Cognitive benefits of sodium-glucose cotransporters-2 inhibitors in the diabetic milieu

Running Title: SGLT2i and Cognition

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Abstract

Patients with diabetes are at higher risk of cognitive impairment and memory loss than the normal population. Thus, using hypoglycemic agents to improve brain function is of importance in these people. Sodium-glucose cotransporters-2 inhibitors (SGLT2i) are a class of therapeutic agents used in the management of diabetes that has some pharmacologic effects enabling them to fight against the onset and progress of memory deficits. Although the exact mediating pathways are not well understood, emerging evidence suggests that SGLT2 inhibition is associated with improved brain function. This study reviewed the possible mechanisms and provided evidence suggesting SGLT2 inhibitors could ameliorate cognitive deficits.

Keywords: diabetes mellitus, Sodium-glucose cotransporters-2 inhibitors, oxidative stress, apoptosis, cognition, memory.

Introduction

The global incidence of diabetes mellitus (DM) is rising rapidly [1]. This metabolic disorder is responsible for a wide variety of complications as well as neuronal problems and behavioural disorders [2, 3]. Epidemiological evidence has confirmed that uncontrolled DM is closely associated with different levels of neuropathies and behavioural complications [3, 4]. Patients with diabetes are at higher risk of cognitive deficits than the normal population [5-7]. On the other hand, different forms of cognitive disorders are a central issue of health in patients with diabetes with significant negative impacts on their quality of life, especially for older adults [8, 9]. These complications now have increasing trends in the Western countries and annually impose a significant economic impact on the health providing systems [10, 11]. Therefore, preventing or lowering the incidence of cognitive impairments are of major significance in patients with diabetes [2].

Sodium-glucose cotransporters-2 inhibitors (SGLT2i) are a new class of hypoglycemic drugs that reduce blood glucose by inhibiting filtrated glucose reabsorption and glucose excretion [12, 13]. These potent anti-diabetic agents lower blood glucose via several mechanisms dependent on the glycosuria [14]. But recent evidence suggested further benefits for SGLT2i in physiologic systems and neuronal networks [15-17]. They may reduce the risk of neuropathies and prevent cognitive impairments through not so well defined pathways [17]. In the current study, we present the possible cognitive benefits of SGLT2 inhibitors and the potential mechanisms behind this.

Classifications of Diabetes Mellitus

The common types of diabetes are type 1 diabetes, type 2 diabetes and gestational diabetes [18]. Type 1 DM (T1DM) mainly refers to lower circulatory insulin due to beta cells dysfunction [18]. Type 2 DM (T2DM) is the most prevalent form of DM, primarily related to insulin resistance in peripheral tissues [18]. Gestational diabetes is another form of DM which occurs in pregnant women due to insulin resistance contributed by pregnancy in high-risk women [19]. Moreover, there are other forms of DM with lower frequency such as LADA (Latent Autoimmune Diabetes in Adults), Maturity-Onset Diabetes of the Young (MODY), secondary diabetes to different conditions such as pancreatitis and secondary diabetes due to medications such as corticosteroids [20, 21].

Cognitive performances in diabetic patients

Patients with uncontrolled DM usually show different levels of cognitive impairment and memory loss, such as Alzheimer's disease (AD), Parkinson's disease (PD), and dementia [6, 7]. Increased neuronal death and brain atrophy due to a higher occurrence of pathologic events such as apoptosis and necrosis is the principal hallmark in brain MRI of patients with uncontrolled diabetes [22, 23]. Multiple pathophysiologic mechanisms induced by DM and related dysfunctional metabolic pathways (e.g. hexosamine, polyol and lipid peroxidation pathways) create a toxic milieu around the neurons and ganglia involved in cognition and memory in central and peripheral nervous systems and so exert substantial negative impacts on physiologic functions of neuronal networks [22]. It has also been suggested that AD and DM

may have the shared pathophysiology of a distinct form of insulin resistance and impaired glucose tolerance in the brain and peripheral tissues [24]. Moreover, some recent reports have suggested similar pathophysiology for DM and PD [25]. Therefore, patients with diabetes are at an increased risk of cognitive complications and memory loss compared with the non-diabetic population [26, 27].

