



How Should We Think About the Role of the Brain in Glucose Homeostasis and Diabetes?

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Although the brain is clearly capable of affecting blood glucose levels, whether such effects are important in day-to-day blood glucose control remains a matter of controversy. In this Perspective, we update and expand on a previously described brain-centric model of glucose homeostasis (1), highlighting recent evidence of the brain's capacity to influence the biologically defended level of circulating glucose in part through rapid and highly coordinated adjustments of both insulin sensitivity and insulin secretion. We also discuss the possibility that dysfunction of this brain-centric system contributes to the pathogenesis of type 2 diabetes by raising the defended level of glycemia. Finally, we discuss the implications of these concepts for the future of diabetes treatment.

Traditionally, the interaction between pancreatic islets and insulin-sensitive tissues has been deemed sufficient to explain most aspects of glucose homeostasis. Whether the brain participates in the physiological control of circulating glucose levels therefore remains a matter of controversy, and the possibility that a dysfunctional central control system contributes to the pathogenesis of diabetes is only beginning to be explored. The overarching goal of this Perspective is to synthesize work from our laboratory and elsewhere that highlights recent progress and identifies emerging research and therapeutic opportunities in these areas.

EVIDENCE OF A ROLE FOR THE BRAIN IN NORMAL GLUCOSE HOMEOSTASIS

There is little question about the brain's ability to influence key determinants of glucose homeostasis (e.g., rates of glucose production or utilization) in response to input from humoral signals, including glucose (2–4) and other nutrients (e.g., amino acids [5] or free fatty acids [6,7]), and nutritionally relevant hormones (e.g., insulin, leptin, ghrelin, and GLP-1 [8–10]). What remains uncertain is the extent to which such effects participate in day-to-day glucoregulation. Studies that use loss-of-function

strategies (e.g., targeted gene deletion, receptor blockade, enzyme inhibitors, etc.) are perhaps most useful in this regard, but the interpretation of such data is often confounded by associated changes of food intake and body weight, by off-target effects (11), or by compensatory adaptations triggered by the experimental intervention. Beyond these concerns, the impact of brain-directed interventions on circulating glucose levels is often seemingly negated by adjustments of islet function. Together, these observations raise the possibility that although the brain can affect glucose homeostasis, day-to-day control of blood glucose levels does not require its active participation. Clearly, new approaches that can tease apart the contributions of brain and islet (and interactions between them) to overall control of glucose homeostasis are needed.

One promising strategy is to start by identifying discrete glucoregulatory neurocircuits and subsequently investigate their physiological role. Recent methodological advances in neuroscience, such as optogenetics and pharmacogenetics, offer unparalleled opportunities in this area, as evidenced by recent work delineating the neurocircuitry involved in the response to hypoglycemia (12–14), food intake control (15,16), and social behaviors (17). A relevant example is the recent identification of a subset of neurons located in the lateral parabrachial nucleus (IPBN) involved in glucose counterregulation that expresses both leptin receptors and the peptide cholecystokinin. Pharmacogenetic activation of these neurons raises blood glucose levels by activating the canonical counterregulatory response to hypoglycemia, including increased secretion of glucagon and corticosterone, and by inhibiting glucose-induced insulin secretion (12). These effects appear to involve ascending projections from the IPBN to the ventromedial nucleus of the hypothalamus (VMN), as optogenetic activation of VMN neurons situated downstream of the IPBN elicits similar, if more potent, effects (14). The next step in this circuit appears to involve projections from VMN to the anterior bed nucleus of the stria

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terminalis (aBNST) (14), a brain area known to integrate and respond to stressful stimuli. As inhibiting these VMM neurons suppresses the counterregulatory response and blocks recovery from insulin-induced hypoglycemia (14), a physiological role for this LPBN→VMN→aBNST circuit in glucose counterregulation is implied.

