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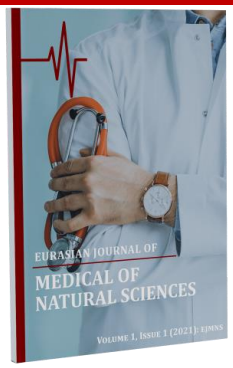

THE ROLE OF MITOCHONDRIAL DYSFUNCTION IN THE DEVELOPMENT OF NEURODEGENERATION

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ABSTRACT

The introduction comprehensively highlights the problem of the role of mitochondrial dysfunction in the development of neurodegeneration, including current understanding of the mechanisms of pathogenesis and therapeutic perspectives. The text is structured logically, emphasizes the relevance of the problem and outlines the prospects for further research, while maintaining the scientific style of presentation and the accuracy of formulations.

Introduction. Neurodegenerative diseases are one of the most pressing problems of modern medicine, due to their growing prevalence, the severity of clinical manifestations and the limited effectiveness of existing treatment methods. In recent decades, more and more data has been accumulating on the key role of mitochondrial dysfunction in the pathogenesis of various forms of neurodegeneration, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis.

Mitochondria, being the energy stations of the cell, play a critical role in maintaining neuronal homeostasis and the functioning of the nervous system. These organelles not only provide the cell with energy in the form of ATP, but also participate in the regulation of calcium homeostasis, apoptosis, production of reactive oxygen species and many other important cellular processes. Neurons are particularly vulnerable to mitochondrial dysfunction due to their high energy requirements and limited ability to regenerate.

Modern research demonstrates that mitochondrial dysfunction can be both a primary pathogenetic mechanism and a secondary link in the development of neurodegenerative processes. Mitochondrial dysfunction is manifested in a decrease in the efficiency of oxidative phosphorylation, increased production of reactive oxygen species, impaired mitochondrial dynamics (fusion and fission processes), changes in mitochondrial transport and quality control.

Of particular importance in the development of neurodegeneration is the formation of a vicious circle, when primary violations of mitochondrial function lead to increased oxidative stress, which in turn causes further damage to mitochondrial DNA, proteins and lipids. This is accompanied by a violation of the bioenergetics of the cell, activation of pro-inflammatory signaling pathways and, ultimately, triggering programmed cell death.

Understanding the molecular mechanisms of mitochondrial dysfunction in neurodegenerative diseases opens up new perspectives for the development of targeted therapies. In recent years, various therapeutic strategies aimed at correcting mitochondrial disorders have been actively explored, including the use of antioxidants, mitochondrial biogenesis modulators, mitophagy regulators, and other potential neuroprotective agents.

The relevance of studying the role of mitochondrial dysfunction in the development of neurodegeneration is confirmed by a growing number of studies demonstrating the relationship between mitochondrial dysfunction and the progression of neurodegenerative diseases. The identification of key mechanisms of mitochondrial dysfunction and the development of methods for their correction represent a promising direction in the search for new therapeutic approaches to the treatment of neurodegenerative diseases.

In this context, a comprehensive study of various aspects of mitochondrial dysfunction, including energy metabolism disorders, oxidative stress, changes in mitochondrial dynamics and quality of control, as well as their role in the initiation and progression of neurodegenerative processes, is of particular importance. This may contribute to the development of more effective strategies for the prevention and treatment of neurodegenerative diseases based on targeted effects on mitochondrial pathogenesis mechanisms.

Major neurodegenerative diseases include Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Huntington's chorea, and Parkinson's disease (PD). It is known that the main cause of the development of these pathological processes are mutations of various proteins with the formation of intracellular aggregates. Such proteins include beta-amyloid precursor (BA), presenilin 1 and 2 (BA), τ-protein (BP), α-synuclein (BP), huntingtin (Huntington's chorea), parkin (BP), superoxide dismutase-1 (BAS), ubiquitin (BA, BP, BAS), frataxin (Friedreich's ataxia) and others.

It has also been established that structural and functional disorders of mitochondria are one of the main pathogenetic links linking the disruption of the structure and functions of these proteins and their accumulation in neurons with the development of degenerative disorders in the nervous tissue. The main manifestations of mitochondrial dysfunction include a decrease in ATP synthesis, the production of reactive oxygen species, and activation of programmed cell death (PHC) mechanisms, including apoptosis, autophagy, and necrosis-like changes. The consequence of these processes is the suppression of energy-intensive processes in neurons, damage by free radicals to cell membrane structures, the development of inflammation in the nervous tissue, death of functional nerve cells, disruption of synaptic signaling, increased release of glutamate from presynaptic terminals, decreased plasticity of synaptic contacts, activation of inflammation. Further study of the mechanisms of formation of mitochondrial dysfunction in the pathogenesis of neurodegenerative processes should help clarify the pathogenetic mechanisms involved in the development of neurodegenerative diseases.

