Sugar Absorption in the Intestine: The Role of GLUT2

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Abstract

Intestinal glucose absorption comprises two components. One is classical active absorption mediated by the Na^+/glucose cotransporter. The other is a diffusive component, formerly attributed to paracellular flow. Recent evidence, however, indicates that the diffusive component is mediated by the transient insertion of glucose transporter type 2 (GLUT2) into the apical membrane. This apical GLUT2 pathway of intestinal sugar absorption is present in species from insect to human, providing a major route at high sugar concentrations. The pathway is regulated by rapid trafficking of GLUT2 to the apical membrane induced by glucose during assimilation of a meal. Apical GLUT2 is therefore a target for multiple short-term and long-term nutrient-sensing mechanisms. These include regulation by a newly recognized pathway of calcium absorption through the nonclassical neuroendocrine L-type channel $Ca_v1.3$ operating during digestion, activation of intestinal sweet taste receptors by natural sugars and artificial sweeteners, paracrine and endocrine hormones, especially insulin and GLP-2, and stress. Permanent apical GLUT2, resulting in increased sugar absorption, is a characteristic of experimental diabetes and of insulin-resistant states induced by fructose and fat. The nutritional consequences of apical and basolateral GLUT2 regulation are discussed in the context of Western diet, processed foods containing artificial sweeteners, obesity, and diabetes.

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INTRODUCTION

Textbooks tell us that glucose is absorbed across the small intestine by Na^+-dependent active transport through the sodium-dependent glucose transporter, SGLT1. It is less widely appreciated that there is also a diffusive mechanism of glucose absorption, which can be several times greater than the active pathway. The diffusive pathway was controversially attributed to paracellular flow, that is, the solvent-induced flow of glucose through tight junctions. However, there were also many reports that the diffusive pathway could not be detected in vitro. As a consequence, a debate developed between proponents of paracellular flow on the one hand and those on the other hand, who argued that the diffusive component did not exist and that all glucose absorption could be accounted for solely by transcellular, active transport (see below). Subsequently, it was proposed that the facilitative transporter, glucose transporter type 2 (GLUT2), could be inserted within minutes into the apical membrane of jejunum in vivo in response to high glucose concentrations, even though GLUT2 was thought to reside normally only at the basolateral membrane. This facilitated or diffusive component of absorption was called the apical GLUT2 pathway. We review here work from a number of laboratories on the mechanism of short-term regulation of GLUT2 at both the apical and basolateral membranes and its physiological and nutritional significance.

Paracellular flow: the flow of nutrients and ions through tight junctions and intercellular spaces between cells as opposed to transcellular flow through cells

The Classical Model of Secondary Active Intestinal Glucose Absorption

Secondary active transport of glucose across the enterocyte apical membrane through SGLT1 is driven by a downhill gradient of Na^+ maintained by the basolateral Na^+/K^+-ATPase (28, 52). When luminal glucose is lower than blood glucose, SGLT1 has the unique ability to transport glucose against its concentration gradient and therefore to act as a very effective scavenger from the lumen in vivo. Once in the enterocyte, glucose crosses the basolateral membrane into the circulation via the facilitative transporter GLUT2. Fructose is transported across the apical membrane by GLUT5 (17), for which it is highly specific in whole intestine. Since plasma fructose is negligible compared with plasma glucose, only a facilitative transporter is necessary; GLUT5 is therefore the low-K_m analogue of SGLT1. In contrast to GLUT5, GLUT2 transports both glucose and fructose, providing a common exit pathway from the enterocyte (19).

The Diffusive Component of Glucose Absorption

The existence of two components of glucose absorption in vivo was reported in 1935 by Donhoffer (33) and confirmed in detail by many other workers (7, 14, 15, 31, 39, 40, 43, 62, 64, 78, 82, 110). The diffusive component is seen far more readily in vivo than in vitro. Of note, Debnam & Levin (31) undertook the first formal kinetic analysis in vivo. The phloridzin-sensitive component displayed the classical saturation kinetics of active absorption with effective saturation occurring around 30 mM glucose; in contrast, the phloridzin-insensitive component was apparently nonsaturable and displayed seemingly linear kinetics from 30–100 mM glucose, consistent with a diffusive component. In different studies, the diffusive component was three- to fivefold greater than the active component (**Figure 1**).

In 1987, Madara & Pappenheimer (81) set the terms of the debate over the physiological importance of the diffusive component in vivo. Specifically, they noted that it accounted for some 75% of total glucose absorption and that, for it to have physiological significance in terms of glucose absorption, it must be dependent upon and occur simultaneously, that is, within minutes, with transport by SGLT1. These terms are important in the context of current work (see below).

Pappenheimer & Reiss (93) observed that glucose transport through SGLT1 induces a cytoskeletal rearrangement of the enterocyte involving contraction of the perijunctional actomyosin ring, loosening of tight junction structure, and widening of the intercellular spaces. Noting that the diffusive component correlates strongly with net water absorption (43), Pappenheimer & Reiss (93) proposed that concentration of glucose in the intercellular spaces by SGLT1 osmotically induced the diffusive flow of glucose by solvent drag through the "open" tight junctions—paracellular flow. For an account of the subsequent debate with Pappenheimer, in which Ferraris and colleagues (38) maintained that glucose absorption could be effectively explained in terms solely of the transcellular classical model, see Kellett (67).

THE MECHANISM OF APICAL GLUT2 TRAFFICKING

Apical GLUT2 Mediates the Diffusive Component of Glucose Absorption

Apical GLUT2: the facilitative transporter GLUT2 inserted in the apical as opposed to its conventional location in the basolateral membrane

The discovery of apical GLUT2 has been described in two previous accounts (67, 68); thus, what follows is a summary to provide sufficient background to understand how apical GLUT2 is controlled by Ca^{2+}, sweet taste receptors, and paracrine and endocrine hormones.

In the classical model of absorption, GLUT2 is located only at the basolateral membrane. However, following work in diabetic rats (26), we discovered that GLUT2 could traffic to and from the apical membrane in normal, fed rats, so that fructose absorption is mediated by both GLUT5 and GLUT2 (54, 55). Apical membrane insertion was very rapid ($t_{1/2} \sim$ 3.5 min) and correlated with activation of the protein kinase C (PKC) βII isoform (56).

The transient presence of GLUT2 in the apical membrane has been detected using four antibodies to epitopes within the C-terminal (rodent) and N-terminal (human) regions and within the large extracellular and large intracellular loops (rodent) (1, 26, 69, 108). Its location in the apical membrane has been confirmed by cell surface biotinylation (4, 55, 108, 111) and by immunogold and immunofluorescence imaging using extracellular loop antibody (1, 4, 46, 47). Apical GLUT2 cannot be detected by immunocytochemistry using C-terminal antibody (1, 107), even though this works well in Western blots, implying that the C-terminal region is masked in intact tissue.

