SGLT-2 Inhibition Beyond Glycemic Control: Exploring the Neuroprotective Properties of Dapagliflozin in Diabetes-Related Neurodegeneration

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Abstract

Background: Diabetes mellitus is increasingly recognized not only as a metabolic disorder but also as a condition that predisposes the central nervous system to accelerated aging and neurodegeneration. Chronic hyperglycemia, oxidative stress, neuroinflammation, and mitochondrial dysfunction collectively contribute to neuronal damage, synaptic impairment, and cognitive decline observed in diabetic patients. In recent years, sodium–glucose cotransporter-2 (SGLT-2) inhibitors, initially developed as glucose-lowering agents, have gained attention for their potential pleiotropic effects beyond glycemic control. Among these, dapagliflozin has emerged as a promising candidate demonstrating cardioprotective, renoprotective, and possibly neuroprotective properties.

The aim of this review is to explore the potential neuroprotective mechanisms of dapagliflozin in diabetes-related neurodegeneration. The article integrates findings from experimental and clinical studies, elucidating how SGLT-2 inhibition might modulate central metabolic and inflammatory pathways to confer neuronal resilience. Dapagliflozin may exert neuroprotective actions through multiple mechanisms, including attenuation of oxidative stress via activation of the Nrf2/ARE pathway, suppression of proinflammatory cytokine release, stabilization of mitochondrial function, and improvement in cerebral microcirculation. Moreover, evidence suggests that dapagliflozin can indirectly enhance insulin sensitivity and modulate neurovascular coupling, which may collectively protect against diabetic encephalopathy and cognitive decline.

Emerging data from preclinical models indicate that dapagliflozin mitigates neuronal apoptosis and preserves synaptic integrity in hyperglycemic conditions. While direct clinical evidence remains limited, preliminary findings from observational studies suggest potential cognitive benefits in diabetic patients treated with SGLT-2 inhibitors. Despite these encouraging results, translational gaps persist, particularly in understanding blood–brain barrier permeability, optimal dosing, and long-term neural outcomes.

In conclusion, dapagliflozin represents a novel pharmacological candidate with neuroprotective potential in diabetes-related neurodegeneration. Its multifactorial mechanisms—spanning metabolic, oxidative, and inflammatory pathways—highlight its promise as an adjunct therapy targeting diabetic brain complications. Further mechanistic studies and dedicated clinical trials are warranted to substantiate these neuroprotective effects and translate them into therapeutic strategies for diabetic patients.

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Keywords: *SGLT-2, Neuroprotective, Dapagliflozin*

Introduction

Diabetes mellitus (DM) has emerged as one of the most significant global health challenges of the 21st century, with its burden extending far beyond glucose dysregulation. Among its systemic complications, the central nervous system (CNS) has increasingly become recognized as a major target of diabetic injury, manifesting as cognitive impairment, increased risk of Alzheimer's disease, and diabetic encephalopathy. Chronic hyperglycemia, insulin resistance, and vascular dysfunction combine to create a neurodegenerative milieu that compromises neuronal metabolism and synaptic integrity. This pathological interplay between metabolic and neurodegenerative processes has prompted a surge of interest in identifying agents that can confer neuroprotection in diabetic states [1].

Traditional glucose-lowering therapies have primarily aimed to maintain glycemic control but have shown limited success in halting the progression of neurological complications. Insulin and metformin, while effective in regulating systemic glucose homeostasis, do not adequately address neuronal oxidative stress or neuroinflammatory cascades associated with chronic hyperglycemia [2]. Thus, there is a growing need for therapeutic strategies that extend beyond glycemic management to target the underlying mechanisms of neuronal injury in diabetes.

Sodium–glucose cotransporter-2 (SGLT-2) inhibitors, a relatively new class of oral antidiabetic agents, reduce plasma glucose by promoting glycosuria through inhibition of glucose reabsorption in the renal proximal tubules. Interestingly, accumulating evidence indicates that these agents exert pleiotropic benefits independent of glucose control, including cardioprotection, renoprotection, and possible neuroprotection [3]. Among the SGLT-2 inhibitors, **dapagliflozin** has shown particular promise due to its favorable safety profile, antioxidant potential, and ability to modulate systemic inflammation and metabolic homeostasis.

