Sodium-glucose transport: role in diabetes mellitus and potential clinical implications

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Abstract

Purpose of review—Current options for glycemic control is less than optimal in terms of efficacy and to reduce complications in the diabetic population. Selective inhibition of SGLT2 in the proximal tubule increases urinary glucose excretion thereby reducing plasma glucose levels, which may present a novel therapeutic approach.

Recent findings—SGLT2 inhibitors enhance glucose excretion and improve glycemic control in patients with type 2 diabetes in the absence of clinically relevant hypoglycemia or sustained changes in volume status or glomerular filtration rate. This is associated with lowering of body weight and may reduce systolic blood pressure. The increased glucosuria appears to increase the risk of genital infections but may not increase the risk of urinary tract infections.

Summary—The ability of SGLT2 inhibitors to reduce plasma glucose without inducing increased insulin secretion, clinically relevant hypoglycemia, or weight gain constitutes a major advance. The ability of increased glucose excretion provides a powerful means to treat caloric excess conditions. Important questions remain to be resolved and more clinical research is needed on the long-term effects of SGLT2 inhibition. Potential extrarenal effects need to be explored in order to determine the safety of these compounds. It also remains to be determined whether these drugs lower the toxicity of glucose directly on renal cells, independent of hyperglycemia, which may slow or prevent the progressive nature of diabetic nephropathy.

Keywords

albuminuria; diabetic kidney disease; glucose transport; glycemic control

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Introduction

Diabetes-associated chronic renal insufficiency is the primary cause of end-stage renal disease (ESRD), yet the pathophysiology is still incompletely understood. Good control of blood glucose levels is important in diabetic patients but difficult to achieve without the potential for hypoglycemia and weight gain. Moreover, existing therapies may not always reduce cardiovascular complications, indicating the need for new therapies with novel mechanisms of action. This review discusses the rationale for the current development of inhibitors of SGLT2 as new antidiabetic drugs and presents newly available clinical data.

Glucose transport in the kidney

The kidney reabsorbs large amounts of glucose, and by extension has a major part in maintaining the overall metabolic balance of the body. In healthy humans, about 180 g/day of glucose are filtered through the renal glomerulus, more than 99% of which is reabsorbed along the tubular system. Transport of glucose across cell membranes is accomplished by two gene families: the facilitative glucose transporters – the GLUTs – and by an active sodium-dependent transport process mediated by the Na^+-glucose cotransporters (SGLT). The latter process allows glucose to be accumulated in cells against the concentration gradient.

The SGLTs are a large family of membrane proteins involved in the transport of glucose, amino acids, vitamins, osmolytes, and some ions [1]. At least two sodium-coupled glucose transporters, SGLT1 and SGLT2, play an important role in the apical membrane of proximal tubular cells in the kidney. The low-capacity, high-affinity SGLT1 is mainly present in the gastrointestinal tract with a minor role in the kidney, whereas the high-capacity, low-affinity SGLT2 transporter is found primarily in the kidney, in which it is responsible for the majority of glucose reabsorption [1–4].

SGLT2 and glucose reabsorption in the proximal renal tubule

The high-capacity, low-affinity SGLT2 is found primarily in the apical membrane of the S1 segment of the proximal tubule, whereas the low-capacity, high-affinity SGLT1 is located more distally in the S3 segment of the proximal tubule. Two basolateral membrane glucose transporters facilitate transcellular glucose transport – the low-affinity GLUT2, which works in concert with SGLT2 in the S1 segment of the renal tubule, and the high-affinity GLUT1, which works with SGLT1 in the S3 segment [5,6].

