

REVIEW

Emerging role of the brain in the homeostatic regulation of energy and glucose metabolism

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Accumulated evidence from genetic animal models suggests that the brain, particularly the hypothalamus, has a key role in the homeostatic regulation of energy and glucose metabolism. The brain integrates multiple metabolic inputs from the periphery through nutrients, gut-derived satiety signals and adiposity-related hormones. The brain modulates various aspects of metabolism, such as food intake, energy expenditure, insulin secretion, hepatic glucose production and glucose/fatty acid metabolism in adipose tissue and skeletal muscle. Highly coordinated interactions between the brain and peripheral metabolic organs are critical for the maintenance of energy and glucose homeostasis. Defective crosstalk between the brain and peripheral organs contributes to the development of obesity and type 2 diabetes. Here we comprehensively review the above topics, discussing the main findings related to the role of the brain in the homeostatic regulation of energy and glucose metabolism.

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CENTRAL REGULATION OF ENERGY METABOLISM

In normal individuals, food intake and energy expenditure are tightly regulated by homeostatic mechanisms to maintain energy balance. Substantial evidence indicates that the brain, particularly the hypothalamus, is primarily responsible for the regulation of energy homeostasis.¹ The brain monitors changes in the body energy state by sensing alterations in the plasma levels of key metabolic hormones and nutrients. Specialized neuronal networks in the brain coordinate adaptive changes in food intake and energy expenditure in response to altered metabolic conditions (Figure 1).^{2,3}

Brain regulation of food intake

The hypothalamus is considered a key organ in the regulation of food intake. The hypothalamic arcuate nucleus (ARC) is adjacent to the median eminence, one of the circumventricular organs, and surrounds the third cerebroventricle. Thus, hormones and nutrients in the systemic circulation and the cerebrospinal fluid can easily access the ARC. Anatomically, the ARC is considered a hypothalamic area that primarily senses metabolic signals from the periphery via the systemic circulation.⁴ In the ARC, there are two distinct neuronal populations: one group of neurons produces the orexigenic neuropeptides neuropeptide Y (NPY) and agouti-related

peptide (AgRP), whereas the other subset of neurons expresses the anorexigenic neuropeptides proopiomelanocortin (POMC), and cocaine- and amphetamine-regulated transcript. These neurons are the first-order neurons on which peripheral metabolic hormones, including leptin, insulin, ghrelin and nutrients, primarily act.⁵ The anorexigenic effect of monoamine serotonin is also mediated by the 5HT-2C receptor in POMC neurons.⁶ POMC neurons project axonal processes to second-order neurons in hypothalamic areas such as the paraventricular nucleus (PVN), ventromedial hypothalamus (VMH) and lateral hypothalamus (LH), and to autonomic preganglionic neurons in the brain stem and spinal cord.⁷

The anorexigenic neuropeptide α -melanocyte-stimulating hormone (α -MSH) is produced by posttranscriptional processing of POMC and is released from the presynaptic terminals of POMC neurons. Upon binding to the melanocortin-3 and -4 receptors (MC3R and MC4R) on second-order neurons, α -MSH activates catabolic pathways, leading to reduced food intake and increased energy expenditure. Targeted deletion of the MC4R in mice induces hyperphagia, reduces energy expenditure and leads to obesity.⁸ In humans, MC4R mutations account for ~6% of severe early-onset obesity cases,⁹ suggesting an important role for the central melanocortin system in the maintenance of normal body weight.

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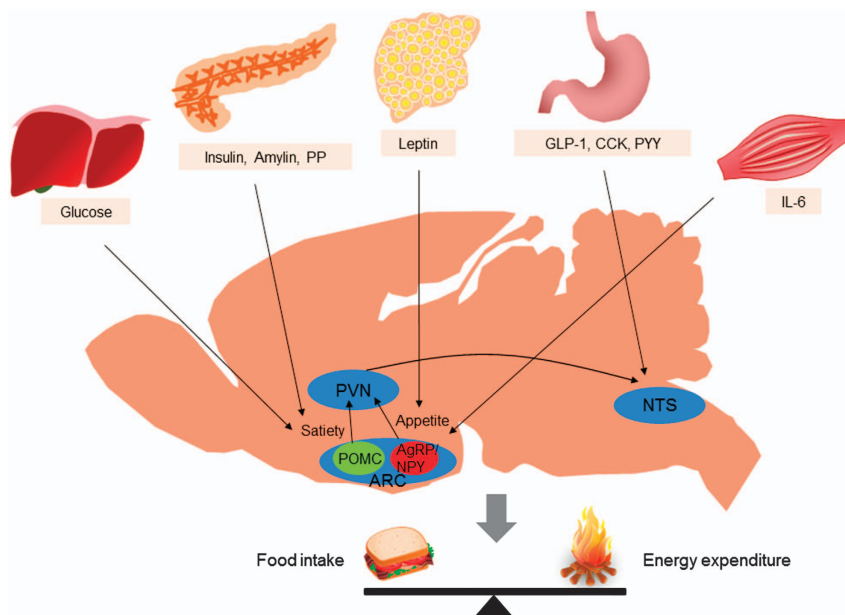