Far less is known about neurocircuits involved in glucose homeostasis in the absence of hypoglycemia (18); indeed, whether they even exist remains uncertain, although several observations suggest that they must. For example, the early finding that intracerebroventricular administration of a low dose of leptin ameliorates hyperglycemia and hyperinsulinemia in leptin-deficient *ob/ob* mice well before substantial weight loss is achieved (19) suggests that deficient leptin signaling in the brain contributes to their diabetic phenotype. Subsequent work extended this finding in unexpected ways. We, and others, reported that in rodents with severe, uncontrolled insulin-deficient diabetes induced by the β -cell toxin streptozotocin—animals that are also severely leptin deficient—intracerebroventricular administration of a low dose of leptin completely normalizes hyperglycemia over the course of a few days (20–23). The fact that this effect occurs without causing hypoglycemia suggests that leptin action in the brain of these animals does not simply lower blood glucose levels. Instead, it would appear that under the influence of leptin, the brain somehow “resets” the defended level of glycemia in the normal range via a mechanism that does not require functional pancreatic β -cells.

This evidence of the brain’s inherent capacity to normalize diabetic hyperglycemia (as opposed to simply lowering blood glucose levels) was extended by work investigating the antidiabetes action of members of the fibroblast growth factor (FGF) family of peptides. Initial reports focused on the potent glucose-lowering effects induced by systemic administration of either of two hormonal members of the FGF family—FGF19 and FGF21—in rodent models of type 2 diabetes (T2D) (24). That the brain is implicated in these effects emerged from subsequent studies showing that intracerebroventricular injection of much lower doses of these peptides can elicit similar effects (25,26), particularly in the case of FGF19, which induces glucose lowering in *ob/ob* mice via mechanisms that, once again, are at least partly insulin independent (25).

Systemic administration of the canonical FGF, FGF1, exerts glucose lowering in mouse models of T2D that is distinguished by a longer duration of action, with a single dose lasting for up to 48 h (27). We reasoned that if this effect, similar to that of FGF19, involves a central site of action, a single intracerebroventricular injection of FGF1 at a dose that is ineffective when administered peripherally should induce potent and long-lived glucose lowering. Yet even with this prediction in mind, we were unprepared for what was observed. Namely, we found that a single intracerebroventricular injection of FGF1 induces diabetes remission across a variety of rodent models of

T2D that can last weeks or even months (28). This extraordinary effect occurs at doses of FGF1 that have no effect when given peripherally and is not secondary to changes in body weight or fat mass. Furthermore, because intracerebroventricular FGF1 does not elicit hypoglycemia even in normal, nondiabetic animals (28), it does not merely lower blood glucose. Rather, it appears to reset the defended level of glycemia at a lower, more normal level.

How might such an effect occur? Although the underlying mechanisms remain uncertain, increased glucose uptake in the basal state (predominantly in skeletal muscle) clearly plays a role, and functional islets may also be required for this effect (unlike what is observed with intracerebroventricular leptin) (28). Whatever the mechanism, these data are consistent with a model in which the brain, similar to pancreatic β -cells, actively senses and integrates information relevant to the prevailing glucose level and, working in cooperation with both islets and peripheral tissues, plays an active role to maintain glycemia within a narrow range (1).

How might the brain sense and respond to changes of ambient glucose levels? One approach to this question focuses on glucose-responsive neurons, which are widely distributed in the brain and especially concentrated in the VMN and other hypothalamic areas involved in metabolic control (29). Two types of glucose-responsive neurons exist: those that are depolarized by glucose (glucose excited) and those that are hyperpolarized (glucose inhibited) (29–31). Recent work suggests that glucose-excited neurons in the VMN respond to a glucose load with mitochondrial responses that activate a signal transduction cascade involving UCP2 and that this effect ultimately promotes systemic glucose lowering via an as-yet-unidentified neurocircuit (32). Future studies using optogenetic or related methods may therefore offer a useful strategy with which to interrogate the role played by VMN UCP2⁺ neurons in day-to-day control of glycemia. If such a role is identified, related tools can then be deployed to identify the circuit of which they are a part and ultimately ascertain the role of this circuit not only in glucose homeostasis but also in glucose lowering induced by intracerebroventricular administration of FGF1, leptin, or other molecules.

