

BRAIN REGULATION OF BLOOD GLUCOSE LEVELS: ITS SIGNIFICANCE IN THE PATHOGENESIS OF TYPE 2 DIABETES

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Abstract: Although the number of studies is rapidly increasing, the role of the brain in regulating normal glucose homeostasis and the pathogenesis of type 2 diabetes remains incompletely understood. In this review, we propose a conceptual framework to better understand the brain's critical role in these processes. This framework is based on evidence showing that the brain, like the pancreas, is capable of sensing changes in circulating glucose levels and responding accordingly. We also examine data suggesting that neuronal glucose sensing plays a fundamental role in determining the defended (physiologically maintained) level of blood glucose and that defects in this regulatory system contribute to the pathogenesis of type 2 diabetes. Furthermore, we discuss the close link between obesity and type 2 diabetes, which may arise from shared dysfunction in highly integrated neurocircuits that regulate both energy and glucose homeostasis. Thus, while obesity is characterized by an elevated defended level of the body's fuel stores (e.g., adipose tissue mass), type 2 diabetes is characterized by an elevated defended level of circulating fuel (e.g., glucose). In both conditions, the underlying pathogenesis is associated with impaired sensing of, or response to, relevant humoral negative feedback signals. This perspective is increasingly supported by preclinical evidence: in type 2 diabetes, restoration of the defended blood glucose level to normal can be achieved through interventions that restore the brain's ability to accurately sense circulating glucose.

Keywords: brain, diabetes, glucose, hypothalamus, obesity, review.

РЕГУЛЯЦИЯ УРОВНЯ ГЛЮКОЗЫ В КРОВИ МОЗГОМ: ЗНАЧЕНИЕ В ПАТОГЕНЕЗЕ САХАРНОГО ДИАБЕТА 2-ГО ТИПА.

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Аннотация: Хотя количество исследований быстро растет, роль мозга в регуляции нормального гомеостаза глюкозы и патогенезе сахарного диабета 2-го типа остается недостаточно изученной. В этом обзоре мы предлагаем концептуальную основу для лучшего понимания критической роли мозга в этих процессах. Эта основа опирается на данные, показывающие, что мозг, как и поджелудочная железа, способен обнаруживать изменения уровня циркулирующей глюкозы и соответствующим образом реагировать. Мы также рассматриваем данные, свидетельствующие о том, что сенсорики глюкозы в нейронах играют фундаментальную роль в определении защищенного (физиологически поддерживаемого) уровня глюкозы в крови, и что нарушения этой регуляторной системы способствуют патогенезу сахарного диабета 2-го типа.

Кроме того, мы обсуждаем тесную связь между ожирением и диабетом 2-го типа, которая может возникать из-за общей дисфункции высоко интегрированных нейросетей, регулирующих как энергетический, так и глюкозный гомеостаз. Таким образом, в то время как ожирение характеризуется повышением защищенного уровня запасов энергии организма (например, массы жировой ткани), диабет 2-го типа характеризуется повышением защищенного уровня циркулирующего топлива (например, глюкозы). В обоих случаях основная патогенез связана с нарушением восприятия или реакции на соответствующие гуморальные сигналы отрицательной обратной связи.

Эта концепция всё больше подтверждается доклиническими данными: при диабете 2-го типа восстановление защищенного уровня глюкозы в крови до нормы может быть достигнуто с помощью вмешательств, которые восстанавливают способность мозга точно ощущать циркулирующую глюкозу.

Ключевые слова: мозг, диабет, глюкоза, гипоталамус, ожирение, обзор.

Introduction

As with other variables regulated in a homeostatic manner, circulating glucose levels in healthy individuals are maintained within a narrow physiological range. The stability of this glucose “set point” is ensured by a complex and highly integrated multi-organ regulatory system that dynamically coordinates the entry of glucose into the circulation with its removal.

