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Development of SGLT1 and SGLT2 inhibitors

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Abstract

Sodium–glucose cotransporters SGLT1 (encoded by *SGLT1*, also known as *SLC5A1*) and SGLT2 (encoded by *SGLT2*, also known as *SLC5A2*) are important mediators of epithelial glucose transport. While SGLT1 accounts for most of the dietary glucose uptake in the intestine, SGLT2 is responsible for the majority of glucose reuptake in the tubular system of the kidney, with SGLT1 reabsorbing the remainder of the filtered glucose. As a consequence, mutations in the *SLC5A1* gene cause glucose/galactose malabsorption, whereas mutations in *SLC5A2* are associated with glucosuria. Since the cloning of SGLT1 more than 30 years ago, big strides have been made in our understanding of these transporters and their suitability as drug targets. Phlorizin, a naturally occurring competitive inhibitor of SGLT1 and SGLT2, provided the first insights into potential efficacy, but its use was hampered by intestinal side effects and a short half-life. Nevertheless, it was a starting point for the development of specific inhibitors of SGLT1 and SGLT2, as well as dual SGLT1/2 inhibitors. Since the approval of the first SGLT2 inhibitor in 2013 by the US Food and Drug Administration, SGLT inhibitors have become a new mainstay in the treatment of type 2 diabetes mellitus. They also have beneficial effects on the cardiovascular system (including heart failure) and the kidney. This review focuses on the rationale for the development of individual SGLT2 and SGLT1 inhibitors, as well as dual SGLT1/2 inhibition, including, but not limited to, aspects of genetics, genetically modified mouse models, mathematical modelling and general considerations of drug discovery in the field of metabolism.

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Contribution statement

Both authors were responsible for drafting the article and revising it critically for important intellectual content. Both authors approved the version to be published.

Duality of interest

Over the past 36 months, VV has served as a consultant and received honoraria from Bayer, Boehringer Ingelheim, Intarcia Therapeutics, Astra-Zeneca, Janssen Pharmaceutical, Eli Lilly and Merck, and received grant support for investigator-initiated research from Astra-Zeneca, Bayer, Boehringer Ingelheim, Fresenius and Janssen.

Keywords

Chronic kidney disease; Drug development; Inhibitor; Intestinal glucose transport; Heart failure; Renal glucose transport; Review; Sodium–glucose cotransporter; Type 1 diabetes; Type 2 diabetes

Introduction

The annual economic costs of diabetes mellitus approximate US$825 billion worldwide [1]. Diabetes is a leading cause of cardiovascular and end-stage renal disease, with the former being the leading cause of death in this patient population [2]. Multiple drug classes are available for the treatment of diabetes mellitus (e.g. insulin, metformin, sulfonylureas, glitazones); however, significant drawbacks include limited effectiveness with regard to improving cardiovascular outcome, and some may even increase the risk of cardiovascular mortality. Sodium–glucose cotransporter 2 (SGLT2) inhibitors, including canagliflozin (Invokana, Janssen pharmaceuticals), dapagliflozin (Forxiga [known as Farxiga in the USA), empagliflozin (Jardiance), and ertugliflozin (Steglatro), have recently been approved by the US Food and Drug Administration as a new class of glucose-lowering compounds (known as the gliflozins) for the treatment of type 2 diabetes mellitus. This review outlines the rationale for the development of individual SGLT2 and SGLT1 inhibitors as well as dual SGLT1/2 inhibitors. The basic concept of the therapeutic strategy is to lower the glucose burden by inhibiting the uptake of dietary glucose in the intestine or excreting the glucose filtered by the kidneys into the urine.

The body's responses to environments with scarce energy resources have been intensively tested and refined over the course of evolution. Given that easy access to exogenous energy resources is a much more recent development, it is not surprising that the body's responses to excess exogenous energy resources can be maladaptive. Therefore, targeting metabolism in the 'periphery' by inhibiting intestinal glucose uptake or spilling glucose into the urine and then using counterregulatory mechanisms to readjust the metabolism, may provide unique benefits as a glucose-lowering approach [3, 4].

Why target glucose handling in the kidney?

In healthy adults, the renal proximal tubule reabsorbs all the filtered glucose (~180 g/day) (Fig. 1). Renal glucose reabsorption requires active basolateral Na^+ removal by the Na^+/K^+-ATPase to generate the electrochemical driving force for apical glucose entry via Na^+-driven sodium–glucose cotransport [5]. On the basolateral side, glucose exits the cells following its concentration gradient primarily via GLUT2 and re-enters the bloodstream [6]. Renal clearance and micropuncture studies in *Sglt1* and *Sglt2* gene knockout mice (*Sglt1*$^{-/-}$ and *Sglt2*$^{-/-}$, also known as *Slc5a1*$^{-/-}$ and *Slc5a2*$^{-/-}$, respectively) demonstrated that SGLT2, which is expressed in the early proximal tubule (Fig. 1), accounts for all glucose reabsorption in this segment and for ~97% of whole kidney fractional glucose reabsorption (FGR) [7–9]. In comparison, SGLT1 is expressed in the later parts of the proximal tubule and accounts for the remaining ~3% of FGR under conditions of normoglycaemia and intact SGLT2 [7–9] (Fig. 1). Thus, under normal physiological conditions, SGLT2 and SGLT1 are together responsible for all renal glucose reabsorption [9].

As regards genetic mutations in SGLT2 in humans, the first occurrence of inherited renal glucosuria was described in 1927 [10] and resulted in urinary glucose losses ranging from 1–150 g/1.73 m^2 per day. This is referred to as familial renal glucosuria (FRG) and almost 50 mutations have been described that cause this condition [11]. FRG is generally considered a benign condition but can be associated with polyuria, polydipsia, nocturnal enuresis, polyphagia and recurrent urinary tract infections. Mutations in SGLT2 are rare and therefore the consequences are not well studied or fully understood. However, no serious complications (e.g. ascending urinary tract infections or impaired kidney function) have been consistently observed in individuals with SGLT2 mutations [11, 12]. This information provided support that SGLT2 inhibitors could potentially be developed as safe glucose-lowering drugs.

