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REVIEW

GLUT2, glucose sensing and glucose homeostasis

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Abstract The glucose transporter isoform GLUT2 is expressed in liver, intestine, kidney and pancreatic islet beta cells, as well as in the central nervous system, in neurons, astrocytes and tanycytes. Physiological studies of genetically modified mice have revealed a role for GLUT2 in several regulatory mechanisms. In pancreatic beta cells, GLUT2 is required for glucose-stimulated insulin secretion. In hepatocytes, suppression of GLUT2 expression revealed the existence of an unsuspected glucose output pathway that may depend on a membrane traffic-dependent mechanism. GLUT2 expression is nevertheless required for the physiological control of glucose-sensitive genes, and its inactivation in the liver leads to impaired glucose-stimulated insulin secretion, revealing a liver-beta cell axis, which is likely to be dependent on bile acids controlling beta cell secretion capacity. In the nervous system, GLUT2-dependent glucose sensing controls feeding, thermoregulation and pancreatic islet cell mass and function, as well as sympathetic and parasympathetic activities. Electrophysiological and optogenetic techniques established that *Glut2* (also known as *Slc2a2*)-expressing neurons of the nucleus tractus solitarius can be activated by hypoglycaemia to stimulate glucagon secretion. In humans, inactivating mutations in *GLUT2* cause Fanconi–Bickel syndrome, which is characterised by hepatomegaly and kidney disease; defects in insulin secretion are rare in adult patients, but *GLUT2* mutations cause transient neonatal diabetes. Genome-wide association studies have reported that *GLUT2* variants increase the risks of fasting hyperglycaemia, transition to type 2 diabetes, hypercholesterolaemia and cardiovascular diseases. Individuals with a missense mutation in *GLUT2* show preference for sugar-containing foods. We will discuss how studies in mice help interpret the role of GLUT2 in human physiology.

Keywords Beta cells · Brainstem · Diabetes · Glucose sensing · Glucose transporter · Hypothalamus · Insulin · Liver · Neurons · Review

Abbreviations

2-DG	2-Deoxy-D-glucose
ChREBP	Carbohydrate regulated element-binding protein
DMNX	Dorsal motor nucleus of the vagus
GE	Glucose excited
GI	Glucose inhibited
GSIS	Glucose-stimulated insulin secretion
i.c.v.	Intracerebroventricular
NPY	Neuropeptide Y
NTS	Nucleus tractus solitarius
POMC	Pro-opiomelanocortin
SGLT	Sodium–glucose linked transporter

Introduction

Glucose is a major source of metabolic energy for most cells of the body and is of critical importance for the brain. Because of its role in cellular energetics and brain function the concentration of glucose in the blood is constantly monitored to adapt cellular and whole body physiology to maintain glycaemia at ~5 mmol/l. Glucose detection mechanisms are multiple and the term 'glucose sensing', as used in this review, refers to any cellular or molecular mechanism whose activity is directly responsive to changes in physiological glucose concentrations. Examples of such glucose-sensing systems include the taste bud cells. These express the sweet taste receptors (T1R2/T1R3) [1], which detect the presence of sugar in the

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food and initiate nervous responses to control the cephalic phase of insulin secretion, as well as food preference [2, 3]. In hepatocytes, high glucose concentrations activate the transcription factor known as carbohydrate response element-binding protein (ChREBP), a key inducer of glycolysis and lipogenesis [4]. ChREBP is also expressed in beta cells where it regulates expression of glycolytic and lipogenic genes and contributes to glucose-stimulated beta cell proliferation [5–7]. A major function of pancreatic beta cells is to secrete insulin in response to a rise in circulating glucose concentrations, and the signalling pathway involved depends on glucose metabolism [8]. In pancreatic alpha cells, an as yet incompletely defined mechanism, which probably also involves glucose metabolism, links hypoglycaemia to the release of glucagon [9]. Importantly, glucose-responsive neurons have been identified in several brain regions involved in the homeostatic control of feeding, energy expenditure and glucose homeostasis [10, 11]. However, glucose detection in the nervous system is not restricted to neurons, but also involves astrocytes and tanycytes.

A large variety of glucose-sensing mechanisms have been described in the nervous system [12, 13]. These include membrane depolarisation following glucose uptake by the electrogenic Na^+-coupled glucose transporter (SGLT)1 [14]; the binding of glucose to SGLT3, which does not transport glucose but can induce a depolarisation signal [15]; the use of beta cell-like glucose-sensing systems, or glucose binding proteins linked to a signalling pathway that closes K^+ leak channels, as described in orexin neurons [16]. The glucose transporter GLUT2 is also associated with various glucose-sensing cells, which are activated by either hypoglycaemia or hyperglycaemia, as further discussed below.

