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R. Sabino-Silva, R.C. Mori, A. David-Silva, M.M. Okamoto, H.S. Freitas and U.F. Machado

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The Na^+/glucose cotransporters: from genes to therapy

R. Sabino-Silva*, R.C. Mori*, A. David-Silva, M.M. Okamoto, H.S. Freitas and U.F. Machado

Departamento de Fisiologia e Biofísica, Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, SP, Brasil

Abstract

Glucose enters eukaryotic cells via two types of membrane-associated carrier proteins, the Na^+/glucose cotransporters (SGLT) and the facilitative glucose transporters (GLUT). The SGLT family consists of six members. Among them, the SGLT1 and SGLT2 proteins, encoded by the solute carrier genes SLC5A1 and SLC5A2, respectively, are believed to be the most important ones and have been extensively explored in studies focusing on glucose fluxes under both physiological and pathological conditions. This review considers the regulation of the expression of the SGLT promoted by protein kinases and transcription factors, as well as the alterations determined by diets of different compositions and by pathologies such as diabetes. It also considers congenital defects of sugar metabolism caused by aberrant expression of the SGLT1 in glucose-galactose malabsorption and the SGLT2 in familial renal glycosuria. Finally, it covers some pharmacological compounds that are being currently studied focusing on the interest of controlling glycemia by antagonizing SGLT in renal and intestinal tissues.

Key words: SGLT1; SGLT2; SLC5A1; SLC5A2; HNF-1; Diabetes

Na^+/glucose cotransporters

Glucose is the main source of energy in eukaryotes and the main fuel providing energy for regular metabolic activity in humans (1). As a polar molecule, glucose is not soluble in the plasma membrane and must be transported across it by carrier proteins, named glucose transporters. Glucose transporters are divided into two families: the facilitative diffusion glucose transporters (GLUTs) and the Na^+/glucose cotransporters (SGLTs) (1). Both GLUTs and SGLTs belong to one of the 43 families of solute carrier genes (SLC1-SLC43).

Glucose transporters play an essential role in the maintenance of euglycemia, not only by determining glucose uptake in all cellular types, but also by releasing glucose from the liver when circulating glucose levels decrease. In addition, these transporters are responsible for absorbing glucose from the diet in the intestine, and for reabsorbing the glucose from the glomerular filtrate in kidneys (2).

Transepithelial glucose transport in cells from the small intestine, the renal proximal tubules and salivary gland ducts occurs by the coordinate action of SGLTs allowing glucose influx through the luminal membrane, and GLUTs allowing glucose efflux through the basolateral membrane (2). This process, in which SGLTs play a key role, will be detailed below.

This review will focus on the SGLTs, which are extremely important for survival, not only by assuring energy substrate taken from food (glucose absorption), but also by preventing its loss in urine and/or saliva (glucose reabsorption).

SGLTs

SGLTs constitute a large family of membrane proteins involved in the transport of glucose, amino acids, vitamins, osmolytes, and some ions across the brush border membrane of the small intestine epithelium and the renal proximal tubules. Although 6 isoforms of Na^+/glucose cotransporters have been described, the SGLT1 and SGLT2 proteins, encoded by the solute carrier genes SLC5A1 and SLC5A2, respectively, are believed to be the most important ones and have been extensively explored in studies focusing on glucose fluxes under both physiological and pathological conditions.

Correspondence: U.F. Machado, Departamento de Fisiologia e Biofísica, ICB, USP, Av. Prof. Lineu Prestes, 1524, 05505-900 São Paulo, SP, Brasil. Fax: +55-11-3091-7285. E-mail: ubiratan@icb.usp.br

*These authors contributed equally to this study.

