The central nervous system (CNS) has been identified as a key regulator of whole body homeostasis. In fact, from the respiratory system to the circulatory system, thermoregulation to energy expenditure, the CNS plays a fundamental role in our body’s homeostatic controls. Within the entire CNS, the hypothalamus in particular is generally accepted to mediate the day-to-day regulation of a number of factors including body temperature (42), blood pressure (44), thirst (5), and hunger (109), and is a fundamental structure for the integration of the nervous and endocrine systems. The record of CNS control of peripheral glucose homeostasis began with the finding by Claude Bernard that punctures in the periphery, from altering hepatic glucose metabolism to modifying extrahypothalamic functions, is to ensure that glucose homeostasis is maintained. In the past decade, the action of insulin has been uncovered to extend beyond the periphery, since neuron-specific insulin receptor disrupted (NIRKO) mice were found to develop mild insulin resistance and elevated plasma insulin levels in association with obesity (18). This suggested, for the first time, that neuronal insulin signaling regulates peripheral glucose homeostasis. Indeed, infusion of insulin or its mimetic into the third cerebral ventricle suppressed hepatic glucose production independent of alterations in body weight or changes in circulating levels of insulin and other glucoregulatory hormones (87). In the same study, antagonism of insulin or its downstream signaling pathway in the brain, including the insulin receptor (IR) and phosphatidylinositol-3 kinase (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 hypothalamus, particularly in the arcuate nucleus (ARC), elicited insulin resistance in rats (84) as similarly seen in NIRKO mice (18). Further delineating the downstream insulin signaling cascade, hypothalamic overexpression of insulin receptor substrate-(IRS)-2 and protein kinase B (PKB, or Akt) via adenoviral gene therapy significantly improved the glycemic response to an insulin injection in streptozotocin (STZ)-induced diabetes (41). Collectively, these findings recognized the CNS as a site of insulin action in regulating glucose homeostasis and, more importantly, implied the criticality of an intact insulin-signaling cascade involving the binding of insulin to its receptor and the subsequent activation of IRS, PI3K, and PKB, in such regulation (FIGURE 1A). Interestingly, with both IRS-1 and -2 being the common isoforms linked to glucose homeostasis (106),

**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.

**Insulin**

The well studied and extensive action of insulin in the periphery, from altering hepatic glucose metabolism to modifying extrahypothalamic functions, is to ensure that glucose homeostasis is maintained. In the past decade, the action of insulin has been uncovered to extend beyond the periphery, since neuron-specific insulin receptor disrupted (NIRKO) mice were found to develop mild insulin resistance and elevated plasma insulin levels in association with obesity (18). This suggested, for the first time, that neuronal insulin signaling regulates peripheral glucose homeostasis. Indeed, infusion of insulin or its mimetic into the third cerebral ventricle suppressed hepatic glucose production independent of alterations in body weight or changes in circulating levels of insulin and other glucoregulatory hormones (87). In the same study, antagonism of insulin or its downstream signaling pathway in the brain, including the insulin receptor (IR) and phosphatidylinositol-3 kinase (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 hypothalamus, particularly in the arcuate nucleus (ARC), elicited insulin resistance in rats (84) as similarly seen in NIRKO mice (18). Further delineating the downstream insulin signaling cascade, hypothalamic overexpression of insulin receptor substrate-(IRS)-2 and protein kinase B (PKB, or Akt) via adenoviral gene therapy significantly improved the glycemic response to an insulin injection in streptozotocin (STZ)-induced diabetes (41). Collectively, these findings recognized the CNS as a site of insulin action in regulating glucose homeostasis and, more importantly, implied the criticality of an intact insulin-signaling cascade involving the binding of insulin to its receptor and the subsequent activation of IRS, PI3K, and PKB, in such regulation (FIGURE 1A). Interestingly, with both IRS-1 and -2 being the common isoforms linked to glucose homeostasis (106),
Hormone (or, more precisely, melanocortin) (110). Belonging to this family is the neuropeptide Y (NPY) and a family of peptidergic neuropeptides that co-express NPY and another peptide, agouti-related peptide (AgRP). NPY and AgRP have opposing effects on food intake (108), leading to the idea that these two neuropeptides compete for the same receptors, thereby modulating food intake (109), leads to the notion that these orexigenic peptides might be the key mediators of food intake regulation (110). Indeed, selective knockout of NPY or AgRP results in a decrease in food intake (108).

