Multifaceted interplay among mediators and regulators of intestinal glucose absorption: potential impacts on diabetes research and treatment

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Chan LK, Leung PS. Multifaceted interplay among mediators and regulators of intestinal glucose absorption: potential impacts on diabetes research and treatment. Am J Physiol Endocrinol Metab 309: E887–E899, 2015. First published October 20, 2015; doi:10.1152/ajpendo.00373.2015.—Glucose is the prominent molecule that characterizes diabetes and, like the vast majority of nutrients in our diet, it is absorbed and enters the bloodstream directly through the small intestine; hence, small intestine physiology impacts blood glucose levels directly. Accordingly, intestinal regulatory modulators represent a promising avenue through which diabetic blood glucose levels might be moderated clinically. Despite the critical role of small intestine in blood glucose homeostasis, most physiological diabetes research has focused on other organs, such as the pancreas, kidney, and liver. We contend that an improved understanding of intestinal regulatory mediators may be fundamental for the development of first-line preventive and therapeutic interventions in patients with diabetes and diabetes-related diseases. This review summarizes the major important intestinal regulatory mediators, discusses how they influence intestinal glucose absorption, and suggests possible candidates for future diabetes research and the development of antidiabetic therapeutic agents.

insulin; glucagon; oxyntomodulin; glucagon-like peptide-1 and -2; glucose-dependent insulino-notropic polypeptide; cholecystokinin; catecholamines; renin-angiotensin system; angiotensin ii; leptin; niacin; polyphenols

diabetes (type 1 or 2 diabetes mellitus, T1DM or T2DM) is a chronic metabolic disease characterized by hyperglycemia that can result from insulin insufficiency and/or insulin resistance. Currently, there are over 300 million diabetic patients, among them 5% being T1DM and 90–95% being T2DM (179). The chronic hyperglycemic state associated with diabetes produces a number of hallmark clinical manifestations, including pathologies of the eyes, kidneys, heart, blood vessels, and nerves.

The vast majority of therapeutic interventions for diabetes target the pancreas, liver, skeletal muscle, adipose tissues, or kidney. Research examining diabetes interventions targeting the small intestine has been somewhat lacking. In this regard, it is important to note that postprandial hyperglycemia has been shown to be closely related to an elevated risk of developing T2DM (88, 122). Given the fundamental role of the small intestine in the absorption of food nutrients, especially glucose, a deeper understanding of the regulators of intestinal glucose uptake would be beneficial for devising new therapeutic strategies, such as potential manipulations of these regulators in the small intestine.

Despite its name, the small intestine is not at all “small” in the sense that it absorbs over 90% of consumed nutrients, leaving only a minority of nutrients to be absorbed by other parts of the intestines. The small intestine is crucial for delivering dietary glucose, as well as substrate molecules for liver gluconeogenesis, into our bloodstream (21); thus, it impacts blood glucose homeostasis on two fronts. The crucial role of intestinal glucose absorption in treating diabetes has been highlighted by several diabetic drugs, such as acarbose (134) and LX4211 (118), which delay the breakdown of carbohydrate via inhibition of α-glucosidase and decrease SGLT1-mediated intestinal glucose absorption, respectively. Moreover, gastric bypass surgery in diabetic patients with weight reduction has been shown to improve diabetic conditions via changes in intestinal glucose absorption (129, 147), thereby underpinning the critical role of the small intestine in glucose homeostasis. A wide variety of regulatory factors play critical roles in the modulation of intestinal glucose transporters, influencing the efficiency of glucose transporters and the amount of glucose absorbed into the bloodstream. The molecular regulation of these glucose transporters and their subsequent glucose uptake behavior have been characterized to a great extent. It should be noted that the small intestine not only absorbs glucose but also utilizes glucose (129); however, a full discussion of this topic is outside the scope of this review, and only intestinal absorption is being focused on here. Prior reviews have discussed hormonal effects on glucose uptake, which were mainly emphasized on certain factors, e.g., growth hormone (153) or tissue levels, e.g., adipose tissue (95). Furthermore, given that there have been substantial scientific advances in the knowledge of modulatory factors on glucose uptake, a wider scope of discussion with current progress is warranted. In view of this, the present review provides a
summary of the normal physiology of intestinal glucose uptake, followed by a discussion of modulatory factors of intestinal glucose uptake, including detailed consideration of the molecular signaling pathways involved in their actions. Knowledge gaps in our understanding of the modulatory factors where we believe future research is needed are also highlighted.

Normal Physiology of Intestinal Glucose Absorption

Intestinal glucose absorption occurs across the small intestinal apical membrane, through the so-called brush border membrane (BBM) of enterocytes, primarily via sodium-dependent glucose cotransporter 1 (SGLT1) (172, 173). SGLT1 functions as a symporter, cotransporting one sodium ion with each glucose molecule that it transports (172). The pivotal role of SGLT1 in intestinal glucose absorption was demonstrated by Gorboulev and colleagues, who found that SGLT1-/- knockout mice develop lethal glucose-galactose malabsorption syndrome if they are maintained on a glucose-based diet (53). Intriguingly, rearing of SGLT1-/- mice on a glucose/galactose-deficient diet prevents development of glucose-galactose malabsorption syndrome and enables them to grow up into viable, healthy, and fertile adult mice despite the fact that they exhibit impaired intestinal glucose absorption (53); these observations of some, albeit reduced, absorption of glucose in SGLT1-/- mice provides evidence of another glucose transporter in the intestinal BBM. Indeed, glucose transporter 2 (GLUT2), which is expressed on the basolateral membrane (BLM) of the small intestine, acts as a facilitative low-affinity, high-frequency glucose uniporter (125).

The existence of two kinds of intestinal glucose transporters was first demonstrated in 1934 by Wertheimer et al. (164).

