SGLT2 Inhibitors: Physiology and Pharmacology

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Abstract

SGLTs are sodium glucose transporters found on the luminal membrane of the proximal tubule, where they reabsorb some 180 g (1 mol) of glucose from the glomerular filtrate each day. The natural glucoside phlorizin completely blocks glucose reabsorption. Oral SGLT2 inhibitors are rapidly absorbed into the blood stream, where they remain in the circulation for hours. On glomerular filtration, they bind specifically to SGLT2 in the luminal membrane of the early proximal tubule to reduce glucose reabsorption by 50–60%. Because of glucose excretion, these drugs lower plasma glucose and glycosylated hemoglobin levels in patients with type 2 diabetes mellitus. The drugs also protect against heart and renal failure. The aim of this review is to summarize what is known about the physiology of renal SGLTs and the pharmacology of SGLT drugs.

Introduction

Rather unexpectedly to endocrinologists, sodium glucose cotransporter-2 (SGLT2) in the kidney has become a major target for the treatment of type 2 diabetes mellitus (T2DM). As a background, the kidneys normally filter 120–180 g (0.67–1 mol) of glucose from plasma every 24 hours, and less than half a gram (3 mmol) is excreted in the urine. Smith et al. reported in 1933 that the reabsorption of the filtered load of glucose was completely inhibited by intravenous phlorizin (phloretin-2'-β-D-glucopyranoside), a naturally occurring plant glucoside (1). Fast forwarding half a century, DeFronzo and colleagues found that “phlorizinising” diabetic rats diminished their hyperglycemia and restored their insulin sensitivity, suggesting phlorizin could be used as a therapy for T2DM (2). Oral phlorizin was not considered to be a viable therapy owing to its hydrolysis by intestinal lactase, and the diarrhea caused by inhibition of intestinal SGLT1.

The pharmaceutical industry set its sights on developing an oral SGLT2 inhibitor to treat T2DM after the cloning and characterizing of the intestinal and renal SGLTs in 1987–1992 (3–10). This was encouraged by reports that familial renal glucosuria (FRG; OMIM 233100) is a benign disorder (11). The initial effort was pioneered by Tsujihara at Tanabe Seryaku in Japan (12), who tested oral phlorizin derivatives on renal glycemia and restored their insulin sensitivity, suggesting phlorizin could be used as a therapy for T2DM (2). Oral phlorizin was not considered to be a viable therapy owing to its hydrolysis by intestinal lactase, and the diarrhea caused by inhibition of intestinal SGLT1.

The functional properties of both transporters have been documented in studies of SGLT1 and SGLT2 expressed in heterologous expression systems. Table 1 summarizes the results obtained in cultured cells at 37°C. Both SGLTs show a similar affinity for glucose, Km 2, and 5 mM, and similar turnover numbers of 30–60 s⁻¹ (the number of complete kinetic cycles per second). The major differences are in the number of sodium ions needed to drive glucose transport, the Na⁺/glucose coupling ratio is 2 for SGLT1 and 1 for SGLT2, and the sugar and inhibitor selectivity.

Figure 1 shows the chemical structure of phlorizin and three of the first inhibitors approved for the
treatment of T2DM. All are glucosides, but empagliflozin (Jardiance), dapagliflozin (Forxiga), and canagliflozin (Invokana) are aryl-C-glucosides that are not cleaved by lactase. These inhibitors are more potent against SGLT2 than SGLT1 with inhibitors constants in the range of 1–12 nanomoles, and are more selective for SGLT2, 2700-fold for Jardiance (Table 1). This difference in potency between SGLT2 and SGLT1 must be due to differences in structure of the aglycones, but this has not been rigorously addressed. However, subtle differences in the structure of aglycones determine whether they are SGLT1 substrates or inhibitors (19). Although the SGLT2 drug inhibitor constants are quite similar, the oral clinical dose is 100–300 mg for Invokana but only 10–25 mg for Jardiance and Forxiga.

