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MITOCHONDRIAL DYSFUNCTION IN NEUROPHYSIOLOGY AND NEURODEGENERATION: A REVIEW

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Abstract

Mitochondrial dysfunction has emerged as a fundamental pathological mechanism underlying the onset and progression of numerous neurodegenerative disorders. Beyond their classical role in adenosine triphosphate (ATP) production, mitochondria regulate calcium homeostasis, redox signaling, apoptosis, mitophagy and neuroimmune responses, all of which are essential for maintaining neuronal integrity and synaptic function. Increasing evidence indicates that disturbances in oxidative phosphorylation, excessive reactive oxygen species generation, mitochondrial DNA damage, impaired mitochondrial dynamics, defective mitophagy and chronic neuroinflammation collectively contribute to neuronal dysfunction and progressive neurodegeneration. These mitochondrial abnormalities have been implicated in the pathogenesis of Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis, highlighting mitochondria as attractive therapeutic targets.

This review comprehensively summarizes the physiological functions of mitochondria in the nervous system and critically discusses the molecular mechanisms linking mitochondrial dysfunction with neurodegenerative diseases. Furthermore, recent advances in mitochondria-targeted therapeutic strategies, including mitochondria-targeted antioxidants (MitoQ), mitophagy activators (urolithin A), NAD^+ augmentation therapies, mitochondrial biogenesis stimulators, metabolic interventions and emerging gene-based approaches, are reviewed with particular emphasis on their mechanisms of action and therapeutic potential. In addition, the review evaluates current challenges in clinical translation, including limited bioavailability, poor blood-brain barrier penetration, disease heterogeneity and the inconsistent outcomes of clinical trials despite encouraging preclinical evidence.

Finally, current controversies, research gaps and future directions are highlighted to provide a critical perspective on the development of effective mitochondria-targeted therapies. A deeper understanding of mitochondrial biology, combined with advances in precision medicine, biomarker discovery and translational neuroscience, may facilitate the development of novel disease-modifying interventions capable of delaying neurodegeneration and improving long-term neurological outcomes.

Keywords: *Alzheimer's disease, Mitochondrial dysfunction, Mitochondria-targeted therapy, Mitophagy, Neurodegeneration, Neuroinflammation, Oxidative stress*

INTRODUCTION

In the nervous system mitochondria are highly specialized intracellular organelles. They play a central role in maintaining neuronal survival and physiological stability. These organelles are primarily responsible for adenosine triphosphate (ATP) production through oxidative phosphorylation. This is a process essential for meeting the high metabolic demands of neurons. Neurons rely heavily on mitochondrial energy generation because of their limited glycolytic capacity and continuous requirement for synaptic transmission, axonal transport and membrane potential maintenance, unlike many other cells. In addition to energy production, mitochondria regulate calcium buffering, reactive oxygen species production, apoptosis and intracellular signaling pathways that are critical for normal neurophysiological activity. Disturbances in mitochondrial integrity have profound effects on neuronal communication and survival making mitochondrial dysfunction an important contributor to several neurological disorders (1).

The human brain consumes approximately 20% of the total oxygen utilized by the body despite comprising only a small proportion of body mass. This high consumption of energy by neuronal tissues leads to increased oxidative stress and mitochondrial burden (2). Neurons require continuous mitochondrial trafficking to maintain local energy supply and calcium homeostasis as they possess elongated axons and extensive synaptic networks. To preserve neuronal functions, proper mitochondrial dynamics, including mitochondrial fusion, fission, transport and mitophagy are essential. Alteration in these processes may impair neuronal adaptability and accelerate cellular degeneration. Recent studies have shown that in several neurodegenerative diseases mitochondrial abnormalities often appear before the onset of clinical manifestations, indicating their early involvement in disease progression (3).

In the nervous system mitochondria also serve as important signaling platforms by regulating intracellular calcium concentration and redox balance. Calcium ions take part in neurotransmitter release, synaptic modulation and neuronal excitability. While mitochondria help in maintaining calcium equilibrium through rapid uptake and release mechanisms. If mitochondrial calcium buffering fails, this may trigger excessive activation of excitatory pathways, leading to excitotoxic neuronal injury (4). Similarly, during mitochondrial dysfunction increased production of reactive oxygen species promotes oxidative damage to proteins, lipids and nucleic acids within neural tissues. Oxidative stress is strongly associated with progressive neuronal loss that is observed in aging and neurodegenerative disorders. It is suggested that oxidative injury and mitochondrial impairment form a vicious cycle that enhances neuronal damage over time (5).

Neurodegenerative diseases are associated with dysfunctional mitochondria such as Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis. Though, these disorders possess their own distinct clinical and pathological features, mitochondrial abnormalities are a common underlying factor in their development (6). Defects in oxidative phosphorylation, mutations in mitochondrial DNA, impaired mitophagy and altered mitochondrial dynamics have all been reported in affected neuronal populations (7). In Alzheimer's disease, mitochondrial dysfunction contributes to amyloid beta accumulation and synaptic failure (8). But in Parkinson's disease, there are defects in mitochondrial quality control proteins such as PINK1 and Parkin. Similarly, in several other neurological disorders, mitochondrial impairment has been involved in motor neuron degeneration and abnormal protein aggregation (9).

In molecular neurobiology, recent studies have improved the understanding of the relationship between mitochondrial dysfunction and neuronal degeneration. Modern technologies are developing in neuroimaging, proteomics, metabolomics and genetic analysis. These technologies enabled researchers for the identification of mitochondrial biomarkers associated with disease progression and therapeutic response. These studies have stimulated developing interests in therapies that target mitochondria including antioxidants, mitophagy modulators, mitochondrial biogenesis stimulators and gene-based interventions. Therapeutic strategies offer promising opportunities for slowing neuronal injury and improving neurological outcomes (10). For the development of diagnostic and therapeutic approaches in neurological medicine, understanding the role of mitochondria in neurophysiology and neurodegeneration is essential (11).

One of the most extensively studied mechanisms is the PINK1 and Parkin signaling pathway controlling mitochondrial quality control. The damaged mitochondria accumulate PINK1 on their outer membrane which subsequently recruits and activates the E3 ubiquitin ligase Parkin under normal conditions. This process marks dysfunctional mitochondria for degradation through the autophagic machinery. The components of this pathway are affected by mutations as they are strongly associated with familial and sporadic forms of Parkinson's disease (12). It is further investigated that disruption of PINK1 Parkin signaling contributes to Parkinsonian pathology and mitochondrial abnormalities observed in Alzheimer's disease, Huntington's disease and amyotrophic lateral sclerosis (13).

Beyond the classical PINK1 Parkin pathway researchers have identified additional mechanisms mediated by receptors that participate in mitochondrial quality control. These alternative pathways provide

compensatory protection when canonical mitophagy becomes damaged and appear particularly important in neuronal tissues where mitochondrial renewal must be precisely regulated throughout life. From the studies in 2025, it has been reported that mitophagy mediated by receptors may represent a critical adaptive response during neurodegeneration. This also provides a promising therapeutic target for preserving neuronal function (14).

Mitochondrial biogenesis is another important aspect of mitochondrial homeostasis. This is the process through which new mitochondria are generated to replace damaged organelles and meet high cellular energy demands. This process is largely regulated by transcriptional networks that involve gamma coactivator 1 alpha (PGC 1α) a receptor that activates the proliferation of peroxisomes, nuclear respiratory factors and mitochondrial transcription factor A. Experimental studies have shown that enhanced mitochondrial biogenesis improves neuronal recovery following cellular stress and may counteract mitochondrial deficits associated with neurodegenerative diseases. Consequently, restoration of mitochondrial biogenesis has emerged as a major area of therapeutic investigation (15).