Although many tissues are involved, the pancreas and the brain play the predominant roles in regulating this process. Following nutrient absorption after a meal, increased insulin secretion enhances glucose uptake in muscle and adipose tissue, while suppressing hepatic endogenous glucose production, thereby minimizing fluctuations in blood glucose concentrations. The brain coordinates not only the magnitude and timing of the insulin response [1] but also insulin-independent mechanisms that suppress glucose production and enhance glucose utilization [2].

In this review, we examine evidence from human and animal studies showing how the brain and the pancreas interact to establish a defended level of blood glucose, and that normal function of this system requires both organs to sense circulating glucose. We further emphasize that impairment of this central regulatory network is a key contributor to the pathogenesis of type 2 diabetes mellitus.

Evidence Linking Brain Glucose Sensing to the Glycemic Set Point. Evolution of Glucose Sensing in the Brain.

Approximately seventy years before the discovery of insulin in 1921, Claude Bernard had already emphasized the central role of the brain in maintaining glucose homeostasis [3]. This view aligned with the understanding that the brain is responsible for homeostatic regulation of many physiological variables essential for life. Given that the brain relies almost exclusively on glucose as its primary fuel source, its involvement in ensuring adequate glucose availability is fully consistent with fundamental physiological principles. Although this concept was overshadowed following the discovery of insulin, recent evidence necessitates a re-evaluation.

Studies in “*Drosophila melanogaster*” [4] demonstrate that systemic glucose levels (in the hemolymph) and the secretion of insulin-like peptides in response to glucose are controlled by a single pair of glucose-sensing neurons. These neurons sense glucose using a cellular mechanism analogous to that of mammalian β -cells. Silencing these neurons leads to increased systemic glucose levels, indicating that they are essential for maintaining normal glucose homeostasis in fruit flies. Surprisingly, this occurs in association with reduced insulin secretion, even though the insulin-producing cells themselves remain intact [4].

These findings suggest that early in evolution, glucose homeostasis may have been regulated primarily by the brain, as initially proposed by Claude Bernard, with insulin secretion functioning as a downstream response to brain glucose sensing. Another important implication is that the cellular mechanisms necessary for glucose detection likely originated in neurons and were later adapted for use in mammalian β -cells.

Although glucose homeostasis in mammals is more complex, evidence suggests that a version of this regulatory architecture has been conserved throughout evolution.

In this review, we propose a model in which normal glucose homeostasis depends on afferent signals to the brain derived from both peripheral and central glucose-sensing mechanisms. These signals regulate glucose-stimulated insulin secretion (GSIS) and other mechanisms governing glucose balance by coordinating the rate of glucose entry into and removal from the bloodstream. Under ordinary physiological conditions, pancreatic islets function with a high degree of autonomy, and minimal central regulation is required as long as glucose levels remain within the defended physiological range [5]. However, once glucose levels deviate from this range, the regulatory influence of the brain becomes increasingly important.

Impairment of Brain Glucose Sensing.

If the brain’s ability to sense circulating glucose becomes impaired—whether due to acquired or genetic factors—the brain may interpret normal glucose levels as abnormally low. Although the precise nature of this defect is not fully understood, several mechanisms have been proposed:

First, increases in circulating glucose are normally paralleled by increased glucose concentration and glucose uptake in the brain; however, this response is blunted in diabetic rodents [6, 7] and humans [8–11].

Second, the neuronal machinery responsible for glucose detection may be dysfunctional [5]. In mice, deletion of brain-specific GLUT2 [12] or glucokinase [13] disrupts glucose homeostasis. In rats, diabetes is associated with reduced hypothalamic glucokinase activity, and restoring this activity improves glucose regulation [14, 15].

Collectively, these findings indicate that in type 2 diabetes, the brain's ability to sense circulating glucose is diminished, leading the brain to raise the "defended" glucose set point. A reduction in GSIS represents a major component of this compensatory response. Further evidence supporting the involvement of such a central (brain-level) defect in the pathogenesis of type 2 diabetes will be discussed in subsequent sections.

Brain Regulation of Glucose Homeostasis During Hypoglycemia.

