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REVIEW ARTICLE

INHIBITORS OF SODIUM/GLUCOSE COTRANSPORT

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ABSTRACT

Sodium/glucose cotransporters (SGLTs) belong to the solute carrier family 5 (SLC5), which has more than 200 members in animal and bacterial cells. This gene family was originally thought to contain only 11 members of the human genome (SLC5A1-SLC5A11), but the GenBank® database also shows the presence of an additional member (SLC5A12). Most of the proteins coded for by these genes behave as cotransporters of diverse solutes such as glucose, amino acids, neurotransmitters, osmolytes, iodide, vitamins and anions. However, some of them have other novel and diverse functions that include water and urea transport, glucosensation and tumor suppression. Of all the members of the SLC5 family, only some transport glucose: SGLT1 and SGLT2 which are expressed at the proximal tubular level, where they reabsorb glucose from the glomerular filtrate. Recently, selective SGLT2 inhibitors have been developed as potential antidiabetic agents due to their ability to enhance glucose and energy loss through the urine, without affecting renal function and minimizing potential side effects associated with the broad tissue distribution of SGLT1. The aim of this article is to describe the biology of the members of the sodium/glucose cotransport family, giving special attention to those which are members of the human genome, and to outline the importance and pharmacological profile of SGLT inhibitors, especially inhibitors of SGLT2.

THE SODIUM/GLUCOSE COTRANSPORTER FAMILY

SLC5 (solute carrier family 5) is an ancient gene family that codes for multifunctional membrane proteins which mainly function carrying out secondary active transport coupled to sodium of sugars, amino acids, neurotransmitters, osmolytes and iodide (1). However, some members of this family behave as uniporters, urea and water channels, and urea and water cotransporters. This gene family was originally thought to contain only 11 members of the human genome (*SLC5A1-SLC5A11*), but the GenBank® database now shows the presence of an additional member (*SLC5A12*) (2). These 12 members of the human genome are expressed in tissues ranging from epithelia to the central nervous system (3).

Sodium/glucose cotransporter 1 (*SLC5A1, SGLT1*)

This was the first cotransporter to be identified and cloned (4), and using a variety of biochemical, molecular, biological and biophysical techniques (5) it has been determined that the *C*-terminal 5-helices of this monomeric 14-transmembrane helix (6) cotransporter contain the sugar selectivity elements and translocation pathway (7).

SGLT1 is mainly expressed in the brush border membrane of mature enterocytes in the small intestine, where it absorbs dietary D-glucose and D-galactose from the gut lumen (8). It is also transcribed in the renal proximal tubule (9), brain (10, 11) and heart (12). In the kidney it accounts for only a small proportion of renal glucose reabsorption due to its low capacity/high affinity for the sugar.

Mutations in the *SGLT1* gene cause malabsorption of glucose and galactose (GGM), and sugar transport is impaired mainly because the mutant proteins are either truncated or are not targeted properly to the cell membrane (13). GGM is characterized by neonatal onset of watery and acidic, severe diarrhea, which is fatal within a few weeks unless lactose (glucose and galactase) is removed from the diet (14, 15). SGLT1 is the target protein for the treatment of secretory diarrhea, such as cholera, by oral rehydration therapy (ORT) (16).

Sodium/glucose cotransporter 2 (*SLC5A2, SGLT2*)

SGLT2 is mainly expressed in the brush border of S1/S2 segments of the proximal convoluted tubule (PCT) in the kidney cortex, where it plays a major role in the reabsorption of glucose from the glomerular filtrate (17) due to its high capacity/low affinity for sugar transport. Expression of SGLT2, although at low levels, has been shown in various tissues, including bovine ciliary body epithelium (18), liver (19) and bovine mammary gland (20), and in lung cancer (21). This transporter is functionally different from SGLT1 because it has lower affinity for glucose and does not transport galactose (16).

Mutations in the *SGLT2* gene are associated with familial renal glucosuria (FRG) (22-25). Although the cDNA coding for human SGLT2

was isolated and sequenced more than a decade ago, there is very little information on the functional properties of this protein due to its low activity when expressed in heterologous systems (26).

