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Central Nervous System Control of Glucose Homeostasis: A Therapeutic Target for Type 2 Diabetes?

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Abstract

Historically, pancreatic islet beta cells have been viewed as principal regulators of glycemia, with type 2 diabetes (T2D) resulting when insulin secretion fails to compensate for peripheral tissue insulin resistance. However, glycemia is also regulated by insulin-independent mechanisms that are dysregulated in T2D. Based on evidence supporting its role both in adaptive coupling of insulin secretion to changes in insulin sensitivity and in the regulation of insulin-independent glucose disposal, the central nervous system (CNS) has emerged as a fundamental player in glucose homeostasis. Here, we review and expand upon an integrative model wherein the CNS, together with the islet, establishes and maintains the defended level of glycemia. We discuss the implications of this model for understanding both normal glucose homeostasis and T2D pathogenesis and highlight centrally targeted therapeutic approaches with the potential to restore normoglycemia to patients with T2D.

1. INTRODUCTION

CNS: central nervous system

BDL_G: biologically defended level of glycemia

T2D: type 2 diabetes

T1D: type 1 diabetes

The circulating level of glucose is determined by the balance between rates of appearance (via synthesis, release from storage, or ingestion) and disappearance (via utilization, uptake, or excretion). This balance is influenced by the ongoing energetic demand of every organ that requires adequate glucose provision to ensure reproductive fitness and survival across ever-changing environmental conditions. While many regulatory checkpoints have evolved to safeguard glucose storage and allocation, the central nervous system (CNS) has the unique capacity to compare the energetic needs of the body with the predicted effects of possible behaviors. By integrating environmental cues of food availability with interoceptive signals of stored and circulating fuel, the CNS works cooperatively with pancreatic islets to adjust glucose production, storage, and utilization to establish the biologically defended level of glycemia (BDL_G) (1) (**Figure 1**). In type 2 diabetes (T2D), the BDL_G is pathologically elevated such that plasma glucose is maintained at a higher level (2, 3), and accumulating evidence implicates both brain and islet dysfunction in this process. Failure to address these pathological processes increasing the BDL_G is a fundamental shortcoming of current antidiabetic medications premised on augmenting insulin action—plasma glucose lowering will be short-lived if competing homeostatic mechanisms that increase glycemia in T2D are not also targeted. This shortcoming is borne out in the disappointing results of current T2D pharmacotherapy: Despite the introduction of more than 40 new US Food and Drug Administration (FDA)-approved drugs over the past decade, the fraction of T2D patients falling short of glycemic targets remains at approximately 50% (4).

Current approaches to T2D treatment are based on an islet-centered view of glucose homeostasis that has dominated the field since insulin was discovered over 100 years ago. According to this view, T2D results when pancreatic beta cells fail to compensate for progressive insulin resistance (5), usually associated with obesity (6). While we agree with this model of T2D pathogenesis, we note that it is incomplete without considering the role of insulin-independent mechanisms of glucose disposal that are also impaired in T2D (see Section 3) (7, 8). Insulin-independent glucose disposal contributes roughly 50% to intravenous glucose tolerance (9), accounts for up to 80% of glucose disposal in the basal state (i.e., in the absence of exogenous nutrients) (9, 10), and is among the first deficits detected in individuals who develop T2D (11, 12). The CNS can potently modulate insulin-independent glucose disposal (13) and synchronously adjust insulin secretion and sensitivity during physiological challenges to glucose homeostasis (14). As T2D is associated with anomalies affecting brain areas and neurocircuits that regulate these processes, a role for the CNS in T2D pathogenesis warrants careful scrutiny.

In this review, we summarize contributions made by both pancreatic islets and insulin-independent mechanisms to overall glucose disposal and T2D pathogenesis, discuss the role of the CNS in these processes, and evaluate the potential of CNS-targeted strategies for future treatment of this common disease.

2. THE ISLET-CENTERED MODEL OF GLUCOSE HOMEOSTASIS

January 12, 2022, commemorates the centennial anniversary of the first administration of insulin to a human (15). The discovery that a crude pancreatic extract could resolve hyperglycemia in type 1 diabetes (T1D), a previously fatal condition, constitutes a landmark achievement in medicine. Insulin's discovery triggered a paradigm shift in the field of diabetes research: It sparked the field of islet biology, led to the identification of insulin-producing beta cells, and heralded a new islet-centered model of glucose homeostasis. Though headlines at the time of insulin's discovery proclaimed the cure to diabetes was imminent, 100 years later, this prediction remains to be fully realized. In this section, we review this islet-centered model of glucose homeostasis and

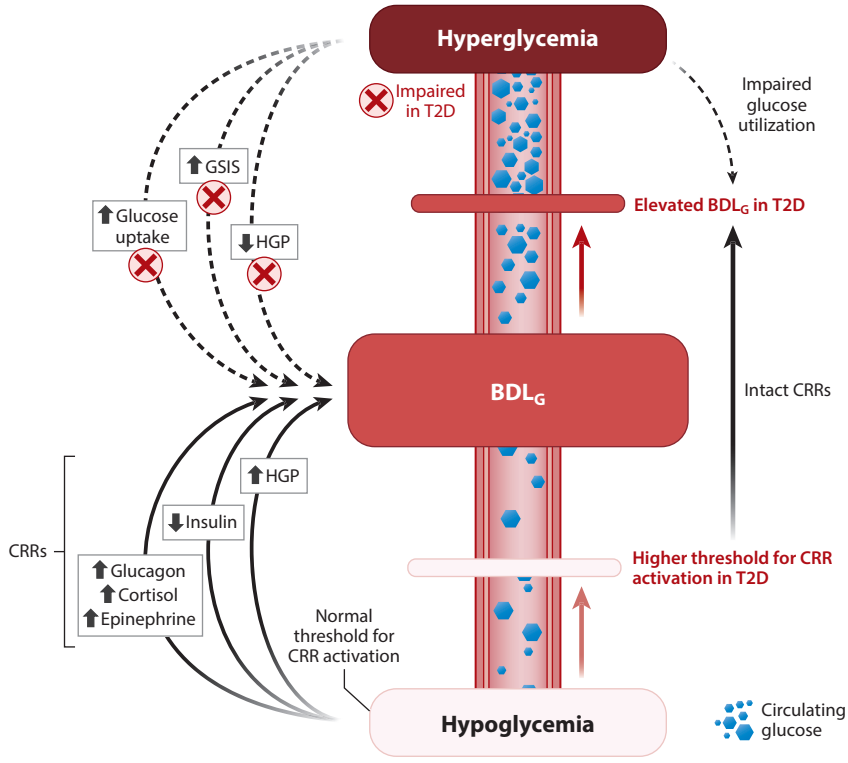


Figure 1

Mechanisms governing the biologically defended level of glycemia (BDL$_G$). The BDL$_G$ is determined by the balance between rates of glucose appearance into and disappearance from the circulation, and imbalance in these rates contributes to the elevated BDL$_G$ in type 2 diabetes (T2D). In health, acute deviations from the BDL$_G$ are counteracted by both insulin-dependent and insulin-independent mechanisms that restore blood glucose levels into the normal range. Responses to rising blood glucose levels (*dashed arrows*) include increased glucose-stimulated insulin secretion (GSIS) by the pancreatic beta cell, which, together with the ability of glucose to independently facilitate its own disposal [termed glucose effectiveness (GE)], increases glucose uptake by peripheral tissues and inhibits hepatic glucose production (HGP). Conversely, a fall in blood glucose levels triggers adaptive neuroendocrine and autonomic counterregulatory responses (CRRs, *solid arrows*) that collectively increase glucose appearance into the circulation and decrease its removal. These responses include increased secretion of glucagon, cortisol, and epinephrine (which stimulate HGP), while insulin secretion is inhibited to prevent a further fall in blood glucose. In T2D, the lower boundary of the BDL$_G$ is increased (as reflected by a higher glycemic threshold for inducing CRRs), and the same is true of the upper boundary of the BDL$_G$, as evidenced by diminished rates of glucose disappearance (owing to reduced GSIS, insulin resistance, and reduced GE) and failure to suppress HGP. The net outcome is a persistently elevated BDL$_G$ in T2D. Figure adapted from images created with BioRender.com.

present evidence that invokes a prominent, collaborative role for CNS mechanisms in both normal and abnormal glucose homeostasis.

