CNS Regulation of Glucose Homeostasis

The central nervous system (CNS) has been identified as a key regulator of whole body homeostasis. In fact, from the respiratory system to the circulatory system, thermoregulation to energy expenditure, the CNS plays a fundamental role in our body’s homeostatic controls. Within the entire CNS, the hypothalamus in particular is generally accepted to mediate the day-to-day regulation of a number of factors including body temperature (42), blood pressure (44), thirst (5), and hunger (109), and is a fundamental structure for the integration of the nervous and endocrine systems. The record of CNS control of peripheral glucose homeostasis began with the finding by Claude Bernard that punctures in the floor of the fourth ventricle resulted in glucosuria (11). It was not until over a century after Bernard’s initial observation that the boom in the field occurred. Over the past decade, it has been shown that the CNS senses insulin (27, 41, 49, 56, 57, 87), namely insulin, leptin, and most recently identified, glucagon-like peptide (GLP)-1, and 2 nutrients (63, 85, 93), namely fatty acids and glucose, to regulate glucose homeostasis. Diabetes, which affects ~179 million individuals worldwide (122), is a disease characterized by a failure in glucose homeostatic control. This impairment is a result of a combination of insulin resistance and inadequate insulin secretion that results in chronic hyperglycemia (30). Since diabetes is characterized by hyperglycemia, the elucidation of defects in hypothalamic hormone and nutrient-sensing pathways that regulate glucose homeostasis will shed light on the central component that perpetuates this metabolic disease. In this review, we discuss the cellular and molecular mechanisms of CNS hormone and nutrient sensing that control glucose homeostasis.

CNS Hormone Action

Insulin

The well studied and extensive action of insulin in the periphery, from altering hepatic glucose metabolism to modifying extrahypothalamic functions, is to ensure that glucose homeostasis is maintained. In the past decade, the action of insulin has been uncovered to extend beyond the periphery, since neuron-specific insulin receptor disrupted (NIRKO) mice were found to develop mild insulin resistance and elevated plasma insulin levels in association with obesity (18). This suggested, for the first time, that neuronal insulin signaling regulates peripheral glucose homeostasis. Indeed, infusion of insulin or its mimetic into the third cerebral ventricle suppressed hepatic glucose production independent of alterations in body weight or changes in circulating levels of insulin and other glucoregulatory hormones (87). In the same study, antagonism of insulin or its downstream signaling pathway in the brain, including the insulin receptor (IR) and phosphatidylinositol-3 kinase (MAPK), another downstream branch of insulin signaling, did not affect central insulin’s potent action on glucose production (87). Consistent with these data, decreased IR expression selectively in the hypothalamus, particularly in the arcuate nucleus (ARC), elicits insulin resistance in rats (84) as similarly seen in NIRKO mice (18). Further delineating the downstream insulin signaling cascade, hypothalamic overexpression of insulin receptor substrate (IRS)-2 and protein kinase B (PKB, or Akt) via adenoviral gene therapy significantly improved the glycemic response to an insulin injection in streptozotocin (STZ)-induced diabetes (41). Collectively, these findings recognized the CNS as a site of insulin action in regulating glucose homeostasis and, more importantly, implied the criticality of an intact insulin-signaling cascade involving the binding of insulin to its receptor and the subsequent activation of IRS, PI3K, and PKB, in such regulation (FIGURE 1A). Interestingly, with both IRS-1 and -2 being the common isoforms linked to glucose homeostasis (106),...
Hormone (e.g., melanocortin) expression is highly detectable in the hypothalamus, including but not limited to the ARC, ventromedial nucleus (VMN), and paraventricular nucleus (PVN) (92). Interestingly, whereas constitutively active IRS-2 in the hypothalamus improved insulin sensitivity (41), genetic knock-out of IRS-2 in the hypothalamus and pancreatic β-cell leads to insulin resistance (66, 68), as is seen with selective brain IRS-2 knockout mice (112).

