THE ROLE OF THE CENTRAL NERVOUS SYSTEM IN GLUCOSE HOMEOSTASIS

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Abstract

Central nervous system, mainly the hypothalamus and the brainstem are important keys in glucose homeostasis. Not only do they use glucose as primary fuel for their functioning but they are part of intricate neuronal circuits involved in glucose uptake and production as was first shown by Claude Bernard. Moreover electrophysiological analysis of hypothalamus revealed the existence of glucosensing neurons whose firing rates are controlled by glucose extracellular level. Further information was obtained regarding the importance of leptin, insulin and free fatty acids as afferent signals received by these neural structures. As for the main efferent pathways, autonomic system is the one connecting CNS with the effector organs (the liver, the pancreas and the adrenal glands).

key words: hypothalamus, brainstem, glucosensing neurons, autonomic system, glucose homeostasis

Brain involvement in glucose homeostasis

The first information regarding the role of the central nervous system (CNS) in glucose homeostasis dates from the 19th century, when Claude Bernard showed that when puncturing the floor of the forth cerebral ventricle in dogs he induced hyperglycemia. His explanation was that there are glucoregulatory connections between the brain and the liver (one of them being responsible for glucose uptake and the other one for its release).

In 1953 Jean Mayer mentioned the existence of two types of cells: glucose excited (GE) neurons-activated by an increase in glucose concentration and glucose inhibited (GI) neurons activated by a decrease in glucose concentration. They were mainly located in the ventromedial (VMH), the arcuate (ARC), lateral (LH), dorsomedial (DMH) and paraventricular (PVH) hypothalamic nuclei and also in the nucleus of solitary tract (NTS), area postrema (AP), the dorsal motor nucleus of the vagus (DMNV) and the basolateral medulla (BLM). Their
main role is represented by plasma glucose regulation.

Twelve years later in 1965, during experiments on rabbits Shimazu and his colleagues proved that electrical stimulation of VMH (containing mainly sympathetic nuclei) upregulated plasma glucose level and decreased hepatic glycogen, while electrical stimulation of LH (containing mainly parasympathetic nuclei) downregulated plasma glucose and barely increased hepatic glycogen. Further studies underlined the importance of CNS in glucose metabolism. An increase in glucose level and hyperglycemic hormones was seen after intracerebroventricular administration of 2-deoxyglucose (2-DG), a glucose antagonist. These effects were altered by hypothalamic deafferentation. At the same time counterregulatory response following insulin administration in dogs was blocked once sectioning the spinal cord or the vagus [1-3].

All these experiments led to a better understanding of the neural structures responsible for glucose metabolism, represented by hypothalamus and a few structures located in the brainstem:

- **Hypothalamus** is one of the most important sites of glucose detection in the brain.

  Numerous experiments on animals sustain its role, and especially the role of the VMH in glucose sensing. Borg showed that chemical lesions of the VMH are responsible for decreased hormonal counterregulation with approximately 75% in case of hypoglycemia. At the same time, he also showed that LH and frontal lobe lesions had no response. Moreover he proved that local microdialysis with 2-DG was responsible for plasma glucose upregulation while local administration of glucose had an opposite effect. Further electrophysiological studies brought into attention the existence of glucose sensing neurons in the hypothalamus.

- **The brainstem** with its neural regions like NTS, DMNV, BLM are responsible for glucose detection. Their importance was underlined by injections with 5-thio-D-glucose (5TG) at different levels of the animal brain. Administration of this compound at the level of NTS was associated with hyperglycemina. Also it was only after 5TG was injected into the fourth ventricle (previously the communicating aqueduct being obstructed) that a hyperglycemic response was obtained. The same consequence was observed after systemic administration of 2-DG in decerebrated rats. All these studies point to the existence of glucosensing neurons in the brainstem [1, 4-7].

**Sites and Mechanism of Glucose Detection**

**GE Neurons**, activated by raised glucose levels, stimulate neurotransmitter release mainly γ aminobutyric acid (GABA) with an inhibitory effect on the counterregulatory response. They are preferentially located in VMH, the ARC and PVH [8, 9] and contribute to glucose detection as follows:

- **GLUT2/GK/K<sub>ATP</sub> pathway** is formed of three important components: low affinity glucose transporter (GLUT2), glucokinase (GK), ATP-dependent K⁺ (K<sub>ATP</sub>) channels. GLUT2 have been identified at different neural levels: neurons located in the hypothalamus and the brainstem, astrocytes, epithelial cells lining the cerebral ventricles. Their importance in
glucose sensing was pointed out by experiments on mice expressing a transgenic GLUT1 transporter in the pancreatic cell and with an inactive GLUT2 gene. GK is found in the hypothalamic nuclei and also in the brainstem. Evidence regarding its role was proved by CNS administration of alloxan (GK inhibitor) which stimulated feeding. Also VMH GK is essential for counterregulatory response to insulin-induced hypoglycemia, as shown by recent studies [8, 10, 11].

