Interactions between the central nervous system and pancreatic islet secretions: a historical perspective

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Begg DP, Woods SC. Interactions between the central nervous system and pancreatic islet secretions: a historical perspective. *Adv Physiol Educ* 37: 53–60, 2013; doi:10.1152/advan.00167.2012.—The endocrine pancreas is richly innervated with sympathetic and parasympathetic projections from the brain. In the mid-20th century, it was established that α-adrenergic activation inhibits, whereas cholinergic stimulation promotes, insulin secretion; this demonstrated the importance of the sympathetic and parasympathetic systems in pancreatic endocrine function. It was later established that insulin injected peripherally could act within the brain, leading to the discovery of insulin and insulin receptors within the brain and the receptor-mediated transport of insulin into the central nervous system from endothelial cells. The insulin receptor within the central nervous system is widely distributed, reflecting insulin's diverse range of actions, including acting as an adiposity signal to reduce food intake and increase energy expenditure, regulation of systemic glucose responses, altering sympathetic activity, and involvement in cognitive function. As observed with central insulin administration, the pancreatic hormones glucagon, somatostatin, pancreatic polypeptide, and amylin can each also reduce food intake. Pancreatic and also gut hormones are released cephalically, in what is an important mechanism to prepare the body for a meal and prevent excessive postprandial hyperglycemia.

cephalic response; conditioning; insulin; islets; pancreatic innervation

THIS ARTICLE is a summary of a presentation given at the meeting of the American Physiological Society in San Diego, CA, in 2012. It was part of a symposium/refresher course on complications of diabetes mellitus, and the specific topic was interactions between the brain and endocrine pancreas.

The pancreatic islets of Langerhans were first identified in the late 19th century (75). As described by Langerhans, the islets are richly innervated (75), and it is now recognized that this innervation includes sympathetic, parasympathetic, and sensory nerves (1). Despite accounting for only 1–2% of the pancreatic mass, islets are highly vascularized, receiving 10–20% of pancreatic blood flow (14, 67, 79). Although most cells found in islets are insulin- and amylin-secreting β-cells (61), there are also significant numbers of α-cells (glucagon) and δ-cells (somatostatin) and small numbers of F cells (pancreatic polypeptide) and ε-cells (ghrelin) (43, 61, 71, 74, 136). In this review, after a brief description of endocrine secretions of the islets, we describe the interactions between the central nervous system (CNS) and pancreatic islets, focusing on cephalic responses, conditioned hypoglycemia, insulin secretion, and the roles of insulin in the CNS. While all pancreatic hormones are discussed, the primary focus throughout this review is upon insulin.

The Endocrine Pancreas and Insulin

Of the many hormones produced in and excreted by cells in the islets, the first identified and best known is insulin. Two decades after the discovery of the islets, Minkowski and von Mering (133) reported that removal of the pancreas produced a diabetic phenotype, and it was subsequently reported that aqueous pancreatic extracts produced moderate reductions in glycosuria (92). The isolation of insulin from pancreatic islets was first performed by Banting and Best (13) in 1922, and exogenous insulin soon became the only effective treatment for insulin-deficient (type 1) diabetes mellitus (123).

Insulin is a 51-amino acid peptide hormone cleaved by proteases from preproinsulin and subsequently from proinsulin in the secretory vesicles of β-cells (104, 105). Insulin's best known action is its ability to reduce circulating glucose by activating glucose transporters on cell membranes, enabling the uptake of glucose into most peripheral tissues, where the glucose is used as a fuel or stored as glycogen (72). Insulin is secreted from β-cells in response to increases of local glucose levels, and both its basal and stimulated levels are directly proportional to body fat, with leaner individuals having reduced insulin secretion relative to individuals with greater adiposity (9, 10, 115, 142).

Shortly after the discovery of insulin, Kimball and Murlin (70) determined that extracts of pancreatic tissue also contain a substance that produces a hyperglycemic response, and this hormone was named glucagon. In the late 1960s and early 1970s, pancreatic polypeptide and somatostatin were described and identified in the pancreas (25, 71). Pancreatic polypeptide is made in and secreted from F cells, and somatostatin is made in and secreted from D cells. Amylin was identified as a pancreatic hormone cosecreted with insulin in the late 1980s (43, 136), and, more recently, ghrelin-secreting epsilon cells have been described in pancreatic islets (100).

