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CONTEMPORARY PATHOGENETIC ASPECTS OF PARKINSON'S DISEASE DEVELOPMENT

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Abstract

The article presents modern views on the role of apoptosis, necrosis, oxidative stress and inflammatory processes, as well as their combination in the pathogenesis of Parkinson's disease. The Parkinson's disease remains one of the global medical and social problems. According to most authors, the number of patients worldwide who suffer from Parkinson's disease exceeds 6 million. The disease is diagnosed in 1% of the population under the age of 60 and 3% at the age of 80 and older. In Ukraine, the prevalence of the disease is 133 cases per 100 thousand populations. High rates of disability, a steady increase in the incidence, still insufficient treatment effectiveness, significant economic costs of treatment, given the relatively high cost of drugs, the need for constant dynamic monitoring of the doctor, the development of rehabilitation measures, make the problem of Parkinson's disease in Ukraine a national one.

According to modern ideas about the pathogenetic changes that are characteristic of Parkinson's disease, one of the leading roles in the development of neurodegeneration in it is played by the presynaptic protein α-synuclein. However, the exact functions of this protein are still insufficiently studied. The key moment of the molecular pathogenesis of Parkinson's disease is the change in the native spatial stacking of α-synuclein with the formation of β-structures and oligomers that have neurotoxicity followed by their fibrillation with the formation of increasing cytoplasmic aggregates. There is evidence that even before the manifestation of a typical clinic for Parkinson's disease pathological synuclein inclusions is found in the olfactory bulbs and neurons of the dorsal motor nucleus n. vagus, after which they can be found in more rostral sections – the nuclei of the suture and the reticular pharmacy, the black substance, etc. Of great importance is the presence of exogenous factors that can reduce the risk of disease, which include smoking, drinking coffee, taking non-steroidal anti-inflammatory drugs, vitamin E, etc. Such changes can be explained by their effect on the molecular properties of α-synuclein. It has been shown that, for example, hydroquinone stabilizes soluble oligomeric forms of α-synuclein and has an inhibitory effect on the formation of fibrils.

Keywords: *Parkinson's disease, pathogenesis, α-synuclein, oxidative stress, apoptosis, necrosis, inflammation.*

The Parkinson's disease (PD) remains one of the global medical and social problems. According to most authors, the number of patients worldwide who suffer from PD exceeds 6 million [*Shadrina* M, *2011*]. The disease is diagnosed in 1% of the population under the age of 60 and 3% at the age of 80 years and older [*Lee A, Gilbert R, 2016*].

In Ukraine, the prevalence of PD is 133 cases per 100 thousand population [*Yurov I, 2012*]. High rates of disability, a steady increase in the incidence, still insufficient treatment effectiveness, significant economic costs of treatment, given the relatively high cost of drugs, the need for constant dynamic monitoring of the doctor, the development of rehabilitation measures, make the problem of PD in Ukraine a national one. A large number of fundamental clinical trials have been devoted to the problem of PD, in which great attention has been paid to the study of the clinical manifestations and stages of PD development, the definition of unified criteria for establishing a diagnosis and unified principles for assessing the severity of the

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disease and monitoring the effectiveness of therapeutic measures. In terms of symptomatology, the staging of the disease course is defined, which remains important today for the adoption of diagnostic, therapeutic and expert decisions.

To date, PD is one of the important factors in the development of acquired cognitive disorders that can progress to dementia [*Batukayeva L, 2010; Levin O, Fedorova N, 2012; Chukhlovina M, 2014; Mazurenko E et al., 2014*]. Therefore, the urgency o f early diagnosis of cognitive disorders and the timely appointment of adequate therapy, with a dynamic assessment of its effectiveness in patients with PD becomes extremely important [*Slobodin T, 2011*]. One of the first manifestations of PD may be psychoemotional and vegetative disorders, which require increased attention and appropriate response to them from the physician.

According to modern ideas about the pathogenetic changes that are characteristic of PD, one of the leading roles in the development of neurodegeneration in PD is played by the presynaptic protein α-synuclein. Under normal conditions, this protein exists in the cell in the form of a tetramer and is possibly involved in the processes of vesicular transport and the regulation of the dopaminergic transmission. However, the exact functions of this protein are still insufficiently studied. The key moment of the molecular pathogenesis of PD is the change in the native spatial stacking of α-synuclein with the formation of β-structures and oligomers that have neurotoxicity followed by their fibrillation with the formation of increasing cytoplasmic aggregates [*Illarioshkin S, 2015*].

