Am J Physiol Gastrointest Liver Physiol 310: G645–G658, 2016.
First published March 3, 2016; doi:10.1152/ajpgi.00015.2016.

Review

Glucosensing in the gastrointestinal tract: Impact on glucose metabolism

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Submitted 11 January 2016; accepted in final form 25 February 2016

Fournel A, Marlin A, Abot A, Pasquio C, Cirillo C, Cani PD, Knauf C. Glucosensing in the gastrointestinal tract: Impact on glucose metabolism. *Am J Physiol Gastrointest Liver Physiol* 310: G645–G658, 2016. First published March 3, 2016; doi:10.1152/ajpgi.00015.2016.—The gastrointestinal tract is an important interface of exchange between ingested food and the body. Glucose is one of the major dietary sources of energy. All along the gastrointestinal tube, e.g., the oral cavity, small intestine, pancreas, and portal vein, specialized cells referred to as glucosensors detect variations in glucose levels. In response to this glucose detection, these cells send hormonal and neuronal messages to tissues involved in glucose metabolism to regulate glycemia. The gastrointestinal tract continuously communicates with the brain, especially with the hypothalamus, via the gut-brain axis. It is now well established that the cross talk between the gut and the brain is of crucial importance in the control of glucose homeostasis. In addition to receiving glucosensing information from the gut, the hypothalamus may also directly sense glucose. Indeed, the hypothalamus contains glucose-sensitive cells that regulate glucose homeostasis by sending signals to peripheral tissues via the autonomous nervous system. This review summarizes the mechanisms by which glucosensors along the gastrointestinal tract detect glucose, as well as the results of such detection in the whole body, including the hypothalamus. We also highlight how disturbances in the glucosensing process may lead to metabolic disorders such as type 2 diabetes. A better understanding of the pathways regulating glucose homeostasis will further facilitate the development of novel therapeutic strategies for the treatment of metabolic diseases.

glucosensing; glucose homeostasis; diabetes

GLUCOSE REPRESENTS ONE of the major sources of energy circulating throughout the body. The tight and continuous control of glycemia in the face of fluctuations in glucose absorption, storage, and production is crucial for all living organisms. Not surprisingly, the gastrointestinal tract constitutes the first anatomic site for the detection of nutrients, including glucose. Glucose detection involves specialized cells referred to as glucosensors (21, 44, 64). These cells, which are present in the oral cavity as well as the small intestine, pancreas, and portal vein, express various glucose transporters and G protein-coupled receptors (GPCRs) implicated in the physiological response to glucosensing (21, 44, 64). Glucosensing by these cells evokes complex neural and endocrine responses that control glucose metabolism. Moreover, glucose detection in the gastrointestinal tract also transmits afferent nervous impulses to the brain, which, in turn, controls peripheral glucose utilization. Indeed, the brain, specifically the hypothalamus, is a key player in the regulation of glucosensing mechanisms. In addition to receiving information via the gut-brain axis, the hypothalamus also contains glucosensitive cells able to detect glucose (91). Upon the integration of these messages, the hypothalamus sends specific signals to the tissues involved in glucose metabolism via the autonomous nervous system (ANS).

Metabolic disorders such as type 2 diabetes (T2D) are considered as epidemics in industrialized countries where accessibility to food exceeds the actual energy need. Although the medical and technological knowledge of these disorders has improved tremendously, the pathogenesis of diabetes remains poorly understood, and efficient therapeutic tools are still lacking. In this respect, the success of gastric bypass surgery and new promising gut-derived pharmacological treatments, such as the use of glucagon-like peptide-1 (GLP-1) analogs, highlights the importance of the gastrointestinal tract in regulating glucose homeostasis (23). Moreover, the so-called "gut-brain axis" is currently an intriguing topic in the search for new antidiabetic tools (23). Thus, a better understanding of the pathways involved in glucosensing inside and outside the gastrointestinal tract will likely contribute to the identification of future therapeutic targets for the treatment of

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diabetes. In this review, we focus on how the gastrointestinal tract and the hypothalamus regulate glucose metabolism under both physiological and pathological conditions.

GLUCOSENSING IN THE GASTROINTESTINAL TRACT

Glucosensing in the Oral Cavity

The oral cavity is the gateway to the digestive tract, where sugars from food are partially digested by salivary enzymes. The tongue is the first organ involved in the detection of sugars, glucose in particular, playing an important part in the regulation of glucose homeostasis.

Cell types involved in glucosensing. The surface of the tongue and the palate epithelium are mapped with different papillae (circumvallate, foliate, and fungiform) within which taste buds are anchored. Taste buds are composed of several taste receptor cells (TRCs) that are differentially expressed across mammalian species (44). Type II TRCs are responsive to local increases in sugar levels, including glucose, within the mouth and function in sweet taste perception while also modulating glucose absorption (44).

Molecular mechanisms of glucosensing. At a molecular level, sweet tastant detection is mediated by two GPCRs called TAS1R2 and TAS1R3 (14). The binding of sweet compounds activates these sweet taste receptors in the taste buds and induces an intracellular transduction cascade leading to the depolarization of the TRCs (44). More precisely, TAS1R2/TAS1R3 activation results in the dissociation of gustducin GPCR subunits (e.g., α-gustducin, Gβ, and Gγ13), leading to increased phospholipase C-β2 activity, which, in turn, results in calcium (Ca^{2+}) release from intracellular stores in a process mediated by inositol 1,4,5-trisphosphate receptor type 3. This pathway allows the opening of transient receptor potential cation channel subfamily M member 5 and leads to the depolarization of membrane TRCs, generating an action potential and ATP release. In turn, the released ATP acts as a transmitter, activating gustatory afferent nerve fibers within the subepithelial connective tissue of the tongue (Fig. 1) (44).

Studies performed in vitro using reporter systems and in vivo with mice deficient for TAS1R3 have shown that the heterodimeric TAS1R2/TAS1R3 receptor is the principal mammalian sweet taste receptor responsive to sweeteners, but it does not directly work via the binding of glucose (14, 19). Damak et al. suggested that additional sugar-sensing mechanisms might exist, depending on the sugar level, but only a supraphysiological glucose concentration was tested in their study (19). Moreover, the presence of glucose transporters in TRCs highlights the functional cross talk between the perception of and the cellular response to a glucose stimulus. TRCs of lingual circumvallate papillae express major glucose transporters, e.g., sodium-glucose cotransporter-1 (SGLT-1) and glucose transporter-2 (GLUT-2), which act as a local glucose monitoring system and mediate active and passive glucose transport, respectively (56). Like intestinal enteroendocrine cells (EECs), TRCs are polarized cells, and the glucose transporters (GLUT-2) are localized to basolateral and/or apical regions of TRCs, in close proximity to TAS1R3 and α-gustducin. Moreover, these cells express voltage-gated sodium and potassium channels and SGLT-1, allowing active glucose transport by the electrochemical gradient (Fig. 1) (21, 56).

Using 2-deoxy-D-glucose (2-DG), a nonmetabolized glucose analog, and α-methyl-D-glucoside, which is specifically transported by SGLT-1, Oyama et al. showed that glucose transporters account for most of the glucose uptake in the oral cavity (69). Glucose uptake stimulates the lingual sodium transport system (57). Modification of the electrophysiological gradient increases a series of intracellular events, with changes in the cytosolic ATP-to-ADP ratio and subsequent closure of ATP-sensitive potassium channels (K_{ATP} channels) leading to TRC depolarization, thereby transforming glucosensing into neural signals (14). In this mechanism, the release of ATP acts on purinergic receptors to activate the gustatory nerve fibers