GLUT2 structure and function

The family of facilitated diffusion glucose transporters (GLUTs, encoded by the *SLC2A* genes) comprises 14 isoforms. These have distinct amino acid sequences, substrate specificities, kinetic properties and tissue and cellular localisations [17]. GLUT2 has a uniquely low affinity for glucose (K_m~17 mmol/l), and can also use mannose, galactose and fructose as low affinity substrates; it has, however, a high affinity for glucosamine (K_m~0.8 mmol/l) [18]. GLUT2 is present in the basolateral membrane of enterocytes and of epithelial cells from the kidney proximal convoluted tubule where it functions in the second step of transepithelial glucose transport, a process initiated by the apical sodium–glucose cotransporters SGLT1 or SGLT2. As discussed further below, knocking out *Glut2* in the mouse revealed that it is dispensable for glucose absorption in the intestine but required for glucose reabsorption in the kidney. GLUT2 is also the major glucose transporter in the plasma membrane of hepatocytes, and studies on *Glut2*-null mice indicated that it is required for glucose uptake but dispensable for glucose output. In rodent pancreatic beta cells, GLUT2 is the major glucose transporter and its genetic inactivation suppresses glucose uptake and glucose-stimulated insulin secretion (GSIS). GLUT2 is also expressed in the central nervous system.

Thus, although the function of GLUT2 is merely to catalyse the passive transport of glucose across plasma membranes, studies of knockout mice have revealed that this transport activity is important for the control of cellular mechanisms impinging on gene expression, regulation of intracellular metabolic pathways, and induction of hormonal and neuronal signals which together form the basis of an integrated inter-organ communication system to control glucose homeostasis (Fig. 1, Table 1). It is important to note that the mouse phenotypes described below are only observed when both *Glut2* alleles are inactivated and that heterozygous knockout mice are indistinguishable from control mice. This is further evidence that glucose transport by GLUT2 is not a rate-controlling step in any of the signalling pathways studied.

GLUT2 in pancreatic islet beta cells

The first indication that GLUT2 was associated with glucose sensing was the observation that it is the major glucose transporter in rodent islet beta cells [19, 20]. Because of its high K_m for glucose and high transport capacity, it allows for fast equilibration of extracellular glucose with that present inside the cell. This gives glucose unrestricted access to glucokinase, the enzyme that catalyses the rate-controlling step in GSIS [21]. In diabetic mice and rats, impaired GSIS is associated with markedly reduced expression of GLUT2 [22, 23]. The loss of GLUT2 expression is regulated at both the mRNA and protein levels. Elevated NEFA suppresses *Glut2* mRNA expression [24] and, in diabetes, the reduced *Glut2* expression is only observed in beta cells and not in liver; this is due to a tissue-specific activity of the transcription factor hepatic nuclear factor-1α (HNF-1α) [25]. The rate of GLUT2 protein degradation can be increased by elevated glucocorticoid levels [26] and, in mice fed a high-fat diet, a reduction in the expression of *N*-acetylglucosamine transferase-4, a Golgi apparatus enzyme involved in N-linked glycosylation, leads to structural alterations in the transporter N-glycan. This suppresses the interaction of GLUT2 with galectin-9, a lectin that normally anchors the transporter at the cell surface, and reduces GSIS [27–29]. Transplantation of islets from diabetic mice in control animals normalised GLUT2 levels and restored GSIS [30, 31]. Thus, the above data suggest that reduced glucose

