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Emerging Neuroprotective Strategies Against Oxidative Stress-Induced Neurotoxicity in Systemic Disorders: Lessons from Diabetes, Malaria, and Hepatic Dysfunction

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ABSTRACT

Oxidative stress is a central, converging mechanism underlying neurotoxicity in a broad range of systemic disorders, including diabetes mellitus, malaria, and hepatic dysfunction. In these conditions, excessive reactive oxygen and nitrogen species (ROS/RNS), impaired antioxidant defenses, mitochondrial dysfunction, and neuroinflammation interact to damage neurons and glia, disrupt the blood–brain barrier (BBB), and impair synaptic and cognitive function. Understanding shared molecular pathways allows cross-fertilization of therapeutic strategies. This review synthesizes current knowledge on oxidative-stress–driven neural injury across diabetes, cerebral malaria, and liver disease, and evaluates emerging neuroprotective strategies: direct and indirect antioxidants, Nrf2 pathway modulators, mitochondrial-targeted therapies, anti-inflammatory and immunomodulatory agents, BBB-stabilizing approaches, nanodelivery systems, metabolic and lifestyle interventions, and regenerative/repair modalities. Preclinical advances-such as mitochondria-targeted peptides, Nrf2 activators, and nanoparticle-facilitated delivery of antioxidants-show promise, and some repurposed drugs (metformin, statins) demonstrate pleiotropic effects across disorders. However, translation is challenged by disease heterogeneity, timing of therapy relative to injury, limited CNS penetration, and inadequate biomarkers. We highlight priority areas for translational research: combination regimens that target oxidative stress and inflammation simultaneously, precision delivery systems to cross or protect the BBB, robust biomarkers for oxidative injury and therapeutic response, and early-intervention trials in stratified patient populations. Integrating mechanistic insights from diabetes, malaria, and hepatic dysfunction can accelerate development of broadly applicable neuroprotective strategies that mitigate oxidative-stress–mediated neural injury in systemic disease.

Keywords: Oxidative stress, neuroprotection, diabetes, cerebral malaria, hepatic encephalopathy

INTRODUCTION

Systemic diseases frequently produce neurological complications that arise, at least in part, from oxidative stress. In diabetes, chronic hyperglycemia and dyslipidemia generate ROS through glucose autooxidation, advanced glycation end-product (AGE) formation, and mitochondrial overload, contributing to diabetic encephalopathy [1]. In malaria-particularly cerebral malaria-parasite sequestration, hemolysis, and immune activation trigger ROS/RNS bursts that damage cerebral endothelium and neurons [2]. Hepatic dysfunction leads to accumulation of neurotoxic metabolites (e.g., ammonia), dysregulated redox balance, and systemic inflammation that precipitate hepatic encephalopathy [3]. Despite distinct initiating triggers, overlapping molecular pathways-mitochondrial dysfunction, redox imbalance, lipid peroxidation, protein oxidation, neuroinflammatory signaling, and BBB disruption-produce convergent neuropathology [3]. This commonality invites therapeutic strategies with cross-disease applicability. Below we summarize mechanisms of oxidative neurotoxicity, examine disease-specific features, and review emerging neuroprotective strategies with translational potential.

Mechanisms Linking Oxidative Stress to Neurotoxicity

Oxidative stress arises when the production of reactive oxygen and nitrogen species (ROS and RNS) exceeds the capacity of cellular antioxidant defenses [4]. Neurons are particularly susceptible to oxidative damage because of their high oxygen consumption, abundant polyunsaturated fatty acids in cell membranes, and limited regenerative potential [5]. The brain's dependence on aerobic metabolism and relatively low antioxidant reserve further increases vulnerability. Mitochondrial dysfunction plays a central role in oxidative neurotoxicity. Excess ROS generated within mitochondria damages mitochondrial DNA, proteins, and lipid membranes, impairing electron transport and ATP synthesis [6]. This dysfunction amplifies ROS production, establishing a vicious cycle that progressively injures neuronal cells. Lipid peroxidation represents another major mechanism whereby ROS attack membrane lipids, causing loss of membrane fluidity, disruption of ion gradients, and compromised neuronal signaling [7]. Protein oxidation and aggregation occur concurrently, as oxidative modification of amino acid residues alters protein folding and enzymatic activity, leading to accumulation of toxic aggregates similar to those observed in neurodegenerative diseases [8]. Neuroinflammation constitutes an additional pathway through which oxidative stress induces neuronal injury. Activated microglia and astrocytes release proinflammatory cytokines, nitric oxide, and additional ROS via NF-κB and inflammasome activation, thereby amplifying tissue damage [9]. Oxidative stress also weakens the blood–brain barrier (BBB) by injuring endothelial cells and degrading tight junction proteins [10]. This increases vascular permeability, allowing peripheral immune cells and toxins to infiltrate brain tissue and exacerbate oxidative and inflammatory cascades. Moreover, ROS-mediated damage affects neurotransmission and synaptic plasticity. Oxidation of synaptic receptors, ion channels, and signaling molecules disrupts neuronal communication, impairs long-term potentiation, and contributes to cognitive decline and behavioral disturbances [11]. These pathological effects are normally counterbalanced by endogenous antioxidant systems such as superoxide dismutase, catalase, glutathione peroxidase, and thioredoxin reductase. Regulation of these enzymes is coordinated by transcriptional factors, most notably nuclear factor erythroid 2–related factor 2 (Nrf2), which activates genes involved in antioxidant defense, detoxification, and mitochondrial protection [12].

Overall, oxidative stress-mediated neurotoxicity is a multifactorial process characterized by a complex interplay between mitochondrial impairment, lipid and protein oxidation, neuroinflammation, BBB disruption, and neurotransmission deficits. Understanding these interconnected mechanisms provides a foundation for developing targeted therapeutic strategies to counteract redox imbalance and preserve neuronal integrity in systemic disorders.