The phenotype of humans carrying gene mutations in the genes for SGLT1 (*SLC5A1*) and SGLT2 (*SLC5A2*) provided much of the evidence for the quantitative contribution of these proteins to renal glucose reabsorption. Gene mutation of SGLT1 has serious consequences for afflicted individuals, who experience glucose-galactose malabsorption, frequent watery diarrhea, and dehydration [7]. However, these individuals have little or no glucosuria. In contrast, those who have SGLT2 gene mutations have persistent renal glucosuria, with glucose excretion of up to 160 g/day in severe cases. A total of 44 different mutations have been described for the SCL5A2 gene, including missense and nonsense mutations, small deletions (in-frame and frame shift), and splicing mutations, scattered throughout the gene

[8]. Although no other complications are known to be consistently associated with mutations of this gene, it is a rare genetic disorder and not well studied [9–12]. New free-flow micropuncture studies in mice lacking SGLT2 confirmed a lack of glucose reabsorption in the early proximal tubule and showed that fractional renal reabsorption of glucose is reduced compared with wild-type mice (36 ± 8 vs. $99.7 \pm 0.1\%$) and varied inversely with the amount of filtered glucose in the knockout mice (between 60 and 10%) [13]. Thus, SGLT2 plays a major role for renal glucose reabsorption.

SGLT2 expression and diabetes mellitus

SGLT2 reabsorbs almost all glucose that occurs in glomerular filtrate; however, there is a transport maximum (T_m) for glucose that depends on the level of protein expression. The issue of gene expression and the possibility of SGLT2 adaptation to hyperglycemia is an area rich for investigation, showing reduced [14], unchanged [15] or increased expression [16] in diabetic rodent models. In-vitro studies indicated that high glucose-induced oxidative stress inhibits Na^+-glucose cotransporter activity in renal proximal tubule cells [17]. New studies in streptozotocin-diabetic rats suggested that the increase in renal SGLT2 mRNA and protein expression in diabetes is mediated by angiotensin II AT1 receptors [18•]. Primary cultures of human exfoliated proximal tubular epithelial cells from fresh urine of patients with type 2 diabetes indicated an increased renal glucose uptake associated with increased expression of SGLT2 and GLUT2 compared with healthy control individuals [19]. Up-regulation of SGLT2 expression in diabetes may involve the transcription factor, hepatocyte nuclear factor (HNF)-1α [20]. New studies provided evidence that the transcriptional activity of both HNF-1α and HNF-3β may contribute to the renal overexpression of GLUT2 mRNA in the kidney of diabetic rats [21•].

Diabetic nephropathy and glucose transport

Diabetes-associated chronic renal insufficiency is the primary cause of ESRD [22]. A number of pathways have been implicated in the development of diabetic nephropathy, including comorbid hypertension and the involvement of the renin angiotensin aldosterone system (RAAS) [22,23]. Other possible pathways include aldose-reductase-polyol, di-acyl glycerol-protein kinase C, advanced glycated end products (AGE), and the hexosamine pathway [24,25]. Many of the proximal pathways culminate in simulation of transforming growth factor beta (TGFb) and CTGF production leading to matrix accumulation and progressive scarring [26,27]. Data on the role that glucose transport may play are beginning to emerge.

Glomerular hyperfiltration is a cardinal feature of early diabetes mellitus and may predispose to the eventual development of diabetic nephropathy [28,29]. According to the 'tubulo-centric principle', the underlying mechanism(s) of diabetic hyperfiltration include(s) a primary increase in proximal reabsorption, which reduces delivery of NaCl to the macula densa [30–32]. The macula densa senses this decline in salt delivery as an error signal and elicits an increase in glomerular filtration rate (GFR), which offsets a portion of the original error signal through negative tubulo-glomerular feedback. In accordance, glomerular hyperfiltration is blunted in early diabetes in mice that lack an intact tubulo-glomerular

feedback response [33]. Enhanced tubular growth and glucose reabsorption have been implicated in proximal hyper-reabsorption and glomerular hyperfiltration in early diabetes [30,32]. In addition to impaired tubular function, diabetes may have direct effects on the afferent arteriole to impair the autoregulatory response. The impaired afferent arteriolar response to increased perfusion pressure is likely contributed by local production of TGF-β [34]. The afferent arteriole becomes dilated, increasing glomerular blood flow and causing distension of the capillary loop early on in kidney disease. In turn, this places stress on mesangial cells, glomerular capillary cells, and podocytes. Stress may lead to podocyte dysfunction or dropout. Microalbuminuria follows and may progress to overt proteinuria. This progression is paralleled by the accumulation of mesangial matrix and basement membrane, glomerular hypertrophy, and increased podocyte dropout. Ultimately, the patient develops glomerular sclerosis, tubulointerstitial disease, tubular atrophy and microvascular disease [35,36] leading to ESRD. The early glomerular changes have been noted to occur in diabetic db/db mice as well [35]. The role of SGLTs in these changes is not known.