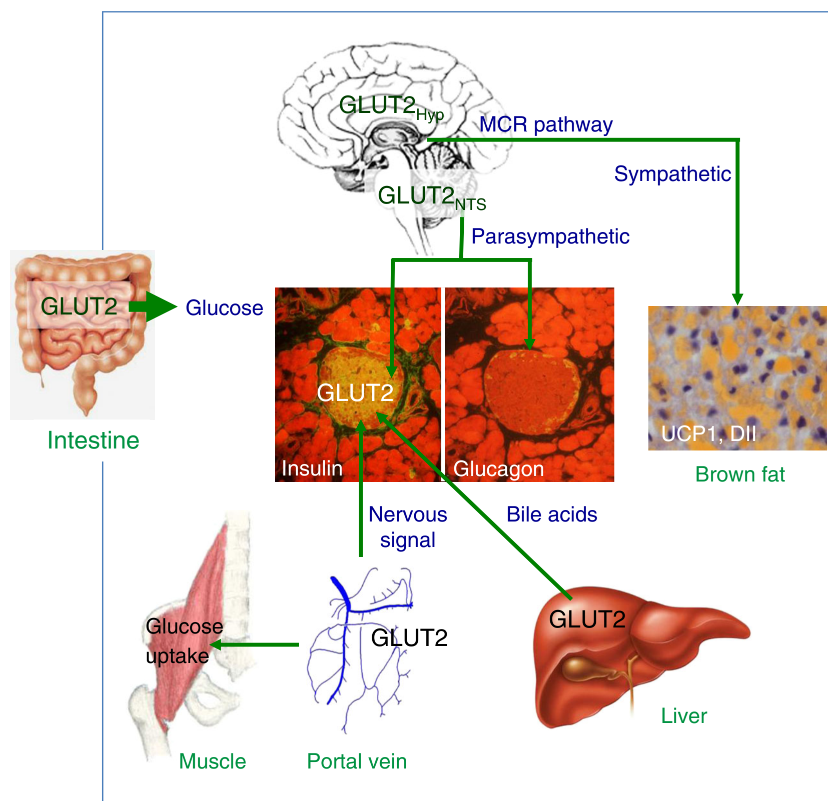

Fig. 1 Sites of GLUT2-dependent glucose transport and sensing in inter-organ communication. GLUT2 is present in the basolateral membrane of intestinal epithelial cells, where it allows entry of glucose in the organism. GLUT2 is present in glucose-sensing cells of the hepatoportal vein region. Activation of these glucose sensors induces a nervous signal that stimulates first-phase insulin secretion, as well as other physiological responses. In hepatocytes, GLUT2 is required for equilibration of cytoplasmic glucose with the extracellular milieu in order to allow appropriate regulation of glucose-sensitive genes during the fed-to-fast transition. These glucose-regulated events modulate bile acid production, which can increase beta cell glucose competence through activation of farnesoid X receptor, a nuclear hormone receptor. GLUT2 is expressed in beta cells; in rodents this transporter is essential for normal glucose-stimulated insulin secretion. GLUT2 is expressed in the brain, in the nucleus tractus solitarius (NTS), in few hypothalamic (Hyp) cells, and in neurons that send projections to neuropeptide Y and pro-opiomelanocortin neurons of the melanocortin (MCR) pathway. Nervous system GLUT2-dependent glucose-sensing cells control the regulation by glucose by both parasympathetic and sympathetic nervous systems. Glucose-regulated parasympathetic activity controls beta cell proliferation during the weaning period and glucose-stimulated insulin secretion in adult mice; it also controls glucagon secretion in response to hypoglycaemia. GLUT2-dependent glucose-sensing cells control the sensitivity to leptin of the melanocortin pathway and sympathetic activity in brown fat to control uncoupling protein 1 and deiodinase-2 expression and thermoregulation

uptake may become limiting in the control of GSIS in the diabetic state.

Whether GLUT2 has unique properties that are required for glucose sensing has been tested in genetic rescue experiments. *Glut2*$^{-/-}$ mice die at around the weaning period [32] and transgenic expression of *Glut1* or *Glut2* in their beta cells (RIP*Glut1;Glut2*$^{-/-}$ or RIP*Glut2;Glut2*$^{-/-}$ mice) restores normal GSIS and glucose-stimulated insulin biosynthesis [33]; a minimum of ~20% of the normal GLUT2 expression level was found to be sufficient to normalise GSIS. Thus, the total transport capacity rather than the specific isoform of glucose transporter expressed at the beta cell surface is necessary for normal GSIS. This is consistent with the observation that human beta cells express several glucose transporters: the low K_m glucose transporters GLUT1 and GLUT3, and GLUT2, which is expressed at a relatively low level (see also the discussion of Fanconi–Bickel patients in the 'GLUT2 in human pathophysiology' section).

A role for GLUT2 in glucose sensing, independent from its transport activity, has been proposed based on the study of liver cells transfected with a cDNA construct encoding a green fluorescent protein fused to the large intracellular loop of GLUT2 (amino acids 237–301). These studies showed that the fusion protein is translocated into the nucleus when the cells are exposed to high glucose concentrations, leading to impaired induction of glucose-regulated genes such as *Glut2* and that encoding L-pyruvate kinase [34]. In subsequent experiments, transgenic mice were produced that expressed the same fusion protein under the control of the actin promoter to achieve ubiquitous expression of the transgene [35]. These mice showed a large diversity

Table 1 GLUT2 involvement in cellular functions and integrated physiology

Organ / cell	Related function	Effect of KO	Reference
Intestine	Transepithelial glucose transport	No impairment in intestinal glucose absorption	[99]
Beta cells (mice)	GSIS	Suppressed GSIS	[32]
Hepatoportal vein glucose sensors	Detection of portal glucose	Suppresses a signal that stimulates glucose uptake by muscles and fat	[46, 47]
Liver	Glucose uptake	Suppression of glucose uptake	[54, 55]
	Glucose output	No impact on glucose output	
	Regulation of glucose-sensitive gene expression	Gene expression maintained to the fed level; impaired expression of cholesterol biosynthesis genes	[52, 53]
Brain (RIP*Glut1*; *Glut2*$^{-/-}$ mice)	Control feeding initiation and termination	Delayed initiation of feeding after a fast	[66]
	Control of glucagon secretion	Elevated glucagonaemia and loss of regulated glucagon secretion during hypo- and hyperglycaemia	[37, 100]
	Thermoregulation	Impaired thermoregulation; fast-induced torpor; reduced UCP1 and deiodinase-2 expression in brown adipose tissue	[63]
	Control of the melanocortin pathway	Impaired regulation of NPY and POMC during the fast-to-refed transition; reduced sensitivity of NPY and POMC neurons to leptin action	[63, 66]
Nervous system (NG2KO mice)	Control of autonomic nervous activity	Impaired stimulation of parasympathetic activity and inhibition of sympathetic activity by glucose	[68]
		Reduced beta cell mass and late-onset glucose intolerance because of reduced GSIS	
Nervous system (NG2KO mice)	Taste preference	Increased preference for sugar-containing foods	(G. Labouèbe, B. Thorens, unpublished observations)
NTS (*Glut2Cre*; *Rosa26ChR2* mice)	Hypoglycaemia detection, activation of vagal activity and glucagon secretion		[75]

