Review

Potential Therapeutic Effects of Sodium Glucose-linked Cotransporter 2 Inhibitors in Stroke

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ABSTRACT

Purpose: Stroke is the second leading cause of death and the third leading cause of disability worldwide. Diabetes mellitus and the associated hyperglycemia are important risk factors for acute ischemic stroke and are associated with poor prognosis. Neurovascular protection is an important therapeutic target to achieve in patients with stroke, especially in those receiving thrombolytic reperfusion therapy. Sodium glucose-linked cotransporter 2 (SGLT2) inhibitors are a novel class of antidiabetic agents that target SGLT2. Hyperglycemia exacerbates the neuronal damage through the SGLT2 transporter. The purpose of this narrative review is to discuss the pleiotropic effects of SGLT2 inhibitors and their role in the treatment and prevention of ischemic stroke in experimental and clinical studies.

Methods: We searched the PubMed database using different term combinations from the date of inception to May 2019. Deselection methods were followed to exclude unrelated articles. The total number of articles included was 14.

Findings: In experimental models, SGLT2 inhibitors have a protective mechanism against neuronal dysfunction and damage through various mechanisms. From a clinical perspective and based on current evidence, SGLT2 inhibitors reduce the risk of cardiovascular events, especially in patients with heart failure.

Implications: SGLT inhibitors may have neurologic and/or vascular protective effect after acute ischemic stroke based on experimental studies. However, getting an accurate judgment of this effect is hard to achieve because only a few animal studies are available. Furthermore, and unlike animale studies, clinical studies provided uncertain answers on whether SGLT2 inhibitors would provide neuroprotective effect. In addition, several studies used combination of drugs along with SGLT2 inhibitors.

Conclusions: It is unlikely that SGLT inhibitors have a positive or negative effect on stroke risk, but the question that remains unanswered is whether SGLT inhibitors can yield a protective effect after acute ischemic stroke. Future observational studies and registries may be the first step to help answer this question. (*Clin Ther*. 2020;42:e242–e249) © 2020 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Key words: canagliflozin, dapagliflozin, empagliflozin, ischemic stroke, pleiotropic effects, SGLT2 inhibitor.

INTRODUCTION

Stroke is the second leading cause of death and the third leading cause of disability worldwide. According to the World Health Organization, 15 million stroke cases occur annually worldwide. Among this number of patients, 5 million have a permanent disability and 5 million die.[1] Diabetes mellitus is considered the second highest risk factor for stroke. A study conducted in the United States found that approximately 40% of patients with ischemic stroke were diagnosed with diabetes.[2] Controlling glucose levels with intensive diabetes

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therapy has proved to reduce the risk of cardiovascular diseases (CVDs) by 42% and CVD recurrent events, including stroke, by 57%.[3] Patients with diabetes reportedly have 2.5 times the risk of having a stroke compared with patients without diabetes and 3.2 times the risk if the duration of diabetes is > 10 years.[4]

Although tissue plasminogen activator is the most and only effective treatment for ischemic stroke, its use is limited because of a tight window of 3–4.5 h from stroke onset to administration.[5] Beyond this window, the risk of hemorrhagic transformation (HT) overweighs the treatment benefit. HT is a complication that occurs because of a series of cellular and metabolic imbalances, leading ultimately to vascular injury and the disruption of the blood brain barrier (BBB). Although stroke, in general, can cause BBB dysfunction through disruption of tight and adherent junctions of endothelial cells, the degree of BBB dysfunction can be potentiated after the incidence of HT. Without an intact BBB, toxic inflammatory substances are secreted, leading to neurovascular death, edema, and hemorrhage.[6–8] Hyperglycemia can increase BBB permeability and the incidence of HT. In fact, persistent hyperglycemia was correlated with an increased risk of HT by > 10-fold.[9] It was also reported that tissue plasminogen activator–treated patients have a 3- to 4-fold increased risk of developing HT. This effect can be potentiated even more in patients with diabetes and those experiencing hyperglycemia.[8,10]

Sodium glucose-linked cotransporter 2 (SGLT2) inhibitors are a novel class of antidiabetic agents that target SGLT2. Although these drugs are primarily indicated for diabetes, several studies have examined their use in the primary and secondary prevention of stroke. An SGLT2 transporter was detected in several body cell types, including the BBB.[7] As mentioned previously, hyperglycemia contributes to BBB dysfunction and HT, and SGLT2 is thought to play a major role in edema formation because of its function as a sodium coupling transporter. Hyperglycemia was also found to exacerbate the neuronal damage through the SGLT2 transporter.[11] In 2012, Yamazaki et al[12] reported that the inhibition of SGLT2 through phlorizin could supress postischemic hyperglycemia exacerbation through reducing the infarct size and improving the neurologic deficit score. In this review, we discuss the pleiotropic effects of SGLT2 inhibitors and their role in the treatment and prevention of ischemic stroke in experimental and clinical studies.