Current therapies for hyperglycemia in type 2 diabetes and unmet needs

Current noninsulin-based therapies for type 2 diabetes mellitus (T2DM) include the alpha-glucosidase inhibitors, incretin mimetics, insulin secretagogues, metformin, sulfonylureas, thiazolidinediones, and more recently glucagon like peptide-1 agonist and dipeptidyl-peptidase-IV inhibitors. Given the progressive nature of T2DM, most patients eventually require combinations of oral antidiabetic medications [37]. The United Kingdom Prospective Diabetes Study (UKPDS) found that after 3 years, only 50% of patients were adequately controlled on a single medication, and that after 9 years, only 25% were controlled on monotherapy [38]. The reasons for the difficulty in achieving glycemic goals are complex. Although the reluctance of medical professionals and patients to intensify treatment may contribute, it seems likely that the progression of the underlying disease process, together with dose-limiting side effects of current therapies, including gastrointestinal effects, fluid retention, weight gain, and hypoglycemia, contribute to the poor glycemic control that is common in T2DM. Furthermore, recent studies have found that further intensive glycemia control (i.e. hemoglobin A1C <6.5%) with existing therapies do not reduce cardiovascular complications [39] and may increase mortality. Given that present therapies may be difficult to provide ideal glycemic control without the potential for hypoglycemia, weight gain and that existing therapies may not always reduce cardiovascular complications, there is a clear need for new therapies with novel mechanisms of action.

Nonselective SGLT inhibition

SGLT inhibition offers the potential to decrease the deleterious effects of hyperglycemia while reducing blood glucose levels by inhibiting renal glucose reabsorption. Impressive results have been achieved in diabetic animal with the nonselective SGLT inhibitor, phlorizin [40], its derivative T-1095 and its metabolite T-1095A [41,42], including beneficial effects on blood glucose levels and HbA$_{1c}$ levels, partial improvement of glucose tolerance and insulin resistance, and suppression of albuminuria and the expansion of the glomerular mesangial area in diabetic rodents [41,43]. Due to their effect on SGLT1, however,

nonselective inhibitors can have unacceptable gastrointestinal side effects and did not proceed to clinical development.

Selective SGLT2 inhibition

Selective SGLT2 inhibitors offer the potential to primarily increase renal excretion of glucose and create a negative energy balance without affecting intestinal function. As inhibition of intestinal absorption of foods has not been accepted by many patients, additional methods to create a negative energy balance may offer strong advantages over present approaches. A major potential advantage is that these compounds will not have direct effects to stimulate insulin release and thus cellular glucose uptake. In the short term increased intracellular glucose uptake will reduce hyperglycemia; however, potentially chronic and persistent increased intracellular glucose uptake could lead to cell dysfunction. Selective SGLT2 inhibition may also provide renoprotection through beneficial effects on glycemia, glomerular hemodynamics, and glucose toxicity of tubular cells. Various SGLT2 inhibitors are currently in development as well as a novel antisense approach to inhibit SGLT2.

ISIS 388626

As shown in preliminary studies, ISIS 388626, a 12-nucleotide SGLT2 antisense oligonucleotide, reduces the mRNA expression of SGLT2 in the proximal tubule of rodents, dogs and nonhuman primates by up to 75–80% and increases glucosuria in these species and improves glycemic control in Zucker diabetic fatty rats [44,45]. ISIS is currently evaluating this compound in a phase 1 study designed to assess the safety and activity of the drug in healthy volunteers.

Dapagliflozin

The compound has a 1200-fold selectivity for SGLT2 over SGLT1 as compared with phlorizin's 10-fold selectivity [46]. Dapagliflozin did not significantly inhibit facilitative glucose transport in human adipocytes [41,47]. In-vivo studies demonstrated that a single dose of dapagliflozin lowers blood glucose levels in streptozotocin-induced diabetic rats [46]. Moreover, dapagliflozin induced significant, dose-dependent glucosuria in normal and ZDF rats, enhanced glucose tolerance in normal rats, and decreased hyperglycemia in ZDF rats after single oral doses and 2-week treatment. Furthermore, the compound caused a significant increase in the glucose utilization rate, which was accompanied by a significant reduction in glucose production and enhanced liver insulin sensitivity without inducing hypoglycemia. No body weight changes compared with vehicle-treated rates were observed [46].