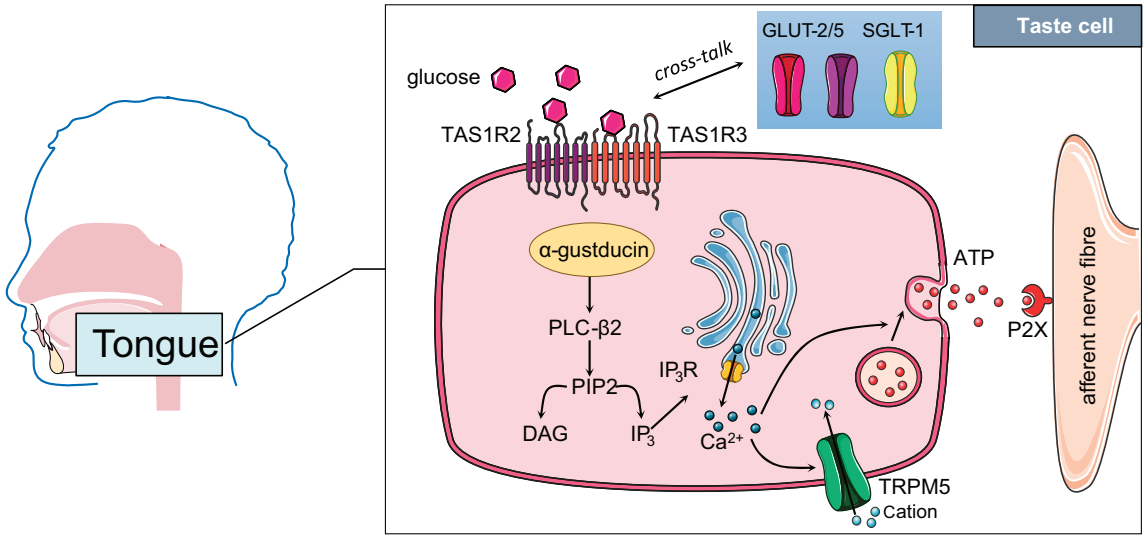

Fig. 1. Molecular mechanisms involved in glucosensing in the oral cavity. In the taste buds, activated TAS1R2/TAS1R3 heterodimers interact with G proteins comprising α-gustducin, leading to phospholipase C-β2 (PLC-β2) activation. In turn, activated PLC-β2 cleaves phosphatidylinositol 4,5-bisphosphate (PIP_2) into inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 stimulates Ca^{2+} release from the endoplasmic reticulum via type III IP_3 receptor activation (IP_3R). The elevated intracellular Ca^{2+} activates the transient receptor potential cation channel subfamily M member 5 (TRPM5) and induces membrane depolarization and ATP release, which stimulates efferent nerve fibers. GLUT-2/5, glucose transporter-2/5; SGLT-1, sodium-glucose cotransporter-1.

within the primary taste nucleus of the solitary tract in the brain stem, involved in taste perception (26).

The functional relationship between sweet-tasting perception and glucosensing is further enhanced by hormonal modulation. Indeed, paracrine hormones, including GLP-1 and glucagon, influence TRC signaling. The functions of these peptides in taste buds are not fully understood, but it is known that they are able to modulate the response of the peripheral gustatory apparatus and glucosensing mechanisms (49). GLP-1 is present in murine α-gustducin/TAS1R3-expressing taste cells in circumvallate papillae, suggesting a potential role for GLP-1 signaling in sweet taste function. Considering the dramatically reduced taste response to sweeteners observed in GLP-1 receptor knockout (KO) mice (90) and the absence of GLP-1 secretion in the circumvallate papillae of TAS1R3 KO mice (31), GLP-1 signaling could potentially maintain or enhance sweet taste sensitivity. Furthermore, dipeptidyl-peptidase 4, which is involved in GLP-1 degradation, is not expressed in taste buds, suggesting an enhanced half-life of GLP-1 in taste tissues, thus ensuring that taste buds have a sufficient level to stimulate their GLP-1 receptors (90). Moreover, similar to GLP-1 expression, glucagon and alternate processing enzyme, which is involved in glucagon biosynthesis, are also found in mouse taste cells and colocalize with TAS1R3 (90). Both genetic and pharmacological disruption of glucagon signaling in mice results in reduced sweet taste responsiveness, indicating a role for local glucagon signaling in the peripheral modulation of this process (13).

Consequences of glucosensing on glucose homeostasis. Sweet gustatory responses to glucose stimuli play an important role in regulating glucose homeostasis through the modulation of neuronal messages to peripheral tissues. There is some evidence demonstrating that, similar to intestinal cells, sugar-sensing cells participate in the maintenance of glucose homeostasis and that hormones binding receptors on taste cells alter the palatability of food (49). For example, the presence of GLP-1 in taste bud cells suggests a role for this peptide in the taste of sweet compounds and in gut hormone secretion after meal ingestion. In animal models deficient for α-gustducin, loss of the GLP-1 response to enteric glucose has been observed, thereby highlighting that the insulinotropic effects of GLP-1 are associated with taste signaling molecules, limiting postprandial glucose excursions (49).

Pathology. Clinical and experimental evidence has revealed that obesity is associated with alterations in taste responsiveness in humans and rodents (13, 21). Taste buds of diabetic rats exhibit enhanced expression of α-gustducin protein and reduced expression of the sweet taste receptor TAS1R3, which may partially explain the sweet taste disorders observed in the diabetic context (96, 97). Although morphometry studies have shown that diabetic rats present no significant difference in papillae size compared with control animals, the innervation of these taste cells is significantly reduced (71). Therefore, the attenuation of sweetness perception may trigger sweet-seeking behaviors in some individuals, potentially increasing the risk of overconsumption of high-energy foods (e.g., rich in glucose) and eventually contributing to the development of obesity (49).

In addition, it has been found that metabolic hormone levels change in obese subjects (13, 49); this may also alter the output of hormonal modulation by taste cells, as described above. These changes may also participate in the altered gustatory sensitivity to tastants and modify glucose intake in obesity (13, 49). Diet-induced obesity in rats causes increased GLP-1 secretion in taste buds, explaining the greater preference for sweet taste observed in obese animals (96). Other studies have highlighted the close association between gustatory pathways and hormonal modulation altered in an obesity context. For example, some studies have demonstrated that the gustatory neural response is enhanced in diabetic Db/Db mice, whereas their threshold to sweet taste compounds is lowered (65, 87).

The tongue is thus an important peripheral organ involved in orchestrating metabolic homeostasis, altered in the context of obesity (21).

Glucosensing in the Small Intestine

The small intestine is the main sensor of ingested carbohydrates and is responsible for secreting numerous hormones involved in the modulation of multiple physiological functions, including glucose homeostasis. In this part of the gastrointestinal tract, glucosensing is performed by different specialized cell types localized in the intestine wall.

Cell types involved in glucosensing. The enterocyte is the most represented epithelial cell type lining the gut mucosa and, consequently, constitutes an important interface between ingested food (glucose) and the rest of the body. Moreover, as absorptive cells, enterocytes mediate nutrient uptake and are responsible for the epithelial secretory process. These functions indicate that enterocytes may play a fundamental role in intestinal glucosensing. This notion is substantiated by the fact that intestinal absorption of glucose triggers discharges of afferent nerves, a phenomenon abolished by phloridzin, a sodium-glucose symporter blocker, and is not initiated by nonabsorbed carbohydrates (55).

In addition to the classical absorptive enterocytes, there is a distinct type of enterocytes called brush cells that are involved in glucosensing in the small intestine (21). These cells are morphologically similar to lingual taste cells and strongly express α-gustducin, a mediator of gustatory signaling (21). Because of this similarity, it has been suggested and subsequently demonstrated that brush cells may participate in sugar sensing by a mechanism analogous to that of taste buds of the lingual epithelium (52).

In addition to enterocytes, EECs are also involved in glucose detection in the small intestine. After detecting glucose, these cells secrete gastrointestinal hormones that inform the body of the nutritional state (75). Among EECs, L cells and K cells, which secrete GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), respectively, are the two major EEC types involved in intestinal glucose detection (21, 75).

Last but not least, enteric neurons also participate in glucosensing within the small intestine. The gut wall is composed of millions of neurons organized into two major plexus: the submucosal plexus, which is directly in contact with the intestinal mucosa, and the myenteric plexus, located between the circular and longitudinal muscular layers (73). Although the enteric nervous system (ENS) is classically known to control intestinal motility, secretion, and absorption, recent evidence suggests its involvement in glucosensing. It has been shown that intraintestinal infusion of glucose increases c-Fos expression, a marker of cell activation, in enteric neurons in conscious rats (84). Moreover, the secretion of gastrointestinal