Since GLUT2 can transport glucose as well as fructose and has a very high K_t (transport constant) for glucose, it was clear that apical GLUT2 had the potential to provide a diffusive (facilitated) component of glucose absorption in vivo. In order to resolve the SGLT1 and apical GLUT2 components, we used phloretin, which

selectively inhibits GLUT2 but not SGLT1 in whole intestine. Normal rat jejunum was perfused in single-pass mode in vivo with modified Krebs-Henseleit buffer containing the stated concentration of glucose osmotically balanced by the addition of mannitol to a total sugar concentration of 100 mM (69); other experiments without mannitol later showed that osmolarity had no effects on the results. We found that glucose absorption comprises a phloretin-sensitive, GLUT2-mediated component and a phloretin-insensitive, SGLT1-mediated component (**Figure 1**). The SGLT1 component shows simple saturation kinetics with an apparent K_t of 27 mM in vivo. The GLUT2 component appeared diffusive, but was in fact cooperative. At high concentrations, the GLUT2 component accounted for ~75% of absorption.

The saturation kinetics of the SGLT1 component were explained by the fact that Western blotting of apical membrane vesicles prepared after a 20- to 30-minute perfusion revealed there was no change in SGLT1 level induced by glucose. At 0 mM glucose, there was a basal level of apical GLUT2, which remained constant up to 20 mM glucose. Consistent with the observed cooperativity, an increase in apical GLUT2 was first detectable at 30 mM glucose, and by 100 mM it was double the basal level (**Figure 1**). This range is significant with respect to the action of intestinal taste receptors (see below). Glucose also increased the level of PKC βII at the apical membrane; inactivation of PKC βII by tissue excision meant that the apical GLUT2 component of absorption was not readily seen in vitro.

At the low perfusion flow rates employed, GLUT2 trafficking depended on SGLT1, so that phloridzin in vivo inhibited not only the SGLT1 component, but also that part of the apical GLUT2 component dependent on SGLT1. However, when GLUT2 trafficking was blocked by perfusion at high flow rate, phloridzin inhibited only the SGLT1 component (31, 53). Moreover, phloridzin and cytochalasin B together inhibited all glucose absorption within experimental error, implying there is no paracellular component of absorption. Similar conclusions were obtained with replacement of Na^+ by choline (no inhibitors) (69).

Calcium Absorption and Enterocyte Cytoskeletal Rearrangement

Biochemical markers suggest that intracellular Ca^{2+} (Ca_i^{2+}) must be important in the glucose-induced insertion of apical GLUT2. Thus insertion is dependent on the conventional PKC βII isoform (55, 69). Moreover, the diffusive component, now identified with apical GLUT2, depends on the enterocyte cytoskeletal rearrangement normally associated with glucose-induced contraction of the perijunctional actomyosin ring (81, 93). Both processes are activated by an increase in Ca_i^{2+}. The importance of Ca^{2+} is demonstrated by its omission from the intestinal perfusate, when the apical GLUT2 component of glucose absorption and apical GLUT2 are both strongly diminished at high (75 mM) sugar concentration (87).

This simple experiment takes us into almost uncharted territory. Since there have been very few studies of how glucose affects Ca^{2+} absorption, the current literature view of Ca^{2+} absorption applies to polarizing conditions and cannot readily explain observations under strongly depolarizing conditions. For example, experiments in the absence of glucose have led to the widely accepted assertion that L-type voltage-dependent Ca^{2+} channels (VDCC) are not present in epithelia (41). Moreover, the literature view has become that Ca^{2+} is absorbed across the apical membrane by the epithelial Ca^{2+} channels transient receptor potential vanilloid (TRPV) 5/6 (59, 94), located largely in the duodenum where there is little glucose absorption (58, 117). Ca^{2+} is then relayed across the cytosol by the vitamin D-dependent calbindin-D_{9K} to the basolateral membrane, where it is actively pumped into the circulation by the Ca^{2+}-ATPase. TRPV5/6 lack the voltage-sensing S4 segment present in L-type channels and are activated by hyperpolarization

in the range of –110 to –90 mV. To complicate matters further, they account for only ~15% of total absorption; the remaining 85% is widely attributed to paracellular flow on the basis of work in the absence of glucose (12). A reexamination of the mechanism of Ca^{2+} absorption under the depolarizing conditions of digestion was required.

Transcripts of an α pore-forming subunit for the nonclassical neuroendocrine L-type VDCC, $Ca_v1.3$, and an associated β_3 subunit were amplified from mucosal cDNA (87, 88). Protein expression of both was localized to the apical membrane. The relative level of $Ca_v1.3$ was minimal in duodenum and distal ileum and maximal in distal jejunum and proximal ileum; moreover, the duodenal transit time of a food bolus is just 2.5 minutes compared with 126 minutes for jejunum and ileum together (12, 88). Thus, $Ca_v1.3$ is expressed maximally in the heart of the digestive center. $Ca_v1.3$ is activated by membrane depolarization, and maximal channel opening occurs at –20 to –10 mV; $Ca_v1.3$ can therefore operate under conditions of sustained, weak membrane depolarization at low-voltage thresholds such as those generated by nutrient absorption (72, 77). Thus, at low glucose (20 mM) and when luminal Ca^{2+} concentration is the same as that for free Ca^{2+} in plasma (1.25 mM), Ca^{2+} entry in rat jejunum is sensitive to inhibitors nifedipine and Mg^{2+} and activator Bay K 8644; none of these standard L-type VDCC effectors act on TRPV5/6 (88). Repolarization of the apical membrane with phloridzin also inhibited Ca^{2+} entry.

The maximal concentration of dietary free Ca^{2+} after a meal is ~10 mM (12), so that there is a large transepithelial gradient. Ca^{2+} absorption is then stimulated some threefold in switching from 75 mM mannitol to 75 mM glucose; stimulation is blocked by nifedipine or phloridzin; the former selectively inhibits the apical GLUT2 component and level, whereas phloridzin inhibits both SGLT1 and that part of apical GLUT2 dependent on SGLT1. These data therefore support the view that, under the strongly depolarizing conditions prevailing during digestion of a meal when dietary Ca^{2+} is plentiful, $Ca_v1.3$ mediates a major route of Ca^{2+} absorption controlled by SGLT1 (87). Activation of this pathway in enterocytes after a sugar-rich meal is shown in **Figure 2**.

How then does Ca^{2+} control insertion? When glucose is transported into the enterocyte by SGLT1, a cytoskeletal rearrangement is induced, so that the enterocyte switches from a nonabsorptive to an absorptive state with respect to glucose, characterized by widening of the intercellular spaces. The cytoskeletal rearrangement involves phosphorylation of myosin II, which is mediated by myosin light-chain kinase (MLCK) (9, 24, 109). Although much emphasis has been placed on the perijunctional actomyosin ring and paracellular flow, it is noteworthy that the original paper of Madara & Pappenheimer (81) also detailed significant changes in the terminal web. Moreover, the latter is a staging post for insertion of PKC βII and apical GLUT2 (4, 47, 50, 101), which provides an alternative explanation to paracellular flow. We therefore showed at 75 mM glucose that omission of luminal Ca^{2+}, perfusion with nifedipine, phloridzin, or ML-7 (an MLCK inhibitor), or replacement of glucose with mannitol, strongly inhibited the phosphorylation of terminal web myosin II, which correlated with the strong inhibition of apical GLUT2 level and associated absorption (80). ML-7 had no effect on Ca^{2+} entry, whereas all other conditions strongly inhibited it; thus, MLCK is downstream of SGLT1 and Ca^{2+} entry by $Ca_v1.3$, which together control the cytoskeletal rearrangement essential for apical GLUT2 insertion.