A ROLE FOR THE BRAIN IN THE RESPONSE TO CONDITIONS THAT CHALLENGE GLUCOSE HOMEOSTASIS

To cope with the innumerable metabolic challenges to which they are exposed, free-living mammals are frequently called upon to adjust rates of glucose utilization and glucose production and to do so in a way that minimizes any impact on glucose homeostasis. Such responses typically involve adaptive changes of tissue insulin sensitivity, and they can be modest and evolve slowly or they can be dramatic and develop quickly. In either case, a compensatory adjustment of insulin secretion

must occur if glucose homeostasis is to be preserved. How this occurs is an important unanswered question.

Cross-sectional studies in humans dating back to the 1990s established that in normal individuals, insulin secretion and insulin sensitivity are coupled to one another such that the product of the two (referred to as the “disposition index,” a major determinant of glucose tolerance) remains constant irrespective of their prevailing level of insulin sensitivity (33–35). Although little is known regarding mechanisms governing this coupling process, there can be no question that it is indispensable for normal glucose homeostasis, as the failure to increase insulin secretion in response to worsening insulin resistance is a cardinal feature of T2D. Here, we consider recent evidence that the brain helps to coordinate the coupling of insulin secretion to adaptive changes of insulin sensitivity that occur in response to the specific environmental challenge posed by cold exposure.

In free-living animals, a considerable fraction of daily energy expenditure is dedicated to maintenance of core body temperature (36). To meet this need, glucose uptake into thermogenic tissues (primarily heart, skeletal muscle, and brown and white adipose tissue) must increase as ambient temperature drops (37). Consequently, moving an animal housed at room temperature into a cold environment markedly increases whole-body glucose utilization via a mechanism involving increased insulin sensitivity of thermogenic tissues (38,39). If hypoglycemia is to be averted, it therefore follows that this sequence of events must be offset by a proportionate decrease of insulin secretion. Moreover, should the external temperature change rapidly, this entire process must unfold in a matter of minutes to hours. Given that pronounced diurnal temperature swings are common throughout much of the world, these dramatic metabolic adaptations are part of daily life for many homeothermic species.

To better understand how these complex responses are orchestrated, we recently performed a detailed metabolic analysis of rats moved from room temperature (22°C) to a cool environment (5°C). Consistent with previous work (40), we found that whole-body insulin sensitivity increased twofold within 24 h of cold exposure. Yet glucose tolerance remained virtually unchanged, owing to a 50% decrease of glucose-induced insulin secretion (41). A key point is that this adaptive reduction of insulin secretion cannot be explained by reduced glucose stimulation of the islet, as blood glucose levels during the glucose tolerance test (which provided the proximal stimulus to insulin secretion) did not differ between cold and warm conditions (41). The fact that each of these responses to cold exposure reverted to normal within 4 h of the return to room temperature attests to the rapidity with which these metabolic adaptations unfold (41).

What is the evidence that the brain might contribute to these rapid and highly coordinated responses? Our finding that each was fully reversed within 30 min by systemic α -adrenergic blockade (41) implies that the

effect of cold to couple reduced insulin secretion to increased insulin sensitivity is coordinated by the sympathetic nervous system (SNS). This conclusion is consistent with evidence that 1) the SNS plays an essential role in the thermogenic response to cold, 2) the brain (hypothalamus, in particular) can increase peripheral tissue insulin sensitivity in response to various hormonal and nutrient-related stimuli via changes in autonomic outflow (42–46), 3) cold exposure increases sympathetic tone to the pancreas (47), and 4) sympathetic stimulation of the islet inhibits insulin secretion (48–50) by activating α_2 -adrenergic receptors on β -cells (51,52). What is remarkable about this conclusion is not that insulin secretion is inhibited by cold-induced SNS activation but that the degree of inhibition appears to be calibrated so as to precisely offset the associated increase of insulin sensitivity and thereby preserve glucose homeostasis (41).

