Review

The role of central nervous system on hypoglycemia and the feasibility of the brain theory in traditional Chinese medicine on treatment of diabetes mellitus

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ABSTRACT: The central nervous system (CNS) plays a key regulatory role in glucose homeostasis. In particular, the brain is important in initiating and coordinating protective counterregulatory responses when blood glucose levels fall. This may due to the metabolic dependency of the CNS on glucose, and protection of food supply to the brain. In healthy subjects, blood glucose is normally maintained within a relatively narrow range. Hypoglycemia in diabetic patients can increase the risk of complications, such as heart disease and diabetic peripheral neuropathy. The clinical research finds that the use of traditional Chinese medicine (TCM) has a positive effect on the treatment of hypoglycemia. Here the authors reviewed the current understanding of sensing and counterregulatory responses to hypoglycemia, and discuss combining traditional Chinese and Western medicine and the theory of iatrogenic hypoglycemia in diabetes treatment. Furthermore, the authors clarify the feasibility of treating hypoglycemia on the basis of TCM theory and CNS and have an insight on its clinical practice.

KEYWORDS: diabetes mellitus; hypoglycemia; counterregulation hormone response; neuroendocrine systems; hypothalamus; brain; review

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1 Introduction

Due to the complicated pathology of diabetes mellitus (DM), especially during episodes of hypoglycemia during treatment, more and more research has been carried out to explore the mechanisms of hypoglycemia. Physiological responses to extremely low blood sugar levels in the central nervous system (CNS), which mainly depends on glucose for energy, can lead to coma, permanent brain injury and death. Thus, during a hypoglycemic episode, the CNS can initiate a series of counterregulatory hormone responses that help to maintain the normal function of the brain. However, in patients with DM, normal protective functions of the CNS against hypoglycemia may be defective[1]. In the theory of the traditional Chinese medicine (TCM), hypoglycemia belongs to “Yunjue”, and “Xufeng” symptom classifications. Over the past thousand years, Chinese physicians have believed that the therapy based on this perspective should guide clinical approaches of treating patients suffering from DM.

2 The response of CNS to hypoglycemia

Counterregulatory hormone responses in the CNS are triggered by falling blood glucose levels. In the normal physiological condition, as blood glucose levels fall, insulin secretion is stopped, and instead, the pancreas releases glucagon. As insulin levels fall, and glucagon levels rise, glycogen is converted to glucose in the liver, raising blood glucose levels. However, currently, the precise mechanism of glucagon release is not clear; it may rely on a combination of several mechanisms, such as local intra-islet response to hypoglycemia[1-3], or stimulation of circulating catecholamines via classic hypothalamus-pituitary-adrenal (HPA) axis[4,5], or a CNS-dependent response of pancreatic tissue[6,7].

Our recent study indicated that the latter pathway can also modulate the hepatic glucose production in addition to intrapancratic hormone responses[8-10] (Figure 1).

The increase in glucagon secretion and complementary reduction in insulin secretion provides a powerful mechanism to correct falling blood glucose, and rapidly restore normal blood glucose levels in healthy subjects. Other counterregulatory neurohumoral changes can also occur. In general, catecholamines can quickly affect the peripheral tissues directly, by reducing glucose uptake, increasing endogenous glucose output (from liver and perhaps kidney), and also indirectly by increasing the supply of gluconeogenic precursors and free fatty acids from muscle and adipose tissue[12-14].

Cortisol levels rise during hypoglycemic events, perhaps as a result of endocrine cells activating neurons in the hypothalamic paraventricular nucleus[15-17]. These neurons in the median eminence subsequently release corticotrophin-releasing factor, which acts on the anterior pituitary, stimulating secretion of adrenocorticotropic hormone (ACTH). The anterior pituitary can also release growth hormone (GH) during hypoglycemia, mainly caused by the changes in releasing factors and inhibitory factors such as somatostatin in hypothalamus[18,19]. Cortisol and GH directly reduce the uptake of glucose by surrounding tissue and promote endogenous glucose production. Hence, they play an important role in mediating persistent hypoglycemia.

Hypoglycemia can also cause many neuroendocrine changes, such as increased release of endorphins and anti-diuretic hormone. The neuroendocrine response to hypoglycemia includes reduced secretion of insulin and increased release of glucagon and epinephrine. Readily observable physiological and behavioral responses associated with shifting hormone balances in response to hypoglycemia (such as palpitations caused by adrenaline activation and sweating caused by the activation of choline), are parts of the metabolic defense system.

A symptom which deserves special mention is hunger, which not only warns of the threat of hypoglycemia, but also increases the appetite to help correct blood glucose levels. The exact mechanism of hunger during hypoglycemia is unclear, but it is worth noting that many brain regions that are thought to be involved in the dynamic balance of glucose, such as the ventromedial hypothalasus (VMH) and lateral hypothalamus, are also thought to play a very important role in controlling appetite and satiety[20-21].

