Mitochondrial Dysfunction in the Pathogenesis of Parkinson Disease: Current Concepts and Potential Therapeutic Strategies

Natalia G. Zhukova, Julia V. Kolobovnikova, Zaynutdinkhuzha F. Sayfitdinkhuzhaev

Siberian State Medical University, Tomsk, Russia

Abstract

Parkinson disease (PD) is a progressive extrapyramidal disorder characterized by the biodegradation of dopaminergic neurons in the substantia nigra. The total number of patients diagnosed with PD worldwide is expected to more than double by 2030, inevitably placing a significant financial burden on healthcare systems. The progression of the disease leads to persistent maladjustment in all aspects of the patient's life, resulting in a loss of human resources. Approximately 85–90% of PD cases are sporadic and multifactorial. The remaining 10–15% are familial forms with conventional inheritance patterns. Current research suggests multiple mechanisms for PD development, but increasing evidence supports a critical role of mitochondrial dysfunction in PD pathogenesis.

*The **aim** of this review was to discuss the key pathogenetic mechanisms of mitochondrial dysfunction in PD pathogenesis. The following keywords and phrases (both in Russian and English) were used to search databases such as eLIBRARY.RU, PubMed, and Web of Science for full-text articles in Russian and English published over the last 20 years: Parkinson disease, neurodegeneration, pathophysiology, mitochondrial dysfunction, bioenergetics, mitophagy, pathogenetic therapy.*

The review describes the factors that cause mitochondrial dysfunction and its impact on PD. Potential therapeutic strategies targeting mitochondrial dysfunction are also described.

Keywords: *Parkinson disease; neurodegeneration; pathophysiology; mitochondrial dysfunction; bioenergetics; mitophagy; pathogenetic therapy*

Source of funding. The study was not supported by any external sources of funding.

Conflict of interest. The authors declare no apparent or potential conflicts of interest related to the publication of this article.

For correspondence: 2, Moskovsky tract, Tomsk, Russia, 634050. Siberian State Medical University.
E-mail: sayfutdinxodjaev2002@gmail.com. Zaynutdinkhuzha F. Sayfitdinkhuzhaev.

For citation: Zhukova N.G., Kolobovnikova J.V., Sayfitdinkhuzhaev Z.F. Mitochondrial dysfunction in the pathogenesis of Parkinson disease: current concepts and potential therapeutic strategies. *Annals of Clinical and Experimental Neurology*. 2025;19(2):74–81.
DOI: https://doi.org/10.17816/ACEN.1219
EDN: https://elibrary.ru/KHXTLY

Received 25.10.2024 / Accepted 04.12.2024 / Published 30.06.2025

Митохондриальная дисфункция в патогенезе болезни Паркинсона: современные представления и потенциальные терапевтические стратегии

Н.Г. Жукова, Ю.В. Колобовникова, З.Ф. Сайфитдинхужаев

Сибирский государственный медицинский университет, Томск, Россия

Аннотация

Болезнь Паркинсона (БП) – прогрессирующее экстрапирамидное заболевание, характеризующееся биодеградацией дофаминергических нейронов чёрной субстанции. Прогнозируется, что общее число пациентов с диагнозом БП к 2030 г. в мире увеличится более чем в 2 раза, что неизбежно приведёт к большой материальной нагрузке на систему здравоохранения. Прогрессирование заболевания характеризуется стойкой дезадаптацией пациентов во всех сферах жизни и, как следствие, потерей человеческих ресурсов. Около 85–90% случаев БП являются спорадическими и имеют мультифакториальную природу. Оставшиеся 10–15% являются семейными формами с традиционными формами наследования. Современные исследования доказывают различные механизмы развития заболевания, однако всё больше данных подтверждают решающую роль митохондриальной дисфункции в развитии БП.

Цель *обзора – рассмотреть ключевые патогенетические механизмы митохондриальной дисфункции в контексте патогенеза заболевания. Нами проведён поиск полнотекстовых публикаций на русском и английском языках в базах данных eLIBRARY.RU, PubMed, Web of Science за последнее 20 лет с использованием ключевых слов и словосочетаний: болезнь Паркинсона, нейродегенерация, патофизиология, митохондриальная дисфункция, биоэнергетика, митофагия, патогенетическая терапия.*

В обзоре подробно рассмотрены факторы, индуцирующие митохондриальную дисфункцию, а также влияние митохондриальной дисфункции на развитие БП. Представлены потенциальные терапевтические стратегии, сопряжённые с митохондриальной дисфункцией.

Ключевые слова: *болезнь Паркинсона; нейродегенерация; патофизиология; митохондриальная дисфункция; биоэнергетика; митофагия; патогенетическая терапия*

Источник финансирования. Авторы заявляют об отсутствии внешних источников финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Адрес для корреспонденции: 634050, Россия, Томск, Московский тракт, д. 2. Сибирский государственный медицинский университет. E-mail: sayfutdinxodjaev2002@gmail.com. Сайфитдинхужаев З.Ф.

Для цитирования: Жукова Н.Г., Колобовникова Ю.В., Сайфитдинхужаев З.Ф. Митохондриальная дисфункция в патогенезе болезни Паркинсона: современные представления и потенциальные терапевтические стратегии. *Анналы клинической и экспериментальной неврологии*. 2025;19(2):74–81.
DOI: https://doi.org/10.17816/ACEN.1219
EDN: https://elibrary.ru/KHXTLY

