

## Surprising Versatility of Na<sup>+</sup>-Glucose Cotransporters: SLC5

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SLC5 is an ancient gene family with 11 members in the human genome. These membrane proteins have diverse, multiple functions ranging from actively transporting solutes, ions, and water, to channeling water and urea, to sensing glucose in cholinergic neurons. Metabolic disorders have been identified that are associated with congenital mutations in two of the human genes.

For over a century, physiologists have been intrigued about the transport of ions, molecules, and water across biological membranes, especially against a concentration gradient. In the 1950s and 1960s it became clear that the energy for active transport comes directly or indirectly from the hydrolysis of ATP, directly in the case of ion pumps and indirectly in the case of cotransporters and antiporters. Crane and colleagues (3) were the first to propose that active solute transport may employ the potential energy inherent in the Na<sup>+</sup> gradient across the cell membrane. Specifically, they postulated that active glucose transport across the brush border of the intestinal epithelium is driven by the Na<sup>+</sup> gradient across the membrane, i.e., Na<sup>+</sup>-glucose cotransport. Following Crane, others, most notably Curran, Schultz, Hopfer, and Murer, provided compelling support for the cotransport hypothesis and broadened the concept to include the active transport of diverse solutes such as amino acids, neurotransmitters, osmolytes, vitamins, and anions. Cotransport (symport or secondary active transport) is now firmly entrenched as the mechanism that explains the active accumulation of solutes in cells of all organisms ranging from Archaea to man (see Refs. 11, 24, and 30).

### The Na<sup>+</sup>-Glucose Cotransporter Gene Family

Our group was the first to identify and then clone a Na<sup>+</sup> cotransporter, and we have pioneered the studies of the physiology, biochemistry, biophysics, and genetics of this class of membrane proteins (e.g., Ref. 27). The gene for the Na<sup>+</sup>-glucose cotransporter (*SGLT1*) is located on human chromosome 22 (22q12.3) and codes for a 73-kDa membrane protein. The evidence that *SGLT1* codes for the intestinal brush border Na<sup>+</sup>-glucose cotransporter is convincing:

1) the gene is predominantly expressed in mucosa of the small intestine;

2) the cDNA was cloned from intestinal mRNA;

3) the open reading frame codes for a 664-amino-acid membrane protein with a predicted weight (73 kDa) consistent with that of the brush border cotransporter;

4) the kinetics, sugar and cation specificity, and inhibitor profile of the clone fit very closely with those for sugar transport in the native tissue;

5) SGLT1 antibodies immunoreact with the brush border of enterocytes; and

6) the inherited disorder glucose-galactose malabsorption (GGM) is due to mutations in *SGLT1* (28, 31).

SGLT1 is the founding member of a large gene family (24), the SGLT or sodium:solute symporter family (SSF), containing over 450 members (see Swiss-Prot entry P13866 in Pfam at <http://www.sanger.ac.uk>). Approximately 230 genes share the common SSF architecture highlighted in **FIGURE 1** and also share the consensus pattern [GS]-2(2)-[LIY]-x(3)-[LIVMFYWSTAG](7)-x(3)-[LIY]-[STAV]-x(2)-G-G-[LMF]-x-[SAP]. Nine of the eleven human genes in this family (SLC5) have a known function (30). The consensus sequence for the six SGLTs and for the Na<sup>+</sup>-myoinositol cotransporter (SMIT1) [R-x-T-x-x-x-x-F-L-A-G-x-x-x-x-W-W-x-x-G-A-S-] is located near the NH<sub>2</sub> terminal of the protein (**FIGURE 1**).

### Versatility of Cotransporters

Whereas most work has focused on the predicted function of these membrane proteins, we have discovered that they have rather unexpected properties. The function of a newly identified gene is generally assigned by its homology to other genes of known function or by functional assays after expressing the gene in cells. Even with functional studies and in those cases in which

cDNAs were isolated by expression cloning (7), the physiological role of genes may not be revealed. The reason is that transporters are multifunctional (FIGURE 2). Examples of unexpected results include the human SGLT3, which is not a glucose transporter but a glucose sensor (5), and SLC5A8, which functions as a tumor-suppression gene as well as a cotransporter (2, 13). What are the functional activities of cotransporter genes?

