Am J Physiol Gastrointest Liver Physiol 310: G887–G898, 2016.
First published March 24, 2016; doi:10.1152/ajpgi.00068.2016.

Review

Intestinal SGLT1 in metabolic health and disease

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Submitted 15 February 2016; accepted in final form 21 March 2016

Lehmann A, Hornby PJ. Intestinal SGLT1 in metabolic health and disease. *Am J Physiol Gastrointest Liver Physiol* 310: G887–G898, 2016. First published March 24, 2016; doi:10.1152/ajpgi.00068.2016.—The Na^+-glucose cotransporter 1 (SGLT1/SLC5A1) is predominantly expressed in the small intestine. It transports glucose and galactose across the apical membrane in a process driven by a Na^+ gradient created by Na^+-K^+-ATPase. SGLT2 is the major form found in the kidney, and SGLT2-selective inhibitors are a new class of treatment for type 2 diabetes mellitus (T2DM). Recent data from patients treated with dual SGLT1/2 inhibitors or SGLT2-selective drugs such as canagliflozin (SGLT1 IC_{50} = 663 nM) warrant evaluation of SGLT1 inhibition for T2DM. SGLT1 activity is highly dynamic, with modulation by multiple mechanisms to ensure maximal uptake of carbohydrates (CHOs). Intestinal SGLT1 inhibition lowers and delays the glucose excursion following CHO ingestion and augments glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) secretion. The latter is likely due to increased glucose exposure of the colonic microbiota and formation of metabolites such as L cell secretagogues. GLP-1 and PYY secretion suppresses food intake, enhances the ileal brake, and has an incretin effect. An increase in colonic microbial production of propionate could contribute to intestinal gluconeogenesis and mediate positive metabolic effects. On the other hand, a threshold of SGLT1 inhibition that could lead to gastrointestinal intolerability is unclear. Altered Na^+ homeostasis and increased colonic CHO may result in diarrhea and adverse gastrointestinal effects. This review considers the potential mechanisms contributing to positive metabolic and negative intestinal effects. Compounds that inhibit SGLT1 must balance the modulation of these mechanisms to achieve therapeutic efficacy for metabolic diseases.

SLC5A1; glucose tolerance; taste receptors; gluconeogenesis; incretin; ileal brake; diarrhea; microbiome; monosaccharide; sodium/hydrogen exchanger isoform 3

THE PRINCIPLE OF INHIBITING uptake of macronutrients in the gut to gain benefit in metabolic diseases such as type 2 diabetes mellitus (T2DM) and obesity has yielded marketed drugs such as α-glucosidase inhibitors (acarbose, voglibose, and miglitol) and pancreatic lipase inhibitors (orlistat and cetilistat). Other macronutrient-altering drugs in development include enteropeptidase inhibitors, which prevent the activation of trypsin, and, secondarily, proenzymes, such as lipase and chymotrypsin, which inhibit amino acid and fatty acid uptake (17). Intestinal Na^+-glucose cotransporter (SGLT) isoform 1 (SGLT1, *Slc5a1* gene) inhibition is another mechanism that would be expected to decrease glucose uptake from the small intestine (SI) and alter postprandial blood glucose excursion.

There are no approved SGLT1 inhibitors; however, the marketed SGLT2 inhibitors for T2DM in the United States, Europe, and/or Japan vary in their selectivity for SGLT2 relative to SGLT1 as follows: 160-fold for canagliflozin (IC_{50} = 4.2 and 663 nM for SGLT2 and SGLT1, respectively), 1,200-fold for dapagliflozin (IC_{50} = 1.2 and 1,400 nM for SGLT2 and SGLT1, respectively), and 2,700-fold for the highly selective empagliflozin (IC_{50} = 3.1 and 8,300 nM for SGLT2 and SGLT1, respectively), as reviewed recently (79). These drugs inhibit SGLT2 reabsorption of glucose in the kidney proximal convoluted tubule, which is physiologically limited by saturation when glucose is ≥35 mM (55), resulting in loss of glucose in the urine and improved glycemic control. At the higher marketed dose (300 mg), canagliflozin also inhibits intestinal SGLT1, which delays the uptake of glucose and increases enteroendocrine cell (EEC) hormone release in healthy humans (88). Therefore, interest in the therapeutic effects of inhibition of SGLT1, alone or in addition to SGLT2, has resulted in the clinical evaluation of a number of dual inhibitors and reports on the metabolic profiles of SGLT1-null ($SGLT1^{-/-}$) mice or after selective SGLT1 inhibition in rodents. Despite these efforts, only a few dual SGLT1/2 or selective SGLT1 compounds have advanced to clinical trials. For this reason, it is timely to review the mechanistic data on intestinal SGLT1 and determine whether there are advantages to a level of inhibition that has tolerable gastrointestinal (GI) effects in metabolic disease.

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Current View of SGLT1 Inhibition in Metabolic Disease

It is broadly accepted that glycated HbA1c levels reflect blood glucose concentrations over time and, therefore, are related to risk for T2DM complications. However, HbA1c does not reflect daily variability of glucose levels, and it has been suggested that high glucose peaks may be an HbA1c-independent risk factor for diabetic complications (36). One advantage of delaying glucose uptake from the small intestine (SI) is that the glucose excursion after an oral glucose tolerance test has a lower peak with a longer shoulder. This has been shown to be the case after administration of 300 mg of canagliflozin (88) and the dual SGLT1/2 inhibitor LX4211/sotagliflozin (149). An effect of canagliflozin on intestinal glucose uptake inhibition in patients with T2DM was further supported by a study in which a second dose of canagliflozin (300 mg) was given 24 h after the first dose: the first dose would be primarily responsible for the lowered blood glucose due to urinary glucose excretion (118), and this second dose, which was administered just prior to a meal, further lowered the glucose excursion relative to the first dose alone (118).