Figure 1 Integration of peripheral metabolic signals and the central nervous system maintains energy homeostasis. The brain integrates metabolic signals from peripheral tissues such as the liver, pancreas, adipose tissue, gut and muscle. Specialized neuronal networks in the brain coordinate adaptive changes in food intake and energy expenditure in response to altered metabolic conditions. Neuropeptide Y/agouti-related protein- and proopiomelanocortin-producing neurons in the hypothalamic arcuate nucleus primarily sense the body energy state. These neurons project to other hypothalamic nuclei and to the nucleus of the solitary tract in the brain stem to control multiple aspects of the homeostatic regulation of energy balance. ARC, arcuate nucleus; CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; IL-6, interleukin-6; PP, pancreatic polypeptide; PVN, paraventricular nucleus; PYY, peptide YY.

The endogenous MC-3/4R antagonist AgRP is released from the terminals of NPY/AgRP-producing neurons to the synaptic space of second-order neurons where it competes with α -MSH for MC3Rs and MC4Rs and antagonizes its effects.¹⁰ Selective ablation of NPY/AgRP neurons in young mice results in a significant decrease in food intake and body weight,¹¹ suggesting that these neurons are critical for promoting food intake and preventing weight loss. Administration of NPY stimulates food intake via Y1 or Y5 receptors.¹² NPY is required for the rapid stimulation of feeding, whereas AgRP stimulates feeding over a prolonged period.¹³

PVN neurons synthesize and secrete neuropeptides that have a net catabolic action, including corticotrophin-releasing hormone, thyrotropin-releasing hormone, somatostatin, vasopressin and oxytocin. On the other hand, PVN neurons control sympathetic outflow to peripheral metabolic organs, resulting in increased fatty acid oxidation and lipolysis.¹⁴ Destruction of PVN and haploinsufficiency of *Sim1*, a critical transcriptional factor in the development of PVN, cause hyperphagia and obesity,¹⁵ implying an inhibitory role of the PVN in food intake and weight gain.

The VMH mainly receives neuronal projections from the ARC and projects their axons to the ARC, dorsomedial nucleus (DMN), LH and brain stem regions. The VMH contains neurons that sense glucose and leptin.^{16,17} Moreover, the anorexigenic neuropeptide brain-derived neurotrophic factor is produced in the VMH.¹⁸ Destruction of the VMH causes hyperphagia, obesity and hyperglycemia.¹⁹ Thus, the VMH is regarded a pivotal area in generating satiety and maintaining

glucose homeostasis. The DMN contains a high level of NPY terminals and α -MSH terminals originating from the ARC.²⁰ Destruction of the DMN also results in hyperphagia and obesity.²¹

In contrast to the PVN, VMH and DMN, destruction of the LH leads to hypophagia and weight loss. Therefore, LH is considered a feeding center. LH contains two neuronal populations producing the orexigenic neuropeptides melanin-concentrating hormone (MCH) and orexin, also called hypocretin. NPY/AgRP- and α -MSH-immunoreactive terminals from ARC neurons are in contact with MCH- and orexin-expressing neurons.²² Orexin-producing neurons are also involved in glucose sensing and the regulation of sleep–awake cycles.²³ Alterations in the orexin receptor-2 and orexin genes produce narcolepsy in animal models and humans.²⁴ On the other hand, depletion of MCH or the MCH-1 receptor in mice attenuates weight gain, suggesting that MCH is an endogenous orexigenic molecule.²⁵

The brain stem is another key brain area involved in the regulation of food intake. Satiety signals from the gastrointestinal tract are relayed to the nucleus tractus solitarius (NTS) through the sensory vagus nerve, a major neuronal connection between the gut and brain. Transection of sensory vagal fibers decreases meal size and meal duration, confirming that vagal afferents transfer meal-related signals to the brain.²⁶ Like the ARC, the NTS is anatomically close to the area postrema, another circumventricular organ.²⁷ Therefore, the NTS is perfectly located for receiving both humoral and neural signals. Meanwhile, the NTS receives extensive neuronal

projections from the PVN and vice versa,²⁸ indicating that there are intimate communications between the hypothalamus and the brain stem. Like hypothalamic neurons, NTS neurons produce appetite-regulating glucagon-like peptide-1 (GLP-1), NPY and POMC, and sense peripheral metabolic signals.²⁹ For instance, NTS POMC neurons show the signal transducer and activator of transcription 3 (STAT3) activation in response to exogenous leptin.³⁰ Thus, circulating hormones and nutrients may relay metabolic signals to the brain by acting on both the hypothalamus and brain stem.

