

The role of brain in the regulation of glucose homeostasis

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Abstract

Brain almost solely depends on glucose for its source of energy. Therefore, it is its vested interest to ensure the maintenance of glucose level at a normal physiological range, thereby ensuring the continuous adequate supply of glucose to brain cells. With recent studies, it is reported that glucose homeostasis is not only regulated by the pancreatic islets but also by a brain-centered gluco regulatory system (BCGS). Studies on glucose-sensitive neurons have implicated their role in counterregulation and meal initiation and termination. This review explores the mechanisms by which the hepatic glucose production (HGP) and systemic glucose homeostasis is controlled by insulin-dependent indirect pathway and insulin-independent glucose disposal mechanisms via the BCGS. The review also discusses the impact of a two-system control that includes the pancreatic islet and the BCGS on diabetes mellitus.

KEY WORDS: Brain-centered gluco regulatory system, counterregulation, glucose homeostasis, glucose sensors

Introduction

The regulation of plasma glucose concentration is an important homeostatic function, which is critical for the normal functioning of the brain. As we know, the brain relies on glucose as its primary fuel for its function, other fuels such as fatty acids or ketone bodies play a very minor role.^[1] Storage of glucose in the form of glycogen in the brain is relatively small and is mainly confined to astrocytes.^[2,3] For a continuous and constant supply of glucose to the brain to occur, a coordinated function of several organs such as the liver, white and brown adipose tissues, muscles, and the brain itself is essentially required. Function of all these organs is again regulated by glucose itself, which behaves similar to a regulatory signal that controls endocrine cells secretion and activation of neurons in the peripheral and central nervous systems.^[4,5] Lately, there has been a report of a glucose-sensing system in the central nervous system, which controls not only the feeding

behavior but also glucose and energy homeostasis.^[5] Renowned physiologist, Claude Bernard, was the first to propose a role for the brain in both glucose homeostasis and diabetes pathogenesis. In his famous experiment, "la pigûre-diabétique," he demonstrated the induction of diabetes resulting in glucosuria by puncturing the floor of the fourth ventricle in rabbits.^[6]

The discovery of insulin, in 1921, and the subsequent identification of liver, muscle, and adipose tissue as principal targets of the powerful effects of insulin on glucose metabolism has overshadowed the importance of brain in glucose homeostasis and prevented the complete understanding of the pathophysiology of diabetes mellitus. The current treatment of diabetes is islet centered and revolves around the role of insulin. Treatment includes, principally, recombinant human insulin preparations, insulin secretagogues, and drugs that increase insulin sensitivity. These drugs are effective in controlling hyperglycemia and in addressing the consequences of diabetes, but they fail to address the underlying cause; hence, they control rather than cure the disease.^[7] The role of the brain to control glucose homeostasis was again brought to light, in 1964, when two laboratories reported neurons within the hypothalamus responding to changes in the plasma glucose.^[8,9] Recent studies of glucose-sensitive neurons in the ventromedial hypothalamic nucleus (VMN), the lateral hypothalamus, the arcuate nucleus, and even in the brain stem that possibly initiates counterregulatory response and

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controls meal initiation and termination further reveals the possible existence of a central mechanism that regulates glucose level and metabolism.^[9,10] Furthermore, there are evidences that these glucose-sensing neurons are not only just sensors responding to a change in glucose level but also capable of responding to metabolic signals, such as leptin, which when administered exogenously controls hyperglycemia via a mechanism that is insulin independent.^[11,12]

Brain Glucose Sensors

It has been discovered that glucose-sensitive neurons in the hypothalamus responded to changes in the extracellular glucose *in vitro*. On applying this finding, studies have shown that neurons in the lateral hypothalamus exhibited heterogeneous responses to changes in plasma glucose. Type 1 neurons exhibited maximal activity when exposed to a plasma glucose level of 5.6 mM or a brain glucose level of 2.1 mM and were completely silent when plasma glucose level rose to 10–12 mM or to a brain glucose level of 3.2–3.4 mM. Types 2 and 3 neurons were only inhibited by plasma glucose levels of 17 mM and higher. Type 4 neurons increases firing rate when the level of blood glucose exceeds 7 mM.^[10,13]

