Review

Influence of VMH fuel sensing on hypoglycemic responses

Owen Chan and Robert Sherwin

Yale University School of Medicine, Department of Internal Medicine, Section of Endocrinology, New Haven, CT 06520, USA

Hypoglycemia produces complex neural and hormonal responses that restore glucose levels to normal. Glucose, metabolic substrates and their transporters, neuropeptides and neurotransmitters alter the firing rate of glucose-sensing neurons in the ventromedial hypothalamus (VMH); these monitor energy status and regulate the release of neurotransmitters that instigate a suitable counter-regulatory response. Under normal physiological conditions, these mechanisms maintain blood glucose concentrations within narrow margins. However, antecedent hypoglycemia and diabetes can lead to adaptations within the brain that impair counter-regulatory responses. Clearly, the mechanisms employed to detect and regulate the response to hypoglycemia, and the pathophysiology of defective counter-regulation in diabetes, are complex and need to be elucidated to permit the development of therapies that prevent or reduce the risk of hypoglycemia.

Physiological response to hypoglycemia

Hypoglycemia elicits a multifaceted hierarchical hormone and autonomic nervous system response that restores glycemia to normal. As plasma glucose levels begin to fall and drop below 80 mg/dl, insulin secretion rapidly decreases, which serves to reduce β cell inhibition of neighboring α cell function. Decreased inhibition from the β cell reduces the secretion of zinc and γ-aminobutyric acid (GABA), which normally inhibit glucagon secretion [1–4]. Together, this allows the rapid release of glucagon into the portal circulation, where it acts on the liver to stimulate glycogenolysis and gluconeogenesis. If glucose levels continue to decline into the 60–70 mg/dl range, epinephrine is released and sympathetic nervous system activity begins to increase, which act in concert to reverse the decline in glucose levels by further enhancing glucagon secretion and exerting insulin antagonist effects on liver, adipocytes, and muscle. In cases of prolonged and/or more severe hypoglycemia, growth hormone and cortisol are mobilized to further stimulate lipolysis and gluconeogenic enzymes as well as inhibit peripheral glucose utilization [5]. Together, this coordinated hormone and neuronal response constitutes a redundant fail-safe mechanism that helps to prevent glucose levels from falling to dangerously low levels. In non-diabetic individuals, glucagon and epinephrine are usually very effective at restoring plasma glucose levels to normal that additional responses are rarely required.

Neural networks that regulate glucose homeostasis

The ability to respond appropriately to hypoglycemia and maintain normal glucose levels depends on the integration of metabolic signals derived from glucose sensors located in both the central nervous system (CNS) and the periphery, including the gut, the portal/mesenteric vein, and the carotid body [6]. Peripheral glucose sensors located in the portal/mesenteric vein detect changes in glucose levels and relay this information to the nucleus of the solitary tract (NTS), the lateral hypothalamus, and the paraventricular nucleus (PVN) through activation of vagal afferents [7,8]. In turn, signals from the hindbrain are carried forth to hypothalamic centers where the predominant glucose sensors are located, and the information is integrated. Although peripheral glucose sensors may play a role in mediating the immediate counter-regulatory responses to hypoglycemia, it is thought that glucosensors located within the brain may serve a redundant regulatory and/or modulatory role in ultimately regulating glucose counter-regulatory responses.

Many of the glucose-sensing components found in pancreatic β cells, including the type 1 sulfonylurea receptor (SUR1) subunit of ATP-sensitive potassium (K_{ATP}) channels, glucose transporters (GLUT) 2, 3, and 4, glucokinase, and monocarboxylate transporters (MCTs), have been identified in the hindbrain [9]. However, it is still unclear whether hindbrain catecholaminergic neurons are directly or indirectly activated by glucose deprivation. Local administration of the potent antimetabolite 5-thioglucose into the hindbrain elicits a rise in plasma glucose and an increase in feeding, suggesting that this region of the brain can respond to glucose deprivation [10]. Moreover, in response to a glucoprivic stimulus stemming from administration of 2-deoxyglucose (2-DG), the hindbrain also exhibits greater Fos immunoreactivity in very distinct catecholaminergic cell groups, indicating that these neurons may play a role in the brain response to glucose deficit [11].

