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Interconnected Roles of Oxidative Stress, Mitochondrial Dysfunction, and Neuroinflammation in Alzheimer's Disease: Mechanistic Insights and Therapeutic Implications

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, synaptic dysfunction, and neuronal loss. While amyloid-beta plaques and tau neurofibrillary tangles are classical pathological hallmarks, increasing evidence demonstrates that oxidative stress, mitochondrial dysfunction, and neuroinflammation are central drivers of disease progression. Oxidative imbalance leads to lipid peroxidation, protein oxidation, and DNA damage, contributing to neuronal vulnerability. Mitochondrial dysfunction impairs energy metabolism and enhances reactive oxygen species production, further aggravating cellular injury. Concurrently, chronic microglial activation sustains inflammatory responses and amplifies oxidative damage. These interrelated processes create a self-propagating cycle that accelerates neurodegeneration. Understanding their molecular interactions provides new opportunities for therapeutic intervention. This review synthesizes current findings on oxidative stress, mitochondrial abnormalities, and neuroinflammatory mechanisms in AD and highlights emerging treatment strategies targeting these interconnected pathways.

Keywords: Alzheimer's disease, oxidative stress, mitochondrial dysfunction, neuroinflammation, microglial activation, reactive oxygen species (ROS), neurodegeneration, inflammatory cytokines

1. Introduction

Alzheimer's disease (AD) is the most prevalent cause of dementia and poses an escalating global health burden. Although amyloid-beta and tau pathology have long dominated research focus, accumulating evidence suggests that oxidative stress and mitochondrial dysfunction are early and pivotal events in AD pathogenesis (Markesbery, 1999; Wang et al., 2014). Oxidative damage has been detected in vulnerable neuronal populations prior to extensive plaque deposition, indicating that redox imbalance may precede classical pathological hallmarks.

Mitochondria are critical regulators of neuronal survival, as they generate ATP, regulate calcium homeostasis, and control apoptotic pathways. In AD, mitochondrial structural abnormalities, respiratory chain impairment, and altered mitochondrial dynamics are consistently reported (Wang et al., 2014; Misrani et al., 2021). These alterations compromise neuronal bioenergetics and increase susceptibility to degeneration.

Neuroinflammation further contributes to AD progression. Activated microglia release pro-inflammatory cytokines and reactive oxygen species, amplifying neuronal injury (Streit, 2010; Leng & Edison, 2020). Chronic inflammatory signaling is now recognized as a major pathogenic driver rather than a secondary response to amyloid accumulation. Recent studies emphasize the integrated nature of oxidative stress, mitochondrial dysfunction, and inflammation, suggesting that these processes interact dynamically to accelerate neurodegeneration (Zhang et al., 2023; Alkhalifa et al., 2025).

This review aims to provide a comprehensive synthesis of current evidence regarding oxidative stress, mitochondrial dysfunction, and neuroinflammation in AD, highlighting their interconnected mechanisms and therapeutic potential.

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2. Oxidative Stress in Alzheimer's Disease

Oxidative stress arises when reactive oxygen species (ROS) production exceeds the capacity of antioxidant defense systems. Early evidence demonstrated elevated lipid peroxidation products and oxidized proteins in AD brains (Markesbery, 1999). These findings suggest that oxidative damage is a central contributor to neuronal dysfunction rather than a mere byproduct of neurodegeneration.

Neurons are particularly vulnerable to oxidative damage due to high oxygen consumption and limited regenerative capacity. ROS-mediated lipid peroxidation disrupts membrane integrity, while protein oxidation alters enzymatic activity and synaptic signaling. Furthermore, oxidative stress promotes amyloid-beta aggregation and tau hyperphosphorylation, thereby linking redox imbalance with classical AD pathology (Wang et al., 2014).

Mitochondrial ROS production is a major source of oxidative stress in AD. Dysfunctional electron transport chain activity increases superoxide generation, overwhelming endogenous antioxidants such as glutathione and superoxide dismutase (Misrani et al., 2021). Persistent oxidative stress activates apoptotic pathways and impairs synaptic plasticity.

Recent research highlights that oxidative stress also interacts with inflammatory mechanisms. Activated microglia generate ROS and nitric oxide, exacerbating neuronal injury (Krause & Müller, 2010). Thus, oxidative stress acts as both a trigger and amplifier of neurodegenerative processes. Therapeutic strategies targeting oxidative pathways include antioxidant compounds and mitochondrial-targeted redox modulators, although clinical translation remains challenging (Alkhalifa et al., 2025).

