CNS Regulation of Glucose Homeostasis

The past decade has hosted a remarkable surge in research dedicated to the central control of homeostatic mechanisms. Evidence indicates that the brain, in particular the hypothalamus, directly senses hormones and nutrients to initiate behavioral and metabolic responses to control energy and nutrient homeostasis. Diabetes is chiefly characterized by hyperglycemia due to impaired glucose homeostatic regulation, and a primary therapeutic goal is to lower plasma glucose levels. As such, in this review, we highlight the role of the hypothalamus in the regulation of glucose homeostasis in particular and discuss the cellular and molecular mechanisms by which this neural pathway is orchestrated.

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 regulation of peripheral glucose homeostasis began with the finding by Claude Bernard that punctures in the cerebral 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 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 extraplastic functions, is to ensure that glucose homeostasis is maintained. In the recent 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 (118). 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 (PI3K), impaired the ability of elevated circulating insulin to suppress glucose production. Of note, the inhibition of mitogen-activated protein 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 hypothalalum, particularly in the arcuate nucleus (ARC), elicited insulin resistance in rats (84) as similarly seen in NIKKO 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 streptozocin (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),
IRS-2 seems to have spotlighted itself in the literature on central glucose regulation. IRS-2 protein is highly detectable in the hypothalamus, including 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 (60, 66), 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<sub>ATP</sub>) channels. The glucose production-lowering effect of systemic or central insulin was established by intracerebroventricular (icv) administration of K<sub>ATP</sub> channel blocker (87, 99). Furthermore, mice lacking the SUR1 subunit of the SUR1/Kir6.2 K<sub>ATP</sub> 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 effent 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 → P3K → PKB) leads to the activation of K<sub>ATP</sub> channels but the involvement of phosphatidylinositol 3,4,5-trisphosphate (PIP<sub>3</sub>) has been suggested. PIP<sub>3</sub> directly activates K<sub>ATP</sub> channels in vitro (68), and, more crucially, constitutive activation of P3K-PIP<sub>3</sub> signaling in pro-opiomelanocortin (POMC) neurons increases K<sub>ATP</sub> channel conductance, which hyperpolarizes neurons and results in a hyperphagic phenotype (98) (FIGURE 1A).

SUR1/Kir6.2 K<sub>ATP</sub> 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 α-melanocyte-stimulating hormone (α-MSH) (110). Belonging to a family of neuropeptides, NPY (NPY) and Agouti-related protein (AgRP) interact with these orexigenic peptides to determine food intake (111).

IRS-2 seems to have spotlighted itself in the literature on central glucose regulation. IRS-2 protein is highly detectable in the hypothalamus, including 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 (60, 66), 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<sub>ATP</sub>) channels. The glucose production-lowering effect of systemic or central insulin was established by intracerebroventricular (icv) administration of K<sub>ATP</sub> channel blocker (87, 99). Furthermore, mice lacking the SUR1 subunit of the SUR1/Kir6.2 K<sub>ATP</sub> 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 effent 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 → P3K → PKB) leads to the activation of K<sub>ATP</sub> channels but the involvement of phosphatidylinositol 3,4,5-trisphosphate (PIP<sub>3</sub>) has been suggested. PIP<sub>3</sub> directly activates K<sub>ATP</sub> channels in vitro (68), and, more crucially, constitutive activation of P3K-PIP<sub>3</sub> signaling in pro-opiomelanocortin (POMC) neurons increases K<sub>ATP</sub> channel conductance, which hyperpolarizes neurons and results in a hyperphagic phenotype (98) (FIGURE 1A).

SUR1/Kir6.2 K<sub>ATP</sub> 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 α-melanocyte-stimulating hormone (α-MSH) (110). Belonging to a family of neuropeptides, NPY (NPY) and Agouti-related protein (AgRP) interact with these orexigenic peptides to determine food intake (111).

IRS-2 seems to have spotlighted itself in the literature on central glucose regulation. IRS-2 protein is highly detectable in the hypothalamus, including 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 (60, 66), 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<sub>ATP</sub>) channels. The glucose production-lowering effect of systemic or central insulin was established by intracerebroventricular (icv) administration of K<sub>ATP</sub> channel blocker (87, 99). Furthermore, mice lacking the SUR1 subunit of the SUR1/Kir6.2 K<sub>ATP</sub> 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 effent 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 → P3K → PKB) leads to the activation of K<sub>ATP</sub> channels but the involvement of phosphatidylinositol 3,4,5-trisphosphate (PIP<sub>3</sub>) has been suggested. PIP<sub>3</sub> directly activates K<sub>ATP</sub> channels in vitro (68), and, more crucially, constitutive activation of P3K-PIP<sub>3</sub> signaling in pro-opiomelanocortin (POMC) neurons increases K<sub>ATP</sub> channel conductance, which hyperpolarizes neurons and results in a hyperphagic phenotype (98) (FIGURE 1A).

