

Neuroprotective effects of physical exercise: Implications in health and disease

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ABSTRACT

Physical exercises have long been linked to numerous health improvements, ranging from cardiovascular to psychiatric. In this review, we take a closer look on its anatomical, physiological and chemical effects on the brain. Starting from the clinical to the cellular level, we will analyze the neurogenesis, anti-inflammatory effects on Brain-Blood Barrier and synaptic plasticity, outlining known molecular aspects that are influenced by physical activity, such as: gene expression, changes of growth factors and neurotransmitter levels and means of reverting molecular mechanisms of ageing. The brain derived neurotrophic factor (BDNF) is one of the central molecules that links the physical exercise to neurogenesis, neuroprotection, cognitive functions, dendritic growth, memory formation and many more. We indicate the correlation between physical activity and mental health in diseases like depression, Alzheimer's dementia and Parkinson's disease.

Keywords: physical exercise, neurogenesis, BDNF, irisin, Sfrp3, depression, neurodegenerative diseases

INTRODUCTION

There is growing evidence that certain lifestyles could contribute to cognitive impairment and dementia, but the physiological steps that link a harmful lifestyle to its negative impact are not always obvious. It is also unclear whether all these harmful lifestyles that contribute to cognitive decline are

linked through the same intermediary steps. Apart from body fitness, physical exercise also have beneficial effects on the brain. A routine of aerobic exercise can improve memory, thinking skills, enhance positive moods and have protective effects against aging (1-3). Exercise has long been known to aid in the treatment of various illnesses, such as cardio-

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vascular disease, diabetes, stroke, obesity and even osteoporosis and cancer (4,5).

However, new data from studies done mostly on rodents have shown that physical exercise can also have a plethora of beneficial effects on the nervous system: boosting neurogenesis in a certain area of the hippocampus, modulating the concentration of a wide range of signaling molecules involved in neuron functions, and protecting against neurodegenerative diseases such as dementia, progressive multiple sclerosis, Alzheimer's disease, Parkinson's disease and major depression disorder, as well as strokes (5-8).

It is noteworthy that these effects are specific to aerobic exercise – the types of exercise that increase heart rate and respiratory rate, such as running, cycling, swimming. Non-aerobic activity, such as muscle building or stretching, do not have the same effect. The effects appear to result from increased blood flow to the brain and subsequent increase in energy metabolism. A certain degree of intensity is necessary to achieve the beneficial outcome. Aerobic exercise increases the production of several growth factors of the nervous tissue, known as neurotrophic factors, among which BDNF (brain derived neurotrophic factor) has a central role. Thus, increasing BDNF levels in the brain is considered an attractive possibility for the prevention/treatment of various brain diseases. BDNF exerts a protective effect on existing neurons, and stimulates formation of new neurons from neural stem cells during the process called neurogenesis. The immediate effect of acute exercise is most remarkable on the body's affective state. A single bout of exercise can promote positive emotions, suppress negative feelings, reduce the body's response to stress. These effects may persist for up to 24 hours, and are thought to result from exercise-induced up-regulation of several substances involved in mood modulation. These include neurotransmitters (dopamine – the neurotransmitter involved in the brain reward pathways, serotonin – commonly known as the substance of well-being and happiness), whose low levels in the brain have been associated with depressive disorders; neuromodulators (beta-endorphins – or endogenous morphine, an endogenous opioid – and anandamide – an endogenous cannabinoid). Endogenous opioids and cannabinoids are known as substances involved in pain modulation, stress and anxiety reduction (9-12).

PHYSICAL EXERCISE, STRUCTURAL CHANGES IN BRAIN

New granule cells are produced in the dentate gyrus, a region of the hippocampus engaged in learning and memory formation tasks (4). Adult neurogenesis is a continuous process, though it

does reduce with age (7,8). An increase in neurogenesis has been linked to superior performance in hippocampus-associated tasks as well as disease prevention, though not complete (13). On the other hand, impaired neurogenesis may be a factor contributing to major depression due to the lowered adaptive plasticity (4).