SGLT2 inhibitors

SGLT2 inhibitors are a newly introduced class of antidiabetic drugs that reduce plasma glucose by inhibiting tubular glucose reabsorption and inducing overt urinary glucose excretion [28, 29]. The sodium-glucose co-transporters are two types of active cotransporters (type 1 and 2) that are mainly located in S2 and S3 segments of proximal renal tubules (as well as in intestines), which reabsorb the most amount of filtrated glucose [13, 30]. They transport glucose, galactose and sodium ions against the concentration gradients (one sodium ion with one D-glucose) [31]. In addition, they are involved in gluconeogenesis, improvement of peripheral tissues insulin sensitivity, glucagon release, and insulin secretion [32-35]. Since discovering phlorizin, the first type of SGLT2 inhibitor, several forms of these agents have been introduced, which all reduce the blood glucose near the level of the capacity of nephrons for glucose reabsorption [36, 37]. SGLT2 inhibitors work entirely independent of insulin hormone (**Figure 1**), and their action is related to serum glucose level and, thereby, is accompanied by reduced risk of hypoglycemia [31]. However, using these drugs has some side effects such as dehydration, dizziness, hypotension, urinary tract infections, and fainting [38]. Canagliflozin, dapagliflozin, and empagliflozin are examples of the approved forms of SGLT2 inhibitors [38].

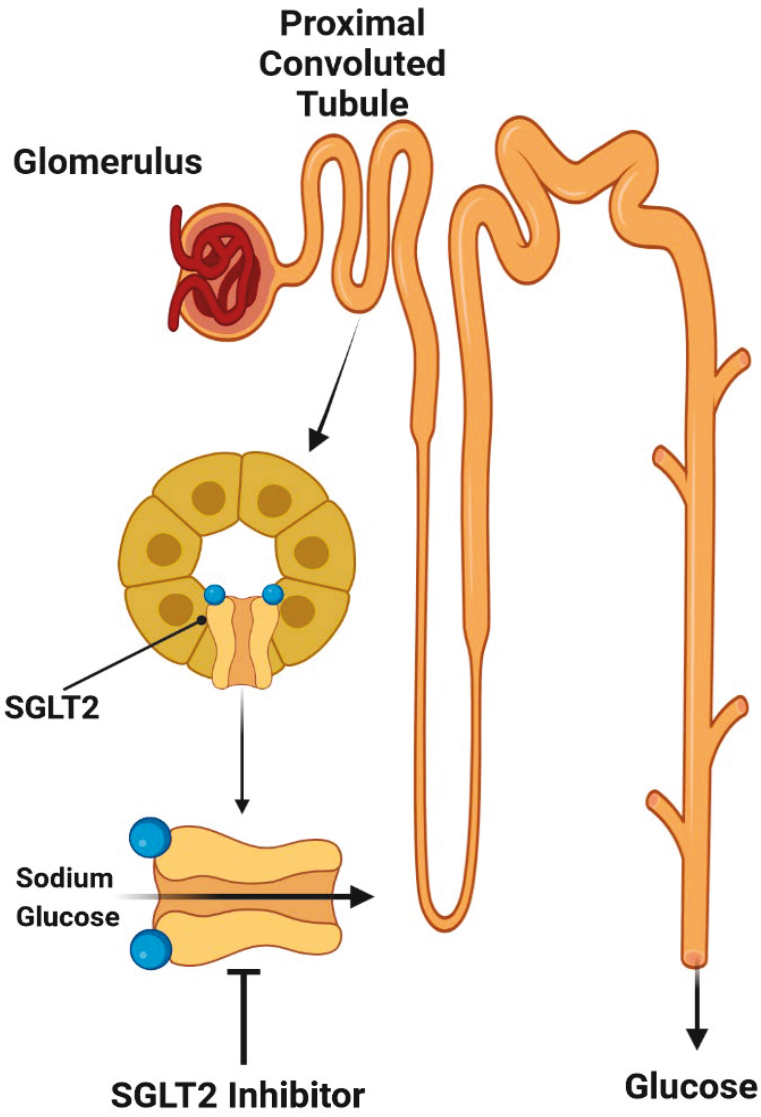

Figure 1; Schematic pic of SGLT2 activities and the effect of SGLT2 inhibitors to induce glycosuria

