NEUROPROTECTIVE MECHANISMS OF PHYSICAL ACTIVITY

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ABSTRACT

It is known that the adaptive capabilities of the brain are not unlimited and deteriorate over time. It is a proven fact that aging is one of the main risk factors for the occurrence of neurodegenerative disorders, mainly due to poorer immune protection and recovery of the body. Therefore, scientists have recently been paying attention to the search for additional methods of management of neurodegenerative pathologies for their more effective prevention. Among the identified methods, special attention is paid to physical activity, the results of which investigation indicate a powerful neuroprotective effect, however, the mechanisms of this phenomenon have not yet been conclusively proven. Therefore, in this systematic review, the main neuroprotective mechanisms of exercise were described and demonstrated using the methods of analysis and systematization of literature sources from PubMed, Web of Science, Elsevier, and Google Scholar databases. As a result of the study, it was established that a significant protective effect on the nervous system is achieved thanks to neuroendocrine regulation due to the influence on the hypothalamic-pituitary-adrenal axis. Another factor is the development of stress due to physical exertion, although the mechanisms of this phenomenon are still a subject of debate among scientists. However, it was proved that the consequence of such influence is the optimization of the work of neurotransmitters, in particular, in the locus coeruleus, as well as the activation of the antioxidant system, which allows to disrupt the number of free radicals in the brain structures. Relatively new is the role of moderate-intensity exercise in increasing the expression of neurotrophins – key factors of neuroplasticity, in particular BDNF, IGF-1, NGF and VEGF, which expands the possibilities of potential effects on the brain and its neuroprotective properties. The obtained results allow the use of physical activity as an additional therapy in the treatment and prevention of neurodegenerative pathologies, however, further practical research is needed to find a specific algorithm and schedule of classes with high application efficiency.

Keywords: *physical activity, neurotrophins, neuroprotection, brain-derived neurotrophic factor, antioxidants.*

Introduction

Neuroprotection is the prevention of cell death by necrosis or apoptosis due to the improvement of its adaptation mechanisms to changes in the external or internal environment. This term is often used to describe neuroplasticity – the ability of nervous structures to change under the influence of stimuli, which also leads to an increase in the adaptive capabilities of the brain and the body as a whole [1]. The concept of neuroprotection has attracted the attention of scientists as one of the points of influence in the treatment of neurological and psychoneurological diseases, including neurodegenerative ones [2]. It has been found that over time the body's adaptive capabilities are lost, and aging is one of the main risk factors in the occurrence of Alzheimer's and Parkinson's diseases, not to mention dementia disorders and psycho-organic syndrome [3]. For example, according to 2019 statistics, about 50 million people in the world suffer from dementia, while every year this indicator increases by 10 million new cases [4]. In Ukraine, the share of people of retirement age is approximately 25% of the population, with a tendency for this indicator to increase annually. According to Fedotova M. S. et al. (2021) as of 2021, the average prevalence rate of dementia in Ukraine was 99.72 persons per 100,000 population,

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and Alzheimer's disease was 5.34 persons per 100,000 population [5].

In addition, although the exact influence of stress factors and war on the susceptibility to the development of dementing disorders is not proven, studies by foreign scientists on the impact of war on the structure and function of the brain indicate a potential increase in the proportion of dementing disorders as a result of a full-scale invasion [6]. A separate topic is the development of various types of neurodegeneration in military personnel as a result of injuries to the central and peripheral nervous systems, which also significantly increases the share of neurodegenerative disorders in the structure of nervous system lesions and increases the urgency of finding and implementing the latest methods of treatment and rehabilitation of patients with these pathologies [7]. The algorithm of prevention and treatment of such disorders includes operative, medicinal and non-medicinal methods. Among the latter, physical activity has long been considered one of the most effective methods of managing dementia and post-traumatic consequences, and early activation has become a routine practice in the work of a doctor of physical rehabilitation medicine [8; 9].

