MOLECULAR-CELLULAR MECHANISMS OF NEURON DEGENERATION IN PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease is a chronic, progressive neurodegenerative disorder characterized by predominant damage to dopaminergic neurons in the substantia nigra of the midbrain and dysfunction of the nigrostriatal system. In recent decades, a significant body of evidence has accumulated indicating that neurodegeneration in Parkinson's disease is underpinned by a complex set of interconnected molecular and cellular mechanisms. Key pathological processes include α-synuclein aggregation, impaired proteostasis, mitochondrial dysfunction, oxidative stress, defects in autophagy and mitophagy, and activation of neuroinflammatory responses. The mutual potentiation of these mechanisms forms a persistent degenerative cascade leading to progressive neuronal death.

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Materials and methods of research. This study is an extensive analytical review of the current scientific literature. It includes data from fundamental and clinical studies published in leading international peer-reviewed journals in neuroscience and neurology. We analyzed the results of in vitro and in vivo experimental studies, clinical observations, as well as systematic reviews and meta-analyses. We focused on publications devoted to the role of α-synuclein, mitochondrial dysfunction, oxidative stress, autophagy, mitophagy, and genetic factors in the pathogenesis of Parkinson's disease. We utilized comparative analysis, pathogenetic modeling, and data synthesis to formulate a comprehensive concept of molecular and cellular neurodegeneration.

Results and discussion. A review of the literature revealed that the pathological aggregation of α-synuclein is a central component in the pathogenesis of Parkinson's disease.

Normally, this protein is involved in the regulation of synaptic transmission; however, when its folding is disrupted, toxic oligomeric and fibrillar structures form, which have a neurotoxic effect. The accumulation of α-synuclein leads to the formation of Lewy bodies and disruption of the cellular proteostatic balance. Mitochondrial dysfunction, manifested by decreased respiratory chain activity, ATP deficiency, and increased production of reactive oxygen species, plays a significant role in the development of neurodegeneration. Oxidative stress damages lipids, proteins, and nucleic acids, which exacerbates neuronal energy deficiency. Of particular importance is the disruption of mitophagy, associated with dysfunction of the PINK1 and Parkin proteins, which leads to the accumulation of defective mitochondria. An additional pathogenic factor is neuroinflammation caused by the activation of microglia and astrocytes. The production of proinflammatory cytokines and inflammatory mediators enhances apoptotic neuronal death and contributes to the chronicity of the degenerative process. Genetic mutations associated with Parkinson's disease potentiate these mechanisms, reducing the adaptive capacity of neuronal cells.

Conclusions

1. Parkinson's disease is a multifactorial neurodegenerative disease with complex molecular and cellular pathogenesis.

2. α-synuclein aggregation and impaired proteostasis play a key role in the initiation of neurodegeneration.

3. Mitochondrial dysfunction and oxidative stress are the leading mechanisms of disease progression.

4. Defects in autophagy and mitophagy contribute to the accumulation of cellular damage.

5. Neuroinflammation and genetic factors enhance the degenerative cascade.

6. A deep understanding of the molecular and cellular mechanisms of Parkinson's disease opens up prospects for the development of pathogenetically based neuroprotective strategies.

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