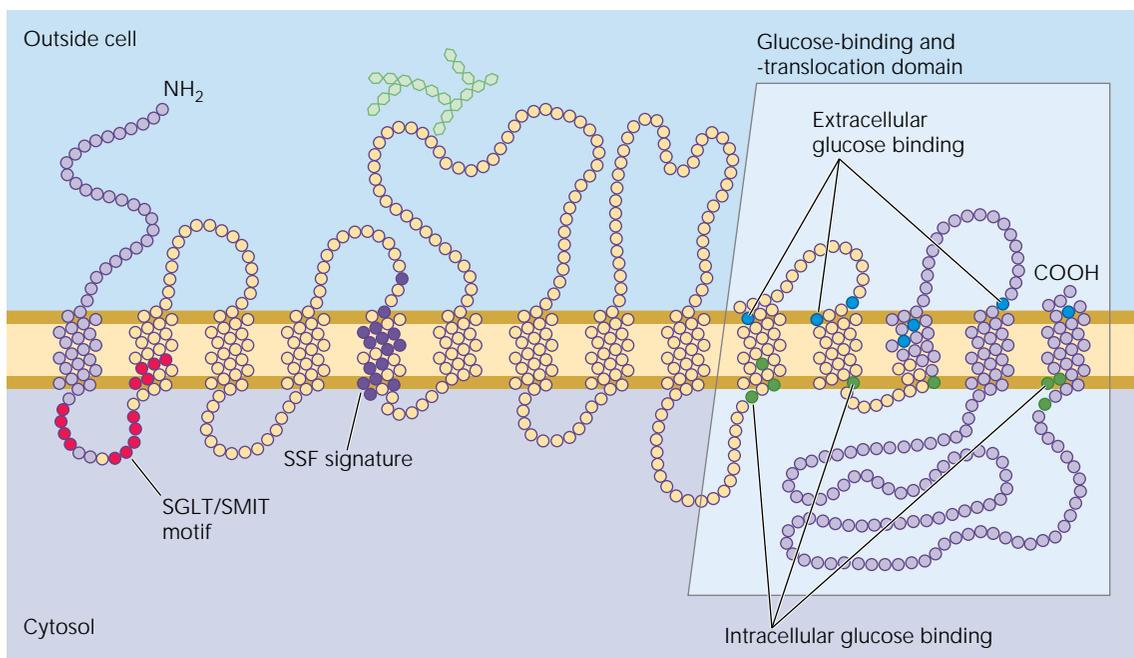
### Cotransport activity

Although functional studies have been carried out on only a few members of the SSF family, it is generally believed that all are sodium-coupled cotransporters for sugars, amino acids, vitamins, osmolytes, and ions such as iodide. In this review we will focus on SGLT1.

The kinetics and selectivity of SGLT1 have been examined by expressing the transporter in oocytes, cultured mammalian and insect cells, and bacteria and by reconstitution of the purified recombinant protein in proteoliposomes (14, 20, 21, 25, 27). Similar results have been recorded for all recombinant SGLT1s tested so far, i.e., human, rabbit, rat, and sheep. These all behave as tightly coupled transporters by which two Na<sup>+</sup> ions are transported simultaneously with one sugar molecule. Cotransport is completely reversible. The direction of transport simply depends on the direction of the sugar- and Na<sup>+</sup>-electrochemical potential gradi-

