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The role of GLUT2 in dietary sugar handling

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GLUT2 is a facilitative glucose transporter located in the plasma membrane of the liver, pancreatic, intestinal, kidney cells as well as in the portal and the hypothalamus areas. Due to its low affinity and high capacity, GLUT2 transports dietary sugars, glucose, fructose and galactose in a large range of physiological concentrations, displaying large bidirectional fluxes in and out the cells. This review focuses on the roles of GLUT2. The first identified function of GLUT2 is its capacity to fuel metabolism and to provide metabolites stimulating the transcription of glucose sensitive genes. Recently, two other functions of GLUT2 are uncovered. First, the insertion of GLUT2 into the apical membrane of enterocytes induces the acute regulation of intestinal sugar absorption after a meal. Second, the GLUT2 protein itself initiates a protein signalling pathway triggering a glucose signal from the plasma membrane to the transcription machinery.

Key words: GLUT2, Sugar transport, Glucose sensing.

Intermittent dietary sugar absorption provides a large portion of daily energy requirement in mammals, but can produce variations of blood glucose that are deleterious especially for the brain. After a meal, the circulating sugars are rapidly captured, used or stored in tissues. Conversely, between meals, these stores are broken down to prevent hypoglycaemic excursions. Glucose homeostasis depends on the ability of the different tissues to detect and signal sugar abundance or scarcity in order to build or mobilise sugar stores. In addition to these acute regulations, tissues are able to adapt in the long term to dietary sugar environment. Interestingly, the intestine, the pancreas and the liver, which are important players in the handling of dietary sugars, are endowed with the glucose/fructose transporter GLUT2. This transporter, a member of the SLC2A gene family, is appropriate to process effi-

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ciently high-sugar concentrations. This review will focus on GLUT2 physiological and pathological roles.

Dietary sugars are transported by GLUT2

The necessary tight regulation of blood glucose levels, in the range of 5 mmol. L^{-1}, involves several tissues. These tissues can sense glucose and respond to the variations of extracellular glucose levels. The intestine contributes to the nutrient flow by providing dietary sugars (Fig. 1).

Intestinal sugar absorption.– Glucose, fructose and galactose are the main natural sugars in human diet. In the classical model of intestinal sugar absorption (Fig. 1, top), the transepithelial transfer of sugars from the lumen to the internal milieu results from two sequential transmembrane transports (44). Dietary glucose and galactose are transported across the apical membrane, by the Na/glucose cotranporter (SGLT1) and dietary fructose by the facilitative-transporter GLUT5. When sugar concentrations are lower in the intestinal lumen than in the blood stream, glucose can be captured by SGLT1 and transported uphill the glucose concentration gradient. SGLT1 is using the energy of the sodium electrochemical gradient, which is maintained by the basolateral Na/K ATPase activity to the expense of metabolic energy (44). A second transport step, through the facilitative transporter GLUT2, is achieved when glucose, fructose and galactose cross the basolateral membrane out of the enterocyte to reach the internal milieu (37). The above model, however, cannot fully explain the rapid transepithelial transfer of glucose immediately after a meal because apical transporters are saturated at low sugar, i.e. in the 10 mmol. L^{-1} concentration range whereas the luminal concentration of sugars can reach 150 mmol. L^{-1} (30).

The apical membrane of enterocytes is structured into microvilli resulting in an enlarged membrane luminal surface. Any change in the protein equipment of this apical membrane will modulate the

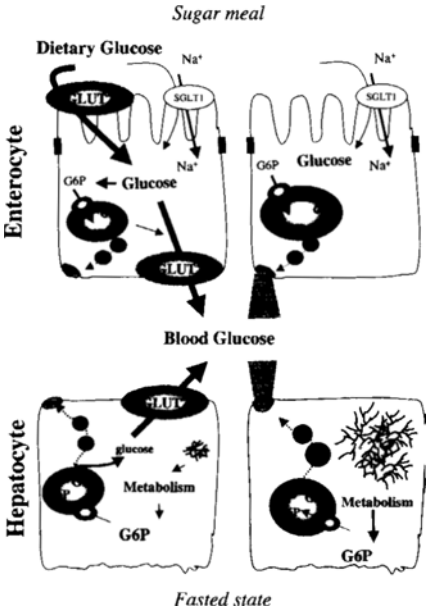

Fig. 1. *Glucose absorption in enterocytes during a sugar meal and glucose production by hepatocytes in the fasted state.*
GLUT2 (left) and GLUT2 deficient (right) cells are compared. In enterocytes, the transcellular transport of sugars, here exemplified by glucose, relies on the equipment of the apical membrane with SGLT1 and GLUT2. GLUT2 ensures the major part of glucose flux through the cell. In cells lacking GLUT2, the amount of glucose export is reduced but not abolished consistent with the presence of an exocytosis pathway (square dots) related to the hydrolysis of glucose-6-phosphate (G6P) into glucose (Glc) in the endoplasmic reticulum (dark elipses). In the fasted state when degradation of glycogen (doted area) or gluconeogenesis, are active in hepatocytes, Glc from G6P hydrolysis is exported by GLUT2. Hepatocytes lacking GLUT2 activate an exocytosis pathway for glucose production but store large amounts of glycogen.