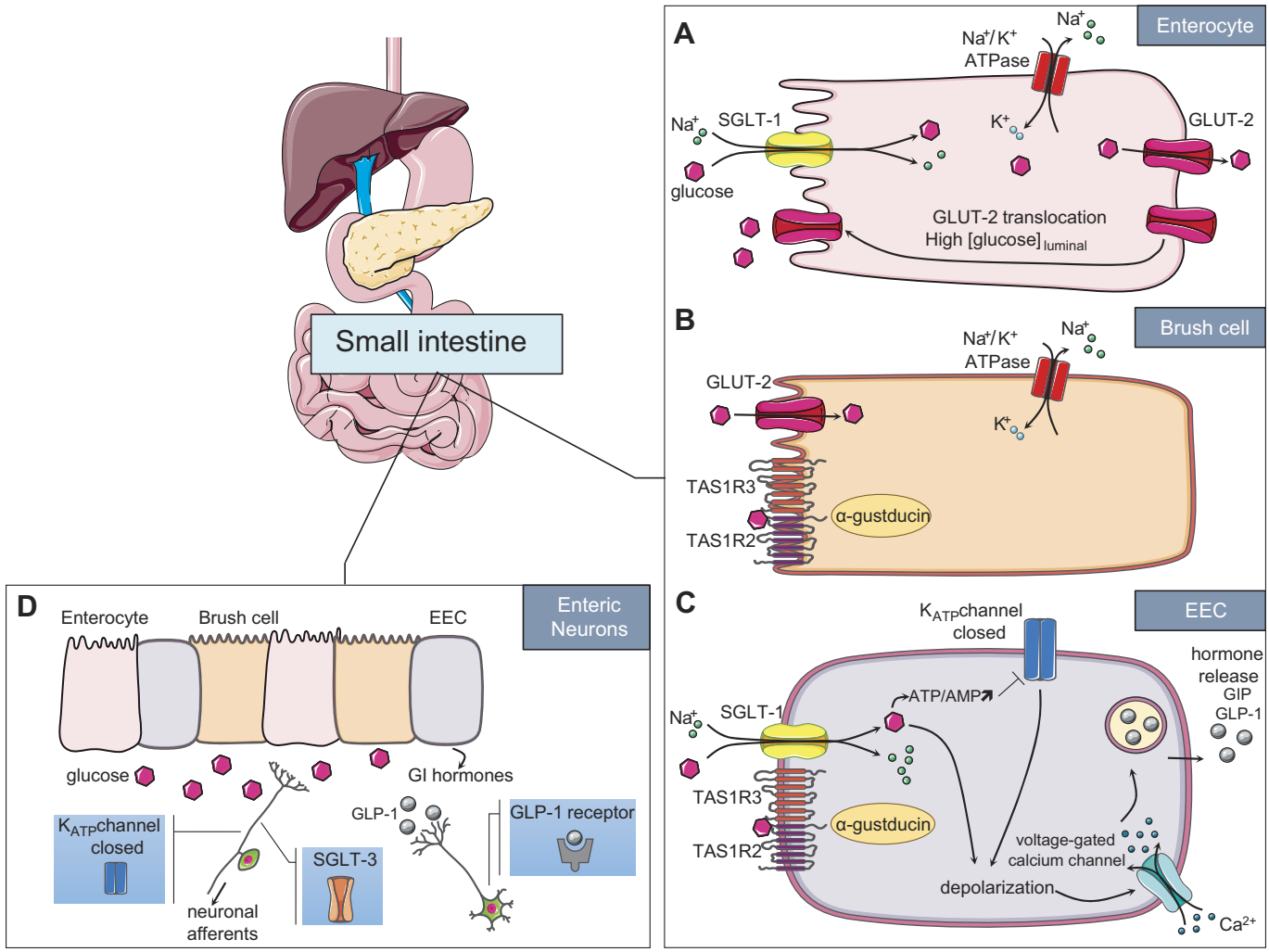

Fig. 2. Molecular mechanisms involved in glucosensing in the gastrointestinal tract. *A*: in enterocytes, transport of glucose occurs by SGLT-1, following the Na^+ electrochemical potential gradient across the apical membrane until its intracellular concentration is sufficiently elevated. Glucose is transported outside of enterocytes by facilitated diffusion through GLUT-2, localized on the basolateral membrane of the cell. Saturation of SGLT-1, depending on the luminal glucose concentration, is associated with an increase of GLUT-2 translocation to the apical membrane. *B*: in brush cells, the glucose trafficking signal transduction pathway involves GLUT-2 transporters. This mechanism is coupled with TAS1R2/TAS1R3 sweet taste receptor activation that was described for taste buds. *C*: enteroendocrine cells (EEC) receive glucose stimulation via sweet taste receptor activation, as described below, but GLUT-2 also trigger the entry of glucose into the glycolytic pathway to generate ATP. This increase in ATP leads to closure of ATP sensitive potassium channels (K_{ATP}) channels, membrane depolarization, opening of Ca^{2+} channels, and release of hormones like glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1); note that membrane depolarization can be induced by glucose itself. *D*: enteric neurons are glucosensitive: extracellular glucose removal leads to hyperpolarization and decreases in their membrane input resistance. The excitation of these neurons is mediated by inhibition of K_{ATP} channels or by SGLT-3. They can also be activated by gastrointestinal (GI) hormones secreted by EECs in response to glucose detection. Enteric neurons can activate neighboring neurons or transmit glycemic information to the brain via nervous afferents.

hormones stimulated by glucosensing EECs might be able to secondarily activate enteric neurons (73). Thus, activation of enteric neurons by intraluminal glucose occurs either directly or indirectly via the EECs.

Molecular mechanisms involved in glucosensing. ENTEROCYTES. Glucose absorption in enterocytes is carried out by two connected transporters. Apical active transport of glucose occurs via SGLT-1, following the sodium electrochemical potential gradient across the apical membrane (94). Consequently, glucose accumulation in the cytosol leads to the elevation of its intracellular concentration. Glucose is then transported out of the enterocyte by facilitated diffusion through GLUT-2, which is localized on the basolateral membrane of the cell. In addition to the GLUT-2 pathway, studies on intestinal absorption in GLUT-2 null mice and in patients with GLUT-2 deficiency suggest an alternative pathway for glucose exit from the enterocyte by exocytosis (94). However, saturation of SGLT-1 has been observed in conditions of increased luminal glucose concentrations. This effect is associated with increased GLUT-2 translocation to the apical membrane. As a consequence, in this context, both inflow and outflow of glucose across the enterocyte are mediated by GLUT-2 (Fig. 2*A*) (42).

BRUSH CELLS. In addition to the involvement of enterocytes and the SGLT-1/GLUT-2 pathway in glucosensing and glucose absorption, studies have shown that brush cells within the small intestine also actively participate in this phenomenon. Brush cells have a similar morphology as lingual taste cells and express sweet taste receptors. As described previously, the

TAS1R2/TAS1R3 heterodimeric sweet taste receptor is able to release ATP, which acts on afferent nerve fibers and leads to taste perception (21, 26). In the gut, perfusion of TAS1R2 and TAS1R3 ligands strongly stimulates glucose absorption through the rapid insertion of apical GLUT-2. This result supports the idea that the ability of brush cells to detect and "taste" glucose could contribute to the complex glucosensing process in the small intestine (Fig. 2*B*) (52).

ENTEROENDOCRINE CELLS. EECs, as enterocytes, are polarized cells. These cells present an apical surface facing the gut lumen, allowing glucosensing, and a basolateral surface from which secretory vesicles are exocytosed in response to glucose detection. A number of mechanisms for glucose-stimulated GLP-1 and GIP release have been proposed for EECs. The most well known is the sodium-coupled glucose uptake performed by SGLT-1, which generates small currents that trigger EEC membrane depolarization, causing Ca^{2+} channels to open and the consequent release of GLP-1 or GIP (Fig. 2*C*). Accordingly, pharmacological inhibition of SGLT-1 in vitro abolishes GLP-1 and GIP secretion, and SGLT-1-deficient mice exhibit reduced GLP-1 and GIP levels following oral glucose administration (75). Additionally, following its transport into L and K cells via SGLT-1, glucose enters into the glycolytic pathway to generate ATP. The increase in ATP leads to closure of K_{ATP} channels, membrane depolarization, opening of Ca^{2+} channels, and release of GIP and GLP-1. Studies showing an enhancement of GLP-1 secretion in vitro in response to a K_{ATP} channel blocker also suggest a potential role for glucose metabolism in gastrointestinal hormone secretion (21).

The activation of sweet taste receptors (TAS1R2/TAS1R3 heterodimers) by glucose and the consequent stimulation of hormone secretion have also been proposed. It has been shown that the G protein α-gustducin colocalizes with GLP-1 and GIP in the small intestine (21, 75). In addition, several sweet taste receptor agonists can elicit GLP-1 secretion from mouse and human EECs in vitro. Conversely, TAS1R3-deficient mice exhibit impaired glucose-stimulated GLP-1 secretion (Fig. 2*C*) (21, 75). Finally, intragastric perfusion of lactisole, an inhibitor of TAS1R2/TAS1R3 receptor, induces a significant reduction in GLP-1 secretion in humans in response to intragastric or intraduodenal perfusion of glucose (32). All of these observations demonstrate that TAS1R2/TAS1R3 receptor is involved in glucose-dependent secretion of gastrointestinal hormones.

Once secreted, gastrointestinal hormones diffuse to the bloodstream or bind to their specific receptors on enteric neurons and/or afferent nerve endings.

ENTERIC NEURONS. Glucose sensing by enteric neurons occurs by direct and indirect pathways, as described above. On the one hand, enteric neurons can be indirectly activated by gastrointestinal hormones secreted by EECs in response to glucose detection. Accordingly, recent technological advances have made possible the generation of GLP-1 receptor-Cre mice crossed with fluorescent reporter strains, facilitating the identification of GLP-1 receptor-positive neuronal cell bodies in the ENS (Fig. 2*D*) (77).

