and anxiety [39–42]. Gentle exercise improves executive function in younger adults [43], and young adults who engage in more aerobic exercise have better memory [44]. Furthermore, exercise can protect healthy people in late middle age by reducing inflammation and minimizing loss of brain volume [45]. In rodent models, increased exercise has been shown to have neuroprotective effects and facilitate functional recovery. Animal studies have found exercise to improve performance in novel object recognition [46], water maze [47], and elevated zero maze [48] tasks, and to affect sucrose preference [49], suggesting that exercise could improve depression-like, anxiety-like, and cognition-like behaviors. Long-term increases in the amount of regular exercise can activate the mechanistic target of the rapamycin (mTOR) pathway in the motor cortex. This leads to potentiated postsynaptic excitation and enhanced neuronal activity. Exercise also increases dendritic spine formation and improves performance on motor learning tasks [50]. During resistance exercise, mTOR could be activated and driving myofibrillar protein synthesis and eventually leading to an increase in muscle mass and strength [51]. The mTOR signaling also induces changes in ribosome biogenesis, autophagy, and the expression of peroxisome proliferator gamma coactivator 1 alpha (PGC-1 α) [52]. Exercise increases p-mTOR in both neurons and glial cells, with voluntary exercise in animals preferentially increasing p-mTOR in astrocytes and forced running increasing p-mTOR in microglia [53]. Physical exercise increases the densities of both mature oligodendrocytes and their precursors. This is due to the contribution of the mTOR pathway to exercise-mediated stress resilience and axonal myelination [54]. Exercise training in

mice was found to promote recovery from sciatic nerve injury, possibly by regulating microglial polarization through BDNF/AKT/mTOR signaling-mediated autophagy flux [27]. It is known that adiponectin (ADN) can pass through the blood-brain barrier and increase cell proliferation in the brain. After exercise, ADN appears to increase hippocampal neurogenesis and reduce depression-like behaviors in rodents by activating the ADNR1/AMPK signaling pathway [55]. Studies have also revealed that the metabolite β -hydroxybutyrate is increased by prolonged physical activity. This, in turn, causes an increase in neurotransmitter release and BDNF expression [56]. Long-term exercise increases the levels of insulin-like growth factor 1 (IGF-1) and PGC-1 α , reduces p-tau levels and glycogen synthase kinase-3 beta activation, some mitochondrial complexes are increased in the hippocampus and cortex by analysis of the oxidative phosphorylation system [57]. Exercise exerts neuroprotective effects in both healthy animals and disease models. In cocaine-exposed mice, treadmill training was found to activate the mTOR-ribosomal protein S6 pathway, restore synaptic deficits, improve spine formation and synaptic transmission, and increase the spontaneous activities of cortical pyramidal neurons [58]. In old mice, dendrites, dendritic spines, and postsynaptic density protein levels increase with physical exercise [59]. The beneficial effects of exercise on synaptic plasticity were found to be mediated by increases in the field potential of long-term potentiation in the hippocampi of AD mice [46]. Furthermore, exercise decreases A β levels in both the cortex and hippocampus [60]. In PD model rats, long-term voluntary exercise significantly reduced gait motor deficits and increased tyrosine hydroxylase-positive neurons in the substantia nigra [61]. In addition, a notable decrease in parvalbumin-positive interneurons has been observed in an animal depression model, but running increased

the expression of PGC-1 α , which increased parvalbumin-positive interneurons, thereby reducing or eliminating depressive behaviors [62]. Overall, exercise appears to increase cell proliferation and neurotrophic factor levels, facilitate neurotransmission, and have beneficial effects on mood and cognitive function.

4 Exercise modulation of glial molecular mechanisms

In a depression model, exercise promoted oligodendrocyte differentiation and myelination in the hippocampus, with beneficial effects outweighing those produced by fluoxetine [63]. In a stress-induced depression model, exercise alleviated depressive symptoms, attenuated the number of microglia, and inhibited microglial activation and neuroinflammation in the hippocampus [49]. Exercise also significantly reduces the number of astrocytes and slows or stops hippocampal volume decline in depression model rats [64]. Hence, the positive effects of exercise on depression involve multiple types of glial cells, including oligodendrocytes, astrocytes, and microglia.