Growing evidence from clinical and experimental research indicates that disturbances in mitochondrial dynamics, impaired mitophagy, defective mitochondrial transport and insufficient mitochondrial biogenesis collectively contribute to neuronal dysfunction. These processes also influence energy metabolism, oxidative stress generation, neuroinflammation and apoptosis. As a result, mitochondrial dysfunction is recognized as a fundamental pathological mechanism. This mechanism links normal aging with progressive neurodegeneration. It is essential to understand these molecular events for the identification of novel biomarkers and developing targeted interventions aimed at preserving neuronal health and slowing disease progression (16).

AIM AND SCOPE OF THE REVIEW

This review aims to provide a comprehensive overview of the role of mitochondrial dysfunction in neurophysiology and its contribution to the pathogenesis of major neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis. This review summarizes the current understanding of oxidative stress, mitochondrial DNA damage, calcium dysregulation, mitochondrial dynamics, impaired mitophagy and neuroinflammation as major mechanisms underlying neurodegeneration. Furthermore, it discusses recent advances in mitochondria-targeted therapeutic strategies while highlighting current challenges, controversies and future directions that may guide the development of effective therapeutic interventions.

MITOCHONDRIAL FUNCTION IN NEUROPHYSIOLOGY

Mitochondria are fundamental regulators and are essential for maintaining the structural and functional integrity of the nervous system. Neurons require high energy and a continuous supply of adenosine triphosphate (ATP) to sustain membrane excitability, neurotransmitter synthesis, vesicle recycling and axonal transport (17). Even slight instabilities in mitochondrial activity can pointedly affect neuronal survival as mature neurons have partial regenerative capacity. Neurons depend on oxidative phosphorylation which makes mitochondrial homeostasis a critical cause of normal brain function and neurological health (3).

In neurons, one of the primary physiological roles of mitochondria is cellular energy production through oxidative phosphorylation. On the inner side of mitochondrial the electron transport chain converts nutrients into ATP through a series of redox reactions. Approximately 90% of neuronal ATP is generated by this process. The ATP acts as energy source and pumps ions such as Na+/K+ ATPase and Ca2+ ATPase. This active pumping of ions maintains electrochemical gradients required for action potential generation and synaptic signaling. Even modest reductions in ATP availability can damage synaptic transmission and compromise neuronal communication (18).

Also, the mitochondria are indispensable regulators of intracellular calcium homeostasis. Calcium enters the cytoplasm during neuronal activity through voltage-gated and ligand-gated channels. Calcium initiates the multiple signalling pathways involved in neurotransmitter release and synaptic plasticity.

Mitochondria rapidly isolate excess calcium and subsequently release it when required. This stops toxic calcium buildup within neurons. In excitatory neurons, this buffering function is particularly important where excessive calcium influx may trigger cellular injury. Recent studies indicate that if mitochondria cannot control calcium levels properly, this contributes to neuronal dysfunction long before apparent neurodegeneration becomes evident (19).

Mitochondrial activity also influences synaptic plasticity. Synaptic plasticity is the biological basis of learning and memory. A substantial amount of energy is required for Long-term potentiation and depression and for the precise regulation of intracellular calcium signalling. Mitochondria are located in the dendritic spines and presynaptic terminals. They provide localized ATP production and buffering of calcium which is necessary for these processes. Experimental studies have revealed that synaptic remodeling and cognitive performance are also disrupted by alterations in mitochondrial distribution and function. Consequently, healthy mitochondrial networks are considered essential for maintaining normal cognitive function throughout life (20).

The natural byproducts of mitochondrial respiration are reactive oxygen species. They play an important physiological role in neuronal signaling. Reactive oxygen species participate in redox-dependent pathways at controlled concentrations that regulate synaptic activity, cellular adaptation and gene expression (21). However, excessive production overcomes antioxidant defense systems and promotes oxidative stress. Because of its high oxygen consumption and abundance of oxidizable lipids the nervous system is particularly vulnerable to oxidative injury. The crucial aspect of mitochondrial function in neurophysiology is to maintain a balance between reactive oxygen species generation and antioxidant protection (22).

Apoptosis is also regulated by mitochondria. Apoptosis is a process necessary for normal nervous system development and tissue homeostasis. Signaling pathways of mitochondria help eliminate damaged or unnecessary cells while they preserve healthy neuronal populations under normal conditions. The controlled release of apoptotic factors and interaction with multiple intracellular signalling cascades facilitate the signalling pathway of mitochondria. Dysregulation of these mechanisms may contribute to pathological neuronal loss that are observed during aging and neurodegenerative disease progression. It is suggested that apoptosis mediated with mitochondria represents a major link between cellular stress and neuronal degeneration (23).

Another important role of mitochondrial physiology is to communicate between the nucleus and mitochondria. According to physiological and environmental demands, this two-directional signalling system permits cells to control metabolic activity. Through retrograde signaling pathways, Mitochondria affect gene expression patterns associated with stress responses, inflammation and cellular adaptation. This communication signalling is necessary in neurons to maintain metabolic flexibility and respond to shifting energy requirements. An important contributor to neurological dysfunction is disruption in nuclear signaling of mitochondria (24).

It is further demonstrated that through interactions with microglia and astrocytes, mitochondria also influence neuroinflammatory responses. Damaged mitochondria can release DNA, reactive oxygen species and other signalling molecules that activate innate immune pathways within the central nervous system. These processes initially provide protective functions; after chronic activation, they may contribute to neuronal injury and disease progression. Consequently, mitochondria are now regarded as metabolic organelles and important regulators of neuroimmune communication and brain homeostasis (25).

Collectively, these observations highlight the various physiological roles of mitochondria in the nervous system. Mitochondria maintain neuronal health as they are involved in energy metabolism, calcium regulation, synaptic plasticity, redox balance, apoptosis, intracellular signalling and neuroimmune interactions. By explaining this functional repertoire, it is unsurprising that mitochondrial dysfunction has emerged as a central mechanism underlying many neurodegenerative disorders. Understanding these physiological roles offers a groundwork for investigating how mitochondrial anomalies contribute to the beginning and development of neurological disease (26).

MECHANISMS OF MITOCHONDRIAL DYSFUNCTION

Mitochondrial dysfunction is a multifactorial process that collectively impairs neuronal function and viability. These mechanisms include oxidative stress, defects in oxidative phosphorylation, mitochondrial DNA damage, and alteration in calcium homeostasis, impaired mitochondrial dynamics and chronic neuroinflammation. Disturbances in these pathways can initiate a cascade of cellular events that ultimately contribute to neurons that heavily depend on mitochondrial metabolism for survival. Current investigations suggest that before the appearance of clinical symptoms, mitochondrial irregularities may arise, highlighting their importance in the initial phases of neurological disorders (27).