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Crane et al. (3) were pioneering researchers who postulated that active glucose transport across the intestinal epithelium is driven by the sodium gradient across the membrane, by means of an Na^+/glucose cotransport (3). Actually, subsequent studies revealed that the sodium electrochemical potential gradient across the brush border membrane promotes sodium influx, providing the energy, which drives glucose into the enterocytes. Sodium that enters the cell along with glucose is then transported into the interstitium by Na^+/K^+ ATPase at the basolateral membrane, maintaining the electrochemical gradient for luminal sodium influx. Thus, the energy for the whole process comes from the adenosine-5'-triphosphate (ATP) consumed by Na^+/K^+ ATPase. Glucose accumulating within the enterocyte is then transported across the basolateral membrane by facilitative diffusion transporters (4). By this process, 1 mole glucose and 2 moles sodium are transported across the enterocyte from the lumen into the interstitium, this being followed by water and 2 moles anions to ensure electroneutrality (4).

SGLT1

SGLT1 is a 75-kDa membrane protein with an Na^+/glucose stoichiometry of 2:1. It contains 14 transmembrane α-helices, a single glycosylation site between transmembrane helices 5 and 6, and two phosphorylation sites between transmembrane helices 6 and 7 and between transmembrane helices 8 and 9 (4,5). The NH_2 and COOH termini are extracellular and intramembrane, respectively, and the glucose binding and translocation domains involve the five transmembrane segments, which are next to the COOH terminus (4).

The SGLT1 protein, encoded by the SLC5A1 gene, is located mainly in the intestine, but has also been detected in the kidney, parotid and submandibular salivary glands as well as in the heart (4,6,7). It has high affinity for glucose, but low capacity of transporting it, and is specifically inhibited by phlorizin. Furthermore, the cotransporter affinity is the same for glucose and galactose (8).

Through the SGLT1, two sodium ions are transported for each molecule of glucose. This cotransport is a secondary Na^+/K^+ ATPase-dependent process, able to transport glucose into the cell against its concentration gradient (9). In the steady state, Na^+ ions entering the cell across the luminal membrane are pumped out by Na^+/K^+ ATPase in the basolateral membrane. Glucose concentrates within the cell, a process that allows it to move downhill to the interstitium through the facilitative diffusion transporters (1).

It is believed that Na^+ and glucose transport by the SGLT1 occurs by a sequential mechanism in which two Na^+ ions on the extracellular side bind to the transporter right before glucose, inducing a conformational change in the glucose binding site and increasing the transporter affinity for this substrate. Then, another conformational change determines the shift of the Na^+ and glucose binding sites to the inner surface of the membrane, with the glucose molecule and immediately after the two Na^+ ions being released within the cell (4,8). Within this process, the SGLT1 protein is able to recycle about one thousand times per second at 37°C (4).

In recent years it has been demonstrated that, besides the two Na^+ ions plus the one glucose molecule, the SGLT1 protein is also able to transport about 264 H_2O molecules. The coupled water transport occurs due to changes induced by ligands (sodium and glucose) in the protein structure during the transport cycle (4,10). The water permeability of the SGLT1 is independent of the grade and direction of the osmotic gradient (4,10), and 35% of total water transport triggered in response to SGLT1 activation is considered to be sugar-coupled water transport in *Xenopus laevis* oocytes expressing SGLT1 (10). Another mechanism is the osmotic transport of water induced by the intracellular sodium and glucose accumulation near the plasma membrane (11), which accounts for 65% of the total water transport that occurs in response to the SGLT1 activation (4,12). In humans, the current 1 mole glucose absorbed per day in the intestine determines absorption of up to 4 liters of water by the sugar-coupled water transport system. Because of that, it is clear that SGLT1 plays an important role in water absorption in the brush border membrane of enterocytes (4).

SGLT2

The SGLT2 protein was originally described as an amino acid cotransporter called Na^+-dependent neutral-amino acid transporter, SAAT1 (13), but was later recognized as a glucose transporter (14). This protein contains 672 amino acids and its NH_2 and COOH termini are extracellular (5). Differently from SGLT1, SGLT2 is a low-affinity and high-capacity glucose transporter, which transports 1 Na^+ ion for each glucose molecule. The SGLT2 encoding gene (SLC5A2) is predominantly expressed in kidneys, but low mRNA expression has also been demonstrated in mammary glands, liver, lungs, intestine, skeletal muscle, and spleen (15).