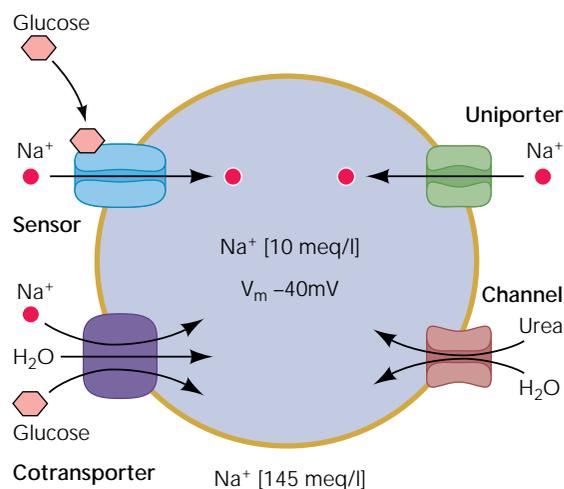
ents. However, the kinetics are very asymmetrical because the apparent ligand affinities are markedly different for transport in the forward and backward directions; e.g., under *zero-trans* conditions (no Na<sup>+</sup> or sugar on the opposite side of the membrane), and the apparent sugar affinity is orders of magnitude lower for influx than for efflux, 0.2 vs. 60 mM (21). Among the natural monosaccharides, D-glucose and D-galactose are the preferred substrates, whereas mannose (or 2-deoxy-D-glucose) is barely accepted. Phlorizin is a high-affinity, non-transported, competitive blocker ( $K_i \sim 0.2 \mu\text{M}$ ). Although Na<sup>+</sup> normally drives cotransport, protons and to some extent Li<sup>+</sup> are able to drive sugar transport. The apparent affinity for protons is 500 times greater than for Na<sup>+</sup> ( $K_{0.5} = 0.007$  vs. 4 mM), but the apparent affinity for sugar is 25 times lower for H<sup>+</sup>-sugar cotransport than for Na<sup>+</sup>-sugar cotransport.

The kinetics for Na<sup>+</sup>-glucose cotransport can be described as an ordered reaction scheme in which two external Na<sup>+</sup> ions bind first to SGLT1, thereby increasing the affinity of the protein for sugar (FIGURE 3). Upon sugar binding, the protein undergoes a conformational change to deliver the two Na<sup>+</sup> ions and sugar to the other side of the membrane, where first the sugar and then the two Na<sup>+</sup> ions dissociate. The unloaded protein finally undergoes another conformational change to again expose the Na<sup>+</sup>- and sugar-binding sites to external solu-



### FIGURE 1. The secondary structure of SGLT1

The 664-amino-acid protein contains 14 transmembrane  $\alpha$ -helical domains (21). Highlighted in yellow is the architecture of common members of the solute symporter family (SSF) gene family with the sodium:SSF signature sequence: [GS]-x (2)-[LIY]-x (3)-[LIVMFYWSTAG] (7)-x (3)-[LIV]-[STAV]-x (2)-G-G-[LMF]-x-[SAP]. The motif shared by the SGLTs and Na<sup>+</sup>-myo-inositol cotransporters (SMITs) is also indicated: R-x-T-x(4)-F-L-A-G-x(4)-W-W-x(2)-G-A-S. The glucose-binding and -translocation domain (C5) is located at the COOH-terminal end of the protein, and the residues proposed to be involved in glucose binding at the extra- and intracellular sides of the membrane are highlighted.



**FIGURE 2. SGLTs are multifunctional proteins**

tion for another turnover cycle. We estimate that SGLT1 can recycle ~1,000 times/s at 37°C. Clear support for the alternating-access kinetic model has been obtained from biochemical and biophysical (optical and charge) experiments (15, 18).

As in the case of other membrane proteins, there is limited information available about the structure. What we do know is that SGLT1 is completely functional as a monomer with 14 transmembrane helices (FIGURE 1). Additional information has emerged from the functional analysis of chimeras, mutants, and truncated proteins. These have shown that the COOH-terminal domain containing the five terminal transmembrane helices (C5, TMH 10–14) are involved in sugar binding and translocation. For example, the truncated protein C5 behaves as sugar uniporter when it is either expressed in oocytes or reconstituted into proteoliposomes, and Gln<sup>457</sup> in TMH 11 has been shown to interact with the oxygens of the carbon 1 hydroxyl and the pyranose ring in D-glucose during binding and translocation (4).