Physical exercise has repeatedly shown to boost and influence all aspects of hippocampal neurogenesis in rodents (4), which correlates with a betterment of cognitive function in the form of learning, memory and attention (4,5). Not all these effects may be due to increased neurogenesis only, since long-term running also influences long-term potentiation (LTP) and neurogenesis (8) in the dentate gyrus, as well as synaptic plasticity (5).

Additionally, exercise has been shown not only to increase neurogenesis, but also neural complexity by boosting dendrite numbers and length, dendritic arborization and spine density, as each type of exercise can induce different changes of neuroplasticity (4,5,7,8). Hippocampal blood flow increases, as well as its volume, enlarging by up to 2% in old age (4, 8), though this effect could also be attributed to changes in dendritic morphology or increased synaptic plasticity, due to a lack of direct evidence concerning boosted neurogenesis in humans (13).

Other morphological changes consist of anti-inflammatory effects, improved endothelial function and blood-brain barrier (BBB) damage by preserving tight junctions, as a study suggests that physical activity regulates claudin-4 and occluding levels, increased antioxidative capacity and even a higher number of brain capillaries (14). Moreover, increased cerebral blood flow, which has a protecting effect against ischemia, and microbiota augmentation effects have been observed (15).

PHYSICAL EXERCISE, CHANGES IN CIRCULATING HORMONES, NEUROTRANSMITTERS AND SIGNALING MOLECULES

It has been shown that physical training affects gene expression, rodent mRNA in the brain being closely related to the distance run (13), can revert aging mechanisms such as synaptic loss by up-regulation of Rho-GTPase (small signaling G proteins, being a subfamily of the Ras superfamily, involved in a wide variety of cell functions, such are: vesicular trafficking, cell cycle, transcriptional dynamics etc.) (15).

Physical exercise also leads to the release of vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF-1) which are both necessary for the enhancement of adult neurogenesis (4,5). VEGF also induces angiogenesis and promotes

vascular health (5, 7). Blocking this angiogenesis using angiotensin II receptor antagonists seems to be sufficient to nullify the effects of physical exercise on neurogenesis (5). In addition, the renin-angiotensin-aldosterone pathway, which is correlated with hypertension and encephalic inflammation is suppressed post exercise (14). IGF-1, which is mostly expressed centrally, helps reducing oligodendrocyte loss and neuronal death in hypoxia, and helps diminishing the decline of performance in memory tasks in rats (7). On the other hand, levels of bone morphogenetic protein (BMP), a negative regulator of adult neurogenesis, are decreased after running (5).

Tryptophan catabolism through the kynurenine pathway can cause brain inflammation and BBB disruption. After tryptophan conversion into kynurenine, the latter can further be metabolized in two distinct compounds: either neuroprotective kynurenic acid or neurotoxic quinolinic acid. Skeletal muscle tissue, during exercise, enhances kynurenine aminotransferase expression, which results in higher neuroprotective compound concentration (14).

Wnt signaling inhibitor secreted frizzled-related protein 3 (Sfrp3) and adipocyte-secreted adiponectin (AND) – a key regulator of insulin sensitivity and tissue inflammation, also function as mediators of hippocampal neurogenesis in relation to physical exercise (4). The former's deletion aids the proliferation of granule cell progenitors, while the latter probably works by up-regulating adiponectin receptor-activated protein kinase signaling pathways (16).

Furthermore, aerobic exercise may also increase cognitive performance by rising the concentration of certain neurotransmitters such as glutamate, noradrenalin and acetylcholine (7). As an example, locus coeruleus, a tremendously important nucleus in cognitive functions, is stimulated by epinephrin levels through the vagus nerve afferents (14). Dopamine, serotonin and gamma-aminobutyric acid (GABA) neurotransmitter systems have also been shown to be impacted by physical exercise (17). Neural growth factor (Ngf) up-regulation, which is achieved in rats after 3 days of access to a running wheel, has also been observed following exercise, though the role it plays in exercise-induced neurogenesis and neuroprotection is still not clear (7). Most likely, it acts in concert with brain-derived neurotrophic factor (BDNF) to achieve different roles concerning the protection of the brain in aging (7).