**K$_{ATP}$ channels** are formed of eight protein subunits. Four of them are sulfonylurea receptor SUR1 (in pancreatic β-cells, brain) or SUR2B (in the brain), while the other four are members of the inward rectifier K$^+$ channel family Kir6.x (Kir6.2 for brain and pancreatic β-cells). Recent study sustained that closing the hypothalamic K$_{ATP}$ channels with glibenclamide (a K$_{ATP}$ channel blocker) damaged the hyperglycemic response to hypoglycemia, while diazoxide (a K$_{ATP}$ channel opener) had a positive effect on the counterregulatory response [12, 13].

The sequence of action consists of neuronal glucose uptake by GLUT2, followed by its phosphorylation to pyruvate by GK (a rate-controlling step) with secondary increase in ATP production. Furthermore, ATP is bound to K$_{ATP}$ channels closing them and reducing K$^+$ efflux from the neurons with membrane depolarization that triggers uptake of Ca$^{2+}$ through voltage-dependent channels. Hence, these will lead to increased neuronal activity and neurotransmitter release [3, 4, 9].

Alternatively the uncoupling protein 2 (UCP2) and the reactive oxygen species (ROS) may interact with this signaling pathway. PROOPIOcéLANOCORTIN (POMC) UCP2 inhibition with genipin increase glucose response [14, 15]. UCP2 are located in the brainstem and also in ARC, VMH, PVH and LH. As for ROS, hypothalamus exposure to increased glucose levels is associated with their formation. Following antimycin/rotenone (known for producing ROS) intracarotid administration insulin production rises [16]. UCP2 may act as a negative modulator of ROS, though ROS may independently act on voltage-gated K$^+$ channels or Ca$^{2+}$ [3, 17].

- **Sodium-glucose cotransporters (SGLTs)** and mainly SGLT1 seem to be linked to glucose peripheral metabolism as proved by central injection of phlorizin which has a positive effect on feeding in rats and inhibits activation of VMH neurons. 3-O-methyl-D-glucose (3-O-MDG) and α-methyl-D-glucopyranoside (α-MDG), nonmetabolizable glucose analogues and substrates for SGLT1, increase hypothalamic GE firing rates. Hypothalamus and ependymal cells of the third and fourth ventricles express SGLT1. Depolarization and increased excitability of GE are the main consequences due to glucose coupling to SGLT1 [3, 4, 9].

- **G-protein-coupled taste receptors (T1R)** is found not only in the tongue and intestine but also in the CNS, PVH, ARC, NTS. At the level of the digestive system they are activated by different metabolites including glucose. However their role in glucose homeostasis it is not yet elucidated [17].

**GI Neurons**, activated by decreased glucose levels, have been associated with several mechanisms. They are most abundant in the LH, ARC and PVH. Their intervention in glucose metabolism is far from being
understood and nor is their neurotransmission. Norepinephrine and glutamate have been considered possible neurotransmitters linked to GI neurons activity. It is important to mention that the majority of VMH neurons contain high levels of the vesicular glutamate transporter.

The following mechanisms have been proposed for GI neurons function:

- **$\text{Na}^+/\text{K}^+\text{-ATPase}$** was the first model proposed for GI. Decrease in extracellular glucose level with secondary downregulation of ATP production lowers $\text{Na}^+/\text{K}^+\text{-ATPase}$ activity, increases intracellular $\text{Na}^+$ and causes membrane depolarization, further leading to the release of neurotransmitters [4, 6, 9].

- Adenosine $5'\text{-Monophosphate-Activated Protein Kinase (AMPK)}$ expression is enhanced in response to hypoglycemia or neuroglucopenia. Injection of 5-amino-4-imidazolecarboxamide riboside (AICAR), an AMPK activator, in the VMH had a positive effect on glucose production, while compound C had an opposite effect [18].

Hypoglycemia activates AMPK as a response to increased AMP/ATP ratio. Furthermore, AMPK phosphorylates neuronal nitric oxide synthases (nNOS) which enhances nitric oxide (NO) synthesis. In turn, NO binds to soluble guanylyl cyclase (sGC) receptors and accelerates cyclic guanosine monophosphate (cGMP) synthesis. This product whether activates AMPK expression or blocks cystic fibrosis transmembrane regulator (CFTR) Cl- conduction producing membrane depolarization and increased firing rates of GI neurons [19, 20].

**Astrocytes-neurons metabolic coupling** is also part of glucose homeostasis, but in an indirect manner. Astrocytes surrounding the blood brain vessels uptake glucose via a GLUT2-dependent mechanism. Here it is stored as glycogen and may be converted to lactate. Further lactate is released in the extracellular space and transferred to neurons through a monocarboxylate transporter (MCT2) being converted to pyruvate by lactate dehydrogenase (LDH) and producing ATP (necessary for glucosensing neurons function) [7, 9, 21].

