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The Importance of Physical Activity in the Treatment of Neurodegenerative and Mental Diseases

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ABSTRACT

The article aims at drawing attention to the possibility of utilizing physical activity in treatment of neurodegenerative illnesses such as Parkinson's, Alzheimer's, multiple sclerosis, dementia and mental disorders, particularly depression and schizophrenia. On the basis of an analysis of the results of research on the effects of physical activity on secretion of neurotrophins, the author present the role of physical exercises in increasing their levels as well as in stimulation of cognitive processes and using them in treatment of neurodegenerative and mental illnesses. The research indicates that physical activity, appropriately dosed in case of various illnesses may be effective, sometimes to a degree similar to pharmaceuticals and in some cases even more effective. The author point out the types of exercises utilized in treatment of neurodegenerative and mental illnesses as well as the possibility of adjusting them to the psychophysical capabilities of the ones exercising. Next, the authors briefly characterize neurotrophins most commonly present in the human body and their role in stabilizing and treating neurodegenerative and mental illnesses and also present secretory functions of muscles during their activity. The concluding part of the article presents factors that stimulate secretion of neurotrophins including the BDNF as well as the types of physical exercises that can be utilized in rehabilitation of adults.

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Introduction

Theories related to the causes of mental and neurological illnesses change along with the publications of consecutive research results. On the turn of the 20th and the 21st century there was much research on the influence of neurotrophic factors on the emergence of numerous mental, neurological and somatic illnesses. A low level of this protein results in lower nutrition of nerve cells, their lower neurogenesis and hyperplasia of neurits eventually leading to a lower number of neural connections. Therefore, there are research results indicating that one of the causes of mental and neurodegenerative illnesses is a lower level of neurotrophic factors including the brain-derived neutotrophic factor in the nervous system and in blood.

Hence started the search for optimal methods of increasing the level of these proteins in the human body. One of the proposed methods was to directly administer neurotrophins in the area of damaged nerves or to implant materials gradually releasing this neurotrophin. The results however, are not satisfactory. Another method, a more natural one, is to introduce physical activity for the patients, adequately selected and optimally intensified. The research on the effects of physical activity in neurodegenerative and mental illnesses has been conducted for a relatively short period of time and their results are promising. It has also been recently discovered that when skeletal muscles contract, myokines secrete, very important proteins having significant effect on the body. Therefore, physical activity might be a valid supplementation of pharmacological treatment.

Neurotrophins and their Types

Neurotrophic factors (neurotrophins) are proteins which feed the central and the peripheral nervous system, cooperate with cell receptors p75NTS and Trk-B and allow proliferation as well as cell differentiation. These important chemical substances stimulate and regulate neurogenesis, axons growth and continued existence, take part in creating synapses both in prenatal and postnatal life [1]. Currently there are many neurotrophins classified and there are new ones being discovered constantly. However, according to the frequency of their presence, there are three groups of neurotrophic factors:

* **Group I** – Classic Neurotrophins which Include:
- **Nerve growth factor (NGF)**,
- **BDNF**,
- **Neurotrophin 3 (NT-3)**,
- **Neurotrophin4 (NT-4)**.

* **Group 2** –Ligands of the Glialcellline-Derivedneurotrophicfactor (GDNF)
* **Group 3** –Neuropoetic Cytokines.

Group I neurotrophins exhibit multidirectional effect on the nervous system as well as other tissues and glands. The nerve growth factor is the best known neurotrophin. It induces differentiation and regulates the longevity of cholinergic neurons of the septum, striate body and the multicellular basal ganglia. It affects Schwann's cells and fibroblasts, increases synthesis and metabolism of acetylcholine and performs numerous other tasks in the central and the peripheral nervous system. The highest density

of that factor is present in the hippocampus. The brain-derived neurotrophic growth factor is the second discovered neurotrophin which is synthesized in sensory neurons. Together with the NGF it acts as apical meristems of neurits in sympathetic ganglions and supervises correct path of a nerve to its destination. BDNF together with neurotrophin NT-3 exhibits neuroregenerative effects, takes part in synaptogenesis, raises serotonin level and affects functions of serotoninergic and glutamatergic neurons of the central nervous system (CNS) and also increases the level of noradrenaline in tissues. Neurotrophin NT-4 together with BDNF stimulates granular cells in the cerebellum and dopaminergic neurons of the midbrain as well as cells of the vestibular ganglion. The BDNF alone has numerous functions, among others it trophically affects the eye retina and its function involving creation of dendrites and axons [1,2].

