Sensing of Glucose in the Brain

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Contents

Abstract The brain, and in particular the hypothalamus and brainstem, have been recognized for decades as important centers for the homeostatic control of feeding, energy expenditure, and glucose homeostasis. These structures contain neurons and neuronal circuits that may be directly or indirectly activated or inhibited by glucose, lipids, or amino acids. The detection by neurons of these nutrient cues may become deregulated, and possibly cause metabolic diseases such as obesity and diabetes. Thus, there is a major interest in identifying these neurons, how they respond to nutrients, the neuronal circuits they form, and the physiological function they control. Here I will review some aspects of glucose sensing by the brain. The

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brain is responsive to both hyperglycemia and hypoglycemia, and the glucose sensing cells involved are distributed in several anatomical sites that are connected to each other. These eventually control the activity of the sympathetic or parasympathetic nervous system, which regulates the function of peripheral organs such as liver, white and brown fat, muscle, and pancreatic islets alpha and beta cells. There is now evidence for an extreme diversity in the sensing mechanisms used, and these will be reviewed.

Keywords Brainstem • Counterregulation • Food intake • Glucogen • Glucokinase • Glucose transporters • Glucose Sensing • Hypothalamus

1 Introduction

Since the initial observation by Claude Bernard that a puncture of the floor of the fourth ventricle of the dog induces diabetes (Bernard 1849), the brain has been recognized as an important regulator of glucose homeostasis. Subsequent studies have demonstrated that feeding behavior was also regulated by central glucose sensing, leading to the glucostatic hypothesis of feeding control by J. Mayer (1953). It was further demonstrated that distinct hypothalamic nuclei were involved in the regulation of feeding and fasting, since lesion of the lateral hypothalamus reduced feeding and body weight, whereas lesion of the ventromedial hypothalamus (VMH) induced hyperphagia and hyperinsulinemia (Bray 1985; Hoebel 1965; King 2006). A widely used animal model of obesity was also established when it was shown that administration of gold thioglucose, which causes the destruction of VMH neurons, induces obesity (Marshall and Mayer 1956; Mayer and Thomas 1967). The toxic effect of gold thioglucose is not duplicated when gold is conjugated with other metabolites or nutrients, suggesting a specific effect on glucose-sensitive neurons. Intracerebroventricular injection of the glucose antimetabolite 2-deoxy-D-glucose, which inhibits glycolysis and creates a glucopenic state mimicking hypoglycemia, has been shown to induce feeding (Miselis and Epstein 1975) and glucagon secretion (Borg et al. 1995). In contrast, i.c.v. injection of glucose reduces feeding in fasted mice (Bady et al. 2006) and can prevent hypoinsulinemia-induced glucagon response (Biggers et al. 1989; Frizzell et al. 1993). A control of energy expenditure through glucose sensing has also been proven by i.c.v. 2-DG injection which induces a marked hypothermic response (Freinkel et al. 1972).

The above-described observations therefore indicated that both hypo- and hyperglycemia can be recognized by central glucose sensing cells to control feeding, energy expenditure, and counterregulation. It has been established for ~50 years that these glucose sensing responses depend on the firing activity of glucose-excited (GE) or glucose-inhibited (GI) neurons that is triggered by, respectively, rises or falls in glucose concentrations (Anand et al. 1964; Oomura and Yoshimatsu 1984; Routh 2002; Yang et al. 2004). Both types of neurons are widely distributed in the hypothalamus and brainstem. In the hypothalamus, GE and GI neurons are present in the arcuate (AN), ventromedial (VMN), paraventricular (PVN), and lateral (LH) hypothalamic nuclei (Dunn-Meynell et al. 1998; Silver and Erecinska 1998; Wang et al. 2004). Both types of neurons are also found in the brainstem, in particular in the nucleus of the tractus solitarius (NTS), the area postrema (AP), and the dorsal motor nucleus of the vagus (DMNX) (Adachi et al. 1984; Dallaporta et al. 1999; Mizuno and Oomura 1984; Yettefti et al. 1997). Recently, it has been suggested that subpopulations of GE and GI neurons in AN are actually responsive to glucose over a high glucose concentration range (5–20 mM) and are referred to as HGE (high-glucose-excited) or HGI (high-glucose-inhibited) neurons, respectively (Fioramonti et al. 2004; Penicaud et al. 2006).