The distribution of SGLTs in human subjects has been limited to gene expression and immunohistochemistry on postmortem and/or surgically resected tissues. However, these methods do not provide information about their functional activity in tissues. To remedy this we have turned to positron emission tomography (PET) with a specific, non-metabolized SGLT tracer, Me4FDG (α-methy-4-[18F]fluoro-4-deoxy-D-glucopyranoside), in both animal and human subjects (20–22). PET is a non-invasive imaging method with high spatial (2 mm) and temporal resolution (seconds) to follow 18F distribution in living subjects (23). Me4FDG is transported by SGLT1 and SGLT2, but not by facilitated glucose transporters, GLUTs (21). Figure 2 shows the steady-state distribution of Me4FDG injected intravenously into two subjects, a control (A) and (B), a patient with FRG (OMIM 2333100) (8,11). This male patient with FRG has a homozygous SGLT2 mutation, Ala305Val, associated with a defect in renal glucose reabsorption resulting in the urinary excretion of 66 g (370 mmol) per 1.73 m² per 24 hours (24).

In the control subject, accumulation of Me4FDG is observed in the renal cortex and regions of the liver, with modest accumulations in skeletal muscle and testis. None is found in the brain or the urinary bladder, the former is

| Table 1. Kinetics of human SGLT2 and SGLT1 |

<table>
<thead>
<tr>
<th>COLUMN ONE</th>
<th>SGLT2</th>
<th>SGLT1</th>
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<tbody>
<tr>
<td>Glucose</td>
<td>$K_m$ (mM)</td>
<td>5</td>
</tr>
<tr>
<td>Galactose</td>
<td>$K_m$ (mM)</td>
<td>$&gt;&gt;100$</td>
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<tr>
<td>aMDG</td>
<td>$K_m$ (mM)</td>
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<tr>
<td>Sodium</td>
<td>$K_m$ (mM)</td>
<td>25</td>
</tr>
<tr>
<td>Na⁺/glucose coupling</td>
<td>1 s⁻¹(38)</td>
<td>30–60 s⁻¹</td>
</tr>
<tr>
<td>Turnover</td>
<td>35 s⁻¹(38)</td>
<td>30–60 s⁻¹</td>
</tr>
<tr>
<td>Phlorizin</td>
<td>$K_i$ (nM)</td>
<td>12</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>$K_i$ (nM)</td>
<td>6</td>
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<tr>
<td>Phlorizin</td>
<td>$IC_{50}$ (nM)</td>
<td>21</td>
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<tr>
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<td>Empagliflozin</td>
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<td>Sotagliflozin</td>
<td>$IC_{50}$ (nM)</td>
<td>2</td>
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All data collected on human SGLT2 and SGLT1 clones expressed in cultured cells at -60 mV and 37°C (35,36), except for the turnover of SGLT2 that was in Xenopus laevis oocytes at 22°C (38). $IC_{50}$ values are for inhibition of aMDG uptakes. aMDG, xx.
due to the lack of SGLTs in the blood-brain barrier, and the latter is due to the reabsorption of Me4FDG from the glomerular filtrate by SGLTs in the proximal tubule. A similar distribution is seen in the patient with FRG, with the exception that in the kidney Me4FDG is shifted from the cortex toward the renal pelvis, and is excreted into the urinary bladder. The time course of Me4FDG excretion into the bladder of the patient with FRG is shown in Figure 3, relative to that for control subjects with or without treatment with Jardiance (empagliflozin). Me4FDG excretion for the patient with FRG reached 3.5% of the injected dose in 75 minutes, compared with none for the control, and 7% after treatment with Jardiance. The SGLT2 inhibitors also inhibited Me4FDG reabsorption in mouse microPET studies (25).