As is true of systems governing both energy homeostasis and glucose homeostasis, thermoregulation depends on circuits situated in the hypothalamus (36,53); by comparison, the neurocircuitry underlying thermoregulation is comparatively well mapped and understood. Temperature changes detected by cutaneous thermosensory neurons are relayed through the dorsal horn of the spinal cord to the LPBN, and from there on to the hypothalamic preoptic area. Within the preoptic area are both cold- and warm-responsive neurons capable of increasing or decreasing SNS outflow to thermogenic tissues, respectively. During cold exposure, cold-responsive neurons both inhibit neighboring warm-responsive neurons and, via projections to the dorsomedial hypothalamic nucleus, activate a descending circuit that ultimately increases SNS outflow to brown adipose tissue (to induce nonshivering thermogenesis), skeletal muscle (to induce shivering), and vasculature (to conserve heat through vasoconstriction) (36,53,54). The overall result is that the sensory experience of cold elicits an adaptive thermogenic response that maintains core body temperature within a narrow physiological range. The possibility that this thermoregulatory circuit also links cold exposure to adaptive adjustments of insulin sensitivity and insulin secretion represents an important opportunity to better understand the brain's role in this aspect of glucose homeostasis.

COMPARING BRAIN-CENTRIC AND ISLET-CENTRIC MODELS OF GLUCOSE HOMEOSTASIS

We submit that many of the foregoing observations are not only consistent with but are best explained by a brain-centric model of glucose homeostasis (1). The core premise of this model is that when the blood glucose level deviates from its defended value, the brain mounts homeostatic responses that return it to the defended range. Similarly, should an intercurrent illness, stress, or other homeostatic challenge necessitate a change in the defended glucose level, the brain ensures that this outcome is achieved, working in partnership with both islets and peripheral tissues (55).

As noted earlier, skeptics of this brain-centric perspective are justified in asking why such a role for the brain is necessary, given that normally functioning islets can by themselves explain most of what is observed on a day-to-day basis. Where this islet-centric model begins to break down, however, is when animals are confronted with a homeostatic challenge (such as cold exposure). As noted earlier, the islet response to adaptive changes of insulin sensitivity can occur in the absence of any detectable change of glycemia and, at least in cold-exposed rats, the central nervous system (CNS) appears to play a key role to mediate this effect (41). A brain-centric model, therefore, appears to account for adaptive coupling of insulin secretion to insulin sensitivity in ways that an islet-centric model cannot, at least in the setting of cold exposure.

If the brain does indeed play this type of role in glucose homeostasis, why has this not been appreciated before now? One possibility is that in a stable, nonthreatening environment, the impact of the brain on the relationship between insulin secretion and insulin sensitivity is already set and consequently its influence is obscured unless steps are taken to disrupt it. Because metabolic research is routinely performed under conditions in which environmental variables are carefully eliminated, it follows that if the brain has already “set the tone” for how islets and peripheral tissues interact, β -cells will respond in what might appear to be an autonomous manner, leading one to conclude incorrectly that the brain played no role.

Another consideration relevant to the brain-centric model proposed here pertains to previously discussed pharmacological evidence that the brain in diabetic animals can reset the biologically defended level of glycemia at a lower value. Most compelling in this regard is the aforementioned finding that a single intracerebroventricular dose of FGF1 can normalize glycemia in rodent models of T2D in a manner that is 1) highly reproducible, 2) sustained for weeks or months, and 3) does not drop blood glucose levels below normal, even in normal, nondiabetic animals (28). We have been hard-pressed to find any explanation for this outcome other than that under the influence of FGF1, the diabetic brain resets the defended level of glycemia at a lower, more normal value. Although this effect may well involve changes of islet function, it is not readily explained by islet-centric models that discount a key role for the brain in glucose homeostasis.