SUR1/Kir6.2 K<sub>ATP</sub> 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 α-melanocyte-stimulating hormone (α-MSH) (110). Belonging to a family of neuropeptides, NPY (NPY) and Agouti-related protein (AgRP) interact with these orexigenic peptides to determine food intake (111).
and activator dephosphorylation in the liver remains to be characterized (106). Resolution of K_Aca, a target of many signaling pathways, is suggested. PIP_2 and, more recently, PI_3 signaling also play a role in the liver. 

**Characteristics and Function of Leptin**

Leptin is a hormone (α-MSH), which by binding the melanocortin receptor 4 (MC4R) inhibits feeding (110). Belonging to the second subtype are neurons that co-express the 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 (108), 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. In the thalamus, particularly that of glucose and fatty acids, "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." 

The discovery of leptin (129) was indeed another milestone in obesity and diabetes research. It is 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).

Leptin is a hormone, and its control of energy homeostasis is largely elicited in the CNS (108). Leptin's glucose homeostatic regulation also has a central component. Acute icv administration of leptin normalized glucose production in high-fat diet-induced insulin resistance (101). Moreover, icv administration of leptin, at a dose that was ineffective when given peripherically, rescued lipodystrophic mice from their insulin resistant and diabetic phenotype (6). Zooming in further, the hypothalamic ARC has been spotlighted as the key CNS site for leptin's effects on glucose homeostasis. With the use of viral gene therapy to selectively rescue leptin receptors in the hypothalamus of leptin receptor-null mice, it was found that unilateral restoration of leptin signaling in the ARC was sufficient to dramatically improve hyperinsulinemia and normalize blood glucose levels compared with pair-fed ob/ob mice (108).

Just as its control of energy homeostasis is largely elicited in the CNS (108), leptin's glucose homeostatic regulation also has a central component. Acute icv administration of leptin normalized glucose production in high-fat diet-induced insulin resistance (101). Moreover, icv administration of leptin, at a dose that was ineffective when given peripherically, rescued lipodystrophic mice from their insulin resistant and diabetic phenotype (6). Zooming in further, the hypothalamic ARC has been spotlighted as the key CNS site for leptin's effects on glucose homeostasis. With the use of viral gene therapy to selectively rescue leptin receptors in the hypothalamus of leptin receptor-null mice, it was found that unilateral restoration of leptin signaling in the ARC was sufficient to dramatically improve hyperinsulinemia and normalize blood glucose levels compared with pair-fed ob/ob mice (108).

It has now come to be known that leptin, upon binding to its receptor in the ARC, activates two independent intracellular signaling cascades, which work in concert to regulate glucose homeostasis (Figure 1A). The first of the two is the well established STAT3-dependent pathway. The long form of leptin receptor (LIRb) belongs to the class I of cytokine receptors (113), and, upon binding of leptin, Janus kinase 2 (Jak2) is activated, leading to the phosphorylation of cytoplasmic targets such as STAT3 (81). The activation of STAT3 is required for leptin's regulation of energy (9) and, more recently considered, glucose homeostasis. Indeed, S/reverted mice, having life-long obliteration in leptin-STAT3 signaling due to a replaced residue in the LIRb (Tyr1138Ser), were found to be severely hepatic insulin resistant (19). In the same study, by using two complementary approaches to prevent central STAT3 activation (specifically Jak2 and the icv infusion of the pharmacological
Traditionally, this gut hormone is thought to regulate and discrete populations of neurons (52). Hormone secreted by the L-cells of the intestines (119) postprandial secretion of incretin hormones such as established that this "incretin effect" is mediated by the glucose homeostasis is partly controlled by gut–intestinal populations was able to increase leptin sensitivity and improve glucose homeostasis (56, 127).

