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Neurotoxicity and Diabetes: Mechanistic Insights into Oxidative Stress Mediated Neuronal Damage and Potential Neuroprotective Interventions

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ABSTRACT

Diabetes mellitus is associated with accelerated neuronal injury manifesting as diabetic peripheral neuropathy, cognitive impairment, and heightened risk of neurodegenerative disease. A large body of evidence implicates oxidative stress-the imbalance between production of reactive oxygen and nitrogen species (ROS/RNS) and antioxidant defenses a central mediator linking hyperglycaemia, dyslipidaemia, and chronic inflammation to neuronal dysfunction. Hyperglycaemia-driven metabolic pathways (polyol flux, advanced glycation end-products, protein kinase C activation, hexosamine pathway), mitochondrial overload, NADPH oxidase activation, and inflammation converge on excessive ROS/RNS generation, which in turn damages neuronal macromolecules, perturbs ion homeostasis, impairs axonal transport and mitochondrial dynamics, and triggers neuroinflammation. Translational research has explored a range of neuroprotective strategies tight metabolic control, repurposed antidiabetic drugs with pleiotropic antioxidant effects, nutraceutical and polyphenol interventions, Nrf2 pathway activators, mitochondria-targeted antioxidants, and novel drug-delivery systems-to interrupt the oxidative cascade. While preclinical studies show consistent neuroprotection by redox-targeted interventions, clinical translation has been mixed due to heterogeneity in patient populations, timing of intervention, bioavailability of compounds, and limited biomarker-guided stratification. Future progress requires biomarker-driven trials, mitochondrial- and blood–brain-barrier–targeted delivery, and combination therapies that preserve physiological ROS signalling while preventing pathological oxidative damage. This review synthesizes current mechanistic insights into oxidative stress–mediated neurotoxicity in diabetes and evaluates the evidence and potential of neuroprotective interventions.

Keywords: Diabetes, oxidative stress, neurotoxicity, neuroprotection, mitochondria

INTRODUCTION

Diabetes mellitus is a global metabolic disorder that profoundly affects both the peripheral and central nervous systems' function. Patients with diabetes experience a high incidence of diabetic peripheral neuropathy (DPN), which manifests as chronic pain, numbness, paresthesia, and an increased risk of foot ulceration and gait instability [1]. Beyond peripheral nerves, diabetes is increasingly associated with central nervous system complications, including cognitive impairment, accelerated brain aging, and elevated risk for dementia and Alzheimer's disease [2]. These neurological sequelae not only compromise quality of life but also significantly increase morbidity and healthcare burden. A central pathological mechanism linking diabetes to neuronal injury is oxidative stress, defined as an imbalance between reactive oxygen and nitrogen species (ROS/RNS) production and endogenous antioxidant defenses [3]. Chronic hyperglycaemia, insulin resistance, dyslipidaemia, and systemic low-grade inflammation converge to promote persistent ROS/RNS generation [4]. At the same time, key antioxidant systems-including superoxide dismutases, catalase, glutathione peroxidase, and glutathione pools-are impaired or depleted in diabetic tissues, creating a pro-oxidant environment [5]. This redox imbalance damages neuronal lipids, proteins, and nucleic acids, alters membrane integrity, disrupts intracellular signaling, and induces mitochondrial dysfunction. These effects collectively compromise neuronal survival, axonal transport, and synaptic function. The deleterious impact of oxidative stress on neurons extends to multiple cellular compartments. Mitochondria, which are highly metabolically active in neurons, are particularly vulnerable. Oxidative damage to mitochondrial DNA and respiratory chain complexes impairs ATP production, generating further ROS and establishing a self-propagating cycle of injury [6]. In addition, chronic oxidative stress activates inflammatory signaling pathways and glial cells,

which release cytokines and secondary ROS/RNS, amplifying neural damage [7]. Endothelial cells and pericytes in the neurovascular unit are also affected, impairing blood–nerve and blood–brain barrier integrity and facilitating infiltration of inflammatory mediators [7]. Understanding these oxidative mechanisms is critical for developing neuroprotective interventions in diabetes. Therapeutic strategies that restore redox homeostasis have the potential to prevent or mitigate peripheral and central neuronal injury, preserve cognitive function, and improve quality of life. Current research emphasizes the importance of targeting mitochondrial dysfunction, enhancing endogenous antioxidant pathways, and modulating inflammatory responses. Lifestyle interventions such as optimized glycaemic control, exercise, and dietary modulation are fundamental but often insufficient, necessitating adjunct pharmacological and nutraceutical approaches. Emerging evidence from preclinical and early clinical studies supports the efficacy of such interventions, although translation to broad clinical practice remains challenging due to patient heterogeneity and variability in oxidative stress burden.

2. Sources of ROS/RNS in Diabetes and How They Target Neurons

Multiple interconnected biochemical pathways drive ROS/RNS generation in diabetic states.