More recently, the safety, tolerability, pharmacokinetics, and pharmacodynamics of dapagliflozin were evaluated in single-ascending dose (SAD; 2.5–500 mg) and multiple-ascending dose (MAD; 2.5–100 mg daily for 14 days) studies in healthy individuals [48•]. The compound induced a dose-dependent glucosuria. Cumulative daily amounts of glucose excreted ranged from 18 to 62 g and were comparable between 1 and 14 days of treatment, with no apparent changes in glycemic parameters. Once-daily doses of approximately 20–50

mg provided close-to-maximal SGLT2 inhibition for at least 24 h [48•,49]. A subsequent multiple-dose study evaluated the safety and efficacy of dapagliflozin in type 2 diabetic patients, which were randomly assigned to one of five dapagliflozin doses (2–50 mg), metformin extended release, or placebo for 12 weeks [50••]. Dapagliflozin induced significant glucosuria (52–85 g urinary glucose/day) and demonstrated glycemic improvements and greater weight loss vs. placebo (HbA$_{1c}$ –0.55 to –0.90 vs. –0.18%; fasting plasma glucose –16 to –31 vs. –6 mg/dl; –2.5 to –3.4 vs. –1.2 kg). Dapagliflozin did not induce clinically significant changes in estimated GFR or volume status and modestly lowered systolic blood pressure and serum uric acid levels. Rates of genital infections were higher with dapagliflozin (especially the higher doses) vs. placebo, whereas bacterial urinary tract infections were not different [50••]. A randomized, double-blind, three-arm, parallel-group, placebo-controlled, 26-center trial was performed to determined whether dapagliflozin lowers hyperglycemia in patients with type 2 diabetes that is poorly controlled with high insulin doses and oral antidiabetic agents (OADs) [51••]. Patients were randomly assigned to placebo, 10 mg dapagliflozin, or 20 mg dapagliflozin, and OADs and 50% of their daily insulin dose. Under these conditions, 12 weeks of dapagliflozin decreased HbA1C, produced better fasting and postprandial plasma glucose levels, and lowered body weight more than placebo. Overall, adverse events were balanced across all groups, although more genital infections occurred in the 20-mg dapagliflozin group than in the placebo group [51••]. Currently, multiple phase III clinical trials with dapagliflozin (mostly as add-on therapies) are being performed.

Sergliflozin

The active entity of sergliflozin etabonate is a highly potent and selective inhibitor of SGLT2. In rats, mice and dogs, oral administration of sergliflozin etabonate results in increased urinary glucose excretion in a dose-dependent manner. It also significantly lowers plasma glucose in a dose-dependent manner when administered to streptozotocin-induced diabetic rats, Zucker fatty diabetic rats or KK-A(y) mice, which have symptoms of obesity and hyperinsulinemia, without stimulating insulin secretion or inducing hypoglycemia [52–54].

More recently, the pharmacokinetics and pharmacodynamics of sergliflozin were evaluated following single oral dose administration of sergliflozin etabonate (5–500 mg) in healthy volunteers and patients with T2DM [55•]. In both populations, sergliflozin etabonate produced a dose-related glucosuria under fasting conditions and following glucose loading but did not appreciably affect urinary electrolyte excretion or fluid balance. Single doses of sergliflozin etabonate 5–500 mg were well tolerated, and there were no clinically significant adverse laboratory findings [55•]. Studies with administration of sergliflozin etabonate (500 or 1000 mg) or placebo three times daily (t.i.d.) for 14 days in healthy overweight or obese human volunteers revealed a mean half-life of the active entity of approximately 2 h [56••]. Sergliflozin etabonate induced a dose-related glucosuria (21 and 51 g/day) associated with unchanged plasma glucose, insulin, and electrolyte levels, whereas body weight was reduced [mean changes from baseline of –1.55 (500 mg) and –1.74 kg (1000 mg) vs. –0.09 kg with placebo, respectively]. Sergliflozin etabonate did not alter creatinine clearance and was generally well tolerated. Excretion in the urine of (micro)albumin, and of the tubular injury

markers, N-acetyl-beta-D-glucosaminidase and β2-microglobulin, were increased in several individuals receiving sergliflozin but the clinical relevance of these effects is uncertain [56••]. The clinical development of sergliflozin etabonate had been discontinued in favor of remogliflozin.