Although the hypothalamic-independent pathway is imperative, it does not stand solo in CNS leptin's control of glucose homeostasis. Several observations suggest possible complementary pathways by which leptin controls glucose homeostasis. First, although hepatic insulin resistance is comparable between db/db mice lacking functional leptin receptors and s/s mice with disrupted Lhb/STAT3 signaling, s/s mice are less hyperglycemic than db/db mice (9, 19). Second, unlike db/db mice, s/s mice pair-fed to control animals do not develop hyperglycemia or glucose intolerance (8). What potentially serves as this complementary pathway? Knowing that leptin, like insulin, requires the activation of hypothalamic PI3K to reduce food intake (82), it seems that the binding of leptin to its receptor to activate PI3K is a likely candidate. Indeed, hypothalamic infusion of PI3K inhibitor curtailed the improvement in insulin sensitivity elicited by restoration of functional ARC leptin receptors in leptin receptor-deficient fat/Δfat rats (86), suggesting that hypothalamic leptin, like insulin, activates PI3K to regulate glucose homeostasis. However, it is highly plausible that the activation of PI3K by leptin and insulin to regulate glucose homeostasis occurs in different neuronal populations since leptin activates PI3K in POMC but not NPY/AgRP neurons (126), whereas insulin signaling in AgRP but not POMC neurons enhances leptin action and improves glucose homeostasis (56). Nonetheless, the role of the downstream effectors of leptin-PI3K signaling cascade that regulate glucose homeostasis remains to be elucidated.

**Glucagon-like peptide 1**

The initial observation that glucose clearance and insulin levels in humans were significantly greater after an oral glucose load compared with the same levels, and a similar increase in insulin secretion upon glucose production-suppressing ability of icv leptin in the ARC was observed with direct icv infusion of a GLP-1 antagonist or agonist, it was found that CNS GLP-1 signaling is involved in regulating peripheral insulin secretion and partitioning of glucose disposal, which collectively increases hepatic glucose disposal, which collectively increases hepatic glycogen storage in preparation for the next fasting state (57). A similar increase in insulin secretion upon an iv glucose tolerance test was observed with direct icv GLP-1 administration (107).

GLP-1 receptor mRNA is widely present in the brain, including but not limited to the hippocampus, hypothalamic nuclei such as the ARC and PVN, and the hindbrain (74). Of these sites, the PVN and hindbrain are known to mediate the anorectic effect of CNS GLP-1 (43, 73, 115). Interestingly, although GLP-1 receptors are found in the ARC and do not regulate food intake, they do mediate GLP-1 action to regulate peripheral glucose homeostasis (107) (FIGURE 1C). Administration of GLP-1 into the ARC effectively lowered hepatic glucose production, a finding not reproducible with GLP-1 administration into the PVN (107). Although the activation of CNS GLP-1 system and the mechanism(s) behind CNS GLP-1 regulation of glucose homeostasis are yet to be clarified, the activation of K<sub>ATP</sub> channels represents a possible candidate as the co-inhition of K<sub>ATP</sub> channel blocker prevented the GLP-1-induced suppression of glucose production (107). Furthermore, this glucose production-suppressing effect of central GLP-1 appears to be POMC-mediated since GLP-1 receptors largely co-localize with POMC and not NPY/AgRP neurons in the ARC (107). In essence, hormones such as insulin, leptin, and GLP-1 have been repeatedly demonstrated to possess glucoregulatory capacities that are, at least in part, mediated centrally. These largely peripheral-derived hormones, transported past the blood-brain barrier, act on respective receptors in the CNS and exert their glucoregulatory effects via seemingly distinct signaling pathways, perhaps converging at some downstream candidates(s). However, much is still to be studied and evaluated to identify the potential convergence or divergence.

**CNS Nutrient Sensing**

In addition to processing input from hormones, the hypothalamus senses nutrients to initiate metabolic responses to regulate energy (28, 29, 63, 76, 85, 122) and nutrient (62, 63, 85) homeostasis. Proposing a role of "nutrient sensing," i.e., the acute accumulation of nutrients, per se in the regulation of homeostasis was not a recent development; glucostatic (7) proposed that circulating amounts of glucose in the brain influence glucose homeostasis. The initial observation that glucose clearance and insulin levels, per se, are increased after an oral glucose load compared with the same levels, and a similar increase in insulin secretion upon glucose production-suppressing ability of icv leptin in the ARC was observed with direct icv infusion of a GLP-1 antagonist or agonist, it was found that CNS GLP-1 signaling is involved in regulating peripheral insulin secretion and partitioning of glucose disposal, which collectively increases hepatic glucose disposal, which collectively increases hepatic glycogen storage in preparation for the next fasting state (57). A similar increase in insulin secretion upon an iv glucose tolerance test was observed with direct icv GLP-1 administration (107).