In the sporadic form of PD, the pathology of α-synuclein is associated with the interaction of exogenous factors, the characteristics of the genome and systemic metabolism. When these factors are imposed on the age-related, a set of changes in the systems of cellular detoxification, the functioning of mitochondria, synaptic transmission and endosomal transport in a particular case arise.

According to many researchers, the role of a number of neurotoxins, and especially of pesticides [*Gatto N et al., 2010*], is the most convincing of the exogenous factors that can be used in PD. One of the representatives of this group is the rotenone. With its help in the experiment it is possible to reproduce the clinical, neurochemical and pathomorphological changes characteristic for PD. Data on an increased average risk of development of PD with farming and living in agro-industrial regions, accompanied by long-term exposure to pesticides, have been obtained by an average of 1.4 times. The molecular basis of this fact is that pesticides, including rotenone, can provoke conformational changes in the molecule of the cellular protein of α-synuclein and substantially accelerate the rate of formation in the neurons of α-synuclein fibrils and Lewy bodies. The functioning of mitochondria through inhibition of complex I of the respiratory chain is also impaired, oxidative stress and apoptosis reactions are induced [*Illarioshkin S, 2015*]. It is important to note the value of this approach in a reliable assessment of the role of the processes of apoptosis, necrosis, inflammation and peroxidation of lipids and their combination in the pathogenesis of the disease, since in the experiment factors that can cause similar changes in the elderly are eliminated.

There is evidence that even before the manifestation of a typical clinic for PD pathological synuclein inclusions is found in the olfactory bulbs and neurons of the dorsal motor nucleus n. vagus, after which they can be found in more rostral sections – the nuclei of the suture and the reticular pharmacy, the black substance, etc. [*Braak H et al., 2003*].

According to the conducted studies, it was noted that even in the latent phase of PD, neurodegenerative changes that correspond to PD were found in peripheral vegetative neurons: in the cells of Meissner's intestinal plexus, pre- and paravertebral ganglions, and some neurotoxins contribute to the secretion of α-synuclein by intestinal neurons, the capture of protein by presynaptic vegetative endings and its retrograde spread into the soma of the cell, which contributes to the progression of pathological changes [*Beach T et al., 2010*]. Secretion of α-synuclein can occur by primary cultures of intestinal neurons by classical exocytosis. Given the presence of such pathogenetic changes, it can be considered possible, according to many authors, to include vegetative neurons of the intestine and olfactory nuclei cells as the earliest sign characteristic of PD, indicating a possible inhalation or alimentary entry of a trigger pathogen, followed by its spread by the fibers of the olfactory and vagus nerves [*Illarioshkin S, 2015*].

Of great importance is the presence of exogenous factors that can reduce the risk of disease, which include smoking, drinking coffee, taking non-steroidal anti-inflammatory drugs, vitamin E, etc. [*Wirdefeldt K et al., 2011*]. Such changes can be explained by their effect on the molecular properties of α-synuclein. It has been shown that, for example, hydroquinone stabilizes soluble oligomeric forms of α-synuclein and has an inhibitory effect on the formation of fibrils.

According to the prion hypothesis of the disease onset, the pathological form of α-synuclein can play the role of a matrix in a cell on which self-replicating anomalous molecules takes place when interacting with normal surrounding α-synuclein molecules. After that there is a gradual increase in the concentration of neuronal protein aggregates to massive structured inclusions – Lewy bodies, which include a large number of other cellular proteins. The possible similarity with prion diseases is indicated by the amyloid nature of α-synuclein aggregates, which are formed in the cytoplasm of neurons [*Hirsch E et al., 2013*]. The possibility of transferring α-synuclein pathology from the neuron to the neuron was confirmed on the models of transgenic animals and cell cultures. α-synuclein can be secreted and captured by various types of central nervous system cells using a number of independent molecular mechanisms.

The role of craniocerebral trauma in the pathogenesis of PD can be explained by rotational damage of fibers of mesencephalic neurons or by violation of the blood-brain barrier, which provokes an immune response from the brain substance and causes activation of acute phase reactions with overexpression of proteins that provoke the formation of α-synuclein aggregates [*Irwin D, Trojanowski J, 2013; Illarioshkin S, 2015*].