SGLT2 is highly expressed in the luminal membrane of the S1 segment of the renal proximal tubule. This isoform is mainly responsible for glucose reabsorption from the glomerular filtrate. In fact, more than 90% of the filtered glucose is reabsorbed in the initial segments of the proximal tubule via SGLT2 (4,16).

Transepithelial glucose transport

Transepithelial glucose transport involves the two classes of glucose transporters, SGLTs and GLUTs. Renal glucose reabsorption occurs mainly in the S1 segment of the proximal tubule by the coordinated action of the SGLT2 and GLUT2 located in the luminal and basolateral membranes,

respectively. Only a small and residual amount of glucose is reabsorbed in the S3 segment, where SGLT1 is present in the luminal membrane, co-expressed with GLUT1 in the basolateral membrane (4). Intestinal glucose absorption occurs mostly in the duodenum and in the initial portion of the jejunum, and involves the co-expression of SGLT1 and GLUT2 (4). In all these processes, SGLTs present in the luminal membrane transport glucose from the lumen into the intracellular medium, where glucose accumulates generating a gradient that favors its transport through the GLUTs in the basolateral membrane, from the cytoplasm to the interstitium (4) (Figure 1).

Other SGLTs

Human SGLT3, encoded by the SLC5A4 gene, is considered to be a glucose-gated ion channel, expressed in the intestine, spleen, liver, kidneys, skeletal muscle, and cholinergic neurons. It does not transport Na^+ or glucose when expressed in *Xenopus laevis* oocytes, but it causes the plasma membrane to depolarize in the presence of glucose in a saturable, Na^+-dependent and phlorizine-sensitive manner (15,16).

It has been demonstrated that porcine SGLT3 expressed in oocytes behaves as an Na^+/glucose cotransporter with very low affinity for glucose (17). However, in humans, SGLT3 is not a functional Na^+/glucose cotransporter, but seems to work as a glucose sensor in the plasma membrane of cholinergic neurons of the enteric nervous system and neuromuscular junctions of skeletal muscle (18), where plasma glucose variations modulate the membrane potential of the neurons.

There are only a few reports on other SGLTs, but it is known that SGLT4, encoded by the SLC5A9 gene, is expressed in the small intestine, kidneys, liver, lung and brain, and SGLT5, encoded by the SLC5A10 gene, is expressed only in the kidneys. Furthermore, SGLT6, encoded by the SLC5A11 gene, is supposed to be a low affinity D-glucose transporter in the small intestine (4).

SGLTs and protein kinases

Protein kinases (PK) may regulate the activity of membrane transporter proteins either directly or indirectly (19). Direct effects occur through phosphorylation of the transporter, thus changing the kinetics of the transporter. It was demonstrated in rat small intestines that the activation of β-adrenoreceptors induces phosphorylation of SGLT1 via PKA, enhancing the cotransporter function, and thus increasing glucose transport (20). Indirect regulations involve changes in the rate of the insertion into or retrieval from the plasma membrane. Membrane proteins are cotranslationally inserted into the endoplasmic reticulum and processed by the Golgi apparatus, where vesicles are formed to deliver the proteins to the plasma membrane (20). Hirsch et al. (19) have demonstrated in *Xenopus laevis* oocytes that PK regulate the SGLT1-induced glucose transport by controlling the distribution of transporters between intracellular compartments and the plasma membrane. Activation of PKA and PKC, respectively, increases and decreases the maximum rate of Na^+/glucose transport, an event accompanied by an increase and decrease, respectively, in the plasma membrane SGLT1 protein content (19). However, SGLT1 translocation seems to be independent of the phosphorylation of potential phosphorylation sites present in the transporter (19). Although some investigators propose that these effects might be extended to other isoforms of SGLTs (4,19), to our knowledge, these mechanisms were demonstrated only for the SGLT1 protein.