Поступила 25.10.2024 / Принята в печать 04.12.2024 / Опубликована 30.06.2025

Introduction

Parkinson disease (PD) is one of the most common neurodegenerative disorders. PD manifests clinically through typical motor and non-motor symptoms. Motor symptoms include resting tremor, bradykinesia, muscular rigidity, hypomimia, and postural instability. Non-motor symptoms, which usually precede motor symptoms during the prodromal period, include cognitive impairment, hyposmia, insomnia, constipation, and depression. The prodromal period lasts for 5–15 years [1]. The clinical symptoms of PD are associated with the death of dopaminergic neurons in the compact region of the substantia nigra in the midbrain. Motor symptoms appear only after 50–80% of these neurons have died. PD is pathologically characterized by the accumulation of Lewy bodies, which are round, eosinophilic intracellular inclusions primarily composed of aberrant alpha-synuclein [2]. The growing elderly population and improved medical care for patients with PD are expected to increase the PD prevalence in the next 20–30 years. It is estimated that the total number of PD patients worldwide will rise from 4.1 million in 2005 to 8.7 million in 2030. This increase will put intense strain on healthcare systems in many countries [2]. The epidemiological parameters of PD prevalence and incidence vary considerably by Russian region. Tomsk has the highest prevalence (238 cases per 100,000 people), whereas Moscow has the lowest prevalence (27 cases per 100,000 people). The incidence rates also vary widely. The lowest incidence rate is reported in Karelia (1.88 cases per 100,000 people per year). The highest rate is reported in the Solnechnogorsky district in the Moscow Oblast (16.3 cases per 100,000 people per year) [3]. In addition, symptomatic therapy becomes less effective as patients' conditions worsen. Currently, there are no treatments that can prevent the onset or progression of PD. Understanding the pathogenesis of PD is critical for the development and clinical implementation of novel, highly effective therapeutic strategies in the near future.

PD is considered a multisystem and multifactorial disease that can be initiated by various etiological factors, including genetic, biological, and environmental factors [3]. From a pathophysiological perspective, familial forms of PD are classified as genetic diseases with Mendelian inheritance patterns. Sporadic forms of PD, which account for 85–90% of cases, belong to multifactorial diseases, meaning that they are genetically predisposed [4]. Sporadic forms have a specific genetic predisposition, but its penetrance depends on environmental factors that induce and potentiate PD development. In recent years, tremendous progress has been made in understanding the molecular basis of PD pathogenesis, leading to various theories. Pathogenetic factors include disturbances in both apoptotic and non-apoptotic programmed neuronal cell death, as well as aberrant autophagy regulation, endoplasmic reticulum dysfunction, and elevated intracellular calcium levels. However, their exact role in neuronal degeneration is still being investigated [5].

Recently, the pathogenetic role of mitochondria in PD has been actively studied. This is because neurons have a complex mitochondrial network extending from the soma to the synaptic terminals. These terminals relay information from one neuron to another. Mitochondria perform many functions, such as adenosine triphosphate (ATP) generation, calcium buffering, and epigenetic neuronal signaling. Unlike many other cell types, neurons have higher bioenergetic needs. For example, ionic homeostasis requires ATP, which is constantly consumed to generate transmembrane ionic fluxes, sequester neurotransmitters into vesicles, facilitate vesicle fusion during synaptic activity, and mediate reuptake during vesicular recycling. ATP is also necessary to maintain and restore a large pool of neurotransmitters. ATP is synthesized

for these processes within the mitochondria. Therefore, mitochondrial dysfunction is considered an essential part of PD pathogenesis [6]. This review focuses on the latest advances in understanding how mitochondrial dysfunction contributes to the development of sporadic and familial forms of PD.

Mitochondrial Dysfunction in the Pathogenesis of Sporadic Parkinson Disease

An electron transport chain (ETC) within mitochondria is the primary source of reactive oxygen species (ROS) in eukaryotic cells. The ETC sequentially reduces molecular oxygen to water. Complexes I and III produce a small amount of superoxide (O_2^-) during this process. Superoxide is formed in the mitochondria and can be converted into hydrogen peroxide by an manganese superoxide dismutase. However, under certain conditions ROS production may exceed the cellular antioxidant capacity. This state, called oxidative stress, can cause irreversible damage to cellular macromolecules and lead to cell death. Markers of oxidative stress, such as oxidized lipids, proteins, and DNA, are found at high concentrations in patients with PD [6]. In addition, patients at risk for PD, including those with frequent constipation, impaired olfactory function, anxiety and depressive thoughts, and sleep behavior disorders, have higher levels of oxidative stress than those at no risk. Increased oxidative stress is one of the effects of complex I deficiency observed in sporadic PD. This is supported by data from a study by Esteves et al., which showed increased oxidative stress and reduced complex I activity in neuronal cells of patients with PD compared to healthy individuals [7].

A major breakthrough in understanding the PD pathogenesis was achieved through the analysis of specific cases of induced parkinsonism in California during the 1980s. Langston et al. (1983) identified individuals with histories of intravenous substance abuse who had inadvertently injected 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a synthetic analog of heroin [6]. They developed parkinsonism within a few days. An autopsy showed significant damage to dopaminergic neurons in the substantia nigra, as well as typical alpha-synuclein inclusions. MPTP easily crosses the blood-brain barrier and is taken up by astrocytes, where it is metabolized into 1-methyl-4-phenylpyridinium (MPP^+) and released into the extracellular space. MPP^+ is a substrate of the dopamine transporter that is selectively taken up by dopaminergic neurons, where it inhibits mitochondrial complex I. After inhibiting complex I, the excess superoxide suppresses the antioxidant capacity of dopaminergic neurons, leading to their death [6]. MPP^+ is toxic to dopaminergic neurons in humans, primates, and rodents. Therefore, MPTP is recommended for use in animal models of parkinsonism by Guidelines for Preclinical Studies of Medicinal Products by the Scientific Center for Expert Evaluation of Medicinal Products.[1] However, MPTP models of PD have some limitations. For example, MPTP experiments rarely result in the formation of Lewy bodies. MPTP induces acute or subacute neurodegeneration, which is differs from the chronic neurodegenerative process in PD. In addition, MPTP-induced parkinsonism models often fail to demonstrate the motor impairments characteristic of PD [8–10]. In experimental settings, other inhibitors of mitochondrial complex I, such as rotenone and annonacin, as well as other pesticides affecting mitochondria (paraquat, maneb, dieldrin, heptachlor, and atrazine), induce pathological, biochemical, and behavioral changes typical of PD [11, 12].

