CNS control of the endocrine pancreas

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Abstract

Increasing evidence suggests that, although pancreatic islets can function autonomously to detect and respond to changes in the circulating glucose level, the brain cooperates with the islet to maintain glycaemic control. Here, we review the role of the central and autonomic nervous systems in the control of the endocrine pancreas, including mechanisms whereby the brain senses circulating blood glucose levels. We also examine whether dysfunction in these systems might contribute to complications of type 1 diabetes and the pathogenesis of type 2 diabetes.

Keywords Autonomic nervous system · Brain · Diabetes · Glucagon · Glucose · Insulin · Islet · Pancreas · Review

Abbreviations

ANS Autonomic nervous system

ARC Arcuate nucleus

BBB Blood–brain barrier

CNS Central nervous system

CRR Counter-regulatory responses

CVO Circumventricular organs

DMNX Dorsal motor nucleus of the vagus

FGF Fibroblast growth factor

GCK Glucokinase

GSIS Glucose-stimulated insulin secretion

GSN Glucose-sensing neuron

HAAF Hypoglycaemia-associated autonomic failure

i.c.v. Intracerebroventricular

IIH Insulin-induced hypoglycaemia

IML Interomedialateral

ISF Interstitial fluid

ME

Median eminence

NTS

Nucleus of the solitary tract

PMV

Portal-mesenteric vein

PNS

Parasympathetic nervous system

POA

Preoptic area

SNS

Sympathetic nervous system

VMN

Ventromedial nucleus

Introduction

Blood glucose levels are maintained within narrow physiological limits. Whenever glucose levels deviate from their defended level, adaptive metabolic responses are engaged to ensure glucose levels return to the normal range. Critical to these responses are the capacities of pancreatic islet alpha and beta cells to coordinately adjust glucagon and insulin secretion, respectively, in response to changes in blood glucose concentrations. However, accumulating evidence suggests that the central nervous system (CNS) works in tandem with the islet to maintain glucose homeostasis [1]. Here, we review key evidence suggesting that: (1) the brain can regulate islet function directly via innervation by parasympathetic nervous system (PNS) and sympathetic nervous system (SNS) branches of the autonomic nervous system (ANS), and indirectly via neuroendocrine mechanisms [2]; (2) the brain senses circulating glucose levels both directly and indirectly, transducing glycaemic information into adaptive glucoregulatory responses [3]; and (3) interventions targeting the brain can regulate glycaemic control, in part, by modulating islet

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function [4]. Finally, we discuss the implications of these concepts for the pathogenesis and treatment of type 2 diabetes.

Autonomic innervation of the endocrine pancreas

The rich autonomic innervation of the islet, first described in 1869 by Langerhans, has been characterised in multiple species by several independent research groups [2, 5]. While rodent islets are extensively innervated by both efferent cholinergic PNS and adrenergic SNS fibres (Fig. 1), initial reports in human islets suggested sparse PNS and less SNS innervation than seen in mice [6]. However, using state-of-the-art tissue clearing and 3D-reconstructive imaging to reduce background and improve clarity and resolution of islet morphology, more-recent work [7, 8] revealed dense PNS innervation of the human islet and more SNS fibres than previously reported [6].

Despite differences in the distribution and innervation of islet endocrine cells, autonomic activation affects islet hormone secretion similarly in rodents and humans. While SNS activation inhibits both basal and glucose-stimulated insulin secretion (GSIS) through release of noradrenaline (norepinephrine), acting via the α 2-adrenergic receptor on pancreatic beta cells, PNS activation augments GSIS via the release and binding of acetylcholine to beta cell muscarinic receptors [5]. In contrast, both PNS and SNS activation stimulates glucagon secretion via activation of muscarinic and β 2-adrenergic receptors, respectively, expressed on islet alpha cells, which are further regulated by insulin secreted from adjacent beta cells [5].

The neural pathways regulating autonomic outflow to the pancreas have been mapped by multiple retroviral tracing studies. These brain-to-pancreas neurocircuits include efferent PNS pathways consisting of preganglionic neurons in the dorsal motor nucleus of the vagus (DMNX), whereas SNS motor neurons are located in the intermediolateral (IML) column of the spinal cord [9, 10] (Fig. 1). However, in addition to a brain-to-pancreas neurocircuit, the SNS can also affect islet secretion indirectly by: (1) increasing outflow to the adrenal medulla, stimulating adrenaline (epinephrine) secretion into the circulation, resulting in inhibition of insulin and stimulation of glucagon secretion; and (2) regulating glucose utilisation by peripheral tissues [11]. The activity of both PNS and SNS outflow to the pancreas is regulated by neural input from multiple overlapping hindbrain, midbrain and forebrain structures [9, 10] (Fig. 2). To illustrate the importance of CNS control of islet function, we consider how the body responds when glucose homeostasis is challenged.