On the basis of previous studies, it was found that physical activity (PA) has a beneficial effect on human cognitive functions and its neuroprotective capabilities [10; 11]. For example, it has been proven that the regular use of PA in the treatment of neurological diseases was associated with better blood supply to the affected areas of the brain and hippocampus, compared to untrained individuals [10]. At the molecular level, this was accompanied by an increase in superoxide dismutase (SOD), endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF), neurotrophins and a decrease in the production of harmful free radicals in the hippocampus region of the brain, which are mainly involved in memory [11]. Studying the mechanisms of PA neuroprotection will improve the possibilities of rehabilitation of patients with neurodegenerative disorders and become an impetus for creating more optimal methods of influencing the restoration of the function of nervous structures.

The Purpose of the work was to analyze and systematize the currently known neuroprotective mechanisms of exercise for their further use in future research.

A systematic literature review was conducted in March-June 2023. All literature sources were analyzed according to PRISMA recommendations [12]. Sources from four databases (PubMed, Web of Science, Elsevier, and Google Scholar) were used to search for studies by keywords.

The inclusion criteria were:

• original studies and meta-analyses on the impact of physical activity on cognitive functions and/or neuroregeneration;

• review works describing possible neuroprotective mechanisms;

• research describing/studying the impact of physical activity on the immune system and antioxidant and neurotrophin systems

• works on the analysis of methods of treatment of neurodegenerative disorders.

Preclinical and in vitro studies, case series, and clinical cases were excluded from the review. Scientific works based on the use of questionnaires and questionnaires without further statistical data processing and all works that did not meet the inclusion criteria were also excluded. All retrieved publications were further screened and any studies not relevant to the topic were excluded. Among the reviewed articles, 43 works were selected for further analysis and inclusion in a systematic review.

Results and Discussion

According to the American College of Sports Medicine (ACSM), physical activity significantly reduces the frequency of diagnosis of metabolic syndrome (hypertensive disease, type II diabetes and obesity) and bone and joint disorders ($p<0.05$) [13]. In addition, statistical data indicate a 20–30% reduction in the risk of ischemic stroke and a 10–20% risk of cardiovascular diseases, regardless of the patient's gender [11].

A similar effect is achieved thanks to a number of mechanisms. For example, systematic exercise leads to hypertrophy and proliferation of myocardial cardiomyocytes with the development of an "adapted" heart, leading to optimization of ATP utilization in cardiomyocytes, increased cardiac output, and improved oxygen delivery to tissues, including the brain. In addition, at the molecular level, PA leads to an increase in the concentration of C-type natriuretic peptide and endothelial natriuretic peptide, whose positive effect in the prevention of heart failure and other cardiovascular diseases has already been sufficiently studied [15].

With this in mind, the ACSM today recommends a program that includes aerobic, strength, flexibility, and balance training for the elderly and patients ≥50 years of age with chronic disorders. Aerobic training should be performed ≥5 days per week for 30 minutes of moderate intensity or ≥3

days per week for 20 minutes of high intensity [13]. However, is such a schedule of physical activity appropriate for neurological pathologies?

It is known that the etiology of neurodegenerative disorders is characterized by its multifactorial nature [16; 17]. Numerous endogenous (age, gender, genetic polymorphisms) and exogenous (smoking, obesity, hypodynamia) factors can both contribute to the development of the disease and prevent it [18]. It was found that among non-medicinal agents, physical exercises have the most pleiotropic effect, due to their influence on the cardiovascular, nervous, and immune systems at both the cellular and molecular levels [9].

The influence of physical activity on neurodegenerative and other neurological disorders has been studied for a long time [9–11]. During this period, several possible points of influence of PA on the brain were identified, which is demonstrated in more detail in the figure (*Fig. 1*). For example, improving the rheological properties of blood and accelerating blood flow as a result of systematic physical activity, which contributes to reducing the risk of acute cerebral blood circulation disorders, was studied as early as the 20th century [19]. At the same time, relatively recent works by Amidfar M. et al. (2020) and Baranowski B.J. et al. (2020), which indicate an increase in the concentration of neurotrophins, in particular BDNF, and antioxidants in the intercellular spaces of the brain, which potentially improves the adaptive capabilities of the brain and reduces the risk of developing Alzheimer's and Parkinson's diseases [20; 21].