intestinal absorption. After a glucose perfusion, GLUT2 is inserted in the apical membrane of enterocytes (25). The translocation of GLUT2 to the apical membrane occurs within minutes after the sugar ingestion and is transient, returning to basal levels as soon as the epithelium is cleared from sugar (13). Importantly, the presence of GLUT2 in the apical membrane increases significantly glucose absorption (13). The role of GLUT2 as a transport protein able to adjust the capacity of sugar transport to the luminal concentration of free glucose or fructose is reviewed in (26). The apical translocation of GLUT2 in enterocytes is also regulated by stress, corticoids (35), fuel availability (19, 42), entero-endocrine hormones (3), and during ontogenesis (4).

This apical translocation is not restricted to intestinal cells. In kidney reabsorbing cells, the epithelial transport machinery is similar to that in the intestine (38). An apical translocation of GLUT2 has been reported in kidney proximal tubules (27).

Sugar transport via GLUT2 in liver cells.– The liver plays a central role in glucose homeostasis, utilizing or producing glucose according to feeding and fasting episodes. The main sugar transporter in the liver plasma membrane is the bidirectional transporter GLUT2 (40). In the absorptive state, when plasma glucose and insulin levels are elevated, the liver stores glucose under the form of glycogen or metabolises it to lipids. In the post absorptive or fasting states, production of glucose by liver is activated (Fig. 1 bottom). The last step of glucose production either from glycogenolysis or gluconeogenesis is the hydrolysis by glucose-6-phosphatase of glucose-6-phosphate into glucose. Glucose is then released in internal media via GLUT2. An alternative pathway for glucose release has been described (Figure 1), which operates in mice lacking GLUT2 (14), but this glucose export has a low efficiency as compared to GLUT2 mediated transport (22).

GLUT2 transport in the pancreas.– In pancreatic β-cells, the uptake of glucose by GLUT2 is the first step of glucose induced insulin secretion. After glucose has been processed by glycolysis and mitochondrial metabolism, factors are generated, which trigger the distal steps of insulin secretion. Indeed, the ATP/ADP ratio controls the ATP-dependent K^+ channel-closure, the membrane depolarization, the opening of voltage-dependent Ca^{2+} channels increasing cytosolic Ca^{2+} concentrations and finally the exocytosis of secretory granules of insulin (20). Once into the cell, glucose is trapped in the cytoplasm by glucokinase phosphorylation. Since glucokinase is the rate-limiting step of the glycolytic flux (28), GLUT2 permits an unrestricted access of glucose to metabolism.

GLUT2 can therefore be viewed as an equilibrator of extra- and intra-cellular glucose concentrations.

The consequences of a lack of GLUT2

Inactivation of the GLUT2 gene in the mouse by homologous recombination leads to a diabetic phenotype: GLUT2 null mice die at weaning time, 2-3 weeks after birth (16). However, these mice can be maintained alive by injections of insulin indicating that the major cause of pup death is a pancreatic defect and its consequences on glucose homeostasis (16). The magnitudes of the glucose-induced insulin secretion and of the glucose-dependent stimulation of insulin

gene transcription are reduced in the islets of GLUT2 null mice (15, 16). The specific expression in β-cell of either GLUT2 or GLUT1 rescues the GLUT2 null mice, which have restored glucose-induced insulin secretion, grow normally and can breed (39).

GLUT2 null mice are characterized by severe glycosuria. The loss of glucose in the urines, which is due to absence of GLUT2 in the kidney proximal convoluted tubule, may account for fasted hypoglycaemia suggesting that GLUT2 is essential for renal glucose re-absorption.

In the absence of GLUT2 expression, hepatic glucose output is ultimately normal. Glucose release from the liver can occur with low efficiency, by an alternative pathway (14), which relies on exocytosis after glucose-6-phosphate is hydrolyzed into glucose in the endoplasmic reticulum (14, 22) (Fig. 1, bottom). The liver of GLUT2 null mice is 40% larger than that of control mice, due to secondary glycogen accumulation and increased cell number. Indeed, in these mice, liver glycogen stores cannot be mobilized during fasting (5). This phenotype is correlated with the persistent high expression of glucose sensitive genes. Re-expression of GLUT2 in the liver rescues this phenotype.

