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, 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 is particularly functional with the central nervous system as a whole (122), to regulate glucose homeostatic control. This impairment is a result of a combination of insulin resistance and inadequate glucose production. Of note, the inhibition of mitogen-activated protein kinase (MAPK), another downstream branch of insulin signaling cascade, hypothalamic overexpression of insulin receptor substrate (IRS)-2 and protein kinase B (PKB; Akt), via adenoviral gene therapy significantly improved the glycemic response to an insulin injection in streptozotocin (STZ)-induced diabetes (41). Consistent with these data, decreased IRS expression selectively in the hypothalamus, 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 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 particular the hypothalamus, directly senses hormones and nutrients to initiate behavioral and metabolic responses to control energy and nutrient homeostasis.

Diabetes, which affects ~170 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 glucose production. Of note, the inhibition of mitogen-activated protein kinase (MAPK), another downstream branch of insulin signaling cascade, hypothalamic overexpression of insulin receptor substrate (IRS)-2 and protein kinase B (PKB; Akt), via adenoviral gene therapy significantly improved the glycemic response to an insulin injection in streptozotocin (STZ)-induced diabetes (41). Consistent with these data, decreased IRS expression selectively in the hypothalamus, 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 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 review.

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The well studied and extensive action of insulin in the CNS hormone and nutrient sensing that control glucose 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, 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.

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 recent decade, the action of insulin has been uncovered to extend beyond the periphery, since neuron-specific insulin receptor disrupted (NIKRO) 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).
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 constitutively 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 (PIP_{3}) has been suggested. PIP_{3} directly activates K_{ATP} channels in vitro (68), and, more crucially, constitutive activation of PI3K-PIP_{3} 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 β-melanocyte stimulating hormone (β-MSH) (110). Belonging to the family of neuropeptide Y (NPY) and a superfamily of orexins (4), POMC neurons co-express NPY and a variety of these neuropeptide-orexin-expressing neurons (109), leading to a competitive binding site at MC4R, or-opioid receptors, to these orexigenic peptides, and their downstream signaling. One theory is that this “hypothalamic orexinergic signaling” is thought to be essential for food intake (111), and glucose homeostatic regulation (112). Indeed, selective brain IRS-2 knockout mice (112) causes insulin resistance (60, 66) and food intake (41), suggesting that IRS-2 seems to have spotlighted itself in the literature on central glucose regulation.

**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 (PIP_{2}) to generate PIP_{3}, which subsequently activating 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: lepin, 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.

