Role of sodium-glucose transporters in glucose uptake of the intestine and kidney

Glucose is essential for energy production in the living body; the glucose transporter plays a critical role in various organs. Glucose transporters are classified into two families: facilitative glucose transporters (GLUTs) and sodium-dependent glucose transporters (SGLTs), through which glucose is transported by facilitated diffusion, and Na^+/glucose are co-transported by an electrochemical gradient across the membrane, respectively. Six isoforms of the *SGLT* gene belong to the *SLC5* gene family and they consist of 15 exons (Table 1). All SGLT proteins have 14 transmembrane helices in topology. SGLT1 and SGLT2 function as a glucose/galactose transporter and a glucose transporter across the membrane, respectively. SGLT3 is not a transporter in some species; for example, in humans, in which SGLT3 is thought to be a glucose sensor expressed in the enteric nervous system and muscle, whereas the functions of SGLT4, SGLT5, and SGLT6 are not known.

SGLT1 is expressed mainly in the intestine and kidney; SGLT2 is expressed highly in the kidney (Figure 1). Recently, Gorboulev *et al.*[1] reported that SGLT1 is expressed in the brush border membrane (BBM) of the intestine, and that glucose absorption across the BBM disappeared in SGLT1-deficient mice, which indicates that intestinal glucose absorption in the intestine is mediated predominantly by SGLT1.

Some studies found that SGLT1 is expressed in incretin-secreting cells and is involved in incretin secretion[2,3]. In addition, it is reported that the SGLT inhibitor, phrorizin, reduces incretin secretion[3]. Incretin is the intestinal hormone that is secreted on meal ingestion and potentiates insulin secretion from pancreatic β-cells in a glucose-dependent manner. Gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), the major incretins, are secreted from K-cells in the proximal small intestine, and from L-cells in the distal small intestine and colon, respectively. Glucose, protein and fat all induce incretin secretions, but fat especially induces GIP secretion in human studies[4]. Gorboulev *et al.*[1] reported that fat ingestion stimulates both GIP and GLP-1 secretion in both wild-type and SGLT1-deficient mice, but that glucose does not in SGLT1-deficient mice, clearly showing that SGLT1 plays a critical role in incretin secretion in response to glucose *in vivo*. Glucokinase, sulfonylurea receptor 1 (SUR1), and Kir6.2, which are associated with glucose-induced insulin secretion in β-cells, are reported to be expressed in both K-cells and L-cells, suggesting that incretin secretion is exerted by glucose metabolism in the cells. In contrast, it has been reported that a-methyl-D-glucopyranoside, which is not metabolized in the glycolytic pathway or tricarboxylic acid cycle, induces incretin secretion[5]. In such a case, membrane depolarization as a result of sodium ion uptake with unmetabolizable glucose into the cell through SGLT1 would be critical for incretin secretion. However, the relative importance in incretin secretion of glucose absorption from the lumen side and from glucose metabolism in the cells remains unclear.

In the kidney, glucose filtered in glomeruli is reabsorbed in proximal renal tubules, and is not usually secreted in the urine. However, when the blood glucose level is over 160~180 mg/dL, glucose reabsorption exceeds reabsorption capacity and glucose does appear in the urine. SGLT1 is expressed mainly in the S2 and S3 segments of the proximal renal tubules, and reabsorbs one glucose molecule coupled with two sodium ions. SGLT2 has 60% homology with SGLT1 and is highly expressed in the BBM of the S1 segment of the proximal renal tubules. SGLT2 has a low affinity to glucose and reabsorbs one glucose molecule coupled with one sodium ion. It is thought that SGLT1 and SGLT2 reabsorb 10 and 90% of filtered glucose, respectively, in the kidney[6]. Considering that SGLT2 is largely involved in glucose reabsorption and that SGLT2 expression is upregulated in the diabetic rat[7], inhibition of SGLT2 might well be a new therapeutic approach to excrete glucose into the urine and manage blood glucose levels in type 2 diabetes mellitus

Table 1 | Subtypes of human sodium-dependent glucose transporter and tissue distribution

SGLT family (gene)	Function	Tissue distribution
SGLT1 (*SLC5A1*)	Glucose/galactose transporter	Intestine, trachea, kidney, heart, brain, testis, prostate
SGLT2 (*SLC5A2*)	Glucose transporter	Kidney, liver, thyroid, muscle, heart
SGLT3 (*SLC5A4*)	Glucose sensor?	Intestine, testis, uterus, lung, brain, thyroid
SGLT4 (*SLC5A9*)	?	Intestine, kidney, liver, brain, trachea, lung, uterus, pancreas
SGLT5 (*SLC5A10*)	?	Kidney, cortex
SGLT6 (*SLC5A11*)	?	Spinal cord, kidney, brain

SGLT, sodium-dependent glucose transporter.