Central distribution of SGLT2

Recent evidence shows that SGLT2 receptors are expressed in different areas of the central nervous system (CNS) and play essential roles in glucose homeostasis in various neuronal networks [39]. They are distributed mainly in Purkinje cells of the cerebellum, hypothalamus (glial cells), hippocampus (granular and pyramidal cells), amygdala, periaqueductal grey, the nucleus of the solitary tract (NTS) as well as in brain microvessels (**Figure 2**) [39-41]. SGLT2is are lipid-soluble molecules that can cross the blood-brain barrier (BBB) to reach the target area in the CNS [42]. So, it is hypothesised that SGLT2 receptors are closely involved in metabolic pathways and glucose homeostasis in the CNS [38]. Also, they

may be involved in other brain-dependent pathways [39]. For example, dapagliflozin, an SGLT2i, has been shown to have anti-seizure activities in a murine model of PTZ[1]-induced epilepsy [43]. Another evidence reported that empagliflozin could reduce neuronal damages dependent on ischemia-reperfusion in rats [44]. It was also able to mitigate diabetes-induced structural abnormalities in endothelial cells, tight and adherens junctions, glia astrocytes, oligodendrocyte and microglia cells, as well as in mitochondria of brain tissues and so provide neuroprotective effects in mice model of T2DM [45]. In a clinical study, Oerter and colleagues in 2019 found the increased levels of SGLT2 receptors expression in the brain of patients with traumatic brain injury (TBI) after 37 h of trauma [46]. They concluded that the level of SGLT2 expression in the brain tissue is probably associated with the time of trauma and extent of injury in these patients [46]. Taken together, SGLT2 receptors have extensive distribution in the brain, suggesting their significant roles in neuronal homeostasis.

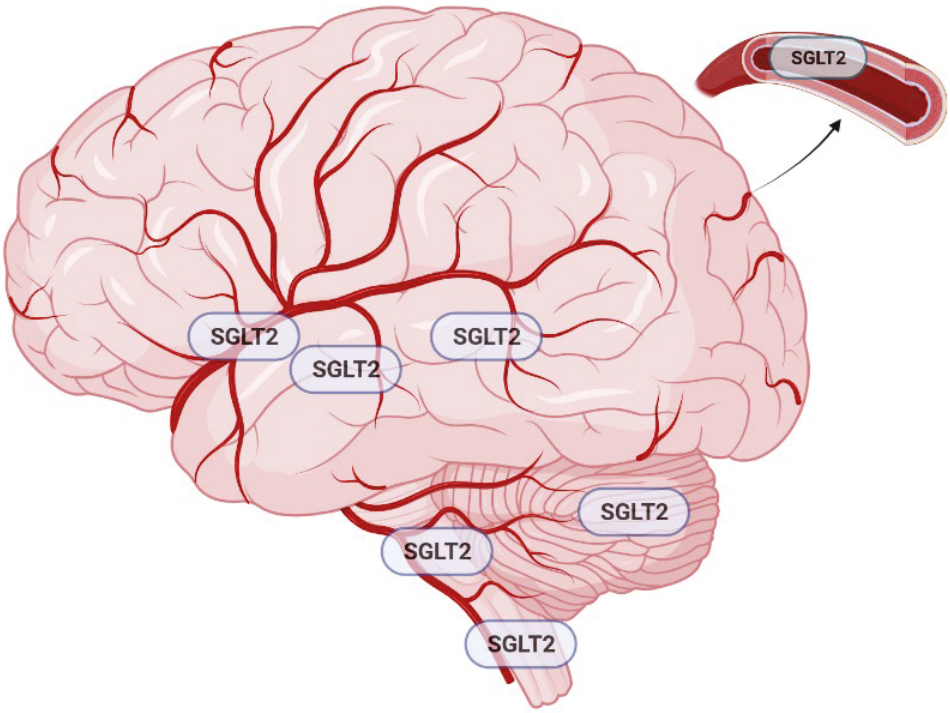

Fig 2; Central distribution of the SGLT2 receptors in cerebellum, hypothalamus, hippocampus, amygdala, periaqueductal grey, the nucleus of the solitary tract and brain microvessels