The islet-centered model suggests that stability of the BDL$_G$ depends largely upon the beta cell's capacity to adjust insulin secretion to changes in circulating glucose levels. When blood glucose levels rise after a meal, for instance, glucose-stimulated insulin secretion (GSIS) returns blood glucose to its preprandial level by both suppressing further glucose production by the liver and facilitating glucose uptake into peripheral tissues. Impairment of either GSIS or insulin action reduces glucose disposal and incompletely suppresses hepatic glucose production (HGP),

GSIS: glucose-stimulated insulin secretion

HGP: hepatic glucose production

yielding hyperglycemia. In health, normal fluctuations in insulin sensitivity occurring daily (e.g., sleep or exercise) and seasonally (e.g., puberty, pregnancy, or aging) are counteracted by adaptive changes in insulin secretion (6). In obesity, associated with persistently reduced insulin sensitivity, a compensatory increase of beta cell function can still preserve glucose homeostasis. In genetically susceptible individuals, failure of beta cells to meet this heightened demand for insulin secretion is proposed to drive the BDL_G out of the normal range, producing T2D (6) (**Figure 1**).

ANS: autonomic nervous system

SNS: sympathetic nervous system

PNS: parasympathetic nervous system

GLP1: glucagon-like peptide 1

Most therapies consequently aim to support or supplant beta cell function by augmenting insulin secretion or sensitivity or by supplementing exogenous insulin itself. Designed to transiently lower blood glucose levels, these approaches can prevent or delay T2D complications, but with the accompanying risk of hypoglycemia and side effect of weight gain. More importantly, strategies designed to simply lower the blood glucose level do not address the underlying pathological processes that elevate the BDL_G and therefore fail to induce sustained diabetes remission.

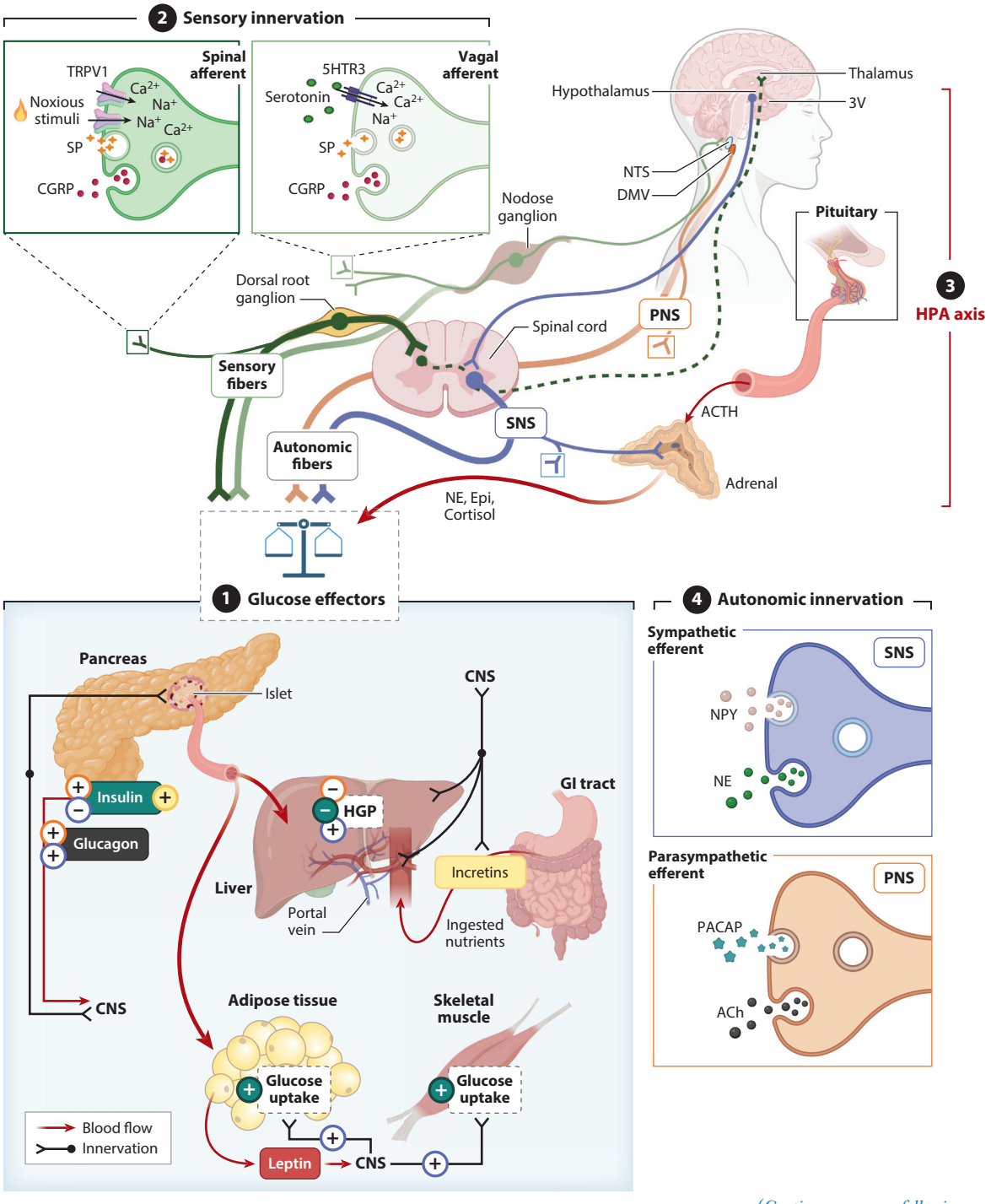
A core issue not addressed by current therapeutic modalities is whether beta cell dysfunction in T2D is a primary disorder or a secondary consequence of severe metabolic derangements that accompany the disease. Indeed, it is possible that both are true. The following discussion addresses this fundamental question.

2.1. Cell-Autonomous and Non-Cell-Autonomous Mechanisms Governing Insulin Secretion

The pancreatic beta cell is a highly specialized cell type that senses and responds to glucose in a cell-autonomous manner, and impaired GSIS is a cardinal feature of T2D (16). Beta cell function is also strongly influenced by factors external to the islet, including input from the CNS. Beta cell regulation by the brain involves both indirect (e.g., via neuroendocrine hormone secretion) and direct [via the autonomic nervous system (ANS) and spinal sensory innervation (**Figure 2**)] mechanisms (for reviews, see 17–19). Despite slight differences between humans and rodents in the anatomy of islet innervation (20, 21), autonomic stimulation affects islet secretion similarly across species. Sympathetic nervous system (SNS) outflow to the beta cell suppresses both glucose-stimulated and basal insulin secretion, while parasympathetic nervous system (PNS) outflow enhances GSIS (17, 22). By contrast, both SNS and PNS outflow to the islet increase glucagon secretion (17). Evidence from multiple species (23, 24) indicates that the PNS is critical for meal-associated GSIS, as muscarinic cholinergic receptor blockade with atropine suppresses postprandial insulin secretion. Interestingly, in humans, atropine suppresses GSIS following an oral, but not intravenous, glucose challenge, suggesting an interaction between the PNS and gut-derived incretin peptides that augment insulin secretion, such as glucagon-like peptide 1 (GLP1) (**Supplemental Appendix 1**) (24). Because vagal (PNS) fibers extensively innervate the gastrointestinal tract and other organs in addition to the pancreas (for detailed reviews, see 25, 26), atropine's effects on islet function may involve gut-vagal-brain hormone sensing (27, 28) or gastric motility, in addition to direct effects on beta cells.

Supplemental Material >

Islets are also innervated by spinal (dorsal root ganglion) sensory neurons. Deletion of TRPV1-expressing spinal afferents (**Figure 2**) suppresses islet inflammation and preserves GSIS and beta cell mass in several diabetic models (29–31). Like vagal afferents, however, spinal afferents innervate multiple tissues, so indirect effects of TRPV1-mediated ablation on GSIS are possible. Target-specific approaches (e.g., via retrograde viral tagging, as in References 32 and 33) are needed to clarify whether sensory neurons directly modulate islet activity and/or sense the islet secretory state. These studies will also help interpret recent work showing increases in nerve density per islet, number of innervated islets, and size of intrapancreatic ganglia in humans with obesity and T2D (21, 34).