Studies over the last several years have started to yield a molecular picture of the mechanisms of glucose sensing by GE and GI neurons. This is, however, still far from being complete, and new studies reveal the extreme diversity of the molecular basis for glucose recognition in the control of neuronal firing, suggesting complex regulatory networks activated by glucose to control physiology.

2 Anatomical Organization of Glucose Sensing Nuclei

2.1 The Melanocortin Pathway

An important site for integration of hormonal, nutritional, and neuronal signals is the melanocortin pathway which consists of AN neurons expressing the anorexigenic peptides POMC and CART as well as neurons expressing the orexigenic peptides NPY and AgRP. AgRP is an antagonist of the melanocortin receptors (MCR) 3 and 4, whereas α-MSH, derived from the POMC prohormone, is an agonist of these receptors. The NPY and POMC neurons project to neurons in the PVN and LH that express the melanocortin 3 and 4 receptors (Gautron and Elmquist 2011; Schwartz et al. 2000). Neurons in the PVN produce the anorexigenic neuropeptides TRH and CRF, whereas neurons in the LH produce the orexigenic peptides MCH and orexin (Schwartz et al. 2000). Together, these neurons form the melanocortin pathway and regulate peripheral metabolism through regulation of the activity of both the sympathetic and parasympathetic branches of the autonomic nervous system; they are also connected to higher brain structures to control feeding behavior, arousal, and reward (Adamantidis and de Lecea 2008; Berthoud 2002; Sakurai 2007).

The neurons in the AN are regulated by several hormones including ghrelin, insulin, PYY3-36, and most importantly leptin. They are also regulated by nutrients including lipids, amino acids, and glucose (Cummings and Schwartz 2000; Gale et al. 2004; Schwartz 2000; Schwartz et al. 2000; Thorens and Larsen 2004; Woods et al. 1998).

Although the role of leptin to regulate this pathway is critical (Gautron and Elmquist), there is also strong evidence for its modulation by glucose. Forty percent of NPY neurons have been found to be glucose inhibited; POMC neurons are typical GE neurons, and orexin neurons in the LH are GI, whereas those expressing MCH are GE neurons.

2.1.1 The Ventromedial Hypothalamus

The VMH has afferent connections with many hypothalamic nuclei, including the medial and lateral hypothalamus, but also with brainstem structures, including the NTS (Canteras et al. 1994). The VMH has been associated with regulation of the counterregulatory response to hypoglycemia, inducing glucagon secretion in response to fall in blood glucose concentrations. Lesion, pharmacological, and genetic studies have demonstrated the role of VMH glucose sensing in counterregulation. For instance, glucagon secretion can be induced by direct injection of 2-DG in the VMH (Borg et al. 1995) or, in contrast, hypoglycemia-induced glucagon secretion can be suppressed by direct VMH injection of glucose (Borg et al. 1997). Interestingly, VMH neurons are predominantly glutamatergic and express the vesicular glutamate transporter vGLUT2. Because the nuclear hormone receptor SF-1 is expressed selectively in VMH neurons, SF-1-Cre mice have been generated that allow specific deletion of floxed genes in the VMH (Dhillon et al. 2006). Deletion of vGLUT2 in the VMH generated mice that had marked defect in glucagon secretion in response to fasting or hypoglycemia (Tong et al. 2007), suggesting that glutamatergic neurons of the VMH are required for the counterregulatory response.

