Chapter 6
The Role of Brain in Glucose Metabolism

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Foreword

. . .Hence we could say that in a diabetic individual the liver secretes too much. The matter which produces sugar cannot be transformed into a product with a more complex organization. The dis-assimilation has become prevalent. Therefore we can consider diabetes as a disease of the nervous system caused by excessive activation of the disassimilator nerve of the liver, which drives the premature disassimilation of [glycogen, translator note] matter that would otherwise be used for nutrition. Hence the treatment of diabetes should address the nervous system. Stimulating the sympathetic nerve could be a valuable tool. But, in order to achieve a treatment with a rationale based on physiology, we should answer many questions, which are still awaiting a solution from the science of physiology.

> Claude Bernard in "Leçons sur les phénomènes de la vie". Cours de physiologies Generale du Museum d'Histoire Naturelle,[1]

Neuroendocrine Control of Glucose Homeostasis

The notion of central nervous system (CNS) control of glucose metabolism has evolved since its initial introduction in the mid-nineteenth century.[2] Claude Bernard first introduced the concept of glucose homeostasis and described a glucoregulatory system involving a brain–liver connection.[1] He observed that blood glucose levels remain surprisingly constant in the face of many physiologic conditions that could affect glucose availability and utilization. Based on his experiments on the puncture of the floor of the fourth cerebral ventricle, he argued that glucose constancy of the "milieu interieur" was regulated by the CNS via two hepatic nerves that would control glucose flux in opposite and physiologically balanced way: the "nerf assimilateur" that stimulates glucose uptake and the "nerf desassimilateur" that stimulates glucose release (Fig. 6.1). The pancreatectomy experiments of Minkwoski in the late nineteenth century and the discovery of the pancreatic hormones insulin and glucagon in the twentieth century shifted the attention to the pancreatic islets as the major site of glucoregulation, substituting neural control of glucose production and utilization to an endocrine control (glucagon and insulin).[2] Work by Shimatzu and colleagues in 1970 underscored the importance of the CNS in the control of glucose homeostasis via innervation of liver and pancreas.[3] In the past few decades, a more complex neuroendocrine model of glucoregulation is emerging (Fig. 6.1c). Several glucoregulatory hormones [including insulin, glucagon-like peptide 1 (GLP1) and some adipokines] initially believed to control glucose homeostasis via their receptors in peripheral organs can affect glucose metabolism via stimulation of their CNS receptors. In addition, circulating nutrients, including glucose and fatty acids, are directly implicated in the regulation of their homeostasis via their ability to stimulate nutrient-sensing pathways in the CNS.

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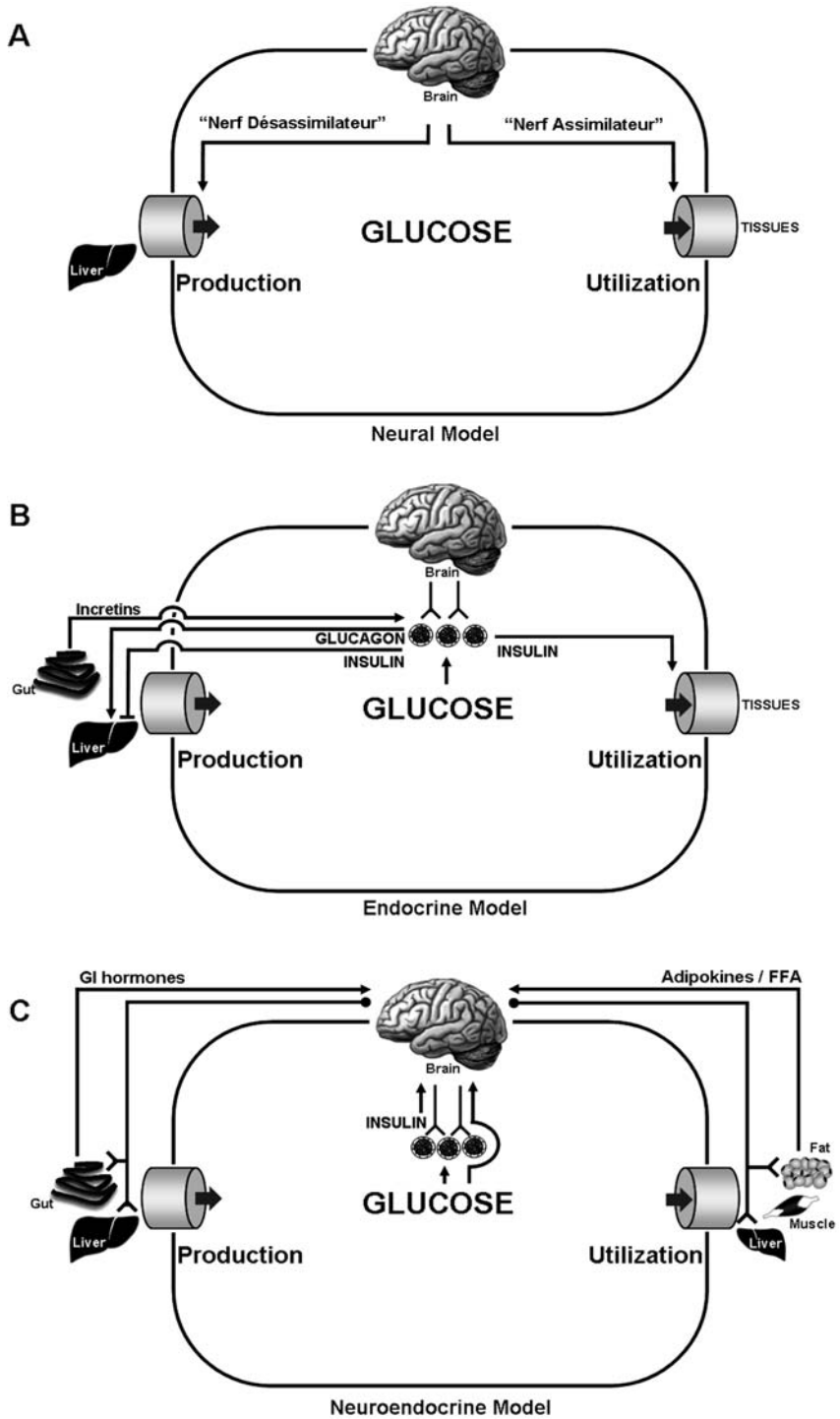

Fig. 6.1 Role of the brain in control of glucose homeostasis: schematic representation of previous and current models. (**a**) Neural model as proposed by Claude Bernard. (**b**) Endocrine (pancreatic) model. (**c**) Neuroendocrine model

This chapter will review the evidence in support of a neuroendocrine model of glucoregulation.

Hypothalamic Insulin Action and Glucose Homeostasis

Although insulin does not appear to influence CNS glucose metabolism, the brain is an insulin-sensitive organ in many respects.[4,5] There is evidence that insulin is promptly transported across the blood–brain barrier via a saturable (receptor-mediated) process and diffusion across the areas of the brain that are outside of the blood–brain barrier.[6] Moreover, insulin levels in the extracellular fluid of hypothalamic nuclei are regulated during meal absorption.[7,8] As in other cell types, the binding of insulin to its receptor triggers a signal transduction cascade initiated by the autophosphorylation of the β-subunit of the insulin receptor (Fig. 6.3) and the phosphorylation and activation of insulin receptor substrate (IRS). Two main downstream pathways of insulin signaling include activation of mitogen-activated protein (MAP) kinases (extracellular signal-regulated kinase 1 and 2 – ERK1, ERK2) and phosphatidylinositol 3-kinase (PI3K). All downstream components of the insulin signaling pathway have been identified in the hypothalamic nuclei.[9–11] The effects of insulin in the CNS include but are not limited to modulation of feeding behavior,[12–14] suppression of neuropeptide Y (NPY) expression,[14–16] hypoglycemia counterregulation,[17] and regulation of autonomic outflow.[5,18,19]

Genetic studies with neural loss of function of the insulin receptor underscore the crucial role of CNS insulin action in the modulation of energy metabolism.[20,21] Ablation of *Insr* gene in nestin-positive neurons results in obesity, hyperinsulinemia, and decreased fertility.[20] In *Caenorhabditis elegans*, the dauer phenotype caused by mutations in the *Insr* ortholog *daf-2* can be rescued by selective re-expression of *daf-2* in the brain.[22]

Hypothalamic Insulin Action Is Sufficient to Modulate Hepatic Glucose Production

Insulin lowers blood glucose by inhibiting endogenous glucose production (EGP) and increasing glucose uptake in insulin-sensitive tissues. Insulin-mediated suppression of EGP occurs via activation of the insulin receptor in hepatocytes (direct effect) and involves the modulation of both glycogen metabolism and gluconeogenesis. The activation of insulin receptors on the surface of hepatocytes leads to the activation of PI3K and serine/threonine-specific protein kinase (Akt) transduction pathway, the phosphorylation of the transcription factor forkhead box O1 (FoxO-1), and the suppression of the expression of gluconeogenic enzymes. Major transcriptional targets of insulin are the promoters of the genes for phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), rate-limiting enzymes for gluconeogenesis and glucose output, respectively. Insulin controls via direct hepatic action the rate of glycogen synthesis and glycogenolysis. In addition, insulin controls hepatic glucose metabolism by acting in extrahepatic sites (indirect effects, such as insulin-mediated suppression of lipolysis and inhibition of glucagon secretion). Recent evidence has uncovered an additional indirect effect of insulin that regulates hepatic glucose production via hypothalamic insulin action.[23] An infusion of small amounts of insulin into the third cerebral ventricle (ICV) is sufficient to inhibit glucose production, in the presence of basal plasma insulin levels. Furthermore, an infusion of a smaller dose of insulin within the parenchyma of the mediobasal hypothalamus[24] results in lower blood glucose and inhibition of hepatic glucose production. These effects are largely due to a marked inhibition of hepatic gluconeogenesis and are associated with decreases in the hepatic expression of PEPCK and G6Pase. Thus, activation of insulin signaling within the mediobasal hypothalamus is sufficient to decrease blood glucose levels via suppression of glucose production.