They classified intestinal glucose transport into phlorizin-sensitive and phlorizin-insensitive components, which correspond to SGLT1 (phlorizin is an SGLT inhibitor) and GLUT2, respectively. Interestingly, during episodes of high luminal glucose loads (e.g., after a meal), GLUT2 is recruited rapidly and transiently from the BLM to enterocyte BBM, yielding a threefold enhancement of glucose uptake (56). Importantly, this GLUT2 recruitment to the BBM requires the involvement of SGLT1 (73). Although, the role of GLUT2 in intestinal glucose absorption has been controversial this issue is not the focus of this review.

Furthermore, the abundance and activity levels of both SGLT1 and GLUT2 are elevated in diabetes (16, 37), suggesting that they may play a role in the pathogenesis of diabetes. Because postprandial hyperglycemia is associated with an increased risk of T2DM (88, 122), any reduction in the postprandial glucose surge is beneficial. Therefore, identification and characterization of the regulatory modulators of glucose transporters and their effects on glucose uptake would be useful for the development of potential therapeutic agents that target these mediators specifically and thus ameliorate diabetic hyperglycemia at the level of small intestine. Regulatory modulators with potential therapeutic value have been selected for discussion below (summarized in Table 1 and Fig. 1).

Peptide Regulators of Intestinal Glucose Absorption

Insulin. Insulin is a 51-amino acid peptide hormone that exerts hypoglycemic effects by acting on various organ levels, including skeletal muscle (27, 74), liver (20), and adipose (27). Insulin can also modulate intestinal glucose uptake; however, the nature of that influence is unclear. At physiological concentrations, insulin has been reported to enhance glucose uptake in the fasted rat (110, 111) and decrease glucose absorption in the fed state (72). This is consistent with the observation that postprandial glucose uptake is increased in streptozotocin-induced diabetic rats which have low circulating insulin levels (72). However, some studies have reported that insulin has no effect on intestinal glucose uptake in the fasted state (75, 76). The mechanism of this apparent discrepancy remains to be elucidated. Interestingly, insulin has been shown to inhibit postprandial glucose uptake in vivo (77) and glucose uptake in isolated intestinal segments from diabetic rats (78). In contrast, insulin has been reported to increase postprandial glucose uptake in vivo (79) and glucose uptake in isolated intestinal segments from control rats (80). These inconsistent results may have been due to differences in experimental models or methodologies. Further studies are needed to clarify the role of insulin in the regulation of intestinal glucose uptake.

Table 1. Summary of regulatory factors that influence intestinal glucose absorption

<table>
<thead>
<tr>
<th>Regulatory Factors</th>
<th>Effects on Glucose Uptake (↑/↓/?/N/A)</th>
<th>SGLT1 Involved?</th>
<th>GLUT2 Involved?</th>
<th>Proposed Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>↑/↓</td>
<td>✓</td>
<td>?</td>
<td>Increased SGLT1 expression (113), with no change in SGLT1 mRNA levels (81). Insulin reversed upregulated SGLT1 activity in STZ-induced diabetic rats (43). *Inhibition of cAMP-PKA signaling pathway (140, 166, 171).</td>
</tr>
<tr>
<td>Glucagon</td>
<td>↑</td>
<td>✓</td>
<td>N/A</td>
<td>Stimulation of insulin release (7), which upregulates SGLT1-mediated uptake (149). cAMP elevation via glucagon receptors. Increased electrochemical gradient for Na⁺ ion (140, 155).</td>
</tr>
<tr>
<td>Glucagon-37</td>
<td>↑</td>
<td>✓</td>
<td>N/A</td>
<td>GLP-1-induced stimulation of glucose uptake might be mediated via neural or hormonal pathways, independent of SGLT1 and GLUT2 (162).</td>
</tr>
<tr>
<td>GLP-1</td>
<td>↑</td>
<td>×/?</td>
<td>✓/?</td>
<td>Promotion of ileal GLUT2 abundance (60) and activity (18, 19). NO-dependent pathway (60).</td>
</tr>
<tr>
<td>GLP-2</td>
<td>↑</td>
<td>N/A</td>
<td>✓/?</td>
<td>Inhibition of intestinal motility (104). PKA phosphorylation (69).</td>
</tr>
<tr>
<td>GIP</td>
<td>↓</td>
<td>N/A</td>
<td>N/A</td>
<td>Increased electrochemical gradient for Na⁺ ion (140, 155).</td>
</tr>
<tr>
<td>CCK</td>
<td>↓</td>
<td>✓</td>
<td>✓</td>
<td>AngII binds to AT1R to inhibit SGLT1 via a GLUT2-independent mechanism. Ang-(1–7) inhibits SGLT1- (but not GLUT2-) mediated glucose uptake (170).</td>
</tr>
<tr>
<td>Leptin</td>
<td>↓</td>
<td>✓</td>
<td>✓</td>
<td>Prevention of translocation of cytosolic preformed SGLT1 to cell membranes (32). Mediated via classic PKC isoforms (32).</td>
</tr>
<tr>
<td>AngII</td>
<td>↓</td>
<td>✓</td>
<td>✓</td>
<td>AngII binds to AT1R to inhibit SGLT1 via a GLUT2-independent mechanism. Ang-(1–7) inhibits SGLT1- (but not GLUT2-) mediated glucose uptake (170). Via Mas receptor, leading to downstream activation of PKC signaling pathway (170).</td>
</tr>
<tr>
<td>Nonpeptide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>↑</td>
<td>N/A</td>
<td>N/A</td>
<td>Action on β-adrenoceptor (107), independent of oxidative metabolism (36).</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>↑</td>
<td>N/A</td>
<td>N/A</td>
<td>Precise mechanism awaits further investigation.</td>
</tr>
<tr>
<td>Niacin</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>cAMP-dependent pathway (Wong et al., unpublished data).</td>
</tr>
<tr>
<td>Polyphenols</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>Precise mechanism awaits further investigation.</td>
</tr>
</tbody>
</table>