Despite this effect on glucose absorption, the dual selective LX4211/sotagliflozin, with 20-fold selectivity (IC_{50} = 1.8 and 30 nM for SGLT2 and SGLT 1, respectively), has not progressed beyond a phase II trial for T2DM, although it is in a phase III trial for type 1 diabetes mellitus (T1DM; Clinicaltrials.gov NCT02531035). In addition, selective SGLT1 inhibitors such as KGA-2727 (390-fold more selective for rat SGLT1 than SGLT2) have shown improved glycemic control in Zucker diabetic fatty rats and increased hepatic portal levels of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) (106). An analog of the KGA-2727 SGLT1-selective inhibitor GSK-1614235 reduced glucose excursion and increased systemic GLP-1 when administered before, but not 30 min after, a meal to healthy volunteers (33). However, it was reported (Clinicaltrials.gov NCT01607385) that GSK-1614235 resulted in a modest increase in the proportion of subjects reporting diarrhea, abdominal pain, and flatulence compared with premeal. Thus, although SGLT1 inhibition alone, or in addition to SGLT2, can have metabolic benefits over highly selective SGLT2 inhibitors, the tolerability profile that could be associated with glucose malabsorption is in question. This topic will be covered later in this review; however, no signs of frank glucose malabsorption or adverse GI effects were reported in T2DM patients treated with 300 mg of canagliflozin twice a day for 4 wk (31) or a single dose of 400 mg of LX4211 (147).

The dual SGLT1/2 inhibitor LX4211 inhibits mouse, rat, dog, and human SGLT1 and SGLT2 and improves glucose control in these species (90). It is more selective for SGLT2 than SGLT1 (~200-fold selectivity for rat SGLT2 and 20-fold selectivity for human SGLT2). In contrast to the SGLT1-selective compound KGA-2727, LX4211 blunts, but does not delay, blood glucose uptake after an oral glucose tolerance test in animal models (91). Evidence for intestinal SGLT1 inhibition locally in the intestine leading to a positive beneficial metabolic effect can be found in reports of increases in colonic glucose concentration and decreases in pH in rats as a result of microbial metabolism of glucose to short-chain fatty acids (SCFAs) after oral administration of LX4211 (18, 91). Also, delayed, but augmented, levels of GLP-1 are noted in LX4211-treated diabetic KKAy mice (90), as well as in healthy humans and T2DM patients (147). A plausible explanation is that glucose escaping into the large intestine is fermented to SCFAs, stimulating GLP-1 and PYY release (147). Such a model is consistent with the elevated concentration of GLP-1 in $SGLT1^{-/-}$ mice (91). Glucose-dependent insulinotropic peptide secretion, in contrast, is reduced after LX4211 treatment in humans (147), in agreement with the low density of K cells in the distal gut.

Compounds with low oral bioavailability also reduce glucose uptake in streptozotocin-treated diabetic rats (43), suggesting that topical enteric SGLT1 inhibition has effects on glucose handling without systemic exposure. Oral administration of a locally acting selective SGLT1 inhibitor in diabetic rat models reduced blood glucose area under the curve by >50%; however, diarrhea occurred at a higher dose (43). It is well known that deletions and functional mutations within the *Slc5a1* gene in humans are associated with severe, life-threatening diarrhea, which can be prevented by exclusion of glucose/galactose from the diet (87, 134, 142).

Based on these clinical and preclinical data, the rest of this review will focus on how SGLT1 is dynamically regulated, evidence for SGLT1 as a glucose sensor, and the relationship of SGLT1 to EEC hormone secretion, all of which may contribute to the metabolic effects observed after SGLT1 inhibition. In addition, the effects of increased luminal glucose and Na^+ in the context of intestinal homeostasis and the microbiome are reviewed. One conundrum is the extent to which our understanding of the intestinal mechanisms related to SGLT1 modulation in rodents may be translational to humans. This is relatively straightforward for glucose dispersal, where human and rodent data can be directly compared, but less well understood in terms of risks for diarrhea and GI discomfort. In this context, the ability to translate the phenotype of $SGLT1^{+/-}$ and $SGLT1^{-/-}$ mice could be important to understand the exact relationship between SGLT1 activity, glucose homeostasis, and diarrhea. Understanding the changes in intestinal homeostasis associated with SGLT1 inhibition may elucidate whether a correct balance of SGLT1 inhibition can be achieved.

Intestinal Monosaccharide Absorption

Complex carbohydrates (CHOs) are broken down by salivary- and pancreatic-secreted α-amylases and by oligo-, tri-, and disaccharidases present in the brush border membrane of enterocytes (34). The resulting monosaccharides (glucose, galactose, and fructose) are absorbed in the SI. Glucose and galactose are actively transported across the apical surface by SGLT1, a high-affinity, low-capacity transporter, first cloned in 1987 (50). The protein consists of 664 amino acids, is encoded by the *Slc5a1* gene, and has 14 putative transmembrane-spanning regions (139). One molecule is cotransported with two Na^+ ions in an electrogenic process, but overall electroneutrality is achieved through Cl^- diffusion (139). The transport of Na^+ and glucose draws osmotically obligated water from the lumen to the blood. The driving force for glucose transport is generated by the activity of Na^+-K^+-ATPase expressed in the basolateral membrane. Glucose/galactose translocation across the basolateral membrane to the systemic side is achieved by glucose transporter (GLUT) 2 (GLUT2) through energy-neutral, facilitated transport. Within

the enterocyte, only a small fraction of glucose is oxidized, with glutamine transported apically into enterocytes being a preferred energy substrate. Glutamine metabolism provides energy for continual replacement of epithelium, which is renewed approximately every 1–2 wk, depending on the cell type. Uptake of fructose on the apical side occurs through facilitated diffusion down a concentration gradient by GLUT5 and basolaterally by GLUT2.

Expression of SGLT1 in the GI tract in different species. In human SI, there is a gradient of SGLT1 mRNA concentration, from highest in the duodenum to lowest in the ileum, with negligible amounts in other regions of the GI tract (22). The BioGPS database and the Human Protein Atlas also report high mRNA levels in the SI but essentially no expression in the colon.

Similarly, in the rat, SGLT1 expression is greatest in proximal SI (jejunum and duodenum), with lower levels in the ileum (8). SGLT1 immunostaining has been reported in the enterocyte brush border, and in the myenteric plexus, EEC (8), and enterochromaffin cells (61). The SI SGLT1 distribution represents a small fraction of the total tissue, and the protein may be underrepresented by quantitative PCR and Western blot analyses. In support of the intestinal distribution, active glucose uptake has been reported in rat colon, but with $V_{max} < 10\%$ of that in the jejunum/ileum (45). Interestingly, rat lingual taste cells express SGLT1 and may be involved in sensing sweet taste (73). Furthermore, SGLT1 is expressed in ductal and acinar cells of rat salivary glands, where it is suggested that SGLT1 reduces salivary flow through uptake of glucose and osmotically obligated water from primary saliva (96, 97).