GLP-1 receptor mRNA is widely present in the brain, including but not limited to the hippocampus, hypothalamic nuclei such as the ARC and PVN, and the hindbrain (74). Of these sites, the PVN and hindbrain are known to mediate the anorectic effect of CNS GLP-1 (43, 73, 115). Interestingly, although GLP-1 receptors are found in the ARC and do not regulate food intake, they do mediate GLP-1 action to regulate peripheral glucose homeostasis (107) (FIGURE 1C). Administration of GLP-1 into the ARC effectively lowered hepatic glucose production, a finding not reproducible with GLP-1 administration into the PVN (107). Although the activation of CNS GLP-1 system and the mechanism(s) behind CNS GLP-1 regulation of glucose homeostasis are yet to be clarified, the activation of K<sub>ATP</sub> channels represents a possible candidate as the co-inhition of K<sub>ATP</sub> channel blocker prevented the GLP-1-induced suppression of glucose production (107). Furthermore, this glucose production-suppressing effect of central GLP-1 appears to be POMC-mediated since GLP-1 receptors largely co-localize with POMC and not NPY/AgRP neurons in the ARC (107). In essence, hormones such as insulin, leptin, and GLP-1 have been repeatedly demonstrated to possess glucoregulatory capacities that are, at least in part, mediated centrally. These largely peripheral-derived hormones, transported past the blood-brain barrier, act on respective receptors in the CNS and exert their glucoregulatory effects via seemingly distinct signaling pathways, perhaps converging at some downstream candidates(s). However, much is still to be studied and evaluated to identify the potential convergence or divergence.

CNS Nutrient Sensing

In addition to processing input from hormones, the hypothalamus senses nutrients to initiate metabolic responses to regulate energy (28, 29, 63, 76, 85, 122) and nutrient (62, 63, 85) homeostasis. Proposing a role of "nutrient sensing," i.e., the acute accumulation of nutrients, per se in the regulation of homeostasis was not a recent development; glucostatic (7) proposed that circulating amounts of glucose in the brain influence glucose homeostasis. The initial observation that glucose clearance and insulin levels, per se, are increased after an oral glucose load compared with the same levels, and a similar increase in insulin secretion upon glucose production-suppressing ability of icv leptin in the ARC was observed with direct icv infusion of a GLP-1 antagonist or agonist, it was found that CNS GLP-1 signaling is involved in regulating peripheral insulin secretion and partitioning of glucose disposal, which collectively increases hepatic glucose disposal, which collectively increases hepatic glycogen storage in preparation for the next fasting state (57). A similar increase in insulin secretion upon an iv glucose tolerance test was observed with direct icv GLP-1 administration (107).
not a recent development. In fact over 50 years ago, the glucostatic (71) and lipostatic (55) hypotheses proposed that circulating nutrients generated in proportionate amounts to storage depots serve as signals to the brain to initiate alterations in energy intake and expenditure. However, only recently has the notion of direct hypothalamic nutrient sensing become a thoroughly demonstrated and credible means of controlling glucose homeostasis.

Glucose

An important source of energy for the majority of mammalian cell types, glucose is particularly vital for the brain where it is essentially the sole substrate for energy metabolism. The discovery of glucose-sensing neurons within the feeding centers of the hypothalamus (4, 89) hinted at potential physiological roles of central glucose utilization (65) beyond serving as a fuel. Indeed, since those seminal studies, central glucose sensing/metabolism has been established to be an essential component in the regulation of feeding (12, 29, 77) and the hypoglycemic counterregulatory response (14, 16). Recent work has also suggested a direct link between central glucose sensing and the regulation of peripheral glucose levels.

Specifically, an acute increase in central glucose resulted in a decrease in blood glucose and insulin levels, and a suppression of hepatic glucose production; this occurred via a curtailing of both gluconeogenesis and glycogenolysis (63). The metabolic fate of brain glucose has been largely clarified by the proposal of the astrocyte-neuron lactate shuttle (96), which is supported by observations that neuronal activity is coupled to glucose utilization (54, 95, 105, 120) and that neurons preferentially utilize glial-derived lactate as an oxidative fuel (69). Indeed, the infusion of icv lactate was able to recapitulate the effects of central glucose on blood glucose levels and hepatic glucose production (63). However, the effects of both icv lactate and glucose were nullified when they were co-infused with oxamate, an inhibitor of hypothalamic lactate dehydrogenase (LDH) activity (63). Since oxamate is an inhibitor of the preferentially lactate-generating LDH-A [the muscle isoform that, within the brain, is expressed exclusively in the glial cells (13)] and the preferentially pyruvate-generating downstream LDH-B [the heart isoform, and the only isoform found in neurons (13)] (17), this finding suggests that metabolism of glucose to lactate and subsequently pyruvate in the hypothalamus is an essential biochemical step in the regulation of glucose homeostasis (Figure 2). Furthering this notion is the suppression of glucose production resulting from the hypothalamic administration of dichloroacetate (DCA) (61), which ultimately promotes the conversion of pyruvate to aceto-CoA via the inhibition of pyruvate dehydrogenase (PDH) kinase, in turn activating PDH (50).

