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Mitochondrial Dysfunction in Neurodegenerative Diseases

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Abstract:
This review discusses the following mechanisms damage and dysregulatory effects on mitochondria: activation of nonspecific response mechanisms to disruption of the native structure of proteins – unfolded protein response (UPR); loss of mitochondrial function proteins; direct toxic effects of defective proteins on mitochondria; mitochondrial activation PGK mechanisms; dysregulation of the processes of utilization, division and fusion of mitochondria; traffic disruption and intracellular distribution of mitochondria.

Keywords: mitochondria, neurodegenerative processes, programmed cell death, endoplasmic reticulum stress. Key words: mitochondria, neurodegenerative processes, programmed cell death, stress of endoplasmic reticulum.

Introduction

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 is mutations of various proteins with the formation of intracellular aggressions. Such proteins include β-amyloid precursor (AD), presenilin 1 and 2 (AD), τ- protein (PD), α-synuclein (PD), huntingtin (Huntington's chorea), parkin (BP), superoxide dismutase-1 (ALC), ubiquitin (AD, PD, ALC), frataxin (Friedreich ataxia), etc..

It was also found that structural and functional disorders of mitochondria are one of the main pathogenetic links that connect disorders of structure and function of these proteins and their accumulation in neurons with the development of degenerative disorders in neural tissue . The main manifestations of mitochondrial dysfunction include reduction of ATP synthesis, production of reactive oxygen species, activation of programmed cell death (PCD) mechanisms, including apoptosis, autophagy and necrosis- like changes. The consequences of these processes are inhibition of energy-intensive processes in neurons, damage of cell membrane structures by free radicals, development of inflammation in nervous tissue, death of functional nerve cells,

disruption of synaptic signal transduction, increased glutamate release from presynaptic terminals, decreased plasticity of synaptic contacts, and activation of inflammation. Further study of the mechanisms of mitochondrial dysfunction formation in the pathogenesis of neurodegenerative processes should contribute to clarification of 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 was established in in vitro experiments on cell lines, extracellular systems, and in vivo on transgenic animals and in experiments with mitochondrial function inhibitors . An increase in the level of defective proteins in the cell under the influence of mitochondrial dysfunction is of great interest, which indicates the possibility of formation of a "vicious circle" between the production of defective proteins and mitochondrial dysfunction. Chronic exposure to low doses of rotenone (25-50 nM, 8 days) was found to promote ubiquitinylated protein accumulation, E1- ubiquitin activation and increased proteasome activity . AOS generation by mitochondria promotes α-synuclein aggregation, which was confirmed in experiments on rotenone-treated cell cultures . The possibility of induction of neurodegenerative changes in rats by rotenone exposure was shown. Disturbances in the activity of respiratory complex I can initiate the accumulation of hyperphosphorylated τ - protein and, to a lesser extent, α-synuclein in nerve cells .

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

UPR development and endoplasmic reticulum stress. Proteasome dysfunction is known to be associated with the development of various neurodegenerative diseases. It was established that the formation of defective protein deposits during neurodegenerative processes leads to the development of UPR and, as a consequence, endoplasmic reticulum (ER) stress . It was established that ER under UPR-mediated stress promotes the development of degenerative changes in mitochondria. The expression of α-synuclein A53T on PC12 cell line culture was shown to reduce proteasome activity, promote ER stress, increase ARF production and increase the frequency of CRP accompanied by cytochrome c release from mitochondria and caspase-9 and -3 activation . Prolonged UPR is known to result in the induction of apoptosis through cytochrome c release from mitochondria and caspase activation. The