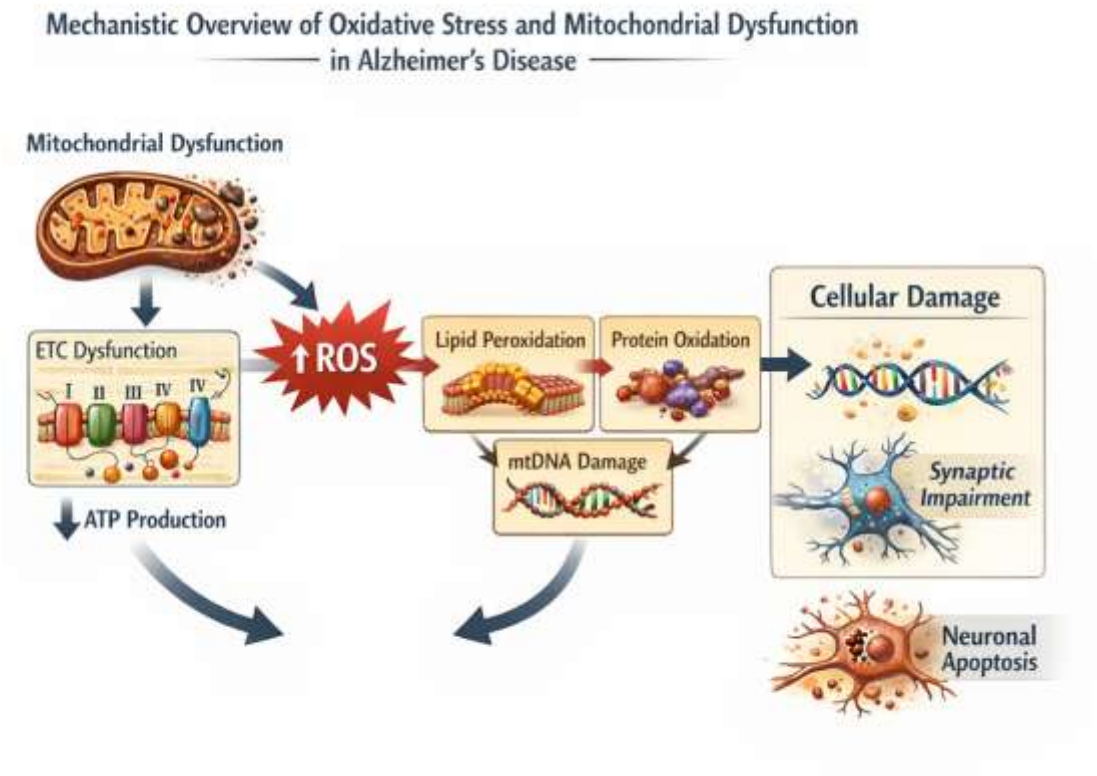

Figure 1. Mechanistic overview of oxidative stress and mitochondrial dysfunction in Alzheimer's disease.
Mitochondrial electron transport chain (ETC) dysfunction increases the production of reactive oxygen species (ROS), leading to lipid peroxidation, protein oxidation, and mitochondrial DNA (mtDNA) damage. These oxidative alterations impair ATP production and disrupt cellular homeostasis. Persistent oxidative damage contributes to synaptic dysfunction and ultimately triggers neuronal apoptosis. The figure illustrates the self-amplifying cycle between mitochondrial impairment and oxidative stress in Alzheimer's disease progression.

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3. Mitochondrial Dysfunction and Bioenergetic Failure

Mitochondrial dysfunction is a defining feature of AD and significantly contributes to neuronal vulnerability. Structural abnormalities, impaired oxidative phosphorylation, and decreased ATP production have been consistently observed in AD models and patient samples (Wang et al., 2014; Misrani et al., 2021).

Altered mitochondrial dynamics—specifically dysregulated fission and fusion processes—lead to fragmented and dysfunctional mitochondria. Impaired mitophagy further results in the accumulation of damaged organelles, increasing ROS production and amplifying oxidative stress (Misrani et al., 2021). Additionally, mitochondrial DNA mutations and oxidative modifications compromise respiratory chain enzyme efficiency.