To distinguish between SGLT1 and SGLT2 in PET studies, we developed a $^{18}$F-labeled SGLT2 inhibitor, 4-$^{18}$Ffluoro-dapagliflozin, F-DAPA, where $^{18}$F replaces the $\text{OH}$ group on C#4 in the pyranose ring (25). In rodent, intravenous (i.v.) injection results in rapid F-DAPA binding to the kidney that is displaced after i.v. dapagliflozin or phlorizin. The specific binding of F-DAPA to the whole kidney was 6× higher than nonspecific binding, and no specific binding was observed for other parts of the body, brain, heart, skeletal muscle, liver, or salivary glands. In human subjects, Jardiance significantly reduced the modest Me4FDG uptake into liver and skeletal muscle, but not the heart (unpublished).

The time course of F-DAPA distribution in the rat is shown in Supplemental Movie 1 (25). After i.v. injection, there was a rapid accumulation of F-DAPA in the renal cortex that approached a steady state in 20 minutes. After i.v. injection of dapagliflozin (or phlorizin, not shown) there was a rapid displacement of F-DAPA from the kidney cortex, reabsorption of the tracer into blood and excretion into the intestine. Of particular note, there was no excretion of F-DAPA into the urinary bladder, before or after displacement with dapagliflozin or phlorizin. The mechanisms of F-DAPA reabsorption from the glomerular filtrate and secretion by the liver are unknown. Similar F-DAPA PET experiments were conducted on human subjects, but these were not successful owing to a very rapid metabolism of the tracer.

The location of specific F-DAPA binding in mouse kidney was refined by autoradiography (Figure 4). In this
Figure 3. | The time course of Me4FDG excretion into the urinary bladder in control subject, a control treated with oral Jardiance (empagliflozin), and the patient with FRG shown in Figure 2. In each, 10 mCi of Me4FDG (370 MBq) was injected intravenously and a dynamic scan over the abdomen was taken for up to 75 minutes. The total activity in the urinary bladder in MBq is plotted against time. The plot + Jardiance is for a control subject given a 25 mg oral dose of Jardiance 2 hours before the PET scan. Wright et al, unpublished.

Glucose Reabsorption

The understanding of glucose handling by the human kidney is that after glomerular filtration of glucose, virtually all of the filtered load is reabsorbed in healthy subjects (Figure 5A). Reabsorption occurs in the proximal tubule because no glucose is found at the end of the straight S3 segment (27). The SGLT2 inhibitors are believed to be freely filtered, as for phlorizin (28), where they then bind to SGLTs in the luminal membrane of the epithelial cells in the proximal tubule. In the dog kidney, the clearance of [3-H]-phlorizin was identical to that for creatinine, and none was excreted in the urine.

The SGLT2 drugs, even at saturating plasma concentrations only inhibit glucose reabsorption by 40–50% (29). The remaining amount in the glomerular filtrate is largely salvaged by SGLT1 activity in S3. This has been confirmed in mice with knockouts of the SGLT1 and SGLT2 genes (21,30), and it is also evident in patients with SGLT2 “knock-out” mutations, where glucose excretion is less than the filtered load (see 8).

SGLTs are expressed in the luminal membrane of the proximal tubule, SGLT2 in the S1/S2 segments (Figure 5B) and SGLT1 in the S3 segment. Glucose uptake into the epithelia across the luminal membrane is driven by the Na+ electrochemical potential gradient across the membrane, then glucose diffuses out into blood across the basolateral membrane through the facilitated glucose transporter GLUT2 (21). Na+ that enters the cells through SGLTs is transported out across the basolateral membrane by Na+/K+ pumps. In the S1 and S2, the net result is that one Na+ is absorbed for every glucose molecule (and one anion to maintain electroneutrality), whereas in S3 two Na+ ions are absorbed for every glucose molecule. Given a glucose reabsorption of 120–180 g (0.67–1 mol) of glucose per day, the stoichiometry of the SGLTs, glucose-coupled sodium absorption only accounts for <10% of the total sodium reabsorption in the proximal tubule. At clinical doses, the SGLT2 inhibitors only reduce total glucose absorption by some 50%, so there is only a modest effect on urinary sodium excretion, given the ability of the distal tubule to reabsorb the increased salt load.

