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REVIEW ARTICLE

Sodium–glucose cotransporters: Functional properties and pharmaceutical potential

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ABSTRACT

Glucose is the most abundant monosaccharide, and an essential source of energy for most living cells. Glucose transport across the cell membrane is mediated by two types of transporters: facilitative glucose transporters (gene name: solute carrier 2A) and sodium–glucose cotransporters (SGLTs; gene name: solute carrier 5A). Each transporter has its own substrate specificity, distribution, and regulatory mechanisms. Recently, SGLT1 and SGLT2 have attracted much attention as therapeutic targets for various diseases. This review addresses the basal and functional properties of glucose transporters and SGLTs, and describes the pharmaceutical potential of SGLT1 and SGLT2.

INTRODUCTION

In mammals, glucose movement into and out of cells is achieved by glucose transporters (GLUTs) on the cell membrane. GLUTs are divided into two structurally and functionally distinct types: (i) GLUTs, which operate by facilitated diffusion[1,2]; and (ii) sodium–glucose cotransporters (SGLTs), which actively transport glucose against the concentration gradient by coupling with sodium[3,4]. GLUTs are located in all body cells to facilitate transport of glucose into the cells, and the concentrations of glucose into and out of the cells become equal with GLUTs operation[1]. In the SGLTs, which comprise a family of at least six different isoforms in humans, glucose and sodium are simultaneously cotransported into the cells using the sodium concentration gradient[5]. Of these SGLTs, SGLT1 and SGLT2 have been frequently investigated, because they play key roles in the transport of glucose and sodium across the brush border membrane of intestinal and renal cells[3,6].

In the intestinal epithelium, glucose influx into the epithelial cells is catalyzed by SGLT1 located in the apical membrane, and the glucose flows into the circulation through GLUT2 located in the basolateral membrane[5,7]. Also, the two types of transporter, GLUTs and SGLTs, work together in the renal tubular cells, with the SGLTs (SGLT2 and SGLT1) transporting glucose into the tubular cells across the apical membrane, and the GLUTs (GLUT2 and GLUT1) transporting the glucose across the basolateral membrane into the blood circulation[7,8].

Recently, SGLT2 inhibitors have been developed, based on a new concept of antidiabetic action by inhibiting renal glucose reabsorption and increasing glucose excretion into urine. SGLT2 inhibitors reduce glucotoxicity by lowering blood glucose, and a decrease in cardiovascular death and the renal protective effects have been reported by large-scale clinical trials[9]. Furthermore, SGLT1 is responsible for glucose absorption in the small intestine and for reabsorption of the part of the filtered glucose load in the kidney[10], and might be an attractive target for the maintenance of good glycemic control and improvement of renal dysfunction[7,11]. In this review, we first present an outline summary of glucose transporters: GLUTs and SGLTs. We then focus on SGLT1 and SGLT2, and describe the functional properties and the pharmacological potential, including new insights.

BASAL PROPERTIES IN GLUTS

The facilitative glucose transporters, GLUTs, use the diffusion gradient of glucose or other sugars across cell membranes, each with unique substrate specificities, kinetic profile and expression profile in tissues[4]. GLUTs are divided into three classes by the similarity of amino acid sequence: class I facilitative transporters, GLUT1–4; class II facilitative transporters, GLUT5, 7, 9 and 11; and class III facilitative transporters, GLUT6, 8, 10, 12 and a proton myo-inositol cotransporter/GLUT13[2,4,5].

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Among the class I facilitative transporters, GLUT1 has ubiquitous expression, with abundant expression in the brain and erythrocytes, and moderate expression in fat, muscle and the liver[4,12–14]. GLUT1 is responsible for constitutive or basal glucose uptake in the cells and can transport aldose, including pentose and hexose[1,15]. GLUT2 is expressed in pancreatic β-cells, the liver, kidney and small intestine. In rodent β-cells, GLUT2 plays a key role in the glucose-sensing mechanism due to the low affinity and high capacity[16,17]. In contrast, in human β-cells, GLUT1 is primarily expressed, and GLUT2 is expressed at an extremely low level[18]. In the liver, GLUT2 is expressed on the sinusoidal membrane and enables the bidirectional transport of glucose[1]. The GLUT2 in the kidney and small intestine is responsible for the movement of glucose out of absorptive epithelial cells into the blood circulation[16]. GLUT3 has a high affinity for glucose, and is known for its specific expression in neurons, in particular the brain. GLUT3 is also expressed in other cells having specific glucose requirements, such as sperm cells and embryos[5,19,20]. Insulin-responsive glucose transporter GLUT4 is expressed in skeletal muscle, adipose tissue and the heart, and is also found in the brain[1,21]. When insulin binds to the insulin receptors, the GLUT4 moves to the cell membrane and facilitates glucose transport into the cells.

