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Orphaned No More? Glucose-Sensing Hypothalamic Neurons Control Insulin Secretion

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Well before Dr. Minkowski discovered the role of the pancreas in regulating blood glucose (1889), Dr. Bernard had discovered the role of the brain (specifically the base of the fourth ventricle) in regulating blood glucose (1849). Bernard's basic observation has been replicated by many interventions involving pharmacological manipulations directed toward the brain stem (1). Nevertheless, the overt production of diabetes by the removal of the pancreas and the eventual discovery of the determinative role of insulin secreted by pancreatic islets in regulating blood glucose by Drs. Banting and Best (1922) led to an overwhelming emphasis in studying islet function (and later insulin sensitivity) in the study of blood glucose regulation.

At about the same time, the function of the hypothalamus began to be studied extensively because of early evidence that damage to the hypothalamus in humans produced a variety of neuroendocrine disturbances, including obesity (Erdheim 1904). However the relative importance of the hypothalamus versus the pituitary in these systemic pathologies continued to be controversial until the classic study by Hetherington and Ransom (2) reported that specific lesions in the ventromedial nucleus (VMN) cause robust obesity in rats, an extremely robust effect replicated in many species, including humans. Subsequent extensions of these studies demonstrated that lesions of an area slightly lateral to the VMN (lateral hypothalamic area [LHA]) produced the opposite effect: starvation. Furthermore, lesions in the paraventricular nucleus (PVN) also produce obesity, although they do not prevent feeding induced by hypoglycemia or 2-deoxy-D-glucose (2-DG) (3).

As early as 1916, Carlson proposed that glucose controlled satiety, but his proposed mechanisms involving stomach contractions as hunger signals were eventually largely discarded. However, in 1953 Mayer (4) revised the so-called glucostat hypothesis, which stated that blood glucose was a key satiety signal that acted on hypothalamic glucose-sensing neurons and it was damage to these neurons that mediated obesity after VMN lesions. A major rationale for this hypothesis was that peripheral injections of gold thioglucose produced obesity and lesions apparently specific to the VMN and, interestingly, to the nucleus tractus solitarius (NTS) of the brain stem, lesions completely dependent on the glucose moiety. Motivated in part by these studies, in 1969 Oomura et al. (5) reported that activity of different neurons in the VMN and LHA could be either excited or inhibited by glucose.

Nevertheless, the glucostat hypothesis was gradually marginalized, especially after the Freidman laboratory discovered leptin and that the signaling form of the leptin receptor is largely confined to hypothalamic areas that regulate energy balance (6,7). However this marginalization left glucose-sensing neurons orphaned, in search of function(s).

Addressing this issue, in 1981 Ritter et al. (8) reported that infusion of the glucose metabolism inhibitor 5-thioglucose, apparently confined to the caudal brain stem, produced hyperglycemia as well as feeding. Furthermore, the Sherwin laboratory reported that the glucose metabolism inhibitor 2-deoxyglucose, confined to the VMN, also produced hyperglycemia and associated counterregulatory responses (9), whereas infusion of glucose into the VMN prevented counterregulatory responses (10). These studies have been extensively corroborated, leading to a broad consensus that glucose-sensing neurons in the VMN and brain stem (almost certainly including the NTS) play a key role in glucose regulation. Subsequent studies supported that in at least some neurons glucose either excites (11) or inhibits (12) glucose-sensing neurons via the putative glucose-sensing enzyme, the pancreatic form of glucokinase (pGK).

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Nevertheless, the mechanisms by which brain glucose-sensing neurons regulate glucose homeostasis have remained unclear. This question is robustly addressed by the study by Rosario et al. (13) in this issue of *Diabetes*. Using elegant improved retrograde pseudorabies viral (PRV) techniques, these investigators traced the connectivity from the brain to the pancreas to β-cells, using an inducible mouse insulin promoter Cre-recombinase construct. Taking advantage of the fact that neurons more directly connected to the β-cells are labeled first, a time course study convincingly demonstrated the order in which the neurons connected: the (presumably afferent) pathway begins in the hypothalamus (labeled last, the LHA, arcuate nucleus [ARC], and VMN, through the PVN), through the periaqueductal gray (PAG) (labeled second), through the brain stem (NTS/dorsal motor nucleus of the vagus (DMX), labeled first), then through autonomic afferents to β-cells (see Fig. 4*C* in ref. 13) (Table 1). Of particular interest, many of the projecting neurons from the ARC, VMN, and LHA coexpressed with pGK, and a significant subset of these neurons also expressed c-fos after intraperitoneal glucose injection. These results convincingly suggest a modulatory role for hypothalamic neurons to regulate β-cell function via this pathway.

