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THE PATHOGENETIC ASPECTS OF PARKINSON'S DISEASE AND POSSIBLE WAYS OF THEIR CORRECTION

Патогенетичні аспекти хвороби Паркінсона і можливі шляхи їх корекції

Abstract

The pathogenetic aspects of Parkinson's disease and possible ways of their correction. Buchakchyiska N. M., Maramukha V. I., Maramukha I. V.

Purpose of the study. *The purpose of the work is to summarize the data available in the literature regarding the role of shock proteins, in particular the HSP 70 protein, in the mechanisms of endogenous neuroprotection and neurodegradation in Parkinson's disease (PD). The article also aims at determining the possible pathogenetic stages of the disease development and the place of mitochondrial dysfunction, apoptotic and antiapoptotic systems in these processes. The modulation of PD MPTP model can help to identify possible ways of influencing the pathogenetic mechanisms of neurodegenerative changes in structures of the extrapyramidal system by stimulating the processes of neuroprotection and slowing of neurodegradation owing to inducing protein level synthesis. After statistical processing of the obtained results, one can interpolate the obtained data on idiopathic PD in the population by matching the relevant neurodegenerative process markers found in the experiment with indicators in PD patients. As a result, it may hypothetically be possible to develop the use of personalized pathogenetic therapy for PD.*

Keywords: *Parkinson's disease, neuroprotection, heat shock.*

Резюме

Патогенетичні аспекти хвороби Паркінсона та можливі шляхи їх корекції. Бучакчийська Н. М., Марамуха В. І., Марамуха І. В.

Мета роботи. *Узагальнити наявні в літературі дані стосовно ролі білків теплового шоку, зокрема білку HSP 70 в механізмах ендогенної нейропротекції та нейродеструкції при хворобі Паркінсона (ХП). Визначити можливі патогенетичні ланки розвитку захворювання та місце в цих процесах мітохондріальної дисфункції, апоптотичних та антиапоптотитичних систем. Завдяки модулюванню MPTP моделі ХП можуть бути отримані результати, що дозволять визначтити можливі шляхи впливу на патогенетичні механізми формування нейродегенеративних змін в структурах екстрапірамідної системи шляхом стимулювання процесів нейропротекції та сповільнення нейродеструкції за рахунок індукції синтезу рівня білків теплового шоку. Після статистичної обробки отриманих результатів інтерполювати отримані дані на ідіопатичну ХП в популяції, співвставивши відповідні маркери нейродегенеративного процесу, що отримані в експерименті з показниками у хворих на ХП. У підсумку гіпотетично може стати можливою розробка застосування персоніфікованої патогенетичної терапії ХП.*

Ключові слова: *хвороба Паркінсона, нейропротекція, тепловий шок*

Despite significant advances in Parkinson's disease (PD) treatment, it continues to be an extremely important medical and social problem. The data from the literature of the last 5 years indicate the positive effects after the use of neuroprotective drugs, but unfortunately, this does not always lead to the expected long-term neuroprotective effect. Therefore, the search for a

scientifically sound strategy of making a rational choice of medicines for basic therapy optimization remains relevant. First of all, it concerns the study of molecular-biochemical changes in PD along with the development of new approaches for their correction, the most promising targets of which, according to some authors, are the activation of endogenous neuroprotection mechanisms and neuroplasticity [2]. The main factor in the antioxidant defense of the neuron is glutathione which regulates and influences the synthesis of heat shock proteins as well as provides regulation of the mechanisms of apoptosis. The increase in the systemic level of heat shock proteins with a molecular weight of 70 kilodalton (kDa) Human Shock Protein (HSP70)) by its inducers is a modern strategy of neuroprotection in PD and is specific for the defeat of neuronal cells. This is confirmed by the literature on the relationship between HSP70 level and the rate of disease progression.

Neuroprotective effects of heat shock proteins. Recently, there have been works on the role of heat shock proteins (HSP) in cerebral ischemia and cancer as indicators of cancer cell resistance to chemotherapy. The role of this class of proteins is also revealed in PD as prognostic markers of the disease progression rate [16, 17, 18].

The synthesis of HSP occurs in the cells of all living organisms in response to the action of multi-stress factors, and the activation of these proteins occurs both in stress and in the process of cell activity as well as apoptosis. Proteins of this class are involved in all life processes of tissues, organs, and the whole organism [15].