The aim of this review is to comprehensively examine the potential neuroprotective properties of dapagliflozin in diabetes-related neurodegeneration, focusing on molecular mechanisms and available experimental and clinical evidence. This paper highlights the critical research gap in understanding the CNS actions of dapagliflozin and the necessity of translational studies bridging metabolic modulation and neuroprotection. Through a synthesis of emerging literature, this review underscores dapagliflozin's therapeutic potential as a multifaceted agent capable of mitigating diabetic neurodegenerative complications [4].

Pathophysiology of Diabetic Neurodegeneration

Diabetes mellitus induces a wide range of metabolic and vascular abnormalities that converge to impair neuronal survival and brain function. Chronic hyperglycemia results in increased oxidative metabolism within neurons, generating reactive oxygen species (ROS) and reactive nitrogen species (RNS) that exceed the capacity of intrinsic antioxidant systems such as glutathione, catalase, and superoxide dismutase. These radicals cause lipid peroxidation, mitochondrial DNA mutations, and damage to membrane proteins, thereby compromising neuronal energy homeostasis. Furthermore, hyperglycemia-driven activation of the polyol and hexosamine pathways amplifies oxidative stress and induces osmotic imbalance, leading to neuronal swelling and degeneration. The resultant oxidative burden triggers apoptosis and disrupts neuroplasticity in critical cognitive regions such as the hippocampus and prefrontal cortex [5].

Neuroinflammation constitutes another major pathogenic driver in diabetic brain injury. Chronic hyperglycemia activates microglia and astrocytes, transforming them from neurotrophic to proinflammatory phenotypes. Activated glial cells release cytokines, including interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), which activate NF-κB and JAK/STAT signaling cascades. These pathways promote oxidative stress, neuronal apoptosis, and synaptic dysfunction. Advanced glycation end products (AGEs), generated by persistent hyperglycemia, interact

with their receptor (RAGE) on neurons and endothelial cells, further amplifying inflammatory signaling. This vicious cycle of oxidative and inflammatory stress results in neuronal loss, particularly within brain regions involved in learning and memory [6].

Mitochondrial dysfunction is central to the pathogenesis of diabetic neurodegeneration. Excess intracellular glucose flux alters the mitochondrial electron transport chain, leading to excessive superoxide generation and impaired ATP production. Damaged mitochondria release cytochrome c and other pro-apoptotic proteins into the cytosol, initiating intrinsic apoptotic cascades through caspase-9 activation. Moreover, hyperglycemia impairs mitochondrial biogenesis by suppressing peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), leading to defective energy metabolism and neuronal vulnerability. Mitochondrial membrane potential depolarization and altered dynamics of fission and fusion exacerbate neuronal death, highlighting mitochondria as both a target and mediator of diabetic brain injury [7].

Vascular dysfunction significantly contributes to neural damage in diabetes by disrupting cerebral perfusion and nutrient delivery. Endothelial injury reduces nitric oxide (NO) bioavailability due to uncoupling of endothelial nitric oxide synthase (eNOS), leading to vasoconstriction and microvascular rarefaction. Concomitantly, increased endothelin-1 production promotes vascular stiffness and impairs autoregulation of cerebral blood flow. These alterations compromise the blood–brain barrier (BBB), allowing influx of inflammatory mediators and immune cells that exacerbate neuroinflammation. Consequently, neuronal energy metabolism becomes impaired, leading to chronic ischemic and hypoxic insults that accelerate neuronal degeneration [8].

Insulin signaling dysregulation within the brain further compounds diabetic neurodegeneration. Insulin acts as a neurotrophic factor, modulating neuronal growth, synaptic plasticity, and neurotransmitter release. In insulin-resistant states, decreased insulin receptor activity in neurons attenuates downstream PI3K/Akt signaling, resulting in reduced glucose uptake, impaired synaptic transmission, and increased susceptibility to oxidative and apoptotic stress. This condition—often termed “type 3 diabetes”—links systemic insulin resistance with neurodegenerative processes akin to those in Alzheimer’s disease. The combined effects of oxidative stress, mitochondrial impairment, neuroinflammation, and vascular injury form the pathological basis for exploring agents such as dapagliflozin that could intervene at multiple mechanistic levels [9].

