Perspectives in Diabetes

Apical GLUT2

A Major Pathway of Intestinal Sugar Absorption

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Understanding the mechanisms that determine postprandial fluctuations in blood glucose concentration is central for effective glycemic control in the management of diabetes. Intestinal sugar absorption is one such mechanism, and studies on its increase in experimental diabetes led us to propose a new model of sugar absorption. In the apical GLUT2 model, the glucose transported by the Na^+/glucose cotransporter SGLT1 promotes insertion of GLUT2 into the apical membrane within minutes, so that the mechanism operates during assimilation of a meal containing high–glycemic index carbohydrate to provide a facilitated component of absorption up to three times greater than by SGLT1. Here we review the evidence for the apical GLUT2 model and describe how apical GLUT2 is a target for multiple short-term nutrient-sensing mechanisms by dietary sugars, local and endocrine hormones, cellular energy status, stress, and diabetes. These mechanisms suggest that apical GLUT2 is a potential therapeutic target for novel dietary or pharmacological approaches to control intestinal sugar delivery and thereby improve glycemic control. *Diabetes* 54:3056–3062, 2005

Diabetes management is directed toward control of postprandial fluctuations or excursions in blood glucose, which reflect the relative rates of delivery from the intestine and disposal to the tissues. While much is known about the impact of disposal mechanisms on blood glucose, rather less is known about delivery mechanisms, including gastric emptying, membrane hydrolysis, and sugar absorption itself.

Intestinal sugar absorption is increased in experimental diabetes (1–3). Knowledge of sugar absorption has been based primarily on the mechanism of Na^+/glucose cotransport by SGLT1 and its long-term regulation by diet (4). Recently, however, we have discovered a new pathway of sugar absorption, the apical GLUT2 pathway, which operates within minutes when high concentrations of primary digestion products, i.e., sugars, disaccharides, and α-limit dextrins, are presented to or generated at the apical membrane of the small intestine (5–7). This process is reversed when these sugars are absent from the lumen in vivo. The first indication of the existence of this mechanism was obtained in a study of the increase in fructose absorption in experimental diabetes (8). Here we review the evidence for the apical GLUT2 model, which is a target of multiple short-term nutrient-sensing mechanisms involving dietary sugars, local hormones, cellular energy status, stress, and diabetes.

THE CLASSICAL MODEL OF SUGAR ABSORPTION

Dietary glucose crosses the apical membrane of the enterocyte by the Na^+/glucose cotransporter (SGLT1) and exits across the basolateral membrane through the facilitative transporter GLUT2 (9). Plasma glucose is maintained at ~5 mmol/l. When the glucose concentration in the lumen is lower than in plasma, SGLT1 transports glucose uphill against its concentration gradient. This transcellular pathway is powered by a downhill gradient of Na^+ across the apical membrane, maintained by the basolateral Na^+/K^+-ATPase. The cloning of SGLT1 by Wright's laboratory (10) and GLUT2 by Thorens' laboratory (9) began the molecular biological era of intestinal nutrient transport

Dietary fructose is transported across the apical membrane by a specific facilitative transporter, GLUT5 (11). In intact intestine, GLUT5 is so specific for fructose that its transport is not inhibited by a 100-fold excess of glucose. GLUT2 in the basolateral membrane, however, transports both glucose and fructose, providing a common exit pathway into the blood (12). Fructose is rapidly cleared from the blood, keeping the effective circulating concentration low. The concentration of fructose against a gradient is not necessary; the entry of fructose is therefore ensured by GLUT5, a facilitative transporter, rather than by an active transport system.

The classical model of intestinal glucose absorption is elegant in its sheer simplicity and effective in its ability to explain glucose absorption in many conditions, most notably at low concentrations of glucose or in experiments using in vitro preparations of intestine, in which the lack of vascular clearance causes tissue accumulation. However, it fails to explain absorption at high glucose or fructose concentrations when SGLT1 and GLUT5, respectively, are saturated.

THE DISCOVERY OF GLUT2 AT THE APICAL MEMBRANE

In the classical model, GLUT2 has an exclusively basolateral location; nevertheless, GLUT2 was first located at the apical membrane in a diabetic rat model (8). The initial objective of those experiments was to investigate the

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AMPK, AMP-activated protein kinase; BBS, brush-border system; GLP, glucagon-like peptide; PKC, protein kinase C.