Among the class II facilitative transporters, GLUT5, which is the specific transporter for fructose, is predominantly expressed in the small intestine, testes and kidneys[4,22]. In the intestine, GLUT5 is responsible for transport of hexose from the villus epithelium with SGLT1. The hexose in the cell leaves the epithelium through GLUT2 located in the basolateral membrane[16]. GLUT7 is primarily expressed in the small intestine and colon, and works as a facilitated hexose transporter[23]. GLUT9 is highly expressed in the kidney and liver[2]. In the human kidney, GLUT9 is expressed in proximal convoluted tubules, and in rodents, it is expressed in distal connecting tubules[24,25]. GLUT9 is reportedly a urate transporter, and some mutations in its sequence induce hypouricemia[26]. GLUT9 is also known as voltage-driven urate transporter 1 on the basolateral membrane[27,28]. Two splice variants of GLUT11, long and short forms (503 and 493 amino acid residues), are expressed in a tissue-specific manner[29,30], and hexose, glucose or fructose is transported. The short form of GLUT11 is predominantly expressed in heart and skeletal muscle, and the long form is detected in the liver, lung, trachea and brain[29,30].

As for the class III facilitative transporters, GLUT6, which is a hexose transporter protein, is highly expressed in the brain, spleen and leukocytes[4]. GLUT8 is mainly expressed in the testis, and lower expressions of messenger ribonucleic acid (mRNA) were detected in other organs, including insulin-sensitive tissues[5]. GLUT8 has been identified as an insulin-responsive glucose transporter, and reportedly has a role in glucose uptake in the mammalian heart, along with GLUT4[31]. GLUT10 plays a role in glucose homeostasis control, and in humans, it has a higher mRNA level in the liver and pancreas[32]. GLUT12, which can facilitate transport of a variety of hexose, is expressed in the heart, small intestine, prostate and insulin-sensitive tissues, including skeletal muscle and fat[33]. Proton myo-inositol cotransporter/GLUT13 has been identified as a proton myo-inositol cotransporter, and is highly expressed in glial cells and some neurons, suggesting that proton myo-inositol cotransporter/GLUT13 might be responsible for myo-inositol metabolism regulation in the brain[34,35].

OVERVIEW OF SGLTS

SGLTs constitute a large family of membrane proteins related to various transports of glucose, amino acids, vitamins and some ions across the apical membrane of the lumen side, including in the small intestine and renal tubules. In humans, six different isoforms have been reported, and two transporters, SGLT1 (solute-carrier [SLC]5A1) and SGLT2 (SLC5A2) proteins, have been widely studied[36]. SGLT1 was discovered by expression cloning in 1987[37], and SGLT2 was identified by homology screening in 1994[38]. GLUTs equilibrate the glucose levels on both sides of the plasma membrane, because the glucose gradient across the membrane is the driving force, whereas SGLT2 can exert differences in glucose concentration, because the transmembrane sodium gradient is the driving force for glucose uptake[3–5].

SGLT1 is responsible for glucose absorption in the small intestine, whereas SGLT2 is responsible for glucose reabsorption in the kidney (Table 1)[38,39]. Considering the physiological functions of SGLT1 and SGLT2, drug recovery research targeting the transporters is reasonable. In 1987, phlorizin, an inhibitor of SGLT1 and SGLT2, was reported to reverse experimental diabetes in partially pancreatectomized rats[40]. SGLT inhibitors have been developed using phlorizin as a lead compound[7,41,42], resulting in the development of SGLT2 inhibitors, which have been successfully launched for the market[42,43].

As for the other SGLTs, SGLT3 (gene name: *SLC5A4*), which is expressed in the intestine, spleen, liver, kidney, skeletal muscle and cholinergic neurons, is not a functional SGLT, and seems to act as a glucose sensor in the plasma membrane of cholinergic neurons[44]. There are only a few reports on the other SGLTs: SGLT4, SGLT5 and SGLT6. SGLT4 (gene name: *SLC5A9*) is expressed in the small intestine, kidneys, liver, lung, brain, trachea, uterus and pancreas; SGLT5 (gene name: *SLC5A10*) is expressed only in the kidneys; and SGLT6 (gene name: *SLC5A11*) is considered to be a low-affinity D-glucose transporter in the small intestine[39,45]. Physiological roles of these SGLTs remain unknown.

Basal properties of SGLT1

The SGLT1 protein, encoded by the *SLC5A* gene on chromosome 22q13.1, is composed of 664 amino acids, comprising 14 transmembrane α-helical domains, a single glycosylation site between transmembrane helices 5 and 6, and two phosphorylation sites, between transmembrane helices 6 and 7, and between 8 and 9[39,45,46]. The NH_2 and COOH terminals are located in extracellular and intracellular membranes, respectively, and the glucose-

Table 1 | Tissue expression and biochemical characteristics of sodium–glucose cotransporter 1 and sodium–glucose cotransporter 2

Characteristics	SGLT1	SGLT2
Site	Mostly in small intestine some kidney, heart, brain etc.	Mainly in kidney
Renal location	S3 segment of proximal tubules	S1 and S2 segments of proximal tubules
Sugar selectivity	Glucose = galactose	Glucose > galactose
Sodium/glucose stoichiometry	1:2	1:1
Affinity for glucose	High (0.5 mmol/L)	Low (2 mmol/L)
Glucose transport capacity	Low	High

SGLT, sodium–glucose cotransporter.

binding domain is supposed to include amino acid residues 457–460[45,47]. SGLT1 is a high-affinity transporter for glucose (Michaelis–Menten constant [K_m] = 0.4 mmol/L) and galactose, whereas fructose is not transported[39,48,49]. Two sodium ions are transported through the SGLT1 for each glucose molecule, and this cotransporter is allowed to transport glucose into the cells against its concentration gradient[4].

