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GLUT2 mutations, translocation, and receptor function in diet sugar managing

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Leturque A, Brot-Laroche E, Le Gall M. GLUT2 mutations, translocation, and receptor function in diet sugar managing. *Am J Physiol Endocrinol Metab* 296: E985–E992, 2009. First published February 17, 2009; doi:10.1152/ajpendo.00004.2009.—Cloned 20 years ago, GLUT2 is a facilitative glucose transporter in the liver, pancreas, intestine, kidney, and brain. It ensures large bidirectional fluxes of glucose in and out the cell due to its low affinity and high capacity. It also transports other dietary sugars, such as fructose and galactose, within the range of physiological concentrations. Sugars and hormones regulate its gene expression. The contribution of GLUT2 to human metabolic diseases previously appeared modest. However, in the past decade, three major features of the GLUT2 protein have been revealed. First, GLUT2 mutations cause the severe but rare Fanconi-Bickel syndrome, mainly characterized by glycogenosis. Recently, a GLUT2 polymorphism has been associated with preferences for sugary food. Second, the GLUT2 location at the cell surface is regulated; this governs cellular activities dependent on glucose in the intestine and possibly those in the liver and pancreas. For instance, GLUT2 translocation from an intracellular pool to the apical membrane after a sugar meal transiently increases sugar uptake by enterocytes (reviewed in 32). Third, GLUT2 functions as a membrane receptor of sugar. Independently of glucose metabolism, GLUT2 detects the presence of extracellular sugar and transduces a signal to modulate cell functions, including β -cell insulin secretion, renal reabsorption, and intestinal absorption according to the sugar environment. These recent developments are examined here in health and metabolic disease, highlighting various unanswered questions.

glucose transporter 2; Fanconi-Bickel syndrome; pancreas; apical membrane; sugar sensing

DIETARY SUGARS PROVIDE A LARGE PORTION of the daily energy requirement in mammals, but sugar consumption is intermittent and can produce variations in blood glucose levels, which are especially deleterious for the brain. After a meal, circulating sugars are rapidly captured, metabolized, or stored in tissues. Conversely, between meals, stores are broken down to prevent hypoglycemic excursions. Glucose homeostasis depends on the ability of the various tissues to detect and signal sugar abundance or scarcity to build or mobilize sugar stores. In addition to such acute regulations, tissues are able to adapt in the long term to the amount of dietary sugar. Interestingly, the intestine, pancreas, kidney, and liver, which all play key roles in the handling of dietary sugars, express the glucose/fructose transporter GLUT2 (5, 14, 72, 73). It is a member of the SLC2A gene family, able to process high sugar concentrations efficiently due to its high V_{\max} and K_m for glucose (17). GLUT2 is abundant, and its transport activity is not limited in physiological conditions; thus, its contribution to pathologies was previously considered very modest.

Regulation of GLUT2 gene expression is complex and has been the matter of several studies focused on tissue specificity. Briefly, refeeding after a fast or low- vs. high-carbohydrate

diets modulate GLUT2 expression in the intestine, kidney, liver, and pancreas (46, 70). Low insulin and high glucose levels in streptozotocin-induced diabetic rodents increase GLUT2 expression in the intestine and liver (47, 84), suggesting that glycemia and insulinemia control GLUT2 expression. Conversely, remarkable reductions in GLUT2 expression have been found in the diabetic pancreas (74), and in the liver and intestine in an animal model of parenteral nutrition (8), showing that other factors, in addition to glucose or insulin, regulate GLUT2 expression.

GLUT2 is a glucose-sensitive gene in liver cells (60), together with the genes encoding L-type pyruvate kinase, and S14, fatty acid synthase (76). Carbohydrate response element-binding protein (ChREBP), a recently identified transcription factor, mediates glucose-induced transcription (77). In hepatocytes, glucose metabolism provides xylulose 5-phosphate, an activator of the protein phosphatase PP2A, which dephosphorylates the transcription factor ChREBP. ChREBP is then transported into the nucleus to trigger glucose-sensitive gene transcription (77). Intriguingly, the GLUT2 promoter does not seem to contain a ChREBP-binding sequence (ChoRE, carbohydrate response element); rather it binds sterol regulatory element-binding protein (SREBP)-1C on a sterol-responsive element (SRE) (78). Indeed, SREBP-1C induces the transcription of some lipogenic genes that require both glucose and insulin (76). In the pancreas, the role of SREBP-1C is empha-

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sized over ChREBP in *GLUT2* transcription (78). *GLUT2* is concomitantly regulated by glucose and by a lipogenic factor; the control of *GLUT2* transcription thus represents a possible step on the way to glucolipotoxicity. By controlling *GLUT2* transcription, the glucose influences its own metabolism, but *GLUT2* is also involved in other aspects of diet sugar managing.