As a physiological consequence of these rapid regulations of SGLT1, we hypothesize that the anticipative and

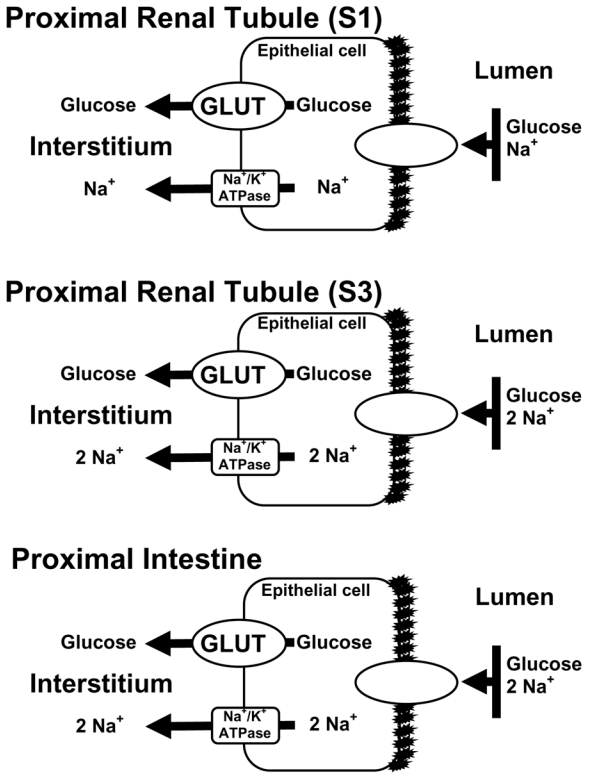

Figure 1. Glucose transport across the renal proximal tubule and proximal intestine. Glucose is transported across the luminal membrane by sodium/glucose cotransporters 1 and 2 (SGLT1 and SGLT2) and then exits through the basolateral membrane by the facilitative glucose transporters 1 and 2 (GLUT1 and GLUT2). The renal cells represent epithelial cells of the S1 and S3 segments of the renal proximal tubule, respectively; the intestinal cells represent enterocytes from the proximal intestine. SGLT1 and SGLT2 in the luminal membranes and GLUT1 and GLUT2 in the basolateral membranes are shown, indicating the glucose flow through the epithelial cell.

the postprandial increases in β-adrenergic activity could contribute to enhancing intestinal glucose absorption by translocating SGLT1.

Transcriptional regulation of SGLTs

Among the transcription factors reported to participate in the regulation of SGLT expression, hepatocyte nuclear factors 1α and 1β (HNF-1α and HNF-1β) can be cited as essential regulators of SGLT1 expression (21). HNF-1α and HNF-1β were originally characterized as liver-specific transcription factors that regulate several genes (22) and were later also implicated in tissue-specific gene regulation in the pancreas, kidney, and intestine. HNF-1α and HNF-1β are developmentally expressed, and their transcriptional effects have been initially related directly to the degree of protein expression.

HNF-1α and HNF-1β contain an NH_2-terminal dimerization domain, and they bind to DNA as homodimers or heterodimers. Isoforms α and β have been reported to have distinct transcriptional activity, and thus the pattern of dimerization plays a key role in the final effect on the transcription of target genes (23,24). In the SLC5A1 gene promoter, there are two cis-regulatory elements for HNF-1α/β, which were demonstrated to be functional by transient promoter assays (21,25,26). The ratio of HNF-1α and HNF-1β dimerization is particularly important in modulating the transcription of SGLT1. Homodimers of HNF-1α are associated with increased SGLT1 transcription, whereas heterodimers of HNF-1α/β decrease SGLT1 transcription (23). A circadian periodicity of intestinal SGLT1 expression was reported in the intestines of *ad libitum*-fed rats: the higher transcriptional rate correlated with HNF-1α homodimers in the morning (10:00 h) and the lower rate with the appearance of HNF-1α/β heterodimers in the afternoon (16:00 h) (23). However, the mechanism by which the dimerization process changes was not determined.