(Caption appears on following page)

Figure 2 (*Figure appears on preceding page*)

Anatomy of glycemic control: central and peripheral mechanisms. (①) After a meal, nutrients digested by the GI tract are delivered into the blood via the hepatic portal vein and circulated throughout the body. Postprandial elevations in blood glucose activate GSIS. Effects of postprandial GSIS (*purple circles*) include suppression of HGP (directly via activation of hepatic insulin receptors and indirectly via inhibition of glucagon release from pancreatic alpha cells) and stimulation of glucose uptake by insulin-sensitive tissues, including skeletal muscle and adipose tissue. Nutrient ingestion also stimulates endocrine cells lining the GI tract to release the incretin hormones, GLP1 and GIP. Incretins augment insulin secretion (*yellow circle*) and, via binding their cognate receptors expressed by sensory afferents innervating the GI tract, convey information to the brain about the size and composition of ingested nutrients (for reviews, see 26, 47, 48). (②) Spinal afferents (*dark green*) have their cell bodies within the dorsal root ganglia, which express molecules such as the ion channel TRPV1 (activated by noxious heat) that processes nociceptive signals conveyed to the brain via the spinothalamic tract. Spinal afferents also can exert effects by releasing inflammatory peptides such as SP and CGRP. Vagal afferents (*light green*) also express SP/CGRP and can sense the local microenvironment through receptors that include the serotonin receptor (5HTR3) in the pancreas and incretin receptors in the GI tract. Cell bodies of vagal sensory neurons are contained within the nodose ganglion and convey sensory information to the CNS via projections to the NTS. In addition to surveilling peripheral tissue function, the CNS can influence peripheral glucose effector function via neuroendocrine systems, including the HPA axis (③) and the ANS. In response to stressful stimuli, activation of the hypothalamic-pituitary-adrenal axis causes the adrenal cortex to secrete cortisol, which stimulates glucose production by the liver. (④) The SNS and PNS branches of the ANS innervate tissues throughout the body to influence glycemia. Stimulation of the SNS (*blue circles* in ①) suppresses GSIS and increases glucagon release from the islets while stimulating increased HGP from the liver via releasing the neurotransmitter NE, which binds to and activates adrenergic receptors on pancreatic islet cells and hepatocytes. Stimulation of the PNS (*orange circles* in ①) increases both insulin and glucagon secretion via binding of the neurotransmitter ACh to muscarinic cholinergic receptors. In the postprandial state, the responses to PNS activation promote glucose uptake and storage. Abbreviations: ACh, acetylcholine; ACTH, adrenocorticotropic hormone; ANS, autonomic nervous system; CGRP, calcitonin gene–related peptide; CNS, central nervous system; GI, gastrointestinal; GIP, glucose-stimulated insulinotropic polypeptide; GLP1, glucagon-like peptide 1; GSIS, glucose-stimulated insulin secretion; HGP, hepatic glucose production; HPA, hypothalamic-pituitary-adrenal; NE, norepinephrine; NPY, neuropeptide Y; NTS, nucleus of the solitary tract; PACAP, pituitary adenylate cyclase–activating polypeptide; PNS, parasympathetic nervous system; SNS, sympathetic nervous system; SP, substance P; TRPV1, transient receptor potential vanilloid 1. Figure adapted from images created with BioRender.com.

While identifying the cause of perturbed islet innervation and its functional consequences for glycemic control requires further study, these observations raise the possibility that aberrant neural input contributes or predisposes to beta cell dysfunction in T2D. Among individuals who develop T2D, beta cells may have an underlying genetic susceptibility to the deleterious impact of influences extrinsic to the islet itself. This view is compatible with clear evidence that beta cell dysfunction can result from sustained hyperglycemia (35) [referred to as glucotoxicity (36)] and obesity-associated metabolic impairment (e.g., hyperlipidemia, systemic inflammation) (37, 38). For these reasons, it remains uncertain the extent to which defective GSIS in T2D involves a primary beta cell defect or instead is secondary to one or more beta cell–extrinsic factors.

2.2. Insights from Genome-Wide Association Studies

A primary beta cell defect in T2D pathogenesis is also inferred from genome-wide association studies (GWAS) data revealing over 400 gene variants associated with T2D risk, many of which are expressed in beta cells (39). However, these variants collectively account for only about 20% of T2D risk (39), and neither the causal role in T2D played by GWAS-identified transcripts (39) nor the significance of their expression in beta cells versus other tissues is known. In fact, many T2D-associated gene variants expressed in the islet are also expressed in the CNS, including genes encoding the glucose phosphorylating enzyme glucokinase (*GCK*) (40) and the ATP-sensitive potassium (K_{ATP}) channel subunits SUR1 (*ABCC8*) and Kir6.2 (*KCNJ11*) (41). The proteins encoded by these genes play important roles in cellular glucose sensing in both the CNS and beta cells (see Section 4). These observations collectively support a model in which individuals that go on to develop T2D have a genetic predisposition to beta cell dysfunction that is aggravated by external challenges to the beta cell, yielding progressive impairment of insulin secretion characteristic of T2D.

2.3. Islet Transplantation

In humans with T1D, implanting healthy donor islets is sufficient to restore normoglycemia (42). Thus, the islet can function independently of CNS input to regulate glucose homeostasis in this pathological setting. However, removing islets from neural control creates a nonphysiological state that does not inform how glucose homeostasis normally works in natural conditions or how it goes awry in T2D. In light of growing evidence that the brain, like the islet, can powerfully impact the BDL_G via both islet-dependent and islet-independent mechanisms (detailed below), we infer that the BDL_G is determined by cooperative interactions between brain and islet. This interaction is exemplified by the adaptive coupling of insulin secretion to increased insulin sensitivity during cold exposure, in which the SNS plays a pivotal role.

2.4. Dynamic Coupling of Insulin Secretion and Insulin Sensitivity During Cold Exposure: A Paradigm for Understanding the Brain's Role in Glucose Homeostasis

To maintain core body temperature in the cold, thermogenic tissues rapidly increase glucose utilization to fuel heat production, including thermogenesis by brown adipose tissue and shivering by skeletal muscle. Enhanced glucose utilization is facilitated in part by increased insulin sensitivity in these tissues (43), which is essential to preserve core temperature in the cold (44). To prevent blood glucose levels from falling during the resultant increase of glucose utilization, an adaptive decrease in insulin secretion occurs with such rapidity and precision that blood glucose levels remain stable throughout the transition to a cold environment. The effect of cold to suppress insulin secretion therefore cannot be attributed to a change in glucose stimulation of beta cells, since glucose levels do not change. These observations illustrate how adaptive coupling of insulin secretion to insulin sensitivity preserves normoglycemia when the energetic demands of tissues change.

Based on the assumption that defective feedback between insulin-sensitive tissues and beta cells underlies glucose intolerance in T2D (6), intensive effort has been devoted to identifying this coupling signal, with candidates that include free fatty acids, intrinsic beta cell glucose metabolism, and sensitivity to incretins (6, 45). While the role played by these factors remains uncertain, a clear role for the SNS has been demonstrated in adaptive coupling during cold exposure. Increased SNS outflow not only drives heat production by thermogenic tissues (44, 46, 47) but also suppresses insulin secretion (47). Blocking SNS outflow (with α-adrenergic receptor antagonists) prevents both the cold-induced suppression of insulin secretion and the increase in insulin sensitivity (14). Collectively, the observations above highlight the difficulty in distinguishing the intertwined roles played by the islet and the CNS in glucose homeostasis—cooperative interactions between them are essential.

2.5. Is Impaired Beta Cell Function a Cause or Consequence of T2D?

This question may have no correct answer and is perhaps not the most scientifically relevant or clinically meaningful question. We view T2D as a heterogenous disorder involving multiple peripheral and central defects, where interactions between them create a vicious cycle that progressively impairs both insulin-dependent and insulin-independent glucose disposal. Impaired beta cell function—whether primary or secondary—plays a key role, but the gradual increase in the BDL_G implicates defective CNS control mechanisms as well.

3. INSULIN-INDEPENDENT MECHANISMS OF GLUCOSE DISPOSAL

FSIGT: frequently sampled intravenous glucose tolerance test

***Sg*:** glucose effectiveness derived from minimal model of glucose kinetics

***Kg*:** glucose disappearance constant derived from FSIGT test

***Si*:** insulin sensitivity index derived from minimal model of glucose kinetics

Supplemental Material >

Our understanding of insulin-independent glucose disposal has been limited by two hurdles: (*a*) the perception that it is a passive, unregulated process with limited relevance to glucose homeostasis, and (*b*) it is hard to measure. The former has been abandoned in light of growing evidence that this process can be rapidly and potently activated by the CNS (see Section 4), and the latter was addressed by the development and validation of Bergman's minimal model of glucose kinetics (**Supplemental Figure 1**), which allowed this variable to be measured. In the original conception of that model—derived by mathematical modeling of frequently sampled intravenous glucose tolerance (FSIGT) test data—glucose effectiveness (designated *Sg* in minimal model analyses) was a parameter that measured "the quantitative enhancement of glucose disappearance due to an increase in the plasma glucose concentration" that was not attributable to the action of insulin (48, p. E673). That is, *Sg* was a measure of the effect of glucose to promote its own disposal down a concentration gradient after an intravenous load (49). However, studies applying the minimal model approach in humans revealed that *Sg* can change during acute experimental intervention (50–52) and in disease (53–55). These seminal findings showed that this underappreciated variable (and the various insulin-independent mechanisms that are represented by *Sg*) contributes significantly to individual variance in glucose tolerance and T2D risk. A notable limitation of *Sg* (glucose effectiveness as a measure of insulin-independent glucose disposal) is that since it is based on the response to a glucose load (i.e., in FSIGT tests), it offers limited insight into insulin-independent glucose disposal in the basal state, where it is quantitatively more important than the insulin-mediated contribution (9, 52).

