CNS Regulation of Glucose Homeostasis

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

The central nervous system (CNS) has been identified as a key regulator of whole body homeostatic processes. 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 floor of the fourth ventricle resulted in glucosuria (11). It was not until over a century after Bernard’s initial observation that the boom in the field occurred. Over the past decade, it has been shown that the CNS senses insulin (27, 41, 49, 56, 57, 87), namely insulin, leptin, and, most recently identified, glucagon-like peptides (GLP-1 and 2) nutrients (63, 85, 93), namely fatty acids and glucose, to regulate glucose 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 insulin secretion that results in chronic hyperglycemia (30). Since diabetes is characterized by hyperglycemia, the elucidation of defects in hypothalamic hormone and nutrient-sensing pathways that regulate glucose homeostasis will shed light on the central component that perpetuates this metabolic disease. In this review, we discuss the cellular and molecular mechanisms of CNS hormone and nutrient sensing that control glucose homeostasis.

CNS Hormone Action

Insulin

The well-studied and extensive action of insulin in the periphery, from altering 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 (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 glyceric 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),...
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 (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 established by intracerebroventricular (ivc) 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 (60), and, more crucially, constitutive activation of PI3K-PKB 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 a-melanocyte stimulating hormone (α-MSH) (110).Belongs in that co-expression of neuropeptide Y (NPY) and a-melanocortin (110) leads to signaling: direct competitive binding at MC4R, of POMC and these orexigenic peptides and their downstream melanocortin, this "hypothalamic set point" thought to be involved in food intake (45). Infusion precludes the generation of a "hyperphagic" state and glucose homeostasis. This is likely caused by the generation of a "hypothalamic set point" thought to be involved in food intake (45). Infusion precludes the generation of a "hyperphagic" state and glucose homeostasis.

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and activator de in the liver remains to be charact eristically known to con- sist of two distinct cascades sum- marized as K_{cat} in the liver and adipose tissue. The ARC con- serves roles of polarizing importance with respect to fueling local energy supply for the brain. “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.”

Just as its control of energy homeostasis is largely elicted 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 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 (14/14) 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 1B). The first of the two is the well established STAT3-dependent pathway. The long form of leptin receptor (LbR) belongs to the class I of cytokine receptors (113), and, upon binding of leptin, Janus kinase 2 (Jak2) is acti- vated, 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/a mice, having life-long obliteration in leptin-STAT3 sig- naling due to a replaced residue in the LbR (Tyr1138Ser), were found to be severely hepatic insulin resistant (19). In the same study, by using two comple- mentary approaches to prevent central STAT3 activation (specifically the icv infusion of the pharmacological
Traditionally, this gut hormone is thought to regulate hormone secreted by the L-cells of the intestines (119) glucagon-like peptide 1 (GLP-1) (31). GLP-1 is a potent derived peptide hormones (72). In fact, it is now established that the insulin secretion is partly controlled by gut-derived peptide hormones (72). In this context, 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 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. Surprisingly, the hypothalamic leptin signaling is not a recent discovery: glucostatic (7) information that the brain is not a recent discovery: glucostatic (7) information that the brain is.
GLP-1-induced hormones, the partitioning of and exert their homeostatic function in 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; this occurred via a curtailing of both gluconeogenesis and glycogenolysis (63). The metabolic fate of glucose in the hypothalamus is an essential biochemical step in the regulation of glucose homeostasis. Interconversion of glucose to acetyl-CoA via the inhibition of dihydroxyacetone (DCA) (63), which ultimately promotes the conversion of pyruvate dehydrogenase (PDH) kinase, in turn activating PDH (50).

The importance of this metabolic coupling between neurons and glia via the generation and intracellular trafficking of lactate in the CNS regulation of glucose homeostasis has also been demonstrated in a few other notable studies. Specifically, the perfusion of the ventromedial hypothalamus (VMH) with lactate was sufficient to severely blunt the counterregulatory hormone response to hypoglycemia, with a marked suppression of both glucagon and epinephrine release during a hypoglycemic clamp, a finding also seen when glucose was perfused into the VMH (15). The caudal hindbrain has also been established as a sensor of local glucoactivation which subsequently activates the neural pathways required to elicit 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.

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_{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 interest, 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 K_{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 hypothalamic ability to regulate glucose homeostasis.
In 2002, it was first demonstrated that the administration of LCFAs into the third cerebral ventricle triggers a neural pathway to regulate energy as well as glucose homeostasis. Of note, these rodents treated with ivc oleic acid had lower plasma insulin and glucose levels, indicating enhanced insulin sensitivity, and with the use of a basal insulin pancreatic clamp this was confirmed, since ivc oleic acid was found to markedly suppress hepatic glucose production (85). Interestingly, the infusion of the medium-chain fatty acid octanoic acid did not yield the same results, revealing a specificity in the nature of the fatty acid-nutrient signal (85). The ivc co-administration of the KATP channel blocker glibenclamide with oleic acid was able to nullify the glucose production-lowering effect of ivc 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 (99). Based on the aforementioned observation that ivc 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 ivc administered LCFAs (FIGURE 2, INSET). With the use of a CPT-1 ribozyme as well as pharmacological CPT-1 inhibitors, it was found that a decrease in CPT-1 activity was sufficient to lead to an increase in the concentration of LCFAs-CoAs and, as a result, elicit a substantial suppression of glucose production (83). Thus the regulatory effects of cellular fatty acids in the 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, 46, 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 ivc 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 ivc 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 glycolysis (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 i) the esterification of LCFAs to LCFAs-CoAs, ii) functional KATP channels, and iii) 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 (163). 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 remains limited. The possibility that hypothalamic amino acid-sensing mechanisms occur via mTOR-dependent or -independent mechanisms is still emerging.

