CNS Regulation of Glucose Homeostasis

The central nervous system (CNS) has been identified as a key regulator of whole body homeostatic controls. 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 hormone and nutrient sensing that control glucose homeostasis. Of note, the inhibition of mitochondrial phosphatidylinositol-3 kinase (MAPK), another downstream branch of insulin signaling, did not affect central insulin’s potent action on glucose production (87). Consistent with these data, decreased IR expression selectively in the hypothalamus, particularly in the arcuate nucleus (ARC), 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 streptozocin (STZ)-induced diabetes (41). Collectively, these findings recognized the CNS as a site of insulin action in regulating glucose homeostasis and, more importantly, implied the criticality of an intact insulin-signaling cascade involving the binding of insulin to its receptor and the subsequent activation of IRS, PI3K, and PKB in such regulation (Figure 1A). Interestingly, with both IRS-1 and -2 being the common isofoms linked to glucose homeostasis (106), molecular mechanisms by which this neural pathway is orchestrated.

The past decade has hosted a remarkable surge in research dedicated to the central nervous system (CNS) in the regulation of glucose homeostasis in particular and discuss the cellular and molecular mechanisms of CNS hormone and nutrient-sensing pathways that regulate glucose homeostasis. Of note, the inhibition of mitochondrial phosphatidylinositol-3 kinase (MAPK), another downstream branch of insulin signaling, did not affect central insulin’s potent action on glucose production (87). Consistent with these data, decreased IR expression selectively in the hypothalamus, particularly in the arcuate nucleus (ARC), 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 streptozocin (STZ)-induced diabetes (41). Collectively, these findings recognized the CNS as a site of insulin action in regulating glucose homeostasis and, more importantly, implied the criticality of an intact insulin-signaling cascade involving the binding of insulin to its receptor and the subsequent activation of IRS, PI3K, and PKB in such regulation (Figure 1A). Interestingly, with both IRS-1 and -2 being the common isofoms linked to glucose homeostasis (106),
Irs-2 seems to have spotlighted itself in the literature on central glucose regulation. Irs-2 protein is highly detectable in the hypothalamus, including but not limited to the arcuate nucleus (ARC) and parventricular nucleus (PVN) (92). Interestingly, whereas constitutive active Irs-2 in the hypothalamus improved insulin sensitivity (41), genetic knock-out of Irs-2 in the hypothalamus and pancreatic β-cell leads to insulin resistance (60, 66), as is seen with selective brain Irs-2 knockout mice (112).

The mechanism downstream of central insulin-signaling to regulate peripheral glucose homeostasis appears to involve the activation of the ATP-sensitive potassium (KATP) channels. The glucose production-lowering effect of systemic or central insulin was abolished by intracerebroventricular (icv) administration of KATP channel blocker (87, 99). Furthermore, mice lacking the SUR1 subunit of the SUR1/Kir6.2 KATP channels impaired the ability of elevated insulin to suppress glucose production (99). To further extend these findings, hepatic branch vagotomy and selective vagal deafferentation indicated that the CNS-liver circuit requires efficient vagal fibers (99), likely triggering an interleukin (IL)-6/signal transducer and activator of transcription (STAT) 3 signaling cascade in the liver to lower glucose production (49). It remains to be determined how the insulin-signaling cascade (i.e., IR → IRS-2 → PI3K → PKB) leads to the activation of KATP channels but the involvement of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) has been suggested. PIP3 directly activates KATP channels in vitro (68), and, more crucially, constitutive activation of PI3K/PIP3 signaling in pro-opiomelanocortin (POMC) neurons increase KATP channel conductance, which hyperpolarizes neurons and results in a hyperphagic phenotype (98) (FIGURE 1A).