The value of age is an important proven independent risk factor for PD. This is due to chronic oxidative stress, a progressive accumulation of mitochondrial DNA mutations, a decrease in the concentration of glutathione, a decrease in the ability of neurons to activate the stress response. Either of these factors or a combination of them leads to the fact that the initial changes in the laying of α-synuclein or other target proteins, which at a younger age would be eliminated by powerful intracellular defense systems, lead to the onset of the fatal cytotoxic cascade and cell death. Therefore, the study of inflammatory markers, vascular wall permeability factors, as possible earliest markers of a possible variant of the disease course and probable prognosis seems to be quite significant.

The role of heredity in the pathogenesis of PD development was established in a large number of epidemiological and population studies. For example, there is evidence that the PINK1 protein interacts with the Parkin in the process of labeling defective mitochondria and ensures their degradation by mitophagy. This confirms the role of mitochondrial dysfunction in the molecular pathogenesis of PD [*Illarioshkin S, 2015*].

PARK7 indicates the significance of oxidative stress in the pathogenesis of PD, since the DJ-1 protein is a mitochondrial antioxidant, neutralizing excess H2O2. It is proved that DJ-1 interacts with Parkin and PINK1 in the regulation of mitochondrial dynamics.

PARK8, a protein product of the dordarin gene, is a cytoplasmic kinase that can be incorporated into the processing of neuronal proteins and the functioning of mitochondria.

Recently, the results of general genomic scanning in PD indicate the presence of 10 new genetic loci associated with the disease (HLMA-DR, BST1, GAK/DGKQ, MCCC1/LAMP3, SYT11/RAB25, FGF20, ACMSD, STK39, RAB7L1, etc.). Attention is drawn to the association of PD with the immune response genes, which confirms the role of inflammatory microglia reactions in the pathogenesis of PD. Microglial inflammation indirectly exerts its effect through the secretion of specific cytokines that enhance the aggregation of α-synuclein [*Illarioshkin S, 2015*].

The great importance in the pathogenesis of PD is the phenomenon of apoptosis. Apoptosis is a programmable cell death, a process that is regulated at the cellular level, the result of which is the fragmentation of the cell into individual apoptotic bodies that are confined to the plasma membrane. Programmed death is an active form of cell death and is the result of the implementation of its genetic program or response to external signals and requires energy and synthesis of macromolecules.

Induction of apoptosis followed by activation of proapoptotic proteins leads to activation of caspases (cysteine proteases) [*Thornberry N, Lazeb-*

nik Y, 1998; Vikulina A, 2015]. There are initiating and effector caspases, that is, caspases function as proteolytic cascades. The effect of effector caspases is the destruction of a variety of proteins that can participate in the maintenance of homeostasis and in the repair of cell components, cell cycle protein regulators, structural proteins, and the like.

The initiation of apoptosis can occur under the influence of external (extracellular) or intracellular factors. For example, as a result of hypoxia, oxidative stress, subnecrotic damage to chemical or physical agents, cross-linking of the corresponding receptors, distortion of cell cycle signals, elimination of growth factors and metabolism, etc. Despite the diversity of initiating factors, two main ways of transduction (transfer) apoptotic signal: a receptor-dependent signaling pathway involving cell death receptors and the mitochondrial pathway [*Shirokova A, 2007*].

Receptor-dependent signaling pathway: the process of apoptosis often begins with the interaction of specific extracellular ligands with cell death receptors, which are expressed on the surface of the cell membrane. Extracellular regions of the death receptors interact with the ligand trimmer (CD95L, TNF, Apo3L, Apo2L, etc.), as a result, the death receptors are trimerized (3 molecules of the receptor are "crosslinked"). Because of the receptor thus activated, interaction with the corresponding intracellular adapter (or adapters) takes place. Adapter associated with the death receptor interacts with effectors – currently still inactive precursors of proteases from the family of initiating caspases – with procaspases. As a result of the "ligand-receptor-adapter-effector" interaction chain, aggregates are formed in which the process of caspase activation begins. Such aggregates are called apoptosomes, apoptotic chaperones or signaling complexes inducing death (from English DISC – death-inducing signaling complex – "signal complex, induces death"). Activated initiating caspases subsequently participate in the activation of effector caspases [*Kaufmann S, Hengartner M, 2001*].

