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Neurotoxicity in Diabetes Mellitus: The Role of Mitochondrial Dysfunction and Redox-Sensitive Signalling Pathways

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ABSTRACT

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia, which exerts profound effects on multiple organ systems, including the nervous system. Neurotoxicity in diabetes is increasingly recognized as a consequence of mitochondrial dysfunction and activation of redox-sensitive signalling pathways. Persistent hyperglycemia induces excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to oxidative stress, mitochondrial damage, and dysregulated cellular signalling. These alterations compromise neuronal bioenergetics, promote inflammation, and precipitate axonal degeneration and synaptic dysfunction. Redox-sensitive transcription factors, including NF-kB, Nrf2, and AP-1, mediate inflammatory and antioxidant responses, while mitochondrial permeability transition, calcium dysregulation, and apoptotic signalling contribute to neuronal death. This review integrates current understanding of the mechanisms underlying diabetic neurotoxicity, highlighting the interplay between mitochondrial impairment and oxidative stress-mediated signalling pathways. Therapeutic strategies targeting mitochondrial function, redox balance, and downstream signalling are discussed, emphasizing their potential to prevent or mitigate diabetic neuropathy and cognitive dysfunction.

Keywords: Diabetes mellitus, neurotoxicity, mitochondrial dysfunction, oxidative stress, redox signaling

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia due to insulin deficiency, insulin resistance, or both [1,2]. While the vascular and renal complications of diabetes are well documented, its impact on the nervous system is increasingly recognized as a major contributor to morbidity. Diabetic neurotoxicity manifests in both the peripheral and central nervous systems, leading to peripheral neuropathy, autonomic dysfunction, cognitive impairment, and increased susceptibility to neurodegenerative diseases [3]. Peripheral neuropathy is characterized by axonal degeneration, demyelination, and impaired nerve conduction, resulting in symptoms such as pain, numbness, and paresthesia [4]. Central complications include hippocampal and cortical dysfunction, contributing to memory deficits and impaired executive function. Mechanistically, diabetic neurotoxicity results from the interplay between chronic hyperglycemia, oxidative stress, mitochondrial dysfunction, and redox-sensitive signalling pathways [5]. Hyperglycemia enhances the generation of reactive oxygen species and reactive nitrogen species, which overwhelm intrinsic antioxidant defenses and damage neuronal macromolecules [6]. Mitochondrial dysfunction further impairs ATP production, destabilizes calcium homeostasis, and promotes apoptosis, particularly in metabolically active neurons. Redox-sensitive transcription factors, including NF-kB, Nrf2, and MAPKs, mediate inflammatory and antioxidant responses, shaping neuronal survival or death [7]. Neurons are especially vulnerable due to their high energy demands, post-mitotic status, and limited regenerative capacity [8]. Understanding these molecular mechanisms is critical for developing interventions that preserve neuronal function, prevent synaptic dysfunction, and mitigate long-term cognitive decline in diabetic patients.

2. Hyperglycemia-Induced Oxidative Stress in Neurons

Persistent hyperglycemia initiates multiple biochemical pathways that contribute to neuronal oxidative stress. The polyol pathway reduces glucose to sorbitol via aldose reductase, consuming NADPH, which is essential for regenerating glutathione, the primary intracellular antioxidant [9]. NADPH depletion therefore weakens neuronal

defenses, increasing susceptibility to ROS-mediated damage. Additionally, chronic hyperglycemia promotes the formation of advanced glycation end-products, which interact with their receptor RAGE to activate NADPH oxidases and induce pro-inflammatory signaling [10,11]. These pathways collectively enhance the production of superoxide, hydrogen peroxide, and peroxynitrite, leading to oxidative modifications of lipids, proteins, and nucleic acids. Mitochondria are central to hyperglycemia-induced ROS generation. Excess glucose increases electron flux through the mitochondrial electron transport chain, causing electron leakage from complexes I and III and superoxide formation [12]. Oxidative damage impairs mitochondrial enzymes, disrupts membrane integrity, and reduces ATP production, compromising synaptic transmission and axonal transport. Reactive nitrogen species, formed from nitric oxide and superoxide interaction, further exacerbate mitochondrial and cytosolic damage, contributing to neuronal apoptosis [13]. These oxidative processes establish a self-perpetuating cycle of mitochondrial dysfunction and redox imbalance, which underlies both peripheral and central neurodegeneration in diabetes.