The renal transport maximum of glucose is reached when blood glucose levels exceed 11.1 mmol/l, and the surplus glucose ‘spills’ into the urine. This renal safety valve can prevent extreme hyperglycaemia. Diabetes may modestly increase the renal transport maximum for glucose as a consequence of tubular growth [13] or primary increases in SGLT2 or SGLT1 expression [14–16]. The enhanced renal glucose reabsorption in diabetes contributes to the maintenance of hyperglycaemia and can therefore be considered maladaptive. When SGLT2 is inhibited (Fig. 1), the renal reabsorptive capacity for glucose declines to the residual capacity of SGLT1, which equates to ~80 g/day. In other words, SGLT2 inhibition causes the renal safety valve to open at a lower threshold and makes it relevant to glucose homeostasis in the normoglycaemic and moderately hyperglycaemic range.

An important clinical aspect of developing a glucose-lowering drug is the risk of hypoglycaemia, since episodes of hypoglycaemia can impair cardioprotective effects, in part due to activation of the sympathetic nervous system [17]. The risk of hypoglycaemia associated with SGLT2 inhibitors is low. This is due to compensation by SGLT1 in the downstream late proximal tubule, which eliminates glucose excretion when the filtered glucose falls below the transport capacity of SGLT1, together with metabolic counterregulatory mechanisms, including the upregulation of hepatic gluconeogenesis [3].

Two SGLT2 inhibitors have been evaluated in major clinical trials in individuals with type 2 diabetes: empagliflozin in the EMPA-REG OUTCOME trial [18, 19] and canagliflozin in the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program [20]. Both trials went beyond the requisite safety parameters to show ~35% reductions in the incidence of heart failure. Potential protective mechanisms include the diuretic and natriuretic effects of SGLT2 inhibition, which reduce volume overload and blood pressure, and body weight reduction [21]. Both trials also discovered salutary renal effects, including 40–50% reductions in the hazard ratios for albuminuria or decline in eGFR.

Could the protective effect in terms of GFR have been predicted, and what can we learn for the development of other drugs? The initial action of SGLT2 inhibition is a reduction in GFR. This is due to the increase in fluid and NaCl delivery to the distal nephron, which lowers GFR through the physiology of tubuloglomerular feedback and by increasing tubular back pressure [3]. This was shown in streptozotocin-induced diabetic rats by micropuncture on the single nephron level with application of the SGLT1/2 inhibitor phlorizin into the free-

flowing early proximal tubule in 1999 [22], and confirmed with dapagliflozin in 2012 [23]. Lowering GFR can lower albuminuria and reduces the oxygen-consuming transport activity in renal tubules, thereby helping to preserve the function (including GFR) and integrity of the remaining nephrons in the long-term [3]. The key point is that the immediate GFR reduction following SGLT2 inhibition is a physiologically expected functional response rather than the result of structural changes and, as such, is reversible. In accordance with this, empagliflozin induced a small decline in eGFR in patients with type 2 diabetes and chronic kidney disease (CKD; stages 2 and 3). This effect was maintained at 52 weeks, associated with reduced urine albumin/creatinine ratios, and, most importantly, was fully reversible after a 3 week washout period [24]. A functional reduction in GFR has the potential for kidney protection, as previously proposed for angiotensin II (AngII) blockers [25]. Since ~80% of patients were co-treated with a form of AngII blockade, the EMPA-REG OUTCOME trial and the CANVAS Program provided evidence that the two strategies are likely additive when applied to patients with initial GFRs of at least 30 ml min^{-1} [1.73 $m]^{-2}$ [18, 20]. This is consistent with the concept that AngII blockade primarily dilates the efferent arteriole, whereas SGLT2 inhibition primarily constricts the afferent arteriole via tubuloglomerular feedback and enhances tubular back pressure [3, 26, 27].

The improvement in glycaemic control in response to SGLT2 inhibition is attenuated in patients with CKD. This is expected due to the reduced absolute filtered glucose. In contrast, the blood pressure-lowering effect of SGLT2 inhibitors and protective effect against heart failure are preserved in individuals with CKD and reduced eGFR [28, 29]. Recently published modelling studies of CKD and nephron loss predicted that SGLT2 inhibition in remaining nephrons with increased single nephron GFR markedly decreases net proximal tubule Na^+ reabsorption and induces a natriuretic and diuretic effect [30]. This is in large part due to the resulting high glucose load on the single nephron level, which osmotically binds water, lowers luminal Na^+ concentrations, and secondarily increases paracellular Na^+ secretion in proximal tubules. The preserved increase in fluid and Na^+ load to the distal tubule also preserves the kaliuretic effect of chronic SGLT2 inhibition. This may reduce K^+ retention in diabetic individuals with CKD and enhance the tolerability of AngII blockade and thus allow their continued use, which is expected to be of therapeutic benefit [30].

Modelling predicted that, in a diabetic normal and CKD kidney, SGLT2 inhibition shifts glucose and Na^+ transport to segments further downstream in the outer medulla, and that SGLT2 inhibition may further reduce the already physiologically low O_2 availability in the renal outer medulla [31, 32]. Indeed, such a reduction has been shown in vivo in non-diabetic and streptozotocin-induced diabetic rats in response to acute dual SGLT1/2 inhibition by phlorizin [33]. The influence on medullary transport and oxygenation would be attenuated by the blood glucose- and GFR-lowering effect of SGLT2 inhibition. Moreover, the proposed SGLT2 inhibitor-induced reduction in oxygen pressure in deep cortex and outer medulla may stimulate hypoxia-inducible factors HIF1 and HIF-2. In *Sglt2*$^{-/-}$mice, renal *Hmox1* mRNA expression (encoding haem oxygenase-1) [14], a HIF-1-α-induced, tissue-protective gene, was increased. Furthermore, activation of HIF-2 may enhance erythropoietin release from renal interstitial cells in response to SGLT2 inhibition [34]. Together with the diuretic effect, HIF-2 activation may contribute to the observed modest increase in haematocrit and haemoglobin in response to SGLT2 inhibition. This may