Glucose-sensing neurons are concentrated within brain regions involved in glucose homeostasis [16], and in mammals the brain determines the lower limit of circulating glucose levels. When glucose levels fall below this limit, the brain initiates counterregulatory responses (CRR) that restore blood glucose to normal [17]. In healthy humans, this lower limit is rarely reached, therefore glucose counterregulation is usually viewed as a response to pathological conditions rather than a component of routine glycemic control.

Nevertheless, specific components of this brain-driven CRR—such as epinephrine secretion—serve as reliable biomarkers of how the brain perceives the defended lower boundary of blood glucose. The stability of this boundary implies the presence of persistent homeostatic signals under neuronal control. This raises the question of whether the brain is capable of elevating the defended glycemic set point, particularly when it senses an internal deficit of fuel.

This capability can be demonstrated experimentally by inducing "neuroglycopenia." Such experiments have been conducted in several mammals, including non-human primates [18]. Neuroglycopenia is induced by administration of 2-deoxyglucose or other non-metabolizable glucose analogs that impair neuronal glucose utilization. The brain's response closely mimics that observed during hypoglycemia: glucose production increases while peripheral glucose utilization decreases, resulting in a stable hyperglycemic plateau that compensates for impaired neuronal glucose sensing.

This hyperglycemia can be fully reproduced in rodents by optogenetic or chemogenetic activation of hypoglycemia-responsive CRR neurons located in the ventromedial nucleus (VMN) of the hypothalamus [19–21]. Although increased insulin secretion would normally be expected in response to hyperglycemia, this response is suppressed because the brain prioritizes the correction of perceived glucose deficiency. Thus, when the brain experimentally senses glucose deprivation, it raises the defended blood glucose level—partly by inhibiting insulin secretion.

Brain Control of Glucose Homeostasis in Diabetic Hyperglycemia.

Importantly, the threshold for the defended lower boundary of glucose rises progressively as glucose metabolism becomes impaired and as individuals transition toward early type 2 diabetes [22]. In other words, the glycemic threshold that activates central counterregulatory responses (CRR) shifts upward, so that CRR becomes engaged at glucose levels higher than normal [22, 23]. This means that in type 2 diabetes, the brain continues to defend an abnormally elevated glycemic set point.

The contribution of the brain to diabetic hyperglycemia has also been demonstrated in mouse studies in which specific subsets of VMN CRR-related gluco-regulatory neurons were selectively inactivated to determine their actual physiological role. In a recent study by Flak and colleagues [21], suppression of a subset of glutamatergic CRR neurons in the VMN expressing the CCK-B receptor reduced blood glucose levels by approximately 25% in healthy mice.

This finding indicates that this particular population of VMN CRR neurons constitutes a physiological determinant of the defended glycemic level. Even more importantly, inactivation of these neurons not only disrupts CRR activation in response to neuroglycopenia [24, 25] but also lowers hyperglycemia in diabetic mice [21]. Thus, the same neurons that mediate brain responses to falling glucose levels also contribute significantly to maintaining hyperglycemia in diabetic animals.

These observations suggest that diabetes involves impaired brain glucose sensing, such that glucose-raising neurocircuits are activated due to a persistent perception of glucose insufficiency. Clinical evidence from individuals with MODY 2 further supports this hypothesis. MODY 2 results from mutations in the glucokinase (GCK) gene [22]. Glucokinase plays a key role in glucose sensing in hypothalamic neurons and in β -cells in both humans and animals [26]. Although individuals with MODY 2 generally maintain relatively stable glucose homeostasis, their glycemic range is slightly elevated compared with healthy individuals.