major role in the suicide signal transduction from ER to mitochondria is assigned to the release of $^{Ca2+}$ and Ire1 protein into cytoplasm. The increase of Ca^{2+} concentration in cytoplasm can induce the release of SCC factors from mitochondria by various mechanisms. One of such processes is the activation of proteins contributing to mitochondrial channel formation: Bax and Bid through calpain activation, and Bad and Bik through calcineurin activation. Another mechanism is the stimulation of Ca^{2+}-sensitive isoform of nitro synthase, which increases oxidative stress in the cell. Another mechanism is the activation of mitochondrial mega channels by excessive Ca^{2+}. One more known mechanism is the damage of mitochondrial membrane due to the activation of phospholipase A2. UPR may be involved in the intensification of mitochondria utilization through the induction of macroautophagic processes in the cell. The increase of the proapoptotic factor HtrA2 level in mitochondria under ER stress conditions was shown, which contributes to the intensification of their mediated suicide signal. Thus, under conditions of neurodegenerative processes development, mitochondria are one of the links integrating ER signals under stress and determine the cell fate 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 function has been shown. There is an opinion that in the initial stages of AD, β-amyloid accumulation and τ-protein hyperphosphorylation may serve as natural mechanisms of cell protection against oxidative stress, which develops as a consequence of mitochondrial dysfunction progression and redox-active metal accumulation. Nevertheless, exceeding a certain threshold level of the concentration of these proteins in the cell contributes to the development of structural and functional disorders in mitochondria. In the brains of AD patients, β-amyloid peptide has been found to accumulate to a high degree in mitochondria, disrupting the activity of glycolysis and Krebs cycle enzymes and activating AFC production . The ability of the extracellular domain of amyloid precursor protein and β-amyloid peptide to inhibit ATP synthesis by the ATP synthase complex under in vitro conditions is interesting. This is determined by the similarity of the structure of this domain with the natural inhibitor of F (1)-subunit of ATP synthase in mitochondria (IF (1)). It was demonstrated that β-amyloid fibrils and its precursor protein are able to bind to the mitochondrial membrane . The β-amyloid precursor protein was found to accumulate predominantly on protein import channels in the mitochondria of the brain tissue of AD patients. 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 results in inhibition of the import into mitochondria of nuclear-encoded

proteins, cytochrome oxidase subunits IV and V b, which leads to inhibition of this protein complex and increases mitochondria production of H O_{22}. High-resolution transmission electron microscopy confirmed the possibility of pore formation in the membranes of mitochondria and other organelles from the oligomers of β- amyloid precursor protein, which disturbs the ionic balance in the cell and causes the development of SCC. The ability of β-amyloid precursor protein to stimulate phospholipase D activity has been shown to change phospholipid spectrum of mitochondrial membranes: the concentration of phosphatidylcholine, phosphatidylethanolamine, and phosphatidic acid increases. It was found that heme binding by β-amyloid peptide leads to heme deficiency in the cell, contributing to the development of disorders in the heme IV complex of the mitochondrial electron-transport chain . In transgenic rats expressing human huntingtin, the aggregation of this protein in mitochondria was observed, which contributed to the development of mitochondrial dysfunction. It was shown that the N-terminal fragment of human α-synuclein carries a latent signal that determines its localization in mitochondria. Imported into mitochondria α-synuclein is preferentially associated with the inner mitochondrial membrane. Accumulation of α-synuclein in the mitochondria of human dopaminergic neurons contributes to a decrease in the activity of respiratory complex I and, as a consequence, an increase in AOS production by mitochondria. Another consequence of the interaction between α- synuclein and mitochondria is the release of cytochrome c 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 can directly interact with various mitochondrial structures: ATP synthase, translocases TOM40 and TIM23, and mitochondrial membranes (pore formation from oligomers of β-amyloid precursor protein).

Activation of mitochondrial SCC mechanisms. In addition to the direct effect of the above defective proteins on mitochondrial function, their ability to activate the release of mitochondrial apoptotic factors through direct or indirect effect on regulatory proteins: p53, Akt, Bad, Bax, Bcl-x(L), calcineurin, etc. Mutant gentingtin was shown to interact with p53, which contributes to an increase in its level in the nucleus. Disruption of p53 activity by RNA interference, gene deletion contributed to the prevention of mitochondrial membrane depolarization and compensated the cytotoxic effect of mitochondrial dysfunction. It was found that β- amyloid peptide induced apoptosis of cerebrovascular endothelial cells through inactivation of Akt protein kinase, which prevents the activation of apoptosis signals involving Bad. A consequence of these events is the development of mitochondrial dysfunction