Insulin and the CNS

Despite Langerhans' early work describing the rich innervation of the islets, there was little early interest in a possible influence of the CNS over the secretion of insulin. Indeed, the *Endocrine Pancreas* volume of the series on endocrinology published by the American Physiological Society in 1972 contained no mention of a possible CNS influence (114). The presumption that there was unlikely to be a significant brain-islet interaction was primarily based on two premises. First, the brain, unlike most other tissues, does not require insulin to take up glucose (63), i.e., the brain was considered to be insulin independent. Second, insulin was considered too large a mol-

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ecule to cross the blood-brain barrier (BBB) (91), deeming it unlikely that the peptide could even enter the brain. The logic was that since insulin was not believed to act on CNS cells and that, in any case, it could not reach CNS cells, there could be no meaningful brain-islet-insulin axis. As a consequence, the prevailing theory leading up to the publication of the volume on the pancreatic islets in 1972 was that insulin was a key negative feedback molecule to prevent hyperglycemia; as glucose levels reaching the islet increased, β-cells responded by secreting insulin and consequently preventing further glucose increases and ultimately returning glucose to basal values (114). However, this model had no explanation as to why there is such a rich innervation of the islets with no known functional significance (151).

At the same time, evidence consistent with a functional role of the nervous system in the pancreatic islets was accumulating. Porte demonstrated that local α-adrenergic stimulation inhibits secretion (96), whereas β-adrenergic agonists stimulate insulin secretion (94, 95), strongly suggesting that insulin secretion is under sympathetic control. Campfield and colleagues (29, 31) subsequently observed that insulin secretion is stimulated by acetylcholine, indicating parasympathetic involvement. Cholinergic stimulation of insulin release was, in turn, decreased in the presence of epinephrine (30, 32), implicating a complex neural control involving both parasympathetic and sympathetic control over β-cells. These early studies paved the way to the currently supported view that the autonomic nervous system can have a powerful influence over the secretion of insulin and indeed all pancreatic hormones.

A Neural Reflex Eliciting Insulin Release

In the late 1960s and early 1970s, using a Pavlovian behavioral paradigm whereby an unconditioned stimulus is paired with a neutral stimulus over the course of several trials resulting in the neutral stimulus becoming a conditioned stimulus, one of us (S. C. Woods) found that rats could be conditioned to secrete insulin and become hypoglycemic (137, 139, 141, 143, 146, 147). In training sessions, experimental rats received a subcutaneous injection of insulin (the unconditioned stimulus) in the presence of a novel stimulus (usually an odor, the conditioned stimulus). Blood glucose decreased in response to insulin (the unconditioned response), whereas it increased slightly in control rats administered a placebo (saline) injection subcutaneously in association with the odor. After several such conditioning trials, a test day occurred in which all rats re-

ceived only saline injections plus the odor, and those that been previously received insulin became hypoglycemic (Fig. 1). Subsequent experiments revealed that the conditioned hypoglycemia required an intact vagus nerve (139), could be blocked with the anti-cholinergic drug atropine (155), and was secondary to conditioned secretion of pancreatic insulin (141).

There are several reviews of these early experiments on conditioned hypoglycemia (81, 138, 144), and it is important to note that the findings generated more questions than they answered. For example, what is the neural circuit that normally leads from the CNS to parasympathetic secretion of pancreatic insulin? Does subcutaneously administered insulin somehow (counterintuitively) trigger a reflex leading to endogenous insulin secretion? Does some of the administered insulin actually get into the brain on conditioning trials? If so, does this imply that brain cells can actually detect and respond to changes of local insulin?

While the phenomenon of conditioned hypoglycemia has been observed in numerous laboratories (e.g., Refs. 5, 45, 52, 53, 84, 120, and 146) and species (for reviews, see Refs. 4, 77, and 144), including humans (48, 118), it should be noted that these early conditioning experiments were not without controversy. Using a purportedly identical protocol, Siegel (110, 111) observed that rats developed a conditioned hyperglycemic response, as opposed to a hypoglycemic response. This makes teleological sense in that when a signal (the odor) occurs that has always previously predicted that the animal was about to receive an injection of exogenous insulin; if the rat learns anything, it should learn to increase its blood glucose to mitigate the inevitable hypoglycemia, i.e., the rat should learn to counter the upcoming reduction of blood glucose. In fact, when smaller, closer-to-physiological doses of insulin are administered on the training days, rats do just that. They develop conditioned hyperglycemia (54, 154).