Sodium/myo-inositol cotransporter 1 (*SLC5A3, SMIT1*)

SMIT1 is one of the transporters responsible for importing myo-inositol (MI) into cells. MI is a precursor for a family of signal transduction molecules, phosphatidylinositol and its derivatives, that regulate many cellular functions (27). This transporter is expressed in many cell types, including brain, heart, kidney, lung and testis (3, 28, 29), and is highly expressed prenatally in the placenta and the CNS, demonstrating the critical importance of SMIT1 in the developing nervous system (30).

Recently, it has been shown that *SMIT1*-null mice died soon after birth due to respiratory failure, but neonatal lethality was prevented by prenatal maternal MI supplementation. MI is essential for the development of peripheral nerves, indicating that lethality of the *SMIT1* knockout mice is most likely due to abnormal development of the nerves that control breathing (27).

It was shown that Sertoli cells cultured in hypertonic medium upregulate *SLC5A3*, probably as a result of their ability to sense and then react to changes in osmolarity by increasing the transport and production of the osmolyte MI (31).

SMIT1 is another sodium-dependent transporter added to the growing list of proteins used by *Mus cervicolor* M813 murine leukemia virus (MuLVs) for cell entry. Characterization of SMIT1 orthologues in different species identified several amino acid variations within two extracellular loops that may restrict susceptibility to M813 infection (32).

Inhibition of MI uptake via SMIT1 has been postulated as a potential mechanism for inositol depletion by mood stabilizers in the treatment of bipolar disorder (33).

Sodium glucose cotransporter 3 (*SCL5A4, SGLT3*)

SGLT3 is not a glucose transporter, but instead a glucosensor (34). It is expressed in the intestinal autonomic nervous system, skeletal muscle, brain and cholinergic neurons in the enteric nervous system and at the neuromuscular junction (1). Recently, Freeman et al. have provided evidence to support the hypothesis that SGLT3 is involved in glucose-sensing in the gut wall, which would be important to mount appropriate reflex control of gastrointestinal secretion and motility in the postprandial period (35).

Sodium/iodide cotransporter (*SLC5A5, NIS*)

NIS is an integral plasma membrane glycoprotein that mediates the active transport of iodide into follicular thyroid cells, the first step in thyroid hormone synthesis. The symporter cotransports two sodium ions along with one iodide ion, with the transmembrane sodium gradient serving as the driving force for iodide uptake. The electrochemical sodium gradient that allows NIS to be functional is maintained by the ouabain-sensitive Na^+/K^+ ATPase. It also mediates active iodide transport into several extrathyroid tissues, in particular the lactating mammary gland. Cloning and molecular characterization of the NIS have allowed the investigation of its key role in thyroid physiology, as well as its potential pathophysiological and therapeutic implications in benign and malignant thyroid diseases (36). Native NIS expression has made possible the use of radioactive iodide to image and treat thyroid disease successfully (37).

Thyroid-stimulating hormone (TSH) regulates iodide transport mainly by two mechanisms: promoting *NIS* gene transcription (38, 39), and inducing the activity of the NIS protein (40, 41), presumably by posttranslational modifications, which are essential for NIS trafficking to the membrane.

NIS offers the unique advantage that it can be used both as a reporter and as a therapeutic gene, so that it is possible to image, monitor and treat the tumor with radioiodide, just as in differentiated thyroid cancer (36). Recently, investigators have identified and characterized inhibitors of NIS function. These small organic molecules represent a starting point in the identification of pharmacological tools for the characterization of NIS trafficking and activation mechanisms (42).

Sodium-dependent multivitamin transporter (*SLC5A6, SMVT*)

This transporter mediates the uptake of water-soluble vitamins, i.e., ascorbic acid, biotin, folate, riboflavin, thiamin and pyridoxine. The transport by human small intestinal epithelial cells of these compounds, essential for normal health, occurs via an efficient Na^+-dependent, carrier-mediated mechanism that saturates at the micromolar range (43).

The human SMVT (hSMVT) system has been cloned, demonstrated to be exclusively expressed at the apical membrane of enterocytes, and shown, by means of gene-specific short interfering RNA (siRNA), to be the main biotin uptake system that operates in human intestinal epithelial cells. The 5′-regulatory region of the human *SMVT* gene has also been cloned and characterized both in vitro and in vivo (44). The hSMVT protein (635 amino acids) is the product of the *SLC5A6* gene, which is located on chromosome 2p23 and consists of 17 exons (45).