Dietary sugars can be absorbed by the intestine in GLUT2 null mice despite the lack of basolateral sugar transporter. Oral glucose load results in normal rate of glucose appearance in blood. In the intestine, an exocytosis pathway, similar to that described in hepatocytes, has been documented (22, 36) (Fig. 1, top). Nevertheless, the lack of GLUT2 in the enterocyte precludes a normal absorption of a sugar-rich meal. Indeed, the uptake of glucose or fructose in intestinal rings of GLUT2 null mice is reduced 3 fold when challenged by a high sugar load (13).

In humans, mutations in the GLUT2 gene are responsible for the Fanconi-Bickel syndrome, an autosomal recessive disorder of carbohydrate metabolism (33). Found in several families, patients suffer from hepatomegaly, nephropathy, fasting-hypoglycaemia, sugar-intolerance and growth-retardation. Some of the identified mutations severely affect the function of GLUT2. These patients do not tolerate simple sugars in their diet, although some of them can absorb uncooked cornstarch. Their insulin secretion is quasi normal. It is important to note, that in humans, at variance from mice, the lack of GLUT2 in pancreatic β-cells does not alter insulin secretion. This is probably related to the 100-fold lower level of GLUT2 in humans as compared to mice pancreatic β-cells (9).

The lack of GLUT2 in pancreatic β-cells is lethal in mice, suggesting that no alternative pathway can restore glucose entry and insulin secretion. In the liver and the intestine, an alternative pathway compensates for the lack of glucose release by GLUT2.

GLUT2 is a glucose-sensitive gene

Several lines of evidence show that the expression of GLUT2 in the intestine, liver and pancreatic β-cells is tightly linked to glucose abundance. Interestingly, GLUT2 expression is specifically regulated by its substrates glucose and fructose.

Regulation of GLUT2 expression by glucose availability and route of delivery.– Fasting refeeding, or low- versus high-carbohydrate diets, modulate GLUT2 expression in the intestine (13), in the kidney, liver and pancreas (38).

A remarkable reduction of GLUT2 expression in the liver and the intestine is revealed in animal model of parenteral nutrition. Artificial nutrition techniques are essential for patients suffering from malnutrition or reduced intestinal absorption. Total parenteral nutrition deteriorates overall insulin-sensitivity characterized by a marked hyperinsulinemia, mild hyperglycaemia and a strong reduction in GLUT2 expression as compared to enteral feeding (8). The profound reduction in GLUT2 levels might participate to insulin resistance.

Conversely, the decrease of insulin concentration and hyperglycaemia that occur in streptozotocin-induced diabetic rodents, increase the expression of GLUT2 in the intestine, the liver and pancreatic β-cells (38).

Glycaemia controls therefore the expression of GLUT2 via direct and indirect mechanisms.

Glucose-induced transcriptional regulation of GLUT2.– In hepatocytes, GLUT2 (2, 31), and L-type pyruvate kinase, S14, fatty acid synthase (12) are glucose-sensitive genes. ChREBP, a recently identified transcription factor, is a mediator of glucose-induced transcription (41). 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 (41). Intriguingly, the GLUT2 promoter does not seem to contain a ChREBP binding sequence (ChoRE, carbohydrate response element), rather it binds SREBP-1C on a sterol responsive element (SRE) (24). Indeed, SREBP-1C induces the transcription of some lipogenic genes that require both glucose and insulin (11). In the pancreas, the role of SREBP1C is emphasized over ChREBP on the transcription of GLUT2 or insulin (43).

By controlling GLUT2 gene transcription, glucose exerts a strong influence on its utilization or storage.

The role of GLUT2 in signalling sugar abundance

The detection of sugar abundance is crucial to adapt hormone secretion, neuronal activation, or gene transcription. GLUT2 triggers a metabolic-signalling cascade that participates to detection of sugar abundance as demonstrated in several tissues (12).

Metabolic glucose signalling.– In pancreatic β-cells, small changes in glucokinase activity significantly affect the threshold for glucose-induced insulin secretion (29). On the other hand, GLUT2 is essential in the process of glucose-induced insulin secretion, since normal glucose uptake and subsequent metabolic signalling cannot be achieved without GLUT2 (16), and modulation of insulin secretion is correlated to GLUT2 expression (45). Furthermore, the overexpression of both GLUT2 and glucokinase improves glucose sensitivity indicating a tight relationship between the two protein activities in insulin producing cells (10). GLUT2 and glucokinase have a high capacity and a low affinity, and can adapt their activities to blood glucose concentrations (29). Thus, the glucose-sensing apparatus of the pancreatic β-cells is of metabolic nature (34).