An additional mechanism that regulates the HNF-1 transcriptional activity is based on its interaction with other proteins. By analyzing DNA sequences implicated in the specific transcriptional regulation of genes by the liver, key nuclear proteins have been identified, such as HNF-3, HNF-4, HNF-6, CCAAT/enhancer binding protein (C/EBP), and D binding protein (DBP), which can cooperatively enhance the transcriptional activity of HNF-1α and/or HNF-1β (24,27). HNF1-α can also interact with caudal-type homeobox protein 2 (CDX2) and GATA-binding protein (GATA) family members to regulate the expression of some intestinal genes (21). Additionally, proteins from the Sp1 family of transcription factors, which bind in GC boxes, in the presence of HNF-1 also act synergistically by up-regulating the transactivation of the promoter of target genes (25). Finally, an important role was attributed to the enhancer of rudimentary homolog (erh) protein, which, by interacting with the dimerization cofactor of HNF-1 (coactivator DCoH), represses the HNF-1 transcriptional activity (28). Most of these cooperative mechanisms have already been reported to modulate the expression of the SGLT1 gene (21,25).

All interactions described above reveal how widespread and complex the HNF-1 transcriptional regulations are. However, little is known about the mechanisms that control these interactions. In this regard, the inhibition of protein phosphatases 1/2A in Caco-2 cells has been shown to enhance HNF-1α/β phosphorylation, decreasing their DNA-binding capacity, and thus repressing the expression of the gene encoding sucrase-isomaltase (29). Furthermore, the mutation of the HNF-1 binding site results in the decrease of the cAMP/PKA-induced HNF-1 promoter activity in HepG2 cells, indicating that this pathway is involved in the transcriptional activity (27).

Fasting- and refeeding- as well as glucose- and insulin-induced regulation of HNF-1 transcriptional activity have been reported mainly in the liver and intestine. Most of these studies involved genes related to glucose metabolism, including the SLC5A1 gene that codes for the SGLT1 protein (21,23,26,27,29). However, the role of dietary proteins or lipids, as well as of insulin and/or its counterregulatory hormones, on HNF-1 transcriptional activity is unknown.

Little is known about HNF-1 regulation of the SLC5A2 gene, which codes for the SGLT2 protein. Impaired renal tubular glucose reabsorption was observed in HNF-1α-deficient mice, suggesting that this transcription factor also regulates renal SGLT2 expression (30). Additional investigations confirmed decreased SGLT2 expression in renal tubular cells of HNF-1α-deficient mice (31). Afterwards, it was shown that HNF-1α directly controls SGLT2 expression in mouse and man (32). More recently, we have demonstrated that increased HNF-1α expression and binding activity in the SLC5A2 promoter is involved in the diabetes-induced overexpression of SGLT2 (33). Moreover, it was observed that diabetes-induced changes in HNF-1α activity and SGLT2 expression are reversed by lowering glycemia, independently of insulinemia (33), indicating that glucose is a major modulator of this transcriptional activity, as described for SGLT1.

SGLTs and diet

It has been reported for a long time that increased dietary sugar enhances the intestinal sodium-dependent glucose transport, suggesting that SGLT1 expression may be increased (34). In fact, alterations in SGLT1 mRNA and protein expression as a consequence of dietary carbohydrate content were reported in ruminant animals (35,36). In addition to induction by dietary carbohydrate, intestinal expression of SGLT1 exhibits circadian periodicity in its activity. SGLT1 mRNA levels in rats vary, with the maximum abundance occurring near the onset of dark and the minimum near the onset of light, variations that are preceded ~6 h before by parallel changes in transcriptional activity,

as described above (23). Furthermore, since the daily variation in SGLT1 activity persists in the absence of food, this variation has been described as an anticipatory response and is regulated at the transcriptional level (23).

Sodium intake also induces important changes in the intestinal and renal glucose cotransporters. Some studies conducted by us in rats have found a significant decrease in SGLT1 mRNA in the upper small intestine with high salt intake. Besides, SGLT1 mRNA increased in the middle segments with low salt intake. These results correlate with a decreased mRNA half-life in the upper segment (on high salt) and an increased half-life in the middle segment with low salt intake (37). Nevertheless, this regulation was not accompanied by alterations in intestinal glucose absorption (37).