Energy deficits particularly affect the hippocampus and cortex, regions essential for memory and learning. Reduced glucose metabolism and impaired mitochondrial respiration correlate strongly with cognitive decline (Wang et al., 2014). Mitochondrial dysfunction also activates intrinsic apoptotic pathways, contributing to progressive neuronal loss.

Emerging therapeutic approaches focus on restoring mitochondrial function through enhancement of mitochondrial biogenesis, stabilization of electron transport chain activity, and promotion of mitophagy (Alkhalifa et al., 2025). These strategies aim to interrupt the cascade linking bioenergetic failure and oxidative stress in AD.

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4. Neuroinflammation and Microglial Activation

Neuroinflammation is increasingly recognized as a major pathological component of AD. Microglia, the brain's resident immune cells, become chronically activated in response to amyloid-beta accumulation and neuronal injury (Streit, 2010). While acute activation may be protective, sustained activation leads to excessive production of pro-inflammatory cytokines.

Microglial-derived cytokines such as IL-1β, TNF-α, and IL-6 promote synaptic dysfunction and neuronal death (Leng & Edison, 2020). Chronic inflammatory signaling also enhances oxidative stress, creating a deleterious feedback loop. Additionally, activated microglia release ROS and reactive nitrogen species, further damaging mitochondrial function (Krause & Müller, 2010).

Recent studies emphasize the heterogeneity of microglial phenotypes in AD. Depending on environmental cues, microglia may adopt neuroprotective or neurotoxic roles (Miao et al., 2023). Dysregulation of these phenotypes contributes to impaired amyloid clearance and sustained inflammation.

Novel therapeutic approaches aim to modulate microglial activation rather than suppress it entirely. Targeted anti-inflammatory strategies, cytokine inhibitors, and signaling pathway modulators are under investigation (Chen et al., 2024; Kamila et al., 2025). Understanding the balance between protective and harmful inflammatory responses is crucial for developing effective interventions.