3.1. Reduced Insulin-Independent Glucose Disposal Predicts T2D Risk

To enable minimal modeling of glucose kinetics in T2D patients, Welch et al. (55) developed an FSIGT protocol using exogenous insulin to compensate for diminished GSIS characteristic of T2D (minimal modeling of FSIGT data requires a dynamic interaction between changing plasma insulin and glucose levels). In addition to the expected reduction in insulin sensitivity, *Sg* was reduced by approximately 40% in T2D patients. Two subsequent studies (11, 56) implicate this defect as causal in T2D pathogenesis.

In the first study (11), 18 lean and obese nondiabetic subjects underwent FSIGT testing and were subdivided into two groups based on quantified glucose tolerance (*Kg*), with body weight tending to segregate, though not exclusively, with *Kg*. Minimal modeling of the FSIGT data revealed that subjects with lower *Kg* had not only the expected lower disposition index (DI, a composite measure of insulin-dependent glucose disposal; **Supplemental Figure 1**) but also twofold lower *Sg*. Glucose intolerance in nondiabetic subjects, therefore, appears to involve reductions in the handling of glucose by both insulin-dependent and insulin-independent mechanisms.

To investigate whether either of these impairments is predictive of future T2D, a prospective cohort study was conducted in 155 normoglycemic offspring of parents who both had T2D (56). FSIGT and minimal model analysis were performed at baseline, and subjects were followed for up to 25 years. In the 25 subjects that developed T2D, reductions of both *Sg* and insulin sensitivity (*Si*) were manifest at least 10 years prior to developing T2D. Remarkably, none of the subjects with *Sg* and *Si* above the median developed T2D, whereas those with *Sg* and *Si* values below the median had a 76% cumulative incidence of T2D over 20 years, with reduced *Sg* imparting the greatest relative risk—15 times greater risk of developing T2D comparing the lowest and highest quintiles of *Sg*. These studies provide compelling evidence linking impaired insulin-independent glucose disposal to T2D pathogenesis. It was only years later that the potent capacity of the brain to regulate insulin-independent glucose disposal came to light (Section 4).

3.2. Reconciling Insulin-Dependent and Insulin-Independent Mechanisms of T2D Pathogenesis

The hypothesis that T2D arises when beta cells fail to compensate for insulin resistance (57) has extensive support, including cross-sectional and longitudinal studies implying that an early beta cell defect develops as a consequence of insulin resistance (for detailed reviews, see 6, 58). Whether assessing groups at high risk for developing dysglycemia (16, 59, 60) or populations that are phenotypically not commonly obese (61, 62), these studies consistently suggest that an early impairment of beta cell function—measured by insulin secretion and/or DI (**Supplemental Figure 1**)—is predictive of T2D.

NHGU: net hepatic glucose uptake, or net hepatic glucose balance

Supplemental Material >

Unexpectedly, recent evidence suggests that insulin hypersecretion, rather than beta cell dysfunction, identifies otherwise normal individuals at risk for T2D. In a recent prospective cohort study conducted by Ferrannini and colleagues (63), 1,168 healthy adults with normal glucose tolerance were stratified according to their level of insulin secretion, and advanced statistical methods were used to ensure virtually identical insulin sensitivity between strata. After a period of 3 years, subjects with higher insulin secretion were more likely to progress to impaired glucose tolerance or T2D than those with lower insulin secretion. This result, which is consistent with other human (64–68) and animal studies (69–73), suggests that primary insulin hypersecretion is a triggering event in T2D pathogenesis (74), possibly by precipitating subsequent insulin resistance (69, 70, 75–79).

A paradoxical finding in the study by Ferrannini and colleagues (63) is that insulin hypersecretors had worse glucose tolerance despite having equivalent insulin sensitivity. Notably, insulin hypersecretion, normal insulin sensitivity, and worsened glucose tolerance simply cannot coexist unless the other key determinant of glucose tolerance—insulin-independent glucose lowering—is reduced. This interpretation is consistent with evidence cited above linking reduced insulin-independent glucose disposal to T2D pathogenesis (11, 56). Although additional work is required to explain the reduced glucose tolerance in this cohort (63), reduced hepatic glucose uptake [regulated largely by insulin-independent mechanisms (81, 82) discussed below] may contribute, as this process is known to be impaired in patients with T2D (83, 84).

3.3. Insulin-Independent Glucose Disposal and Hepatic Glucose Flux

As the recipient of portal venous blood from the gastrointestinal tract, the liver is uniquely placed to monitor glucose appearance after a meal (1). Following meal ingestion, the glucose level entering the liver through the portal system is much greater than that of the arterial circulation. First described in dogs by Cherrington and colleagues (81, 85), this negative arterial-portal glucose gradient (termed the portal signal) is specific to the postprandial setting and produces a robust, insulin-independent increase in net hepatic glucose uptake (NHGU), in effect directing the liver to switch rapidly from glucose output in the fasted state to glucose uptake following a meal. Cherrington and colleagues (86, 87) provide evidence that (*a*) in the fasted state, basal sympathetic tone to the liver blocks NHGU, and the portal signal suppresses sympathetic activity to produce a sharp rise in NHGU; (*b*) within hepatocytes, this response involves increased activity of glucokinase and glycogen synthase, which increase glucose uptake and glycogen synthesis, respectively (88); (*c*) chronic high-fat diet (HFD)/high-fructose diet feeding abolishes portal signal induction of NHGU together with reductions in glucokinase content and activity, glycogen synthase activity, and glucose tolerance (89, 90); and (*d*) sympathetic denervation along the common hepatic artery in the HFD/high-fructose diet–fed dog partially restores NHGU, independent of insulin, thereby improving glucose tolerance (91).

VMN: ventromedial nucleus

ARC: arcuate nucleus

This work thus suggests that overnutrition heightens sympathetic tone to the liver and blocks the ability of the portal signal to drive the normal meal-induced increase of NHGU. This interpretation is supported by earlier work in dogs in which long-term epinephrine infusion, to mimic effects of chronic sympathetic activation, induces a nearly two-thirds drop in *Sg*, with no difference in *Si* or insulin secretion (92). How might these findings impact our understanding of T2D pathogenesis?

3.4. Evidence for Autonomic Dysfunction in T2D Pathogenesis

Several studies suggest that autonomic dysfunction and excessive sympathetic tone are early precursors of T2D (93). Prospective cohort studies have shown that both baseline norepinephrine levels and sympathetic reactivity predict future T2D risk (94–96). Two large prospective cohort studies in ethnically distinct patient populations recently demonstrated that reduced heart rate variability, a biomarker of dysautonomia with sympathetic-parasympathetic imbalance (favoring sympathetic tone), was associated with significantly increased T2D risk (97, 98). Cross-sectional studies show increased resting muscle sympathetic nerve activity in T2D patients compared to patients with impaired glucose tolerance (99) or obesity alone (100). Other human (101–104) and animal (105) studies suggest that diet-induced obesity (DIO) is associated with chronically elevated sympathetic nerve activity.

Thus, in addition to the role played by beta cell dysfunction, both reduced *Sg* and dysautonomia (characterized by increased sympathetic tone) are consistently predictive of increased risk for T2D. Since insulin-independent mechanisms predominate in the control of basal glycemia, explaining up to 80% of overall glucose disposal (9, 52), and since reduced *Sg* is an expected consequence of increased sympathetic tone to the liver, we propose that an individual's propensity to develop T2D may depend on primary or acquired defects in these centrally controlled parameters.

4. AN INTEGRATIVE MODEL FOR CNS CONTROL OF GLUCOSE HOMEOSTASIS AND T2D PATHOGENESIS

Many brain regions have the capacity to influence glycemia, including several nuclei within the mediobasal hypothalamus [such as the ventromedial nucleus (VMN), arcuate nucleus (ARC), paraventricular nucleus, and lateral hypothalamus] and the hindbrain (including the nucleus of the solitary tract) (**Figures 2** and **3**). Neurons in these regions are anatomically well positioned to influence rates of glucose production and disposal by polysynaptic relays involving both limbs of the ANS, as well as via neuroendocrine secretion (26, 106) (**Figure 2**). Many neuronal subsets in these brain regions also express the molecular machinery necessary for intrinsic glucose sensing (see the sidebar titled Cellular Mechanisms of Glucose Sensing) and receptors for hormones and nutrients, raising the possibility that their effects on glucose homeostasis are regulated by circulating cues of energetic status, in addition to afferent neural input.