improve the oxygenation of the kidney outer medulla and cortex, and may also facilitate oxygen delivery to the heart and other organs. Notably, changes in haematocrit and haemoglobin from baseline explained 51.8% and 48.9%, respectively, of the effect of the SGLT2 inhibitor empagliflozin vs placebo on the risk of cardiovascular death [35]. In other words, and in addition to its volume effect, SGLT2 inhibition may simulate systemic hypoxia to the oxygen sensor in deep cortex and outer medulla of the kidney, and the induced response then helps the failing heart and the kidney [30]. Finally, the model predicted that hyperglycaemia facilitates the diuretic and natriuretic potential of SGLT2 inhibition in CKD [30]. This may explain why effects of SGLT2 inhibitors on volume status rather than HbA_{1c} levels were the most important mediators reducing the risk of cardiovascular death [35]. Thus, the attenuated blood glucose-lowering effect of SGLT2 inhibitors in CKD may not be completely disadvantageous [30].

Why target glucose handling in the intestine?

Elevations in blood glucose after meals are associated with an increased risk of diabetic complications [36]. The small intestine is the major site of dietary glucose uptake into the body, and SGLT1 plays a pivotal role in luminal glucose uptake [7, 37] (Fig. 2). Glucose subsequently exits via facilitative glucose transport (GLUT2) in the basolateral membrane and enters the bloodstream (Fig. 2). Glucose uptake by intestinal SGLT1 also modulates the secretion of intestinal hormones that regulate glucose homeostasis, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) [4, 7, 38] (Fig. 2). In accordance with a primary role in intestinal absorption, humans with mutations in the *SGLT1* gene and mice lacking SGLT1 (*Sglt1*$^{-/-}$) suffer from glucose/galactose malabsorption, which, especially in newborns, can be associated with massive osmotic diarrhoea, dehydration and metabolic acidosis [7, 37]. Removal of lactose, sucrose and glucose from the diet can control symptoms in these individuals, and *Sglt1*$^{-/-}$ mice can be rescued by a glucose/galactose-free diet [7].

Rodent studies have indicated that diabetes increases intestinal SGLT1 expression [39, 40] and glucose uptake [41, 42]. Consistent with the importance of SGLT1 in intestinal glucose uptake and, consequently, postprandial hyperglycaemia, *Sglt1*$^{-/-}$ mice show a strongly reduced blood glucose increase during an OGTT [43, 44]. Consistent with this, pre-meal, in contrast to post-meal, dosing of the selective SGLT1 inhibitor GSK-1614235 in healthy volunteers delayed intestinal glucose absorption [45]. Furthermore, the SGLT1 inhibitor enhanced circulating levels of GLP-1 and GIP for 2 h [45]. These hormones then act on pancreatic beta cells and increase insulin secretion in a glucose-dependent manner. GLP-1 decreased pancreatic glucagon secretion and appetite, and increased beta cell mass in preclinical studies [46]. All these effects contribute to the glucose-lowering effect of GLP-1 receptor agonists, which are approved for the treatment of type 2 diabetes [47]. Of note, lack of SGLT1 in mice attenuates the acute secretion of GLP-1 in response to a glucose bolus [7]. However, blocking glucose uptake via SGLT1 in the early intestine shifts glucose downward towards further distal intestinal segments [45, 48, 49]. At these sites, glucose has been proposed to be metabolised by the gut microbiome, and the resulting formation of shortchain fatty acids (SCFAs) may induce a sustained release of GLP-1 (Fig. 2). The latter has been observed with selective SGLT1 inhibition in healthy volunteers [45], in mice treated with a

non-absorbable selective SGLT1 inhibitor (LX2761) [48], and in *Sglt1*$^{-/-}$ mice [49]. Thus, inhibition of intestinal SGLT1 has a dual effect on glucose homeostasis: (1) a direct effect by inhibiting glucose uptake, and (2) an indirect effect via promoting a sustained release of glucose-lowering incretin hormones (Fig. 2).

Somewhat unexpectedly, the selective SGLT1 inhibitor GSK-1614235 and the dual SGLT1/2 inhibitor sotagliflozin (LX4211) can be taken orally at doses that measurably inhibit glucose transport in the intestine without severe gastrointestinal side effects [45, 50]. While these promising findings indicate a potential therapeutic application for partial SGLT1 inhibition, long-term studies are needed to better document the intestinal responses and safety.

In multiple species, including humans, SGLT1 protein is also expressed in the parotid and submandibular salivary glands, liver, lung, skeletal muscle, heart, pancreatic alpha cells and brain [4]. The role of SGLT1 at many of these sites, as well as the consequences of SGLT1 inhibition, are poorly understood. Based on studies in rodents, SGLT1 inhibition in the diabetic heart could be a two-edged sword (for review see [4]): SGLT1 might be involved in the progression of diabetic cardiomyopathy by triggering reactive oxygen species and/or facilitating the accumulation of glycogen in cardiomyocytes, but could also protect against ischaemia reperfusion injury by replenishing ATP stores in ischaemic cardiac tissues by enhancing glucose availability. While inhibition of SGLT1 merits evaluation for its therapeutic potential in diabetes, there is a clear need for a more comprehensive understanding of its function, including in the heart and brain, in health and disease.

Development of SGLT inhibitors

Given the findings discussed in the previous two sections, targeting hyperglycaemia by inhibiting intestinal and/or renal glucose reabsorption is an appealing therapeutic strategy. Phlorizin, a molecule found in the root bark, leaves, shoots and fruit of the apple tree, was discovered over 150 years ago and soon thereafter was found to increase urinary glucose excretion in healthy humans [51]. Studies in insulinresistant (due to partial pancreatectomy) diabetic rats showed that subcutaneous phlorizin administration normalised plasma glucose profiles and insulin sensitivity [52, 53]. However, because of the poor solubility of phlorizin in water, poor oral bioavailability and unselective SGLT1 and SGLT2 inhibition, phlorizin was not an ideal therapeutic candidate. T-1095 overcame some of these limitations but did not continue into clinical development [54]. Subsequent efforts led to the identification of the novel *C*-glucoside-containing selective SGLT2 inhibitor dapagliflozin. SGLT2 inhibitors such as canagliflozin, empagliflozin and ertugliflozin are based on the same meta *C*-glycosylated diarylmethane pharmacophore. In contrast to the *O*-glucosides phlorizin and T-1095, *C*-glycosylation makes these molecules resistant to hydrolysis by β-glucosidases, increasing their half-life [41, 55, 56]. Differences between the approved SGLT2 inhibitors include their respective selectivity profiles for SGLT2 over SGLT1, ranging from ~260:1 for canagliflozin to ~2700:1 for empagliflozin [41].