SGLT1 mRNA expression has been detected by reverse transcription polymerase chain reaction in the following tissues in humans: small intestine, kidney, skeletal muscle, liver, lung, heart, trachea, prostate, testis, cervix of the uterus, stomach, mesenteric adipose tissue, pancreatic α-cells, colon and brain[50–53]. SGLT1 protein expression has been localized to the apical brush border of the small intestine and the late proximal tubules, and has also been detected in the following tissues in humans: salivary gland, liver, lung, skeletal muscle, heart and pancreatic α-cells[37,53–55].

SGLT1 reportedly exerts the transport activity by many molecular regulations, including protein kinases. SGLT1 contains strain-specific regulation sites by protein kinase A (PKA) and protein kinase C (PKC): one PKA site in humans and rabbit, none in rat; five consensus PKC sites in humans and rats, and four sites in rabbits[56,57]. PKA activation led to an increase in the number of SGLT1 proteins in the membrane of the small intestine in rats[58], and PKA activator, 8-bromo-cyclic adenosine monophosphate, or forskolin increased the SGLT capacity and the SGLT1 activity in the plasma membrane[56,58]. The expression and activity of SGLT1 is positively regulated by PKA activity, and the effects on SGLT1 activation was inhibited by PKA inhibitor, H-89[59,60]. PKC-mediated effects on SGLT1 are also reported, but obvious species differences are admitted and the effects are controversial. PKC activation decreased the SGLT1 transport capacity in rats and rabbits, but increased the capacity in humans[56].

In other reports, adenosine monophosphate-activated protein kinase activation increased maximal sodium-dependent glucose transport[61,62], knockout of the serum- and glucocorticoid-inducible kinase 3 caused a decrease of intestinal SGLT1 activity[63], and Ste20p-related proline alanine-rich kinase caused a decrease of SGLT1 abundance in the plasma membrane[64].

Intestinal SGLT1 activity and expression are regulated by dietary carbohydrate content. The SGLT1 activity and expression increased in mice, rats and sheep fed a high-sugar diet[65], and is maintained by the presence of luminal nutrients in the human intestine[66]. In addition, SGLT1 activity and expression are related to a diurnal rhythm that correlates waking hours with the highest expression of SGLT1[67,68].

Basal properties of SGLT2

The SGLT2 protein, encoded by SLC5A2, is composed of 672 amino acids and its NH_2 and COOH termini are extracellular[46]. The K_m values in human SGLT2 for glucose and sodium are 2 and 25 mmol/L, respectively, and, differently from SGLT1, SGLT2 is a low-affinity and high-capacity glucose transporter[39,51]. SGLT2 is predominantly expressed in the kidney of rodents and humans, and low mRNA expressions were detected in the mammary glands, testis, liver, lung, intestine, skeletal muscle, spleen and cerebellum[39,51,52,69,70]. Also, SGLT2 is reportedly expressed in pancreatic α-cells and related to glucagon secretion[53]. SGLT2 is localized in the luminal membrane of the segment (S)1 and S2 segments of renal proximal tubules in humans and rodents, whereas SGLT1 is localized in the luminal membrane of the S3 segment[39,52,70,71]. SGLT2 is mainly responsible for glucose reabsorption in nephron, and ≥80% of the filtered glucose is reabsorbed in the S1 and S2 segments of the proximal tubules through SGLT2[45,72].

Protein kinase A and PKC activation increased glucose uptake by 225 and 150%, respectively, in human embryonic renal cells expressing SGLT2[73]. As for the mechanisms, the PKA-mediated effect might be related to an increased rate of vesicle fusion with the membrane; however, no such mechanism was found on the PKC-mediated effect. Also, SGLT2 expression reportedly increased through the activation of exchange protein directly activated by cyclic adenosine monophosphate/PKA through extracellular signal-regulated kinase/p38 and mitogen-activated protein kinase[73,74]. In the renal pig cell line, interleukin-6 and tumor necrosis factor-α increased SGLT2 mRNA and protein expressions[75], and similarly, the phosphorylation of transforming growth factor-β1 and the downstream transcription factor, smad3, increased the SGLT2 protein level in human renal proximal tubular cells[76].

Functional properties of SGLTs in the small intestine

SGLT1 in the small intestine is localized in the apical cell membrane composing brush border (Figure 1)[6,52,54]. SGLT1 is

responsible for the transport of glucose or galactose from the lumen into the epithelial cells, whereas the facilitative transporter, GLUT2, is subsequently responsible for the transport of glucose from the basolateral membrane into the blood circulation[77,78].

The level of SGLT1 expression provides the capacity for glucose absorption and undergoes short-term and long-term regulations depending on the luminal nutrients[65,66]. A high-glucose diet or a high-sodium diet reportedly increases the level of SGLT1 expression in the small intestine[65,66]. Also, an increase in the luminal glucose concentrations induces GLUT2 translocation to the brush border membrane[78,79].