Possible cognitive benefits of SGLT2 inhibitors

SGLT2is provide additional therapeutic benefits by reducing the neurobehavioral comorbidities and improving cognitive functions in the diabetic milieu through ill-defined

[1] Pentylenetetrazol

pathways (**Figure 3**). The following sections discuss the possible involved mechanisms and cellular pathways (table 1).

1. Brain Insulin Signaling

An intact brain insulin signalling is critical for normal cognitive performances [47, 48]. In addition to metabolic roles, it is now confirmed that insulin plays essential functions as a neuromodulator, and it is involved in the cognition and memory [48]. Insulin is involved in many neuronal processes such as dendritic sprouting, cell growth and repair, and neuronal stem cell activation [49]. Also, it can provide neuroprotective effects via control of phosphorylated tau levels and proinflammatory cytokines, which are associated with the β-amyloid (Aβ) depositions in the brain [49, 50]. Evidence demonstrates that insulin receptors (IRs) are expressed in the brain area involved in memory and cognition, such as hippocampus [51, 52], amygdala [53, 54], olfactory bulb, neocortex, cerebellum and hypothalamus [55-57]. Also, their expression pattern is associated with behavioural activities and may be related to some cognitive disorders such as depressive moods [56]. Moreover, glucose transporters of Glut-4[2] are expressed in the cerebellum, neocortex, astrocytes and hippocampus, suggesting a role for insulin-dependent glucose uptake in neuronal activities [58]. Furthermore, other molecules in intracellular insulin signalling machinery such as Akt[3], PI3K[4], mTOR[5], GSK3-β[6], CREB[7] and FOXO[8] are present in neuronal tissues and play important roles in brain cognitive functions [57, 59-61].

Insulin elicits memory pathways and food memory in the hypothalamus [55, 56]. It has regulatory roles in hippocampal synaptic plasticity through several pathways such as NMDA[9] and PI3K dependent signalling [62]. Also, spatial memory training increases hippocampal insulin receptor expression where the insulin receptors have higher distributions than other brain area [51, 52]. Similarly, an experimental model of hippocampal insulin resistance was related to reduced synaptic plasticity and cognitive deficits in rats [63]. Moreover, genetic knockout of insulin receptors in CNS suppresses synaptic plasticity, diminishes cognitive capacities and impairs hippocampal memory [64]. These findings emphasise the role of insulin signalling in normal cognitive abilities.

Patients with diabetes have been shown to have impaired brain insulin signalling, which facilitates the development of cognitive deficits [47, 48]. But some recent evidence suggests that SGLT2 inhibition can reverse these changes [65]. In an animal model of obesity-induced brain insulin resistance, dapagliflozin provided neuroprotective and cognitive benefits via improving the brain insulin signalling, hippocampal synaptic plasticity and mitochondrial integrity [65]. Also, another experimental study demonstrated that empagliflozin ameliorates

[2] glucose transporters-4
[3] Protein kinase B
[4] phosphatidylinositol 3-kinase
[5] target of rapamycin
[6] glycogen synthase kinase 3-beta
[7] transcription factors cAMP response element-binding protein
[8] forkhead box O
[9] N-methyl-d-aspartate

cognitive disorders by improving central insulin signalling in diabetic mice [66]. In an experimental study, dapagliflozin improved cognitive performance via reestablishing the brain insulin signalling in diabetic animals [67].