From a teleological perspective, a neural-based glucoregulatory system makes sense given the brain's substantial energetic demands and its dependence upon glucose as a fuel. Phylogenetic evidence supports the notion that glucoregulatory functions, including glucose sensing and insulin secretion, originated in neural cell types that preceded the evolution of pancreatic islets (117). Interestingly, the beta cell shares many morphological, transcriptional, and electrophysiological properties with nerve cells (118) despite originating from a distinct embryonic germ layer (endoderm). These observations have spurred the hypothesis that specialized endodermal cells adopted a neuronal transcription program during beta cell evolution, while glucoregulatory systems in the brain were largely preserved (117). This concept, though speculative, fits well with accruing

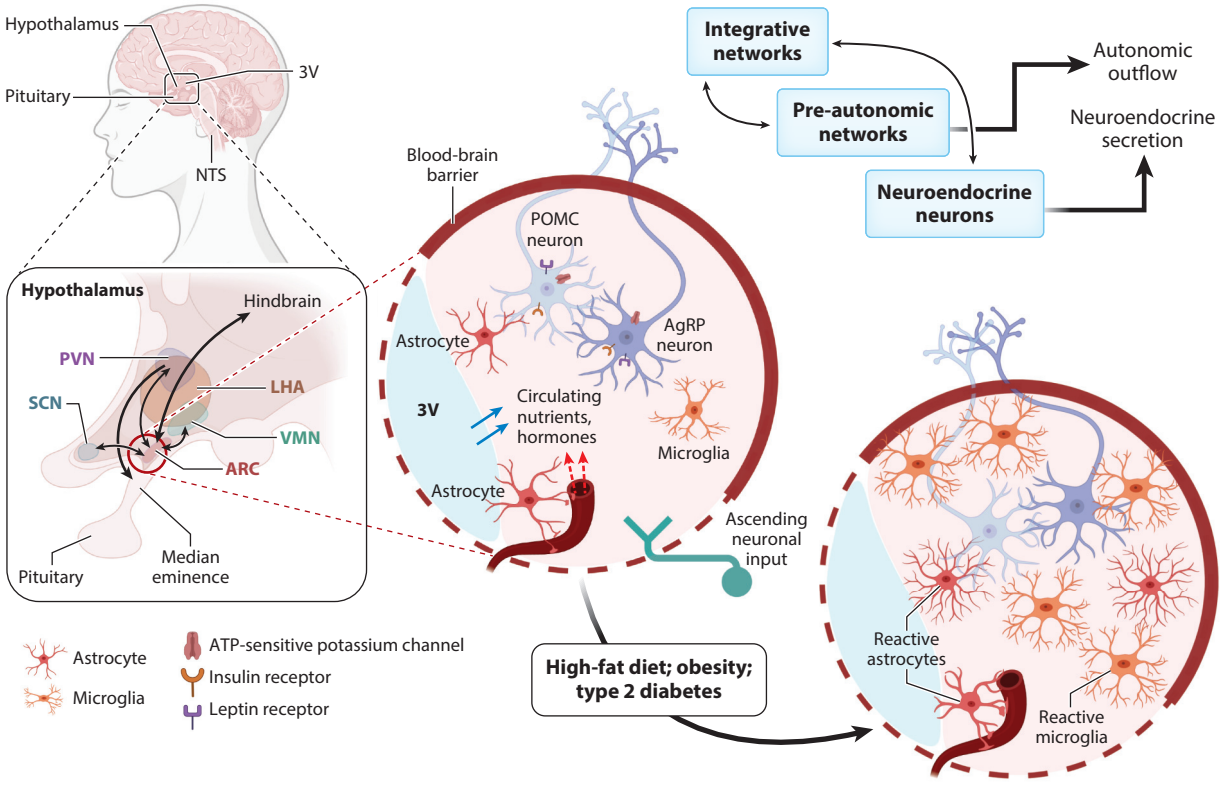


Figure 3

Hypothalamic neurocircuits in glycemic control. The hypothalamus is a forebrain structure situated ventral to the thalamus and dorsal to the pituitary gland and median eminence. It is an important component of the hypophyseal portal system. The mediobasal hypothalamus exhibits reciprocal connectivity with hindbrain structures, including the nucleus of the solitary tract (NTS), as well as with neighboring hypothalamic nuclei (*arrows* indicate connectivity in hypothalamus inset). The median eminence is a circumventricular organ with fenestrated capillaries that increase vascular permeability (indicated by *dashed red lines* in circular insets) and that receives dense innervation from hypothalamic neurons [including from parvocellular neurons of the paraventricular nucleus (PVN)], which release hypophysiotropic hormones (e.g., corticotropin-releasing factor) into the pituitary portal system, thereby directing pituitary secretions. Heightened vascular permeability of the median eminence exposes neurons in the adjacent arcuate nucleus (ARC) to higher levels of circulating nutrients and hormones than seen by brain regions located behind the blood-brain barrier (*bold red line*), such as the ventromedial nucleus (VMN), PVN, and lateral hypothalamic area (LHA). The ARC is also adjacent to the third ventricle (3V), permitting access to factors circulating in the cerebrospinal fluid, and receives afferent neuronal input from multiple brain regions conveying information about energetic demands, environmental cues of time and food availability, and cue-reward associations. These dynamic and varied inputs are integrated by pro-opiomelanocortin (POMC)- and agouti-related peptide (AgRP)-expressing neurons in the ARC that are regulated in a reciprocal manner and drive opposing effects on glycemia and energy balance, in part, by engaging melanocortin receptor signaling in downstream neurons. Hypothalamic network activity is also shaped by interactions with neighboring glia, including astrocytes and microglia. In addition to providing structural support for neurons and their projections, astrocytes and microglia play critical roles in neurovascular coupling, neurotransmitter uptake, synaptic pruning, immune surveillance, and inflammatory signaling (for a detailed review, see 116). In the setting of overnutrition, these cell types engage in a hypothalamic-specific reactive gliosis—characterized by cellular morphological changes, including enlarged, extended processes and heightened release of proinflammatory cytokines—that contributes to the metabolic consequences of diet-induced obesity. Figure adapted from images created with BioRender.com.

CELLULAR MECHANISMS OF GLUCOSE SENSING

As recently reviewed (107–110), glucose-excited and glucose-inhibited neurons increase their electrical activity in response to a rise or fall, respectively, in ambient glucose levels. Glucose-excited neurons and pancreatic beta cells employ analogous glucose-sensing strategies: After GLUT2-mediated glucose entry and phosphorylation by glucokinase, glycolysis and oxidative phosphorylation of glucose increase cytosolic ATP levels, triggering the closure of ATP-sensitive potassium (K_{ATP}) channels and cell depolarization. In contrast, glucose-inhibited neurons are activated when glucose is low via a mechanism involving reduced glucose phosphorylation by glucokinase, elevation of AMP:ATP levels, AMP kinase activation, and closure of membrane chloride channels. Whether neuronal glucose sensing is required for normal neuronal activity and central nervous system control of glycemia is debated. Although brain glucose levels parallel circulating levels, brain glucose entry is tightly controlled by the blood-brain barrier (BBB), and glucose concentrations in brain interstitium (0.7–2.5 mmol/L) are considerably lower than in the circulation (3.9–5.6 mmol/L in health) (109, 111). Thus, direct neuronal glucose sensing is more likely to be relevant in specialized brain regions, called circumventricular organs, not protected by the BBB. Alternatively, neuronal glucose sensing may involve indirect mechanisms such as the metabolism of lactate released from neighboring glia (112) and/or afferent neural input from peripheral glucose sensors (26, 113–115).

evidence of the central control of glycemia and provides a framework for understanding the complex contribution of the mammalian CNS to glucoregulatory functions delegated to the islets.

We hypothesize that glucose homeostasis depends upon the ability of the CNS to (*a*) reliably detect interoceptive signals regarding the circulating glucose level, (*b*) rapidly and precisely compute the anticipated homeostatic consequences of possible behaviors, and (*c*) regulate the balance between rates of glucose production and glucose utilization by adaptively adjusting autonomic and neuroendocrine outflow to glucose effector organs, including the pancreas and liver. Combined with evidence that normal islets can compensate for progressive impairment of glucose effectiveness or insulin sensitivity, we infer that normal CNS and islet function may be permissive for normal glucose homeostasis, with islet compensation (e.g., insulin hypersecretion) limiting the consequences of central glucoregulatory dysfunction (e.g., impaired *Sg*) when it is mild but not when it is more advanced. Defects in both central control and islet function may therefore be required for disease progression. Here, we consider the cause(s) of central glucoregulatory dysfunction with the potential to raise the BDL_G in T2D.