Sotagliflozin (LX4211) shows only a 20 times higher potency for SGLT2 over SGLT1 and is considered a dual SGLT1/2 inhibitor [57]; it is currently undergoing Phase 3 clinical trials. GSK-1614235 is ~390:1 selective for SGLT1 over SGLT2 and has been tested in Phase 1 clinical trials [45]. Mizagliflozin is a novel selective SGLT1 inhibitor that has been

investigated for its potential to improve chronic constipation [58]. The novel non-absorbable SGLT1 inhibitor LX2761 was recently developed by modifying sotagliflozin [48]. Another compound, LIK066, is currently in clinical trials for the treatment of obesity (NCT03100058) and polycystic ovary syndrome (NCT03152591). Regarding the potential use of LIK066 for obesity, further studies are also needed to determine the usefulness of intestinal SGLT1 inhibition in hyperleptinaemic obese individuals. Hyperleptinaemia (*db*/*db* mice), but not hypoleptinaemia (*ob*/*ob* mice), reduces intestinal SGLT1 abundance and blood glucose elevations in response to oral glucose loading [43]. The reduction in abundance in *db*/*db* mice is possibly via activation of leptin receptor isoform A (LEPRa).

From a metabolic standpoint, is it worth inhibiting both SGLT2 and SGLT1 in the kidney? Under normal conditions, inhibition of renal SGLT1 alone induces only a small glucosuric effect (Fig. 1). This effect, however, is increased up to the transport maximum of SGLT1 when more glucose is delivered to the late proximal tubule, which may occur in hyperglycaemia or in response to SGLT2 inhibition. In response to treatment with SGLT2 inhibitors in humans [59–61] and pharmacological inhibition or in *Sglt2*$^{-/-}$ mice [7, 9], FGR is only reduced to ~40–50%, despite the fact that SGLT2 normally contributes to >95% of FGR (Fig. 1). This is the consequence of a compensatory role of SGLT1 in the late proximal tubule [9]. Studies in *Sglt1*$^{-/-}$ and *Sglt2*$^{-/-}$ mice allowed us to estimate that the basal overall glucose reabsorption capacities for SGLT2 vs SGLT1 in a non-diabetic mouse kidney is in the range of 3:1 to 5:1 [62]. Based on these observations, simultaneously blocking SGLT1 and SGLT2 in the kidney could be advantageous compared with SGLT2 inhibition alone with regard to blood glucose lowering [63]. The impact of intestinal SGLT1 inhibition on blood glucose control discussed above is expected to be additive to the renal effects. On the other hand, the risk of hypoglycaemia may increase with dual SGLT1/2 inhibition, and the expected stronger diuretic effect could place patients at greater risk of hypotension, prerenal failure, complications related to haemoconcentration and diabetic ketoacidosis.

Perspectives

Large clinical outcome trials will be needed for selective SGLT1 and dual SGLT1/2 inhibitors. Selective SGLT2 and dual SGLT1/2 inhibitors are also currently being tested in individuals with type 1 diabetes as an add on to insulin. In general, these compounds improve glycaemic control [64–67], and overall are expected to have a similar protective effects as those reported in type 2 diabetes [68]. A serious concern is the greater incidence of diabetic ketoacidosis in these patients [65, 69]. Since the effects of SGLT2 inhibitors on GFR, natriuresis and diuresis can occur in the absence of hyperglycaemia [3], they are also being tested in non-diabetic people with heart failure or CKD [70].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AngII	Angiotensin II
CANVAS	Canagliflozin Cardiovascular Assessment Study
CKD	Chronic kidney disease
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon-like peptide-1
FGR	Fractional glucose reabsorption
FRG	familial renal glucosuria
HIF	Hypoxia-inducible factor
SCFA	Short-chain fatty acid
SGLT	Sodium–glucose cotransporter

References

[1]. NCD Risk Factor Collaboration (2016) Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. Lancet 387: 1513–1530 [PubMed: 27061677]

[2]. Laakso M (2010) Cardiovascular disease in type 2 diabetes from population to man to mechanisms: the Kelly West Award Lecture 2008. Diabetes Care 33: 442–449 [PubMed: 20103560]

[3]. Vallon V, Thomson SC (2017) Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. Diabetologia 60: 215–225 [PubMed: 27878313]

[4]. Song P, Onishi A, Koepsell H, Vallon V (2016) Sodium glucose cotransporter SGLT1 as a therapeutic target in diabetes mellitus. Expert Opin Ther Targets 20: 1109–1125 [PubMed: 26998950]

[5]. Dennis VW, Brazy PC (1978) Phosphate and glucose transport in the proximal convoluted tubule: mutual dependency on sodium. Adv Exp Med Biol 103: 79–80 [PubMed: 717124]

[6]. Cramer SC, Pardridge WM, Hirayama BA, Wright EM (1992) Colocalization of GLUT2 glucose transporter, sodium/glucose cotransporter, and gamma-glutamyl transpeptidase in rat kidney with double-peroxidase immunocytochemistry. Diabetes 41: 766–770 [PubMed: 1350259]

[7]. Gorboulev V, Schurmann A, Vallon V, et al. (2012) Na^+-D-glucose cotransporter SGLT1 is pivotal for intestinal glucose absorption and glucose-dependent incretin secretion. Diabetes 61: 187–196 [PubMed: 22124465]