UCP1, uncoupling protein 1

of phenotypes associated with deregulation of glucose metabolism [35] and feeding behaviour [36]. However, even though the transgenic mice show a clear and intriguing phenotype, this is induced by overexpression of a soluble fusion protein that can migrate to the nucleus. It is not clear how these observations can support a role for GLUT2, a membrane protein that has so far never been reported to be present in the nucleus, as a glucose sensor that directly controls biological processes in the nucleus. Nevertheless, a role for GLUT2 in transducing an intracellular glucose-dependent signal, independent from its glucose transport activity, cannot be excluded.

GLUT2 is required for GSIS in rodent islets; GLUT2 is dispensable in human beta cells since they also express GLUT1 and GLUT3.

GLUT2 and the hepatoportal glucose sensor

The finding that GLUT2 is required for glucose signalling in beta cells prompted the assessment of an association of the transporter with other glucose-sensing systems. A first indication that this was the case came from studies assessing the regulation of glucagon secretion in response to hypo- or hyperglycaemia. Initial observations with *Glut2* knockout mice revealed strong hyperglucagonaemia [32]. Using RIP*Glut1;Glut2*$^{-/-}$ mice it was observed that the stimulation of glucagon secretion by hypoglycaemia or its suppression by hyperglycaemia were lost [37]. As GLUT2 is not expressed in pancreatic alpha cells, this indicated that glucose sensing by extra-pancreatic GLUT2-expressing cells were involved in glucagon secretion. In addition, since the hyperglucagonaemia of the knockout mice could be normalised by ganglionic blockade, this suggested that these

extrapancreatic GLUT2-dependent glucose sensors control autonomic nervous activity.

The hepatoportal vein is richly innervated by vagal afferents [38, 39], which are activated following intestinal glucose absorption [40, 41], leading to several physiological responses: suppression of glucagon secretion [42, 43], feeding termination [44] and stimulation of glucose uptake by some muscles and brown fat [45]. Studies of RIP*Glut1;Glut2*$^{-/-}$ mice showed that the signal generated by glucose infusion into the portal vein and that stimulates glucose utilisation by peripheral tissues required GLUT2 expression [45, 46]. Studies of mice with inactivation of GLUT4 or of the insulin receptor specifically in muscles indicated that the signal generated by the hepatoportal sensor was distinct from insulin, required GLUT4 expression, and was suppressed by expression of a dominant negative form of 5′ AMP-activated protein kinase in muscle [47]. Inactivation of this sensor also suppressed first-phase insulin secretion following i.p. glucose injection; however, insulin secretion from perifused islets isolated from the same mice displayed normal first-phase insulin secretion [48]. This therefore shows that in vivo, the control of first-phase insulin secretion depends on an indirect signal activated by glucose entering the hepatoportal vein area, and probably transmitted to beta cells by the nervous system.

Hepatic GLUT2, bile acids and beta cell glucose competence

GLUT2 is the major glucose transporter of hepatocytes in rodents and humans [19, 49]. The generally accepted role of this transporter is to take up glucose during the absorptive phase and to release it in the blood during fasting. In hepatocytes, glucose can be stored as glycogen, degraded through the glycolytic pathway or converted to fatty acids by the lipogenic pathway. The release of glucose in the circulation follows degradation of glycogen or gluconeogenesis.

Glucose also modifies cellular metabolism by allosteric and transcriptional regulation. Glucose inhibits glycogenolysis by activating glycogen phosphorylase kinase, which inactivates glycogen phosphorylase, the rate-limiting enzyme in glycogen breakdown; glucose 6-phosphate, on the other hand, is an allosteric activator of glycogen synthase [50]. Thus, increased absorption and phosphorylation of glucose stimulates glycogen deposition by allosteric stimulation of glycogen synthesis and inhibition of its degradation. A fraction of the absorbed glucose is metabolised through the pentose shunt pathway, which produces xylulose 5-phosphate, an activator of the protein phosphatase that dephosphorylates ChREBP [4, 51]. This induces translocation of ChREBP into the nucleus, where it activates the transcription of the gene encoding L-pyruvate kinase, a key regulator of glycolysis, and lipogenic genes such as those encoding acetyl-CoA carboxylase and fatty acid synthase. These allosteric and transcriptional responses are important in the absorptive phase to control glucose uptake, storage and conversion into fat.

Investigation of the impact of *Glut2* inactivation in hepatocytes led to three surprising findings. First, *Glut2* inactivation in hepatocytes of adult mice using a tamoxifen-dependent recombination system (LG2KO mice) [52] suppressed hepatic glucose uptake but did not modify glucose homeostasis in the fed, fasted, or fasted and refed states. Measurement of tissue glucose uptake in LG2KO mice showed increased uptake in the tibialis anterior and extensor digitorum longus muscles. Thus, glucose fluxes were redirected to other tissues to preserve normal control of glycaemia in the absorptive state.

