WJPMR, 2026, 12(4), 435-438

Research Article

Impact Factor: 7.555

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

ISSN (O): 2455-3301
ISSN (P): 3051-2557
Coden USA: WJPMBB

OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION IN NEUROLOGICAL DISORDERS

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DOI: https://doi.org/10.5281/zenodo.19674491

How to cite this Article: Dilara Aliyeva*[1], Irada Aliyeva[2], Gulnara Valiyeva[1], Asiya Aghayeva[1], Azada Rustamzada[1], Sabina Mashadiyeva-Bayramova[2]. (2026). Oxidative Stress and Mitochondrial Dysfunction In Neurological Disorders. World Journal of Pharmaceutical and Medical Research, 12(4), 435–438.

Article Received on 05/03/2026 **Article Revised on 25/03/2026** **Article Published on 01/04/2026**

KEYWORDS: Oxidative stress; mitochondrial dysfunction; neurodegenerative diseases; reactive oxygen species; apoptosis; neuroinflammation; mitochondrial DNA.

INTRODUCTION

Neurological disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis, constitute a heterogeneous group of conditions that collectively impose a substantial burden on global healthcare systems. These disorders are characterized by progressive neuronal degeneration, synaptic dysfunction, and irreversible impairment of cognitive and motor functions. Despite differences in clinical presentation and etiology, accumulating evidence suggests that they share common molecular and cellular mechanisms, among which oxidative stress and mitochondrial dysfunction play central and interdependent roles. Advances in molecular neuroscience and cellular bioenergetics have highlighted that neuronal survival is critically dependent on mitochondrial integrity, given the essential functions of mitochondria in ATP production, intracellular calcium buffering, and regulation of programmed cell death pathways.

Neurons are uniquely susceptible to mitochondrial impairment due to their high energy demands, reliance on oxidative phosphorylation, and limited capacity for regeneration. In addition, the extended morphology of neurons, particularly the length of axons, requires efficient mitochondrial transport and distribution, making them highly sensitive to disruptions in mitochondrial dynamics. Any disturbance in mitochondrial function can therefore lead to energy deficits, impaired synaptic transmission, and eventual neuronal loss. Furthermore, mitochondrial DNA (mtDNA), which lacks protective histones and has limited repair capacity, is especially vulnerable to damage, further exacerbating mitochondrial dysfunction and cellular instability.

Oxidative stress emerges when there is a disequilibrium between the generation of reactive oxygen species (ROS) and the efficiency of endogenous antioxidant defense systems, including enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. Under physiological conditions, ROS are produced as natural byproducts of mitochondrial respiration and play important roles in cellular signaling. However, under pathological conditions, excessive ROS accumulation leads to widespread oxidative damage affecting lipids, proteins, and nucleic acids. Lipid peroxidation disrupts membrane integrity, protein oxidation alters enzymatic activity and structural stability, and oxidative modifications of nucleic acids contribute to genomic instability.

Mitochondria occupy a dual role in this context, acting both as a major source of ROS and as a primary target of oxidative damage. Dysfunction of the electron transport chain results in electron leakage and enhanced ROS production, which in turn damages mitochondrial components, including mitochondrial membranes, respiratory chain complexes, and mtDNA. This establishes a self-perpetuating cycle in which oxidative stress and mitochondrial dysfunction mutually reinforce each other, amplifying cellular injury. Such a feedback loop is widely recognized as a fundamental feature of neurodegenerative processes and plays a critical role in driving neuronal apoptosis and necrosis.[1,6]

In addition to direct cellular damage, oxidative stress and mitochondrial dysfunction also influence other pathogenic pathways, including neuroinflammation and excitotoxicity. Elevated ROS levels can activate microglial cells and promote the release of pro-inflammatory mediators, thereby creating a chronic inflammatory environment that further accelerates neuronal damage. Simultaneously, mitochondrial impairment disrupts calcium homeostasis, contributing to excitotoxic neuronal injury through excessive activation of glutamatergic signaling pathways. Collectively, these interconnected mechanisms underscore the pivotal role of oxidative stress and mitochondrial dysfunction as key drivers in the pathogenesis of neurological disorders.

MATERIALS AND METHODS

This study was designed as a comprehensive narrative review with the primary objective of integrating and critically evaluating contemporary evidence on the role of oxidative stress and mitochondrial dysfunction in neurological disorders. Given the complexity and multidimensional nature of these mechanisms, a narrative approach was selected to allow a flexible yet systematic synthesis of findings derived from experimental, clinical, and translational research. The review process was guided by a structured search strategy to ensure both breadth and relevance of the included literature.

A systematic literature search was conducted across major scientific databases, including PubMed, Scopus, and Web of Science, with a focus on publications released between 2020 and 2025. This timeframe was deliberately chosen to capture the most recent advancements in molecular neuroscience, mitochondrial biology, and neurodegenerative disease research. Search queries were constructed using combinations of controlled vocabulary terms and free-text keywords, including "oxidative stress," "mitochondrial dysfunction," "reactive oxygen species," "mitochondrial DNA damage," "neurodegeneration," and "neurological disorders."

To ensure the scientific robustness of the review, clearly defined inclusion and exclusion criteria were implemented. Eligible studies included peer-reviewed original research articles, clinical studies, and high-quality review papers that specifically addressed molecular and cellular mechanisms linking oxidative stress and mitochondrial dysfunction to neurological pathologies. Particular emphasis was placed on studies exploring mitochondrial bioenergetics, electron transport chain alterations, ROS-mediated damage, mitochondrial dynamics (fusion and fission), mitophagy, and neuroinflammatory interactions. Additionally, studies investigating emerging therapeutic strategies targeting these pathways were also considered relevant and included in the analysis.