Interestingly, a recent randomised, double-blind, placebo-controlled, phase 2 trial study confirmed it and reported that empagliflozin improves brain insulin signalling in prediabetic people [68]. They found that eight weeks of empagliflozin therapy was statistically correlated to increased hypothalamus insulin sensitivity and improved brain insulin responsiveness in these people [68]. Although it needs further examination, it seems that improving brain insulin signalling is a central link between SGLT2 inhibition and cognitive functions in the diabetic milieu.

2. Oxidative Damages

It was well confirmed that oxidative stress has prominent roles in the pathophysiology of many compilations and cognitive deficits [69, 70]. This pathologic state is commonly correlated with mitochondrial dysfunction, inflammatory responses, impaired neuronal signalling, and reduced synaptic plasticity [71]. Also, it is a potent risk factor for Aβ deposition and incidence of many cognitive disorders such as AD, PD, Down syndrome (DS) and dementia [72-74]. It is even linked to cognitive impairments in healthy population [70]. Increased levels of oxidative injury occur before the onset of Aβ deposition and tau protein hyperphosphorylation in the brains of patients with cognitive deficits [72-74]. So readjusting the oxidative balance and normalising the redox state in the diabetic milieu is an important approach to preventing neuronal damage and improving the neurobehavioral functions [16, 75].

SGLT2 inhibitors potentially have antioxidative impacts in the diabetic milieu [30]. They can prevent or attenuate oxidative damage by lowering the free radical generation or potentiating the antioxidant defence system [30]. Earlier, we explained that SGLT2 inhibition ameliorates free radical species by modifying different pathways as pro-oxidant enzymes, AGE-RAGE[10] crosstalk, hemodynamic changes, mitochondrial dysfunction, RAS[11] system and pro-inflammatory pathways [30]. They can suppress pro-oxidant enzymes of NADPH oxidase (Nox), eNOS[12], and xanthine oxidase and reduce oxidative and nitrosative free radicals [76-78]. Mitochondrial dysfunction is another prominent source of free radicals that may be suppressed by these antidiabetic agents [65, 79-82]. They can improve mitochondrial integrity and prevent mitochondria-dependent free radical production[80-82]. Also, SGLT2 inhibitors potentiate intrinsic antioxidative defence by increasing involved elements' expression/activity [30]. Sugizaki and colleagues in 2017 demonstrated that SGLT2 inhibitor of TA-1887 upregulates main antioxidative enzymes of MnSOD[13] and CAT[14] enzymes in diabetic animals [83]. Likewise, Shin et al. in 2016 revealed that dapagliflozin restored MnSOD, CAT and

[10] Advanced glycation end products- receptor for advanced glycation end products
[11] Renin-angiotensin system
[12] Endothelial nitric oxide synthase
[13] Superoxide dismutase
[14] Catalase

Cu/Zn SOD expression in kidneys of diabetic animals [84]. Taken together, this evidence highly suggests that SGLT2 inhibition is associated with lower oxidative injuries [30]. Also, another evidence demonstrated that empagliflozin up-regulates glutathione and CAT antioxidative enzymes in circulating leukocytes in patients with T2DM [85].

We have evidence suggesting that SGLT2 inhibitors improve cognitive functions by preventing or reducing oxidative injuries [86]. Lin et al. in 2014 found that ten weeks of empagliflozin therapy increased cognitive functions in obese and T2DM mice via improving the redox state [86]. Another evidence in 2017 revealed that dapagliflozin has cognitive benefits in diabetic animals via attenuation of oxidative damages [65]. It was also able to improve DM-induced cognitive impairments via exerting the antioxidative impacts in rats [67]. A newer form of SGLT2i of Luseogliflozin has improved the cognitive function in a more recent experiment through pathways dependent on lowering the free radical species in diabetic rats [87]. SGLT2 inhibitors may also attenuate brain oxidative stress by modulating resident macrophages' activities as the primary source of free radicals in the neuronal networks [39, 88, 89].