4.1. Does Reduced Brain Glucose Sensing Contribute to T2D Pathogenesis? Lessons from the Defense Against Hypoglycemia

One possible explanation for the increased BDL_G in T2D is that it is a CNS response to a perceived glucose deficiency. The brain response to a fall in blood glucose is well characterized, involving highly coordinated neuroendocrine and autonomic counterregulatory responses (CRRs) that collectively restore normoglycemia (for detailed reviews, see 114, 119). These responses include secretion of epinephrine, corticosterone/cortisol, and glucagon, which, combined with suppression of insulin secretion and elevation of HGP, rapidly return low blood glucose levels back to the BDL_G (**Figure 1**). Multiple research groups have identified subsets of VMN neurons whose activity is required for full CRR generation during systemic hypoglycemia, implicating the VMN as a central node in the underlying neurocircuitry (120–123). If the same neurons are activated experimentally when glucose levels are not limiting (i.e., during normoglycemia by optogenetic or chemogenetic stimulation), diabetes-range hyperglycemia is rapidly

CRR: counterregulatory response

elicited by activating CRRs normally reserved for the response to hypoglycemia—including, paradoxically, suppression of GSIS despite profound hyperglycemia (120–122, 124). As diminished GSIS, hyperglucagonemia, and elevated HGP are features common to both CRRs and T2D, pathological overactivation of neurocircuits (e.g., VMN) that function to mobilize glucose may contribute to diabetic hyperglycemia. This is a provocative idea, but both direct and indirect evidence support this possibility.

The glycemic threshold for triggering CRRs (presumably, the level at which the brain perceives a glucose deficit) is elevated by 40% or more in people with T2D compared to nondiabetic individuals (125, 126). Despite this elevated threshold for CRR activation, the magnitude of CRRs (and their ability to raise blood glucose) is preserved, implying that adaptive responses to glucose deficiency are intact, but the degree of hypoglycemia needed to mount them has lessened. This effect is even more pronounced in monogenic diabetes resulting from glucokinase mutations (126), suggesting that defective glucose metabolism (and putatively cellular glucose sensing) raises the glycemic threshold for CRR initiation. Although glucokinase is expressed in multiple tissues, including brain and islets, a specific role for central glucokinase activity is supported by rodent studies in which increasing glucokinase activity in the ARC improves GSIS and glucose tolerance (127). Together, these findings support a model of T2D pathogenesis in which the central representation of glucose deficiency occurs at a blood glucose level higher than the normal hypoglycemia threshold (**Figure 1**).

Additional support stems from evidence that brain glucose uptake is reduced in humans with obesity and T2D (128, 129). While the underlying mechanisms are poorly understood, a role for overnutrition in hypothalamic dysfunction has been proposed. In rodents, 3 days of HFD feeding is sufficient to induce hypothalamic gliosis (130) (reactive astrocyte formation and proinflammatory microglial infiltration with deleterious consequences for resident neurocircuits; for a detailed review, see 116) (**Figure 3**). Further, obesity is attenuated in mice fed a HFD by interventions that block this microglial inflammatory activation (131). HFD feeding also suppresses brain glucose uptake via endothelial downregulation of the glucose transporter, GLUT1 (132); over time, these responses are associated with hypothalamic angiogenesis, which may reflect compensatory vascular remodeling (132, 133). Studies in humans have similarly shown that both hypothalamic gliosis (134) and the number of hypothalamic arterioles (133) are increased in obesity and T2D. Addressing whether and how these vascular changes affect brain glucose sensing, neurocircuit function, and T2D pathogenesis are priorities for future studies.

4.2. Hypothalamic Glucoregulatory Neurocircuits: the Melanocortin System

Among the brain's distributed network of glucoregulatory neurons, those in the hypothalamic ARC have received the most attention. By virtue of their privileged anatomical position nestled between the circumventricular median eminence and the third ventricle (**Figure 3**), ARC neurons can sense nutrients and hormones circulating in both the blood and cerebrospinal fluid (for reviews, see 135, 136). ARC neurons not only adjust their activity according to energetic state (137), feed-forward cues of nutrient availability (137, 138), and metabolic demand (139) but also exert strong effects on energy (140, 141) and glucose (41, 142) homeostasis, many of which involve the central melanocortin system.

The melanocortin system, a highly conserved cellular signaling pathway, directs catabolic and anabolic metabolism depending upon the balance of melanocortin 4 receptor (MC4r) binding to two opposing ligands, each expressed by a distinct subset of ARC neurons (143). The anabolic arm is activated by agouti-related peptide (AgRP), an inverse agonist of MC4r that is released in response to caloric insufficiency. By reducing MC4r signaling, AgRP promotes increased food

intake, reduced energy expenditure, and weight gain (1, 143). Conversely, the catabolic arm is driven by the MC4r agonist α-melanocyte stimulating hormone [α-MSH, derived from its precursor pro-opiomelanocortin([POMC)] in response to caloric excess. MC4r activation by α-MSH suppresses appetite and raises energy expenditure (143). Loss-of-function MC4r mutations in rodents and humans result in profound early-onset obesity; polymorphisms at the *POMC* gene locus are associated with T2D risk (144–146). Growing evidence suggests that reduced melanocortin signaling due to AgRP and POMC neuron dysfunction predisposes to glycemic abnormalities characteristic of T2D (147, 148).

4.3. CNS Regulation of Insulin-Independent Glucose Disposal

Among the most impressive examples of central glucoregulatory capacity is the finding that intracerebroventricular infusion of the adipocyte-derived hormone leptin restores normoglycemia to rodent models of insulin-deficient T1D [induced by streptozotocin (STZ), a beta cell toxin] (for a review, see 149). Leptin-mediated glucose normalization is associated with increased autonomic outflow to the liver (150), suppressed gluconeogenesis and HGP (151), reduced hyperglucagonemia (151, 152), and increased brain and peripheral tissue glucose uptake (151). These findings raise the question, how can leptin action in the brain ameliorate diabetes induced by beta cell destruction unless the brain plays a role in the hyperglycemia of insulin deficiency (2)?

To address this question, we consider recent evidence that inactivation of select glucoregulatory VMN neurons (whose activity promotes CRRs during hypoglycemia) greatly diminishes STZ-mediated hyperglycemia (123). This suggests that hyperglycemia elicited by severe insulin deficiency requires activation of these neurons. Earlier evidence similarly implicated VMN activity in diabetic hyperglycemia, as intra-VMN delivery of brain-derived neurotrophic factor (153) or leptin (154) comparably resolves STZ-mediated hyperglycemia via insulin-independent mechanisms. However, given that leptin deficiency develops as a consequence of insulin deficiency and fat loss in STZ-treated mice, whether centrally driven hyperglycemia in this setting is due to insulin versus leptin deficiency per se is unclear.

Evidence suggests that both may contribute. For example, HGP is suppressed by central administration of either insulin or leptin (151, 155), primarily via K_{ATP}-mediated neuronal hyperpolarization (41, 155). Consistent with this notion is recent evidence of an important role for K_{ATP} channels in the control of ARC AgRP neuron activity in relation to glucose homeostasis. Specifically, (*a*) genetic deletion of K_{ATP} channels in AgRP neurons elicits their hyperactivity, leading in turn to hyperglycemia, insulin resistance, and obesity (41), and (*b*) central administration of K_{ATP} channel openers (resulting in neuronal silencing) reduces blood glucose by suppression of HGP (156). In humans, systemic delivery of K_{ATP} channel antagonists blunts hyperglycemia-induced suppression of HGP by nearly 50%, suggesting that similar brain mechanisms may contribute to glycemic control in humans (13). These findings highlight hypothalamic regulation of HGP as a promising target for glucose lowering in T2D.

4.4. CNS Control of Insulin Sensitivity

The CNS is capable of driving rapid, parallel changes in insulin secretion and sensitivity during cold exposure, suggesting that aberrant neural activity could conceivably underlie defective coupling of these determinants of glycemia during T2D progression. Multiple brain regions have the capacity to drive rapid and reversible changes in peripheral insulin sensitivity (157), and daily changes in insulin sensitivity appear to be orchestrated by the central circadian system (158). Magnetic resonance imaging (MRI)-based evidence in humans has linked obesity-induced

hypothalamic gliosis to systemic insulin resistance and glucose intolerance, suggesting that a hypothalamic defect contributes to obesity-associated metabolic impairment (134). Metabolic improvement induced by bariatric surgery in women with T2D is associated with an improved MRI signature of hypothalamic gliosis (159), suggesting that the underlying neuropathological process may be reversible. Future studies that clarify the contribution of gliosis and associated mechanisms driving aberrant neurocircuit activity to insulin resistance and T2D pathogenesis are a scientific priority.

