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REVIEW

Mitochondrial dysfunction and oxidative stress in Parkinson's disease: mechanisms, biomarkers, and therapeutic strategies

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ABSTRACT

Background: Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by motor symptoms and progressive degeneration of dopaminergic neurons. Accumulating evidence indicates that mitochondrial dysfunction and oxidative stress are major contributors to PD pathogenesis.

Objectives: This review explores the molecular mechanisms underlying PD, emphasizing mitochondrial dysfunction and oxidative stress. It also examines genetic and environmental contributors, emerging biomarkers, and future treatment strategies.

Methods: An extensive literature review was conducted, focusing on mitochondrial biology, oxidative stress, genetic mutations, and environmental toxins relevant to PD. Investigations into treatment options – including redox therapies, gene therapies, and lifestyle approaches – were also examined.

Results: Mitochondrial dysfunction in PD includes disrupted oxidative phosphorylation and elevated reactive oxygen species (ROS). This also affects calcium homeostasis, especially in substantia nigra neurons. Genetic mutations (PINK1, Parkin, DJ-1, LRRK2, GBA) impair mitophagy and antioxidant defenses. Environmental toxins (e.g. MPTP, rotenone) further damage mitochondrial function and contribute to dopaminergic neuron loss. Emerging biomarkers involve measurements of lipid peroxidation and mitochondrial DNA damage. Promising therapeutic strategies include mitochondria-targeted antioxidants (e.g. MitoQ), PINK1-based gene therapy, Parkin activation, ketogenic diet, and exercise-induced mitochondrial biogenesis.

Conclusions: Mitochondrial dysfunction and oxidative stress are central to PD pathophysiology. Strategies targeting these mechanisms may slow disease progression. Future research should emphasize combination therapies and early intervention trials, alongside biomarker integration, to enhance clinical outcomes.

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Introduction

Parkinson's disease (PD) is a multifaced, progressive, and slowly neurodegenerative disorder primarily characterized by bradykinesia, resting tremor and rigidity, with postural instability emerging in the later stages of the disease. As the second most prevalent neurodegenerative disease after Alzheimer's disease (AD)[1], PD affects approximately 0.5–1% among those 65–69 y of age, rising to 1–3% among persons 80 y of age and older[2,3]. Given the demographic shift toward an aging global population, PD incidence is projected to rise by over 30% by 2030[4], imposing significant societal, healthcare, and economic burdens.

Pathologically, PD is marked by two key hallmarks: (i) the progressive and slow decrease of dopaminergic neurons in the part of the brain that is substantia nigra pars compacta, resulting in loss of dopamine in the striatum and subsequent disruption of basal ganglia circuitry, and (ii) the accumulation of Lewy bodies – intracytoplasmic aggregates composed of fibrillar α-synuclein[5]. Although the precise etiological factors that trigger neurodegeneration in PD remain unclear, growing evidence highlights mitochondrial dysfunction and the oxidative stress as central determinants in the pathophysiological mechanisms underlying disease progression. Several previous studies have explored mitochondrial dysfunction in PD and the potential for therapies targeting this pathway. However, a comprehensive analysis of mitochondrial dysfunction with a particular focus on mitochondrial dynamics and their reciprocal interactions with oxidative stress,

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neuroinflammation, and genetic susceptibility remains lacking. This review aims to bridge this knowledge gap by offering an integrated discussion on these intertwined mechanisms.

Mitochondria are critical for maintaining neuronal function, with their dysfunction being closely associated with PD pathology[6]. Oxidative phosphorylation couples redox and phosphorylation reactions within the inner mitochondrial membrane, generating ATP via the electron transport chain (ETC), composed of complexes I – IV. However, this process also generates reactive oxygen species (ROS), which accumulate in excess, and disrupt cellular homeostasis. In PD, mitochondrial dysfunction means impaired mitochondrial biogenesis, unstable membrane potential, reduction in oxidative phosphorylation efficiency, and increased ROS production[7]. The overproduction of ROS exceeds the capacity of cellular antioxidant defense mechanisms, resulting in oxidative damage of lipids, proteins, and mitochondrial DNA (mtDNA), thereby exacerbating neuronal degeneration[7]. Moreover, mutations in genes such as PINK1[8], Parkin, and DJ-1[9], which regulate mitochondrial quality control and oxidative stress response, have been linked to both familial and sporadic PD, highlighting the significant role of mitochondrial dysfunction in disease progression.

In this review, mitochondrial dynamics refers to the continuous processes of mitochondrial fission, fusion, biogenesis, and selective degradation (mitophagy), which collectively govern mitochondrial morphology, distribution, and functional integrity in neurons. Disruption of these dynamics plays a critical role in PD pathology.

Furthermore, it is important to note that PD patho-mechanisms are multi-directional. For instance, oxidative stress can not only result from mitochondrial dysfunction but also aggravate it, creating a vicious cycle of damage. In light of this, Figure 1 has been modified to reflect these bi-directional relationships, illustrating how oxidative stress, mitochondrial damage, and other cellular impairments interconnect in the progression of PD.