2.1.2 Brainstem, The Dorsal Vagal Complex, and the Basolateral Medulla

The hindbrain structures involved in glucose-dependent regulation of feeding and glucose homeostasis include the dorsal vagal complex (DVC), which consists of the AP, the NTS, and the DMNX, as well as the basolateral region (BLM) that contains the A1/C1 catecholamine neurons. The role of the hindbrain in glucoregulation has been proven by intracerebroventricular (i.c.v.) injection of 2-DG, which stimulates feeding only if the cerebral aqueduct is open to allow access of the injected substance to the brainstem (Berthoud and Mogenson 1977; Ritter et al. 1981), and food uptake can be activated by direct injection of 5-thioglucose (5-TG) into the NTS, DMNX, or BLM (Ritter et al. 2000). The importance of the NTS neurons in glucose sensing is also demonstrated by their sensitivity to small variations of blood glucose concentrations as determined by extracellular recording of their firing activity (Yettefti et al. 1995). Neurons from the NTS project to the LH and PVN, whereas neurons from the BLM project to the AN. Destruction by immunotoxins of the BLM projections to the AN suppresses the effect of 2-DG on food intake and on regulated expression of AgRP and NPY, suggesting a highly functional interrelationship between glucose-sensitive neurons from the brainstem and hypothalamus in integrated control of feeding (Fraley and Ritter 2003; Ritter et al. 2001).

3 Mechanisms of Glucodetection by GE and GI Neurons

3.1 *Glucose-Excited Neurons: The Glut2/Glucokinase/K_{ATP} Channel Signaling Pathway*

The mechanism of glucose sensing by GE neurons is thought to be similar to that of the pancreatic beta cells (Fig. 1), which depends on glucose metabolism and production of coupling factors, mostly derived from mitochondrial metabolism, which induce depolarization of plasma membrane prior to Ca^{2+} entry and stimulated secretion. In the beta-cell signaling pathway, Glut2 is the major glucose transporter isoform that allows a fast equilibration of glucose between the extra- and intracellular compartments. Glucokinase then phosphorylates glucose, and this is the rate-controlling step in glucose utilization and production of the coupling factors, the major one being the increase in the ATP/ADP ratio, which induces the closure of ATP-dependent K^+ (K_{ATP}) channels. This channel closure depolarizes the plasma membrane and opens voltage-gated calcium channels, resulting in Ca^{2+} influx which triggers insulin secretion. The Glut2/GK/K_{ATP} channel signaling pathway is probably also active in hypothalamus and brainstem to control neuronal excitability and control of feeding, energy expenditure, and glucose homeostasis. However, so far there is no direct proof that the three components of the Glut2/GK/K_{ATP} channel signaling pathway are present together in any given neuron.

POMC neurons in arcuate nucleus are GE neurons that express the K_{ATP} channel subunits SUR1 and Kir6.2 (Ibrahim et al. 2003). The importance of this channel in glucose sensing and glycemic control has been shown in mice in which a mutated form of Kir6.2, which prevents channel closure in response to increased ATP/ADP ratio, is expressed selectively in POMC neurons. The neurons of these mice no longer respond to glucose when tested by electrophysiological recording, and this is associated with the presence of mild glucose intolerance (Parton et al. 2007). As for pancreatic beta cells, expression of the uncoupling protein UCP2 in mitochondria is thought to reduce the production of ATP and therefore reduces glucose-stimulated membrane depolarization and induced firing. In agreement with this hypothesis, inhibition of UCP2 in POMC neurons by genipin increases their glucose responsiveness (Parton et al. 2007). In beta cells, it is, however, still debated whether the effect of UCP2 on secretion is explained only by its effect on intracellular ATP levels or whether it acts as a regulator of reactive oxygen species (ROS) production (Pi et al. 2009; Pi et al. 2007; Zhang et al. 2001). Indeed, ROS are also intracellular signaling molecules (Rhee 2006) that can regulate the activity of voltage-gated K^+ channels (Archer et al. 2004; Pan et al. 2008) or Ca^{2+} influx (Kraft et al. 2004; Tabet et al. 2004; Todt et al. 2001). ROS may also be part of the mechanisms controlling glucose signaling in the hypothalamus. For instance,