Mechanism of Na+ Glucose Transport

Much more is known about the mechanism of glucose transport by SGLT1 than for SGLT2, simply due to the much higher activity of SGLT1 in heterologous expression systems such as Xenopus laevis oocytes (6,8,9). This has been partially rectified by the discovery that coexpression of MAP17 increased SGLT2 expression in oocytes (31). MAP17 (PDZK1IP1) is small protein expressed in the plasma membrane, endoplasmic reticulum, and Golgi apparatus of many cell types, and is involved in cargo transport between the Golgi and plasma membrane. In the mouse proximal tubule, MAP17 is expressed in the brush border membrane of the S1 and S2 segments, where it is involved in the endocytosis of the sodium phosphate cotransporter NaPi-IIa from the brush border into the trans-Golgi network (32). MAP17 interacts indirectly with the cytoplasmic C-terminal domain of NaPi-IIa through a PDZ protein. However, there is no comparable C-terminal domain of SGLT2, but there is evidence that MAP17 may be a β-subunit of SGLT2 in the plasma membrane of the S1 and S2 segments (31,33).

SGLT2 is robustly expressed in cultured mammalian cells at 37°C (34–37), and there is no MAP17 in these cells (32,33). The kinetic properties of SGLT2 in cultured cells and oocytes are similar (35,38), and those for HEK293T cells are summarized in Table 1.

The kinetics of SGLT2 and SGLT1 are very similar in that they are sodium cotransporters with an obligatory coupling of glucose and sodium transport that is specifically blocked by phlorizin. The glucose affinities are 5 and 2 mM for glucose, with maximum enzymatic turnover numbers of 30–60 s⁻¹. Such data refute earlier claims that these are low-affinity, high-capacity, and high-affinity, low-capacity
transporters. The major kinetic differences between SGLT2 and SGLT1 are: (1) stoichiometry of Na$^+$ and glucose transport (1 for SGLT2, and 2 for SGLT1); (2) sugar specificity (galactose is transported by SGLT1 but rather poorly for SGLT2); (3) the requirement of SGLT2 for MAP17; (4) the high selectivity of SGLT2 for inhibitors; and (5) high SGLT1 capacitive currents are evident for SGLT1 but not SGLT2 (these have been instrumental in developing kinetic models, see Figure 6).

A kinetic model for Na$^+$ and glucose transport by SGLT2 is presented in Figure 6. This is largely on the basis of the wealth of experimental biochemical, molecular, and biophysical data collected for SGLT1 (see 8,17). The transporter is represented as a double-gated membrane protein that exists in a minimum of interconvertible five states (C1, C2, C3, C4, C6). The distribution of these depends on the Na$^+$ and glucose concentrations on each side of the membrane, and the voltage across the membrane. Under physiologic conditions, with the extracellular Na$^+$ and glucose concentrations of 145 m-equiv/l and 5 mM, and a membrane potential of -60 mV, and the direction of Na$^+$/glucose is into the cell. In the kinetic scheme, extracellular Na$^+$ binds first to open the extracellular gate (C1-C2) and, after extracellular glucose binding, the external gate closes (C2-C3). The intracellular gate then opens to permit Na$^+$ and glucose to exit into the cytoplasm (C4-C6). The intracellular release of ligands is presumed to be stochastic, unlike our original symmetrical model with a C5 state (8,17,39). The final step is the transition of the inward to outward facing conformations (C6-C1). The apo-transporter is charged, valance -1, and the major effect of voltage in on the distribution between C6 and C1, and this