In order to stimulate the above protective response,
the body must first experience hypoglycemia. The exact brain nuclei and the dominant nucleus involved in sensing hypoglycemia remain a controversy. However, the important role that brain nuclei play in response to hypoglycemia is well documented\(^{[8,10,11]}\).

Outside of the brain, the reduction in blood glucose of healthy subjects is very important in suspending the release of insulin, which in turn may lead to glucagon release. It is worth noting that to a great extent the switch between insulin and glucagon secretion may be because, within the islets of Langerhans in the pancreas, blood flows from the rich center of insulin-secreting β cells to the periphery, where glucagon-secreting α cells are located\(^{[12]}\). Although the exact role of these areas in response to counterregulation during hypoglycemia is unclear, a glucose-sensing mechanism is no doubt present in the liver and/or hepatic portal vein. In order to test the role of a blood glucose-sensing apparatus in this region, researchers cut the hepatic nerve in dogs. In these experiments the sensitivity of epinephrine decreases during hypoglycemia\(^{[13]}\). Similarly, through selective glucose infusion, when glucose levels in the portal vein (and liver) maintained at an elevated level, the ability of the adrenal medulla to cope with systemic hypoglycemia was decreased\(^{[14]}\).

However, other studies have shown only a minor role for a liver/hepatic portal vein-based glucose-sensing apparatus during hypoglycemia. Neither blocking the vagus loops of rats to reduce the transmission of the liver afferent nerve\(^{[15]}\), nor transplanting denervated liver in humans disrupt the counterregulatory response to hypoglycemia\(^{[16]}\). In addition, increasing the level of glucose above the systemic glucose level could enhance the counterregulatory hormone response in hypoglycemic subjects. This indicated that the hepatic glucose sensor plays a role on glucose sensing, but not on initiating on counterregulatory hormone response to hypoglycemia\(^{[17]}\).

In conclusion, although the hepatic portal vein is important in sensing blood glucose levels, the function of hepatic sensors in the counterregulatory response to hypoglycemia is unclear. It may be that these sensors initiate a distal counterregulatory response through the coordination of the CNS.

The exact area for detecting hypoglycemia in the CNS also remains controversial. Borg and his colleagues\(^{[18,19]}\) pointed out that the ventromedial hypothalamic nucleus (VMH) is an important area. For example, in rats, damage to the VMH weakens the counterregulatory response to hypoglycemia\(^{[20]}\).

Further studies have shown that a counterregulatory response can be triggered by\(^{[10,30-32]}\), 1) using trace dialysis technology to exchange the substrate and make it enter into the hypothalamus directly; 2) perfusing a non-metabolizable glucose analog (2-deoxy-glucose (2-DG)) into the VMH and 3) transporting glucose through the VMH during systemic hypoglycemia to reduce glucose. Many studies have also demonstrated that blood glucose-sensing neurons can be found in the VMH.

However, a large number of studies have shown that the brain stem is likely to play a major role in sensing blood glucose levels. The non-metabolizable glucose analog 5-thioglucose (5-TG) can trigger appetite and hyperglycemia response more effectively when entering into the fourth ventricle than into the lateral ventricle\(^{[23]}\). Acute closed brain aqueduct blocked 5-TG into the lateral ventricle, but did not prevent them into the fourth ventricle. The direct injection of 5-TG into many areas of brain parenchyma around the fourth ventricle stimulated appetite and/or high blood glucose response. But, other regions of the hypothalamus showed no response to this stimulation. Similar to the hypothalamus, the brain stem areas such as the solitary nucleus and the neurons of the medulla area have been confirmed to respond to changes in peripheral blood sugar concentrations\(^{[14-16]}\).

Evidence for several different pathways for sensing low blood glucose across mammalian models suggests the importance of adequate control over these counterregulatory responses. These different sensing fields, whether in the brain or other possible areas outside the CNS, can detect low glucose and trigger counterregulatory responses. It is likely that counterregulatory responses to systemic hypoglycemia are elicited by coordinated information from many different sensors, rather than one system alone.

### 3 Hypoglycemia detection mechanisms

Although the mechanism for detecting hypoglycemia through the CNS remains to be identified, an acute lowing on brain nutrient can trigger the counterregulatory responses. Infusion of the non-glucose substrate, lactate or β-hydroxybutyric acid, during hypoglycemia, demonstrates that a rise of plasma level of any of these substrates will reduce counterregulatory responses\(^{[24]}\). This suggests that the decline of metabolism in specific areas of the brain is a sign of the initiation of a counterregulatory response, rather than a result of the falling blood glucose levels. Consistent with this view, lactic acid spreading to the VMH area is enough to trigger counterregulatory responses during hypoglycemia.

Some special neurons can change their excitability in response to peripheral blood glucose concentration, allowing indirect measurement of changes in the CNS metabolism. For a long time, however, it was believed that the changes in peripheral blood sugar concentration would more generally affect activity of neurons in specific brain areas. Oomura first described the VMH neuron response to changes in glucose level: rising blood glucose can increase the activity of these neurons, however at the same time, the activity of the hypothalamus lateral neurons is inhibited. Silver and
Erecinska\textsuperscript{[38]} reported that 30\% of the lateral hypothalamic neurons respond to changes in glucose concentration. Similarly, activity of VMH neurons involved in responding to changes in glucose concentration increases with rising blood glucose levels.

