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# Carbohydrates and the Brain: Roles and Impact

*Xavier Fioramonti and Luc Pénicaud*

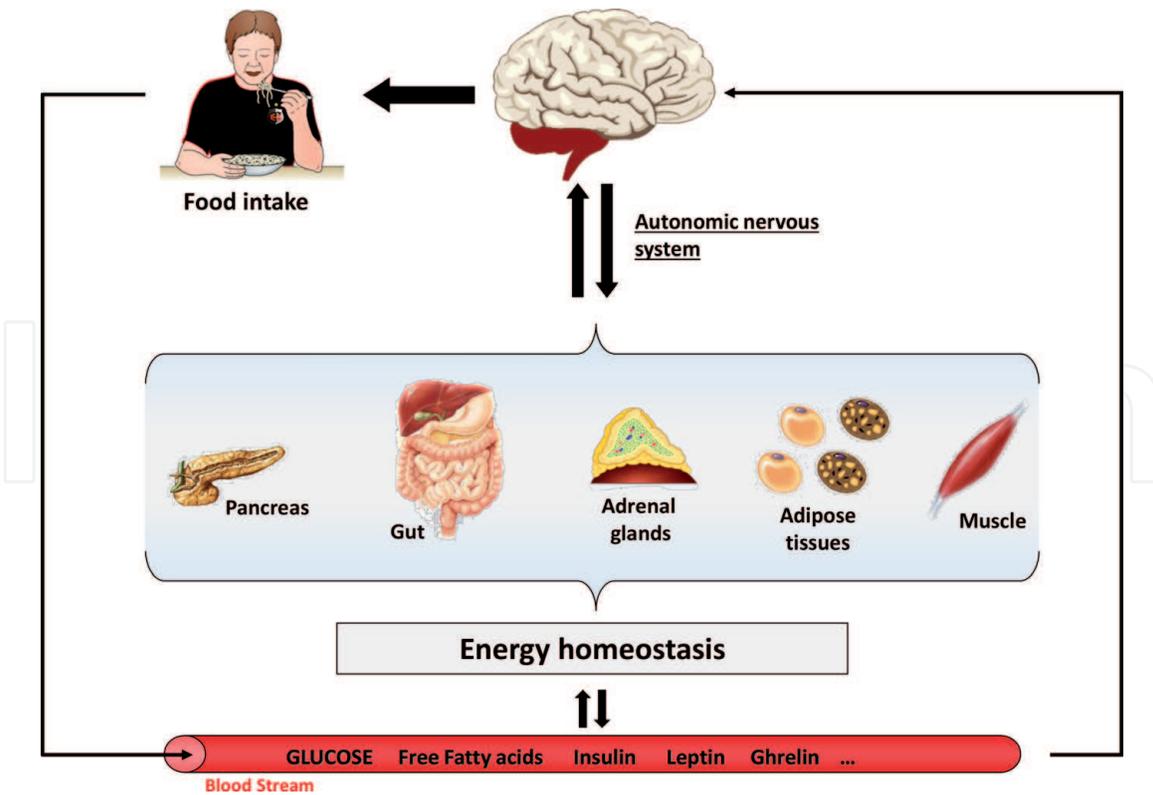
## Abstract

Even if its size is fairly small (about 2% of body weight), the brain consumes around 20% of the total body energy. Whereas organs such as muscles and liver may use several sources of energy, under physiological conditions, the brain mainly depends on glucose for its energy needs. This involves the need for blood glucose level to be tightly regulated. Thus, in addition to its fueling role, glucose plays a role as signaling molecule informing the brain of any slight change in blood level to ensure glucose homeostasis. In this chapter, we will describe the fueling and sensing properties of glucose and other carbohydrates on the brain and present some physiological brain functions impacted by these sugars. We will also highlight the scientific questions that need to be answered in order to better understand the impact of sugars on the brain.