METHODS

A review of experimental and clinical studies was conducted using the PubMed and Google Scholar databases from the date of inception to December 2019. Our search strategy used the following combinations of terms based on title and abstract: *stroke, ischemic stroke, cerebrovascular ischemia, neuroprotection,* and *vascular protection* as well as *SGLT2, SGLT2 inhibitor, sodium glucose transporter inhibitor, empagliflozin, dapagliflozin, canagliflozin*, and *sodium glucose-linked cotransporter inhibitor*. Articles were screened based on reading the title and abstract. Articles were excluded based on the following criteria: the written language was other than English, full text was not available, and article was a reply to author or editorial. A total of 94 articles were selected based on the title and abstract. Articles were also excluded based on the following: short articles or reports and review articles. A total of 37 eligible articles were selected, including 6 experimental or animal articles and 31 clinical or human articles. Eligible articles were fully reviewed for the objectives of this systematic review. Overall, the total number of articles included in the systematic review was 14, of which 6 were animal studies and 8 were clinical articles.

RESULTS

SGLT2 Inhibitors

The SGLT2 transporter is mostly expressed in the proximal tubules in the kidney but is found also in other organs, such as the liver, thyroid, muscle, and heart. The receptor's function is to reabsorb glucose coupled with sodium ion from the excreted urine back to the blood.[13] As a therapy for diabetes, SGLT2 inhibitors inhibit glucose reabsorption, which leads to the excretion of the extra glucose from the blood to the urine glucosuria.[14] Currently, 3 SGLT2 inhibitors have been approved: empagliflozin, dapagliflozin, and canagliflozin. Empagliflozin has higher selectivity for SGLT2 (2500-fold) than dapagliflozin (1200-fold) and canagliflozin (250-fold).[15] Apart from glucose lowering, SGLT2 inhibitors have other pleiotropic effects. These benefits lead to cardiovascular protection through

decreasing weight, lowering blood pressure, increasing the elasticity of the arteries and reducing its stiffness, lowering lipid production, decreasing systemic inflammation and the release of inflammatory biomarkers, increasing insulin production, decreasing insulin resistance, and decreasing uric acid levels.[16,17] Among studies reporting these benefits was a study conducted on apolipoprotein E–deficient mice. These mice were fed a Western diet for 20 weeks and were treated with empagliflozin for 8 weeks. Treatment produced a significant decrease in insulin resistance and atherosclerotic plaque in the aorta. Empagliflozin acted as an anti-inflammatory by decreasing the expression of tumor necrosis factor α, interleukin 6, monocyte chemoattractant protein 1, serum amyloid A, and infiltration of inflammatory cells. It decreased mice's weight, fat mass, and adipose cell size. Furthermore, it decreased urinary microalbumin, which was correlated significantly with decreased plaque size.[18] Another study reported a cardioprotective effect of SGLT2 inhibitors through the inhibition of the sodium hydride exchanger in cardiac cells, which results in reducing the interstitial cardiac fibrosis, the superoxide concentration, and the macrophage infiltration.[17]

SGLT2 Inhibitors and the Brain

SGLT2 inhibitors are partially lipid soluble drugs and can cross the BBB. Several studies confirmed the presence of the SGLT2 receptor in the brain, which may emphasize the potential therapeutic role of SGLT2 inhibitors in brain injury in the future.[19] Yu et al[20] reported the presence of SGLT2 receptors in several regions of rats' brain, including the cerebellum and hippocampus. The expression of the SGLT2 protein was concentrated in neuronal cell bodies, exons, and dendrites. Furthermore, SGLT2 was found to be a multifunctional protein that can transport molecules other than glucose and sodium, such as water and urea. Acting as a glucose sensor, SGLT2 in the hypothalamus plays a role in sleep regulation and appetite through glucose excited-neurons.[20–23] Erdogan et al[24] found that pentylenetetrazol seizure–induced rats treated with dapagliflozin have a significant reduction in seizure activity. They explained that the inhibition of SGLT2 may have led to a decrease in the glucose consumption by neurons, thus decreasing their membrane excitability and total depolarization events.