The mechanism downstream of central insulin-signaling to regulate peripheral glucose homeostasis appears to involve the activation of the ATP-sensitive potassium (K_{ATP}) channels. The glucose production-lowering effect of systemic or central insulin was established by intracerebroventricular (icv) administration of K_{ATP} channel blocker (87, 99). Furthermore, mice lacking the SUR1 subunit of the SUR1/Kir6.2 K_{ATP} channels impaired the ability of elevated insulin to suppress glucose production (99). To further extend these findings, hepatic branch vagotomy and selective vagal deafferentation indicated that the CNS-liver circuit requires efficient vagal fibers (99), likely triggering an interleukin (IL)-6/signal transducer and activator of transcription (STAT) 3 signaling cascade in the liver to lower glucose production (49). It remains to be determined how the insulin-signaling cascade (i.e., IR→IRS-2→PI3K→PKB) leads to the activation of K_{ATP} channels but the involvement of phosphatidylinositol 3,4,5-trisphosphate (PIP3) has been suggested. PIP3 directly activates K_{ATP} channels in vitro (58), and, more crucially, constitutive activation of PI3K-PIP3 signaling in pro-opiomelanocortin (POMC) neurons increases K_{ATP} channel conductance, which hyperpolarizes neurons and results in a hyperphagic phenotype (98) (FIGURE 1A).

SUR1/Kir6.2 K_{ATP} channels are characteristically found in pancreatic β-cells (2) and the CNS (32), including hypothalamic ARC neurons known to control energy and glucose homeostasis. The ARC contains an array of neuronal subtypes that are involved in energy and glucose homeostatic regulations, of which two are most extensively studied. The first are neurons that express the anorexigenic products of the peptide POMC. POMC is posttranslationally cleaved to a series of smaller peptides; of note is β-melanocyte stimulating hormone (92). Belonging that co-express Y (NPY) and a signaling cascade (109), leads to a competitive binding site at MC4R, of POMC and these orexigenic and their downstream actions in this "hypothalamic axis" have been thought to be mediated by NPY and glucose homeostasis of NPY action on the generation of pancreatic insulin and its effect on food intake (110). NPY infusion precluding food intake (109) leads to the competitive binding site at MC4R, contributing directly to the competitive binding site at MC4R, of orexigenic and their downstream actions.

As with insulin, leptin plays a critical role in regulating peripheral glucose homeostasis. In leptin or its receptor (59, 117) deficient ob/ob mice, POMC neurons are reduced and not POMC neurons (3, 24) deficient ob/ob mice, POMC neurons are reduced, which increases glucose homeostasis. Indeed, insulin’s action on glucose homeostasis is mediated by the phosphatidylinositol (3,4,5)-trisphosphate (PIP3) signaling pathway, which activates the PI3K-PIP3 signaling cascade in POMC neurons (98). This signaling cascade leads to the activation of K_{ATP} channels in POMC neurons, which hyperpolarizes neurons and results in a hyperphagic phenotype (98).