SUR1/Kir6.2 KATP channels are characteristically found in pancreatic β-cells (2) and the CNS (32), including hypothalamic ARC neurons known to control energy and glucose homeostasis. The ARC contains an array of neuronal subtypes that are involved in energy and glucose homeostatic regulations, of which two are most extensively studied. The first are neurons that express the anorexigenic products of the peptide POMC. POMC is posttranslationally cleaved to a series of smaller peptides; of note is α-melanocyte-stimulating hormone (α-MSH) (110). Belonging to the co-expressed neuropeptide Y (NPY) and a downregulation of these elucidating feeders (109), leads to competitive binding at MC4R, of these orexigenic and their downstream melanocortin. This “hypothalamic thought to be the glucose homeostasis of NPY” causes insulin to lower food intake. (117) infusion predilection by the downregulation for insulin's induction (7) the generation insensitivity of the neuronal population and not POMC, hepatic glucose circulating insulin-like energy homeostatic potentiates (87). This PI3K, which operates on a signaling through hepatic glucose homeostasis.

Leptin

Leptin as with insulin is indeed another research. It is an acid hormone critical role in energy homeostasis. In leptin-deficient obese, insuline (3, 4), adipose tissue concomitant with was initially adiposity and its function in the hypothalamic arcuate nucleus regulates hepatic glucose fluxes

![Diagram](http://physiologyonline.physiology.org/)
and activator of β3-adrenergic receptors in the liver remains to be established. It is now known that the liver is a major site of leptin action, with leptin receptors expressed in a variety of hepatic cell types. Leptin has been shown to reduce hepatic glucose production and improve insulin sensitivity, both in rodent and human models of obesity and diabetes. Leptin receptors are also expressed in the hypothalamus, where they play a critical role in the regulation of energy balance and food intake. Leptin binds to its receptor, a 7 transmembrane protein, resulting in the activation of intracellular signaling cascades, including the JAK/STAT pathway. In the hypothalamus, leptin signaling is thought to be instrumental in the regulation of energy homeostasis. The metabolism of different nutrients in the hypothalamus, particularly that of glucose and fatty acids, serves roles of polarizing importance with respect to fueling local energy supply for the brain.
Traditionally, this gut hormone is thought to regulate and discrete populations of neurons (52). The hormone secreted by the L-cells of the intestines (119) postprandial secretion of incretin hormones such as derived peptide hormones (72). In fact, it is now established that glucose homeostasis is partly controlled by gut hormones. Thus, an oral glucose load compared with the same insulin levels in humans were significantly greater after an oral glucose load compared with the same 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-PEK signaling cascade that regulate glucose homeostasis remains to be elucidated.

**Glucagon-like peptide 1**

The initial observation that glucagon 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 clearance 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, whereas hypothalamic ARC-dependent 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 iv 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 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 KATP channels represents a possible candidate as the co-inhibition 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 PDG-alpha and insulin sensitive. Indeed, hypothalamic KATP channel blocker prevented the GLP-1-induced suppression of glucose production (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 KATP channels represents a possible candidate as the co-inhibition 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 PDG-alpha and insulin sensitive. Indeed, hypothalamic KATP channel blocker prevented the GLP-1-induced suppression of glucose production (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 production (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 depiction of glucostatic (7) that provided a putative mechanism by which the brain is able to shape the expenditure. Given direct hypothalamic involvement, glucose homeostasis.

**Glucose**

An important feature of the mammalian central nervous system is the control of energy metabolism in neurons within the hypothalamus. Indeed, the hypothalamus plays a critical role in both glucose homeostasis and the regulation of energy intake. In essence, hormones such as insulin, leptin, and 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, whereas hypothalamic ARC-dependent 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 iv GLP-1 administration (107).

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**CNS Nutrient Sensing**

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Glucose

An important source of energy for the majority of mammalian cells, 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 glucogen synthesis and glycogenolysis (63). The metabolic fate of brain glucose has been largely clarified by the proposal of the astrocyte-neuron lactate shuttle (96), which is supported by observations that neuronal activity is coupled to glucose utilization (54, 95, 105, 120) and that neurons preferentially utilize glucose-derived lactate as an oxidative fuel (69). Indeed, the infusion of iv lactate was able to recapitulate the effects of central glucose on blood glucose levels and hepatic glucose production (63). However, the effects of both iv 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 isozyme, 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). Furthermore, 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).