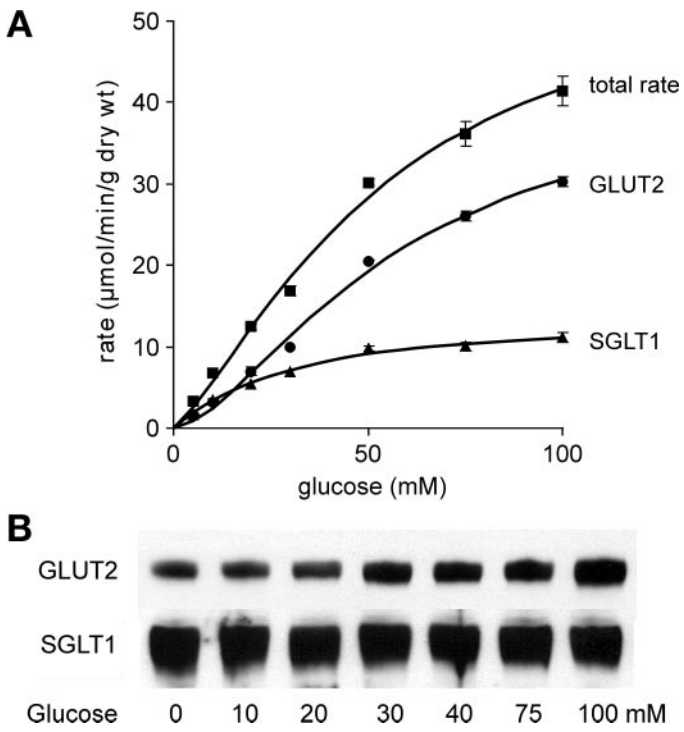

FIG. 1. Apical GLUT2 provides a major route of glucose absorption in vivo. *A*: Jejunum from rats maintained on a diet containing carbohydrate was perfused in vivo with glucose in the absence and presence of phloretin. At high glucose concentrations, the phloretin-sensitive GLUT2-mediated component (●) is almost three times that of the phloretin-insensitive SGLT1-mediated component (▲). The sum of the two components gives the total rate of absorption (■). *B*) Western blots of apical membrane vesicles reveal that GLUT2 insertion increases with glucose concentration; SGLT1 is unaltered. Reproduced with permission (ref. 7).

effect of diabetes on fructose absorption by GLUT5 in jejunum. Diabetes enhanced fructose absorption by ~60%. However, this increased absorption was strongly inhibited in either whole intestine or vesicles by glucose, phloretin, or cytochalasin B, suggesting the presence of a member of the facilitative transporter family at the apical membrane. The only transporters known to transport fructose were GLUT5 and GLUT2, but only GLUT2 is inhibited by glucose, phloretin, or cytochalasin B. Apical membrane vesicles from diabetic rats revealed not only GLUT5, but also large amounts of GLUT2 protein. In contrast, normal rats did not reveal significant apical GLUT2 (but see below). Thus, targeting of apical GLUT2 appeared to reflect the pathology of diabetes.

Could we convert normal intestine to display a "diabetic" phenotype by perfusion of fructose with effectors of protein kinase C (PKC)-, extracellular signal–related kinase–, p38-, and phosphatidylinositol 3-K–dependent pathways? Significant progress revealed alterations in the intrinsic activities of GLUT5 and GLUT2 over a five- and ninefold range, respectively, between different conditions (5,6). Most excitingly, in several sets of conditions, large amounts of GLUT2 were inserted into the apical membrane by trafficking from an internal pool to produce large changes in fructose transport (5). In particular, perfusion with the PKC activator phorbol myristic acid rapidly stimulated fructose transport by causing a fourfold increase in the level of apical GLUT2 without change in GLUT5 (6). Apical GLUT2 insertion correlated with the activation of the conventional isoform PKC βII. All regulation happened within the 30 min necessary to ensure that effectors had time to act; thus, we were looking for the first time at the short-term regulation of fructose transport in intestine.