Mouse SI also has a gradient in SGLT1 mRNA, with the highest expression in the duodenum (146) and a maximal Na^+-dependent uptake of glucose in the duodenum that decreases toward the ileum (39). SGLT1 mRNA levels in human and mouse duodenum were comparable (62). In contrast to humans, however, SGLT1 expression is also low in mouse colon and rectum (146). However, no functional significance of colonic SGLT1 has been demonstrated, and infusion of glucose into the mouse colon has no effects on GLP-1 secretion (78).

In dogs, Na^+-dependent glucose uptake does not differ between the proximal, mid, and distal SI (9). We confirmed comparable intestinal mucosal SGLT1 mRNA levels in cynomolgus and humans and high levels in the duodenum and jejunum and lower expression in the ileum in the rat. A similar pattern was seen in the dog SI mucosa; in the dog, however, the levels were generally much lower than in the rat, human, and cynomolgus (Fig. 1), consistent with the low intake of CHOs in the dog. Low SGLT1 mRNA levels were detected in the large intestine in all the species (Fig. 1).

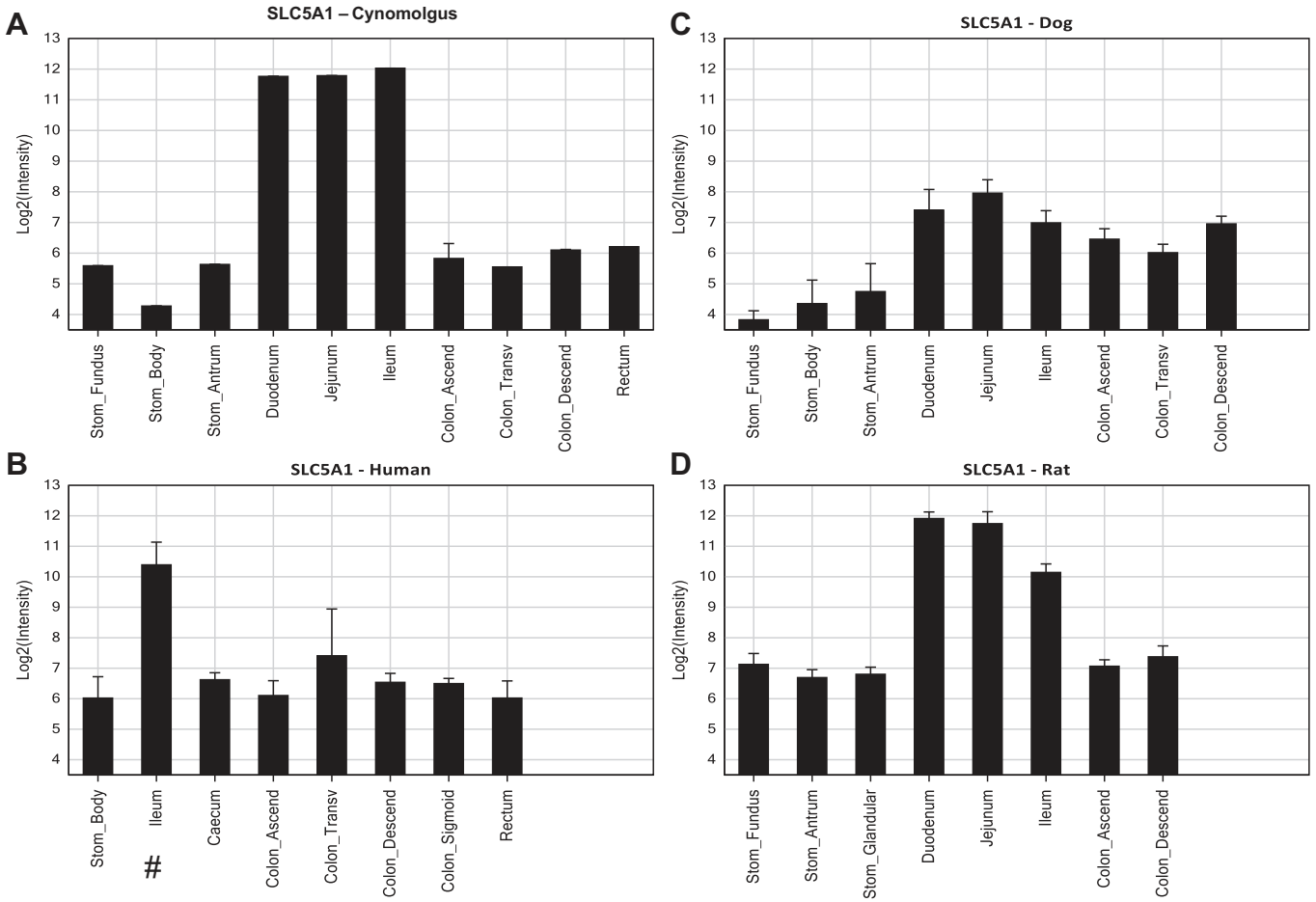

Fig. 1. Direct comparison of SLC5A1 mRNA expression by microarray in mucosal tissue isolated from gastrointestinal tracts of cynomolgus macaques (*A*), humans (*B*), canine beagles (*C*), and rats (*D*). Highest levels of SLC5A1 mRNA in all species are in small intestinal mucosa: stomach ≤ colon < small intestine. Cautious-comparison $\log_2$ intensity of ileum across species: dog < rat ≤ human < cynomolgus. #, Only ileum human mucosa was available from SI.