Figure 4. | The distribution of SGLT2 in the mouse kidney as determined by 4-[18F]fluoro-dapaglifozin (F-DAPA) autoradiography. A mouse was injected intravenously with 4 mCi of F-DAPA and the kidney was harvested after 60 minutes and prepared for autoradiography. The figure shows the grain density and hematoxylin and eosin staining for a section of the whole kidney (A), a higher magnification view of the outer cortex (B), and a higher magnification view of tubules surrounding a single glomerulus. The scale bars are 1 mm in (A), and 100 μm in (B) and (C). These result shows that SGLT2 is confined to the outer cortex in the mouse kidney, specifically to some tubules surrounding the glomeruli. Reprinted from Ghezzi et al. 2017 (25).
is the origin of the fast, transient SGLT1 capacitive currents in the absence of ligands (8,40,41).

The model accounts for the strict coupling between Na and glucose transport that is completely reversible—the direction and rate of transporter simply depends on the ligand concentrations on each side of the membrane and the membrane potential. In the case of SGLT1, the capacitive currents provide an entree into estimating the rate constants for each step in the kinetic cycle, and determining the total number of transporters in the plasma membrane. This topic is beyond the scope of this review, but interested readers are directed elsewhere (8,17). Suffice to say that a single set of rate constants account for SGLT1 kinetics.

**SGLT Inhibitors**

Phlorizin and other SGLT blockers are high-affinity, competitive inhibitors that are only active from the extracellular surface in the presence of Na (17,37,39,42,43). Inhibition is reversible, but the OFF-time constants are slower for the specific SGLT2 inhibitors than phlorizin (15,36). Phloretin, the phlorizin aglycone, is a low affinity nonspecific inhibitor of SGLTs (8). This, together with the high affinity of phlorizin relative to glucose, has led to the view that the glucose moiety of phlorizin binds to the glucose-binding site of SGLTs, and the phloretin binds at an adjacent site within 15 Å (44).

A molecular interpretation of inhibitor interactions with SGLTs is illustrated in Figure 7. Phlorizin and the SGLT2 drugs bind to the external surface of SGLTs in the outside open Na+ bound conformation. As shown in Figure 7A, phlorizin enters with the glucose moiety approaching the glucose binding site, and the aglycone approaching an external vestibule. Once bound, the inhibitors lock the transporter in an outward-facing conformation. Although binding is reversible, the OFF rate is slow due to the interactions the aglycone and the vestibule, and this accounts for the high affinity of phlorizin relative to glucose.

Structural models on the basis of the atomic structure of the bacterial isoform, vSGLT (45,46) provide additional insight into inhibitor binding (47). The transporters have a core structure composed of 10 transmembrane helices with a central sugar binding site (N75, H80, E99, K321, Y290, and W291), external (L84, F98, F453), and internal (Y290) gates, and a Na2 sodium-binding site centered around S393 (Figure 7B). All these residues are conserved between SGLT2, SGLT1, and vSGLT (see 8,17), and their functional importance in SGLT1 has been confirmed by studies of cysteine mutants (40,48,49,50). Similar studies with SGLT2 have not yet been carried out.

The precise location of the inhibitor-binding site shown in Figure 7, B-D. This has been determined by molecular-docking studies on SGLT1 and SGLT2 structural models, and verified for SGLT1 by mutations of coordinating amino acids.
residues (47). The glucose moiety of phlorizin binds in the glucose binding site, and the aglycone is found in an external vestibule bounded by the external ends of TM1, TM2, TM3, and TM10. Phloretin overlaps with the aglycones. Mutation of SGLT1 side-chains predicted to interact with inhibitors, for example, F101, reduces phlorizin binding by 200-fold without influencing glucose transport. In SGLT2, the bound inhibitors are capped by H80, F98, and H268 on the long extracellular loop connecting TM5 and TM6. This cap forms an aromatic cage around the central aromatic ring of the aglycone tail in SGLT2 but not SGLT1, and so may contribute to the differences in selectivity of SGLT inhibitors.