ATP-sensitive potassium (K_{ATP}) channels are expressed in the hypothalamus[25] and can be activated by insulin in selective hypothalamic neurons.[26,27] Studies by Pocai and colleagues show that the activation of hypothalamic K_{ATP} channels with diazoxide is sufficient to lower blood glucose levels, decrease glucose production and hepatic gluconeogenesis. In addition, like CNS insulin action, diazoxide decreases liver G6Pase and PEPCK mRNA levels. Thus, direct activation of central K_{ATP} channels is per se sufficient to recapitulate the action of hypothalamic insulin on hepatic glucose production and gluconeogenesis and on hepatic expression of G6Pase and PEPCK. Insulin-mediated activation of hypothalamic K_{ATP} channels is abolished by

the K_{ATP} blockers sulfonylureas.[26,27] ICV co-administration of insulin and glibenclamide abolishes the hypothalamic effects of insulin on hepatic glucose metabolism. Thus, modulation of K_{ATP} channel activity within the arcuate nucleus of the hypothalamus can modulate neural output to the liver and control hepatic glucose metabolism.

Some hypothalamic neuronal fibers project to the brain stem and connect with motornuclei of the vagus nerve that innervates the gastrointestinal tract. These areas of the hindbrain are involved in the control of visceral functions including short-term regulation of ingestive behavior[28,29] and the modulation of liver metabolism.[30] Pocai and colleagues have shown that hypothalamic insulin action requires the activation of hepatic efferent vagal fibers because hepatic branch vagotomy abolishes the effects of ICV insulin on EGP and the expression of gluconeogenic enzymes.[24]

Hypothalamic Insulin Action Is Required to Suppress Hepatic Glucose Production

Although these studies establish the existence of a brain–liver neural connection activated by hypothalamic action of insulin, they do not demonstrate that this circuitry is required for the insulin-mediated control of glucose homeostasis. Is hypothalamic insulin action required for the physiologic suppression of glucose production induced by hyperinsulinemia? Obici and colleagues have examined this question by assessing in vivo glucose metabolism during physiologic hyperinsulinemia and simultaneous and selective blockade of insulin action in the hypothalamus.[23] Inhibition of hypothalamic insulin action was achieved in several ways: ICV infusion of anti-insulin antibodies, delivery of antisense oligonucleotides to lower insulin receptor expression, infusion of inhibitors of PI3K. Selective hypothalamic antagonism of insulin action markedly diminishes plasma insulin's ability to inhibit glucose production during hyperinsulinemic clamp procedures.[31] Additionally, ICV or intrahypothalamic infusion of a K_{ATP} blocker markedly impairs the effects of physiologic increases in plasma insulin on glucose production.[24] Similarly, hepatic branch vagotomy impairs the inhibitory effects of systemic insulin on glucose production, gluconeogenesis, and hepatic expression of G6Pase and PEPCK.

The role of K_{ATP} channels in the regulation of hepatic glucose metabolism is supported by the observation that mice with the genetic ablation of the sulfonylurea receptor subunit 1 (SUR1) display a selective impairment of glucose production and gluconeogenesis to insulin-mediated suppression.

The identity of the hypothalamic neurons and circuits responsible for insulin-dependent control of glucose production is still under investigation. Studies using antisense against the insulin receptor indicate that its down-regulation in the medial portion of the arcuate nucleus is sufficient to impair insulin action on glucose production. This area of the arcuate nucleus is enriched with NPY- and AgrP-containing neurons. Indeed, genetic and selective ablation of the insulin receptor in AgrP-positive neurons leads to impaired ability of hyperinsulinemia to suppress glucose production.[32]

Taken together, these results are consistent with a role of hypothalamic insulin action in activating a negative feedback system that controls and restrains the appearance of nutrients in the circulation (Fig. 6.2a). This hypothalamic restraint on glucose output is required for the maintenance of glucose homeostasis and its failure could lead to glucose intolerance. In addition, these experiments imply that impaired hypothalamic insulin signaling is a possible cause of hepatic insulin resistance.

The neuronal circuitry responsive to insulin plays an important role in modulating hepatic gluconeogenesis in response to physiologic elevations of plasma insulin. Since increased gluconeogenesis is a main cause of fasting and postprandial hyperglycemia in type 2 diabetes, impaired hypothalamic insulin signaling might play an important role in the pathogenesis of diabetes.[33]

This novel role of insulin, however, remains to be directly demonstrated in humans.

Hypothalamic Leptin Action

The cloning of leptin, the product of the ob (obese) gene, in the early 1990s has renewed the interest in the relationship between brain and control of energy balance and metabolism. Although the notion that the

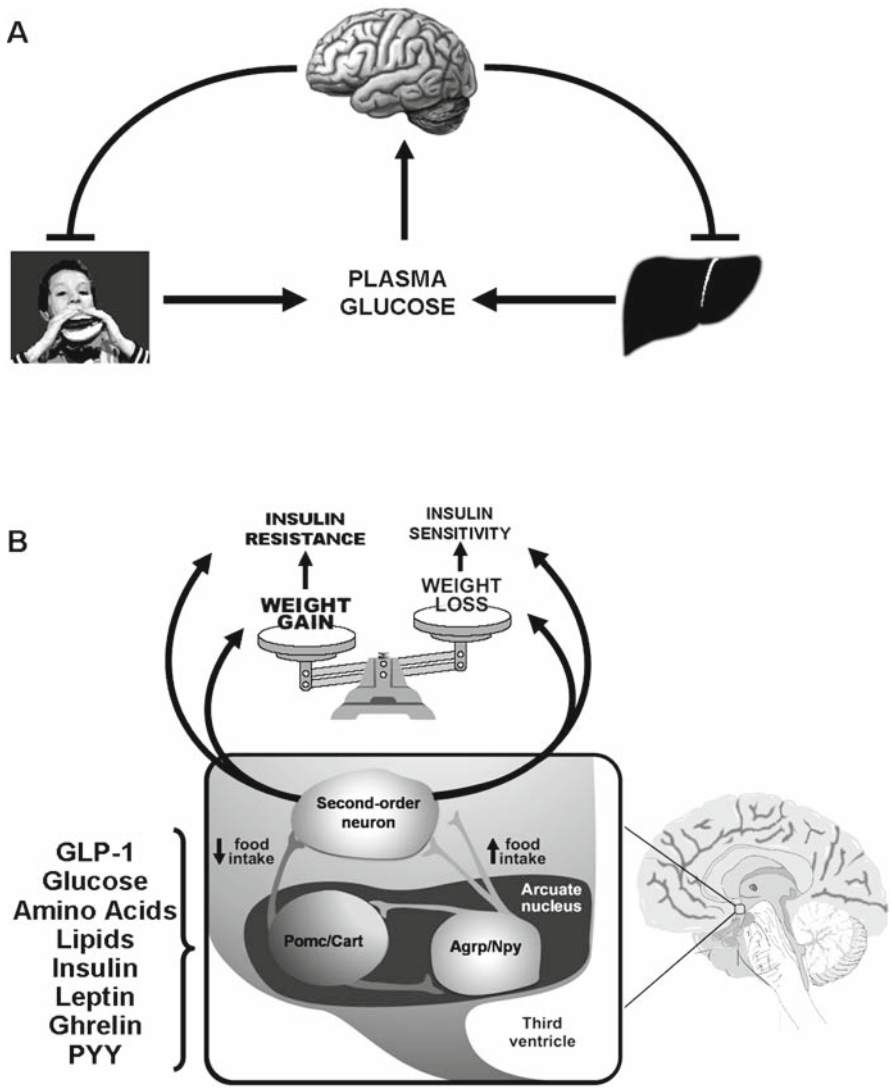

Fig. 6.2 CNS control of the glucose and energy homeostasis. (**a**) The brain senses circulating levels of glucose and nutrients and responds to their fluctuations by modifying the availability of exogenous fuel (feeding behavior) or endogenous fuel (hepatic production). (**b**) Specialized arcuate neurons receive and integrate a variety of peripheral humoral signals that are proportional to fat mass and/or nutritional state. This information is relayed to second-order neurons and used to maintain the homeostasis of energy stores by coordinated changes in food intake and energy expenditure. CNS control of glucose homeostasis may occur through two major mechanisms: (1) alterations in energy balance and body composition occur primarily and result in changes in insulin sensitivity and (2) glucose homeostasis and insulin sensitivity are modulated independently of changes in fat mass or body composition