Adaptive changes in intestinal SGLT1. Within minutes, enterocytes can upregulate Na^+-dependent glucose transport after exposure to glucose (105), and the rapid appearance of SGLT1 in the apical membrane is a result of recruitment of intracellular transporters (52, 140). In addition to rapid recruitment, SGLT1 activity varies diurnally to meet the fluctuating availability of glucose in the gut lumen, a pattern that has been described in rats, rhesus monkeys (94), and mice (39). Maximal transport capacity shows a periodicity that was also a reflection of mRNA synthesis (7, 39, 123). SGLT1 activity is maximal when food is anticipated, and studies using time-restricted feeding suggest that this is entrained by intestinal nutrient availability and, possibly, regulated by clock genes (5, 6). Diurnal rhythmicity of SGLT1 is retained even in isolated jejunal loops (114). Both insulin-resistant lean and diabetic obese Zucker rats showed disturbed diurnal variations in food intake and jejunal glucose uptake; however, there was no simple relationship between these variations in food intake and rhythmic changes in SGLT1 mRNA expression, and neither GLUT2 nor the sweet taste receptor T1R2 had a diurnal pattern of expression in this study (13).

SGLT1 expression also changes in response to the overall luminal supply of CHO. Feeding pigs slowly digestible CHOs stimulated ileal expression of SGLT1, probably as a result of higher concentrations of glucose more distally in the gut (137). Rats offered high-starch diets had elevated SGLT1 expression in the SI, partially mediated by acetylation of histones H3 and H4 (54). Rats previously on a CHO-free regimen expressed higher levels of SI SGLT1 mRNA when glucose was added to the diet (77). High-fructose or -sucrose diets increased SGLT1, GLUT5, and GLUT2 mRNA expression in rat jejunum, but in this case a high-glucose diet had no effect on expression of these transporters (63). Even medium-chain triacylglycerols (144) or a glycerol-containing diet (77) increased SGLT1 expression. Conversely, the markedly attenuated absorption in critically ill patients was paralleled by a 50% reduced level of mRNA for SGLT1 and GLUT2 (30).

The sweet taste receptors T1R2 and T1R3 (heterodimeric family C G protein-coupled receptors) were first characterized in lingual taste buds but may also have sensing functions in the GI tract. Luminal exposure of the SI to low glucose (69) and apical exposure in cell lines (150) increased glucose uptake. Furthermore, SGLT1 was upregulated after feeding or duodenal perfusion of mice with artificial sweeteners (115), suggesting the involvement of T1R2/3. Increased SGLT1 expression associated with CHO-induced upregulation of glucose transport in mice was reported to be T1R3-dependent; however, neither an agonist nor an antagonist of the sweet taste receptor altered glucose absorptive capacity in rat jejunum in vivo (25, 71). Also, it is difficult to reconcile the T1R2/3 regulation of glucose-induced SGLT1 expression with the circadian pattern of SGLT1 expression, but not T1R2/3 (13).

Some lines of evidence suggest that GLUT2, which is normally located on the basolateral membrane to allow facilitated diffusion of glucose, translocates to the apical surface in response to high luminal glucose levels or in diabetes (58, 59, 136). This would enable SGLT1-independent glucose uptake at high luminal glucose concentrations. The evidence for this is as follows: in the IEC-6 rat gut epithelial cell line (without measurable GLUT2) transfected with GLUT2 cDNA, the transporter was expressed in the apical membrane after incubation with glucose (151); after short-term perfusion of rat jejunum with high glucose concentration, GLUT2 immunostaining was increased in the brush border membrane (60, 69), and, in mice on a low-CHO diet switched to a CHO-rich meal, GLUT2 was highly expressed in the brush border membrane (47). The translocation of GLUT2 does not occur in $SGLT1^{-/-}$ mutants (46). Others have reported no increase in GLUT2 immunoreactivity in the apical membrane after glucose administration to mice by gavage and suggest that GLUT2 detected by Western blotting in isolated brush border membrane fractions may be due to contamination from the basolateral membrane (95). Glucose perfusion (100 mM) of rat jejunum or in isolated everted rat jejunal sleeves augmented facilitative glucose transport without altering GLUT2 content in the brush border membrane (21). It has been claimed that protein kinase C and cytoskeletal proteins mediate translocation of GLUT2 to the brush border membrane (51), but this claim is also controversial (103). It is possible that literature discrepancies are more apparent than real and that brush border membrane expression of GLUT2 is highly sensitive to the experimental conditions, which questions the extent to which translocation is a robust physiological response.

Adaptive changes in intestinal SGLT1 in metabolic disease. In T2DM patients, mRNA and protein levels of SGLT1, GLUT2, and GLUT5 are elevated (35). Morbidly obese diabetic subjects express more GLUT2 in both apical brush border and endosomal membranes (1). This enhanced endosomal/brush border membrane GLUT2 in obese T2DM patients may reflect enterocyte insulin resistance (1), and it has been reported in mice that insulin reversed that GLUT2 translocation in response to oral glucose challenge (126). However, much less is understood about enterocyte insulin resistance than about the effects of insulin on metabolically important cells (e.g., hepatocytes and skeletal muscle cells), and there are more conflicting data. For example, insulin either inhibited (86) or stimulated (104a) glucose uptake in rat jejunum, in the latter case through increased glucose transporters.

The strongest evidence for a causative role for SGLT1 in obesity was shown in mice, where deletion of the gene for the SGLT1-regulatory protein RS1 was associated with a sevenfold-increased expression of SGLT1 protein, enhanced SI glucose uptake, and obesity (84). Another link was suggested by the upregulation of SI SGLT1 mRNA in Otsuka Long-Evans Tokushima fatty rats (42). Similarly, both glucose uptake and SGLT1 expression were increased in morbidly obese, nondiabetic humans (82). Overall, however, it is unclear whether SGLT1 upregulation alone could be causal in metabolic diseases, and the related SGLT3 may be as important for nutrient signaling in obesity and T2DM (76).