According to the studies performed on brain slices using patch clamp recording method, glucose sensory neurons in the VMN are basically of two types, the glucose-excited neurons (GE) and the glucose-inhibited (GI) neurons.^[13,14] GE neurons increase their action potential when extracellular glucose increases from 0.1 to 2.5 mM, and they respond to glucose via ATP-sensitive potassium (K ATP) channel. Their action potential decreases when they are exposed to extracellular glucose below 1 mM for less than 10 min. GI neurons, however, showed decreased action potential, as extracellular glucose level increased from 0.1 to 2.5 mM and respond to glucose level via a chloride channel that is sensitive to intracellular ATP levels or the CTFR channels.^[14,15]

But, glucose sensing in the VMN is not so simple as it seems, because it involves a complex convergence of pre- and postsynaptic mechanisms. There are three subtypes of glucose sensing neurons in VMN that are modulated presynaptically by glucose. The first is the PED neurons or the presynaptically excited by decrease glucose neurons, which are excited when extracellular glucose falls below 2.5 mM. The other two are PER neurons or presynaptically excited by raised glucose neurons and PIR neurons or presynaptically inhibited by raised glucose neurons, both respond to an increase in the extracellular glucose from 2.5 to 5 or 10 mM. VMN neurons receive glucose-controlled presynaptic input in response to decreased glucose, but they also receive glucose-controlled presynaptic input in response to increased glucose.^[14,16,17]

The function of the glucose-sensing neurons in the brain is basically to regulate and maintain glucose homeostasis. Studies have reported that all neurons are silent when they are exposed to extremely low glucose level below 1 mM for more than 12–15 min.^[18] Routh (2002)^[19] reported that exposure to

0.1 mM glucose for over 15 min leads to irreversible damage for most neurons. Therefore, brain has a vested interest to ensure the regulation of glucose levels within normal physiological range.

The glucose-sensing neurons fulfill this need to ensure a constant supply of the primary fuel glucose to the brain by the initiation of a counterregulatory response, regulation of meal initiation and termination.

Counterregulatory Response

When plasma glucose level falls below 5 mM, a counterregulatory response is initiated, which consists of activation of a cell of the pancreas to secrete glucagon and activation of the sympathoadrenal system. The activation of the sympathoadrenal system increases plasma epinephrine, norepinephrine, and glucagon, which then stimulate hepatic glycogenolysis and inhibit insulin secretion by the pancreas.^[20]

Sherwin and coworkers^[21,22] showed that the secretion of counterregulatory hormones, epinephrine and glucagon, is influenced by neurons in the VMN. Routh^[19] pointed out that the neurons influencing counterregulation are the GE neurons in the VMN.^[19] The same is also indicated in the study done by Miki *et al.*^[23] who used Kir 6.2 knockout mice that lacks functional KATP channels showing attenuated counterregulation in response to hypoglycemia.^[23]

However, we cannot ignore the peripheral glucose sensors and their critical role in counterregulation. Hevener *et al.*^[24] demonstrated their importance when they showed a severe attenuation in the secretion of epinephrine and norepinephrine during hypoglycemia after the vagal afferents from the portal veins were destroyed.^[24]

Meal Initiation and Termination

Louis-Sylvestre and Le Magnen^[25] indicated in their study that meal initiation was preceded by a drop in the plasma glucose by as little as 6% to 8%.^[25] Another study conducted few years after this, used on-line glucose monitoring and demonstrated that initiation of meal occurred during a rise in plasma glucose, which was preceded by a drop of the plasma glucose by about 10%.^[26]

If, under euglycemic condition, the brain extracellular glucose is about 1–2 mM, a 10% drop would correspond to about 100–200 μ M. According to Routh,^[19] the GE neurons were shown to be sensitive to 100 μ M increments in extracellular glucose level. Moreover, a number of investigators have indicated the presence of these neurons in areas of the brain, which are associated with food intake and energy balance. Taking the findings of all these studies into account, a derivation can, thus, be made, which points to glucose-sensing neurons or the GE neurons as possible players in meal initiation and termination.^[19]

GI neurons decrease their action potential frequency when glucose levels increase from 0.1 to 2.5 mM. However,

GI and PED neurons also respond to a decrease in the extracellular glucose from 2.5 to 1 mM, which places the glucose sensitivity of these neurons in the low range of brain glucose levels. Therefore, these neurons may be involved in initiation of the meal. PER and PIR neurons are sensitive to glucose changes between 2.5 and 5 mM, which is in the range that the brain perceived as a plasma glucose level transition from euglycemia to hyperglycemia. This can be a signal that triggers these neurons to modulate meal termination or increase sympathetic activation. It must be noted that the responses of the GE and GI neurons can be biphasic, because of the existence of presynaptic inputs and postsynaptic conditions.^[14,17,23]

