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 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 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 peptide (GLP)-1, and leptin, and most recently identified, glucagon-like peptides (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 peptide (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 hepatic glucose metabolism to modifying extrahepatic 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 (10). 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 this 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 NIKKO mice (18). Further delineating the downstream insulin signaling cascade, hypothalamic overexpression of insulin receptor substrate (IRS)-2 and protein kinase-B (PKB, or Akt) via adenoviral gene therapy significantly improved the glycemic response to an insulin injection in streptozotocin (STZ)-induced diabetes (41). Collectively, these findings recognized the CNS as an integral component of 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 regulations (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 is in the hypothalamus improved insulin sensitivity (41), genetic knock-out of IRS-2 in the hypothalamus and pancreatic β-cell leads to insulin resistance (60, 66), as is seen with selective brain IRS-2 knockout mice (112).

The mechanism downstream of central insulin-signaling to regulate peripheral glucose homeostasis appears to involve the activation of the ATP-sensitive potassium (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 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 → PPIK → 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 vivo (68), and, more crucially, constitutive activation of PPIK-PKB signaling in pro-opiomelanocortin (POMC) neurons increases 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 family of neuropeptides Y (NPY) and a significant role in feeding is its receptor: MC4R, which is expressed in the ARC as well as other hypothalamic nuclei (109). The MC4R is a G protein-coupled receptor that co-expresses Y (NPY) and α-MSH, and signaling mediated through the MC4R is thought to be competitive to that of orexigenic neuropeptides such as NPY and their downstream pathways. This “hypothalamic” feeding circuit is thought to be a major determinant of feeding behavior and glucose homeostasis.

As with most hormones, insulin has a significant role in the regulation of sugar metabolism, and its role in the regulation of glucose homeostasis is well established. Insulin plays a critical role in energy balance and glucose homeostasis. It is secreted in response to increased plasma glucose concentrations and is essential for the regulation of glucose metabolism in peripheral tissues, including the liver, muscle, and adipose tissue. Insulin binds to its receptor, which is a transmembrane protein with an extracellular domain and an intracellular domain. The activation of the insulin receptor leads to the activation of two major downstream signaling pathways: the insulin receptor substrate (IRS)-PI3K-Akt pathway and the phosphatidylinositol 3-kinase (PI3K)-Akt pathway. These pathways play a crucial role in the regulation of glucose metabolism, lipid metabolism, and protein synthesis.

**Figure 1. Hormonal action in the hypothalamic arcuate nucleus regulates hepatic glucose fluxes**

A: insulin, binding to its receptor, activates IRS and PISK, PI3K phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP2) to generate PIP3, which subsequently activates PPK2, which subsequently activates the SUR1/Kir6.2 KATP channels to alter signaling in neurons such as the NPY/AgRP neuron. B: lepomin binding to its receptor, activates JAK/STAT3 pathway, which results in a decrease in hepatic glucose production. C: more recent, ARC GLP-1 has been shown to decrease hepatic glucose production, likely through SUR1/Kir6.2 KATP channel-dependent mechanisms in the POMC neurons.
and activator de in the liver remains to be cascade (i.e., IR hormone (α-MSH), which by binding the melanocortin receptor 4 (MC4R) inhibits feeding (110). Belonging to the second subtype are neurons that co-express the orexigenic peptides neuropeptide Y (NPY) and agouti-related peptide (AgRP). The activation of these orexigenic neurons, in addition to stimulating feeding by increasing NPY/AgRP signaling (109), leads to a twofold inhibition of anorexigenic signaling: directly synapsing with POMC neurons or competitive binding of AgRP to the α-MSH binding site at MC4R, collectively resulting in the antagonism of POMC’s anorexigenic effects. The interplay between these orexigenic and anorexigenic neuronal subsets and their downstream effectors 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 NPY or melanocortin receptor antagonist causes insulin resistance independent of changes in food intake (1, 70, 117). More importantly, icv NPY infusion precludes the inhibition of glucose production elicited by circulating insulin, suggesting that the downregulation of NPY release is likely a prerequisite for insulin’s ability to suppress hepatic glucose production (117). Moreover, it was elegantly shown with 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 MC3/4R antagonist did not alter the effect of circulating insulin to inhibit hepatic glucose production (87). Together, these data suggest that insulin operates on a melanocortin-independent pathway, signaling through NPY/AgRP and not POMC, to regulate hepatic glucose production (Figure 1A).

Leptin

As with insulin, the discovery of leptin (129) was indeed another milestone in obesity and diabetes research. It is well documented that this 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).