The SGLT1 expression in the small intestine is reportedly increased in diabetes, which is considered to be related to the response to greater dietary glucose intake. Intestinal SGLT1 mRNA expression increased in diabetic animal models, such as streptozotocin-induced diabetic models and Otsuka Long-Evans Tokushima Fatty rats[80,81]. In type 2 diabetes patients, the intestinal SGLT1 mRNA and protein expressions in the brush border membrane were higher, and also the intestinal glucose uptake was elevated[82]. The upregulation of SGLT1-mediated glucose uptake in the small intestine is considered to induce the rapid postprandial hyperglycemia in diabetes[83,84].

Functional properties of SGLTs in the kidney

In the kidney, glucose is transported through the apical membrane of the proximal convoluted tubule by SGLT2 and SGLT1, and exits through the basolateral membrane of the proximal tubule by the facilitative transporters GLUT2 and GLUT1[39,85]. SGLT2 is expressed in the upper part of the proximal tubule,

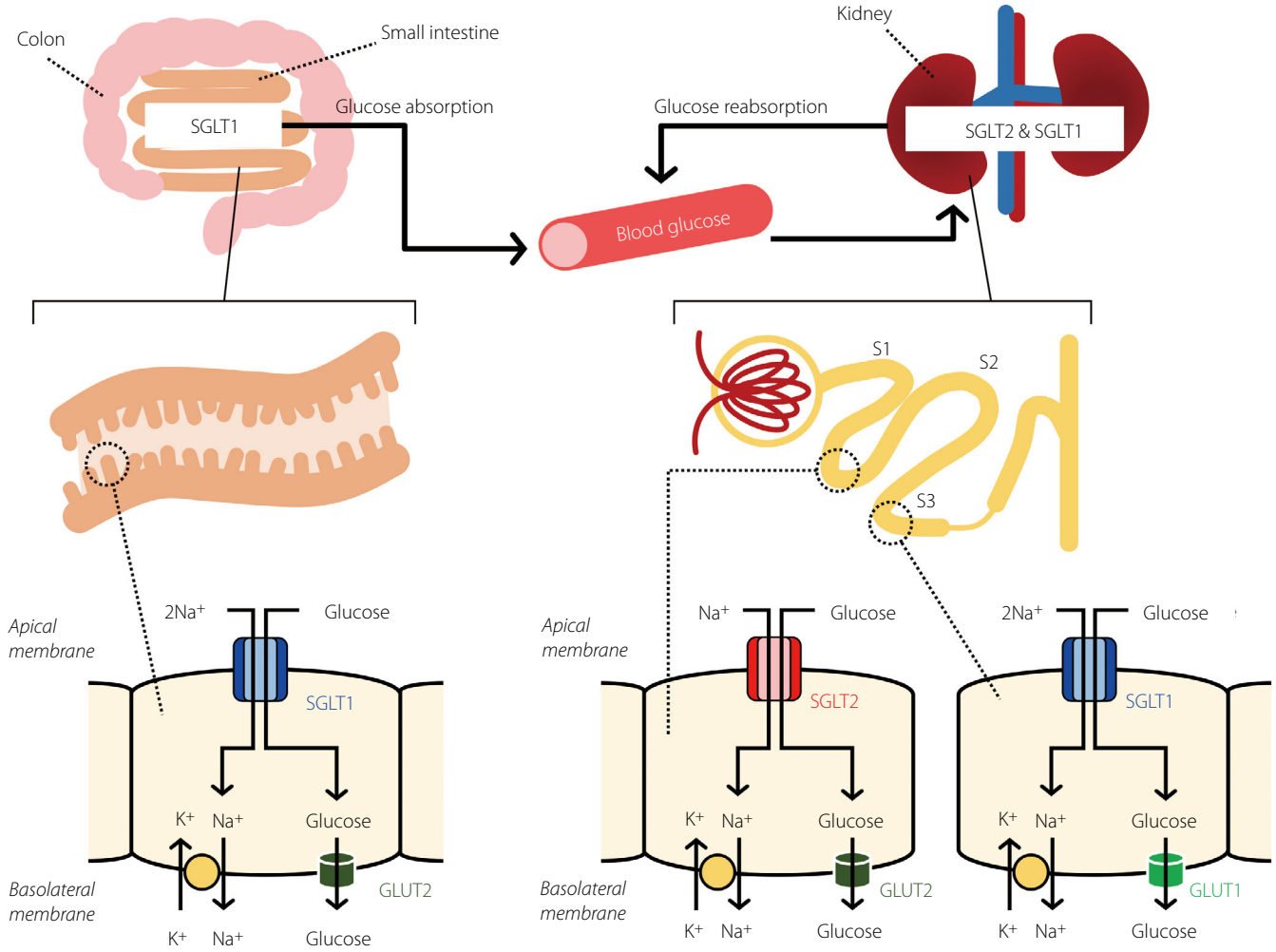

Figure 1 | Glucose handling through sodium–glucose cotransporter (SGLT)1 and SGLT2. In the small intestine, dietary glucose is mainly absorbed by SGLT1 on the brush border membrane. SGLT1 has a high-affinity (Michaelis–Menten constant [K_m] = 0.4 mmol/L) for glucose, and transports sodium and glucose with a 2:1 stoichiometry. In the kidney, filtered glucose by the renal glomerulus is reabsorbed by SGLT2 and SGLT1 expressed in the luminal membrane of the segment (S)1 and S2 segments, and S3 segment of proximal tubules, respectively. The affinity of SGLT2 for glucose is lower (K_m = 2 mmol/L), and transport of sodium and glucose by SGLT2 occurs with a 1:1 stoichiometry. GLUT, glucose transporter.

