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DEVELOPMENT OF SCIENCE KNOWLEDGE VS. TEACHER TRAINING

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Neuroprotective role of some microelements in the course of neurodegenerative diseases

Introduction

Neurodegenerative diseases are now one of the most serious health problems faced by the humanity around the world. According to the World Health Organization, in 2030 the number of people suffering from these diseases can reach up to 120 million. The cause of these diseases is primarily the aging of the population and, consequently, its homeostasis disorder at the cellular level. Neurodegenerative diseases include, among others Parkinson's disease (PD), Alzheimer's Disease (AD), Huntington Disease (HD) and Amyotrophic Lateral Sclerosis (ALS). The mechanism of symptom formation in these diseases is also seen in some diseases of the retina, such as glaucoma (Glaucoma).

Neurodegenerative diseases are a symptom of disturbances in the functioning of the central or peripheral nervous system resulting from the loss of nerve cells. Despite the different clinical picture and the different course of these diseases, it is believed that they are a consequence of the progressive dying of neurons (Jellinger, 2009). The loss of neurons may be the result of necrosis combined with induction of inflammation or apoptosis, i.e. programmed cell death. Aggregation of specific areas of the central nervous system, such as β-amyloid, in nerve cells is considered to be the cause. These proteins contain numerous molecules of glutamine, microtubules connected to the tau protein, or dysfunctional mitochondria and the associated oxidative stress (Martin, 2010).

Cellular homeostasis and microelements

Homeostasis is an essential condition for the proper functioning of the system. In order to maintain homeostasis, i.e. internal stability in changing environmental conditions, the human body must maintain such parameters of the internal body environment as body temperature, blood pressure, body fluid volume, blood pH value. A disruption of homeostasis means an illness.

In the complex mechanisms of maintaining homeostasis, microelements play an important role, which include, among others, transition group metals such as iron, copper, zinc, as well as non-metallic selenium belonging to the aerobes (Klecha and Bukowska, 2016). The biochemical properties of these elements' ions are based on basic biological processes occurring at the level of each cell and on the scale of

the whole organism, and the condition of proper functioning of the body is the daily supply of these microelements, mechanisms maintaining their concentration within physiological norms and interactions between them.

Both a deficiency or excess of these micronutrients can induce systemic disorders leading, among others, to pathological changes in the nervous tissue, which may in some specific areas of the nervous system direct the metabolism to the path of apoptosis or necrosis of neurons.

Role of iron in maintaining intracellular homeostasis The effects of excess or deficiency

Adequate supply and maintenance of optimal iron concentration in the body is of particular importance for the proper conduct of basic biological processes. The physiological level of this element in the human body ranges from 2 to 3 grams (Kuras et al., 2015). Iron is part of the prosthetic groups of metalloproteins – hemoglobin and myoglobin. It is also a cofactor of cytochromes – enzymes that are part of the respiratory chain – and is part of peroxidases and catalase, which protect cells against oxidative stress (Hentze et al., 2010). Iron deficiency is the main cause of anemia, which is indirectly associated with disorders of the development and function of the nervous system. The phenomenon of hypomyelination of nerve fibers in the brain and medulla spinal cord is also associated with iron deficiency in infancy (Lozoff et al., 2013). Neurological symptoms of iron deficiency in the early, neonatal phase of individual development are manifested in school-age children as, among others, reduced cognitive ability and learning difficulties. These disorders do not retreat later in life, even after the iron levels have been adjusted. In demyelinating diseases, such as multiple sclerosis, the cause of myelinogenesis is iron deficiency (He et al., 2007).

Deregulation of homeostatic mechanisms leading to an increase in iron concentration in the body causes its excessive accumulation in various structures of the nervous system and is one of the elements that seems to play a role in the pathogenesis and development of neurodegenerative diseases (Ndayisaba et al., 2019). The accumulation of iron in the subcortical nuclei of the striatum, pale globe and reticular part of the black matter, as well as in the cerebellar toothed nuclei is a characteristic feature of a wide group of genetically and clinically heterogeneous diseases referred to as Neurodegeneration With Brain Iron Accumulation (NBIA) (Dusek and Schneider, 2012). These diseases are usually inherited recessively autosomal, and their neurological symptoms depend on the type of neurodegeneration with brain iron accumulation and may appear in various periods of individual development (from early childhood to 40 years of age). Nervous system degenerations involving excessive iron accumulation occur not only in NBIA syndromes, but also in a number of other neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease, or ALS, for which the risk factor is often old age (Millan et al., 2007).