accompanied by the release of endonuclease G and Smac from mitochondria. It was established that β-amyloid peptide activates cytochrome c release from mitochondria through dephosphorylation of Bad under the influence of calcineurin. The phosphorylated form of τ-protein was shown to activate the mechanisms of apoptosis characterized by the decrease in mitochondria transmembrane potential, the increase in JNK, Bim, Bad, Bax and caspase-3. In an experiment with neuronal cultures from cerebellum, striatum and substantia nigra transfected with mutant gene ataxin-3, it was shown that the latter activates cytochrome C and Smac release through activation of Bax expression and suppression of Bcl-x(L) expression. The accumulation of ceramides in neurons, observed in various neurodegenerative processes, may contribute to the activation of SCC by inducing the release of some pro- apoptotic mitochondrial proteins: cytochrome C, Omi, SMAC and AIF. Summarizing the above, under the conditions of neurodegenerative processes development, defective proteins affect various links of the CCP system interacting with mitochondria. An increase in the intensity of suicide signals exposure to mitochondria contributes to a decrease in the transmembrane mitochondrial potential, mitochondria production of ROS and release from these organelles the factors initiating the mechanisms of programmed cell death.

Deficiencies in mitochondrial protein function. It has been established that one of the mechanisms of ALS development can be catalysis by a mutant variant of mitochondria-specific superoxide dismutase-1 of atypical biochemical reactions, the product of which can be various free radicals, including superoxide anion, hydroxyl radical, hydrogen peroxide and peroxynitrite. High levels of reactive oxygen species can damage mitochondrial structures and participate in the development of mitochondrial dysfunction. Mutations of this enzyme were found to impair anterograde mitochondrial transport in neuronal sprouts. In mixed primary culture of astrocytes and motor neurons showed that 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 the astrocytes themselves and in those cultured together motor neurons. Disturbances in the structure of the DJ-1 protein (PARK7), a component of the antioxidant protection of mitochondria, the nucleus, and a modulator of transcritical activity were found to contribute to the development of recessively inherited parkinsonism. Point mutations of mitochondrial protein HtrA2 (PARK13) were shown to be a susceptibility factor for PD. Low expression level of mitochondrial iron-binding protein frataxin observed in Friedreich's ataxia contributes to iron accumulation in mitochondria, disruption of iron-sulfur clusters and high sensitivity to oxidative stress. Mutations in the gene HSPD1 encoding the

mitochondrial chaperone Hsp60 have been identified in patients with an autosomal dominant form of hereditary spastic paraplegia. This is probably the cause of the defective mitochondrial protein recycling system. Thus, functional deficiency of various mitochondrial proteins contributes to the impairment of mitochondrial systems of antioxidant protection, iron homeostasis, and utilization of defective proteins, which promotes the development of structural and functional disorders of mitochondria in conditions of neurodegenerative processes.

Disruption of mitochondrial fission and fusion processes. A close relationship between the processes of mitochondrial fragmentation and fusion and activation of mitochondrial PKC mechanisms has now been shown. PINK1 (PTEN- induced putative kinase 1) and parkin have been shown to be components of the mitochondrial fusion/ fission system and are involved in the maintenance of mitochondrial integrity and integrity. Mutations of PINK1 and parkin genes are observed in patients with recessive forms of PD. Simulation of such disorders on Drosophila melanogaster showed the presence of structural abnormalities of mitochondria (enlargement, swelling) of various tissues of the body, including muscle and dopaminergic neurons. Parkin (PARK2) mutations were found to contribute to impaired elimination of defective mitochondrial forms by autophagosomes. Overexpression of β-amyloid precursor protein by M17 cells is accompanied by mitochondria fusion/separation system disorders: the levels of dynamino- like protein-1 and OPA-1 significantly decrease, while the level of Fis-1 significantly increases [4. To summarize the above, congenital and acquired defects in the mitochondrial fragmentation/ fusion system, contributing to the development of mitochondrial dysfunction and activation of SCC processes, are involved in the formation of neurodegenerative processes.