The cytoplasmic *C*-terminal tail of the hSMVT polypeptide is essential for targeting the protein to the apical membrane domain. Intracellular trafficking of the hSMVT protein is dependent on an intact microtubule network and involves distinct trafficking vesicles. The minus-end–directed microtubule motor protein dynein seems to regulate the polarized delivery of hSMVT protein to the apical cell surface (46). This transporter is also distributed in the placenta, testis, skeletal muscle and liver (47). Mutations in this transporter could provoke deficiencies in some essential micronutrients, and thus may lead to a variety of clinical abnormalities. Recently, considerable attention has been paid to target this nutrient transport system for delivering drugs (such as biotin-conjugated prodrugs) with poor permeability (48, 49).

High affinity choline transporter 1 (*SLC5A7, CHT1*)

The *CHT* genes identified in mice, rats and humans reside on chromosomes 17, 9 and 2, respectively. The structure of mammalian *CHT* genes is well conserved: each has 9 exons and spans ~25 kb of genomic sequence. The sequence similarity between *CHT* and other *SLC5A* family members, as well as hydrophilicity analyses and topology prediction algorithms, have led to a new prediction comprising

13 transmembrane domains with an extracellular *N*-terminus and a cytoplasmic *C*-terminus, a consensus site for *N*-linked glycosylation present at residue N301 in the fourth extracellular loop and several potential serine and threonine phosphorylation sites in the fifth intracellular loop and *C*-terminus that could serve to regulate CHT function (50).

CHT immunoreactivity is present both in the cell bodies and presynaptic terminals of cholinergic neurons (51). Choline present at the synaptic cleft after hydrolysis of acetylcholine (ACh) by acetylcholinesterases (AChE) is efficiently recaptured by CHT to sustain new ACh synthesis. Pharmacological studies reveal that ACh release cannot be sustained without presynaptic transporter-mediated recapture of choline. Once transported, ACh is very efficiently resynthesized by choline acetyltransferase (ChAT), loaded into synaptic vesicles by the vesicular ACh transporter (VAChT), and the cycle continues (50).

CHT may be an important target gene for disorders associated with deficits in cholinergic function. Alzheimer's disease (AD) patients may be vulnerable to deficits in *CHT* expression or regulation, bearing in mind that a loss of nucleus basalis cholinergic neurons occurs in the brains of AD patients (52) and that the symptoms of dementia can be relieved with AChE inhibitors (53). To date, the only drugs available to target CHT have been blockers with lethal effects, but the stage is now set to identify positive modulators of CHT that could provide relief from cholinergic deficiency (50). For example, the CHT enhancer MKC-231 improves cholinergic hypofunction by enhancing high-affinity choline uptake, subsequently facilitating ACh synthesis and release in vitro and in vivo (54).

Sodium-coupled monocarboxylate transporter 1 (*SLC5A8, SMCT1*)

SMCT1 is a sodium-coupled transporter for several monocarboxylates, including L-lactate, short-chain fatty acids and ketone bodies, contributing to the maintenance of energy status and the function of neurons (55). Gopal et al. have shown that human SMCT1 also transports nicotinate and its structural analogues. SMCT1 is also expressed on the luminal membrane of the epithelial cells lining the intestinal tract, and this transporter may therefore participate in the intestinal absorption of monocarboxylate drugs (56). Martin et al. demonstrated for the first time the differential and cell type-specific expression of these transporters in the retina, where they have biological importance in terms of transcellular transfer of lactate and ketone bodies (57).

The principal physiological function of the transporter may vary from tissue to tissue. In the colon, the transporter mediates the Na^+-coupled entry of short-chain fatty acids from the lumen into colonocytes. In the kidney, it is responsible for the active reabsorption of lactate from the glomerular filtrate. In the thyroid gland, SMCT1 is expressed in the apical membrane of thyroid follicular cells. Since pyruvate and lactate are produced as byproducts of thyroid hormone synthesis within thyroid follicular cells, the gating of the iodide channel by these monocarboxylates may have physiological significance, providing a mechanism to link the synthesis of thyroid hormones to the release of iodide into the colloidal lumen (58).

