

Oxidative Stress and Mitochondrial Dysfunction in Stroke

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Introduction

Stroke is a complex neurological disorder characterized by abrupt disruption of cerebral blood flow, leading to ischemic or hemorrhagic injury and subsequent neuronal death. Beyond the immediate vascular event, secondary injury cascades play a crucial role in determining the extent of brain damage and functional outcomes. The brain is particularly vulnerable to oxidative stress due to its high oxygen consumption, abundant lipid content and relatively low antioxidant defenses. During stroke, excessive generation of Reactive Oxygen Species (ROS) overwhelms the endogenous antioxidant capacity, resulting in lipid peroxidation, DNA damage and protein oxidation. This oxidative imbalance not only amplifies neuronal injury but also disrupts intracellular signaling pathways essential for cell survival and repair. Mitochondria, the primary source of cellular energy, are both generators and targets of oxidative stress in stroke. Ischemia-reperfusion injury and excitotoxicity impair mitochondrial function, leading to reduced ATP production, calcium overload, release of pro-apoptotic factors and further ROS generation in a vicious cycle. This mitochondrial dysfunction exacerbates neuronal death, blood-brain barrier disruption and neuroinflammation, ultimately worsening stroke outcomes. Emerging research highlights the interplay between oxidative stress, mitochondrial dynamics and cell death pathways such as apoptosis, necroptosis and autophagy [1].

Description

Oxidative stress is a critical pathological mechanism in the progression of ischemic and hemorrhagic stroke. The brain is highly vulnerable to oxidative damage because it consumes approximately 20% of the body's oxygen while possessing relatively weak antioxidant defenses. During ischemia, the abrupt cessation of blood flow depletes oxygen and glucose, impairing oxidative phosphorylation and leading to an accumulation of metabolic by-products. Upon reperfusion, the sudden reintroduction of oxygen paradoxically exacerbates injury by triggering a burst of reactive oxygen species (ROS), including superoxide anions, hydrogen peroxide and hydroxyl

radicals. ROS also act as mediators of neuroinflammation, stimulating microglial activation and the release of pro-inflammatory cytokines. The imbalance between excessive ROS production and inadequate antioxidant defenses drives a self-perpetuating cycle of injury that extends beyond the initial vascular event. Importantly, oxidative stress does not act in isolation but interacts closely with mitochondrial dysfunction to amplify neuronal injury. Understanding this interplay is essential for designing therapeutic interventions that can interrupt these destructive cascades [2].

Mitochondrial dysfunction is a hallmark of stroke pathology and plays a pivotal role in determining neuronal survival. Mitochondria are the primary sites of ATP production through oxidative phosphorylation and their failure during ischemia and reperfusion leads to catastrophic cellular consequences. Energy depletion impairs ion homeostasis, causing calcium overload and neuronal depolarization. Excess intracellular calcium further disrupts mitochondrial function, leading to opening of the mitochondrial permeability transition pore (mPTP), collapse of the mitochondrial membrane potential and release of pro-apoptotic factors such as cytochrome c. These events initiate caspase-dependent apoptosis and other forms of programmed cell death. Mitochondria also serve as major generators of ROS and their dysfunction during stroke amplifies oxidative damage in a vicious feedback loop. In hemorrhagic stroke, toxic products of hemoglobin degradation impair mitochondrial respiratory chain function, worsening energy failure. Thus, mitochondrial dysfunction lies at the crossroads of excitotoxicity, oxidative stress and inflammation, making it a critical determinant of stroke severity and recovery [3].

The interplay between oxidative stress and mitochondrial dysfunction forms a destructive cycle that amplifies neuronal injury in stroke. ROS generated during ischemia-reperfusion not only damage cellular macromolecules but also impair mitochondrial respiratory chain complexes, leading to further ROS generation. This feed-forward mechanism establishes a state of sustained oxidative stress, which perpetuates mitochondrial injury. Calcium dysregulation adds another layer of complexity, as calcium overload within mitochondria

accelerates ROS production and triggers mPTP opening. Together, these processes lead to neuronal apoptosis, necrosis and in some cases necroptosis or ferroptosis, each contributing to lesion expansion. Neuroinflammation also feeds into this cycle, as activated microglia and infiltrating immune cells release additional ROS and reactive nitrogen species (RNS). This inflammatory amplification extends tissue injury beyond the ischemic core into the penumbra, a region that remains potentially salvageable. Mitochondrial dysfunction further compromises synaptic activity and impairs neuroplasticity, limiting functional recovery. The persistence of oxidative and mitochondrial injury even after reperfusion therapy highlights the limitations of current treatments. Addressing this interlinked pathology offers opportunities to extend the therapeutic window and improve outcomes. Therapeutic strategies targeting both oxidative stress and mitochondrial stability are therefore of significant interest in contemporary stroke research [4].

Given their central role in stroke pathophysiology, oxidative stress and mitochondrial dysfunction have become key targets for novel therapeutic interventions. Traditional antioxidants such as vitamins C and E have shown limited efficacy in clinical trials due to poor bioavailability and inability to cross the blood–brain barrier effectively. Newer approaches involve mitochondrial-targeted antioxidants, such as MitoQ and SS-31, designed to accumulate within mitochondria and directly neutralize ROS. Beyond pharmacological therapies, lifestyle interventions such as caloric restriction, exercise and dietary antioxidants may support mitochondrial health and reduce oxidative stress in stroke prevention. Stem cell therapies and exosome-based approaches are being explored for their ability to deliver mitochondrial components and antioxidant enzymes to damaged neurons. While many of these therapies remain experimental, their integration with established reperfusion treatments could expand the therapeutic window and improve functional outcomes. The challenge moving forward lies in translating promising preclinical findings into safe, effective and widely applicable clinical solutions [5].

Conclusion

Oxidative stress and mitochondrial dysfunction represent interconnected hallmarks of stroke pathology, driving neuronal injury, neuroinflammation and long-term deficits. The excessive generation of reactive oxygen species, coupled with impaired mitochondrial energy production and calcium dysregulation, creates a self-perpetuating cycle of cellular damage. This cascade not only worsens the acute phase of injury but also limits repair and recovery in the post-stroke period. Targeting these mechanisms offers promising avenues for therapeutic innovation, particularly through mitochondrial-directed antioxidants, permeability transition inhibitors and agents that

enhance mitochondrial biogenesis and quality control. Advances in nanomedicine, gene therapy and stem cell-based approaches may further expand treatment possibilities by improving drug delivery and restoring cellular homeostasis. However, translating these experimental strategies into effective clinical practice remains a major challenge due to issues of safety, bioavailability and heterogeneity of patient populations. Continued research into the molecular interplay between oxidative stress and mitochondrial dysfunction will be essential to develop interventions that not only mitigate acute injury but also promote long-term neurological recovery.

Acknowledgment

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Conflict of Interest

None.

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