*Unconfirmed potential clues for further investigation. See text for definitions. N/A, not studied.
absorption in rat intestinal sac preparations (87). Additionally, in experiments employing an in situ perfusion technique (i.e., measuring jejunal glucose absorption in anesthetized rats), insulin increased the luminal uptake of glucose via increased SGLT1 expression (139). Interestingly, insulin was shown in an early study to restore upregulated SGLT1 activity in streptozotocin (STZ)-induced diabetic rats (43), with the effect not being attributable to changes in blood glucose concentrations, because it was not reversed by starvation. This finding was somewhat surprising given that renal Na\(^+\)/glucose cotransporters are regulated by changes in blood glucose concentration (175). Furthermore, it has been reported that an acute inhibition of glucose absorption can be attributed entirely to SGLT1 (113). Hence, further investigations are warranted to clarify the actions of insulin on intestinal glucose uptake (i.e., stimulatory or inhibitory), as well as to answer the question why insulin would reverse upregulated SGLT1-mediated intestinal glucose uptake in STZ-induced diabetic rats.

Although the exact mechanism involved in insulin-mediated regulation of glucose uptake remains ambiguous, studies have indicated that Sglt1 mRNA levels in insulin-treated diabetic rats are comparable to those in STZ-induced diabetic rats, suggesting that insulin-mediated control of intestinal SGLT1 activity is mediated downstream of translation, such as at translation or posttranslationally (81). This inference was confirmed experimentally by studies showing that insulin enhances SGLT1 protein expression in HCT-116 intestinal cells in culture (8) and that infusion of insulin into the portal vein results in an acute increase of intestinal glucose in anesthetized mice (149).

Insulin is known to reduce cellular concentrations of 3\',5'-cyclic adenosine monophosphate (cAMP) and to inhibit lipid metabolism in adipocytes (76). Given that cAMP promotes SGLT1-mediated glucose uptake in the small intestine of rats (140, 166), if the action of insulin were inhibitory, it would be plausible to speculate that insulin might inhibit SGLT1 activity via inhibition of cAMP. The messenger molecule cAMP is involved in the activation of protein kinase A (PKA), a well-characterized cAMP-dependent kinase in the so-called cAMP/PKA pathway. Indeed, previous studies have shown that SGLT1 activity is dependent on PKA signaling, with PKA activity upregulating SGLT1 activity (171). Therefore, it may be that insulin downregulates intracellular cAMP levels, which in turn inhibits PKA signaling, thus subsequently hindering SGLT1-mediated intestinal glucose uptake. However, the possibility that insulin may inhibit SGLT1 via the cAMP/PKA pathway has yet to be confirmed experimentally.

Insulin has also been reported to diminish transepithelial transfer of sugars and protein expression of GLUT2 on the BBM and BLM sides of Caco2/TC7 cells in vitro and to inhibit intestinal glucose absorption in mice, apparently by regulating the membrane localization of GLUT2 in enterocytes (161). However, there is little information regarding this potential interaction between insulin and GLUT2 in enterocytes.

**Glucagon.** Glucagon (glucagon-29) is a 29-amino acid peptide hormone (13, 156). The glucagon gene, which encodes the 160-amino acid polyprotein proglucagon, is expressed in the α-cells of the endocrine pancreas and in the L-cells of the small intestine. Proglucagon is modified posttranslationally by limited proteolysis to yield tissue-specific peptides. In enteric L-cells, proteolytic cleavage of proglucagon yields three major peptide molecules, namely glucagon-37 (aka oxyntomodulin; amino acids 33–69, i.e., glucagon-29 extended by a COOH-terminal octapeptide), glucagon-like peptide-1 (GLP-1; amino acids 72–108), and glucagon-like peptide-2 (GLP-2; amino acids 126–158) (115). Discovered in 1922 as a hyperglycemic hormone in glucose homeostasis regulation and has been implicated in T2DM pathogenesis (3). Intravenous glucagon has...
Glucagon-mediated elevation of blood glucose levels stimulates the release of insulin (7), which can induce short-term upregulation of SGLT1-mediated glucose uptake (149). Incubation of isolated rat jejunal enterocytes with glucagon (10 nM) has been reported to enhance glucose uptake within 15 min (25). Furthermore, glucagon incubation (0.1–100 nM) increased intracellular cAMP levels dose dependently in enterocytes over a similar time course (140). Consistently, addition of dibutyryl cAMP and theophylline raised cAMP levels and then stimulated glucose uptake (140). Hence, glucagon has been shown to stimulate intestinal glucose uptake in enterocytes, perhaps via increased cAMP levels. Aside from the cAMP-mediated pathway, other studies have indicated that glucagon exerts a stimulatory action on glucose uptake through an increased electrochemical gradient for Na⁺ ions (140, 155).

**Glucagon-37.** As suggested by its name, glucagon-37, or oxyntomodulin, is comprised of 37 amino acids. In contrast to glucagon-29, which is released by the pancreas, glucagon-37 is produced by enteric L-cells (115). In the stomach, glucagon-37 antagonizes pentagastrin- and histamine-stimulated acid secretion via somatostatin release (31, 119). Meanwhile, in the small intestine, glucagon-37 promotes intestinal glucose absorption acutely; this effect was demonstrated in isolated perfused small intestine and villus tip enterocytes from the rat (151) and appears to involve stimulation of SGLT1 (150). This stimulatory action of glucagon-37 was abolished in the presence of the cAMP antagonist Rp-cAMPS and therefore appears to be mediated via a cAMP-dependent mechanism (151).