OXIDATIVE STRESS AND REACTIVE OXYGEN SPECIES

One of the most extensively studied consequences of mitochondrial dysfunction is oxidative stress. Mitochondria produce small amounts of reactive oxygen species as natural metabolic byproducts during normal oxidative phosphorylation. However, excessive reactive oxygen species production overwhelms endogenous antioxidant defense systems under pathological conditions resulting in oxidative damage to proteins, lipids and nucleic acids (28). Because of their high oxygen consumption and relatively limited antioxidant capacity, neurons are particularly vulnerable to oxidative injury. Persistent oxidative stress disrupts synaptic signalling, damages the enzymes of mitochondria and promotes progressive neuronal loss observed in many neurodegenerative disorders (29).

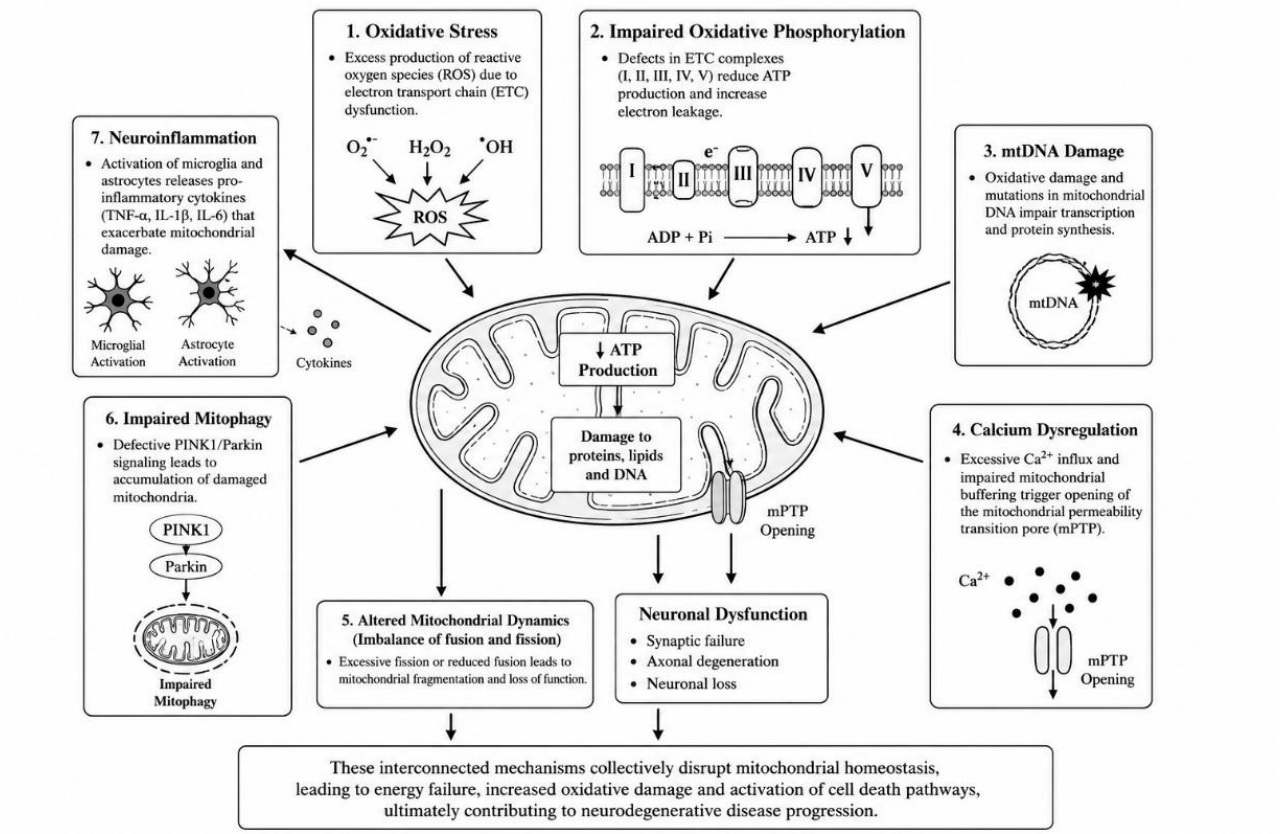

Fig. 1. Molecular mechanisms underlying mitochondrial dysfunction in neurodegeneration

Mitochondrial dysfunction is characterized by interconnected pathological processes, including oxidative stress, impaired oxidative phosphorylation, mitochondrial DNA (mtDNA) damage, calcium dysregulation, altered mitochondrial dynamics, defective PINK1/Parkin-mediated mitophagy and chronic neuroinflammation. These mechanisms collectively impair ATP production, increase reactive oxygen species (ROS) generation, disrupt neuronal homeostasis and promote neuronal dysfunction and progressive neurodegeneration. The shared mitochondrial abnormalities illustrated in this figure contribute to the pathogenesis of major neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis. Created by the authors based on published literature (3, 11, 13, 15, 21, 23, 25, 30, 38, 39)

Excess in the production of reactive oxygen species creates a self-perpetuating cycle of mitochondrial injury. Oxidative damage to mitochondrial membranes impairs electron transport chain efficiency which in turn increases electron leakage and further production of reactive oxygen species (30).

This vicious cycle progressively reduces cellular energy production and accelerates neuronal dysfunction. Recent evidence indicates that oxidative stress may represent one of the earliest detectable abnormalities in both experimental models and patients with neurodegenerative diseases and it is progressing with apparent pathological changes such as protein aggregation and neuronal death (31).

DEFECTIVE OXIDATIVE PHOSPHORYLATION

On the inner side of the mitochondrial membrane, there is an electron transport chain that is responsible for generating the majority of neuronal ATP. Defects in oxidative phosphorylation reduce ATP synthesis and compromise on numerous neuronal processes that depend on energy. In several neurodegenerative conditions, impaired activity of respiratory chain complexes, particularly complex I and complex IV has been reported (32). Reduced ATP availability contributes to various neurological declines as it affects ion channel functions, neurotransmitter release, axonal transport and synaptic plasticity (33).

Recent investigations have shown that oxidative phosphorylation abnormalities are not restricted to neurons alone. Furthermore, mitochondrial metabolic dysregulation also affects glial cells, including astrocytes and microglia. They alter their physiological functions and promote inflammatory responses in the nervous system. These investigations revealed that impaired mitochondrial bioenergetics leads to disease progression through both non-neuronal and neuronal mechanisms (34).

MITOCHONDRIAL DNA DAMAGE

Unlike nuclear DNA, Mitochondrial DNA exists in proximity to the electron transport chain and lacks many of the defensive mechanisms accessible within the nucleus. Therefore, mitochondrial DNA is highly vulnerable to oxidative impairment and mutational growth. Damage of mitochondrial DNA leads to the faulty synthesis of crucial respiratory chain proteins, resulting in oxidative stress and imperfect energy production. Mutations in the mitochondrial DNA are also linked with aging and several neurodegenerative illnesses, suggesting an important part in disease initiation and development (35).

It is reported that acquired or inherited mutations disturb mitochondrial maintenance. This can lead to severe neurological phenotypes. The relationship between mitochondrial DNA damage and neurodegeneration is further strengthened by this evidence. When the DNA integrity of mitochondria declines, neuronal resilience decreases and makes the neurons more susceptible to environmental stressors, inflammation and cellular damage related to age. This progressive decline contributes to the chronic nature of neurodegenerative diseases (36).