hypothalamus is a major control center for energy homeostasis was previously well established, the discovery that leptin acts in the hypothalamus to regulate food intake and energy expenditure has greatly advanced our understanding of the neuroendocrine control of energy metabolism.[28] A major target of leptin action in the hypothalamus is the modulation of hypothalamic neuropeptidergic neurons. Leptin can reduce food intake and increase energy expenditure by simultaneously downregulating "orexic" peptides [that promote food intake and energy efficiency, such as neuropeptide Y (NPY), melanocyte-concentrating hormone, MCH, and orexins] and increasing the expression of anorectic peptides (such as the α-melanocyte-stimulating hormone, α-MSH,

and corticotrophin releasing hormone, CRH). Two populations of neurons in the arcuate nucleus of the hypothalamus are highly responsive to leptin (Fig. 6.2b). One of these populations responds to leptin by increasing the expression of proopiomelanocortin (POMC), the precursor of α-MSH. The other population of neurons responds to leptin by markedly decreasing the expression of NPY and the agouti-related protein (AgRP). The latter is a natural antagonist of the melanocortin pathway acting on the MC4 (and MC3) receptors.[34,35] The peptide α-MSH is the natural ligand for the CNS melanocortin receptors (MC3 and MC4). The MC4 receptor is expressed in the hypothalamus and has been convincingly implicated in the regulation of energy homeostasis.[36] In particular, genetic knockout of the MC4 receptor gene and ICV administration of agonists and antagonists for this receptor result in dramatic effects on feeding behavior and energy balance.[19–39] Since obesity is tightly associated with insulin resistance, hypothalamic leptin action plays a major role in carbohydrate metabolism and insulin action.[40–43] For example, rodents with a genetic deficiency of leptin function, such as the ob/ob and db/db mice, and the Zucker fa/fa rats, are markedly resistant to insulin action and develop diabetes mellitus later in life. Prolonged leptin administration in leptin-deficient ob/ob mice markedly decreases both plasma insulin and glucose concentration.[44,45] Administration of leptin to ob/ob mice at doses insufficient to induce weight loss rapidly normalizes blood glucose levels, suggesting that leptin has insulin-sensitizing effects independent of its anorectic action.[46] Leptin was also shown to regulate glucose tolerance, insulin signaling/action, and lipid metabolism independently of its anorectic effects.[41,47–52]

Leptin regulates food intake and body adiposity partly via activation of melanocortin receptors in the hypothalamus and in other areas within the central nervous system.[29,45] Bidirectional modulation of central melanocortin action leads to significant changes in peripheral insulin action.[39] On the other hand, the prolonged administration of either leptin or melanocortin agonists or antagonists also impacts on the distribution of body adiposity and on lipid homeostasis.[44,45] The loss of adiposity is likely to influence insulin action, since it is well established that changes in fat mass and/or fat distribution similar to those associated with long-term treatment with either leptin or melanocortin agonists can alter insulin action, particularly in insulin-resistant and obese animals. Thus, short-term administration studies, in the absence of changes in fat mass, might provide a glimpse on the direct role of hypothalamic leptin in the modulation of glucose metabolism.

Leptin appears to exert its pleiotropic behavioral, metabolic, and neuroendocrine actions via multiple neural pathways. What pathways are responsible for the action of CNS leptin on glucose metabolism? Leptin activates central melanocortin receptors mainly via increased biosynthesis of the physiological ligand α-MSH and via decreased biosynthesis of an antagonist agouti-related protein (AgRP) at the level of the hypothalamus.[34] The activation of the central melanocortin pathway mediates in great part leptin action on food intake, energy expenditure, sympathetic nervous system, insulin secretion, and body fat distribution.[40,49,53–55] The acute central activation of melanocortin receptors stimulates the expression of gluconeogenic enzymes within the liver, markedly increases the rate of gluconeogenesis, and decreases the suppressive effect of insulin on glucose production.[43] These rapid metabolic effects of the CNS melanocortin pathway on liver metabolism are completely different from the insulin-sensitizing effects obtained by prolonged stimulation of the CNS melanocortin receptors.[39] In fact, a week-long infusion of α-MSH leads to decreased visceral adiposity and improved insulin action.[39] Similarly, genetic ablation of the MC4 receptor results in hyperphagia, obesity, hyperinsulinemia, glucose intolerance, or diabetes.[38] The contrast between acute and chronic effects of central melanocortin modulation is likely due to the dramatic effects of this pathway on body fat mass and distribution, lipid oxidation and storage, and sympathetic nervous system activity. Acutely, the activation of the melanocortin pathway in the CNS is likely to enhance autonomic outflow to peripheral organs in the absence of changes in visceral adiposity and lipid storage.[38,39] In the liver, an increase in adrenergic tone leads to increased expression of G6Pase and PEPCK and to increased fat oxidation, which in turn can drive up gluconeogenesis.

The effects of leptin on hepatic glucose fluxes appear to be more complex than those of α-MSH. In lean, postabsorptive rats, short-term leptin infusion does not alter systemic insulin action on glucose production or utilization. However, systemic or ICV leptin induces a remarkable redistribution of intrahepatic glucose fluxes, greatly increasing the contribution of gluconeogenesis and simultaneously decreasing the contribution of glycogenolysis to hepatic glucose output.[41,48] Co-administration of a melanocortin receptor antagonist and leptin blunts the stimulatory effect on gluconeogenesis and inhibits the rate of glycogenolysis, consequently

enhancing the insulin-mediated inhibition of glucose production.[43] These experiments indicate that hypothalamic leptin action acutely controls gluconeogenic fluxes via the activation of hypothalamic melanocortin receptors. However, when central melanocortin action is blocked, CNS leptin action leads to a marked enhancement of hepatic insulin sensitivity.

The neural mechanisms responsible for leptin amelioration of hepatic insulin sensitivity are still largely unknown. Leptin binding to the long isoform of its receptor activates the Janus kinase-signal transducer–activator of transcription 3 (JAK/STAT3) pathway. This transduction pathway is linked to obesity, because transgenic mice carrying a point mutation of the leptin receptor abolishing JAK2/STAT3 activation are obese and hyperphagic. However, its role in modulating glucose homeostasis is still under investigation. In addition, like insulin, leptin can activate and exert its anorectic action via the PI3K pathway.[56,57] Since the effect of ICV insulin on hepatic glucose production requires central activation of PI3K,[31] the melanocortin-independent action of leptin on hepatic insulin sensitivity might be mediated by its activation of PI3K in neurons.

NPY and insulin action. Neuropeptide Y (NPY) is a potent orexigenic peptide, widely distributed in the mammalian brain and co-expressed in AgRP-positive neurons, whereby it is strongly downregulated by insulin and leptin. Injection of NPY into the hypothalamus or cerebral ventricles has potent and rapid effects on whole body metabolism.[58–60] Leptin and insulin may modulate feeding behavior and glucose homeostasis at least in part by suppressing the release and expression of NPY in the arcuate nucleus. Intracerebroventricular (ICV) injection of NPY decreases hepatic insulin sensitivity.[61] A recent study shows that ICV infusion of NPY impairs hepatic insulin sensitivity via modulation of liver sympathetic innervation.[62]

Hypothalamic Nutrient Sensing

There is a growing body of evidence indicating that circulating nutrients are sensed in the brain and directly participate in the homeostatic control of energy balance and peripheral metabolism. The hypothalamic arcuate nucleus is a regulatory site whereby lipids, glucose, and amino acids levels and their flux are sensed as integrated with other neural and hormonal signals to regulate food intake and energy metabolism. In particular, we will discuss the role of CNS lipid and glucose sensing vis à vis the regulation of hepatic glucose metabolism.