Besides the nervous system, BDNF is also present in the heart, skeletal muscles, smooth muscle cells, lungs, blood platelets and fibroblasts. It contributes to the development of stem cells (later on, these form the eventual body cells) and their transformation into their final forms. Together with the NGF it increases the longevity of sensory neurons in the spinal cord. Neurotrophins have vast significance in slowing down the aging processes of the brain, in repair processes of the nervous system in various neurological deficits also in mental illnesses. Releasing BDNF activates a series of genes which develop new cells and paths in the brain. Thanks to high quality of BDNF, learning is faster, aging processes are slower and the memory works better. Each of the abovementioned neurotrophins has slightly different features and affects nerve cells in a different way, but all of them have similar structure [3].

Group II consists of ligands of the glialcellline-derived neurotrophic factor (GDNF) produced by glial cells. It is responsible for keeping the dopaminergic neurons alive and prevents apoptosis of motor neurons, regulates the development of spermatogenesis and wound healing, also nourishes nerve cells.The GDNF was discovered relatively late – in 1991 and research on its effects on various systems are still being conducted.

Group III are neuropoetic cytokines. They include i.a.: IL-6, the factor halting leukaemia, ciliary neurotrophic factor which is induced after a nerve has been damaged in order to perform its regeneration and repair. The tasks of this group of substances vary but usually involve neuroprotective and anti-flammatory functions.

Apart from the abovementioned neurotrophic factors, there are many others and new ones are still being discovered. A theoretical analysis of the literature and research results indicates that they are vital for a human being to function correctly in every mental and physical aspect [2].

Physical Activity as an Important Factor Supporting Secretion of Neurotrophins

Physical activity is every movement which engages skeletal muscles which results in energy cost and significantly involves the work of skeletal muscles, increases heart rate and the number of breaths and forces the person exercising to make an effort.

A meta-analysis of 35 selected research results indicates a significance of physical activity in achieving an improvement of memory, learning, better general mental and physical sensation for people of all ages and particularly for the elderly. Numerous research indicate a possibility of utilizing physical exercises in treating mental and neurological disorders such as: schizophrenia, depression, cyclophrenia or Alzheimer's, Parkinson's as well as other neurodegenerative illnesses [2,4-6].

Preliminary research was conducted on animal models and proved that intensive physical activity increases expression of the BDNF gene. The mice participating in the experiment and running a treadmill learnt their way in the maze faster and remembered it better in comparison to the mice which had restricted movement and did not perform the activity. The experimental group exhibited increased neurogenesis and proliferation of nerve cells [7]. The next research we want to mention also indicates a significance of physical activity in stimulation of cognitive functions. In one of the research experiments by three groups were evaluated [8]. The people in the first two groups suffered from schizophrenia, the third group consisted of healthy people. The first group exercised on a cycloergometerfor three months, the second group played table football and the third went on walks. The participants from the first group achieved an improvement of short-term memory of 34%, from the second – 28% and the third – 17% in relation to the preliminary evaluation. The first group achieved the best results in the range of short-term memory improvement and was also determined to have the highest increase in the size of the hippocampus, the second group was at the second position, and the third group in this regard achieved poorer results, but still noting improvement.

Research into the effects of physical activity on cognitive processes proved that it is crucial how long the exercises are performed (a minimum of 3 months), their type and intensity. While researching 120 elderly people aged 60 and above it was observed that after a physical exercise training lasting 3 months the participants exhibited an increase of blood perfusion in brain areas that are responsible for cognitive functions and in increase of the presence of BDNF in blood serum. In post-tests these people achieved results indicating an improvement of memory, learning, better general sensation and feeling of increased energy as well as will to act [5].

Other research also show that regular exercise, in this case aerobic (such as: fast walks, Nordic walking, cycling), improve thinking, declarative and spatial memory, information processing speed, spatial orientation, improve general sensation and self-esteem and, what's very important, improve stress-resistance. Oxygen exercises, those which oxygenate the whole body while they're conducted, are also a strong anti-depressant and euphoric factor [9].

Research indicate that people who participated in experiments related to the effects of physical activity on brain functioning and cognitive processes noted increased size of the hippocampus, the frontal lobes and to a lesser degree – temporal lobes, and also an increased size of the corpus callosum. In these areas there was a growth of grey and white matter and an increase of neurotransmitters production, neurogenesis and the number of neural connections and the blood had an increased level of BDNF. Apart from the benefits for the central and the peripheral nervous systems, there was an increase of muscle strength, growth of capillaries which resulted in better blood supply for the brain and the whole body and facilitated the process of enzyme secretion [9-11].

The results of these research as well as others are important since they can help design optimal programmes for treating mental and neurological illnesses, taking into account inclusion of programmes involving physical activity with adequate intensity

and selection of exercises.

The Secretory Function of Skeletal Muscles while Conducting Physical Exercises

In the last dozen of years, research have proven that skeletal muscles also perform secretory functions, as while they contract, numerous substances are produced, including proteins called myokine being part of the cytokines group. Myokines have autocrine, paracrine and endocrine effects, which means that:

- Autocrine Effects – Occurs when a cell synthesizes a hormone which affects the cell itself;
- Paracrine Effects – The synthesized hormone locally affects neighbouring cells;
- Endocrine Effects – The hormone is released into the blood and affects distant body organs.