“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). Glucagon-like peptide 1 (GLP-1) (31). GLP-1 is a potent published that this "incretin effect" is mediated by the load given intravenously gives rise to the thoughts that after an oral glucose load compared with the same insulin levels in humans were significantly greater. The initial observation that glucose clearance and...leptin to activate PI3K is a likely candidate of the JAK-STAT pathway, suppressor of cytokine signaling (SOCS-3), in selective brain regions and neuronal populations was able to increase leptin sensitivity and improve glucose homeostasis (56, 127). Although the hypothalamic leptin receptor-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 P3K to reduce food intake (82), it seems that the binding of leptin to its receptor to activate P3K is a likely candidate. Indeed, hypothalamic infusion of P3K inhibitor curtailed the improvement in insulin sensitivity elicited by restoration of functional ARC leptin receptors in leptin receptor-deficient fa/fa rats (86), suggesting that hypothalamic leptin, like insulin, activates P3K to regulate glucose homeostasis. However, it is highly plausible that the activation of P3K by leptin and insulin to regulate glucose homeostasis occurs in different neuronal populations since leptin activates P3K in POMC but not NPY/AgRP neuron (126), whereas insulin signaling in AgRP but not POMC neurons activates glucose homeostasis (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 glucostatic effects of central GLP-1 action are an essential component of the CNS glucostatic feedback loop that neurons derived lactate dehydrogenase (LDH) effectors are co-infused in the ARC effectively lowered hepatic glycogen storage in preparation for the next fasting state (57). A similar increase in insulin secretion upon an iv glucose tolerance test was observed with direct icv GLP-1 administration (107). GLP-1 receptor mRNA is widely present in the brain, including but not limited to the hippocampus, hypothalamic nuclei such as the ARC and PVN, and the hindbrain (74). Of these sites, the PVN and hindbrain are known to mediate the anorectic effect of CNS GLP-1 (43, 73, 115). Interestingly, although GLP-1 receptors are found in the ARC and do not regulate food intake, they do mediate GLP-1 action to regulate peripheral glucose homeostasis (107) (FIGURE 1C). Administration of GLP-1 into the ARC effectively lowered hepatic glucose production, a finding not reproducible with GLP-1 administration into the PVN (107). Although the activation of CNS GLP-1 system and the mechanism(s) behind CNS GLP-1 regulation of glucose homeostasis are yet to be clarified, the activation of KATP channels represents a possible candidate as the co-infusion of KATP channel blocker prevented the GLP-1-induced suppression of glucose production (107). Furthermore, this glucose production-suppressing effect of central GLP-1 appears to be POMC-mediated since 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 infusion of a GLP-1 antagonist or agonist, it was found that CNS GLP-1 signaling is involved in regulating peripheral insulin secretion and partitioning of glucose disposal, which leptin controls glucose homeostasis (107). Specifically, GLP-1 receptor mRNA was found to be present in both brain levels, and a recent observation, this occurs in the hypothalamic and brain glucose homeostasis (107). 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not a recent development. In fact over 50 years ago, the glucostatic (71) and lipostatic (55) hypotheses proposed that circulating nutrients generated in proportionate amounts to storage depots serve as signals to the brain to initiate alterations in energy intake and expenditure. However, only recently has the notion of direct hypothalamic nutrient sensing become a thoroughly demonstrated and credible means of controlling glucose homeostasis.

Glucose

An important source of energy for the majority of mammalian cell types, glucose is particularly vital for the brain where it is essentially the sole substrate for energy metabolism. The discovery of glucose-sensing neurons within satiety and feeding centers of the hypothalamus (4, 89) 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 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 lactate was able to recapitate 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 the preferentially lactate-generating downregulation of LDH-A [the muscle isoform that, within the hypothalamus, is expressed exclusively in the glial cells (13) (17), this finding suggests that metabolism of glucose to lactate and subsequently pyruvate in the hypothalamus is an essential biochemical step in the regulation of glucose homeostasis (FIGURE 2). Furthering this notion is the suppression of glucose production resulting from the hypothalamic administration of dichloroacetate (DCA) (63), which ultimately promotes the conversion of pyruvate to acetyl-CoA via the inhibition of pyruvate dehydrogenase (PDH) kinase, in turn activating PDH (50). The importance of this metabolic coupling between neurons and glia via the generation and intracellular trafficking of lactate in the CNS regulation of glucose homeostasis has also been demonstrated in a few other notable studies. Specifically, the perfusion of the ventromedial hypothalamus (VMH) with lactate was sufficient to severely blunt the counterregulatory hormonal response to hypoglycemia, with a marked suppression of both glucagon and epinephrine release during a hypoglycemic clamp, a finding also seen when glucose was perfused into the VMH (15). The caudal hindbrain has also been established as a sensor of local glucoprivation which subsequently activates a response to restore glycemia; and in an attempt to uncover the potential metabolic sensors involved, the role of lactate in particular was recently examined (94). Indeed, infusing an inhibitor of monocarboxylate transporters (which lactate transport is dependent on) into the caudal fourth ventricle of rodents resulted in increased blood glucose levels (94). Conversely, an increase in caudal hindbrain lactate worsened insulin-induced peripheral hypoglycemia (94).