Lipids

The accumulation of lipids in adipose tissue, the site of long-term energy stores, is highly regulated by the brain via the coordinated regulation of feeding behavior (energy intake) and energy expenditure. The "lipostatic hypothesis" maintains that peripheral signals proportional to the size of fat mass communicate energy status to brain centers that in turn regulate energy intake and expenditure.[28,63] Leptin and insulin are classical examples of peripheral signals of energy store size because their plasma levels are proportional to adiposity and they act in the CNS to decrease energy intake.[45,63–65] Recent evidence supports the notion that the lipostatic hypothesis may include CNS control of circulating energy in the form of macronutrients such as fatty acids and glucose. Increased levels of plasma glucose and lipids can stimulate secretion and biosynthesis of insulin and leptin. These signals of adiposity and nutrient availability in turn reach hypothalamic centers and induce rapid shifts in metabolic fluxes of peripheral tissues such as liver and skeletal muscle.[41,52] In addition, hypothalamic neurons are also capable of directly sensing the levels of circulating nutrients.[23,66] The administration of oleic acid in the third cerebral ventricle results in the inhibition of food intake and endogenous glucose production.[31] The CNS effect of oleic acid, a long-chain fatty acid (18 carbons), is not elicited by delivery of medium-chain fatty acids such as octanoic acid (8 carbons). This suggests that the mere availability of macronutrients for oxidation to ATP is not a sufficient signal to the brain for regulation of energy metabolism. Although the brain largely relies on glucose for energy supply, lipids are oxidized in the CNS in small quantities. Studies with radiotracer techniques have shown that, although up to 50% of fatty acids delivered to the whole brain are oxidized to acetate, the bulk of palmitate and oleate incorporated into brain lipids is derived from circulating FAs and not from newly synthesized long-chain

fatty acid-coenzyme A (LCFA-CoA).[67] Fatty acids are transported from the circulation to the brain and into cells (Fig. 6.3), converted into LCFA-CoAs, and further metabolized in oxidative (β-oxidation in mitochondria) or biosynthetic pathways (incorporation in phospholipids). Neuronal lipid metabolism has recently been implicated in the control of energy intake and metabolism as a neuronal biochemical sensor of energy flux. Inhibitors of fatty acid synthase have potent anorexic effects mediated via CNS mechanisms.[68] The effect of FAS inhibitors on food intake requires the accumulation of malonyl-CoA, a product of glucose metabolism and potent allosteric inhibitor of carnitine palmitoyltransferase 1 (CPT1). This enzyme is the first committed step for the transport of LCFA-CoAs into mitochondria, where they undergo β-oxidation (Fig. 6.3). In peripheral tissues (liver and muscle), malonyl-CoA has been identified as a fuel sensor that controls the rate of fatty acid oxidation and consequently determines the intracellular levels of LCFA-CoAs.[16,69] Recent evidence suggests that a similar biochemical sensor operates in the brain, and in particular in the hypothalamus.[70] Accumulation of malonyl-CoA by inhibition of fatty acid synthase (FAS) leads to anorexia,[68] whereas lowering malonyl-CoA by overexpression of malonyl-CoA decarboxylase (MCD) causes hyperphagia.[71,72] In addition, MCD overexpression in arcuate prevents the accumulation of arcuate LCFAs and prevents LCFA-mediated inhibition of glucose production.[71] As predicted by the physiologic role of malonyl-CoA as inhibitor of CPT1 and fatty acid oxidation, inhibition of hypothalamic CPT1 increases neuronal levels of LCFA-CoAs and results in anorexia and inhibition of endogenous glucose production.[73] In physiologic conditions, the levels of malonyl-CoA in the hypothalamus vary according to nutritional status, being low in the fasting state and high during refeeding.[74] Taken together, these experiments suggest that peripheral circulating macronutrients (LCFAs and carbohydrates) may represent signals of nutrient availability and activate a neural "lipid-sensing" signal of negative feedback on feeding behavior and glucose production to restrain circulating nutrients from "exogenous" (food) or "endogenous" sources (liver-derived glucose/lipids).

Hypothalamic lipid sensing modulates hepatic glucose fluxes via a neural circuit involving efferent vagal innervation (Fig. 6.3c). The suppression of glucose production elicited by central inhibition of fatty acid oxidation (via CPT1 inhibition) is abolished by selective hepatic vagotomy, whereas vagal deafferentation has no effect.[75]

Hypothalamic sensing of circulating LCFA and hepatic glucose production. CNS delivery of oleic acid results in decreased plasma glucose levels, hepatic glucose production, and expression of hepatic G6Pase.[76,23] These effects are apparently paradoxical because elevated plasma LCFAs are known to increase hepatic glucose production and expression of G6Pase.[77] Indeed, elevated plasma LCFAs in the presence of hyperinsulinemia markedly decrease insulin inhibitory action on glucose production. However, in some circumstances, circulating FFAs do not increase glucose production. In the presence of basal insulin levels, the elevation of plasma LCFA concentration via lipid infusions stimulates gluconeogenesis but does not alter glucose production in nondiabetic humans and animals because of a compensatory decrease in hepatic glycogenolysis.[77] This rapid metabolic adaptation is called hepatic autoregulation. Lam and colleagues have shown that plasma FFA-induced hepatic autoregulation is disrupted when hypothalamic FFA uptake and action are prevented or follow hepatic vagotomy.[78] Thus,

Fig. 6.3 (continued) Hypothalamic control of hepatic glucose metabolism. (**a**) Insulin controls hepatic glucose production in part via the activation of its receptors in the arcuate nucleus of the hypothalamus (see text). (**b**) Effects of hypothalamic leptin action on hepatic glucose fluxes. Leptin receptors in the arcuate activate two major distinct signaling pathways: Jak/STAT and IRS/PI3K. Leptin action in the arcuate leads to stimulation of proopiomelanocortin (POMC) neurons and inhibition of NPY/AgRP neurons. The direct and acute effects of CNS leptin action on heptic glucose fluxes can be classified into melanocortin dependent (activation of hepatic gluconeogenesis) and melanocortin independent (decreased glycogenolysis). (**c**) Hypothalamic lipid sensing and brain–liver connection. Circulating LCFAs can alter glucose metabolism by direct action on liver or via an indirect neural circuit. In the hypothalamus, LCFAs are esterified to LCFA-CoAs. Elevation of LCFA-CoAs in the arcuate nucleus results in the opening of K_{ATP} channels and the stimulation of the vagal efferent fibers. These motor neurons originate in the vagal nucleus of the brain stem (NTS/DMX) and innervate the liver. The accumulation of LCFA-CoAs is controlled by the levels of malonyl-CoA, a glucose-derived precursor of fatty acids and potent allosteric inhibitor of CPT1. Increased levels of malonyl-CoA inhibit CPT1 activity, decrease LCFA-CoA oxidation, and increase cytoplasmic LCFA-CoAs levels. This in turn activates a neural hepatic signal for the suppression of glucose production. BBB, blood–brain barrier