IMPLICATIONS FOR THE PATHOGENESIS OF T2D

Lessons Learned From the Energy Homeostasis System

The natural history of T2D is characterized by a gradual rise in the defended level of glycemia owing to a progressive failure of β -cells to mount the increase of insulin secretion necessary to compensate for insulin resistance (35,56). For decades, it has been assumed that this uncoupling of insulin secretion from insulin sensitivity is the consequence of a defect in the β -cell. Although the search for such a defect remains a major focus of T2D

research, alternative possibilities can and should be considered until definitive answers are obtained. Here, we consider the possibility that a defect in the brain-centric glucoregulatory control system plays a causal role and that β -cell dysfunction in T2D is at least in part secondary to this defect. The type of defect envisioned here is one that is characterized by a gradual but progressive failure of the brain to sense and/or respond to information relevant to the defended level of glycemia. The logical way to compensate for such a glucose-sensing defect is by increasing glucose delivery to the brain and, consequently, the biologically defended blood glucose level gradually increases over time.

This type of regulatory dysfunction resembles that implicated in the pathogenesis of obesity. By matching energy intake to energy expenditure over time, the energy homeostasis system serves to maintain body fat stores within a narrow physiological range, and the neurobiological underpinnings of this system (situated in the hypothalamus and elsewhere) are increasingly well understood (57–60). As total fat mass represents the body's supply of stored fuel and the circulating glucose level represents fuel that is available for immediate use, it makes teleological sense to invoke a role for the brain in the control of each.

How is this information relevant to obesity pathogenesis? Although many factors can predispose to excess weight gain, obese individuals appear to defend their elevated body weight in a manner indistinguishable from lean individuals (61,62). Thus, obesity can be described as a disorder in which the biologically defended level of body fat mass is increased outside of the normal range, akin to the defense of elevated blood pressure in patients with hypertension. To explain this phenomenon, we and others hypothesize that obesity pathogenesis involves a defect in the ability of key energy homeostasis neurocircuits to sense and/or respond to afferent input used by the brain to establish the defended level of fat stores (e.g., circulating leptin levels), and available data support this possibility (61–64).

Could a similar defect give rise to the progressive increase in the biologically defended level of blood glucose characteristic of T2D? Certainly, the fact that obesity and T2D are tightly linked metabolic disorders (65) is consistent with this possibility. Beyond this link, the aforementioned concept that the brain participates in the coupling of insulin secretion to insulin sensitivity predicts that a progressive disorder of glucose-sensing within the brain-centric glucoregulatory system would result in the secretion of insulin in amounts that maintain circulating glucose levels at a level sufficiently elevated to compensate for the underlying central defect. In addition to impaired neuronal glucose sensing, the underlying defect could potentially involve defective integration of relevant sensory input, an impaired capacity to mount an appropriate efferent response to this input, or any combination thereof. The higher the defended level of glycemia, the

more abnormal the insulin secretion is predicted to be—despite the fact that the defect resides outside of the β -cell. As more is learned about the underlying neurocircuitry, new opportunities to test this hypothesis will likely present themselves.

A Role for the Brain in the Pathogenesis of β -Cell Dysfunction in T2D?

The notion that β -cell dysfunction in T2D involves regulatory defects residing outside of the β -cell might seem heretical to some. Certainly, this possibility seems at odds with known structural defects that accompany β -cell dysfunction in this setting, the presence of which can be taken as evidence of an intrinsic β -cell lesion. Yet there is ample precedent for severe structural as well as functional deterioration of otherwise healthy endocrine cells resulting from a change of regulatory input. Consider, for example, the profound atrophy and hypofunction of the adrenal cortex induced by prolonged pharmacological glucocorticoid administration. In this example, the effect arises from removal of the trophic effect of ACTH (secretion of which is suppressed by glucocorticoid excess), and the resulting adrenal atrophy and hypofunction can be associated with pathological features that persist months after the underlying problem is corrected. A similar phenomenon is observed in virtually any endocrine tissue deprived of its trophic support.