Apical GLUT2 meets all the terms for physiological significance laid down by Pappenheimer for paracellular flow (see above) and so provides an alternative explanation for the diffusive component. We have tested this proposition directly in rat jejunum in four different ways (80): by investigating the absorption of mannitol (the gold standard of inert paracellular probes), net water flow (said to provide solvent drag for paracellular flow), and the absorption of Ca^{2+} (which has a molecular radius

$Ca_v1.3$: nonclassical neuroendocrine L-type voltage-dependent calcium channel (VDCC)

ML-7: an inhibitor of myosin light-chain kinase (MLCK)

much less than mannitol or glucose and is supposed to occur mainly by paracellular flow); we also studied all three in the presence and absence of ML-7, which is a specific inhibitor of MLCK and thereby blocks the cytoskeletal rearrangement. There was no change in mannitol absorption as measured by ^{14}C-tracer in switching from 75 mM mannitol to 75 mM glucose; absorption measured in this way remained at a negligible 0.28% of glucose absorption. Similarly, whereas $^{45}Ca^{2+}$ absorption increased in response to glucose, neither Ca^{2+} nor mannitol absorption were affected by ML-7. Changes in water absorption correlated with an increase in glucose absorption, but decreases in water absorption induced by ML-7 correlated only with decreases in apical GLUT2 at high glucose concentrations. Our perfusion system is a single-pass system in which a steady state of absorption is achieved in just 15 minutes. On this time scale, paracellular flow of glucose (and of Ca^{2+}) is undetectable in rat jejunum, even though glucose absorption is huge (53, 69).

Human GLUT2 cotransports just 35 mols water per mol 3-O-methylglucose compared with 210 for SGLT1 (116). Nevertheless, since the apical GLUT2 component is three- to fivefold that of SGLT1 at high glucose concentrations, GLUT2 could account for some 33% to 45% of intestinal water transport during a meal.

Intestinal Sweet Taste Receptors

The full increase in Ca^{2+} absorption induced by glucose is achieved at 20 mM glucose when there is no apical insertion of GLUT2 over the basal level (80). However, since at 75 mM glucose insertion is strongly inhibited by omission of luminal Ca^{2+}, it is apparent there is a second signal downstream of Ca^{2+} absorption that operates in the range of 30 to 100 mM glucose to control insertion. This concentration range coincides with that for activation of sweet taste receptors by simple sugars (76, 79).

The lingual T1R family of sweet taste receptors comprises T1R1, T1R2, and T1R3; the latter is a common subunit involved in the formation of T1R1+T1R3 (amino acid and umami taste) and T1R2+T1R3 (sweet taste) heterodimers (76, 86, 87, 91). T1R2+T1R3 operate through two G-protein-mediated signaling systems involving α-gustducin and/or transducin, which are linked either to phospholipase C (PLC) β2 or protein kinase A, thereby increasing intracellular Ca^{2+} and diacylglycerol or cAMP, respectively (83). When T1R2+T1R3 are expressed heterologously, natural sweeteners such as glucose, fructose, and sucrose induced maximal increases in Ca_i^{2+} at concentrations in the hundred-mM range, whereas artificial sweeteners, such as acesulfame potassium, sucralose, and saccharin did so in the low-mM range (76).

For the past decade, a major theme of nutrient sensing has been the idea that the intestine may "taste" nutrients to induce a response (32, 36, 60, 61, 97). A key early observation was that rat intestine contains brush cells, which are morphologically similar to lingual taste cells and strongly express α-gustducin (61). Following the discovery of the taste receptor families, it was reported that STC-1 enteroendocrine cells and intestine contain transcripts for some bitter taste (T2R) and sweet taste family members and T1R protein (10, 23, 35, 99).

In 2007, four papers reported functional demonstrations of intestinal sweet taste receptors (66, 75, 79, 84). The first reported that the artificial sweetener sucralose (1 mM) doubles absorption of 20 mM glucose within minutes by selectively tripling apical GLUT2 (79); on this time scale, SGLT1 was unaffected. Blocking G-protein-coupled activation of PLC β2 with U-73122 prevented the increase in apical GLUT2 induced by sucralose. Moreover, U-73122 also blocked insertion by 75 mM glucose but had no effect on the basal level at 20 mM glucose. Since sucralose did not increase absorption at 75 mM glucose, it seems that sucralose and high glucose concentrations use the same PLC β2–dependent pathway to increase apical GLUT2. Saccharin, acesulfame potassium, and sucralose increased the apical GLUT2 component of

absorption in parallel with their potency in increasing cytosolic Ca_i^{2+} in a heterologous expression system (76, 79).

Western blotting of apical membrane vesicles revealed that all the necessary taste reception components are present in rat jejunum and traffic to and from the apical membrane within minutes. Moreover, 75 mM glucose and 1 mM sucralose at 20 mM glucose caused the rapid internalization of T1R2, T1R3, α-gustducin, and PepT1 while simultaneously causing insertion of T1R1, transducin, PLC β2, and GLUT2 into the apical membrane. The rapid and reversible regulation of established transporters in strict concert with taste reception components is consistent with the presence of the latter in enterocytes.

Immunocytochemistry revealed that taste reception components are colocalized to different extents in three major sites: enterocytes, Paneth cells, and solitary chemosensory cells (SCCs) labeling with either gustducin or transducin, which therefore include enteroendocrine cells, brush cells, and bipolar SCCs (10, 102). Enterocytes contain all the necessary signaling machinery to account for the stimulation of glucose absorption by apical insertion of GLUT2 in response to high sugar concentrations and artificial sweeteners, namely all T1Rs, α-gustducin, transducin, and high levels of PLC β2 in the apical membrane along the full villus length, consistent with the PLC β2-dependent mechanism. However, because levels of other components are generally much lower than levels in SCCs, it is essential to use appropriate imaging techniques such as spectral unmixing.

The secretory granules of the Paneth cells contain colocalized T1R1, T1R3, and transducin scattered every five or so crypts. Their presence suggests they may well be involved in a rapid response to feeding after starvation (2). Their detection will depend crucially on long-term diet and how the intestine is treated before analysis; in particular, they are observed readily in glucose-perfused intestine from fed rats but rarely in nonperfused intestine.