SMCT1 also transports butyrate and pyruvate, which are inhibitors of histone deacetylases. The silencing of SMCT1 occurs in cancers of a variety of tissues. Re-expression of SMCT1 in cancer cell lines leads to growth arrest and apoptosis in the presence of butyrate or pyruvate, suggesting that the transporter may function as a tumor suppressor. Since tumor cells selectively regulate these nutrient transporters to support their rapid growth, these transporters have potential as drug targets for cancer therapy (58, 59).

Sodium/glucose cotransporter 4 (*SLC5A9, SGLT4*)

SGLT4 is an essential transporter for mannose, 1,5-anhydro-D-glucitol and fructose. It was found to be highly expressed in the intestine and kidney and moderately expressed in the liver, suggesting that this transporter may play a pivotal role in the homeostasis of these sugar derivatives in the mammalian body (60). The homeostasis of mannose is controlled largely by transporter-mediated reabsorption in the kidney (61, 62). However, it has been reported that an elevation of serum mannose is associated with invasive candidiasis (63), diabetes (64) and metabolic syndrome (65). Therefore, control of the serum concentrations of mannose could be useful for the treatment of such pathological conditions. SGLT4 might therefore be a potential therapeutic target in patients with the above-mentioned disorders (60).

Sodium/glucose cotransporter 5 (*SLC5A10, SGLT5*)

SGLT5 is almost exclusively expressed in the renal cortex, but at present its function is unknown (16).

Sodium/myo-inositol cotransporter 2 (*SLC5A11, SGLT6, SMIT2*)

SMIT2 is a high-affinity sodium/myo-inositol transporter abundantly expressed in the brain and the kidney, where its role could be the accumulation of inositol for metabolism and/or osmoregulation (1). Recently it has been shown that SMIT2 mediates MI uptake in apical membranes of rat small intestine (66). In the rabbit kidney, SMIT2 is predominantly expressed in the cortex, where it is probably responsible for the apical transport of MI into the proximal tubule (67). This isoform also behaves as a glucose transporter, and it is believed that it could play a role in glucose uptake in those cells where it is expressed (16). SMIT2 has greater affinity for glucose than does SMIT1 and is thus more likely to be affected by increased glucose levels in untreated diabetes (68).

Sodium-coupled monocarboxylate transporter 2 (*SLC5A12, SMCT2*)

SMCT2 is very similar to SMCT1 in substrate selectivity and Na^+ dependence. A major difference between the two transporters lies in the relative affinity for their substrates, SMCT1 being a high-affinity transporter and SMCT2 a low-affinity transporter. Jorgensen and Sheikh had already shown that there were two distinct transport systems for lactate in the kidney, one being a low-affinity system found in the superficial cortex and the other a high-affinity system found in the outer medulla (69). While SMCT2 is broadly expressed along the entire length of the proximal tubule (S1/S2/S3 segments), the expression of SMCT1 is mostly limited to the S3 segment. This suggests that the low-affinity transporter SMCT2 initiates lactate absorption in the early parts of the proximal tubule, followed by the participation of the high-affinity transporter SMCT1 in the latter parts of the proximal tubule (70).

The expression of SMCT2 is limited to only three tissues: kidney, small intestine and skeletal muscle. Srinivas et al. clearly demonstrated by RT-PCR the presence of both SMCT1 and SMCT2 transcripts in the skeletal muscle. These transporters are likely to play a critical role in the handling of lactate by the skeletal muscle. SMCT2 is expressed predominantly in the proximal part of the small intestine and is absent from the cecum and colon, while SMCT1 is expressed in the distal part of the small intestine and in the cecum and colon. The proximal regions of the small intestine, where SMCT2 is expressed, are relatively sterile, with minimal bacterial colonization. It therefore appears that the physiological function of SMCT2 may be to absorb lactate and other monocarboxylates from dietary sources, while the primary function of SMCT1 in the intestine could be the absorption of bacterial metabolites, such as acetate, propionate and butyrate (2).

SGLT INHIBITORS: IMPORTANCE IN THE CONTROL OF HYPERGLYCEMIA

Of all the members of the SLC5A family, only some transport glucose, the most important and well studied being SGLT1 and SGLT2. Both proteins are expressed at the proximal tubule level, where they reabsorb glucose from the glomerular filtrate. Recently, special attention has been given to SGLT2 as a molecular target to induce glucose excretion and thereby normalize glucose levels in patients with type 2 diabetes, without increasing insulin secretion and minimizing the risk of hypoglycemia. Compounds selective for SGLT2 minimize potential side effects associated with the broad tissue distribution of SGLT1, which is expressed in other organs and tissues such as the blood–brain barrier and heart, in addition to the intestine and kidney (71).