Of course, pancreatic islets differ from most other endocrine tissues in that a β -cell trophic factor has yet to be identified and that, unlike most other endocrine cell types, β -cells are highly responsive to nutrient stimulation in a manner that is regulated by both hormonal and neural input. Pancreatic islets are richly innervated by parasympathetic, sympathetic, and sensory nerves (66,67), and whereas basal and glucose-stimulated insulin secretion are inhibited by increased sympathetic tone (as noted earlier), parasympathetic activation stimulates insulin secretion via activation of muscarinic receptors (68). In addition to effects on islet function, sympathetic innervation plays a key role in both structural and functional aspects of islet development, with defects in this input during development having lasting effects that predispose to metabolic impairment (69). By comparison, autonomic regulation of α -cell function differs in that glucagon secretion is increased with both parasympathetic and sympathetic stimulation (70).

Beyond their well-documented involvement in the response to hypoglycemia (71,72), islet nerves are increasingly implicated in the link between brain glucose sensing and day-to-day function of pancreatic islets. Support for this hypothesis stems in part from work focused on the glucose transporter *Glut2*, a key mediator of cellular glucose sensing. In addition to β -cells and hepatocytes, *Glut2* is expressed in hypothalamic areas implicated in glucose homeostasis, and brain-specific *Glut2* deletion impairs neuronal glucose sensing in mice (73). How are β -cells affected when the brain cannot sense glucose properly?

On the basis of the brain-specific *Glut2* deletion mouse model, the consequences include not only impaired cephalic and first-phase insulin secretion and glucose intolerance but also reduced β -cell mass and altered responsiveness to hypoglycemia (73,74). A direct link can therefore be drawn between defective brain glucose sensing and impairments of both islet structure and function reminiscent of those seen in human T2D. Although the relevance of this work to humans awaits further study, a link between T2D risk and variants of the gene encoding *Glut2* (*SLCA2A*) has been established by genome-wide association studies (75).

In considering this evidence of a role for the brain in the pathogenesis of β -cell dysfunction in T2D, we note that neither islet structure nor function is substantially altered by denervation of the pancreas in mature animals (69). Thus, loss of SNS input cannot explain the deterioration of β -cells characteristic of T2D, which in turn implies that islet innervation does not provide trophic support to pancreatic β -cells in adults. This conclusion, however, does not preclude the possibility that aberrant signals originating in the brain have deleterious effects on β -cells; indeed, data from mice with neuron-specific *Glut2* deletion noted above (74) offer direct support for this possibility. Reduced islet innervation is also associated with glucose intolerance and islet dysfunction in diabetic Chinese hamsters (76), whereas cholinergic stimulation improves insulin secretion and glucose tolerance in insulin-resistant, high-fat diet-fed mice (77).

In summary, while acknowledging that a key role for the brain in the pathogenesis of β -cell dysfunction in T2D constitutes a clear departure from mainstream thought, evidence presented here suggests that this possibility should be taken seriously. This is especially true given that a primary, β -cell-autonomous cause has eluded detection despite decades of intensive research. Until this situation changes, investigation into alternative possibilities, including a role for the brain, is warranted.

Role of Glucagon

In addition to β -cell dysfunction, T2D is also characterized by both elevated plasma glucagon levels and aberrant control of glucagon secretion from islet α -cells (78). As glucagon's effects on glycemia—mediated primarily by stimulation of hepatic glucose production—oppose those of insulin, a role for excess glucagon in the pathogenesis of T2D has been proposed (78,79). Indeed, a considerable investment has been made by the pharmaceutical industry to develop glucagon receptor antagonists for the treatment of this disease (80).

One potential mechanism to explain elevated glucagon levels in T2D is based on evidence that insulin has a direct inhibitory effect on α -cells. As β -cells fail, therefore, the secretion of glucagon increases (81). Because glucagon secretion is also regulated by islet nerves, however, a neural mechanism can be considered, and several observations support this possibility. First, either electrical

stimulation (82) or optogenetic activation of VMN neurons (14) stimulates glucagon secretion (and raises blood glucose levels), whereas the glucagon response to hypoglycemia is blunted by either silencing VMN neurons (14) or by intra-VMN administration of glucose (83). Second, the effect of severe insulin-deficient diabetes to increase plasma glucagon levels in rats results from leptin deficiency, as physiological leptin replacement reverses this effect (84,85). This leptin effect appears to be mediated centrally because it is replicated by administration of leptin directly into the brain at a dose below that needed to affect glucose homeostasis when given systemically (21,22).