From Genotype to Phenotype

Life without *GLUT2*, the Fanconi-Bickel syndrome. In humans, some mutations in the *GLUT2* gene are responsible for the Fanconi-Bickel syndrome, an autosomal recessive disorder in carbohydrate metabolism (65). Patients with this rare disorder suffer from hepatomegaly, nephropathy, fasting hypoglycemia, sugar intolerance, and growth retardation with variable penetrance (66). A large glycogen accumulation is reported in *GLUT2*-expressing tissues. For some of the identified *GLUT2* mutations, the transporter function is abolished (64). These patients do not tolerate simple sugars in their diet, but some of them can absorb uncooked (highly branched glucose) cornstarch. It is important to note that, in humans, inhibition of *GLUT2* functions does not greatly alter insulin secretion, as insulin treatments were not reported. Fanconi-Bickel patients display severe glucosuria, suggesting that, in humans, *GLUT2* inactivation is highly detrimental to glucose reabsorption by the kidney. The loss of glucose in urine due to a deficient *GLUT2* protein may account for growth retardation and fasting hypoglycemia. Glucose elimination in urine is a strategy designed to get rid of extra glucose to prevent hyperglycemia in patients suffering from diabetes (28) or to eliminate extra calories to prevent weight gain in obese patients (29). Sodium-dependent glucose transporter 2 (SGLT2) is a target of the inhibitors of glucose reabsorption, but not yet *GLUT2*.

Inactivation of *GLUT2* in mice by homologous recombination provokes severe glucosuria (21) but, in contrast to the human disease, leads to a lethal diabetic phenotype after weaning. *GLUT2*-null mice thrive during milk feeding and often die due to deficient insulin secretion when the pups eat the standard high-carbohydrate pellets (21). Thus, *GLUT2* invalidation is lethal in mice but not in humans. Nevertheless, if mice had permanent access to a low-sugar diet, they might survive *GLUT2* invalidation.

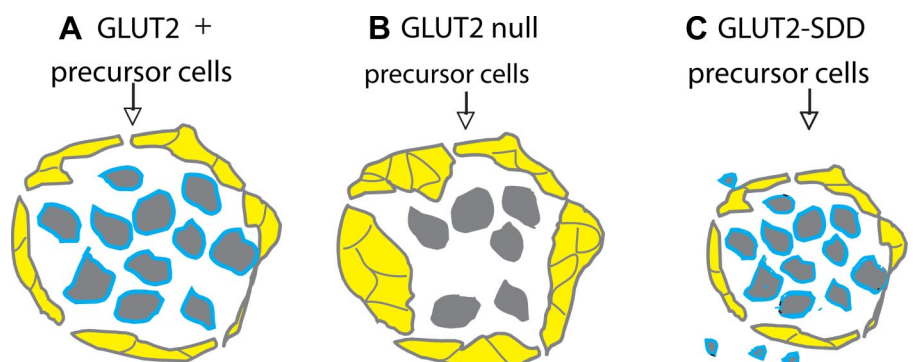
A fundamental discrepancy is observed when one compares human and murine pancreas: it is related to *GLUT2* abundance (9). A lower level of *GLUT2* is reported in human than in mouse pancreatic β -cells (58). The glucose-induced insulin secretion is first initiated by the uptake of glucose. Then, ATP