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**REVIEWS**

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and activator de in the liver remains to be cascade (i.e., IR in the liver) suggested. PIP3 cascade (i.e., IR 2 PIP3 signaling con- trols medicine (98) known to con- volve in the liver phenotype (98) The ARC con- trols are involved in invasive signaling: directly synapsing with POMC neurons or competitive binding of AgRP to the control in the antagonism of POMC’s anorexigenic effects. The interplay between these orexigenic and anorexogenic 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 administra- tion of a melanocortin agonist improves peripheral glucose homeostasis (36, 86). Oppositely, icv adminis- tration 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 produc- tion elicited by circulating insulin, suggesting that the downregulation of NPY release is likely a prerequisite for insulin’s ability to suppress hepatic glucose pro- duction (117). Moreover, it was elegantly shown with the ARC of leptin receptor-deficient Koletsky (fak/fak) rats that selective restoration of leptin receptors in the ARC was sufficient to dramatically improve metabolism (27). Selective restoration of leptin receptors in the ARC was ineffective when given peripherally, rescued lipodystropic mice from their insulin resistant and diabetic phenotype (6). Zooming in further, the hypo- thalamic 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 recep- tors 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 while only modestly reducing food intake and body fat mass (27). Selective restoration of leptin receptors in the ARC of leptin receptor-deficient Koletsky (a/a/a) rats also improved insulin sensitivity (80). It has now come to be known that leptin, upon bind- ing to its receptor in the ARC, activates two independent intracellular signaling cascades, which work in concert to regulate glucose homeostasis (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 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 dereg- ulations (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 adi- posity and feeding (20, 45, 57), later observations strongly suggest that leptin, just as insulin, can also reg- ulate glucose homeostasis independent of its effects on weight loss. Chronic increases in plasma leptin, inde- pendent 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 lipodystropic 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 hypo- thalamus, 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). hormone secreted by the L-cells of the intestines (119) published that this “incretin effect” is mediated by the derived peptide hormones (72). In fact, it is now established that the binding of leptin to its receptor to activate PI3K is a likely candidate of the JAK-STAT pathway, suppressor of cytokine suppressor of cytokine signal transducer and activator of transcription 3 (STAT3). Although the observed STAT3-dependent pathway is imperative, it does not stand alone in CNS leptin’s control of 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 candida. 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/fat rats (80), 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 dif- ferent neuronal populations since leptin activates PI3K in POMC but not NPY/AgRP neurons (126), whereas insulin signaling in AgRP but not POMC neuron regu- lates glucose homeostasis. Consistent with this view, selective deletion of SOCS3 in POMC neurons enhances leptin action and improves glucose homeo- ostasis (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 clearance and insulinemia 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 (31). 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 homeosta- sis through direct central GLP-1 action. Of note, utilizing 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 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 KATP channels representing a possible candidate as the co-infusion of KATP 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 PDMP-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 peripherally derived hormones, transported past the blood-brain barrier, act on respective receptors in the CNS and exert their glucoregulatory effects via seemingly distinct signal- ing pathways, perhaps converging at some down- stream candidate(s). However, much is still to be studied and evaluated to identify the potential conver- gence 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, 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 discovery. Glucostatic (7) hypothesized that circulating amounts of nutrients directly affect expenditure. Indirect hypothalamic regulation of glucose homeostasis (7) by glucose is an important mechanism. In the brain, glucose is derived from peripheral fuels such as hypothalamus, i.e., local hypothalamic responses to glucose. A recent study showed that the hypothalamus senses circulating and gut-derived fuels by the JH2 complex to glucose homeostasis, including those that are involved in energy metabolism, e.g., ketone bodies (86) and the amino acids, the branched chain amino acids (87). Importantly, this action is supported by well-established studies showing that central administration of carbohydrates results in a change in glucose levels, and a direct link between central glucose production and glucose homeostasis. CNS glucose homeostasis appears to be an essential mechanism, not only for the control of food intake (115) but also for the regulation of central glucose metabolism. Centralization of the enzymatic activities of the gluconeogenic system, i.e., liver and kidney, is achieved by the brain’s control of hypothalamic cellular glucose homeostasis. Therefore, CNS glucose homeostasis appears to be an essen- tial mechanism, not only for the control of food intake (115) but also for the regulation of central glucose metabolism. Centralization of the enzymatic activities of the gluconeogenic system, i.e., liver and kidney, is achieved by the brain’s control of hypothalamic cellular glucose homeostasis. Therefore, CNS glucose homeostasis appears to be an essen- tial mechanism, not only for the control of food intake (115) but also for the regulation of central glucose metabolism.
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 satiety and feeding centers of the hypothalamus (4, 89) hints 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 glucose within the hypothalamus' ability to regulate 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 gluco- orlipohypothalamic nutrient sensing. The next fasting response upon food deprivation has been to mediate hepatic glucose homeostasis and 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 K\textsubscript{ATP} 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 \(	ext{\beta}\)-cell, it was recently demonstrated that the POMC neuron-specific expression of a mutated K\textsubscript{ATP} 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.
undoubtedly further its physiological relevance. Fatty acid sensing on glucose homeostasis should promote the formation of hypothalamic malonyl-CoA, which is perhaps an important step in the regulation of glucose production (85). Interestingly, the infusion of the medium-chain fatty acid octanoic acid did not yield the same results, revealing a disparity 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 (96). 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 cytokine-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 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 cytokinetic (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 food intake and body weight but also resulted in lower body glucose levels during a glucose tolerance test, increased glucose uptake during a hyperglycemic–euglycemic clamp, and increased liver glycogen synthesis (21). Thus 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 KATP channel blocker was administered during an intravenous lipid infusion, there was a significant elevation in glucose production, which was attributed to an increase in glucose glycogenolysis (64). The results of these pharmacological findings were confirmed with a genetic approach using mice deficient in the KATP channel subunit Sur1 (64). Pharmacological inhibition of hypothalamic acyl-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 studies illustrate 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 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 (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 (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 of a hypothalamic amino acid-sensing mechanism is elusive local effects of amino acids comes to mind. Central amino acid-sensing mechanisms may serve as a link between amino acid metabolism and hypothalamic CNS-mediated responses (FIGURE 2).