Two subsequent papers by Margolskee and colleagues (66, 84) provided the important discovery that a taste receptor-dependent pathway can stimulate glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 secretion from human and mouse proximal gut K and L cells. In these cells, α-gustducin, T1R2, and T1R3 are colocalized to different extents; α-gustducin is also colocalized with GLP-1 and GLP-2. Of note, α-gustducin knockout mice show deficits in GLP-1 secretion and hence in the regulation of plasma insulin and glucose in response to gavage-administered glucose (550 mM). Sucralose-induced GLP-1 secretion was blocked by lactisole in the human L-cell line NCI-H716 and in the mouse GLUTag cell line by gurmarin; lactisole and gurmarin block the sweet taste receptor response in human and rodent cell lines, respectively, by inhibiting T1R3. Wild-type mouse fed for two weeks on a high-sucrose diet (70%) doubled SGLT1 mRNA, protein, and function compared with mice fed a low-sucrose (1.9%) diet containing 2 mM sucralose (84). These effects were blocked in T1R3 knockout and in α-gustducin knockout mice. The sensor controlling glucose-induced cAMP-dependent SGLT1 synthesis in sheep is therefore presumably the T1R2+T1R3 sweet taste receptor (36).

The fourth paper is therefore of particular relevance in reporting that human Caco-2/TC7 cells possess transcripts for T1R3 and α-gustducin and that T1R2/3 protein is expressed mainly in plasma membranes (75). Furthermore, a ninefold increase in SGLT1 mRNA induced by 48 hours in a fructose-containing medium was halved when T1R3 was inhibited by lactisole. Caco-2/TC7, a clonal enterocytic cell line, displays sugar sensing by metabolic-dependent, GLUT2 protein-dependent, and sweet taste receptor–dependent pathways (75, 108). It is proposed that enterocytes express all the necessary taste-signaling machinery to control physiology and nutrition in the regulation of apical GLUT2. However, as described below, there are important roles for endocrine and paracrine hormones in the regulation of intestinal sugar absorption.

GIP: glucose-dependent insulinotropic polypeptide

GLP-1 and GLP-2: glucagon-like peptides 1 and 2

K_{ATP}: ATP-dependent potassium channel

There are significant differences between the four studies; for example, jejunum in fed rat (79) and duodenum in starved mouse (66, 84). Rat duodenum does not have significant levels of apical GLUT2 and its level of SGLT1 is ~40% that in jejunum (P. Helliwell, personal communication). Thus, the regulation of glucose absorption in duodenum is quite different from jejunum, which is the digestive center of the gastrointestinal tract; indeed, with limited absorptive capacity, short length, and very rapid transit of food, duodenum appears to be more about signaling than absorption. Jejunum was perfused directly with fixed concentrations of sweeteners, whereas mouse duodenum was investigated after a gastric bolus or chow diet. Alterations in rapid protein trafficking with sugar concentration, differences in protocols, and differences in intestinal regions or clonal enterocytic cell lines on which studies were focused reveal different aspects of the physiological and nutritional importance of intestinal taste receptors.

Figure 2 summarizes the control of apical GLUT2 insertion in jejunal enterocytes after a sugar-rich meal. Membrane-depolarization by SGLT1 results in a large Ca^{2+} influx through $Ca_v1.3$, which induces a global cytoskeletal rearrangement, permitting protein trafficking through the terminal web in both directions. Further research is necessary to delineate the next steps precisely. In the simplest view, however, high concentrations of sugars, both glucose and fructose, then activate the T1R2+T1R3 receptor in the apical membrane. In unstimulated cells, both PLC β2 and PKC βII reside as inactive forms in the cytosol, but traffic rapidly to their target membrane on stimulation. In response to the taste signal, therefore, PLC β2 and PKC βII traffic to the apical membrane, where PLC β2 generates diacylglycerol to complete the activation of PKC βII, resulting in apical GLUT2 insertion. Fructose is not transported by SGLT1; however, it can in principle depolarize the apical membrane by a metabolic route through closure of K_{ATP} channels (48).

ENDOCRINE AND PARACRINE REGULATION OF SUGAR ABSORPTION

Insulin, Insulin Resistance, and Diabetes

Insulin secreted in response to a sugar-rich meal promotes lowering of blood glucose within minutes by a tenfold increase of glucose uptake by skeletal muscle and adipose tissue via GLUT4 translocation to the plasma membrane (63). Studies of insulin effects on intestinal sugar absorption have generated conflicting results over the past 60 years, and insulin action on transport was often interpreted in terms of altered metabolism (70, 95, 113).

Figure 3 shows the integration of endocrine and paracrine regulation of sugar absorption; for clarity, the enterocyte-based mechanisms shown in **Figure 2** have been omitted. Insulin binds to its enterocyte receptor (IR), resulting in rapid trafficking of GLUT2 away from both apical and basolateral membranes (108). These data were obtained in conscious mice within two hours after insulin perfusion in stable euglycemic clamp conditions. Moreover, insulin was able to prevent insertion of GLUT2 into the apical membrane, even when luminal glucose was high. Insulin attenuated transepithelial absorption, limiting the magnitude of postprandial plasma glucose excursions. These results were confirmed in vitro in human enterocytic Caco-2/TC7 cells incubated for 15–30 minutes with insulin in the presence of a fixed glucose concentration (108).

The lack of insulin and associated hyperglycemia in experimental diabetes (16) and in human diabetic patients (37) increases sugar transporter abundance. Apical GLUT2 was also dramatically increased in experimental diabetes characterized by hyperphagia, hyperglycemia, and insulinopenia; large amounts of GLUT2 were permanently located in the apical membrane, so that fructose absorption was mediated by both GLUT5 and GLUT2 (26). Thus a high rate of sugar absorption is maintained despite abnormally elevated blood glucose. In

normal rat jejunum, simultaneous inhibition and activation of the ERK and p38 pathways, respectively, resulted in fructose absorption with a diabetic phenotype (54). Apical GLUT2 in kidney cells of diabetic rats correlates with high glucose concentrations in glomerular filtrates (44).

Chow-fed, insulin-sensitive mice express apical GLUT2 transiently (**Figure 4**). However, insulin resistance can be induced by feeding a fructose-rich diet for 30 days or a saturated high-fat diet for 12 weeks (108). Impaired insulin action then results in a permanent insertion of GLUT2 in the apical membrane and cellular redistribution. The presence of GLUT2 in the apical membrane was unrelated to total GLUT2 protein. Indeed, in fructose-induced resistant mice, total GLUT2 was ~threefold greater than in fat-fed resistant mice that expressed only basal GLUT2 levels. Not only was GLUT2 present in the apical membrane of mice fasted overnight, but also insulin perfusion was unable to internalize GLUT2 in hyperinsulinemic-euglycemic clamp conditions.

Taken together, these results highlight a previously unknown hypoglycemic action of insulin on enterocytes. The end result is to smooth glycemic excursions during the course of a meal, a known risk factor for cardiovascular disease in type 2 diabetic patients (51). Defective insulin action, either by decreased pancreatic production or by tissue resistance, leads to the permanent presence of functional GLUT2 in the apical membrane of enterocytes, reinforcing lack of glycemic control in diabetes.