S1 and S2 segments, whereas SGLT1 is expressed in the downward part of the proximal tubule, the S3 segment in humans and rodents (Figure 1)[52,71,86].

In the capacity of filtered glucose reabsorption in euglycemia, SGLT2 exerts the main function, showing the aforementioned ≥80% glucose reabsorption, whereas SGLT1 reabsorbs the remaining glucose or approximately 5% of the filtered glucose[77,86,87]. As a point to be noted, the coupling ratio of glucose and sodium is different between the two cotransporters: SGLT2 transports glucose and sodium in a 1:1 ratio, whereas SGLT1 transports glucose and sodium in a 1:2 ratio[38,39]. The transport property of SGLT2 enhances the concentrating power to reabsorb the glucose delivered to the distal part S3 segment of the proximal tubule[49]. Furthermore, it is reported that SGLT1 prepares the highly reserved ability of glucose reabsorption[72,87,88]. When pharmacological SGLT2 inhibition induces the glucose flow downstream in the distal proximal tubule, SGLT1 can compensate for the reabsorption of glucose. As a result, euglycemic humans treated with SGLT2 inhibitors maintained a fractional glucose reabsorption of 40–50%[72,87], and the mean value of fractional glucose reabsorption in euglycemic SGLT2 knockout (KO) mice was 36%[86]. In wild mice, SGLT2 inhibitor, empagliflozin, dose-dependently increased the urinary glucose excretion, whereas the dose–response curve was shifted leftward and the maximum response doubled in SGLT1 KO mice[87]. The compensatory effect of SGLT1 is also supported by studies in SGLT1/SGLT2 double KO mice[89,90] and SGLT1 KO mice treated with SGLT2 inhibitor[87]. Sustained hyperglycemia, which induces exceeding of the transport capacity of the proximal SGLT2, increased the glucose flow to the distal proximal tubule and enhanced the SGLT1-mediated glucose reabsorption[7]. The reserved ability of glucose reabsorption and compensatory effect of SGLT1 are notable properties in consideration of the physiological function.

In type 1 and type 2 diabetes animal models, the renal SGLT2 protein level was reportedly increased[42,91], whereas the reported results for renal SGLT1 levels are controversial. Streptozotocin rats showed increased mRNA and protein expressions of SGLT1 in the renal cortex[92,93]. Also, renal SGLT1 mRNA expression in Zucker fatty rats was increased[94]. In *ob*/*ob* mice, the renal membrane SGLT1 protein level was increased, but the mRNA expression was decreased[95]. In contrast, it was reported that the renal membrane SGLT1 protein level was decreased in diabetic Akita mice[96]. SGLT2 and SGLT1 properties in renal glucose reabsorption in euglycemic condition are well understood; however, those properties in the diabetic state remain poorly understood, and in particular, a better understanding of the physiological significance in the renal SGLT1 regulation is a pivotal subject for the future.

Functional properties of SGLTs in the heart

The localization of SGLT1 protein was found in capillaries of the heart in humans and rats[52,97], whereas the expression was not found in capillaries of the small intestine[97]. Also, SGLT1 was reportedly expressed in the cell membrane of cardiomyocytes in humans and mice[98,99]. Thus, cardiac SGLT1 might be involved in glucose transport from capillaries into the cardiomyocytes. In contrast, SGLT2 is not expressed in the heart. In the heart, two facilitated glucose transporters, GLUT1 and GLUT4, play a primary role in glucose uptake: GLUT1 for basal glucose uptake, and GLUT4 for insulin-dependent glucose uptake[100]. In consideration of the physiological roles of SGLT1 in the heart, the involvement with the facilitated glucose transporters is essential and cannot be bypassed.

Cardiac SGLT1 mRNA expression is reportedly increased in patients with type 2 diabetes and diabetic cardiomyopathy[101]. In streptozotocin diabetic rats, GLUT4 mRNA and protein expressions were decreased, whereas GLUT1 mRNA expression was not significantly changed[102,103]. The reduction of cardiac GLUT4 activity led to a decrease of glucose uptake and development of diabetic cardiomyopathy, whereas the physiological roles of GLUT1 in the heart remain unclear[104–106].

A recent study reported that chronic cardiac overexpression of SGLT1 in mice led to pathological cardiac hypertrophy and left ventricular failure, and cardiac knockdown of SGLT1 attenuated the disease phenotype[107]. In contrast, a recent study also reported that dual SGLT1/SGLT2 inhibitor exacerbated cardiac dysfunction after experimental myocardial infarction in rats[108]. Considering that SGLT2 is not expressed in the heart, this effect might be linked to SGLT1 inhibition. Whether cardiac SGLT1 inhibition exerts protective effects on cardiovascular disease still remains unclear. Further research is required.