Central glucose sensors are also located in the lateral hypothalamus, the paraventricular nucleus, the dorsal hypothalamus, the amygdala, and the ventromedial hypothalamus (VMH) [12]. Hypothalamic glucose sensors and, more specifically, those located in the VMH, are crucial for detecting falling blood glucose levels and regulating the

Corresponding author: Sherwin, R. (robert.sherwin@yale.edu).
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counter-regulatory responses [13], and are probably the best characterized (reviewed in [14]). The VMH is ideally situated to receive information regarding the metabolic status of the organism. Being located next to the third ventricle and median eminence, the VMH has projections that allow it to sample glucose and hormones which regulate metabolism. Two types of glucose-sensing neurons have been identified in the VMH: (i) 'glucose-excited' or GE neurons that increase their firing rate in response to rising glucose levels, and (ii) 'glucose-inhibited' or GI neurons which decrease their firing rate in response to increasing glucose levels. Although glucose-sensing neurons respond to changes in extracellular glucose levels by altering their firing rate, the mechanisms used by each subclass of neurons are believed to be very different [14].

GE neurons

The GE neurons in the VMH are the best characterized and they contain much of the same glucose-sensing machinery as pancreatic β cells [15,16]. They predominantly express GLUT3 and to a lesser extent GLUT2, as well as glucokinase (GK) which regulates the first rate-limiting step in glycolysis – the phosphorylation of glucose to glucose-6-phosphate (G6P). The importance of glucokinase as a regulator of glucose-sensing is supported by data showing that pharmacological inhibition or RNA interference reduces the sensitivity of VMH glucose-sensing neurons [17] and that its expression is increased in rodent models of defective glucose-sensing [18,19].

Once glucose is phosphorylated to G6P, this intermediate is metabolized to generate ATP. An increase in the [ATP]/[ADP] ratio causes ATP-sensitive potassium (K_{ATP}) channels to close, and this depolarizes the neuron membrane and opens voltage-gated calcium channels. The influx of extracellular Ca^{2+} leads to exocytosis of vesicular contents (Figure 1). Thus, as glucose levels rise, these neurons continue to fire. By contrast, during hypoglycemia these neurons are largely silenced due to lack of glucose, production of G6P, and thus ATP production. Glucose-excited neurons express the SUR1-containing ATP-sensitive K^+ channel (K_{ATP}) that couples changes in energy status with electrical activity of GE neurons. In this