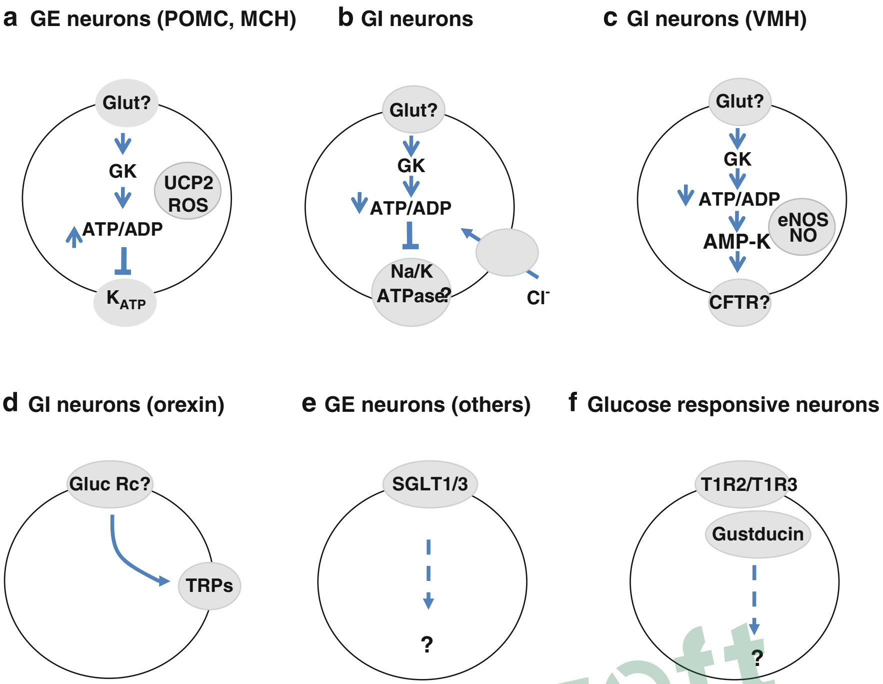

Fig. 1 Schematic representation of the glucose sensing mechanisms. (**a**) The classical model for GE neurons, found in POMC and MCH neurons, depends on glucose uptake and metabolism leading to increased ATP/ADP ratio and closure of K_{ATP} channels, and membrane depolarization induces influx of Ca^{2+} to induce firing activity. UCP2 and ROS can modulate this signaling pathway. (**b**) The initial description of glucose sensing by GI neurons suggested that decreases in intracellular ATP levels consequent to fall in extracellular glucose reduce the activity of the Na/K-ATPase. The resulting increase in intracellular Na^+ then closes a chloride conductance to induce nerve firing. (**c**) GI neurons of the VMH respond to hypoglycemia by activating AMPK, which can be further upregulated by an eNOS/NO/guanylate-cyclase-dependent mechanism; AMPK finally activates the chloride conductance of the CFTR. (**d**) The GI neurons of the LH orexin neurons are activated by low glucose in a glucose intake and metabolism-independent manner, possibly secondary to glucose interaction with a cell surface receptor that controls a K^+ conductance. (**e**) A large fraction of hypothalamic GE neurons, in dispersed neuronal populations, can be activated by the nonmetabolizable SGLT substrate α-MDG. This requires substrate and Na^+ uptake, which depolarizes the plasma membrane, and is independent of K_{ATP} channel activity. (**f**) The sweet receptors T1R3 and gustducin are present in neuronal populations. This receptor could contribute another glucose sensing mechanism

exposing hypothalamic slices to 20 mM glucose stimulates ROS generation. Also, intracarotid administration of antimycin or rotenone, which induces ROS formation, mimics the effect of glucose on activity of AN neurons and subsequent insulin release mediated by efferent neurons (Leloup et al. 2006).

A role for AMP-kinase has also been proposed for the regulation by glucose of POMC neuron activity. In mice with genetic inactivation of the α2 subunit of AMPK (and with only one allele of the α1 subunit), the POMC neurons no longer respond to extracellular glucose as assessed by electrophysiological recordings (Claret et al. 2007). How this kinase, which is activated only at low glucose concentration, can prevent the response to high glucose of these neurons is not clear.

In the lateral hypothalamus, the MCH neurons are also GE and probably share the same glucose signaling pathway as the POMC neurons. The same requirement for a functional K_{ATP} channel has been established, and knockout of UCP2 specifically in MCH neurons increases their glucose responsiveness (Kong et al. 2010). Genetic inhibition of the K_{ATP} channel also leads to glucose intolerance.

