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Potential Effects Of Sglt-2 Inhibitors on Parkinson Disease

Sglt-2 İnhibitörlerinin Parkinson Hastalığı Üzerindeki Potansiyel Etkileri

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ÖZET

Parkinson hastalığı (PD), hem merkezi hem de periferik sinir sistemlerini etkileyen ilerleyici bir nörodejeneratif bozukluktur. Substansiya nigradaki dopaminerjik nöronların kaybı ile karakterize edilir ve striatumdaki dopamin seviyelerinde önemli bir düşüşe neden olur. Bu arada, tip 2 diabetes mellitus (T2DM) genel sağlık için ciddi bir tehdit oluşturmaktadır. T2DM'nin patofizyolojisinin önemli bir yönü, artan oksidatif stresi içerir. Kanıtlar, T2DM'li bireylerin PD geliştirme riskinin yüksek olabileceğini düşündürmektedir. Oksidatif stres ve enflamasyon gibi altta yatan ortak mekanizmalar, her iki durumun da gelişmesine katkıda bulunabilir. T2DM'yi yönetmek için onaylanan SGLT-2 inhibitörleri olarak bilinen ilaçlar, böbreklerde glikoz geri emilimini engelleyerek kan şekerini düşürür. Glikoz düşürücü etkilerinin ötesinde, bu ilaçların enflamasyonu azalttığı, mitokondriyal sağlığı koruduğu ve reaktif oksijen türlerinin üretimini azalttığı bilinmektedir. Bu özellikleri nedeniyle SGLT-2 inhibitörleri, PD dahil olmak üzere nörodejeneratif hastalıklardaki potansiyel faydaları açısından araştırılmaktadır. Örneğin empagliflozin, Parkinson hastalığının fare modellerinde motor fonksiyonları iyileştirme, nöroinflamasyonu azaltma ve nöroplastisiteyi teşvik etme yeteneğini göstermiştir. Bununla birlikte, mevcut araştırma sınırlıdır ve genellikle metodolojik olarak kusurludur, bu da bu bulguları doğrulamak için daha büyük, daha titiz çalışmalara duyulan ihtiyacı vurgulamaktadır. Bu derleme, T2DM ve PH arasındaki ilişkiyi araştırmayı, mevcut literatürü özetlemeyi ve SGLT-2 inhibitörlerinin PH ilerlemesi üzerindeki potansiyel etkisini değerlendirmeyi amaçlamaktadır. Ancak literatürdeki bilgiler kısıtlı olduğundan dolayı bu konu ile ilgili daha fazla çalışmaya ihtiyaç vardır. Gelecekteki araştırmalar yeni terapötik yaklaşımların önünü açabilir ve bu ilaçların nörodejeneratif süreçleri nasıl etkileyebileceğine dair anlayışımızı derinleştirebilir.

Anahtar kelimeler: Parkinson hastalığı, Diabetus Mellitus, SGLT-2 inhibitörü, nöroinflamasyon

ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder that impacts both the peripheral and central nervous systems. It is characterized by the deficit of dopaminergic neurons in the substantia nigra, resulting in a significant decline in dopamine levels within the striatum. Meanwhile, type 2 diabetes mellitus (T2DM) poses a serious threat to overall health. A key aspect of T2DM's pathophysiology involves increased oxidative stress. Evidence suggests that individuals with T2DM may have a heightened risk of developing PD. Shared underlying mechanisms, such as oxidative stress and inflammation, could contribute to the development of both conditions. Medications known as SGLT-2 inhibitors, which are approved for managing T2DM, reduce blood sugar by blocking glucose reabsorption in the kidneys. Beyond their glucose-lowering effects, these drugs are known to decrease inflammation, maintain mitochondrial health, and reduce the production of reactive oxygen species. Due to these properties, SGLT-2 inhibitors are being explored for their potential benefits in neurodegenerative diseases, including PD. For example, empagliflozin has demonstrated the ability to improve motor functions, lower neuroinflammation, and promote neuroplasticity in mouse models of Parkinson's disease. However, current research is limited and often methodologically flawed, highlighting the need for larger, more rigorous studies to confirm these findings. This review aims to explore the relationship between T2DM and PD, summarize the existing literature, and evaluate the potential impact of SGLT-2i on PD progression. However, due to the limited information available in the literature, further research on this topic is needed. Future investigations could pave the way for new therapeutic approaches and deepen our understanding of how these drugs might influence neurodegenerative processes.