The development of mitochondrial dysfunction under the influence of defective proteins specific for neurodegenerative processes has been established in in vitro experiments on cell lines, extracellular systems, and in vivo in transgenic animals and in experiments using inhibitors of mitochondrial functions. Of considerable interest is the increase in the level of

defective proteins in the cell under the influence of mitochondrial dysfunction, which indicates the possibility of forming a "vicious circle" between the production of defective proteins and mitochondrial dysfunction. It was found that chronic exposure to low doses of rotenone (25-50 nM, 8 days) promotes the accumulation of ubiquitinated proteins, activation of E1-ubiquitin, and increased proteasome activity. The generation of ROS by mitochondria promotes the aggregation of α-synuclein, which is confirmed in experiments on cell cultures treated with rotenone. The possibility of inducing neurodegenerative changes in rats by exposure to rotenone has been shown. In this case, disturbances in the activity of respiratory complex I can initiate the accumulation of hyperphosphorylated t-protein and, to a lesser extent, α—synuclein in nerve cells.

The stated facts characterize mitochondrial dysfunction as an active link in the pathogenesis of neurodegenerative processes. This determines the need to study the mechanisms of development of structural and functional disorders of mitochondria in the context of the development of neurodegenerative diseases. The results of experimental studies indicate a significant variety of processes contributing to the formation of structural and functional disorders in the mitochondria of nerve cells.

This review discusses the following mechanisms of damage and dysregulatory effects on mitochondria: activation of non—specific mechanisms of response to disruption of the native structure of proteins - unfolded protein response (UPR); loss of function of mitochondrial proteins; direct toxic effects of defective proteins on mitochondria; activation of mitochondrial mechanisms of PHC; dysregulation of processes of utilization, division and fusion of mitochondria; disruption of transport and intracellular distribution of mitochondria.

UPR development and endoplasmic reticulum stress. The relationship of proteasome dysfunction with the development of various neurodegenerative diseases is well known. It has been established that the formation of deposits of defective proteins during neurodegenerative processes leads to the development of UPR and, as a result, stress on the endoplasmic reticulum (ER). It has been established that ER, which is in a state of UPR-mediated stress, contributes to the development of degenerative changes in mitochondria. In PC12 cell culture, it was shown that the expression of A53T α-synuclein contributes to a decrease in proteasome activity, the development of ER stress, an increase in ROS production and an increase in the frequency of PGK, accompanied by the release of cytochrome C from mitochondria and the activation of caspases-9 and -3. Prolonged UPR is known to result in the induction of apoptosis due to the release of cytochrome C from mitochondria and activation of caspases. The main role in transmitting the suicide signal from the ER to the mitochondria is assigned to the release of Ca^{2+} and Ire1 protein into the cytoplasm. An increase in the concentration of Ca^{2+} in the cytoplasm can induce the release of PHC factors from mitochondria through various mechanisms. One of these processes is the activation of proteins that contribute to the formation of mitochondrial channels: Bax and Bid due to the activation of calpains, as well as Bad and Bik through the activation of calcineurin. The next mechanism is to stimulate the Ca^{2+}-sensitive isoform of nitrosynthase, which contributes to an increase in oxidative stress in the cell. Another mechanism is the activation of mitochondrial megachannels due to exposure to excessive amounts of Ca^{2+}. Another known mechanism is damage to the mitochondrial membrane due to activation of phospholipase A2.

UPR may be involved in the intensification of mitochondrial utilization through the induction of macroautophagy processes in the cell. An increase in the level of proapoptotic factor HtrA2 in mitochondria under ER stress conditions has been shown, which contributes to an increase in the intensity of the suicide signal mediated by them. Thus, in the context of the development of neurodegenerative processes, mitochondria are one of the links integrating signals from the ER under stress and determine the fate of the cell depending on the state of this system.