Why was GLUT2 not detectable earlier in the apical membrane by immunocytochemistry? Thorens et al. (9) cloned and localized GLUT2 to the basolateral membrane using antibody to the COOH-terminal sequence, which did not detect GLUT2 at the apical membrane. We have confirmed these results (13), which suggest that the COOH-terminal of apical GLUT2 is masked. Fortunately, antibody to a sequence within the large extracellular loop between transmembrane domains 1 and 2 readily detects apical GLUT2; the immunocytochemical results then correlated with the functional data (13–15). Masking of GLUT2 COOH-terminal could occur by interaction with regulatory proteins or by phosphorylation, which regulates GLUT2 intrinsic activity (16,17).

Could experimental design lead to a failure to detect apical GLUT2? Early in this work, we adopted procedures to prevent rapid changes in trafficking occurring during membrane vesicle isolation: jejunum was flushed with ice-cold perfusate and vesicles isolated exclusively at 4°C. Two crucial results followed immediately. First, experiments revealed GLUT2 present in the apical membrane even in normal jejunum in vivo. We could therefore no longer view apical GLUT2 simply as a pathological phenomenon associated with diabetes; it must have an important physiological function. Second, if intestine were flushed with warm perfusate, then, as jejunum was excised before vesicle preparation, most GLUT2 was lost from the membrane within minutes; this occurred because PKC βII was rapidly inactivated by removal from activating sugars and local hormones. Failure to arrest GLUT2 trafficking was a second reason why we had not detected this component before in normal intestine during the diabetes work (8).

Could apical GLUT2 provide an explanation for the long-known, stereospecific diffusive component attributed to paracellular flow described in in vivo studies but not in most in vitro preparations of intestine? Absorption for both animals and humans in vivo continues to increase in an apparently diffusive fashion up to concentrations as high as 200 mmol/l (revs. in 18,19). Debnam and Levin (20) reported that absorption in vivo comprises two components: the first is a saturable, phloridzin-sensitive component mediated by SGLT1, the second a nonsaturable phloridzin-insensitive diffusive component, some three times greater than the active component. Pappenheimer and Reiss (18) attributed the diffusive component to paracellular solvent drag through tight junctions. We have now demonstrated that this component is due to apical GLUT2 (7,21).

Could apical GLUT2 also explain the brush-border system (BBS)2 component described in guinea pig intestine? Glucose transport in guinea pig and pig brush-border membrane vesicles comprises two systems (22,23); BBS1 is a high-affinity transporter identified with SGLT1, whereas the low affinity BBS2 is sensitive to cytochalasin B, a facilitative transport inhibitor, but not to α-methylglucoside, a highly specific SGLT1 substrate. The lack of a species-specific antibody means that BBS2 has not been formally identified with GLUT2. Nevertheless, it is noteworthy that BBS2 is abolished by starvation (24) and increased in pig intestine by a glucose-rich diet (25). Although BBS2 showed some Na^+ dependence, probably