[8]. Vallon V, Platt KA, Cunard R, et al. (2011) SGLT2 mediates glucose reabsorption in the early proximal tubule. J Am Soc Nephrol 22: 104–112 [PubMed: 20616166]

[9]. Rieg T, Masuda T, Gerasimova M, et al. (2014) Increase in SGLT1-mediated transport explains renal glucose reabsorption during genetic and pharmacological SGLT2 inhibition in euglycemia. Am J Physiol Renal Physiol 306: F188–F193 [PubMed: 24226519]

[10]. Hjarne U (1927) A study of orthoglycaemic glycosuria with particular reference to its hereditability. Acta Med Scand 67: 495–571

[11]. Santer R, Calado J (2010) Familial renal glucosuria and SGLT2: from a Mendelian trait to a therapeutic target. Clin J Am Soc Nephrol 5: 133–141 [PubMed: 19965550]

[12]. Wright EM, Loo DD, Hirayama BA (2011) Biology of human sodium glucose transporters. Physiol Rev 91: 733–794 [PubMed: 21527736]

[13]. Thomson SC, Deng A, Bao D, Satriano J, Blantz RC, Vallon V (2001) Ornithine decarboxylase, kidney size, and the tubular hypothesis of glomerular hyperfiltration in experimental diabetes. J Clin Invest 107: 217–224 [PubMed: 11160138]

[14]. Vallon V, Rose M, Gerasimova M, et al. (2013) Knockout of Na-glucose transporter SGLT2 attenuates hyperglycemia and glomerular hyperfiltration but not kidney growth or injury in diabetes mellitus. Am J Physiol Renal Physiol 304: F156–F167 [PubMed: 23152292]

[15]. Vallon V, Gerasimova M, Rose MA, et al. (2014) SGLT2 inhibitor empagliflozin reduces renal growth and albuminuria in proportion to hyperglycemia and prevents glomerular hyperfiltration in diabetic Akita mice. Am J Physiol Renal Physiol 306: F194–F204 [PubMed: 24226524]

[16]. Wang XX, Luo Y, Wang D, et al. (2017) A dual agonist of farnesoid X receptor (FXR) and the G protein-coupled receptor TGR5, INT-767, reverses age-related kidney disease in mice. J Biol Chem 292: 12018–12024 [PubMed: 28596381]

[17]. Khunti K, Davies M, Majeed A, Thorsted BL, Wolden ML, Paul SK (2015) Hypoglycemia and risk of cardiovascular disease and all-cause mortality in insulin-treated people with type 1 and type 2 diabetes: a cohort study. Diabetes Care 38: 316–322 [PubMed: 25492401]

[18]. Wanner C, Inzucchi SE, Lachin JM, et al. (2016) Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 375: 323–334 [PubMed: 27299675]

[19]. Zinman B, Wanner C, Lachin JM, et al. (2015) Empagliflozin, Cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 373: 2117–2128 [PubMed: 26378978]

[20]. Neal B, Perkovic V, Mahaffey KW, et al. (2017) Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 377: 644–657 [PubMed: 28605608]

[21]. Inzucchi SE, Zinman B, Wanner C, et al. (2015) SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. Diab Vasc Dis Res 12: 90–100 [PubMed: 25589482]

[22]. Vallon V, Richter K, Blantz RC, Thomson S, Osswald H (1999) Glomerular hyperfiltration in experimental diabetes mellitus: potential role of tubular reabsorption. J Am Soc Nephrol 10: 2569–2576 [PubMed: 10589696]

[23]. Thomson SC, Rieg T, Miracle C, et al. (2012) Acute and chronic effects of SGLT2 blockade on glomerular and tubular function in the early diabetic rat. Am J Physiol Regul Integr Comp Physiol 302: R75–R83 [PubMed: 21940401]

[24]. Barnett AH, Mithal A, Manassie J, et al. (2014) Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2: 369–384 [PubMed: 24795251]

[25]. Holtkamp FA, de Zeeuw D, Thomas MC, et al. (2011) An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. Kidney Int 80: 282–287 [PubMed: 21451458]

[26]. Petrykiv S, Laverman GD, de Zeeuw D, Heerspink HJL (2018) Does SGLT2 inhibition with dapagliflozin overcome individual therapy resistance to RAAS inhibition? Diabetes Obes Metab 20: 224–227 [PubMed: 28685934]

[27]. Skrtic M, Cherney DZ (2015) Sodium-glucose cotransporter-2 inhibition and the potential for renal protection in diabetic nephropathy. Curr Opin Nephrol Hypertens 24: 96–103 [PubMed: 25470017]

[28]. Wanner C, Lachin JM, Inzucchi SE, et al. (2018) Empagliflozin and clinical outcomes in patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic kidney disease. Circulation 137: 119–129 [PubMed: 28904068]

[29]. Petrykiv S, Sjostrom CD, Greasley PJ, Xu J, Persson F, Heerspink HJL (2017) Differential effects of dapagliflozin on cardiovascular risk factors at varying degrees of renal function. Clin J Am Soc Nephrol 12: 751–759 [PubMed: 28302903]

[30]. Layton AT, Vallon V (2018) SGLT2 inhibition in a kidney with reduced nephron number: modeling and analysis of solute transport and metabolism. Am J Physiol Renal Physiol 10.1152/ajprenal.00551.2017

[31]. Layton AT, Vallon V, Edwards A (2016) Predicted consequences of diabetes and SGLT inhibition on transport and oxygen consumption along a rat nephron. Am J Physiol Renal Physiol 310: F1269–F1283 [PubMed: 26764207]

[32]. Layton AT, Vallon V, Edwards A (2015) Modeling oxygen consumption in the proximal tubule: effects of NHE and SGLT2 inhibition. Am J Physiol Renal Physiol 308: F1343–F1357 [PubMed: 25855513]

[33]. O'Neill J, Fasching A, Pihl L, Patinha D, Franzen S, Palm F (2015) Acute SGLT inhibition normalizes O_2 tension in the renal cortex but causes hypoxia in the renal medulla in anaesthetized control and diabetic rats. Am J Physiol Renal Physiol 309: F227–F234 [PubMed: 26041448]

