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The potential mechanisms of exercise-induced cognitive protection: A literature review.

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Abstract

Dementia has become a major health concern for the aging population of the United States. Studies indicate that participation in moderate exercise, with training, has been shown to have a beneficial impact on cognition. Thus, exercise and its effects on cognitive function has become an important area of research. This review summarizes the current literature on the potential mechanisms of the benefits of exercise for cognitive function.

Keywords

cognitive function; dementia; exercise; BDNF; PGC-1α; IL-6

Introduction

Dementia is a major cause of death and disability in the United States(1). Family, friends, and caregivers pay a terrible toll in supporting the individual with dementia(1, 2). Even more concerning, we have no effective therapies for attenuating dementia progression once symptoms commence(1). Thus, the importance of understanding lifestyle factors that can be modified to improve cognitive function cannot be overly stressed. Studies have found that exercise can improve aspects of brain health related to cognition (3–16); however, there are still gaps in knowledge regarding the mechanisms controlling these relationships. This review focuses on exercise-induced influences on cognition and addresses some of the potential mechanisms behind observed improvements in cognitive function with exercise.

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Conflict of interest
The authors have no conflicts of interest to disclose.

Exercise and cognitive function

Exercise has been demonstrated to improve cognitive function in healthy older adults(3–7). A twelve week randomized control trial demonstrated that older adults who participated in the exercise group had improved memory and executive functions when compared to the control group(3). Additionally, an 8 year longitudinal study found that older adults who were physically active during leisure time had better subsequent cognitive function and a slower rate of cognitive decline than those who were not(5). Further, a randomized controlled trial in older adults demonstrated changes in brain activity in specific brain regions with exercise training(11). Other studies, in animals and young adults, support this finding and indicate that exercise can induce changes in the hippocampus(8–10). In mice, running enhanced hippocampal neurogenesis and learning(9). In rats, treadmill running reduced activation of inflammatory signaling pathways in the hippocampus and resulted in better cognitive performance(10). Hippocampal changes are specifically relevant to dementia, as it is important in memory processes and has been of specific focus in the study of Alzheimer's disease(17) Studies have also shown preservation of both white and gray matter with increased exercise(12–15). A recent study demonstrated that wheel running in mice not only improved cognitive function, but also reduced amyloid β plaques and reduced neuroinflammation associated with aging(16). These studies have demonstrated that exercise is an appropriate modifiable factor for reducing the risk of developing dementia.

Physical activity in youth is also important for cognitive function(8, 15, 18–23). Participation in a physical activity program has been shown to improve executive control and data shows that physical activity may improve childhood cognition(24). Additionally, children participating in an exercise program have improved white matter integrity when compared to children involved in a sedentary after-school program(25). These studies and others have provided the rationale for the application of exercise programs in children and adolescents for cognitive benefits.

Research indicates that different types of exercise can have different effects on the brain. Regular moderate aerobic exercise has been shown to promote antioxidant capacity in brain, while anaerobic or high-intensity exercise, aerobic-exhausted exercise, or the combination of these types of training are believed to reduce antioxidant response(26). Studies have indicated beneficial effects of resistance exercise on cognitive function, potentially by enhancing hippocampal synaptic plasticity-related molecules(27). Studies have shown brain structural changes related to strength training in white matter, gray matter, and putamen volume in the healthy adult brain(14, 28–30). Further, long-term mild, rather than intense exercise and sustained aerobic exercise, rather than high intensity interval or resistance training were found to produce hippocampal neurogenesis(31, 32). Thus, a combination of moderate aerobic and resistance exercise would provide an ideal benefit to overall cognitive function.

Adverse effects of extreme exercise

Although exercise has beneficial effects on brain health, studies indicate that training is important and that acute, extreme, or too vigorous of exercise can be detrimental. Extreme exercise has been shown to lead to an increase in plasma S100B, a proposed marker of blood-brain barrier disruption and brain damage(33). Exercise to exhaustion has resulted in increased brain IL-6 levels in rats, but long-term training protects from an increase in hippocampal IL-6(34). Acute bouts of cardiovascular exercise can momentarily alter executive control and increase performance instability in lower fit individuals, while this was reduced in higher fit individuals(35). Further, a study found that moderate-intensity exercise produced a beneficial effect on cognitive function, but this effect was lost with high-intensity exercise(36). Although many prior studies have documented the beneficial effects of exercise, most studies have not considered the potential adverse effects of extreme exercise. In future studies, researchers should take these adverse effects into consideration. In addition, recommendations about exercise should specify that training is important and that acute and extreme exercise without training may not be beneficial.