Keywords: Parkinson's Disease, Diabetus Mellitus, SGLT-2 Inhibitor, neuroinflammation

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INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting both the central and peripheral nervous systems. It is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra, leading to a marked reduction of dopamine levels in the striatum (1). While research has traditionally focused on the basal ganglia's role in PD, emerging evidence suggests that the loss of Purkinje cells in the cerebellum, which regulate movement via GABAergic signaling, may also contribute to motor and cognitive deficits (2, 3). Globally, PD affects about 1% of individuals over 60 and up to 5% of those over 85 years old (4). A hallmark pathological feature of Parkinson's disease (PD) is the accumulation of misfolded alpha-synuclein (α-syn) proteins, which aggregate to form intracellular inclusions known as Lewy bodies. These aggregates disrupt normal cellular homeostasis, impair proteasomal and lysosomal degradation pathways, and contribute to mitochondrial dysfunction and oxidative stress. As a result, the progressive accumulation of Lewy bodies leads to neuronal dysfunction and death, particularly within dopaminergic neurons of the substantia nigra, thereby driving the characteristic motor and non-motor symptoms of PD (5). Mutations in genes such as Parkin and DJ-1 also contribute to PD development. Parkin mutations disrupt mitochondrial function, whereas DJ-1 mutations impair antioxidant defense mechanisms (6). Oxidative stress is considered a major driver of PD pathology (7), with elevated levels of oxidative damage to proteins, lipids, and DNA observed in the substantia nigra of PD patients (8). Dopaminergic neurons are especially vulnerable due to the activity of ROS-generating enzymes, including tyrosine hydroxylase (TH) and monoamine oxidase (MAO) (7, 9). Neuroinflammation further contributes to PD progression, mainly through microglial activation and the release of proinflammatory cytokines (10). In addition, insulin resistance has been implicated in accelerating PD pathology (11). Recent hypotheses propose that DOPAL, a toxic dopamine metabolite produced via MAO, may promote α-synuclein aggregation and Lewy body formation (10).

Type 2 Diabetes Mellitus (T2DM) is another major global health concern, affecting 9.3% of the world's population in 2019. It is associated with microvascular and macrovascular complications such as cardiovascular disease, nephropathy, and retinopathy (12). Oxidative stress plays a central role in T2DM pathogenesis, where hyperglycemia promotes ROS production and chronic inflammation, leading to endothelial dysfunction. Conversely, elevated oxidative stress and inflammation can worsen insulin resistance and glycemic control. Several enzymatic pathways including xanthine oxidase, NADPH oxidases, eNOS, and AGEs

contribute to oxidative stress and systemic complications in T2DM (13-16). Effective management of oxidative stress and hyperglycemia through lifestyle changes and pharmacological treatments (such as statins, antihypertensives, probiotics, antiplatelet therapies, and antidiabetic drugs) is crucial for preventing disease progression (13, 17-19).

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors represent a newer class of antidiabetic drugs that lower blood glucose by inhibiting renal glucose reabsorption. Agents such as empagliflozin, dapagliflozin, canagliflozin, and others have been approved by regulatory agencies including the FDA (20, 21). Beyond glycemic control, SGLT-2 inhibitors show potential neuroprotective effects, including anti-inflammatory actions, preservation of mitochondrial function, and reduction of oxidative stress, suggesting possible benefits for neurodegenerative diseases (21, 22). Although preclinical data are limited, studies with empagliflozin in a rotenone-induced mouse model of PD demonstrated improved motor function, reduced neuroinflammation, enhanced neuroplasticity, dopaminergic neuron preservation, and increased autophagy (23, 24). Epidemiological studies also suggest that T2DM may increase the risk of developing PD (25), potentially due to shared pathological mechanisms such as inflammation and oxidative stress (26).

Experimental research indicates that insulin modulates dopaminergic neuron function, whereas chronic hyperglycemia impairs it (27). T2DM may also contribute to tau pathology (28) and cognitive decline in elderly populations (29). Between 8% and 30% of PD patients develop diabetes, and 50% to 80% exhibit insulin resistance (30-37). Diabetes appears to influence the clinical course of PD, being associated with more severe gait disturbances (38-40) and faster cognitive decline (40, 41) (table.1).