After increased exercise, old mice showed attenuated cognitive decline, decreased numbers of activated astrocytes, decreased numbers of microglia, and increased expression of the astrocytic water channel aquaporin 4 (AQP4) [59]. In contrast, the proportion of microglia colocalized with BDNF was increased [65]. In 5-month-old APP/PS1 AD transgenic mice, A β deposition and astrocyte activation significantly reduced after 5 months of increased exercise, whereas the activation of microglia was unaffected [19]. However, when the exercise protocol began later in life, at the age of 7 or 24 months, microglial activation was significantly reduced, but the number of A β plaques did not decrease [66]. Conversely, in a study that combined

exercise with antioxidant treatment, 10-month-old APP/PS1 mice showed no observable change in astrocyte activation or the number of microglia [67]. In a sporadic AD model produced by the intracerebroventricular administration of streptozotocin, the astrocytic glutathione content of the CA1 region was increased after 5 weeks of exercise [68]. Astrocytes in the hippocampus displayed an increase in the number of primary branches and the size of the soma area, an increase in astrocytic BDNF, and the restoration of PSD-95 levels [21]. These data suggest that exercise may delay and treat age-related memory decline, mostly enhance the dendritic spine density, synaptic protein expression, and synaptic plasticity in the cortex and hippocampus.

In PD, glial cells contribute to decreased dopamine transmission and the effects of the disease on motor and cognitive functions [69]. Treadmill exercise was found to reduce Ibal-1 expression, TNF- α and IL-1 β levels in MPTP mice, and to suppress the TLR2/MyD88/NF- κ B signaling pathway, reducing motor deficits and the decline in dopamine levels [70]. In 6-OHDA-induced Parkinsonism, the morphology of striatal astrocytes and GFAP levels returned to normal to some degree after exercise [71]. The 6-OHDA PD mice showed increased activation of astrocytes, microglia, and oxidative species before exercise, and exercise prevented the neuroinflammatory response [72].

In other disease models, a combination of exercise and caloric restriction significantly increased glutamate uptake from the extracellular space, indicating that astrocytes help to avoid excitotoxic damage [73]. Moreover, microglia activation and motor neuron counts were observed to increase with exercise in ALS model mice [74]. Together, these data indicate that exercise provides a potential means of modulating the activation of glial cells, the neuroinflammatory process, and neuronal activity. This further

supports the possible use of exercise as a nonpharmacological method of managing neurological diseases.

5 The effects of exercise on central and peripheral factors

The mechanisms underlying exercise-induced neuroprotection involve several neurotrophic factors [75]. BDNF is involved in the differentiation, maturation, and survival of neurons [76]. Several studies have shown that exercise promotes the expression of BDNF, which increases synaptic plasticity and improves memory [56, 77, 78]. Glial cell-derived neurotrophic factor (GDNF) enhances the survival of midbrain dopaminergic neurons [79]. Short-term exercise was found to increase GDNF levels in the spinal cord of rats [80], while long-term exercise increased GDNF expression and enhanced structural neuroplasticity at neuromuscular junctions [81]. Vascular endothelial growth factor (VEGF) is a signaling protein that promotes the growth of new blood vessels. In older adults, gentle exercise may trigger weak VEGF expression through both hypoxic and nonhypoxic mechanisms [82]. Another neurotrophic factor involved in exercise-facilitated neuroprotection is IGF-1. This is a wide-spectrum angiogenic growth factor that participates in vascular remodeling in the adult brain [83]. Studies have shown exercise to significantly increase serum IGF-1 levels and these increases are exercise duration and intensity-dependent. After exercise training, serum IGF-1 levels reach their highest concentration but overexercise was found to increase unfavorable and unbound IGF-1 levels and to increase the risk of hormone cancer and osteoarthritis [84]. IGF-1 also improved obesity-related cognitive dysfunction following exercise interventions through improvement of neurogenesis, synaptic plasticity or inflammation. [85]. IGF-1 is also a key regulator of the differentiation and myelination of oligodendrocyte

progenitor cells [86–88]. Oligodendrocytes and their progenitors affect synaptic transmission and the intrinsic excitability of axons to contribute to long-term memory, memory consolidation, and recall in associative learning [89].

The involvement of neurotrophic factors in the modulation of the effects of physical exercise on the brain has been confirmed [75] and other central or peripheral factors have also been implicated. Irisin is a recently identified myokine that is released into the circulation during exercise. This is cleaved from fibronectin type III domain-containing protein 5 (FNDC5) [90] and research has shown that FNDC5/irisin expression is reduced in the hippocampus and cerebrospinal fluid of AD mice. Thus, increasing the expression of FNDC5/irisin through exercise could potentially reduce AD-induced memory impairments [46]. Moreover, exercise has been found to suppress cancer onset and progression through direct regulation of natural killer (NK) cell trafficking, with epinephrine-dependent mobilization of NK cells into the circulation, followed by their IL-6-dependent redistribution to tumors [91]. NK cells are white blood cells that destroy infected, diseased, or cancerous cells. These studies indicate that the neuroprotective effects of exercise are achieved through the regulation of the expression of central and peripheral factors.