Leptin

Leptin released from adipose tissue and stomach in response to nutrient ingestion is delivered to the circulation and to the small intestinal lumen. Leptin receptors are expressed at the apical and basolateral membranes of enterocytes (8). Leptin inhibits active transport through a reduction in SGLT1 in the apical membrane but does not affect apical GLUT2-dependent glucose uptake (34, 65).

Paracrine Hormones

Cheeseman and colleagues have already provided significant insights into the paracrine regulation of sugar absorption, particularly by GIP and proglucagon-derived peptides GLP-1 and GLP-2 (4, 20, 22). **Figure 3** shows that luminal sensing may occur through taste receptor-, SGLT1-, SGLT3-, and metabolic K_{ATP}-based sugar sensors (42, 48, 66). GIP is secreted from K cells predominantly in duodenum, and GLP-1 and GLP-2 are secreted simultaneously from L cells predominantly in ileum in response to GIP (6). Nevertheless, L cells are scattered through the more proximal regions of intestine and possess a thin process extending to the luminal surface for the sampling of sugars. Proximal secretion may contribute to the early phase of GLP-1 release (**Figure 3**), which is more usually attributed to GIP-induced vagal stimulation of ileal L cells.

GLP-2R: glucagon-like peptide-2 receptor

GLP-2 receptors are abundant in the upper small intestine, but there seems no convincing evidence for GIP, GLP-1, or GLP-2 receptors (GLP-2R) on jejunal enterocytes themselves (**Figure 3**). In rat, GLP-2Rs are localized to vagal afferents, enteric neurons, and 5-hydroxytryptamine-positive enteroendocrine cells (90). GLP-2 rapidly stimulates apical GLUT2 insertion in jejunum within minutes (**Figure 3**), as shown by vascular infusion in vivo in the absence of luminal glucose (4). Interestingly, vascular GLP-2 has no effect in a dual luminally and vascularly perfused preparation, in which the neural route of control seems unavailable, but luminal glucose has an effect similar to that of GLP-2 in vivo. Cheeseman therefore argued that glucose can exert a direct effect on enterocytes to upregulate apical GLUT2 independently of GLP-2 (4). GLP-2 also upregulates basolateral GLUT2 transport within 2–6 hours through effects on GLUT2 intrinsic activity and level (not shown in **Figure 3**) (21, 22). Vascular infusion of GIP in rats has similar effects to GLP-2, the effects being completely blocked by GLP-2 antibodies; GLP-1 on the other hand has no effect (21, 22). GLP-2 also increases the apical level of SGLT1 (**Figure 3**); however, the process

WAS: water avoidance stress

is much slower than for GLUT2 trafficking, taking at least one hour under optimal conditions (20). Upregulation of SGLT1 is most likely mediated by synthesis and dependent on cAMP, which diminishes total GLUT2 levels (20). Cholecystokinin-8 (CCK-8) rapidly inhibits SGLT1 by reducing its abundance at the apical membrane; although it therefore seems clear that SGLT1 can traffic to and from the membrane, conditions have yet to be found under which trafficking is regulated on a time scale of minutes by glucose. CCK-8 does not seem to be involved in apical GLUT2 translocation (57).

GLP-1 acts to inhibit gastric emptying in vivo (6), thereby slowing nutrient delivery. Moreover, GLP-1 and GIP may exert their incretin effect to enhance insulin secretion, which induces internalization of GLUT2 away from the apical and basolateral membranes (108). These actions combine to diminish transepithelial sugar transport significantly. In contrast, GLP-2 promotes apical GLUT2 translocation by indirect action through GLP-2R (4), but the precise route of control is unknown. These antagonistic effects can be reconciled by assuming that the end result is to maintain glucose homeostasis during a sugar-rich meal. GLP-2 might therefore function as a gatekeeper to inform the proximal intestine that transport capacity is insufficient to clear ingested sugar from the gut lumen; such action would provide a safety factor to help prevent sugars from reaching the colon, where they would cause bacterial overgrowth and osmotic diarrhea. In keeping with this view, chronic GLP-2 administration during total parenteral nutrition in piglets strongly upregulates SGLT1 in ileum (**Figure 3**) but downregulates apical GLUT2, possibly by a reduction in luminal sugar reaching the ileum (27).

Stress and Glucocorticoids

A classical response to chronic stress is elevated plasma corticosterol, which is associated with gastrointestinal disorders of various intensities. Environmental stress created by perturbed housing conditions inhibited the apical GLUT2-component of glucose absorption while preserving the SGLT1 component (103); this effect was mimicked by pretreatment of the animals with dexamethasone. These results differ from those produced by water avoidance stress (WAS) (11) or long-term (phase III) starvation and refeeding (50). WAS-induced reduction of energy-dependent transport by SGLT1 was attributed to alteration of Na^+K^+/ATPase activity since SGLT1 protein levels were unchanged. However, GLUT2-mediated transport was severalfold higher in WAS than in controls because of a large increase in apical GLUT2 localization. In phase III fasted rats, protein catabolism increased glucose absorption via SGLT1; refeeding of these animals rapidly recruited GLUT2 to the apical membrane (50). Increased SGLT1 in phase III fast may thus prepare intestine for immediate glucose absorption on refeeding. This stress effect is transient; for SGLT1, protein decreased with falling plasma corticosterone concentration. Both conditions resulted in reciprocal regulation of energy-dependent SGLT1 and energy-independent GLUT2-mediated transport. Stress caused by energy depletion effects can be mimicked by the use of 5-aminoimidazole-4-carboxamide riboside, an AMP-activated protein kinase (AMPK) activator. In this case, the adenosine monophosphate-to-adenosine triphosphate ratio increases and AMPK activity rises, so that GLUT2 translocates to the apical membrane and glucose absorption increases strongly and rapidly when luminal sugar becomes available; however, total SGLT1 is markedly reduced within 30 minutes, effecting a marked shift toward energy-independent absorption (111). Distinct mechanisms apparently develop in response to different stresses.

NUTRITION AND GLUT2

Widespread Species Distribution of Apical GLUT2

Since its discovery in rat (69), apical GLUT2 has been reported for mice (45), sheep

(J. Aschenbach, personal communication), pig (27), and recently insects (18). Moreover, brush-border system 2 in guinea pig (15) is now thought to be apical GLUT2. It has also been found in human intestinal Caco-2 cell lines (74, 108), but appropriate conditions to detect apical GLUT2 in human small intestine remain to be reported (37). Interestingly, GLUT2 also traffics in the epithelium of the kidney proximal tubule to enhance glucose reabsorption (44). The widespread distribution of apical GLUT2 argues strongly for the nutritional significance of GLUT2 trafficking in the adaptation of sugar absorption.