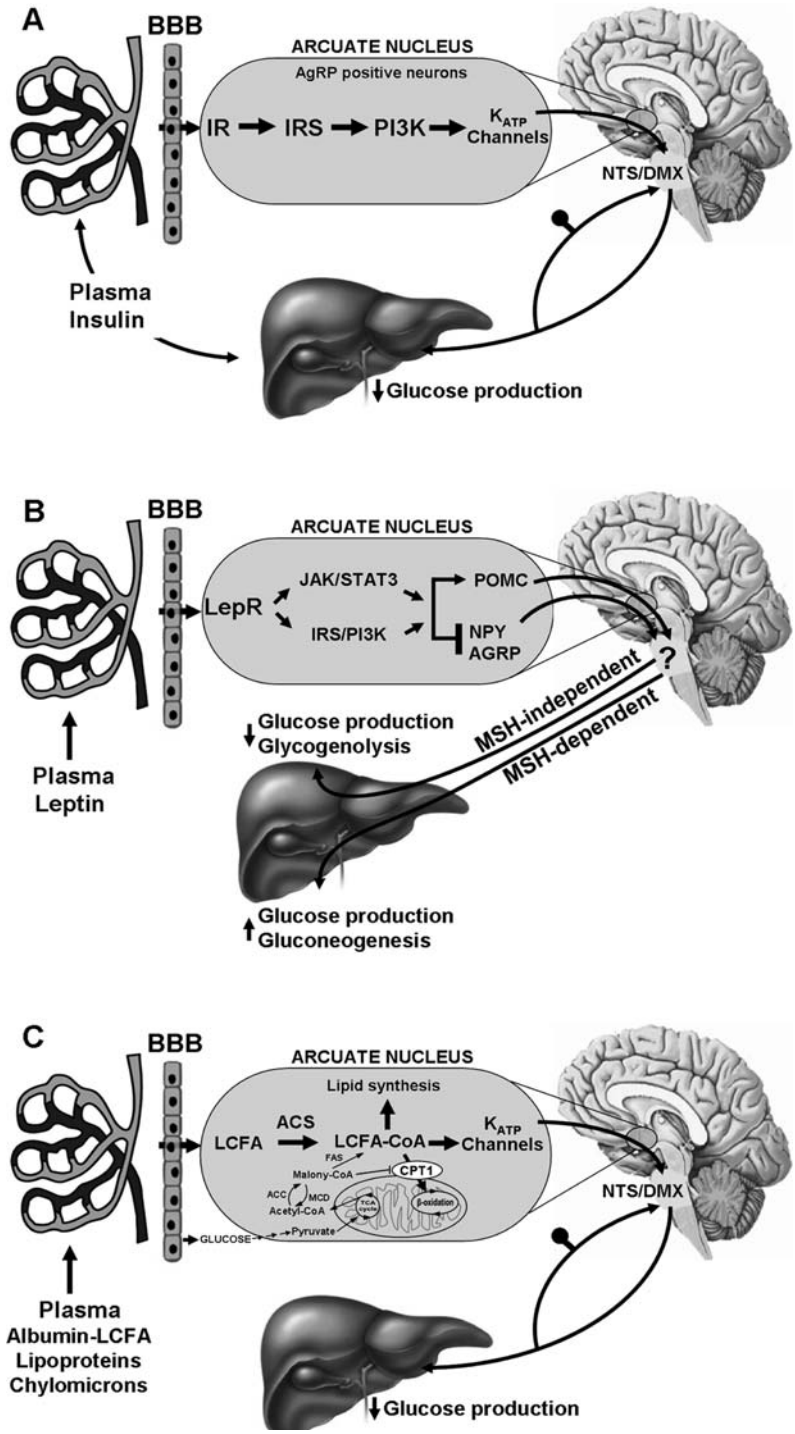

Fig. 6.3 (continued)

circulating LCFAs can alter hepatic glucose production via hepatic and extrahepatic mechanisms. The latter include the stimulation of hypothalamic circuits traveling along the efferent branch of the vagus nerve. Since CNS action of circulating LCFA is required to counteract LCFA-induced stimulation of gluconeogenesis and to prevent an increase in glucose production, FFA-induced hepatic autoregulation might result from the simultaneous activation of hepatic and hypothalamic signals. Interestingly, hypothalamic overexpression of MCD results in the inability to accumulate LCFA-CoA in the arcuate nucleus during peripheral infusion of lipid and in the disruption of FFA-induced hepatic autoregulation.[71] Similarly, hepatic autoregulation is impaired in type 2 diabetes since reciprocal changes in glycogenolysis fail to compensate for changes in gluconeogenesis when the plasma LCFA concentrations are experimentally manipulated.[79]

Glucose

Mayer's "glucostatic" hypothesis postulated the existence of peripheral and neuronal glucose sensors involved in the homeostatic control of energy balance and metabolism.[80] Indeed specialized neurons can alter their firing frequency and membrane potential in response to changes in extracellular glucose levels. Glucose sensing is an essential component of the CNS defense against hypoglycemia and hyperglycemia that triggers counterregulatory responses and attempts to restore normoglycemia. Homeostatic control seemingly operates in the physiologic range of blood glucose (∼5 mM), which is in equilibrium with glucose concentration in the extracellular space in brain (∼2 mM). Lam and colleagues have shown that moderate increases in glucose levels within the hypothalamus lower blood glucose via the inhibition of hepatic glucose production.[81] Furthermore, the restraining effect of CNS glucose on hepatic fluxes requires its conversion to pyruvate and the activation of hypothalamic K_{ATP} channels. In nondiabetic subjects, hyperglycemia is per se sufficient to suppress glucose production. However, hyperglycemia fails to suppress EGP in the presence of hypothalamic blockade of glucose metabolism or K_{ATP} channel activation. Thus, glucose regulation of hepatic glucose production might be mediated in part by extrahepatic, hypothalamic mechanisms. Notably, in diabetic individuals, hyperglycemia fails to decrease glucose production, suggesting a possible impairment of brain glucose sensing.

Other CNS Modulators of Glucose Metabolism

GLP-1

Glucagon-like peptide-1 (GLP-1) is an enteric peptide recently implicated in the neural control of glucose metabolism. GLP-1 is known to stimulate glucose-dependent insulin secretion,[82] reduce glucagon secretion,[83] and inhibit gastric emptying.[84] GLP-1 and its agonists are effective hypoglycemic agents for the treatment of type 2 diabetes.[85] Improved glycemia with GLP-1 is likely due to its multiple actions. GLP-1-induced increase in insulin and decrease in glucagon secretion restrain hepatic glucose production, favor peripheral glucose utilization, and, in concert with delayed gastric emptying, effectively limit postprandial glycemic excursions.[86] Recent evidence suggests that GLP-1 released from intestinal L cells may interact locally with its receptor located on vagal afferent fibers projecting to the nucleus of the solitary tract (NTS) in the brain stem, and ultimately to the arcuate nucleus in the hypothalamus. This would result in the generation of an efferent signal from the arcuate nucleus to increase insulin secretion and decrease hepatic glucose production and muscle glucose utilization.[87] Notably, Sandoval and colleagues have recently shown that direct GLP-1 administration into the arcuate nucleus is sufficient to inhibit hepatic glucose production and glucose uptake. Like insulin, the hypothalamic action of GLP-1 on hepatic glucose metabolism requires the activation of hypothalamic K_{ATP} channels.[88]

Resistin

Resistin is a plasma protein derived from adipose tissue that has been implicated in insulin resistance and inflammation.[89] Acute systemic infusions of resistin result in marked hepatic insulin resistance. ICV or intrahypothalamic infusion of resistin reproduces its systemic effects on hepatic glucose production and inflammation. Of interest, the central administration of resistin markedly and selectively impaired the inhibitory action of insulin on hepatic glycogenolysis with no changes in circulating levels of glucoregulatory hormones or effect on hepatic expression of the key gluconeogenic enzymes. It supports the idea that resistin centrally increased hepatic glucoses fluxes predominantly via glycogenolytic activation.[90] Other studies report that the effects of CNS resistin on glucose production are abrogated in mice lacking NPY or in wild-type mice pretreated with antagonists of the NPY Y1 receptor.[91]

Neurotransmitters

A large body of evidence supports the notion that CNS monoamine neurotransmitters affect energy balance and glucose homeostasis. Hyperphagia and obesity are associated with abnormal hypothalamic dopamine and serotonin tone.[92] Conversely, experiments with streptozotocin-induced diabetic rats show that alterations in insulin and glucose homeostasis can influence mesoaccumbens dopamine and lower striatal concentrations of dopamine.[93] Treatment with dopamine receptor agonists reverts elevated hypothalamic levels of NPY and decreases body weight and hyperglycemia in obese leptin-deficient mice.[94] Agonists of 5-HT receptors are potent anorexic agents. A targeted deletion of the serotonin 5-HT_{2C} receptor gene leads to adult-onset obesity, insulin resistance, and glucose intolerance.[95] Conversely, a selective agonist for 5-HT_{2C} receptors improves glucose tolerance and insulin resistance in diet-induced, insulin-resistant mice, at doses that do not cause changes in fat mass. The beneficial effect of 5-HT_{2C} receptor activation on glucose metabolism requires functional MC4 receptors.[96]

Recent evidence links the use of atypical antipsychotics for the treatment of psychiatry disorders to the onset of obesity, hyperlipidemia, and type 2 diabetes, and underscores the important role of a normal monoaminergic tone in the control of glucose homeostasis. Experiments in dogs show that a short-term treatment with olanzapine causes increased adiposity and markedly reduced hepatic insulin sensitivity.[97] Recent studies in rats show that atypical antipsychotics can acutely impair hepatic insulin sensitivity in the absence of changes in fat mass.[98,99]

A Neural Model of Integration of Peripheral Nutrients and Hormonal Signals

The brain is emerging as an essential regulator of energy metabolism. In particular, the regulation of glucose homeostasis is achieved through complex and still poorly understood neural mechanisms.[100] A major aspect of neural control of glucose metabolism involves the ability of neurons to sense energy flux and glucose availability. As discussed above, nutrients are sensed in neurons either directly or indirectly via the action of nutrient-dependent hormonal signals on neurons. Arcuate neurons are able to alter their firing rate upon changing the extracellular levels of glucose. The presence of K_{ATP} channels in glucose-responsive neurons provides molecular and physiologic mechanism for the ability of neurons to process and integrate nutrients and hormonal signals and translate them into a membrane potential signal (Fig. 6.4). In addition to the postulated role of K_{ATP} channels in the conterregulatory responses to hypoglycemia, these channels have been recently implicated in the neural control of hepatic glucose production.[101] Indeed, several signals converging onto K_{ATP} channels can influence their function and ultimately lead to changes in neuronal electrical activity. As discussed above, glucose, insulin, and LCFA-CoAs can modulate glucose production via activation of K_{ATP} channels in the arcuate nucleus. Nutrients can modulate K_{ATP} channel activity by providing energy for the production of ATP, as demonstrated for glucose-sensing neurons.[102] Parton and colleagues have shown that the selective expression of a mutant K_{ATP} channel unable to bind ATP in POMC neurons results in a mouse with an impaired glucose sensing in POMC neurons