Therefore, they affect the body metabolism and the communication among tissues. Secretion of myokines depends on muscle contraction. Contracting muscles also produce myonectin, myostatin, vascular endothelium growth factor, irisin and other substances. Myokine receptors are located in muscle, fat, liver, pancreas, bone, heart, resistance and brain cells [12,13].

Due to a large number of myokines, they perform numerous functions. Above all, they participate in metabolic changes during and after physical activity. They also participate in regenerating and repairing various tissues, maintaining the body's healthy functioning, strengthening the immunity system and cell signalling, expression and differentiation of cells.

Myostatin is the main regulator of muscle development. It acts locally and globally. Its expression improves incorrect carbohydrate and insulin-resistant economy. A suitable level of its concentration affects fat content and improves glucose metabolism. Hence, among others, physical exercises are utilized in treating obesity and diabetes [14].

Irisine (Ir) is a not well-known myokine discovered in 2008. Quoting "…The name of irisine was derived from the name of the goddess Iris from Greek mythology, who performed the function of the Olympian gods' emissary [14]. She did not perform the gods' order, but only relayed them. She also had the ability to form a rainbow connecting The Sky and The Earth which symbolized the bond between them. Irisine is released as a result of physical exercises of skeletal muscles and is a substance quite significantly affecting energy metabolism, which results in decreasing body mass, better glucose tolerance and decrease of insulin-resistance as well as an increased regeneration of pancreas cells". Hence, the obtained results give hope for the possibility of using irisine in treating diabetes. The details of the mechanic of secretion and capture by the receptors is not well-known, it seems variable, dependent on the training level of a given person. This protein was also found in Purkinje cells in rodents' cerebellum as well as hippocampus. In experimental conditions, the researchers applied a treatment dose with high concentration of Ir which resulted in a growth of cells in the hippocampus by as much as 70% percent. Due to a direct dependency of Alzheimer's and the functioning of the hippocampus and the confirmed positive effect of physical exercises on treating this illness, Ir may be applicable in the therapy in the future. Ir is also present in vestibular nuclei and medulla oblongata [13,14].

The protein in question can also be found in bones. It strengthens them, protects from osteoporosis and probably has autocrine effects. The best exercises include resistance training and strength training while using equipment. Decreased concentration of the protein in blood serum correlates with an increased number of osteoporotic fractures (caused by lower bone density). Research results also show a negative correlation between the level of irisine in the serum and the morbidity rate of coronary disease as well as decreasing the dysfunction of the endothelium of blood vessels and vessels inflammation, affecting the decrease of the influx of macrophages and T-lymphocytes [14,15].

In their research, also confirm the effects of physical exercises on the increased production of myokines, which regulate the brain's functioning, including cognitive functions [16]. Working muscles also produce cathepsin B regulating cell immunity, improve the functioning of the cardio-vascular system, which positively affects blood supply for the brain.

According to, physical activity decreases the risk of numerous illness. Working muscles act as an endocrine organ which produces hundreds of myokines [17]. They affect cognitive functions, lipid metabolism, bronzing of white fat, forming bones and strengthening them. The abovementioned authors suggest that myokines may become biomarkers for monitoring instructions related to exercises for people with neurodegenerative illnesses, diabetes and cancers.

These scientific research results may indicate a beneficial effect of contracting muscles during physical exercises on all body tissues, including nerve tissue and positively affect their functioning.

The Role of BDNF and other Neurotrophins in the Stabilization of the Work of the Nervous System and Treatment of Neurodegenerative and Mental Illnesses

Neurotrophins have numerous common characteristics, they work and affect various processes, i.a. they influence the development of neurons and their physiological functions, development of dendritic connections, inhibition of the process of apoptosis. They also stimulate the process of neuroregeneration in illnesses of the nervous system i.a. by activating receptors TrkB and p75NTR. The most common neurotrophin is BDNF, which additionally suppresses brain inflammation, acts like a natural anti-depressant, prevents negative effects of stress. Lower level of neurotrophins results in the occurrence of neurodegeneration of neurons, including dopaminergic neurons observed in Parkinson's, Alzheimer's, multiple sclerosis, motor, cognitive, mental disorders such as depression, schizophrenia, mood disorders, lower stress resistance and so on. BDNF is located in a nerve cell's cytosol, which is the main location of its synthesis. It is also located near dendritic spines and outside the nervous system in lymphocytes T, lymphocytes B, monocytes and thrombocytes [1,7,19]. It has been proven that neurotrophins may have autocrine, paracrine and endocrine effects by attaching to particular receptors located in the cell membrane or the nucleus. This gives them the possibility to affect various tissues, also located further away.