Genetic Alteration of Intestinal Sugar Transporters

The nutritional and physiological role of apical GLUT2 was confirmed in studies comparing fructose absorption in intestinal rings from normal and GLUT2-null mice (45). When wild-type mice were given a gastric bolus of simple sugars (fructose, glucose, or sucrose) after an overnight fast, there was a large increase in insertion of apical GLUT2 and associated absorption within 30 min, provided that mice were first adapted to a long-term fructose- or glucose-rich diet. The increase did not happen in GLUT2-null mice, which showed only the same level of GLUT5-mediated fructose absorption as observed for wild-type mice in the presence of the specific GLUT2 inhibitor cytochalasin B. Analogous results were obtained for glucose absorption in apical membrane vesicles. The maximal GLUT2-mediated fructose or glucose absorption was some threefold greater than that by GLUT5 and SGLT1, respectively.

Genetic defects can alter transepithelial sugar transport at both apical and basolateral membranes. Strikingly, GLUT2-deficient patients do not appear to display sugar malabsorption (100); indeed, Fanconi-Bickel patients, like GLUT2-null mice (105), may release glucose from enterocytes by a microsomal membrane transport pathway. This exit pathway was estimated to represent about 15% of total transport in wild-type mice; in conditions of low sugar intake, therefore, this pathway seems likely to compensate for GLUT2 deficiency.

SGLT1 mutations underlying glucose-galactose malabsorption cause severe diarrhea and dehydration in human infants (114). The therapy for these sugar-intolerant patients is to withdraw all dietary glucose and galactose. Other pathways can depolarize the apical membrane, for example, H^+/peptide and Na^+/amino acid cotransport, and thereby increase the Ca^{2+} absorption necessary for cytoskeletal rearrangement. The translocation of GLUT2 into the apical membrane that might compensate for the lack of Na^+/glucose cotransport has not yet been reported. However, other depolarizing nutrients may not be able to provide the downstream taste receptor signal for insertion or they may not be present at an appropriate concentration; glucose, for example, promotes insertion at high but not low concentrations.

Fructose is an activator of GLUT2 trafficking in mice (45). In glucose-galactose malabsorption and Fanconi-Bickel syndrome, fructose absorption is normal. By analogy with pancreatic β-cells and GLUTag cell lines, fructose could depolarize the apical membrane through closure of K_{ATP} channels (48) and can, of course, provide a taste signal (**Figure 2**). Interestingly, defects in the GLUT5 gene have not been reported to explain human fructose malabsorption (112). However, the possibility cannot be excluded that defects in GLUT5-mediated transport are compensated for by apical GLUT2.

Total Parenteral Nutrition

Total parenteral nutrition (TPN) is often required to prevent malnutrition and dehydration when the enteral route is clinically prohibited (for example, through feeding intolerance in premature infants). TPN provides nutrients only to the basolateral side of enterocytes, but leads to adverse effects by rapidly provoking intestinal atrophy; such behavior underlines the necessity of understanding the differences

TPN: total parenteral nutrition

between luminal and basolateral nutrient signals.

Vascular or luminal glucose concentration upregulates enterocyte basolateral membrane transport in 4–8 hours, probably as a consequence of gene transcription and new protein synthesis (21, 22). In rat pups fed a high-fructose or -glucose diet for five days, GLUT2 mRNA abundance was enhanced in intestine and bypassed segments (Thiry-Vella loops), indicating that systemic factors increased expression (29). Consistent with these observations, basolateral provision of glucose or fructose to Caco-2/TC7 cells enhanced GLUT2 mRNA promoter activity (75). Although dietary sugars increase apical GLUT2 insertion (reviewed in 68), vascular perfusion of glucose designed to mimic hyperglycemia in diabetes does not seem to induce apical GLUT2 location (C.I. Cheeseman, personal communication).

TPN-induced mucosal atrophy is associated with diminished SGLT1 expression. In contrast, apical GLUT2 is strongly enhanced in parenterally fed piglets, but glucose fluxes are reduced (27). The discrepancy might reflect the difficulty of comparing very different membrane samples because parenteral nutrition provokes marked atrophy. The intestinotrophic properties of GLP-2 have been shown to prevent mucosal atrophy and reduced nutrient absorption caused by lack of luminal nutrient stimulation during TPN. In TPN-fed piglets, apical GLUT2 abundance in jejunum was high and remained unchanged by GLP-2 treatment. GLP-2, however, increased glucose and galactose absorption, consistent with increased SGLT1 and reduced glucose utilization (25, 27). Apical GLUT2 translocation does not participate in the intestinotrophic effect of GLP-2.

Natural and Processed Foods: Artificial Sweeteners

In the Western diet, simple dietary sugars are provided by honey, fruits, vegetables, and processed foods, such as syrups, candies, cakes, table sugar, and fizzy drinks. Consumption of a fructose-rich meal by unanesthetized wild-type mice promotes apical GLUT2 insertion, so that simple sugar absorption can triple within minutes in mice (45); a similar recruitment of GLUT2 to the apical membrane was seen with sucrose, but dietary glucose appeared less efficient than fructose at increasing tissue uptake. In sharp contrast, a low-glycemic-index diet, i.e., one containing little carbohydrate or primarily complex carbohydrate that releases absorbable simple sugars only slowly during membrane hydrolysis, fails to induce recruitment of apical GLUT2 and, furthermore, blocks the rapid induction of apical GLUT2 by a sugar bolus (45).

The concentration of sugars generated at the apical membrane during hydrolysis of digestion products, such as disaccharides and α-limit dextrins, bears directly on the physiological role of the diffusive component. In rat, indirect estimates of maximal concentrations range from less than 48 mM (38) to as much 300 mM (92). Taste receptors operate in the 100-mM range: Stimulation of T1R2+T1R3 by simple sugars at 30 and 100 mM corresponds to 15% and 85% of the maximal increase in Ca_i^{2+} in a heterologous expression system (76). These concentrations coincide with those observed independently for apical GLUT2 induction by T1R2+T1R3 in perfusions (69, 79), confirming that such concentrations must be routinely generated at the apical membrane during digestion. In this context, the local buildup of sugar concentration in the vicinity of transporters and sensors is important. It has been proposed that the glycocalyx might play a role in its ability to cause the retention of sugars and electrolytes (3, 13). Thus, apical GLUT2 might well mediate disaccharidase-related transport (96); moreover, ingestion of complex sugar with a low glycemic index might avoid a steep rise of simple sugars in the lumen, keeping concentrations at the vicinity of the membrane below required levels for GLUT2 trafficking. Interestingly, a physiological shift from suckling to weaning in rat, which is characterized by a change from lipid- to carbohydrate-rich food, is associated with increased apical GLUT2

consistent with a switch from a low to a high luminal sugar concentration (5).

The Western diet has been considerably enriched in high-glycemic-index sugars, especially by the addition of high-fructose corn syrups in processed foodstuffs. Such a diet can result in indiscriminate ingestion of readily absorbable sugars. The chronic ingestion of a sugar-rich diet in rodent increases the expression of proteins required for sugar absorption (45, 71, 85). Furthermore, the GLUT2 component of sugar absorption is increased in mice fed a sugar-rich diet for five days (45). In GLUT2-null mice, the missing transport capacity could not be compensated fully by the increased expression of SGLT1 or GLUT5 in response to sugar-rich diets. Consistent with reduced absorptive capacity in upper jejunum, GLUT5 was increased in ileum. Long-term dietary adaptation primes jejunum for acute induction of apical GLUT2-mediated sugar absorption.