Further insight into the structure of the SGLT1 sugar-binding site(s) is obtained from a consideration of binding sites in other proteins, e.g., the bacterial H<sup>+</sup>-lactose symporter (1). First, the interactions involved in sugar binding mirror those in sugar-binding proteins; second, analysis of 60 sugar-binding proteins reveals a high propensity for some (Trp >> His > Tyr > Glu ~ Arg > Asp) and a low propensity for other residues (Pro < Thr < Lys < Val < Ser < Ala < Cys < Ile < Gln < Leu < Me < Asn < Phe) at the sugar-binding site (23). Extending this to the conserved residues in the Na<sup>+</sup>-sugar cotransporters leads to the hypothesis that there are two sugar-binding sites in the C5 domain of SGLT1: one on the outside face of the membrane, possibly the high-affinity site, and the other on the inside face, possibly the low-affinity site (FIGURE 1).

Limited functional studies have been carried out with SGLT2, SGLT3, the bacterial Na-sugar cotransporter (vSGLT), and SGLT6 (SMIT2). SGLT2 has all the hallmarks of the low-affinity renal transporter (8), even though it has very low activity in expression systems. Pig SGLT3 expresses in oocytes, where it behaves as a low-affinity Na<sup>+</sup>-glucose cotransporter with a very low affinity for galactose (see Ref. 27). Human SGLT3 is expressed to a high level in the plasma membrane of oocytes, but it does not transport sugar (see below). So far, there are no reports on the function of human SGLT4–6, but rabbit and *Xenopus* SGLT6s (SMIT2) transport both inositols and glucose (see Ref. 30). The function of the bacterial cotransporter, vSGLT, closely resembles SGLT1, but there are some differences in terms of sugar specificity, coupling, and sensitivity to phlorizin (25). Likewise, there is experimental evidence that other SLC5 proteins, e.g., SMIT1 (Na<sup>+</sup>-myo-inositol), NIS (Na<sup>+</sup>-iodide), SMVT (Na<sup>+</sup>-vitamin), and CHT (Na<sup>+</sup>-choline), are cotransporters (30).

#### Uniport

In the absence of sugar, the SGLT family members (SGLT1, pig SGLT3, SMIT1, and NIS) transport Na<sup>+</sup>. The rate of Na<sup>+</sup> transport ranges from 8 to 34% of the maximum cotransport rate. Uncoupled Na<sup>+</sup> transport by SGLT1 is a saturable function of the Na<sup>+</sup> concentration ( $K_{0.5} = 4$  mM; Hill coefficient = 2), is blocked by phlorizin ( $K_i = 4$  μM), and has an activation energy of 20 kcal/mol (16). These properties are consistent with carrier-mediated Na<sup>+</sup> transport or uniport.

#### Glucosensor

Both pig and human SGLT3 are widely expressed in tissues throughout the body and are not restricted to epithelial tissues, e.g., skeletal muscle (5). Surprisingly, human SGLT3 does not transport sugar. Instead, glucose generates an inward Na<sup>+</sup> current that depolarizes the membrane potential. We have suggested that SGLT3 is the missing glucose sensor (see below).

#### Channel

SGLT1 and other cotransporters behave as channels for water and small hydrophilic solutes when expressed in oocytes (17, 19). The rate and direction of the osmotic flow of water is directly proportional to the osmotic gradient. The osmotic and urea permeabilities are blocked by the SGLT1 inhibitor phlorizin ( $K_i = 1$ –5 μM), and each has an activation energy (5 kcal/mol) similar to those observed with aquaporins. The urea channel is located in the C5 domain of SGLT1. The significance of the SGLT1 channel is that aquaporins and urea transporters are absent from the intestinal brush border, and therefore SGLT1

may play an important role in fluid and urea transport across the intestine.

### Water cotransport

We have also found that cotransporters behave as water pumps (17). In *Xenopus laevis* oocytes expressing SGLT1, we found that activation of Na<sup>+</sup>-glucose cotransport by the addition of sugar triggers the immediate uptake of water. There is a stoichiometric relationship between the rate of Na<sup>+</sup>-glucose cotransport and the rate of water transport (2 Na<sup>+</sup>:1 glucose ~ 260 water molecules). Coupled-water transport is independent of the osmotic gradient and even occurs against it. Both the initial rates of Na<sup>+</sup>-glucose cotransport and water transport are proportionally altered by rapid (millisecond) jumps in the membrane potential. In control experiments on ion channels, there are no immediate changes in water transport upon rapid jumps in membrane potential. The cotransport of water is explicable in terms of the ligand-induced changes of the cotransporter during the transport cycle (see FIGURE 3). We estimate that under steady-state conditions, 35% of water transport occurs by Na-glucose-water cotransport, 35% occurs by osmosis through SGLT1, and 30% occurs by osmosis through the plasma membrane.