3. Neuroinflammatory pathways

Inflammatory responses have strong relationships with the onset and progression of cognitive disorders in children and adults [90]. Evidence has well demonstrated that patients with cognitive problems have increased chronic low-grade inflammation levels that are closely implicated in neuropathophysiological pathways involved in neuronal death and brain atrophy leading to reduced cognitive capacities [90, 91]. So an inflammatory hypothesis was developed to emphasise the role of inflammatory mediators in cognitive deficits [92, 93].

SGLT2 inhibitors can exert anti-inflammatory effects via suppressing the expression/release of inflammatory mediators [13, 94]. In this context, empagliflozin inhibited the gene expression of MCP-1, IL-1[15] and TGF-β[16] in cultured human renal cells [95]. Also, empagliflozin reduced the mRNA expression and circulating levels of MCP-1[17], IL-6 and TNF-α[18] in adipose tissue and aortic plaques of diabetic mice [96], as well as Nf-κb[19] and IL-6 levels in renal tissues of diabetic Akita mice [97]. Moreover, dapagliflozin decreased the expression of inflammatory mediators of TNF-α, IL-6 and CRP[20] in liver cells and adipocytes of diabetic mice [98]. It was also reported that empagliflozin attenuates inflammatory processes by reducing the Iba1+[21] (the primary marker of brain inflammation) in brain tissue of diabetic animals with AD [66]. Sa-Nguanmoo et al., in 2017, provided data indicating dapagliflozin have cognitive benefits via a decrease of inflammatory responses in diabetic animals [65]. They found that 16 weeks of SGLT2 inhibition reduces inflammation and related apoptosis and preserved cognitive abilities in the experimental model of the T2DM [65]. SGLT2i

[15] Interleukine-1
[16] Transforming growth factor beta
[17] Monocyte chemoattractant protein-1
[18] Tumor necrosis factor alpha
[19] Nuclear factor kappa B
[20] C-reactive protein
[21] Allograft inflammatory factor 1

physiologically increases ketone bodies level such as β-hydroxybutyrate as byproducts of lipid metabolism, which can, in turn, modify NLRP3 inflammasome-IL-1β signalling, a critical pathologic pathway involved in the AD development [99, 100].

Also, these antidiabetic drugs can attenuate systemic inflammation by dealing with other pathways such as oxidative stress, hemodynamic changes, hyperglycemia-induced cytokines release, renin-angiotensin system (RAS), immune system, and immune system obesity-dependent inflammation [13, 94]. These pathways have multiple interactions with the release of inflammatory mediators and play prominent roles in the systemic inflammation development [13]. Taken together, we conclude that SGLT2 inhibitors have extraglycemic effects of anti-inflammation, which enable them to fight against onset and progress of cognitive deficits in the diabetic milieu.