Moreover, the threshold for CNS-dependent CRR activation during hypoglycemia—such as epinephrine secretion—is increased in MODY 2 patients, closely resembling the pattern observed in type 2 diabetes [22, 23]. While MODY 2 mutations impair glucose sensing in both β -cells and neurons, the upward shift in the defended lower glycemic boundary is mediated solely by the brain, not by β -cells. Thus, the elevated threshold for epinephrine secretion in MODY 2 provides direct evidence that defects in neuronal glucose sensing alone are sufficient to raise the defended glycemic lower limit, just as occurs in type 2 diabetes. Fully mapping and characterizing the neurocircuits involved in this response remains a key research priority.

Central Nervous System Regulation of Islet Function.

One of the most direct mechanisms by which the brain maintains glucose homeostasis is through its control of pancreatic islet function. Over the past 50 years, studies in humans and animals have consistently shown that insulin and glucagon secretion are regulated by the nervous system in response to circulating and sensory signals [27, 28].

Neurons connecting the brain to the islets are located in the hypothalamus and brainstem nuclei. Many of these neurons are glucose-sensing, and some partially overlap with neurocircuits governing feeding behavior and adiposity. These neurons relay signals to the islets through multiple synapses in the autonomic nervous system. When various internal or external stimuli disrupt the normal activity of these neurocircuits, plasma insulin levels can change rapidly.

Thus, a precise and well-established central mechanism exists for controlling islet hormone secretion, and although these neurocircuits are not yet fully characterized, they overlap with pathways involved in energy homeostasis.

Autonomic Regulation via the Sympathetic and Parasympathetic Nervous Systems.

The islets receive innervation from both sympathetic (SNS) and parasympathetic (PNS) nerve fibers. Recent three-dimensional imaging of human pancreatic tissue has demonstrated dense innervation comparable to that seen in rodents [29]. SNS and PNS activity modulates insulin and glucagon secretion, exerting powerful effects on circulating glucose levels.

During feeding, PNS activation enhances insulin secretion. During hypoglycemia, SNS activation increases glucagon secretion and suppresses glucose-stimulated insulin secretion (GSIS). Sympathetic fibers projecting to the liver are also activated as part of the CRR (central

counterregulatory response). In parallel, epinephrine released from the adrenal medulla, together with glucagon, enhances hepatic glucose production, thereby helping to restore normoglycemia [32]. The suppression of insulin secretion occurs via SNS activation or elevated circulating epinephrine acting on β -adrenergic receptors on β -cells [33, 34].

Regulation of Glucagon Secretion.

Central regulation of glucagon secretion is even more firmly established [28]. During hypoglycemia, SNS activation triggers glucagon release from α -cells, promoting hepatic glucose production [37]. If the islets are denervated—for example, following transplantation or due to diabetic neuropathy—this response is diminished [38]. The CNS also participates in postprandial glucagon regulation [39], which in turn plays an important role in meal-induced insulin secretion [40]. Thus, PNS-derived signals to the islets during feeding coordinate the integrated endocrine response.

Role of the Brain in Hepatic Glucose Control.

The brain also plays a key role in regulating hepatic glucose metabolism. In both humans and animals, normal K_{ATP} channel activity is required to suppress endogenous glucose production during hyperglycemia (a major component of glucose effectiveness, i.e., glucose's ability to dispose of itself) [2]. Thus, the brain supports glucose homeostasis not only through the regulation of islet function but also by modulating glucose effectiveness.

Restoring Normoglycemia in Rodents Through Brain-Targeted Interventions. Transient Glucose Lowering in Diabetes.

Some of the clearest evidence for the brain's ability to regulate blood glucose comes from rodent models of type 1 and type 2 diabetes, in which centrally targeted interventions reduce hyperglycemia. These studies repeatedly demonstrate that glucose lowering in diabetic animals often occurs via insulin-independent mechanisms.

One of the earliest studies involved intracerebroventricular (i.c.v.) administration of leptin to mice or rats with uncontrolled diabetes resulting from severe insulin deficiency [45]. Surprisingly, continuous central leptin infusion fully normalized hyperglycemia, and the dose required to produce this effect was far lower than that needed when leptin was administered peripherally. Another unexpected finding was that although central leptin exerted rapid biological effects within minutes to hours, full correction of hyperglycemia required 4–5 days of sustained infusion. I.c.v. leptin normalized both the excessive hepatic glucose production and the reduced peripheral glucose utilization characteristic of diabetic hyperglycemia, even when profound insulin deficiency persisted. This demonstrates the brain's ability to activate insulin-independent glucose-lowering mechanisms [46].