[34]. Sano M, Takei M, Shiraishi Y, Suzuki Y (2016) Increased hematocrit during sodium-glucose cotransporter 2 inhibitor therapy indicates recovery of tubulointerstitial function in diabetic kidneys. J Clin Med Res 8: 844–847 [PubMed: 27829948]

[35]. Inzucchi SE, Zinman B, Fitchett D, et al. (2018) How does empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME trial. Diabetes Care 41: 356–363 [PubMed: 29203583]

[36]. Ceriello A (2005) Postprandial hyperglycemia and diabetes complications: is it time to treat? Diabetes 54: 1–7 [PubMed: 15616004]

[37]. Turk E, Zabel B, Mundlos S, Dyer J, Wright EM (1991) Glucose/galactose malabsorption caused by a defect in the Na+/glucose cotransporter. Nature 350: 354–356 [PubMed: 2008213]

[38]. Moriya R, Shirakura T, Ito J, Mashiko S, Seo T (2009) Activation of sodium-glucose cotransporter 1 ameliorates hyperglycemia by mediating incretin secretion in mice. Am J Physiol Endocrinol Metab 297: E1358–E1365 [PubMed: 19808907]

[39]. Miyamoto K, Hase K, Taketani Y, et al. (1991) Diabetes and glucose transporter gene expression in rat small intestine. Biochem Biophys Res Commun 181: 1110–1117 [PubMed: 1722397]

[40]. Ogata H, Seino Y, Harada N, et al. (2014) K_{ATP} channel as well as SGLT1 participates in GIP secretion in the diabetic state. J Endocrinol 222: 191–200 [PubMed: 24891433]

[41]. Grempler R, Thomas L, Eckhardt M, et al. (2012) Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: characterisation and comparison with other SGLT-2 inhibitors. Diabetes Obes Metab 14: 83–90 [PubMed: 21985634]

[42]. Fujita Y, Kojima H, Hidaka H, Fujimiya M, Kashiwagi A, Kikkawa R (1998) Increased intestinal glucose absorption and postprandial hyperglycaemia at the early step of glucose intolerance in Otsuka Long-Evans Tokushima Fatty Rats. Diabetologia 41: 1459–1466 [PubMed: 9867213]

[43]. Dominguez Rieg JA, Chirasani VR, Koepsell H, Senapati S, Mahata SK, Rieg T (2016) Regulation of intestinal SGLT1 by catestatin in hyperleptinemic type 2 diabetic mice. Lab Invest 96: 98–111 [PubMed: 26552046]

[44]. Roder PV, Geillinger KE, Zietek TS, Thorens B, Koepsell H, Daniel H (2014) The role of SGLT1 and GLUT2 in intestinal glucose transport and sensing. PLoS One 9: e89977 [PubMed: 24587162]

[45]. Dobbins RL, Greenway FL, Chen L, et al. (2015) Selective sodium-dependent glucose transporter 1 inhibitors block glucose absorption and impair glucose-dependent insulinotropic peptide release. Am J Physiol Gastrointest Liver Physiol 308: G946–G954 [PubMed: 25767259]

[46]. Vilsboll T (2009) The effects of glucagon-like peptide-1 on the beta cell. Diabetes Obes Metab 11 Suppl 3: 11–18 [PubMed: 19878257]

[47]. Drucker DJ, Nauck MA (2006) The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 368: 1696–1705 [PubMed: 17098089]

[48]. Goodwin NC, Ding ZM, Harrison BA, et al. (2017) Discovery of LX2761, a sodium-dependent glucose cotransporter 1 (SGLT1) inhibitor restricted to the intestinal lumen, for the treatment of diabetes. J Med Chem 60: 710–721 [PubMed: 28045524]

[49]. Powell DR, Smith M, Greer J, et al. (2013) LX4211 increases serum glucagon-like peptide 1 and peptide YY levels by reducing sodium/glucose cotransporter 1 (SGLT1)-mediated absorption of intestinal glucose. J Pharmacol Exp Ther 345: 250–259 [PubMed: 23487174]

[50]. Zambrowicz B, Freiman J, Brown PM, et al. (2012) LX4211, a dual SGLT1/SGLT2 inhibitor, improved glycemic control in patients with type 2 diabetes in a randomized, placebo-controlled trial. Clin Pharmacol Ther 92: 158–169 [PubMed: 22739142]

[51]. Chasis H, Jolliffe N, Smith HW (1933) The action of phlorizin on the excretion of glucose, xylose, sucrose, creatinine and urea by man. J Clin Invest 12: 1083–1090 [PubMed: 16694183]

[52]. Rossetti L, Smith D, Shulman GI, Papachristou D, DeFronzo RA (1987) Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats. J Clin Invest 79: 1510–1515 [PubMed: 3571496]

[53]. Rossetti L, Shulman GI, Zawalich W, DeFronzo RA (1987) Effect of chronic hyperglycemia on in vivo insulin secretion in partially pancreatectomized rats. J Clin Invest 80: 1037–1044 [PubMed: 3308956]

[54]. Oku A, Ueta K, Arakawa K, et al. (1999) T-1095, an inhibitor of renal Na^+-glucose cotransporters, may provide a novel approach to treating diabetes. Diabetes 48: 1794–1800 [PubMed: 10480610]

[55]. Choi CI (2016) Sodium-glucose cotransporter 2 (SGLT2) Inhibitors from natural products: discovery of next-generation antihyperglycemic agents. Molecules 21:E1136 [PubMed: 27618891]

[56]. Isaji M (2011) SGLT2 inhibitors: molecular design and potential differences in effect. Kidney Int Suppl: S14–S19

[57]. Lapuerta P, Zambrowicz B, Strumph P, Sands A (2015) Development of sotagliflozin, a dual sodium-dependent glucose transporter 1/2 inhibitor. Diab Vasc Dis Res 12: 101–110 [PubMed: 25690134]