3.1.1 Other Glucose Sensing Mechanisms in GE Neurons

Variations from the Glut2/GK/K_{ATP} channel signaling pathway have been described in the stimulation by glucose of different GE neurons (Fig. 1). First, there is no evidence that Glut2 is expressed in POMC or MCH neurons, and the isoform of glucose transporter expressed by these neurons is not yet established, although genetic inactivation of Glut2 prevents the normal regulation of POMC expression in response to i.c.v. glucose or during the fast-to-refed transition. This suggests that the regulation by glucose of these neurons in physiological conditions may be indirect, through interaction with Glut2-expressing neurons (see discussion of Glut2 in central glucose sensing below). Second, there is evidence that glucose can excite neuronal activity through mechanisms that require glucose recognition by the Na^+-dependent glucose transporters SGLT1 or SGLT3. SGLT1 may play a role in central glucose sensing as suggested by the effect of i.c.v. injection of phlorizin, a specific inhibitor, which enhances food intake in rats (Tsujii and Bray 1990) and inhibits activation of GE neurons in the VMH (Yang et al. 1999). Strikingly, analysis of isolated hypothalamic neurons shows that a majority of GE neurons can be activated by α-MDG, a specific SGLT1 substrate. Furthermore, tolbutamide cannot increase the activity of these α-MDG-sensitive neurons, indicating that the K_{ATP} channel may not be involved in this signaling pathway (O'Malley et al. 2006).

SGLT3 is a member of the SGLT family, which has been reported to be a glucose sensor in cholinergic neurons present in the small intestine and at the neuromuscular junctions (Diez-Sampedro et al. 2003). In *Xenopus oocytes* expressing SGLT3, glucose produces a phlorizin-sensitive inward current that depolarizes the membrane potential by up to 50 mV (Diez-Sampedro et al. 2003). As SGLT3 mRNA is expressed in both cultured hypothalamic neurons and adult hypothalamus, this suggests that it may also be involved in central glucose sensing (O'Malley et al. 2006).

The G-protein-coupled taste receptors of the T1R family form heterodimers for sensing sweet taste (T1R2; T1R3) or amino acids (umami taste) (T1R1; T1R3). The sweet receptors are activated by a large number of artificial sweeteners but also by sucrose and glucose. These receptors are localized in the taste buds of the tongue, in the intestine where they may control secretion of the gluco-incretin hormone GLP-1

(Jang et al. 2007; Steinert et al. 2011), and in diverse brain areas, but in particular, in the hypothalamic PVN and AN (Ren et al. 2009). They are also found in the brainstem, in the NTS (Lemon and Margolskee 2009). Whether these receptors participate in the regulation of glucose homeostasis or of feeding behavior is not yet established.

3.2 Glucose-Inhibited Neurons

Glucose-inhibited neurons increase their firing activity when glycemic levels decrease. Several models have been proposed to account for the induction of membrane depolarization induced by hypoglycemia (Fig. 1). A first model proposed that a decrease in glucose uptake reduces ATP production, leading to a lower activity of the Na^+/K^+ ATPase and an increase in intracellular Na^+ that drives membrane depolarization through activation of a chloride conductance (Silver and Erecinska 1998). In recent years, other models have been suggested, with different mechanisms being proposed for GI neurons in the VMH and orexin neurons in the LH.

In VMH neurons, hypoglycemia induces firing by a glucose-metabolism-dependent signaling pathway. The glucose transporter involved in glucose uptake may be Glut1, Glut2, or Glut3, as different subpopulations of GI neurons express these transporters, as assessed by single-cell RT-PCR analysis (Kang et al. 2004). There is also evidence that glucose sensing by VMH neurons requires glucokinase expression (Kang et al. 2006). The following steps leading to neuronal firing in these neurons have been proposed by the group of V. Routh: A reduction in glucose metabolism leads to an increased intracellular AMP concentration. This activates AMPK which in turn triggers production of NO by eNOS. The activation of guanylate cyclase by NO further activates AMPK. The critical part is the subsequent regulation of the chloride conductance of the CFTR by AMPK which induces neuronal firing (Canabal et al. 2007; Fioramonti et al. 2010; Murphy et al. 2009).