Bariatric surgery, especially Roux-en-Y gastric bypass (RYGB), is an effective way to reverse T2DM and obesity. Glucose control is markedly improved, and, in addition to the beneficial effect of weight loss, there is an early antidiabetic effect of largely unknown mechanism. A few studies have addressed changes in SGLT1 after bariatric surgery. In patients after RYGB, intestinal mucosal SGLT1 mRNA was increased and physiological glucose absorption was enhanced (81). These changes occurred along with intestinal hypertrophy, which is presumably an intestinal adaptation to mitigate possible CHO malabsorption. In rats, RYGB was associated with hypertrophy of the mucosa of the Roux limb (the section of the

SI anastomosed with the gastric remnant) (117), which was also noted in human biopsy samples 1 yr after RYGB (20). Counterintuitively, reduced glucose uptake was associated with increased SGLT1 mRNA, which was attributed to post-transcriptional regulation of SGLT1 (117). Supportive of this, in a different rat RYGB surgery study, SGLT1 protein expression was decreased in the alimentary limb (122); however, in yet another study, the level of SGLT1-mediated glucose transport activity of the Roux limb measured in Ussing-type flux chambers at 14 days was twofold greater than in control rats (20). More consistent data have been obtained in mice, where duodenal-jejunal bypass was associated with impaired glucose uptake and lower levels of both SGLT1 mRNA and protein (143), but not in rats after vertical sleeve gastrectomy (20). Diet-induced obese rats have increased SGLT1 activity in the duodenum and jejunum; when treated with a high-fat diet and low-dose streptozotocin followed by duodenal-jejunal bypass surgery, they showed improved oral glucose tolerance, with 50% blunting of SGLT1-mediated glucose uptake (56). Thus, different surgical interventions can result in different findings related to the glucose transporters. Overall, these data suggest that multiple adaptive changes occur in the mucosa immediately after surgical intervention. In the short term, decreased glucose uptake after surgery may seem counterintuitive to the increased SGLT1 activity, unless one considers that the glucose may be more locally utilized to support the adaptive increase in intestinal growth. An example is that, despite several reports of an increased number of GLP-1 cells in patients after RYGB (93), this could not be confirmed to occur independently of mucosal hyperplasia (20). Thus, apparent changes in transporter expression and function due to a high-fat diet or after RYGB may be confounded by multiple other adaptations to the intestinal surgery and should be interpreted with this in mind. The additional confounder, the microbiota changes associated with gastric bypass, is considered further below (see *Intestinal CHO and the Microbiome*).

Intestinal CHO and the Microbiome

Bacterial fermentation. Under normal conditions, most digestible CHOs are absorbed in the SI. Inhibition of SI digestion of disaccharides by acarbose, an α-glycosidase inhibitor, treats T2DM by delaying the digestion and intestinal absorption of dietary CHO. In effective doses, acarbose induces passage of CHO into the colon; however, despite this energy loss through bacterial fermentation, this compound has insignificant effects on weight loss (12) or prevention of weight regain in (post)obese humans (49). The effect of such chronic CHO delivery to the colon, assessed in patient rectal biopsies, confirmed little difference in fecal macronutrient output, but pH was decreased and total SCFA, butyrate, and acetate output was markedly increased (53).

The bacterial community in the colon is dominated by obligate anaerobes of the phyla Bacteroidetes, Firmicutes, and Actinobacteria. In the colon, 10^{11}–10^{12} colony-forming units of bacteria per milliliter contribute up to 60% of fecal mass and require ~70 g of CHO per day (109); therefore, altering their energy supply is a way to modulate microbial populations. A major source of energy supporting the microbiota comes from dietary plant cell wall polysaccharides, storage polysaccharides, and oligosaccharides that are not digestible by the host. Through fermentation, bacterial growth is stimulated, and this is reflected in increased production of gases and SCFAs (butyrate, acetate, and propionate). It was calculated that there is insufficient CHO from dietary fiber alone to support the colonic bacterial population in humans, and this shortfall (CHO gap) can be made up by energy from host-derived glycans, where glycoproteins comprise ~65% of intestinal dry weight (2). Interestingly, the abundance of the mucin-degrading bacterium *Akkermansia muciniphila* inversely correlates with body weight in humans and improves the metabolic profile in diabetic mice (37). Another source of energy to make up the CHO gap comes from digestible CHOs that are mostly absorbed in the SI, but with significant amounts "escaping" from the host into the colon (4, 14, 119) to provide energy for the microflora (102). This so-called starch malabsorption amounts to ~10–20% of a large starch meal based on hydrogen breath test. In the latter study, this amounted to 2–20% of ingested CHO from smaller test meals (20 or 60 g of starch) in different subjects, with no increase in hydrogen breath test compared with lactulose. These studies are consistent with increasing the availability of unabsorbed digestible CHOs up to ~40 g/day to the colon as tolerable malabsorption.

Since SGLT1 inhibition in the gut reduces the uptake of glucose from the SI, this could theoretically increase the amount of escaping glucose that enters the colon. It is unknown whether SGLT1 inhibition can be tuned to the equivalent tolerable level as suggested by these studies, i.e., the amount of glucose escaping into the colon would be ~10 g/meal consumed. Improving bacterial nourishment by increasing the availability of glucose could be beneficial in diabetes. For example, administration of dietary inulin-type fructans to obese women led to an increase in bacteria that was negatively correlated with serum lipopolysaccharide levels and an increase in bacteria associated with a slight decrease in fat mass and with plasma lactate (32). The prebiotic concept is to increase growth of beneficial indigenous bacterial genera, such as *Lactobacilli* and *Bifidobacteria*, butyrate-producing Firmicutes, and polysaccharide-degrading Bacteroidetes. This in turn can reduce insulin resistance and increase SCFA, which can stimulate GLP-1 secretion through free fatty acid receptor (FFAR) 3/2 [G protein-coupled receptor (GPR) 41/43]-dependent mechanisms (reviewed in Ref. 38). While glucose is not a prebiotic, it is an optimal energy source for bacteria and could enhance energy harvest in obese patients, a concept that has been described as a therapeutic strategy (131). As would be expected, *Bifidobacteria* and *Lactobacilli* grow well on glucose when cultivated in vitro. However, while most probiotic strains of *Bifidobacteria* also grew well on alternative CHO such as maltodextrin, a number of *Lactobacillus* strains showed good growth only during fermentation of glucose and lactose. Glucose/CHO fermentation by *Bifidobacteria* and *Lactobacilli* results in mostly lactate and/or acetate, with some strains of *Bifidobacteria* producing lactate as the major metabolite from fermentation of glucose (72).