**FIGURE 1.** Hormonal action in the hypothalamic arcuate nucleus regulates hepatic glucose fluxes

A: insulin, binding to its receptor, activates IRS and PI3K. PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to generate PIP3, which subsequently activates the SUR1/Kir6.2 K_{ATP} channels to alter signaling in neurons such as the NPY/AgRP neuron. Via a melanocortin-independent pathway, which is relayed through the vagus nerve, hepatic glucose production is decreased. B: leptin, upon binding to the long form of the leptin receptor, activates two distinct pathways: 1) activation of the JAK2/STAT3 pathway and 2) activation of PI3K. Together, these signaling cascades summate to an increase in POMC neuron activity, which results in a decrease in hepatic glucose production. C: more recently, ARC GLP-1 has been shown to decrease hepatic glucose production, likely through SUR1/Kir6.2 K_{ATP} channel-dependent mechanisms in the POMC neurons.
and activator of STAT3. The development of leptin in the liver remains to be elucidated (112). Belonging to the second subtype are neurons that co-express orexigenic peptides neuropeptide Y (NPY) and agouti-related peptide (AgRP). The activation of these orexigenic neurons, in addition to stimulating feeding by increasing NPY/AgRP signaling (106), leads to a twofold inhibition of anorexigenic signaling: directly synapsing with POMC neurons or competitive binding of AgRP to the α-MSH binding site at MC4R, collectively resulting in the antagonism of POMC's anorexigenic effects. The interplay between these orexigenic and anorexigenic neuronal subsets and their downstream effector signaling form the melanocortin signaling system; it is the activation of this "hypothalamic melanocortin tone" (25) that is thought to be instrumental in the regulation of energy and glucose homeostasis. Indeed, direct activation of the central melanocortin system by central administration of a melanocortin agonist improves peripheral glucose homeostasis (36, 86). Oppositely, icv administration of NPY or melanocortin receptor antagonist causes insulin resistance independent of changes in food intake (1, 70, 117). More importantly, icv NPY infusion precludes the inhibition of glucose production elicited by circulating insulin, suggesting that the downregulation of NPY release is likely a prerequisite for insulin's ability to suppress hepatic glucose production (117). Moreover, it was elegantly shown with the use of a saline perfusate and specific neuronal populations that only AgRP-IR knockout mice, and not POMC-IR knockout mice, failed to suppress hepatic glucose production in response to elevated circulating insulin and had reduced insulin-stimulated hepatic IL-6 expression independent of changes in energy homeostasis (39). Indeed, icv infusion of a potent MC3/4R antagonist did not alter the effect of circulating insulin to inhibit hepatic glucose production (87). Together, these data suggest that insulin operates on a melanocortin-independent pathway, signaling through NPY/AgRP and not POMC, to regulate hepatic glucose production (FIGURE 1A).

Leptin

As with insulin, the discovery of leptin (129) was indeed another milestone in obesity and diabetes research. It was well documented that this 167-amino acid hormone, secreted by the adipose tissue, holds a critical role in the regulation of energy and glucose homeostasis. In both rodents and humans, deficiency in leptin or its functional receptors leads to profound obesity, insulin resistance and other endocrine deregulations (3, 24, 39). Leptin replacement in both leptin-deficient ob/ob mice and humans markedly induced adipose tissue-specific weight loss (37, 45). Although a concomitant improvement in glucose homeostasis was initially attributed as secondary to reduced adiposity and feeding (20, 45, 57), later observations strongly suggest that leptin, just as insulin, can also regulate glucose homeostasis independent of its effects on weight loss. Chronic increases in plasma leptin, independent of changes in weight, enhances both hepatic and extrahepatic insulin action under pancreatic clamp settings as well as reverses insulin resistance and improves glucose homeostasis in lipodystrophic rodents (7, 33, 111). Furthermore, leptin-treated ob/ob mice had a 40% reduction in glucose and insulin levels compared with pair-fed ob/ob mice (108).

"The metabolism of different nutrients in the hypothalamus, particularly that of glucose and fatty acids, serves roles of polarizing importance with respect to fueling local energy supply for the brain."
Traditionally, this gut hormone is thought to regulate and discrete populations of neurons (52).

Glucagon-like peptide 1 (GLP-1) (31). GLP-1 is a potent postprandial secretion of incretin hormones such as published that this "incretin effect" is mediated by the derived peptide hormones (72). In fact, it is now estab-

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on the β-cells, with fat intake (115). These findings suggest that the brain is programmed for an “in)elegant” response to hypoglycemia (115).

Indeed, infusing an inhibitor of monocarboxylate transporters (which lactate transport is dependent on) into the caudal fourth ventricle of rodents resulted in increased blood glucose levels (94). Conversely, an increase in caudal hindbrain lactate worsened insulin-induced peripheral hyperglycemia (94).

An acute elevation in circulating glucose is known to markedly suppress liver glucose production (75, 105, 114). When plasma glucose levels were doubled in the presence of a concurrent intrahypothalamic infusion of oxamate, this inhibitory action of acute hyperglycemia on glucose production was blunted by 40% (63), revealing that the activation of hypothalamic lactate metabolism is a critical component of the effectiveness of glucose per se. Circulating lactate has also been demonstrated to regulate hepatic glucose fluxes (51), and it was recently shown that the inhibition of either hypothalamic LDH or KATp channels during a physiological increase in circulating lactate led to an increase in hepatic glucose production (58).