Another molecular hypothesis suggests that the mitochondrial defects in PD result from the accumulation of point mutations in mitochondrial DNA (mtDNA). In eukaryotic cells, mtDNA is organized into nucleoids, which consist of proteins and nucleic acids. Each nucleoid contains an average of 1.4 million copies of mtDNA, and cells can contain up to 2,000 nucleoids [6]. mtDNA is circular and encodes 13 proteins, as well as mitochondrial transfer RNA (tRNA) and ribosomal RNA (rRNA) [6]. The proteins encoded by mtDNA include subunits from all parts of the ETC. Six of these genes encode subunits of complex I [6]. Therefore, point mutations in any of six genes can affect the activity of complex I. Therefore, mitochondria are involved in the pathogenesis of Parkinson-like syndromes. Mitochondrial dysfunction has been reported in the neurons of the substantia nigra, as well as in the myocytes, platelets, lymphocytes, and fibroblasts of patients with PD. These findings support the idea that mitochondrial dysfunction is not limited to neurons alone and is an important feature of PD's multisystem nature.

Alpha-synuclein, a characteristic marker of PD, binds to voltage-dependent anion-selective channel 1 (VDAC1), translocase of the outer membrane (TOM) 40, and TOM20, thereby mediating mitochondrial dysfunction [13, 14]. In sporadic PD, reduced levels of VDAC1 are found in neurons of the substantia nigra due to alpha-synuclein aggregation, which contributes to mitochondrial dysfunction [15]. In addition, alpha-synuclein activates a channel that depolarizes the mitochondrial membrane, leading to mitochondrial fragmentation and degradation. The aggregation of alpha-synuclein disrupts proteostasis, impairing function and transport within the endoplasmic reticulum, the Golgi apparatus, and the autophagolysosomal system. This process destabilizes organelle connections and contributes to mitochondrial dysfunction. Oxidative stress is closely related to mitochondrial dysfunction. Mitochondria produce up to 90% of cellular ROS [16]. Synucleinopathy, oxidative stress, and mitochondrial dysfunction appear to form a vicious cycle in the pathogenesis of sporadic PD [17]. The accumulation of iron in the substantia nigra of patients with sporadic PD can also cause increased ROS production and enhanced alpha-synuclein aggregation [15, 18]. Mitochondria actively exchange iron with the cytoplasm. This exchange is necessary for the synthesis of various enzyme systems that are integral components of mitochondrial complexes I and III [18]. The inhibition of complex I by rotenone, MPTP, and paraquat leads to iron accumulation and induces the development of PD [19]. Inhibition of the ubiquitin-proteasome system also causes an imbalance of iron in cells, further enhancing ROS generation and alpha-synuclein aggregation [20].

[1]Guidelines for Preclinical Studies of Medicinal Products. Part 1. Moscow; 2012. 944 p. URL: https://rsmu.ru/fileadmin/templates/DOC/Zakon_RF/Mironov_Rukovodstvo_po_provedeniju_doklinicheskikh_issledovanii_lekarstvennykh_sredstv.pdf

Mitochondrial Dysfunction in the Pathogenesis of Autosomal Dominant Parkinson Disease

Alpha-synuclein was first associated with PD due to its presence in Lewy bodies. Subsequently, the *SNCA* gene, which encodes alpha-synuclein, was identified as the first gene responsible for autosomal dominant PD [21]. Alpha-synuclein is a small polypeptide consisting of 140 amino acids. It mediates neurotransmitter release in presynaptic terminals and interacts with the membranes of various organelles, including mitochondria. Mullin et al. discovered that alpha-synuclein is present in mitochondrial membranes, where it directly influences the structure and function of organelles [22]. Both *in vitro* and *in vivo* models have demonstrated that *SNCA* gene mutations (*A53T*, *E46K* and *H50Q*) lead to the production of a defective protein, resulting in mitochondrial fragmentation and excessive ROS production [23]. Alpha-synuclein is normally located in a specialized structure called the mitochondria-associated endoplasmic reticulum membrane (MAM). The MAM acts as a barrier between the endoplasmic reticulum and the mitochondria and plays a critical role in regulating calcium signaling and apoptosis. Negative mutations in the *SNCA* gene decrease alpha-synuclein binding to MAM and increase mitochondrial fragmentation. These findings suggest that alpha-synuclein is involved in the regulation of mitochondrial morphology [14, 24]. Overexpression of mutant alpha-synuclein causes the dissociation of mitochondria from MAM, disrupting calcium exchange and reducing mitochondrial energy production [25]. Ryan et al. discovered that alpha-synuclein directly influences mitochondrial morphology and biogenesis by regulating the PGC1α receptor [26].

Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene, which encodes a protein called dardarin, are a frequent cause of autosomal dominant and familial forms of PD [27]. LRRK2 is a multifunctional protein kinase, where PD-associated mutations lead to increased kinase activity. Increased mitochondrial sensitivity to toxins, defects in mitochondrial homeostasis, and increased ROS production have been demonstrated in experimental animal models with mutant *LRRK2* associated with PD [23]. Studies have shown that the *G2019S* mutation in the *LRRK2* gene is associated with mitochondrial abnormalities in dopaminergic neurons of the substantia nigra in patients with PD [26], as well as in PD mouse models [27].

Several proteins interact with LRRK2, mediating pathological effects on mitochondria. For example, the mitochondrial fission protein, dynamin-related protein 1 (DRP1), acts as an effector of mitochondrial fragmentation through LRRK2-mediated phosphorylation [28]. In addition, LRRK2 appears to interact with other mitochondrial fission proteins, including mitofusin and the dynamin-like protein [29]. Excessive activity of uncoupling proteins 2 and 4 may cause increased proton leakage and LRRK2-mediated loss of mitochondrial membrane potential [30]. The *G2019S* mutation in the *LRRK2* gene impairs the proteasomal degradation of an outer mitochondrial membrane protein, which connects mitochondria to microtubule motor proteins, contributing to defective mitophagy [31].