is generated during glucose processing through glycolysis and mitochondrial metabolism. The increased ATP/ADP ratio promotes ATP-dependent K^+ channel closure, membrane depolarization, and opening of voltage-dependent Ca^{2+} channels, thereby increasing cytosolic Ca^{2+} concentrations and finally the exocytosis of insulin granules (24). In these cells, the *GLUT2* transporter provides an unrestricted supply of glucose for metabolism, whereas glucokinase is the rate-limiting step of the glycolytic flux (45). Once in the cell, the glucose is trapped, phosphorylated by glucokinase. *GLUT2* can therefore be viewed as an equilibrator of extra- and intracellular glucose concentrations. Only a significant decrease in glucose transport activity is likely to limit glycolytic flux and insulin secretion. A second discrepancy is that *GLUT2* invalidation may be compensated for in human pancreatic- β -cells but not in mouse. There may be another transporter system in human pancreatic β -cells, as observed in murine enterocytes and hepatocytes (68); however, this remains to be investigated.

Two studies recently reported the presence of *GLUT2* in human fetal pancreas (58, 61). This highlights a possible role for *GLUT2* during early pancreatic differentiation. Indeed, *GLUT2* is found in the endodermal domain containing the pancreatic primordium (56). In a similar study, a pool of potential β -cell precursors was recently characterized as *GLUT2*-positive/insulin-negative cells (79). Furthermore, *GLUT2* invalidation in mice disrupts islet architecture, and endocrine α -cells are favored at the expense of β -cells (21). This suggests that *GLUT2* contribution in β -cell differentiation occurs after precursor split between α - and β -lineage, i.e., after NeuroD expression (81). The contribution of *GLUT2* in the development and maturation of pancreatic α - and β -cells is shown (Fig. 1, A and B). More studies are necessary to fully appreciate the role of *GLUT2* in pancreas endocrine lineage. This would help us understand the mechanisms for β -cell mass enlargement and maturation, for the benefit of diabetic patients.

Single nucleotide polymorphisms in *GLUT2*: sugar rewards. Polymorphisms in the *GLUT2* gene have provided conflicting results concerning their association with risk of type 2 diabetes (4, 35, 80). Thr¹¹⁰Ile, a common single nucleotide polymorphism (SNP) of *GLUT2*, leading to a missense mutation in transmembrane domain 2, was identified early in 1994 (69). This Thr¹¹⁰Ile variant did not show any decrease in transport activity (49), but it was recently found in a Canadian population that preferentially ate 14% more sugars than the Thr¹¹⁰Thr matched cohort (12). This result requires confirmation before *GLUT2* is considered to be a susceptibility gene for food intake disorders. Neuronal *GLUT2* functions might help us under-

Fig. 1. Structure of pancreatic islets in relation to the presence of *GLUT2* in the precursor cells. A: classically, precursors, some being *GLUT2* positive, give rise to α - (yellow) and β - (gray) cells, the ratio being favorable to β -cells. B: in *GLUT2*-null mice, precursors are all devoid of *GLUT2*, and the ratio is now in favor of α - over β -cells (21). C: in *GLUT2*-SDD (*GLUT2* sugar detection-deficient) mice, the size of the islets is reduced; several small islets are observed (67). Thus, *GLUT2* may contribute to β -cell differentiation at steps involved in determining β -cell lineage and islet size.



stand the role of GLUT2 in food preference and more generally in the central regulation of food intake. The distribution of GLUT2 in brain nuclei, neurons, glial cells, and astrocytes is a crucial issue but is still a matter for debate (2, 3, 43, 63). Given that GLUT2 is a transporter of elevated concentrations of glucose, GLUT2 should be found in the high-glucose-sensing neurons (37). This has not been established yet, probably due to technical limits. Surprisingly, GLUT2 is involved in the sensing of hypoglycemia in glial cells rather than hyperglycemia (43). Alternative explanations are suggested: one is that GLUT2 transport kinetics might be different in brain cells from those in other cell types (57); a second is that GLUT2-mediated sensing might be independent of glucose metabolism, as GLUT2 can act as a plasma membrane receptor of alternative sugars (see *Glut2 and insulin receptor cointernalization to reduce hepatic glucose reduction?*).

The analysis of GLUT2, from genotype to phenotype, may help uncover other physiological GLUT2 functions.