Few articles to date have looked at glucose sensing in specific neuronal cell types. Of particular note, by operating on the proposal that glucose sensing in the anorexigenic pro-opiomelanocortin (POMC) neurons of the hypothalamus mechanistically mimics that of the pancreatic β-cell, it was recently demonstrated that the POMC neuron-specific expression of a mutated KATp channel subunit Kir6.2 was sufficient to impair glucose homeostasis, as determined by an oral glucose tolerance test (93). Furthermore, electrophysiological analyses determined that a high-fat diet was able to impair glucose sensing by POMC neurons, and this impairment was linked to an upregulation in the mitochondrial uncoupling protein UCP2 (93).

Fatty acids

Although the brain does not use fatty acids as a primary source of energy, fatty acids likely serve as a signal of nutrient abundance. Indeed, it has been demonstrated recently that select enzymes and intermediates of fatty acid metabolism contribute to the hypothalamus’ ability to regulate glucose homeostasis.
Indeed, when an icv infusion of a KATP channel blocker fatty acid sensing on glucose homeostasis should access the brain and recapitulate the effect of central lysis triggers a neural pathway to regulate energy as well as glucose homeostasis. Of note, these rodents treated with icv oleic acid had lower plasma insulin and glucose levels, indicating enhanced insulin sensitivity, and with the use of a basal insulin pancreatic clamp this was confirmed, since icv oleic acid was found to markedly suppress hepatic glucose production (85). Interestingly, the infusion of the medium-chain fatty acid octanoic acid did not yield the same results, revealing specificity in the nature of the hypothalamic nutrient signal (85). The icv co-administration of the KATP channel blocker glibenclamide with oleic acid was able to nullify the glucose production-lowering effect of icv oleic acid alone (85). Moreover, this was in line with a later study demonstrating that hypothalamic-KATP channel activity per se can regulate glucose production (99). Based on the aforementioned observation that icv oleic acid but not octanoic acid, a medium-chain fatty acid that does not require CPT-1 for mitochondrial entry (85), has suppressive effects on glucose production, it was then tested whether central CPT-1 activity-mediated changes in cytosolic-long chain fatty acids (LCFAs) can recapitulate the effects observed with icv administered LCFAs (FIGURE 2, INSET). With the use of a CPT-1 ribozyme as well as pharmacological CPT-1 inhibitors, it was found that a decrease in CPT-1 activity was sufficient to lead to an increase in the concentration of LCFAs-CoAs and, as a result, elicit a substantial suppression of glucose production (83). Thus the regulatory effects of cellular fatty acids in the hypothalamus are extramitochondrial and are likely cytosolic (FIGURE 2, INSET).

The activity of CPT-1 is regulated by malonyl-CoA, which is generated from acetyl-CoA by acetyl-CoA carboxylase (ACC) as the committed step of de novo fatty acid generation (121). Numerous studies have revealed a role of hypothalamic malonyl-CoA in the regulation of feeding and energy expenditure (22, 46, 48, 67, 124), but to date the application of the "malonyl-CoA hypothesis" to the regulation of glucose homeostasis remains limited. Citrate, an intermediate metabolite produced in the mitochondria in the citric acid cycle, is an allosteric effector of ACC activity, and it was recently demonstrated that icv citrate not only decreased an allosteric effector of ACC activity, but also a concomitant decrease in LCFAs-CoA abundance (46). Recently, we have demonstrated that this increase in circulating lipids lowers glucose production via a hypothalamic protein kinase C (PKC)-dependent mechanism (103). Furthermore, the pharmacological activation of hypothalamic PKC was sufficient to lower hepatic glucose production, an effect that was nullified with the pharmacological or molecular disruption of hypothalamic KATP channels (103); altogether, these results support the notion that the activation of hypothalamic PKC is necessary for central lipid-sensing mechanisms to lower glucose production via the KATP channel-dependent pathway (FIGURE 2, INSET).