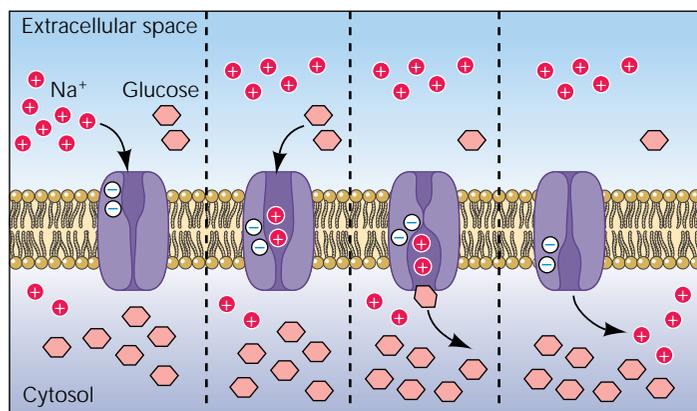
The mechanism of sugar-coupled water flow has been challenged by another group (6, 12). Although it is acknowledged that they cannot disprove our water-cotransport hypothesis, they have suggested that intracellular accumulation of glucose next to the plasma membrane may account for the fast component of water transport associated with the activation of the cotransporter. Incidentally, this would not account for either the rapid turnoff of water and Na<sup>+</sup>-glucose cotransport on depolarizing the membrane potential or the sugar-activated urea transport through SGLT1 (17, 32). Irrespective of the molecular mechanism of water transport, either osmotic flow through SGLT1, or a combination of water cotransport and osmosis, it is clear that SGLT1 plays a significant role in water transport across the intestinal brush border membrane (see below).

### Other cotransporter genes

Functional data is not available for many of the SSF genes in the databases, and their function is only inferred by sequence homology. In some cases functional assays have been attempted, but no results were obtained. These orphans may not be trafficked properly to the plasma membrane of heterologous expression systems because they are targeted to other membranes in the cell or because a chaperone is missing from the expression system. Alternatively, if the protein is in the plasma membrane the appropriate functional assay may not have been performed. One consequence is that the databases undoubtedly contain erroneous information about the presumed function of SSF genes, e.g., human SGLT3 is listed as a Na<sup>+</sup>-glucose cotransporter, but it is in reality a glucosensor. The function assigned to SSF genes will depend on where they are expressed and whether their major function is to behave as cotransporters, channels, or receptors.

### Physiological Roles of SGLTs

The definitive approach to the physiological function of SGLTs is to determine the precise cellular location of the protein and to compare and contrast the function of the protein in the native tissue and in heterologous expression systems. We have done this for SGLT1 expressed in the brush border membrane of the intestinal epithelium. The functional properties of SGLT1 in the brush border and in heterologous expression systems are remarkably similar (see above). Glucose transport across the intestine occurs in two steps (FIGURE 4), the first being Na<sup>+</sup>-glucose cotransport across the brush border and the second being downhill transport from the cell interior across the basolateral membrane into blood (29). The gene encoding for glucose transport across the brush border cotransporter is *SGLT1*, and that for transport across the basolateral membrane is the facilitated transporter *GLUT2*. Patients with *SGLT1* mutations are unable to accumulate sugars within



**FIGURE 3. A model for Na<sup>+</sup>-glucose cotransport**

The inward Na<sup>+</sup> gradient drives glucose transport into the cell against the glucose concentration gradient. External Na<sup>+</sup> first binds to the negatively charged protein to allow glucose to bind with high affinity. Two Na<sup>+</sup> ions and one glucose molecule are then transported across the membrane, where first the sugar and then Na<sup>+</sup> are released into the cytoplasm due to the low affinity for glucose and the low intracellular concentration of Na<sup>+</sup>. The ligand-free protein then returns to the original conformation largely because of the negative membrane potential and the high external Na<sup>+</sup> concentration.