The metabolic fueling of the hypothalamus, which serves a role in the CNS-mediated control of food intake, is clearly a metabolically complex process that requires a modulated fueling local environment to maintain the appropriate nutrient homeostasis to support hypothalamic function. In this context, the hypothalamus has evolved a multi-faceted system of nutrient sensing that selectively serves hypothalamic glucose-sensing mechanisms in the regulation of food intake and CNS-mediated neural response.
As lipid infu-
sion reduces glucose produc-
tion, increased glucose use in brain astrocytes is necessary for proper function subunit Ser1 (Ser1) and Ser2 (Ser2) functional coupling via the mitochondrial permeability transition pore (mPTP). Taken together, these findings support the hypothesis that the metabolism of different nutrients in the hypothalamus, particularly glucose and fatty acids, serves roles of polarizing importance with respect to fueling local energy supply for the brain. However, 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). 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 understanding 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 (90). Additionally, these neuronal XBP1 and placed on a high-fat diet exhibited hyper-protein folding and trafficking to combat ER stress; among other proteins, ER chaperones, which assist in activated in the UPR and upregulates genes encoding,

Furthering 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 PK3 signaling via adenosine gene therapy was found to enhance the ability of peripherally administered insulin to lower glucose levels, whereas pharmacological inhibition of hypothalamic PI3K signaling blunted insulin-mediated glucose lowering (41). In normal rodents, the infusion of icv insulin lowers glucose production (47), however, this regulatory ability of hypothalamic insulin was lost after merely 1 day of high-fat feeding (88). The diminished phosphorylation of hypothalamic Akt and unchanged hepatic insulin signaling revealed that this acute overfed model had selective hypothalamic insulin resistance (88). Furthermore, these rodents had significantly increased S6K activity, and the adenoviral overexpression of dominant negative S6K in the MBH was able to reverse the observed hypothalamic insulin resistance in the high-fat diet-fed rats, restoring the ability of hypothalamic insulin to suppress glucose production (88).

LCFAs serve as a central signal of nutrient abundance, in turn triggering the series of neuronal signaling cascades necessary to regulate nutrient intake and production. Shortly after the effects of ivc oleic acid were published, it was then evaluated whether short-term alterations in nutrient availability affect the ability of central oleic acid to regulate energy and glucose homeostasis. In rats that overfed on a 3-day high-fat diet, an ivc oleic acid bolus was unable to inhibit food intake or suppress GP under conditions of a pancreatic-ic basal insulin clamp. Interestingly, by pair-feeding rats on the high-fat diet, the ability of ivc oleic acid to suppress hepatic GP was restored (78). This provides compelling evidence that the hypothalamic responses triggered by an acute increase in central LCFAs are nutritionally regulated, and along with the aforementioned hypothalamic insulin resistance that developed in rodents fed a high-fat diet for 1 day (88), presents a startling reality in terms of how rapidly intrinsic homeostatic mechanisms can fail. Since the rise in central LCFAs-CoAs is a critical initiator of the fatty acid-mediated homeostatic regulation, the authors specifically postulated that the increase in lipid availability by

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able to reverse the

observed hypothalamic insulin resistance in the high-fat diet-fed rats, restoring the ability of hypothalamic insulin to suppress glucose production (88).