One of the main features of cellular aging is characterized of autophagy dysfunction that increases neurotoxicity and neurodegeneration. Fortunately, treadmill exercise in rodents regulated

Beclin1, a protein that finely regulates autophagy (15).

BDNF AND ITS ROLES IN NEUROPROTECTION

BDNF (brain-derived neurotrophic factor) has emerged as one of the most important molecules involved in neuroprotection. It has been shown that low cerebral levels of BDNF, playing a critical role in many brain functions, have been implicated in neurodegenerative, neurological and psychiatric diseases; changes in BDNF levels are observed throughout the brain but are most remarkable in the hippocampus (responsible for memory and learning). In fact, regular exercise has been shown to increase the size of the hippocampus and improve cognitive functions. While acute exercise, defined as a single workout, can produce significant changes in BDNF levels and subsequent improvements in learning performance, a regular exercise program progressively increases BDNF baseline levels and makes its response steadier overtime (11,18).

BDNF higher concentration has been linked to physical exercise, as a correlation that has been established between distance of running and BDNF mRNA levels. Its expression increases in brain (beside hippocampus, in caudal neocortex, amygdala, claustrum, nucleus of the solitary tract), blood and even skeletal muscle (19). Interestingly, its gene transcription in prenatal stage is limited, which indicates that is involved in postnatal neurogenesis (5). In addition to BDNF concentration fluctuations, its receptor TrkB (tropomyosin receptor kinase B) undergoes higher phosphorylation rates during running (4), and its deletion completely ceases the neurogenesis enhancements by exercise (5).

Some of the reported functions of BDNF include: dendritic growth, neuronal survival, synaptic plasticity and efficacy, increase cognitive function, memory formation, and neurogenesis (8,14,19). Interestingly, significantly low BDNF levels have been associated with major depressive disorders, post-traumatic stress disorders and suicidal behavior. Fortunately, 8-12 weeks of treatment with antidepressant medication resulted in closer to physiological concentration of the neurotrophic factor (19). BDNF appears to coordinate its actions with at least two other growth factors: insulin-like growth factor (IGF-1) and vascular endothelial growth factor (VEGF), whose expressions levels also increase following aerobic exercise. BDNF interacts with IGF-1 to induce neurogenesis, while VEGF stimulates growth of new blood vessels, a process known as angiogenesis (18,20).

Regarding other interactions of BDNF, beta-endorphins have been proved to greatly influence it.

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 FNDC5 increased BDNF levels, while RNAi knockout of FNDC5 resulted in low BDNF levels (8). Noradrenaline can also stimulate its production through $\beta 1/\beta 2$ and $\alpha 2$ -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 linked to females that exercised during pregnancy (15,26).