Therefore, based on the available modern data, scientists put forward a number of hypotheses regarding the possible mechanisms of the neuroprotective function of physical activity, which are described below.

Neuroendocrine regulation

According to the research of Hackney A.C. (2006), with sufficient intensity and duration of physical activity, they can play the role of an activator of the neuroendocrine system and its adaptation to stress. In response to submaximal loads, the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system are activated, resulting in the release of hormones from the adrenal glands (cortisol, adrenaline) and the hypothalamus (vasopressin, corticolipin, and beta-endorphin), which contributes to greater utilization of metabolic substrates. The result of this is improved blood circulation, optimization of vascular tone and better delivery of oxygen to tissues [22].

At the same time, physical activity has an effect on neurotransmitters, namely on the central dopaminergic, serotonergic and noradrenergic systems. Tai F. et al. (2020) found that systematic

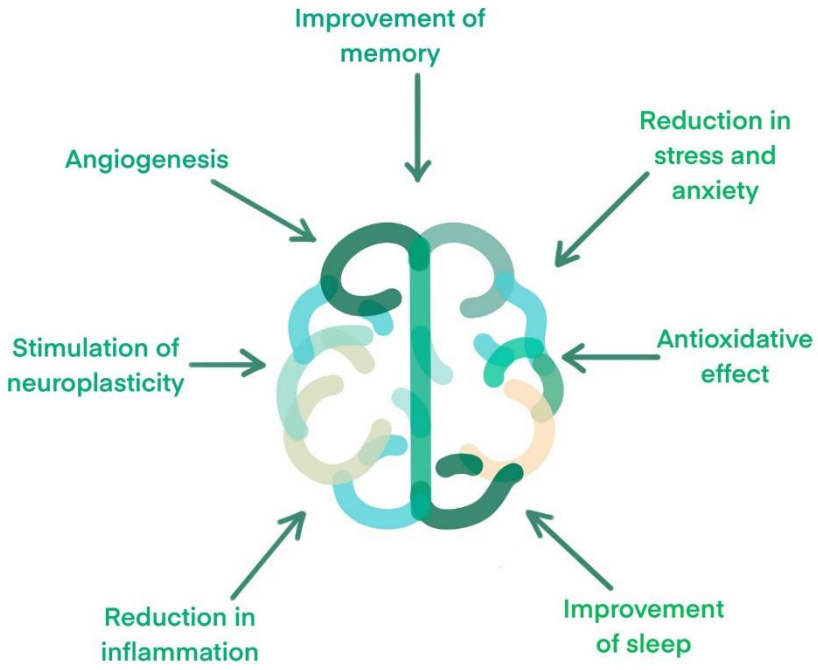

Fig. 1. General effects of physical activity on the human brain.

physical activity significantly increases the release of mediators in these systems and the extracellular concentration of dopamine, norepinephrine, serotonin, and neurotrophins, which is primarily explained by an increase in serum calcium levels in the blood as a result of exercise [23].

Neural adaptation in response to uncontrolled stress is associated with the effect on neurotransmitter systems. Sciolino N.R. et al. (2012) found that neuroprotection occurs through the expression of galanin in the locus coeruleus, which hyperpolarizes noradrenergic neurons, thereby reducing the excessive release of norepinephrine that causes feelings of fear and anxiety. Since the main source of the mediator for the frontal cortex and the amygdala is the locus coeruleus, the inhibitory effect of PA on this area of the brain leads to the optimization of norepinephrine levels and the prevention of anxiety-like behavior [24]. In addition, norepinephrine in normal concentrations is involved in memory consolidation and recovery, which especially plays a role in the case of patients prone to neurodegenerative disorders [25].

The influence of PA on the serotonergic system depends on the region of the brain and the intensity of training. For example, running at a moderate pace for a month reduced 5-HT levels in the hippocampus, while 7 days of high-intensity training led to increased levels of the mediator. This indicates the potential antidepressant and anxiolytic effects of exercise, which was also found in studies by Mahalakshmi B. et al. (2020) [9].