Potential mechanisms of improved cognition with exercise

Brain glycogen, a critical energy source for neurons, is primarily localized to astrocytes(37). Prolonged exhaustive exercise with hypoglycemia leads to decreases in brain glycogen(38). However, one study indicates that the brain, like skeletal muscle, overcompensates for the loss of astrocyte glycogen(38). Another study supports the theory that glycogen depletion in astrocytes limits the ability of the brain to accelerate its metabolism during activation(39). This would indicate that regular exercise would increase astrocyte glycogen stores, giving the brain increased protection from future bouts of hypoglycemia and improving cognition.

Many studies in animals have demonstrated that exercise can increase hippocampal neurogenesis or rescue the process from various insults, including: restricted cerebral blood flow, lipopolysaccharide exposure, irradiation, and intracerebroventricular amyloid β injection(29, 31, 32, 36, 40–43). The mechanisms by which this occurs are not completely understood, however research has provided some insights into potential mediators of the process. Studies have implicated brain-derived neurotrophic factor (BDNF), serotonin, and adiponectin in the process of exercise-induced hippocampal neurogenesis(36, 40, 42, 44–48).

Exercise is associated with changes in levels of neurotransmitters, neurotrophic factors, and growth factors, alongside increases in temporal lobe functional connectivity(8, 19, 49–54). One of these factors, BDNF, is indicated to function to alter the brain mitochondrial respiratory efficiency; however the presence of inflammatory cytokines appears to block this function(55). The main function of BDNF in the adult brain is to regulate synapses, with structural and functional effects on both excitatory and inhibitory synapses, in many brain regions(56). BDNF regulates energy homeostasis by controlling patterns of feeding and physical activity, and modulating peripheral glucose metabolism(22, 55–61). The role of BDNF in cognitive impairment is unclear, but does seem to have an important role, as mice with knockout of BDNF in restricted areas of the brain manifest object recognition deficiency(62). Previous studies have shown that mice consuming a high-fat diet increase BDNF in multiple regions of the brain(57, 63, 64). On the other hand, exercise was shown to reverse memory impairment caused by a high fat diet and elevate BDNF in neurons of the hippocampal CA3 region(22, 57–59, 65, 66). Further, recent evidence suggests that myokines released by exercising muscles affect the expression of BDNF synthesis in the dentate gyrus of the hippocampus(67). These studies suggest that BDNF is a key mediator of the effects of exercise on cognitive function.

Peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α appears to have a role in facilitating some of the effects of exercise on brain health. PGC-1α has been found to be part of the mechanism by which exercise induces hippocampal BDNF expression(68). One study indicated that exercise training is a more effective at reducing age-associated inflammation than resveratrol supplementation and that PGC-1α was required for these anti-inflammatory effects(69). Exercise training of skeletal muscle changes kynurenine metabolism and protects from stress-induced depression(70–73). Activation of PGC-1α1 can increase skeletal muscle expression of kynurenine aminotransferases, which facilitate the conversion of kynurenine into kynurenic acid, a metabolite unable to cross the blood-brain barrier(73). Reducing plasma kynurenine protects the brain from stress-induced changes associated with depression; skeletal muscle-specific PGC-1α1 transgenic mice have been found to be resistant to depression induced by chronic mild stress or direct kynurenine administration(73–76). These studies indicate that PGC-1α in both muscle and brain may mediate the effects of exercise on cognitive function.