In our laboratory, we have also demonstrated that a high sodium diet increases the expression of SGLT2, GLUT2 and GLUT1 in renal proximal tubules (38). In the renal cortex from rats fed a high sodium diet, the very high sodium filtration rate improves the cellular glucose influx in the early S1 segment. Most of the filtered glucose flows rapidly into the epithelial cells in this segment and the high-capacity/low-affinity GLUT2 transporter cannot proportionally increase the cellular efflux of glucose. Therefore, the S1 epithelial cells may be temporarily submitted to a high glucose concentration, which is enough to determine the increase of SGLT2 and GLUT2. On the other hand, although the luminal sodium concentration is also very high in the S3 segments of high salt-fed rats, the modulation of the glucose transporters is not the same as that in the S1 segments. The SGLT1 mRNA remains unchanged, whereas the GLUT1 protein strongly increases (38). This may be explained by the intracellular glucose concentration (39), which could be very low in S3 epithelial cells. Since the high filtration rate of sodium provides almost complete glucose reabsorption in S1 segments, no substrate would be available for reabsorption in the S3 territory. This may occur despite high sodium concentration and consequently intracellular glucose may decrease.

A diet-induced mechanism of SGLT1 expression has been recently described, involving the intestinal luminal glucose content and a sugar sensor located at the luminal membrane of the enterocyte. It has been demonstrated that the sweet taste receptor subunit T1R3 and the taste G protein gustducin, expressed in enteroendocrine cells, underlie cellular sugar sensing (40), triggering a signal linked to the cAMP-PKA pathway, which eventually leads to enhancement of SGLT1 mRNA and protein expression (35).

SGLTs and diabetes

Dyer et al. (41) have reported that brush border Na^+/glucose cotransport SGLT1 mRNA and protein levels in duodenal biopsies are 3- to 4-fold higher in diabetic subjects than in controls. They have concluded that there is an increased capacity to absorb glucose in diabetic subjects and that this is due to both a rise in transporter expression and structural changes in the brush border membrane.

In diabetic kidneys of rats with both spontaneous and pharmacologically induced diabetes, there is increased transtubular glucose flux accompanied by increased SGLT2 and GLUT2 expression (33,42-44). This increased glucose transporters expression is part of a regulatory mechanism, which intends to avoid glucose loss. However, it also results in increased glucose concentration in the proximal tubule interstitium, favoring the development of glomerulosclerosis and nephropathy in uncontrolled diabetes (45,46).

It is important to emphasize that alterations in SGLT expression in diabetes involve mechanisms of regulation at the transcriptional level, as recently demonstrated by studies from our laboratory using alloxan-induced diabetic rats. In those animals, diabetes increased both SGLT2 and HNF-1α mRNA expression and there was a correlation between the expression of SGLT2 and HNF-1α binding to the SGLT2 promoter in the renal cortex, as demonstrated by both electrophoretic mobility and chromatin immunoprecipitation (ChIP) assays (33).

An important public health issue related to diabetes concerns the diabetes-associated oral health complications, which include xerostomia, periodontal diseases, increased incidence and severity of caries, tooth loss, and candidiasis (47). These alterations may be linked to salivary gland dysfunctions, such as reduced salivary flow rate (48) and altered composition of the saliva, e.g., increased glucose concentration (49).

Recent studies have made important contributions to this area, showing that, SGLT1 mRNA expression increases in the parotid and submandibular glands of diabetic rats with decreased basal salivary secretion. Furthermore, SGLT1 protein expression increases in the luminal membrane of ductal cells, a process that can exacerbate water reabsorption from primary saliva (7). Considering the ability of SGLT1 to act as a water pump in salivary ducts, this protein probably regulates salivary flow, and changes in its expression may alter the secreted volume of saliva. All of these functional and molecular changes contribute to explaining the reduced salivary flow of diabetic subjects and, importantly, they are all reversed by insulin therapy (7).

Genetic disorders involving the SLC5A1 and SLC5A2 genes

There are two types of genetic disorders involving the Na^+/glucose cotransporters: glucose-galactose malabsorption (GGM, OMIM 182380) and familial renal glycosuria (FRG, OMIM 233100), both involving a single gene mutation.

