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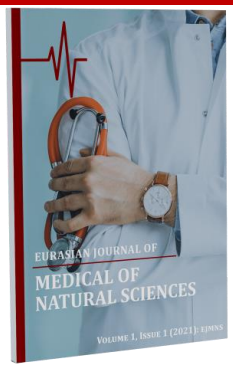

RELATIONSHIP BETWEEN MITOCHONDRIAL DYSFUNCTION AND NEURODEGENERATIVE PROCESSES

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ABSTRACT

Neurodegenerative diseases are a group of progressive pathological conditions characterized by the selective death of certain populations of neurons, which leads to the development of specific neurological and cognitive disorders. In recent decades, convincing evidence has been accumulated that mitochondrial dysfunction plays a central role in the pathogenesis of these diseases, acting both as a primary pathogenetic mechanism and an important modulator of the progression of neurodegenerative processes.

Introduction. Mitochondria, being key organelles in ensuring cellular energy metabolism, maintaining calcium homeostasis and regulating programmed cell death, are especially important for the functioning of nervous tissue. Neurons with high energy requirements and limited regenerative capacity show increased sensitivity to mitochondrial function disorders.

Modern research shows that mitochondrial dysfunction manifests itself at various levels of cellular organization and includes disorders of energy metabolism, oxidative stress, changes in mitochondrial dynamics, disorders of mitophagy and qualitative control of mitochondria. These changes are observed in various neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis. Of particular importance is the study of the mechanisms of the vicious circle formation, when primary violations of mitochondrial function lead to increased oxidative stress and damage to mitochondrial DNA, which in turn exacerbates mitochondrial dysfunction and contributes to the progression of neurodegeneration. Understanding these mechanisms opens up new perspectives for the development of targeted therapeutic strategies. In recent years, the possibilities of therapeutic effects on various aspects of mitochondrial dysfunction have been actively explored, including the use of antioxidants, modulators of mitochondrial biogenesis, regulators of mitophagy, and other potential neuroprotective agents. Of particular interest is the development of integrated approaches aimed at the simultaneous correction of several pathogenetic mechanisms. The relevance of studying the relationship between mitochondrial dysfunction and neurodegenerative

processes is due not only to its fundamental importance for understanding the pathogenesis of neurodegenerative diseases, but also to the practical need to develop new therapeutic strategies based on the correction of mitochondrial disorders.

Insufficiency of mitochondrial protein functions. It has been established that one of the mechanisms of ALS development may be the catalysis by a mutant variant of mitochondrial-specific superoxide dismutase-1 of atypical biochemical reactions, the product of which may be various free radicals, including superoxide anion, hydroxyl radical, hydrogen peroxide and peroxynitrite. High levels of reactive oxygen species can damage mitochondrial structures and contribute to the development of mitochondrial dysfunction. It has been established that mutations of this enzyme contribute to the weakening of the anterograde transport of mitochondria in the processes of neurons. In a mixed primary culture of astrocytes and motor neurons, it was shown that the expression of the mutant form of superoxide dismutase-1 SOD1(G93A) by astrocytes contributes to a decrease in the mitochondrial potential and redox status of mitochondria both in astrocytes themselves and in co-cultured motor neurons. It has been established that the development of recessively inherited Parkinsonism is facilitated by structural disorders of the DJ-1 protein (PARK7), a component of the antioxidant protection of mitochondria, the nucleus, and a modulator of transcriptional activity. It has been shown that point mutations of the mitochondrial HtrA2 protein (PARK13) are a factor of susceptibility to PD [34]. The low level of expression of the mitochondrial iron-binding protein frataxin, observed in Friedreich's ataxia, contributes to the accumulation of iron in mitochondria, disorders of iron-sulfur clusters, and high sensitivity to oxidative stress. Mutations of the HSPD1 gene encoding the mitochondrial chaperonin Hsp60 have been identified in patients suffering from an autosomal dominant form of hereditary spastic paraplegia. This is probably the reason for the disruption of the system of disposal of defective mitochondrial proteins. Thus, the functional insufficiency of various mitochondrial proteins contributes to the disruption of antioxidant defense systems in mitochondria, iron homeostasis, and the utilization of defective proteins, which contributes to the development of structural and functional disorders of mitochondria in the context of the development of neurodegenerative processes.

Disruption of mitochondrial fission and fusion processes. Currently, a close relationship between the processes of mitochondrial fragmentation and fusion with the activation of mitochondrial PHC mechanisms has been shown. It has been established that PINK1 (PTEN-induced putative kinase 1) and parkin are components of the mitochondrial fission fusion system and are involved in maintaining their integrity and functional integrity. Mutations of the PINK1 and Parkin genes are observed in patients with recessive forms of PD. Modeling of such disorders on Drosophila melanogaster showed the presence of structural mitochondrial disorders (enlargement, swelling) of various body tissues, including muscles and dopaminergic neurons. It has been established that parkin mutations (PARK2) contribute to the disruption of the elimination of defective forms of mitochondria by autophagosomes. Overexpression of the beta—amyloid precursor protein by M17 cells is accompanied by disruptions of the mitochondrial fusion system: levels of dynamin-like protein-1 and OPA-1 decrease significantly, while the level of Fis-1 increases significantly. Summarizing the above, congenital and acquired defects of the mitochondrial fusion fragmentation system,

contributing to the development of mitochondrial dysfunction and activation of PHC processes, participate in the formation of neurodegenerative processes.