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 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<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 PI3K-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 ß-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 -melanocyte stimulating hormone (α-MSH) (110). Belonging to this family is the neuropeptide Y (NPY) and a family of peptidergic neuropeptides that co-express NPY and another peptide, agouti-related peptide (AgRP).

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 in the hypothalamus improved insulin sensitivity (41), genetic knock-out of IRS-2 in the hypothalamus and pancreatic β-cell leads to insulin resistance (66, 68), as is seen with selective brain IRS-2 knockout mice (112).

The mechanism downstream of central insulin-signaling to regulate peripheral glucose homeostasis appears to involve the activation of the ATP-sensitive potassium (K<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 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<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 PI3K-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).

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and activator of POMC neurons such as the ARC contains leptin receptors. As such, leptin signaling in the ARC is critical for leptin’s regulatory effect on food intake, and circulating leptin to inhibit hepatic glucose production (117). Moreover, icv infusion of leptin, at a dose that was ineffective when given peripherally, 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 glucose homeostasis independent of changes in weight, enhances both hepatic and extrahepatic insulin action under pancreatic clamp settings as well as reverses insulin resistance and improves glucose homeostasis in lipodystrophic rodents (7, 33, 111). Furthermore, leptin-treated ob/ob mice had a 40% reduction in glucose and insulin levels compared with pair-fed ob/ob mice (108).

The metabolism of different nutrients in the hypothalamus, particularly that of glucose and fatty acids, serves roles of polarizing importance with respect to fueling local energy supply for the brain. 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 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).

“Prominent orexigenic and anorexigenic neuronal subsets have developed a series of POMC's anorexigenic effects. The interplay between these orexigenic and anorexigenic neuronal subsets and their downstream effector signaling form the melanocortin signaling system; it is the activation of this "hypothalamic melanocortin tone" (25) that is thought to be instrumental in the regulation of energy and glucose homeostasis. Indeed, direct activation of the central melanocortin system by central administration of a melanocortin agonist improves peripheral glucose homeostasis (36, 86). Oppositely, icv administration of POMC or melanocortin receptor antagonist causes insulin resistance independent of changes in food intake (1, 76, 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 IR 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 MCR3/4B 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).

Just as its control of energy homeostasis is largely elicited in the CNS (109), 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 peripherally, 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 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 (86). 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 1B). 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/s 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 f the icv infusion of the pharmacological
GLP-1 appears to be POMC-mediated since GLP-1 receptors are found in the ARC and do not regulate food intake, (43, 73, 115). Interestingly, although GLP-1 receptors 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 lowers 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) of the glucose production-suppressing ability of icv 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 (SOCS3), in select 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 restoration of functional ARC leptin receptors in leptin receptor-deficient fat/mice (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 regulates glucose homeostasis. Consistent with this view, selective deletion of SOCS3 in 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 load given intravenously gives rise to the thoughts that glucagon-like peptide 1 (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 homeostasis through direct central GLP-1 action. Of note, utilizing iv cingulation 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 leptin controls glucose homeostasis (107) (FIGURE 1C). Administration of GLP-1 into the ARC effectively lowers 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_{ATP} channels represents a possible candidate as the co-infusion of K_{ATP} 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 peripherally 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 candidate(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, 61, 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 demonstration that metabolites (7) proposed that circulating nutrients affect the brain by altering nutrient expenditure. In essence, CNS nutrient sensing may be directly hypothalamic or an extrinsic nutrient sensor(s) in the brain regulating glucose homeostasis (76, 127).
on the β-cells, biosynthesis, of 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, 28, 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, which has been associated with an increase in circulating lactate (51), and it was recently shown that the inhibition of either hypothalamic LDH or KATP channels during glucose co-infusion of either hypothalamic LDH or KATP channels during glucose co-infusion of 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)), 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 (13). 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% (65), 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 (50). 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 mutant 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. Fatty acid sensing on glucose homeostasis should be regulated by malonyl-CoA is perhaps an important step in the regulation of glucose homeostasis (21). Thus promoting the formation of hypothalamic lipids on glucose production (46). According to 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 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 activity varies with nutritional status (116). Its activity is sensitive to various nutrients, including glucose and 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 (46K), an effector of mTOR activity, in the hypothalamus (28); these effects were confirmed in a recent study in a dose-dependent manner (102). However, the role of central amino acid sensing per se in controlling circulating glucose levels and the possibility that hypothalamic amino acid sensing mediated by mTOR (FIGURE 2, INSET) to regulate glucose homeostasis (64). Pharmacological inhibition of hypothalamic acetyl-CoA carboxylase (ACC) by triacsin C2 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 LCFA 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 (103). Furthermore, the pharmacological activation of hypothalamic PKC was sufficient to lower hepatic glucose production, an effect that was nullified with the pharmacological or molecular disruption of hypothalamic KATP channels (103); altogether, these results support the notion that the activation of hypothalamic PKC is necessary for central lipid-sensing mechanisms to lower glucose production via the KATP channel-dependent pathway (FIGURE 2, INSET).