**Amino acids**

Recent studies have pushed for a physiological role of central amino acid sensing. The mammalian target of rapamycin (mTOR) is a regulator of cell growth, and much like AMPK it is a cellular energy sensor whose kinase activity varies with nutritional status (116). Its activity is sensitive to various nutrients, including glucose and some fatty acids and particularly the branched-chain amino acid leucine (125). Indeed, when a low dose of leucine was administered into the third cerebral ventricle of rodents, leading to the activation of mTOR signaling, a marked decrease in short-term food intake and body weight was observed (28). This leucine-mediated anorectic effect was nullified when hypothalamic mTOR activity was inhibited via rapamycin treatment (28). The anorectic effects mediated by central leucine administration correlated with an increase in the phosphorylation of S6 kinase (S6K), an effector of mTOR activity, in the hypothalamus (28); these effects were confirmed in a recent study in a dose-dependent manner (102). However, the role of central amino acid sensing per se in controlling circulating glucose levels and the possibility that hypothalamic amino acid sensing occurs via mTOR-dependent mechanisms remains to be determined.

The metabolic coupling of feeding and energy expenditure serves roles not only in the regulation of body weight, but also in fueling local energy needs. This comes to mind when one considers the nutrient-sensing hypothalamic-metabolic CNS-mediated anorectic response (FIGURE 2), which emerged as a natural response to integrate the hypothalamic fatty acid sensing mechanisms with the possibility that the anorectic pathways integrate both nutrient-sensing and possible glucoregulatory pathways.
As lipid influx increases, glucose production increases in the hypothalamus, particularly the subunit Sur1 of the glucose sensor. However, the extent to which hypothalamic glucose and fatty acid metabolism is involved in the regulation of glucose homeostasis remains unknown. As such, evaluating the possibility for amino acids to regulate glucose homeostasis and determining whether this regulation occurs via mTOR pathway-dependent or -independent mechanisms remains an utmost priority.

The metabolism of different nutrients in the hypothalamus, particularly that of glucose and fatty acids, serves roles of polarizing importance with respect to fueling local energy supply for the brain. But when it comes to maintenance of whole body homeostasis, these nutrients appear to form a united front and collectively serve as a nutrient surfeit signal, activating hypothalamic pathways that ultimately initiate the CNS-mediated regulation of glucose homeostasis (FIGURE 2).

LCFA-CoA and malonyl-CoA have emerged as the molecules of focus that are poised to integrate the activation of glucose- and fatty acid-sensing mechanisms in the hypothalamus; however, the extent to which hypothalamic nutrient-sensing pathways interact with those of the previously detailed hormone sensing is uncertain. As such, the integration and possible co-dependence of central nutrient and hormone-sensing pathways remains an area of interest that is open to further scrutiny.

Implications for Diabetes and Obesity

The numerous studies outlined thus far in this review have been instrumental in advancing the importance of brain, in particular the hypothalamus, in processing acute changes in hormonal signaling and nutrient availability and triggering a neuronal circuit to regulate glucose homeostasis. When it comes to this homeostatic regulation in the face of metabolic disease characterized by nutrient excess and/or dysregulated hormone action, experimental evidence, in general, points to a decreased effectiveness of this circuitry; however, there are some notable exceptions.