The most studied is the protein of this family with a molecular weight of 70 kDa or HSP70. The HSP70 protein is an inducible representative of the heat shock protein family and HSP70; this is the first protein called chaperone. The action of chaperones in the cell leads to the fact that they bind to damaged or re-synthesized polypeptides and promote the adoption of native conformation, as well as the delivery of proteins to certain organelles. The HSP70 family proteins are among the main elements of protein quality control systems, which confirms their protective function. Thus, chaperone eliminates a large number of factors, including those that cause apoptosis, and removes proteins that cannot be corrected through the proteosomal mechanism. This has been confirmed by numerous in vitro and in vivo studies using a wide range of experimental models. The analysis of the data obtained has suggested the possibility of increasing the stability of the neuron by increasing the content of intracellular HSP70. Some authors substantiate the possibility of using the protective properties of extracellular HSP70, which probably interacts with neighboring cells and protects them from death. Thus, exogenous HSP70 exhibits protective properties similar to intracellular chaperone and interacts with glial cells and neurons in the Central Nervous System (CNS) [19].

Recently, there has been evidence of a regulatory effect of heat shock proteins on the mitochondrial dysfunction resulting from a pathobiochemical cascade of events. These data mainly refer to studies of the cerebral circulation acute disorders, but given that apoptosis is a typical pathological process, it is also relevant to pathological processes characteristic of PD.

According to many researchers, the activation of neuroapoptosis causes the development and progression of persistent impaired function of the extrapyramidal system. Apoptosis is a cascade process accompanied by the activation of specific pro- and anti-apoptotic protein formation, as well as proteolytic enzymes - caspase. Among the factors involved in the activation of apoptosis one should mention the formation of reactive oxygen species owing to the impaired oxidative metabolism in the cell. Several studies have found that mitochondria play a central role in this process due to changes in the permeability of their membranes caused by the formation of a specific complex of mitochondrial pores [11].

Currently, researchers use the generalized concept "mitochondrial dysfunction" which leads to a violation of the reuptake of catecholamine, dopamine, serotonin mediators, to impaired ion transport, impulse generation and conduction, impaired translation and transduction efficacy, as well as activation of inefficient energy-generating reactions in cells along with the energy deficiency formation in the neuron [1].

The results of recent biochemical studies have shown the impaired energy metabolism in cells, hyperproduction of excitotoxic amino acids, reduction in the normal accumulation of Ca in mitochondria, damage to the mitochondrial membrane by active forms of oxygen, which enhances the opening of pores and creates conditions for the release of apoptogenetic proteins from the damaged mitochondria [8].

The mitochondrial pore is a channel that passes through both mitochondrial membranes and consists of three proteins: an adenine nucleotide translocator, a potential dependent anion channel, and a benzodiazepine receptor. When binding this complex to Ca, agents with low molecular weight begin to flow through the membrane pore. This leads to a decrease in membrane potential and swelling of the matrix, the integrity of the outer membrane is broken, and apoptosis proteins enter the cytoplasm from the cytoplasm. The apoptosome complex is formed and caspases are activated, which causes a structural protein cleavage along with the formation of biochemical and morphological features of apoptosis [9].

However, there exist anti-apoptotic systems

that counteract pro-apoptosis ones, among which the most interesting is the protein of Bcl-2 type, whose activity affects a group of genes encoding superoxide dismutase and other antioxidant and anti-apoptotic proteins. The studies conducted have investigated some of the molecular mechanisms by which proteins of the Bcl-2 family regulate apoptosis: the mitochondrial pathway and the caspase activation process. In the first case, proteins of this family affect the permeability of the mitochondrial membrane, thereby controlling the release of cytochrome C from the mitochondria. The process by which the activation of the caspase cascade occurs is initiated both by the participation of Bcl-2 and by the presence of cytochrome C in the cell cytosol [10, 12, 13].

The main mechanism of the antiapoptotic action of the Bcl-2 protein is the inactivation of proapoptotic homologs and blocking of cytochrome C, which is needed for activation of the caspase cascade, from mitochondria [3]. Given that the role of Bcl-2 in the described apoptosis mechanisms has not been fully investigated, the molecular mechanism of anti- and pro-apoptotic protein action requires further study. The data that will be obtained in subsequent scientific studies can be used as prognostic markers for the later stages of the disease [5].