Prolonged exposure to hyperglycemia is now recognized as a major factor in the pathogenesis of diabetic complications. Hyperglycemia induces a large number of alterations at the cellular level of different tissues. Several studies have shown diverse mechanisms that explain most of the pathological alterations observed in the hyperglycemic diabetic environment. These include (72):

- Nonenzymatic glycosylation of proteins and lipids which can interfere with their normal function by disrupting molecular conformation, altering enzymatic activity, reducing degradative capacity and interfering with receptor recognition. The interaction of glycosylated proteins with their receptors results in the induction of oxidative stress and proinflammatory responses.
- Protein kinase C (PKC) activation with subsequent alteration in growth factor expression
- *O*-Linked glycosylation of various enzymes, which alters normal enzymatic function
- Increase in oxidative stress through several pathways, for example overproduction of the superoxide anion (O_2^-) by the mitochondrial electron transport chain
- Induction of inflammation through the secretion of cytokines by several cell types including monocytes and adipocytes

To prevent the development or progression of diabetic kidney disease, good glycemic control remains the cornerstone in the management of diabetic patients (73). The most important management strategy for type 2 diabetes involves lifestyle changes that promote body weight loss, especially diet and exercise. When this is not sufficient to maintain a good energy balance, antidiabetic drugs are required (74). Therapeutic strategies to ameliorate hyperglycemia have traditionally focused on developing molecules that enhance endogenous insulin secretion and/or improve insulin sensitivity. However, at present, the inhibition of renal glucose uptake is used because it has been demonstrated that this strategy plays a key role in reducing plasma glucose concentrations during hyperglycemia (75, 76).

Diabetes is a leading cause of end-stage renal disease. Hyperglycemia increases the filtered load of glucose at the glomerulus, and glomerular hyperfiltration itself is also associated with diabetes. The progression of renal dysfunction in type 2 diabetes involves injury of the tubular epithelium, as well as the glomerulus, and it is thought that increased glucose fluxes through epithelial pathways result in the increased expression and activity of aldose reductase, protein kinase C (PKC) and transforming growth factor β (TGF-β), which have all been implicated in diabetic nephropathy (77).

SGLT2 inhibitors are being developed as potential antidiabetic agents offering a renoprotective effect by decreasing transcellular epithelial glucose fluxes, preventing at least some of the cellular mechanisms that lead to diabetic renal complications (77). On the other hand, SGLT2 inhibitors can be used in monotherapy or in combination with other oral agents such as metformin or even insulin, if needed. Besides, they have the advantage of a dual effect, both on glycemic control and weight loss, and may also be effective in type 1 diabetes, especially for reducing postprandial glucose levels (47).

INHIBITORS OF SGLT2 FOR THE TREATMENT OF TYPE 2 DIABETES

Nonselective inhibitors

Phloridzin

Phloridzin (Fig. 1A), isolated from the root bark of the apple tree, was the first SGLT inhibitor to be evaluated. This drug is a β-D-glucoside and consists of a glucose moiety and an aglycone in which two aromatic carbocycles are joined by an alkyl spacer (74). Phloridzin is a dual inhibitor of both SGLT1 and SGLT2 and increases glucose excretion in the urine by suppressing renal glucose reabsorption, and concomitantly decreases plasma glucose levels (78).

Hirayama et al. provided evidence that phloridzin interacts with SGLT1 at two distinct sites: the sugar moiety binds to the substrate binding site and the aromatic rings of the aglycone bind to a second site which produces transport inhibition (79). Recently, site-directed mutagenesis experiments suggested that Cys610 in human SGLT1 (hSGLT1) and the analogous Cys615 in hSGLT2 may be important in maintaining the structure of the inhibitor binding site, but these residues are not likely to bind directly to inhibitors (26).