Central control of the endocrine pancreas

Perhaps the most robust example of central control of the endocrine pancreas is the counter-regulatory response (CRR) to hypoglycaemia. In response to a fall in blood glucose levels (i.e. insulin-induced hypoglycaemia [IIH]), a coordinated set of adaptive responses is engaged to restore normoglycaemia, including increased secretion of glucagon, glucocorticoids and adrenaline, and inhibition of GSIS [12]. These effects are driven largely by hypoglycaemia-induced activation of both PNS and SNS outflow to the islet, and increased SNS outflow to the adrenal medulla to drive adrenaline secretion. Accordingly, surgical or pharmacological ablation of autonomic outflow markedly reduces glucagon and adrenaline responses to IIH, thereby impairing glucose recovery [5]. Moreover, recurrent iatrogenic hypoglycaemia (common during intensive insulin therapy) produces a brain adaptation termed hypoglycaemia-associated autonomic failure (HAAF), which results in reduced autonomic outflow during subsequent IIH, thereby increasing susceptibility to, and severity of, future episodes of hypoglycaemia [13]. HAAF is of particular concern for individuals with type 1 diabetes, in whom impaired glucagon response to IIH is frequent. While the precise explanation for impaired glucagon secretion is unclear, putative mechanisms include the loss of not only beta cells, but also SNS fibres selectively within the islet [14], and a role for the brain has been identified [15].

Within the brain, subsets of neurons within the hypothalamic ventromedial nucleus (VMN) are implicated in mediating CRRs, as VMN-specific glucopaenia triggers CRRs during systemic normoglycaemia, while infusion of glucose within the VMN blunts CRRs during IIH [16]. Moreover, recent studies using advanced neuroscience approaches have identified multiple subsets of neurons in the VMN, the activity of which is both sufficient to robustly raise blood glucose levels of normoglycaemic mice by activating hormonal CRRs, and required for intact hormonal CRRs and recovery from IIH [17–19]. Whether these neurons play a physiological role in the primary sensing of circulating glucose levels or are secondarily engaged as part of the brain's efferent limb to drive CRRs are questions awaiting further study.

The defence of core body temperature during cold exposure represents another physiological challenge where the energy needs of thermogenic tissues pose a challenge to glucose homeostasis [20]. This challenge is met through coincident, adaptive reductions in insulin secretion that allow glucose to be directed to thermogenic tissues, while avoiding a fall in blood glucose levels [21]. The brain is implicated in these effects since: (1) cold exposure increases sympathetic tone to both the pancreas and thermogenic tissues [20, 22]; and (2) pharmacological blockade of α -adrenergic receptors rapidly reverses the cold-induced inhibition of insulin

Fig. 1 Sensory and autonomic innervation of the endocrine pancreas. The islet receives efferent innervation (solid lines) from both sympathetic (orange) and parasympathetic (green) branches of the ANS, as well as sensory afferent fibres (dashed lines). Projecting from the lateral horn of the spinal cord, the cell bodies of sympathetic efferent fibres are positioned within the celiac ganglia (CG) and superior mesenteric ganglia (SMG). These fibres enter the islet along blood vessels (inset) and release noradrenaline from their terminals, stimulating glucagon secretion through binding to β -adrenergic receptors on alpha cells and inhibiting insulin secretion through activation of beta cell α_2 -adrenergic receptors. Afferent sympathetic fibres have their cell bodies in the dorsal root

ganglia (DRG) and project to the laminae I and IV of the spinal cord. Efferent parasympathetic fibres originate in the DMNX and innervate intrapancreatic ganglia (IPG), which, in turn, sends cholinergic input to the islet to stimulate increased glucagon secretion from alpha cells and to potentiate insulin secretion through local release of acetylcholine via muscarinic receptors on beta cells (inset). Pseudounipolar afferent parasympathetic neurons have their cell bodies within the nodose ganglion (NG), and terminals in the islet and NTS. In response to hypoglycaemia, increased sympathetic activity inhibits insulin secretion, while both increased sympathetic and parasympathetic activity stimulates glucagon secretion. This figure is available as part of a [downloadable slideset](#)

secretion [21], implying that SNS tone to the islet helps maintain normoglycaemia despite increased demand for glucose.

