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 homeostatic control. Within the entire CNS, the hypothalamus is particularly well studied due to 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 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 role in our body's homeostatic controls. Over the past decade, the CNS has been shown to be a fundamental 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.

In this review, we focus on the role of the CNS in the regulation of glucose homeostasis, particularly in the hypothalamus, which has emerged as a key regulator of whole body homeostatic control. In fact, from the respiratory system to the circulatory system, the CNS has become increasingly recognized as a key regulator of whole body homeostasis. In fact, from the respiratory system to the circulatory system, the CNS has become increasingly recognized as a key regulator of whole body homeostasis.
IRS-2 seems to have spotlighted itself in the literature on central glucose regulation. IRS-2 protein is highly detectable in the hypothalamus, including but not limited to the ARC, ventromedial nucleus (VMN), and paraventricular nucleus (PVN) (92). Interestingly, whereas constitutive active IRS-2 is 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_{ATP}) channels. The glucose-production-lowering effect of systemic or central insulin was abolished 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 efferent 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 (69), and, more crucially, constitutive activation of PI3K-PIP3 signaling in pro-opiomelanocortin (POMC) neurons increase 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 α-melanocyte-stimulating hormone (110). Belonging to the melanocortin (MC) family of peptides, POMC is thought to be the primary mechanism that co-express Y (NPY) and α-MSH (111). GI tract growth and gut motility are directly regulated by the MC4R (112), leading to competitive hypothalamic suppression of appetite and weight regulation (113).

Leptin

As with insulin, leptin is another hormone that has a critical role in energy homeostasis. In leptin or insulin receptor-deficient ob/ob or db/db mice, leptin deficiency results in obesity, insulin resistance (3, 24), and decreased glucose production (99). The leptin receptor (ObR) is constitutively expressed in pancreatic β-cells and the hypothalamic ARC (114). The leptin receptor is activated by leptin, leading to a complex signaling cascade that involves several downstream effectors. Leptin receptor activation leads to the phosphorylation of IRS-2 protein, which is highly detectable in the hypothalamus, including but not limited to the ARC, VMN, and 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).

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**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 JAK/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.

**FIGURE 2.** Leptin signaling

Leptin signaling in the hypothalamic arcuate nucleus involves the activation of IRS-2 and PI3K, leading to the activation of POMC neurons. Activation of POMC neurons results in the release of α-MSH, which acts on the pancreatic β-cells to decrease glucose production. This pathway is independent of melanocortin receptors and is mediated by the vagus nerve.
and activator deins in the liver remains to be explored due to the liver’s role in regulating the levels of leptin and insulin. Leptin is a hormone (α-MSH), which binding to the melanocortin receptor 4 (MC4R) inhibits feeding (110). Leptin also decreases the levels of the orexigenic peptides 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 orexigenic signaling: directly suppressing the downstream binding of AgRP to 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 icv knockout mice in 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 is well documented that this I67-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 body 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).

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Traditionally, this gut hormone is thought to regulate and discrete populations of neurons (52). The hormone secreted by the L-cells of the intestines (119) glucagon-like peptide 1 (GLP-1) (31). GLP-1 is a potent establishment that this “incretin effect” is mediated by the derived peptide hormones (72). In fact, it is now estimated that glucose homeostasis is partly controlled by gut hormone, PI3K inhibitor curtailed the improvement in insulin sensitivity elicited by restoration of functional ARC leptin receptors in leptin receptor-deficient fa/fa 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 ARC neurons while insulin signaling in AgRP neurons is involved in 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 load given intravenously gives rise to the thoughts that glucose homeostasis is partly controlled by gut-derived peptide hormones (72). In fact, it is now established that this “incretin effect” is mediated by the postprandial secretion of incretin hormones such as glucagon-like peptide 1 (GLP-1) (31). GLP-1 is a potent hormone secreted by the L-cells of the intestines (119) and discrete populations of neurons (52). Traditionally, this gut hormone is thought to regulate glucose homeostasis via directly acting on the β-cells to stimulate insulin secretion and biosynthesis, decrease glucagon secretion, and promote pancreatic β-cell growth (51). GLP-1’s action centrally has been associated with the control of food intake (115). Interestingly, however, emerging studies are pointing at GLP-1’s regulation of peripheral glucose homeostasis through direct central GLP-1 action. Of note, utilizing ivc 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 results in improved 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 ivc 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, consequently, 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_B channels represents a possible candidate as the co-injection of K_B 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 glucostatic effects of central hypothalamic glucose production-suppressing ability of ivc leptin in overfed rats was nullified, affirming the requirement of STAT3 activation in this regulation (19). In line with this, the inactivation or deficiency of a negative regulator of the JAK-STAT pathway, suppressor of cytokine signaling (SOCS) 3, in selective brain regions and neuronal populations was able to increase leptin sensitivity and improve glucose homeostasis (56, 127).

