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The Effect of Physical Activity on Cognition – Physiological Mechanisms

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REVIEW

ABSTRACT

The presumption that physical activity, i.e. exercise, as an independent and separated factor influences different aspects of cognitive mechanisms is substantially supported by the literature. The investigations of the influence of physical activity on cognitive functioning have offered several mechanisms which could explain this relationship. Physiological mechanisms including increased cerebral blood flow, changes in neurotransmitter release, structural changes in central nervous system and altered arousal levels are based on physical changes that occur in the body as a consequence of the physical activity. There is evidence that physical training selectively increases angiogenesis, synaptogenesis and neurogenesis. The role of central (BDNF) and peripheral (estrogens, corticosteroids, growth hormone, IGF-1) factors in mediation of the effects of physical exercise on brain functions, has been promoted. Also, there is convergent data on molecular and cellular level, as well as on behavioral and systemic level which support the presumption that physical activity is beneficial to cognition. These data emphasizes the importance of promotion of physical activity during the life span for the prevention of contemporary (obesity, diabetes and cardiovascular) diseases and cognitive decline in humans.

Key words: cognition, physical activity, physiology.

1. INTRODUCTION

There is a bulk of information obtained from studies, performed on humans, as well as on experimental animals, regarding the presumption that physical activity, especially aerobic training could demonstrate positive effect on many aspects of brain functions and cognition. The evidence from studies on animals have identified molecular and cellular changes that have occurred under the influence of physical training and could be related to the exerted effects of fitness on cognition. It has been proven that physical training selectively increases angiogenesis, synaptogenesis and neurogenesis (especially in gyrus dentatus in the hippocampus), as well as it initiates the up regulation of numerous neurotrophic factors in rat brain (1, 2). Nevertheless, there are numerous unanswered questions left regarding this issue. From a practical point of view there is little information on the subject of the design of an intervention which will enable an optimal effect of physical exercise on cognition and mental health. Future studies should answer questions such as when it is the best time to start the physical training, which types and which intensity of physical training are the most efficient.

2. PHYSIOLOGICAL MECHANISMS WHICH EXPLAIN THE EFFECT OF PHYSICAL TRAINING ON COGNITION

The investigations of the influence of physical activity on cognitive functioning have proposed several mechanisms which could explain this relationship (3, 4, 5, 6). Physiological mechanisms including increased cerebral blood flow, changes in neurotransmitter release, structural changes in central nervous system and altered arousal levels are based on physical changes that occur in the body as a consequence of the physical activity.

One of the fundamental physiological mechanisms that explains the influence of physical activity on cognition is the increased blood flow through the brain. Studies using contemporary imaging techniques, have confirmed that medium and high intensity physical training significantly increases the blood flow through the brain, providing increased supply of necessary nutrients. The stimulation of brain neurotransmitter release after acute bout of exercise has also been suggested by several authors. Increased levels of norepinephrine and its precursors (7, 8), epinephrine

(adrenaline A) (9) and serotonin (10, 11) have been documented. Another physiological explanation of the effects of physical activity on brain functions includes structural changes in the brain as a result of exercise. Studies on animals have shown that rats exposed to increased physical activity showed increased cerebral cortex vascularization and had shorter vascular diffusion distance compared to non-exercise rats (12).

3. THE ROLE OF BDNF ON COGNITION

Numerous investigations of brain functions on molecular level have revealed an important mechanism of the effect of physical exercise on cognition. The latest studies of the physiology of cognitive processes have discovered that BDNF (Brain Derived Neurotrophic Factor) is the key molecule engaged in learning and memory. The finding that physical exercise increases the production of this molecule seems to be very important. It has been suggested that this neurotrophic factor is responsible for neuron genesis, their survival and resistance to stress, which all together facilitate the learning process. Some researches call the BDNF, “Miracle Gro” (miracle growth factor for the brain). It has also been discovered in the hippocampus, the brain region which is directly involved in learning (13, 14). For example, the learning capacity has been connected to the effect of BDNF on synaptic plasticity, which is a potential basis of cognitive processes (15, 16). This substance can increase the learning and memory capacity of rats for a short period of time, that is only one week of running on a wheel (17). The effect of physical training on BDNF system is exerted through the functions of the intracellular signaling system, including calcium- calmodulin kinase II and mitogen activating protein kinase. They execute the final effects on the synthesis and on the function of CAMP response element binding protein (CREB). There is evidence suggesting that physical training significantly increases the levels of mitochondrial uncoupling protein 2, which is a factor of protection of the energy homeostasis exerted through the preservation of calcium homeostasis, the production of ATP and the control of free radicals.