Phloridzin has been a very useful pharmacological tool for elucidating the role of SGLT2 in glucose homeostasis. However, it is not used as an antidiabetic agent because it has very poor oral bioavailability (71) due to hydrolysis by lactase-phlorizin hydrolase in the intestine (74). In addition, due to its lack of selectivity, SGLT1 is also inhibited,

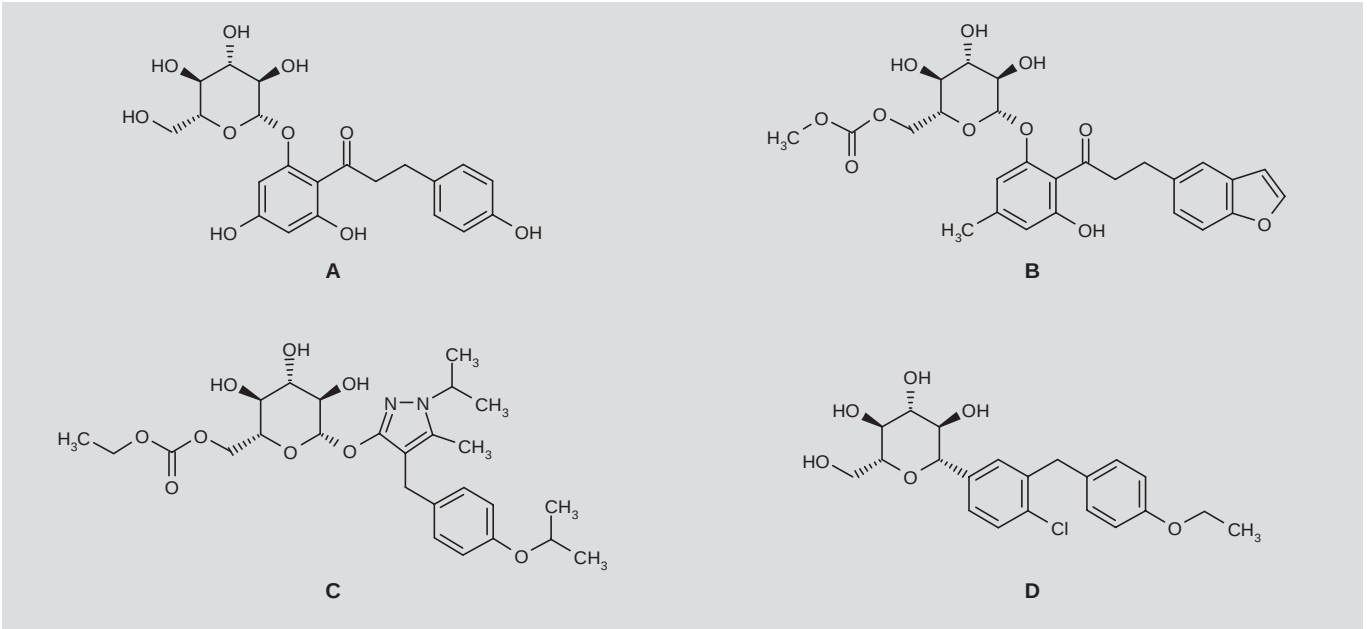

Figure 1. Inhibitors of SGLT2 for the treatment of type 2 diabetes.

with undesirable side effects such as diarrhea. Furthermore, phloretin, the aglycone of phloridzin, was found to inhibit other transporters such as GLUT1 and monocarboxylate transporter 1, which transport glucose and monocarbohydrates, respectively, in different tissues (74, 78). Therefore, due to the unwanted adverse effects of phloridzin, newer compounds have been developed.

T-1095

An analogue of phloridzin, T-1095 (Fig. 1B) is a methyl carbonate prodrug with good absorption that can be administered orally. It is converted to its metabolite, T-1095A, in the liver after intestinal absorption, and it would thus not affect glucose absorption in the intestine. This drug lowers blood glucose by inhibiting the function of renal SGLTs and increasing urinary glucose excretion (80). In fact, T-1095A inhibits SGLT2 activity with 4-fold greater potency relative to SGLT1.

T-1095 was shown to effectively suppress marked postprandial hyperglycemia in streptozotocin (STZ)-induced diabetic rats, and with long-term T-1095 treatment both blood glucose and glycosylated hemoglobin (HbA1c) levels were reduced in STZ-induced diabetic rats and obese insulin-resistant KK mice. This suggested that T-1095 exerts an antihyperglycemic effect irrespective of the presence of endogenous insulin secretion. In addition, T-1095 treatment improved the hyperinsulinemia in genetically diabetic yellow KK-Ay mice, an obese type 2 diabetes model with typical insulin resistance, which suggested improvement in insulin resistance in that murine model (80).