Dapagliflozin binding also involves the glucose moiety binding to the glucose site, and the aglycone tail overlaps with the phlorizin tail in the external facing vestibule, but with the minor difference that dapagliflozin lies deeper in the pocket. Simulations of inhibitor binding also indicate the external gate partially closes after binding, due to a rigid rotation of TM9, an inward bend of the outer half of TM10, and the inward movement of the extracellular loop between TM5 and TM6. These helical rearrangements have been observed in real time by fluorescence measurements on fluorophores covalently bound within the sugar-binding site (17,50).

Unfortunately, the structural models do not account for the selectivity of inhibitors for SGLT2 over SGLT1 (Table 1). Nevertheless, they do account for the sidedness of inhibitor binding as cytoplasmic phlorizin and SGLT2 drugs fail to gain access to the sugar binding site due to steric clashes (47).

To date, there are few reports of SGLT1 specific inhibitors, but there has been some interest in the pharmaceutical companies in dual SGLT1/SGLT2 inhibitors, such as sotagliflozin (Table 1). The objectives were to control blood glucose, especially in type 1 diabetes, by reducing intestinal absorption, and inhibiting renal SGLT2 and SGLT1 (see 51).

SGLT2 Inhibitors in Heart and Kidney Failure

An unanticipated outcome of the Jardiance cardiac safety trial was that patients who were diabetic and treated with Jardiance showed a remarkable reduction in hospitalization and mortality for heart failure (52). This cardio protection is a SGLT2 inhibitor class effect, and it persists in patients who are nondiabetic (53–55). SGLT2 inhibitors are now approved for the treatment of heart failure. Although there is no direct evidence for a relationship between the kidney and heart in the effects of SGLT2 inhibitors, there is rodent data suggesting an off-target effect on cardiac sodium transport.

Figure 6. | A model for glucose transport by SGLT2. The transporter in the plasma membrane is shown as a double-gated protein where, in the absence of ligands, both gates are closed. The binding of external sodium (green circle) to the Na2 site opens the external gate to allow external glucose (yellow hexagon) to bind. After glucose is bound, the external gate closes after sugar binding to trap the sugar in the middle of the protein before the inner gate opens to permit Na+ and glucose to exit into the cytoplasm in one step. Finally, the transporter returns to the starting position. The net result is strict coupling of one sodium and one glucose transport across the membrane during one transport cycle.
proton exchangers (NHE1). The most compelling experiments come from Zuurbier’s group, who tested the effect of SGLT2 inhibitors on the intracellular Na\(^+\) and Ca\(^{2+}\) concentrations in isolated cardiac myocytes, and the onset of contraction in an ischemic mouse heart model (56–58). At pharmacologically relevant doses, 0.25–1 μM, the inhibitors produce fast lowering of the intracellular Na and Ca concentrations that are consistent with inhibition of NHE1. Indirect support was achieved by molecular docking studies of the drugs with a homology model of NHE1. The glucose moiety of the drugs reportedly binds to the Na\(^+\) binding site and the aglycone to the adjacent extracellular vestibule (our preliminary studies also find vestibule leading canonical glucose binding site, Bisignano et al., unpublished). The effect of SGLT2 inhibitors on cardiac NHE1 are consistent with the current thinking that elevated myocyte Na and Ca intracellular concentrations are drivers of heart failure and cardiac death. Whether these rodent studies will translate into patients is unknown, but I do note that clinical trials on other potent NHE1 inhibitors have not been successful, such as the cariporide GUARDIAN and EXPEDITION trials (59).

After the cardiac safely trials, it emerged the SGLT2 inhibitors produced a comparable reduction in the progression of CKD in patients who were diabetic and nondiabetic (60,61). The underlying mechanisms are not understood, because it is unclear at what points the inhibitors act in the natural progression of kidney disease. In particular, the potential importance of renal sodium protein exchangers, principally NHE3 in the proximal tubule, has yet to be clarified.