Here, we review the contribution of mitochondrial dysfunction and oxidative stress in the pathogenesis of Parkinson's disease, their effects on neuronal survival and the molecular mechanisms underlying neurodegeneration. It further explores the involvement of PD-associated genes in regulating mitochondrial homeostasis and oxidative stress responses. Additionally, we discuss potential biomarkers and therapeutic strategies targeting these pathways to mitigate disease progression.

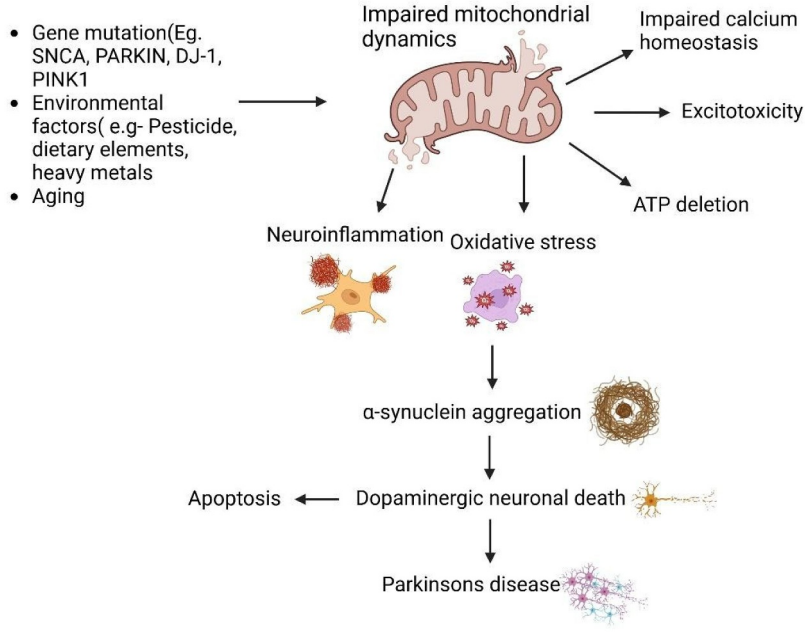

Figure 1. Mitochondrial dysfunction triggers multiple harmful effects, driving neurodegeneration across various diseases. The inability to clear damaged mitochondria severely impacts the central nervous system, resulting in cellular stress, damage, and ultimately neuronal loss. Arrows indicate increases (up) or decreases (down) in specific processes.

Mitochondrial dysfunction in Parkinson's disease

Recent studies have revealed endoplasmic reticulum (ER)-mitochondrial signaling in roles, specifically within neurons, which impact many cellular functions[10,11]. Advanced electron microscopy has revealed the presence of this signaling within cell bodies, axons, dendrites, and synaptic regions[12–14]. One key function of ER-mitochondrial signaling is the regulation of Ca2+ homeostasis, a crucial process for maintaining cellular functions. The ER releases Ca^{2+} into the cytoplasm through inositol 1,4,5-trisphosphate receptors (IP3Rs), allowing mitochondria to take up Ca^{2+} via voltage-dependent anion channel (VDAC) proteins in the outer mitochondrial membrane (OMM) and the mitochondrial Ca^{2+} uniporter (MCU) in the inner membrane (IMM). Disruption of Ca^{2+} homeostasis impairs synaptic transmission and plasticity, processes that altered in PD.

In addition to ER – mitochondrial interactions, classical features of mitochondrial dysfunction in Parkinson's disease include impairments in the electron transport chain (ETC), particularly at Complex I, which result in reduced ATP synthesis and increased production of reactive oxygen species (ROS). Deficiencies in ETC function are among the earliest biochemical abnormalities observed in PD and are linked to energy failure and oxidative stress.

Presynaptic Ca^{2+} levels regulate neurotransmitter release, while fluctuations in dendritic Ca^{2+} control synaptic activity and plasticity[15,16]. Furthermore, Ca^{2+} release from intracellular stores plays a pivotal role in neurogenesis by coordinating migration, differentiation, and proliferation[17].

Increased concentrations of mitochondria in the synaptic terminals are known due to the increased levels of ATP that is required for synaptic activity[18]. Synaptic activity depends on the depletion of the dynamin-related protein 1(Drp1), a mitochondrial fission protein that stabilizes the interaction between mitochondria and ER[19]. Additionally, the two organelles' impaired signaling is directly linked to synaptic transmission loss and ensuing degradation[20].

Another key pathological mechanism in PD is the disruption of mitochondrial quality control. This includes dysregulation of mitophagy and the selective degradation of damaged mitochondria. Genes such as PINK1 and Parkin are crucial in maintaining mitochondrial quality through this pathway. When these proteins are mutated or functionally impaired, damaged mitochondria accumulate, leading to oxidative damage and neuronal death.

Axonal damage is one pathological condition that has caused ER and mitochondria to be directed to the damaged site.[21,22]. Interestingly, in many studies, it has been reported that there is a regrowth of injured axons as soon as ER-mitochondrial tethering increases and Ca2+ transfers to mitochondria[23], suggesting potential therapeutic targets in neurodegenerative disease.