Arakawa et al. (81) demonstrated the acute and chronic antihyperglycemic effects of T-1095 in C57BL/KsJ-*db/db* mice, a strain that exhibits many of the metabolic disturbances of human type 2 diabetes, including hyperglycemia, obesity, early hyperinsulinemia and renal pathological changes similar to those observed in diabetic patients (81-83). These investigators showed that chronic oral administration of T-1095 decreased blood glucose and HbA1c levels and improved glucose intolerance in *db/db* mice. Furthermore, they found that the drug suppressed both the development of albuminuria and the expansion of glomerular mesangial area in these mice, indicating its ability to prevent the progression of diabetic nephropathy (81).

Another animal model, Goto-Kakizaki (GK) rats, a spontaneous, nonobese model of type 2 diabetes (84), was also used to demonstrated the efficacy of T-1095. T-1095 administered as a dietary admixture significantly reduced blood glucose and HbA1c levels, partially improved glucose intolerance and insulin resistance, and prevented the development of diabetic neuropathy in GK rats (85).

More recently, it was demonstrated that a reduction in the transport maximum for glucose of at least 70-80% with T-1095A is necessary for suppressing postprandial hyperglycemia in normal dogs (86). On the other hand, it was reported that T-1095 does not increase sodium levels in urine, nor affect plasma osmolarity and the contents of electrolytes in diabetic KK mice (87). Thus, this SGLT inhibitor does not appear to influence the electrolyte balance in plasma and urine (86).

The development of T-1095 reached phase II clinical trials but was subsequently discontinued (74).

Selective inhibitors

Remogliflozin etabonate

Remogliflozin etabonate (Fig. 1C) is a prodrug based on a benzylpyrazole glucoside and is metabolized to its active form, remogliflozin, in the body. Since its skeleton differs from that of phloridzin, T-1095 or sergliflozin, remogliflozin etabonate belongs to a new category of SGLT2 inhibitor.

Remogliflozin is a potent and highly selective SGLT2 inhibitor, having a selectivity ratio of 365 and a K_i of 12.4 nM in COS-7 cells. This drug produces its antidiabetic effect by increasing urinary glucose excretion; the antihyperglycemic effect of remogliflozin etabonate does not depend on an increase in insulin secretion. Remogliflozin etabonate may be useful over a range of diabetes from mild to severe, since it showed an antihyperglycemic effect in *db/db* mice, which have more severe hyperglycemia than STZ-induced diabetic rats.

Clinical trials on remogliflozin etabonate are currently in progress (88).

Dapagliflozin (BMS-512148)

Dapagliflozin (Fig. 1D) is a *C*-aryl glycoside identified as a potent and selective inhibitor of human SGLT2, which reduces blood glucose levels by as much as 55% in hyperglycemic STZ rats. The selectivity ratio for this compound is 1,200 in CHO cells stably expressing human SGLT2 and SGLT1. However, the selectivity for rat SGLT2 versus SGLT1 decreased to 200-fold.

This compound displays a favorable absorption, distribution, metabolism and excretion (ADME) profile. It is a potent, metabolically robust, selective SGLT2 inhibitor that is not subject to *O*-glucosidase degradation, resulting in a prolonged pharmacokinetic half-life and duration of action (47). Dapagliflozin is expected to be orally bioavailable in humans based on its high (> 150 nm/s) permeability value in the Caco-2 cell monolayer assay and 84% oral bioavailability in rats (89).

Dapagliflozin is currently undergoing phase IIb/III clinical development by Bristol-Myers Squibb and AstraZeneca (47).

Other SGLT2 inhibitors under development

The following SGLT2 inhibitors are in earlier stages of development and no publications are yet available:

- SAR-7226: phase I (sanofi-aventis)

  As this compound possesses sugar residues, it was evaluated whether it could interfere either directly with the activity of glucokinase (GK) or with the interaction between GK and the GK-regulatory protein (GKRP), which is regulated by carbohydrates such as glucose or fructose 1-phosphate. In enzymatic assays the activity of purified GK was not affected by SAR-7226. In addition, SAR-7226 does not affect the GK–GKRP interaction at pharmacologically relevant concentrations; hence, this compound does not interfere with a key step of hepatic carbohydrate metabolism (90).