Summary

Oral SGLT inhibitors are rapidly absorbed from the gastrointestinal tract into blood, where they bind to plasma proteins and circulate throughout the vascular tree with a half-life of 10–14 hours. The free drugs are filtered from plasma at the glomerulus where they then bind to the luminal membrane of the proximal tubule. The SGLT2

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**Figure 7.** Inhibitor binding to SGLT2. (A) External phlorizin approaching the glucose binding site binding in the sodium bound outward open conformation. The glucose moiety of phlorizin binds to the glucose binding pocket and the aglycone moiety is stuck in the outer vestibule. (B) A structural model of SGLT2 with glucose in the occluded binding site, and the location of the Na\(^2\) binding site. From Ghezzi et al. 2018 (27). The protein has a core structure of 10 transmembrane helices (TM 10 not shown for clarity) with glucose. We propose that the external gate formed by residues L84, F98, F453, and the extracellular helical loop EL8b. Glucose is bound through H-bonds to N75, H80, E99, K321, and W291, and hydrophobic binding to Y290. These residues are conserved in SGLT1. Y290, at least in part contributes to the internal gate. (C) The SGLT phlorizin binding site in the center of the membrane protein. The glucose moiety binds to the glucose binding site, and the aglycone occupies an outer vestibule bounded by the external ends of TM1, TM2, TM3, and TM10 (17). Y290, the internal gate is highlighted in yellow. (D) An atomic model of phlorizin and dapaglifoxin bound to SGLT2 (47). This shows the superimposition of the glucose moiety of dapaglifoxin and phlorizin with glucose in the sugar site, and the superimposition of the aglycones in the external vestibule. H80, F98 and H268 form a cage above the inhibitor (H268 is replaced by D268 in SGLT1).
inhibitors bind to SGLT2 in the luminal membrane of the early (S1 and S2) segments of the nephron, where they may block up to 60% of glucose reabsorption. Glucose that escapes reabsorption in S1 and S2 segments is normally salvaged by SGLT1 in the late proximal tubule (S3). The non-specific inhibitor phlorizin binds to SGLT2 in S1 and S2, and to SGLT1 in S3, causing complete inhibition of glucose reabsorption. In mice, this has been confirmed using SGLT2 and SGLT1 null-mice, and may be inferred in humans with “knock-out” mutations of SGLT2 (FRG). There have been efforts to develop dual SGLT2/SGLT1 inhibitors, such as sotagliptin (Table 1), but these have not yet gained Food and Drug Administration approval for the treatment of diabetes. Considerable progress has been made in understanding the mechanism of action of SGLT inhibitors at a molecular level, but additional work remains to account for their selectivity for SGLT2 over SGLT1.

There is a remarkable ability of SGLT2 drugs to lower the progression of heart and kidney disease, and, at least for heart disease, this may be due to an off-target effect on the cardiac sodium proton exchanger NHE1.

Disclosures

E. Wright reports being a consultant on SGLTs for various pharmaceutical companies, including Boehringer Ingelheim, from 2006 to 2015.

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Author Contributions

E. Wright conceptualized the study, was responsible for the investigation, and wrote the original draft.

Supplemental Material

This article contains supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0002772021/-/DCSupplemental.

Supplemental Movie 1. The time course of the distribution of F-DAPA in abdomen of the rat. After i.v. delivery there was rapid distribution throughout the vascular tree, peaking at 2 minutes (3% I.D. per gram of plasma) before falling to a quasi-steady value of 0.35% I.D. per gram. In contrast, there was rapid binding to the kidney cortex, at 5.5% I.D. per gram, which is displaced by i.v. dapagliflozin (and phlorizin, not shown). No F-DAPA appeared in the urine throughout the experiment, but it was transiently found in the renal vein, and then the liver and small intestine. Taken from Ghezzi et al. 2017 (25).

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