Orexin neurons from the LH have been proposed by the group of Burdakov to function in a very different manner (Karnani and Burdakov 2011). Most strikingly, data published by this group indicate that the activation of these neurons can be triggered by the nonmetabolizable analogue 2-DG, that lactate cannot reproduce the glucose response, and glucokinase inhibitors did not prevent glucose activation (Gonzalez et al. 2008) in agreement with the reported absence of this enzyme from orexin neurons (Dunn-Meynell et al. 2002). This led to the suggestion that glucose activates a surface receptor that leads to regulation of channel activity. This activity was originally proposed as being controlled by tandem pore K^+ channels (TRPs) (Burdakov et al. 2006), but recent studies on TRP knockout mice failed to directly support this hypothesis (Gonzalez et al. 2009). Interestingly, these authors also showed that orexin GI neurons are sensitive to changes in ambient glucose concentrations rather than to absolute glycemic levels.

At the level of the brainstem, where both GE and GI neurons are detected, electrophysiological recordings indicate that GI neurons are activated in response to glucose removal by a signaling pathway that requires the presence of glucokinase and the regulation of a K^+ current (Balfour et al. 2006; Balfour and Trapp 2007).

In the arcuate nucleus, inactivation of AMPK is part of the response to leptin and insulin, whereas hypoglycemia or 2-DG activates AMPK. The activation by low glucose or neuroglucopenia of AMPK is observed only in the AN and PVN but not in the VMH, DMH, and LH nuclei (Minokoshi et al. 2004). Adenoviral delivery of constitutively active or dominant negative forms of AMPK in medial hypothalamic nuclei activates or, respectively, inhibits feeding (Minokoshi et al. 2004). How AMPK activity in hypothalamic neurons controls feeding is not fully understood. In neuronal cell lines and on ex vivo hypothalamic explants, low glucose concentrations and AICAR increase AMPK activity and AgRP expression (Lee et al. 2005). In accordance with these observations, the specific deletion of the α2-subunit of AMPK in POMC and AgRP neurons suppressed glucose sensing by these cells but preserved normal leptin or insulin action (Claret et al. 2007).

Together, the above-described data indicate that during evolution, the brain has developed several mechanisms for sensing hypoglycemia, either to induce counterregulatory hormone secretion or to induce a feeding response. This variety of mechanisms may be explained by the almost exclusive dependence of the brain on glucose as a source of metabolic energy. Fall of glucose below the normoglycemic concentrations dose-dependently impairs brain function, possibly leading to coma and death. Therefore, the multiplicity of mechanisms involved may reflect an adaptive process to ensure constant, optimal brain function and to maximize the chances of survival.

4 Indirect Control of Neuronal Activity by Glucose: Glial Cells and Tanycytes

4.1 Glial Cells

The utilization of glucose by neurons has been proposed to be mostly secondary to its initial uptake and metabolism by astrocytes that first produce lactate. Lactate is then transferred to neurons via specific monocarboxylate transporters, MCT1 present in astrocytes and MCT2 present in neurons, and utilized by neurons for ATP production (Magistretti et al. 1999; Pellerin et al. 2007). This metabolic coupling between astrocytes and neurons may also be used in some glucose sensing and glucoregulatory functions.

For instance, it has been shown that methyl sulfoximide, an astrocyte-specific inhibitor of glycolysis, blocks the increase in c-fos labeling in the AN induced by intracarotid or brainstem 2-DG injections (Guillod-Maximin et al. 2004; Young et al. 2000). It was also hypothesized that the release of lactate from neighboring glial cells is involved in glucose response of hypothalamic neurons (Ainscow et al. 2002; Lam et al. 2005). In the brainstem, the involvement of astrocyte-derived lactate in the control of glucose-sensitive neurons in the AP and NTS has been demonstrated by c-fos labeling studies, when monocarboxylate transporter is inhibited by α-cyano-4-hydroxycinnamate injected in the fourth ventricle. This treatment leads to elevations in blood glucose concentrations (Briski and Patil 2005; Patil and Briski 2005a, b).