The mitochondrial signaling pathway of apoptosis is realized through the release of apoptogenic proteins from the intermembrane space of the mitochondria into the cytoplasm of the cell. The release of apoptogenic proteins can probably be carried out in two ways: through the rupture of the mitochondrial membrane or by the opening of highly permeable channels on the outer membrane of the mitochondria. Activated in this way, caspase-9 conducts recruitment of procaspase-3, which in turn is activated prior to caspase-3. The rupture of the outer membrane of the mitochondria can be explained by the increase in the volume of the mitochondrial matrix. This process is associated with the opening of the pores of the mitochondrial membrane, which leads to a decrease in the membrane potential and high-amplitude swelling of the mitochondria as a result of osmotic imbalance. The opening of pores is stimulated by such factors: depletion of cells with reduced glutathione; formation of reactive oxygen species; an increase in the Ca2 + content in the cytoplasm of the cell; depletion of the mitochondrial pool of adenosine triphosphate, etc. Cytochrome C, prokaspase 2, -3 and -9 are released into the cytoplasm; apoptosis inducing factor. With the participation of cytochrome C, apoptosis is formed together with the Apaf-1 protein ("apoptosis protease activation factor"). Previously, Apaf-1 undergoes conformational changes due to the reaction proceeding with the energy expenditure of ATF. It is assumed that the transformed Apaf-1 acquires the ability to bind cytochrome C. In addition, the access of the Apaf-1 CARD (Caspase activation and recruitment domain) for procaspase-9 is opened, due to which oligomerization of at least 8 subunits of the transformed Apaf-1 protein involving cytochrome C and procaspase- 9. So an apoptosis is formed, activating caspase-9. Mature caspase-9 binds and activates procaspase-3 to form effector caspase-3[*Bernardi P et al., 2001*, [*Vikulina A, 2015*] .

During the effector phase (the caspase cascade), various initiating pathways are transformed into one (or more) common pathway of apoptosis. As a rule, activation of the cascade of effector proteins and regulating protein-modulators occurs. The main effector of apoptosis is caspase [*Earnshaw WC et al., 1999*]. Caspases involved in apoptotic processes are divided into initiating and effector. With the help of initiating caspases, effector caspases are activated, which in turn provoke and directly participate in the transformation of the cell. One of the main functions of effector caspases is direct and indirect destruction of cellular structures.

The result of programmed cell death, regardless of the initial initiation effect, is the degradation of

the cell (the degradation phase) by fragmentation into individual apoptotic bodies bounded by the membrane. Fragments of the dead cell are phagocytosed by macrophages or neighboring cells, bypassing the development of the inflammatory reaction, which in principle distinguishes apoptosis from necrosis, which is characterized by the presence of inflammation, which finds its exposure in the corresponding concentration of pro-inflammatory cytokines [*Vikulina A, 2015*]

In PD, it is especially important to pay attention to the apoptosis of cells in the state of "cellular stress". Exposure to cells of reactive oxygen species, which in its intensity can not cause necrosis, leads to the initiation of apoptosis.

In the question of the pathogenetic mechanisms of the functioning of the caspase cascade, it is important to study the activity of caspase 3 and 9, which are mainly found in the mitochondria. For its intracellular redistribution and activation, a necessary condition is the destruction of the outer mitochondrial membrane, which occurs in the early stages of apoptosis. In the process of activation, caspase-3 forms diameters. Cytochrome C/Apaf-1/ caspase-9 form apoptosome, which enhances the caspase cascade. Activated caspase-3 refers to the central complex of apoptosis pathways.

In the presence of processes in the central nervous system, accompanied by the destruction of the synaptic apparatus of neurons, as well as the death of the nerve cells, their dendritic apparatus, synapses, a local inflammatory reaction is triggered, in which microglial structures take an active part. When inflammation in the neural tissue cytokines accumulate. All this is accompanied by a violation of glucose metabolism in the nervous tissue, energy deficiency, increased peroxidation, damage and progressive insufficiency of antioxidant systems of neurons, inferiority of acetylcholine and other transmitter systems of the brain. It is now established that one of the main mechanisms leading to the death of neurons is their apoptosis. Apoptosis of neurons can be triggered in several ways. First, damage to neurons increases oxidative stress, leads to intracellular accumulation of reactive oxygen species, which in turn causes the activation of N-methyl-D-aspartate (NMDA) receptors, followed by the opening of calcium channels in the neuronal membrane. An increase in the level of Ca^{++} in protoplasm of neurons activates procaspases and, subsequently, the entire caspase cascade. Secondly, in view of the fact that some neurons die due to the development of necrobiosis and necrosis, the inflammation develops in the nerve tissue and, as its constant companion, the accumulation of pro-inflammatory cytokines occurs. Contact of these cytokines with the "death receptors" of the cell triggers the "instructive apoptosis" mechanism. Thirdly, the synapses are destroyed, and the nerve cells lose contact with each other. To assess the severity of oxidative stress, the activity of the levels of superoxide dismutase 1 (Cu, Zn-SOD) and superoxide dismutase 2 (MN-SOD) and the state of the glutathione system are used.