Emerging neuroprotective strategies

1. Direct and indirect antioxidants

Traditional antioxidants (vitamin E, vitamin C, N-acetylcysteine [NAC]) scavenge free radicals or replenish glutathione. NAC, by restoring intracellular glutathione, has shown neuroprotective effects in models of diabetes and hepatic encephalopathy [13]. However, limitations include poor BBB penetration and mixed clinical efficacy when used alone. Interest is growing in indirect antioxidants—compounds that upregulate endogenous defenses (see Nrf2 activators).

2. Nrf2 pathway modulators

Nrf2 is a master regulator of antioxidant response elements. Small-molecule Nrf2 activators (e.g., electrophilic phytochemicals) enhance expression of glutathione-related enzymes and detoxifying proteins [14]. Preclinical studies indicate benefit in diabetic neuropathy models and in attenuating neuroinflammation after systemic insults [15]. Controlled activation is crucial because chronic overactivation may be maladaptive.

3. Mitochondrial-targeted therapies

Mitochondrial health is central. Strategies include mitochondria-targeted antioxidants (e.g., peptide-based mimetics), agents that stabilize the electron transport chain, and compounds that promote mitophagy to remove damaged mitochondria [16]. Mitochondria-penetrating compounds have shown superior efficacy in reducing neuronal ROS compared with untargeted antioxidants [17].

4. Anti-inflammatory and immunomodulatory agents

Because oxidative stress and inflammation are intertwined, agents that dampen microglial activation (e.g., minocycline, selective cytokine inhibitors) can reduce oxidative mediators [18]. Repurposed drugs with pleiotropic effects, metformin (AMPK activator) and statins (endothelial stabilizers) demonstrate antioxidant and anti-inflammatory properties in translational studies [19].

5. BBB protection and endothelial stabilizers

Protecting or restoring BBB integrity reduces CNS exposure to peripheral oxidative mediators. Approaches include stabilizing tight junction proteins, modulating endothelial nitric oxide synthase (eNOS) to normalize redox signaling, and targeting matrix metalloproteinases (MMPs) implicated in junctional breakdown [20].

6. Nanodelivery and targeted therapeutics

Nanoparticle carriers improve CNS delivery of antioxidants, small molecules, and nucleic acids. Lipid- or polymer-based nanoparticles can be engineered to cross the BBB, provide sustained release, and target specific cell types

(neurons, astrocytes, microglia). Such systems have enhanced efficacy in preclinical models by delivering functional payloads directly to vulnerable cells [21].

7. Metabolic and lifestyle interventions

Glycemic control, weight management, exercise, and dietary interventions (e.g., omega-3 fatty acids, polyphenol-rich diets) reduce systemic oxidative burden and confer neuroprotective benefits [22]. Exercise upregulates endogenous antioxidant enzymes and supports mitochondrial biogenesis, offering a low-cost adjunctive strategy [23].

8. Regenerative and cell-based approaches

Stem cell therapies and strategies to promote endogenous neurogenesis and synaptic repair may mitigate oxidative injury's long-term consequences [24]. Cell-based therapies can exert trophic, immunomodulatory, and antioxidant effects, though safety and delivery challenges remain. [25]

Translational Challenges and Opportunities

The translation of antioxidant-based neuroprotective strategies from laboratory models to clinical settings remains challenging due to the multifaceted nature of oxidative stress and its integration with other pathological processes [26]. One major issue is the timing and disease stage at which the intervention occurs. Antioxidant therapies tend to show maximal efficacy during early or subclinical phases, when oxidative cascades can still be interrupted [27]. Once neuronal loss and synaptic degeneration become advanced, recovery is limited. Therefore, early diagnosis and stratification of patients using biomarkers of oxidative damage could substantially improve therapeutic success.

Blood-brain barrier (BBB) penetration and targeted delivery represent another major obstacle. Many potent antioxidants fail to achieve therapeutic concentrations within the central nervous system because of limited permeability [28]. Emerging strategies such as nanodelivery systems, liposomal encapsulation, and prodrug formulations are being developed to enhance CNS bioavailability and facilitate targeted release at affected regions.

The development of reliable biomarkers and clinical endpoints is equally critical. Biomolecules such as oxidized lipids, protein carbonyls, and circulating mitochondrial DNA fragments could serve as disease-agnostic indicators of oxidative injury and treatment response [29]. Combinatorial therapy is increasingly recognized as a promising approach. Because oxidative stress interacts closely with inflammation, mitochondrial dysfunction, and metabolic imbalance, combining antioxidants with anti-inflammatory, metabolic, or mitochondrial-supportive drugs may yield synergistic neuroprotective effects [30].

Finally, safety and chronicity must be carefully managed. Since low levels of ROS are vital for cellular signaling, immune responses, and synaptic plasticity, long-term antioxidant use requires precise dosing and monitoring to prevent adverse effects and maintain physiological redox signaling.

CONCLUSION

Oxidative stress is a unifying driver of neurotoxicity in diabetes, malaria, and hepatic dysfunction. Emerging strategies-from Nrf2 activation and mitochondrial-targeted therapeutics to nanodelivery and lifestyle interventions-offer promising avenues to protect the brain from redox-mediated injury. Translational success will depend on precise targeting, appropriate timing, validated biomarkers, and rational combination therapies that address oxidative stress and its inflammatory and metabolic collaborators. Cross-disease learning accelerates progress; by leveraging mechanistic overlaps, the field can move toward broadly applicable neuroprotective regimens that improve neurological outcomes for patients with systemic disease.

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