An acute elevation in circulating glucose is known to markedly suppress liver glucose production (75, 105, 114). When plasma glucose levels were doubled in the presence of a concurrent intrahypothalamic infusion of oxamate, this inhibitory action of acute hyperglycemia on glucose production was blunted by 40% (63), revealing that the activation of hypothalamic lactate metabolism is a critical component of the effectiveness of glucose per se. Circulating lactate has also been demonstrated to regulate hepatic glucose fluxes (53), and it was recently shown that the inhibition of either hypothalamic LDH or KATP channels during a physiological increase in circulating lactate led to an increase in hepatic glucose production (58). In recent years to date there 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.
undoubtedly further its physiological relevance.

fatty acid sensing on glucose homeostasis should
malonyl-CoA is perhaps an important step in the regu-
lycemic clamp, and increased liver glycogen synthesis
food intake and body weight but also resulted in lower
ly demonstrated that icv citrate not only decreased
an allosteric effector of ACC activity, and it was recent-
boxylase (ACC) as the committed step of de novo fatty
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
citrated 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-
activity was sufficient to lead to an increase in the concentration of LCFAs-CoAs and, as a result, elicited
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 car-
boxylase (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 recent-
ly demonstrated that citrate not only decreased food intake and body weight but also resulted in lower
blood glucose levels during a glucose tolerance test, increased glucose uptake during a hyperglycemic-eug-
lycemic clamp, and increased liver glycogen synthesis (21). Thus promoting the formation of hypothalamic
malonyl-CoA is perhaps an important step in the regu-
lation 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 iv infusion of a KATP channel blocker
was administered during an intravenous lipid infu-
was there a significant elevation in glucose pro-
duction, which was attributed to an increase in glucose
lysogenesis (64). The results of these pharmacologi-
cal findings were confirmed with a genetic approach
using mice deficient in the KATP channel subunit Sur1
(64). Pharmacological inhibition of hypothalamic
acyl-CoA synthetases (ACS) by triacsin C, as well as a
hepatic branch vagotomy, negated the effects of circu-
lating lipids on glucose production (64). Taken togeth-
er, the study illustrates that circulating LCFAs can
generate glucose homeostasis via a hypothalamically
triggered mechanism that is dependent on i) the
estronization of LCFA to LCFAs-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 regu-
late 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 abun-
dance (46). Recently, we have demonstrated that this
increase in circulating lipids lowers glucose produc-
tion via a hypothalamic protein kinase C (PKC)-
dependent mechanism (161). 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
(163); 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 glu-
cose and some fatty acids and particularly the
branchi-amylyz isolated amino acid leucine (125). Indeed,
when a low dose of leucine was administered into the
third cerebral ventricle of rodents, leading to the activa-
tion 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 medi-
ated 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

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As lipid infu-
sion increases glucose produc-
tion, the role of the hypothalamic
systemSur1
subunit as a glucose or
acetoacetate sensor 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 -independ-
ent mechanisms remains an utmost priority.

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. But when it
comes to maintenance of whole body homeostasis,
these nutrients appear to form a united front and col-
lectively 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 inter-
est 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 regu-
late glucose homeostasis. When it comes to this home-
ostatic 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 function-
able 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