Alterations in the number of intestinal glucose transporters have been shown to induce increased glucose absorption under certain circumstances, including pregnancy (116), lactation (116), STZ-induced diabetes (40), high-carbohydrate diets (93), and experimental hypo- and hyperinsulinemia (165). In view of the results, questions were raised as to whether the stimulatory action of glucagon-37 on intestinal glucose uptake may also be due to increased de novo synthesis of intestinal glucose transporters. However, experimental data excluded such a possibility; the acute onset (within minutes) of the enhanced glucose uptake induced by glucagon-37 was too rapid to be accounted for by an increase in the abundance of intestinal glucose transporters (151). The possibility that the increase in glucose uptake was mediated by cAMP signaling, however, remains viable.

Other observations have also been confounding, including changes in vascular perfusion rate, changes in intestinal motility, and changes in effective mucosal flow following intestinal redistribution of total flow. However, thus far, glucagon-37 appears not to affect total vascular flow, superior mesenteric artery flow, celiac trunk flow, or intestinal motility (151). Hence, these factors seem unlikely to contribute to glucagon-37-induced enhancement of glucose uptake.

**GLP-1.** GLP-1, synthesized and secreted by enteroendocrine L-cells, is a type of incretin hormone that modulates postprandial glucose excursions via potentiation of glucose-stimulated insulin secretion (68, 123). Previous data demonstrating that plasma GLP-1 and intestinal glucose absorption are only weakly correlated are consistent with the possibility that GLP-1-induced stimulation of glucose uptake might be mediated via neural or hormonal pathways (162) rather than by direct action on intestinal glucose transporters. Notwithstanding, there has been little examination of a potential direct role of GLP-1 in intestinal glucose uptake; therefore, further investigation into this question is warranted.

**GLP-2.** GLP-2 is a 33-amino acid peptide derived from proglucagon that is produced postprandially by intestinal enteroendocrine L-cells (106). It has long been known for its promotion of intestinal growth and crypt villus height in the small intestine via enhancement of crypt cell proliferation and inhibition of enterocyte apoptosis (29, 177). Additionally, enteral feeding in humans and piglets has been shown to enhance GLP-2 secretion rapidly, indicating that GLP-2 is also active in gut metabolism regulation (54, 174). In terms of its effect on intestinal glucose uptake, GLP-2, when infused intravenously, increased carrier-mediated glucose uptake across the intestinal BLM in situ in rats (19). Studies have also demonstrated that GLP-2 stimulates intestinal glucose uptake in piglets via a nitric oxide (NO)-dependent mechanism (60). The involvement of a NO-dependent pathway was demonstrated by the observation that coinfusion of GLP-2 with a direct inhibitor of nitric oxide synthase blocked stimulation of glucose uptake completely (60). The potential possibility of GLUT2 involvement in this GLP-2 effect has been raised based on the findings that GLP-2 infusion leads to promotion of ileal GLUT2 abundance (60) as well as GLUT2 activity at the intestinal BLM (18, 19). However, this elevated GLUT2 abundance in the ileum may be of little physiological relevance given that GLUT2-mediated changes in NO expression and activity are confined to the proximal jejunum (60). Nevertheless, further study aimed at unraveling the specific glucose metabolic pathways that might mediate GLP-2-stimulated glucose uptake is needed.

**GIP.** GIP, also known as gastric inhibitory polypeptide, is an incretin hormone composed of 42 amino acids that is synthesized by duodenal K-cells. It has an inhibitory action on histamine-induced gastric acid secretion, which gave rise to its original name, GIP. As suggested by its name, GIP is now known primarily for its potentiating influence on glucose-stimulated insulin secretion (50). Contrary to this original name, GIP is now known primarily for its potentiating influence on glucose-stimulated insulin secretion (35, 112), consistent with its contemporary name of glucose-dependent insulinotropic polypeptide.

Ogawa et al. found that intraperitoneal GIP delivered in a single-pass perfusion impaired intestinal glucose uptake in a concentration-dependent fashion (104), potentially attributable, at least in part, to GIP-mediated inhibition of intestinal motility. However, in the same study, measurement of intestinal glucose uptake by everted mouse intestinal rings did not show an inhibitory effect on glucose; the authors suggested that this negative result was due to the rings being set inside-out and distended to a considerable extent, such that the model might not reflect the general conditions of intestinal motility. In line with these findings, intestinal motility has been shown to correlate positively with intestinal absorption across the intestinal BLM (128, 143). Enhanced intestinal motility promotes glucose delivery to BBM transporters by increasing the intestine’s functional surface area as well as unsettling the static water layer in the intestine (121, 167). Hence, thus far, the evidence supports
the notion that GIP may inhibit intestinal glucose uptake by inhibiting intestinal motility.

**Cholecystokinin.** Cholecystokinin (CCK) is a gastrointestinal peptide released after food intake and is well known for its roles in regulating various physiological functions, including pancreatic exocrine secretion, gallbladder contraction, and bowel motility (100). CCK was first recognized for its ability to delay gastric emptying, an effect that affects intestinal glucose absorption indirectly (24, 83, 84). Later, it was discovered that CCK also has a direct effect on the rate of glucose absorption across the small intestinal BBM in rats (67); this effect is accompanied by a parallel reduction in SGLT1 expression on the intestinal BBM (66). Furthermore, CCK has been reported to reduce postprandial hyperglycemia in humans (84).

Slowed glucose entry into systemic circulation has been reported to improve other glucose homeostatic systems’ capacities to handle glucose load, thereby contributing to a normalization of the plasma glucose concentration (66). Cholecystokinin octapeptide (CCK-8) has been shown to decrease the rate of SGLT1-mediated 3-O-methyl-glucose absorption, but not GLUT2-mediated D-fructose, transport, suggesting that the CCK hypoglycemic effect involves SGLT1 but not GLUT2 (65). More specifically, immunoblotting experiments demonstrated that CCK decreased SGLT1 posttranscriptionally at the level of protein expression (66).