GLUT2 in the liver initiates a metabolic pathway that signals glucose abundance to stimulate gene transcription (12). This metabolic pathway of glucose signalling

involves the activation of the transcription factor ChREBP by a glucose metabolite, the xylulose-5-phosphate (41).

GLUT2 is a transporter-detector triggering protein signalling.– The metabolic pathway described above, however cannot fully account for glucose effect. Indeed, GLUT2 cannot always be replaced by another GLUT isoform. When β-cells are engineered with glucose transporter isoforms to provide a similar glucose flux, only GLUT2 allows a normal insulin production in response to glucose (23). Furthermore, a close correlation between the level of GLUT2 and glucose-sensitive gene expression is observed in hepatoma cells (1) and in engineered β-cells (21). In addition, only GLUT2-transported sugars are efficient stimulators of the transcription of glucose-sensitive genes (31). More direct evidence comes from GLUT2-null mice in which the lack of GLUT2 impairs the stimulation by glucose of sensitive gene expression, e.g. the insulin gene in the pancreatic β-cells and L-pyruvate kinase in the liver (16). These data indicate that the GLUT2 protein is required to mediate the effect of glucose in liver and pancreatic β-cells.

If GLUT2 can function as a sensor of extra cellular glucose, able to trigger a signal into the nucleus, it implies that at least one intracytoplasmic domain of the protein is activated after the addition of sugar. In yeast, many glucose-sensing pathways have been described, two of which are downstream of glucose transporter-detectors (32). They produce a sugar signal mediated by protein-protein interactions starting at the plasma membrane via a cytoplasmic domain of the protein (32). In hepatoma cells, the expression of GLUT2-cytoplasmic domains allows to uncover a similar signalling pathway (17). The expression of the cytoplasmic TM 6-7 loop but not of other cytoplasmic peptides of GLUT2 inhibits the transcription of glucose sensitive genes without any effect on glycogen synthesis. Adding to its metabolic action, GLUT2, can thus signal sugar abundance to the transcription machinery in the nucleus (Fig. 2).

A nuclear importer, karyopherin α2, is involved in the glucose-sensing pathway initiated at the plasma membrane by the GLUT2 TM 6-7 loop. This protein-partner of the GLUT2-loop was identified by a two-hybrid screen (18). An appropriate amount of karyopherin α2 is required for

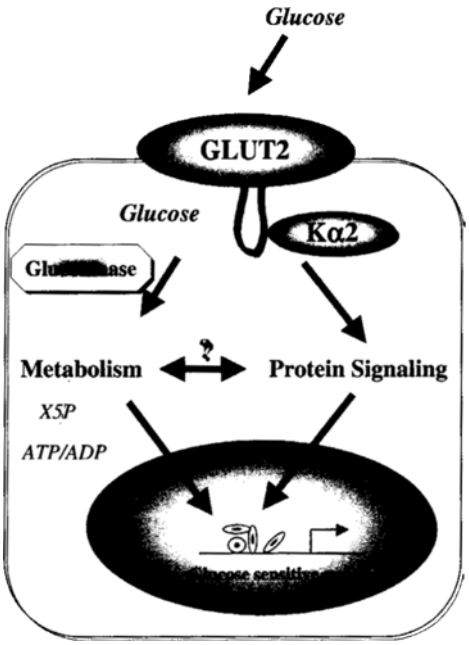

Fig. 2. *GLUT2-dependent transcription of glucose sensitive genes in liver cells.*
At the plasma membrane, GLUT2 initiates two pathways: a metabolic pathway that increases energy production (ATP/ADP ratio) and xylulose-5-phosphate (X5P) and a protein signalling pathway starting at the TM 6-7 intracytoplasmic loop of GLUT2. A nuclear import protein, karyopherin α2 (Kα2), interacts with GLUT2 and shuttles in and out of the nucleus to deliver the sugar signal.

the proper expression of glucose sensitive genes in hepatoma cells. Furthermore, the movements of fluorescent karyopherin α2 in living cells depend on extracellular glucose changes. Glucose not only accelerates the net nuclear efflux but also the shuttling rate of karyopherin α2, suggesting that the location of karyopherin α2 cargos are regulated by glucose (7). These cargo proteins could be responsible for the ultimate stimulation of glucose-sensitive gene transcription. A cross talk of the metabolic and protein pathways of glucose signalling is possible at the level of cytoplasmic or transcription factors.