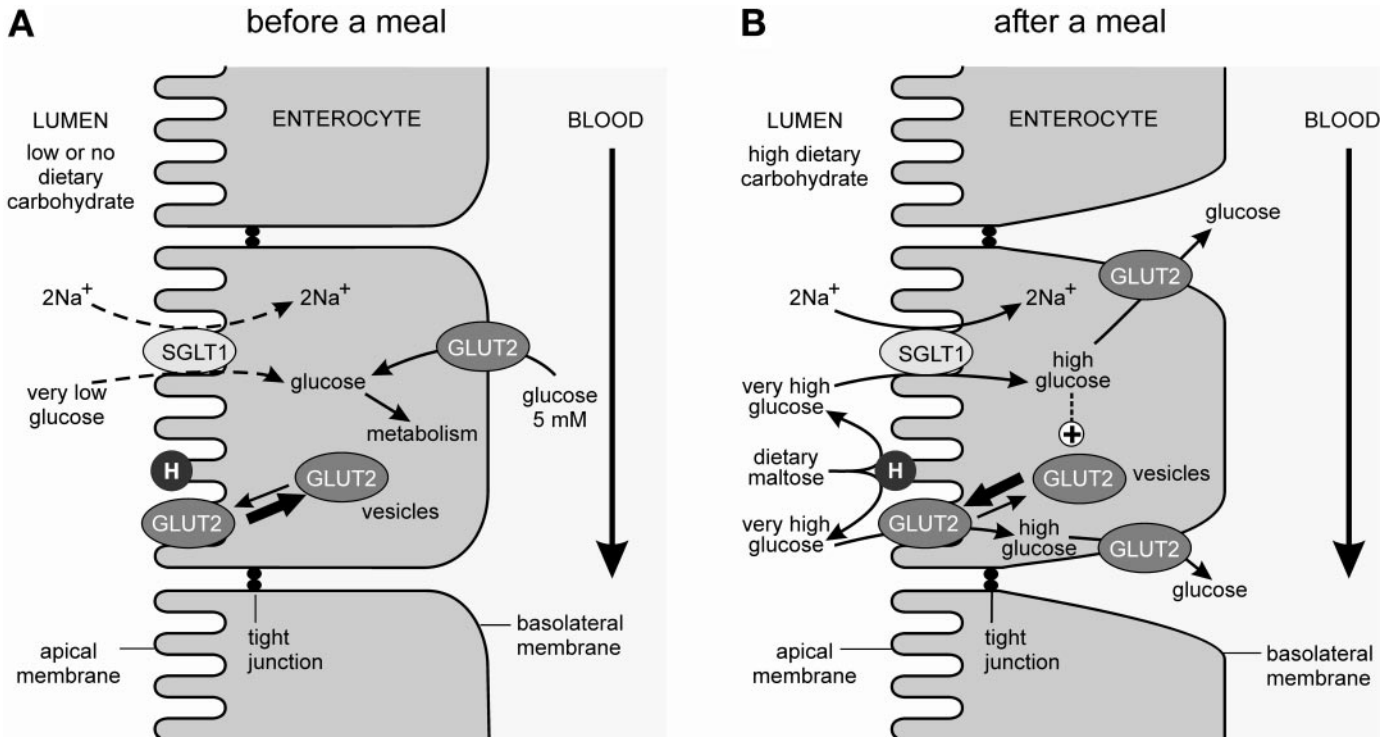

FIG. 2. The apical GLUT2 model of intestinal glucose absorption before (*A*) and after (*B*) a meal. See REGULATION OF SUGAR ABSORPTION DURING AND BETWEEN MEALS for explanation. H, hydrolase.

due to a contribution of SGLT1 to insertion, its other features are close to those of GLUT2. Our recent findings therefore suggest that BBS2 should be reassessed as GLUT2.

How do the kinetic properties of GLUT2 modulate apical glucose absorption? Two components of absorption are observed as a function of glucose concentration. The high affinity, low capacity SGLT1 shows a saturation response (Fig. 1*A*), with no change of SGLT1 protein level in our experiments (Fig. 1*B*). The low-affinity, high-capacity GLUT2, however, was not saturated and gradually accounted for the major part of absorption as high glucose concentrations were reached. Detailed analysis revealed that the concentration dependence of GLUT2 response to glucose is in fact cooperative because both activation of GLUT2 and its protein level in the apical membrane increase with glucose concentration. The data clearly show that GLUT2 and SGLT1 together effectively accounted for total glucose absorption (7,21).

REGULATION OF SUGAR ABSORPTION DURING AND BETWEEN MEALS

The apical GLUT2 model is illustrated in Fig. 2. Before a meal (Fig. 2*A*), the concentration of glucose in the lumen is much less than that of 5 mmol/l in plasma. Any glucose is rapidly captured by SGLT1, which is ideal for this purpose, being a low-capacity, high-affinity transporter and the only transporter capable of moving glucose against a concentration gradient. GLUT2 is a high-capacity, low-affinity facilitative transporter that equilibrates glucose between plasma and enterocyte. Hence, when there is little glucose in the lumen before a meal, GLUT2 is very low at the apical membrane (Figs. 1*B* and 3) and basolateral GLUT2 operates in the opposite direction to supply glucose from the blood and maintain the energy requirements of enterocytes (Fig. 2*A*). Even when there is little glucose in the lumen before a meal, there may be some GLUT2 at the apical membrane in vivo (Figs. 1*B* and 2*A*). In principle, apical GLUT2 in this situation could lead to disastrous secretion of glucose, since the gradient is downhill from plasma to lumen. This is avoided or minimized by several factors: apical GLUT2 is diminished at low luminal glucose concentrations and is lost completely after an overnight fast (Fig. 3); the intrinsic activity of any residual GLUT2 is low, and glucose is rapidly utilized through the very active glycolytic pathway. Any secreted glucose is rapidly recycled up the concentration gradient by SGLT1. Secretion of glucose in rat jejunum has been clearly demonstrated. It is consistent with apical GLUT2, since the rate of secretion is proportional to the difference in glucose concentration between blood and lumen and occurs in the presence of luminal mannitol when the tight