Disruption of mitochondrial utilization. It is suggested that excessive activity of autophagic processes may lead to a decrease in the number of mitochondria in the cell. Inhibition of proteasome activity is observed in neurodegenerative diseases, which disturbs mitochondria homeostasis in the cell and contributes to mitochondrial dysfunction progression. The possibility of induction of mitochondrial dysfunction by proteasome function inhibitors is objectively confirmed . The consequence of these processes is the activation of mitochondrial macroautophagic and the accumulation in lysosomes of lipofuscin, a product of incomplete degradation of mitochondrial components, which leads to a decrease in the activity of protein degradation through autophagy. Lipofuscin accumulation with aging is demonstrated in microglia cells accompanied by an increase in mRNA concentration of proinflammatory (TNF-α, IL-1β, IL-6) and anti-inflammatory (IL-10, TFR-β1) cytokines. In general, impaired

mitochondrial utilization leads to a decrease in the number of functionally complete mitochondria, accumulation of products of their incomplete decay in nerve cells, weakening of resistance, and development of neurodegenerative changes.

Disruption of transport and intracellular distribution of mitochondria. Suppression of mitochondrial axonal transport by defective forms of τ-protein and huntingtin leads to disruption of energy supply to nerve cell spines, the main consequence of which is disruption of synaptic transmission and degeneration of synapses. Overexpression of human τ- protein in motor neurons of Drosophila melanogaster larvae was found to result in the reduction of functionally complete mitochondria in presynaptic terminals, thus impairing synaptic signal transmission. Transfection of the τ-protein gene into mature hippocampal neurons resulted in disruption of its distribution in cells, suppression of transport of mitochondria and other organelles with subsequent degeneration of synapses . Expression of mutant huntingtin was found to attenuate axonal transport of nerve cell organelles, including mitochondria. Thus, impaired mitochondrial transport and distribution in neurons is an additional factor contributing to the development of degenerative processes in nerve tissue.

Conclusion:

Thus, mechanisms of mitochondrial dysfunction formation under conditions of neurodegenerative processes are multifaceted and highly complex. This is determined by the diversity of mutant proteins associated with neurodegenerative diseases and the complexity of their negative impact. The universal mechanism of mitochondrial dysfunction development in this case is ER stress, which contributes to the increase of Ca^{2+} concentration in cytosol, activation of mitochondrial CRP mechanics and mitophagy process. A number of mutant proteins and their aggregates (β- amyloid precursor protein, α-synuclein) 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 results in decreased ATP production, disturbed electron transport chain and decreased mitochondria transmembrane potential. Interesting is the development of neurodegenerative processes as a consequence of abnormalities in several mitochondrial proteins: superoxide dismutase-1, DJ-1, frataxin, and mitochondrial Hsp60. Expression of these proteins contributes to disruption of antioxidant protection, iron homeostasis, and utilization of defective proteins in the mitochondria.

Intracellular mitochondrial dynamics abnormalities observed in neurodegenerative processes also have a negative effect on the function of these organelles. Hereditary and acquired functional insufficiency of the mitochondrial fragmentation and fusion system associated with the development of parkinsonism and AD leads to mitochondrial dysfunction and activation of SCC processes. High mitophagy activity in nerve cells as well as weakened elimination of organelles with structural and 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 neural tissue is the impaired transport and distribution of mitochondria in neurons that leads to the formation of mitochondria-deficient areas in nerve cell spines and impaired synaptic signal transduction with decreased plasticity of synaptic contacts.

Thus, in the pathogenesis of neurodegenerative diseases, mitochondria are an important link that integrates signals of ER under stress, direct and indirect effects of mutant proteins. Patterns considered in this review require further study, which will contribute to a more holistic picture of the pathogenesis of many neurodegenerative diseases. The diversity of mechanisms of mitochondrial dysfunction and uniformity of its involvement in the pathogenesis of various neurodegenerative changes is of great scientific and practical interest for the development of preventive and treatment strategies for neurodegenerative diseases.

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