Functional properties of SGLTs in the brain

SGLT1 mRNA expression was found in the brains of humans, rabbits, pigs and rodents[109–111]. In rabbits and pigs, SGLT1 mRNA expression was found in neurons of the frontal cortex, Purkinje cells of the cerebellum and neurons of the hippocampus[50]. In rodents, SGLT1 mRNA expression was found in neurons of the brain cortex, hippocampus, hypothalamus, corpus striatum and cerebellum[50,111]. The SGLT1 protein was reportedly expressed in small vessels of the rodent brain[109]. Also, a radioactively labeled SGLT1 selective glucose analog could not pass the blood–brain barrier, suggesting that SGLT1 is only localized in the luminal membrane of endothelial cells[50]. In consideration of the localization and function of SGLT1, SGLT1 in the brain might play a key role as an energy supply source for neurons on increased glucose demand, such as in hypoxemia and hypoglycemia.

Functional properties of SGLTs in other organs

There are some reports of SGLT1 in the lung, liver, pancreas and T lymphocytes. SGLT1 mRNA was detected in the trachea, bronchi and lung tissue in humans[51,52], and SGLT1 protein was detected in alveolar type 2 cells, and in the luminal membrane of Clara cells in bronchioles in humans and rats[52]. SGLT1-mediated glucose uptake might be responsible for fluid absorption, and provides energy for the production of

surfactants in alveolar type 2 cells, and for mucin and surfactants in Clara cells.

SGLT1 mRNA was detected in the liver and gallbladder in humans[51], and SGLT1 protein was detected in the apical membrane of bile duct epithelial cells in humans and rats[52,71].

Small amounts of SGLT1 mRNA were detected in the pancreas of humans, and SGLT1 mRNA and protein expressions were found in pancreatic α-cells of humans and mice[51,53]. Also, SGLT1 mRNA expression was found in activated T lymphocytes of mice[112]. Physiological roles of SGLT1 in the liver, pancreas and T lymphocytes are not well understood.

THERAPEUTIC POTENTIAL OF SGLT1 AND SGLT2 INHIBITION

The therapeutic potential of selective SGLT2 inhibitors as an antihyperglycemic strategy has been well established. In contrast, the therapeutic potential, including efficacy and safety, of dual SGLT2/SGLT1 inhibitor or selective SGLT1 inhibitor remains less clear (Table 2).

SGLT2 inhibitors

Selective SGLT2 inhibitors – dapagliflozin, canagliflozin, empagliflozin, ipragliflozin, luseogliflozin and tofogliflozin – have been approved for the treatment of type 2 diabetes[113]. These SGLT2 inhibitors reduce plasma glucose levels by a different mechanism than other antidiabetic drugs, involving an increase of the renal glucose excretion through SGLT2 in the proximal tubule leading to diminished glucose toxicity. In contrast, mechanisms of other drugs are as for metformin: inhibition of gluconeogenesis in the liver; sulfonylurea derivatives, glucagon-like peptide (GLP)-1 analogs and dipeptidyl peptide-4 inhibitors: increase of insulin secretion in the pancreas; and thiazolidinediones: enhancement of insulin sensitivity. These SGLT2 inhibitors have different selectivity for inhibition of SGLT2 versus SGLT1. SGLT2/SGLT1 selectivity is ≥1,000-fold higher in dapagliflozin, empagliflozin, luseogliflozin and tofogliflozin, whereas the selectivity of canagliflozin and ipragliflozin is lower, at 190- and 250-fold, respectively[113].

Table 2 | Preclinical and clinical sodium–glucose cotransporter 1, sodium–glucose cotransporter 2 and dual sodium–glucose cotransporter 1/2 inhibitors

Selective SGLT1 inhibitors	Selective SGLT2 inhibitors	Dual SGLT1/2 inhibitors
KGA-2727	Dapagliflozin	Sotagliflozin
GSK-1614235 (mizagliflozin)	Canagliflozin	Licogliflozin
LX2761	Empagliflozin	
JTT-662	Ipragliflozin	
	Luseogliflozin	
	Tofogliflozin	
	Ertugliflozin	

SGLT, sodium–glucose cotransporter.

In preclinical studies in diabetic animal models, the SGLT2 inhibitors decreased fasting and non-fasting glucose levels, hemoglobin A1c levels, and blood pressure, and improved glucose intolerance[114–117]. Furthermore, SGLT2 inhibitors have a different mechanism from the other antidiabetic drugs, as described above, and can be used in combination with those drugs, as well as in monotherapy for the treatment of type 2 diabetes[118–122].

Recent studies reported that SGLT2 inhibitors had a renal protective effect in animal models of diabetic nephropathy[122–124]. The renal protective effects of SGLT2 inhibitors also have been shown in clinical trials[9,125,126]. The mechanism of action is speculated as follows: SGLT2 inhibitor increases the amount of sodium delivery to the distal tubule by suppressing sodium absorption in the proximal tubule. As a result, the tubuloglomerular feedback through the macula densa is activated, and this allows afferent arteriolar contraction and normalizes the glomerular filtration rate[127].

SGLT1 inhibitors

Postprandial hyperglycemia is a risk factor for cardiovascular failure and diabetic microangiopathy, including retinopathy[128–130]. As glucose absorption from the small intestine is mostly mediated by SGLT1, an improvement of postprandial hyperglycemia with SGLT1 inhibitor would definitely be a useful therapy. In diabetic rats, a single dose of KGA-2727, a selective SGLT1 inhibitor, improved postprandial hyperglycemia, and its chronic administration reduced hemoglobin A1c levels[131], suggesting that SGLT1 inhibition might maintain good glycemic control for the long term. In an oral glucose tolerance test with KGA-2727, plasma insulin levels, as well as plasma glucose levels, were reduced, and protective effects on the pancreas are also expected.