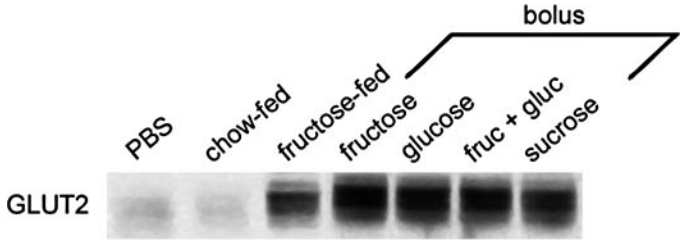

FIG. 3. Dietary regulation of apical GLUT2. Wild-type mice were maintained on 50% complex sugar diet ("chow-fed") or fructose-rich (65%) diet ("fructose-fed"). Some fructose-fed mice were fasted overnight before they received a gastric bolus of either PBS, glucose, fructose, glucose + fructose, or sucrose ("bolus"). Apical GLUT2 was very low in chow-fed or in fasted animals receiving a PBS bolus. The presence of GLUT2 was high in the apical membrane of animals fed ad libitum with the fructose-rich diet and in the apical membrane of mice receiving a bolus of simple sugar. Reproduced with permission (ref. 15).

junctions are closed (26). Blocking of reabsorption with phloridzin increases the net rate of secretion. Secretion and recycling through SGLT1 occur at a low rate in normal rats but are increased threefold in diabetic rats, which also have vastly increased apical GLUT2 (8). Recycling increases Na^+ absorption and may well provide a compensatory mechanism for urinary loss in diabetes.

After a meal (Fig. 2*B*), the initial digestion products of high–glycemic index carbohydrate, primarily disaccharides and α-limit dextrins, arrive at the apical membrane of the jejunum within 30 min; these are rapidly hydrolyzed by membrane-bound hydrolases (H) to produce a high effective glucose concentration at the surface of the apical membrane. The exact local concentration is, of course, the big unknown but estimates range from 50 to 300 mmol/l (27,28). As the concentration of free glucose increases, initial transport across the apical membrane occurs through SGLT1, causing activation of PKC βII. These events result in rapid ($t_{1/2}$ ~3.5 min) activation of apical GLUT2 already in the membrane and further insertion of GLUT2 into the apical membrane from intracellular vesicles underlying the membrane, as seen in immunocytochemistry. Apical GLUT2 is now the major pathway of absorption. Then, as glucose is absorbed and its concentration in the lumen falls, the whole signaling system is reversed so that GLUT2 is inactivated and traffics away from the apical membrane to restore the situation before a meal. During the assimilation of a meal, fructose is transported across the apical membrane by both GLUT5 and GLUT2 (see below).

The physiological role of apical GLUT2 has been confirmed in studies with GLUT2 knock-out mice. The mice lack GLUT2 in enterocytes, yet show normal transepithelial glucose absorption rates in combined intestine/liver perfusion experiments. Stumpel et al. (29) convincingly demonstrated an alternative pathway to GLUT2 for glucose exit, involving glucose 6-phosphate translocase in endoplasmic reticulum and exocytosis of glucose-containing vesicles at the basolateral membrane. In wild-type mice, this pathway accounts for 15% of glucose transport but is upregulated in GLUT2-null mice to give apparently normal rates of transport. This mechanism also operates in human patients with a Fanconi-Bickel syndrome who suffer from nonfunctional GLUT2 (30). When the apical GLUT2 model was proposed, Gouyon et al. (15) reinvestigated the absorption of fructose or glucose in mice maintained on diets enriched in simple carbohydrates. When wild-type mice adapted to a fructose- or glucose-rich diet were challenged with a gastric bolus of fructose, glucose, or sucrose after an overnight-fast, there was a large increase in intestinal apical GLUT2 insertion within 30 min (Fig. 3). There was then a large, GLUT2-mediated (cytochalasin B-sensitive) component of fructose absorption in apical membrane vesicles that was not present in GLUT2-null mice (Fig. 4). The cytochalasin B-insensitive absorption in wild-type mice was mediated by GLUT5 and was the same as total absorption in the jejunum of GLUT2-null mice. Similarly, the total uptake of glucose could be accounted for by SGLT1 and GLUT2 transport activities. The GLUT2-mediated fructose or glucose absorption was some threefold greater than that of GLUT5 and SGLT1, respectively. Consistent with the limited local absorption of sugar in the jejunum of GLUT2-null animals, the expression of GLUT5 in ileal enterocytes was increased by downstream unabsorbed fructose (15).