3. Mitochondrial Dysfunction in Diabetic Neurotoxicity

3.1 Bioenergetic Impairment

Neurons rely heavily on mitochondria for ATP generation through oxidative phosphorylation. Hyperglycemia and oxidative stress impair electron transport chain complexes, particularly complexes I and III, leading to electron leakage and energy deficits [14]. Reduced ATP availability compromises synaptic vesicle cycling, ion pumping, and axonal transport, rendering neurons highly susceptible to injury and degeneration [15].

3.2 Mitochondrial ROS Generation

Damaged mitochondria become a major source of reactive oxygen species, producing superoxide and hydrogen peroxide that amplify oxidative damage to mitochondrial DNA, proteins, and lipids. Accumulation of mitochondrial DNA mutations and deletions in neurons triggers apoptosis and cellular senescence, perpetuating neurotoxicity [16].

3.3 Calcium Dysregulation and Mitochondrial Permeability

Oxidative stress disrupts intracellular calcium homeostasis, causing mitochondrial calcium overload. Elevated calcium triggers the opening of the mitochondrial permeability transition pore, leading to loss of membrane potential, cytochrome c release, and activation of intrinsic apoptotic pathways [17]. This mechanism of cell death is central to both peripheral and central manifestations of diabetic neurotoxicity, contributing to axonal degeneration, synaptic dysfunction, and cognitive impairment [18].

4. Redox-Sensitive Signalling Pathways in Diabetic Neurons

4.1 NF-kB Signalling

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) is a key transcription factor sensitive to changes in the intracellular redox state [19]. In diabetic neurons, elevated reactive oxygen species activate NF-kB through phosphorylation and degradation of its inhibitor IκB, allowing NF-kB translocation to the nucleus [20]. Once activated, NF-kB upregulates the transcription of pro-inflammatory cytokines, including tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6. These cytokines mediate neuroinflammation, recruit glial cells, and promote oxidative injury in both neurons and supporting glial networks. Chronic NF-kB activation creates a feed-forward loop whereby inflammation further increases ROS production, amplifying mitochondrial dysfunction and neuronal apoptosis [21]. In addition, NF-kB influences the expression of adhesion molecules, chemokines, and matrix metalloproteinases, which alter neuronal microenvironment and exacerbate synaptic damage.

4.2 Nrf2 Pathway

Nuclear factor erythroid 2-related factor 2 (Nrf2) serves as a master regulator of the cellular antioxidant response [22]. Under oxidative stress, Nrf2 dissociates from its inhibitor Keap1 and translocates to the nucleus, where it binds antioxidant response elements to drive expression of enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and heme oxygenase-1[23]. These enzymes neutralize reactive oxygen species and maintain redox homeostasis. In the context of diabetes, persistent hyperglycemia and chronic ROS accumulation impair Nrf2 activation through oxidative modification of Keap1 and epigenetic alterations, reducing neuronal antioxidant capacity [24]. The resulting vulnerability to oxidative damage contributes to mitochondrial dysfunction, synaptic deficits, and cell death. Pharmacological activation of Nrf2 has emerged as a potential strategy to restore redox balance and prevent neurodegeneration in diabetic conditions [25].

4.3 MAPK and AP-1 Signalling

Mitogen-activated protein kinases, including p38 MAPK and c-Jun N-terminal kinase, are sensitive to redox fluctuations and regulate apoptosis, inflammation, and cytoskeletal remodeling in neurons [26]. Their downstream effector, activator protein-1 (AP-1), coordinates the transcription of pro-apoptotic genes and inflammatory mediators. Hyperglycemia-induced ROS activate MAPK pathways, leading to dendritic retraction, axonal degeneration, and synaptic dysfunction [27]. These structural and functional impairments contribute to both peripheral neuropathy and cognitive deficits in diabetic patients.

4.4 AGE-RAGE Axis

Advanced glycation end-products accumulate in neurons under chronic hyperglycemia and bind to their receptor, RAGE, on the cell surface. AGE-RAGE interaction stimulates NADPH oxidase-dependent ROS generation, activating NF-kB and further amplifying oxidative stress. This pathway disrupts mitochondrial function, promotes neuronal apoptosis, and contributes to axonal degeneration [28]. AGE-RAGE signalling has been implicated in the pathogenesis of diabetic peripheral neuropathy, autonomic dysfunction, and cognitive decline, linking metabolic dysregulation to long-term neurodegenerative outcomes [29].