enterocytes. In both patients and rodent models with GLUT2 deficiency, there is a failure to absorb 3-*O*-methyl-D-glucoside, the nonmetabolized glucose analog that is a substrate for SGLT1 and GLUT2. The fact that glucose absorption appears to be unimpaired in GLUT2 deficiency (26) indicates an alternative pathway for glucose exit from the cell via the endoplasmic reticulum and exocytosis (FIGURE 4). Finally, one has to be aware that genes other than those in the SGLT family may have a role in secondary active sugar transport (10).

It is well known that glucose stimulates massive amounts of water absorption from the small intestine. This follows from the model for glucose absorption (FIGURE 4). Glucose increases Na<sup>+</sup> entry across the brush border membrane via the Na<sup>+</sup>-glucose cotransporter, and then Na<sup>+</sup> is pumped out across the basolateral membrane by the Na<sup>+</sup>/K<sup>+</sup> pump. Glucose and Na<sup>+</sup> absorption across the epithelium is followed by anions (chiefly Cl<sup>-</sup> and HCO<sub>3</sub><sup>-</sup>) and water, resulting in fluid absorption that is isotonic. Glucose, salt, and water absorption are blocked by the SGLT1 inhibitor phlorizin. Our studies suggest that SGLT1 plays an important role in water transport, either directly as a water cotransporter or indirectly as a water channel. About 1 mol of glucose is absorbed from the intestine each day, and we estimate that this results in ~6 liters of water.

In the kidney, the reabsorption of glucose from the glomerular filtrate in the proximal tubule is carried out by an isoform of SGLT1 (SGLT2), and GLUT2 appears to be the only mechanism for sugar exit across the basolateral membrane. SGLT1-deficient patients only show a mild renal glucosuria, whereas SGLT2- and GLUT2-deficient patients

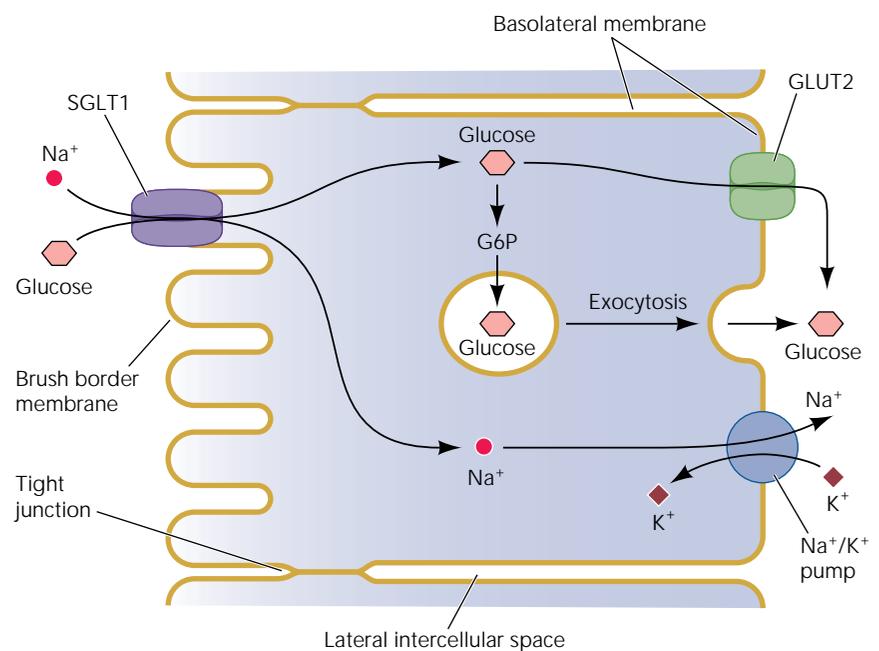
have severe glucosuria (see below). Unlike the small intestine, glucose plays a minor role in the absorption of water across the proximal tubule; of the 150 liters of fluid reabsorbed each day, we estimate that Na<sup>+</sup>-glucose-water cotransport accounts for only 2% of the total.