In a recent report on SGLT1-selective inhibition by KGA-2727 in rodents and recovery of 3-*O*-methylglucose (3-OMG), Dobbins et al. (33) found the expected decrease in urine tracer recovery and increase in fecal recovery but increase in "unrecovered" fraction of 23–43%, which they suggested could be due to variable bacterial fermentation to ^{3}H or SCFA. Incuba-

tion of *Escherichia coli* in either glucose or OMG demonstrated that bacteria can utilize OMG as a carbon source, albeit at concentrations higher than glucose (27). As noted previously, bacteria, in turn, generate SCFAs, of which butyrate is a particularly important substrate for colonocytes (102). Apart from their direct effects on GLP-1 secretion from the colon, SCFAs expand the number of colonic FFAR2/GPR43-positive GLP-1-synthesizing EECs, as demonstrated after chronic administration of an indigestible CHO to rats (57).

The enrichment of genes involved in CHO transport and metabolism has been observed in human gut bacterium genome analysis. These predicted genes are >10% of the genes annotated, although there are few functional studies of these genes, despite the CHO sources of energy and carbon for the human gut bacteria. The substrate specificity (both isomaltose and maltose) of the *Ruminococcus obeum* (reclassified *Blautia obeum*) enzyme α-glucosidase suggests the potential for digestible CHO uptake and glucose production. At least one bacterium studied to date, *Bacteroides thetaiotaomicron*, has evolved to harvest glycans as energy with numerous CHO-active enzymes (125). The glucose metabolism pathways in the human gut microbiome need to be further explored to understand their potential impact on the human physiology of glucose metabolism (121).

Interrelationship of microbiome, glucose, and bariatric surgery. Intestinal gluconeogenesis may contribute to positive metabolic effects of propionate (29) produced by microbiota. Although the liver and kidney are considered to be the primary organs for gluconeogenesis, some studies support the existence of intestinal gluconeogenesis and suggest that it is a key factor behind protein-induced satiety. During fasting, glucose generated by the intestine reaches the hepatic portal blood, which is followed by activation of hepatic portal vagal afferents. The vagal-brain-sympathetic reflex pathways modulating metabolism are due to the disparate sensing of higher levels of hepatic portal glucose and lower levels of fasting systemic glucose. Mice lacking the intestinal glucose-6 phosphatase catalytic unit to prevent gluconeogenesis more rapidly develop hyperglycemia under a high-fat/sucrose diet and have a metabolic phenotype that is corrected for by portal glucose infusion (110). However, whether SGLT1 inhibition would interfere with hepatoportal vagal afferent signaling in this regard is unknown but is probably unlikely, since the impact is on glucose uptake that occurs postprandially, rather than during fasting.

Intestinal gluconeogenesis may contribute to the beneficial effects of gastric bypass surgery (75, 130). Mice fed a high-fat diet and subjected to surgery somewhat similar to RYGB (pyloric sphincter ligation and anastomosis to the midjejunum) had improved hepatic insulin sensitivity and increased intestinal gluconeogenesis (130). Other beneficial bacterially derived metabolites, such as γ-amino butyric acid and butyrate, are increased in the feces in rodent models of gastric bypass surgery (65). Furthermore, a large metabolomic analysis of patients who underwent gastric bypass surgery reported changes in a number of bacterially derived metabolites following surgery, which functionally demonstrates an altered gut microbiome (99). Although many studies have demonstrated population shifts (metagenomic fecal bacterial analysis) after RYGB, the beneficial effects of weight loss and diabetes resolution include changes in diet, enteroendocrine hormones, and bile acids, all of which influence the microbiota, and vice versa; therefore, cause-and-effect is difficult to determine (reviewed in Ref. 120). Colonization of germ-free mice with stool transfer from patients who have improved metabolic profiles after gastric bypass resulted in reduced fat deposition in recipient mice (128), suggesting causality of the microbiome. However, the germ-free animal models are artificial, and variability of results after fecal microbial transfer is to be expected on the basis of the influence of diet and behavior of the donors. Therefore, these experiments are difficult to reproduce in a manner that can help define the underlying mechanisms for the observed host phenotypic response and bacterial populations responsible.

SGLT1 Relationship to EECs and Neuronal Function

By virtue of its depolarizing effect secondary to transport of Na^+ into EECs, SGLT1 activity raises intracellular Ca^{2+}. This induces fusion of hormone-containing granules and secretion of the hormones and, therefore, promotes the incretin effect for efficient glucose dispersal. Primary colonic L cells from SGLT1$^{-/-}$ mice do not release GLP-1 in response to glucose (85), and glucose-stimulated incretin secretion was obliterated in SGLT1$^{-/-}$ mice (46, 95) but intact in GLUT2 knockouts (95). In seeming contrast, GLP-1 secretion was enhanced, but delayed, in SGLT1$^{-/-}$ mice (89). This effect was probably due to glucose metabolism to SCFAs in the large intestine (89), which in turn activates release of GLP-1 through GPR41/43 (FFAR3/2).

The sweet taste receptor T1R2/3 is present on the EECs, but artificial sweeteners do not cause GLP-1 secretion in humans. Circulating GLP-1 was elevated in healthy volunteers given glucose or 3-OMG (nonmetabolizable SGLT1 substrate) but was not increased following administration of sucralose (141). Sucralose also did not affect GLP-1 in healthy volunteers when co-infused with glucose or 3-OMG into the duodenum (68), and sucralose did not alter PYY secretion in healthy volunteers (40).

The presence of nutrients in the intestines reduces food intake and gastric emptying to match digestive and absorptive capacity with nutrient delivery. This negative feedback is particularly powerful when nutrients (predominantly lipids) are present in the ileum (70), and the term "ileal brake" to describe this was originally coined by Spiller et al. (112). This mechanism has both endocrine and neuronal components, where the humoral factors are predominantly GLP-1 and PYY, both of which retard gastric emptying. There is some evidence for involvement of SGLT1 in ileal brake function. Perfusion of the rat SI with SGLT, but not GLUT2, substrates reduced gastric emptying in conscious rats. Since galactose (a poor SLGT3 ligand in contrast to glucose) was devoid of these effects, SGLT3, rather than SGLT1, may be involved (41). Both glucose and galactose inhibit food intake in rats after their infusion directly into the duodenum, mid-SI, or colon (74). Glucose infusion also inhibited gastric motility and was SGLT1-dependent, and in rats fed a high-CHO diet to augment glucose SI uptake capacity, ileal brake activation by SGLT1 substrates was decreased (92). This latter result was presumably secondary to lower GLP-1/PYY release because of reduced glucose exposure of the distal SI, where L cells are most prevalent (92). In summary, SGLT1 stimulation activates the

ileal brake, which, by virtue of its inhibitory effects of gastric emptying, may help control blood glucose levels.