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As lipid infusion increases glucose production, the role of amino acids in glucose homeostasis remains unknown. As such, evaluating the possibility for amino acids to regulate glucose homeostasis and determining whether this regulation occurs via mTOR pathway-dependent or -independent mechanisms remains a 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...
and obesity and/or overfed rodent models (38) are paradoxically elevated. Leptin’s effects are largely carried out in the brain (108), and experimental findings are consistent with the notion of impaired leptin access to the brain being a key component of leptin resistance. After chronic high-fat diet feeding, food intake and body weight were resistant to peripherally administered leptin; however, a single bolus of icv leptin in these mice maintained its robust suppressive effects on these parameters (118). Additionally, when 3-day overfed rodents received icv leptin, there was a marked inhibition of food intake (101). However, there is an upper limit to circumventing the resistance to peripherally administered leptin via direct icv leptin administration, since during the course of chronic overfeeding the extent of hypothalamic STAT3 activation by both peripheral and icv leptin administration diminishes (34). Protein tyrosine phosphatase 1B (PTP1B) has been shown to be involved in the blockade of leptin signaling, and indeed neuron-specific PTP1B knockout mice on a chronic high-fat diet had lower fed blood glucose and serum insulin levels, and as such displayed improved insulin sensitivity and glucose tolerance (10). This finding was paralleled by a recent study that demonstrated that the neuron-specific knockout of SOCS3, another suppressor of a leptin-signaling pathway (JAK-STAT), was resistant to chronic high-fat diet-induced weight gain and hyperleptinemia, and were more insulin sensitive as measured by glucose- and insulin-tolerance tests (79), observations that were similarly seen in mice with a haplosufficiency in whole body SOCS3 that were maintained on a high-fat diet (47).

Endoplasmic reticulum (ER) stress, the cellular condition generally characterized by a disruption in protein synthesis and processing, and the subsequent activation of the compensatory unfolded protein response (UPR) has been demonstrated to hold an important role in the progression of obesity-induced peripheral insulin resistance and the establishment of Type 2 diabetes (81). Quite recently, it has been shown that the development of ER stress in the hypothalamus confers leptin resistance. Particularly, mice on a chronic high-fat diet developed ER stress and subsequent UPR activation in the hypothalamus (as determined by upregulated PERK-like ER-resident kinase, or PERK), and when mice were administered icv tunicamycin to upregulate PKR-like UPR activation in the hypothalamus, the development of hypothalamic ER stress in the hypothalamus, leptin-induced hypothalamic STAT3 phosphorylation was abolished (90). XBP1 is a transcription factor that is selectively induced ER stress in the hypothalamus, leptin-induced hypothalamic STAT3 phosphorylation was abolished (90). XBP1 is a transcription factor that is activated in the UPR and upregulates genes encoding, among other proteins, ER chaperones, which assist in protein folding and trafficking to combat ER stress; indeed, mice displaying a neuron-specific knockout of XBP1 showed relatively higher fasting blood glucose and insulin sensitivity (90). Overnutrition-induced hypothalamic ER stress has also been shown to activate a mediator of metabolic inflammation, IKKβ/NF-κB (128). This study also demonstrated that mice that had constitutively active IKKβ in the MBH impaired the activation of Akt and the generation of PIP3 in response to icv insulin and 2) the phosphorylation of STAT3 in response to icv leptin; furthermore, the suppressive effects of icv insulin and leptin on short-term food intake was blunted in these mice (128). Thus the activation of IKKβ/NF-κB in the MBH causes both central leptin as well as central insulin resistance.