Remogliflozin etabonate is a prodrug that is metabolized to its active form, the selective SGLT2 inhibitor, remogliflozin, in the body [57]. Orally administered remogliflozin etabonate increased urinary glucose excretion and showed antihyperglycemic effects in both streptozotocin-induced diabetic rats in oral glucose tolerance and in db/db mice. In high-fat diet-fed Goto-Kakizaki rats, remogliflozin etabonate improved hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and insulin resistance [57]. Preliminary studies in patients with type 2 diabetes supported the safety of its administration with metformin with minimal risk of hypoglycemia [58]. Further preliminary studies in these patients revealed a plasma half-life of 120 min and dose-dependent increases in urinary glucose excretion [59]. The clinical development of remogliflozin etabonate, however, has been discontinued in 2009 as a result of extenuating circumstances, including the development status of SGLT2 inhibitors by competitors.

Other SGLT2 inhibitors in development include AVE2268 [60], BI10773 [61], BI44847 [62], canagliflozin [62], LX4211 [62], ASP1941 [62] and TS-071 [63], but no clinical data are available or published yet.

Implications of current findings

On the basis of preclinical and the first clinical studies, SGLT2 inhibition shows promise as a potential therapy for improving glycemic control and possibly offering renoprotection in T2DM. The ability of a class of agents to reduce plasma glucose without inducing increased insulin secretion, clinically relevant hypoglycemia, or weight gain constitutes a major advance.

However, important questions remain to be resolved and more clinical research is needed on the long-term effects of SGLT2 inhibition on kidney function, blood pressure and bone health. The available studies find no increase in bacterial urinary tract infection in response to SGLT2 inhibition. The incidence of genital fungal infections, however, may be increased, which requires close observation. These drugs are lipid-soluble, and therefore will cross the blood brain barrier (BBB). The SGLTs are found within the hypothalamus in which they sense and respond to changes in glucose concentrations [64]. Real-time PCR suggested SGLT2 RNA expression in many human tissues [65] but, due to the lack of good antibodies, the implication for extrarenal protein expression of SGLT2 is unclear. It is critical that potential extra-renal effects are explored in order to determine the safety of these compounds.

Potential benefits of renoprotection must be investigated thoroughly as well. Do these drugs affect kidney growth and hyperfiltration in early diabetes? Does SGLT2 inhibition have direct effects on cells to inhibit matrix production and cell dysfunction? Studies are needed to determine if there are beneficial effects on cytokines such as TGFβ1 and CTGF to

determine whether these compounds can slow or prevent the progressive nature of diabetic nephropathy. It will be challenging to prove that any benefits are over and above the reduction of systemic hyperglycemia. Ultimately, their effects in patients with early and established kidney disease must be explored. A preferential reduction in albuminuria and markers of tubular damage with SGLT2 inhibitors will be of major interest. Those questions notwithstanding, SGLT2 inhibition appears to offer substantial hope for a unique and effective diabetes therapy, with an acceptable adverse effect profile, and potential beneficial effects on the kidneys.

Conclusion

SGLT2 mediates glucose reabsorption in the early proximal tubule and the majority of the overall glucose reabsorption by the kidney. The available clinical studies show the ability of SGLT2 inhibitors to enhance the urinary excretion of glucose in patients with T2DM, thereby reducing plasma glucose levels without inducing increased insulin secretion, clinically relevant hypoglycemia, or weight gain. Benefits to diabetic kidney disease will likely be due to overall improved glycemic control without weight gain, and potentially direct benefit by inhibiting glucose uptake in renal cells.

Acknowledgments

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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