Several studies have reported possible neuroprotective effects of melatonin as an HSP70 inducer, and clarified the issues of the epiphysis and melatonin physiology, given that the hormone is synthesized in specific cellular elements (pinealocytes) from the precursor of serotonin. Due to the high degree of lipophilicity, exogenous melatonin enters brain structures easily and quickly. The possible pathogenetic dependence of PD on defects in melatonin secretion is indicated by experimental observations, according to which, with PD, the dynamics of the secretory activity of the epiphysis in the form of nocturnal hormone secretion is disturbed. The treatment with levodopa makes it possible to normalize this process, in comparison with patients who have not yet received levodopotherapy. The identified changes can probably be explained by the fact that melatonin acts as a modulator of the central nervous system, including the nigrostriatal, dopaminergic transmission [20]. The secretory activity of the epiphysis itself, in turn, is under the control of dopaminergic mechanisms.

The most common PD experimental model is behavioral disorders that occur in rats after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration. At the same time there is akinesia, rigidity, and tremor, which are typical for this disease and often accompanied by violations of the synaptic role of nigrostriatal dopamine with simultaneous deviations in plasma melatonin concentration.

The models used enabled identifying possible neuroprotective properties of melatonin in the form of attenuation of behavioral responses by motor functions and conditional reflex activity due to MPTP introduction in rats [7].

At the same time, epiphysectomy or a prolonged exposure of animals to bright light, which inhibits the natural secretion of melatonin, leads to more severe inhibition of motor and cognitive function in animals after neurotoxin administration. This theoretically substantiates the feasibility of using melatonin as an inducer of heat shock protein synthesis in patients with PD.

Recently, the greatest attention of researchers has been drawn to the possibility of pharmacological regulation of synaptic processes with the participation of GABA, a derivative of which is «Noophen». GABA interacts with GABA-A, GABA-B, and GABA-C receptors. Due to this, it is possible to influence the synthesis and biotransformation, neuronal and glial uptake of GABA, with a change in its concentration in the CNS. GABA-B receptors have been studied in less detail. Due to their location on pre- and postsynaptic membranes, they are bound to adenylate cyclase by G-protein. This leads to an increase in c-AMP (c-adenosinemonophosphate) levels, which reduces the permeability of ion channels for Ca. Many authors have noted a significant metabolic effect, a positive effect on the bioenergy of the neuron, a decrease in the concentration of oxidative stress products and slowing of glutamate excitotoxicity due to the impact on the GABA-ergic system [4]. The data presented by the researchers need further study in the context of the potential influence on the pathogenetic processes inherent in PD.

In recent years, studies have been conducted to evaluate the efficacy of choline alfoscerate («Gliatilin»), which contains 40% of choline, which is converted into a metabolically active form – phosphatidylcholine, which has the ability to penetrate the blood-brain barrier and activate the synthesis of acetylcholine in the presynaptic terminals of neurons. Owing to the fact that it is a donor of acetylcholine, there is a renewal of interneuronal connections and improvement of neurotransmission. It plays an important role in the repair of neuronal membranes by reducing the severity of free fatty acids degeneration. In addition, it stimulates the synthesis of glycerophospholipids due to the formation of membrane phospholipid precursors from the products of their disintegration, which is of great importance in conditions of apoptotic cell death [6].

Considering the fact that there are many pathogenetic mechanisms for the development of PD, it is advisable to study the average effective dose of melatonin, «gliatilin» and «noophen» in the PD model with a dynamic assessment of neurological deficiency in the experiment. It is

important to evaluate the functional state of mitochondria and energy metabolism in the brains of animals, determine the role of these drugs in the mechanisms of endogenous neuroprotection according to the influence on the intensity of HSP70 synthesis and HSP70 mRNA (matrix Ribonucleic acid) expression in the brain tissues of the experimental animals [14].

The assessment of neuroprotective action in conditions of toxic MPTP doses is relevant. The data obtained in the experiment may allow us to optimize a personalized approach to the treatment of this category of patients. This requires the construction of highly sensitive statistical and mathematical models, taking into account the fluctuations in the concentration of HSP70 protein and Bcl-2 protein before and during the therapy as well as the impact of these integrated indicators on the motor and cognitive sphere, the rate of disease progression with a parallel evaluation of the intensity of apoptotic processes and apoptotic efficacy using highly sensitive statistical methods to confirm the high probability of the results obtained and their possible implementation into clinical practice.

The presented literature correlates with the results obtained by us in studies studied changes in the levels of markers of endogenous neuroprotection and neurodestruction, as well as mitochondrial dysfunction and energy changes of substantia nigra neurons in an experimental model of Parkinson's disease.

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