On the other hand, there was evidence supporting the counterintuitive position. Peripheral administration of glucose had been previously used as the unconditioned stimulus in some classical conditioning experiments, and a slight conditioned hypoglycemia was developed relative to controls (90, 102). The glucose administration on conditioning trials presumably elicited endogenous insulin secretion, and subsequent experiments later determined that a change of blood glucose on conditioning trials is not a crucial component of the conditioning process; rather, during conditioning trials, the important factor for the development of a conditioned hypoglycemic

Fig. 1. A: the conditioned hypoglycemic response. Saline injection in animals previously conditioned with a series of insulin injections produced a transient hypoglycemia relative to control animals injected with saline on the conditioning trials. B: conditioned insulin secretion. Animals conditioned with multiple injections increasing plasma and brain insulin have a fourfold increase of plasma insulin on a saline injection test trial. Graphs were redrawn from Woods et al. (147) (A) and from Woods et al. (141) (B).
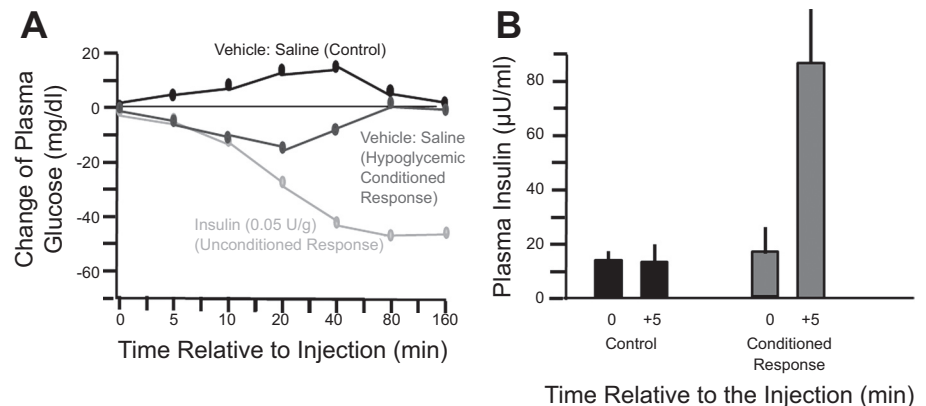
response is the increase of insulin (137). Overall, the data suggest that an increase of insulin (either exogenous or endogenously produced) rather than a decrease of blood glucose is sufficient to produce conditioned hypoglycemia (and concomitant conditioned insulin secretion).

The implication, as well as the important point, from all of these studies reporting conditioned insulin secretion and hypoglycemia was that a sudden increase of insulin triggered a reflex reaction in which neurally elicited pancreatic insulin secretion occurred. Such a reflex had in fact been reported in dogs, but it only occurred when the administered insulin actually gained direct access to the brain (38, 124, 125). Only later was it recognized that when large doses of insulin are administered systemically, some insulin actually penetrates the BBB, i.e., after an intravenous administration of exogenous insulin, the level of insulin in the blood rises rapidly and glucose in both plasma and the cerebrospinal fluid (CSF) decreases (152). A sudden increase of insulin in the CSF, in and of itself, elicits a transient, neurally elicited increase of pancreatic insulin secretion (36, 148). In summary, when sufficient exogenous insulin is administered that some of it enters the CNS, the insulin acts on brain circuits to trigger a vagally mediated parasympathetic increase of insulin secretion from the islets, and this reflexive response can be conditioned.

Subsequent experiments found insulin receptors on neurons and other brain cells in many areas of the CNS. In fact, by the mid 1980s, insulin receptors had been found to be abundant and widely distributed throughout both the developing and adult CNS (44, 62). The distributions of insulin and its receptor in the brain have been extensively characterized by immunohistochemistry (16), autoradiography (130, 131), and in situ hybridization of insulin receptor mRNA (83). High levels of insulin receptors are found in the choroid plexus, olfactory bulbs, and arcuate nucleus of the hypothalamus. The insulin receptor is also abundant in many other regions, including the cerebellum, cerebral cortex, hippocampus, and several hypothalamic nuclei (15, 16, 82, 83, 130, 131).