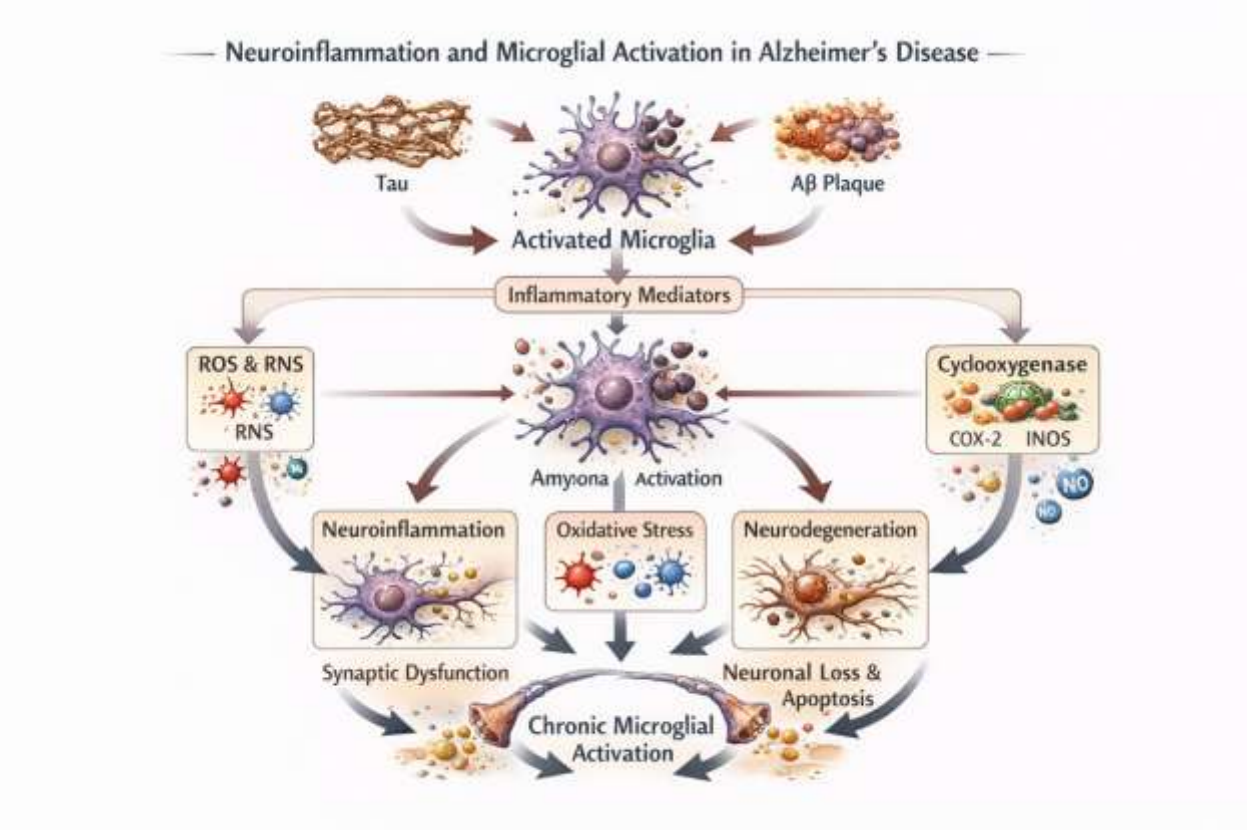

Figure 2 → Neuroinflammation and Microglial Activation Pathway

Amyloid-beta (Aβ) plaques and hyperphosphorylated tau aggregates stimulate microglial activation in the Alzheimer's disease brain. Activated microglia release inflammatory mediators, including pro-inflammatory cytokines (IL-1β, TNF-α, IL-6), reactive oxygen species (ROS), and reactive nitrogen species (RNS). Upregulation of inflammatory enzymes such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) further amplifies oxidative and inflammatory stress. Sustained inflammatory signaling promotes synaptic dysfunction, neuronal loss, and apoptosis. The figure illustrates the self-perpetuating cycle of chronic microglial activation that contributes to progressive neurodegeneration in Alzheimer's disease.

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5. Integrated Crosstalk Among Pathogenic Mechanisms

Oxidative stress, mitochondrial dysfunction, and neuroinflammation are not isolated phenomena but interconnected processes that reinforce each other. Mitochondrial impairment increases ROS production, which activates inflammatory pathways. In turn, inflammatory mediators further disrupt mitochondrial function, perpetuating oxidative damage (Zhang et al., 2023).

Microglial activation amplifies redox imbalance through cytokine release and oxidative burst activity. Oxidative modifications of mitochondrial components reduce ATP production and enhance apoptotic susceptibility. This bidirectional interaction accelerates synaptic degeneration and cognitive decline (Alkhalifa et al., 2025).

Systems-level analyses suggest that AD progression results from convergence of metabolic failure, oxidative imbalance, and chronic inflammation rather than a single pathogenic trigger. Therefore, multi-target therapeutic strategies addressing these interconnected pathways may yield superior outcomes compared to monotherapies.

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6. Therapeutic Perspectives and Future Directions

Current AD treatments primarily target amyloid pathology or provide symptomatic relief. However, emerging evidence underscores the importance of addressing oxidative and inflammatory mechanisms. Antioxidant therapies, although promising in preclinical models, have shown limited clinical efficacy, possibly due to late-stage intervention (Markesbery, 1999).

Mitochondrial-targeted therapies aim to restore bioenergetic capacity and reduce ROS generation (Misrani et al., 2021). Compounds enhancing mitochondrial biogenesis and mitophagy are gaining research attention. Similarly, selective modulation of inflammatory signaling pathways offers potential for reducing chronic neuroinflammation without impairing protective immune functions (Chen et al., 2024).

Future research should focus on early detection biomarkers of oxidative and mitochondrial dysfunction, enabling timely intervention. Personalized therapeutic strategies considering individual redox and inflammatory profiles may improve treatment efficacy.

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7. Conclusion

Oxidative stress, mitochondrial dysfunction, and neuroinflammation are deeply interconnected processes that play central roles in Alzheimer's disease pathogenesis. Rather than acting independently, these mechanisms form a pathological network that drives neuronal degeneration and cognitive decline. A comprehensive understanding of their molecular interplay is essential for developing effective disease-modifying therapies. Future therapeutic strategies should adopt multi-targeted approaches to interrupt the vicious cycle of oxidative damage, bioenergetic failure, and chronic inflammation, offering renewed hope for individuals affected by Alzheimer's disease.

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