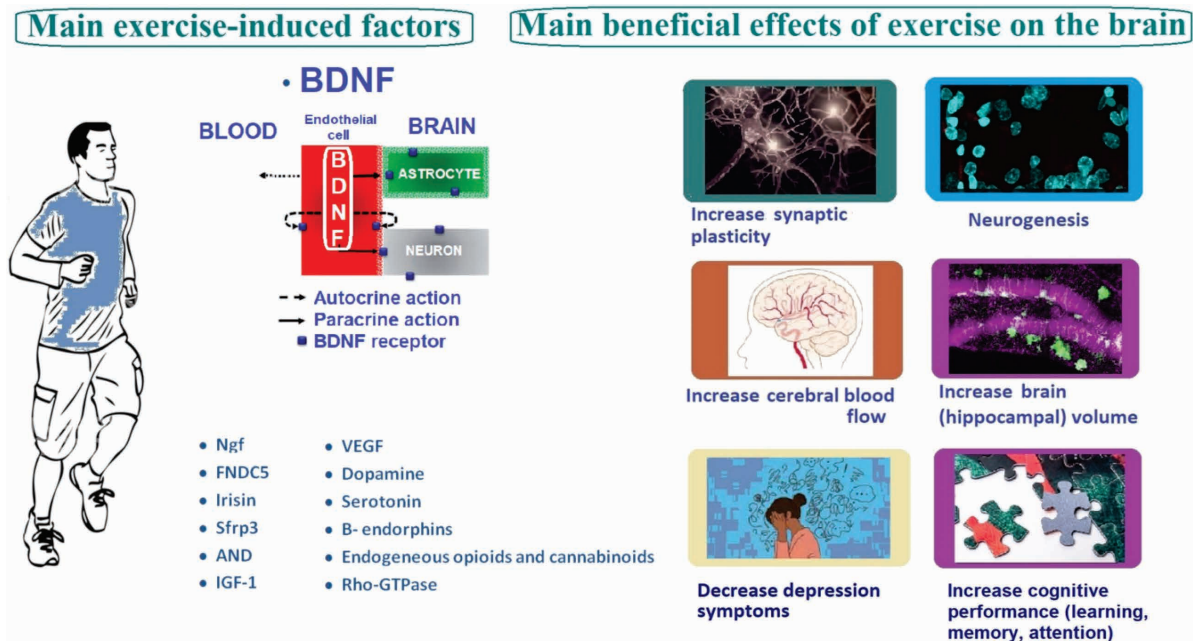


FIGURE 1. Beneficial effects of physical exercise on the brain; central role of BDNF beside other known exercise-induced factors – adapted after (21).

Ngf – neural growth factor; *FNDC5* – fibronectin type III domain containing 5; *Sfrp3* – secreted 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.

TABLE 1. Studies on types of exercise training and effects on BDNF levels in depressed patients