Sodium–Glucose Cotransporter-2 (SGLT-2) Inhibitors: Overview

SGLT-2 inhibitors are a class of oral antidiabetic drugs that lower blood glucose by blocking renal tubular reabsorption of glucose, thus promoting glycosuria. Their mechanism is independent of insulin secretion or action, offering therapeutic benefit even in insulin-resistant states. Clinical outcome trials, including EMPA-REG OUTCOME and DECLARE-TIMI 58, demonstrated significant cardiovascular and renal benefits, prompting interest in their pleiotropic properties. The reduction in cardiovascular mortality and slowing of renal decline observed with SGLT-2 inhibition suggest systemic effects that extend beyond glycemic control, potentially encompassing neuroprotective actions as well [10].

The pleiotropic benefits of SGLT-2 inhibitors stem from multiple mechanisms including reduction of systemic inflammation, oxidative stress, and blood pressure. By promoting mild ketogenesis, these agents shift cellular metabolism from glucose to ketone utilization, a process that enhances mitochondrial efficiency and reduces ROS generation. Ketone bodies, particularly β-hydroxybutyrate, serve as efficient energy substrates for neurons and have been shown to activate anti-oxidative transcription factors such as Nrf2. Therefore, the metabolic reprogramming induced by SGLT-2 inhibition may provide neurons with a more stable and energy-efficient environment, offering protection against diabetes-induced metabolic stress [11].

Although SGLT-2 expression is largely restricted to renal tissue, indirect CNS benefits of these inhibitors are increasingly recognized. Improved endothelial function, reduced systemic cytokine levels, and attenuation of oxidative stress collectively enhance cerebral perfusion and blood–brain barrier integrity. Furthermore, preclinical studies suggest that some SGLT-2 inhibitors might exert partial

SGLT-1 inhibition, which is expressed in the brain and may influence neuronal glucose transport. These systemic and possibly central actions together create a neuroprotective milieu that may mitigate the structural and functional brain changes seen in diabetes [12].

Dapagliflozin: Pharmacological Profile

Dapagliflozin is a highly selective SGLT-2 inhibitor with an inhibitory constant (IC50) around 1 nM, making it one of the most potent agents in its class. It demonstrates excellent oral bioavailability and a terminal half-life of 12–13 hours, allowing once-daily administration. The drug undergoes extensive hepatic metabolism via UDP-glucuronosyltransferase (UGT1A9) and is primarily excreted through the kidneys. Dapagliflozin's pharmacological profile provides stable glucose-lowering efficacy across different populations with low risk of hypoglycemia and favorable tolerability, features that enhance its suitability for chronic use in diabetic patients [13].

Beyond glucose regulation, dapagliflozin exerts notable anti-inflammatory and antioxidant effects. Studies have reported significant reductions in plasma levels of TNF-α, IL-6, and high-sensitivity C-reactive protein following chronic administration. Additionally, markers of oxidative stress such as malondialdehyde (MDA) and 8-hydroxy-2′-deoxyguanosine (8-OHdG) decrease, while antioxidant enzyme activities—including catalase and glutathione peroxidase—are enhanced. These effects are associated with reduced NF-κB activation and improved mitochondrial respiration. The convergence of these systemic actions suggests that dapagliflozin may indirectly mitigate neuronal oxidative injury, aligning with the pathophysiological targets relevant to diabetic neurodegeneration [14].

Mechanistic Insights into Neuroprotection by Dapagliflozin

Dapagliflozin's neuroprotective properties are believed to arise from its ability to modulate oxidative stress and inflammation, two key drivers of neuronal damage in diabetes. Experimental data suggest that dapagliflozin activates the nuclear factor erythroid 2–related factor 2 (Nrf2) signaling pathway, a major regulator of antioxidant gene expression. Activation of Nrf2 enhances transcription of antioxidant enzymes such as heme oxygenase-1 (HO-1), superoxide dismutase (SOD), and glutathione peroxidase (GPx), restoring redox balance within neurons. Concurrently, dapagliflozin suppresses NADPH oxidase activity and decreases mitochondrial ROS production, thereby preventing oxidative damage to neuronal membranes and mitochondria. Through these mechanisms, the drug enhances neuronal survival and maintains synaptic integrity in the diabetic brain [15].

