Central glucose level can modify neural activity through sodium-glucose co-transporter 1 (SGLT1) as well as glucose transporters.

A recent publication from Fan et al.1 revealed a new glucose-sensing mechanism in the central nervous system (CNS). Many previous studies have pointed out the existence of glucose-sensing neurons utilizing similar components in pancreatic β-cells, including glucose transporters (GLUTs), glucokinase, and adenosine triphosphate (ATP)-sensitive potassium channels (KATP). In addition to these components, they proved that SGLT1, the high-affinity SGLT, was also expressed in the ventromedial hypothalamus (VMH). This novel player has a significant role in the detection of hypoglycemia and activation of counter-regulatory responses to hypoglycemia (Figure 1).

Glucose is the most dominant and essential nutrient for the brain, which is responsible for approximately 25% of the body’s glucose consumption. Numerous biological studies regarding glucose metabolism and signaling have established three families of glucose carriers: GLUTs, SGLTs and “sugars will eventually be exported transporters.” Although the GLUT family has been extensively explored in the central nervous system (CNS), knowledge about the SGLT family is sparse, and the characteristics of “sugars will eventually be exported transporters,” which have been mostly investigated in plants, are still unclear in mammals.

Many studies have linked the roles of GLUTs to the function of glucose-excited (GE) neurons in the hypothalamus. In 1964, a group of neurons whose spontaneous discharges increased with the rising of glucose levels was described as GE neurons2. Rigorous studies following the suggested concept of glucose-sensing neurons have provided considerable evidence including the distribution of GE neurons in many hypothalamic regions and the mechanism of glucose sensing. GE neurons are distributed throughout the arcuate nucleus, ventromedial hypothalamus, anterior hypothalamus, paraventricular nucleus and the lateral hypothalamus. The glucose-sensing mechanism used by GE neurons has been well-characterized in VMH. Most GE neurons exploit similar glucose-sensing machinery to that utilized by pancreatic β-cells. Extracellular glucose enters neurons through GLUTs, predominantly GLUT3, and is phosphorylated to glucose-6-phosphate by glucokinase. Subsequently, glucose-6-phosphate is metabolized to generate ATP, and an increase of the ATP/ADP ratio provokes the closing of KATP channels and depolarization of the plasma membrane followed by electrical excitation of GE neurons. In this context, the significant roles of KATP channels in GE neurons have been shown in the hypoglycemic status. Hence, the KATP channel closer glibenclamide attenuated the counter-regulatory responses to hypoglycemia and the KATP channel opener, diazoxide, amplified the responses. Recent work carried out by Fan et al.1 added the novel player, SGLT1, to the glucose-sensing mechanism1. As SGLT1 has a lower “Michaelis constant Km” for D-glucose compared with SGLT2, GLUTs or physiological glucose levels in the CNS, SGLT1 can operate as an alternative gateway for glucose entry during hypoglycemia.

NEURAL SGLT1 ALTERS NEURAL EXCITABILITY ONLY UNDER GLUCOPRIVATION

Regarding glucose levels in the brain, hypothalamic glucose levels are regulated from 0.7 to 4.5 mmol/L between physiological fasted and fed states. When blood glucose levels fall to ~2.8 mmol/L during hypoglycemia, brain glucose levels also decline to ~0.3 mmol/L3. According to a long-standing dogma, SGLT1 is a high-affinity transporter for glucose. In fact, Panayotova-Heiermann et al.4 determined that SGLT1 in rats and humans had a similar Km of ~0.4 mmol/L for glucose. Based on this report, Fan et al.1 concluded that SGLT1 should be saturated under physiological blood glucose levels, and the amount of glucose entering neurons through SGLT1 would start decreasing only under hypoglycemia. They developed and proved this hypothesis indirectly through their experiments in which the augmentation of counter-regulatory responses to hypoglycemia was recognized in SGLT1 knocked-down rats with acute or recurrent hypoglycemic bout(s).

Fan et al.1 knocked down the expression levels of SGLT1 messenger ribonucleic acid in rat VMH using microinjections of an adeno-associated viral vector containing the SGLT1 short hairpin ribonucleic acid. These rats were exposed to recurrent bouts or a single bout of hypoglycemia induced by hyperinsulinemic-hypoglycemic clamp procedures. During hypoglycemia, the glucose infusion rate decreased, glucagon and epinephrine levels increased, and hepatic glucose production increased in SGLT1 knocked-down rats.