Recently, a link was discovered between PD and the vacuolar protein sorting 35 (*VPS35*) gene in European patient cohorts with a family history of PD, suggesting autosomal dominant transmission [27, 32]. VPS35 is an essential component of a complex that mediates the retrograde delivery of substances from endosomes to the Golgi apparatus and the recycling of substances from endosomes to the cell surface (33). Early studies showed that PD-associated mutations in the *VPS35* gene made cells more vulnerable to the mitochondrial toxin MPP^+ *in vitro* [34]. The primary function of *VPS35* in mitochondria appears to be the regulation of mitochondrial dynamics through interaction with fission and fusion proteins. Recent studies have demonstrated that the mutant *VPS35* protein may cause mitochondrial fragmentation and lead to neurodegeneration [14]. This may occur through decreased degradation of the E3 ubiquitin ligase-1 protein, which increases mitofusin degradation [35], or by enhancing DRP1 complex turnover through vesicle-mediated transport from mitochondria to lysosomes [36]. In addition, the *D620N* mutation in the *VPS35* gene is shown to increase mitochondrial fragmentation, disrupting the assembly and activity of complex I [37].

Another gene, *CHCHD2* (*coiled-coil-helix-coiled-coil-helix domain-containing 2)*, has mutations that have been identified as a potential cause of late-onset, autosomal dominant PD in three Japanese families [38]. This gene produces a protein containing a coiled-coil-helix-coiled-coil-helix domain, which is found in the intermembrane space of mitochondria and the cell nucleus. CHCHD2 is usually found in mitochondria and associated with complex IV. The under-expression of CHCHD2 suppresses the activity of complex IV, which leads to increased ROS production and mitochondrial fragmentation [39]. It should be noted that CHCHD2 translocates into the nucleus and acts as a transcription factor under stress conditions, thereby regulating the expression of subunit 4 isoforms of mitochondrial complex IV [40]. In addition, Drosophila with low CHCHD2 [41] expression or PD-linked *CHCHD* gene mutations exhibit mitochondrial structural and biochemical abnormalities resulting in dopaminergic neurodegeneration in the substantia nigra and motor dysfunction. These findings strongly suggest that the *CHCHD2* gene mutation leads to nigrostriatal neurodegeneration and the development of PD specifically due to mitochondrial dysfunction.

Mitochondrial Dysfunction in the Pathogenesis of Autosomal Recessive Parkinson Disease

The most common cause of autosomal recessive PD is mutations (>120) in the *Parkin*gene, which encodes the Parkin protein. The Parkin protein is a cytosolic E3 ubiquitin ligase that attaches ubiquitin to target proteins for signaling or proteasomal degradation. Parkin primarily functions in association with mitochondria. Parkin-deficient models show severe defects in mitochondrial morphology and function [43]. The E3 ubiquitin ligase plays different functions in maintaining mitochondrial homeostasis and regulating mitochondrial biogenesis and mitophagy. Mitophagy is the process by which dysfunctional mitochondria are removed from a healthy mitochondrial pool and degraded using the autophagolysosomal pathway [44]. During the early stages of mitochondrial degradation, Parkin is recruited to damaged or dysfunctional mitochondria and activated by kinase 1, leading to ubiquitylation of proteins and subsequent proteasomal degrada-

tion [14]. Pickrell et al. demonstrated a defect in Parkin-mediated mitophagy in distal neuronal axons in a rodent model of age-related dopaminergic neurodegeneration accompanied by PD symptoms [45]. These findings further highlight the pathophysiological importance of Parkin-mediated mitophagy in PD, as opposed to data from *in vitro* studies. Apart from its role in mitophagy, Parkin maintains a functional mitochondrial pool by regulating biogenesis [43]. Parkin normally mediates the degradation of peroxisome proliferator-activated receptor gamma coactivator (PGC1α), which leads to its translocation to the nucleus and the activation of transcription of mitochondrial-related genes [46]. Therefore, Parkin dysfunction suppresses mitochondrial biogenesis, resulting in a decrease in the number and function of mitochondria [47]. These results also highlight a key role of Parkin in maintaining the balance between mitochondrial biosynthesis and biodegradation.

Mutations in the *PINK1* gene are the second most common cause of early-onset, autosomal recessive PD [48]. PINK1 (PTEN-induced putative kinase 1) is a serine-threonine kinase associated with mitochondria and plays a critical role in maintaining mitochondrial homeostasis. PINK1 is shown to enhance mitochondrial fission by increasing the activation of protein kinase A [49] and to modulate mitochondrial biogenesis by regulating Parkin-dependent degradation [50]. A defective *PINK1* gene impairs mitochondrial function, resulting in the destruction of mitochondria. Mitophagy is the most widely studied function of PINK1 [45, 51]. PINK1 activates Parkin through two mechanisms: direct phosphorylation [52] and transactivation via the phosphorylation of ubiquitin, followed by Parkin binding [51, 53, 54]. In addition, PINK1 can mediate mitophagy independently of Parkin by recruiting nuclear dot protein and optineurin [55]. Like LRRK2, PINK1 promotes mitophagy by arresting mitochondrial transport through phosphorylation, followed by proteasomal degradation [56]. Experiments on Drosophila and mice have shown that partially inhibiting PINK1 results in various mitochondrial dysfunctions. This is primarily due to the loss of PINK1/Parkin-mediated mitophagy. However, PINK1 regulates mitochondrial homeostasis through another mechanism [43]: a PINK1 deficiency leads to mitochondrial calcium overload [57] and a decrease in mitochondrial complexes I and III [58].

A rare form of autosomal recessive juvenile PD, Kufor–Rakeb syndrome, is caused by mutations in the *ATP13A2* gene [59]. This gene encodes a P5B-type ATPase that mainly localizes to the endolysosomal compartment. Although ATP13A2 is believed to transport cations across organelle membranes [59], its transport activity is not fully defined. However, a loss of ATP13A2 in cells in patients with PD reveals increased sensitivity to Zn^{2+} and Mn^{+}, suggesting a critical role for ATP13A2 in maintaining the balance of these trace elements [14, 59]. The association between the *ATP13A2* gene and mitochondrial dysfunction was first identified in skin fibroblasts from patients with mutations in this gene [14, 60]. Grünewald et al. [60] and Ramonet et al. [61] demonstrated mitochondrial dysfunction, characterized by reduced ATP production, increased mitochondrial fragmentation, and elevated ROS production, in a model of ATP13A2-deficient cells [60, 61]. Park et al. proposed that ATP13A2 has a broader impact on cellular bioenergetics. They found that loss of ATP13A2 worsens glycolysis and causes more severe mitochondrial dysfunction [62]. In addition, the literature describes ATP13A2 mutations that cause Zn^{2+} homeostasis disruption due to an imbalance in vesicular sequestration, resulting in mitochondrial dysfunction [61]. Disruption in Zn^{2+} metabolism can also cause lysosomal dysfunction [63] and contribute to defective mitophagy. This highlights the complex relationship between interconnected intracellular processes in PD pathogenesis.