Experimental Studies of SGLT2 Inhibitors and Stroke

Effect on Stroke Risk Factors

Hyperglycemia, hypertension, dyslipedmia, and obestiy are among the most important risk factors for stroke. Several studies reported improvements in these parameters in diabetic and obese or stroke-prone mice and rats after treatment with SGLT2 inhibitors. In 2017, Sa-nguanmoo et al[25] reported weight and visceral fat reduction in rats on treatment with dapagliflozin through the improvement of the peripheral insulin sensitivity and decreasing caloric intake mediated by enhanced urine glucose excretion. Another study on mice with streptozotocin-induced diabetes treated with dapagliflozin coupled with liraglutide found a beneficial effect on β cells through enhancement of insulin sensitivity.[26] Combining the 2 treatments also decreased the weight and level of both triglycerides and corticosterone hormone. Mice had an increased level of glucagon and glucagon-like peptide 1, leading to better control in the rate of glucose production through fatty acids breakdown.[26] In an experiment performed on different *in vitro* and *in vivo* models, including spontaneously hypertensive stroke–prone rats, Zhang et al[27] found that the SGLT2 inhibitor significantly increases survival of spontaneously hypertensive stroke–prone rats by 67% compared with controls. Zhang et al[27] observed that SGLT2 inhbitor–treated rats had weight reduction, which could possibly explain the reduced stroke risk and increased survival. Furthermore, treated rats had increased urine output; thus, water consumption increased as a compensatory mechanism to maintain hydration. It was hypothesized that the increased urine output and sodium excretion helped in decreasing the rats' blood pressure, which further decreased the risk of stroke.[27]

Effect on the Oxidative Stress and Inflammation in the Brain

Several studies reported that SGLT2 inhibitors can decrease inflammation and oxidative stress caused by obesity or diabetes in murine models. In a model of high-fat diet–induced obese rats, dapagliflozin acted as an antioxidant and anti-inflammatory and improved the brain mitochondrial function. Treated obese rats had significantly decreased levels of the

brain malondialdehyde,[28] a marker for oxidative stress. In addition, brain mitochondrial function was improved through a decrease in the mitochnodrial reactive oxygen species, membrane swelling, and depolarization. Dapagliflozin also had antiapoptotic activity through decreasing the proapoptotic marker (Bax) and increasing the antiapoptotic marker (Bcl2) in treated rats. Furthermore, dapagliflozin had an anti-inflammatory effect through decreasing the ratio of phosphorylated nuclear factor−κB and p-65 against the unphosphorylated ones.[25] Recently, Hayden et al[29] reported that increased reactive oxygen species and nitrogen species could be the reason for the intracellular structure remodeling in the neurovascular unit of the brain. On treatment with empagliflozin, a protective effect against this pathologic remodeling of proteins, lipids, and nucelic acid was achieved.[29]

Effect on the Microvascular Structure of Brain Cells and Cognitive Function of the Brain

Remodeling of the neurovascular unit is one of the sequalae of hyperglycemia that can ultimately lead to deterioration in brain cognitive function. A recent study[29] focused on the toxic effect of hyperglycemia on the microvascular structure of the brain, including loss of myelin and axon collapse of neurons, detachment of astrocyte, loss of pericyte, thickening of basement membrane, and loss of tight and adherent junction of endothelial cells. The study[29] found that empagliflozin had a protective effect against this glucotoxicity and was able to prevent this aberrant remodeling in diabetic mice. Another study[26] reported the neuroprotective effect of dapagliflozin-liraglutide in mice with diabetes. Treated mice had increased generation of immature neurons and increased expression of doublecortin and synaptophysin of neurons, which ultimately increased neurogenesis and synaptic denisty and improved cognitive function.[26] Dapagliflozin-liraglutide−treated mice overcame the cognitive impairment and were able to discriminate between novel objects and familiar ones similar to healthy control mice. Similar conclusions were drawn from a different study[25] performed on obese rats. The study[25] found that LDL causes impairment in the hippocampal synaptic plasticity, an effect that was reversed with the use of dapagliflozin through increasing the electrical long-term potentiation of synapses in the hippocampus.