Disruption of mitochondrial utilization. It is assumed that excessive activity of autophagic processes can lead to a decrease in the number of mitochondria in the cell. In neurodegenerative diseases, inhibition of proteasome activity has been revealed, which disrupts mitochondrial homeostasis in the cell and contributes to the progression of mitochondrial dysfunction. This is objectively confirmed by the possibility of inducing mitochondrial dysfunction using proteasome function inhibitors. The consequence of these processes is the activation of mitochondrial macroautophagy and the accumulation of lipofuscin in lysosomes, a product of incomplete degradation of mitochondrial components, which leads to a decrease in protein degradation activity through autophagy. Accumulation of lipofuscin with aging is shown for microglial cells, accompanied by an increase in the concentration of mRNAs of proinflammatory (TNF-α, Il-1b, Il-6) and anti-inflammatory (Il-10, TFR-β1) cytokines. In general, violations of the processes of mitochondrial utilization lead to a decrease in the number of functionally complete mitochondria, accumulation of products of their incomplete decay in nerve cells, weakening of resistance, and the development of neurodegenerative changes.

Disruption of transport and intracellular distribution of mitochondria. Suppression of axonal transport of mitochondria under the influence of defective forms of t-protein and huntingtin leads to a violation of the energy supply of nerve cell processes, the main consequence of which is a violation of synaptic transmission and degeneration of synapses. It has been established that overexpression of human t-protein in the motor neurons of Drosophila melanogaster larvae leads to reduction of functionally complete mitochondria in presynaptic terminals, contributing to disruption of synaptic signaling. When the t-protein gene was transfected into mature hippocampal neurons, its distribution in cells was disrupted, and transport of mitochondria and other organelles was suppressed, followed by synapse degeneration. It was found that the expression of mutant huntingtin weakens the axonal transport of nerve cell organelles, including mitochondria. Thus, disruption of the transport and distribution of mitochondria in neurons is an additional factor contributing to the development of degenerative processes in the nervous tissue. Thus, the mechanisms of formation of mitochondrial dysfunction in the context of the development of neurodegenerative processes are characterized by versatility and high complexity. This is determined by the variety of mutant proteins associated with neurodegenerative diseases and the complexity of their negative effects. In this case, the universal mechanism of development of mitochondrial dysfunction is ER stress, which contributes to an increase in the concentration of Ca2+ in the cytosol, activation of the mitochondrial mechanisms of PHC and the process of mitophagy. A number of mutant proteins and their aggregates (β-amyloid precursor protein, α-synuclein) they can have a toxic effect directly on mitochondria. These proteins form complexes with mitochondrial structures, inhibit the activity of ATP synthase, disrupt the processes of protein import into mitochondria from the cytosol by translocases (TOM40, TIM23) and can form pores in membranes. This contributes to a decrease in ATP production, disruption of the electron transport chain and a decrease in the transmembrane potential of mitochondria. The development of neurodegenerative processes as a

consequence of disorders of certain mitochondrial proteins is interesting: superoxide dismutase-1, DJ-1, frataxin, and mitochondrial Hsp60. The expression of these proteins contributes to the disruption of antioxidant protection, iron homeostasis, and the utilization of defective proteins in mitochondria.

Disorders of the intracellular dynamics of mitochondria observed in neurodegenerative processes also have a negative effect on the functions of these organelles. Hereditary and acquired functional insufficiency of the mitochondrial fragmentation and fusion system, associated with the development of Parkinsonism and asthma, leads to the formation of mitochondrial dysfunction and activation of PHC processes. The high activity of mitophagy in nerve cells, as well as the weakening of the elimination of organelles with structurally functional disorders, can contribute to a shift in the balance between functionally complete and defective mitochondria. An additional factor contributing to the development of degenerative processes in the nervous tissue is a violation of the transport and distribution of mitochondria in neurons, which leads to the formation of areas with mitochondrial deficiency in the processes of the nerve cell and impaired synaptic signal transmission with a decrease in the plasticity of synaptic contacts.

Conclusions: Thus, in the pathogenesis of neurodegenerative diseases, mitochondria are an important link integrating signals from ER under stress, direct and indirect effects of mutant proteins. The patterns discussed in this review require further study, which will contribute to creating a more holistic picture of the pathogenesis of many neurodegenerative diseases. The variety of mechanisms of development of mitochondrial dysfunction and the universality of the principles of its participation in the pathogenesis of various neurodegenerative changes is of significant scientific and practical interest for the formation of strategies for the prevention and treatment of neurodegenerative diseases.

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