Potential Therapeutic Strategies

Since mitochondrial dysfunction plays a significant role in the development of PD, novel pathogenetic approaches are needed to treat PD. Various strategies are being developed to improve mitochondrial function in both familial and sporadic forms of PD. An effective approach to treating PD appears to involve targeting the mitophagy process in defective mitochondria. Increasing the activity of the cytosolic ubiquitin ligase E3 (Parkin) by nilotinib, which inhibits phosphorylation, is shown to provide a neuroprotective effect [64]. Inhibition of the deubiquitinating enzymes increases Parkin-mediated mitophagy because a ubiquitin-specific peptidase counteracts Parkin's effects, whereas inhibition of the ubiquitin-specific peptidase increases mitochondrial degradation [14, 65]. In addition, activation of mitophagy in PD may create alternative conditions that restore mitochondrial function. Hamacher-Brady et al. demonstrated that the proteins FUNDC1 (FUN14 domain containing 1) and Ambra1 (autophagy and Beclin 1 regulator 1) are able to modulate mitophagy independently of PINK1 or Parkin activity [66]. However, it has been discovered that Nip3-like protein-mediated mitophagy [14, 67] restores mitochondrial function and prevents neurodegeneration in case of Parkin or PINK1 deficiency, which justifies this mechanism as a new potential target for PD treatment [14].

Another neuroprotection strategy involves increasing mitochondrial biogenesis. Hayashi et al. demonstrated in animal experiments and human subjects that dimethyl fumarate (BG-12) increases mitochondrial biogenesis through the transcription factor NRF2 (nuclear factor erythroid 2-related factor 2) [68]. Phase III clinical trials demonstrated the efficacy of BG-12 in treating relapsing multiple sclerosis [69], and the agent was approved for patient use. These findings highlight the potential use of BG-12 in PD treatment. Other activators of the NRF2-mediated pathway include synthetic triterpenoids, which have demonstrated protective effects on dopaminergic neurons against MPTP [70]. Johri et al. reported that PGC-1α, a powerful inducer of mitochondrial biogenesis, might be another candidate for a target in PD treatment [71]. Other studies on animal models of neurodegeneration have demonstrated that bezafibrate [71] and quercetin [72] increase mitochondrial numbers. These findings open up opportunities for developing new PD treatment strategies.

Conclusion

A literature review has revealed the significant role of mitochondrial dysfunction in PD development. Both exogenous environmental factors and endogenous factors, such as genetic aberrations characteristic of familial forms of PD, can

lead to mitochondrial dysfunction. Mitochondria are affected by these etiological factors directly and indirectly, through the activation or inhibition of secondary messenger systems. Pathogenetically, mitochondrial dysfunction can arise from either defective mitophagy or disrupted mitochondrial biogenesis. Therefore, new treatment strategies for PD should aim to enhance mitophagy of defective mitochondria or increase the biogenesis of new mitochondria.