Insulin and the BBB

Once insulin had been identified within the brain and CSF, it was hypothesized that insulin enters the CSF from plasma via the choroid plexus, subsequently passing through the ependymal lining and acting at insulin receptors on nearby neurons

(149). This seemed a reasonable explanation given the dense insulin binding sites in the choroid plexus and the observation that numerous nuclei in the ventral hypothalamus are close to the wall of the CSF-containing third ventricle and have a high density of insulin receptors (15, 59, 60, 130, 132, 157). However, more mechanistic experiments assessing the dynamics of insulin uptake into the CSF and the brain later determined that rather than entering the CNS via the choroid plexus and CSF, insulin is transported into the brain via an insulin receptor-mediated, saturable pathway in brain capillary endothelial cells (see Fig. 2) (17). Thus, the normal movement of insulin to the CNS fits a three-compartment model (plasma to brain interstitial fluid to CSF) (11, 12, 80, 106).

Cephalic Responses

Neurally elicited insulin secretion normally occurs at mealtime, and this natural reflex is easily conditionable to cues that reliably predict meal onset (155). These cues include food-predicting odors or the time of day that meals normally occur. These meal-related responses are called "cephalic" because insulin is not secreted in response to a local change of glucose or other nutrient in the pancreas but rather to a neural signal emanating from the brain. The importance of cephalic insulin to normal physiology is demonstrated by the observation that if cephalic insulin is blocked or prevented, animals appear diabetic when they eat, experiencing abnormally high elevations of blood glucose. The secretion of a small amount of insulin as the meal begins thus enables individuals to consume large caloric loads without becoming hyperglycemic, and in its absence, only small meals are generally consumed (140). There are many reviews of cephalic insulin and its importance (1, 23, 69, 99, 118, 119, 127, 128).

During meals, and especially during large meals, there are large fluxes of nutrients into and then out of the gastrointestinal system, into and out of the blood, and ultimately into tissues for immediate use or storage. Cephalic responses enable the body to prepare for these processes in advance and consequently to allow them to proceed smoothly and with the least metabolic perturbation (153). Importantly, many processes other than insulin secretion are involved. Before anticipated meals, there is also evidence for the cephalic secretion of other islet hormones, including pancreatic polypeptide (126), amylin (76), and glucagon (107). Gastrointestinal hormones are also se-
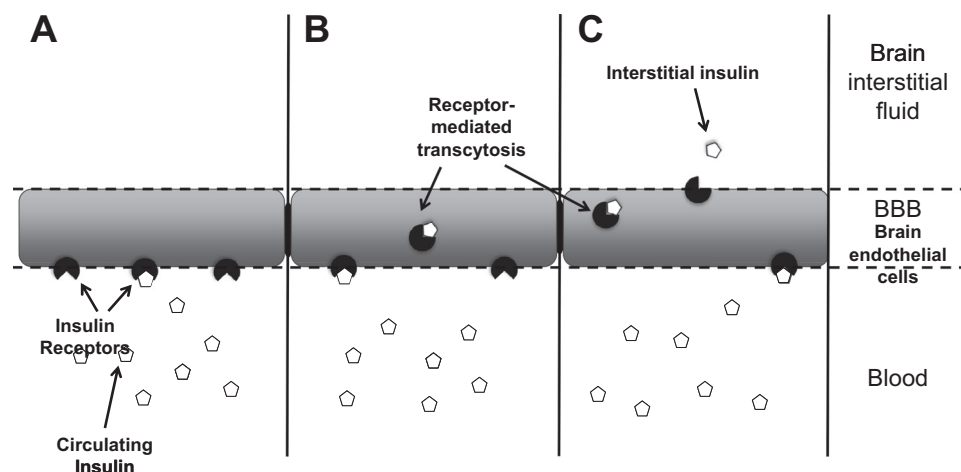
Fig. 2. Transport of circulating insulin from the blood into the central nervous system. *A*: circulating insulin, which has been released into the blood from β-cells in the pancreas, binds to receptors on endothelial cells of the blood-brain barrier (BBB). *B*: insulin is transported through the endothelial cells via receptor-mediated transcytosis. *C*: insulin is released into the brain interstitial fluid, where it can then act on neuronal insulin receptors.

creted cephalically before the actual onset of eating, including ghrelin (46, 122), cholecystokinin (50), and glucagon-like peptide 1 (129). The important point is that the CNS initiates and coordinates a complex mix of premeal events that help the individual adequately prepare for and deal with the caloric load (see Fig. 3).