The Brain-Centered Glucoregulatory System (BCGS)

In recent days, there is a growing evidence of the existence of a BCGS that is capable of lowering blood glucose levels via insulin-dependent and insulin-independent mechanisms. Much have been documented on the glucoregulatory effects of pharmacological or genetic intervention, targeting neurons in the hypothalamus and brainstem.^[7]

The insulin-dependent mechanism control glucose homeostasis by regulating HGP through direct action on hepatocytes and via another proposed indirect mechanism that regulate HGP through insulin action at a remote site.^[27,28] Direct action of insulin on hepatocytes activates insulin receptor substrate phosphatidylinositol 3-OH [IRS-PI (3)K], which in turn activates Akt that inhibits Forkhead box protein 01 (Fox01), a transcription factor that stimulates gluconeogenesis and glycogenolysis, the two determinants of HGP.^[28]

Evidence of an indirect pathway for insulin control of HGP comes from a recent study of TLKO mice with liver-specific deletion of Fox01 and the two Akt isoforms. In these mice, insulin cannot directly regulate HGP through the Akt–Fox01 pathway. In spite of the absence of this pathway, what is revealing is that there is no loss of regulation in response to even exogenous insulin, as both HGP and systemic glucose homeostasis are found to be normally controlled in TLKO mice.^[29]

Therefore, a speculated mechanism that possibly mediates the indirect control of HGP by insulin as in the TLKO mice is the BCGS, which is found to be both activated by insulin and capable of controlling HGP in humans and in mice.

Another mechanism controlling glucose homeostasis is the insulin-independent glucose disposal by the BCGS. Studies have demonstrated the effect of direct infusion of leptin into the brain ventricles of rats and mice with insulin-deficient diabetes at doses too low to have any effect outside the brain, which normalizes the markedly increased blood glucose level.^[11,12] The implication of this study is that, even in the absence of insulin, the brain has the mechanism to normalize HGP and restore euglycemia in diabetic animal. There has been suggestions that this is mediated by leptin and that the mode of action of leptin in the brain involves the inhibition of the hypothalamic–pituitary–adrenal axis and the

associated lowering of elevated circulating glucocorticoid levels.^[30]

Many other agents have also been implicated to be involved in improving glucose tolerance, but one such agent that possibly involves the brain is the gastrointestinal hormone, fibroblast growth factor (FGF) 19, which is a regulator of hepatic bile acid homeostasis and is normally secreted after a meal. When intracerebroventricular ICV injection of FGF19 is given (at a dose when administered peripherally causes no lowering of glucose) to genetically obese and leptin-deficient *ob/ob* mice, the mice displayed markedly improved glucose tolerance despite no change in insulin secretion or sensitivity.^[31,32]

Conclusion

We can, therefore, summarize that factors such as rising glucose levels, increased plasma concentrations of insulin, FGF19, leptin, and others such as meal consumption generate diverse signals that activate the BCGS, which then take part in the glucose disposal via insulin-dependent or insulin-independent mechanisms in concert with the pancreatic islet responses.

These new revelations lead to a proposal of a two-system control of glucose homeostasis, which consists of the pancreatic islet responses and the BCGS responses. If this is to be accepted, then the question that will arise is, is diabetes a failure of the two systems? The failure of the pancreatic islet responses in diabetes today is a well-documented fact. So, where is the evidence that defects in the BCGS function leads to diabetes? Some recent studies have shown the association of rodent models of obesity and type 2 diabetes (T2D) with hypothalamic injury and gliosis, which we can say is a potential cause of BCGS dysfunction. There is also evidence that BCGS function depends on the normal function of the islet. BCGS is shown to be relying on inputs from insulin and other hormones whose secretion depends on normal islet function.^[33,34]

The two-system control is a plausible mechanism; however, the bridge linking the two is still a haze in the maze that calls for a more in-depth study to shed more light into the complete and integrated understanding of the complex control of glucose homeostasis. With a rising T2D population of 347 million currently, which is projected to increase to 552 million by 2030,^[35] it is imperative to urgently evolve a complete understanding of glucose homeostasis, which will help usher a treatment for diabetes that will possibly cure the disease and not just control it.

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