In mice that are genetically obese and lack functional leptin (ob/ob), the administration of leptin potently reverses obesity, lowering their food intake and body weight and normalizing plasma glucose and insulin levels (97). However, leptin levels in obese humans...
leptinemia, hyperinsulinemia, and elevated fasting XBP1 and placed on a high-fat diet exhibited hyper-
indeed, mice displaying a neuron-specific knockout of protein folding and trafficking to combat ER stress; among other proteins, ER chaperones, which assist in activated in the UPR and upregulates genes encoding, abolished (90). XBP1 is a transcription factor that is tin-induced hypothalamic STAT3 phosphorylation was upregulated PKR-like kinase, or PERK), a mediator of metabolic inflammation, IKK/NF-B (100). An important mechanism by which the hypothalamic response to icv insulin and 2) the phosphorylation of STAT3 in response to icv leptin; furthermore, the suppressive effects of icv insulin and leptin on short-term food intake was blunted in these mice (128). Thus the acti-
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Furhter the role of central insulin resistance in the pathogenesis of diabetes, it was determined that hypothalamic insulin signaling via the PI3K pathway was markedly reduced in rodents with STZ-induced uncontrolled diabetes (41). Furthermore, enhancing PI3K signaling via adenoviral gene therapy was found to enhance the ability of peripherally administered insulin to lower glucose levels, whereas pharmacologi-
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overfeeding fails to translate into this increase in the intracellular pool of LCFA-CoA (100). This was indeed the case: when a systemic lipid emulsion designed to double plasma LCFA and hypothalamic LCFA-CoAs (64) was administered to overfed rats, the circulating lipids failed to increase hypothalamic LCFA-CoAs (100). An impeded blood-brain barrier LCFA transport mechanism is far from being complete. Notably, the specific role of hypothalamic insulin and nutrient-sensing mechanisms in the CNS that regulate hypothalamic lipid sensing to regulate glucose homeostasis in normal rodents with experimentally induced hypoinsulinemia and, more significantly, in normal rodents with overfed rodents (100). Thus inhibiting hypothalamic lipid oxidation via the inhibition of CETP hyperactivity is sufficient to restore energy balance as well as glucose homeostasis in overfed rodents. However, interestingly, not all central nutrient sensing mechanisms are disrupted in models of obesity and/or diabetes. We have recently demonstrated that the activation of PKC in the hypothalamus, a necessary mediator of hypothalamic lipid sensing to regulate glucose homeostasis, was sufficient to suppress hepatic glucose production in a 3-day overfed rodent model (101) in which hypothalamic lipid sensing per se is impaired (78). Additionally, an acute increase in central lactate has been shown to lower plasma glucose levels and glucose production in an acute hypoglycemia model of STZ-diabetes (23). Furthermore, ivc lactate suppressed glucose production in normal rodents with experimentally induced hypoinsulinemia and, more significantly, in diet-induced insulin resistance resulting from a 3-day high-fat diet (23). Clearly, further investigation is necessary to elucidate the exact mechanism underlying this selective preservation in central nutrient sensing in models of metabolic disease.

Concluding Remarks

This review highlights the importance of hormone- and nutrient-sensing mechanisms in the CNS that control glucose homeostasis. The pieces are presented individually, yet the puzzle remains to be assembled and is far from being complete. Notably, the specific neurons that mediate CNS control of glucose homeostasis and their physiological relevance remains to be elucidated. Nonetheless, the studies as a whole suggest that, in response to an acute rise of nutrients, the brain triggers peripheral metabolic responses to decrease plasma glucose levels.

Graduate Award from BBDC, University of Toronto. T. K. T. Lam holds the John Kitson McIvor Chair in Diabetes Research at the Toronto General Research Institute and University of Toronto. We apologize to colleagues whose work has not been specifically referenced due to space limitations.

References


γ-Amino butyric acid and the activation of GABA control throughout the periphery becomes clear as a development of many diseases that GABA can control tumor cell growth. In most cases, GABA is an essential component for the development of stem cells. However, only limited evidence has been provided to support the claim that GABA can control tumor cell proliferation and function. For example, in a recent study, it was found that the presence of GABA can inhibit tumor cell proliferation and function.

Aside from traditional signaling molecules, GABA is also involved in the development of adult stem cells. Both the brain and the peripheral organs (if not adult stem cells) contain adult stem cells. In the brain, adult stem cells reside (separated from the peripheral stem cells) and maintain various microenvironments such as tight GABAergic signaling. In the peripheral organs, adult stem cells may be altered and can play different roles in the development of tumor cells. In other signaling molecules, tumor cells may be affected.