Evidence also suggests a neural link to the cephalic and first phases of insulin secretion, wherein insulin is secreted prior to nutrient absorption during sensory stimulation of the oral cavity as food is ingested [23]. The PNS is implicated in cephalic insulin release since it is suppressed by vagotomy, ganglionic blockade and by antagonism of muscarinic receptors in rodents [24]. However, the extent to which these

findings apply to humans remains uncertain due to differences in study paradigms [23, 25].

Together, these observations support a model in which the brain integrates and transduces afferent information regarding fuel availability and cooperates with the islet to maintain blood glucose levels in the face of anticipated metabolic demand [3]. Yet, critical questions remain as to how the brain senses circulating blood glucose levels to mediate these adaptive responses.

Fig. 2 Central neurocircuits implicated in efferent outflow to the islet. Motor neurons of the SNS and PNS receive input from extensively overlapping brain nuclei, including both hypothalamic and hindbrain regions. Motor neurons of the SNS lie within the IML of the spinal cord and receive synaptic input directly from premotor neurons within the NTS. These sympathetic premotor neurons receive input from hypothalamic regions, including the paraventricular nucleus (PVN) and lateral hypothalamic area (LHA), which, in turn, receive input from the VMN and ARC,

amongst other brain areas. In contrast, efferent PNS pathways consist of preganglionic neurons in the DMNX, intrapancreatic ganglia and postganglionic neurons in the pancreas. The DMNX, in turn, receives input from hypothalamic areas, including the PVN, LHA and VMN, via the periaqueductal grey (PAG) and/or raphe pallidus (Ra) and noradrenergic cell group 5 (A5). AP, area postrema. This figure is available as part of a [downloadable slideset](#)

Mechanisms of central glucose sensing

The brain has the capacity to detect glycaemic status via primary sensory fibres innervating peripheral organs and intrinsic sensing of glucose levels within the brain (Fig. 3). Indeed, sensory fibres extensively innervate peripheral organs, including the pancreas and gastrointestinal tract, and the portal-mesenteric vein (PMV) and carotid body [26]. Evidence suggests that some sensory neurons innervating the gastrointestinal tract detect glucose and other nutrient-related inputs [27], while those that innervate the PMV are critical for establishing CRRs to slow-onset hypoglycaemia [28], with each transmitting this information to the nucleus of the solitary tract (NTS) in the hindbrain. Sensory fibres innervating the pancreas may also play a role in glucose homeostasis, as their ablation increases beta cell mass and GSIS [29], and protects against diabetes progression in multiple rodent models [2, 30, 31]. Whereas rodents exhibit dense sensory innervation within the islet, human sensory fibres predominantly localise to intrapancreatic ganglia and the peri-islet area but do not penetrate the islet core [8]. Thus, the extent to which sensory innervation of the pancreas contributes to CNS control of blood glucose levels, and whether afferent fibres sense glucose or other signals within the islet microenvironment, remain undetermined.

Within the brain, evidence suggests that neurons, astrocytes and other glial cell types play a role in glucose sensing (see previous publication [32]), although neurons have received the most attention. Glucose-sensing neurons (GSNs) are subdivided into either glucose-excited (GE) or glucose-inhibited (GI) subsets, which increase their firing rates when extracellular glucose concentrations increase or decrease, respectively [26]. Although GSNs express the cellular machinery (e.g. GLUT2, glucokinase [GCK] and the Kir6.2 subunit of the ATP-sensitive potassium [K_{ATP}] channel) required to respond to changes in ambient glucose levels [26], the majority reside behind the blood–brain barrier (BBB), where glucose concentrations in brain interstitial fluid (ISF) are nearly sevenfold lower and temporally decoupled from changes in circulating glucose levels [33]. Conversely, neurons in circumventricular organs (CVOs), such as the arcuate nucleus (ARC)-median eminence (ME) of the hypothalamus, or the area postrema (AP) of the hindbrain, are not protected by the BBB and, therefore, have greater inherent potential to directly sense circulating blood glucose and relay this information to glucoregulatory systems behind the BBB [34].

To better understand the physiology of brain glucose sensing, we consider how the brain detects and responds to a change of ambient temperature. For instance, during cold exposure, thermal information, detected by temperature-