Recent studies reported that SGLT1 KO mice and mice treated with phloridzin had lower plasma total GLP-1 levels 5 min after glucose challenge than wild-type mice and control mice, respectively[77,132]. This result suggests that SGLT1 is required to trigger GLP-1 secretion in the early phase after glucose stimulation. In contrast, another study reported that SGLT1 KO mice had high plasma total GLP-1 levels from 30 min to 6 h after a glucose-containing meal[89]. The increase of plasma total GLP-1 in the late phase after a meal was also observed in healthy humans treated with SGLT1 inhibitor[84] and patients with type 2 diabetes treated with SGLT1/2 inhibitor[83]. One possible mechanism of delayed GLP-1 release is fermentation of glucose to short-chain fatty acids (SCFAs). SGLT1 inhibition in the early intestine reduces glucose absorption and thereby increases glucose delivery to the more distal parts of the small intestine, where glucose is used by the microbiome to form SCFAs. SCFAs induce glucagon-like peptide-1 secretion through G protein-coupled receptors, including G protein-coupled receptor 41 and G protein-coupled receptor 43[133]. From the above, although SGLT1 inhibition reduces glucose-stimulated GLP-1 release in the early phase, SCFAs generated by fermentation of

glucose induce GLP-1 release in the late phase, suggesting that SGLT1 inhibitor increases net circulating GLP-1 levels.

As a concerning point, in the small intestine, the SGLT1 inhibitor is considered to induce gastrointestinal side-effects, including diarrhea, but no serious gastrointestinal side-effects were observed in the treatment of selective SGLT1 inhibitors, GSK-1614235 and KGA-2727, or a dual SGLT1/SGLT2 inhibitor, sotagliflozin[83,84,134].

The SGLT1 inhibitors induce a delay of absorption of monosaccharides and thus their retention, and the SGLT1 inhibitors might improve the intestinal condition in diabetes patients through changes in gut microbiota. An increase in colonic microbiol production of propionate with increased glucose exposure reportedly contributed to positive intestinal metabolic effects[10].

SGLT1 is expressed in the brush border membrane of the S3 segment of proximal tubule in the kidney, and reabsorbs glucose that escapes from SGLT2-mediated reabsorption in the S1 and S2 segments[39,52]. Studies on SGLT2 KO mice and selective SGLT2 inhibitors described the renal transport capacity of SGLT1, showing that the SGLT1-mediated glucose reabsorption is maintained at 40–50% on inhibition of SGLT2 under euglycemic conditions (Figure 2)[87]. Inhibition of SGLT2 under the conditions of prolonged and severe hyperglycemia that exceeds the transport capacity of SGLT2 activates the full renal transport capacity of SGLT1, and SGLT1 exerts a compensatory