Lastly, ER-mitochondria signaling also controls autophagy and mitophagy, which is the selective destruction of damaged mitochondria. Furthermore, autophagic failure is a fundamental feature of numerous neurodegenerative disorders[24]. Nonetheless, there is still debate regarding the function of ER-mitochondria interactions in autophagy. According to later research, the loss of ER-mitochondria contacts stimulates autophagy[11]. However, it was first demonstrated that autophagosome production occurs at ER-mitochondria contacts[25]. This could be because different techniques are employed to induce autophagy.

The dynamic structure of ER-mitochondria interaction is now recognized and adapted in response to physical stimuli, with the help of synaptic activity that enhances their formation[26], but the mechanism governing these alterations remains unclear. Several proteins have been identified to promote or disrupt the ER-mitochondria contacts. Some of these proteins, such as the Sigma-1 receptor (SigmaR1), function directly at the contact sites, whereas others, like the ALS-associated protein TAR DNA-binding protein 43 (TDP-43, also called TARDBP) and fused in sarcoma (FUS), influence the connections indirectly by triggering downstream signaling pathways[27,28]. The mitochondria-associated membrane (MAM) is the place where SigmaR1 is located, where it serves as a chaperone for inositol 1,4,5-triphosphate receptors (IP3Rs), facilitating calcium (Ca2+) transfer to mitochondria via ER and supporting ATP production[27,29]. In hippocampal neuron development, SigmaR1 plays an important role by regulating dendritic spine formation and activating Rac1, a little Rho GTPase that is also involved in neuronal growth and plasticity.[30]

Oxidative stress in Parkinson's disease

Mitochondria are known to produce ATP (adenosine triphosphate) by the help of respiration and oxidative phosphorylation, also known as the cell's primary energy source. Oxidative phosphorylation efficiently generates ATP by combining phosphorylation and redox processes. In electron transport chain (ETC), it has complexes I – IV that produce a proton gradient near the inner mitochondrial membrane by moving electrons from either FADH2 (flavin adenine dinucleotide) or NADH (nicotinamide adenine dinucleotide) or FADH2 (flavin adenine dinucleotide). This comprises of a pH gradient (ΔpH) and an electrical gradient ($\Delta\psi$), drives the ATP synthase (complex V) enzyme to convert adenosine diphosphate (ADP) into ATP[31].

Signs of mitochondrial dysfunction include reduced mitochondrial biogenesis, altered membrane potential, fewer mitochondria, and disrupted oxidative protein activity due to ROS accumulation in cells and tissues[7]. A difference in the level of the generation of reactive oxygen species (ROS) and also the antioxidant defenses of the cell lead to the oxidative stress in the cell, where the negative effects of ROS outweigh the protective advantages of antioxidants.

By interacting with mitochondrial and cellular components like DNA, proteins, and lipids, ROS produced in mitochondria during the OXPHOS process predominantly results in mitochondrial dysfunction[32,33]. Increased ROS generation is encouraged by higher glucose levels, changing the structure of mitochondria[34]. Dopaminergic neurons of the substantia nigra pars compacta (SNpc), one of the various neuronal types affected by PD, are principally to blame for the distinctive motor symptoms and is the driving force behind symptomatic treatments[35,36].

Dopaminergic neuronal degeneration is largely caused by oxidative stress and mitochondrial dysfunction[37–41]. Oxidative stress-induced toxins include 1,1'-dimethyl-4,4'-bipyridinium dichloride, rotenone, and 1-methyl-4-phenyl 1,2,3,6 tetrahydropyridine (MPTP). The use of paraquat and 6-hydroxydopamine (6-OHDA) imitate PD has further demonstrated a relationship between oxidative stress and dopaminergic neuronal degeneration[42–45]. Toxins that cause oxidative stresses, such as rotenone, 1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine (MPTP), 1,1'-dimethyl-4,4'-bipyridinium dichloride (paraquat), 6-hydroxydopamine (6-OHDA), and 1-methyl-4-phenyl 1,2,3,6tetrahydropyridine (MPTP), have been employed as PD model, confirming the connection in oxidative stress and also dopaminergic neuronal degeneration[42–46]. When the biological system's ability to produce ROS is exceeded to eliminate reactive intermediates during oxidative stress, cellular damage ensues.

By activating enzymes like nitric oxide synthase (NOS) and NADPH oxidases, ROS may be produced indirectly or directly through the Fenton and Haber-Weiss reactions, which include redox-active metals and oxygen species. For the most free radicals to generate chemically, molecular oxygen must be activated[47]. H2O2, ($O2^{-}$), and (−OH) are some of the examples of ROS. The electron transport chain's mitochondrial complexes I and III are the primary sources of superoxide anions, which are reactive and readily diffuse through the inner mitochondrial membrane, where they are reduced to H2O2[41]. Peroxisomes also produce H2O2. The enzyme catalase, found in peroxisomes, converts H2O2 into water, preventing its accumulation. However, when peroxisome enzymes are downregulated or damaged, H2O2 is released into the cytosol, contributing to oxidative stress. The Fenton reactions can further convert H2O2 into the highly reactive hydroxyl radical in the presence of reduced metals such as ferrous iron (Fe^{2+})[48].