Their research design, consisting of an SGLT1 knocked-down model and a recurrent hypoglycemia model, was
elegant. However, we would like to suggest two limitations in their work. First, they examined no transport capacity of glucose through SGLT1 in the knocked-down VMH. In general, transport capacity depends on both the copy number and the turnover rate of the transporter proteins. Direct verification of reduced electrical discharge frequency in neurons infected with SGLT1 short hairpin ribonucleic acid is expected in the future. Second, a recent study⁴ showed that human SGLT1 has a relatively lower affinity for D-glucose, inconsistent with the previously reported value; that is, $K_{0.5}$ 2 mmol/L versus Km 0.4 mmol/L. As Hummel et al.⁵ proved the kinetics of glucose transport using only human SGLT1, the characteristics might vary in rat SGLT1. Readers should carefully interpret the report by Fan et al.¹, and consider the possible differences between humans and rodents.

**CLARIFICATION OF GLUCOSE-SENSING MECHANISM IN THE CNS WILL PROVIDE A USEFUL SOLUTION METHODOLOGY FOR HYPOGLYCEMIA**

Iatrogenic hypoglycemia in diabetic patients currently invites serious clinical attention because of its possible influence on quality of life and cardiovascular motility. Impaired glucose counter-regulation response is one of the most important factors that elicit severe and/or recurrent bouts of hypoglycemia. Although the mechanisms of the impairment have not yet been fully expounded, it appears acceptable that glucose sensing and assembling metabolic information from the periphery in CNS contributes to the deficit. In addition to GE neurons as aforementioned, other crucial participants, glucose-inhibited or glucose-inhibited neurons, have been defined, investigated and characterized as key players in the counter-regulatory response to hypoglycemia. Glucose-inhibited as well as GE neurons are distributed throughout the hypothalamus including the VMH. They increase the frequency of spontaneous action potential discharge through an interaction between adenosine monophosphate activated protein kinase (AMPK) and nitric oxide. In recurrently hypoglycemic model rats or type 1 diabetic model rats, Fan et al.⁷ also reported that the counter-regulatory responses were amplified by the activation of AMPK in the VMH with aminomimidazole carboxamide ribonucleotide. In contrast, the counter-regulatory responses were lessened in neuronal nitric oxide synthase knocked-out mice.

When considering the recent finding from Fan’s laboratory,¹ VMH glucose-sensing neurons have three distinct mechanisms for detecting hypoglycemia: (i) the KATP channel pathway in GE neurons; (ii) the SGLT1 pathway in GE neurons; and (iii) the AMPK–nitric oxide pathway in glucose-inhibited neurons. In addition to these VMH neurons, there are several contributors to glucose-sensing mechanisms, including orexin neurons in lateral hypothalamus, neuropeptide Y neurons in arcuate nucleus and lateral hypothalamus, and hypothalamic glial cells. In particular, as Fan et al.¹ also specified in their recent study, numerous hypothalamic glial cells express various glucose-sensing molecules. An increasing body of evidence suggests that hypothalamic glial cells might play a relevant role in glucose sensing and fuel homeostasis utilizing a glial metabolic substrate lactate.

To develop applicable therapeutic strategies to prevent hypoglycemia, we must clarify the interaction and integration of inter-/intracellular cross-talk among these glucose-sensing cells mediated by various neurotransmitters and neuroendocrine hormones; for example. γ-aminobutyric acid, glutamate, norepinephrine, serotonin and corticotrophin-releasing hormone. For instance, it was recently shown that serotonin, a monoamine neurotransmitter, has an important role in regulating adrenomedullary responses to glucoprivation at the
perifornical hypothalamus. It has also been reported that the administration of selective serotonin re-uptake inhibitors augments the counter-regulatory responses to hypoglycemia. Hence, as several types of cells throughout the CNS have been proven to be glucose-sensing cells, we must consider the vast heterogeneity among these cells, and carefully investigate this research field with well-designed studies in the future.

In conclusion, Fan et al. proved a novel type of GE neurons, which detect hypoglycemia through decreasing glucose entry through SGLT1. To conquer hypoglycemia unawareness, which limits an appropriate approach to tight control of the blood glucose level, the mechanisms of counter-regulation responses to hypoglycemia must be rigorously investigated and clarified. The work achieved by Fan et al. releases an alternative pathway to approach and resolve the problem.

**DISCLOSURE**

The authors declare no conflict of interest.

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