Hypothalamic regions such as the VMN are critical for normal glucose homeostasis and also participate in leptin-induced glucose lowering [47], indicating overlap between neurocircuits controlling energy balance and those regulating glucose metabolism.

Additional evidence arises from the glucose-lowering effects of members of the fibroblast growth factor (FGF) family. Two FGF hormones—FGF21 and FGF19, secreted primarily by the liver and gastrointestinal tract, respectively—have been extensively studied. When administered peripherally at pharmacological doses, these peptides transiently normalize blood glucose in rodent models of type 2 diabetes [48]. Although initial studies proposed a peripheral mechanism,

subsequent work revealed that pharmacological FGF21 and FGF19 act predominantly, if not entirely, through the brain to lower glucose, again via insulin-independent pathways [49, 50].

Sustained Glucose Lowering.

These studies were extended by investigating the glucose-lowering effects of central administration of another member of the FGF family—FGF1. Intracerebroventricular (i.c.v.) injection of FGF1 in rodent models of type 2 diabetes normalizes hyperglycemia; however, unlike FGF19 or FGF21, a single injection of FGF1 produces effects that last for weeks or even months [51]. This action is mediated through the mediobasal hypothalamus (MBH) [52], predominantly via insulin-independent mechanisms, although protective effects on basal insulin secretion and beta-cell mass have also been reported [53, 54].

The mechanisms underlying the sustained glucose-lowering action of FGF1 in the MBH are not yet fully elucidated, but recent studies indicate a role for glia–neuron interactions and FGF1-induced alterations in the extracellular matrix [55, 56]. Regardless of the precise mechanism, evidence suggests that hyperglycemia in type 2 diabetic rodents arises from pathological processes that can be corrected or suppressed through the hypothalamic action of FGF1.

Revisiting the Relationship Between Obesity and Type 2 Diabetes. Progression from Obesity to Type 2 Diabetes.

The theoretical basis for this model stems from our understanding of obesity, as obesity is closely associated with metabolic dysfunction. Although multiple factors can contribute to excessive weight gain, the body's fat mass is biologically defended, even when it exceeds the normal range in individuals with obesity (Fig. 2). In other words, obesity represents a condition in which the defended level of the body's primary stored energy source (triacylglycerol) gradually increases. Consequently, weight lost through caloric restriction is often regained, regardless of an individual's initial body size [62].

The increase in adiposity observed in obesity can be explained by reduced central sensitivity to negative feedback signals such as leptin—i.e., the development of central resistance to these signals [62, 63]. This resistance causes the brain to perceive the actual fat mass as lower than it truly is, thereby activating responses aimed at increasing fat stores. Ultimately, a new steady state is achieved in which fat mass and circulating negative feedback signals rise to levels sufficient to overcome this central resistance. Although this mechanism does not fully explain all aspects of obesity, it likely plays a major role in the defended elevation of fat mass in many individuals with obesity [62].

We propose a similar model for type 2 diabetes: the defended level of the body's primary circulating energy source (glucose) also gradually increases. This can explain why insulin and other glucose-lowering therapies often exhibit only temporary effects—once the treatment effect dissipates, blood glucose returns to its defended level, regardless of the presence or absence of type 2 diabetes.

Furthermore, we hypothesize that this pathological sequence is initiated or exacerbated by impaired central sensing of blood glucose levels—a form of “brain glucose resistance” [64] (Fig. 1). Although direct evidence is currently lacking that misperception of circulating glucose by the brain is a primary cause of type 2 diabetes, impaired central responses to glucose in humans with type 2 diabetes are well documented [8–10]. Further exploration of this hypothesis represents an important research priority.