Despite strong evidence supporting oxidative stress in Parkinson's disease (PD), it remains unclear whether ROS accumulation is a cause or a consequence of other cellular pathways. Since mitochondria serve as both a source and a target of ROS, mitochondrial dysregulation is strongly implicated in the pathophysiology of PD.

Mitochondria are dynamic organelles with multiple functions, including calcium homeostasis, stress responses, and energy production. Consequently, mitochondrial dysfunction induces cellular damage and contributes to neurodegeneration.

Neuroinflammation and mitochondrial dysfunction are interconnected in PD pathogenesis[39]. Pro-inflammatory cytokines can impair mitochondrial function, inducing oxidative stress and disrupting oxidative phosphorylation (OXPHOS). On the other hand, mitochondrial dysfunction may initiate immune responses and worsen neuroinflammation[49–51]. The genes Parkin and PINK1, which regulate mitochondrial quality control through mitophagy, are notable examples[52]. Mechanistic studies on human and animal models indicate that mitophagy may mitigate neuroinflammation by preventing the release of damage-

associated molecular patterns (DAMPs), which activate innate immunity[53]. Elevated interleukin-6 levels suggest that activating the cyclic GMP-AMP synthase/stimulator of the interferon gene pathway diminishes innate immune system activity[52,53].

Another important consequence of ROS-induced damage is lipid peroxidation, which occurs when lipids and ROS combine to form lipid radicals[48]. By initiating chain reactions that compromise membrane integrity, these radicals lead to the dysfunction of organelles and cells. Polyunsaturated phospholipids in cell membranes are particularly vulnerable to lipid peroxidation, which has been intimately associated with the pathophysiology of Parkinson's disease[53]. Elevated lipid peroxidation levels in the substantia nigra of PD patients have been linked to increased neuronal cell death[54].

Mitochondrialdysfunction and dopaminergicNeuron degeneration

Recently, in several studies, the death of a specific set of neuronal cell populations would be one of the key features. Every disorders have certain patterns; in case of PD, it is the degeneration and the affected neurons, which determines the clinical symptoms that is typically associated with the condition. In PD conditions, the motor activity of a person is linked with the death of a specific set of neuronal cell populations of dopaminergic neurons[55]. This SNc is a neuronal population that is projecting to caudate and putamen that are critical for regulating basal ganglia circuitry. Recent clinical trials have proven that 50–60% of SNc Da neurons have degenerated[56,57]. There are some motor symptoms, but there are some autonomic symptoms that include olfactory dysfunction, constipation, sleep disturbances, depression, and anxiety[58].

Recently in some studies, it is mentioned that these DA neurons are at danger generally because they produce toxic molecules in specific conditions by the generation of neurotransmitters that are reactive quinones during its oxidation[59]. For the production of neuromelanin in the SNc DA neurons this oxidation is important, and these DA quinones interact with and negatively impact the function of mitochondrial protein complexes I, II, and V[60] and of other protein-like tyrosine hydroxylase, which is the DA transporters and α-synuclein[61]. Some of these byproducts can lead to the promotion of mitochondrial dysfunction, aggregation of α-synuclein and the oxidative stress[62]. The continuous degeneration of DA neuron in PD condition can be decreased by increasing the number of vesicular packaging of DA, while another method can be downregulating vesicular packaging has the reverse effect[63–65]. Nevertheless, this cannot explain the vulnerability of various dopaminergic neuron subgroups or the potential susceptibility of non-dopaminergic neurons in PD. Even though DA toxicity undoubtedly plays a role in the degeneration of SNc DA neurons, it is not the only factor responsible for neuronal death in PD, there are many other factors that are playing a role in the degeneration of dopaminergic neurons, that is iron, that can generate ROS by the help of Fenton reaction. In many of the studies, it has been shown to accumulate with age in SNc. It is also very important for ETC to function as it relies on iron-sulfur clusters, mainly due to the high bioenergetic demand of SNc neurons[66,67]; if there is an increase in the iron content, it could lead to increases and sustained mitochondrial activity. Interesting features to see is that iron in the Da neurons can be chelated by neuromelanin, which makes it unavailable for mitochondrial function. Despite the lower affinity of iron for neuromelanin, the loss of ferritin concentration with decrease in age may impact mitochondrial function and can lead to cell death[68].