Second, hepatic glucose production was quantitatively normal in fasted LG2KO mice. This was surprising because the last steps in glucose release from hepatocytes are classically described as involving the transport of glucose 6-phosphate into the endoplasmic reticulum where the active site of the glucose 6-phosphatase is located. Glucose 6-phosphate is hydrolysed into glucose and phosphate, and glucose is transported back into the cytosol to be exported from the cell by GLUT2. Our data indicated that absence of GLUT2 suppressed glucose uptake but, unexpectedly, did not impair glucose output. This revealed the existence of a second pathway for glucose output that does not require transport of glucose back into the cytoplasm. Investigation of this export mechanism suggested that glucose release was dependent on a membrane traffic-based pathway originating in the endoplasmic reticulum [53–55]. Although not yet fully characterised, this second pathway could offer a major regulatory advantage. Indeed, compartmentalising glucose away from the cytoplasm when hepatic glucose production is needed, i.e. in the fasted state, would prevent the redirection of glucose to glycogen storage, glycolysis and lipogenesis. In the fasted state, GLUT2 expression in the plasma membrane is nevertheless required for normal hepatic glucose metabolism. Indeed, since part of the glucose generated from glucose 6-phosphate in the endoplasmic reticulum can be transported back into the cytoplasm, it needs to be equilibrated with the extracellular glucose. Preventing this equilibration in LG2KO hepatocytes leads to the accumulation of glucose and glucose 6-phosphate in the cytoplasm, which causes a permanent increase in nuclear ChREBP and a paradoxical upregulation of the gene encoding L-pyruvate kinase and the lipogenic genes in the fasted state [52, 53]. The presence of GLUT2 in hepatocytes is therefore required for the normal control by glucose of gene expression under physiological conditions.

The third surprise was that, even though *Glut2* gene inactivation in adult mouse liver had no immediate impact on whole body glucose homeostasis, LG2KO mice progressively developed glucose intolerance as a result of a defect in GSIS [52]. Thus, altered glucose metabolism in hepatocytes induced progressive beta cell dysfunction. However, beta cell mass and insulin content were normal. To identify possible signals from

the liver that control beta cell function, we performed gene expression analysis of livers of fasted and fed control and LG2KO mice. Gene set enrichment analysis revealed that, besides modifications of glycolytic and lipogenic gene expression, most cholesterol biosynthesis genes were downregulated. However, this was not associated with changes in plasma cholesterol in either the fed or fasted stated. As cholesterol is also the precursor of bile acids, we measured their concentrations in faeces and plasma. Faecal bile acids were reduced by 30% in LG2KO mice as compared with control mice, and the plasma bile acid concentration was also lower in the mutant mice. When islets from control mice were incubated for 24 h in the presence of bile acids, GSIS measured in subsequent incubations was strongly increased, and this effect was not seen in islets from mice with genetic inactivation of *Fxr*, which encodes a nuclear receptor for bile acids. An acute role of bile acids on GSIS, through *Fxr*-dependent effects on K_{ATP} channels has also been reported [56]. Thus, bile acids may form a functional link between hepatic glucose metabolism and beta cell function.

In hepatocytes, GLUT2 is required for glucose uptake but is dispensable for glucose output, which takes place through a separate, probably membrane traffic-based release pathway. GLUT2 is nevertheless required to equilibrate intracellular and extracellular glucose concentrations to ensure proper control of glucose-sensitive gene expression in the liver. Failure of this process, as seen in LG2KO mice, reveals a new role of hepatocytes in linking glucose sensing to the long-term preservation of beta cell glucose competence by a mechanism likely involving bile acids.

GLUT2 in the nervous system

GLUT2 is expressed in the central nervous system of humans [57, 58], rodents and zebrafish [59]. In rats, a careful immunohistochemical mapping of GLUT2 expression at the light and electron microscopy levels revealed its presence in most brain structures, and expression was found in neurons, astrocytes, endothelial cells and tanycytes, which are specialised astrocytes lining the lower part of the third ventricle [60–62]. In mice, using a genetic reporter system in which a fluorescent protein is expressed under the control of the *Glut2* promoter (*Glut2-Cre* transgenic mice crossed with *Rosa26tdTomato* mice), the distribution of GLUT2 expressing cells in the brain was found to be very similar to that of the rat [63].

Glucose sensing, feeding and thermogenesis

Initial investigations of the role of rat brain GLUT2 in glucose homeostasis and feeding control used intracarotid [64] or intracerebroventricular (i.c.v.) [65] injections of specific antisense oligonucleotides to silence *Glut2* expression. In the first study this led to reduced body weight with no change in feeding and a reduced insulin response to intracarotid glucose administration. In the second one, *Glut2* silencing reduced feeding and body weight gain. Using RIP*Glut1;Glut2*$^{-/-}$ mice the feeding response to i.c.v. (as well as to i.p.) glucose or 2-deoxy-D-glucose (2-DG) injections was lost and this was associated with impaired regulation of the orexinergic (neuropeptide Y [NPY], agouti-related peptide [AGRP]) and anorexigenic (pro-opiomelanocortin [POMC], cocaine and amphetamine regulated transcript [CART]) neuropeptides of the melanocortin pathway during the fast-to-refed transition or following i.c.v. glucose injection [66]. These data indicated that central GLUT2-dependent glucose sensing regulates feeding through control of the melanocortin pathway.