Mitochondrial overload occurs when excess glucose and fatty acid oxidation increases electron donors (NADH and $FADH_2$), resulting in electron leakage at complexes I and III of the electron transport chain and elevated superoxide production [8]. This ROS accumulation damages mitochondrial DNA and respiratory proteins, establishing a feedback loop that amplifies oxidative injury. NADPH oxidases (NOX) are activated by hyperglycaemia and pro-inflammatory cytokines in neurons, glial cells, and vascular endothelium, producing bursts of superoxide that exacerbate neuronal oxidative stress [9]. The polyol pathway contributes to redox imbalance by consuming NADPH to convert glucose into sorbitol, reducing availability of this cofactor for glutathione regeneration and weakening antioxidant defenses [10]. Advanced glycation end-products (AGEs) interact with the receptor for AGEs (RAGE) on neurons, microglia, and endothelial cells, activating NF-κB and NOX-mediated pro-oxidant and pro-inflammatory cascades [11]. Nitrosative stress arises from inducible nitric oxide synthase (iNOS) overactivity in inflamed neural tissue, generating nitric oxide that reacts with superoxide to form peroxynitrite, a highly reactive species that damages proteins, lipids, and DNA [12].

These ROS and RNS converge to injure neuronal axons and soma through multiple mechanisms: oxidation of lipids and proteins, disruption of ion channel function, impairment of axonal transport, and mitochondrial dysfunction [13]. Long peripheral nerves are particularly susceptible due to their high metabolic demands. Furthermore, oxidative injury to endothelial cells and pericytes compromises the neurovascular unit, weakening the blood–nerve and blood–brain barriers, reducing perfusion, and facilitating infiltration of inflammatory cells, which further exacerbate neuronal damage [14]. This complex interplay of metabolic, oxidative, and inflammatory pathways underlies the widespread neurotoxicity observed in diabetes, providing a mechanistic rationale for interventions targeting oxidative stress and its downstream effects.

3. Cellular and Molecular Consequences of Oxidative Neuronal Injury

Oxidative stress exerts profound effects on neurons and glial cells through multiple, interrelated mechanisms that compromise structural integrity, cellular signaling, and functional performance. Mitochondrial dysfunction is a primary target: reactive oxygen species damage mitochondrial DNA and proteins, impairing electron transport chain function and uncoupling oxidative phosphorylation. The resulting reduction in ATP production is particularly detrimental to neurons, which rely on sustained high-energy flux for ion pumping, synaptic transmission, and axonal transport [15]. Mitochondrial impairment also increases further ROS generation, establishing a self-perpetuating cycle of injury [16].

Impaired axonal transport and cytoskeletal damage are critical downstream effects. Oxidative modification of motor proteins such as kinesin and dynein, along with cytoskeletal components including tubulin and neurofilaments, slows the trafficking of mitochondria, vesicles, and signaling molecules along axons [17]. Distal axonal degeneration emerges as a hallmark of length-dependent neuropathy, explaining why long peripheral nerves are often the earliest and most severely affected in diabetes [18].

Excitotoxicity and calcium dysregulation further exacerbate neuronal injury [19]. Oxidative stress impairs glutamate uptake and modulates receptor activity, resulting in excessive excitatory signaling [20]. Intracellular calcium overload activates proteases, phospholipases, and endonucleases, compounding structural damage to membranes, cytoskeleton, and organelles [21]. This dysregulation also affects synaptic plasticity and neurotransmitter release, linking cellular damage to functional deficits.

DNA damage and poly (ADP-ribose) polymerase (PARP) overactivation represent additional molecular consequences [22]. Oxidative lesions in nuclear and mitochondrial DNA activate PARP, which consumes NAD+ and ATP in attempts to repair damage [23]. Persistent overactivation leads to energetic collapse and triggers programmed cell death pathways, including apoptosis and parthanatos, particularly in metabolically stressed neurons [24].

Neuroinflammation is tightly intertwined with oxidative stress. Microglia, the resident immune cells of the central nervous system, become primed toward pro-inflammatory phenotypes under oxidative conditions. Activated

microglia release cytokines, ROS, and reactive nitrogen species, establishing a feed-forward loop that amplifies neuronal injury and propagates inflammatory signaling across neural networks [25]. Astrocytes and oligodendrocytes also exhibit functional impairment, contributing to reduced support for axons, myelin instability, and further metabolic vulnerability [26].

Synaptic dysfunction and cognitive deficits emerge as higher-order consequences of these cellular and molecular insults. Oxidative modification of synaptic proteins, neurotransmitter receptors, and signaling pathways disrupts long-term potentiation and synaptic plasticity, which underlies learning and memory [27]. Clinically, these processes manifest as cognitive impairment, slowed information processing, and increased susceptibility to neurodegenerative disorders in individuals with diabetes.

Collectively, these mechanisms operate across multiple scales-from redox-sensitive signaling pathways at the molecular level to conduction deficits in peripheral nerves and cognitive decline in the central nervous system. The convergence of mitochondrial dysfunction, cytoskeletal impairment, excitotoxicity, DNA damage, and neuroinflammation explains the heterogeneity and severity of diabetic neuroclinical phenotypes. Understanding these interconnected pathways is crucial for the development of targeted neuroprotective strategies aimed at mitigating oxidative neuronal injury and preserving both peripheral and central nervous system function.