Artificial, nonabsorbable sugars are used as calorie-free sweeteners in processed foods for human consumption on the assumption that they are nutritionally inert. Replacement of simple sugars in processed foods is normally partial, since some natural sugar is required to maintain bulk and mouth feel. The affinities of taste receptors for artificial sweeteners are some hundredfold greater than for natural sugars (76); moreover, natural and artificial sweeteners can bind simultaneously to taste receptors to activate downstream targets synergistically (106). In intestine, activation of T1R2+T1R3 by sucralose and low concentrations of glucose drives GLUT2 to the apical membrane, increasing glucose absorption within minutes (79). On a time scale of hours in human Caco-2/TC7 cells, activation of T1R2+T1R3 by fructose stimulated SGLT1 and GLUT5 but not GLUT2 expression, indicating selectivity of activating pathways (75). In agreement with this finding, sucralose added to a low-sugar mouse chow for two weeks increased SGLT1 protein and mRNA expression (84).

The consequences for obesity and diabetes of the fact that artificial sweeteners are not in fact inert, but signal to a major food-sensing system to exert short-term (trafficking) and long-term (transcriptional) stimulation of sugar absorption, are open to debate. On one hand, it is argued that GLP-1 release may increase insulin secretion so that manipulation of intestinal taste receptors might offer valuable opportunities for beneficial intervention as alternatives to development of GLP-1 receptor agonists (66). On the other hand, poor eating habits, such as "grazing" on processed foods containing both simple sugars and artificial sweeteners, may result in repeated and increased plasma glucose/insulin excursions, which will ultimately promote increased sugar uptake and fat storage by adipose tissue. The development of insulin-resistance and permanent apical GLUT2 in mice fed a fructose-rich diet suggest that the latter is the dominant mechanism in normal animals (108).

Similar considerations apply to gastric emptying, which varies inversely with dietary calories and is a significant determinant of glycemia. Thus, activation of sweet taste receptors by a diet rich in simple, caloric sugars stimulates GLP-1 release, which inhibits gastric emptying. What happens, then, if dietary sugar is partially replaced by artificial sweeteners? An indication of the answer may be provided by a study in which male human volunteers consumed a fixed measure of vodka mixed with either a regular mixer to give a total of 478 kcal or a diet mixer to give a total of 225 kcal (115). Gastric emptying for the diet mixer drink was almost twice as fast as that for the regular mixer, resulting in an increase in the peak blood alcohol concentration of 56%. GLP-1 release was not reported for this study.

If the above findings were to be confirmed in human with the necessary level of detail, then even though a review of 16 recent, carefully controlled 12-week studies concludes that substitution of sucrose in soft drinks with artificial sweeteners reduces calorie intake by about 10% (30), it is conceivable that substitution could have the opposite effect to that intended in the longer term. Nevertheless, there seems little evidence that artificial sweeteners reduce the

overall caloric intake in many of those who use them in the uncontrolled conditions of daily life. A more pressing scenario might therefore be where poor eating habits mean that large volumes of fizzy drinks containing artificial sweeteners are consumed indiscriminately with a carbohydrate-containing diet, for example, diet cola and fries. The importance of this question is such that it clearly deserves clinical investigation. Although limited clinical studies did not reveal adverse effects of high doses of artificial sweeteners (49), new investigations should now be considered in the light of recent advances.

A closely related phase II clinical trial, based on apical GLUT2, is therefore of particular interest (89). The clinical trial aims to establish whether quercetin, an inhibitor of GLUT2, exerts antihyperglycemic effects in humans. Fruit, vegetables, and red wine provide the main sources of dietary polyphenols (98); quercetin, a naturally occurring flavonoid in human diet, strongly inhibits apical GLUT2-mediated sugar uptake in Caco-2E cells (74). When ingested with glucose, quercetin diminishes hyperglycemic excursions by 40% in diabetic Zucker fa/fa rats that express apical and basolateral GLUT2 (104). SGLT1 and GLUT2, but not GLUT5, transport activities were inhibited by quercetin (73, 74). Whether inhibition of SGLT1 activity by quercetin then affects the apical location of GLUT2 remains to be investigated.

SUMMARY POINTS

1. This review is centered on the short-term regulatory events that occur within minutes during assimilation of a sugar-rich meal. The physiological role of apical GLUT2 is to provide a major pathway of absorption at high sugar concentrations as the limited capacity of SGLT1 is exceeded.
2. There is evidence for sensing roles for SGLT1, SGLT3, K_{ATP} channels, and Ca^{2+}, to which the discovery of functional roles for intestinal taste receptors in enterocytes and enteroendocrine cells add a powerful new dimension. Luminal, basolateral, and metabolic sensors play different roles.
3. Control of sugar absorption by sugars is exerted at the level of enterocytes and through endocrine and paracrine hormones, endocytosis, and gastric emptying. It is necessary to understand the systems biology of intestine, how the multiplicity of mechanisms essential for a single organ that mediates the input side of homeostasis operates and interacts under different conditions.
4. New insights into how nutrition controls sugar absorption include how simple sugars and complex carbohydrates regulate apical GLUT2, the fact that high-sugar or -fat diets lead to insulin resistance characterized by permanent apical GLUT2, and the realization that artificial sweeteners signal through taste receptors to stimulate sugar absorption.

FUTURE ISSUES

1. How do the multiple systems involved in absorption interact? How does absorption of one nutrient affect that of another?
2. What are the detailed signaling mechanisms controlling absorption, and how do they fail in disease, especially in obesity and diabetes?

3. What other roles do intestinal taste receptors have; for example, do they control food intake, and is intake causally related to absorption?
4. What are the clinical consequences of partial replacement of sugars with artificial sweeteners in processed foods? How do different dietary components such as polyphenols and artificial sweeteners interact through effects on apical GLUT2? What are the possibilities for beneficial dietary and pharmaceutical intervention?

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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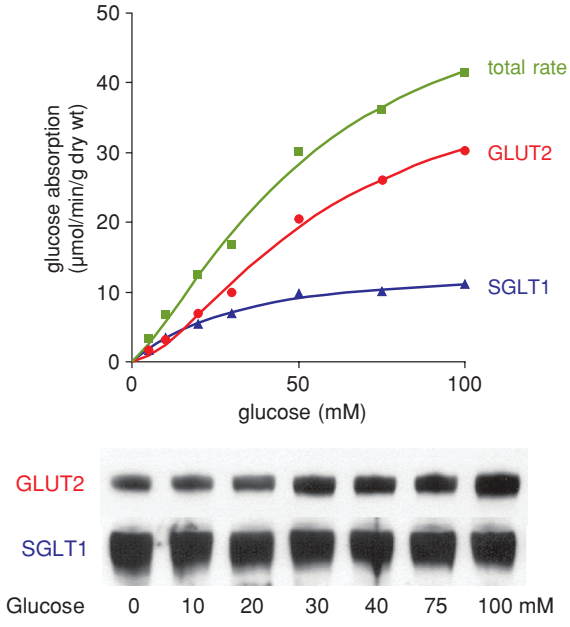

Figure 1

Apical glucose transporter type 2 (GLUT2) provides a major, diffusive pathway of glucose absorption in vivo. (*Top panel*) Jejunum was perfused with glucose in fed rats in vivo. Total absorption was resolved into two components mediated by the sodium-dependent glucose transporter 1 (SGLT1) and apical GLUT2. (*Bottom panel*) Western blots of apical membrane vesicles reveal that GLUT2 insertion increases with glucose concentration; SGLT1 is unchanged. Figure reproduced with permission from (69).