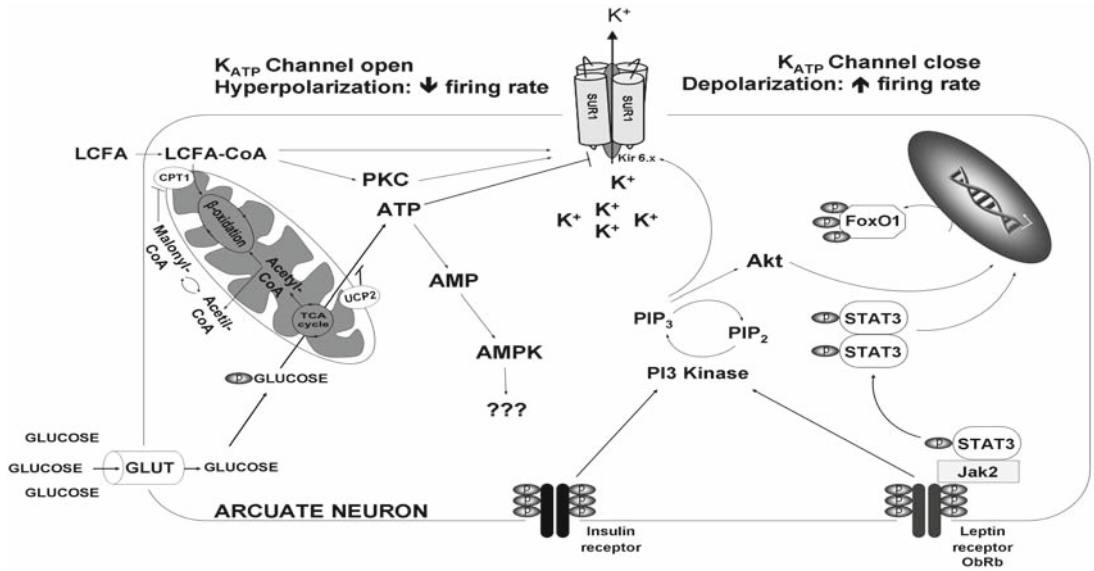

Fig. 6.4 Molecular mechanisms leading to changes in electrical activity in arcuate neurons. A variety of nutrients and hormones can modulate the activity of ATP-sensitive potassium channels (KATP) and rapidly alter neuronal excitability. In addition, modulation of transcriptional activity can alter gene expression for neuropeptides and neurotransmitters

and an impaired systemic tolerance to a glucose load.[103] In addition, LCFA-CoAs can bind directly to the Kir6.2 subunit and modify its sensitivity to ATP. Alternatively, LCFA-CoAs have been shown to activate the channels via activation of PKC.[104] Moreover, insulin and leptin open K_{ATP} channels via PI3K-dependent production of phosphatidylinositol-3,4,5-biphosphate (PIP3).[26,27] Additionally, nutrients and hormonal signals will affect neuronal activity by inducing transcriptional changes that result in the modulation of neuropeptide expression, neurotransmitter metabolism, and synaptic plasticity.

Summary

The concept that brain controls glucose homeostasis goes back to the nineteenth century with the pioneering studies of Claude Bernard, who proposed that the brain controls liver glucose production via its hepatic nerves. The current view is that plasma glucose regulation is under the control of complex neural and endocrine mechanisms. Nonetheless, recent evidence suggests that the CNS is a crucial organ for the control of glucose homeostasis. Circulating nutrients and nutrient-induced hormones (such as insulin and leptin) activate signals of increased energy availability in brain centers that control energy balance and endogenous glucose production. This in turn activates efferent pathways that restrain food intake and excessive endogenous glucose production. This neuroendocrine system of negative feedback ensures the physiologic constancy of plasma glucose levels. The arcuate nucleus of the hypothalamus receives and integrates all peripheral signals of nutrient availability and controls hepatic glucose metabolism via efferent vagal fibers. A major neural mechanism for the integration of metabolic signals is the control of membrane potential through K_{ATP} channels. These channels respond to changes in energy flux (ATP levels) as well as to intracellular changes in second messengers (PIP). Opening of K_{ATP} channels in the arcuate is implicated in the restraint of hepatic glucose production and can occur rapidly in the absence of changes in gene expression. In addition, nutrient and hormones can lead to changes in the expression of neuropeptides (NPY, MSH, AgRP) that have been implicated as CNS modulators of hepatic glucose metabolism. The implication of this recent evidence is that defects in the neural circuitry controlling glucose metabolism can contribute to the pathogenesis of diabetes. There is ample evidence that this occurs in animal models of obesity

and type 2 diabetes. An important future challenge is to determine whether these mechanisms play a role in the control of glucose homeostasis in human pathophysiology of glucose metabolism.

References

1. Bernard C. *Leçons sur les phénomènes de la vie. Cours de physiologies generale du Museum d'Histoir Naturelle*. Paris: Librairie Delagrave; 1859.
2. Unger RH. The milieu interieur and the islets of Langerhans. *Diabetologia*. 1981;20:1–11.
3. Shimazu T 1998. *The Hypothalamus and Metabolic Control*. Minatomachi and Matsuyama, eds. Ehime, Japan: Ehime University School of Medicine.
4. Schwartz MW, Porte D Jr. Diabetes, obesity, and the brain. *Science*. 2005;307:375–379.
5. Davis SN, Colburn C, Dobbins R, et al. Evidence that the brain of the conscious dog is insulin sensitive. *J Clin Invest*. 1995;95:593–602.
6. Schwartz MW, Sipols A, Kahn SE, Lattemann DF, Taborsky GJ, Jr., Bergman RN, Woods SC, Porte D, Jr. Kinetics and specificity of insulin uptake from plasma into cerebrospinal fluid. *Am. J. Physiol* 1990;259:E378–E383.
7. Gerozissis K, Rouch C, Nicolaidis S, Orosco M. Brain insulin response to feeding in the rat is both macronutrient and area specific. *Physiol Behav.* 1998;65:271–275.
8. Gerozissis K, Orosco M, Rouch C, Nicolaidis S. Insulin responses to a fat meal in hypothalamic microdialysates and plasma. *Physiol Behav.* 1997;62:767–772.
9. Unger JW, Betz M. Insulin receptors and signal transduction proteins in the hypothalamo-hypophyseal system: a review on morphological findings and functional implications. *Histol. Histopathol.* 1998;13:1215–1224.
10. Marks JL, Porte D, Jr., Stahl WL, Baskin DG. Localization of insulin receptor mRNA in rat brain by in situ hybridization. *Endocrinology* 1990;127:3234–3236.
11. Baskin DG, Gierke EP, Wilcox BJ, Matsumoto AM, Schwartz MW. Food intake and estradiol effects on insulin binding in brain and liver. *Physiol Behav.* 1993;53:757–762.
12. Richardson RD, Ramsay DS, Lernmark A, Scheurink AJ, Baskin DG, Woods SC. Weight loss in rats following intraventricular transplants of pancreatic islets. *Am. J. Physiol* 1994;266:R59–R64.
13. Woods SC, Lotter EC, McKay LD, Porte D, Jr. Chronic intracerebroventricular infusion of insulin reduces food intake and body weight of baboons. *Nature* 1979;282:503–505.
14. Sipols AJ, Baskin DG, Schwartz MW. Effect of intracerebroventricular insulin infusion on diabetic hyperphagia and hypothalamic neuropeptide gene expression. *Diabetes* 1995;44:147–151.
15. Schwartz MW, Marks JL, Sipols AJ, Baskin DG, Woods SC, Kahn SE, Porte D, Jr. Central insulin administration reduces neuropeptide Y mRNA expression in the arcuate nucleus of food-deprived lean (Fa/Fa) but not obese (fa/fa) Zucker rats. *Endocrinology* 1991;128:2645–2647.
16. Sahu A, Dube MG, Phelps CP, Sninsky CA, Kalra PS, Kalra SP. Insulin and insulin-like growth factor II suppress neuropeptide Y release from the nerve terminals in the paraventricular nucleus: a putative hypothalamic site for energy homeostasis. *Endocrinology* 1995;136:5718–5724.
17. Davis SN, Dunham B, Walmsley K, Shavers C, Neal D, Williams P, Cherrington AD. Brain of the conscious dog is sensitive to physiological changes in circulating insulin. *Am. J. Physiol* 1997;272:E567–E575.
18. Liang C, Doherty JU, Faillace R, Maekawa K, Arnold S, Gavras H, Hood WB, Jr. Insulin infusion in conscious dogs. Effects on systemic and coronary hemodynamics, regional blood flows, and plasma catecholamines. *J. Clin. Invest* 1982;69:1321–1336.
19. Rowe JW, YounG JB, Minaker KL, Stevens AL, Pallotta J, Landsberg L. Effect of insulin and glucose infusions on sympathetic nervous system activity in normal man. *Diabetes* 1981;30:219–225.
20. Bruning JC, Gautam D, Burks DJ, et al. Role of brain insulin receptor in control of body weight and reproduction. *Science*. 2000;289:2122–2125.
21. Okamoto H, Obici S, Accili D, Rossetti L. Restoration of liver insulin signaling in Insr knockout mice fails to normalize hepatic insulin action. *J Clin Invest*. 2005;115:1314–1322.
22. Wolkow CA, Kimura KD, Lee MS, Ruvkun G. Regulation of C. elegans life-span by insulinlike signaling in the nervous system. *Science* 2000;290:147–150.
23. Obici S, Zhang BB, Karkanias G, Rossetti L. Hypothalamic insulin signaling is required for inhibition of glucose production. *Nat Med*. 2002;8:1376–1382.
24. Pocai A, Lam TK, Gutierrez-Juarez R, et al. Hypothalamic K(ATP) channels control hepatic glucose production. *Nature*. 2005;434:1026–1031.
25. Karschin C, Ecke C, Ashcroft FM, Karschin A. Overlapping distribution of K(ATP) channel-forming Kir6.2 subunit and the sulfonylurea receptor SUR1 in rodent brain. *FEBS Lett.* 1997;401:59–64.
26. Spanswick D, Smith MA, Groppi VE, Logan SD, Ashford ML. Leptin inhibits hypothalamic neurons by activation of ATP-sensitive potassium channels. *Nature*. 1997;390:521–525.
27. Spanswick D, Smith MA, Mirshamsi S, Routh VH, Ashford ML. Insulin activates ATP-sensitive K+ channels in hypothalamic neurons of lean, but not obese rats. *Nat Neurosci*. 2000;3:757–758.