CALCIUM DYSREGULATION AND MITOCHONDRIAL DYNAMICS

Another critical mitochondrial function is the maintenance of calcium homeostasis, which becomes disrupted during neurodegeneration. Mitochondria buffer a momentary rise in cytosolic calcium and help coordinate intracellular signalling pathways. Declined in calcium buffering capacity, resulting in intracellular calcium excess. Initiation of calcium-dependent proteases and eventual neuronal damage are unveiled by dysfunctional mitochondria. Mitochondrial respiration is additionally impaired by prolonged calcium imbalance and excites apoptotic pathways that contribute to neuronal damage (37).

For the maintenance of healthy mitochondrial networks, mitochondrial fusion and fission are equally significant. Mitochondrial quality control systems under pathological conditions are disrupted by Excessive mitochondrial fragmentation, impaired fusion and defective mitophagy. These irregularities reduce energy production, increase oxidative stress and promote the buildup of dysfunctional organelles within neurons (38). Growing evidence indicates that disturbances in mitochondrial dynamics are common features of Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis (6).

NEUROINFLAMMATION AND MITOCHONDRIAL DYSFUNCTION

Chronic neuroinflammation has emerged as an important consequence and driver of mitochondrial dysfunction. Damaged mitochondria release mitochondrial DNA, reactive oxygen species, cardiolipin and

other danger-associated molecular patterns that activate innate immune pathways. These signals stimulate microglial activation and promote the release of proinflammatory cytokines that further damage neuronal mitochondria. Consequently, a bidirectional relationship develops in which mitochondrial dysfunction promotes inflammation while inflammation exacerbates mitochondrial injury (39).

Current investigations show that this communication between mitochondrial dysfunction and neuroinflammation may characterize a common pathological pathway across many neurodegenerative disorders. Continuous activation of inflammatory pathways contributes to synaptic dysfunction, neuronal death and disease progression. Understanding this connection has created significant attention in therapeutic approaches targeting both mitochondrial function and inflammatory pathways simultaneously (40).

Table I. Mitochondrial dysfunction and pathological features in major neurodegenerative diseases

Disease	Key mitochondrial dysfunction	Major molecular mechanisms	Neuropathological consequences	Representative recent references
Alzheimer's disease (AD)	Oxidative stress, impaired oxidative phosphorylation, mtDNA damage, defective mitophagy	Amyloid-β accumulation, tau pathology, ROS overproduction, calcium dysregulation, impaired mitochondrial quality control	Synaptic dysfunction, hippocampal atrophy, cognitive decline and dementia	(42, 44, 47, 48, 50, 54)
Parkinson's disease (PD)	Complex I deficiency, impaired mitophagy, mitochondrial fragmentation, oxidative stress	α-Synuclein aggregation, PINK1/Parkin dysfunction, calcium dysregulation, neuroinflammation	Degeneration of dopaminergic neurons, motor dysfunction, neuronal loss	(56, 58, 59, 61, 62, 69)
Huntington's disease (HD)	Defective oxidative phosphorylation, impaired mitochondrial transport, reduced mitochondrial biogenesis	Mutant huntingtin toxicity, impaired PGC-1α signaling, altered mitochondrial dynamics	Striatal degeneration, cognitive impairment, psychiatric manifestations	(70, 71, 73, 74)
Amyotrophic lateral sclerosis (ALS)	Mitochondrial fragmentation, impaired axonal transport, calcium dysregulation, oxidative stress	SOD1, TARDBP, FUS and C9orf72 mutations, neuroinflammation, defective mitophagy	Motor neuron degeneration, muscle weakness, respiratory failure	(75- 79)

MITOCHONDRIAL DYSFUNCTION IN ALZHEIMER'S DISEASE

Alzheimer's disease is the most common neurodegenerative disorder and represents a major cause of cognitive decline and dementia worldwide (41). Although the disease is classically characterized by extracellular amyloid beta plaques and intracellular neurofibrillary tangles, growing evidence indicates that mitochondrial dysfunction plays a central role in its pathogenesis. Mitochondrial abnormalities have been detected in patients with Alzheimer's disease many years before the appearance of severe cognitive impairment, suggesting that mitochondrial dysfunction is an early pathological event rather than a secondary consequence of neuronal degeneration (42).

One of the principal mechanisms linking mitochondria to Alzheimer's disease involves the interaction between amyloid beta and mitochondrial structures. Amyloid beta peptides can accumulate within mitochondria and interfere with respiratory chain activity leading to impaired ATP synthesis and excessive production of reactive oxygen species. Neuronal metabolism is disrupted by these alterations and this disruption also increases oxidative injury in vulnerable brain regions such as the hippocampus and cerebral cortex (8). Studies have demonstrated that mitochondrial dysfunction induced by amyloid beta peptides contributes significantly to synaptic failure and progressive memory impairment in Alzheimer's disease (43).

Oxidative stress is strongly associated with neuronal injury in Alzheimer's disease. Increased generation of reactive oxygen species promotes oxidation of proteins, membrane lipids and mitochondrial

DNA; therefore, they damage neuronal integrity and accelerate neurodegeneration. Amyloid beta aggregation and tau hyperphosphorylation are also increased by oxidative stress, further amplifying pathological changes within the brain. Recent experimental evidence indicates that oxidative injury and mitochondrial dysfunction create a self-reinforcing cycle that progressively worsens disease severity (44).

Tau pathology represents another important contributor to mitochondrial dysfunction in Alzheimer's disease. Microtubule stability is disrupted by hyperphosphorylated tau and impairs axonal transport of mitochondria, preventing their efficient distribution to synaptic terminals (45). Consequently, in the regions with high metabolic demand, neurons experience localized energy deficiency and defective calcium buffering. Abnormal tau accumulation has also been linked with impaired mitochondrial dynamics, increased mitochondrial fragmentation and reduced mitophagy. Neuronal survival and synaptic communication are further compromised by these alterations (46).

In Alzheimer's disease the major pathological mechanism is defective mitophagy. To preserve cellular homeostasis, damaged mitochondria are selectively removed under normal physiological conditions. However, studies have demonstrated that mitophagic pathways become progressively impaired during Alzheimer's disease progression which leads to the accumulation of dysfunctional mitochondria and enhanced oxidative stress. Reduced expression of proteins related to mitophagy has been observed in both experimental models and postmortem brain tissues from affected individuals (47). For slowing neurodegeneration, restoration of mitophagy is therefore being explored as a potential therapeutic strategy (48).

In Alzheimer's disease, neuroinflammation further contributes to mitochondrial dysfunction. Inflammatory mediators and reactive oxygen species are released by activated microglia that damage the mitochondrial membranes and impair respiratory chain activity. Conversely, dysfunctional mitochondria release their DNA and oxidized proteins that stimulate inflammatory signalling pathways. This chronic neural injury and cognitive decline are accelerated and promoted by reciprocal interaction between mitochondrial dysfunction and neuroinflammation. Evidence suggests that suppression of neuroinflammatory pathways may provide neuroprotective effects through preservation of the functions of mitochondria (49).

In Alzheimer's disease bioenergetic abnormalities are consistently observed. They may precede the onset of clinical symptoms. In patients with mild cognitive impairment and early Alzheimer's disease, brain imaging studies have revealed reduced glucose metabolism and impaired mitochondrial respiration (50). Reduced ATP availability affects synaptic plasticity, neurotransmission and neuronal repair mechanisms. This ultimately contributes to memory deficits and cognitive deterioration. These findings support the hypothesis that the fundamental component of Alzheimer's disease pathology is mitochondrial energy failure (20).