Based on this model, we propose that, just as the defended elevation in fat mass in obesity may represent a compensatory physiological response [62], defended hyperglycemia in type 2 diabetes may likewise result from brain glucose resistance (Fig. 2). Specifically, in type 2 diabetes, disrupted central glucose sensing activates MBH glucoregulatory neurons, thereby raising the blood glucose “set point” as a compensatory mechanism. Suppression of glucose-stimulated insulin secretion (GSIS) is also a key component of this adaptive response.

Additional support for the conceptual overlap between obesity and type 2 diabetes comes from their strong epidemiological association and from the substantial anatomical and functional overlap between brain regions governing energy and glucose homeostasis (including the VMN and adjacent hypothalamic nuclei) [16, 61]. Therefore, we propose that the pathogenesis of both disorders involves dysfunction within two closely interconnected brain regulatory systems—those responsible for energy homeostasis and glucose homeostasis.

Just as the defended level of stored energy (triacylglycerol) can be viewed as a consequence of reduced sensitivity to adipocyte-derived negative feedback signals, we also suggest that, in individuals with obesity who progress to type 2 diabetes, the primary defect additionally involves impaired central sensing of the circulating energy substrate (glucose). This leads to the defended elevation in blood glucose levels.

Accordingly, beta-cell dysfunction leading to type 2 diabetes may arise, at least in part, as a secondary consequence of this central defect. Under conditions of reduced central glucose sensing, suppression of GSIS via central pathways becomes necessary to raise blood glucose levels sufficiently to compensate for impaired sensing.

In genetically predisposed individuals, a vicious cycle may arise: hyperglycemia and associated metabolic decompensation further worsen beta-cell dysfunction. Testing this hypothesis represents a critical area for future research.

A particularly intriguing and initially paradoxical finding is that hyperinsulinemia is a predictor of future type 2 diabetes risk [57, 65, 66]. The mechanisms underlying this excessive insulin secretion and its relationship to type 2 diabetes pathogenesis remain unclear. Nevertheless, hyperinsulinemia also occurs in normoglycemic individuals, and because it is not associated with insulin resistance [65], affected individuals may have impaired glucose effectiveness (otherwise, one would expect lower blood glucose). Indeed, reduced glucose effectiveness is a known predictor of future type 2 diabetes in humans [67].

These findings raise two important questions for future investigation:

1. Could hyperinsulinemia serve as a biomarker of reduced glucose effectiveness in individuals at risk for type 2 diabetes?
2. Does the brain—which has the capacity to regulate glucose effectiveness—play a role in the mechanisms underlying reduced glucose effectiveness?

Conclusion.

Here, we propose a model in which normal glucose homeostasis depends on the brain’s accurate sensing of circulating glucose levels, and in which impairment of this sensing—potentially arising in association with obesity—plays a central role in the pathogenesis of type 2 diabetes. Partial support for this model comes from evidence that the brain can normalize defended blood

glucose levels in rodent models of type 2 diabetes [51, 52]. This suggests that the primary defect underlying hyperglycemia resides in the brain and can be targeted therapeutically using peptides such as FGF1.

Despite significant progress, the mechanistic role of the brain in glucose homeostasis and the pathogenesis of type 2 diabetes remains in its early stages, with substantial opportunities for conceptual advancement. Key outstanding questions include:

How does the brain sense circulating glucose?

To what extent does this process involve neuronal versus non-neuronal cell types (e.g., astrocytes, oligodendrocytes, tanycytes)?

Which mechanisms underlie “brain glucose resistance” in type 2 diabetes?

Is this defect related to mechanisms governing the defended elevation in fat mass in obesity?

How does the brain regulate glucose effectiveness?

Addressing these questions may ultimately enable therapeutic strategies that not only transiently lower blood glucose levels but reset them to a truly normalized defended level. Otherwise, the effectiveness of most existing therapies will remain limited, and beta cells—poorly equipped to withstand sustained metabolic stress—will continue to deteriorate.

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