Another critical mechanism underlying dapagliflozin's neuroprotective effects involves the attenuation of neuroinflammation. By inhibiting NF-κB translocation and downregulating Toll-like receptor-4 (TLR4) signaling, dapagliflozin suppresses the release of proinflammatory cytokines from activated glial cells. The drug also decreases expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), leading to reduced nitric oxide and prostaglandin-mediated neuronal toxicity. These anti-inflammatory effects may not only protect neuronal cells directly but also preserve blood–brain barrier integrity by preventing cytokine-induced endothelial damage. Collectively, the suppression of neuroinflammatory cascades contributes to a more stable neural microenvironment resistant to hyperglycemia-induced injury [16].

Mitochondrial protection is another crucial dimension of dapagliflozin's proposed neuroprotective mechanism. The drug improves mitochondrial biogenesis through upregulation of PGC-1α and sirtuin-1 (SIRT1), both of which play vital roles in maintaining mitochondrial health and energy production. By enhancing mitochondrial membrane potential and promoting oxidative phosphorylation efficiency, dapagliflozin helps prevent ATP depletion and neuronal energy failure. Additionally, evidence from animal models suggests that dapagliflozin reduces mitochondrial swelling and cytochrome c release, thereby inhibiting intrinsic apoptotic pathways. This mitochondrial stabilization may underlie its ability to preserve neuronal viability under metabolic stress conditions typical of diabetes [17].

Autophagy modulation has also been implicated in the neuroprotective actions of dapagliflozin. Autophagy, a cellular process essential for degrading damaged proteins and organelles, becomes dysregulated in diabetes. Dapagliflozin restores autophagic flux by modulating AMP-activated protein

kinase (AMPK) and mammalian target of rapamycin (mTOR) pathways. Activation of AMPK and inhibition of mTOR enhance cellular resilience by promoting clearance of dysfunctional mitochondria and toxic protein aggregates. This process not only sustains neuronal homeostasis but also limits neuroinflammation, highlighting dapagliflozin's potential to restore multiple metabolic pathways simultaneously [18].

Another emerging mechanism involves the preservation of blood–brain barrier (BBB) integrity. Hyperglycemia disrupts BBB function by increasing endothelial permeability and tight-junction protein degradation. Dapagliflozin has been reported to upregulate tight junction proteins such as occludin and claudin-5 while decreasing matrix metalloproteinase-9 (MMP-9) expression, thereby maintaining BBB stability. Improved endothelial function and reduced vascular leakage prevent neuroinflammation and secondary neuronal injury. Together, these mechanisms indicate that dapagliflozin provides multi-layered neuroprotection that addresses both neuronal and vascular aspects of diabetic neuropathology [19].

Evidence from Preclinical Studies

Preclinical studies have provided compelling evidence for dapagliflozin's neuroprotective potential in diabetic and ischemic models. In streptozotocin-induced diabetic rats, dapagliflozin treatment significantly improved learning and memory performance in the Morris water maze test while reducing oxidative stress markers in hippocampal tissue. Histological analyses revealed preservation of neuronal density and decreased glial activation compared to untreated diabetic controls. Additionally, treatment restored antioxidant enzyme levels and decreased expression of apoptotic proteins such as Bax and caspase-3, suggesting a robust anti-apoptotic effect within the CNS [20].

Further investigations demonstrated that dapagliflozin reduces microglial activation and astrocyte hypertrophy in the hippocampus, accompanied by lower expression of inflammatory mediators including TNF-α and IL-1β. These findings indicate suppression of neuroinflammatory cascades that contribute to neurodegeneration. Importantly, in rodent models of cerebral ischemia, dapagliflozin administration reduced infarct size and improved neurological outcomes, implicating improved mitochondrial function and oxidative resilience as key contributors. Such results support the hypothesis that dapagliflozin's benefits extend beyond glucose control to confer direct neuroprotection under pathological conditions involving oxidative and inflammatory stress [21].