These SGLT genes are expressed in other tissues in the body, e.g., SGLT1 is found in the heart, trachea, and prostate and SGLT2 is found in brain and liver. This begs questions about their function in these tissues. SGLT3 is expressed in the intestinal autonomic nervous system, skeletal muscle, and brain, among others, and this may be related to our hypothesis that SGLT3 is a glucosensor. For example, in neuroendocrine cells glucose and the non-metabolized sugar analog α-methyl-D-glucopyranoside, but not galactose, stimulate glucagon-like peptide secretion, and this stimulation is blocked by phlorizin (see Ref. 5). Secretion is mediated by a depolarization of the membrane potential and the subsequent increase in firing of action potentials. SGLT3 is also expressed in cholinergic neurons in the enteric nervous system, and it is well established that cholinergic neurons mediate enteric reflexes after a meal. Thus SGLT3 is predicted to play a role in determining intestinal motility. In both pigs and humans, SGLT3 may carry out the same function even though one transports glucose and the other does not; in both cases, changes in glucose concentration depolarize the membrane potential. SGLT1 and SGLT2 may also behave as glucose receptors in such tissues as heart and brain.

SGLT6, like SMIT1, is abundantly expressed in the brain and kidney, where its most likely role may be the accumulation of inositol for metabolism

**FIGURE 4. Sugar transport across the intestinal epithelium**

Glucose (and galactose) are transported across the brush border membrane by SGLT1 and then exit through the basolateral membrane by either GLUT2 or exocytosis. The low intracellular Na<sup>+</sup> is maintained by the basolateral Na<sup>+</sup>/K<sup>+</sup> pump. The net result is that glucose, salt, and water are absorbed from the gut lumen, and this provides the rationale for oral rehydration therapy.



and/or osmoregulation. The primary function of NIS, the Na<sup>+</sup>-iodide cotransporter, is the accumulation of iodide in the thyroid gland and other tissues, but it too is a multifunctional protein.

### SGLTs and Disease

Probably the most clinical significance of SGLT1 relates to its role in oral rehydration therapy used to treat infectious diarrhea (9). This therapy, based on glucose stimulation of salt and fluid absorption across the intestine (FIGURE 4), saves countless lives in children afflicted with cholera. Mutations in *SGLT1* cause the diarrhea associated with GGM (OMIM #182380). The high frequency of GGM in consanguineous unions and the lack of vertical transmission demonstrate an autosomal recessive pattern of inheritance. This is consistent with the fact that SGLT1 is a monomer, with our studies of the inheritance of GGM in several families, and with the fact that, among nearly all of the 82 patients examined so far, each has a unique mutation(s). The defect in sugar transport in each case is caused by production of either truncated, nonfunctional protein or of full-length protein that does not reach the brush border membrane (28, 31). Mutations in *SGLT2* also appear to be responsible for the inherited form of renal glucosuria, but some doubt remains in the absence of functional studies of the mutant renal protein (22). Unlike GGM, renal glucosuria is a benign condition. It is noteworthy that SGLT2 has become a target for the drug industry searching for therapeutic tools to treat diabetic patients. So far, the only other SGLT gene linked to a genetic disease is NIS (OMIM #60184). Finally, the growth of colon tumors is related to the silencing of the *SLC5A8* gene (13), a function that may be related to the loss of short-chain fatty acid accumulation (2).

### Summary

SGLT (SLC5, SSF) is an ancient gene family, and despite the fact that a major function of these proteins is to carry out secondary active transport of sugars, amino acids, neurotransmitters, osmolytes, and iodide, they are in fact multifunctional proteins. The diverse functions include sodium, water, and urea transport; glucosensation; and tumor suppression. A challenge is to determine the physiological significance of these diverse functions. ■

We are grateful to the many talented students, fellows, and collaborators who contributed to the success of the work that provides the foundation for this review and for financial support from the National Institute of Diabetes

and Digestive and Kidney Diseases (grant nos. DK-19567, DK-44602, and DK-44582).

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