28. Schwartz MW, Woods SC, Porte D Jr., Seeley RJ, Baskin DG. Central nervous system control of food intake. *Nature*. 2000;404:661–671.
29. Grill HJ, Schwartz MW, Kaplan JM, Foxhall JS, Breininger J, Baskin DG. Evidence that the caudal brainstem is a target for the inhibitory effect of leptin on food intake. *Endocrinology*. 2002;143:239–246.
30. Matsuhisa M, Yamasaki Y, Shiba Y, Nakahara I, Kuroda A, Tomita T, Iida M, Ikeda M, Kajimoto Y, Kubota M, Hori M. Important role of the hepatic vagus nerve in glucose uptake and production by the liver. *Metabolism* 2000;49:11–16.
31. Obici S, Feng Z, Morgan K, Stein D, Karkanias G, Rossetti L. Central administration of oleic acid inhibits glucose production and food intake. *Diabetes*. 2002;51:271–275.
32. Konner AC, Janoschek R, Plum L, et al. Insulin Action in AgRP-Expressing Neurons Is Required for Suppression of Hepatic Glucose Production. *Cell Metab*. 2007;5:438–449.
33. Magnuson MA. Tissue-specific regulation of glucokinase gene expression. *J Cell Biochem*. 1992;48:115–121.
34. Cowley MA, Smart JL, Rubinstein M, et al. Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. *Nature*. 2001;411:480–484.
35. Cowley MA, Pronchuk N, Fan W, Dinulescu DM, Colmers WF, Cone RD. Integration of NPY, AGRP, and melanocortin signals in the hypothalamic paraventricular nucleus: evidence of a cellular basis for the adipostat. *Neuron* 1999;24: 155–163.
36. Butler AA, Cone RD. Knockout studies defining different roles for melanocortin receptors in energy homeostasis. *Ann.N Y.Acad.Sci.* 2003;994:240–245.
37. Butler AA, Kesterson RA, Khong K, Cullen MJ, Pelleymounter MA, Dekoning J, Baetscher M, Cone RD. A unique metabolic syndrome causes obesity in the melanocortin-3 receptor-deficient mouse. *Endocrinology* 2000;141:3518–3521.
38. Huszar D, Lynch CA, Fairchild-Huntress V, et al. Targeted disruption of the melanocortin-4 receptor results in obesity in mice. *Cell*. 1997;88:131–141.
39. Obici S, Feng ZH, Tan JZ, Liu LS, Karkanias G, Rossetti L. Central melanocortin receptors regulate insulin action. *J Clin Invest*. 2001;108:1079–1085.
40. Barzilai N, She L, Liu L, et al. Decreased visceral adiposity accounts for leptin effect on hepatic but not peripheral insulin action. *Am J Physiol*. 1999;277:E291–E298.
41. Liu L, Karkanias GB, Morales JC, et al. Intracerebroventricular leptin regulates hepatic but not peripheral glucose fluxes. *J Biol Chem*. 1998;273:31160–31167.
42. Fan W, Dinulescu DM, Butler AA, Zhou J, Marks DL, Cone RD. The central melanocortin system can directly regulate serum insulin levels. *Endocrinology* 2000;141:3072–3079.
43. Gutierrez-Juarez R, Obici S, Rossetti L. Melanocortin-independent effects of leptin on hepatic glucose fluxes. *J Biol Chem*. 2004;279:49704–49715.
44. Halaas JL, Gajiwala KS, Maffei M, et al. Weight-reducing effects of the plasma protein encoded by the obese gene. *Science*. 1995;269:543–546.
45. Halaas JL, Boozer C, Blair-West J, Fidahusein N, Denton DA, Friedman JM. Physiological response to long-term peripheral and central leptin infusion in lean and obese mice. *Proc Natl Acad Sci USA*. 1997;94:8878–8883.
46. Pelleymounter MA, Cullen MJ, Baker MB, et al. Effects of the obese gene product on body weight regulation in ob/ob mice. *Science*. 1995;269:540–543.
47. Schwartz MW, Baskin DG, Bukowski TR, Kuijper JL, Foster D, Lasser G, Prunkard DE, Porte D, Jr., Woods SC, Seeley RJ, Weigle DS. Specificity of leptin action on elevated blood glucose levels and hypothalamic neuropeptide Y gene expression in ob/ob mice. *Diabetes* 1996;45:531–535.
48. Rossetti L, Massillon D, Barzilai N, et al. Short term effects of leptin on hepatic gluconeogenesis and in vivo insulin action. *J Biol Chem*. 1997;272:27758–27763.
49. Barzilai N, Wang J, Massilon D, Vuguin P, Hawkins M, Rossetti L. Leptin selectively decreases visceral adiposity and enhances insulin action. *J Clin Invest*. 1997;100:3105–3110.
50. Muoio DM, Dohm GL, Fiedorek FT, Jr., Tapscott EB, Coleman RA, Dohn GL. Leptin directly alters lipid partitioning in skeletal muscle. *Diabetes* 1997;46:1360–1363.
51. Muoio DM, Dohm GL, Tapscott EB, Coleman RA. Leptin opposes insulin's effects on fatty acid partitioning in muscles isolated from obese ob/ob mice. *Am. J. Physiol* 1999;276:E913–E921.
52. Minokoshi Y, Kim YB, Peroni OD, et al. Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. *Nature*. 2002;415:339–343.
53. Balthasar N, Coppari R, McMinn J, et al. Leptin receptor signaling in POMC neurons is required for normal body weight homeostasis. *Neuron*. 2004;42:983–991.
54. da Silva BA, Bjorbaek C, Uotani S, Flier JS. Functional properties of leptin receptor isoforms containing the gln–>pro extracellular domain mutation of the fatty rat. *Endocrinology*. 1998;139:3681–3690.
55. Haynes WG, Morgan DA, Djalali A, Sivitz WI, Mark AL. Interactions between the melanocortin system and leptin in control of sympathetic nerve traffic. *Hypertension*. 1999;33:542–547.
56. Niswender KD, Morton GJ, Stearns WH, Rhodes CJ, Myers MG Jr., Schwartz MW. Intracellular signalling. Key enzyme in leptin-induced anorexia. *Nature*. 2001;413:794–795.
57. Niswender KD, Morrison CD, Clegg DJ, et al. Insulin activation of phosphatidylinositol 3-kinase in the hypothalamic arcuate nucleus: a key mediator of insulin-induced anorexia. *Diabetes*. 2003;52:227–231.