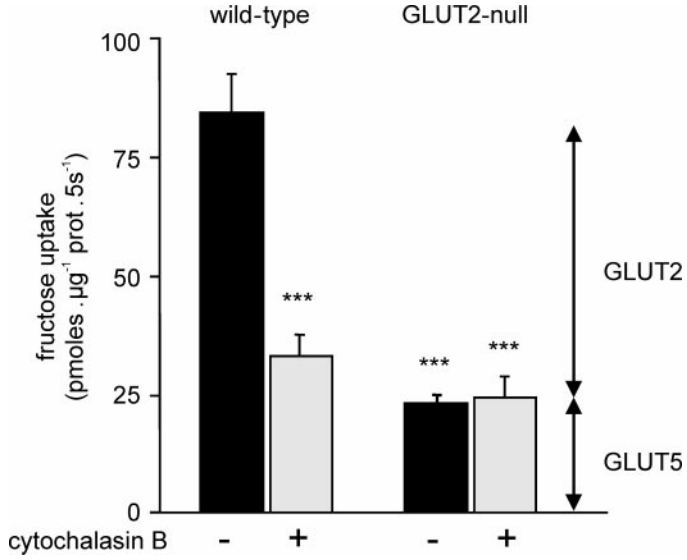

FIG. 4. Fructose uptake in GLUT2-null mice. Apical membrane vesicles were prepared 30 min after administration of a gastric bolus of fructose to wild-type and GLUT2-null mice maintained on a high fructose diet. The uptake of 10 mmol/l fructose was determined in the presence and absence of cytochalasin B, which inhibits GLUT2 but not GLUT5. GLUT2-null mice have the same GLUT5-mediated absorption as wild-type mice but lack the large GLUT2 component. Reproduced with permission (ref. 15).

REGULATION OF APICAL GLUT2

Long-term diet. Regulation involving apical GLUT2 insertion depends on the nature of the long-term diet on which mice are maintained (15). In particular, if wild-type mice received a complex diet containing low–glycemic index carbohydrate, then GLUT2 insertion was minimal (Fig. 3). When mice were maintained on such a diet, no difference in apical glucose absorption between wild-type and GLUT2-null mice was seen (28). Since biopsy practice requires that the gut is empty of food, this presumably explains why GLUT2 was not detected in the apical membrane of human intestine (31). However, since human glucose absorption continues to rise at concentrations far greater than required to saturate SGLT1, then apical GLUT2 must also operate in humans (27). Conversely, maintenance of mice on a long-term diet rich in simple (high–glycemic index) sugars primes the intestine for rapid apical GLUT2 insertion in response to a short-term sugar load. We therefore speculate that eating high–glycemic index carbohydrate diets common in the developed world might result in high levels of apical GLUT2, increased delivery of glucose into the blood, and excessive postprandial excursions. It is well established that SGLT1 is regulated by long-term diet (4 and refs. therein). Since apical GLUT2 is dependent on glucose transport by SGLT1, long-term regulation of SGLT1 may also be reflected in changes in apical GLUT2. In phase three starvation (protein catabolism), SGLT1 protein increased threefold and apical GLUT2 was abolished (32), confirming the data of Gouyon et al. (15) on the effect of a minimal diet. On refeeding for just 2 h, SGLT1 levels returned to control values and large amounts of GLUT2 appeared at the apical membrane.