Current research are targeted at seeking methods of compensating the deficits of BDNF. One of the methods, which was already mentioned above, is direct application of BDNF to the areas of damaged nerve cells and implanting it directly into the brain's structures and administering materials which gradually release this neurotrophin. Another method, a more natural one, is using correctly intensified physical activity, as BDNF exhibits expression at the time when neurons are active and energetic processes occur inside them. What happens inside the nerve cell then are changes of potentials. As a result of these processes, neurotransmitters

are created, which facilitates the reconstruction of the synaptic network and allows new branches to be created. If such changes do not occur inside nerve cells, they lose the possibility to reconstruct and modify and their functioning becomes limited. It is confirmed by numerous research, including the works of Mattson and Mennerick and co-authors which show that the lack of energetic transformations results in lowering cascade biochemical processes, inhibition of neurotransmitters production and limiting the synthesis of the BDNF [3]. For a correct functioning of the central and peripheral nervous systems, it is vital to stimulate it [1,19].

Utilizing Physical Activity with the Aim of Treating NDG and Mental Illnesses

Due to the vital significance of neurotrophins in our body, we ask ourselves the question: "when does the highest and simultaneously optimal stimulation of the neurotrophins' secretion occur?" The abovementioned research results indicated that it occurs during physical activity since movement initiates production of trophic growth factors, definitely less during cognitive activity, adequate diet or moderate exposure to sunlight. Increased secretion of BDNF in the nervous system during physical exercises results in the fact that the brain is more resistant to stress and the occurrence of various disorders in the nervous system and the mind, including depression. The connection between the BDNF and physical exercises has been known for a long time, but the research dated to as late as the end of the 20th century showed that physical exercises actually activate the gene which sends the signal with the information about the need for larger synthesis and secretion of the BDNF [20].

Therefore, the question remains: how can the amount of neurotrophins, including the BDNF, be increased to an optimal level, so that they can perform their function best? How long does one have to exercise and how hard in order for it to have healing effects?

What kinds of exercises need to be used and at what intensity in order for them to optimally stimulate the induction of neurotrophins?

Analysing the professional experience of a physiotherapist and the knowledge of neurophysiology and the existing mental and neurodegenerative disorders, it should be assumed that the optimum is a minimum of 150 minutes per week for the elderly and less fit. It is important to adjust the physical activity to the psychophysical conditions of the exercising person, starting with smaller doses. For people who exercise more and are fitter, it should be 300 minutes per week. It is possible to utilize aerobic exercises involving the possibility of oxygenation during exercises which results in good oxygenation of the body including the brain and lack of severe fatigue, e.g. fast walking, Nordic walking, cycling [14]. Then it is possible to use resistance exercises which involve strength training, e.g. weightlifting during which one strengthens their muscles.

The next group of exercises, also important, are whole body motor coordination exercises, motor-visual coordination or motor-auditory coordination. Also balance exercises, fast reaction, target practice, stretching exercises etc. These exercises are suitable for people suffering from Parkinson's and other neurodegenerative illnesses. This group of people should begin with walks with accelerations followed by adding more exercises. It is advised to use aerobic exercises, also stretching and coordinating in every training. The first effects, as research show, can be observed after 3 months although treatment or experimental programmes should last for at least 6 months. Bearing in mind the intention to keep the beneficial effects, the procedure should not be stopped after that period, but rather continued, as the achieved effect will disappear after a few weeks [21].

Conclusion

An analysis of research results proves that adequately intensified physical activity positively affects the secretion of neurotrophic factors, particularly BDNF and increases the size of some parts of the brain. An adequate level of neurotrophins in the nervous system may protect from neurodegenerative illnesses and mental disorders, especially depression. The metaanalysis of the research results also shows that adequately selected physical exercises improve memory, learning and spatial orientation. While skeletal muscles are working, myokines are produced. Similarly to neurotrophins, they affect the whole body and communication among tissues, hence physical exercises are also utilized in cases of diabetes, obesity and other somatic illnesses. The conducted observations provide proof that adequately intensified and adjusted physical activity may perform a supplementary function in treating Parkinson's, Alzheimer's or depression. It may also successfully perform preventative function.

Results show that a good effect is achieved by utilizing aerobic exercises along with coordination exercises, adequately intensified, adjusted to the psychophysical condition of the people exercising. In order to achieve the healing effect, they should be conducted for at least 150 minutes per week for a period of at least 3 months and even better if longer, up to 6 months. For fitter people the dose should be 300 minutes per week.

Analysing the research results, it can be concluded that physical exercises perform a healing function, and also a preventative one in the range of mental, neurodegenerative and somatic illnesses, they constitute a universal antidote for keeping mental and physical health [22-25].

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