58. Menendez JA, Mcgregor IS, Healey PA, Atrens DM, Leibowitz SF. Metabolic effects of neuropeptide-y injections into the paraventricular nucleus of the hypothalamus. *Brain Res*. 1990;516:8–14.
59. Billington CJ, Briggs JE, Grace M, Levine AS. Effects of intracerebroventricular injection of neuropeptide-y on energy-metabolism. *Am J Physiol*. 1991;260:R321–R327.
60. Marks JL, Waite K. Some acute effects of intracerebroventricular neuropeptide Y on insulin secretion and glucose metabolism in the rat. *J Neuroendocrinol*. 1996;8:507–513.
61. Marks JL, Waite K. Intracerebroventricular neuropeptide Y acutely influences glucose metabolism and insulin sensitivity in the rat. *J Neuroendocrinol*. 1997;9:99–103.
62. van den Hoek AM, van Heijningen C, Schroder-van der Elst JP, et al. Intracerebroventricular administration of neuropeptide Y induces hepatic insulin resistance via sympathetic innervation. *Diabetes*. 2008;57:2304–2310.
63. Baskin DG, Figlewicz LD, Seeley RJ, Woods SC, Porte D Jr., Schwartz MW. Insulin and leptin: dual adiposity signals to the brain for the regulation of food intake and body weight. *Brain Res*. 1999;848:114–123.
64. Schwartz MW, Figlewicz DP, Baskin DG, Woods SC, Porte D Jr. Insulin in the brain: a hormonal regulator of energy balance. *Endocr Rev*. 1992;13:387–414.
65. Seeley RJ, van Dijk G, Campfield LA, et al. Intraventricular leptin reduces food intake and body weight of lean rats but not obese Zucker rats. *Horm Metab Res*. 1996;28:664–668.
66. Levin BE, Dunn-Meynell AA, Routh VH. Brain glucose sensing and body energy homeostasis: role in obesity and diabetes. *Am J Physiol*. 1999;276:R1223–R1231.
67. Miller JC, Gnaedinger JM, Rapaport SI. Utilization of plasma fatty acids in rat brain: distribution of 14C-Palmitate between oxidative and synthetic pathways. *J Neurochem*. 1987;49:1507–1514.
68. Loftus TM, Jaworsky DE, Frehywot GL, et al. Reduced food intake and body weight in mice treated with fatty acid synthase inhibitors. *Science*. 2000;288:2379–2381.
69. McGarry JD, Mannaerts GP, Foster DW. A possible role for malonyl-CoA in the regulation of hepatic fatty acid oxidation and ketogenesis. *J Clin Invest*. 1977;60:265–270.
70. Obici S, Rossetti L. Minireview: nutrient sensing and the regulation of insulin action and energy balance. *Endocrinology*. 2003;144:5172–5178.
71. He W, Lam TKT, Obici S, Rossetti L. Molecular disruption of hypothalamic nutrient sensing induces obesity. *Nat Neurosci*. 2006;9:227–233.
72. Hu Z, Dai Y, Prentki M, Chohnan S, Lane MD. A role for hypothalamic malonyl-CoA in the control of food intake. *J Biol Chem*. 2005;280:39681–39683.
73. Obici S, Feng Z, Arduini A, Conti R, Rossetti L. Inhibition of hypothalamic carnitine palmitoyltransferase-1 decreases food intake and glucose production. *Nat Med*. 2003;9:756–761.
74. Wolfgang MJ, Lane MD. The role of hypothalamic malonyl-CoA in energy homeostasis. *J Biol Chem*. 2006;281:37265–37269.
75. Pocai A, Obici S, Schwartz GJ, Rossetti L. A brain–liver circuit regulates glucose homeostasis. *Cell Metab*. 2005;1:53–61.
76. Morgan K, Obici S, Rossetti L. Hypothalamic responses to long-chain fatty acids are nutritionally regulated. *J Biol Chem*. 2004;279:31139–31148.
77. Lam TK, Carpentier A, Lewis GF, van de WG, Fantus IG, Giacca A. Mechanisms of the free fatty acid-induced increase in hepatic glucose production. *Am J Physiol Endocrinol Metab*. 2003;284:E863–E873.
78. Lam TK, Pocai A, Gutierrez-Juarez R, et al. Hypothalamic sensing of circulating fatty acids is required for glucose homeostasis. *Nat Med*. 2005;11:320–327.
79. Boden G, Chen X, Capulong E, Mozzoli M. Effects of free fatty acids on gluconeogenesis and autoregulation of glucose production in type 2 diabetes. *Diabetes*. 2001;50:810–816.
80. Mayer J. Glucostatic mechanism of regulation of food intake. *N Engl J Med*. 1953;249:13–16.
81. Lam TK, Gutierrez-Juarez R, Pocai A, Rossetti L. Regulation of blood glucose by hypothalamic pyruvate metabolism. *Science*. 2005;309:943–947.
82. Holst JJ, Gromada J. Role of incretin hormones in the regulation of insulin secretion in diabetic and nondiabetic humans. *Am J Physiol Endocrinol Metab*. 2004;287:E199–E206.
83. Schirra J, Nicolaus M, Roggel R, et al. Endogenous glucagon-like peptide 1 controls endocrine pancreatic secretion and antro-pyloro-duodenal motility in humans. *Gut*. 2006;55:243–251.
84. Willms B, Werner J, Holst JJ, Orskov C, Creutzfeldt W, Nauck MA. Gastric emptying glucose responses, insulin secretion after a liquid test meal: effects of exogenous glucagon-like peptide-1 (GLP-1)-(7-36) amide in type 2 (noninsulin-dependent) diabetic patients. *J Clin Endocrinol Metab*. 1996;81:327–332.
85. Zander M, Madsbad S, Madsen JL, Holst JJ. Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, beta-cell function in type 2 diabetes: a parallel-group study. *Lancet*. 2002;359:824–830.
86. Sandoval D. CNS GLP-1 regulation of peripheral glucose homeostasis. *Physiol Behav*. 2008;94:670–674.
87. Knauf C, Cani PD, Perrin C, et al. Brain glucagon-like peptide-1 increases insulin secretion and muscle insulin resistance to favor hepatic glycogen storage. *J Clin Invest*. 2005;115:3554–3563.
88. Sandoval DA, Bagnol D, Woods SC, D'Alessio DA, Seeley RJ. Arcuate glucagon-like peptide 1 receptors regulate glucose homeostasis but not food intake. *Diabetes*. 2008;57:2046–2054.
89. Mojiminiyi OA, Abdella NA. Associations of resistin with inflammation and insulin resistance in patients with type 2 diabetes mellitus. *Scand J Clin Lab Invest*. 2007;67:215–225.

90. Muse ED, Lam TK, Scherer PE, Rossetti L. Hypothalamic resistin induces hepatic insulin resistance. *J Clin Invest*. 2007;117:1670–1678.
91. Singhal NS, Lazar MA, Ahima RS. Central resistin induces hepatic insulin resistance via neuropeptide Y. *J Neurosci*. 2007;27:12924–12932.
92. Meguid MM, Fetissov SO, Varma M, et al. Hypothalamic dopamine and serotonin in the regulation of food intake. *Nutrition*. 2000;16:843–857.
93. Murzi E, Contreras Q, Teneud L, et al. Diabetes decreases limbic extracellular dopamine in rats. *Neurosci Lett*. 1996;202: 141–144.
94. Pijl H. Reduced dopaminergic tone in hypothalamic neural circuits: expression of a "thrifty" genotype underlying the metabolic syndrome?. *Eur J Pharmacol*. 2003;480:125–131.
95. Nonogaki K, Strack AM, Dallman MF, Tecott LH. Leptin-independent hyperphagia and type 2 diabetes in mice with a mutated serotonin 5-HT2C receptor gene. *Nat Med*. 1998;4:1152–1156.
96. Zhou L, Sutton GM, Rochford JJ, et al. Serotonin 2C receptor agonists improve type 2 diabetes via melanocortin-4 receptor signaling pathways. *Cell Metab*. 2007;6:398–405.
97. Ader M, Kim SP, Catalano KJ, et al. Metabolic dysregulation with atypical antipsychotics occurs in the absence of underlying disease: a placebo-controlled study of olanzapine and risperidone in dogs. *Diabetes*. 2005;54:862–871.
98. Houseknecht KL, Robertson AS, Zavadoski W, Gibbs EM, Johnson DE, Rollema H. Acute effects of atypical antipsychotics on whole-body insulin resistance in rats: implications for adverse metabolic effects. *Neuropsychopharmacology*. 2007;32:289–297.
99. Chintoh AF, Mann SW, Lam L, et al. Insulin resistance and decreased glucose-stimulated insulin secretion after acute olanzapine administration. *J Clin Psychopharmacol*. 2008;28:494–499.
100. Rother E, Konner AC, Bruning JC. Neurocircuits integrating hormone and nutrient signaling in control of glucose metabolism. *Am J Physiol Endocrinol Metab*. 2008;294:E810–E816.
101. Prodi E, Obici S. Minireview: the brain as a molecular target for diabetic therapy. *Endocrinology*. 2006;147:2664–2669.
102. Levin BE, Dunn-Meynell AA, Routh VH. Brain glucosensing and the K(ATP) channel. *Nat Neurosci*. 2001;4:459–460.
103. Parton LE, Ye CP, Coppari R, et al. Glucose sensing by POMC neurons regulates glucose homeostasis and is impaired in obesity. *Nature*. 2007;449:228–232.
104. Ross R, Wang PY, Chari M, et al. Hypothalamic protein kinase C regulates glucose production. *Diabetes*. 2008;57:2061–2065.