**Afferent and Efferent Pathways in Glucose Homeostasis**

Glucose is the main energetic substrate for the brain and its level is maintained constant by neuronal circuits. Information regarding blood sugar activates brain receptors through indirect and direct mechanism. The regulatory effect of interstitial brain glucose level (under physiologic conditions maintained at 1-3mM) on CNS receptors can be considered the direct mechanism. As for glucose indirect stimulation of neural structures, vagal afferent pathway is one of the most important. Moreover, after information is integrated at CNS level efferent sympathetic or parasympathetic pathways will be activated. Both of them are connected with the liver, the pancreas and the adrenal glands responsible for a hyperglycemic or hypoglycemic response.

**Increased level of glucose** may be sensed by taste receptors located in the mouth, may activate cholinergic neurons of the submucosal and myenteric plexus in the gut (due to glucose binding to SGLT3 or activation of $K_{\text{ATP}}$ase) and may activate receptors in the hepatoportal vein. All of them are connected to afferent vagal fibres that project to the NTS, parabrachial nucleus (PBN) and DMNV. However blood sugar
variation independently activates the same brainstem structures and also the basal hypothalamus. NTS, PBN, DMNV are linked to the hypothalamus that elaborates the proper response through a parasympathetic efferent pathway. Increased insulin production by the pancreas and decreased hepatic glucose production are effects of vagal innervation.

**Decreased level of glucose** may be sensed in the periphery by a GLUT2-dependent glucose sensor located in the portal vein and further the data collected reach the brainstem and the hypothalamus via vagal fibres. At the central level hypoglycemia informs GLUT2-astrocytes, in particular those located in the brainstem. Finally, a proper response is achieved via the efferent sympathetic pathway. These autonomic fibres reach the liver through the splanchnic nerves and their postganglionic fibres originate from the celiac ganglia producing increased glucose production and decreased glycogen storage. The pancreas receives its efferent sympathetic fibres through the celiac plexus, the response consisting in decreased insulin production via the α-adrenoreceptors and increased glucagon release. Finally the adrenal glands response to hyperglycemia mediated by splanchnic nerves and lumbar ganglia consists of increased epinephrine and glucocorticoids secretion [1, 7, 22, 23].

**Other Regulatory Mechanisms Involved in Glucose Homeostasis**

**Leptin** is an adipokine produced by adipocytes whose role in the neural circuits responsible for food intake and energy balance is mediated by hypothalamus. ARC nucleus with its anorexigen POMC neurons producing α-melanocyte-stimulating hormone (αMSH) and its orexigen neurons secreting neuropeptide Y (NPY) and agouti-related peptide (AgRP) are leptin main sites of action. αMSH is an agonist of the melanocortin-4 receptor (MC4R) while NPY and AgRP are antagonist. Both NPY/AgRP and αMSH are regulated by leptin: inhibiting the former, stimulating the latter and leading to reduced food consumption [24, 25].

Also several experiments on laboratory animals revealed leptin’s role in carbohydrate metabolism starting with intracerebroventricular leptin injection with secondary increase in glucose turnover and uptake. Looking closer leptin seems to mediate its effect on glucose homeostasis through a MC4R dependent pathway, including the POMC neurons and their projections to the dorsovagal complex (including DMNV), the vagus nerve and its connection with the liver [25-28]. There may be another mechanism as leptin injection into the VMH stimulates glucose uptake, that does not depend on MC4R, possible including PVH due to its connection with the pre-ganglionic autonomic neurons, but further investigations are needed [25]. As for the molecular implication of their actions GK the K_{ATP}-channel seem to be the key [1].

**Insulin** injection into the carotid artery, the cerebral vessels or intracerebroventricular administration downregulates glucose production. Insulin receptors are located in different regions of the brain including the hypothalamus and its ARC nucleus. Due to insulin POMC receptors, the hormone acts as a modulator of the melanocortin pathway. It seems that it acts through a K_{ATP}-channel mechanism [1].

Alternatively, blocking norepinephrine uptake and activating glial β-adrenoreceptors with glucose release from their stores, insulin can provide energetic substrate for the neurons [29].
Decreased activity

Free Fatty acids (FFAs) located in the CNS may come from local synthesis or may have plasma origin. FFAs seem to act as an afferent signal in glucose metabolism, influencing the firing rate of glucosensing neurons located in the VMH or LH [30]. Central injection of oleic acid decreased hepatic glucose production, possibly through a $K_{ATP}$-dependent mechanism, as previous study showed [31, 32].

Conclusions

Thus it is possible to synthesize the following circuit. After crossing the blood-brain barrier through a GLUT1-dependent transport, glucose enters the neurons but also the astrocytes. Further, glucose is metabolized providing the necessary energy for GE and GI neurons functioning. Also, their activity is guided by blood sugar level, by numerous signals received via the vagal pathway from periphery. Neurons-astrocytes connection is
also source of energetic substrate. Furthermore, the metabolic information is processed through different molecular mechanisms and the CNS establishes connection via the autonomic system with the liver, the pancreas and the adrenal glands, organs responsible for generating the proper response (Figure 1).

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