**Keywords:** brain, glucose, fructose, food intake, glucose-sensing neurons

## 1. Introduction

The mammalian brain essentially depends on glucose for its energy needs. Because neurons have the highest energy demand in the adult brain, they require continuous delivery of glucose from the blood. In man, the brain represents ~2% of the body weight but uses ~20% of glucose-derived energy, making it the main consumer of glucose [1]. As a consequence, a tight regulation of glucose metabolism is critical for brain physiology. A fine feedback loop between the brain and various organs and tissues has been demonstrated, allowing, in normal conditions, to maintain blood glucose level rather constant around 1 g/l (7–8 mM) in the blood and ~2 mM in the brain (see below Section 5) [2, 3]. The brain needs a precise and clear feedback on the metabolic state of the whole body [4]. To achieve this aim, various brain areas, especially the brainstem and the hypothalamus, integrate peripheral signals delivered by neural input from various organs, as well as by metabolites (glucose, fatty acids) and hormones (leptin, insulin, ghrelin) via the blood [2–4]. Thus, specialized nutrients- and hormones-sensing neurons in which the firing rate varies in response to changes in extra-cellular nutrients or hormones concentration have been described. In response, the brain will generate appropriate response by modulating food intake and peripheral organs' activity via the autonomic nervous system to maintain energy status and glucose homeostasis (**Figure 1**). Thus, we will describe in this chapter that in the central nervous system, glucose has a dual role and is considered as a fueling as well as a sensing metabolite to ensure glucose homeostasis and appropriate fueling of brain cells.

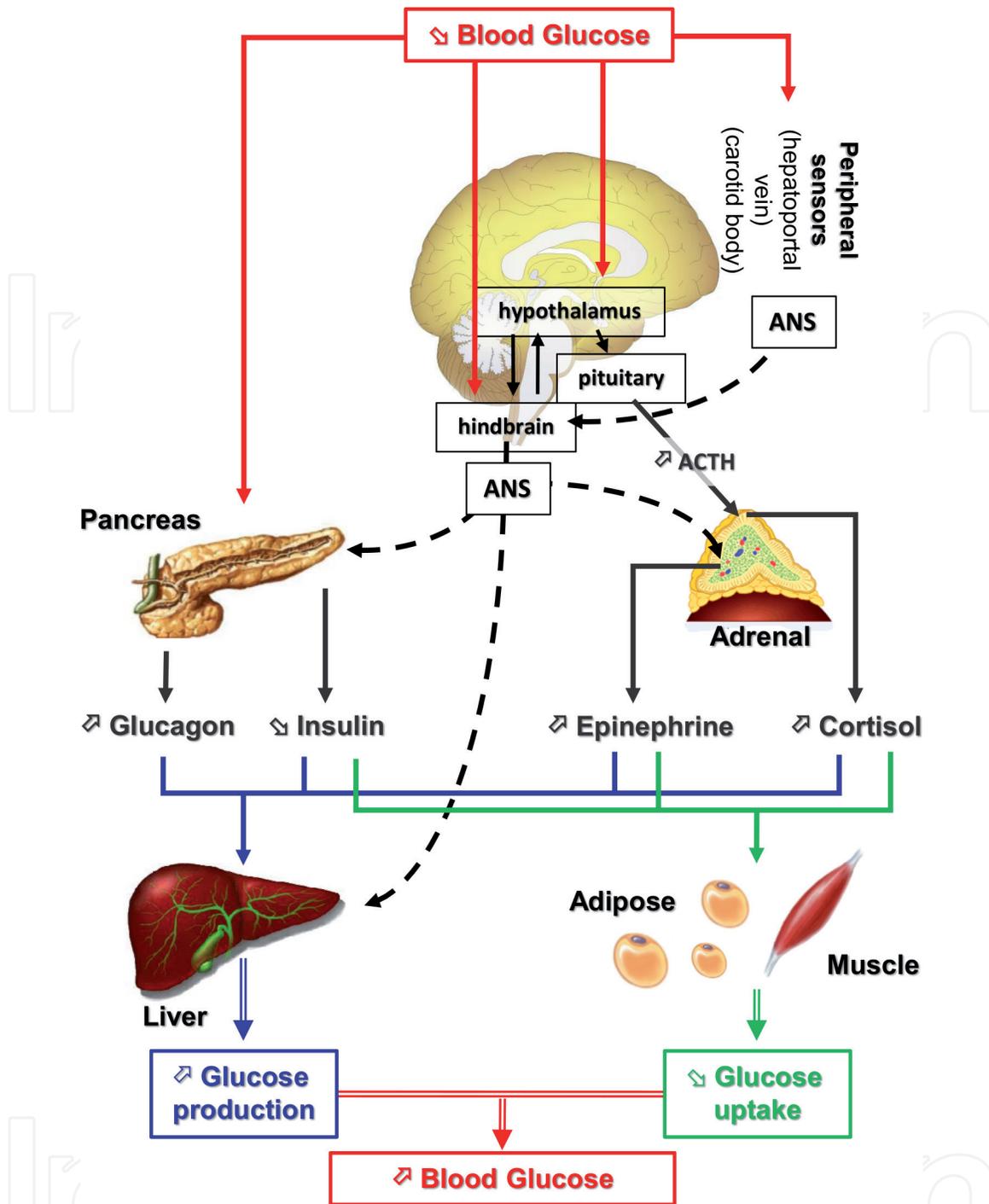


**Figure 1.** Role of the brain in the control of energy homeostasis. The brain integrates peripheral signals delivered by neural input from various organs, as well as by metabolites (glucose and fatty acids) and hormones (leptin, insulin, and ghrelin) via the blood. In response, the brain generates appropriate response by modulating food intake and peripheral organs' activity via the autonomic nervous system to maintain energy homeostasis.