Given that the physiological effects of CCK are localized to the intestinal BBM, some researchers have reasoned that it is more likely that CCK effects are mediated via a cytosolic second messenger than via receptor-mediated endo- or exocytosis (66). Cholecystokinin octapeptide (CCK-8) has been shown to decrease the rate of SGLT1 might be modulated by PKA phosphorylation (69); however, no apparent consensus PKA phosphorylation sites could be identified in rat SGLT1 (65), making this possibility less attractive. Notwithstanding, activation of PKA has been shown to increase the maximal rate of glucose transport mediated by SGLT1, with the effect being dependent on the SGLT1 sequence that mediates the chaperone protein interactions that regulate SGLT exocytosis and endocytosis. That is, replacement of single residues within this interaction sequence had dramatic effects on the influence of PKA on SGLT1 activity (171).

**Leptin.** Leptin, a hormone encoded by the ob gene, was discovered in 1994 as a protein, secreted by adipose cells, that possesses weight-reducing properties (178). Consequently, leptin was viewed initially as a prominent adipostatic signal that might control body weight and adiposity. Subsequent research revealed that leptin regulates a variety of other functions, including neuroendocrine functions (1), fertility (55), and angiogenesis (109). More importantly, pertaining to satiety and weight control in obesity, it has been established that leptin is a critical regulator of long-term energy balance and suppression of food intake (77).

In addition to adipocytes, leptin is also produced by tissues within the gastrointestinal tract, such as the salivary glands (59) and stomach (6, 144), as well as by the placenta (89). Stomach-derived leptin is secreted together with gastric acid (6, 144); astoundingly, leptin remains active in the highly acidic (pH 2) gastric environment (59). Upon reaching the small intestine, leptin exists as both free and macromolecule-bound leptin (61). Leptin binds leptin receptors along the small intestinal BBM, thereby initiating physiological processes that regulate the transport of sugars (86) and peptides (17) across the small intestine.

Concerning the role of leptin in intestinal glucose transport, circulating leptin released by adipocytes has been shown to inhibit sugar transport by way of inhibiting SGLT1 activity (86). On a local level, addition of leptin to the mucosal side of the rat small intestine induces a rapid, marked inhibition of SGLT1-mediated glucose transport, which is achieved by preventing the translocation of cytosolic SGLT1 to the cell membrane (32). Leptin-mediated inhibition of glucose transport was abolished completely by Go-6976, a selective classical (Ca2+-dependent) protein kinase C (PKC) isoform inhibitor, but not by mallotoxin, a novel (Ca2+-dependent; DAG-dependent) PKC isoform inhibitor (32). Alternatively, leptin can regulate intestinal glucose uptake in rats indirectly by stimulating intestinal secretion of CCK (61) and GLP-1 (5), which are both involved in the regulation of glucose absorption. Aside from leptin’s effect on SGLT1, orally administered leptin has been reported to increase GLUT2 mRNA levels in the jejunum, where GLUT2 is a direct target of luminal leptin (131). Elucidation of the influence of this leptin-induced effect on GLUT2 and subsequent glucose uptake by the jejunum will require further investigation.

**Local Renin-Angiotensin System in the Small Intestine**

Over the last century, the renin-angiotensin system (RAS) has become well known for its crucial roles in fluid/electrolyte homeostasis, cardiovascular pathophysiology, pulmonary diseases, and renal diseases. The story of RAS began in 1898 when renin was first discovered and dubbed a “pressor substance” by Robert Adolph Armand Tigerstedt and Per Gustav Bergman, paving the way for the establishment of the concept of a “circulating” or “systemic” RAS (157). Later, in a groundbreaking discovery of the 1990s, it was demonstrated that pharmacological inhibition of angiotensin-converting enzyme (ACE) could be used clinically in the management of cardiac arrest and hypertension.

Around the same time, the existence of a local RAS was revealed, leading to a paradigm shift in how we viewed the RAS as only a circulating system (38, 85, 110). This new notion of a localized RAS was derived from the discoveries of various RAS components in rather “unusual” places in the body, such as the localization of renin, typically found in the kidney, in the brain, which could not be explained by our prior understanding of an endocrine RAS (48, 49). In addition, intracellular generation of a key peptide hormone of the RAS has been observed (80). These findings revealed that the RAS was more diverse and complex than appreciated previously, having not only endocrine actions but also paracrine and intracrine actions.

Following the discovery of a local RAS, there was an intensification of efforts to uncover RAS components in various tissues, including the brain, pancreas, gastrointestinal tract, heart, blood vessels, adipose, lymphatic tissue, gonads, placenta, and kidney (111). The evidence demonstrating local RAS components within the small intestine in particular are summarized in Table 2; efforts have been made to characterize these components and analyze their functional impacts on glucose uptake, as highlighted below.
Angiotensin II. Angiotensin II (AngII) is an 8-amino acid peptide that serves as the major angiotensin peptide in the RAS. Synthesized from cleavage of angiotensin I by ACE and chymase, or alternatively from angiotensinogen by kallikrein (94), AngII is a major regulator of blood pressure, hydroelectrolyte balance, and various endocrine functions, including functions related to cardiovascular disease (92). In our laboratory, we found that AngII inhibits SGLT1-mediated intestinal glucose uptake via a GLUT2-independent mechanism, a previously unknown role for AngII in intestinal BBM (168). Specifically, the addition of L162313, a nonpeptide analog of AngII, to mucosal fluid resulted in a dose-dependent inhibition of rat jejunal glucose uptake, with the inhibitory effects becoming significant at a concentration of 1 nM. At a 100 nM dose, glucose uptake was reduced by ~60%, to 90 (from 225) pmol glucose (mg dry wt)/s. Pretreatment of jejunal tissue with 1 μM losartan did not alter jejunal glucose uptake in the absence of AngII but abolished the inhibitory effect of 100 nM AngII, demonstrating that AngII inhibition of glucose uptake requires involvement of the angiotensin type I receptor (AT1R).