4.5. CNS Regulation of Beta Cell Mass

As discussed in Section 2, the CNS has the capacity to surveil and regulate islet activity during acute challenges to glucose homeostasis such as meal intake, insulin-induced hypoglycemia, and cold exposure. Beyond these functions, the ANS also affects the development and plasticity of the endocrine pancreas (160). Animal models with reduced parasympathetic activity during postnatal development exhibit diminished beta cell mass and GSIS in adulthood (161), whereas beta cell proliferation is increased when cultured islets are treated with muscarinic agonists. Since adrenergic stimulation has the opposite effect, available evidence points to direct and counteracting roles for the two limbs of the ANS in regulating beta cell mass (162–165). Manipulating the balance between sympathetic and parasympathetic outflow, therefore, may present a promising therapeutic approach to the preservation of both beta cell mass and function in T2D.

4.6. Targeting the Brain to Induce Sustained Diabetes Remission

Preclinical studies have demonstrated the ability of multiple centrally administered peptides, in addition to leptin, to elicit diabetes remission in rodent T2D models. Peptides in the fibroblast growth factor (FGF) family have received the most attention, based on evidence that central administration of FGF19 (166), FGF21 (167), and FGF1 (168–171) promotes insulin-independent glucose lowering in rodent models of T2D via activation of FGF receptors in the mediobasal hypothalamus. Strikingly, the glucose-lowering effects of FGF1 are quite long lived: A single intracerebroventricular administration of FGF1 normalizes glycemia for months in the leptin-deficient (*ob/ob*) mouse model of T2D (168) via an action in the ARC (170). Unlike conventional antidiabetic medications that elicit glucose lowering, FGF1 treatment does not increase the risk of hypoglycemia, nor does it alter insulin secretion or sensitivity. Instead, FGF1 appears to mediate its effects by restoring the BDL_G to normal (168). Investigation into mechanisms underlying this FGF1 effect has identified extracellular matrix remodeling (172) and sustained inhibition of AgRP neurons coupled with increased melanocortin signaling (173) as likely targets for this effect. Clarifying where, how, and why FGF1 works to normalize BDL_G in T2D is a priority for future work.

5. CNS-TARGETED THERAPEUTIC STRATEGIES FOR T2D: LOOKING TO THE FUTURE

Growing evidence that CNS-targeted therapies can normalize the BDL_G in preclinical T2D models (151, 168) underscores their untapped potential as future T2D treatments. **Supplemental Table 1** lists currently approved antidiabetic drug classes (and examples) with CNS-based metabolic effects. Below we discuss the most promising of the approved agents, the GLP1R agonists (**Supplemental Appendix 1**), to highlight the potential of centrally mediated drug action even when the drug's development was not predicated on central action. We then propose future therapeutic strategies targeting both central and peripheral glucoregulatory neural control

Supplemental Material >

mechanisms with the potential to enhance both insulin-dependent and insulin-independent glucose disposal as a path toward T2D remission/disease modulation.

5.1. GLP1R Agonists

Long-acting GLP1R agonists are among the more promising new drugs for T2D. Semaglutide, a once-weekly subcutaneously administered GLP1R agonist, was evaluated in the SUSTAIN clinical trial program in over 8,000 patients across the T2D spectrum. These trials demonstrated superior glycemic control and weight loss with semaglutide versus all comparators (including insulin, other GLP1R agonists, and dipeptidyl peptidase inhibitors) (174, 175). Semaglutide also has shown efficacy for clinically meaningful (~15%) weight loss in obese patients without diabetes (176).

GLP1R agonists elicit multiple glucose-lowering effects that include augmentation of GSIS (via a direct effect on beta cells) and reductions of food intake and body weight that are mediated centrally. Identifying contributions of various subnetworks of GLP1R+ neurocircuits (**Supplemental Appendix 1**) to the pleiotropic effects of GLP1 is an active area of research. Another active area of research involves the development and validation of intermixed, unimolecular, multiagonist peptides involving combinations of GLP1, glucagon, and/or glucose-stimulated insulinotropic polypeptide (GIP) (177). The goal of this strategy is to enhance GLP1's activity by broadening tissue targets and synergizing within tissues (e.g., brain and islet) that express multiple receptors. Several preclinical (178, 179) and Phase I and II clinical studies (180, 181) have demonstrated that these drugs may outperform single agonists in sustained glycemic improvement and weight loss and provide a promising path forward for GLP1-related agents (177). The roles of the brain and the islets as targets for these drugs are an active area of study, and it is likely that both contribute.

Supplemental Material >

5.2. Future Prospects for CNS-Targeted T2D Remission

Perhaps the most important lesson from preclinical models of T2D is that CNS-targeted therapies have the potential to induce T2D remission by restoring BDL_G to normal (unlike current nonsurgical treatment options). Two notable examples are intracerebroventricular injection of FGF1 in rodent models of T2D (168) and of leptin in rodent models of T1D (151). In both cases, BDL_G normalization appears to require suppression of abnormally hyperactive ARC AgRP neurons, possibly coupled with POMC neuron activation, thereby increasing melanocortin signaling (41, 173). FGF1 is ineffective in normalizing BDL_G in T2D models with deficient melanocortin signaling (173). Leptin is ineffective in normalizing BDL_G in T1D models in which leptin receptors are deleted from AgRP neurons (41).

How does one pursue translation of these preclinical models? A first step would be to test the safety and efficacy of the agents themselves in large animal models. One such study is underway for FGF1 in a nonhuman primate model of T2D. Safety and efficacy of centrally administered leptin has been tested in nonhuman primates (182, 183). A pilot study of peripheral administration of metreleptin (modified to increase half-life, which is approved for use in lipodystrophic diabetes) has been completed in T1D patients (184). While glycemia was not significantly improved in this study, preclinical findings suggest that leptin must be administered directly into the brain for its antidiabetic effects to be observed (151). A pilot study to test the safety and efficacy of central administration of leptin in T1D patients is therefore a priority. Such a strategy has the potential to elicit effective and sustained normalization of glucose without the risks of hypoglycemia (185) and weight gain (186).

Parallel efforts aimed at translation may further dissect the cellular and molecular mechanisms of promising agents. At multiple time points after intracerebroventricular FGF1 injection into obese diabetic mice, a recent comprehensive transcriptomic analysis across mediobasal hypothalamic cell types revealed other potentially druggable pathways (173). Notably, the transcriptomic response of astrocytes displayed prominent neuroprotective and neuron-interacting phenotypes, with evidence suggesting increased astrocytic coverage of AgRP neuron synapses. Some of these cellular signatures are common to other neurological disease processes, including ischemic stroke, and therefore may highlight the potential of drug candidates co-opted from other disease states.

A critical consideration for any centrally targeted pharmaceutical will be the pharmacokinetic nuances of drug delivery to the brain. This highlights the therapeutic potential of strategies that increase hypothalamic melanocortin signaling for treatment of T2D and associated metabolic disorders. The close proximity of AgRP neurons to the median eminence, which has a fenestrated blood-brain barrier (BBB), suggests that drugs aimed at silencing these neurons might access them via the circulation. In other cases, however, centrally targeted therapies that are administered systemically will have to traverse the BBB and contend with unique pharmacokinetic properties of CNS drug delivery (187). Promising alternative possibilities include intranasal (188) or catheter-based intrathecal delivery (189) (**Figure 4**).

In addition to pharmaceuticals, other therapeutic modalities for restoring brain neural circuit disorders include (*a*) deep brain stimulation, currently FDA-approved for Parkinson's disease, essential tremor, dystonia, obsessive compulsive disorder, and epilepsy (190), and (*b*) CNS gene therapy via antisense oligonucleotides (191) or stereotactic virally delivered gene therapy (192), which are being investigated in Huntington's and Parkinson's diseases, respectively, with promising results.

Deep brain stimulation relies on modulating neural circuit activity using controlled electrical fields emitted from chronically implanted electrodes. While future iterations of this technique may provide a strategy for modulating glucoregulatory neural circuits, a current limitation of this approach is that the electric fields generated are rather large compared to the relatively small and cellularly heterogenous nuclei of the mediobasal hypothalamus. CNS gene therapy is an increasingly viable strategy in select neurodegenerative disorders, with improved techniques for gene delivery and coverage of the brain region of interest and an understanding of the genetic targets that are most tractable (i.e., therapeutic gain versus loss of gene function) (192). The potential of this approach in T2D is intriguing in light of preclinical studies demonstrating improved glucose tolerance with ARC-specific transduction of the glucokinase gene (127), conferring improved neuronal glucose sensing, and the aforementioned evidence of reduced brain glucose sensing in T2D pathogenesis. Further investigation and refinement of the safety and efficacy of CNS gene therapy for severe neurodegenerative diseases should ultimately lay the groundwork in the potential application of this approach to chronic neural circuit disorders, including T2D.