Effect on Neuronal Damage After Acute Ischemia

In addition to the effect of SGLT2 inhibitors on cognitive function, microvascular structure, oxidative stress, and stroke prevention, SGLT2 inihibtors were also studied in acute cerebral ischemia. Phlorizin (a specific and competitive inhibitor of SGLT) was administered immediately after reperfusion in a temporary bilateral carotid artery occlusion mice model. Compared with controls, phlorizin markedly reduced the development of ischemic neuronal damage, behavioral abnormalities, and memory disturbance. This study found that phlorizin was able to reverse the postischemic hyerglycemia-induced neuronal damage through SGLT inhibition. However, the authors did not explore other antioxidant or anti-inflammatory mechanisms of SGLT inhibitor that could have contributed to this effect.[30] A summary of the SGLT2 inhibitor effect on stroke based on experimental studies is presented in the Fig..

Clinical Studies for SGLT2 Inhibitors and Stroke

SGLT2 inhibitors have emerged as a novel antidiabetic class that have therapeutic benefits beyond glucose lowering. Early studies on SGLT2 inhibitors focused on glycemic levels and diabetes-related effects as primary outcomes. Given the small sample size of these studies, SGLT2 inhibitor effects on CVD outcomes were not prominent. However, pooling results from different studies were able to signal the benefit of these drugs in CVD.[31] During the past 5 years, the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME),[32] Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS),[33] Dapagliflozin Effect on Cardiovascular Events−Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58),[34] and Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF)[35] studies found that SGLT2 inhibitors reduce the risk of CVD in general, with more prominent effect on cardiovascular death and hospitalization for heart failure. A previous systematic review[36] to assess the cardiovascular effects of the SGLT2 inhibitors also found that canagliflozin, dapagliflozin, and empagliflozin reduce all-cause mortality (odds ratio [OR], 0.79; 95% CI,

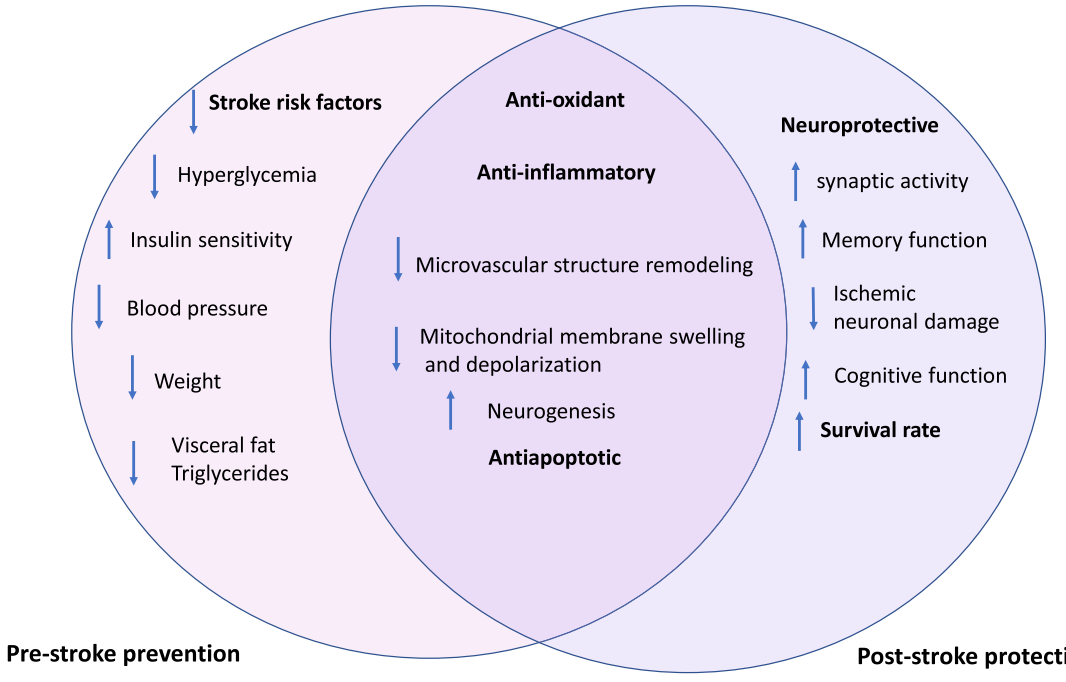

Figure. Pleiotropic effects of sodium glucose-linked cotransporter 2 (SGLT2) inhibitors favoring their therapeutic potential in stroke. The figure represents the effect of the SGLT2 inhibitor in prestroke prevention and poststroke protection. The overlapped circle represents function both before and after stroke. SGLT2 inhibitors decrease the risk factors of stroke, such as diabetes, hypertension, and obesity; thus, they could prevent stroke occurrence. SGLT2 inhibitors work against inflammation, oxidative stress, apoptosis, and brain microvascular structure remodeling, which could be increased because of the presence of several risk factors, such as diabetes and obesity. These inhibitors produce long-term neuroprotection by inducing neurogenesis, synaptic activity, and cognitive function. These protective mechanisms could decrease the risk of stroke occurrence and, most importantly, could protect against neuronal damage that could occur because of ischemia after stroke. The survival rate was reported to be increased in rats after ischemic stroke.