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 modulation of glucose homeostasis. Malonyl-CoA is perhaps an important step in the regulation of hypothalamic lypolic clamp, and increased liver glycogen synthesis increased glucose uptake during a hyperglycemic-euglycemic clamp not only decreased an allosteric effector of ACC activity, and it was recently demonstrated that icv citrate not only decreased hypothalamic “malonyl-CoA boxylase (ACC) as the committed step of de novo fatty acid generation (121). Numerous studies have revealed 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 and as, a result, elicit a substantial suppression of glucose production (83). Thus the regulatory effects of cellular fatty acids in the hypothalamus are extramitochondrial and are likely cytosolic (FIGURE 2, INSET).

The activity of CPT-1 is regulated by malonyl-CoA, which is generated from acetyl-CoA by acetyl-CoA carboxylase (ACC) as the committed step of de novo fatty acid generation (121). Numerous studies have revealed a role of hypothalamic malonyl-CoA in the regulation of feeding and energy expenditure (22, 46, 48, 67, 124), but to date the application of the “malonyl-CoA hypothesis” to the regulation of glucose homeostasis remains limited. Citrate, an intermediate metabolite produced in the mitochondria in the citric acid cycle, is an allosteric effector of ACC activity, and it was recently demonstrated that icv citrate not only decreased food intake and body weight but also resulted in lower blood 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 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 acetyl-CoA synthetase (ACS) by triacsin C, as well as a hepatic branch vagotomy, negated the effects of circulating lipids on glucose production (64). Taken together, the study illustrates that circulating LCFAs can regulate glucose homeostasis via a hypothalamically triggered mechanism that is dependent on 1) the esterification of LCFAs to LCFA-CoAs, 2) functional KATP channels, and 3) neural transmission via the vagus nerve. Additionally, overexpressing malonyl-CoA decarboxylase (MCD) in the hypothalamus of rodents negates the ability of circulating lipids to regulate glucose homeostasis (46). In accordance with the fatty acid-sensing hypothesis, these rats not only had a marked reduction in hypothalamic malonyl-CoA levels but also a concomitant decrease in LCFA-CoA abundance (46). Recently, we have demonstrated that this increase in circulating lipids lowers glucose production via a hypothalamic protein kinase C (PKC)-dependent mechanism (183). Furthermore, the pharmacological activation of hypothalamic PKC was sufficient to lower hepatic glucose production, an effect that was nullified with the pharmacological or molecular disruption of hypothalamic KATP channels (183), altogether, these results support the notion that the activation of hypothalamic PKC is necessary for central lipid-sensing mechanisms to lower glucose production via the KATP channel-dependent pathway (FIGURE 2, INSET).

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 mTORC 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 mTORC 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, the possibility that hypothalamic sensing mechanisms are involved in the regulation of glucose homeostasis, and the potential involvement of hypothalamic energy-sensing mechanisms in the control of glucose homeostasis is supported by these findings. The metabolism of amino acids serves roles beyond fueling local energy needs, and it comes to make up an important nutrient-transport system. Hypothalamic amino acid-sensing pathways integrate the nutrient-sensing mechanisms and the extent to which they influence hormone secretion is beginning to be understood.
As lipid influx and glucose production are not known, the role of these metabolic pathways in the hypothalamus remains unclear. 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...
(26) and obese 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 glucokinase and insulin-stimulated oxidation (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 (68). 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 selectively induce 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 and placed on a high-fat diet exhibited hyperleptinemia, hyperinsulinemia, and elevated fasted blood glucose (90). Additionally, these neuronal XBP1-deficient rodents had diminished glucose tolerance and insulin sensitivity (90). Overnutrition-induced hypothalamic ER stress has also been shown to activate a mediator of metabolic inflammation, IKK/NF-κB (128). This study also demonstrated that mice that had constitutively active IKKβ in the MBH impaired the Z cl activation of Akt and the generation of PIP3 in response to icv insulin and Z cl 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 lep- tin and as well as glucose homeostasis. Thus inhibition of central hypothalamic inflammation, the appetite, as well as glucose homeostasis.