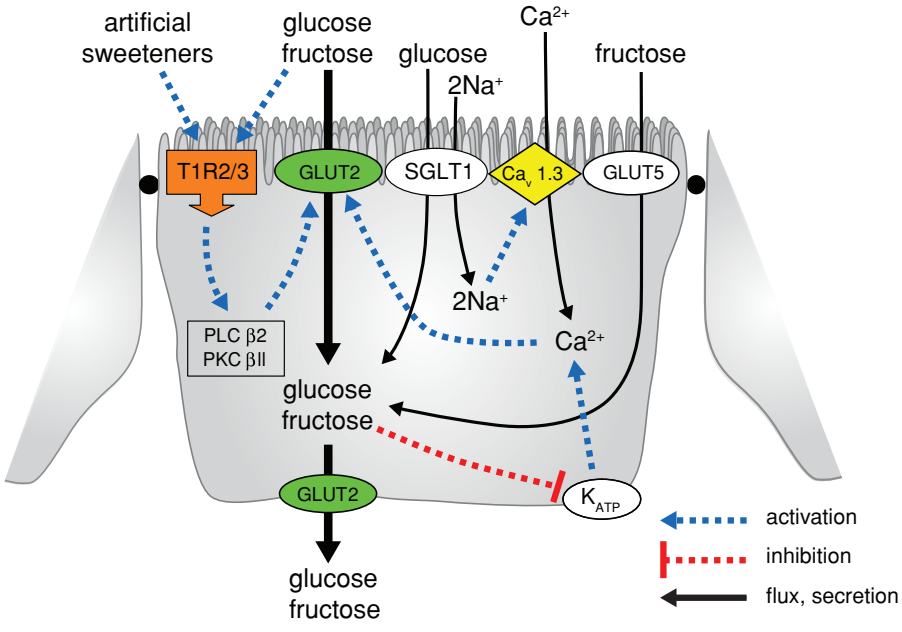

Figure 2

Regulation of apical GLUT2 in enterocytes by calcium and taste receptors. GLUT, glucose transporter; PKC, protein kinase C; PLC, phospholipase C; SGLT, sodium-dependent glucose transporter.

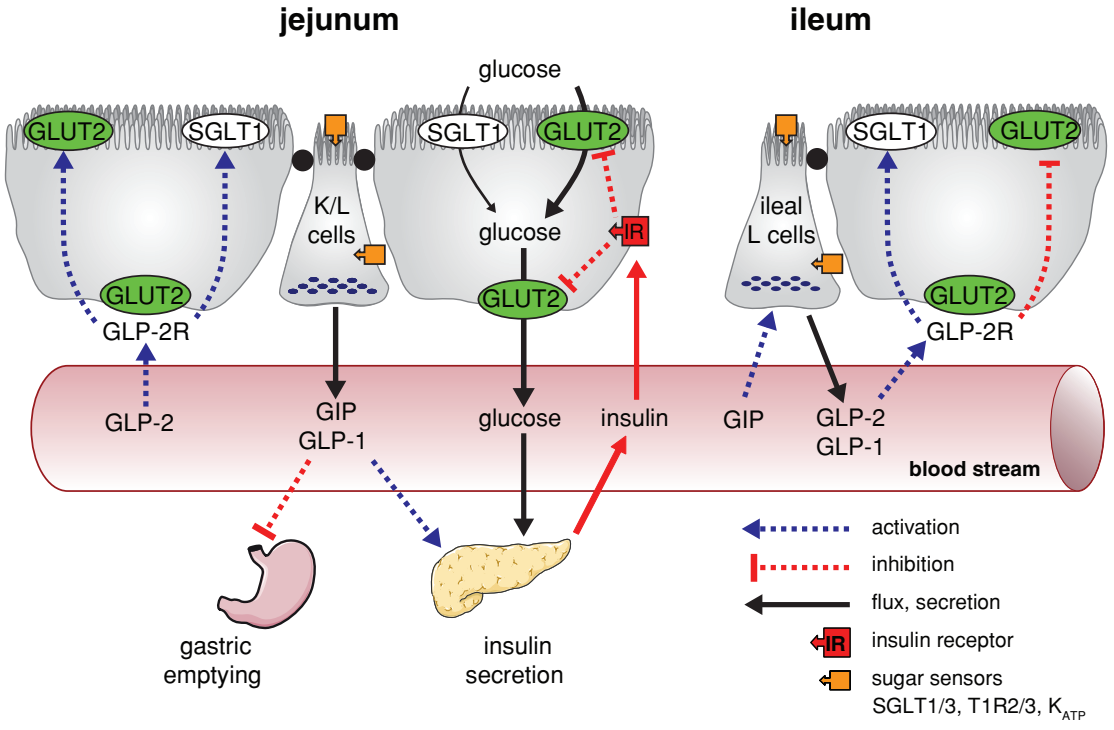

Figure 3

Endocrine and paracrine regulation of intestinal sugar absorption. GIP, glucose-dependent insulinotropic polypeptide; GLUT, glucose transporter; SGLT, sodium-dependent glucose transporter.

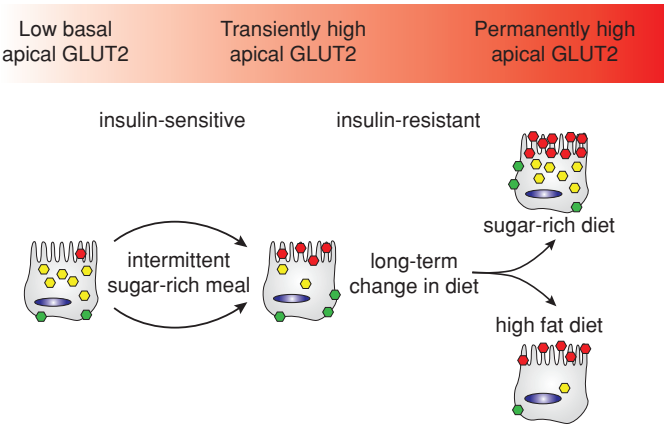

Figure 4

Development of insulin resistance in response to dietary sugar and fat results in permanent apical glucose transporter type 2 (GLUT2). *Red pentagons* denote apical GLUT2; *yellow pentagons*, internalized GLUT2 in vesicles; *green pentagons*, basolateral GLUT2.

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Errata

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