[58]. Inoue T, Takemura M, Fushimi N, et al. (2017) Mizagliflozin, a novel selective SGLT1 inhibitor, exhibits potential in the amelioration of chronic constipation. Eur J Pharmacol 806: 25–31 [PubMed: 28410751]

[59]. Komoroski B, Vachharajani N, Boulton D, et al. (2009) Dapagliflozin, a novel SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects. Clin Pharmacol Ther 85: 520–526 [PubMed: 19129748]

[60]. Heise T, Seewaldt-Becker E, Macha S, et al. (2013) Safety, tolerability, pharmacokinetics and pharmacodynamics following 4 weeks' treatment with empagliflozin once daily in patients with type 2 diabetes. Diabetes Obes Metab 15: 613–621 [PubMed: 23356556]

[61]. Sha S, Devineni D, Ghosh A, et al. (2011) Canagliflozin, a novel inhibitor of sodium glucose cotransporter 2, dose dependently reduces calculated renal threshold for glucose excretion and increases urinary glucose excretion in healthy subjects. Diabetes Obes Metab 13: 669–672 [PubMed: 21457428]

[62]. Gallo LA, Wright EM, Vallon V (2015) Probing SGLT2 as a therapeutic target for diabetes: basic physiology and consequences. Diab Vasc Dis Res 12: 78–89 [PubMed: 25616707]

[63]. Powell DR, DaCosta CM, Gay J, et al. (2013) Improved glycemic control in mice lacking Sglt1 and Sglt2. Am J Physiol Endocrinol Metab 304: E117–E130 [PubMed: 23149623]

[64]. Sands AT, Zambrowicz BP, Rosenstock J, et al. (2015) Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in type 1 diabetes. Diabetes Care 38: 1181–1188 [PubMed: 26049551]

[65]. Garg SK, Henry RR, Banks P, et al. (2017) Effects of sotagliflozin added to insulin in patients with type 1 diabetes. N Engl J Med 377: 2337–2348 [PubMed: 28899222]

[66]. Dandona P, Mathieu C, Phillip M, et al. (2017) Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. Lancet Diabetes Endocrinol 5: 864–876 [PubMed: 28919061]

[67]. Henry RR, Thakkar P, Tong C, Polidori D, Alba M (2015) Efficacy and safety of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to insulin in patients with type 1 diabetes. Diabetes Care 38: 2258–2265 [PubMed: 26486192]

[68]. Fattah H, Vallon V (2018) The potential role of SGLT2 inhibitors in the treatment of type 1 diabetes. Drugs 10.1007/s40265-018-0901-y

[69]. Pieber TR, Famulla S, Eilbracht J, et al. (2015) Empagliflozin as adjunct to insulin in patients with type 1 diabetes: a 4-week, randomized, placebo-controlled trial (EASE-1). Diabetes Obes Metab 17: 928–935 [PubMed: 26080652]

[70]. Heerspink HJ, Desai M, Jardine M, Balis D, Meininger G, Perkovic V (2017) Canagliflozin slows progression of renal function decline independently of glycemic effects. J Am Soc Nephrol 28: 368–375 [PubMed: 27539604]

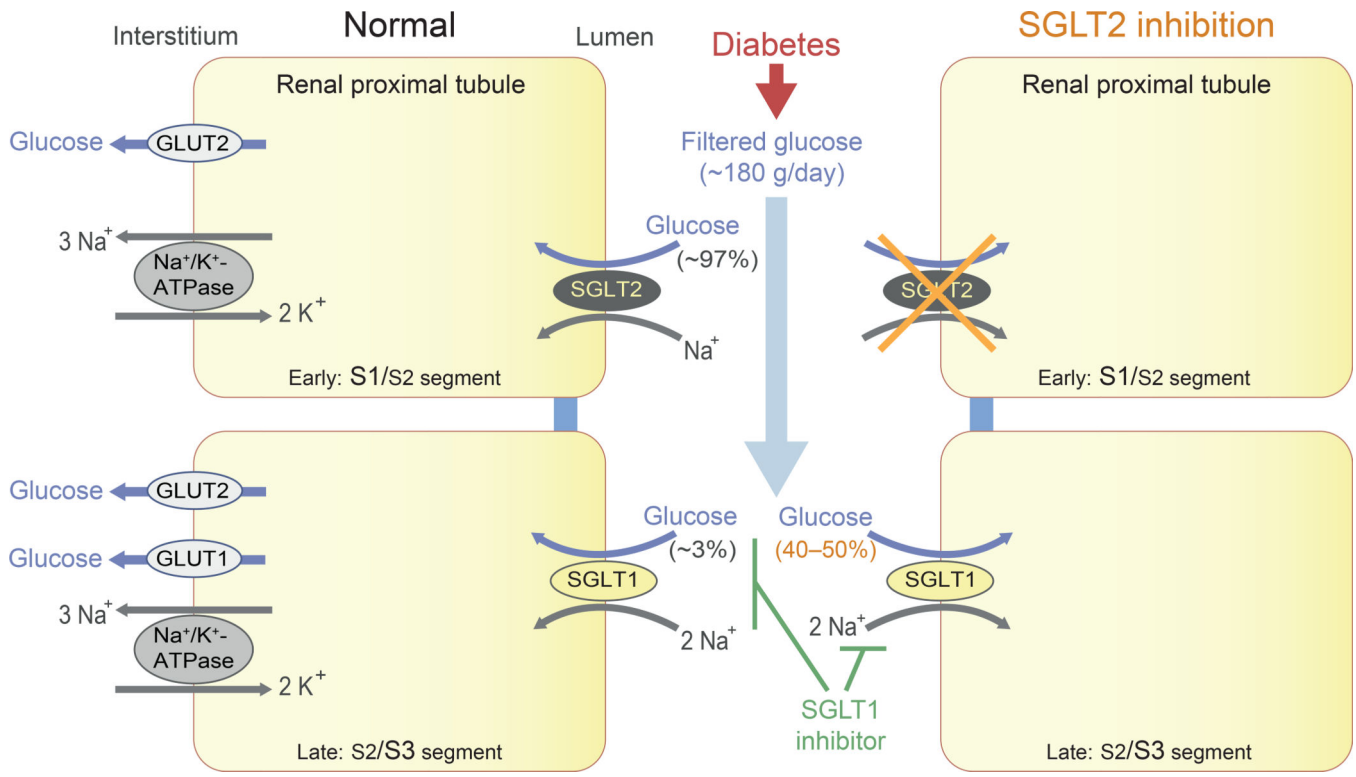

Fig. 1.