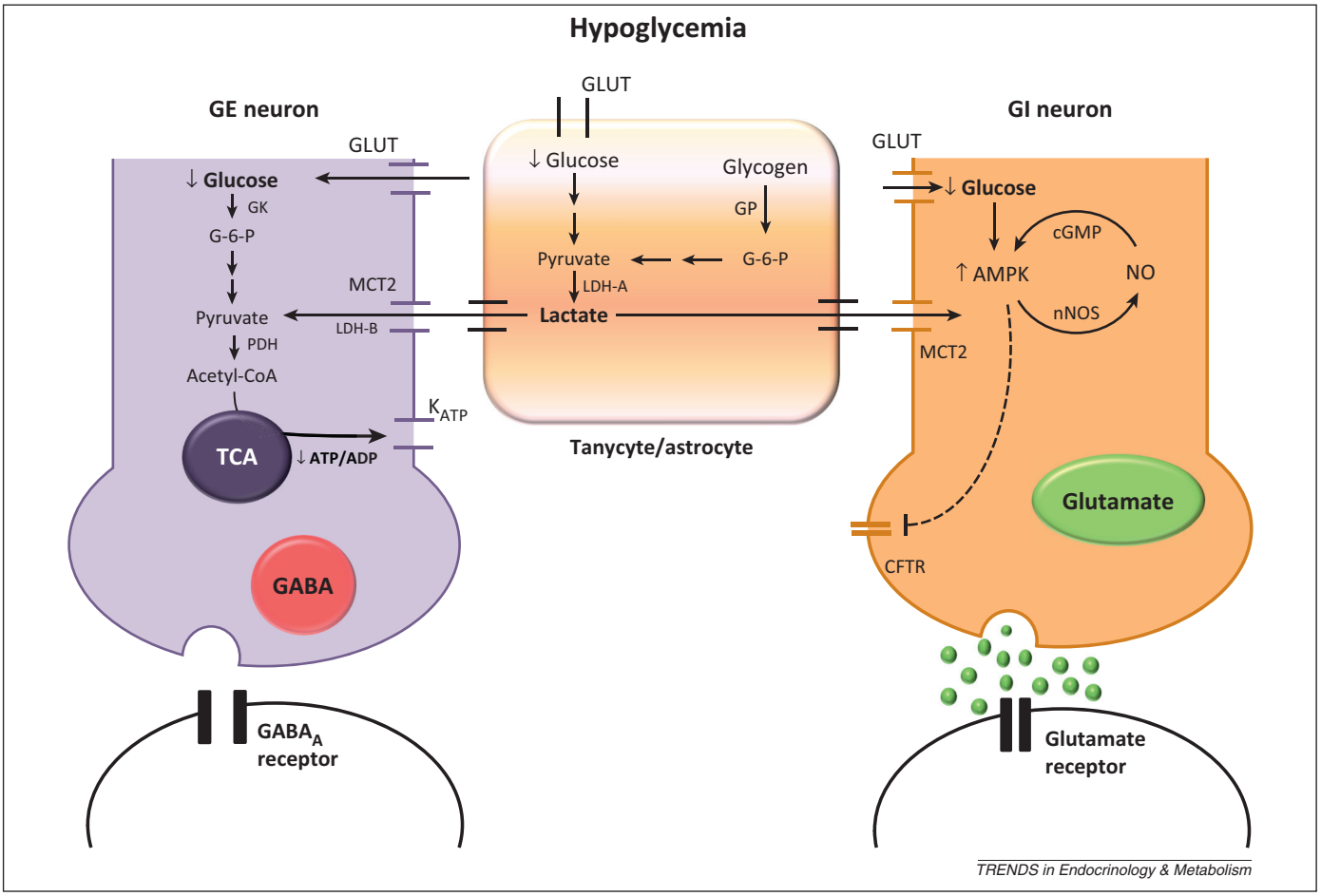

Figure 1. Ventromedial hypothalamus (VMH) glucose-sensing mechanisms during acute hypoglycemia. Schematic showing pathways in the VMH involved in glucose-sensing in response to an acute bout of hypoglycemia in the non-diabetic hypoglycemia-naive condition. In glucose-excited (GE) neurons it has been postulated that a decrease in glucose entering the neuron leads to a reduction in the ATP/ADP ratio. Decreases in this ratio causes ATP-sensitive potassium channel (K_{ATP}) to open, and this in turn hyperpolarizes GE neurons and prevents the release of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA). By contrast, hypoglycemia, which stimulates glucose-inhibited (GI) neurons, leads to activation of AMP-activated protein kinase (AMPK). AMPK then increases the production of nitric oxide (NO), which in turn further enhances the level of AMPK activation through secondary messengers. This amplification of AMPK activity then inactivates (dotted line) the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel, resulting in depolarization of glucose-inhibited neurons and release of a neurotransmitter, likely glutamate. In the astrocytes/tanycytes, a reduction in glucose entry leads to the breakdown of stored glycogen and the production of lactate. Lactate is exported from the astrocyte through monocarboxylic acid transporters 1 or 4 (MCT1 or 4) and enters nearby neurons through MCT2 where it is oxidized. Additional abbreviations: GK, glucokinase; GLUT, glucose transporter; GP, glycogen phosphorylase; LDH, lactate dehydrogenase; nNOS, neuronal NO synthase; PDH, pyruvate dehydrogenase; TCA, tricarboxylic acid cycle.