GLUT2 Location

A regulated translocation of GLUT2 in apical membranes. Regulated GLUT2 translocation was first described at the apical membrane of rat enterocytes (33), and the physiological relevance of this process was rapidly established (18). Indeed, glucose, fructose, and galactose, which are the main natural sugars in the human diet, are taken up from the lumen to be transferred into the blood circulation through enterocytes (82). The low sugar levels of glucose and galactose, i.e., between meals, are taken up at the apical membrane by SGLT1, a Na/glucose cotransporter; fructose is taken up by GLUT5, a facilitative transporter; both display high affinity for sugar. If concentrations are lower in the intestinal lumen than in the blood, glucose can be captured by SGLT1 and transported against the glucose concentration gradient. SGLT1 uses the energy of the sodium electrochemical gradient maintained by the basolateral Na-K-ATPase activity at the expense of metabolic energy (82). The second transport step at the basolateral membrane is ensured by GLUT2, which transports glucose, fructose, and galactose out of the enterocyte toward the blood stream (82). If meals contain sugars above SGLT1 and GLUT5 saturating concentrations (17), unsaturated GLUT2 is rapidly translocated to the apical membrane (18). High sugar concentrations can thus be taken up from the lumen within minutes of sugar ingestion (18). Then, GLUT2 is internalized by a mech-

anism driven by insulin action (75). GLUT2 operates in the intestine as a transport protein able to adjust the capacity of sugar transport according to the luminal concentration of glucose (32). GLUT2 internalization by insulin thus constitutes a means to limit blood glucose excursions, a primary action of the hormone. The apical translocation of GLUT2 in enterocytes is also regulated by stress, corticoids, and glucagon-like peptide-2 (GLP-2) enteroendocrine hormone and during ontogenesis (31). Nutrient availability to intestinal cells coordinates GLUT2 translocation by at least two signaling pathways. One is associated with calcium absorption through the Cav1.3 Ca^{+} channel, and the other is triggered by sweet-taste receptors activated by natural sugars and artificial sweeteners (39, 48). Notably, this mechanism of apical GLUT2 translocation clarifies the previously unexplained issue of glucose absorption of sugar-rich meals by intestinal cells equipped with low- K_m SGLT1 (Fig. 2). Furthermore, the apical GLUT2 translocation in enterocytes is a mechanism reported in various species, from insects to mammals (31). The clinical relevance of such a fine regulation of postprandial blood glucose levels is yet to receive experimental support. In metabolic diseases, i.e., in insulin resistance in mice, GLUT2 remained permanently in the apical membrane of enterocytes (75). The contribution of GLUT2 to diabetes, obesity, and insulin resistance should be reinvestigated by assessing its membrane location. Moreover, this may lead to the discovery of stimuli other than insulin that induce GLUT2 internalization.

The apical translocation is not restricted to intestinal cells. In kidney reabsorbing cells, the epithelial transport machinery is similar to that in the intestine, and an apical translocation of GLUT2 has been reported in proximal tubules of streptozotocin-treated rats, a mechanism abolished by starvation (42). Regulated GLUT2 apical translocation can now be considered a feature of monocellular epithelial cells. It remains unclear whether this mechanism is true for other GLUT2-expressing cell types.

GLUT2 cell surface mislocation: a deficiency of protein targeting? In pancreatic β -cells, GLUT2 was described as being more abundant at the microvilli than at the basolateral membrane (54). GLUT2 was also found inside β -cells in two genetically modified mice, affecting either their protein glycosylation (52) or caspase-induced apoptosis (79). Indeed, it was reported that GLUT2 cell surface expression controls glucose-induced insulin secretion (52). A misglycosylation induced by