On the other hand, enteric neurons seem to be able to sense glucose directly. In 1999, Liu et al. identified glucoresponsive neurons in the small intestine of guinea pigs (48). These glucoresponsive neurons could be distinguished from other neuronal populations because of their hyperpolarization and the decrease in their membrane input resistance observed in response to glucose removal from the extracellular milieu. This effect was reversed by the reintroduction of glucose or by the K_{ATP} channel inhibitor tolbutamide, suggesting that the glucose-induced excitation of enteric neurons is mediated by the inhibition of these channels. In addition, immunofluorescence analysis has demonstrated that enteric neurons in both the submucosal and myenteric plexus express SGLT-3 (22). In this study, the authors showed that D-glucose causes depolarization of membrane potential in oocytes expressing SGLT-3. These findings suggest that SGLT-3 could also function as a glucose sensor in enteric neurons (Fig. 2*D*).

Once activated by glucose, enteric neurons could activate neighboring enteric neurons within the ENS or transmit the glycemic information centrally to the brain stem via nerve afferents.

ENTERIC GLIAL CELLS. Another intestinal partner potentially involved in glucosensing is the enteric glial cell (EGC). Nevertheless, the role of EGCs in glucosensing is not as clear as those of the other cell populations described above. Only a couple of studies in the last decade have tried to elucidate the function of EGCs in glucose metabolism. These investigations suggest that EGCs are indirectly involved in glucose homeostasis through a fine cross talk with pancreatic β-cells. Specifically, EGCs communicate with β-cells via the release of glial-derived neurotrophic factor (GDNF). Once released, GDNF binds specific receptors, i.e., Ret receptor tyrosine kinase and the glycosylphosphoinositol-anchored coreceptor (GFRα), on β-cells. This interaction influences β-cell function and mass and protects them from damage, e.g., in the diabetic state (62). The GFRα receptor in particular represents an important link between the nerve and the endocrine compartments within the pancreas. Indeed, it has been shown that the signaling evoked by the GDNF-GFRα interaction is needed for the establishment of parasympathetic innervations in the islets, which are crucial for the regulated secretion of pancreatic hormones (79). All together, these mechanisms account for the indirect role of EGCs in the regulation of glucose homeostasis.

Consequences of GLP-1 and GIP release on glucose homeostasis. As described earlier in this review, the gastrointestinal tract is a specialized sensory system responsible for the detection of ingested glucose and the subsequent relay of information to peripheral tissues or the brain to regulate glucose metabolism. Here, we discuss the role of the different organs involved in the regulation of glucose homeostasis.

PANCREAS. In healthy subjects, oral administration of glucose causes a two- to threefold higher insulin response compared with intravenous infusion of glucose, known as the incretin effect. This incretin effect reflects the capacity of gastrointestinal hormones, released in the portal vein, to increase insulin secretion by the pancreas. Among gastrointestinal hormones, it is now well established that GLP-1 and GIP are the two most important incretins. First, the receptors for GLP-1 and GIP are expressed by β-cells in the pancreas (40). Second, in experiments where GLP-1 and GIP were infused together with glucose, both elicited insulin secretion to an extent that can fully explain the insulin response (40). In contrast, the use of GLP-1 and GIP receptor antagonists abolishes this response (40). Finally, when glucose levels are at or above fasting levels, GLP-1 strongly inhibits glucagon secretion (40).

INTESTINE. Incretins also have extrapancreatic functions. First, it has been shown that GLP-1 has a profound inhibitory

effect on gastric emptying of a liquid mixed test meal in healthy normoglycemic volunteers (63). The decrease in gastric emptying slows the gastric transit of nutrients from the stomach to the intestine, thus reducing the importance of postprandial glycemia and helping to normalize glycemic levels. The mechanism by which GLP-1 mediates the inhibition of gastrointestinal motility has not been fully established. However, recent evidence suggests that the GLP-1 inhibitory effect is mediated through nitric oxide (NO) release by enteric neurons. Approximately 30% of neurons in the small intestine coexpress the GLP-1 receptor and neuronal NO synthase (nNOS) (4). Furthermore, in vitro studies have demonstrated that inhibition of nNOS abolishes the inhibitory effect of GLP-1 on small intestine contractility in mice (4).

LIVER. Beyond the digestive system, incretin hormones can also target the liver. During hyperglycemic clamp, GLP-1-treated mice exhibited reduced hepatic glucose production associated with increased [^{13}C]lactate labeling from glucose in the liver (34). This last result was reinforced by the increased rate of glycogen synthesis found in the liver of GLP-1-treated mice during the clamp experiment. All of these findings indicate that, in addition to enhancing glucose storage by the liver, GLP-1 can inhibit hepatic glucose production.

ADIPOSE TISSUE. In vitro costimulation of adipocytes with insulin and GIP elicits GLUT-4 (the insulin-sensitive glucose transporter) translocation to the membrane, demonstrating that GIP can enhance insulin sensitivity in adipose tissue (60). Moreover, in rat adipocytes, GLP-1 increased insulin-stimulated 2-DG uptake and triggered rises in glycogen synthesis and oxidation (72).

HYPOTHALAMUS. Incretins released into the portal vein can directly target peripheral tissues to control glucose metabolism. However, these incretins are rapidly degraded by enzymes in the blood of the portal vein, forcing them to use a second route to affect peripheral tissues. In line with this concept, Knauf et al. proposed the following model: at the beginning of a meal, detection of glucose by the intestine elicits GLP-1 release, leading to an afferent nervous message to the brain (45). Integration of this enteric message by the brain stem generates GLP-1 production by this structure. Thus, secreted GLP-1 reaches the hypothalamus where its receptors are present. Central GLP-1 receptor activation leads to secretion of catecholamines providing input to sympathetic preganglionic neurons (95). Therefore, central GLP-1 is linked to the regulation of the ANS. Via this ANS pathway, the GLP-1-sensitive cells then signal the pancreas to secrete insulin and skeletal muscles to prepare for glucose storage. At the end of a meal, when systemic hyperglycemia is evident, the brain directly detects the glucose. Subsequently, a signal opposite to the one sent by enteric glucose detectors would then be sent to the muscles, leading to temporary muscular insulin resistance, permitting the redirection of glucose toward the liver to prepare for the fasting period between two meals (43).

Using specific NO amperometric probes implanted directly into the hypothalamus of mice, our group has demonstrated that NO release is stimulated in response to the activation of enteric glucose sensors (25). Hypothalamic NO is known to cause increased blood flow in mice, which is associated with enhanced glucose utilization (12). Conversely, the application of NO synthase inhibitors in the hypothalamus leads to peripheral hyperglycemia and insulin resistance (24). Thus, we could speculate that hypothalamic NO may be a target of enteric glucose detection that, in return, modulates glucose homeostasis.

Pathology. As described above, enteric detection of glucose is crucial for glucose homeostasis. It is therefore well established that impaired glucose detection in the intestine may result in profound metabolic disorders, such as T2D.

Knauf et al. have shown that, compared with normal mice, high-fat diet (HFD)-induced diabetic mice exhibited reduced c-Fos expression in the hypothalamus in response to intragastric infusion of glucose (43). The impaired enteric detection of glucose in diabetic mice is associated with a failure to induce changes in the glucose utilization rate. Following this project, our group has observed abnormalities in hypothalamic NO release in Db/Db genetically induced diabetic mice in response to intragastric perfusion of glucose (25). In parallel, the diabetic mice used in this study exhibited increased oxidative, inflammatory, and endoplasmic reticulum stress markers in the gut, whereas the same markers were only slightly affected in the hypothalamus. This last result suggests that the development of intestinal cellular stress leads to changes in brain NO-dependent glucose sensing in T2D.

Glucosensing in the Pancreas

Sensors located in the pancreas continuously monitor variations in blood glucose levels. Indeed, the presence of glucosensors in the endocrine part of the pancreas allows the modulation of hormonal secretions, emphasizing the crucial role played by these sensors in glucose homeostasis.

Cell types involved. β- and α-Cells are pancreatic glucose sensors located in the islets of Langerhans, representing 65 and 35% of total cellular islets, respectively. Similar to neurons, β- and α-cells are considered to be excitable upon glucose detection, due to the generation of a membrane potential. While β-cells respond to increases in glucose levels, α-cells are sensitive to variations in low glucose concentrations. Although the glucosensing role of β-cells is clearly established, the involvement of α-cells in this process is still debated (33).

Molecular mechanisms. β-CELLS. Pancreatic β-cells sense glucose through a two-step mechanism: the first involves the entry of glucose into the cell and subsequent glycolysis, followed in a second step by insulin secretion.

Glucose is transported into the cell by facilitated diffusion through GLUT-2, a glucose transporter characterized by rapid glucose uptake with low affinity. After its entry into β-cells, glucose is phosphorylated to glucose 6-phosphate by hexokinase IV. This enzyme allows β-cells to adjust glucose 6-phosphate formation rates according to blood glucose levels. Indeed, in β-cells, the glucokinase (GK) gene is constitutively transcribed, but hexokinase IV abundance is regulated by posttranscriptional mechanisms that are activated when blood glucose levels allow acceleration of intracellular glucose transport (54, 85). This results in an increase in glucose 6-phosphate formation rates during the postprandial period, when blood glucose levels are elevated. Thus, hexokinase IV plays an essential role in glucose detection by pancreatic β-cells. Once phosphorylated, glucose enters the glycolysis pathway to produce pyruvate and NADH coenzyme. Both cytosolic pyruvate and NADH then enter mitochondria and are metabolized to produce ATP (Fig. 3).