Thermoregulation in RIP*Glut1;Glut2*$^{-/-}$ mice is abnormal due to a defect in central glucose sensing. This was shown by the much lower hypothermic response induced by i.c.v. 2-DG injections in RIP*Glut1;Glut2*$^{-/-}$ as compared with control mice [63]. This was secondary to reduced activation of brown fat uncoupling protein 1 and deiodinase-2 expression by the sympathetic nervous system and was associated with fasting-induced torpor in the *Glut2*-null mice. Abnormal sympathetic tone was caused, at least in part, by the reduced sensitivity to leptin of arcuate nucleus neurons, further supporting a role for central GLUT2-dependent glucose sensing in the control of the melanocortin pathway. Analysis of mice that express the red fluorescent protein tdTomato in *Glut2*-expressing cells revealed that NPY and POMC neurons do not express this transporter. However, they are in contact with nerve terminals from *Glut2*-expressing neurons, which probably have their soma outside the arcuate nucleus, suggesting an indirect control by glucose of the melanocortin pathway.

GLUT2 is required for glucose sensing by cells of the central nervous system. Absence of central GLUT2-dependent glucose sensing impairs the normal sensitivity of the melanocortin pathway to leptin and is associated with impaired control of feeding and thermoregulation.

Nervous glucose sensing and the regulation of islet cell mass and function

Analysis of mice with genetic inactivation of *Glut2* in the nervous system (NG2KO mice), generated by crossing *Glut2*^{flox} mice with a strain of *nestin-Cre* mice that do not show any metabolic or growth abnormalities [67], provided a new view of the role of nervous glucose sensing in autonomic regulation of the endocrine pancreas [68]. Direct recording of

nerve activity showed that the firing rate of the parasympathetic nerve was lower in NG2KO mice than in control mice and was not increased by i.p. glucose injections. Sympathetic nerve activity was similar in the basal state in NG2KO and control mice but was not suppressed by glucose in NG2KO mice. Thus, *Glut2* is required for normal control by glucose of both branches of the autonomic nervous system.

Absence of parasympathetic nerve regulation by glucose had two consequences. First, the proliferation rate of beta cells during the weaning period was reduced by half in NG2KO mice vs control mice and this lower rate of proliferation led to a 30% reduction in adult beta cell mass. However, the difference in proliferation rates was not seen when the mice were weaned on a high-fat, carbohydrate-free diet. Thus, during the weaning period, when there is a high rate of beta cell proliferation [69] and when the diet changes from a lipid-rich milk to a carbohydrate-rich chow [70], GLUT2-dependent nervous glucose sensing and parasympathetic activity play a critical role in stimulating beta cell proliferation to achieve normal adult beta cell mass.

The second consequence of the lack of glucose regulation of the autonomic nervous system was a loss of first-phase insulin secretion. In vivo, this early secretion response depends on nervous glucose sensing, in particular activation of the hepatoportal glucose sensor. This response was lost in NG2KO mice, whereas first-phase insulin secretion from isolated and perifused islets from young mice was normal. Thus, the defect in achieving normal adult beta cell mass together with the loss of first-phase insulin secretion led to the progressive development of glucose intolerance. This became evident at around 24 weeks of age and was caused by a defect in GSIS observed in vivo as well as in isolated islets. These physiological defects were accelerated by high-fat-diet feeding and were also associated with the development of hyperglucagonaemia.

> Nervous GLUT2-dependent glucose sensing is required for the normal control by glucose of the sympathetic and parasympathetic nervous activity. Absence of this sensing mechanism prevents normal beta cell expansion in the postnatal period and achievement of normal adult beta cell mass. Over time this leads to development of glucose intolerance due to a defect in GSIS.

Optogenetic control of *Glut2*-expressing neurons to stimulate glucagon secretion

In order to better define the role of *Glut2*-expressing neurons in glucose regulation, we studied a small group of such cells present in the nucleus tractus solitarius (NTS). This brainstem structure is at the crossroad of afferent signals coming from different segments of the absorptive track, it can directly sense changes in nutrient and hormone concentrations, and the neurons forming this structure send projections not only to neighbouring nuclei such as the area postrema (AP) and the dorsal motor nucleus of the vagus (also referred to as the DMNX or DMV) but also to various forebrain regions [71–73]. The DMNX is of particular interest since it is formed by the somas of the vagus nerve neurons and NTS neurons send numerous projections to the DMNX to control vagal activity [74].