Sensory afferents are also necessary for the ileal brake (127), and myenteric transmitters, such as 5-HT acting on 5-HT_3 receptors, which reduce proximal SI motility after ileal perfusion of fat in dogs, have been implicated (66). SGLT1 was detected on myenteric neurons (8), and SI glucose infusion activated submucosal neurons (101). While unlikely to be the major component of the beneficial effects of SGLT1 inhibition, the enteric nervous system may modulate the expression and response to SGLT1 activation, as reviewed previously (107). Recently, a method to visualize both EEC and afferent autonomic neuron activation was developed (135). The method is based on detection of phosphorylated Ca^{2+}-calmodulin-dependent kinase II (pCaMKII). This technique has been used to show that gavage of glucose induces pCaMKII in enterochromaffin, L, and K cells in rat SI (64). Also, content of pCaMKII was increased in enteric and vagal afferent neurons after SI glucose administration. With the exception of K cells, this pattern of activation was suppressed in a T2DM rat model (64). The role of SGLT1 in glucose-stimulated vagal afferent activity is unknown and may not be direct, since release of 5-HT has been implicated in in vivo experiments (100, 152). On the other hand, an in vitro study showed that glucose excites some vagal afferents through ATP-dependent K^+ channel blockade and requires GLUT3, but the role or presence of SGLT1 in vagal afferents was not determined (48). Moreover, a vagal-dependent, 5-HT_3 receptor-mediated mechanism has been invoked in glucose-induced intestinal upregulation of SGLT1 (115). Vagal afferents may control glucose uptake, as evidenced by a lack of upregulation of glucose transport in guinea pig jejunum after transition from a low- to a high-CHO diet in animals treated with capsaicin (10). Similarly, capsaicin deafferentation disrupted SGLT1 expression at a posttranslational (116), but not transcriptional (124), level. Vagal afferents appear to control dynamic regulation of SGLT1 expression, and vagal deafferentation reduced visceral abdominal fat in rodents (113). In summary, in the SI, glucose regulates vagal afferent activity, but this is probably not directly mediated by SGLT1 but, rather, by release of signaling molecules from EECs and enterochromaffin cells. In the colon, parasympathetic afferent activity may be triggered by SCFAs (29), which may occur as a consequence of increased glucose after SGLT1 inhibition.

GI Motility and Secretion Associated With SGLT1 Inhibition

In clinical trials of the dual inhibitors, such as sotagliflozin, there was not much evidence for adverse GI effects in T2DM patients or in healthy subjects (147–149). An appropriate therapeutic margin may be obtained in T1DM patients, where the goal is to improve glycemic control while reducing the amount of bolus insulin, which has the advantage of improving weight management and reducing the risk for hypoglycemia (98). A phase II clinical trial (NCT01915849) of another dual SGLT1/2 inhibitor, LIK066, administered over 4 days, was associated with adverse GI effects, with 8 of 12 patients reporting diarrhea at the highest (150 mg) dose. Thus effects such as diarrhea are rapidly observed and are dose-related. Therefore, the mechanisms for SGLT1-induced diarrhea will be considered to try to determine whether there is a threshold below which it is tolerable for patients.

Genetic deletion of SGLT1 activity. Resection of the SI alone, depending on the length of the remaining bowel, can result in watery diarrhea (3). Glucose-galactose malabsorption (GGM) is a rare autosomal recessive disease caused by >40 different loss-of-function mutations of the *Slc5a1* gene and can be diagnosed by an abnormal glucose hydrogen breath test and severe persistent diarrhea (87, 142). If undiagnosed, it is fatal due to dehydration; however, exclusion of glucose and galactose from the diet completely reverses these symptoms. Likewise, mice with a deletion of the *Slc5a1* gene develop GGM but are healthy on a diet devoid of these CHOs (46, 89). $SGLT1^{-/-}$ mice fed a high-fat diet had improved oral glucose tolerance (46, 89). The translational ability of these mice to predict GI effects of GGM is questionable, since enhanced SI and cecal glucose levels were not associated with watery or soft fecal pellets (46, 89). In suckling GGM human neonates, severe diarrhea was observed, whereas suckling $SGLT1^{-/-}$ mice showed no obvious diarrhea (46, 89). However, the latter finding may be due to the lower concentration of lactose (a disaccharide converted by lactase-isomaltase to glucose and galactose) in murine than human milk.

Na^+ and Ca^{2+} intestinal homeostasis. People in the Western world consume an average of ~1 mol of glucose daily (138), which is taken up by SGLT1 together with ~46 g of Na^+. This Na^+ is offset by secretory loss into the lumen of the crypts, where Na^+ secretion passively follows actively secreted Cl^- (23). Another mechanism to prevent excessive uptake of Na^+ cotransported with glucose involves a neurally mediated reflex pathway (108). This autoregulatory effect also supplies Na^+ to the microenvironment, where it is needed the most to sustain glucose transport.

The addition of glucose to oral rehydration solutions increases fluid absorption in the SI and reduces dehydration due to the stoichiometry of Na^+ uptake of SGLT1 with glucose. However, increasing glucose in the SI does not reduce diarrhea, in part because of intraluminal glucose stimulation of Ca^+-activated Cl^- secretion (145). SGLT1 inhibition may therefore be associated with increased diarrhea because of the reduction in the Na^+ gradient combined with glucose-enhanced Ca^+-activated Cl^- secretion. Stimulation of SGLT1 is known to promote activity of the main Na^+ uptake protein in the brush border membrane, the Na^+/H^+ exchanger (NHE) isoform 3 (67), by increased trafficking of NHE3 to the brush border membrane. A reciprocal regulation of SGLT1 and NHE3 was noted using siRNA knockdown in cell cultures, so that suppression of one enhances expression and activity of the other (24). Further evidence lies in Caco-2 intestinal epithelial cell monolayers, where intracellular pH increased during SGLT1-dependent glucose uptake and the NHE3-selective inhibitor S-3226 prevented this alkalinization (132). Dietary K^+ loading may also modify glucose transfer in the rat jejunum. In rats fed a control diet, the uptake of glucose in the jejunum was unaffected by acute administration of amiloride, an inhibitor of epithelial Na^+ channel and NHE1 transport activity; however, in some animals fed a high-K^+ diet there was an increased flux of glucose that became sensitive to amiloride (19). It is unclear how SGLT1 inhibition would affect intestinal Na^+ transport, except for one report using brush border membrane vesicles isolated from a jejunal biopsy from a GGM patient that showed NHE3 transporter activity equivalent to control tissue, despite Na^+-dependent D-glucose