Recent therapeutic researches focusing on mitochondrial dysfunction in Alzheimer's disease. Experimental interventions, including mitochondrial antioxidants, mitophagy activators, calcium stabilizers and mitochondrial biogenesis enhancers, have demonstrated promising neuroprotective effects in preclinical studies. The compounds such as coenzyme Q10 (51), nicotinamide riboside (52), urolithin A (53) and antioxidants that target mitochondria are currently being investigated for their ability to improve neuronal bioenergetics and reduce oxidative stress. Although most of these approaches remain under clinical evaluation, they represent promising strategies for modifying disease progression through restoration of mitochondrial homeostasis.

Collectively, current evidence strongly supports the involvement of mitochondrial dysfunction in the initiation and progression of Alzheimer's disease. Disturbances in oxidative phosphorylation, mitophagy, mitochondrial transport, calcium regulation and neuroinflammatory signalling collectively contribute to neuronal degeneration and cognitive decline. A better understanding of these mitochondrial mechanisms may facilitate the development of novel therapeutic approaches who aimed to slow disease progression and to preserve neuronal function in affected individuals (54).

MITOCHONDRIAL DYSFUNCTION IN PARKINSON'S DISEASE

The second most common neurodegenerative disorder is Parkinson's disease. This disease is primarily characterized by progressive loss of dopaminergic neurons within the substantia nigra. Clinically, the symptoms include tremors, muscular rigidity, bradykinesia and postural instability. Although several genetic and environmental factors contribute to disease development, mitochondrial dysfunction is considered one of the central mechanisms involved in neuronal degeneration (55). Because of their high metabolic activity, elevated oxidative burden and dependence on efficient calcium regulation, dopaminergic neurons are particularly vulnerable to mitochondrial injury (56).

One of the earliest indications that link mitochondria to Parkinson's disease emerged from studies demonstrating the impaired activity of mitochondrial complex I in affected individuals. Complex I deficiency disrupts oxidative phosphorylation and reduces ATP generation resulting in impaired neuronal energy metabolism (57). Simultaneously, defects in electron transport enhance reactive oxygen species production and promote oxidative stress within dopaminergic neurons. This oxidative environment contributes to lipid peroxidation, protein oxidation and mitochondrial DNA damage, all of which accelerate neuronal degeneration (58).

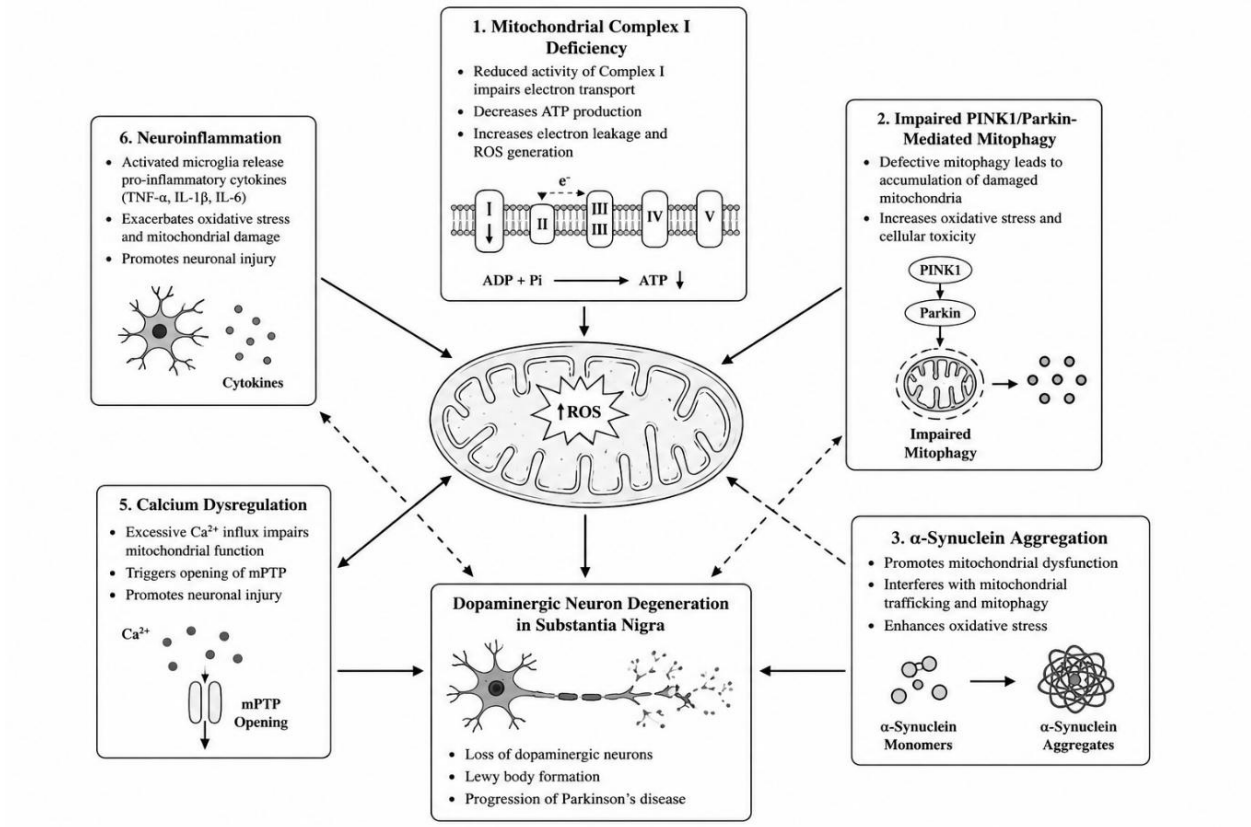

Fig. 2. Molecular pathways linking mitochondrial dysfunction to Parkinson's disease pathogenesis
The schematic summarizes the principal mitochondrial mechanisms involved in the pathogenesis of Parkinson's disease. Environmental factors, aging and genetic susceptibility contribute to mitochondrial complex I deficiency, resulting in impaired oxidative phosphorylation, reduced ATP production, and excessive reactive oxygen species (ROS) generation. Mitochondrial dysfunction further promotes α-synuclein aggregation, impaired PINK1/Parkin-mediated mitophagy, calcium dysregulation and chronic neuroinflammation, creating a self-amplifying cycle of neuronal injury. These interconnected pathological processes culminate in the progressive degeneration of dopaminergic neurons within the substantia nigra leading to the characteristic motor manifestations of Parkinson's disease, including bradykinesia, rigidity, resting tremor and postural instability. Created by the authors based on published literature (40, 55-69)

The mutations in genes that are associated with mitochondrial quality control have further strengthened the relationship between mitochondrial dysfunction and Parkinson's disease. The genes, PTEN-induced kinase 1 (PINK1) and Parkin, play essential roles in mitophagy by identifying and removing damaged mitochondria. Dysfunctional mitochondria accumulate PINK1 on the outer mitochondrial membrane under physiological conditions leading to recruitment of Parkin and activation of mitochondrial

degradation pathways. Either mutation affects protein, impairs mitophagy and permits the accumulation of defective mitochondria in neurons, thereby increasing oxidative stress and cellular vulnerability (59).

In Parkinson's disease the aggregation of alpha-synuclein also contributes significantly to mitochondrial abnormalities. Misfolded alpha-synuclein proteins can interact directly with mitochondrial membranes and it can also disrupt respiratory chain function. Experimental studies have shown that alpha-synuclein accumulation impairs mitochondrial transport, reduces ATP production and promotes mitochondrial fragmentation. Furthermore, abnormal alpha-synuclein may interfere with mitophagy and exacerbate oxidative injury, creating a pathological cycle that accelerates dopaminergic neuronal death (60, 61).