Mice expressing a fluorescent protein in *Glut2*-expressing neurons (*Glut2Cre;Rosa26tdTomato*) were used to prepare acute brainstem slices for patch-clamp analysis. NTS *Glut2*-expressing neurons were shown to be activated by hypoglycaemia by a signalling pathway that involves glucose metabolism, stimulation of AMP kinase and the control of K^+ leak channels [75]. The *Glut2-Cre* mice were then crossed with *Rosa26ChR2* [76] mice to express channelrhodopsin-2, a light-sensitive cation channel [77], in *Glut2*-expressing neurons. Patch-clamp analysis demonstrated that pulses of blue light could induce firing of the NTS *Glut2*-expressing neurons. Stimulation by light in living mice with simultaneous recording of vagal activity showed that activation of the NTS *Glut2*-expressing neurons increased vagal nerve firing and this led to a strong stimulation of glucagon secretion [75]. Thus, *Glut2*-expressing neurons from the NTS are part of a neuronal circuit that links hypoglycaemia detection to the counter-regulatory response. These observations are also in agreement with the fact that when hypoglycaemia develops, vagal activity is increased first and sympathetic activity increases only at deeper hypoglycaemic levels [78]. They are also relevant in the context of the insulin treatment of type 1 and type 2 diabetes. Indeed, insulin-treated patients are at risk of developing hypoglycaemia, a risk that increases following antecedent hypoglycaemic episodes [79]. This condition, referred to as hypoglycaemia-associated autonomic failure, is due to impaired hypoglycaemia detection. The identification of an NTS glucose-sensing system involved in glucagon secretion provides a new pathway to investigate the molecular mechanisms of counter-regulation control and defects in these.

> *Glut2*-expressing neurons of the NTS are glucose-inhibited (GI) neurons that are activated by hypoglycaemia and control vagal nerve activity and glucagon secretion.

GLUT2 in human pathophysiology

GLUT2 mutations The role of GLUT2 in human physiology and pathogenic processes can be inferred from genetic studies. First, inactivating mutations in the *GLUT2* gene cause

Fanconi–Bickel syndrome, a condition associated with hepatomegaly, growth retardation and renal Fanconi syndrome [80, 81]. The liver and kidney phenotypes of the Fanconi–Bickel patients are very similar to those of *Glut2* knockout mice [82]. There is a similar increase in liver weight and increased glycogen accumulation, but a preserved hyperglycaemic response to glucagon injection, indicating that glycogen degradation can be followed by hepatic glucose release in the absence of GLUT2, both in humans and mice. Patients with Fanconi–Bickel syndrome have aminoaciduria, hyperphosphaturia and hypercalciuria, which are also observed in the *Glut2*-null mice [83]. In the mouse, exaggerated secretion of phosphate is linked to the suppressed expression in the proximal tubule of the type 2 sodium–phosphate cotransporter (NPT2C). Thus, defects in glucose reabsorption in the proximal tubule leads to secondary changes in other transporters expression, which may explain the observed renal syndrome.

Impaired GSIS in adult Fanconi–Bickel patients have only been reported in a few cases [84–86], but inactivating mutations in *GLUT2* have been found to cause transient neonatal diabetes mellitus [87]. As this condition disappears after approximately 18 months, this indicates that there is a transient requirement for GLUT2 for the control of insulin secretion in the first months of life. However, transient neonatal diabetes was not reported in all Fanconi–Bickel patients. This may be because such cases went undiagnosed. Alternatively, defects caused by *GLUT2* mutations may be compensated for by the expression of other genes. For instance, human beta cells express the low K_m glucose transporters GLUT1 and GLUT3 in addition to GLUT2, thereby providing multiple means of efficiently taking up glucose to ensure that glucokinase remains the rate-controlling step in GSIS.

Another, attractive possible explanation for the impact of the mutation is that GLUT2 expression in the nervous system has similar functions in humans as in mice. If this were the case, impaired GLUT2 expression in glucose-sensing cells of the nervous system would prevent the normal expansion of beta cell mass in the postnatal period and prevent first-phase insulin secretion, leading to hyperglycaemia. Glycaemia is, however, normalised at a later stage of development, when other signals, independent from autonomic nervous activity, are activated to increase beta cell mass, leading to a sufficient insulin secretion capacity.

Interestingly, a role for GLUT2 expression in the control of food preference has been suggested by studies of two cohorts of individuals with the common Thr110Ile variant of GLUT2 [88]; these individuals show a significant preference for high-sugar-containing food. A similar preference for glucose solutions has been observed in cohorts of NG2KO mice (G. Labouèbe, B. Thorens, unpublished observations). However, when expressed in *Xenopus* oocytes the GLUT2 Thr110Ile variant is normally transported to the cell surface and its glucose transport activity is normal [89]. Thus, in humans, the genetic mutation that codes for the Thr110Ile variant may also be involved in mechanisms regulating GLUT2 expression at a pretranslational level; alternatively, it may suppress a putative signalling mechanism that is distinct from GLUT2 sugar transport activity and is dependent on Thr110.

> Inactivating mutations in *GLUT2* in humans cause Fanconi–Bickel syndrome, characterised by hepatomegaly, growth retardation and renal syndrome. Patients with Fanconi–Bickel syndrome have been observed to have transient neonatal diabetes mellitus, indicating a link between GLUT2 and insulin secretion in human neonates.