However, one has to keep in mind that given the dietary mutations that occurred in recent decades, sugars other than glucose are part of our diet and could influence brain fueling and sensing. This is indeed the case for example of fructose. Fructose and glucose are rather simple molecules but there are differences in the way the body processes them. This is definitely true for the way the brain uses and reacts to them. These differences could explain the consequences observed after a high consumption of fructose, on food intake and whole-body glucose metabolism.

## 2. Brain's control of glycemia

In humans, the value for normoglycemia is around 1 g/l. Although the endocrine pancreas is the main regulator of blood glucose level via the secretion of insulin and glucagon, the brain plays a major role in controlling glycemia. This is achieved through different pathways involving the autonomic nervous system and its projection to several organs and tissues such as the endocrine pancreas, the adrenal gland, the liver, skeletal muscles, and white and brown adipose tissues. As illustrated in **Figure 2**, in case of a drop in blood glucose, there is an activation of sympathetic nerves and consequently an increase in glucagon secretion by the alpha cells and a decrease in that of insulin by the beta cells of the pancreas, as well as an increase in epinephrine and cortisol secretion by the adrenal gland. These changes in hormone levels together with a direct effect of the sympathetic system will lead to an increased glucose production by the liver, and a decreased glucose utilization by fat deposits and muscles, leading thus to a normalization of blood glucose.



**Figure 2.** Neuroendocrine pathways involved in the counter-regulatory response to hypoglycemia. Decreased blood glucose is detected by central (hypothalamus and hindbrain) and peripheral (pancreas, hepatoportal vein, and carotid body) glucose sensors. Together, these glucose sensors coordinate physiological responses, which raise blood glucose levels. The initial response to hypoglycemia involves activation of the autonomic nervous system (ANS), inhibition of insulin secretion, and stimulation of pituitary ACTH secretion. Activation of the autonomic nervous system increases glucagon and epinephrine secretion from the pancreas and adrenal medulla, respectively. ACTH stimulates cortisol release from the adrenal cortex. Increased glucagon, epinephrine, and cortisol together with decreased insulin stimulate hepatic glucose production and decrease adipose and muscle glucose uptake. The net result of the neuroendocrine counter-regulatory response to hypoglycemia is to increase blood glucose levels and restore euglycemia.

### 3. Glucose: the fuel of brain's neurons

Brain function and glucose metabolism are intimately linked [1]. Indeed, glucose is the main, if not the only, energy substrate of this organ. Hypoglycemia (below 0.7 g/l) causes rapid brain repercussions, but fortunately, most of the time quickly

reversible after correction of hypoglycemia. With regard to hyperglycemia, acute situations such as ketoacidosis and hyperosmolarity can lead to a coma, with significant mortality. The chronic effects of hyperglycemia on the brain remain unclear, apart from the risk of ischemic stroke. However, microangiopathy is intimately linked to chronic hyperglycemia, and can cause irreversible diffuse vascular lesions and cerebral ischemia, resulting in cortical atrophy and diabetic encephalopathy.

The brain uses glucose as its main source of energy, although it can utilize other metabolites (mainly ketone bodies) in special situations such as fasting. It has very high energy consumption for its size, mainly due to the high energy supply needed to maintain its functions (potential difference across nerve cell membranes, transport along axons and dendrites, tissue plasticity and repair).

Glucose enters the brain by facilitated diffusion across the blood-brain barrier, and enters brain cells mainly via a range of glucose transporters. Most human cells import glucose by members of the GLUT (SLC2A) family of membrane transport proteins (see review [5]). Of these, GLUT1 is abundant at the BBB and in astrocytes, regulated mainly by steady-state levels of plasma glucose. GLUT2 appears to serve glucose sensors in the brain. GLUT3 ensures efficient glucose uptake by neurons. Although the brain is considered as a non-insulin-dependent organ, insulin crosses the blood-brain barrier and binds to receptors on neurons and glial cells [6]. There is controversy as to whether insulin resistance for glucose is present in the CNS, but emerging data suggest that insulin insensitivity may play an important role in the pathogenesis of obesity, type 2 diabetes, and Alzheimer's disease [7, 8]. GLUT5 and GLUT7 are present at low levels in the brain and have specificity for fructose. GLUT6 is expressed in the brain but has low affinity to glucose. Studies of mice suggest roles of GLUT8 in hippocampal neuronal proliferation. GLUT13 is a myoinositol transporter expressed primarily in the brain and is the only GLUT protein that appears to function as a proton-coupled symporter (see review [5]).