In Parkinson's disease, mitochondrial dynamics are profoundly altered. Excessive mitochondrial fission and impaired fusion lead to fragmented mitochondrial networks, which exhibit reduced metabolic efficiency and increased susceptibility to apoptosis. Dysregulation of proteins such as protein 1, which is involved in dynamics and mitofusins, has been reported in both experimental models and tissues driven by patients. These alterations impair mitochondrial trafficking along neuronal axons and compromise synaptic function, which ultimately contributes to progressive motor dysfunction (62).

In Parkinson's disease, calcium dysregulation is another important feature of mitochondrial dysfunction. Dopaminergic neurons of the substantia nigra rely on calcium-dependent pacemaker activity for maintaining neuronal signalling. Persistent calcium influx imposes considerable metabolic stress on mitochondria and increases reactive oxygen species generation. Dysfunctional mitochondria lose their ability to buffer intracellular calcium effectively, which results in activation of apoptotic pathways and neuronal injury. Recent evidence suggests that mitochondrial stress mediated by calcium may significantly influence disease progression (63,64).

Neuroinflammation also participates actively in Parkinsonian neurodegeneration. Activated microglia release inflammatory cytokines and reactive oxygen species that further impair mitochondrial function in surrounding neurons. At the same time, damaged mitochondria release their DNA and other pro-inflammatory molecules which are capable of activating innate immune pathways. This interaction between mitochondrial dysfunction and neuroinflammation amplifies neuronal damage that contributes to chronic disease progression (65).

Recent therapeutic approaches for Parkinson's disease are focusing on restoring mitochondrial function and improving neuronal bioenergetics. Experimental interventions targeting oxidative stress (66), mitophagy enhancement (67), mitochondrial biogenesis and calcium stabilization (68) have demonstrated neuroprotective effects in preclinical studies. Compounds such as coenzyme Q10, nicotinamide adenine dinucleotide precursors, mitochondrial antioxidants and mitophagy activators are currently being explored for their potential to slow neuronal degeneration. Although definitive clinical success remains limited, mitochondria-targeted therapies continue to represent promising strategies for disease modification in Parkinson's disease (69).

Overall, current evidence strongly supports mitochondrial dysfunction as a major contributor to Parkinson's disease pathogenesis. Impaired oxidative phosphorylation, defective mitophagy, oxidative stress, calcium dysregulation, alpha-synuclein toxicity and neuroinflammation collectively participate in dopaminergic neuronal degeneration. Improved understanding of these mitochondrial mechanisms may provide opportunities for developing more effective therapeutic interventions aimed at slowing disease progression and preserving neurological function.

MITOCHONDRIAL DYSFUNCTION IN HUNTINGTON'S DISEASE AND AMYOTROPHIC LATERAL SCLEROSIS

Huntington's disease is an inherited neurodegenerative disorder. It is characterized by progressive motor dysfunction, psychiatric disturbances and cognitive decline. The cause of this disease is the abnormal expansion of CAG, which repeats within the huntingtin gene. Following the production of mutant huntingtin protein which exerts toxic effects on neuronal cells (70). Evidence indicates that the major contributor to Huntington's disease pathology is dysfunctional mitochondria. Mutant huntingtin interferes

with mitochondrial trafficking, oxidative phosphorylation, calcium buffering and mitochondrial biogenesis, which ultimately impairs neuronal energy metabolism and survival. In these mitochondrial abnormalities neurons in the striatum are particularly vulnerable because of their high metabolic demands and sensitivity to oxidative stress (71).

The defects of the mitochondrial respiratory chain are frequently observed in Huntington's disease and are associated with reduced ATP generation and enhanced oxidative injury. Experimental studies demonstrated that mutant huntingtin impairs the activity of respiratory complexes leading to excessive reactive oxygen species production and mitochondrial membrane depolarization. In addition, the abnormal interactions between mutant huntingtin and mitochondrial proteins disrupt mitochondrial transport along neuronal axons as a result there is low energy at synaptic terminals. These alterations contribute significantly to synaptic dysfunction and progressive neuronal degeneration observed during disease progression (72).

Impaired mitochondrial biogenesis also plays an important role in Huntington's disease. Studies have shown that mutant huntingtin suppresses expression of peroxisome proliferator-activated receptor gamma coactivator 1 alpha, a major regulator of mitochondrial generation and oxidative metabolism (73). Reduced mitochondrial biogenesis compromises neuronal adaptability to metabolic stress and increases susceptibility to apoptosis. Furthermore, defective mitophagy permits the accumulation of dysfunctional mitochondria, further amplifying oxidative stress and cellular injury within affected neuronal populations (74).

Another progressive neurodegenerative disease is amyotrophic lateral sclerosis. This disease is strongly associated with mitochondrial dysfunction. The disorder is characterized by degeneration of upper and lower motor neurons that leads to progressive muscle weakness, paralysis and respiratory failure. The mechanisms that are the basis of amyotrophic lateral sclerosis are not understood. Mitochondrial abnormalities are consistently observed in both familial and sporadic forms of the disease. Structural mitochondrial defects, impaired oxidative phosphorylation, alteration in calcium homeostasis and excess in oxidative stress have all been involved in motor neuron degeneration (75).

Mutations in genes such as superoxide dismutase 1, TAR DNA binding protein 43, fused in sarcoma and chromosome 9 open reading frame 72, are linked with mitochondrial dysfunction in amyotrophic lateral sclerosis (76). These mutations damage mitochondrial dynamics and also disrupt axonal transport of mitochondria within motor neurons. Since motor neurons possess exceptionally long axons, they have high metabolic requirements. Defects in mitochondrial trafficking severely compromise neuronal function and survival. Further, the mitochondrial fragmentation and impaired mitophagy also contribute to the progressive motor neuron degeneration and muscular weakness (77).

In amyotrophic lateral sclerosis, neuroinflammation significantly contributes to mitochondrial dysfunction. Inflammatory mediators that increase oxidative stress and impair mitochondrial integrity within motor neurons are released by activated microglia and astrocytes. Simultaneously, damaged mitochondria release mitochondrial DNA and pro-inflammatory molecules that activate innate immune pathways, creating a cycle of chronic inflammation and neuronal injury. These interactions between mitochondrial dysfunction and neuroinflammation are increasingly recognized as major contributors to disease progression in amyotrophic lateral sclerosis (30).

Current evidences support that mitochondrial dysfunction as an important pathological mechanism in both Huntington's disease and amyotrophic lateral sclerosis. The disturbances in oxidative metabolism, mitochondrial trafficking, calcium regulation, mitophagy and neuroinflammatory signaling collectively contribute to neuronal degeneration and disease progression. Continued investigation into mitochondrial biology may therefore facilitate the development of novel therapeutic approaches aimed at preserving neuronal survival and improving clinical outcomes in these devastating neurological disorders (78).

THERAPEUTIC STRATEGIES TARGETING MITOCHONDRIA

Mitochondrial dysfunction acts as a central mechanism in neurodegenerative diseases. These diseases have stimulated considerable interest in therapeutic approaches that target mitochondria. Oxidative

stress, impaired energy metabolism, calcium dysregulation, defective mitophagy and neuronal apoptosis are caused by mitochondrial dysfunctions. Therapeutic interventions that restore mitochondrial function may provide neuroprotective benefits. Recent experimental and clinical findings suggest that modulation of mitochondrial homeostasis is a promising approach in declining neurodegenerative progression (79).