5.3. Antidiabetic Strategies Targeting the Autonomic Nervous System

In addition to developing T2D therapies directed at the brain, the ANS presents an attractive target based on its role as an essential relay between central neurocircuits and peripheral glucose effectors. Modulating the PNS and/or SNS branch of the ANS in T2D may facilitate the balancing of mechanisms governing BDL_G. Vagal efferents innervating beta cells not only stimulate GSIS (193, 194) but can also promote beta cell proliferation and expansion (163–165), thereby offering potential T2D disease-modifying treatment. Although uncertainty remains regarding the extent to which the liver parenchyma is innervated by vagal efferent fibers (195), activation of these fibers offers a potentially viable approach to inhibit expression of gluconeogenic genes, gluconeogenesis, and HGP (196).

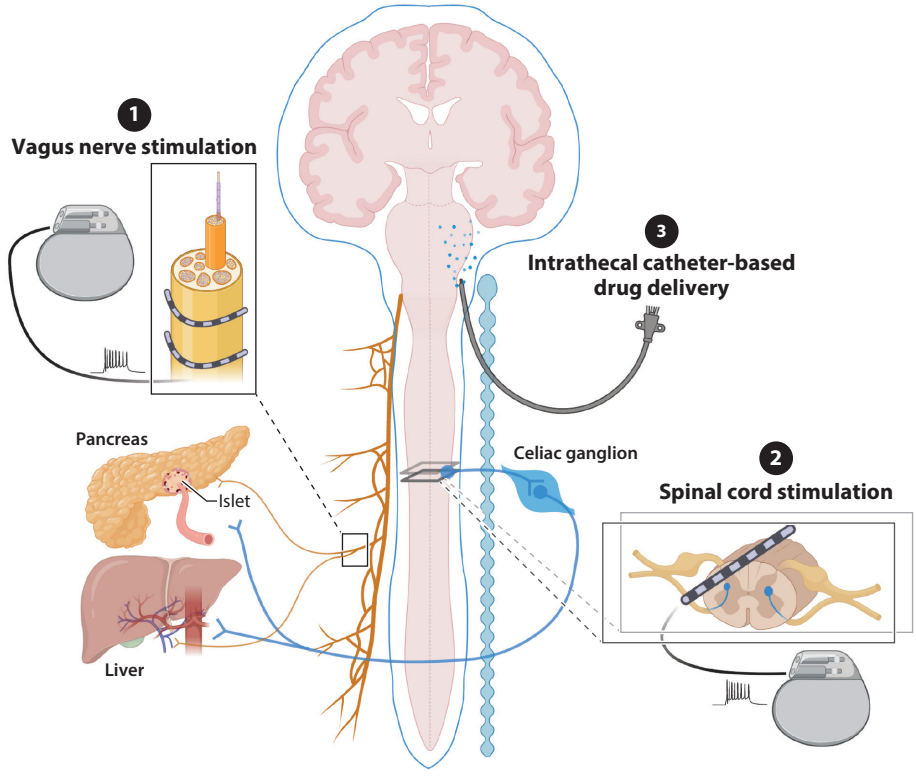


Figure 4

Future prospects for central nervous system (CNS)-targeted type 2 diabetes (T2D) remission/disease modulation. Device-based, CNS-targeted approaches to T2D disease modulation include (❶) vagal nerve stimulation targeting fascicles innervating liver, portal vein, and pancreatic islets, (❷) spinal cord stimulation with electrodes placed epidurally to target preganglionic sympathetic nerves in the intermediolateral cell column (*blue cell bodies* in inset) innervating the celiac ganglion (~T5–T9 levels), and (❸) intrathecal catheter-based targeted drug delivery (e.g., leptin, fibroblast growth factor analogs) with infusion via an implanted subcutaneous reservoir or pump. Figure adapted from images created with BioRender.com.

Conversely, vagal afferents are well documented to innervate the hepatic portal vein and are a critical component of the glucose-sensing machinery that provides input relevant to the circulating glucose level to central neurocircuits (e.g., for the response to hypoglycemia or the portal glucose signal) (115, 197–201). Recent work (115) characterizes a vago-vagal circuit, originating with vagal afferents innervating the portal vein wall, directly contacting vagal efferents in the hindbrain dorsal motor nucleus of the vagus (which in turn modulates hepatic and islet function). Therapeutic strategies targeting these neurons, perhaps in combination with reduced SNS tone at the liver and pancreas, may have the potential to lower the BDL_G in patients with T2D.

While cholinergic/anticholinergic drugs may be limited by off-target effects on other organs, device-based neuromodulation using implantable vagal nerve stimulators (VNSs) offers a more targeted approach. For example, if the vago-vagal circuit supplying the hepatic portal vein could be specifically targeted with a VNS device, the circuit could potentially be dialed up or down as needed to optimize the BDL_G. Considerations in the development of this strategy will include optimal placement of the electrode along the central-peripheral axis of the nerve (to reduce the number of vagal fascicles destined for nonglucoregulatory organs) and the stimulation parameters

(i.e., pulse width/frequency/duration to engage the highest fraction of desirable efferent/afferent glucoregulatory vagal fascicles) (202–204). VNS is already FDA approved for use in epilepsy and depression, and early proof-of-principle studies in patients with obesity and T2D show promising results (205, 206) (**Figure 4**).

Alternatively, therapeutic strategies could target SNS modulation of the BDL_G. As discussed above, increased sympathetic tone on beta cells suppresses GSIS (14), while stimulating glycogenolysis and gluconeogenesis in hepatocytes, thus increasing HGP (26, 208, 209); conversely, sympathetic denervation of the liver in DIO dogs improves glucose tolerance (91). Similarly, catheter-based renal sympathetic denervation in patients—developed for treatment-resistant hypertension—surprisingly appears to reduce whole-body sympathetic nerve activity (210) and in small early studies showed reduced fasting plasma glucose and insulin levels, suggesting improved insulin sensitivity (211). Larger studies of this approach for T2D have not been conducted, but meta-analyses of small studies failed to show that the antidiabetic effect is reliable (212). Inconsistent results from this approach extend to its initial indication—hypertension—with randomized, controlled studies showing both positive and negative outcomes for its efficacy (caveats cited for negative studies included variability in denervation technique across study sites and patient selection criteria) (213).

Analogous to the considerations discussed for VNS above, effective SNS modulation may be better achieved with more targeted, device-based neuromodulation. Implantable epidural spinal cord stimulators are currently FDA approved and widely used as a targeted treatment for chronic neuropathic pain (214). In Europe, targeted spinal cord stimulators are also used for ischemic pain (e.g., angina) related to arterial insufficiency and have been shown to produce sympathetic blockade as part of their mechanism of action (215, 217). By extension, spinal cord stimulation (SCS) modulation of SNS innervation of the islet and liver, by way of preganglionic sympathetic nerves located in the intermediolateral cell column and projecting to the celiac ganglion, may provide a tunable strategy for normalizing the BDL_G in T2D. Furthermore, in patients with neuropathic pain, SCS appears to modulate dorsal horn–dorsal column spinal sensory pathways that include direct inputs from TRPV1+ dorsal root ganglion neurons (216), subsets of which innervate the islets at the upper thoracic levels as discussed above (29–31). SCS thus offers multiple potential mechanisms by which to modulate neural activity to and from peripheral glucose effectors.

Development of new therapeutic strategies targeting CNS control of glucose homeostasis will be a formidable challenge. However, growing and undeniable evidence that the CNS plays a fundamental role in normal and abnormal glucose metabolism is a sign of an emerging era of CNS-centered research and drug discovery in T2D.

SUMMARY POINTS

1. Insulin-independent glucose disposal mechanisms predominate in the control of the basal glucose level.
2. Type 2 diabetes (T2D) is associated with impaired insulin-independent glucose disposal. Evidence that this impairment is primary in T2D pathogenesis is as compelling as the evidence of a causal role played by a beta cell defect.
3. In rodent models of type 1 diabetes and T2D, the brain can be targeted to normalize the biologically defended level of glycemia (BDL_G) via mechanisms that are largely, if not exclusively, insulin independent.

4. The mediobasal hypothalamus is the only known brain area capable of normalizing the BDL_G in preclinical models of T2D, with increased melanocortin signaling engaged by neurons in the arcuate nucleus likely playing a key role.
5. In both humans and preclinical models, obesity and T2D are associated with hypothalamic pathology, including activation of glial cells (reactive gliosis) in areas involved in glucose homeostasis; this pathological response may contribute to elevation of the BDL_G by reducing neuronal sensing of (or responsiveness to) the circulating glucose level.
6. Neuronal subsets in the hypothalamic ventromedial nucleus that normally orchestrate counterregulatory responses to glucose deficiency may aberrantly promote the elevated BDL_G in T2D; inactivation of these neurons in rodent T2D models elicits insulin-independent glucose lowering.
7. Future therapeutic strategies and drug discovery focused on central nervous system control of both insulin-independent and insulin-dependent glucose disposal offer significant untapped potential yet to be addressed by current T2D treatments.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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