In summary, contrary to earlier beliefs, insulin is now recognized to cross from the periphery to the brain via an insulin receptor-mediated transport process through brain capillary endothelial cells. Within the brain, insulin stimulates insulin receptors, which are abundantly located in many areas of the CNS. The widespread distribution of insulin and its receptors within the CNS suggests that there are diverse actions of insulin in the brain, likely influencing many behaviors in addition to those directly related to energy homeostasis.

The Functions of Central Insulin

Once within the CNS, insulin has a diverse range of actions. Central insulin alters food intake and energy expenditure (19, 106, 108) and systemic glucose responses to meals and fluctuations of plasma glucose (51, 78, 113). Insulin in the brain is also involved in reproductive function/development (28), hedonic responses (49), and sympathetic activity (101, 134). A particularly exciting topic at the present time concerns the ability of insulin, acting on receptors in the hippocampus and elsewhere in the CNS, to improve cognitive function (37, 116, 117). Most of these aspects of CNS insulin action are beyond the scope of this review.

Insulin and the Regulation of Body Adiposity

Soon after a specific insulin assay became available, it was determined that both basal insulin and insulin secreted in response to a glucose load are directly correlated with body weight, with insulin being elevated in individuals with greater adiposity (9, 10). Because insulin levels in the blood increase when humans (112) or animals (22) overeat and become fat, it was proposed that because insulin is able to enter the CNS, it may act as a negative feedback controller of adiposity (150).

The concept was simple, i.e., if an individual overeats and gains weight, the elevated blood and consequently brain insulin would provide a signal triggering corrective responses to eat less and return weight to its former level. Conversely, if an individual fasts or diets, the reduced brain insulin signaling would trigger a reflex to eat more and regain weight. To test this hypothesis, Woods et al. (145) infused insulin into the CSF of baboons and observed a dose-dependent decrease of food intake and body weight over a several-week period, and these effects were reversed after the cessation of the infusions. Many studies have confirmed the effects of central insulin administration to reduce food intake and body weight, most commonly in rodents (2, 3, 64, 85). Importantly, the anorexia and weight loss are not secondary to aversion (35) or to decreased mobility of animals after insulin infusion (33). Consistent with these data, when the insulin signal in the CNS is reduced, by local administration of antibodies to insulin, by genetically knocking out insulin receptors on all CNS neurons, or by interfering with the insulin receptor mRNA message locally in the hypothalamus, animals have increased food intake and body weight (28, 56, 85, 121).

Central insulin-induced hypophagia has been observed in many species, including rats (2, 3, 21, 26, 42, 64, 93), baboons (145), mice (27, 66), chicks (109), and sheep (55). Importantly, humans also have reduced food intake after central insulin administration. With the use of an intranasal insulin administration technique to increase CSF insulin levels, a dose-dependent reduction of food intake was observed in human volunteers (58), and daily treatment resulted in significant weight loss after 6 wk (58). Followup experiments found that men were more sensitive to the anorectic effects of insulin than women (20). Similarly, in the rat, males are relatively more sensitive to the anorectic effects of central insulin, whereas females are relatively more sensitive to the anorectic effect of central leptin (40, 42). Consistent with this, females have higher circulating leptin and lower circulating insulin than comparably obese males (40). This appears to be related to fat distribution, as females generally have more subcutaneous fat,