Fig. 3 Model for central glucose sensing. Circulating blood glucose levels are detected in both the periphery, by sensory afferent fibres (e.g. that innervate the hepatic portal vein), and central CVOs, including the ARC-ME and the area postrema (AP). This afferent information is relayed to neural centres located behind the BBB that comprise the efferent limb of the brain's glucoregulatory system. These neurons also have the capacity to detect concentrations of glucose in brain ISF and, when activated, regulate both neuroendocrine and autonomic mechanisms through peripheral tissues, via both direct and indirect mechanisms, to regulate circulating blood glucose levels. This figure is available as part of a [downloadable slideset](#)

sensitive receptors in the skin, is transmitted via a well-mapped peripheral-to-central relay that is integrated by neurons in the hypothalamic preoptic area (POA) and transduced into adaptive responses that maintain core temperature [20]. According to this model, neurons within the POA comprise the integrative/efferent limb of the brain's thermoregulatory system and, while not involved in directly sensing ambient temperature under physiological conditions, they retain intrinsic thermal-sensing properties that enable them to respond to changes in local hypothalamic temperature. Therefore, while subsets of POA neurons have the capacity to directly sense temperature change, just as subsets of neurons behind the BBB have the capacity to sense glucose, it is unclear if changes in local brain temperature or interstitial glucose levels occur unless a challenge to homeostasis is prolonged or severe.

Instead, just as afferent input regarding external temperature is transmitted primarily by neurons innervating the skin and other peripheral tissues, we anticipate that afferent information regarding the circulating glucose level is provided by GSNs that lie outside the BBB (i.e. within CVOs and/or peripheral glucose sensors) and is subsequently transmitted to glucoregulatory circuits sheltered behind the BBB. While

these latter neurons putatively comprise the integrative/efferent limb, rather than the sensory/afferent limb of the brain's glucoregulatory system, many retain intrinsic glucose-sensing properties, such that changes of local glucose availability can activate these neurons with potent consequences for systemic glucose homeostasis [34]. For example, pharmacological glucoprivation of NTS neurons activates both ascending [35] and descending [36] circuits, with the net outcome being a potent CRR analogous to that induced by hypoglycaemia. These findings are consistent with a model in which GSNs situated behind the BBB do not function as primary sensors of the circulating glucose level but can detect and respond to changing glucose levels in brain ISF should they deviate from the normal range. Future studies are needed to identify and characterise the physiological roles played by different populations of GSNs (Fig. 3).

Implications for the pathogenesis of type 2 diabetes

Maintenance of normal glucose tolerance hinges on the capacity of the beta cell to adjust insulin secretion in response to

changes of both blood glucose concentration and insulin sensitivity [37]. During conditions of increased insulin sensitivity (e.g. cold exposure, exercise), insulin secretion must be reduced to avoid a fall in blood glucose concentration, while, conversely, during insulin-resistant conditions (e.g. pregnancy, puberty and obesity), insulin secretion must increase proportionately to maintain glucose tolerance. Failure of the beta cell to compensate for insulin resistance is a characteristic feature in individuals with type 2 diabetes and is associated with a gradual rise in the defended level of blood glucose levels [38].

As functional beta cells normally regulate neighbouring alpha cells and suppress glucagon secretion, hyperglucagonaemia, resulting from unregulated alpha cells, is also implicated in the pathogenesis of both type 1 diabetes and type 2 diabetes, as the beta cells are destroyed or fail, respectively [39]. To further support this notion, it has been reported that: (1) the effect of hyperglycaemia to suppress glucagon secretion is blunted in diabetes; (2) glucagon receptor-null mice are protected from streptozotocin-induced diabetes; and (3) suppression of glucagon secretion has been suggested as a strategy for treatment of type 2 diabetes [39, 40].

Together, these observations suggest that the capacity of the beta cell to adapt to conditions of insulin resistance constitutes a primary defence against type 2 diabetes [38]. Consistent with this, genome-wide association studies (GWAS) indicate that the majority of gene variants associated with type 2 diabetes regulate beta cell function or mass [38]. Since the mechanism that mediates the crosstalk between insulin-sensitive tissues and the islet is yet to be identified, we consider the possibility that the brain plays a role.

Compelling evidence of a direct role for brain glucose sensing in glucose homeostasis stems from work examining the role of GLUT2, the glucose transporter utilised by glucose-sensing cells in the pancreas, liver and brain. Mice with chronic inactivation of *Glut2* (also known as *Slc2a2*) specifically in the brain (NG2KO mice) exhibit impaired cephalic and first-phase insulin secretion and impaired glucose tolerance [41], as well as reduced beta cell mass, mediated, in part, by reduced PNS activity [41]. In addition, NG2KO mice also exhibit elevated plasma glucagon levels [41]. GLUT2 neurons within the NTS are implicated in this effect, as acute activation of NTS GLUT2 neurons increases vagal nerve activity and drives glucagon secretion in vivo [36].