5. Impact on Peripheral and Central Nervous Systems

5.1 Peripheral Neuropathy

Oxidative stress and mitochondrial dysfunction impair axonal transport and myelin integrity, leading to distal axon degeneration characteristic of diabetic peripheral neuropathy. Schwann cells are also affected, reducing myelin maintenance and further compromising conduction velocity [30]. Symptoms include numbness, paresthesia, and neuropathic pain, which correlate with biomarkers of oxidative damage.

5.2 Central Nervous System Dysfunction

Diabetic neurotoxicity affects hippocampal and cortical neurons, contributing to cognitive deficits and increased risk of dementia. Mitochondrial impairment, ROS accumulation, and chronic inflammation disrupt synaptic plasticity, reduce neurogenesis, and promote neuronal apoptosis [31]. Altered redox-sensitive signalling contributes to impaired learning, memory, and executive function.

6. Biomarkers of Neurotoxicity in Diabetes

The identification of reliable biomarkers is essential for early detection, monitoring, and prognostication of diabetic neurotoxicity. Biomarkers reflecting oxidative stress, mitochondrial dysfunction, and dysregulated redox signalling provide insight into the ongoing neuronal injury and can guide therapeutic interventions [32].

6.1 Oxidative Damage Markers

Markers of oxidative injury, including lipid peroxidation products such as malondialdehyde and 4-hydroxynonenal, accumulate in neuronal and glial membranes under chronic hyperglycemia. These reactive aldehydes disrupt membrane integrity, interfere with ion transport, and promote apoptotic signaling [33]. Protein carbonyls, formed through direct oxidation of amino acid residues, indicate oxidative modification of structural and enzymatic proteins, impairing cellular function. Oxidative damage to nucleic acids is reflected by elevated 8-hydroxydeoxyguanosine, a marker of DNA oxidation, which correlates with neuronal dysfunction and apoptosis [34]. Clinically, increased plasma or cerebrospinal fluid levels of these molecules have been associated with the severity of peripheral neuropathy and cognitive decline, suggesting their utility in risk stratification and monitoring disease progression.

6.2 Mitochondrial Dysfunction Indicators

Mitochondrial integrity is central to neuronal survival, and its compromise can be assessed using functional biomarkers [35]. Alterations in mitochondrial membrane potential, as measured by fluorescent dyes, reflect early mitochondrial depolarization and susceptibility to apoptosis. Release of cytochrome c into the cytosol is a hallmark of intrinsic apoptotic pathway activation [36]. ATP depletion in neuronal tissue or peripheral blood mononuclear cells indicates bioenergetic failure and impaired neuronal function. These markers serve as surrogates for mitochondrial health and can predict the extent of neurodegeneration in diabetic patients.

6.3 Redox-Sensitive Transcription Factor Activity

The activity of redox-sensitive transcription factors, including NF-kB, Nrf2, and MAPKs, provides insight into the balance between pro-inflammatory and antioxidant responses [37]. Elevated NF-kB activity indicates ongoing neuroinflammation, whereas impaired Nrf2 signalling reflects reduced cellular antioxidant capacity. MAPK pathway activation is associated with apoptosis and cytoskeletal alterations in neurons [38]. Quantifying these signalling pathways in patient-derived samples may offer predictive value for neurotoxicity progression and serve as pharmacodynamic markers for therapeutic interventions aimed at restoring redox homeostasis [39,40]. Collectively, these biomarkers provide a comprehensive framework for evaluating oxidative and mitochondrial contributions to diabetic neurotoxicity and may inform the development of targeted neuroprotective strategies.

CONCLUSION

Neurotoxicity in diabetes mellitus arises from the interplay of mitochondrial dysfunction, oxidative stress, and dysregulated redox-sensitive signalling pathways. Persistent hyperglycemia triggers ROS overproduction, lipid and protein oxidation, mitochondrial impairment, and activation of inflammatory and apoptotic transcription factors, culminating in neuronal injury and functional deficits. Peripheral neuropathy and central nervous system dysfunction are common clinical manifestations, with biomarkers of oxidative damage and mitochondrial stress providing insight into disease progression. Therapeutic strategies targeting mitochondrial bioenergetics, redox balance, and signalling pathways, in combination with tight metabolic control, offer the most promising avenues for preventing or mitigating diabetic neurotoxicity. Continued research into molecular mechanisms and translational interventions is essential for developing personalized therapies that preserve neuronal function and improve quality of life in patients with diabetes.

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