Infusion of BDNF in humans enhances learning (18), while deficiency of BDNF causes disturbances in learning capacity. The fact that physical exercise rises BDNF suggests that physical exercise has a potential to enhance learning. In addition to the hypothesis that the increased BDNF caused by physical training is one of the key mechanisms of the positive effect of physical activity on learning, it is also possible that physical activity modulates some other factors that are involved in gaining new knowledge. Hippocampal neurogenesis which is a result of physical exercise, or placement of animals in enlarged environment (19, 20) is related to enhanced performance on spatial memory tests.

Recent genetic studies have accentuated the importance of the role of BDNF in human brain functioning. They have discovered a series of BDNF gen polymorphisms, and have determined their possible essential role in human cognition. The substitution of an amino-acid in the coding region of the BDNF gene (val/meth) results in damaged processing

and release of BDNF (21). The genetic research has shown that carriers of meth-BDNF allele have weaker memory function and abnormal hippocampal activity. These cognitive effects were revealed in a sample of healthy young subjects who had not shown any noticeable signs of cognitive or neurological abnormalities (25-45 years, 641 subjects) (22). Other studies additionally pointed out that meth-BDNF and separately BDNF polymorphism represent risk factors for Alzheimer disease (23, 24). These studies have clearly indicated that when there is a malfunction in BDNF, cognitive functions suffer long-term decline.

Recent studies have noted BDNF as a simple non-pharmacological potential factor of brain function improvement. Most recent reports confirm that regulation of BDNF protein is controlled by the expression of the BDNF gene in neurons, and the level of gene expression is modulated by a sequence of neurotransmitter interactions. Peripheral factors like blood level of circulating hormones (for example: estrogen, corticosteroids and insulin like growth factor 1) also influence BDNF and its function in the brain (25). The CNS (neurotransmitter) mechanism that is involved in the regulation of BDNF gene expression is the neuronal activity. In CNS, glutamate is the predominant excitatory neurotransmitter which promotes neuronal activity. The transmission of signals by glutamate is essential for mediation of up-regulation of BDNF levels in hippocampus. Gene regulation of BDNF is additionally sensitive to numerous other neurotransmitters which have converting effects on the modulation of glutamatergic neuronal function in hippocampus. The neurotransmitter systems: acetylcholine, GABA, serotonin and noradrenalin which act as mediators in regulation of BDNF in hippocampus related to physical activity have been investigated until now (26, 27).

4. PERIPHERAL REGULATORY MECHANISMS

In addition to the leading role of central factors in mediation of the effects of physical activity on brain function, it is necessary to point out the importance of peripheral influences. The peripheral control of the effects of physical activity on brain function involves estrogen, corticosteroids and IGF-1. These hormones control BDNF and also modulate the neurogenesis, which is an important element of the mechanism by which physical activity exerts its effect on brain function. **Estrogen:** there are several possible mechanisms which could be involved in the regulation of the effect of physical activity on BDNF expression by the estrogen. The estrogen could both have a direct molecular effect on BDNF gene expression and an indirect one through stimulation of physical activity. Some beneficial effects of estrogen on the brain could be mediated by regulation of the expression of BDNF gene, aiming to increase the availability of this trophic factor. In women the presence of estrogen has proved to be necessary for the regulation of BDNF by physical activity (28). The physical activity has failed to increase the levels of BDNF mRNA in rat hippocampus, after two months of estrogen deprivation. Though, when physical activity is combined with estrogen substitution, the level of BDNF is significantly increased compared to solitary

estrogen substitution. The presence of estrogen in women could be a permissive factor necessary for the regulation of BDNF with physical activity. It could be pointed out that the level of voluntary physical activity depends on estrogen status. In absence of estrogen, the women are less active, while estrogen substitution returns the physical activity on normal levels (29).

5. CORTICOSTEROIDS/STRESS

Represent another neuro-endocrinological mechanism which could influence the level of BDNF and may modulate the effect of physical exercise on the brain. These hormones, which are released by the adrenal gland as an answer to stressful events, can enter the brain and can bind to specific glucocorticoid receptors in order to perform a modification of gene expression. The concentration of glucocorticoid receptors in hippocampus makes this brain region particularly sensitive to the effect of stress and to glucocorticoids. Physical exercise is considered to have protective features against the negative effects of stress exposure. One of the mechanisms by which this protective features could be mediated may be through the regulation of BDNF—increased levels of glucocorticoids reduce hippocampal BDNF mRNA and protein expression (30). Physical activity may neutralize stress and may confront its negative effect on two levels: behavioral and neurochemical. BDNF has been considered to have a key role in this protective effect of exercise against the consequences of stress (31).