Patients with GGM present little or no renal glycosuria at all, which is in accordance with the limited role of SGLT1 and a much larger one of SGLT2 in the kidney. This disease was reported simultaneously by a group from Sweden and

another one from Belgium, in 1962. Severe diarrhea and dehydration occur due to water retention in the intestinal lumen, caused by the osmotic loss generated by non-absorbed glucose, galactose and sodium in the intestine (50). This recessive homozygous autosomal disease is rare and usually results from consanguineous relationships. Mutations in the coding sequence of the SGLT1 gene are responsible for this disease (51), characterized by neonatal onset of watery and acidic diarrhea, which becomes fatal within a few weeks unless glucose- and galactose-containing nutrients are removed from the diet (51).

FRG is a rare benign genetic condition of the kidneys characterized by an isolated defect in glucose reabsorption. FRG patients present various degrees of polyuria and polydipsia and the urinary loss of glucose occurs even in normoglycemia. Individuals are homozygous or compound heterozygous for an SGLT2 mutation. Approximately 21 different gene mutations have been described for SGLT2, leading to persistent renal glycosuria, with glucose excretion of up to 160 g/day (52). At the higher level of excretion, there is a complete absence of glucose reabsorption from the glomerular filtrate (52,53).

SGLTs as therapeutic targets

Oral rehydration therapy (ORT) was the first therapeutic approach based on the sodium/glucose cotransporter capacity to induce water transport, as a consequence of the intestinal sodium/glucose cotransport (54). ORT is an inexpensive, simple and surprisingly effective treatment in which sodium and glucose are offered together with water for intestinal absorption. As a consequence of the sodium and glucose cotransport through SGLT1 in the apical membrane of enterocytes, water is highly absorbed by both direct cotransport and sodium/glucose-induced osmosis. Stoichiometry of SGLT1 determines that recovery of 2 moles sodium for each mole of glucose absorbed is accompanied by 6 to 8 liters of water (4). This therapy saves countless lives in children afflicted with infectious diarrhea, and has been considered the greatest medical contribution to human health in the 20th century (54).

More recently, SGLT1 has been targeted for diabetic therapy. By blocking glucose reabsorption in the proximal renal tubule, reduction of glycemia might be achieved in diabetic patients. The first drug developed for this purpose was T-1095 (55), a phlorizin analogue, which is absorbed in the intestine, converted to its active form in the liver, and then filtered by the kidney where it blocks glucose reabsorption through SGLT2 and SGLT1. However, because of the side effects caused by the inhibition of SGLT1 in other territories, this drug could not be indicated for clinical use (56).

Specific SGLT2 inhibitors have been studied as possible options for diabetes treatment in the future. One example is dapagliflozin (BMS-512148), a compound containing C-glycosylation, which confers on it a longer half-life than that of phlorizin (57). In addition, compared to SGLT1, it is 1220-fold more selective for SGLT2, whereas phlorizin is only 10-fold more selective (58). *In vitro* studies have indicated a comparable inhibitory potency against rat SGLT2 or human SGLT2. Dapagliflozin administration to diabetic rats resulted in a 55% reduction in blood glucose 5 h after a single dose (58).

Another selective drug being tested for the treatment of hyperglycemia and/or obesity in patients with type 1 or type 2 diabetes is Sergliflozin (KGT-1251). It is a competitive SGLT2 inhibitor able to enhance glucose and energy loss through the urine. Based on the observation that individuals with familial renal glycosuria maintain normal long-term kidney function, it is believed that this mode of action will not adversely affect renal function (59). Even better, the drug might prevent the development of glomerulosclerosis by reducing the interstitial glucose concentration in the cortical area.

Intense research has led to the discovery of novel SGLT inhibitors, each with different chemical, pharmacodynamic and pharmacokinetic profiles (60) and some will probably be available for clinical use soon.

Perspectives

The extensively growing knowledge about SGLT1 and SGLT2 has extended their physiological role in the tissues where they are expressed, as well as their participation in the pathophysiology of several diseases. As a therapeutic target, SGLT1 and SGLT2 selective agonists and antagonists should make remarkable contributions to human health in the not too distant future.

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