Genetic and environmentalInfluences on mitochondrial dysfunction in PD condition

Figure 2 illustrates the crosstalk between genetic mutations, toxins present in like pesticide, and aging in promoting mitochondrial dysfunction that leads to the oxidative stress in Parkinson's disease (PD). Mutations in these genes such as PINK1, PARKIN, DJ-1, LRRK2, SNCA, and GBA can disrupt mitochondrial biogenesis, that is leading to impaired mitophagy and increase in the production of reactive oxygen species (ROS). Environmental toxins, including MPTP, rotenone, and paraquat, as well as aging-related mitochondrial decline, further exacerbate oxidative stress and energy deficits by inhibiting complex Iof the electron transport chain. These mitochondrial impairments contribute to α-synuclein aggregation, which overwhelms cellular clearance mechanisms such as the autophagy-lysosomal pathway, leading to dopaminergic neuron degeneration and PD progression. PGC- 1α, which is aregulator of mitochondrial function, it

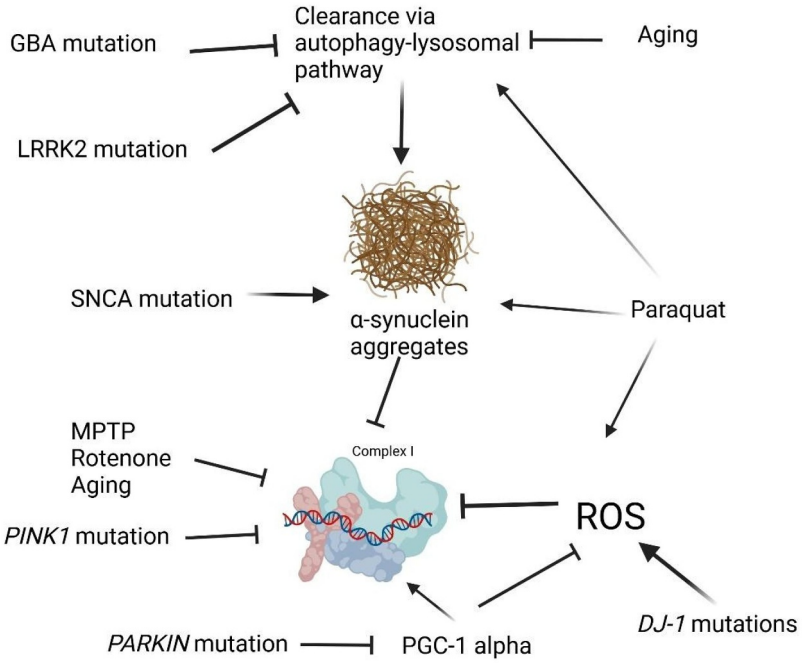

Figure 2. Crosstalk between genetic mutations.

is implicated in modulating oxidative stress responses. Autosomal dominant Parkinson's disease patients are associated with a mutation in the alpha-synuclein gene. PD risk is influenced by additional genetic variables. Even in patients with sporadic Parkinson's disease, these high-penetrant mutations helped reveal that Lewy bodies are the main component of alpha-synuclein, despite the fact that they are comparatively rare in families. Subsequently, autosomal PD patients were identified, indicating that the etiology of PD involves high alpha-synuclein levels. Singleton et al.[69]. According to Kitada et al.[70] and Valente et al.[71], mutations in PARKIN and PINK are linked to the early onset of autosomal recessive Parkinson's disease. PARKIN and PINK1 have been linked to a cellular pathway that enables macro-autophagy, or "mitophagy," to selectively degrade malfunctioning mitochondria in lysosomes. It has been discovered that sporadic Parkinson's disease (PD) has low levels of PGC-1alpha, a crucial transcriptional regulator that manages the expression of genes for mitochondrial functioning as well as multiple antioxidant defenses. PARKIN indirectly regulates this[72]. Mitochondrial turnover disorder in Parkinson's disease is linked to these genetic connections to mitochondrial biosynthesis and degradation.

Upon vulnerable to the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can result in Parkinson's disease (PD). It produces a quick start of parkinsonian phenotype and kills dopaminergic neurons in the SN, most likely as a result of inhibiting mitochondrial complex I activity. In a number of studies, pesticides like rotenone are connected to Parkinson's disease (PD) by causing chronic exposure in mice. Rotenone is also an inhibitor of the mitochondrial complex I, which can cause dopaminergic neurons to degenerate[73.74]. In almost every organism, from bacteria to mammals, PARK7 encodes DJ-1, a tiny (~20 kDa) protein. Because of the uncontrolled death of dopaminergic neurons, mutations in the human gene PARK7 result in an early appearance of Parkinson's disease (PD)[75]. DJ-1 has antioxidant effects going through multiple pathways, including as promoting glutathione synthesis and controlling NRF2, a transcription factor that upregulates several antioxidant defenses[76].