Once transported into the cell, glucose is phosphorylated by a hexokinase, an enzyme with such high affinity toward glucose that it rapidly transforms glucose into glucose-6-phosphate. Glucose-6-phosphate is metabolized further, mainly in the glycolytic pathway, where it is converted to pyruvate. Glucose-6-phosphate is also substrate for the pentose phosphate shunt and the generation of glycogen only in glial cells. Pyruvate is metabolized either in the Krebs cycle after transport into the mitochondria, or converted to lactate by means of the lactate dehydrogenase. A large part of the pyruvate transported into brain mitochondria is devoted to the oxidative phosphorylation of ADP to ATP.

The energy supply to the brain is provided by blood vessels. In most brain structures, these vessels are surrounded by a blood-brain barrier which does not allow molecules to cross it and as a consequence isolates the brain from the circulatory network. Under these conditions, the energy input is partly indirect and passes partly through the cells that constitute this barrier, namely the astrocytes [9]. These cells can store energy as glycogen or transform it as lactate. This energy is released on demand, when the neurons need it [10]. This lactate is produced in astrocytes by degradation of glucose in pyruvate when the neurons need it. The lactate is then sent to neurons, which synthesize pyruvate and use it in the Krebs cycle. This role of astrocytes and lactate as the main energy substrate of neurons is still a matter of debates.

#### **4. Glucose: a signaling molecule for the brain**

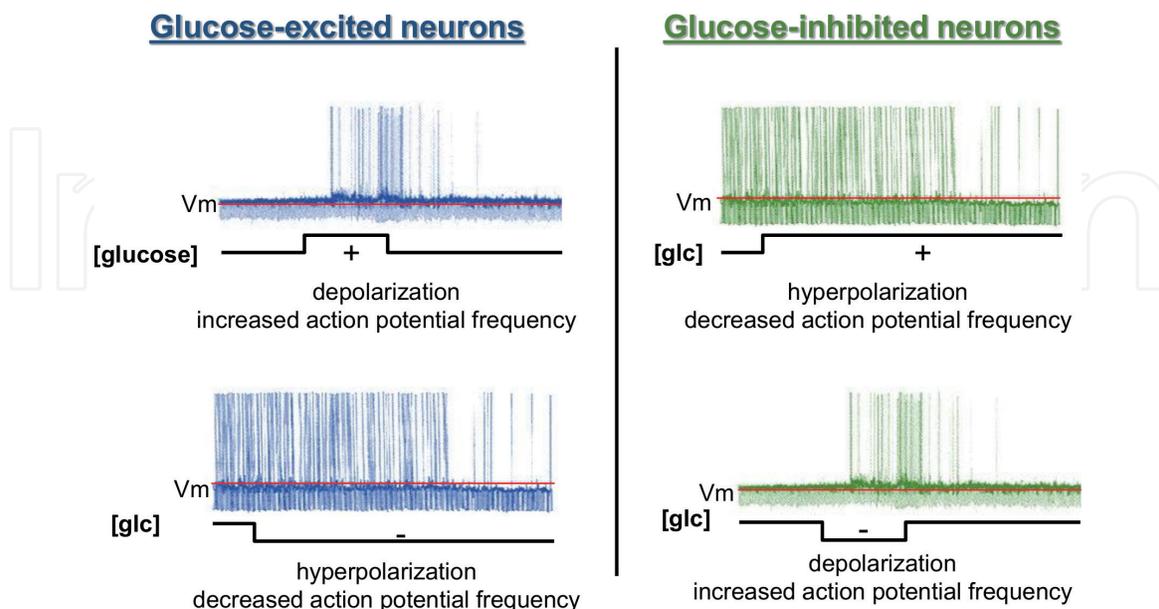
In the previous part, we discussed the fact that the brain relies on glucose to function. This implies that blood glucose level must remain stable. Any decrease in blood glucose level would have immediate consequences on brain functions. Increased blood level will not have acute consequences but sustained hyperglycemia will be

deleterious in the long term as seen in patients with uncontrolled diabetes mellitus. The brain plays a critical role in the regulation of blood glucose level to ensure whole-body glucose homeostasis. Thus, to be able to control the level of blood glucose, the brain must be able to sense any change. In this part, we will discuss the idea that glucose is more than a fueling molecule and it is able to play the role of a signaling molecule in some neurons or brain cells called glucose-sensing cells.