Genome-wide association studies

Genome-wide association studies have found that variants in *GLUT2* (including the Thr110Ile variant encoded by the rs5400 single nucleotide polymorphism) are associated with impaired fasting glucose [90, 91], type 2 diabetes and an increased risk of transition from impaired fasting glycaemia to diabetes [90, 92–94]. When *GLUT2* SNPs are investigated in association with other phenotypes, such as intensity of exercise, the presence of the major allele predicts that low physical activity increases the risk of developing type 2 diabetes by about threefold as compared with high physical activity; the presence of the minor allele has no predictive value [93]. A search for genetic regions associated with plasma lipid profiles and adjusted for diet and physical activity found that the *GLUT2* locus has a major influence on serum cholesterol levels [95]. Another study found that out of 46 genetic variants examined, only the minor risk allele of *GLUT2* was significantly associated with a risk of cardiovascular diseases [96].

These genetic studies therefore indicate that *GLUT2* is involved in regulatory mechanisms that control impaired fasting glucose, the risk to transition to type 2 diabetes, preference for sugar-containing foods, as well as cholesterol levels and risk of cardiovascular disease. Because GLUT2 is only one of the glucose transporters present in beta cells, it is unlikely that slight changes in expression could have an impact on insulin secretion. Studies in mice showed that *Glut2* expression in the nervous system controls glucose-regulated autonomic nervous activity, which could impact liver, adipocytes and heart function. It is tempting to speculate that *GLUT2* has a dominant role in glucose sensing in the nervous system in humans and that its deregulation precedes the development of type 2 diabetes.

Genome-wide association studies have reported that GLUT2 variants are associated with fasting hyperglycaemia and an increased risk of type 2 diabetes.

Summary and perspectives

Studies of the facilitated diffusion glucose transporters have revealed a multitude of novel regulatory systems controlling glucose homeostasis [17, 97]. The investigations of GLUT2 function reported here shed light on some unique regulatory mechanisms, in particular related to blood glucose monitoring and the control of pancreatic hormone secretion, activity of the autonomic nervous system, and feeding and thermoregulation. The results of mouse physiological studies and human genetic-physiological studies to date suggest that, in humans, the association of *GLUT2* mutations with transient neonatal diabetes, fasting hyperglycaemia, and risk of type 2 diabetes may be best explained by defects in neuronal glucose sensing, which induce loss of first-phase insulin secretion, deregulated feeding behaviour, hyperglucagonaemia, and progressive development of glucose intolerance and impaired GSIS. This suggests that loss of nervous glucose sensing may actually precede the establishment of the alpha and beta cell defects that are characteristic of overt type 2 diabetes. Thus, it would be highly interesting to test the loss of nervous glucose sensing in humans. The investigations could include assessment of the cephalic phase of insulin secretion, which relies on nervous glucose sensing. If this response shows a conserved pattern in healthy individuals, a decreased response may indicate a prediabetic state. Designing specific clinical investigations to test this hypothesis could be an important goal of future research.

A still unresolved question is why is a high K_m glucose transporter required in glucose-sensing cells in the brain when the parenchymal glucose concentration is approximately one-third of that in the blood [11], i.e. much lower than the K_m of GLUT2 for glucose? And why is GLUT2 associated with both GI and glucose-excited (GE) neurons? Related to the first question, it is still unknown whether the high K_m for glucose represents an advantage for glucose sensing in the brain or whether GLUT2 has signalling properties that are independent of its transport capacity. Concerning the role of GLUT2 in both GI and GE neurons, we previously proposed a model to explain the observation that plasma glucagon levels in *Glut2*-null mice are elevated in the basal state and no longer increased by hypoglycaemia or suppressed by hyperglycaemia [37]. This model proposes that during hypoglycaemia, GI neurons generate a positive signal to stimulate autonomic nervous activity and glucagon secretion; in the absence of GLUT2 this positive signal can no longer be suppressed when euglycaemia is restored. On the other hand, when glycaemia increases GE, neurons generate an inhibitory signal that suppresses autonomic activation of alpha cells; in the absence of GLUT2, this signal cannot be generated. Thus, *Glut2* knockout leads to permanently elevated stimulation of glucagon secretion [98]. Our studies on NTS *Glut2*-expressing neurons have shown that these are indeed activated by hypoglycaemia to control parasympathetic activity and glucagon secretion [75]. On the other hand, *Glut2*-expressing neurons of the basolateral medulla are activated by glucose injections as revealed by c-fos immunostaining [63]. Whether they are GE neurons that negatively control glucagon secretion will, however, require direct analysis using electrophysiological and optogenetic techniques. These studies will be important to further validate our hypothesis that GE and GI *Glut2*-expressing neurons functionally interact to fine-tune autonomic nervous activity and glucagon secretion. The identification of these neurons will also pave the way to a new understanding of the mechanisms leading to hypoglycaemia-associated autonomic failure.

Finally, because knocking out *Glut2* in the nervous system leads to suppressed regulation of parasympathetic activity by glucose and impaired control of beta cell mass and function [68], it will be important to identify the glucose-sensing neurons that control this autonomic activity. Identification of these glucose sensing cells may lead to alternative ways of improving insulin secretion capacity in diabetic patients.

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