One of the most extensively explored therapeutic approaches is to reduce mitochondrial oxidative stress by using antioxidants. Excess in the production of reactive oxygen species contributes significantly to neuronal damage in neurodegenerative disorders. Neuronal integrity may be preserved by the compounds capable of neutralizing oxidative molecules or improving endogenous antioxidant defenses. In experimental models several antioxidants, including coenzyme Q10 (80), vitamin E (81), mitoquinone and edaravone have demonstrated protective effects by reducing oxidative injury and improving mitochondrial respiration. These agents may help stabilize mitochondrial membranes and reduce apoptosis associated with neuronal degeneration (82).

In neurodegenerative diseases, enhancement of mitophagy has also emerged as an important therapeutic strategy. As defective mitophagy permits accumulation of dysfunctional mitochondria, neuronal survival may be improved by pharmacological activation of mitochondrial quality control pathways. The compounds that stimulate PINK1 Parkin signaling, autophagic flux or lysosomal degradation have demonstrated encouraging neuroprotective effects in experimental studies (83). Restoration of mitophagy may reduce oxidative stress, improve cellular bioenergetics and limit inflammatory activation within the nervous system (84).

Mitochondrial biogenesis is another promising therapeutic direction. Activation of transcriptional regulators such as PGC-1α enhances mitochondrial biogenesis and improves oxidative phosphorylation capacity (85). Experimental interventions that promote mitochondrial biogenesis have shown beneficial effects in neuronal recovery, synaptic maintenance and resistance to oxidative stress. The agents that have potential for improving mitochondrial metabolism and reducing neurodegenerative pathology in preclinical investigations include resveratrol (86), nicotinamide riboside (52) and exercise mimetics (87).

Table II. Mitochondria-targeted therapeutic strategies for neurodegenerative diseases: mechanisms of action, therapeutic benefits and disease relevance

Therapeutic strategy	Mechanism of action	Therapeutic benefits	Disease relevance	Representative recent references
Conventional antioxidants (Coenzyme Q10, Vitamin E, Edaravone)	Scavenge reactive oxygen species (ROS), reduce oxidative stress, and preserve mitochondrial membrane integrity	Decreased oxidative neuronal injury, improved mitochondrial function, and enhanced neuronal survival	Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis	(80 - 82)
Mitochondria-targeted antioxidant (MitoQ)	Selectively accumulates within mitochondria, reducing mitochondrial ROS and improving electron transport chain function	Enhanced ATP production, improved mitochondrial bioenergetics, and reduced oxidative damage	Alzheimer's disease, Parkinson's disease	(78, 79)
Mitophagy activators (Urolithin A, PINK1/Parkin modulators)	Promote selective removal of damaged mitochondria through activation of mitophagy pathways	Improved mitochondrial quality control, reduced oxidative stress, and enhanced neuronal survival	Alzheimer's disease, Parkinson's disease, Huntington's disease	(48, 84, 90)
Mitochondrial biogenesis stimulators (Nicotinamide riboside, PGC-1α activators)	Stimulate mitochondrial biogenesis and oxidative phosphorylation through activation of	Increased ATP synthesis, improved cellular metabolism, and enhanced neuronal resilience	Alzheimer's disease, Huntington's disease	(52, 74, 85)

	mitochondrial regulatory pathways			
Metabolic therapies (Ketogenic diet and ketone supplementation)	Provide alternative energy substrates and improve mitochondrial metabolism	Enhanced ATP production, reduced oxidative stress, and improved neuronal function	Alzheimer's disease, Parkinson's disease	(92)
Gene-based therapeutic approaches	Regulate mitochondrial quality-control pathways and restore mitochondrial homeostasis	Potential disease-modifying effects and improved neuronal survival	Experimental studies in multiple neurodegenerative disorders	(88, 95)
Mitochondrial membrane stabilizer (Elamipretide, SS-31)	Stabilizes mitochondrial membranes, preserves ATP synthesis, and limits oxidative injury	Improved mitochondrial bioenergetics and neuronal protection	Alzheimer's disease, Parkinson's disease (preclinical and early clinical studies)	(91)

CLINICAL TRANSLATION AND CURRENT THERAPEUTIC CHALLENGES

Although considerable progress has been achieved in identifying mitochondria-targeted therapeutic strategies, successful translation from experimental models to clinical practice remains limited. Numerous pharmacological agents have demonstrated significant neuroprotective effects in cellular and animal models by improving mitochondrial bioenergetics, reducing oxidative stress, enhancing mitophagy and preserving neuronal survival. However, these encouraging preclinical findings have not consistently translated into meaningful clinical benefits in patients with neurodegenerative disorders.

One of the most extensively investigated mitochondrial therapies is coenzyme Q10 (CoQ10), an essential component of the mitochondrial electron transport chain and a potent endogenous antioxidant. Experimental studies demonstrated that CoQ10 improves mitochondrial respiration, reduces reactive oxygen species generation and attenuates neuronal apoptosis in models of Alzheimer's disease and Parkinson's disease (80). Despite these promising findings, several randomized clinical trials reported minimal or no significant improvement in disease progression or neurological function. Similar observations have been reported for vitamin E supplementation, which effectively reduced oxidative damage in experimental studies but failed to demonstrate consistent clinical efficacy in large patient populations (81).

Several factors may explain the discrepancy between experimental success and clinical failure. Most patients are diagnosed after substantial neuronal loss has already occurred, limiting the effectiveness of mitochondria-targeted therapies initiated during advanced disease stages. Furthermore, poor blood-brain barrier penetration, limited oral bioavailability, short biological half-life and inter-individual variability in mitochondrial dysfunction significantly reduce therapeutic efficacy (88). Differences between experimental animal models and the complex pathological mechanisms present in human neurodegenerative diseases further complicate successful clinical translation. These findings suggest that future therapeutic interventions should emphasize earlier diagnosis, optimized drug delivery systems, patient stratification based on molecular biomarkers and combination therapies targeting multiple pathogenic mechanisms simultaneously (89).

Recent advances have introduced several promising next-generation mitochondrial therapeutics. MitoQ, a mitochondria-targeted derivative of coenzyme Q10, accumulates selectively within mitochondria and has demonstrated improved antioxidant activity compared with conventional antioxidants. Likewise, urolithin A has emerged as a promising mitophagy activator capable of enhancing mitochondrial quality control, restoring lysosomal function and improving neuronal energy metabolism. NAD^+ precursors, including nicotinamide riboside and nicotinamide mononucleotide, have also shown considerable potential by enhancing mitochondrial biogenesis, improving oxidative phosphorylation and promoting neuronal resilience (90). In addition, the mitochondria-targeted peptide elamipretide (SS-31) has demonstrated encouraging preclinical results through stabilization of mitochondrial membranes, preservation of ATP

synthesis and reduction of oxidative injury. Although these therapies remain under active clinical investigation, they represent promising candidates for disease-modifying treatment of neurodegenerative disorders (91).