6 Conclusions

The benefits of regular exercise and physical activity are well-known and easily observed in fit individuals. Studies have also demonstrated the neurological benefits of exercise. Recently, there has been increased research interest in the functions of glial cells. Exercise has been found to promote morphological and functional changes in the brain, not only in neurons but also in glial cells. Clinical studies and animal models have shown the favorable effects of exercise on the brain and somatic functions to extend to the glial cells. This is apparent in morphological changes in astrocytes, the elimination of plaques of microglial plaques, and the promotion of differentiation and myelination of oligodendrocytes (Fig. 1). There is evidence that exercise speeds functional recovery from physical trauma or illness, aids emotional healing, improves memory, and facilitates the recovery of motor function after its impairment. Exercise has also demonstrated neuroprotective effects in both healthy and diseased animal models, including increased synaptic plasticity and neurotrophic factor levels. Exercise can both directly regulate the morphology and function of glial cells and influence downstream pathway signaling to modulate the activation of glial cells and

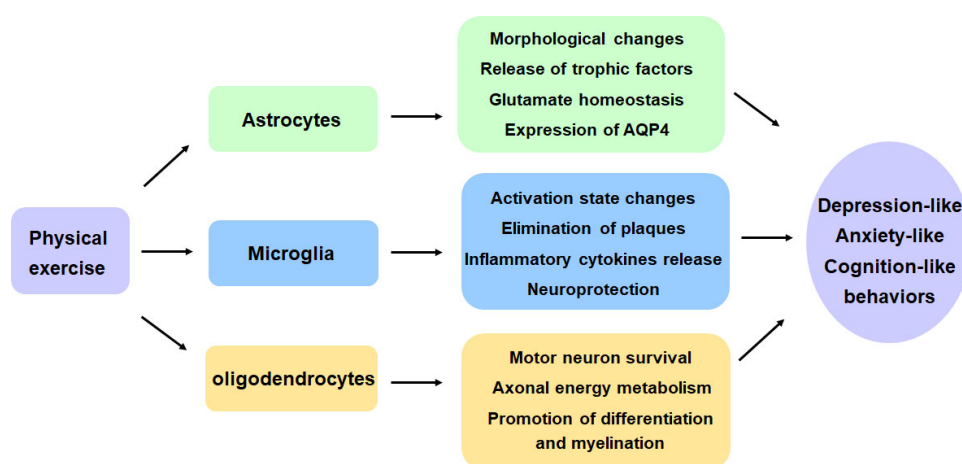


Figure 1 Flow diagram illustrating glial cell mediation of the beneficial effects of exercise on the brain and somatic functions.

neuroinflammatory processes. It affects physical functions and phenotypes via central and peripheral factors.

Although overexercizing can increase the risk of unpredicted diseases [84], moderate physical exercise can be instrumental in improving clinical and pathological phenotypes and has overall health benefits. This review provides insights into the use and effects of exercise as an intervention for brain disorders.

Funding information

This work was funded by STI2030-Major Projects (2022ZD0207600) to L.Z., National Key Research and Development Program of China (2020YFA0113600) to L.Z., National Natural Science Foundation of China (U22A20301 to K.F.S., 32070955 to L.Z., No.82104416 to Y.L.), Key Research and Development Plan of Ningxia (2022BEG01004) to K.F.S, and Guangdong Basic and Applied Basic Research Foundation (2023B1515040015) to L.Z., Science and Technology Program of Guangzhou (No. 202201011178 to Y.L.), The project of Administration of Traditional Chinese Medicine of Guangdong Province of China (No. 20221101 to Y.L.), China Postdoctoral Science Foundation (No. 2022M710059 to Y.L.).

Acknowledgements

None.

Author contribution

Y.L. collected literatures and wrote the manuscript, with the help from S.R. L.Z. and Y.L. revised the manuscript, under the supervision of K-F.S. All authors have commented on previous versions of the manuscript and approved the final version.

Declaration of conflicting interests

All authors declare no conflict of interest.

Data availability statement

There is no data for this review.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

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