Immune-inflammatory regulation

It is known that sharp physical activity is accompanied by an increase in the levels of pro-inflammatory cytokines, which is explained by the reaction to a sudden stress factor [26]. However, Flynn M.G. et al. (2007) found that regular physical exercises of moderate activity, on the contrary, are associated with a decrease in the levels of the main markers of the inflammatory process in the body, which is explained by the immunomodulatory effect of PA [27].

For example, Koh Y. et al. (2018) in their study found that daily gymnastics of moderate and low intensity led to a decrease in the expression of cell adhesion molecules - one of the key factors in "luring" immune cells to the focus of inflammation. At the same time, high-intensity exercises, on the contrary, increased the intensity of these markers. The mechanism of this phenomenon consists in the epigenetic regulation of the transcription of genes responsible for the synthesis of cell adhesion molecules and inflammatory cytokines, as well as the effect of physical activity on the antioxidant system [28].

Thus, the systemic immunomodulatory effect of exercise is the result of a combination of regulation of the activity of pro-inflammatory cells, neuroendocrine effects, activation of metabolism and reduction of visceral fat mass, and an increase in the levels of antioxidants in the blood.

Optimizing the function of antioxidant systems

It is known that the brain accounts for approximately 20% of the total use of oxygen and glucose by the body [29]. Accordingly, the degree of generation of free radicals in the brain is also significant, which is fully compensated by the work of antioxidants (enzymes and other substances capable of neutralizing free forms of oxygen). However, with age, their effect decreases and the level of oxidative damage to the nervous system increases, which is currently considered one of the main elements in the pathophysiology of neurodegenerative diseases [30].

In recent years, a number of studies have demonstrated an inverse correlation between different degrees of physical activity and the state of oxidative stress in the body. Thus, according to research of Li T. et al. (2015) high-intensity training leads to temporary stress in the body and an initial increase in the level of oxidative stress, since muscle cells are the main source of free radicals during exercise. However, it promotes the activation of compensatory systems and increases the expression of antioxidants, in particular catalase, glutathione peroxidase and superoxide dismutase, which are present in the body for a long time and contribute to the reduction of oxidative stress not only in muscles, but also in other systems, in particular, the brain [31]. This is confirmed by the work of Bojarczuk A. et al. (2022), who found a statistically significant difference in a higher level of antioxidants in athletes compared to untrained individuals [32].

However, the concept of using high-intensity loads is not appropriate in the elderly, who are the main risk group for the occurrence of neurodegenerative disorders. In this case, low-intensity exercises with their systematic application can also be useful, as according to the same study by Li. T. et al. (2015) leads to a compensatory increase in antioxidant levels, however, more evenly than during high-intensity exercise [31]. The effectiveness of this type of load is explained by the theory of hormesis, highlighted in the work of Radak Z. et al. (2008), which is graphically demonstrated in the figure (*Fig. 2*) [33].