Список источников | References

1. Зарипов Н.А., Додхоев Д.С., Абдуллозода С.М., Джамолова Р.Д. Немоторные симптомы болезни Паркинсона. *Вестник Авиценны.* 2021;23(3):342–351. Zaripov NA, Dodxoev DS, Abdullzoda SM, Zhamalova RD. Nonmotor clinic Parkinson's disease. *Avicenna's Bulletin.* 2021;23(3):342–351. doi: 10.25005/2074-0581-2021-23-3-342-351
2. Dorsey ER, Constantinescu R, Thompson JP, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology.* 2007;68(5):384–386. doi: 10.1212/01.wnl.0000247740.47667.03
3. Катунина Е.А., Бездольный Ю.Н. Эпидемиология болезни Паркинсона. *Журнал неврологии и психиатрии им. С.С. Корсакова.* 2013;113(12):81–88. Katunina EA, Bezdolniy YuN. Epidemiology of Parkinson's disease. *S.S. Korsakov Journal of Neurology and Psychiatry.* 2013;113(12):81–88.
4. Polito L, Greco A, Seripa D. Genetic profile, environmental exposure, and their interaction in Parkinson's disease. *Parkinsons Dis.* 2016;2016:6465793. doi: 10.1155/2016/6465793
5. Zaltieri M, Longhena F, Pizzi M, et al. Mitochondrial dysfunction and α-synuclein synaptic pathology in Parkinson's disease: who's on first? *Parkinsons Dis.* 2015;2015:108029. doi: 10.1155/2015/108029
6. Hauser DN, Hastings TG. Mitochondrial dysfunction and oxidative stress in Parkinson's disease and monogenic parkinsonism. *Neurobiol Dis.* 2013;51:35–42. doi: 10.1016/j.nbd.2012.10.011
7. Esteves AR, Arduíno DM, Swerdlow RH, et al. Oxidative stress involvement in alpha-synuclein oligomerization in Parkinson's disease cybrids. *Antioxid Redox Signal.* 2009;11(3):439–448. doi: 10.1089/ars.2008.2247
8. Blesa J, Przedborski S. Parkinson's disease: animal models and dopaminergic cell vulnerability. *Front Neuroanat.* 2014;8:155. doi: 10.3389/fnana.2014.00155
9. Lindholm D, Mäkelä J, Di Liberto V, et al. Current disease modifying approaches to treat Parkinson's disease. *Cell Mol Life Sci.* 2016;73(7):1365–1379. doi: 10.1007/s00018-015-2101-1
10. Mustapha M, Mat Taib CN. MPTP-induced mouse model of Parkinson's disease: a promising direction of therapeutic strategies. *Bosn J Basic Med Sci.* 2021;21(4):422–433. doi:10.17305/bjbms.2020.5181
11. Freire C, Koifman S. Pesticide exposure and Parkinson's disease: epidemiological evidence of association. *Neurotoxicology.* 2012;33(5):947–971. doi: 10.1016/j.neuro.2012.05.011
12. Inden M, Kitamura Y, Abe M, et al. Parkinsonian rotenone mouse model: reevaluation of long-term administration of rotenone in C57BL/6 mice. *Biol Pharm Bull.* 2011;34(1):92+96. doi: 10.1248/bpb.34.92
13. Pozo Devoto VM, Falzone TL. Mitochondrial dynamics in Parkinson's disease: a role for α-synuclein? *Dis Model Mech.* 2017;10(9):1075–1087. doi: 10.1242/dmm.026294
14. Park JS, Davis RL, Sue CM. Mitochondrial dysfunction in Parkinson's disease: new mechanistic insights and therapeutic perspectives. *Curr Neurol Neurosci Rep.* 2018;18(5):21. doi: 10.1007/s11910-018-0829-3
15. Chu Y, Goldman JG, Kelly L., et al. Abnormal alpha-synuclein reduces nigral voltage-dependent anion channel 1 in sporadic and experimental Parkinson's disease. *Neurobiol Dis.* 2014;69:1–14. doi: 10.1016/j.nbd.2014.05.003
16. Perfeito R, Cunha-Oliveira T, Rego AC. Revisiting oxidative stress and mitochondrial dysfunction in the pathogenesis of Parkinson disease-resemblance to the effect of amphetamine drugs of abuse. *Free Radic Biol Med.* 2012;53(9):1791–1806. doi: 10.1016/j.freeradbiomed.2012.08.569
17. Ganguly G, Chakrabarti S, Chatterjee U, Saso L. Proteinopathy, oxidative stress and mitochondrial dysfunction: cross talk in Alzheimer's disease and Parkinson's disease. *Drug Des Devel Ther.* 2017;11:797–810. doi: 10.2147/DDDT.S130514
18. Carboni E., Lingor P. Insights on the interaction of alpha-synuclein and metals in the pathophysiology of Parkinson's disease. *Metallomics.* 2015;7(3):395–404. DOI: 10.1039/c4mt00339j
19. Carboni E, Lingor P. Insights on the interaction of alpha-synuclein and metals in the pathophysiology of Parkinson's disease. *Metallomics.* 2015;7(3):395–404. doi: 10.1039/c4mt00339j
20. Muñoz Y, Carrasco CM, Campos JD, et al. Parkinson's disease: the mitochondria-iron link. *Parkinsons Dis.* 2016;2016:7049108. doi: 10.1155/2016/7049108
21. Polymeropoulos MH, Lavedan C, Leroy E, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science.* 1997;276(5321):2045–2047. doi: 10.1126/science.276.5321.2045
22. Mullin S, Schapira A. α-Synuclein and mitochondrial dysfunction in Parkinson's disease. *Mol Neurobiol.* 2013;47(2):587–597. doi: 10.1007/s12035-013-8394-x
23. Ryan BJ, Hoek S, Fon EA, Wade-Martins R. Mitochondrial dysfunction and mitophagy in Parkinson's: from familial to sporadic disease. *Trends Biochem Sci.* 2015;40(4):200–210. doi: 10.1016/j.tibs.2015.02.003
24. Guardia-Laguarta C, Area-Gomez E, Rüb C, et al. α-Synuclein is localized to mitochondria-associated ER membranes. *J Neurosci.* 2014;34(1):249–259. doi: 10.1523/JNEUROSCI.2507-13.2014
25. Paillusson S, Gomez-Suaga P, Stoica R, et al. α-Synuclein binds to the ER-mitochondria tethering protein VAPB to disrupt Ca^{2+} homeostasis and mitochondrial ATP production. *Acta Neuropathol.* 2017;134(1):129–149. doi: 10.1007/s00401-017-1704-z
26. Ryan SD, Dolatabadi N, Chan SF, et al. Isogenic human iPSC Parkinson's model shows nitrosative stress-induced dysfunction in MEF2-PGC1α transcription. *Cell.* 2013;155(6):1351–1364. doi: 10.1016/j.cell.2013.11.009
27. Yue M, Hinkle KM, Davies P, et al. Progressive dopaminergic alterations and mitochondrial abnormalities in LRRK2 G2019S knock-in mice. *Neurobiol Dis.* 2015;78:172–195. doi: 10.1016/j.nbd.2015.02.031
28. Reinhardt P, Schmid B, Burbulla LF, et al. Genetic correction of a LRRK2 mutation in human iPSCs links parkinsonian neurodegeneration to ERK-dependent changes in gene expression. *Cell Stem Cell.* 2013;12(3):354–367. doi: 10.1016/j.stem.2013.01.008
29. Santos D, Esteves AR, Silva DF, et al. The Impact of mitochondrial fusion and fission modulation in sporadic Parkinson's disease. *Mol Neurobiol.* 2015;52(1):573–586. doi: 10.1007/s12035-014-8893-4
30. Papkovskaia TD, Chau KY, Inesta-Vaquera F, et al. G2019S leucine-rich repeat kinase 2 causes uncoupling protein-mediated mitochondrial depolarization. *Hum Mol Genet.* 2012;21(19):4201–4213. doi: 10.1093/hmg/dds244
31. Hsieh CH, Shaltouki A, Gonzalez AE, et al. functional impairment in Miro degradation and mitophagy is a shared feature in familial and sporadic Parkinson's disease. *Cell Stem Cell.* 2016;19(6):709–724. doi: 10.1016/j.stem.2016.08.002
32. Vilariño-Güell C, Wider C, Ross OA, et al. VPS35 mutations in Parkinson disease. *Am J Hum Genet.* 2011;89(1):162–167. doi: 10.1016/j.ajhg.2011.06.001
33. Zimprich A, Benet-Pagès A, Struhal W, et al. A mutation in VPS35, encoding a subunit of the retromer complex, causes late-onset Parkinson disease. *Am J Hum Genet.* 2011;89(1):168–175. doi: 10.1016/j.ajhg.2011.06.008
34. Small SA, Petsko GA. Retromer in Alzheimer disease, Parkinson disease and other neurological disorders. *Nat Rev Neurosci.* 2015;16(3):126–132. doi: 10.1038/nrn3896