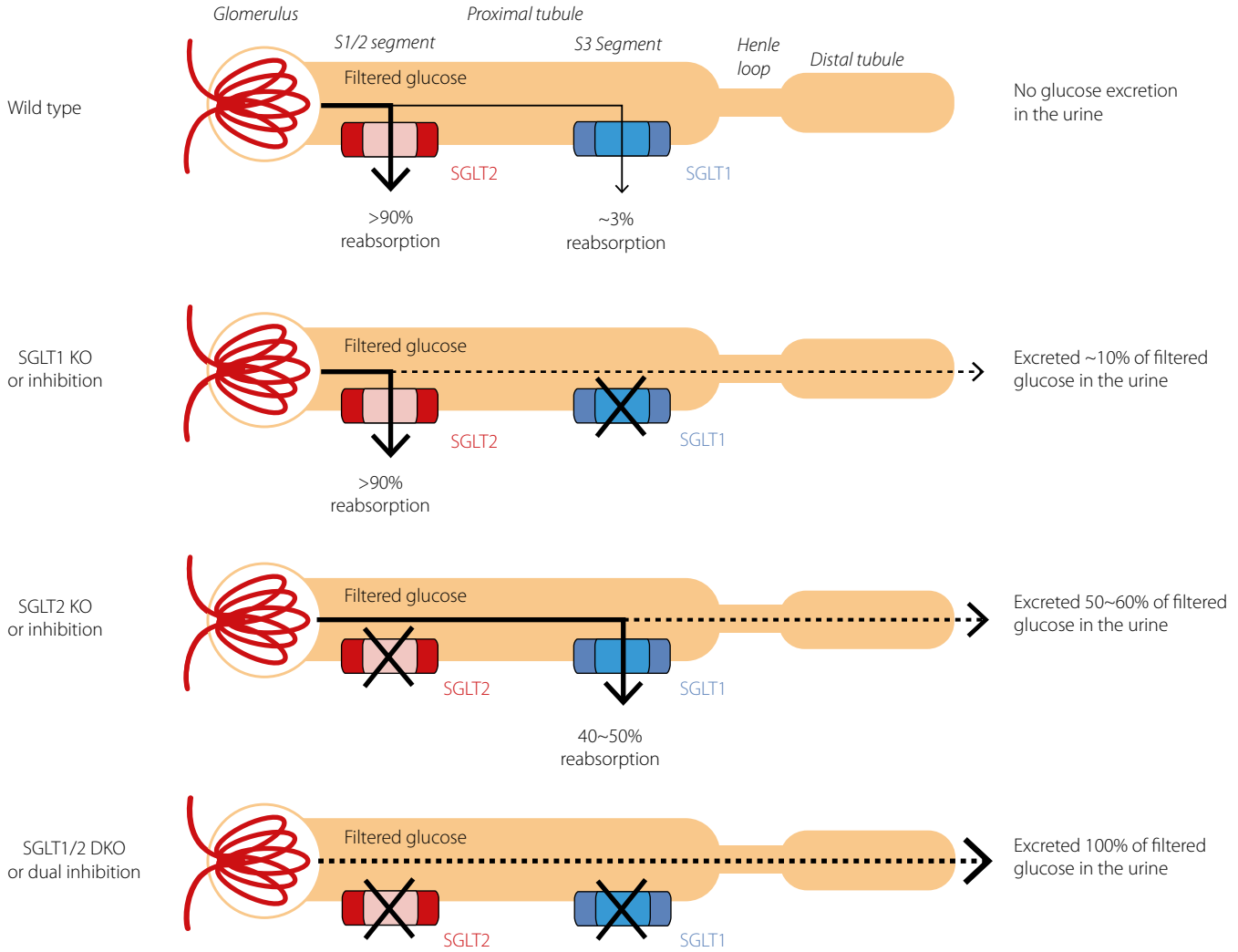

Figure 2 | Capacity of sodium–glucose cotransporter (SGLT)1 and SGLT2 for filtered glucose reabsorption under euglycemic conditions. Under euglycemic conditions, most filtered glucose is reabsorbed by SGLT2 expressed in the segment (S)1 and S2 segments of proximal tubules, and the remaining is reabsorbed by SGLT1 expressed in the S3 segment of proximal tubules, resulting in no glucose being detected in the urine. Complete suppression of transport activity of SGLT1 (e.g., SGLT1 knockout [KO] or inhibition) only slightly increases the urinary glucose excretion, because most filtered glucose is reabsorbed by SGLT2. If SGLT2 is absent (e.g., SGLT2 KO or inhibition), SGLT1 reabsorbs 40–50% of filtered glucose. If both SGLT1 and SGLT2 are absent (e.g., SGLT1/2 double KO [DKO] or dual inhibition), almost all of the filtered glucose is excreted in the u-rine.

function in renal reabsorption of glucose. Therefore, the combination therapy of an SGLT1 inhibitor and an SGLT2 inhibitor or a dual SGLT1/SGLT2 inhibitor is expected to induce significantly greater glucosuria and glycemic control than either an SGLT1 or SGLT2 inhibitor alone[87,89,135]. Also, a stronger effect of dual SGLT1/SGLT2 inhibition on blood glucose levels was observed in mice with modest hyperglycemia, as well as those with euglycemia[87,89]. Thus, the combined effects of dual SGLT1/SGLT2 inhibition might induce synergistic effects on the early and distal proximal tubules.

Although selective SGLT1 inhibitors are not on the market yet, some compounds (e.g., LX2761 and JTT-662) are under development for the treatment of diabetes.

CONCLUSION AND PERSPECTIVE

In this review, we described the basal properties of GLUTs and SGLTs, and also the functional properties of SGLT1 and SGLT2, and focused on the pharmacological potential of SGLT1 or SGLT2 inhibition alone, and the dual inhibition of SGLT1 and SGLT2. These glucose transporters have diverse multiple functions, and are attractive as therapeutic targets for metabolic diseases.

In basic studies of the kidney in SGLT2 KO mice and using an SGLT2 inhibitor, a high reserved ability of glucose reabsorption has been disclosed. Six selective SGLT2 inhibitors have been approved for treatment of diabetes, and the usefulness is widely admitted.

Based on the phenotype of loss-of-function of the SGLT1 gene in humans and mice, it is clear that SGLT1 is the main transporter of glucose absorption in the small intestine. As described above, it is expected that SGLT1 inhibitors would improve postprandial hyperglycemia in diabetes patients by reducing glucose absorption in the small intestine. This mechanism of action would be beneficial, particularly in diabetes patients with declining renal function, because SGLT2 inhibitors are less effective in such patients.

A dual SGLT1/SGLT2 inhibitor or a combination of an SGLT1 inhibitor and SGLT2 inhibitor might be good option for the treatment of diabetes, because dual inhibition leads to blockade of both intestinal and renal glucose absorption, thus lowering blood glucose levels robustly. Combined treatment of SGLT1 inhibitor and dipeptidyl peptide-4 inhibitor might also be a good strategy, because the combination could effectively increase active GLP-1 levels.

Diabetes is a leading cause of end-stage kidney disease and cardiovascular disease. Despite the emergence of a large variety of antihyperglycemic agents, it is still difficult to maintain good glycemic control with monotherapy over a long-term period. These agents also have potential risks and side-effects (e.g., hypoglycemia, ketoacidosis and more). For these reasons, other antihyperglycemic agents with different mechanisms of action are required. Inhibition of SGLT1 or dual inhibition of SGLT1/2 are novel therapeutic strategies for glycemic control in diabetes patients. However, further studies are required to confirm the long-term efficiency and safety of these strategies.

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DISCLOSURE

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