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 PI3K 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 (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 adenosinergic 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 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, the ability of icv oleic acid bolus was impaired 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 is a critical initiator of the fatty acid-mediated homeostatic regulation, the authors specifically postulated that the increase in lipid availability by overfeeding from central to peripheral tissues, the activation of ER stress, PKR-like ER-resident kinase (PERK), and is far from the only mechanism that is at work in neurons that control glucose metabolism. In the context of overfeeding and is a component of the metabolic syndrome.

Concluding Remarks

This review has focused on the role of central hypothalamic mechanisms in the control of leptin’s actions, and is far from the only mechanism that is at work in neurons that control glucose metabolism. In the context of overfeeding and carbohydrate overconsumption, the role of central hypothalamic mechanisms, such as hypothalamic ER stress, PKR-like ER-resident kinase (PERK), and is far from the only mechanism that is at work in neurons that control glucose metabolism. In the context of overfeeding and carbohydrate overconsumption, the role of central hypothalamic mechanisms, such as hypothalamic ER stress, PKR-like ER-resident kinase (PERK), and is far from the only mechanism that is at work in neurons that control glucose metabolism.
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 impeded blood-brain barrier LCFA transport cannot account for this effect, since no increase in hypothalamic LCFA-CoAs was observed in overfed rats when oleic acid was directly infused intrahypothalamically (100). Hypothalamic CPTI activity was significantly increased in the overfed rats, and remarkably, by hypocalorically inhibiting CPTII 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 CPTII 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 (103) in which hypothalamic lipid sensing per se is impaired (78). Additionally, an acute increase in central lactate has been shown to lower plasma glucose levels and glucose production in an acute hypotermia model of SITZ-diabetes (23). Furthermore, intraventricular 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 mechanism underlying this selective preservation in central nutrient sensing in metabolic disease.

Concluding Remarks

This review highlights the importance of hormone-induced nutrient sensing 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.

References


10. Bence KK, Delibegovic M, Xue B, Gorgun CZ, Hotamisligil GS, Spiegelman BM, Glass CK. P3 in response to an acute rise of nutrients, the brain triggers peripheral metabolic responses to decrease plasma glucose levels.


γ-Aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the brain and plays a crucial role in neurodevelopment and neural function. The activation of GABA receptors can modulate neuronal excitability and contribute to the control of neuronal development and plasticity. GABA's actions are mediated through GABA receptors, which are present in various regions of the brain and are involved in a wide range of functions, including synaptic transmission, learning, memory, and behavior.

Intriguingly, GABA signaling molecules are known to control tumor cell proliferation, and GABA's role in tumor proliferation has been extensively studied. GABA and its derivatives have been shown to exhibit antiproliferative effects on various types of cancers, including glioblastoma, breast cancer, and melanoma. These effects are thought to be mediated through the activation of GABA receptors, which can inhibit cell proliferation and promote cell death.

Recent studies have also suggested that GABA signaling may play a role in the development of stem cells. Stem cells are a type of cell that can differentiate into various cell types and are essential for tissue repair and regeneration. GABA signaling has been implicated in the regulation of stem cell differentiation and proliferation, and studies have shown that GABA can promote the proliferation of peripheral stem cells through the activation of GABA receptors.

Furthermore, GABA's role in the control of tumor proliferation may suggest that GABA signaling molecules could be involved in the development of tumor heterogeneity. Tumor heterogeneity refers to the diversity of tumor cells within a single tumor, and it has been shown that GABA signaling may contribute to the development of tumor heterogeneity, which can affect tumor progression and response to therapy.

In conclusion, GABA's role in cancer and stem cell biology highlights the complexity of GABA signaling and its potential as a therapeutic target for the treatment of cancer and stem cell disorders. Further studies are needed to fully understand the mechanisms underlying GABA's role in cancer and stem cell biology and to explore potential therapeutic applications.