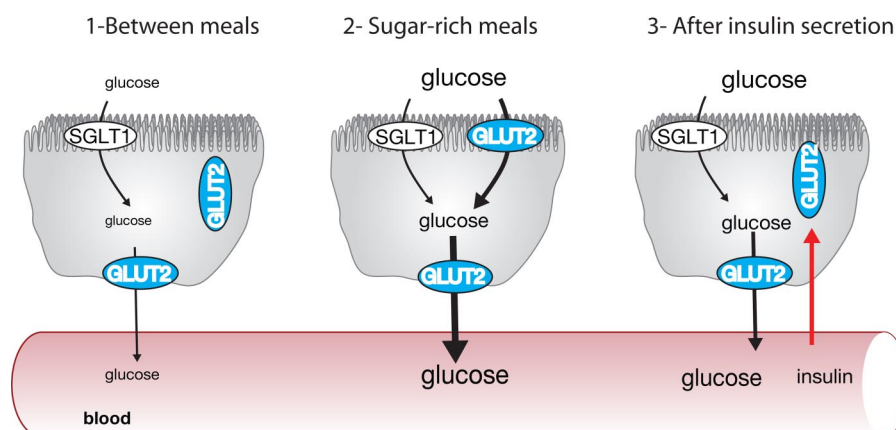


Fig. 2. Regulated translocation of GLUT2 in food-facing enterocyte membranes. If sugar concentrations are low in the lumen, glucose uptake is ensured by Sodium-dependent glucose transporter 1 (SGLT1), and glucose release in blood is ensured by GLUT2. A pool of GLUT2 in intracellular vesicles is ready to translocate in the apical membrane when a sugar-rich meal is taken. This translocation increases ≤ 3 -fold for glucose uptake (18). Insulin is secreted in response to a sugar meal. The hormone internalizes GLUT2 and reduces sugar uptake (75). Thus, regulating the location of GLUT2 in enterocytes is a mechanism that controls the magnitude of postprandial hyperglycemia, a strategy that would benefit patients suffering from metabolic diseases.

genetic invalidation of glucosamine transferase- α promotes GLUT2 endocytosis (52). This process was mimicked by the consumption of a high-fat diet (52, 59). Genetic misglycosylation specifically in β -cells provokes a reduction of GLUT2 cell surface levels to 15% (52). Moreover, if β -cell apoptosis is induced by targeted activation of caspase 8 (PANIC-ATTAC mice), GLUT2 cell surface expression is lost, and GLUT2 remains inside the β -cells (79). This effect is fully reversible, and GLUT2 cell surface expression in β -cells 8 wk after treatment arrest is similar to that in control mice (79). Wang et al. (79) suggest that intracellular retention of GLUT2 protects β -cells from hyperglycemia. They also reported a pool of potential β -cell precursors expressing GLUT2. The location of GLUT2 at the surface of cells represents an interesting observation: if confirmed in wild-type mice, it would make GLUT2 an excellent membrane marker to isolate β -cell precursors.

From these studies with genetically modified mice, it is still difficult to predict whether GLUT2 undergoes regulated translocation in β -cells in physiological conditions. Yet, to modulate glucose-induced insulin secretion, the control exerted by GLUT2 cell membrane location must be large in mice but more discrete in humans, in whom GLUT2 is less abundant.

GLUT2 and insulin receptor cointernalization to reduce hepatic glucose production? In liver, GLUT2 was first located in the basolateral (sinusoidal) plasma membrane domain of hepatocytes (72). Lately, GLUT2 internalization in endosomal fractions has highlighted a new regulatory step driven by the amount of GLUT2 present at the hepatocyte surface. Two groups (11, 16) reported in murine hepatocytes that GLUT2 and the insulin receptor (IR) seemed to colocalize and cointernalize in the endosomal fraction in response to insulin action. Such IR-GLUT2 complexes were increased in a mouse model of improved hepatic insulin sensitivity (PTP1B-null mice) (16). This could be relevant to the inhibitory effect of insulin on hepatic glucose production. Indeed, the liver plays a central role in glucose homeostasis, utilizing or producing glucose according to feeding and fasting episodes. In the postabsorptive or fasting states, the liver produces glucose. The last step of glucose production, from either glycogenolysis or gluconeogenesis, is the hydrolysis of glucose 6-phosphate into glucose, which is then released into the blood through GLUT2. In the absorptive state, when plasma glucose and insulin levels rise, the liver stores glucose in the form of glycogen or metabolizes it into lipids. Endogenous glucose production is stopped by the inhibition of gluconeogenic enzymes. Thus, removing GLUT2 from the plasma membrane might add another efficient mechanism to prevent glucose exit from hepatocytes, thus reducing endogenous glucose production. A high-fat diet induced GLUT2 internalization in rat liver cells, which did not occur in rats with chronic glucose intolerance, probably because of unrestrained hepatic glucose production (50). In rats fed a high-fat diet, a modest 30% alteration of GLUT2 cell surface levels was sufficient to alter liver function significantly, indicating that GLUT2 location might be a regulatory step in liver physiology.