Future clinical translation will require multidisciplinary approaches integrating precision medicine, advanced neuroimaging, artificial intelligence-assisted drug discovery, multi-omics technologies and validated mitochondrial biomarkers to identify patients most likely to benefit from targeted interventions. Well-designed multicenter clinical trials with standardized outcome measures, longer follow-up periods and disease-stage-specific therapeutic strategies will be essential for determining the true clinical potential of mitochondria-targeted therapies. Continued advances in mitochondrial biology and translational neuroscience are expected to accelerate the development of safe and effective disease-modifying treatments for neurodegenerative disorders.

Recent studies have also explored the role of metabolic therapies in preserving mitochondrial function. For neurons experiencing impaired glucose metabolism, the ketogenic diet and ketone-based metabolic supplementation may provide alternative energy substrates. Ketone bodies support mitochondrial ATP production and can also bypass defects in glucose utilization while simultaneously reducing oxidative stress. In certain neurodegenerative diseases, metabolic interventions may improve cognitive performance and neuronal resilience in certain neurodegenerative conditions. Further large-scale studies are required to confirm their long-term therapeutic value (92).

Despite several investigations of mitochondrial physiology, there are many challenges that remain to implement experimental outcomes into effective clinical practices. Neurodegenerative diseases involve complex and multifactorial pathological mechanisms, making it unlikely that a single therapeutic strategy will completely halt disease progression. Furthermore, variability in disease stage genetic background and mitochondrial susceptibility may influence treatment outcomes. However, ongoing advances in mitochondrial biology continue to provide valuable insights into novel therapeutic opportunities. Future strategies combining antioxidants, mitophagy modulators, metabolic therapies and gene-based interventions may offer more comprehensive approaches for preserving neuronal survival and slowing neurodegeneration (93).

CHALLENGES, LIMITATIONS AND FUTURE PERSPECTIVES

Despite substantial advances in understanding mitochondrial dysfunction in neurodegenerative diseases, several important scientific and clinical challenges remain unresolved. Mitochondrial dysfunction is a multifactorial process involving oxidative stress, impaired oxidative phosphorylation, mitochondrial DNA damage, calcium dysregulation, defective mitophagy, altered mitochondrial dynamics and neuroinflammation. These mechanisms interact through complex signaling networks rather than acting independently, making it difficult to identify a single therapeutic target capable of modifying disease progression. Furthermore, considerable heterogeneity exists among patients with Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis suggesting that disease-specific and patient-specific mitochondrial alterations should be considered when developing targeted therapeutic strategies (73).

Another major challenge is the inconsistent understanding of mitophagy during neurodegeneration. Although impaired mitophagy has been widely reported in Alzheimer's disease and Parkinson's disease, several recent investigations suggest that mitophagy may initially increase as a compensatory response before becoming dysfunctional during later disease stages. These apparently conflicting observations may reflect differences in disease stage, experimental models, brain regions examined and analytical methods used to evaluate mitochondrial turnover. Consequently, additional longitudinal human studies are required to clarify the temporal regulation of mitophagy and to determine the optimal timing for mitophagy-targeted therapeutic interventions (94).

Translating promising experimental therapies into successful clinical treatments remains another significant limitation. Numerous antioxidant compounds, including coenzyme Q10 and vitamin E, demonstrated encouraging neuroprotective effects in preclinical models but failed to produce consistent

clinical benefits in large human trials. Several factors may contribute to these disappointing outcomes, including poor blood-brain barrier penetration, limited bioavailability, delayed therapeutic intervention after irreversible neuronal injury, differences between animal models and human disease and substantial genetic and pathological heterogeneity among patients. These findings emphasize that future therapeutic strategies should prioritize earlier diagnosis, improved patient stratification, optimized drug delivery systems and combination therapies targeting multiple pathological pathways simultaneously (88).

Recent studies have identified several promising mitochondria-targeted therapeutic approaches that may overcome some of these limitations. Urolithin A, a natural mitophagy activator has demonstrated the ability to improve mitochondrial quality control, reduce oxidative stress, restore lysosomal function and improve cognitive performance in experimental models of Alzheimer's disease (90). Likewise, mitochondria-targeted antioxidants such as MitoQ, NAD^+ precursors and pharmacological modulators of the PINK1/Parkin signaling pathway are being actively investigated because of their potential to selectively restore mitochondrial function while minimizing systemic adverse effects (83). Although these approaches remain under clinical evaluation, they represent encouraging advances toward disease-modifying therapies for neurodegenerative disorders.

Future research should focus on integrating multi-omics technologies, artificial intelligence-assisted drug discovery, precision medicine, advanced neuroimaging and sensitive mitochondrial biomarkers to facilitate early diagnosis and individualized therapeutic strategies. Emerging technologies including gene editing, mitochondrial transplantation, nanotechnology-based drug delivery and personalized mitochondrial medicine may further improve treatment efficacy (95). Well-designed multicenter clinical trials with standardized outcome measures and long-term follow-up will be essential for translating advances in mitochondrial biology into effective clinical interventions capable of delaying or preventing neurodegenerative disease progression (96).

CONCLUSION

Mitochondrial dysfunction is increasingly recognized as a central pathological mechanism underlying the initiation and progression of major neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis. Disturbances in oxidative phosphorylation, excessive reactive oxygen species generation, mitochondrial DNA damage, impaired mitochondrial dynamics, defective mitophagy, calcium dysregulation and chronic neuroinflammation collectively contribute to progressive neuronal dysfunction and degeneration. Advances in molecular neuroscience have considerably improved our understanding of the complex relationship between mitochondrial homeostasis and neuronal survival establishing mitochondria as promising therapeutic targets for neurodegenerative diseases.

Recent progress in mitochondria-targeted therapeutics including mitochondria-targeted antioxidants, mitophagy activators, NAD^+ augmentation therapies, mitochondrial biogenesis stimulators, metabolic interventions and emerging gene-based strategies has demonstrated encouraging neuroprotective potential in experimental models. However, the successful translation of these approaches into clinical practice remains limited because of poor bioavailability, restricted blood-brain barrier penetration, disease heterogeneity and the multifactorial nature of neurodegenerative disorders. These challenges emphasize the need for better disease models, sensitive biomarkers, optimized drug-delivery systems and carefully designed clinical trials.

Future research should focus on integrating precision medicine, multi-omics technologies, artificial intelligence-assisted drug discovery, advanced neuroimaging and personalized therapeutic strategies to better characterize mitochondrial dysfunction and improve patient-specific treatment approaches. Furthermore, large-scale multicentre clinical studies are required to validate the long-term safety and therapeutic efficacy of emerging mitochondria-targeted interventions. Continued advances in mitochondrial biology and translational neuroscience are expected to facilitate the development of effective

disease-modifying therapies capable of delaying neurodegeneration, preserving neuronal function and improving the quality of life of affected patients.

Conflict of interest:

The authors declare no conflict of interest.

Authors' contribution:

MN Conceptualization, literature search, data collection and manuscript drafting; AE Literature screening and data extraction; AJ Data organization and content development; MBA Manuscript formatting and reference management; RR Data verification and quality assessment; LJ Literature review and manuscript editing; LS Reference cross-checking and proofreading; MM Critical review and intellectual content contribution; AS Manuscript writing and revision, figure design and preparation, scientific content development, overall coordination of the study, corresponding author responsibilities and final approval of the manuscript. All authors read and approved the final manuscript.

Declaration of generative AI-assisted tools:

Generative AI-assisted tools were used only for grammar correction. All scientific content, analysis, interpretations and conclusions were developed, reviewed and approved by the authors who take full responsibility for the manuscript.

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