The hepatoportal glucose sensor.– The hepatoportal glucose sensor that triggers hormonal and neuronal counter-regulation relies on the presence of GLUT2 (6), but to date, the exact cellular location of this sensor is unknown and could be either at the level of endothelial cell or mediated through glucose-sensitive neurons.

So far, two glucose-signalling pathways mediated by GLUT2 have been identified in mammalian cells: a metabolic and a protein pathway. Work is in progress to describe these pathways, to identify the protein partners and to find out the cross talks of these glucose-sensing systems.

Conclusion

Important advances have been made in the understanding of the role of GLUT2 in the handling of dietary sugars. First, GLUT2 can transport dietary sugars through the plasma membrane in a bidirectional mode. Second identified role is the capacity of GLUT2 to provide unlimited sugar to a metabolic pathway affecting glucose signalling e.g. glucose induced gene transcription and insulin secretion. Very recently, two other roles for GLUT2 were uncovered. GLUT2 contributes to the acute regulation of sugar absorption by its transient insertion into the apical membrane of enterocytes and kidney cells. The protein GLUT2 is also an important element of glucose sensing apparatus. The protein GLUT2 in the

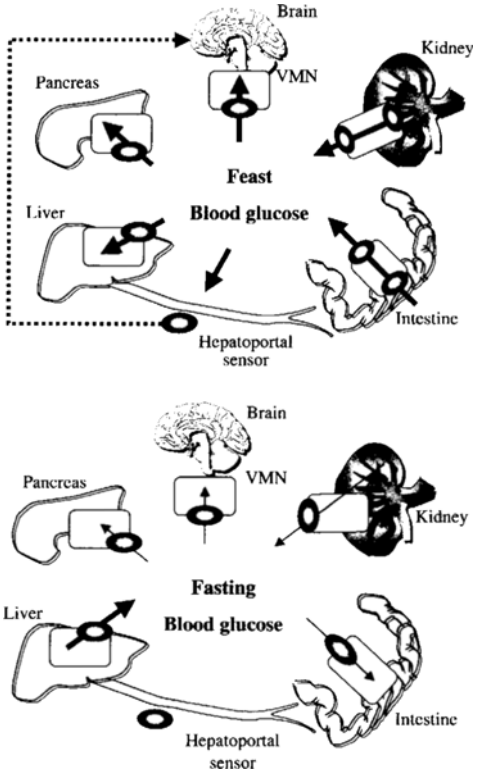

Fig. 3. *GLUT2 expressing tissues and control of blood glucose levels.*
Tissues involved in glucose fluxes endowed with GLUT2 (filled ellipses) are presented in the contrasted physiological situations of fast and feast (sugar diet or meal). Arrows indicate the direction and size of glucose fluxes in the different tissues. Note that renal and intestinal epithelial cells can transiently traffic GLUT2 to the apical membrane facing high glucose to increase luminal absorption and reabsorption capacities. VMN, hypothalamic ventromedial nucleus.

plasma membrane can detect glucose and trigger both a metabolic pathway and a protein-signalling cascade targeting the transcription of glucose-sensitive genes. GLUT2 might provide a unifying message to the whole body signalling sugar abundance (Fig. 3).

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A. LETURQUE, E. BROT-LAROCHE, M. LE GALL, E. STOLARCZYK y V. TOBIN. *Papel del GLUT2 en la utilización de los azúcares de la dieta* (minirrevisión). J. Physiol. Biochem., **61** (4), 527-538, 2005.

GLUT2 es un transportador equilibrativo de glucosa localizado en la membrana plasmática de células hepáticas, pancreáticas, intestinales y renales, asi como en áreas portales e hipotalámicas. Debido a su baja afinidad y alta capacidad, GLUT2 transporta los azúcares de la dieta glucosa, fructosa y galactosa, en un amplio margen de concentraciones fisiológicas, dando lugar a amplios flujos bidireccionales hacia dentro y fuera de las células. La presente revisión trata sobre las funciones de GLUT2. La primera función identificada para GLUT2 es su capacidad para avivar el metabolismo y proporcionar metabolitos que estimulan la transcripción de genes sensibles a la glucosa. Recientemente se han descubierto otras dos funciones. Primera, la inserción de GLUT2 en la membrana apical de los enterocitos induce una regulación aguda de la absorción intestinal de glucosa tras la ingesta. Segunda, la propia proteína GLUT2 inicia una ruta de señalización para la glucosa desde la membrana a la maquinaria de transcripción.

Palabras clave: GLUT2, Transporte de azúcares, Sensor de glucosa.

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