LCFAs serve as a central signal of nutrient abundance, in turn triggering the series of neuronal signaling cascades necessary to regulate nutrient intake and production. Shortly after the effects of ivc oleic acid were published, it was then evaluated whether short-term alterations in nutrient availability affect the ability of central oleic acid to regulate energy and glucose homeostasis. In rats that overfed on a 3-day high-fat diet, an ivc oleic acid bolus was unable to inhibit food intake or suppress GP under conditions of a pancreatic-ic basal insulin clamp. Interestingly, by pair-feeding rats on the high-fat diet, the ability of ivc oleic acid to suppress hepatic GP was restored (78). This provides compelling evidence that the hypothalamic responses triggered by an acute increase in central LCFAs are nutritionally regulated, and along with the aforementioned hypothalamic insulin resistance that developed in rodents fed a high-fat diet for 1 day (88), presents a startling reality in terms of how rapidly intrinsic homeostatic mechanisms can fail. Since the rise in central LCFAs-CoAs is a critical initiator of the fatty acid-mediated homeostatic regulation, the authors specifically postulated that the increase in lipid availability by
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 cannot account for this effect, since no increase in hypothalamic LCFA-CoAs was also observed in overnight fed rats when oleic acid was directly infused intrahypothalaminically (100). Hypothalamic CPT activity was significantly increased in the overnight fed rats, and remarkably, by hypothalaminically inhibiting CPT activity or expression, the authors were able to suppress food intake as well as glucose production in overnight fed rodents (100). Thus inhibiting hypothalamic lipid oxidation via the inhibition of CPTI hyperactivity is sufficient to restore energy balance as well as glucose homeostasis in overnight fed rodents. But 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 overnight fed 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 rats (62) and model of diet-induced diabetes (23). Furthermore, icv lactate suppressed glucose production in normal rodents with experimentally induced hypoinsulinemia and, more significantly, in overfed rodents (100). Thus inhibiting hypothalamic lipid oxidation via the inhibition of CPTI hyperactivity is sufficient to restore energy balance as well as glucose homeostasis in overnight fed rodents.

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. Nonetheless, the evidence so far suggests that, in response to an acute rise of nutrients, the brain triggers peripheral metabolic responses to decrease plasma glucose levels.

References


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γ-Amino butyric acid (GABA) is a key neurotransmitter that plays a crucial role in various physiological and pathological processes.

### Development and Function of GABAergic Neurons

GABAergic neurons develop from pluripotent stem cells that reside throughout the periphery. Both the brain and peripheral organs (if not adult stem cell niches exist in these tissues) likely contain adult stem cells. However, these cells may be altered by environmental factors.

GABAergic neurons demonstrate both nerve and glial characteristics, indicating that they are multipotent in nature. In adulthood, GABAergic neurons are involved in various physiological and pathological processes, including synaptic plasticity, learning, memory, and neurodegeneration.

### GABAergic Neuron Differentiation

The differentiation of GABAergic neurons from pluripotent stem cells is not only limited to the brain but also occurs in the periphery. This process is controlled by various signaling molecules, such as bone morphogenetic proteins (BMPs), neural stem cell factor (NSF), and fibroblast growth factor (FGF).

### GABAergic Neuron Proliferation and Function

GABAergic neurons are generated from neural progenitor cells through a process of symmetric and asymmetric divisions. The proliferation of GABAergic neurons is controlled by factors such as the Wnt/β-catenin signaling pathway, which regulates the expression of transcription factors such as Pax6 and Ngn2.

### GABAergic Neuron Function

GABAergic neurons are involved in various physiological and pathological processes, including synaptic plasticity, learning, memory, and neurodegeneration. The function of GABAergic neurons is regulated by various signaling molecules, such as glutamate (Glu), dopamine (DA), and serotonin (5-HT).

### GABAergic Neuron Inhibition

GABAergic neurons are an important inhibitory neurotransmitter system that plays a crucial role in various physiological and pathological processes. The inhibition of GABAergic neurons is controlled by factors such as the GABA transporters (GATs), which regulate the reuptake of GABA from the synaptic cleft.

### GABAergic Neuron AllostERIC Inhibition

GABAergic neurons are targets for allosteric inhibitors, which are substances that bind to the GABA receptor complex and modulate its function. Allosteric inhibitors of GABAergic neurons are used in the treatment of various neurological disorders, such as epilepsy and schizophrenia.

### References