To address the functional significance of this pathway, Rosario et al. (13) assessed the effect of overexpressing hexokinase I (HK1) in hypothalamic neurons on pancreatic function. A similar manipulation in β-cells basically mimics the effects of glucose, enhancing basal insulin secretion but not glucose-stimulated insulin secretion, although overexpression of HK1 enhanced insulin secretion relative to controls even in the stimulated state (14). If hypothalamic neurons behaved similarly, the expectation would be that overexpression of hypothalamic HK1 would mimic glucose signaling. As overexpression of HK1, at least in the ARC and VMN, reduced insulin secretion rather than enhanced it, the most logical conclusion is that the dominant effect of HK1 in the these nuclei was in glucose-inhibited neurons, analogous perhaps to glucagon expression in α-cells. Inhibition of VMN neurons also appears to be mediated by pancreatic-like mechanisms, including a role for pGK and glycolysis (12). These results are supported by more specific activation of pGK-expressing neurons in the VMN that also reduced insulin secretion, whereas specific inhibition of these neurons stimulated insulin secretion (15). These glucose-inhibited VMN neurons likely mediate counterregulatory responses as they are activated by 2-DG (12), and lesions of the VMN block counterregulatory responses to hypoglycemia (16).

As with all good studies, the study by Rosario et al. (13) should stimulate many further studies. For example, it will be of great interest to assess which subset of hypothalamic neurons mediates the effects of HK1 on insulin secretion. NPY/AgRP neurons are activated by 2-DG (17) and inhibited by glucose via glycolysis (18), so these neurons would plausibly mediate effects of HK1 in the ARC on pancreatic function. Analyses of other hypothalamic neurons would be similarly compelling.

Table 1—Order of connectivity from the brain region indicated to pancreatic islets, from first to last, as indicated by viral tracing in Rosario et al. (13)

Order of connectivity	Metabolic phenotype
1. NTS/DMX	GTG lesion POMC expression Activated by glucopenia Lesions produce mild hyperphagia
2. PAG	Little if any
3. PVN	Lesion produces hyperphagia and obesity Lesion-induced obesity blocked by pair-feeding Lesion causes increased blood glucose and insulin Activated by hypoglycemia Low expression of GK
3. LHA	Lesions produce starvation and impaired response to glucopenia Predominantly glucose inhibited Activated by hypoglycemia GK overlaps with projections to pancreas Enhanced hexokinase decreases glucose, no change in insulin
4. ARC	Neonatal MSG lesions produce modest obesity Adult lesions (AgRP/NPY neurons) by diphtheria toxin produce starvation AgRP/NPY neurons inhibited by glucose AgRP/NPY neurons activated by hypoglycemia and fasting POMC neurons Activated by glucose, inhibited by fasting Enhanced POMC expression reverses diabetes GK overlaps with projections to pancreas Enhanced hexokinase increases glucose, decreases insulin
4. VMN	Lesion produces hyperphagia, reduced metabolism, and obesity Lesion-induced obesity not prevented by pair-feeding Lesion produces hyperinsulinemia, not hyperglycemia GTG lesion overlaps with POMC neurons Genetic ablation of several VMH genes (Sf1, BDNF) produces obesity Lesion blocks counterregulatory response to hypoglycemia Local glucopenia produces counterregulatory responses Local infusion of glucose prevents counterregulatory responses GK overlaps with projections to pancreas Enhanced hexokinase decreases insulin, no change in glucose

Phenotypes as derived by a variety of studies, including the study by Rosario et al. (13). GTG, gold thioglucose; MSG, monosodium glutamate; POMC, proopiomelanocortin.

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