FIGURE 2. Glucose and fatty-acid sensing pathways in the hypothalamus

Glucose is taken up by astrocytes where it is glycolytically metabolized to pyruvate. In astrocytes, pyruvate is pref-
erentially converted to L-lactate by lactate dehydrogenase A (LDH-A). Lactate is then taken up by neurons and is
preferentially converted back to pyruvate by means of LDH-B. Finally, pyruvate is converted to acetyl-CoA by pyru-
ivate dehydrogenase (PDH). Intracellular long-chain fatty acids (LCFAs) are immediately esterified to LCFA-
CoAs upon entry into cells via acyl-CoA synthetases (ACS), and LCFA-CoA gain access to the mitochondria to
undergo β-oxidation via the acyltransferase carnitine palmitoyltransferase-1 (CPT-1), located on the outer mito-
chondrial membrane. Cellular fat oxidation is regulated by the availability of malonyl-CoA, which potently inhibits
CPT-1 activity. Malonyl-CoA, in turn, is mainly derived from acetyl-CoA via the enzyme acetyl-CoA carboxylase
(ACC), which marks a point of convergence between glucose- and fatty acid-sensing mechanisms. Finally, ACC is
allosterically inhibited by AMP-activated protein kinase (AMPK)-mediated phosphorylation. The increased flux
through both hypothalamic glucose and fatty acid metabolism has been shown to lower hepatic glucose produc-
tion via a K<sub>ATP</sub> channel-dependent mechanism.
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 adipocyte lipolysis, which is typically resistant to leptin in rodents (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 reduced food 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. Particukarly, mice on a chronic high-fat diet developed ER stress and subsequent UPR activation in the hypothalamus (as determined by upregulated PKE-like ER-resident kinase, or PERK), and when mice were administered icv minocyclin 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 XBP1f 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, IKKβ/NF-κB (100). This study also demonstrated that mice that had constitutively active IKKβ in the MBH impaired the IC 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 glucose insensitivity (101).

Furtheing 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 (47); however, this regulatory ability of hypothalamic insulin was lost after merely 1 day of high-fat feeding (88). The diminished phosphorylation of hypothalamic Akt and unchanged heptic insulin signaling revealed that this acute overfed model had selective hypothalamic insulin resistance (88). Furthermore, these rodents had significantly increased S6K activity, and the adenosine 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 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 LCPAs is a critical initiator of the fatty acid-mediated homeostatic regulatory system, the authors specifically postulated that the increase in lipid availability by overfeeding fuels intracellular signaling pathways.

Conclusion

This review highlights the impact of overnutrition on the brain and nutrient control glucose metabolism. Although the role of leptin and its receptors is far from fully elucidated, we have demonstrated that there is a strong relationship between obesity and the impairment of leptin signaling in the brain. It is clear that both leptin and insulin play a role in the control of energy balance and glucose metabolism. A better understanding of these mechanisms is crucial for the development of effective treatments for obesity and type 2 diabetes.
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 LCFAa 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 in overfed rats when oleic acid was directly infused intrahypothalamically (100). Hypothalamic CPTI activity was significantly increased in the overfed rats, and remarkably, by hypothalaminically inhibiting CPTI 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 CPTI 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 lipids 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 early onset model of STZ-diabetes (23). Furthermore, icv lactate suppressed glucose production in normal rodents with experimentally impaired the observed high-fat diet-induced insulin to glucose production in an early onset model of STZ-diabetes (103) in which hypothalamic lipid sensing per se is impaired (64). This provides a possible mechanism by which increased circulating lactate failed to increase hypothalamic LCFA-CoA and hypothalamic CPTI activity in overfed rats, the circulating lipids failed to increase hypothalamic LCFA-CoAs (100). Thus inhibiting hypothalamic lipid oxidation via the inhibition of CPTI hyperactivity is sufficient to restore energy balance as well as glucose homeostasis in overfed rodents.

Concluding Remarks

This review highlights the importance of hormone- and nutrient-sensing mechanisms in the CNS that control glucose homeostasis. The pieces are presented individually, yet the puzzle remains to be assembled. This provides a possible mechanism by which increased circulating lactate failed to increase hypothalamic LCFA-CoA and hypothalamic CPTI activity in overfed rats, the circulating lipids failed to increase hypothalamic LCFA-CoAs (100). This was indeed the case: when a systemic lipid emulsion designed to double plasma LCFAa 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 also 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 hypothalaminically inhibiting CPTI 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 CPTI 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 lipids 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 early onset model of STZ-diabetes (23). Furthermore, icv lactate suppressed glucose production in normal rodents with experimentally impaired 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.


168


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γ-Amino butyric acid and the activation of GABA control throughout the development of many different organs (if not only limited to containing adult stem cells. Here may be altered by 10.220.32.246 on June 17, 2017 http://physiologyonline.physiology.org/ Downloaded from

GABA's Control of Peripheral Tumor Proliferation

Aside from tumor proliferation, GABA has been shown to control tumor cell proliferation through GABA receptors. In many cases, the GABA signaling molecule has been shown to inhibit tumor growth and induce apoptosis. In most cases, GABA receptors are present on tumor cells and may be altered to reduce tumor proliferation. 

References