4.2 Tanycytes

Tanycytes are glial cells lining the lateral lower part and the floor of the third ventricle. Their apical pole faces the ventricular lumen. They also have extended basal processes that reach regions of the median eminence devoid of blood–brain barrier and sometimes are in direct contact with microvessels present in the median eminence. These processes form extended contact with AN neurons, in particular NPY neurons (Akmayev and Fidelina 1974; Flament-Durand and Brion 1985; Kozlowski and Coates 1985). These cells express the glucose transporter Glut2 and glucokinase (Garcia Mde et al. 2003; Millan et al. 2010). Because of their strategic location, contacting both the cerebrospinal fluid and the general circulation, and because they express genes involved in glucose sensing, they may have a role in glucoregulation. A functional link between these cells and NPY neurons has been shown to rely on tanycytes expressing deiodinase II, and converting T4 into T3, thereby modulating glucose sensing in NPY cells by inducing UCP2 expression (Coppola et al. 2007). More studies are clearly needed to assess the potential role of tanycytes on glucoregulation, but the available information clearly suggests a potentially important function.

5 Glut2-Expressing Cells in Central Glucose Sensing

5.1 Glut2-Expressing Cells in the Brain

The glucose transporter Glut2 catalyzes the first step in the Glut2/GK/K_{ATP} signaling pathway that controls insulin secretion from beta cells. Glut2 is expressed in the mouse brain, in neurons, astrocytes, tanycytes, and endothelial cells (Arluison et al. 2004a; Arluison et al. 2004b; Marty et al. 2007a). However, because of the low level of Glut2 expression in the brain, its immunocytochemical distribution is relatively difficult to establish. As a result, there is no solid information about a colocalization of Glut2 with well-characterized GE or GI neurons of the melanocortin pathway or of other brain structures. In fact, the available evidence points to Glut2 not being present in NPY, POMC, orexin, or MCH neurons

(Mounien et al. 2010). By quantitative RT-PCR analysis, Glut2 expression has been found to be relatively low in the rat AN, VMH, PVN, and LH and at somewhat higher levels in brainstem nuclei, in particular nucleus 12 and inferior olive; it is also present in the AP and NTS (Li et al. 2003). In the VMH, single-cell RT-PCR analysis revealed expression of Glut2 in approximately one third of the GE, GI, and of non-glucose-sensitive neurons (Kang et al. 2004). Very good evidence demonstrates the expression of Glut2 in tanycytes and ependymal cells (Garcia Mde et al. 2003), as discussed above. In human brain, Glut2 is expressed at highest level in the hypothalamus and brainstem, where it is often colocalized with glucokinase (Roncero et al. 2004). Interestingly, in trout, Glut2 is expressed not only in the insulin secreting cells of the Brockmann body (which contain the insulin secreting cells) but also in the hypothalamus and hindbrain (Polakof et al. 2007). In the zebrafish, it is also present in the brain, although the exact localization has not yet been established (Castillo et al. 2009).

Collectively, the above-described information indicates that Glut2 is present in brain regions involved in glucoregulation, but not in clear association with the principal neurons of the melanocortin pathway, and that it is only present in a small subset of neurons in the VMH. In the brainstem, it is not possible to establish expression of Glut2, since glucose sensing cells in the DVC and the BLM cannot be identified by histological markers.

In an attempt to identify the Glut2-expressing cells, Mounien et al. (Mounien et al. 2010) generated transgenic mice expressing the Cre recombinase under the control of the Glut2 gene promoter (query: change correct? see changes). These transgenic mice were then crossed with Rosa26eYFP mice, and expression of the fluorescent reporter gene was used to identify sites of Glut2 expression. Expression of eYFP was found only in neurons. In the hypothalamus, the highest concentrations of eYFP cells were detected in the LH and the zona incerta; it was present in a few cells in the VMH, and no positive cells were detected in the AN. In this nucleus, however, numerous nerve endings were found associated with NPY and POMC neurons, suggesting synaptic contacts with Glut2-positive neurons located outside of the AN. In the brainstem, eYFP positive neurons were found in the NTS, the DMNX, the parasolitary tract, and in the A1/C1 region of the BLM. These eYFP neurons are glucose sensitive as demonstrated by their costaining with c-fos following i.p. glucose or 2-DG injection. In fact, at the brainstem level, the BLM eYFP neurons were activated following glucose but not 2-DG injections. In contrast, the eYFP neurons of the NTS and DMNX were activated by 2-DG but not glucose injections, suggesting that these are GI neurons. In LH, a similar fraction of neurons were activated by glucose or by 2-DG, suggesting that eYFP neurons in this structure are either GE or GI.