Furthemore, the role of insulin sensitivity in the pathogenesis of diabetes, it was determined that hypothalamic insulin signaling via the PI3K pathway was markedly reduced in rodents with STZ-induced hyperinsulinemia (100). An important role for hypothalamic insulin resistance when obese and/or overfed rodents (64) was administration of icv tunicamycin, which significantly increased hypothalamic STAT3 activation, the authors postulated that the increase in lipid availability by overfeeding for intracellular protein folding increased the activity of hypothalamic STAT3 (101). This study also demonstrated that mice that had constitutively active IKKβ in the MBH impaired the activation of Akt and the generation of PIP3 in response to icv insulin and 2) the phosphorylation of STAT3 in response to icv leptin; furthermore, the suppressive effects of icv insulin and leptin on short-term food intake was blunted in these mice (128). Thus the activation of IKKβ/NF-κB in the MBH causes both central leptin as well as central insulin resistance.

In rodents, the infusion of icv insulin lowers glucose production (87); 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). LCPAs 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 icv 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 icv oleic acid bolus was unable to inhibit food intake or suppress GP under conditions of a pancreatic- or hepatic insulin clamp. Interestingly, by pair-feeding rats on the high-fat diet, the ability of icv oleic acid to suppress hepatic GP was restored (78). This provides compelling evidence that the hypothalamic responses triggered by an acute increase in central LCPAs 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 LCPA-CoAs is a critical initiator of the fatty acid-medi-ated homeostatic regulation, the authors specifically postulated that the increase in lipid availability by

Concluding Remarks

This review highlights the role of intrinsic homeostatic mechanisms in the regulation of energy balance and is far from elucidated. Not the least, it is worth emphasizing that, in rodents, the blockade of leptin signaling, and indeed neuron-specific PTP1B knockout mice on a chronic high-fat diet had lower fed blood glucose and serum insulin levels, and as such displayed improved insulin sensitivity and glucose tolerance (10). This finding was paralleled by a recent study that demonstrated that the neuron-specific knockout of SOCS3, another suppressor of a leptin-signaling pathway (JAK-STAT), was resistant to chronic high-fat diet-induced weight gain and hyperleptinemia, and were more insulin sensitive as measured by glucose- and insulin-tolerance tests (79), observations that were similarly seen in mice with a haplosufficiency in whole body SOCS3 that were maintained on a high-fat diet (47).

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overfeeding fails to translate into this increase in the intracellular pool of LCFA-CoA (100). This was indeed the case: when a systemic lipid emulsion designed to double plasma LCFA and hypothalamic LCFA-CoA (64) was administered to overfed rats, the circulating lipids failed to increase hypothalamic LCFA-CoAs (100). An impaired blood-brain barrier LCFA transport cannot account for this effect, since no increase in hypothalamic LCFA-CoAs was also observed in overfed rats when oleic acid was directly infused intrahypothalamic ally (100). Hypothalamic CPT activity was significantly increased in the overfed rats, and remarkably, by hypothalamically inhibiting CPT activity or expression, the authors were able to suppress food intake as well as glucose production in overfed rodents (100). Thus inhibiting hypothalamic lipid oxidation via the inhibition of CPT hyperactivity is sufficient to restore energy balance as well as glucose homeostasis in overfed 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 overfed rodent model (100) 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 a pancreas-islet model of STZ-diabetes (23). Furthermore, ivc lactate suppressed glucose production in normal rodents with experimentally induced hypoinsulinemia and, more significantly, in diet-induced insulin resistance resulting from a 3-day high-fat diet (23). Clearly, further investigation is necessary to elucidate the exact mechanism underlying this selective preservation in central nutrient sensing in models of metabolic disease.

Concluding Remarks

This review highlights the importance of hormone- and nutrient-sensing mechanisms in the CNS that control glucose homeostasis 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 peripherally mediated responses to decrease plasma glucose levels.

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Aside from trauma, GABA can control tumor cell proliferation throughout the body. 

γ-Amino butyric acid and the activation of GABA receptor (GABA_A) have been found to control tumor cell proliferation. In most cases, the control of tumor cell proliferation is mediated by GABA_A receptors. 

Intriguingly, GABA signaling molecules can inhibit tumor cell proliferation. In some cases, GABA signaling molecules can inhibit tumor cell proliferation. 

A recent study has shown that GABA_A receptor activation can inhibit tumor cell proliferation. 