We confirmed that both AT1R and AT2R are expressed on the intestinal BBM. These findings led to the establishment of a functional local RAS in the small intestinal BBM (168) through which AngII hampers SGLT1-mediated glucose uptake. However, the mechanism by which AngII inhibits SGLT1 remained elusive. Our recent investigation has suggested that AngII might inhibit SGLT1 via inhibition of apical sodium-hydrogen exchanger 3 (NHE3) (unpublished data). Interestingly, hypertension that is related to NHE3 has been shown to affect glucose transport by altering Na⁺ gradients (90). Additional work is under way to test this possibility.

**ACE2-Ang-(1–7)-Mas axis.** Emerging evidence has suggested that AngII is not the only active peptide of the RAS. For instance, the baroreflex and vascular actions of Ang-(1–7) have been reported to oppose the actions of AngII (41, 132). Indeed, there appears to be an ACE2-Ang-(1–7)-Mas axis acting in opposition to the classical ACE-AngII-AT1R axis in the heart, kidney, and liver. This oppositional axis may serve as a compensatory mechanism for the cellular effects of altered expression of ACE-AngII-AT1R axis components in diabetes (9).

The first component of the ACE2-Ang-(1–7)-Mas axis is ACE2. ACE2 is an exopeptidase that is structurally similar to ACE but is resistant to inhibition by ACE inhibitors (158). The primary physiological function of ACE2 is to catalyze the conversion of AngII to Ang-(1–7) (42); it also catalyzes the conversion from AngI to Ang-(1–9), but the binding affinity of ACE2 for AngII is ~400-fold higher than that for AngI. ACE2 expression has been observed in a wide variety of tissues in rats, including the heart (47), lung (51), kidney (82), brain (46), and pancreas (159); in humans, ACE2 has been found in the heart and kidney (28), and also in the small intestine and colon (160).

Ang-(1–7) is an endogenous ligand of Mas, a G protein-coupled receptor (133). Ang-(1–7) is generated, primarily, from the processing of AngI or AngII by prolyl-endopeptidase or from the processing of AngII by carboxypeptidase (58, 103, 105, 154). In the context of intestinal glucose uptake, recent experiments in our laboratory showed that enterocyte levels of Ang-(1–7), ACE, and the Mas receptor are elevated in T1DM patients, with Ang-(1–7) inhibiting Mas receptor-mediated jejunal glucose uptake in a dose-dependent manner (170). Given that AngII has been reported to inhibit ACE2 formation (46, 47), these recent findings complement our previous results in T1DM model rats showing that diminished ACE and AT1R expression in T1DM reduced enterocyte production of AngII (169), which in turn increased expression of ACE2 and Ang-(1–7), resulting in an upregulated ACE2-Ang-(1–7)-Mas axis in jejunal enterocytes. Interestingly, our findings indicate that, in contrast to the dynamics observed in other tissues, AngII and Ang-(1–7) peptides do not appear to oppose each other in the case of enterocyte glucose uptake. Conversely, we have found that both peptides suppress SGLT1-mediated glucose uptake, independently of GLUT2.

We conducted follow-up experiments examining the cellular signaling mechanism underlying Ang-(1–7)’s inhibition of enterocyte glucose uptake and found that the effect is dependent on Ang-(1–7) binding of the Mas receptor (i.e., blocked by Mas receptor antagonist A-779) and downstream activation of PKC (i.e., blocked by PKC inhibitor GF-109203X hydrochloride) (170). The underlying mechanistic relationship between Mas receptor activation, PKC activation, and a blunted SGLT-mediated glucose transport in the jejenum has yet to be delineated. Notwithstanding, the establishment of an ACE2-Ang-(1–7)-Mas axis that affects enterocyte glucose uptake has important implications for the control of postprandial glycaemia in diabetes. It is important to note that treatment of diabetic rats with Ang-(1–7) improved glucose tolerance significantly after an oral but not

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**Table 2. Summary of RAS components identified locally in the small intestine**

<table>
<thead>
<tr>
<th>RAS Component</th>
<th>Supportive Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renin</td>
<td>Renin gene expression in human and mouse intestine (138).</td>
</tr>
<tr>
<td>ACE</td>
<td>Localization of ACE in the BBM of human jejunum (148). High ACE mRNA, protein, and activity levels in the BBM fraction of rat proximal to mid-small intestine (39, 176). Strong ACE immunoreactivity in absorptive epithelial cells of human intestinal mucosa, particularly in the microvilli and BBM of the small intestine (14). Prominent surface expression of ACE protein localized in enterocytes of the small intestine was noted (64). Highly enriched ACE activity in the intestinal brush border of the rat (163). AT1R mRNA and protein identified <em>in vitro</em> on RIE-1 rat intestinal epithelial cells (142). In vitro autoradiography revealed that AngII receptors are most abundant in the colon, followed by the ileum, duodenum and jejunum (33). AT2R and, to a lesser extent, AT2R detected in rat intestine by autoradiography; specific AngII binding sites found to be moderately abundant in jejunal and ileal mucosa (137). Functional AT1R present in rat ileum and duodenum (135).</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; BBM, brush border membrane; GLUT2, glucose transporter 2; RAS, renin-angiotensin system. See text for definitions.
an intravenous glucose load, pointing to a local action of Ang-(1–7) on intestinal glucose transport.

**Nonpeptide Regulators of Intestinal Glucose Absorption**

**Catecholamines.** Catecholamines are monoamines comprised of a catechol group (i.e., 1,2-dihydroxybenzene) with an amine side chain. The catecholamine synthesis reactions are well defined (12). Perhaps the best known of the catecholamines, epinephrine (aka adrenaline) and norepinephrine (noradrenaline) trigger “fight-or-flight” responses and are fundamental neuromodulators in the central nervous system (CNS). Epinephrine administration raises intestinal glucose uptake significantly, in parallel with increased oxygen uptake into the bloodstream (57).