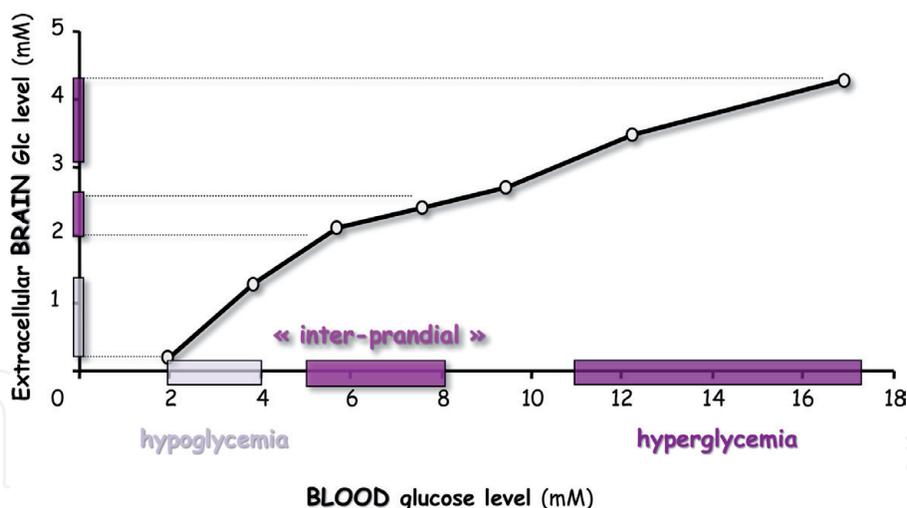
**Glucose-sensing neurons:** The first hypothesis that specialized cells within the brain could detect changes in glucose level originated from studies by Oomura' and Anand's groups, in which they showed that neurons within the hypothalamus had their electrical activity modified in response to intravenous injection of glucose [11, 12]. While these studies suggested that neurons able to detect glucose were present in the brain, they did not prove that glucose could directly affect these neurons since glucose was injected intravenously. Thus, later, Oomura demonstrated the presence of specialized glucose-sensing neurons in showing that the direct application of glucose in the lateral hypothalamus of rats altered the activity of specific neurons [13]. These so-called glucose-sensing neurons are now defined as cells able to adapt their electrical activity in response to changes in extracellular glucose level. By definition, glucose-excited (GE) neurons increase their electrical activity, whereas glucose-inhibited (GI) neurons decrease their activity when glucose level rises. By opposition, when glucose level decreases, GE neurons decrease their electrical activity whereas GI neurons increase it (**Figure 3**).

It is important to note that glucose-sensing neurons use glucose, not only as fuel, but as a signaling molecule that modulates their electrical activity. In addition, it must be mentioned that glucose-sensing neurons directly detect changes in glucose level and not through indirect presynaptic modulation. Finally, their responses to decreased glucose level are distinct from the “run-out-of-fuel” silencing of every neuron by nonphysiological low glucose levels.

**Brain glucose level:** The notion that, by definition, glucose-sensing neurons respond to physiological changes in brain glucose level raises the question of the



**Figure 3.** Schematic representation of the electrical activity of glucose-sensing neurons in response to changes in glucose level. Glucose-excited (GE) neurons increase their electrical activity (depolarization and increased action potential frequency), whereas glucose-inhibited (GI) neurons decrease their activity (hyperpolarization and decreased firing rate) when glucose level rises. By opposition, when glucose level decreases, GE neurons decrease their electrical activity whereas GI neurons increase it. Abbreviations: glucose or glc, extracellular glucose level;  $V_m$ , basal membrane potential.