Fig. 3. Meal parameters and signals in anticipation of, during, and after a meal. Cephalically induced neuropeptide and hormone release occurs to prepare the body for the incoming nutrients and prevent potentially damaging hyperglycemia. During a meal, numerous factors may act as satiation signals, and when the meal is completed, leading to the postprandial period, many of the same signals help complete the digestion process. NPY, neuropeptide Y; GLP, glucagon-like peptide; CCK, cholecystokinin; PYY, peptide YY.
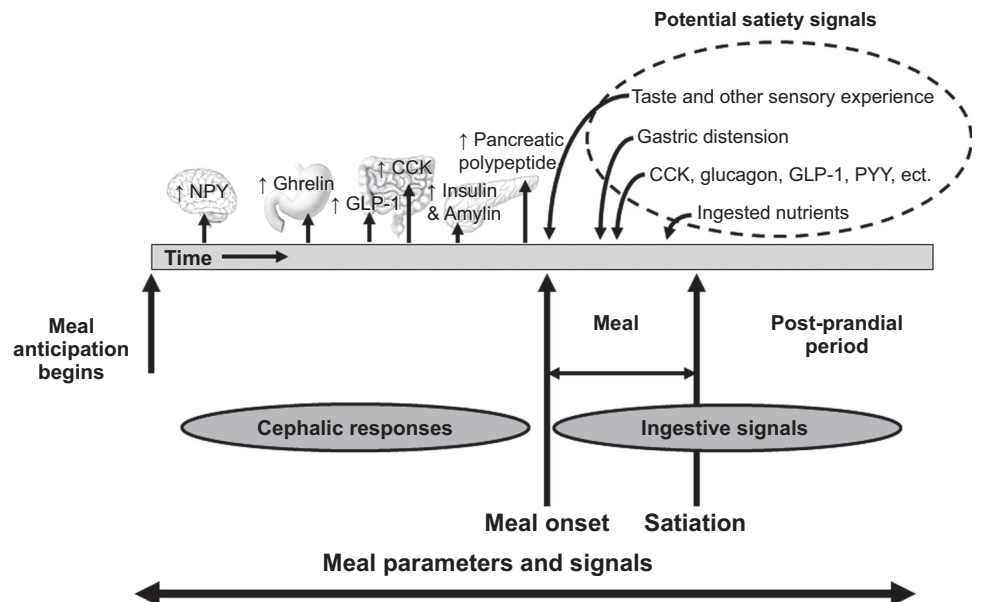
whereas males tend to have a higher proportion of visceral fat (24, 88), and leptin is secreted disproportionately more from subcutaneous fat (47, 86), whereas insulin secretion is more proportional to visceral fat (98). Sex differences observed in hypophagia after the central administration of insulin are due to the actions of estrogen in the hypothalamus, i.e., estrogen inhibits insulin effects on food intake while potentiating the effects of leptin (87). It should be noted that central insulin administration does not necessarily lead to a negative energy balance; rather, the magnitude of the brain insulin signal reduces the amount of body adiposity that is homeostatically maintained (i.e., central insulin infusion will not obligatorily reduce food intake) (33). These examples point to some of the complexities involved in the "regulation" of food intake and energy balance.

Central insulin administration is ineffective at reducing food intake in obese Zucker rats lacking functional leptin receptors (64), and the response to central insulin infusion is also reduced in animals made obese using diet-induced obesity models (7, 34, 39, 41) as well as in obese humans (57). This indicates that obesity results in insulin resistance in the CNS as well as in peripheral tissues. The transport of insulin through the BBB is also compromised in diet-induced obesity (18, 65), and it is possible that this effect is secondary to the leptin resistance that occurs with weight gain (73), given that there is some evidence indicating that the hypophagic effects of insulin require leptin functioning (64, 156). When insulin and leptin are both administered centrally, most doses elicit additive leptin-insulin hypophagic effects. However, at some doses, the reduction of food intake is significantly less than the sum of the individual effects (3). The interactions between insulin and leptin resistance in obesity remain an important area for future research, and a key question that remains is whether endogenous insulin has the same hypophagic action as exogenous insulin.

Other Pancreatic Hormones and the CNS

The hormones produced in the pancreas are all capable of being neurally stimulated, with insulin, amylin, glucagon, and pancreatic polypeptide all released during cholinergic stimulation (29, 68, 89), whereas somatostatin secretion is controlled adrenergically (103). Although they have different and sometimes opposite effects on blood glucose and other parameters, each of the islet hormones reduces food intake. Insulin, pancreatic polypeptide, and somatostatin all act at the hypothalamus to decrease food intake (6, 8, 145), whereas amylin acts at the area postrema in the hindbrain (97) and glucagon acts on the vagal afferent neurons (135). As stated above, pancreatic hormones are released cephalically, in what is an important mechanism for the body to prepare for a meal and prevent diabetes-like symptoms.

Summary

It is now well established that there are complex interactions between the brain and pancreatic islets. Cells within the islets are stimulated by CNS parasympathetic or sympathetic outputs to alter the secretion of peptide hormones, including insulin. Insulin acts within the brain to reduce the amount of body adiposity that is homeostatically maintained, generally reducing food intake and increasing energy expenditure. All other major islet hormones, including pancreatic polypeptide, somatostatin, amylin, and glucagon, reduce food intake, indicating mechanisms of feedback to the CNS from the endocrine pancreas.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: D.P.B. prepared figures; D.P.B. drafted manuscript; D.P.B. and S.C.W. edited and revised manuscript; D.P.B. and S.C.W. approved final version of manuscript.

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