Given that epinephrine can yield increased oxygen uptake, it was debated whether the parallel effect on glucose uptake was an indirect effect related to the increase in oxygen uptake rather than a direct effect of epinephrine per se. However, the increase in glucose uptake far exceeded what could be accounted for on the basis of oxidative metabolism alone (36). Moreover, Oyebola et al. conducted several important experiments examining the induction of elevated intestinal glucose uptake by intravenous injection of epinephrine in rabbits (107). Specifically, they took blood flow and glucose measurements via a vein draining a segment of the upper jejunum and then calculating the difference in glucose concentration between arterial and venous blood. Interestingly, the hyperglycemic response to epinephrine was abolished by propranolol (a β-adrenergic antagonist) but not prazosin (an α1-adrenergic antagonist), demonstrating that the effect was mediated via apical β-adrenoceptors (107). These findings revealed a previously unappreciated important role of the sympathetic nervous system in glucose absorption, providing new insights into neural-gastrointestinal interactions.

Similarly to epinephrine, intravenous norepinephrine increases intestinal glucose uptake within minutes (57), raising both arterial and venous levels of glucose. However, the mechanism of the norepinephrine effect has not been explored.

**Niacin.** Niacin (vitamin B3 or nicotinic acid) is a nutritional supplement widely used for elevating high-density lipoprotein levels and reducing low-density lipoprotein levels. Accordingly, niacin has been reported to ameliorate dyslipidemia in diabetic patients and to be beneficial for patients being treated for dyslipidemia-associated cardiovascular diseases that are commonly comorbid with diabetes (62). Given that diabetic patients have an elevated risk of suffering coronary event-associated mortality, which is closely related to dyslipidemia, the benefits of niacin in the treatment of dyslipidemia have been encouraging. However, notwithstanding the aforementioned health benefits, more and more recent studies have revealed that niacin can induce glucose intolerance in patients, evidenced by increased blood glucose levels in euglycemic patients after three years of niacin treatment (114). Recent findings in our laboratory suggest that this phenomenon may be related to a previously unknown role of niacin in intestinal glucose uptake. We found that niacin enhanced intestinal glucose uptake in db/db T2DM model mice as well as glucose uptake in human Caco2 (epithelial colorectal adenocarcinoma) cells through activation of the nicotinic receptor GPR109a (167a). We further confirmed that niacin is localized to the jejunal BBM, where it exerts a local modulatory action on the glucose uptake of enterocytes, and we observed that niacin-induced elevation of intestinal glucose uptake involved SGLT1 and GLUT2. These findings indicate that niacin and its apical receptor GPR109a are involved in the local control of intestinal glucose uptake. Hence, the niacin-induced hyperglycaemia observed in euglycemic patients could be due to this local enterocyte modulation via GPR109a.

**Polyphenols.** Polyphenols are bioactive compounds that are ubiquitous in the plant kingdom. They constitute an integral part of the human diet (88, 122) and are renowned for their abilities to exert a multitude of beneficial effects on disease states, from inflammation to cardiovascular disease and cancer (91). Intake of beverages rich in dietary phenols can alter the pattern of intestinal glucose uptake (70, 71). For instance, the phenolic compounds in apple juice were found to delay intestinal glucose uptake (70). Additionally, chlorogenic acid (a group of dietary phenols in coffee) was shown to exhibit a similar inhibitory effect on intestinal glucose uptake, as well as to improve glucose tolerance in humans (71).

The first demonstration of blunted glucose transport in response to phenolic compounds dates back to 1922, when Nakazawa showed that phlorizin, a flavonoid glucoside, inhibited glucose uptake in the rabbit small intestine (102). However, at that time, only functional data regarding changes in the absorption of glucose, fat, protein, water, and salt were reported. The precise mechanism was unknown until 1967, when Alvarado reported that the key to the decrease in glucose uptake was competitive inhibition of SGLT1 across the intestinal BBM (4). More recently, green tea polyphenols, including epigallocatechin gallate and epicatechin gallate, were shown to inhibit glucose transport, potentially through SGLT1 inhibition (78). Moreover, flavonoid (a group of polyphenols found in a great variety of edible plants) has been shown to inhibit GLUT2-mediated glucose uptake (145). Hence, it appears that both SGLT1 and GLUT2 may participate in polyphenol-mediated regulation of intestinal glucose uptake.

**Interplay of Intestinal Regulatory Mediators**

Mediators of intestinal regulation do not function independently. Rather, they interact with one another to give rise to an intricate network of interactions among organ systems, including gut-brain-liver and gut-brain-pancreas axes, as summarized in Fig. 2 and discussed below.

**Gut-brain-liver axis.** During embryogenesis, the parasympathetic ganglia of the brain and gut are derived from the neural crest. Owing to this common origin, various gut hormones and peptides and their respective receptors are also located in the brain; thus, many peptide hormones secreted by the gut have been dubbed “brain-gut” hormones. Indeed, the small intestine is richly innervated by primary visceral afferents from both the sympathetic and parasympathetic divisions of the autonomic nervous system (45).

After ingestion of a meal, the presence of nutrients generates neural signals that are sent to hindbrain nuclei for integration; those nuclei project to various forebrain regions, including the hypothalamus (124, 152). Furthermore, the intestinal regulatory peptide leptin, introduced above, modulates energy balance through its actions on the hypothalamic long-form leptin receptor (Leprβ) (98, 101). It has been reported that leptin...
stimulation of phosphatidylinositol 3-kinase (PI3K) in the hypothalamus can improve insulin sensitivity (99) and reduce glucose production in high-fat-fed rodents (15). Similarly, leptin reduces glucose production and glucose levels in STZ-induced diabetic rodents (44, 52). These findings underscore the importance of leptin effects on the hypothalamus in the modulation of insulin sensitivity.