- YM-543 and ASP 1941: phase II (Astellas Pharma)

  Both drugs are novel hypoglycemic agents effective in a broad spectrum of patients irrespective of the pathology (impaired insulin secretion or insulin resistance). They prevent weight gain and are suitable for combination therapy with all types of hypoglycemic agents (91).

- TA-7284: phase II (Mitsubishi-Tanabe Pharma and Johnson & Johnson) (92)

- CSG-452 (R-7201): phase I (Chugai, codeveloped with Roche) (93)

- BI-10773 and BI-44847: phase II (Boehringer Ingelheim) (94-96)

- JNJ-28431754: phase II (Johnson & Johnson)

  This orally administered SGLT2 inhibitor is also being tested as a drug to promote weight loss in overweight and obese patients who do not have diabetes (97).

- LX-4211: phase I (Lexicon Pharmaceuticals)

  Orally delivered small molecule under development as a potential treatment for diabetes. In preclinical studies, animals treated with LX-4211 demonstrated increased urinary glucose excretion and decreased blood HbA1c levels (a marker of long-term blood sugar levels). Importantly, urinary glucose excretion returned to baseline after treatment was discontinued (98).

- LX-4212: preclinical (Lexicon Pharmaceuticals) (98)

Antisense drugs

Antisense technology consists of the inhibition of different gene products and has allowed the rapid evaluation of many potential targets for the treatment of complex metabolic diseases such as diabetes and obesity in well-established animal models.

- ISIS-388626: phase I (Isis Pharmaceuticals)

  ISIS-388626 effectively and specifically inhibits the production of SGLT2 in the kidney tissue, without having any effect on the related gene product SGLT1. In preclinical studies, Isis demonstrated in several animal species that ISIS-388626 and other antisense inhibitors of SGLT2 effectively reduce target mRNA levels, increase urinary glucose excretion and consequently lower blood glucose levels and HbA1c without causing hypoglycemia. ISIS-388626 is also unique due to its length of 12 nucleotides rather than the more typical 18-21-nucleotide sequences of other antisense drugs. This attribute simplifies manufacturing and may also contribute to its unusually high potency. This drug is administered subcutaneously (99, 100).

CONCLUSIONS

The multifunctional properties of the SLC5 sodium/glucose cotransport family have attracted the interest of many investigators in order to determine its physiological significance. On the other hand, the pharmaceutical industry has focused its attention on some members of this family of proteins as targets for the development of novel therapeutic drugs:

- SGLT1 is the target protein for the treatment of secretory diarrhea, such as cholera, by oral rehydration therapy (ORT)

- Inositol depletion via inhibition of SMIT1 was proposed as a therapeutic mechanism in the treatment of bipolar mood disorder and the transporter may be a target for mood stabilizers.

- Recently, investigators have identified and characterized inhibitors of NIS function which will allow the characterization of NIS trafficking and activation mechanisms.

- Considerable attention has been paid to targeting the nutrient transport system SMVT as a tool for delivering drugs (as biotin-conjugated prodrugs) with poor permeability.

- *CHT* may be an important target gene for disorders associated with deficits in cholinergic function such as AD. Therefore, rather than inhibitors, in this case the strategy could be the development of CHT enhancers or positive modulators to improve cholinergic function.
- It has been suggested that SMCT1 may function as a tumor suppressor. This transporter may therefore have potential as a drug target for cancer therapy.
- SGLT4 may be a therapeutic target in patients with disorders that are accompanied by an elevation in serum mannose, such as invasive candidiasis, diabetes and metabolic syndrome.
- Undoubtly, SGLT2 is the transporter of this family that has attracted the greatest interest in recent years as a target to control blood glucose in diabetic patients. Selective SGLT2 inhibitors may control hyperglycemia, improve insulin resistance and preserve pancreatic β-cell function without affecting gastrointestinal functions or inducing body weight gain. This new class of antidiabetic agents has the advantages of good potency and safety.

In addition, the future development of specific inhibitors for these transporters and/or gene knockout will provide important information about their physiological function.

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