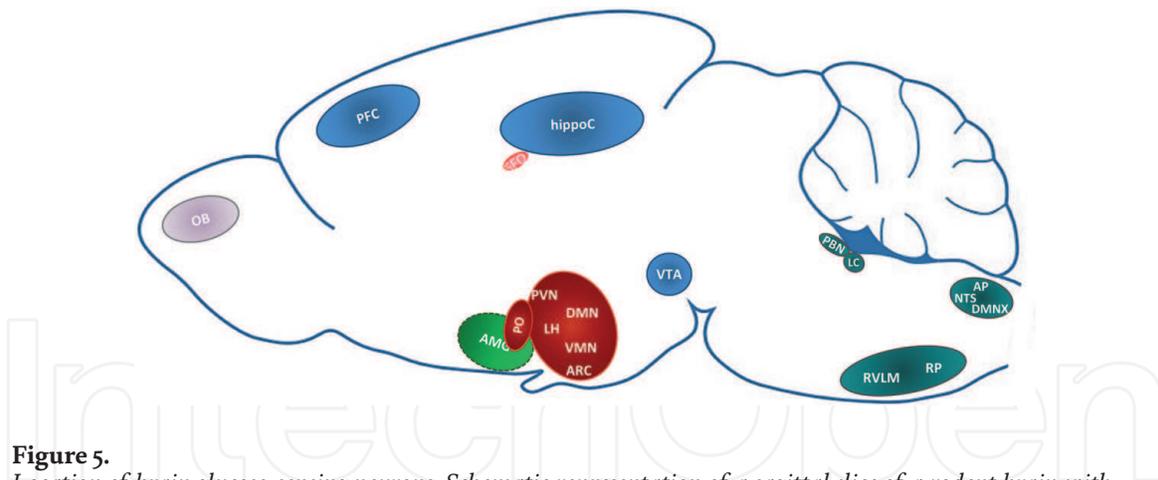
**Figure 4.**

*Extracellular brain glucose levels versus plasma glucose levels. Plasma glucose levels of about 2–4 mM (50–80 mg/dl) observed during hypoglycemia correlate brain levels of about 0.1–1 mM. Plasma levels of about 5–8 (80–120 mg/dl) are related to levels seen during meal-to-meal variation and correlate to brain levels of about 2–2.5 mM. Plasma glucose levels over 8 mM or 140 mg/dl are seen during uncontrolled hyperglycemia and correlate with brain level above 3 mM but not exceeding 4.5–5 mM. Adapted from Ref. [19].*

glucose level in the brain. The level of brain glucose is a process finely regulated by GLUT1, the glucose transporter expressed at the BBB. The high affinity of this transporter ( $K_M = 2\text{--}3\text{ mM}$ ) for glucose justifies the level found in the brain, which is about 30% of the blood level. Thus, several studies using glucose oxidase electrode methods or zero net flux method for microdialysis consistently indicate that physiological levels of glucose within the brain vary within a fairly tight range from 0.7 to 2.5 mM. On the other hand, extracellular brain glucose levels below 0.7 mM and above 2.5 mM are associated pathological hypo- and hyperglycemia, respectively. This is the case in all brain areas where it has been measured including the hypothalamus, the hippocampus, and striatum for instance [14–18] (**Figure 4**).

**Location and role of glucose-sensing neurons:** Most of the glucose-sensing neurons have been described in the hypothalamus in response to changes in the window between 0.1 and 5 mM, which represents the physiological changes observed in the brain (see for review [20, 21]). Nevertheless, our group found that within the arcuate nucleus (ARC), four populations of glucose-sensing neurons actually exist. We showed that the “classical” GE and GI neurons detect changes below 2.5 mM whereas so-called HGE or HGI neurons (for high-glucose-excited or -inhibited neurons) are respectively activated or inhibited by changes above 5 mM [22–25]. Interestingly, the electrical activity of HGE and HGI neurons is only changed in response to glucose change below 2.5 mM and not altered by changes in glucose level above it [22, 23]. Similarly, we found that HGE and HGI neurons only change their electrical activity in response to changes in glucose level above 5 mM but not below this level [23]. Finding these different subpopulations of glucose-sensing neurons raised the question of the actual glucose level present in the arcuate nucleus of the hypothalamus in which the BBB is fenestrated [16, 26] and suggested that, in confined areas, glucose level could be increased closer to levels found in the blood.

Not everything is known yet regarding these different populations of glucose-sensing neurons. Their proportion within the different nuclei of the hypothalamus is difficult to estimate since not every study uses the same changes in glucose level. However, we could estimate that they represent around 10% of hypothalamic neurons. A question which has been poorly addressed is their interconnection. We think that some HGE or HGI neurons from the ARC may connect some VMN neurons found to be indirectly modulated to increased glucose level above



**Figure 5.** Location of brain glucose-sensing neurons. Schematic representation of a sagittal slice of a rodent brain with different areas where glucose-sensing neurons have been found. Abbreviations: AMG, amygdala; AP, area postrema; ARC, arcuate nucleus; DMNX, dorsal motor nucleus; DMN, dorsomedial nucleus; HippoC, hippocampus; LC, locus coeruleus; LH, lateral hypothalamus; NTS, solitary nucleus; OB, olfactory bulb; PBN, parabrachial nucleus; PFC, prefrontal cortex; PO, preoptic area; PVN, paraventricular nucleus; RP, Raphae pallidus; SFO, subfornical organ; VMN, ventromedial nucleus; VTA, ventral tegmental area.