Physical exercise intervention	Subjects	Results	Ref.
One bout of aerobic exercise: Incremental exercise test on treadmill (initial walking speed 3 km/h). Speed and inclination increased simultaneously every 3 min	n = 35 women with depressive episode of RUD; Age: 61.1 ± 7.2 y	↑BDNF (soon after exercise cessation); at 30 min of recovery, BDNF after exercise cessation	27
Strength training & combined aerobic: strength training, 3x/week; 40 min of aerobic exercises at 65% and 80% age-predicted max. heart rate, 3x/week; Duration: 10 weeks	n= 451 community-dwelling older women, RCT; Age: 65–89 y	↑BDNF, both aerobic and strength trainings: ↓GDS score	28
Aerobic exercise: 3x/week, targeted dose of 16.5 cal/kg/week of aerobic exercise, single-stage submaximal treadmill walking test	n = 26 depressed in patients, RCT; Age: 42.81± 12.4	↑ BDNF after 2 weeks	29
One bout of aerobic exercise: 30 min stationary bicycle; blood taken before and within 10 min after completion of each session	n = 24 women with depression; Age: 38.6 ± 14.0 y	↑BDNF, improvement in depressed mood, not intensity depended	30
Trainings sessions, 3/per week for each 45 min. at moderate intensity: a load test at 50% of the max. workload achieved during the initial incremental exercise test. All patients trained in the aerobic-anaerobic transition zone. Duration: 6 weeks	n=42 depressed in patients (on antidepressant drugs), exercise intervention plus treatment as usual (EXERCISE, n = 22), or treatment as usual (TAU, n = 20), RCT; Age: 18 - 60 y	↑BDNF in the EXERCISE group and slightly ↓in the TAU group.	31
Combined aerobic and strength trainings: 3x/week, 3 sets of 10 rpts and 30 s interval during 30 min. Resistance bands exercises. Intensity: 50% of 1RM initially; 75% of 1RM in 3rd month. At the end of session: 30 min walk with 75-85% HRmax, duration: 3 months	n = 31 women independent and non-demented subjects; Age: 80 - 97 y	↑BDNF, ↓depression symptoms, ↑cognitive performance, ↑muscle strength of lower limbs and aerobic condition	32
Combined aerobic and strength trainings: 20 min, 3x/week; aerobic training: 60 min, 60-80% of their age-predicted HRmax; main muscles at 95% of the 10 RM, Duration: 8 weeks	n = 16 MDD patients and physical inactive; Age: 39.31 ± 7.02 y	↑ BDNF levels, ↓depression symptoms, ↑sleep quality and cognitive function	33
Aerobic training: 15min/day on treadmill; speed at 6 km/h, duration: 28 days	n = 70 women; 35 with depression vs. non-depressed women; Age: ≥50 y	↑BDNF 35.3% in depressed and 16% from initial values in non-depressed women	34
One bout of aerobic exercise: Graded exercise test on a cycle ergometer starting at 25w with progression of 25 w every 2 min, until exhaustion	n = 30 MDD patients (n = 17 women); 23 patients with current depressive disorder; Age: 39.2 ± 11.4 y	↑ BDNF, larger BDNF increase in women with smaller number of platelets.	35
Stretching exercise: 9 sessions of stretching activity. A protocol consisting of 2-min stage with speed and grade increasing over time, Duration: 16 weeks	n = 29 sedentary adults with MDD/PDD with a current major depressive episode; Age: 18–65 y	↑BDNF at 4th, 8th and 16th week	36
Aerobic exercise: 3 sessions in the 1 st week, 2 sessions for 2 nd week, and 1 session in the 3 rd week. Duration: 12 weeks	n = 13 adolescents with depression and physically inactive; Age: 14.4-15.5 y	After 12 weeks: ↑BDNF, ↓depression symptoms, ↓CDRS-R	37
6-month home-based randomized trial of exercise vs. attention-control group, weekly progress towards the 150 min weekly exercise goal; blood take pre- and post-intervention. Duration: 6 months	n = 144 ovarian cancer survivors women who had stage I-IV ovarian cancer; Age: 57.3 ± 8.6 y	↓depression symptoms (with 18%); the exercise intervention was not associated with change in serum BDNF	38

Legend: BDNF: brain-derived neurotrophic factor; CES-D: Epidemiologic Studies Depression Scale; GDS: geriatric depression scale; HRmax: maximal heart rate; MDD: major depressive disorder; PDD: persistent depressive disorder; RM: repetition maximum; PDD: persistent depressive disorders; RUD: recurrent unipolar depression; CDRS-R score: children's depression rating scale revised; RCT: randomized controlled trial; rpts: repeats; VO₂max: maximal oxygen consumption; TAU: treatment as usual.

It should be mentioned that genetic associated studies discussed the genetic polymorphisms in genes involved in many cerebral functions (BDNF, promoter region of serotonin transporter 5-HTTLPR or 5-HTT gene linked polymorphic region), as modifiers of neuropsychiatric disorders susceptibility or other disease-related conditions. Val66Met (rs6265) single-nucleotide polymorphism in the BDNF gene exhibits one of the highest variabilities in terms of allelic distribution between populations, and a number of controversies, including small effect sizes, sampling of allele inheritance are discussed to direct future research (39,40).

Improvements in exercising mice with Parkinson's disease have been observed. Some of the candidate mechanisms are mitochondrial biogenesis, lower apoptosis rates and decreased inflammatory cytokines (15). Multiple sclerosis has also been shown to ameliorate through physical activity. One main reason of demyelination is increased BBB permeability which allows T and B cells to cross this structure. The beneficial effects of exercise include decreases in BBB permeability markers, higher hippocampus and grey matter volumes and better white matter structure (14,41).

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 (A β) 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.

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