The phosphoinositide-3 kinase/Akt/TORC1 (target of rapamycin complex) pathway is activated by nutrients. It can be constitutively activated in tuberous sclerosis complex 2 (TSC2)-null mice, where it reduces glucose uptake by regulating GLUT4 and GLUT2 trafficking (30). This was the first report of a parallel regulation of GLUT4 and GLUT2 transporter traffick-

ing. The molecular mechanisms driving GLUT2 (31) and GLUT4 translocation (85) might reveal similarities. Nevertheless, in intestine and hepatocytes, insulin internalizes GLUT2, whereas in adipocytes and muscles insulin externalizes GLUT4. Again, more studies are necessary to clarify the similarities and contradictions in insulin action on sugar transporter trafficking to and from the plasma membrane.

Sugar Sensing: GLUT2 a Sugar Receptor

GLUT2 feeds a metabolic pathway signaling glucose abundance. The sensing of sugar abundance is a mechanism ensuring the survival of mammals by adapting hormone secretion, neuronal activation, or gene transcription to environmental sugar abundance. GLUT2 is generally considered to be a minor actor in the glucose-sensing apparatus for glucose-induced insulin secretion by pancreatic β -cells, glucokinase being the major player (44). In the liver, GLUT2 feeds a metabolic pathway signaling glucose abundance to stimulate gene transcription (76). This metabolic pathway of glucose signaling involves the activation of the transcription factor carbohydrate response element-binding protein (ChREBP) by a metabolite messenger, xylulose 5-phosphate (77). Other glucose transporters can also feed the metabolic signaling pathway, but, due to their low K_m for glucose, they are not considered to be sensors of sugar abundance.

GLUT2: a plasma membrane receptor of sugar. Glucose receptors (or detectors) at the plasma membrane trigger a glucose signal inside the cells. In yeast, sugar receptors at the membrane are either G protein-coupled receptors (Gpr1), or transporter-like detectors (Snf3 and RGT2), and their signaling pathways are well documented (25). In higher eukaryotes, knowledge on glucose receptors is just emerging. From the GPCR family, the sweet taste receptors trigger sugar signaling in taste buds (7) but also in gut cells after activation by sugars and artificial sweeteners (36, 38, 41). Boss, a GPCR in *Drosophila*, responds to extracellular glucose to regulate sugar and lipid metabolism (34). In addition, the transporter-like SGLT3 in enteric neurons (10) and the transporter SGLT1 in neurons (15) are suspected to trigger nonmetabolic pathways of glucose signaling. GLUT2 contributes to the sensing of sugar (71) not only by fueling the metabolic-signaling cascade but also by triggering a specific protein-signaling pathway. Indeed, GLUT2 cannot always be replaced by another GLUT isoform, suggesting that the GLUT2 protein has particular qualities (51). When β -cells are engineered with GLUT isoforms to provide a similar glucose flux, only GLUT2 allows normal insulin production in response to glucose (27). Furthermore, there is a close correlation between the level of GLUT2 and glucose-sensitive gene expression in hepatoma (1) and in engineered β -cells (26). In addition, only GLUT2-transported sugars are efficient stimulators of the transcription of glucose-sensitive genes (23). This is directly supported by studies with GLUT2-null mice, in which the absence of GLUT2 impairs the stimulation by glucose of sensitive gene expression, e.g., the insulin gene in pancreatic β -cells and L-pyruvate kinase in liver and intestine (18, 19, 21). These mice were rescued by the overexpression of GLUT1 in pancreas, which could induce the second phase of insulin secretion (21), but only GLUT2 could rescue the first phase of insulin secretion (20). These data indicate that both the GLUT2 protein and the glucose flux are

required to sense glucose in various cell types. Therefore, the GLUT2 protein can be considered to be a receptor involved in glucose sensing.