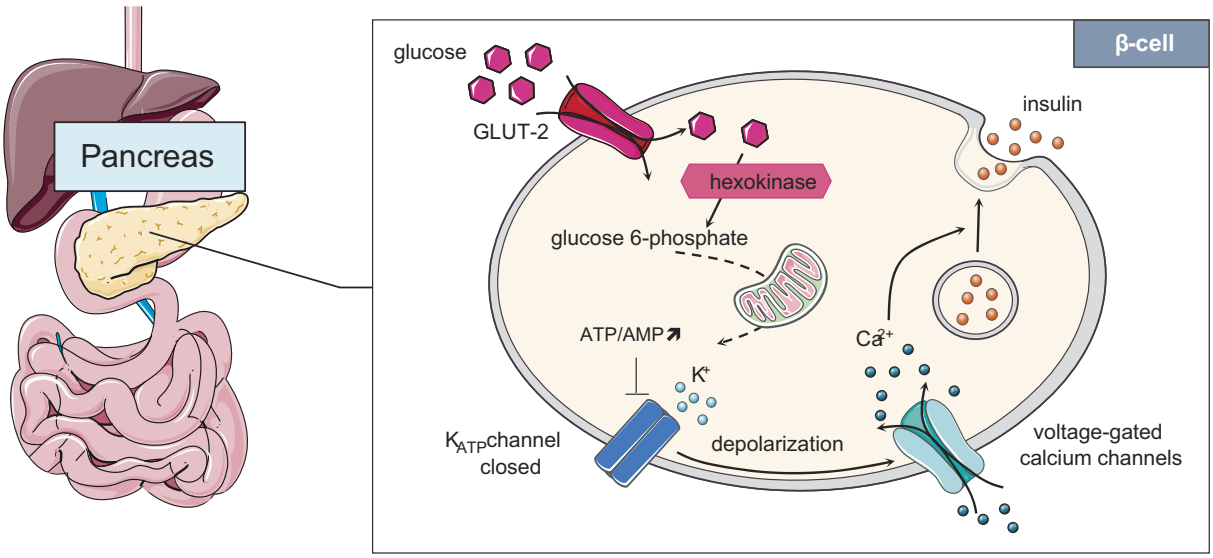

Fig. 3. Molecular mechanisms involved in glucosensing in the pancreas. In pancreatic β-cells, glucose is transported by GLUT-2, phosphorylated to glucose 6-phosphate by hexokinase IV, and subjected to the glycolysis pathway. This leads to an increase in ATP, followed by K_{ATP} channel closure and membrane depolarization. This depolarization, in turn, activates voltage-dependent Ca^{2+} channels, leading to Ca^{2+} accumulation in the cytoplasm and insulin secretion.

The subsequent increase in cytosolic ATP concentration inactivates K_{ATP} channels and induces depolarization of the β-cell membrane, leading to the opening of voltage-gated Ca^{2+} channels (51). Massive entry of Ca^{2+} allows the mobilization and exocytosis of secretory insulin vesicles. While the membrane potential is exclusively controlled by glucose, the exocytosis of insulin granules is also under the control of body energy needs. For this reason, β-cells have various functional insulin pools, which include an intracellular reserve pool (representing ~90% of the insulin store), a docked pool (~10%), and a pool ready for delivery, which is determined by the initial secretory response (between 0.3 and 2%) (Fig. 3) (78).

Interestingly, it should be added that other mechanisms are implicated in pancreatic β-cell glucosensing. As previously described under *Glucosensing in the Oral Cavity*, sweet taste receptors also play a key role in β-cells. Using an inhibitor of taste receptor type 1 member 3 receptor, Hamano et al. have shown that this receptor is required to induce insulin secretion by sweeteners (35). Moreover, Leloup et al. highlighted a major implication of reactive oxygen species (ROS) signaling in β-cell glucosensing. Glucose induces a transient and moderate H_2O_2 production in β-cells that is an obligatory stimulus for insulin secretion, whereas oxidative stress may disturb its signaling function (46).

α-CELLS. Pancreatic α-cells have also been reported to be glucosensitive. Indeed, α-cells express essential components for glucodetection found in β-cells: the K_{ATP} channel and GK (37). However, α-cells do not express GLUT-2 (68), and their glucosensor functions are debatable. Glucagon secretion appears to be more controlled by ANS than by glucosensing α-cells, since atropine (a cholinergic antagonist that acts by binding to muscarinic receptors) inhibits hypoglycemia-induced glucagon secretion (36). The regulation of glucagon secretion by ANS activity and hypothalamic centers will be extensively discussed under EXTRAGASTROINTESTINAL GLUCOSENSING: THE ROLE OF THE BRAIN below.

Based on different studies of the molecular mechanisms involved in glucose-dependent regulation of glucagon secretion, several models have been postulated (41, 76), but a large number of pathways remain to be unraveled. For example, the involvement of the K_{ATP} channel is controversial, and the link between glucose incorporation and inhibition of Ca^{2+} influx remains unclear. Consequently, much work still needs to be done to explain the molecular glucosensing mechanisms of α-cells.

Consequences of insulin and glucagon on glucose homeostasis. INSULIN. Insulin is secreted by β-cells in response to high blood glucose levels. In the liver, glucose flux is controlled by GK enzymes, not by its transport across the cell. Insulin increases the rate of glucose uptake by stimulating GLUT-4 translocation from intracellular pools to the cell surface (86). Moreover, by increasing glucose uptake, insulin promotes two limiting steps of glycolysis and enhances the activity of hexokinase and 6-phosphofructokinase (83).

In liver, muscle, and adipose tissues, insulin increases the rate of glycogen synthesis while also decreasing the rate of glycogen breakdown in muscle and liver. Insulin activates glycogen synthase by inducing its dephosphorylation through the inhibition of kinases (18). Insulin also inhibits the activity of glycogen phosphorylase (92). The liver is a crucial glucose-producing organ implicated in the maintenance of constant blood glucose levels, especially during the fasting period. Insulin directly controls the activities of gluconeogenesis enzymes, leading to the inhibition of this pathway (83).

There is a tight balance between hormones secreted by the exocrine part of the pancreas, with each being able to inhibit the other. Indeed, in hyperglycemic conditions, insulin inhibits glucagon release from α-cells.

GLUCAGON. Normally, glucagon, which is secreted by α-cells, exerts opposite effects to those of insulin. It is a hyperglycemic hormone secreted when blood glucose levels are too low. Glucagon mainly targets hepatic cells, but it can also act on other tissues involved in glucose metabolism, such

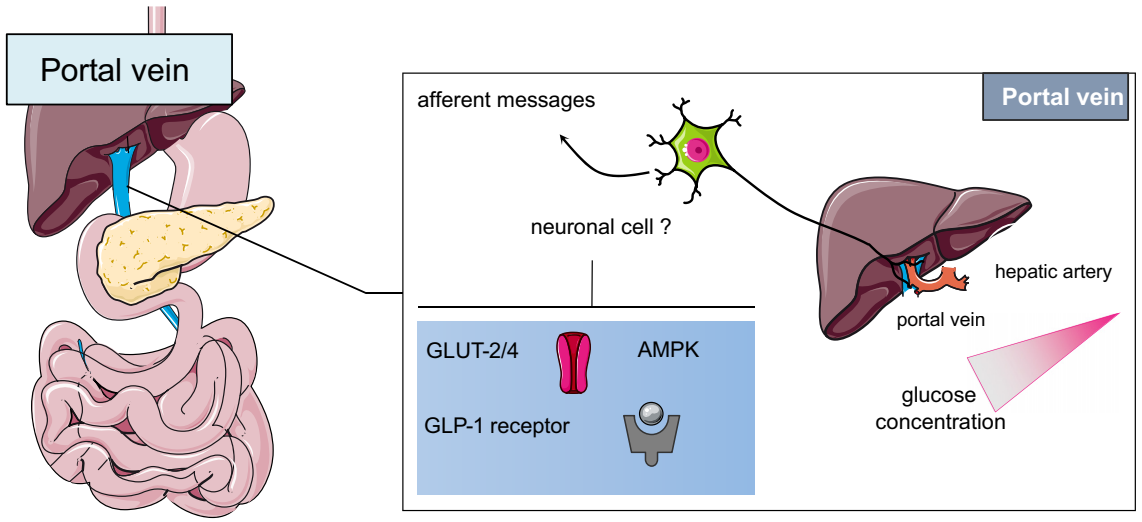

Fig. 4. Molecular mechanisms involved in glucosensing in the portal vein. In hepatoportal glucosensor cells, portal glucose concentrations are inversely correlated with the firing rate of hepatic afferent nerves. Little is known about the molecular mechanisms involved in hepatoportal glucosensing, but several actors are required, including GLUT-2, GLUT-4, AMP-activated protein kinase (AMPK), and GLP-1 receptor.

as the brain and adipose tissues (50). The release of glucagon from α-cells during hypoglycemia stimulates glucose release and production by the liver by activating glycogenolysis and gluconeogenesis. Glucagon can also initiate lipolysis in the liver and adipose tissues (50). Like insulin, glucagon modulates insulin secretion from β-cells, inhibiting it through a paracrine mechanism (3).