The R144G mutation, for example, has a far higher penetrance than the G2019S mutation, which is predicted to have a penetrance of about 25%. These mutations are responsible for roughly 5% of the familial PD cases and are present in 1% to 2% of all PD cases. But in some groups, such as Ashkenazi Jews and North African Berbers, their prevalence is noticeably higher. Both Alessi and Sammler,[77]. Mutations in LRRK2 are associated with increased kinase activity[78]; some earlier research has suggested that it also has a protective effect[79], albeit it may also contribute to the loss of LRRK2 function[80]. A gene mutation linked to autosomal

recessive Gaucher disease causes GBA, another common genetic factor that increases the risk of Parkinson's disease (PD)[81]. GBA carriers are around four times more likely to develop Parkinson's disease (PD) though this varies according to the particular GBA mutation. GBA mutation-associated Parkinson's disease (PD) has been linked in recent studies to a higher risk of dementia[82]. In Parkinson's disease (PD), research has shown that a mutation in the GBA gene reduces the activity of lysosomal glucocerebrosidase (GCase). Balestrino and Schapira[83] state that substances that increased GCase activity and substrate reduction therapy are currently advancing to clinical trials after showing promise in animal models.

The R144G mutation, for example, has a far higher penetrance than the G2019S mutation, which is predicted to have a penetrance of about 25%. These mutations are responsible for roughly 5% of the familial PD cases and are present in 1% to 2% of all PD cases. But in some groups, such as Ashkenazi Jews and North African Berbers, their prevalence is noticeably higher. In both Alessi and Sammler,[77] any mutations in the gene LRRK2 are related to an increase in the kinase activity[78]; some earlier research has suggested that it also has a protective effect[79], albeit it may also contribute to the loss of LRRK2 function[80]. In particular, α-synuclein that is present in the intracellular, where the homeostasis is usually maintained by the help of ubiquitin-proteasome and lysosomal autophagy systems. α-Synuclein cleavage is also linked to extracellular proteases that are not part of either system. Therefore, the weakening of these degradation pathways may increase the accumulation of α-synuclein. Oxidative stress (OS) is an important aging factor that directly harms the central nervous system. Free radicals, or ROS, are essential for host defense, apoptosis, gene transcription, and the regulation of brain plasticity in physiological conditions[84]. NADPH oxidase (NOX), which is crucial for starting OS and neurotoxicity, is believed to be the most important ROS generator. According to Bedard and Krause[85], Halliwell[86], and Kovac et al.[87], mitochondria are another significant generator of ROS.

Therapeutic strategies targeting mitochondrial dysfunction and oxidative stress

Among the nutritional alternatives utilized in the dietary supplementation approach to treat mitochondrial dysfunction are vitamin B2, creatine, CoQ, and carnitine. Carnitine protects cells by transporting long-chain fatty acids to mitochondria and preventing their accretion through its interaction with acyl-CoA[88,89]. According to Hernández-Camacho et al.[90], ubiquinone, sometimes referred to as CoQ, inhibits lipid peroxidation and encourages the transfer of electrons from Complexes I and II to Complex

III. This prevents oxidative damage to lipoproteins and cell membranes. Skeletal muscle acts as an energy buffer reserve because creatine can reestablish ATP by forming a molecule with phosphoric acid[91]. When there is not enough glucose available, human metabolism uses ketone bodies to give different organs alternative energy. Fatty acid oxidation in the liver's mitochondrial matrix is the main process that produces these ketone molecules, which include acetoacetate, β-hydroxybutyrate (βOHB), and acetone. The ketogenic diet (KD), with its high fat and low carbohydrate intake, mimics the metabolic state of extended fasting. Exogenous ketone body supplements and ketogenic diets have been found in preclinical research to be beneficial in preventing advanced heart failure, spinal cord damage, AD, PD, MELAS, ischemic stroke, and intractable infantile epilepsy.

Mitochondrial dysfunction and oxidative stress are key contributors to various neurodegenerative diseases, metabolic disorders, and aging. Therapies targeting these dysfunctions focus on antioxidant supplementation, gene therapy to enhance mitochondrial repair, and lifestyle modifications to boost mitochondrial health. Below are the main strategies:

Redox-based therapies

Glutathione enhancers and thiol-based treatments help neutralize oxidative stress and protect mitochondrial integrity. Smith et al.[92] demonstrated that thiol-based antioxidants, such as N-acetylcysteine (NAC), partially restore mitochondrial redox balance and reduce oxidative damage, though full functional recovery remains limited. Thiol-based antioxidants (e.g., N-acetylcysteine (NAC) and glutathione precursors) offer partial protection against oxidative damage by restoring mitochondrial redox balance. However, the findings suggest that while thiol-based treatments reduce oxidative burden, their efficacy in fully restoring mitochondrial function remains limited. The authors highlight the need for

combination therapies involving gene therapy (PINK1/Parkin activation), mitochondria-targeted antioxidants (like mitoQ), and lifestyle interventions (exercise and diet) to achieve more effective neuroprotection." Mitochondria-Targeted Antioxidants: A New Era of Redox-Based Therapeutics." [93] Mitochondrial dysfunction plays a central role in the pathogenesis of Parkinson's disease, contributing to oxidative stress, impaired bioenergetics, and neuronal apoptosis. Emerging research suggests that mitochondria-targeted antioxidants – such as MitoQ, SkQ1, and SS peptides – offer promising neuroprotective effects by selectively neutralizing mitochondrial reactive oxygen species (ROS), restoring mitochondrial membrane potential, and improving cellular energy metabolism. Studies indicate that these antioxidants prevent dopaminergic neuron degeneration, reduce α-synuclein aggregation, and mitigate neuroinflammation, which are key pathological features of PD. They also enhance mitophagy and mitochondrial biogenesis, promoting cellular homeostasis in dopaminergic neurons. Despite encouraging preclinical and early clinical data, challenges remain regarding optimal dosing, long-term safety, and efficacy in human trials. Table 1 is depicting the therapeutic approached that are targeting mitochondrial dysfunctions and oxidative stress in PD. Future research should focus on clinical validation, combination therapies, and targeted delivery approaches to maximize therapeutic potential.