Although the hypothalamic STAT3-dependent 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 Ldb1/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 ivc 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 ivc leptin in the PVN (107). Although the aforementioned STAT3-dependent pathway is imperative, it does not stand solo in CNS glucose homeostasis (56). Nonetheless, the role of the downstream effectors of leptin-PI3K signaling cascade that regulate glucose homeostasis remains to be elucidated. CNS Nutrient Sensing

In addition to processing input from hormones, the hypothalamus senses nutrients to initiate metabolic responses to regulate energy balance (28, 29, 63, 76, 85, 123) 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 central neural circuitry amounts of the brain to regulate expenditure. Is direct hypothalamically driven glucose homeostasis

An important role for the mammalian CNS in the brain where energy metabolism occurs is the control of hypothalamic glucostatic roles of central energy metabolism as a fuel. Indeed, glucose sensing is an essential response (14), direct link between regulation of glucose homeostasis and central glucose metabolism, which leptin controls glucose homeostasis. Several observations suggest possible complementary pathways by which leptin controls glucose homeostasis. First, leptin may act on respective receptors in the CNS and exert their glucostatic (7)

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not a recent development. In fact over 50 years ago, the glucostatic (71) and glucostatic (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 satiety and 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 curtailment of both glucogenolytic and glycogenolysis (63). The metabolic fate of glucose has been largely clarified by the proposal of the hypothalamic 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 glucose-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 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) (63), which ultimately promotes the conversion of pyruvate to acetyl-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 intracellular 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 (15). The caudal hindbrain has also been established as a sensor of local glucoprivation which subsequently activates a response to restore glycemia; 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 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 KAT_P channel blocker undoubtedly further its physiological relevance. Fatty acid sensing on glucose homeostasis should access the brain and recapitulate the effect of central regulation of glucose homeostasis. Malonyl-CoA is perhaps an important step in the regulation of glucose homeostasis via the KAT_P channel-dependent pathway (103). Altogether, these results support the notion that the activation of hypothalamic PGC is necessary for central lipid-sensing mechanisms to lower glucose production via the KAT_P 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, it 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, 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 of homeostasis occurring via mTOR-dependent mechanisms remains limited.

The hypothalamus, part of the brain, serves roles in fueling local energy needs in addition to regulating overall body energy homeostasis through efferent neural pathways. The hypothalamic-pituitary-adrenal (HPA) axis integrates the hypothalamic and efferent neural pathways into the fueling local energy needs. The role of hypothalamic sensing mechanisms in the degree of energy expenditure and possibly feeding and energy expenditure (22, 40, 46, 48, 67, 121). Numerous studies have revealed that central fatty acid-sensing hypothesis, these rats not only had a marked reduction in hypothalamic malonyl-CoA levels 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 PGC was sufficient to lower hepatic glucose production, an effect that was nullified with the pharmacological or molecular disruption of hypothalamic KAT_P channels (103), altogether, these results support the notion that the activation of hypothalamic PGC is necessary for central lipid-sensing mechanisms to lower glucose production via the KAT_P channel-dependent pathway (FIGURE 2, INSET).