How receptors convert changes in extracellular glucose concentrations into appropriate signals is key to understanding nutrient sensing. Several glucose-sensing pathways have been described in yeast (62), two of which are downstream from glucose transporter detectors (55). They produce a sugar signal mediated by protein-protein interactions, starting at the plasma membrane and passing via a COOH-terminal cytoplasmic domain of the protein (55). Indeed, intracellular domains of transporter detectors are likely to trigger the first step of the signaling pathway. In mammals, the receptor function of GLUT2, activated in response to extracellular glucose, is transduced by the cytoplasmic loop between transmembrane domains (TM) 6-7. Using this domain of GLUT2 as a molecular tool, we provided experimental evidence for the signaling pathway. The expression in large excess of this tool can inhibit, probably by titration, the transcription of glucose-sensitive genes with no effect on glycogen synthesis in hepatoma cells (22). GLUT2 signals sugar abundance to the transcription machinery in the nucleus. A nuclear importer, karyopherin- $\alpha 2$, is a relevant partner protein of GLUT2 TM 6-7 loop (23) and an appropriate amount of karyopherin- $\alpha 2$ is required for the expression of glucose-sensitive genes in hepatoma cells. Furthermore, the nucleocytoplasmic movements of a fluorescent

karyopherin- $\alpha 2$ in living cells depend on changes in extracellular glucose concentrations. Glucose accelerates the shuttling rates of karyopherin- $\alpha 2$ and its net nuclear efflux, suggesting that the location of karyopherin- $\alpha 2$ cargoes are regulated by glucose (6). These cargo proteins could contribute to the ultimate steps in the stimulation of glucose-sensitive gene transcription. Thus, the identification of karyopherin- $\alpha 2$ cargo proteins may help identify new steps in this glucose-signaling pathway.

The relative contribution of metabolic- over receptor-mediated glucose signaling pathways (Fig. 3) is an important issue. Modulation of glucose sensing by metabolic inhibitors is hampered *in vivo*, as most cell functions and vital parameters would be affected. The creation of a GLUT2 sugar detection-deficient (SDD) mouse has allowed this investigation (67). GLUT2-SDD mice display urinary glucose loss, low insulin secretion, growth retardation, and a significantly different glucose homeostasis (67). In GLUT2-SDD mice, the ratio of α -over β -cells was conserved, but the number of small islets was increased (Fig. 1C) (67), suggesting that GLUT2 receptors are involved in islet structures. In addition, GLUT2-SDD mice have altered food intake behavior (Stolarczyk E, Guissard C, Even P, Lorsignol A, Pénicaud L, Brot-Laroche E, Leturque A, Le Gall M, unpublished data). The phenotype of these mice highlights the importance of GLUT2 as a receptor of extracel-