Evidence from Clinical and Translational Studies

While direct clinical evidence remains limited, growing translational research supports potential cognitive benefits of SGLT-2 inhibitors in humans. Observational studies have shown that diabetic patients receiving SGLT-2 inhibitors display better cognitive performance compared with those on traditional oral antidiabetic agents. Although these associations are preliminary, they suggest improved cerebral metabolism or reduced neuroinflammation as possible underlying mechanisms. Moreover, analysis of cardiovascular outcome trials revealed secondary benefits such as reduced incidence of stroke and transient ischemic attacks, indicating possible cerebrovascular protection [22].

Neuroimaging studies are beginning to explore the effects of SGLT-2 inhibitors on brain metabolism and structure. Early functional MRI and PET imaging results suggest that SGLT-2 inhibition may improve cerebral perfusion and glucose utilization in regions associated with memory and executive function. Additionally, reduced systemic inflammation and oxidative stress biomarkers have been correlated with improved cognitive trajectories in elderly diabetic cohorts treated with these agents. These findings underscore the translational potential of dapagliflozin and its class as modulators of brain metabolism and vascular health [23].

Comparative Evaluation with Other SGLT-2 Inhibitors

Among SGLT-2 inhibitors, dapagliflozin shares mechanistic similarities with empagliflozin and canagliflozin but exhibits subtle pharmacodynamic distinctions that may influence neuroprotective potential. Empagliflozin has demonstrated significant anti-inflammatory and antioxidative effects in both animal and human studies, yet dapagliflozin appears to exert stronger effects on mitochondrial

biogenesis and endothelial function. Canagliflozin, on the other hand, possesses partial SGLT-1 inhibition, which could directly affect neuronal glucose transport but may also increase the risk of adverse gastrointestinal effects. Comparative experimental studies suggest that dapagliflozin's balance of efficacy and safety, combined with potent anti-oxidative effects, may render it particularly advantageous for long-term neuroprotective therapy [24].

9. Potential Molecular Targets and Pathways

The pleiotropic actions of dapagliflozin involve multiple signaling networks that converge on neuroprotection. Activation of Nrf2 enhances the antioxidant response, while AMPK and SIRT1 modulate energy metabolism and mitochondrial quality control. Concurrent inhibition of NF-κB signaling dampens neuroinflammatory cascades, and normalization of endothelial function preserves neurovascular coupling. Recent evidence also implicates modulation of microglial polarization from proinflammatory M1 to anti-inflammatory M2 phenotypes as an additional protective mechanism. Through these pathways, dapagliflozin exerts system-level effects that synchronize metabolic, vascular, and neuronal homeostasis in the diabetic brain [25].

Future Directions and Conclusion

Despite compelling preclinical data, the clinical translation of dapagliflozin's neuroprotective potential remains incomplete. Key research gaps include the lack of randomized controlled trials specifically evaluating cognitive and neurobiological outcomes, limited understanding of its penetration across the blood–brain barrier, and uncertainty regarding long-term neural safety. Future studies should employ multimodal approaches combining neuroimaging, cognitive testing, and biomarker profiling to elucidate the full spectrum of dapagliflozin's CNS actions. Moreover, exploration of synergistic effects with other agents such as GLP-1 receptor agonists or antioxidants may reveal additive neuroprotective benefits [26].

In conclusion, dapagliflozin represents a promising pharmacological candidate with multifaceted mechanisms that address the metabolic, oxidative, and inflammatory components of diabetes-related neurodegeneration. By improving mitochondrial health, reducing neuroinflammation, and preserving vascular integrity, this SGLT-2 inhibitor transcends its original glycemic role to emerge as a potential neurotherapeutic agent. While current evidence is encouraging, rigorous clinical validation is essential before dapagliflozin can be firmly positioned within the therapeutic arsenal for diabetic neurodegeneration [27].

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