5 mM [20, 23, 27]. Nevertheless, no study has directly studied their interconnection to determine whether they could work as a synchronous network. By opposition, the molecular mechanisms involved in their detection to changes in glucose level are pretty much known (see for review [20, 21]). The nature of these glucose-sensing neurons in terms of neurotransmitter expressed and released, however, is not clear for all the subpopulations [20]. Knowing better the identity of glucose-sensing neurons will be necessary to better understand the physiological functions they control, which are not fully understood yet. It is however clear that these neurons are involved in the control of food intake, thermogenesis, and glucose homeostasis (glucose tolerance, insulin secretion, and hepatic glucose production). Several studies have described that inhibiting molecular mechanisms involved in their glucose sensitivity alters some of these functions.

Glucose-sensing neurons can be found in extra-hypothalamic areas (Figure 5). To our knowledge, HGE and HGI neurons have only been found in so-called circumventricular organs, brain areas where the BBB is fenestrated including the area postrema of the hindbrain, the subfornical organ and the vascular organ of lamina terminalis. All the other brain areas where glucose-sensing have been found present neurons modulated by glucose changes below 2.5 mM glucose. This raises the question of the physiological role of these neurons in these extra-hypothalamic areas. One hypothesis is that these neurons present in different places of the brain detect decreased glucose level, which could be associated to hypoglycemia. They may play the role of detectors of energy availability and inform about a potential “crisis” since glucose is the principal fuel of neurons and its brain level needs to be finely controlled. Nevertheless, we cannot exclude that these neurons take part in physiological functions including memory, motivation olfaction, in view of their location in areas such as the hippocampus, striatum, olfactory bulb for instance. Significant work is still needed to fully understand the functions controlled by these hypothalamic or extra-hypothalamic neurons.

**Glial cells are also able to detect glucose:** Astrocytes represent the major class of macroglial brain cells and occupy about 50% of the total brain volume. Beyond their role of structural neuronal supporting cells, astrocytes are now recognized to take an acting part in brain homeostasis and participate in increasingly large number of functions including neuronal proliferation, synaptogenesis, synaptic transmission, and neurotransmitter homeostasis as well as neuronal fueling and nutrient sensing.

The first evidence suggesting a role of astrocytes in hypothalamic glucose-sensing was the expression of some key “glucose-sensing” protein in this cell population. Thus, our group was the first to show that GLUT2 is expressed in hypothalamic astrocytes [28–30]. Other glucose sensors such as  $K_{ATP}$  channels and glucokinase are also found in astrocytes. We also showed that increased central glucose level increases the expression of the cell activation marker c-fos in hypothalamic astrocytes [31]. More recently, studies showed that glial cells are directly glucose-sensing using primary culture. Thus, increased glucose level increases calcium waves in hypothalamic tanycytes (astrocyte-like cells present in the ventral hypothalamus) suggesting that these cells are activated by glucose as shown in neurons [32, 33]. Even though these studies started to decipher mechanisms involved in astrocyte glucose-sensing (involvement of ATP release, purinergic channels, connexins), further work is still needed to better understand the signaling pathways involved in their glucose-sensing. A question that needs to be answered is the mechanisms by which astrocytes and neurons are coupled in order to ensure brain glucose-sensing. Studies from our group and others suggested that the gliotransmitter ACBP (AcetylCoA-Binding Protein), released by astrocytes in response to increased glucose level, activates pro-opiomelanocortin neurons of the arcuate nucleus, neurons highly known to control food intake, thermogenesis, and glucose homeostasis [34, 35]. ACBP is not the only gliotransmitter involved in glucose-sensing, other studies also showed the importance of ATP or lactate. Interestingly, glucose-excited neurons responding to increased glucose level are also activated by lactate [36]. Thus, in addition to be a fueling substrate for neurons, lactate, as glucose, is also considered as a signaling-like nutrient for glucose-sensing neurons. More studies are still needed to highlight other potential glucose-sensing gliotransmitter and to fully understand the role of astrocytes in brain glucose-sensing. Also, different isoforms of glucose transporters or hexokinases are expressed in other glial cells including microglia or oligodendrocytes [37]. Nevertheless, except a putative fueling role, it is not known whether these glial cell types are able to sense changes in glucose levels as neurons or astrocytes do.