Recent evidence suggests that leptin may have actions outside the brain as well. Intestinal leptin has been reported to activate the CNS via a leptin receptor-PI3K pathway that is independent of the STAT3 pathway in the regulation of glucose homeostasis (120). This novel finding is in line with previous studies indicating that nutrient sensing is mediated by intestinal vagal innervation and that this nutrient sensing controls glucose homeostasis through a so-called gut-brain axis (11), which could potentially be targeted therapeutically in the treatment of diabetes.

Intestinal CCK (introduced above) has also been shown to control glucose production by activation of the gut CCK-A receptor and a gut-brain-liver neuronal axis independently of changes in circulating insulin levels (22). In rats, CCK-A receptor deficiency results in the development of an elevated rate of hepatic glucose production, obesity, and diabetes (10, 72, 97, 141). These findings suggest that the CNS conveys peptide hormone–glucose homeostasis–regulating signals initiated in the intestine or brain. Moreover, these findings may be relevant for understanding the mechanisms underlying observed improvements in glucose tolerance that are independent of weight loss in diabetic/obese patients that have had gastric duodenal bypass surgery (127).

**Gut-brain-pancreas axis.** The normal physiological glucose signals for insulin release in the pancreas act in concert with messages triggered by glucagon and incretin hormones (e.g., GLP-1 and GIP) binding their cognate receptors (30). Enterohormones, such as CCK, have been found to stimulate pancreatic enzyme secretion by activating sensory nerves and by triggering long vagovagal enteropancreatic reflexes (79). Concerning gut-pancreas interactions, islet autonomous nerve activity has been shown to be closely related to the nutritional state of the organism (2). Meanwhile, it has been postulated that measurement of blood glucose by hypothalamic neurons regulates the autonomous nervous component of the endocrine pancreas (136).

Neural effectors regulate insulin and glucagon release as well as glucose sensors in α- and β-pancreatic cells. As plasma glucose drops (e.g., between meals or during prolonged fasting), an increase in sympathetic output via the splanchnic nerves has been reported (130). This increased sympathetic activity of the pancreatic islet nerves stimulates glucagon release and inhibits insulin release directly (2), possibly via the actions of the neurotransmitter norepinephrine (117) and the neuropeptide galanin (34). These findings provide strong evidence suggesting that glucose homeostasis, particularly that mediated by the small intestine, interacts with that of the pancreas via the CNS.

**Intestinal Taste Receptors as Novel Regulators of Glucose Absorption**

Roux-en-Y gastric bypass surgery (RYGB) is a surgical procedure commonly performed on T2DM patients to alleviate obesity (126). However, the underlying mechanisms remained elusive until recent research breakthroughs have revealed that there exists a jejunal nutrient-sensing mechanism at the jejunum required for the restoration of metabolic homeostasis. In this regard, recent data have proposed that a gut-brain-liver network is responsible for lowering endogenous glucose production in normal rats induced by intrajejunal nutrient administration (11). As mentioned previously in the section Gut-brain-liver axis, the observed weight-independent improvements in glucose tolerance after RYGB might be attributable to the activation of CCK-A receptor and the subsequent gut-brain-liver neuronal axis by the action of intestinal CCK. Furthermore, solid evidence has also shown that the detection of intraluminal glucose load is mediated by the glucose-sensing protein SGLT3, located at the proximal intestine (108). The stimulation of SGLT3 was found to increase the rate of glucose absorption in the distal small intestine, followed by an increase in GLP-1 secretion, where the integrity of the vagus nerve is necessary for the pathway to function. Since the proximal small intestine constitutes the greatest part for nutrient-sensing response, studies have also revealed isolation of this region by RYGB from enteric nutrients; thus, sweet-taste sensing diminishes SGLT1 expression and improves oral glucose handling (146). Therefore, these studies provide potential mechanistic
insights into foregut exclusion by RYGB, which disrupts the glucose-sensing mechanism. In light of these findings, the novel sensing mechanisms localized at the jejunum should open an exciting avenue for the development of potential therapeutic targets for the treatment of human T2DM.

Future Perspectives

Identification and characterization of novel regulatory factors in the control of intestinal glucose uptake would be helpful for improving our understanding of the intricate relationships and interactions among the regulatory factors in various critical organ systems and thus our understanding of their influences on systemic glucose homeostasis as a whole. Most of the data discussed here were obtained in animal models, tissues, or cells. Therefore, the validity of the current body of data will need to be extended and assessed in human subjects and specimens to enable greater clinical applications. The relative roles of genetic versus environmental factors should also be considered to develop a complete picture of the roles of these regulatory factors. Genetically modified models (e.g., knockout and transgenic rodents) can be utilized further to investigate the genetics of glucose homeostasis. Genetic manipulation experiments related to leptin (96) and the growing body of transcription factors that regulate protein expression levels of insulin and glucose sensors (63) would be particularly important. Additionally, more work, including large-scale genome analyses, is needed to identify the genetic variants associated with obesity and diabetes.

Summary

Small intestinal glucose transport is a sophisticated physiological process that is intricately regulated by a multitude of regulatory factors. Dietary glucose enters the body in the small intestine, particularly the jejunum. Over the past decade, novel regulatory factors have been identified and characterized, with an emphasis on their roles in mediating intestinal glucose uptake. Elucidation of the physiology of intestinal glucose uptake and blood glucose homeostasis will require understanding the key regulatory factors modulating the functions of glucose transporters and their underlying molecular pathways. Such knowledge can be used in the development of therapeutic agents that target the regulatory factors that control intestinal glucose uptake, postprandial hyperglycemia, and the homeostasis of blood glucose levels. Indeed, a growing body of literature in this area points to potential clinical applications of manipulating these regulatory factors. Considerable physiology remains to be explored, particularly with respect to uncovering novel molecular signaling pathways involved in the functions of regulatory factors and glucose transporters.

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AUTHOR CONTRIBUTIONS


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