Following the selection process, the identified studies were subjected to a critical appraisal focusing on methodological design, sample size, experimental models, and the validity of reported findings. Data extraction was performed to capture key information, including study objectives, experimental approaches, major outcomes, and proposed mechanistic insights. The synthesized data were then organized into thematic categories to facilitate a coherent interpretation of the complex interplay between oxidative stress and mitochondrial dysfunction.

Rather than a simple descriptive summary, this review emphasizes the integration of findings into a unified conceptual framework that highlights causal relationships, feedback mechanisms, and clinical implications. Special attention was given to identifying converging evidence across different neurological disorders, thereby underscoring shared pathogenic pathways. This integrative approach enables a deeper understanding of disease mechanisms and provides a foundation for the development of targeted therapeutic interventions.

RESULTS AND DISCUSSION

The synthesis of recent evidence clearly indicates that oxidative stress and mitochondrial dysfunction are not independent phenomena but rather tightly interrelated processes that collectively drive the onset and progression of neurological disorders. Mitochondrial impairment leads to excessive generation of reactive oxygen species (ROS), primarily due to inefficiencies within the electron transport chain. Elevated ROS levels subsequently induce oxidative damage to mitochondrial DNA (mtDNA), proteins, and phospholipid membranes, resulting in structural and functional deterioration of mitochondria. This establishes a self-propagating cycle in which mitochondrial damage enhances ROS production, further aggravating cellular dysfunction and ultimately leading to neuronal degeneration.[4,6,11]

A central mechanism underlying this pathological cascade is the disruption of the electron transport chain (ETC), particularly at complexes I and III, where electron leakage is most prominent. Impaired electron transfer results in incomplete reduction of oxygen and increased formation of superoxide radicals. This not only diminishes ATP synthesis but also compromises cellular energy homeostasis. Given that neurons depend heavily on oxidative phosphorylation for their energy requirements, even subtle mitochondrial inefficiencies can lead to significant functional deficits, including impaired synaptic transmission and reduced neuronal viability.[10,11] Furthermore, oxidative stress-induced alterations in mitochondrial membrane integrity can trigger the opening of the mitochondrial permeability transition pore (mPTP), leading to loss of membrane potential, release of pro-apoptotic factors such as cytochrome c, and activation of caspase-dependent cell death pathways.[2,13]

In addition to bioenergetic failure, impairment of mitochondrial quality control systems plays a critical role in the progression of neurodegenerative processes. Under physiological conditions, damaged mitochondria are selectively removed through mitophagy, while mitochondrial biogenesis ensures the replenishment of functional organelles. However, in neurological disorders, these regulatory mechanisms are often disrupted, leading to the accumulation of dysfunctional mitochondria and amplification of oxidative stress.[1,3,5] Alterations in mitochondrial dynamics, including imbalances in fusion and fission processes, further contribute to mitochondrial fragmentation and functional decline.[7]

Another important dimension of mitochondrial dysfunction is its impact on intracellular calcium homeostasis. Mitochondria act as key regulators of calcium buffering, and their impairment leads to abnormal calcium accumulation within neurons. This dysregulation enhances excitotoxicity, particularly through overactivation of glutamatergic receptors, ultimately resulting in neuronal injury and cell death.[12,13] The convergence of energy failure, oxidative damage, and calcium dysregulation creates a highly toxic intracellular environment that accelerates neurodegeneration.

Oxidative stress also serves as a potent modulator of neuroinflammatory responses. Elevated ROS levels activate microglial cells and astrocytes, leading to the release of pro-inflammatory cytokines and chemokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). This inflammatory response not only exacerbates oxidative damage but also contributes to a chronic neurotoxic milieu that further impairs neuronal survival.[3,12] In addition, oxidative stress-mediated signaling pathways have been shown to amplify inflammatory cascades and disrupt redox homeostasis in the central nervous system.[9,14]

These interconnected mechanisms manifest across various neurological disorders, albeit with disease-specific features. In Alzheimer's disease, mitochondrial dysfunction and oxidative damage contribute to synaptic loss and accumulation of pathological protein aggregates, ultimately impairing cognitive function.[6,9] In Parkinson's disease, defects in mitochondrial function within dopaminergic neurons of the substantia nigra lead to increased oxidative burden and progressive neuronal loss.[15] Similarly, Huntington's disease and amyotrophic lateral sclerosis are characterized by disrupted mitochondrial dynamics, elevated oxidative stress markers, and impaired cellular energy metabolism, highlighting a shared molecular basis among these conditions.[8,16]

In recent years, significant attention has been directed toward the development of therapeutic strategies targeting oxidative stress and mitochondrial dysfunction. Approaches such as the use of mitochondria-targeted antioxidants, activation of mitochondrial biogenesis pathways, and modulation of mitochondrial dynamics have demonstrated promising results in preclinical studies.[2,17] Furthermore, emerging evidence suggests that enhancing endogenous antioxidant systems and protecting mitochondrial integrity may provide additional therapeutic benefits.[14,17] Nevertheless, the translation of these findings into effective clinical therapies remains challenging, largely due to the multifactorial nature of neurodegenerative diseases and the intricate interplay between oxidative stress, mitochondrial dysfunction, and other pathogenic mechanisms.

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