Table.1. Epidemiological evidence linking T2DM to PD

Study / Year	Study Type	Sample Size	PD Risk in T2DM (HR/OR)	95% CI
Xu et al., 2011(42)	Prospective cohort	2,017,115	1.32	1.18 – 1.48
De Pablo-Fernández et al., 2018 (43)	Systematic review & meta-analysis	7 studies	1.38	1.18 – 1.62
Cereda et al., 2011 (44)	Meta-analysis	8 studies	1.37	1.21 – 1.55
Sun et al., 2012 (45)	Cohort study	51,552	1.36	1.04 – 1.77
Schernhammer et al., 2011 (46)	Prospective cohort	288,662	1.32	1.08 – 1.62

Abbreviations: HR: Hazard Ratio, OR: Odds Ratio, CI: Confidence Interval

This compilation study examined studies published in the PubMed, Scopus, and Web of Science databases. The keywords were determined as “SGLT-2 inhibitors,” “Parkinson's disease,” “oxidative stress,” and “neuroinflammation.”

Effects of SGLT-2 Inhibitors on Parkinson's Disease

Most SGLT-2 inhibitors are lipid-soluble, enabling them to effectively cross the blood-brain barrier (BBB) (47). Empagliflozin has been shown to alleviate cognitive deficits in mice by reducing cerebral oxidative stress, decreasing the expression of NADPH oxidase subunits (gp91), enhancing BDNF levels, and minimizing albuminuria and glomerular injury mechanisms that may underlie its neuroprotective effects (48-50). However, studies investigating the impact of SGLT-2 inhibitors in PD models remain limited. Notably, empagliflozin was reported to attenuate neurodegeneration in a rotenone-induced PD rat model by modulating α-synuclein and PARK2 expression, as well as by exerting antioxidant and anti-inflammatory effects (51). Additionally, empagliflozin improved locomotor function, reduced α-synuclein accumulation, alleviated oxidative stress and inflammation, and activated the AMPK/SIRT-1/PGC-1α and Wnt/β-catenin signaling pathways in this model (52). Similarly, dapagliflozin was found to significantly ameliorate motor deficits and neuronal damage through the ROS-dependent AKT/GSK-3β/NF-κB and DJ-1/Nrf2 pathways in another rotenone-induced PD rat model (53). A limited number of case reports also suggest that treatment with

SGLT-2 inhibitors in PD patients may improve metabolic profiles and overall health outcomes (21, 54) (Table 2).

Glucose serves as the brain's primary energy source and is essential for maintaining normal neuronal function (55). After crossing the BBB, glucose is transported into neurons and glial cells via specific carrier proteins. Two main types of glucose transporters are involved: sodium-dependent glucose transporters (SGLTs) and facilitated diffusion glucose transporters (GLUTs) (56). Neurons predominantly express GLUT3, whereas glial cells and the endothelial cells of the BBB primarily express GLUT1 (57).

SGLT transporters were originally identified in the kidney and small intestine (58, 59). However, recent research has demonstrated that these transporters are also expressed in several regions of the brain, including the frontal cortex, hippocampus, caudate nucleus, putamen, parietal cortex, and the paraventricular nucleus of the hypothalamus, though their presence is less prominent in the brainstem (60). The partial lipid solubility of SGLT-2 inhibitors, their ability to cross the blood–brain barrier, and the confirmed presence of SGLT-2 in the brain have increased interest in their potential use for treating neurological disorders (61-63). (Figure 1).

Table.2. Effects of SGLT-2 inhibitors in Parkinson's disease (54)

Medicine	Mechanism of action	Effect on the PD model	Clinical evidence in PD
SGLT-2 inhibitors	reduces the kidneys' reabsorption of glucose	• reduces neurodegeneration in Parkinson's disease caused by rotenone • Promotes more locomotor activity • Reduces the buildup of α-syn • Wnt/β-catenin and AMPK/SIRT-1/PGC-1α pathways are activated • Decreases neuronal damage via pathways dependent on ROS	Potential advantages, such as neuroprotective effects, are suggested by several observational studies