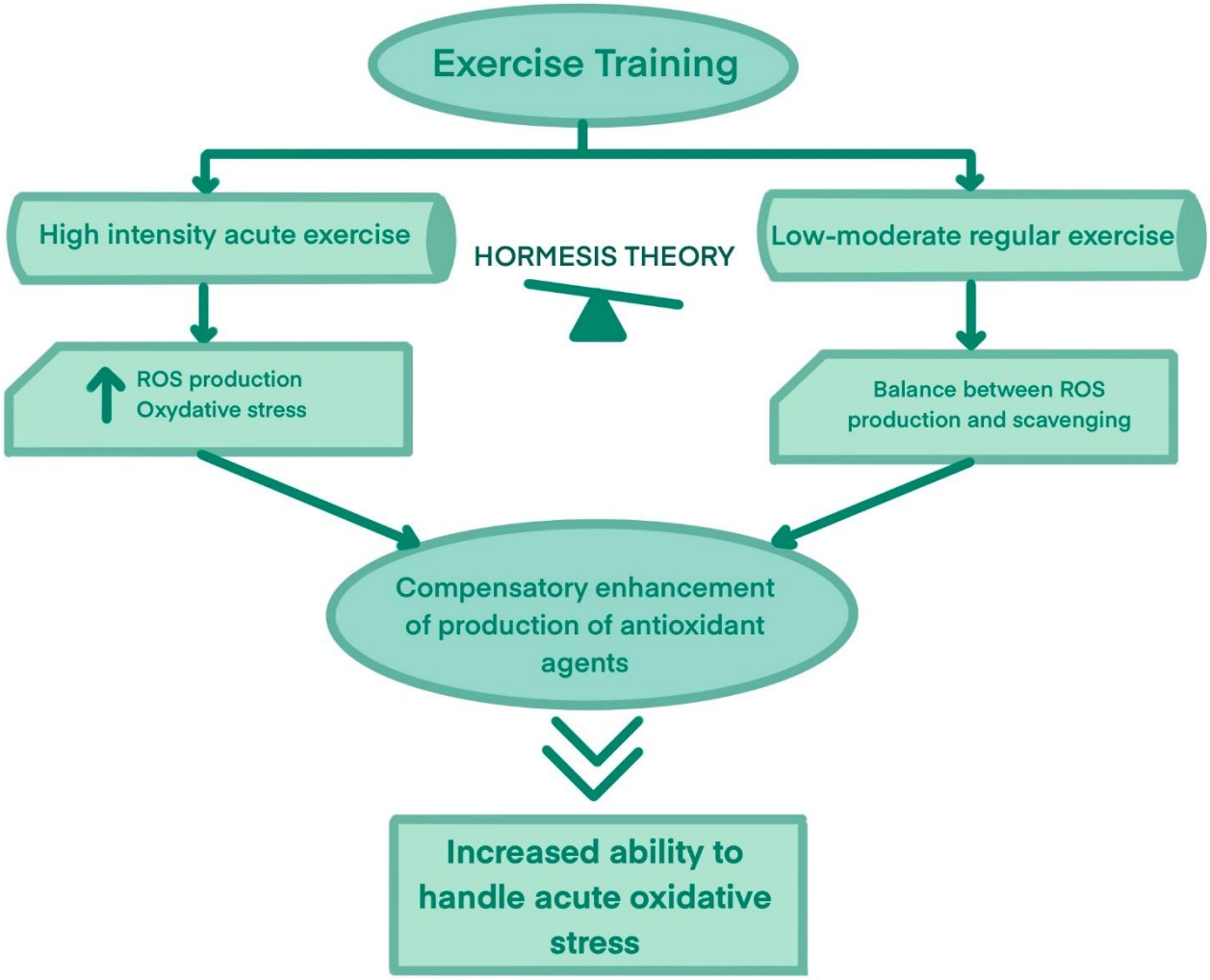

Fig. 2. Schematic representation of the theory of hormesis in the context of physical activity [33].

According to the work of scientists, a low dose of any agent that is harmful at high altitudes causes an adaptive beneficial effect on the cell or organism. In the context of physical activity, their low intensity will lead to a gradual increase in antioxidants as a compensatory response to moderate physical stress, without the occurrence of oxidative stress, while high intensity, on the contrary, will promote its development, resulting in the activation of antioxidants [33].

Thus, it is more appropriate to use low-intensity exercises in the elderly, taking into account their comorbidity, while in young patients with an organism adapted to loads, it will be appropriate to use high-intensity exercises in combination with low-intensity ones for better adaptation of the body.

Influence on neuroplasticity

Neuroplasticity is the ability of the nervous system to adapt in response to endo- and exogenous stimuli through structural and functional restructuring.

Relatively recently, it was discovered that in response to physical activity, proteins-neurotrophins are released, the main effect of which is not carried out by neural networks of the brain. Basically, they have neurotrophic activity (stimulate synaptogenesis, growth and differentiation of new neurons), which significantly increases the neuroprotective potential of a specific individual. Their effect on the brain was primarily detected after an ischemic stroke, as it was found that after ischemic stroke, the concentration of neurotrophic factors such as BDNF and IGF-1, as well as the substance VEGF, which is one of the main proangiogenic factors, in the impression zone increases significantly [34]. Recent studies also indicated their role in the prevention of neurodegenerative disorders, in particular, Alzheimer's disease and other types of dementia [35–41].