Role of renal SGLT2 and SGLT1 in glucose reabsorption under normoglycaemic conditions and when SGLT2 is inhibited. SGLT2 and SGLT1 are expressed in the luminal membrane of the early (S1 and S2 segment) and late proximal tubule (S3 segment), respectively. They reabsorb ~97% (SGLT2) and ~3% (SGLT1) of filtered glucose under normoglycaemic conditions. A significant capacity of SGLT1 to reabsorb glucose is unmasked by SGLT2 inhibition and during hyperglycaemia (~40–50% reabsorption), which both enhance glucose delivery to the late proximal tubule. As a consequence, diabetes-induced hyperglycaemia or SGLT2 inhibition increase the SGLT1 inhibition-induced rise in glucose excretion, the latter providing the renal rationale for dual SGLT1/2 inhibition. Adapted with permission from [4]. This figure is available as part of a downloadable slideset

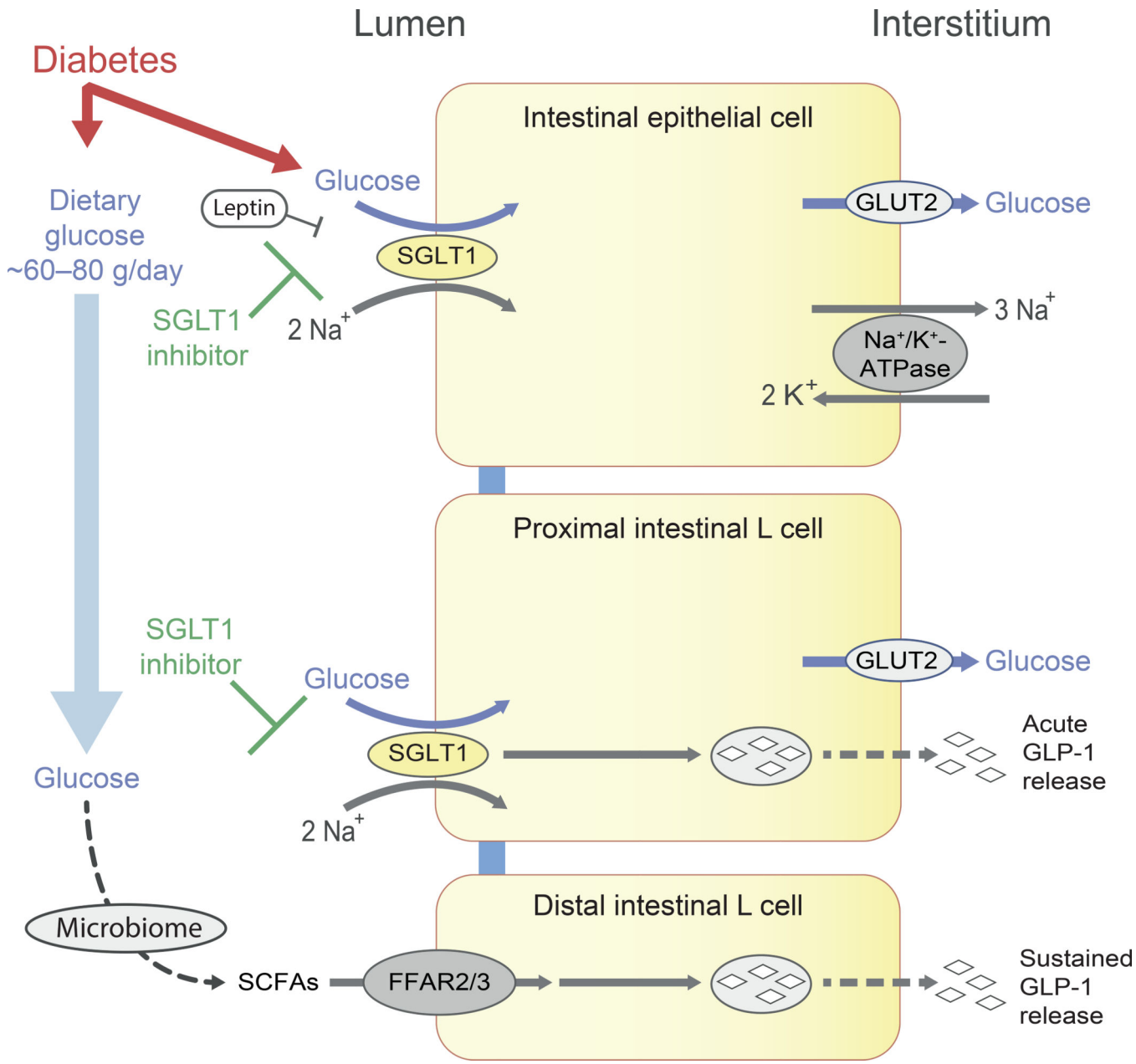

Fig. 2.

Role and regulation of intestinal SGLT1 for glucose uptake and potential therapeutic applications of SGLT1 inhibitors. In the small intestine, luminal SGLT1 mediates glucose/galactose absorption. SGLT1 expression is regulated by multiple signalling cascades and is upregulated in diabetes and downregulated by leptin [43]. SGLT1 in L cells in the proximal intestine sense dietary glucose, which subsequently triggers the ‘acute’ release of GLP-1. SGLT1 inhibition in the early intestine reduces glucose absorption and thereby increases glucose delivery to the more distal portions of the small intestine, where glucose is used by the microbiome to form SCFAs. SCFAs enter the distal L cells by free fatty acid receptors

(FFAR2/3) and trigger a ‘sustained’ release in GLP-1. Adapted with permission from [4]. This figure is available as part of a downloadable slideset