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 diffusion1,2; and (ii) sodium–glucose cotransporters (SGLTs), which actively transport glucose against the concentration gradient by coupling with sodium3,4. 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 operation1. 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 gradient5. 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 cells3,6.

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 membrane5,7. 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 circulation7,8.

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 trials9. Furthermore, SGLT1 is responsible for glucose absorption in the small intestine and for reabsorption of the part of the filtered glucose load in the kidney10, and might be an attractive target for the maintenance of good glycemic control and improvement of renal dysfunction7,11. 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 tissues4. 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/GLUT135,45.

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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. GLUT1 is responsible for constitutive or basal glucose uptake in the cells and can transport aldose, including pentose and hexose. 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 its high affinity and capacity. In contrast, in human β-cells, GLUT1 is primarily expressed, and GLUT2 is expressed at an extremely low level. In the liver, GLUT2 is expressed in the sinusoidal membrane and enables the bidirectional transport of glucose. The GLUT2 in the kidney and small intestine is responsible for the movement of glucose out of absorptive epithelial cells into the blood circulation. GLUT3 in the intestine is responsible for the movement of glucose out of absorptive epithelial cells into the blood circulation. GLUT7 is primarily expressed in the small intestine epithelium through GLUT2 located in the basolateral membrane. GLUT8 has been identified as a proton hexose transporter protein, with expression in the brain, in particular the brain. GLUT9 is highly expressed in the kidney and liver. 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. 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. 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. The NH2 and COOH terminals are located in extracellular and intracellular membranes, respectively, and the glucose-
binding domain is supposed to include amino acid residues 457–460\(^4,47\). SGLT1 is a high-affinity transporter for glucose (Michaelis–Menten constant \([K_m] = 0.4 \text{ mmol/L}\) 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 \(\alpha\)-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 \(\alpha\)-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 intestine 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\(^{59,68}\). 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\(^{38,51}\). 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 \(\alpha\)-cells and related to glucagon secretion\(^5\). 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\(^{23,74}\). In the renal pig cell line, interleukin-6 and tumor necrosis factor-\(\alpha\) increased SGLT2 mRNA and protein expressions\(^{75}\), and similarly, the phosphorylation of transforming growth factor-B1 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\(^7\).\(^8\)

The level of SGLT1 expression provides the capacity for glucose absorption and undergoes short-term and long-term regulations depending on the luminal nutrients\(^6\).\(^5\).\(^6\) A high-glucose diet or a high-sodium diet reportedly increases the level of SGLT1 expression in the small intestine\(^6\).\(^5\).\(^6\). Also, an increase in the luminal glucose concentrations induces GLUT2 translocation to the brush border membrane\(^7\).\(^8\).\(^9\).

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\(^8\).\(^0\).\(^1\). 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\(^8\).\(^2\). The upregulation of SGLT1-mediated glucose uptake in the small intestine is considered to induce the rapid postprandial hyperglycemia in diabetes\(^8\).\(^3\).\(^8\).

**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\(^3\).\(^9\).\(^8\). SGLT2 is expressed in the upper part of the proximal tubule, mRNA expression increased in diabetic animal models, such as streptozotocin-induced diabetic models and Otsuka Long-Evans Tokushima Fatty rats\(^8\).\(^0\).\(^1\). 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\(^8\).\(^2\). The upregulation of SGLT1-mediated glucose uptake in the small intestine is considered to induce the rapid postprandial hyperglycemia in diabetes\(^8\).\(^3\).\(^8\).

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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 glucose72,86,87. 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 ratio38,39. The transport property of SGLT2 enhances the concentrating power to reabsorb the glucose delivered to the distal part S3 segment of the proximal tubule49. Furthermore, it is reported that SGLT1 prepares the highly reserved ability of glucose reabsorption72,87,88. When pharmacological SGLT2 inhibition induces the glucose flow downstream in the 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 mice87. The compensatory effect of SGLT1 is also supported by studies in SGLT1/SGLT2 double KO mice89,90 and SGLT1 KO mice treated with SGLT2 inhibitor47. 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 reabsorption7. 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 increased42,91, whereas the reported results for renal SGLT1 levels are controversial. Streptozotocin rats showed increased mRNA and protein expressions of SGLT1 in the renal cortex92,93. Also, renal SGLT1 mRNA expression in Zucker fatty rats was increased42. In ob/ob mice, the renal membrane SGLT1 protein level was increased, but the mRNA expression was decreased95. In contrast, it was reported that the renal membrane SGLT1 protein level was decreased in diabetic Akita mice96. 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 rats52,97, whereas the expression was not found in capillaries of the small intestine97. Also, SGLT1 was reportedly expressed in the cell membrane of cardiomyocytes in humans and mice30,98,99. 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 uptake100. 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 cardiomyopathy101. In streptozotocin diabetic rats, GLUT4 mRNA and protein expressions were decreased, whereas GLUT1 mRNA expression was not significantly changed102,103. 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 unclear104–106. 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 phenotype107. In contrast, a recent study also reported that dual SGLT1/SGLT2 inhibitor exacerbated cardiac dysfunction after experimental myocardial infarction in rats108. 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 rodents109–111. In rabbits and pigs, SGLT1 mRNA expression was found in neurons of the frontal cortex, Purkinje cells of the cerebellum and neurons of the hippocampus50. In rodents, SGLT1 mRNA expression was found in neurons of the brain cortex, hippocampus, hypothalamus, corpus striatum and cerebellum50,111. The SGLT1 protein was reportedly expressed in small vessels of the rodent brain109. 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 cells50. 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 humans51,52, and SGLT1 protein was detected in alveolar type 2 cells, and in the luminal membrane of Clara cells in bronchioles in humans and rats52. SGLT1-mediated glucose uptake might be responsible for fluid absorption, and provides energy for the production of fluid.
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\(^5\), and SGLT1 protein was detected in the apical membrane of bile duct epithelial cells in humans and rats\(^5\). Small amounts of SGLT1 mRNA were detected in the pancreas of humans, and SGLT1 mRNA and protein expressions were found in pancreatic \(\alpha\)-cells of humans and mice\(^5,13\). Also, SGLT1 mRNA expression was found in activated T lymphocytes of mice\(^12\). 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 \(\geq\)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\(^113\).

**SGLT1 inhibitors**

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\(^127\).

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**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            | Luseogliflozin         |
| LX2761                    | Empagliflozin             | Tofogliflozin          |
| JTT-662                   | Ipragliflozin             | Ertugliflozin          |

SGLT, sodium–glucose cotransporter.

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In particular, 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\(^127\).
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, sitagliptin.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

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**Figure 2** | Capacity of sodium–glucose cotransporter (SGLT1) 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 urine.
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\textsuperscript{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\textsuperscript{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 peptidase-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, ketoadiposis 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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Ryuhei Sano and Yuichi Shinozaki are employees of Japan Tobacco Inc. Takeshi Ohta declares no conflict of interest.

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