# Oxidative phosphorylation dysregulation in neurodegenerative disorders.

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## Introduction

Oxidative phosphorylation (OXPHOS) is the primary mechanism through which eukaryotic cells generate adenosine triphosphate (ATP), the universal energy currency required for vital cellular functions. This process occurs in the mitochondria, where electrons derived from nutrients pass through the electron transport chain (ETC) composed of five multi-subunit complexes embedded in the inner mitochondrial membrane. The energy from electron flow is used to pump protons across the membrane, creating an electrochemical gradient that drives ATP synthesis by ATP synthase [1]. In the central nervous system (CNS), where neurons are highly dependent on oxidative metabolism due to their elevated energy demands and limited glycolytic capacity, the integrity of OXPHOS is essential. Dysregulation of this finely tuned system has emerged as a central contributor to the pathophysiology of numerous neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). The vulnerability of neurons to mitochondrial dysfunction stems from their long lifespan, high energy requirements, limited regenerative capacity, and susceptibility to oxidative stress [2].

In Alzheimer's disease, one of the most prevalent forms of dementia, mitochondrial dysfunction and impaired oxidative phosphorylation occur early in the disease process, often preceding classical hallmarks such as amyloid-beta plaques and tau tangles. Reduced activity of cytochrome c oxidase (complex IV) and ATP synthase, as well as decreased mitochondrial respiration, have been reported in both brain tissue and peripheral cells of AD patients [3]. These impairments lead to a bioenergetic deficit that compromises synaptic function and plasticity, processes that are energetically demanding and essential for learning and memory. Moreover, defective OXPHOS increases the production of reactive oxygen species (ROS), which further damage mitochondrial DNA (mtDNA), proteins, and lipids, creating a vicious cycle of oxidative stress and energy failure. Amyloid-beta itself has been shown to accumulate within mitochondria, interacting with ETC complexes and exacerbating dysfunction. In addition, tau pathology disrupts mitochondrial trafficking and dynamics, impairing the ability of neurons to transport mitochondria to areas of high energy demand, such as synaptic terminals [4].

In Parkinson's disease, characterized primarily by the degeneration of dopaminergic neurons in the substantia nigra, mitochondrial dysfunction has long been implicated in disease etiology. Complex I deficiency is one of the most consistent biochemical abnormalities observed in PD patients and experimental models. This defect reduces ATP production and enhances ROS generation, which damages cellular components and contributes to the selective vulnerability of dopaminergic neurons [5]. Mutations in genes associated with familial PD, such as PINK1, Parkin, DJ-1, and LRRK2, affect mitochondrial quality control, mitophagy, and OXPHOS. For example, PINK1 and Parkin coordinate the removal of damaged mitochondria via mitophagy, a process essential for maintaining mitochondrial health. Loss-of-function mutations in these genes impair mitochondrial turnover and allow dysfunctional mitochondria to accumulate, promoting neurodegeneration. Environmental toxins that inhibit complex I, such as MPTP and rotenone, reproduce Parkinsonian symptoms in animal models, further supporting a causal role of oxidative phosphorylation dysregulation in PD [6].

Huntington's disease is a genetic neurodegenerative disorder caused by a CAG repeat expansion in the huntingtin gene, leading to a toxic polyglutamine tract in the mutant protein. HD is characterized by progressive motor dysfunction, cognitive decline, and psychiatric disturbances. Neuronal loss, particularly in the striatum and cortex, is accompanied by mitochondrial abnormalities and impaired energy metabolism. Studies have shown reductions in complex II, III, and IV activities in HD brains, contributing to a chronic energy deficit and elevated ROS levels. Mutant huntingtin protein directly interacts with mitochondria, impairing their calcium handling and enhancing their susceptibility to permeability transition and cell death. Moreover, transcriptional dysregulation of genes involved in mitochondrial biogenesis and respiration, including peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), has been observed in HD. The downregulation of PGC-1α reduces the expression of OXPHOS components and antioxidant enzymes, making neurons more vulnerable to metabolic stress [7].

Amyotrophic lateral sclerosis, a progressive motor neuron disease, also features mitochondrial dysfunction as a key element in its pathogenesis. Both sporadic and familial forms of ALS exhibit defects in mitochondrial structure and function, particularly within spinal cord motor neurons. Mutations in genes such as SOD1, TARDBP, FUS, and C9orf72 disrupt various aspects of mitochondrial physiology, including oxidative phosphorylation, dynamics, transport, and calcium buffering. Mitochondria in ALS often show swelling, cristae disorganization, and reduced respiratory chain complex

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activity. SOD1 mutations, for instance, lead to the misfolding of the enzyme, which associates with mitochondria and impairs complex IV function. These alterations compromise ATP production and elevate oxidative damage, promoting motor neuron death. The impaired transport of mitochondria along axons, a process essential for neuronal survival, further exacerbates the energy deficiency at neuromuscular junctions, accelerating disease progression [8].

Beyond individual diseases, a common theme emerges wherein oxidative phosphorylation dysregulation serves as a final common pathway in neurodegeneration. The convergence of mitochondrial defects across disorders suggests that targeting mitochondrial bioenergetics may offer broad therapeutic potential. However, developing effective treatments is challenged by the complexity and multifactorial nature of mitochondrial dysfunction. Interventions aimed at enhancing OXPHOS function include antioxidants, mitochondrial biogenesis stimulators, and metabolic modulators. Coenzyme Q10, a component of the electron transport chain with antioxidant properties, has shown modest benefits in some trials but has not demonstrated consistent efficacy in large-scale studies. Similarly, creatine, which buffers cellular ATP levels, has been explored in PD, HD, and ALS with limited success. More recently, drugs that activate PGC-1α or modulate NAD+ metabolism, such as nicotinamide riboside and nicotinamide mononucleotide, are being investigated for their ability to enhance mitochondrial function and resilience to stress [9].

Gene therapy and stem cell-based approaches offer additional avenues for correcting mitochondrial dysfunction. Mitochondrial-targeted gene delivery to restore defective OXPHOS components or improve quality control pathways is under active investigation. Induced pluripotent stem cells (iPSCs) derived from patients with neurodegenerative disorders have become invaluable tools for modeling disease and testing therapeutic strategies in a patient-specific context. Moreover, lifestyle interventions such as exercise and caloric restriction, known to enhance mitochondrial biogenesis and efficiency, are gaining attention as non-pharmacological approaches to support brain health and delay neurodegeneration [10].

## Conclusion

In conclusion, oxidative phosphorylation is a central determinant of neuronal health and function. Its dysregulation contributes significantly to the pathogenesis of major neurodegenerative disorders, including Alzheimer's, Parkinson's, Huntington's disease, and ALS. The intricate relationship between impaired energy production, oxidative stress, and neuronal vulnerability highlights mitochondria as a critical hub in neurodegeneration. While therapeutic strategies targeting mitochondrial dysfunction face numerous challenges, they also offer promising opportunities for disease modification. A comprehensive understanding of the molecular underpinnings of OXPHOS dysregulation, coupled with advances in diagnostics and therapeutics, holds the potential to transform the management of neurodegenerative diseases and improve outcomes for affected individuals.

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