Sugar sensing. The apical GLUT2 model envisages a new role for SGLT1 not just as a scavenger and transporter, but as a glucose sensor involved in control of apical GLUT2 insertion. This role is dependent on the ability of luminal sugar to activate PKC βII, which is then turned over very

rapidly by dephosphorylation, followed by ubiquitylation and degradation. Such rapid activation and turnover is ideally suited to the short-term modulation of absorptive capacity to match dietary intake. The signaling mechanism involves Ca^{2+}, which activates PKC βII and is necessary for contraction of the perijunctional actomyosin ring essential for the glucose-induced cytoskeletal rearrangement of the enterocyte. Nifedipine-sensitive Ca^{2+} entry is blocked by phloridzin, so that SGLT1 is a part of the sensing mechanism (33). Moreover, nifedipine and removal of Ca^{2+} from the luminal perfusate prevent apical GLUT2 insertion, whereas glucose stimulates Ca^{2+} absorption (E.L. Morgan and O.J. Mace, personal communication). Ca^{2+} entry may involve the nonclassical L-type channel $Ca_v1.3$ in the apical membrane (33), the same channel that is preferentially coupled to glucose-stimulated insulin secretion in INS-1 cells (34).

However, while SGLT1 is undoubtedly very important, it is not the only player involved in apical GLUT2 regulation. Fructose, for example, promotes activation and insertion but enters the cell initially through GLUT5; the mechanism is unknown, but one possibility might be closure of ATP-sensitive K^+ channels leading to membrane depolarization and Ca^{2+} entry, as happens in pancreas and the L-cell model GLUTag cell line (35). This cell line contains not only SGLT1 but also SGLT3a, which may be a glucose-gated Na^+ channel involved in sensing (36); both may play important roles in sugar sensing by GLUTag cells leading to glucagon-like peptide (GLP)-1 release through ATP-sensitive K^+ channel closure at low glucose concentrations when depolarization is low or through direct SGLT-dependent membrane depolarization seen at high concentrations of nonmetabolizable sugars.

Energy sensing. Of great interest, apical GLUT2 is the target of a cellular energy-sensing mechanism. Energy depletion provokes activation of AMP-activated protein kinase (AMPK), which causes activation of p38 and then insertion of apical GLUT2 (37). The antidiabetic drug metformin also activates AMPK (38) and promotes apical GLUT2 insertion; while this might potentially lead to an increased rate of delivery, glycemic control is in fact better because intestinal utilization is enhanced (39). Madsen et al. (37) note that under conditions of metabolic stress, the cell faces conflicting demands: there is a need to increase ATP by increasing glucose supply, but the very process of Na^+/glucose-dependent absorption utilizes ATP. The increase in Na^+/K^+-ATPase activity and therefore AMP has the potential to stimulate AMPK/p38 leading to apical GLUT2 insertion and activation; this facilitative pathway then provides the cell with a large increase in absorption that makes no further energy demand.

Incretins. Plasma concentrations of local hormones, including GLP-1 and -2, secreted by enteroendocrine cells in response to nutrient ingestion, are determined by variability in the rate of gastric emptying (40). Cheeseman's laboratory reported (14) that GLP-2 rapidly promotes apical GLUT2 insertion, upregulating jejunal fructose transport. Gastrointestinal polypeptide released from K-cells in the duodenum and jejunum in response to luminal glucose promotes secretion of GLP-1 and -2 from L-cells in rat ileum and distal colon, where both SGLT1 and SGLT3 may play a role in sugar sensing (35). GLP-2 promotes apical GLUT2 insertion, while GLP-1 enhances insulin secretion from the pancreas and hence glucose uptake in the peripheral tissues. Although some essential details are not known, especially the interacting time dependencies of events (40), most of the basic elements seem to be in place to suggest that a highly coordinated enteroendocrine system might permit high concentrations of dietary sugars to provide the signal that ensures not only their disposal in the tissues, but also their efficient transport into the body. It has yet to be established whether satiety signals including CCK8 and leptin, which both inhibit SGLT1, can in turn regulate apical GLUT2 (41,42).