Toxic effect of mutant proteins on mitochondria. The possibility of a direct effect of defective proteins and their deposits on mitochondrial functions has been shown. It is believed that at the initial stages of AD development, the accumulation of β-amyloid and the hyperphosphorylation of t-protein can serve as natural mechanisms for protecting cells from oxidative stress, which develops as a result of the progression of mitochondrial dysfunction and the accumulation of redox metals. Nevertheless, exceeding a certain threshold level of concentration of these proteins in the cell contributes to the development of structural and functional disorders in the mitochondria. It has been established that in the brains of patients with AD, beta-amyloid peptide is able to accumulate to a high degree in the mitochondria and disrupt the activity of glycolysis and Krebs cycle enzymes, and activate ROS production. The ability of the extracellular domain of the amyloid precursor protein and the β-amyloid peptide to inhibit ATP synthesis by the ATP synthase complex in vitro is interesting. This is determined by the similarity of the structure of this domain with the natural inhibitor of the F(1) subunit of ATP synthase in mitochondria (IF(1)). It has been shown that beta-amyloid fibrils and its precursor protein are able to bind to the mitochondrial membrane. It has been established that the beta—amyloid precursor protein accumulates mainly on protein import channels in the mitochondria of the brain tissue of patients with asthma. Interacting with the mitochondrial membrane, this protein forms stable 480 kDa complexes with translocase TOM40 and 620 kDa complexes with both translocase TOM40 and TIM23. This leads to the suppression of the import of proteins encoded by the nuclear genome into mitochondria: cytochrome oxidase subunits IV and Vb, which leads to the inhibition of this protein complex and an increase in the production of H2O2 by mitochondria. High—resolution transmission electron microscopy has confirmed the possibility of the formation of pores in the membranes of mitochondria and other organelles from oligomers of the beta-amyloid precursor protein, which contributes to the disruption of the ion balance in the cell and causes the development of PHC. The ability of the beta—amyloid precursor protein to stimulate the activity of phospholipase D has been shown, which leads to a change in the phospholipid spectrum of mitochondrial membranes: the concentration of phosphatidylcholine, phosphatidylethanolamine, and phosphatidic acid increases. It has been established that the binding of heme by the β-amyloid peptide leads to its deficiency in the cell, contributing to the development of disorders in the heme-containing IV complex of the mitochondrial electron transport chain. In transgenic rats expressing human huntingtin, aggregation of this protein in the mitochondria was observed, which contributed to the development of mitochondrial dysfunction. It has been shown that the N-terminal fragment of human α-synuclein carries a hidden signal that determines its localization in mitochondria. Alpha-synuclein imported into the mitochondria is predominantly associated with the inner mitochondrial membrane. The

accumulation of α-synuclein in the mitochondria of human dopaminergic neurons contributes to a decrease in the activity of the I respiratory complex and, as a result, an increase in the production of ROS by mitochondria. It has been established that another consequence of the interaction of α-synuclein with mitochondria is the release of cytochrome C from them into the cytosol. In general, the above data objectively show the possibility of accumulation of mutant proteins and their aggregates in the mitochondrial matrix and their association with mitochondrial membranes. These proteins are able to directly interact on various structures of mitochondria: ATP synthase, translocases TOM40 and TIM23, mitochondrial membranes (the formation of pores from oligomers of the precursor protein β-amyloid).

Activation of the mitochondrial mechanisms of PHC. In addition to the direct effect of the above-mentioned defective proteins on mitochondrial functions, their ability to activate the release of mitochondrial apoptotic factors has been established due to direct or indirect effects on regulatory proteins: p53, Akt, Bad, Bax, Bcl-x(L), calcineurin, etc. It has been shown that mutant huntingtin interacts with p53, which contributes to an increase in its level in the nucleus. Disruption of p53 activity due to RNA interference and gene deletion helped prevent depolarization of mitochondrial membranes and compensated for the cytotoxic effect of mitochondrial dysfunction. It was found that β-amyloid peptide induces apoptosis of cerebrovascular endothelial cells due to inactivation of Akt protein kinase, which prevents activation of apoptosis signals involving Bad. The consequence of these events is the development of mitochondrial dysfunction, accompanied by the release of endonuclease G and Smac from the mitochondria. It was found that the β-amyloid peptide activates the release of cytochrome C from mitochondria due to dephosphorylation of Bad under the influence of calcineurin. The ability of the phosphorylated form of t-protein to activate apoptosis mechanisms characterized by a decrease in the transmembrane potential of mitochondria, an increase in the levels of JNK, Bim, Bad, Bax, and caspase-3 has been shown. In an experiment with a culture of neurons from the cerebellum, striatum, and substantia nigra transfected with the mutant ataxin-3 gene, it was shown that the latter activates the release of cytochrome C and Smac by activating Bax expression and suppressing Bcl-x(L) expression. The accumulation of ceramides in neurons, observed in various neurodegenerative processes, may contribute to the activation of PHC by inducing the release of certain pro-apoptotic mitochondrial proteins: cytochrome C, Omi, SMAC, and AIF. Summarizing the above, in the context of the development of neurodegenerative processes, defective proteins affect various parts of the PHC system interacting with mitochondria.

Conclusions: Thus, an increase in the intensity of the effect of suicide signals on mitochondria contributes to a decrease in the transmembrane mitochondrial potential, the production of ROS by mitochondria, and the release of factors from these organelles that initiate the mechanisms of programmed cell death.

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