6. GROWTH HORMONE (GH) AND INSULIN DERIVED GROWTH FACTOR (IGF-1)

Another peripheral mechanism which could mediate the effects of exercise on BDNF in the brain is the GH/IGF-1 axis. Exercise increases circulating GH which is the main stimulator of IGF-1 production. Major quantity of circulating IGF-1 is produced in the liver, but many other tissues, including the brain, can also produce IGF-1. IGF-1 may have multiple biological effects on processes like neurogenesis, learning, cognition, amyloid processing and other systematic effects (30,31). IGF-1 and BDNF act through different signal pathways. It has been supposed that in order to promote the health of the brain and its plasticity these factors could act separately and also in a synergistic way.

Basic scientific research on animal models provide documented evidence of the positive effects of physical activity on brain health as well as its positive effects on cognition and learning which could lead to more efficient adaptation. Physical activity induces BDNF mRNA production in glutamate neurons in hippocampus and some other brain regions (32). In current literature on research on humans it has been strongly suggested that BDNF influences cognitive functions, while BDNF polymorphism (related to protein processing and release) in animals has been related with reduced cognitive function. This has been a very important discovery which suggests that animal studies could be translated into human studies. In human research there has been a small number of clinical studies with placebo control related to BDNF and cognition. Most of the studies

are descriptive, based on retrospective analyzes. Never the less, the existing literature suggests that physical exercise i.e. increased aerobic fitness is one of the variables that consistently appears as a predictor of higher cognitive functions as well as of lower depressiveness in humans (21, 22).

Long term physical exercise increases the expression of neurotrophic factors. It may also have a neurogenerative and neuroprotective effect in the brain, which could be exerted by stimulation of new cells growth and development and by the protection of neurons from ischemic damages (1).

Influence of other lifestyle factors on cognition

Some interesting and intriguing studies have been conducted with an aim to determine whether physical activity interacts with other lifestyle factors during its influence on cognition and brain health. For example, Molten and all (32) have investigated the interaction between the effect of diet and exercise on molecular level, through their effects on BDNF and learning. They reported that physical exercise diminishes the negative effects of diet rich with lipids on BDNF and learning. In another study, the effects of physical activity on hippocampal neurogenesis have substantially been reduced and postponed in a group of socially isolated rodents, compared to those animals which were kept in group (33). These results suggest that further research on the interaction between social factors and physical activity and their effect on brain function and cognition in humans should be conducted. In current literature, there are several epidemiological prospective studies on influence of different lifestyle factors and physical exercise on cognition and neurodegenerative disorders. Carp and al, have reported that cognitive, physical and social activities reduced the risk of dementia in 778 adult subjects during three year period. Subjects with highest scores on all three mentioned variables showed biggest benefit (34).

Despite the research reviewed above, there are several gaps in our understanding of the relation of physical activity and cognitive functions. To date, the majority of research studies assessing this relationship have been cross-sectional in nature. Longitudinal randomized controlled trials are necessary to elucidate causal influence between physical activity, brain structure and brain processes. Research is needed to understand the optimal physical activity criteria that target cognitive and brain health: the frequency, the duration, the intensity and the mode of physical activity. While some understanding of the mechanisms supporting exercise-induced changes in cognition is provided through animals models, many molecular and cellular details in the human brain still remain to be discovered.

7. CONCLUSION

The number of studies which indicate the beneficial effects of physical activity on different cognitive functions is constantly growing (35). These studies suggest that physical activity improves executive functions (36, 37, 38), attention (39, 40), cognitive speed (40, 41) and episodic memory (42). Cardiovascular training has been related to improvement of cognitive functions in aging people (43). Sedentary subjects who participated in a protocol with cardio aerobic exercise had significant benefit in the volume of both grey and white matter in several brain regions, such as prefrontal

and temporal cortex (44). It has been suggested that those brain regions undergo negative structural changes related to aging. These studies are compatible with reports of neuronal proliferation and survival, growth of capillary vessels and an increased number of dendrite extensions in certain brain structures, which could be related to beneficial effects of physical exercise on cognition in humans and animals (13, 20, 45, 53).

It has been suggested that aerobic exercise is potentially important not only for stopping the neuronal decline caused by aging process, but also is a potentially efficient mechanism for roll-back of some normal functions that have been disturbed due to reductions in brain structure related to aging (54-60).

Physical activity has been suggested to be a useful tool for the reduction of the risk for cognitive impairment related to aging. Future randomized studies should investigate different levels of physical activity and its type, that could be recommended with an aim to prevent or postpone cognitive decline.

There is convergent evidence on molecular and cellular level, also on behavioral and systemic levels, which emphasizes the importance of promotion of physical activity during the life span for the prevention of contemporary (obesity, diabetes and cardiovascular) diseases and cognitive and neurologic decline in people. In addition to its role in health promotion, physical activity could also reduce the economic burden to society related to chronic degenerative diseases.

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