## 5. The impact of other sugars on the brain: the example of fructose

The patterns of sugar consumption have changed considerably in recent decades. Glucose is not the only monosaccharide present in our alimentation, which can cross the intestinal barrier and be present in the bloodstream. Fructose is the other main monosaccharide we eat. Fructose is the *partner* of glucose in the sucrose we consume. In addition to its natural presence in fruit and honey, it is also present in soda, biscuits, and all sorts of processed food. Thus, while fructose consumption was <5 g/day until the 70s, it consumption has dramatically increased since and currently reaches 50–80 g/day in developed countries. In addition, the ending of European sugar quota in 2017 will likely further increase by 8–15% its intake in the next decade.

So far, the increase in fructose consumption has raised health issues regarding liver function and development of metabolic syndrome [38]. Increases in fructose consumption have paralleled the increasing prevalence of obesity, and high-fructose diets are thought to promote weight gain and insulin resistance. Thus, fructose has been pointed out by the French Anses agency as potentially harmful (saisine n° 2012-SA-0186). The agency demands “more studies aiming at understanding the effect of selective sugars including fructose, on brain functions and mental health.” Thus, the impact fructose overconsumption could have on other organs or physiological functions has been somehow neglected. It has been reported that

when consumed in low amount, the intestine metabolizes fructose into glucose with almost no fructose spill over into the bloodstream. Even if spill over may happen in the portal vein, fructose will be metabolized and transformed into fatty acids by the liver. Nevertheless, when consumed in excess, fructose spills over into the bloodstream and may enter organs including the brain [39].

The fact that the brain is fully equipped to uptake and metabolize fructose supports the concept that fructose could affect the activity of brain networks. The main fructose transporter GLUT5 and the ketohexokinase (KHK, the principal fructose-metabolizing enzyme) are expressed in the brain and at the BBB [40]. Both human and animal studies have shown that the brain reacts to high fructose intake. For instance, studies from K Page showed that fructose ingestion does activate some brain regions but which are different to the one activated by a glucose load [41, 42]. Interestingly, they showed that fructose load does not decrease the hunger sensation as compared to glucose. This would suggest that fructose does not send a satiety signal to the brain as powerful as glucose does. In support of this, studies in animal models showed that intracerebral injection of fructose stimulates food intake [43, 44]. Fructose overconsumption may also alter other brain functions including cognition and mood. Studies showed that rodents fed a high-fructose diet present memory deficits or anxiety-related behaviors [45–49]. Interestingly, it seems that the adolescence may be a more sensitive period to high fructose exposition [47, 49, 50]. This is particularly puzzling since adolescents are the population eating fructose and transformed food the most. Nevertheless, in all these animal studies with high-fructose feeding, the effect of fructose diet cannot be segregated from its impact of glucose homeostasis. It is not clear yet whether fructose may directly alter neuronal network. Many more studies need to be performed to fully understand the direct effect of fructose on brain cells and the brain functions impaired by fructose overconsumption. In addition, many other questions have not been answered yet. Can fructose be used as glucose to fuel brain cells, even though its basal blood level is extremely low? Do fructose-sensing neurons or glial cells exist within the brain? These open questions must be answered rapidly in order to improve the nutritional recommendation regarding the consumption of this sugar.

## **6. Conclusions**

Over the last 50 years or so, our vision of the impact of sugars on the brain has significantly evolved. Knowing for its fueling role to brain cells, glucose is also considered as a signaling molecule informing the brain of the whole-body energy status and availability thanks to the discoveries of specialized glucose-sensing neurons. The findings that not only neurons are able to sense changes in glucose level and the fact that glial or neuronal glucose sensors are present all over the brain show the importance of detecting glucose level for a proper control of energy homeostasis. Nowadays, the nutritional mutation we are facing raises other concerns. The brain would be somehow protected to glucose overconsumption in view of the transporter present at the blood-brain barrier, which is saturated around 2–2.5 mM. However, the impact on brain of the metabolic changes induced by such increase in sugar consumption is yet to be evaluated further. Which brain networks and brain functions are altered by increased sugar consumption? In addition, the change in the nature of the sugars we eat raises others questions as described here for fructose. Years of research are still needed to improve our understanding of the impact of sugars on the brain in order to propose optimal nutritional recommendations.

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## **Conflict of interest**

The authors declare no conflict of interest.

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