Thus, it can be assumed that it is possible that in the nervous tissue processes of apoptosis, necrosis, inflammation of oxidative stress, competing with each other and potentiating each other, further deepening the negative impact on the course of the disease and its prognosis are simultaneously taking place.

Another pathogenetic mechanism in PD is autophagy – degradation of organelles and cytoplasmic material, which occurs with the involvement of intracellular membrane structures [*Manskih V, 2007*]. With autophagy de novo, specialized structures are formed – autophagosomes. Possible factors of autophagy are: absence of growth factors or lack of nutrients; presence in the cytoplasm of damaged organelles, for example, mitochondria. With a shortage of nutritional compounds, the cell begins to utilize part of its cytosolic proteins and organelles with autophagy. There are three types of autophagy – microautophagy, macroautophagy and chaperone-dependent autophagy. The actual type of PD is precisely type 3 - chaperone-dependent autophagy. In this case, directed transport of partially denatured proteins to the cytoplasm through the lysosome membrane into its cavity occurs where they are digested. This type of autophagy is induced by stress. This occurs with the participation of cytoplasmic chaperone proteins of the hsc-70 family, accessory proteins and LAMP-2 (Lysosome-associated membrane protein), which serve as the membrane receptor of the chaperone complex and the protein to be transported to the lysosome.

In the processes of the neurons of affected areas of the brain, an accumulation of immature autophagosomes is observed, which are not trans-

ported to the body of the cell and do not merge with lysosomes. Mutant alpha-synuclein is absorbed and digested with chaperone-dependent autophagy, and activation of this process prevents the formation of their aggregates in neurons.

Inflammation is most often a catastrophe for surrounding cells. The presence or absence of inflammation is used as a sign that distinguishes apoptosis from necrosis. From the above, it follows that necrosis is characterized by rupture of the cytoplasmic and intracellular membranes, which leads to the destruction of the organelles, the release of lysosomal enzymes, and the release of cytoplasmic contents into the intercellular space. The above-mentioned changes are also aggravated by a violation of the permeability of the blood-brain barrier, one of the methods for determining it is the endothelial factor of type A. The concept of "programmable necrosis" was formed on the basis of the evidence that there is a signaling pathway for initiating necrosis in response to receptors binding of such molecules as TNF, against the background suppression of apoptosis [*Fiers W et al., 1999*]. Programmed necrosis in turn can be suppressed if the cells are influenced by antioxidants or inhibit the activity of RIP protein kinase [*Holler N et al., 2000*]. Interestingly, RIP protein kinase is one of the targets of caspase action. This means that the initiation and implementation of apoptosis actively suppress the development of necrosis in cells. The same can be said with respect to PARP (poly (ADP-ribose) polymerase).

Thus, taking into account all the above, given the timely correction of the revealed violations based on the established relationships between the parameters of the antioxidant protection system, local inflammation in the zone of neurodegeneration, the degree of apoptosis, the state of the blood-brain barrier, it may be possible to identify individuals at risk for rapid PD progression. It is necessary to continue the scientific search to determine the progression factors of PD at the level of SOD 1 (Cu, Zn-SOD) and SOD 2 (MN-SOD), IL-1β, IL-2, IL-6, IL-8, IL-10, VEGF -A-factor, caspase 3. It is expedient to evaluate the possibilities of laboratory diagnostics of oxidative stress with the determination of the activity of various SOD subtypes to ensure timely neuroprotective correction of adaptation mechanisms and cytoprotection in patients with PD. Taking into account the clinical-neuropsychological, molecular-biochemical effectiveness of differentiated use of neuroprotective drugs (citicoline, amantadine sulfate), it is necessary to improve the pathogenetically grounded patterns of their appointment to patients with PD with an individual approach to the patient and taking into account the effect of each drug on the status of SOD, IL-cascade, and caspase mechanism.

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