Oxidative stress and inflammatory processes are closely interconnected. In a rat model of isoprenaline-induced renal oxidative injury, treatment with canagliflozin inhibited the expression of iNOS and NOX4, activated antioxidant and anti-inflammatory pathways such as AMPK, AKT, and eNOS, and subsequently reduced oxidative damage while restoring depleted antioxidant reserves (64). Given that the redox state reflects a delicate and dynamic balance between oxidative and antioxidative forces, numerous studies have concurrently examined both systems. For example, in streptozotocin-induced diabetic mice, SGLT-2 inhibition using phlorizin reduced the levels of nitrogen-derived free radicals, particularly 3-nitrotyrosine (3-NT), while also restoring the activity of key antioxidant enzymes, such as glutathione peroxidase (GPx) and catalase (CAT), in the kidney (65).

Furthermore, evidence suggests that SGLT-2 inhibition can restore manganese/copper/zinc-dependent superoxide dismutases and catalase activity in diabetic animal kidney tissues, contributing to reduced oxidative stress (66, 67). Overall, these findings suggest that SGLT-2 inhibitors have antioxidant and anti-inflammatory effects, especially in the kidneys. In human proximal tubular cells under high-glucose conditions, tofogliflozin reduced oxidative stress, lowered MCP-1 levels, and prevented cell death (68). Similarly, in cultured mouse renal proximal tubular cells, dapagliflozin reduced the expression of genes linked to oxidative stress and inflammatory cytokines, highlighting its role in alleviating hyperglycemia-induced inflammation and oxidative stress in diabetic nephropathy (69). Additionally, canagliflozin was found to inhibit glucose-induced excessive ROS production in cultured mouse mesangial cells by blocking the protein kinase C/NADPH oxidase signaling pathway (70).

Oxidative stress occurs when a biological system fails to maintain redox homeostasis, leading to an imbalance between the production and clearance of reactive oxygen species (ROS). A significant association exists between oxidative stress and the pathophysiology of PD, with oxidative damage contributing to the degeneration of dopaminergic neurons and the progression of neurodegeneration, where pathological mechanisms such as alpha-synuclein aggregation, neuroinflammation, mitochondrial dysfunction, and abnormal dopamine metabolism contribute to heightened oxidative damage (71). Consequently, targeting oxidative stress-related signaling pathways could offer therapeutic potential for managing PD (72). Given the established association between oxidative stress and PD, it is plausible that SGLT-2 inhibitors may exert indirect neuroprotective effects in the context of Parkinson’s disease.

