Mice lacking this compound were unable of neurogenesis. Moreover, beta-endorphin stimulates BDNF gene expression in the dentate gyrus (5). Irisin precursor, FNDC5, can as well stimulate the neurotrophic factor production. Forced expression of FDNC5 increased BDNF levels, while RNAi knockout of FNDC5 resulted in low BDNF levels (8). Noradrenaline can also stimulate its production through β1/β2 and α2-adrenergic receptors (14). Together, these processes improve survival of existing neurons, produce new brain cells, and constitute the brain's enhanced plasticity that underlies the exercise-induced protective effects against aging, injuries and degenerative diseases.

PROTECTION AGAINST NEURODEGENERATIVE DISORDERS AND OTHER BRAIN CONDITIONS

Multiple studies found that physical exercise improves the outcome of several neurological conditions, such as major depression disorder, dementia, Alzheimer's disease, Parkinson's disease, depression and even traumatic brain injury (4,22). It is also well-known that physical activity is correlated with better academic achievement, retrieval of relational material, spatial learning performance and even larger hippocampal volume in children (4,23). The effect of physical exercise in adolescents may be more pronounced due to the elevated neuroplasticity during this life period, though the exact mechanism of action is unknown (4). A study on rats suffering from fetal alcohol spectrum disorder (FASD), which in humans has negative effects on the hippocampal anatomy and function, has shown that 12 days of exercise has positive effects on neurogenesis and hippocampus-dependent memory (24), which are affected by FASD (4).

Regarding depression, it has been found that the hippocampus decreases in volume in patients suffering from this condition, due to decreased neurogenesis, since neurodegeneration is not a symptom of depression in these patients (4), although no causal link between decreased neurogenesis and the onset of depressive disorders has yet been completely proven (25). Physical exercise has been shown to alleviate depressive symptoms and led to a lower probability of developing major depressive disorder (MDD) (25). The expression of hippocampal BDNF might be involved, as not only do BDNF-knockout mice present a less effective antidepressant response, but the infusion of BDNF or overexpression of TrkB gene are themselves capable of ameliorating the depressive symptoms (4). In addition, prenatal depression, as well as shorter first stage of labor, have been liked to females that exercised during pregnancy (15,26).

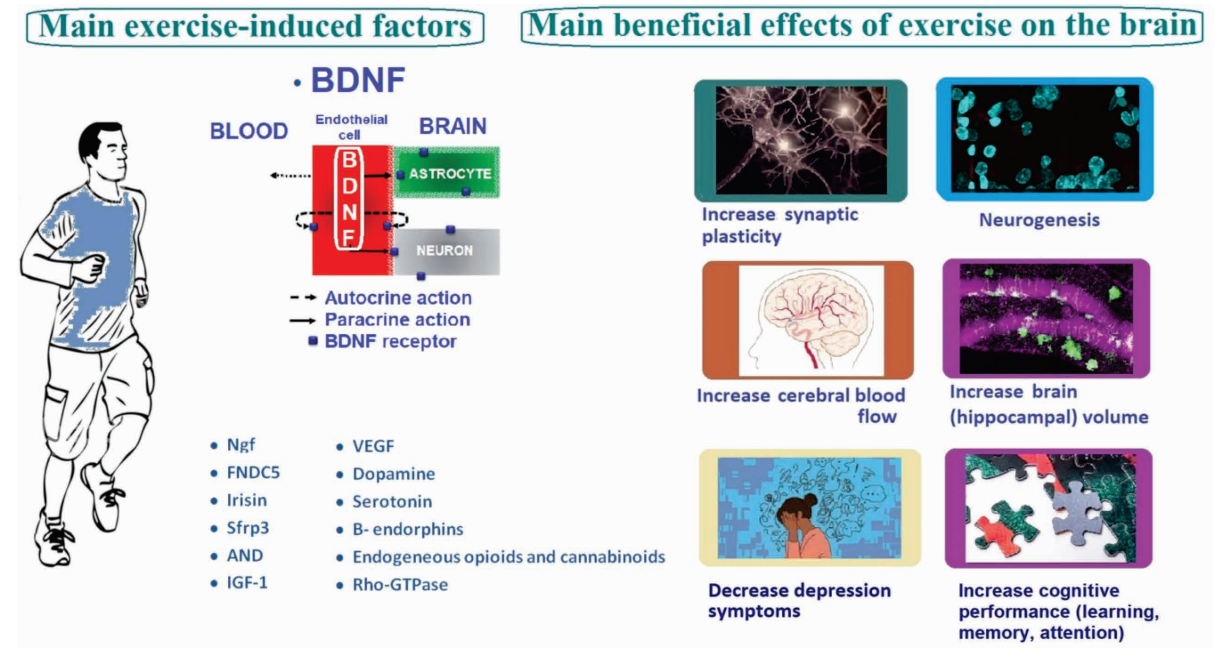

FIGURE 1. Beneficial effects of physical exercise on the brain; central role of BDNF beside other known exercise-induces factors – adapted after (21).

Ngf – neural growth factor; FNDC5 – fibronectin type III domain containing 5; Sfrp3 – xecreted frizzled-related protein 3; AND – adipocyte-secreted adiponectin; IGF-1 – insulin-like growth factor; VEGF: vascular endothelial growth factor; BDNF – brain-derived neurotrophic factor; Rho-GTPase – a subfamily of the Ras superfamily, involved in vesicular trafficking, cell cycle, transcriptional dynamics etc.

Another disorder whose incidence is inversely correlated with physical activity is Alzheimer's disease (AD) (42). Even 30 minutes of daily exercise is helpful in decreasing the number of hospitalizations in AD patients as well as increasing their quality of life (4). In mouse models, exercise decreases the amount of amyloid-beta (Aβ) oligomers that accumulate in the hippocampus; it also reduces neuroinflammation and neurons apoptosis in the same site (6). Increased levels of synaptotagmin-1, synaptobrevin-1, synaptophysin and PSD95 – synaptic markers involved in the AD pathogenesis – were also reported in certain areas of the brain, such as the hippocampus and cerebral cortex after exercise training (43).

Physical exercise could also help in mitigating traumatic brain injury (TBI) symptoms. Exercise preceding TBI in mice enhanced the recovery of several brain functions, while also decreasing lesions size and neuronal loss (44). Another neuroprotective effect of exercise involves up-regulation of tight-junction-associated proteins of the BBB which act as a barrier to harmful circulating molecules. Microglia activation and levels of cytokines in the hippocampus have also been found to be decreased by running in aged mice (7).

CONCLUSION AND FURTHER RESEARCH

Overall, physical exercise aids in decreasing the risk of neurodegenerative disease and combating cognitive decline with age. The extent of age-related atrophy in brain has been proven to be lower in people who exercise, and reductions in neurogenesis due to age and disease can be countered by exercise in old animals. BDNF plays a major role in linking exercise to anatomical and physiological changes in the brain. As it is predominantly expressed in the hippocampus, its main effects are related to neurogenesis and cognitive functions, as well as psychiatric disorders prevention.

All these point towards an inexpensive, powerful and universally available alternative approaches of treatment and prevention of brain disease and intellectual decline in old age.

Further research on human brain tissue is necessary, though difficult to achieve. So far, mostly mice models have been used, despite contrasting findings regarding the extent of adult neurogenesis in mice and human. Though there is no doubt that physical exercise provides numerous health benefits and has neuroprotective effects; the complete mechanisms of action through which physical exercise modulates brain structure and function in human remain to be elucidated.

Note

The first two authors have equal contribution.

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