Gene therapy approaches

Some strategies, such as PINK1/Parkin-based gene therapy, aim to prevent neurodegeneration and promote mitophagy, or mitochondrial autophagy. "PINK1-Parkin Pathway Modulation in Mitochondrial Diseases: Therapeutic Implications,"[94]. The PINK1-Parkin pathway, which ensures the selective removal of damaged mitochondria to prevent cellular stress and neurodegeneration, is crucial for maintaining mitochondrial quality control through mitophagy. This system's malfunction has been directly connected to the etiology of Parkinson's disease (PD), which leads to the accumulation of damaged mitochondria, increased oxidative stress, and neuronal death, particularly in dopaminergic neurons. In Parkinson's disease and other mitochondrial illnesses, treatment options that boost PINK1-Parkin activity offer intriguing neuroprotective potential. According to preclinical studies, mitophagy, Parkin recruitment, and PINK1 expression can reduce oxidative damage, restore mitochondrial homeostasis, and stop dopaminergic neuron degeneration. Gene therapy methods, CRISPR-based drugs, and tiny molecules that target this system offer the potential to alter the disease rather than only cure its symptoms. However, challenges remain, including the need for long-term validation in human models, potential off-target effects, and effective delivery techniques. Future research should assess patient-specific medicines, combination therapy with mitochondrial antioxidants, and druggable targets within the PINK1-Parkin pathway in order to improve treatment outcomes. The study emphasizes its potential in Parkinson's illness and mitochondrial encephalopathies. "CRISPR-Based Gene Therapy for Mitochondrial Dysfunction: Advances and Challenges." Gonzalez & Patel[95] investigate CRISPR/Cas9- based PINK1/Parkin upregulation and its therapeutic effects in models of mitochondrial dysfunction. This study discusses potential clinical applications and limitations.

Table 1. Summary of therapeutic approaches targeting mitochondrial dysfunction and oxidative stress in PD.

Study	Study Model	Therapeutic Strategy	Key Findings
Smith et al.[92]	Preclinical (cellular)	NAC, glutathione precursors	Partial redox restoration; limited mitochondrial recovery
Zhang & Lee[93]	Preclinical (animal)	MitoQ, SkQ1 (mitochondria-targeted antioxidants)	Reduced dopaminergic neuron loss and α-synuclein aggregation
Kim et al.[94]	Preclinical (rodent models)	Gene therapy (PINK1/Parkin activation)	Enhanced mitophagy and neuroprotection
Gonzalez & Patel[95]	Experimental models	CRISPR-mediated PINK1 upregulation	Promoted mitochondrial homeostasis and reduced ROS
Wang et al.[96]	Dietary (rodent and cellular)	Ketogenic diet, NAD^+ precursors	Boosted mitochondrial function, reduced ROS levels
Jones et al.[97]	Clinical review	Exercise	Increased PGC-1α expression and mitochondrial biogenesis

Lifestyle and nutritional interventions

While nutritional therapies (such as ketogenic diets and NAD+ precursors) boost mitochondrial function, exercise promotes mitochondrial biogenesis. "Exercise-Induced Mitochondrial Biogenesis: Mechanisms and Benefits." Jones et al.[97] The study looks at how exercise helps maintain mitochondrial health and how it may affect neurodegenerative conditions like Parkinson's disease (PD). The association between Parkinson's disease and mitochondrial dysfunction is influenced by numerous factors. Some of them have already been mentioned:

(A) Exercise stimulates PGC-1α, a key regulator of mitochondrial biogenesis, which enhances energy production and reduces oxidative stress in neuronal cells.
(B) Regular physical activity improves mitophagy, the process of removing damaged mitochondria, which is particularly impaired in PD due to PINK1/Parkin dysfunction.
(C) Endurance exercise increases antioxidant defenses, reducing the accumulation of reactive oxygen species (ROS) and delaying neuronal degeneration.
(D) Exercise enhances dopamine metabolism, potentially slowing the progression of dopaminergic neuron loss in PD.