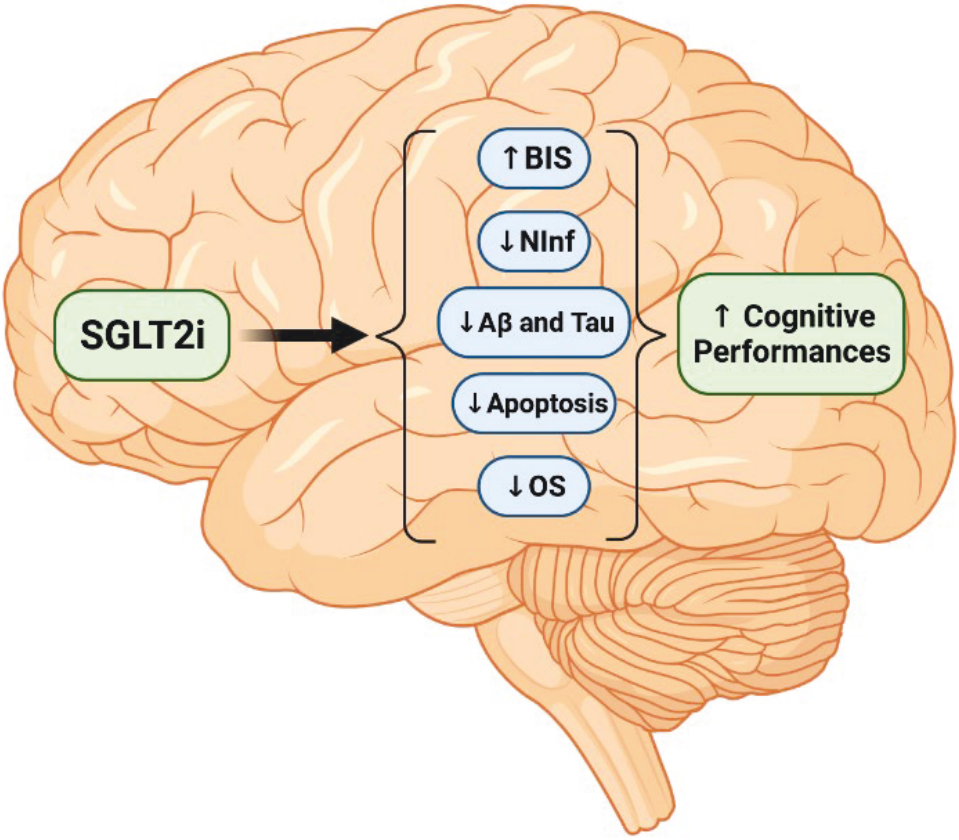

Fig 3; SGLT2 inhibition improves cognitive abilities thru five cellular pathways as improve in brain insulin signalling (BIS), reducing the neuroinflammation (Ninf), reducing the Aβ and Tau protein deposition/accumulation, reducing the neuroapoptosis and lowering the oxidative stress (OS) in brain tissue

4. Neuroapoptosis

Apoptosis is a physiologic event of programmed cell death involved in many biological processes such as growth, maturation, and migration [101]. It is a highly controlled cellular process that occurs under many factors and stimuli and is necessary during the cell cycle [101]. But in uncontrolled and pathologic states, it can induce histological damages in various tissues and neuronal structures, leading to brain atrophy [101]. It has been confirmed that neuroapoptosis is included in the pathophysiology of many neuronal disorders and is involved in most forms of cognitive problems and memory loss such as AD, PD and dementia [102, 103]. Thus, many pharmacologic agents have been tested to preserve brain function and improve cognitive and memory abilities [104-106].

SGLT2 inhibitors have pharmacologic capacities to fight against the neuroapoptosis [107]. They may directly suppress it, but it seems that most anti-apoptotic effects of SGLT2 inhibitors are indirect via suppressing inducer pathways such as oxidative stress or inflammation [108]. We have strong evidence suggesting SGLT2 inhibition is correlated to lower apoptotic death in various tissues. Shin and coworkers in 2016 stated that dapagliflozin attenuated apoptotic processes by decreasing renin-angiotensin system (RAS) activity and lowering oxidative stress in renal tissue of diabetic animals [84]. Shibusawa et al. in 2019 demonstrated that dapagliflozin reduces ER[22] stress-dependent apoptosis in renal cells of diabetic mice [109].

Moreover, Staels et al. in 2017 suggested the anti-apoptotic potentials of SGLT2i in the cardiovascular system as cardioprotective effects of these antidiabetic agents [110]. SGLT2 inhibitors may deal with apoptosis cellular machinery [111, 112]. Lee and coworkers in 2018 demonstrated that empagliflozin protects against renal proximal tubular cells' apoptosis by reducing intra-renal lipotoxicity in HK2 cells treated with high glucose concentration [111]. They also found that empagliflozin upregulated the Bcl-2 and down-regulated the t-Bid, Bax and cytochrome-C and inactivated the caspase-3, 8 and 9 (which are essential mediators of apoptosis) in kidney tissues [111]. SGLT2 inhibition modulates Erk and caspase activities in malignant cells [112]. A more recent study demonstrated that dapagliflozin reduces apoptotic events via caspase-3 dependent pathway [113]. We have limited direct evidence about the anti-apoptotic properties of SGLT2i in neuronal tissues. But presented data highly suggest that SGLT2 inhibitors have modulatory effects on apoptotic events. Sa-nguanmoo and coworkers reported that dapagliflozin reduces neuroapoptosis by preventing inflammation and oxidative stress in brain tissue and improving cognitive function in obesity-induced diabetic rats [65]. However, more investigations are still needed.