Myokines play roles in maintaining biological homeostasis, including energy metabolism, angiogenesis, and myogenesis(77, 78). Interleukin (IL)-6, among other myokines, is dependent upon contraction and plasma levels increase during exercise; this indicates that it may serve as an exercise factor, providing a potential mechanism for the association between sedentary behavior and many chronic diseases(8, 34, 78–89). Although IL-6 is often thought of as pro-inflammatory, some evidence indicates that it can have anti-inflammatory effects as well. Skeletal muscle derived IL-6 produced during exercise has been shown to decrease the production and activity of IL-1β and TNF-α(90). Wheel running mice were shown to have measurable training effects and significantly lower hippocampal TNF-α and higher IL-6, IL-1rα, and IL-12 expression in the hippocampus compared to controls(91). One study indicated that an exercise-induced increase in IL-6 within the brain may serve a neuroprotective role(92). Additionally, the release of IL-6 from the brain when exercise is prolonged may serve as a signal of metabolic stress within the brain(39). Findings suggest that the systemic inflammatory response to acute exercise is different in lean compared to overweight and obese subjects, with overweight and obese individuals exhibiting a more pronounced increase in inflammatory markers (93). Fatigue associated with recovery from muscle damage due to eccentric exercise has recently been linked to increases in brain and muscle pro-inflammatory cytokines(94). Thus, exercise, particularly with training, may alter production of IL-6 and other myokines to produce a beneficial effect on inflammatory markers and brain health.

Summary and Conclusions

Moderate physical exercise with training appears to be a modifiable lifestyle factor which can provide benefits to cognitive function, these effects and some of the potential mechanisms behind this are summarized in Figure 1. Exercise has been demonstrated to preserve white and gray matter, induce changes in the hippocampus, including neurogenesis, and improve cognitive function. Although the complete details of the mechanisms are not known, researchers have described some aspects of the process. Increased astrocyte glycogen storage, increased expression of BDNF, PGC-1α signaling, and altered skeletal muscle IL-6 production appear to mediate some of the benefits of exercise for cognitive function. Further understanding of these mechanisms may provide insight into potential targets for the development of therapeutics for the prevention and treatment of dementia. Current evidence provides a compelling argument for the participation in moderate physical exercise, consisting of both aerobic and resistance training, as a strategy for improving cognitive function and preventing cognitive decline, perhaps preventing the development of dementia and other neurodegenerative diseases, such as Parkinson's disease and multiple sclerosis.

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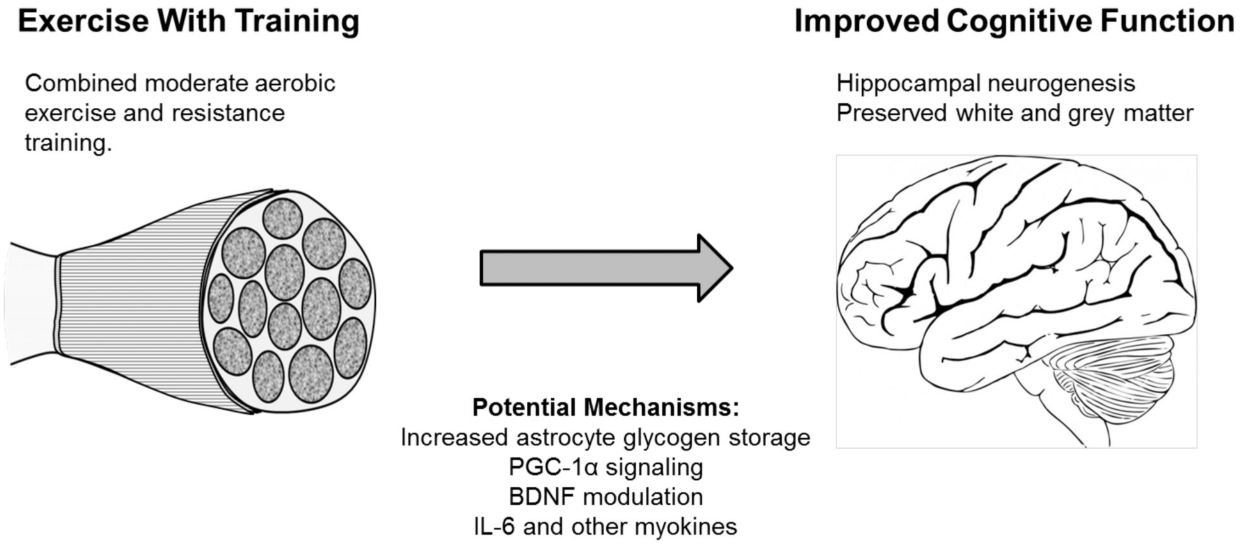

Figure 1.

Summary of the effects of exercise on cognitive function and potential mechanisms by which they occur.