In particular, Kuga G.K. et al. (2017) found that under physiological conditions, BDNF, IGF-1, and VEGF transduce intracellular signals in hippocampal neurons to maintain their integrity and function. However, with mutations in the genes encoding the specified factors, the risk of dementia disorders increases significantly, which was demonstrated in [35]. In addition, Lovatel G. A. et al. (2013) found that IGF-1 dysfunction leads to a decrease in aversive memory and an increase in inflammatory markers, in particular, interleukins 1, 4 and tumor necrosis factor [36].

At the same time, it was established that the use of physical exercises reliably improves the neuroprotective capabilities of the body [36; 37]. For example, in the same study Lovatel G. A. et al. (2013), the use of daily running for 20 minutes for a period of 2 weeks reduced the level of pro-inflammatory markers and increased IGF-1 signaling in hippocampal neurons. At the same time, Lin T. W. et al. (2015) found that 10 weeks of regular treadmill training can delay the development of Alzheimer's disease. This is because exercise promoted synaptogenesis, specifically increasing the dendritic chain of CA1 and CA3 neurons, which led to improved memory associated with the amygdala and hippocampus. At the same time, the scientists found an increase in BDNF/TrkB signaling molecules (p-AKT, p-PKC and p-TrkB) in the hippocampus and amygdala, as well as a decrease in amyloid-β levels in these areas, which further indicates a positive neuroprotective effect of neurotrophic factors [37].

In addition to BDNF and IGF-1, exercise also regulates the expression of VEGF, which is responsible for endothelial cell proliferation and angiogenesis, which is critically necessary for neurotrophic and neuroprotective processes in the brain, as revealed by Ben-Zeev T. et al. (2022) Scientists found that exercise-induced increases in VEGF concentrations led to improved neurogenesis and microangiogenesis, as well as increased levels of ciliary neurotrophic factor neurotrophin (CNTF) fibroblast growth factor 21 (FGF21), whose effects on the brain are currently poorly understood [38] . In addition, studies have been described on the neuroprotective effect of neuron growth factor (NGF) and neurotrophin-4, which contribute to the induction of growth and remodeling of the innervation of motoneurons of the spinal cord and brain, however, their proof of their role in neuroprotection and the connection with physical activity is still not sufficiently studied, which can be a topic for further research [39–41].

A separate neuroprotective mechanism of exercise is its effect on autophagy – the breakdown and circulation of the body's own substances, mediated by lysosomes. Physiologically, this process is necessary for the destruction of damaged intracellular components and the use of the obtained substrate for obtaining energy or the synthesis of new structures [42]. Thanks to the work of Rocchi A. et al. (2017) found that defects in the normal course of autophagy are associated with stress sensitivity and neurodegenerative disorders. For example, a mutation in the Beclin 1/Becn 1 gene is accompanied by a significant increase in β-amyloid in brain cells, which physiologically is also an autophagic substrate. At the same time, researchers found that voluntary physical activity of moderate intensity is a physiological inducer of autophagy, which is accompanied by a protective effect similar to the work of Beclin 1/Becn 1 regarding the preservation of memory function and the onset of dementia, however, the exact mechanism of this phenomenon is still not well understood [43].

Thus, due to the effect of physical activity on the system of neurotrophins and autophagy, a pronounced neuroprotective effect is potentially achieved, which can reduce the tendency to develop neurodegenerative and other psycho-neurological diseases.

Conclusions

Our findings indicate that regular physical activity of moderate and active intensity reliably leads to the improvement of the cognitive skills of athletes and their adaptability to the occurrence of neurodegenerative disorders. In particular, it was found that due to physical activity neuromuscular transmission, synthesis of neurotrophins, autophagy is optimized, the expression of serotonin, dopamine and norepinephrine mediators improves, which leads to a reduction in the risk of neurodegeneration, as well as a number of other neuropsychological pathologies, for example, depression and anxiety disorders. The obtained results allow the use of physical activity as an additional therapy in the treatment and prevention of neurodegenerative pathologies, however, further practical research is needed to find a specific algorithm and schedule of classes with high application efficiency.

DECLARATIONS:

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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