Pathology. As previously described, pancreatic β-cells respond to conditions of glucose excess by secreting insulin. This ability is lost in the case of T2D. Indeed, it has been shown in T2D patients that there is increased insulin release during the early diabetic stage, while at later stages, the rate of blood insulin declines and does not counterbalance the hyperglycemia. This defect in insulin secretion could be explained in part by impairment of glucosensing in β-cells, but it is instead generally considered the consequence of a multifactorial failure (99). GK plays a fundamental role in glucosensing, since genetic defects in GK lead to a form of diabetes, the so-called maturity-onset diabetes of the young, which develops gradually in adults (54). Glucosensing in α-cells also appears to be altered in T2D. Patients with T2D exhibit hyperglucagonemia, leading to overstimulation of glucose production by the liver during the fasting state. This is also associated with a deficit in glucagon secretion removal by insulin, a result of β-cell failure (11).

Glucosensing in the Portal Vein

Following digestion of nutrients by the digestive tract, glucose is absorbed by the intestinal epithelium and then released in the blood flow of the portal vein. Thus, the liver, via the portal vein, is perfectly located to regulate postprandial glucose levels through glucosensing mechanisms.

Cell types involved in glucosensing. The existence of glucoreceptors in the liver was first postulated by Russek in 1963 (82). He suggested that receptors send a signal to the central nervous system in response to the glucose present in portal venous blood. In the 1980s, Niijima and his collaborators described the suppressive effect of D-glucose infusion in the portal vein on the rate of afferent discharges of fibers in the hepatic branch of the vagus nerve (64). Only infusion of D-glucose decreased in discharge rates (i.e., there were no effects of D-fructose, D-mannose, or D-arabinose) (64), since it is the only sugar metabolized and used as an energy source by nerve cells. Adachi et al. in 1984 established the connection between glucose detection in portal venous blood and message integration in the central nervous system. For the first time, they highlighted the link between vagal endings in the portal vein and the brain stem (1). In 1997, Hevener and Bergman confirmed the neuronal origin of the detection mechanism by showing that glucose infusion in the portal vein induced a 66% decrease in epinephrine secretion compared with an infusion in the jugular vein (38). This inhibition was also found in portal denervation experiments (39). Therefore, hepatoportal glucosensing depends on glucose detection by vagal nerve endings.

Molecular mechanisms. Hepatoportal glucosensor cells respond to a gradient of glucose concentrations in the portal vein. The firing rate of hepatic afferent nerves is inversely related to the portal glucose concentration, with the rate of firing decreasing when the portal glucose level increases (64). This effect is observed over a range of portal blood glucose concentrations from 5.5 to >20 mM, which represents the physiological glucose levels found in this site. These findings clearly show that glucosensors send messages to the central nervous system in response to glucose fluctuations in the portal vein (Fig. 4).

The molecular partners involved in hepatoportal glucosensing are poorly understood. Nonetheless, in the early 2000s, Burcelin et al. showed that the GLUT-2 receptor is required for glucose detection in fasted mice, as well as for pancreatic β-cell glucosensing (9). In their study, the authors demonstrated that GLUT-2-deficient mice do not increase their peripheral glucose utilization in response to portal vein glucose infusion (Fig. 4).

The same group also identified the GLP-1 receptor as a second critical partner for portal glucosensing. They found that coinfusion of glucose and exendin-9 (a GLP-1 receptor antagonist) in the portal vein inhibited glucose clearance and in-

duced a transient increase in glycemia (8). They then demonstrated that the effects of hepatoportal glucosensing on muscle glucose utilization required other muscle players, including GLUT-4 and AMP-activated protein kinase (AMPK). Indeed, the infusion of glucose in the portal vein of mice with muscle-specific deletion of GLUT-4 induced similar glucose utilization in muscles to that observed after a femoral vein glucose infusion (7). Moreover, taking a similar approach, the authors showed that transgenic overexpression of a dominant-negative form of AMPK in mice also led to decreased glucose utilization (Fig. 4).

More recently, researchers have implicated SGLT-3 in portal glucosensing in conditions of low glucose flux. While portal glucose detection was inhibited by phlorizin (a specific inhibitor of SGLTs), infusion of 3-*O*-methylglucose (a nonmetabolizable glucose analog that is a substrate for all SGLTs but not GLUTs) activated portal glucosensing (20). These observations suggest the existence of a SGLT-3-dependent sensing mechanism in the portal vein.

Consequences on glucose homeostasis. The portal vein is the major site at which the organism receives the glucose absorbed by the intestine. Thus, by informing the body of glycemia changes, this site acts as a key player in the control of glucose homeostasis.

LIVER. The effects of portal vein glucosensing on the liver have been illuminated through the work of Gardemann et al. (30). These authors have developed a model to reproduce the glucose concentration gradient between the portal vein and the hepatic artery. By infusing high glucose concentrations in the portal vein and low concentrations in the hepatic artery of anesthetized rats, they were able to reproduce a feeding state and explore the consequences on hepatic glucose metabolism. When the glucose concentration is higher in the portal vein than in the hepatic artery, portal glucosensing leads to tissue glucose uptake in the first 10 min, ceasing in favor of hepatic storage (30). More details have been provided by Pagliassotti et al., who showed that portal signaling induces glycogen synthesis by the liver via glycogen synthase activation. Consequently, in response to portal glucosensing, there is a significant glycogen accumulation in this organ (70).

In the last few years, another mode of regulation has been revealed. The gut can also produce glucose through a gluconeogenesis pathway, but to a lesser extent than the liver. Similarly to the glucose in food, the glucose produced by the intestine moves into the portal vein and triggers a signal. Mithieux et al. suggested that information is transferred from the portal vein to the brain as a result of glucosensor stimulation, leading to an afferent nervous message. Integration of these messages in the central nervous system elicits suppression of hepatic glucose production (59).

SKELETAL MUSCLE AND ADIPOSE TISSUE. Portal glucosensing also has extrahepatic effects, since stimulation of portal sensors increases peripheral glucose utilization in a number of tissues. Infusion of 2-deoxy-[^{14}C]glucose (a nonmetabolizable radiolabeled glucose analog) has facilitated the quantification of glucose uptake by different tissues, revealing that portal infusion of glucose promotes glucose utilization by oxidative muscles and brown adipose tissue (BAT) compared with infusion of glucose in the femoral vein (10). This concurs with Gardemann's experiments showing the kinetics of glucose distribution after portal glucosensing, as explained above (30). This system provides for the distribution of glucose in the body according to its needs. Moreover, the mechanism by which the portal signal is transmitted to other tissues is certainly dependent on the activation of the ANS (10). This view is confirmed by the fact that hepatoportal glucosensors are connected to afferent branches of the vagus nerve, which are able to change the activity of hypothalamic neurons, which, in turn, modify peripheral glucose utilization (Fig. 5).

PANCREAS. Portal glucosensors are sensitive to blood glucose changes. A wide variety of mechanisms control the balance between insulin and glucagon release to maintain glycemia at physiological values. Therefore, it is conceivable that portal vein glucosensors may also target the pancreas to control the release of these two hormones. Along this line, it has been clearly shown that a portal glucose bolus triggers the release of insulin by the pancreas, specifically during the first secretion phase (5). Nevertheless, the mechanisms linking portal glucosensing and glucagon release are still unknown.

Pathology. In T2D, the capacity for glucosensing in the portal vein is altered. Moore et al. showed that, in the pathological HFD condition, the signal sent by portal sensors in response to glucose detection is altered (61). More specifically, T2D is associated with enzymatic changes that alter portal glucose sensing. While glucosensing in the portal vein is associated with increases in GK and glycogen synthase in the liver, in T2D induced by HFD, the expression of these enzymes is decreased (15). This could explain the aberrant postprandial hepatic glucose metabolism observed in this pathology.

EXTRAGASTROINTESTINAL GLUCOSENSING: THE ROLE OF THE BRAIN

As described above, the brain is continuously informed about glucose fluctuations in the gastrointestinal tract via the gut-brain axis. The modulation of hypothalamic neuronal activity in response to gut signals controls metabolic functions, including peripheral glucose utilization. Furthermore, the brain is also able to directly detect glucose variations through specialized hypothalamic cells identified as glucosensors. In response to all of this glycemic information, the hypothalamus sends peripheral signals via the ANS to control whole body glucose metabolism.