The role of iron accumulation in the etiopathogenesis of neurodegenerative diseases has not yet been clarified. It is not known whether iron is a factor generating the occurrence of the disease or just a secondary symptom of the development

of other pathological processes that damage neurons. However, the contribution of iron to neurodegenerative processes seems to be obvious. Free iron ions Fe^{+2} (unbound to transport or storage protein) are highly toxic and in the presence of hydrogen peroxide (H_2O_2) initiate the Fenton reaction. The Fenton reaction creates free radicals that destroy the cell membrane (Altamura and Muckenthaler, 2009). The hydroxyl radical (-OH) that is formed as a result of this reaction is one of the most reactive oxidants and causes lipid peroxidation and structural changes in DNA and protein molecules. The consequence of these changes is cell death by apoptosis. The presence of free radicals can also contribute to the aggregation of β-amyloid proteins and play a role in the development of neurodegenerative diseases, such as Alzheimer's disease for example (Lovell et al.,1998).

Role of copper in maintaining intracellular homeostasis The effects of excess or deficiency

Copper is an element that plays an important role in the course of biological oxidation-reduction reactions. Its physiological level in the human body ranges from 100 to 150 mg. Copper is a cofactor for many enzymes such as ceruloplasmin, superoxide dismutase and cytochrome c oxidase (Wang and Wang, 2019). Ceruloplasmin, also known as copper oxidase, is a glycoprotein that contains up to six copper atoms and acts as the main transporter of this element in blood plasma. As an enzyme with oxidase and ferroxidase activity, ceruloplasmin is also involved in the metabolism of copper and iron. It catalyzes the oxidation of Fe^{+2} to Fe^{+3} ions, enabling them to be combined with iron transporting or storage proteins. Superoxide dismutase is a metalloprotein whose prosthetic group containing copper and zinc or manganese acts as an active center. This enzyme plays an important role in the cell's defense mechanisms as a scavenger of free oxygen radicals. Cytochrome c oxidase as the last protein complex of the respiratory chain reduces oxygen by transferring electrons from cytochrome c to its molecule. The high oxidoreductive potential of copper and copper-dependent protein complexes causes that the disruption of their homeostasis can have serious consequences for the body.

In the conditions of copper deficiency, the activity of copper-dependent enzymes decreases and the amount of free radicals increases. The consequences of these metabolic disorders are mitochondrial damage, worsening of oxidative stress and ultimately apoptotic cell death (Lombardo et al., 2003). A decrease in plasma copper concentration and a decrease in superoxide dismutase activity in the cerebrospinal fluid has been observed in the most common neurodegenerative diseases such as Alzheimer's, Parkinson's disease and amyotrophic lateral sclerosis (Boll et al., 2008). Lower levels of copper in the hippocampus and amygdala than in healthy individuals have also been reported in Alzheimer's disease patients with severe histopathological disorders (Rossi et al., 2001). This demonstrates the generating effect of copper deficiency on the course of degenerative processes in the nervous system.

Excess of copper is as toxic to cells as its deficiency. It can cause oxidation of proteins and nucleic acids and peroxidation of membrane lipids, as well as stimulate

the formation of free radicals in Haber-Weiss and Fenton reactions, thus causing oxidative stress (Valko et al., 2005). Another mechanism triggered in conditions of increased copper concentration is the promotion of protein deposits formation in the cytoplasm of nerve cells that contribute to the development of neurodegenerative diseases (Dobson, 2003).

Role of zinc in maintaining intracellular homeostasis The effects of excess or deficiency

Zinc is one of the basic micronutrients associated with maintaining homeostasis of the body. Its total content in the body ranges from 1.5 to 4.0 grams (Puzanowska-Tarasiewicz et al., 2009). The biological importance of this microelement results from its presence in the composition of many proteins, including enzymatic ones. At present, about 400 such proteins are known that have zinc in their composition, which is also the only metal necessary for the proper functioning of enzymes in all six of their classes (Andreini et al., 2006). In enzyme molecules, zinc can act as a cofactor permanently associated with its molecule or as an activator that is not permanently associated with the enzyme causing its activation and often a significant increase in the rate of catalyzed reaction. Zinc plays a special role in maintaining redox and oxidative balance in cells by participating in the construction of superoxide dismutase, a superoxide radical neutralizing enzyme. It also participates in the inhibition of iron and copper-dependent lipid peroxidation (Oteiza, 2012).

Any disruption of zinc intra-body balance, both in the direction of deficiency and elevated concentration, can lead to serious impairment of vital functions. It has been shown that zinc deficiency can lead, among others, to growth inhibition, impaired immune function, cognitive impairment and even autism (Tian and Diaz, 2012). Disorders resulting from too high a concentration of zinc are not very common due to well-developed mechanisms that maintain intracellular homeostasis of this microelement. The central nervous system is particularly sensitive to zinc, in which disturbances in its balance may be one of the factors leading to the emergence and development of neurodegenerative diseases (Craddock et al., 2012). High levels of zinc in the central nervous system lead to inhibition of neuronal growth and differentiation, and even their death (Wang et al., 1999). High levels of zinc can also induce apoptosis of nerve cells, both by activating proapoptotic proteins and directing neurons to the path leading to apoptosis, as well as by inhibiting energy metabolism causing damage to mitochondrial membranes, the outflow of enzymes into cytosol and, consequently, the induction of programmed cell death. Another effect of high levels of zinc in the body is oxidative stress caused by a reduction in the content of reduced glutathione in the cell (Craddock et al., 2012).