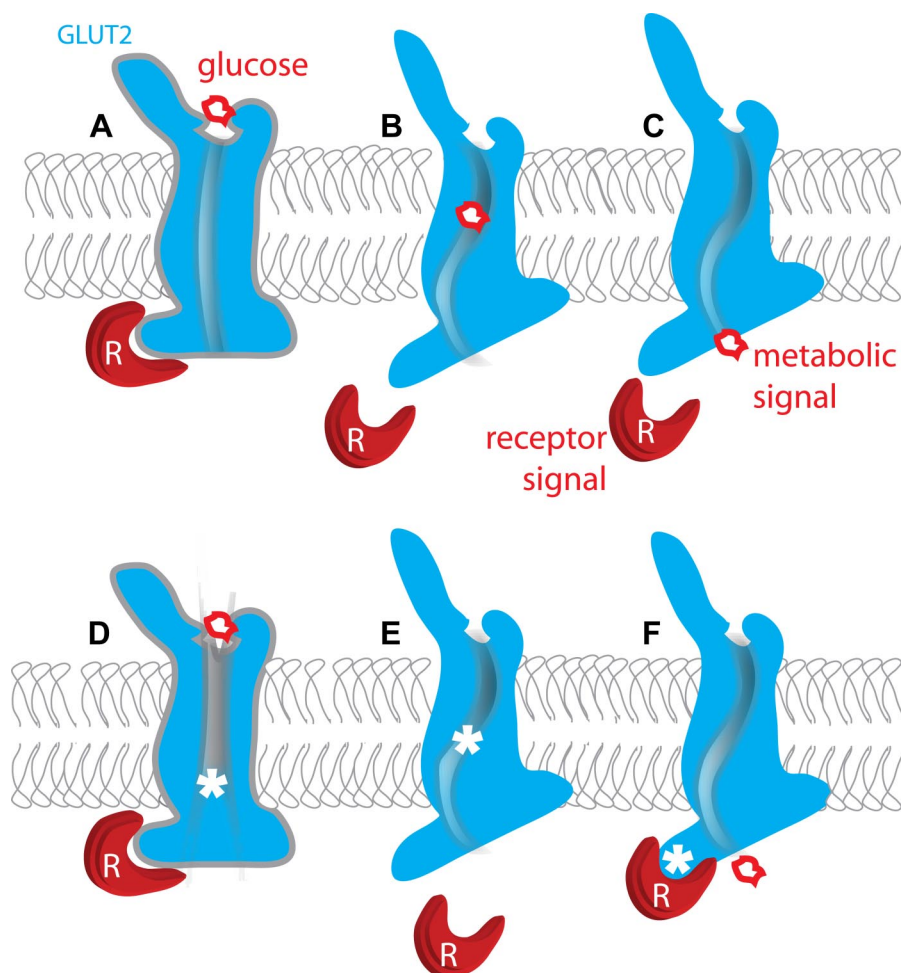


Fig. 3. GLUT2 conformations and signaling activities. On the basis of models established for other sugar transporters, two GLUT2 conformations (in blue) are predicted, with an outward-facing, nonsignaling conformation (A) and an inward-facing, signaling conformation (C). This conformation can trigger both pathways of metabolic- and receptor-mediated (R) sugar signaling. We can hypothesize that the conformational shift triggers the sugar-signaling pathway if a glucose molecule (in red) is bound to an internal site of the channel (B). GLUT2 mutations (star) that block the transport activity might also invalidate sugar signaling (D). Mutations (stars) that modify the sugar-signaling pathway might occur in the sugar channel (E) or in domains involved in receptor activity (F).

lular glucose involved in multiple aspects of glucose homeostasis.

Only a low metabolic flux of glucose is required to initiate or sustain the protein pathway. Cross talk of the metabolic and protein pathways of glucose signaling is possible at the level of cytoplasmic factors or transcription factors, but these mechanisms remain to be determined.

How does a transporter-receptor transduce a sugar signal? The structure-function analysis of the glucose transporter indicates that transport occurs by binding sugar onto docking sites in the channel, causing shifts in protein conformations from outward- to inward-facing configurations (53). This was confirmed recently by a crystal structure model of the outward-facing conformation of a SGLT protein from *Vibrio parahaemolytica*, which provided an insight into structural rearrangements for active transport (13). Similar signaling and nonsignaling conformations may exist for GLUT2 (Fig. 3). Indeed, a model structure for a transporter-like receptor for amino acid transport and sensing has been proposed (83). In this model, occupation of the internal binding sites seemed to stabilize the transporter-receptor in signaling conformations. In GLUT2 mutants, the binding of extracellular glucose on an internal site in the sugar channel may constrain the protein into an active signaling conformation. An intriguing question is whether GLUT2 mutations that alter the signaling conformations can be found among Fanconi-Bickel patients (Fig. 3). Importantly, a plasma membrane receptor of sugar should trigger a signal appropriate to both high and low glucose concentrations. The molecular signaling triggered by low glucose concentration remains to be investigated in mammalian cells.

Aided by the identification of various fructose binding sites in GLUT2 (40), the identification of GLUT2-specific ligands might also facilitate the understanding of the GLUT2 receptor function. Moreover, synthetic ligands of GLUT2 sugar receptors may provide excellent clues for the treatment of metabolic diseases. GLUT2 may thus constitute a drug target for obesity and diabetes.

Conclusion

The biological functions of GLUT2, revealed by genetic and signal transduction studies, display unique signaling characteristics compared with other members of the facilitative glucose transporter protein (SLC2A) family. GLUT2 has the ability to provide a unifying message to the whole body by signaling both sugar scarcity and abundance. New opportunities for reevaluating GLUT2 in diabetes, obesity, and insulin resistance are provided by the regulation of GLUT2 location. Remaining challenges include detailed analysis of GLUT2 receptor function in physiological and pathological conditions, taking advantage of its drug accessibility at the plasma membrane.

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