**FIGURE 2.** In 2002, it was first demonstrated that the 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, 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 a specificity in the nature of the fatty acid nutrient signal (85). The icv co-administration of the KAT_P 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 KAT_P 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 LCFAs-CoAs and, as a result, elicit a substantial suppression of glucose production (83). Thus the regulatory effects of cellular fatty acids in the hypothalami 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 citrate not only decreased food intake and body weight but also resulted in lower blood glucose levels during a glucose tolerance test, increased glucose uptake during a hyperglycemic-arginine clamp, and increased liver glycogen synthesis (21). This promoting the formation of hypothalamic malonyl-CoA is perhaps an important step in the regulation of glucose homeostasis. Illustrating that circulating plasma fatty acids can access the brain and recapitulate the effect of central fatty acid sensing on glucose homeostasis should undoubtedly further its physiological relevance. Indeed, when an icv infusion of a KAT_P channel blocker was administered during an intravenous lipid infusion, there was a significant elevation in glucose production, which was attributed to an increase in glycogenolysis (64). The results of these pharmacological findings were confirmed with a genetic approach using mice deficient in the KAT_P channel subunit SUR1 (64). 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 LCFAs-CoAs, 2) functional KAT_P 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 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 PGC was sufficient to lower hepatic glucose production, an effect that was nullified with the pharmacological or molecular disruption of hypothalamic KAT_P channels (103); altogether, these results support the notion that the activation of hypothalamic PGC is necessary for central lipid-sensing mechanisms to lower glucose production via the KAT_P channel-dependent pathway (FIGURE 2, INSET).
As lipid infu- sion increases glucose pro-duction, the metabolic approach of subunit Sur1 in hypothalamic glucose sensing 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 is not only had a regulatory role of central target of glucose production (116). Its including glucose phosphorylation (125). Indeed, glucose sensing is critical to the activation of central target of glucose production (125). Indeed, glucose sensing is critical to the activation of central nutrient-sensing pathways.

Glucose is taken up by astrocytes where it is glycolytically metabolized to pyruvate. In astrocytes, pyruvate is preferentially converted to L-lactate by lactate dehydrogenase A (LDH-A). Lactate is then taken up by neurons and is preferentially converted back to pyruvate by means of LDH-B. Finally, pyruvate is converted to acetyl-CoA by pyruvate dehydrogenase (PDH). In astrocytes, the two enzymes responsible for the conversion of pyruvate to acetyl-CoA are pyruvate dehydrogenase (PDH) and pyruvate dehydrogenase phosphatase (PDP1). These enzymes are inhibited by AMP-activated protein kinase (AMPK) and activated by the mTOR signaling pathway. The increased flux through both hypothalamic glucose and fatty acid metabolism has been shown to lower hepatic glucose production via a KATP channel-dependent mechanism.
and insulin sensitivity (90). Overnutrition-induced hypothalamic ER stress has also been shown to activate a mediator of metabolic inflammation, IKKβ/NF-κB (100). In addition, these neurons that overfed intracellularly when subjected to high-glucose feeding (64) was associated with heightened hypothalamic inflammation, which is mediated by hypothalamic IL-1β and TNF-α (100). An important point is that the expression of hypothalamic IL-1β is not increased by hypothalamic inflammation, the authors noted, and acute treatment with the anti-inflammatory agent curcumin inhibits hypothalamic inflammation in high-fat diet-fed rats (100). Thus, inhibition of hypothalamic inflammation can ameliorate the development of obesity-related hypothalamic inflammation and peripheral inflammation (78). This is consistent with the notion of impaired hypothalamic insulin sensitivity in obesity, which is due to chronic hyperleptinemia and hypothalamic inflammation. Thus, hypothalamic inflammation is a key mediator of obesity-related hypothalamic insulin resistance.

In conclusion, hypothalamic inflammation is an important contributor to the development of obesity-related hypothalamic insulin resistance. The precise mechanisms by which hypothalamic inflammation contributes to hypothalamic insulin resistance remain to be elucidated. However, it is clear that hypothalamic inflammation plays a central role in the development of obesity-related hypothalamic insulin resistance.

**References**


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.

Concluding Remarks

This review highlights the importance of hormone- and nutrient-sensing mechanisms in the CNS that control glucose homeostasis. These 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.

References


Aside from traditional signaling molecules (e.g., insulin and leptin) on hypothalamic neurons (J. Clin. Invest. 115: 951–958, 2005), there is emerging evidence that 

\[ \text{GABA} \]

controls tumor cell proliferation through a developmental process involving stem cells. In the periphery, stem cell niches may be altered by certain signaling molecules (Nature 372: 425–432, 1994). Intriguingly, signaling molecules can directly influence the proliferation of tumor cells (Cell 135: 61–73, 2008). 

...and the activation of 

GABA control throughout development. In many cases, both the brain and peripheral tissues may be involved in the activation of GABA control (Endocrinology 149: 5654–5661, 2008). 

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