The metabolic and functional role of central amino acid-sensing mechanisms is not limited to the hypothalamus, but rather extra-adrenal tissues and other endocrine glands also respond to circulating amino acids, revealing specificity in the nature of the amino 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 (163). 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).
As lipid infusion increases glucose production and a rise in adipocytes, the role of the hypothalamus in the regulation of 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 an utmost priority.

The metabolism of different nutrients in the hypothalamus, particularly that of glucose and fatty acids, serves roles of polarizing importance with respect to fueling local energy supply for the brain. But when it comes to maintenance of whole body homeostasis, these nutrients appear to form a united front and collectively serve as a nutrient surfeit signal, activating hypothalamic pathways that ultimately initiate the CNS-mediated regulation of glucose homeostasis (FIGURE 2). LCFA-CoA and malonyl-CoA have emerged as the molecules of focus that are poised to integrate the activation of glucose- and fatty acid-sensing mechanisms in the hypothalamus; however, the extent to which hypothalamic nutrient-sensing pathways interact with those of the previously detailed hormone sensing is uncertain. As such, the integration and possible co-dependence of central nutrient and hormone-sensing pathways remains an area of interest that is open to further scrutiny.

**Implications for Diabetes and Obesity**

The numerous studies outlined thus far in this review have been instrumental in advancing the importance of brain, in particular the hypothalamus, in processing acute changes in hormonal signaling and nutrient availability and triggering a neuronal circuit to regulate glucose homeostasis. When it comes to this homeostatic regulation in the face of metabolic disease characterized by nutrient excess and/or dysregulated hormone action, experimental evidence, in general, points to a decreased effectiveness of this circuitry; however, there are some notable exceptions. In mice that are genetically obese and lack functional leptin (ob/ob), the administration of leptin potently reverses obesity, lowering their food intake and body weight and normalizing plasma glucose and insulin levels (97). However, leptin levels in obese humans...
deficient rodents had diminished glucose tolerance (90). Overnutrition-induced hypohalamic 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 J1 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 (101).

Furthemore, the role of central insulin resistance in the pathogenesis of diabetes, it was determined that hypohalamic insulin signaling via the PI3K pathway was markedly reduced in rodents with STZ-induced uncontrolled diabetes (41). Furthermore, enhancing PI3K signaling via adenoaviral gene therapy was found to enhance the ability of peripherally administered insulin to lower glucose levels, whereas pharmacological inhibition of hypohalamic 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 adenoviral overexpression of dominant-negative S6K in the MBH was able to reverse the observed hypohalamic 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-fat 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-CoA is a critical initiator of the fatty acid-mediated homeostatic regulatory, the authors specifically postulated that the increase in lipid availability by overfeeding for circulating periphery.}


thus, the authors concluded that overfeeding for circulating periphery. This review highlights the importance of intracellular and extracellular signaling in the hypothalamus. Specifically, the study of ICV-based models of nutrient availability and signaling within the hypothalamic nuclei is vital for our understanding of the complex mechanisms that control food intake and energy balance. Future studies should aim to elucidate the specific contributions of each signaling pathway to the regulation of energy homeostasis, particularly in the context of obesity and type 2 diabetes.


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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-CoA (100). An impeded blood-brain barrier LCFA transport cannot account for this effect, since no increase in hypothalamic LCFA-CoA was also observed in overfed rats when oleic acid was directly infused intrahypothalamically (100). Hypothalamic CPT1 activity was significantly increased in the overfed rats, and remarkably, by hypothalamically inhibiting CPT1 activity or expression, the authors were able to suppress food intake as well as glucose production in overfed rodents (106). Thus inhibiting hypothalamic lipid oxidation via the inhibition of CPT1 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 a rodent model of STZ-diabetes (23). Furthermore, i.c.v. 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 models of metabolic disease.

Concluding Remarks

This review highlights the importance of hormone- and nutrient-sensing mechanisms in the CNS that control glucose homeostasis. The pieces are presented individually, yet the puzzle remains to be assembled and is far from being complete. Notably, the specific mechanisms 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 effect the ability to inhibit food intake and decrease plasma glucose levels.

Graduate Award from BBDC, University of Toronto. T. K. T. Lam holds the John Kitson McIvor Chair in Diabetes Research at the University of Toronto. We apologize to colleagues whose work has not been specifically referenced due to space limitations.

References


γ-Amino butyric acid (GABA) is a neurotransmitter that plays a crucial role in the brain and peripheral nervous system. Its activation throughout development becomes clear as a control mechanism in many diseases, including cancer.

Both the brain and peripheral organs (if not adult stem cells) may contain adult stem cells. Here, it is suggested that GABA may control tumor allosteric inhibitors by reducing tumor growth.