In response to fluctuation glucose levels in the blood and brain, the CNS plays an important role in maintaining various of homeostatic functions, such as central control of endogenous glucose production, insulin secretion, and the appetite/feeding pathway. Sensitivity to hypoglycemia may thus represent a functional response that depends on coordination of sensory information from neurons and perhaps also peripheral glucose sensors in order to control the fuel supply to the CNS.

4 Changes in CNS response to hypoglycemia in DM

As mentioned above, the CNS plays an important role in controlling defenses against hypoglycemia, thus stabilizing its fuel supply. In DM, a large number of these defenses, both inside and outside of the CNS, may malfunction, resulting in increasing risk of severe hypoglycemia. Diabetes patients treated with insulin or insulin secretagogues are unable to reduce insulin secretion into the blood as glucose levels decline; this causes an absolute and relative surplus of insulin in the blood.

In addition, most patients with type 1 diabetes produce insufficient glucagon and become seriously depleted during hypoglycemia within the first five years after diagnosis. The deficiency of glucagon secretion results in that the patients mainly depend on catecholamine as the major hormone to preventing hypoglycemia\textsuperscript{[39]}. Unfortunately, many diabetic patients develop additional defects in the catecholamine response to hypoglycemia\textsuperscript{[39]}. In diabetic subjects, the defects in production of glucagon, the adrenomedullary/catecholamine responses and the impaired ability to detect hypoglycemia significantly increase the risk of suffering severe hypoglycemia and its complications\textsuperscript{[4,40]}

The exact cause of counterregulation in diabetes is unclear. Most patients with insulin-deficient DM exhibit an abnormal glucagon response. This is most likely caused by changes in local islets, although CNS adaptation may also play a role\textsuperscript{[41-44]}. Normally, during hypoglycemia caused by insulin release, insulin secretion and production will decline. However, in the insulin-deficient diabetic pancreas, exogenous insulin leads to a rise in islet insulin levels, and inhibits the release of glucagon. Defects in the catecholaminergic secretion during hypoglycemia, are considered to be the result of an adaptation occurring in those areas of the brain that are sensitive to hypoglycemia and launch counterregulatory responses\textsuperscript{[49]}. For the counterregulatory hormone response, the most important factors affecting abnormal counterregulation are intensified glycemic control, long duration of diabetes, and the previous episode of hypoglycemia.

Interestingly, hypoglycemia occurring in diabetic patients may be lead to depression of the counterregulatory responses in subsequent hypoglycemic events occurring over the course of the next few weeks. Healthy subjects that suffer a moderate to severe hypoglycemia episode show a temporary decline in counterregulatory responses to following hypoglycemic events\textsuperscript{[45,46]}. Subsequent studies confirm that both in diabetic patients and healthy subjects, previous low blood glucose events can reduce counterregulatory response to hypoglycemia\textsuperscript{[47,48]}. This can also occur in both type 1 and advanced type 2 diabetes. The phenomenon of insensitivity to hypoglycemia is called hypoglycemia-associated autonomic failure (HAAF)\textsuperscript{[45,46]}.

5 Nourishing qi provides a therapeutic insight on the treatment of HAAF

Ancient Chinese clinicians recognized that “qi” is a key factor for the treatment of HAAF. An ancient Chinese medical textbook called Suwen (Plain Conversation, a fascicle of the Huangdi Neijing (Yellow Emperor’s Canon of Medicine)) mentioned the idea of “nourishing of qi” in the treatment of diabetes. In the clinical practice, we found that Chinese herbs for “nourishing of qi” improved the symptoms and strengthened hormone response in patients suffering their second bout of hypoglycemia. This indicated that the compounds in these herbs could initiate the counterregulatory hormone response to hypoglycemia. Our recent study indicated that Huangqi (Radix Astragali), a Chinese herb, that helped to improve the symptoms in the patient with hypoglycemia, could also initiate glucagon and epinephrine response to hypoglycemia in rats. In this study, the animals were pretreated with Radix Astragali for a few days, followed by exposure to standard hyperinsulinemic-hypoglycemic clamp\textsuperscript{[49]}. Radix Astragali amplified the glucose counterregulatory response to hypoglycemia in both intact and recurrent hypoglycemic rats. Brain-staining studies suggested this might be associated with the neuronal activation in the key central glucose-sensing regions of the hypothalamus\textsuperscript{[49]}.

In conclusion, TCM theory indicates that hypoglycemia belongs to an unbalance of yin-yang. Applying TCM theory to brain-associated hypoglycemia will improve clinical and laboratory treatment of HAAF and provide an alternative therapeutic modality to the treatment of diabetes mellitus.

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7 Conflict of interests

All authors have no actual or potential conflict of interests including any financial, personal or other relationships with other people or organizations.

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