Role of selenium in maintaining intracellular homeostasis The effects of excess or deficiency

Selenium was discovered in 1817 and until 1957 it was considered a toxic element. It is a trace element whose content in the human body is estimated at 10–30

milligrams. It occurs in all tissues and organs, but its highest concentration is observed in the liver and muscles. Selenium as an element has no biological effect. On the other hand, its compounds show biological activity. Most often they are the amino acids selenocysteine and selenomethionine, in which the sulfur atom was replaced with selenium atom. Thanks to this, selenium participates in the construction of many proteins – selenoproteins, including enzymatic proteins (Pitts et al., 2014). The enzymes in which selenium occurs can be divided into three main groups: glutathione peroxidases, iodothyronine deionidases and thioredoxin reductases. There are also several individual selenoproteins in the human body, of which selenoprotein P is of the greatest importance. These enzymes are associated primarily with the processes of cell defense against oxidative stress caused by free radicals, thyroid hormone production, inflammatory processes and the regulation of the programmed cell death pathway – apoptosis (Steinbrenner et al., 2016).

The association of selenium with neurodegenerative diseases is mainly associated with the action of glutathione peroxidase, thioredoxin reductase, or selenoprotein P, which are considered free radical scavengers (Pillai et al., 2014). Selenium has been proven to help protect neurons from the harmful effects of lipid peroxidation products and β-amyloid in Alzheimer's disease and can be used to alleviate Parkinson's disease symptoms such as bradykinesia (Ellwanger et al., 2015). Too high a concentration of selenium causes a set of symptoms called selenosis. Typical symptoms for selenosis are diarrhea, nausea, fatigue and joint pain. According to some researchers, excessive selenium supplementation can lead to the development of type 2 diabetes and that excess selenium may induce oxidative stress (Fairweather-Tait et al., 2011). While selenium can be helpful in treating or alleviating the effects of many diseases, including neurodegenerative diseases, its excess can have the opposite effects, such as induction of oxidative stress.

Glaucoma as a neurodegenerative disease? Glaucoma neuroprotection

Neuroprotection in the light of recent discoveries arouses great interest and is associated with a lot of hope, because until recently retinopathies such as glaucoma or age-related macular degeneration (AMD) were treated as exclusively ophthalmic diseases, which is one of the most common causes of blindness. In 2006, glaucoma was similar to neurodegenerative diseases of the central nervous system disease, such as Alzheimer's or Parkinson's disease (Vasudevan et al., 2011). It is now known that the pathogenesis of neurodegenerative diseases is associated with the loss or death of neurons in specific areas of the central and peripheral nervous system. Within the retina of the eye, the ganglion cells and their axons forming the optic nerve are selectively killed (Rusciano et al., 2017).

The presence of similar mechanisms of nerve cell death in these diseases suggests that patients with glaucoma can receive similarly beneficial effects of neuroprotective treatment as in neurological diseases. Clinical studies have confirmed the good effect of neuroprotective treatment in glaucoma.

As it turns out, zinc and selenium play an important neuroprotective role in retinal metabolism and condition the proper activity of enzymes of this organ, such as retinol dehydrogenase and catalase. Reduced zinc supply increases the risk of age-related macular degeneration. A beneficial effect of zinc therapy in patients with AMD was also shown in comparison with the placebo group.

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Neuroprotective role of some microelements in the course of neurodegenerative diseases

Abstract

Neurodegenerative diseases are characterized by progressive loss of nerve cells in specific areas of the nervous system. Until now, it has not been clearly defined which mechanism is responsible for the death of nerve cells in neurodegenerative diseases, but as the results of research indicate, apoptosis is responsible for this process. The death of neurons causes disturbances in the functioning of the nervous system. The process of nerve cell degeneration is accompanied by the appearance of pathological changes resulting from the aggregation of misfolded proteins. Studies indicate that disruption of the balance between production and degradation of misfolded proteins causes an increase in their concentration, and consequently, aggregation leading to the development of neurodegenerative diseases such as Alzheimer's, Parkinson's and glaucoma. As it results from the presented data on the share of selected microelements in maintaining intracellular oxidation-reduction balance, they can show a protective effect, protecting cells against oxidative stress.

Keywords: homeostasis, microelements, neurodegenerative diseases

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