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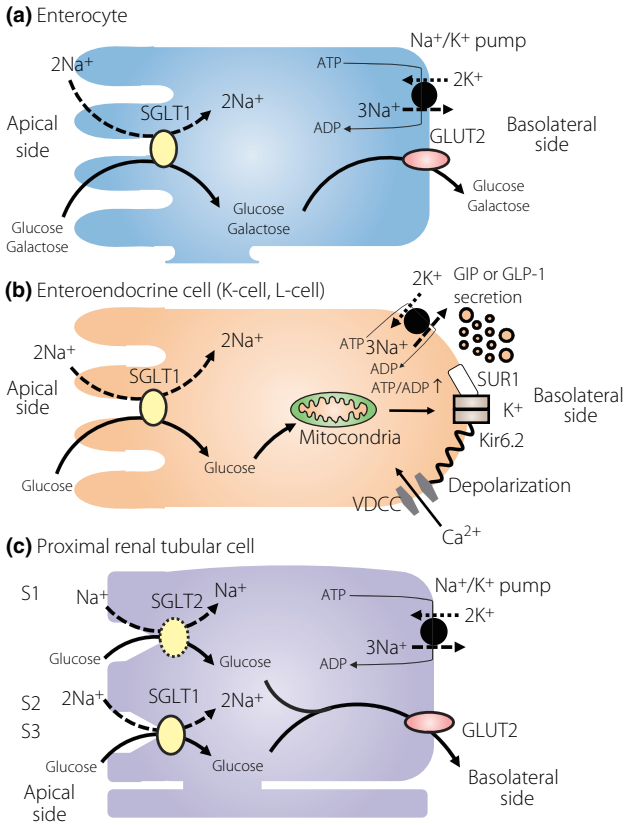

Figure 1 | Glucose absorption through sodium-dependent glucose transporter 1 (SGLT1) in (a) an enterocyte and (b) an enteroendocrine cell, and (c) glucose reabsorption through SGLT1 and sodium-dependent glucose transporter 2 (SGLT2) in a proximal renal tubular cell. ADP, adenosine diphosphate; ATP, adenosine triphosphate; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; GLUT, glucose transporter; SUR1, sulfonylurea receptor 1; VDCC, voltage-dependent calcium channel.

patients. To date, various SGLT2 inhibitors have been developed for treatment of type 2 diabetes mellitus. Interestingly, Gorboulev *et al.* showed that SGLT1-deficient mice lose just ~3% of the filtered glucose into the urine, whereas SGLT2-deficient mice lose ~60% of the filtered glucose into the urine, suggesting that wild-type mice do not use the maximal transport capacity of SGLT1 under normoglycemic conditions[1]. In diabetic patients, the glucose concentration is overwhelming in early proximal tubules and is even more in the patients with a SGLT2-specific inhibitor. In this condition, SGLT1 transporter might be performing at full capacity and minimizes the effects of the drug. In this context, SGLT1 inhibition might have therapeutic potential. However, it might reduce incretin secretion and induce side-effects, such as diarrhea and polyurea, the main symptoms of glucose–galactose malabsorption in patients with *SGLT1* gene mutations.

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REFERENCES

1. Gorboulev V, Schürmann A, Vallon V, *et al.* Na(+)-D-glucose cotransporter SGLT1 is pivotal for intestinal glucose absorption and glucose-dependent incretin secretion. *Diabetes* 2012; 61: 187–196.
2. Reimann F, Habib AM, Tolhurst G, *et al.* Glucose sensing in L cells: a primary cell study. *Cell Metab* 2008; 8: 532–539.
3. Gribble FM, Williams L, Simpson AK, *et al.* A novel glucose-sensing mechanism contributing to glucagon-like peptide-1 secretion from the GLUTag cell line. *Diabetes* 2003; 52: 1147–1154.
4. Yamane S, Harada N, Hamasaki A, *et al.* Effects of glucose and meal ingestion on incretin secretion in Japanese subjects with normal glucose tolerance. *J Diabetes Invest* 2012; 3: 80–85.
5. Moriya R, Shirakura T, Ito J, *et al.* Activation of sodium–glucose cotransporter 1 ameliorates hyperglycemia by mediating incretin secretion in mice. *Am J Physiol Endocrinol Metab* 2009; 297: E1358–E1365.
6. Ferrannini E, Solini A. SGLT2 inhibition in diabetes mellitus: rationale and clinical prospects. *Nat Rev Endocrinol* 2012; (Epub ahead of print). doi: 10.1038/nrendo.2011.243.
7. Freitas HS, Anhê GF, Melo KF, *et al.* Na(+)-glucose transporter-2 messenger ribonucleic acid expression in kidney of diabetic rats correlates with glycemic levels: involvement of hepatocyte nuclear factor-1alpha expression and activity. *Endocrinology* 2008; 149: 717–724.