0.70–0.89; $P < 0.001$), major adverse cardiac events (OR, 0.8; 95% CI, 0.76–0.92; $P < 0.001$), nonfatal myocardial infarction (OR, 0.85; 95% CI, 0.73–0.98; $P = 0.03$), and heart failure or hospitalization for heart failure (OR, 0.67; 95% CI, 0.59–0.76; $P < 0.001$) in patients with type 2 diabetes mellitus. Another study that is currently ongoing is the Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular (VERTIS-CV) outcomes trial.[36] This trial is examining whether ertugliflozin carries cardiovascular benefits similar to the rest of the SGLT2 class. Apart from benefits in patients with diabetes, dapagliflozin has been recently tested in patients with established heart failure and reduced ejection fraction with and without diabetes mellitus. This landmark trial, DAPA-HF,[35] found that dapagliflozin reduced the risk of worsening heart failure or cardiovascular death by 26% (hazard ratio [HR], 0.74; 95% CI, 0.65–0.85; $P < 0.001$). Findings were consistent in patients with and without diabetes.

Despite the perceived cardiovascular benefits of SGLT2 inhibitors, especially in heart failure, the effects of SGLT2 inhibitors on stroke prevention were contradictory. For example, there was a slight trend toward an increased risk of stroke with

empagliflozin (HR, 1.18; 95% CI, 0.89−1.56; $P = 0.26$) in the EMPA-REG OUTCOME trial, although this finding was not statistically significant. This trend was attributed by some to be related to the elevation in the hematocrit in the empagliflozin arm, which may lead to an increase in blood viscosity and hence stroke risk.[37] On the other hand, there was a trend toward reduction in the risk of stroke with canagliflozin (HR, 0.87; 95% CI, 0.69−1.09) in the CANVAS trial that was not also statistically significant. Even meta-anlyses found controversial results. In 2016, Wu et al[38] analyzed data from 6 regulatory submissions and 57 clinical trials on 7 SGLT2 inhibitors and found that SGLT2 inhibitors increased the risk of nonfatal stroke by 30% (HR, 1.3; 95% CI, 1−1.68; $P = 0.049$). However, a more recent meta-analysis found that SGLT2 inhibitors had no effect on stroke risk (OR, 1.02; 95% CI, 0.85−1.21; $P = 0.87$).[31]

DISCUSSION

This systematic review covers an important novel area but is not without limitations. First, few animal studies were available, which limits the external validity and the review generalizability. In addition, some of the studies used combinations of drug treatments of SGLT2 and other drugs related to diabetes treatment; therefore, judging the effect of SGLT2 inhibitor as having neuroprotective alone is not sufficient. Additional research studies using appropriate experimental models are warranted to facilitate having a more accurate judgment.

In conclusion, experimental models found that SGLT2 inhibitors have a protective mechanism against neuronal dysfunction and damage through various mechanisms. The increased the survival of stroke-prone rats and play an important role to eliminate the risk factors of stroke through decreasing the glucose level, insulin resistance, triglycerides, and fat mass in the body. SGLT2 inhibitors are neuroprotective, an effect that is mediated primarily through antioxidant, anti-inflammatory, and antiapoptotic mechanisms. In addition, SGLT2 inhibitors improve the ultrastructural histologic features of neurons and the BBB, which can be promising in stroke therapy. However, more studies are required to confirm the effect of SGLT2 inhibitor after ischemia on the acute, subacute, and long-term stroke outcomes. From a clinical perspective and based on current evidence, SGLT2 inhibitors reduce the risk of cardiovascular events, especially in patients with heart failure. It is unlikely that SGLT2 inhibitors have a positive or negative effect on stroke risk, but the question that remains unanswered is whether SGLT2 inhibitors have neurologic and/or vascular protective effect after acute ischemic stroke. Future observational studies and registries may be the first step to help answer this question.

DISCLOSURES

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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