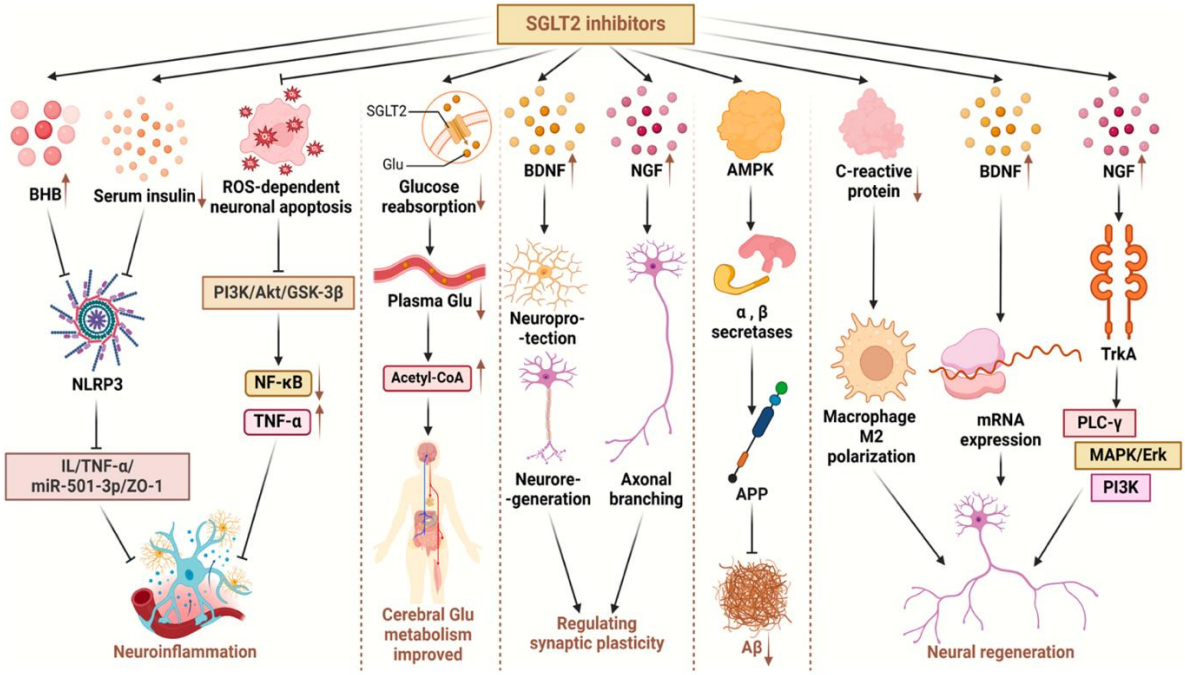

Figure 1. ways that SGLT-2 inhibitors regulate the survival of neurons

1. SGLT-2 inhibitors reduce the activation of the NLRP3 inflammasome in macrophages by increasing serum levels of β-hydroxybutyrate (BHB) and lowering circulating insulin levels. This results in the downregulation of the NLRP3/IL-1/TNF-α/miR-501-3p/ZO-1 signaling axis. Additionally, SGLT-2 inhibitors suppress the PI3K/Akt/GSK-3β pathway, prevent ROS-induced neuronal cell death, and inhibit the activation of the NF-κB and TNF-α pathways, thereby effectively mitigating neuroinflammation 2. The primary mechanism of action of SGLT-2 inhibitors involves targeting SGLT-2 transporters in the renal proximal tubules, promoting urinary glucose excretion and reducing glucose reabsorption. This metabolic shift enhances cerebral glucose metabolism by favoring a transition from carbohydrate utilization to fatty acid oxidation in the brain 3. SGLT-2 inhibitors enhance synaptic plasticity by increasing the expression of neurotrophic factors such as BDNF and NGF 4. By activating adenosine monophosphate-activated protein kinase (AMPK) through liver kinase B1 (LKB1) and modulating the expression of α- and β-secretases, SGLT-2 inhibitors effectively reduce the production of amyloid-beta (Aβ) from amyloid precursor protein (APP), thereby potentially mitigating the accumulation of amyloid plaques associated with neurodegenerative diseases. 5. SGLT-2 inhibitors promote the polarization of macrophages towards the M2 phenotype, which plays a key role in supporting nerve regeneration. These inhibitors also significantly elevate tissue levels of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF).

BDNF enhances mRNA expression, thereby increasing the intrinsic regenerative capacity of neurons, while NGF binds to the pro-myosin receptor kinase A (TrkA), triggering a cascade of biochemical pathways that promote neural repair and regeneration (63).

CONCLUSION AND DISCUSSION

SGLT-2 inhibitors, originally developed for the management of T2DM, have recently attracted attention for their potential neuroprotective effects in neurodegenerative diseases such as PD. Preclinical studies have demonstrated that these agents can improve cerebral glucose metabolism, enhance neuronal plasticity, and reduce oxidative stress and neuroinflammation processes central to PD pathogenesis (47, 52). In addition, their ability to modulate mitochondrial function and attenuate microglial activation may contribute to slowing disease progression (73). Despite these promising findings, the current body of literature is both limited and, in certain aspects, contradictory. While some studies report significant neuroprotective effects (54), others have found minimal benefit or raised concerns about potential off-target actions that could diminish their therapeutic value (74).

These inconsistencies may result from heterogeneity in experimental models, dosing regimens, treatment durations, and study populations, underlining the need for standardized and reproducible research protocols. Given the pharmacodynamic overlap between the mechanisms of SGLT-2 inhibitors and the pathophysiological processes underlying PD such as impaired energy metabolism, oxidative stress, and chronic inflammation repurposing these agents as neuroprotective drugs represents a compelling research avenue. Future studies should aim to address current evidence gaps through well-designed longitudinal animal models and large-scale randomized clinical trials. As a result, SGLT-2 inhibitors are considered one of the promising therapeutic options of the future not only in the treatment of diabetes but also in the management of neurodegenerative diseases.

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