Stress. Activation of the hypothalamopituitary adrenal axis in response to stress releases glucocorticoids with potential to play a pathogenetic role in metabolic syndrome, which includes obesity, insulin resistance, diabetes, and hyperlipidemia (43). Glucocorticoids rapidly inhibit apical GLUT2 insertion as part of the body's emergency response in activating the hypothalamopituitary adrenal axis, which enables mobilization of peripheral energy stores (44). Inhibition of apical GLUT2 insertion parallels inhibition of GLUT4 translocation by glucocorticoid in muscle (45). The first indication of this mechanism was obtained in opportunistic studies from a real-life situation, as a stress response in rats was caused by noise and vibration from renovation and construction during expansion of the Biology Department at the University of York. During more intense work, a rapid decline in the GLUT2 component of absorption and concomitant reduction in apical GLUT2 was observed; SGLT1 was unaffected (44). The effects of stress were blocked by metyrapone, and dexamethasone rapidly mimicked the effects of stress when injected into unstressed rats. When the peripheral energy stores of muscle and adipose tissue are mobilized by cortisol, the resulting primary metabolites, including lactate, amino acids, and glycerol, are recovered by enhanced gluconeogenesis. The concomitant inhibition of intestinal glucose delivery by cortisol seems necessary to prevent restriction of gluconeogenesis and the emergency response; during limited exposure to glucocorticoids, restriction is also prevented by insulin secretion and increased tissue disposal in response to raised blood glucose. Repeated exposure to glucocorticoids in stressful situations, however, might diminish insulin secretion and also peripheral glucose uptake by inhibition of GLUT4 translocation in muscle and adipose tissue, contributing eventually to various aspects of metabolic syndrome (43).

Diabetes. Apical GLUT2 is a potential therapeutic target. Thus, increased delivery by apical GLUT2 might be a factor in repeated insulin spikes associated with poor eating habits, such as "grazing" on junk food, ultimately contributing to insulin resistance, obesity, and type 2 diabetes. Apical GLUT2 is strongly regulated by long-term diet. Dietary manipulation to reduce the level of apical GLUT2 may therefore represent an important approach for modulation of absorption, especially in conjunction with other therapies. Apical GLUT2 is diminished by a low–glycemic index diet (15); moreover, Thomson et al. (46) have shown that altering the proportion of saturated and unsaturated fats improves glycemic control and diminishes total GLUT2.

Understanding apical GLUT2 control may be of direct relevance to the use of metformin and glucosidase inhibitors. Thus, metformin efficiently promotes apical GLUT2 insertion (see ENERGY SENSING). Improvement of type 2 diabetes has been achieved by restriction of delivery using α-glucosidase inhibitors such as acarbose (47). Sucrose is effective in promoting apical GLUT2 insertion (Fig. 3), emphasizing the importance of membrane hydrolysis of

dietary sugars (15). A large part of dissacharidase-related transport is Na^+ independent (48) and therefore might be mediated by apical GLUT2.

Apical GLUT2 has been reported in the kidney of streptozotocin-induced diabetic rats (49). The increased level of intestinal apical GLUT2 seen in experimental diabetes may lead to increased sugar recycling by SGLT1 and thereby provide a compensatory mechanism for urinary Na^+ loss.

CONCLUSIONS

Apical GLUT2 is primed by a long-term diet containing high–glycemic index sugars, insertion is rapidly induced by simple dietary sugars, and the apical GLUT2 component of absorption is several times greater than the active component at high glucose concentrations. Apical GLUT2 and SGLT1 act in tandem to cover the entire concentration range with SGLT1 playing an important regulatory role in the control of apical GLUT2. Apical GLUT2 is not only tightly regulated by long- and short-term supply of dietary sugars, but also by local and endocrine hormones, cellular energy status, stress, and diabetes; regulation occurs through a network of intracellular signaling pathways. Accordingly, apical GLUT2 can provide a major route of sugar absorption by which absorptive capacity is rapidly and precisely upregulated to match the dietary intake of sugars during assimilation of a meal. Apical GLUT2 provides a safety factor by preventing high sugar loads from reaching the colon (50); moreover, the consequent rapid delivery of sugar into the blood might increase the postprandial excursions, especially when glycemic control is poor. Apical GLUT2 is therefore a potential therapeutic target for novel dietary or pharmacological approaches to control intestinal sugar delivery and thereby improve glycemic control.

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