The importance of this metabolic coupling between neurons and glia via the generation and intracerebral trafficking of lactate in the CNS regulation of glucose homeostasis has also been demonstrated in a few other notable studies. Specifically, the perfusion of the ventromedial hypothalamus (VMH) with lactate was sufficient to severely blunt the counterregulatory hormone response to hypoglycemia, with a marked suppression of both glucagon and epinephrine release during a hypoglycemic clamp, a finding also seen when glucose was perfused into the VMH (13). The caudal hindbrain has also been established as a sensor for local glucose secretion which subsequently activates a response to restore glyceremia; and in an attempt to uncover the potential metabolic sensors involved, the role of lactate in particular was recently examined (94). 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 hypoglycemia (94).

An acute elevation in circulating lactate 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 onanogenic pro-opiомelanocortin (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 undoubtedly further its physiological relevance. 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 (98). 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 LCFA-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, 68, 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 the activity of ACC but also concomitantly decrease its LCFA-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 (183). 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 (183); 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 merits the possibility that homeostasis occurs via mTOR-dependent mechanisms.

The metabolic role of hypothalamus, particularly the PVN, serves to integrate feeding local energy sources using neural and endocrine mechanisms (Figure 2). In 2002, it was first demonstrated that administration of LCFAs into the third cerebral ventricle 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, with icv oleic acid alone (85). Pharmacological inhibition of hypothalamic acetyl-CoA synthetases (ACS) by triacsin C, as well as a hepatic branch vagotomy, negated the effects of circulating lipids on glucose production (64). Taken together, the study illustrates that circulating LCFAs can regulate glucose homeostasis via a hypothalamically triggered mechanism that is dependent on 1) the esterification of LCFAs to LCFA-CoAs, 2) functional KATP channels, and 3) neural transmission via the vagus nerve. Additionally, overexpressing malonyl-CoA decarboxylase (MCD) in the hypothalamus of rodents negates the ability of circulating lipids to regulate glucose homeostasis (46). In accordance with the fatty acid-sensing hypothesis, these rats not only had a marked reduction in hypothalamic malonyl-CoA levels but also a concomitant decrease in LCFA-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 (183). 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 (183); 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).
As lipid infusions increase glucose production, the role of the hypothalamus in glucose homeostasis is 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...
deficient rodents had diminished glucose tolerance and insulin sensitivity (90). Overnutrition-induced hypothalamic ER stress has also been shown to activate a mediator of metabolic inflammation, IKKβ/NF-κB (64) was administered to intraperitoneal injections to induce ER stress in hypothalamic neurons that control glucose homeostasis. Thus, inhibition of C/EBPα signaling could be a potential therapeutic target for the treatment of diabetes.

Conclusions

This review highlights the potential of microbial nutrient and nutrient-status homeostatic mechanisms to control glucose metabolism and body weight homeostasis. A better understanding of these mechanisms is crucial for the development of novel strategies to prevent and treat obesity and type 2 diabetes. The authors’ findings support the importance of targeting gut-brain communication in the development of new therapies for obesity and diabetes.
In normal glucose presence, the hypothalamic lipid sensing circuits that mediate the acute control of food intake are sensitive to the availability of acute nutrients, but not long-term food intake (23). Clearly, further investigation is necessary to elucidate the exact mechanism underlying this selective preservation in central nutrient sensing in response to an acute rise of nutrients, the puzzle remains to be assembled.

This review highlights the importance of hormone-dependent and -independent signals in central nutrient sensing in the regulation of glucose homeostasis. The pieces are presented individually, yet the puzzle remains to be assembled.

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.

T. K. T. Lam is supported by grants from the Canadian Institutes of Health Research (CIHR, MOP-86554 and 82701) and the Banting and Best Diabetes Centre (BBDC). University of Toronto. C. K. L. Lam is supported by a Canadian Graduate Scholarship from CIHR. M. Chai is supported by an Ontario Graduate Scholarship and a Graduate Award from BBDC, University of Toronto. T. K. T. Lam holds the John Kiteon Mckior 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 become clear throughout development and differentiation (187). In many cases, both the brain and peripheral organs (if not adult stem cells) contain adult stem cells. Here, we suggest that GABA can control tumor cell proliferation (187) and induce tumor cell growth and function in peripheral stromal cells (e.g., GABAergic tumor cells). Intriguingly, GABA signaling molecules inhibit tumor proliferation.