4. Biomarkers and Experimental Models

Accurate assessment of oxidative neuronal injury requires both direct and indirect biomarkers. Lipid peroxidation products such as F2-isoprostanes and 4-hydroxynonenal reflect oxidative damage to cellular membranes [28]. Protein carbonyls and nitrotyrosine indicate oxidation and nitration of structural and enzymatic proteins, while DNA oxidation markers, including 8-hydroxy-2′-deoxyguanosine (8-OHdG), track genomic and mitochondrial damage [29]. Redox status can be quantified via ratios of reduced to oxidized glutathione (GSH:GSSG) and activities of key antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase [30].

Functional and structural correlates are provided by neurophysiologic tests, including nerve conduction studies, electromyography, and assessments of sensory thresholds. Histopathological evaluation of skin and sural nerve biopsies allows direct visualization of axonal degeneration and myelin pathology [31]. Advanced neuroimaging techniques, including magnetic resonance spectroscopy and diffusion tensor imaging, provide in vivo assessment of neural integrity and oxidative metabolic changes.

Experimental models have been indispensable in elucidating mechanisms of oxidative neurotoxicity and evaluating potential interventions. Streptozotocin-induced diabetic rodents replicate hyperglycaemia-driven neuropathic features, while high-fat diet and insulin resistance models mimic metabolic dysfunction in type 2 diabetes [32]. Transgenic animals allow targeted manipulation of oxidative stress pathways, including NADPH oxidases, mitochondrial enzymes, and antioxidant systems [33]. Despite their utility, translational gaps remain due to species differences, differences in disease progression, and timing of intervention, highlighting the need for careful extrapolation to human clinical contexts.

5. Neuroprotective Strategies: Mechanisms and Evidence

Given oxidative stress's centrality, redox-focused neuroprotection spans several complementary approaches.

Metabolic control and lifestyle: Tight glycaemic control, weight reduction and exercise reduce substrate-driven ROS production, improve mitochondrial dynamics and lower inflammation [34]. Clinical data show that good metabolic control lowers incidence and progression of DPN and may slow cognitive decline [35]. Repurposed antidiabetic drugs with neuroprotective effects: Metformin, GLP-1 receptor agonists and SGLT2 inhibitors exhibit pleiotropic benefits-mitigating mitochondrial dysfunction, lowering inflammation and reducing oxidative stress-shown in preclinical and emerging clinical studies to improve neural outcomes [36]. Antioxidant nutraceuticals and polyphenols: Compounds such as resveratrol, curcumin, epigallocatechin gallate and flavonoids reduce ROS, activate Nrf2-mediated antioxidant responses, and attenuate microglial activation [37]. Preclinical models show preservation of nerve structure and function; clinical trials demonstrate improved oxidative biomarkers and symptomatic relief in some cohorts, though heterogeneity and bioavailability limitations temper conclusions. [5] Nrf2 activators and endogenous pathway enhancers: Pharmacologic activation of Nrf2 boosts transcription of glutathione synthesis and phase II detox enzymes, offering broad cytoprotection [38]. Early-stage compounds and natural activators (sulforaphane, bardoxolone-like agents) show promise but require careful safety evaluation. Mitochondria-targeted antioxidants and delivery systems: Molecules designed to accumulate in mitochondria (e.g., mitoQ, SS peptides) have succeeded in reducing mitochondrial ROS and improving nerve function in animal models [39]. Nanoparticle-based delivery and blood–brain-barrier–permeable formulations are active areas to improve CNS targeting and bioavailability [6,40]

Anti-inflammatory strategies: Targeting microglial activation, cytokine signaling (IL-1β, TNF-α) and PARP pathways can blunt the oxidative–inflammatory feedback loop. Combination therapies that simultaneously reduce oxidative burden and inflammation show additive benefits in preclinical studies [41]. Symptom-directed and regenerative approaches: Neurotrophic factors, Schwann cell support, and therapies that enhance axonal

regeneration (e.g., growth factor delivery, cell therapies) are being tested alongside antioxidant strategies to restore function rather than solely halting degeneration [42].

CONCLUSION

Oxidative stress is a central mechanistic nexus linking metabolic derangements in diabetes to neuronal injury. The oxidative cascade damages mitochondria, perturbs ion homeostasis and axonal transport, and fuels neuroinflammation-collectively leading to peripheral neuropathy and cognitive dysfunction. Neuroprotective strategies that target redox imbalance-when coupled with improved metabolic control, targeted delivery, and biomarker-driven patient selection-offer realistic promise for mitigating diabetic neurotoxicity. Realizing that promise will require rigorous translational pipelines, precision clinical trials, and therapies that preserve physiological ROS-dependent signalling while preventing pathological oxidative damage.

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