5.2 *Evidence for Glut2 in Central Glucose Sensing*

Studies of genetic inactivation of Glut2 in mice (with transgenic expression of glucose transporter in their beta cell to normalize glucose-stimulated secretion), were analyzed to assess the role of brain glucose sensing in the control of counterregulation, feeding, and thermoregulation (reviewed in (Marty et al. 2007b; Thorens 2003). The critical findings can be summarized as follows. In this mouse model, plasma glucagon levels were elevated in the fed state but could be normalized by ganglionic blockers, indicating that in the absence of Glut2, there was an abnormally high autonomic tone to the alpha cells stimulating glucagon secretion (Burcelin and Thorens 2001). In complementation experiments, transgenic reexpression of Glut2 in glial cells, but not in neurons, of the Glut2-null mice restored hypoglycemia-induced glucagon secretion. This was associated with a restoration of c-fos labeling in the dorsal vagal complex following i.p. 2-DG injections (Marty et al. 2005). This suggests that astrocyte–neuron coupling is required for normal hypoglycemia detection and counterregulatory response. In these experiments, however, c-fos labeling in the VMN induced by 2-DG injection was similar in the presence and absence of Glut2, suggesting that this transporter is not involved in neuroglucopenia activation of VMN neurons.

Absence of Glut2 was also associated with a defect in refeeding following a fast, and with hyperphagia in ad libitum–fed mice. These mutant mice also failed to respond to i.p. or i.c.v. injections of 2-DG (which normally stimulates feeding) or of glucose (which normally reduces feeding). This was further associated with a loss of regulated expression of NPY and POMC in the AN during the fast-to-refed transition, or following i.c.v. injections of glucose (Bady et al. 2006). A defect in thermogenesis was also described, with an impaired capacity of the Glut2-null mice to maintain their body temperature when exposed to 4°C, and their spontaneous entry into torpor when fasted overnight (Mounien et al. 2010). This was secondary to reduced activation of thermogenesis, as revealed by reduced UCP-1 and deiodinase II expression in the brown adipose tissue. Impaired activation of thermogenesis may be secondary to a defect in leptin action on AN neurons. Absence of Glut2 indeed led to a reduction in leptin signaling as assessed by phosphorylation of STAT3 in NPY and POMC neurons during the fast-to-refed transition or following i.p. injection of leptin.

Collectively, these results suggest that glucose sensing by Glut2-expressing cells is required for the normal sensitivity to leptin of NPY and POMC neurons. They also indicate that even though NPY and POMC neurons may be directly responsive to changes in glycemia, as assessed in hypothalamic slices, in physiological conditions their glucose responsiveness is also controlled by Glut2-expressing cells. These can be neighboring tanycytes or neurons located in other brain regions and which send projections to the AN. Finally, these data suggest that Glut2-expressing neurons may form a distinct class of GE and GI neurons that act as modulator of the more classical GE and GI neurons of the AN, LH, and VMH.

6 Conclusions

The studies reviewed here indicate a very high diversity in the mechanisms involved in detecting variations in blood glucose levels or glucose availability by the brain. The picture that is emerging is that there are multiple sites of glucose sensing located mostly in the hypothalamus and brainstem, regions involved in homeostatic regulation of feeding, energy expenditure, and glucose homeostasis. These regions are connected to peripheral sites of glucose sensing such as the gut and hepatoportal vein regions (Marty et al. 2007a), which monitor peripheral glycemic levels, and also to regions of the brain involved in control of feeding behavior and reward. It is puzzling to observe such diverse glucose sensing systems, and so far there is no real hypothesis for the importance of this diversity. It may be related to the fact that different GI neurons may be required for activation of counterregulatory hormone secretion, glucagon and catecholamines, at different hypoglycemic levels, in order to induce feeding or thermogenesis. These responses may be coordinated but still controlled differentially. Alternatively, different glucose sensing neurons may be recruited at different levels of hypoglycemia, in analogy to the activation of various TRP-expressing, temperature-sensitive neurons that are responsive to different temperature ranges (Voets et al. 2005).

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