A third key observation is that plasma glucagon levels are elevated in mice with impaired CNS glucose sensing induced by brain-specific Glut2 deletion (73,74). As noted above, these mice are also characterized by reduced β -cell mass, loss of first-phase insulin secretion, and glucose intolerance. Each of these effects is consistent with what might be predicted to result when the brain is unable to properly sense ambient glucose levels. To compensate for this defect, the brain engages responses that raise blood glucose levels, including changes of neural input to the islet that reduce insulin while enhancing glucagon secretion. These observations collectively support a model in which the brain, acting via islet nerves, participates in the increase of circulating glucagon levels observed in T2D.

The Brain and Reduced Insulin-Independent Glucose Disposal in T2D

Impairment of insulin-independent glucose disposal is yet another aspect of T2D that fits with the central regulatory defect explored here. That T2D is associated with a major defect in this component of glucose disposal is well established (86,87). Indeed, reduced insulin-independent glucose disposal was found to be predictive of the future development of T2D in an at-risk human population (87). As glucose utilization in the basal state is predominated by insulin-independent mechanisms (86), this defect likely contributes to fasting hyperglycemia in patients with T2D. How might this observation fit with a role for the brain in T2D pathogenesis?

In leptin-deficient *ob/ob* mice, hyperglycemia is associated not only with severe insulin resistance but also with a marked reduction of insulin-independent glucose disposal (86,88), and the latter is selectively ameliorated by central administration of FGF19 (25). Combined with evidence that intracerebroventricular leptin normalizes glycemia in rodents with severe, insulin-deficient diabetes (20–23), the brain is clearly capable of promoting glucose lowering via this mechanism. It therefore follows that the link between impaired brain glucose sensing and the defense of elevated blood glucose levels can potentially involve reduced insulin-independent glucose disposal in addition to the uncoupling of insulin secretion from insulin sensitivity, impairment of β -cell structure and function, and elevation of plasma glucagon levels. As each of these abnormalities is also observed in T2D, additional work is

warranted to investigate the extent to which they originate within the brain.

THE BRAIN AS A TARGET FOR T2D TREATMENT

Standard medical therapy for patients with T2D revolves around daily administration of drugs that transiently lower blood glucose levels combined with frequent glucose monitoring. Although some individuals can achieve adequate glycemic control with this approach, a large percentage does not (89,90). Moreover, the risk of hypoglycemia increases with efforts to achieve tight control, and an increase in hypoglycemic events is associated with health risks that offset the benefits of tight glucose control (91,92). Plainly, there is room for improvement.

An ideal diabetes treatment is one that is easy to administer, serves to normalize rather than simply lower blood glucose levels (and does so in a manner that is sustained rather than transient), and does not increase the risk of hypoglycemia or have other untoward effects. That diabetes remission can be safely achieved with certain bariatric surgical procedures (93–96) raises the possibility that medical approaches might one day achieve this goal (97–99). Until the mechanism underlying surgically induced diabetes remission is better understood, however, progress in this area will continue to be limited.

In a previous review (1), we reasoned that if the brain plays a key role to establish the biologically defended level of glycemia, therapies targeting the brain might one day be identified with the potential to safely induce sustained diabetes remission. Our recent finding in rodent models of T2D that sustained diabetes remission can be induced by a single intracerebroventricular injection of FGF1 lends credence to this possibility (28). Although the mechanisms underlying this effect remain to be elucidated, our emerging understanding of the brain's role in glucose homeostasis points to the untapped potential of interventions targeting the CNS to improve treatment outcomes for patients with T2D.

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