35. Bi F, Li F, Huang C, Zhou H. Pathogenic mutation in VPS35 impairs its protection against MPP(+) cytotoxicity. *Int J Biol Sci.* 2013;9(2):149–155. doi: 10.7150/ijbs.5617
36. Tang FL, Liu W, Hu JX, et al. VPS35 deficiency or mutation causes dopaminergic neuronal loss by impairing mitochondrial fusion and function. *Cell Rep.* 2015;12(10):1631–1643. doi: 10.1016/j.celrep.2015.08.001
37. Wang W, Wang X, Fujioka H, et al. Parkinson's disease-associated mutant VPS35 causes mitochondrial dysfunction by recycling DLP1 complexes. *Nat Med.* 2016;22(1):54–63. doi: 10.1038/nm.3983
38. Chou L, Wang W, Hoppel C, et al. Parkinson's disease-associated pathogenic VPS35 mutation causes complex I deficits. *Biochim Biophys Acta Mol Basis Dis.* 2017;1863(11):2791–2795. doi: 10.1016/j.bbadis.2017.07.032
39. Funayama M, Ohe K, Amo T, et al. CHCHD2 mutations in autosomal dominant late-onset Parkinson's disease: a genome-wide linkage and sequencing study. *Lancet Neurol.* 2015;14(3):274–282. doi: 10.1016/S1474-4422(14)70266-2
40. Aras S, Bai M, Lee I, et al. MNRR1 (formerly CHCHD2) is a bi-organellar regulator of mitochondrial metabolism. *Mitochondrion.* 2015;20:43–51. doi: 10.1016/j.mito.2014.10.003
41. Meng H, Yamashita C, Shiba-Fukushima K, et al. Loss of Parkinson's disease-associated protein CHCHD2 affects mitochondrial crista structure and destabilizes cytochrome c. *Nat Commun.* 2017;8:15500. doi: 10.1038/ncomms15500
42. Tio M, Wen R, Lim YL, et al. Varied pathological and therapeutic response effects associated with CHCHD2 mutant and risk variants. *Hum Mutat.* 2017;38(8):978–987. doi: 10.1002/humu.23234
43. Scarffe LA, Stevens DA, Dawson VL, Dawson TM. Parkin and PINK1: much more than mitophagy. *Trends Neurosci.* 2014;37(6):315–324. doi: 10.1016/j.tins.2014.03.004
44. Pickrell AM, Youle RJ. The roles of PINK1, Parkin, and mitochondrial fidelity in Parkinson's disease. *Neuron.* 2015;85(2):257–273. doi: 10.1016/j.neuron.2014.12.007
45. Pickrell AM, Huang CH, Kennedy S, et al. Endogenous Parkin preserves dopaminergic substantia nigral neurons following mitochondrial DNA mutagenic stress. *Neuron.* 2015;87(2):371–381. doi: 10.1016/j.neuron.2015.06.034
46. Shin JH, Ko HS, Kang H, et al. PARIS (ZNF746) repression of PGC-1α contributes to neurodegeneration in Parkinson's disease. *Cell.* 2011;144(5):689–702. doi: 10.1016/j.cell.2011.02.010
47. Stevens DA, Lee Y, Kang HC, et al. Parkin loss leads to PARIS-dependent declines in mitochondrial mass and respiration. *Proc Natl Acad Sci U S A.* 2015;112(37):11696–11701. doi: 10.1073/pnas.1500624112
48. Lill CM. Genetics of Parkinson's disease. *Mol Cell Probes.* 2016;30(6):386–396. doi: 10.1016/j.mcp.2016.11.001
49. Pryde KR, Smith HL, Chau KY, Schapira AH. PINK1 disables the anti-fission machinery to segregate damaged mitochondria for mitophagy. *J Cell Biol.* 2016;213(2):163–171. doi: 10.1083/jcb.201509003
50. Lee Y, Stevens DA, Kang SU, et al. PINK1 Primes Parkin-mediated ubiquitination of PARIS in dopaminergic neuronal survival. *Cell Rep.* 2017;18(4):918–932. doi: 10.1016/j.celrep.2016.12.090
51. Geisler S, Holmström KM, Skujat D, et al PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1. *Nat Cell Biol.* 2010;12(2):119–131. doi: 10.1038/ncb2012
52. Kondapalli C, Kazlauskaite A, Zhang N, et al. PINK1 is activated by mitochondrial membrane potential depolarization and stimulates Parkin E3 ligase activity by phosphorylating Serine 65. *Open Biol.* 2012;2(5):120080. doi: 10.1098/rsob.120080
53. Kazlauskaite A, Kondapalli C, Gourlay R, et al. Parkin is activated by PINK1-dependent phosphorylation of ubiquitin at Ser65. *Biochem J.* 2014;460(1):127–139. doi: 10.1042/BJ20140334
54. Kane LA, Lazarou M, Fogel AI, et al. PINK1 phosphorylates ubiquitin to activate Parkin E3 ubiquitin ligase activity. *J Cell Biol.* 2014;205(2):143–153. doi: 10.1083/jcb.201402104
55. Lazarou M, Sliter DA, Kane LA, et al. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. *Nature.* 2015;524(7565):309–314. doi: 10.1038/nature14893
56. Wang X, Winter D, Ashrafi G, et al. PINK1 and Parkin target Miro for phosphorylation and degradation to arrest mitochondrial motility. *Cell.* 2011;147(4):893–906. doi: 10.1016/j.cell.2011.10.018
57. Kostic M, Ludtmann MH, Bading H, et al. PKA phosphorylation of NCLX reverses mitochondrial calcium overload and depolarization, promoting survival of PINK1-deficient dopaminergic neurons. *Cell Rep.* 2015;13(2):376–386. doi: 10.1016/j.celrep.2015.08.079
58. Amo T, Saiki S, Sawayama T, et al. Detailed analysis of mitochondrial respiratory chain defects caused by loss of PINK1. *Neurosci Lett.* 2014;580:37–40. doi: 10.1016/j.neulet.2014.07.045
59. Park JS, Blair NF, Sue CM. The role of ATP13A2 in Parkinson's disease: clinical phenotypes and molecular mechanisms. *Mov Disord.* 2015;30(6):770–779. doi: 10.1002/mds.26243
60. Grünewald A, Arns B, Seibler P, et al. ATP13A2 mutations impair mitochondrial function in fibroblasts from patients with Kufor-Rakeb syndrome. *Neurobiol Aging.* 2012;33(8):1843.e1–7. doi: 10.1016/j.neurobiolaging.2011.12.035
61. Ramonet D, Podhajska A, Stafa K, et al. PARK9-associated ATP13A2 localizes to intracellular acidic vesicles and regulates cation homeostasis and neuronal integrity. *Hum Mol Genet.* 2012;21(8):1725–1743. doi: 10.1093/hmg/ddr606
62. Park JS, Koentjoro B, Veivers D, et al. Parkinson's disease-associated human ATP13A2 (PARK9) deficiency causes zinc dyshomeostasis and mitochondrial dysfunction. *Hum Mol Genet.* 2014;23(11):2802–2815. doi: 10.1093/hmg/ddt623
63. Tsunemi T, Krainc D. Zn^{2+} dyshomeostasis caused by loss of ATP13A2/PARK9 leads to lysosomal dysfunction and alpha-synuclein accumulation. *Hum Mol Genet.* 2014;23(11):2791–2801. doi: 10.1093/hmg/ddt572
64. Karuppagounder SS, Brahmachari S, Lee Y, et al. The c-Abl inhibitor, nilotinib, protects dopaminergic neurons in a preclinical animal model of Parkinson's disease. *Sci Rep.* 2014;4:4874. doi: 10.1038/srep04874
65. Dikic I, Bremm A. DUBs counteract parkin for efficient mitophagy. *EMBO J.* 2014;33(21):2442–2443. doi: 10.15252/embj.201490101
66. Hamacher-Brady A., Brady N.R. Mitophagy programs: mechanisms and physiological implications of mitochondrial targeting by autophagy. *Cell Mol Life Sci.* 2016;73(4):775–795. doi: 10.1007/s00018-015-2087-8
67. Koentjoro B, Park JS, Sue CM. Nix restores mitophagy and mitochondrial function to protect against PINK1/Parkin-related Parkinson's disease. *Sci Rep.* 2017;7:44373. doi: 10.1038/srep44373
68. Hayashi G, Jasoliya M, Sahdeo S, et al. Dimethyl fumarate mediates Nrf2-dependent mitochondrial biogenesis in mice and humans. *Hum Mol Genet.* 2017;26(15):2864–2873. doi: 10.1093/hmg/ddx167
69. Linker RA, Gold R. Dimethyl fumarate for treatment of multiple sclerosis: mechanism of action, effectiveness, and side effects. *Curr Neurol Neurosci Rep.* 2013;13(11):394. doi: 10.1007/s11910-013-0394-8
70. Kaidery NA, Banerjee R, Yang L, et al. Targeting Nrf2-mediated gene transcription by extremely potent synthetic triterpenoids attenuate dopaminergic neurotoxicity in the MPTP mouse model of Parkinson's disease. *Antioxid Redox Signal.* 2013;18(2):139–157. doi: 10.1089/ars.2011.4491
71. Johri A, Calingasan NY, Hennessey TM, et al. Pharmacologic activation of mitochondrial biogenesis exerts widespread beneficial effects in a transgenic mouse model of Huntington's disease. *Hum Mol Genet.* 2012;21(5):1124–1137. doi: 10.1093/hmg/ddr541
72. Li X, Wang H, Gao Y, et al. Quercetin induces mitochondrial biogenesis in experimental traumatic brain injury via the PGC-1α signaling pathway. *Am J Transl Res.* 2016;8(8):3558–3566.