transport being 10% of controls (16). Given the dynamic interplay between SGLT1 and NHE3, it is possible, in terms of Na^+ uptake, that NHE3 compensates for reduced activity of SGLT1. While pharmacological inhibition of NHE3 in the gut can produce diarrhea (111), any possible contribution of Na^+ to osmotic diarrhea in profound SGLT1 inhibition has not been investigated, but, on the basis of the overall assessment above, it seems likely that NHE3 would compensate for moderately reduced Na^+ balance due to SGLT1 inhibition.

Lactase deficiency results in lactose intolerance, as reflected by GI symptoms such as bloating, flatulence, and osmotic diarrhea (11, 34, 80). These symptoms are caused by lactose fermentation in the large intestine and are prevented by exclusion of dairy products from the diet or supplementation of lactase. Similar to the symptom threshold for lactose-intolerant patients, there may be a level of SGLT1 inhibition that can be tolerated at any given CHO intake. Based on studies of partially gastrectomized patients with diarrhea, it was suggested that absorption of CHOs does not follow a fixed ratio but is characterized by a threshold effect (15). In a subgroup of patients with unexplained diarrhea, rapid orocecal transit with large intestinal CHO overload may underlie the condition (104). Interestingly, one-third of a small T2DM population without GI symptoms showed signs of CHO malabsorption as measured by H^+ and methane gas exhalation (133). This indicates that CHO malabsorption may be more common in this population and that it may not cause symptoms.

Fermentation of CHOs to SCFAs reduces colonic pH and increases the ionized fraction of Ca^{2+} and other divalent cations (83). As a consequence, increased passage of CHOs to the colon enhances Ca^{2+} absorption. It may be speculated that acidification of the colonic lumen secondary to synthesis of SCFAs and followed by higher concentrations of ionic Ca^{2+} activates the Ca^{2+}-sensing receptor expressed in colonocytes (44). Finally, at toxicological, rather than pharmacological, doses of canagliflozin in rats, increased urinary excretion of Ca^{2+} was noted and, by using $^{45}CaCl_2$, was consistent with increased absorption of dietary Ca^{2+} (28). However, rats are relatively sensitive to alteration of CHO absorption by a variety of substances (e.g., lactose, sorbitol, and mannitol), all of which can be associated with increased Ca^{2+} absorption and urinary Ca^{2+} excretion. This physiological effect has been demonstrated in humans (25, 129) after ingestion of a soluble or a partly soluble fiber-rich diet based on the apparent absorption of Ca^{2+} (25).

Summary and Perspective

Intestinal SGTL1 is finely tuned at the gene and protein level, as well as in terms of intracellular trafficking to the apical brush border membrane and its activity. This regulates the host response to CHO intake and related nutrient-signaling molecular mechanisms. The intestinal uptake of glucose from the gut is integral to neural and endocrine modulation of feeding behavior and satiation. There is no predictable way that SGLT1 functionality correlates with metabolic health and disease, and the alteration of its activity is not causal to T2DM, probably since adaptive mucosal changes also occur. Nevertheless, there are clear metabolic benefits of a level of SGLT1 inhibition in the gut. This inhibition will reduce and delay the glucose uptake from the SI and enhance downstream colonic hormone secretion. In the large intestine, increased glucose and Na^+ resulting from extreme loss of functional SGLT1 could alter intestinal homeostasis and, therefore, be related to adverse GI effects. It has been challenging to attain a level of selective SGLT1 inhibition that prevents glucose uptake and does not perturb intestinal homeostasis. This difficulty is compounded by apparent lack of adverse GI effects in rodents that do not readily translate to tolerability in humans. In addition, how an increase in colonic glucose can alter, if at all, the microbiome in detrimental ways is unknown. A threshold of glucose "escape" into the large intestine may be beneficial in terms of supporting the bacteria with an energy source.

The difficulty in achieving the correct "balance" of SGLT1 inhibition may contribute to the few dual or selective SGLT1 inhibitors that have advanced through clinical trials for T2DM. Marketed SGLT2 drugs such as canagliflozin have a selectivity profile that includes intestinal SGLT1 inhibition and show good overall efficacy. Dual SGLT1/2 inhibitors, such as sotagliflozin, may benefit T1DM patients by reducing bolus insulin dosing and risk of hypoglycemia. It is unlikely that an SGLT1-selective inhibitor can match the efficacy of SGLT2-selective or dual inhibitors, and with the additional concerns about GI tolerability and the question of cardiovascular risk due to the possible presence of SGLT1 in cardiac tissue, it would be challenging to mitigate these concerns for minimal additional benefit to patients. A enteric-restricted SGLT1 inhibitor may meet the needs of metabolic disease patients in a manner similar to other locally acting nonabsorbed drugs available in some countries, such as α-glucosidase inhibitors.

ACKNOWLEDGMENTS

The authors appreciate the input from and discussions with many Janssen colleagues. The authors especially thank Drs. Raul Camacho, Fuyong Du, and Simon Hinke (Cardiovascular and Metabolic Discovery, Janssen, Spring House, PA), who contributed to the approach to the mechanisms; Dr. Xiang-Yao (Computational Biology, Janssen, La Jolla, CA), who compiled the data for SLC5A1 mRNA expression in different species; and Dr. David Polidori (Cardiovascular and Metabolic Early Development, La Jolla, CA) for careful reading of the manuscript and valuable feedback on earlier versions of this review.

DISCLOSURES

P. J. Hornby is employed by Janssen Research and Development, LLC.

AUTHOR CONTRIBUTIONS

A.L. and P.J.H. developed the concept and designed the research; A.L. and P.J.H. drafted the manuscript; A.L. and P.J.H. edited and revised the manuscript; P.J.H. interpreted the research; P.J.H. prepared figures; P.J.H. approved the final version of the manuscript.

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