5. Aβ and Tau protein deposition/accumulation

Accumulation or deposition of some proteins such as Aβ, Tau protein and α-synuclein have prominent roles in the aetiology of some cognitive disorders, e.g. AD and PD [114, 115]. Aggregated and insoluble forms of these proteins make cortical plaques and Lewy bodies in the brain area related to cognitive functions and disaster their normal function thru well-defined pathways [116, 117]. These plaques, the primary neuro-histological markers of AD and PD, are generated by Aβ accumulation or tau protein hyperphosphorylation [117]. Also, their increased levels in blood or CSF are main predictors of cognitive impairments [116]. Recent evidence suggested that patients with diabetes are at higher risk of cognitive problems partly

[22] Endoplasmic reticulum

via a higher incidence of protein accumulation in the brain [118, 119]. Hence, using the antidiabetic drug, which can modify these proteins, will benefit patients with diabetes.

We have limited data indicating SGLT2 inhibitors attenuate cortical plaque formation in the diabetic milieu [66, 120]. They may decrease the cortical Aβ accumulation and tau hyperphosphorylation in the AD model of mice with T2DM [107]. In a recent study, empagliflozin reduced the senile cortical plaque and improved cognitive functions in an animal model of AD and T2DM [66]. Also, they may reduce plaque formation through the mTOR[23] inhibition [49, 121], which is involved in mitochondrial dysfunction, tau hyperphosphorylation and Aβ deposition [122]. SGLT2 inhibition reduces mTOR signalling activity, which is a shared mechanism between DM and AD, thereby reducing the probability of Aβ accumulation and AD [49]. The GSK[24], a main metabolic enzyme involved in hyperphosphorylated tau deposition in glial cells [123], maybe another link because it can be modulated by the SGLT2 inhibition [124]. Also, a recent study demonstrated that natural SGLT2 inhibitors of Acerogenin A, ε- viniferin, and Sophoraflavanone could deal with BACE-1[25] activity, a rate-limiting enzyme in Aβ deposition/accumulation; and so decrease the cortical plaque formation [125]. These reports highly suggest that SGLT2 inhibition may attenuate Aβ plaque deposition/accumulation; however, ongoing studies are still required to confirm it.

Mechanism	Effects of SGLT2i	References
Brain insulin signaling	Improve insulin signaling in the brain tissue toward improved brain function	[65-68]
Oxidative stress	Ameliorate oxidative pathways in neuronal tissues	[86, 87]
Neuroinflammation	Attenuate/suppress inflammatory processes	[65, 99, 100]
Aβ and tau protein deposition/accumulation	Prevent or reduce cortical plaque formation via damping the Aβ and tau protein deposition/accumulation	[66, 120, 125]
Neuroapoptosis	Reduce neuroapoptosis and prevent brain atrophy	[65]

Table 1, possible cognitive benefits of SGLT2 inhibitors

Conclusion

Due to the pathophysiologic pathways dependent on chronic hyperglycemia, cognitive deficits in diabetic patients have a higher incidence than in the normal population. So preserving brain function and preventing diabetes-induced cognitive impairments is one of the main goals in treating patients with diabetes. SGLT2 inhibitors have extra-glycemic effects,

[23] mammalian target of rapamycin
[24] Glycogen synthase kinase-3
[25] beta-site amyloid precursor protein cleaving enzyme 1

which protect brain function and prevent cognitive deficits. They can reduce the risk of cognitive impairment and prevent progressive memory loss by modulating pathways such as brain insulin signalling, oxidative stress, neuroinflammation, Aβ and tau protein deposition/accumulation, and neuroapoptosis.

Conflict of Interests

None of the authors has any conflict of interest regarding this study.

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