Information about the authors

Natalia G. Zhukova – Dr. Sci. (Med.), Professor, Professor, Department of neurology and neurosurgery, Siberian State Medical University, Tomsk, Russia, https://orcid.org/0000-0001-6547-6622
Julia V. Kolobovnikova – Dr. Sci. (Med.), Associate Professor, Dean, Faculty of medicine and biology, Head, Department of normal physiology, Professor, Department of pathophysiology, Siberian State Medical University, Tomsk, Russia, https://orcid.org/0000-0001-7156-2471
Zaynutdinkhuzha F. Sayfitdinkhuzhaev – research assistant, Department of scientific and educational laboratory of cognitive neurophysiology of psychosomatic relationships, Siberian State Medical University, Tomsk, Russia, https://orcid.org/0009-0007-2184-2708

***Authors' contributions**: Zhukova N.G.* – manuscript editing; *Kolobovnikova Yu.V.* – concept, approval of the final version of the article for publication; *Sayfitdinkhuzhaev Z.F.* – concept, writing the text, editing the manuscript.

Информация об авторах

Жукова Наталья Григорьевна – д-р мед. наук, профессор, профессор каф. неврологии и нейрохирургии СибГМУ, Томск, Россия, https://orcid.org/0000-0001-6547-6622
Колобовникова Юлия Владимировна – д-р мед. наук, доцент, декан медико-биологического факультета, зав. каф. нормальной физиологии, профессор каф. патофизиологии СибГМУ, Томск, Россия, https://orcid.org/0000-0001-7156-2471
Сайфитдинхужаев Зайнутдинхужа Фазлиддинхужа угли – лаборант-исследователь кафедральной научно-образовательной лаборатории когнитивной нейрофизиологии психосоматических отношений СибГМУ, Томск, Россия, https://orcid.org/0009-0007-2184-2708

***Вклад авторов:** Жукова Н.Г.* – редактирование рукописи; *Колобовникова Ю.В.* – концепция, утверждение окончательного варианта статьи для публикации; *Сайфитдинхужаев З.Ф.* – концепция, написание текста, редактирование рукописи.