Another study, "Dietary Strategies to Enhance Mitochondrial Function: The Role of Ketogenic Diets and NAD+ Precursors." According to Wang et al.[96], oxidative stress, poor energy metabolism, and neuronal degeneration are all consequences of mitochondrial dysfunction, which is a key factor in the pathophysiology of Parkinson's disease (PD). By improving mitochondrial function, lowering oxidative damage, and promoting neuronal survival, new research indicates that dietary approaches – in particular, ketogenic diets (KDs) and nicotinamide adenine dinucleotide (NAD^+) precursors – offer encouraging therapeutic promise. By increasing β-oxidation, improving ATP production, and decreasing the formation of reactive oxygen species (ROS), ketogenic diets increase mitochondrial efficiency. The switch to ketone metabolism gives neurons a different source of energy, which could make up for the deficiencies observed in Parkinson's diseases.

Deep brain stimulation (DB) in a PD patient

This FDA-approved neurosurgical technique uses an electrode inserted into the deeper brain structure to provide electrical stimulation. It has a very good connection to a subclavicular battery source that is implanted. Although deep brain stimulation (DBS) is primarily a neurosurgical intervention for motor symptoms in PD, some studies have suggested it may indirectly impact mitochondrial activity and oxidative stress through modulation of neuronal activity and energy demand[98]. However, this relationship remains speculative and is not the central focus of mitochondrial-targeted therapies reviewed herein. Globus pallidus internus (GPI) and the subthalamic nucleus (STN) are the target areas. The ventral intermediate (VIM) nucleus of the thalamus is less frequently targeted for ablation because VIM DBS only works for PD symptoms that resemble tremors. But it does not help with other PD symptoms. DBS has the extra benefit of being easier to target the STN and GPi than other complex methods. Continuous guidance alone, in conjunction with microelectrode recordings, or both may be used. Additionally, patients might get a warning before beginning these procedures, such as microelectrode recording or anesthesia, as is customary in imaging-alone-based surgeries. Although there may be a noticeable decrease in the rates of bleeding and infection with general anesthesia, this treatment may also have additional adverse effects. According to Ho et al.[99], there is a possibility that the clinical motor outcomes will differ considerably less.

Despite strong preclinical evidence supporting the therapeutic potential of targeting mitochondrial dysfunction and oxidative stress, clinical trials have yielded disappointing results. For example, interventions involving MitoQ or Coenzyme Q10 have not demonstrated clear neuroprotective effects in PD patients[100]. One reason may be the limited translational relevance of toxin-based models used in early research. Agents like MPTP, rotenone, and 6-OHDA induce rapid and widespread dopaminergic cell death – changes that are not reflective of the slow, progressive neurodegeneration characteristics of idiopathic PD. Indeed, individuals exposed to MPTP develop Parkinsonian symptoms in just days, whereas

in idiopathic PD, neurodegeneration unfolds over the years. This discrepancy raises concerns that such models may not capture the pathophysiological complexity or tempo of the human condition.

An alternative and emerging hypothesis is the "single-neuron degeneration" model of PD pathogenesis, which proposes that dopaminergic neuron loss in idiopathic PD is driven by intrinsic, neuron-specific mechanisms. A key candidate in this model is the endogenous neurotoxin aminochrome, a metabolic byproduct of dopamine oxidation within neuromelanin-containing neurons. Aminochrome has been shown to impair mitochondrial function, induce α-synuclein aggregation, and promote oxidative stress. Unlike exogenous neurotoxins, aminochrome's effects are localized and non-spreading, leading to the gradual loss of individual neurons[101]. This process may account for the slow progression of PD and the challenges in detecting therapeutic efficacy using conventional clinical endpoints. Future strategies should consider this model and prioritize interventions that mitigate endogenous toxin accumulation and single-cell vulnerability over long time scales.

Conclusion and future direction

Parkinson's disease is the second most neurodegenerative disorder, in that there are several components that play but most importantly there are two components that play a major role, that is mitochondrial dysfunctional and oxidative stress. The evidence reviewed here highlights how impaired mitochondrial biogenesis leads to defects in the electron transport chain (ETC) and irregular functioning of mitophagy leads to neuronal loss leading to PD. The oxidative stress that is caused due to the excessive reactive oxygen species (ROS) production, increase in the protein misfolding and DNA damage, all that leads to the degeneration of dopaminergic neurons. As mentioned in some of the studies that there are certain genes like PINK1, DJ-1 and LRRK2 and environmental toxins like rotenone, pesticides that further lead to an imbalance of mitochondrial and the oxidative stress, leading to the PD pathophysiology.

Recently, there have been many advancements in understanding PD mechanisms, but then also current therapies still remain in debate, with no exact cure of the disease. Nevertheless, there is some hope left still with the ongoing research of antioxidants, mitochondrial-targeted therapies, and also with gene therapy as it is found to be effective but still some of the clinical studies are still going on to prove it. There are some biomarker that has been identified for mitochondrial dysfunction and oxidative stress, but still research is going on and remains an active area of research. This may be promising for earlier diagnosis and targeted interventions. Additionally, as mentioned in earlier lifestyles, it plays an important role such as exercise and dietary modifications that still remain a potential field of research. Given the complexity of PD, an important approach combining genetic, metabolic, and neuroprotective strategies holds the most promise in altering disease and improving patient outcomes.

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