Cell Types Involved

In 1964, Oomura et al. showed that hypothalamic neurons have the unusual ability to modify their firing rates in response to changes in glucose concentration (Fig. 5) (67, 91). Currently these neurons are classified into two categories based on their responses to physiological changes in extracellular glucose, i.e., neurons excited by glucose ("glucose-excited") and neurons inhibited by glucose ("glucose-inhibited") (81). During a meal, there is a rise in brain glucose levels (from 1 to 5 mM), which activates glucose-excited neurons and keeps glucose-inhibited neurons inactive. On the contrary, during a fasting period, reduction of the brain glucose concentration to 0.1 mM activates glucose-inhibited neurons and inhibits glucose-excited neurons (81). In the hypothalamus, glucose-excited neurons are found in the lateral part of the arcuate nucleus (ARC), whereas glucose-inhibited neurons are localized to

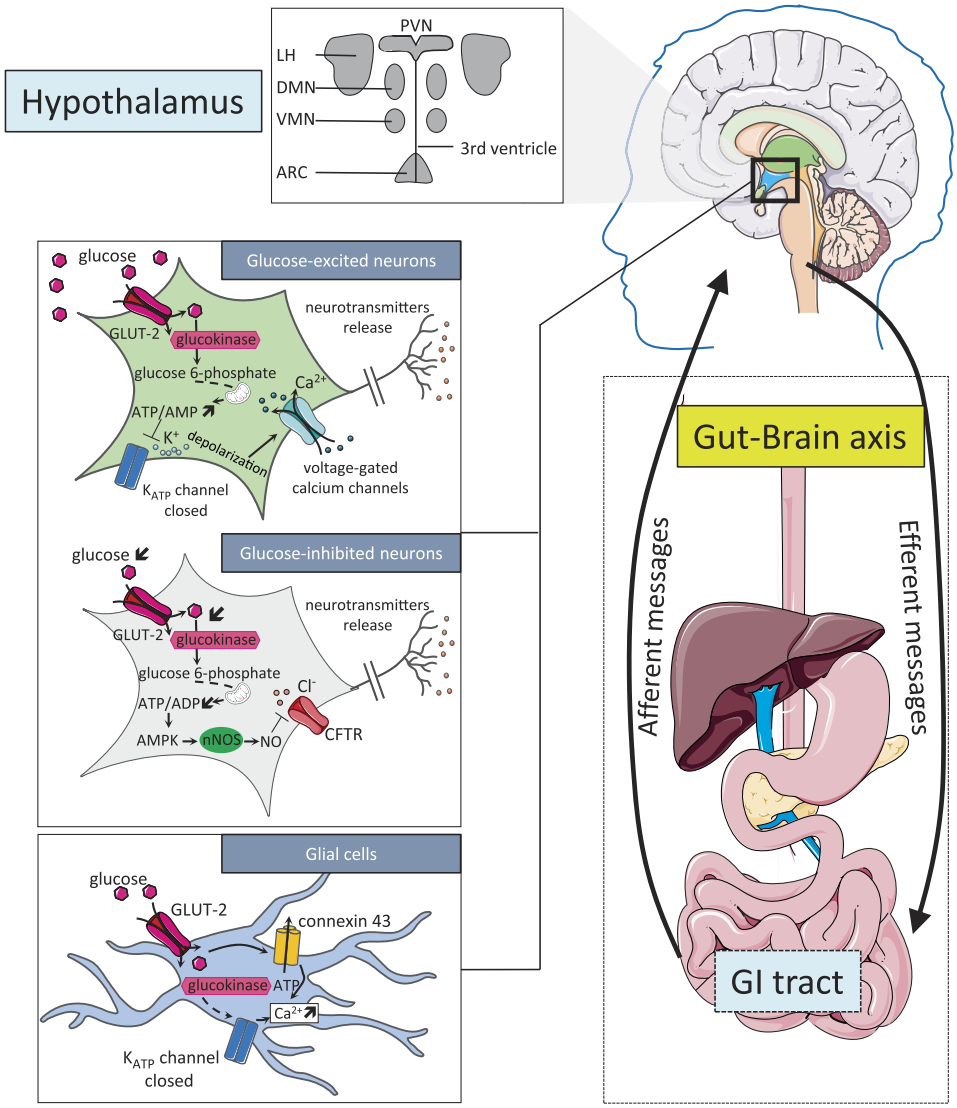

Fig. 5. The gut-brain axis and the key role of hypothalamic glucosensing. *Top*, schematic representation of a coronal section showing different hypothalamic nuclei, including the arcuate nucleus (ARC), ventromedial nuclei (VMN), dorsomedial nuclei (DMN), the lateral hypothalamus nucleus (LH), and paraventricular nuclei (PVN). The remainder of the figure highlights molecular mechanisms in different hypothalamic cell types involved in glucosensing, which contribute to glucose homeostasis via the gut-brain axis. In glucose-excited neurons, glucose enters via GLUT-2, is converted to glucose 6-phosphate by glucokinase, and is then used in the glycolytic pathway to generate ATP. The resultant increase in intracellular ATP levels inactivates K_{ATP} channels, leading to membrane depolarization and opening of Ca^{2+} channels. The massive influx of Ca^{2+} causes release of neurotransmitters. Conversely, glucose-inhibited neurons are sensitive to decreases in the glucose concentration. Here, less glucose enters the neurons through GLUT-2 and is metabolized by the glycolytic pathway, thus producing less cellular ATP. The decrease in the ATP-to-ADP ratio is detected by AMPK, which activates production of gaseous messenger nitric oxide (NO) by neuronal NO synthase (nNOS). Production of NO leads to the inhibition of specific chloride channels, including the cystic fibrosis transmembrane regulator (CFTR), which is responsible for membrane depolarization. In glial cells, glucose enters into intracellular compartments via GLUT-2 and increases intracellular Ca^{2+} waves, a mechanism dependent on ATP release by connexin 43.

the medial part of the ARC and the ventromedial nuclei (VMN) (Fig. 5) (91).

Evidence indicates that, in addition to providing structural and functional support to neurons, brain glial cells are also involved in glucose detection. A peritoneal injection of 2-DG, which mimics peripheral hypoglycemia, typically leads to an increase of c-Fos labeling in neurons. However, this labeling is reduced when the animals are pretreated with a specific inhibitor of carbohydrate metabolism in glial cells (the methionine sulfoximine) (80). Among glial cells, hypothalamic astrocytes and tanycytes lining the third ventricle are the most studied in glucosensing (81). In addition, due to the strategic location of glial cells all along the blood vessels in the brain and the physical connection between astrocytes and endothelial cells via connexin 43, it is not difficult to imagine that these cells can directly sense glucose levels and convey signals to their neighboring neurons.

Molecular Mechanisms

Glucose-excited neurons. Glucose-excited neurons and β-cells of the pancreas share similarities in glucose responsiveness (81). Glucose enters via GLUT-2 into glucose-excited neurons, where it is converted to glucose 6-phosphate by GK and then used in the glycolytic pathway to generate ATP. The resultant increase in intracellular ATP level inactivates K_{ATP} channels, generating membrane depolarization and consequently the opening of Ca^{2+} channels. This massive influx of Ca^{2+} causes the release of neurotransmitters. The role of GLUT-2 in brain glucosensing has been clearly established: specific inhibition of GLUT-2 by antisense oligonucleotides suppressed the insulin response to intracarotidian glucose injection toward the brain (80). In addition to GLUT-2, glucose-excited neurons express other transporters that might participate in neuronal glucosensing mechanisms, namely the insulin-sensitive GLUT-4 and SGLT-1 (81). GK seems to play a key role in neuronal glucosensing, since knockdown of this enzyme by small-interfering RNA is associated with a decrease in glucosensitive neurons, both glucose-excited and glucose-inhibited varieties (80). In mice, deficiency of Kir6.2, a K_{ATP} channel subunit, leads to a loss of glucose responsiveness in glucose-excited neurons and a severe defect in glucagon secretion in response to systemic hypoglycemia (58). These

results demonstrate that K_{ATP} channels are also involved in neuronal glucosensing (Fig. 5). Finally, the involvement of mitochondrial ROS in hypothalamic glucosensing has clearly been shown. Indeed, bolus of glucose stimulates ROS generation on ex vivo hypothalamic slices (47). Moreover, intracarotid injection of glucose (therefore only perceived by the hypothalamus) in rats causes a significant increase in neuronal activity in the arcuate nucleus, and this effect is abolished by coinjection of antioxidant enzymes (47).