While GLUT2 is important for cellular glucose import, GCK activity is required for intracellular glucose metabolism and neuronal glucose sensing [42]. Indeed, GSNs are absent in mice with GCK knockdown, while, conversely, increased *Gck* expression heightens sensitivity of GSNs to ambient glucose [42]. Furthermore, brain-specific GCK inhibition in mice impairs glucose tolerance and blunts GSIS [43], while increasing *Gck* expression in the ARC has the opposite effect [44]. Combined with additional evidence that ARC *Gck*-expressing

neurons are a source of polysynaptic innervation of the pancreas [9], these findings suggest that hypothalamic GSNs have the capacity to regulate islet secretion via neurocircuits modulating ANS flow, raising the question of whether dysfunctional brain glucose sensing impairs glucose homeostasis. The relevance of these findings to human type 2 diabetes is bolstered by evidence that both *GCK* and *GLUT2* (also known as *SLC2A2*) are expressed in the human brain [45], and that *GLUT2/GCK* gene variants are associated with impaired fasting glucose and increased risk of type 2 diabetes [46, 47]. Indeed, loss of function *GCK* mutations produce maturity-onset diabetes of youth (MODY) in humans [47]. However, additional studies are required to determine the extent to which glucose homeostasis is perturbed by the impact of *GLUT2/GCK* variants on the function of pancreatic islets vs GSNs.

If impaired glucose sensing in the brain contributes to elevated blood glucose levels in type 2 diabetes, can the brain be targeted to treat this disease? In support of this, intracerebroventricular (i.c.v.) administration of leptin in both genetic (i.e. *ob/ob*) and acquired (i.e. severe insulin-deficient type 1 diabetes) rodent models of leptin-deficiency ameliorates hyperglycaemia suggesting that deficient leptin signalling in the brain contributes to the diabetic phenotype. This effect occurs independently of changes in energy balance and is associated with normalisation of elevated plasma glucagon and corticosterone levels. In addition, i.c.v. leptin administration modulates GSIS via the SNS in rodent models of type 2 diabetes [48] and improves glucose homeostasis in high-fat-diet-fed rats [49], while systemic administration of leptin to a polygenic model of type 2 diabetes normalises fasting plasma glucose levels in association with decreased glucagon concentrations and elevated pancreatic insulin content [50]. However, evidence suggests that the degree of hyperleptinaemia necessary to achieve adequate brain signalling can exert effects that paradoxically undermine leptin's central action [51]. This may explain why subcutaneous metreleptin therapy was not efficacious in improving blood glucose levels in patients with type 1 diabetes, although it did reduce daily insulin requirements [52]. Additional work is warranted to investigate whether central leptin administration can ameliorate hyperglycaemia without the need for insulin in patients with type 2 diabetes.

The capacity of the brain to normalise hyperglycaemia in diabetes is also clear from studies examining the glucose-lowering actions of fibroblast growth factor (FGF) peptides. Recent work demonstrates that a single i.c.v. injection of FGF1 is sufficient to induce sustained diabetes remission across several rodent models of type 2 diabetes [53]. This effect involves FGF1 signalling in the ARC-ME [54] and is mediated, in part, by preservation of beta cell mass and function, thus delaying the progressive decline of basal insulin levels that parallels hyperglycaemia in controls [55]. Importantly, rather than simply lowering blood glucose levels,

FGF1 appears to act in the brain to lower the defended level of blood glucose, as i.c.v. FGF1 has no effect on blood glucose levels in nondiabetic rodents [53]. This observation suggests that FGF1 resets the glycaemic set-point to normal, without increasing the risk of iatrogenic hypoglycaemia, a critical factor limiting tight glycaemic control in people with diabetes. Although the mechanisms underlying the effects of FGF1 remain uncertain, these findings raise the possibility that therapeutic interventions that target both the brain and islet may be more effective for the treatment of diabetes than current treatments targeting the islet alone, which, though effective acutely, fail to sustainably preserve beta cell function over the long term in either adults or children with type 2 diabetes [56].

Conclusions

In conclusion, cooperation between the brain and islet is fundamental to glucose homeostasis and involves both neuroendocrine and autonomic mechanisms. While the brain contains GSNs and has the capacity to sense circulating glucose levels, it also receives glycaemic information from peripheral glucose sensors. The next key steps in the field are to: (1) distinguish the neuronal subsets that comprise the afferent vs efferent limb of the brain's glucoregulatory system; and (2) examine whether defective activity in either the afferent or efferent limb occurs in human type 2 diabetes. Recent advances in neuroscience technology (including cell-type-specific viral tract tracing, chemo- and optogenetics to selectively activate or inhibit neuronal populations, and in vivo fibre photometry techniques for monitoring the activity of discrete neuronal subsets in conscious, free-living mice) create numerous exciting avenues and opportunities to advance this field.

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