Glucose-inhibited neurons. When the central concentration of glucose decreases, the amount of glucose entering the neuron by GLUT-2 transporters also decreases. Consequently, there is less glucose entering the glycolytic pathway via GK and thus less cellular ATP. The decrease in the ATP-to-ADP ratio is detected by AMPK, which induces the production of the gaseous messenger NO by nNOS. Production of this neurotransmitter leads to the inhibition of specific chloride channels in glucose-inhibited neurons, particularly the cystic fibrosis transmembrane regulator. These channels are responsible for the membrane depolarization of glucose-inhibited neurons (80). Many effects of NO are mediated by the activation of soluble guanylyl cyclase receptor, both of which are critical for glucosensing in glucose-inhibited neurons (Fig. 5) (80).

Glial cells. Neurons are not the only glucose-sensitive cells in the brain. Indeed, tanycytes also express GLUT-2, GK, and K_{ATP} channels, suggesting that they are able to sense glucose (91). Moreover, studies have shown that glucose increases intracellular Ca^{2+} waves in cultured tanycytes, a mechanism dependent on ATP release by connexin 43 (91).

Astrocytes also play a role in glucosensing, since they express GLUT-2. Indeed, GLUT-2 KO mice fail to increase plasma glucagon levels following glucose deprivation. In addition, astrocyte-specific restoration of GLUT-2 expression in these mice is sufficient to restore glucagon production in response to hypoglycemia (Fig. 5) (53). As for tanycytes, connexin 43 seems to be required in brain glucose sensitivity through astrocytes. Astroglial connexins 43 form channels, allowing for the intercellular transfer of small molecules, such as glucose, throughout the astroglial networks. The inhibition of connexin 43 in the mediobasal hypothalamus attenuated hypothalamic glucose sensitivity in rats, which was demonstrated by a pronounced decreased insulin secretion in response to brain glucose challenge (45). Furthermore, in a second step, this glucose detection by astrocytes allows the activation of glucose-sensitive neurons. Indeed, glucose can enter into astrocytes via GLUT-2 transporter, to be stored as glycogen, or to be converted into lactate by the lactate dehydrogenase A. This lactate could leave these astrocytes by monocarboxylate transporters-1 and -4, and enter into glucose-sensitive neurons via the monocarboxylate transporter-2. At this site, lactate will continue its oxidation and participate in these neurons activation (45). This lactate shuttle between astrocytes and glucose-sensitive neurons is also suggested in hypoglycemia detection and involve NO signaling (28). All of these observations reinforce the role of astrocytes in brain glucosensing mechanisms.

Consequences for Glucose Homeostasis

In response to glucose detection, the hypothalamus maintains glucose homeostasis by generating messages that are transmitted to peripheral tissues by the ANS. The targeted tissues are the pancreas, the liver, skeletal muscles, and adipose tissues (both white and brown).

Pancreas. The pancreas secretes two hormones that govern glucose metabolism, insulin and glucagon. As previously described in this review (see *Glucosensing in the Pancreas* above), increases in blood glucose are detected by β-cells, leading to exocytosis of insulin-containing vesicles. This insulin release is also controlled by the ANS, more particularly by the parasympathetic nervous system (PNS) (2). In the rat hypothalamus, an intracarotid glucose load induces a peak in plasma insulin 1–3 min later, without modifying peripheral glucose levels (47). Coadministration of antioxidant molecules inhibits this insulin secretion, suggesting a key role of brain ROS in the insulin secretion induced by the cerebral glucose load (47).

Similar to insulin, glucagon secretion is controlled by the hypothalamus. Hypoglycemia increases the activity of the sympathetic nervous system (SNS) by stimulating α-cells to release glucagon (98). Glucagon secretion in response to hypoglycemia is abolished by glucose injection in the VMN (98). The main hypothalamic actor involved in this hypoglycemia detection in the VMN seems to be NO, since intra-VMN injection of a NOS inhibitor slowed the recovery of euglycemia after hypoglycemia (27).

Liver. The hypothalamus is extensively involved in the liver's contribution to glucose metabolism via the ANS. Indeed, electrical stimulation of the VMN, as well as direct activation of hepatic sympathetic nervous fibers, triggers an increase in hepatic glucose production (88, 89). Conversely, electrical stimulation of the lateral hypothalamic area or direct activation of hepatic parasympathetic nervous fibers leads to a decrease in hepatic glucose production (88, 89). K_{ATP} channels seem to play a key role in these mechanisms, since intracerebroventricular injection of a channel blocker prevented the inhibition of hepatic glucose production mediated by insulin (74).

Skeletal muscles. The brain also impacts glucose metabolism in muscles via the ANS. For example, activation of the SNS leads to an increase in glucose uptake and glycogenesis in skeletal muscles (66).

Adipose tissues. BAT contributes to the regulation of body temperature in response to cold by inducing thermogenesis mechanisms. This activity is also controlled by the SNS. Moreover, intracerebroventricular injection of glucose increases SNS activity in BAT, whereas intracerebroventricular injection of 2-DG reduces SNS activity in BAT, leading to hypothermia (91). These results demonstrate the impact of central glucosensing on thermogenesis.

White adipose tissue stores excess blood glucose in the form of lipid droplets. This activity is also promoted by the brain, since SNS activation induces glucose uptake in this tissue through an increase in GLUT-4 translocation (66).

Pathology

Given the involvement of central glucosensors in glucose homeostasis, evidence suggests that impaired glucosensing in

the hypothalamus could trigger metabolic disorders such as T2D. Indeed, if glucosensing neurons become hypersensitive to small decreases in glucose levels, they could send inappropriate energy deficit signals to the brain. The consequence would be the activation of energy-sparing mechanisms to counteract the perceived deficit, thereby leading to the development of obesity and T2D. In support of this hypothesis, Colombani et al. showed that intracarotidian injection of a low glucose concentration (that does not raise the systemic glucose level) is sufficient to produce an increase in plasma insulin in obese Zucker rats, but not in their lean littermates (16). This result is consistent with an increased response of glucose-inhibited neurons to decreased glucose concentrations. Moreover, inhibition of VMN glucose-excited neurons to midrange decreases in glucose is significantly enhanced in diabetic Db/Db mice (17). Thus, in the case of T2D, the brain perceives glucose deficits under conditions of energy sufficiency/excess, leading to pathological exacerbation.

CONCLUSION

Gastrointestinal glucosensing fulfills a fundamental role in postprandial glucose homeostasis, orchestrating specific multieffector responses to the glucose ingested with food. The increasing attention paid to the gastrointestinal tract in the regulation of whole body glucose metabolism has led to significant progress in elucidating the molecular mechanisms underlying its ability to sense glucose. Indeed, the oral cavity, small intestine, pancreas, and portal vein act in concert, releasing hormones or activating nerve routes, to maintain glycemia in the face of glucose variations. Furthermore, all of these organs are in close communication with the hypothalamus, itself able to detect glucose and to adjust its production and utilization. The gastrointestinal tract plays an important glucoregulatory role, but not only in the glucosensing process, since intestinal lipid sensing also sends afferent nervous messages to the hypothalamus to regulate glycemia (6). Thus, the gut-brain axis represents a major regulatory checkpoint in the control of energy homeostasis.

In addition to the well-described chemosensing mechanisms, it is becoming clear that modifications of intestinal motility can also impact hypothalamic neuronal activity and, subsequently, glycemic control (29, 93). Because impaired glucose chemosensing is observed in diabetic contexts, further studies based on intestinal mechanosensing and peripheral glucose utilization via the gut-brain axis are needed to open new perspectives on the development of novel therapeutic strategies for the treatment of metabolic diseases.

ACKNOWLEDGMENTS

We thank the Societe Francaise de Nutrition (SFN) and the Fondation Recherche Médicale (FRM) (Grant ING20150532586) for financial support. P. D. Cani is the recipient of grants from the FNRS (convention J.0084.15, convention 3.4579.11), PDR (Projet de Recherche, convention: T.0138.14), FRM (Fondation Recherche Medicale), and ARC (Action de Recherche Concertée-Communauté française de Belgique convention: 12/17-047). P. D. Cani is also a recipient of an ERC Starting Grant 2013 (European Research Council, Starting grant 336452-ENIGMO). C. Cirillo is a postdoctoral fellow of the Fonds voor Wetenschappelijk Onderzoek (FWO, Belgium).

GRANTS

This work was supported by the Fonds de la Recherche Scientifique-FNRS for the FRFS-WELBIO under grant WELBIO-CR-2012S-02R. This work was also supported in part by the Funds InBev-Baillet Latour (Grant for Medical Research 2015).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.F., A.M., A.A., and C.P. prepared figures; A.F., A.M., A.A., C.P., P.D.C., and C.K. drafted manuscript; A.F., A.M., A.A., C.P., C.C., P.D.C., and C.K. edited and revised manuscript; A.F., A.M., A.A., C.P., C.C., P.D.C., and C.K. approved final version of manuscript.

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