On the other hand, the brain reward system is involved in the control of hedonic feeding, that is, intake of palatable foods. Like other addiction behaviors, the mesolimbic and mesocortical dopaminergic pathways are involved in hedonic feeding. Intake of palatable foods elicits dopamine release in the ventral tegmental area (VTA), which in turn activates the neural pathways from the VTA to the nucleus accumbens via the medial forebrain bundles. Interestingly, hedonic feeding is modulated by metabolic signals. Leptin acts on the dopaminergic neurons in the VTA to suppress feeding.³¹ Conversely, hedonic feeding can override satiety signals. Mice lacking the D₂ receptor are more sensitive to leptin.³²

Brain regulation of energy expenditure

The brain modulates various processes that consume energy, such as locomotor activity, fatty acid oxidation in the skeletal muscle and thermogenesis.³³ Tumor growth factor- α , produced in the suprachiasmatic nucleus in a circadian manner, strongly inhibits locomotor activity by acting on the epidermal growth factor receptors expressed in the hypothalamic subparaventricular zone.³⁴ Orexin-A produced by LH neurons promotes locomotor activity and wakefulness through orexin-1 and orexin-2 receptors.³⁵ A role for orexin in food-seeking behavior in food-deprived conditions has been suggested.³⁶ Leptin stimulates locomotor activity via a mechanism that depends on hypothalamic POMC neurons³⁷. Leptin also enhances fatty acid oxidation in skeletal muscle via both central and peripheral mechanisms.³⁸

Thermogenesis is the process that dissipates energy as heat to maintain body temperature. Thermogenesis mainly occurs in brown adipose tissue (BAT).³⁹ Brown fat-like adipocytes, so-called browning of white adipose tissue (WAT), are found in the subcutaneous inguinal WAT under certain circumstances. Cold exposure or intracerebroventricular (ICV) coinjection of insulin and leptin induces WAT browning.⁴⁰ Induction of WAT browning results in increased energy expenditure and attenuation of diet-induced obesity in mice. Conversely, inhibition of WAT browning by depletion of Prdm16 leads to obesity.³⁹

The brain regulates BAT thermogenesis through modulation of the sympathetic nervous system. Norepinephrine released from sympathetic nervous terminals acts on the β ₃-adrenergic receptors in adipocytes in the BAT and inguinal fat pads. Activation of adrenergic receptors triggers cyclic-adenosine monophosphate signaling, which in turn increases the expression of uncoupling protein-1 in the mitochondria. BAT

thermogenesis is important for maintaining body temperature in response to cold exposure and dissipating excess energy after high-calorie intake. Because metabolic fuel substrates such as glucose and fatty acid are consumed during BAT thermogenesis, BAT thermogenesis can affect body weight and body fat mass.⁴¹ In the past, BAT was thought to be present only in human infants. However, ¹⁸F-fluorodeoxyglucose positron emission tomography revealed the presence of BAT in the adult humans. Human BAT depots are distributed in the supraclavicular area and in perivascular and periviscus areas (for example, around the heart, airway, gut, liver and adrenal gland) of the chest and abdomen.⁴² BAT activity, determined by ¹⁸F-fluorodeoxyglucose positron emission tomography, is affected by outdoor temperature, age, sex, body mass index and the coexistence of diabetes. Because the amount of BAT is inversely correlated with body mass index, especially in older subjects, a potential role of BAT in adult human metabolism has been suggested.⁴³

In thermogenic regulation, the hypothalamus integrates the sensation of body temperature with efferent sympathetic outflow. Hypothalamic areas such as the preoptic area, VMH, DMN and ARC modulate thermogenic activity by influencing the sympathetic nervous system.⁴⁴ The preoptic area is an important area in the control of body temperature.⁴⁵ VMH was the first hypothalamic nucleus to be studied regarding the regulation of BAT activity. The DMN also contains sympathoexcitatory neurons,⁴⁶ which regulate thermogenic activity.^{47,48} BAT thermogenesis is also related to the ARC melanocortin system because α -MSH stimulates BAT activity.⁴⁹

Hormonal- and nutrient-mediated metabolic signals can influence sympathetic outflow to the BAT. Central administration of leptin, MC3/4R agonist, glucagon and GLP-1 stimulates BAT activity.^{50,51} Central administration of insulin either stimulates or inhibits BAT thermogenesis, depending on the insulin dose. Central administration of high doses of insulin increases sympathetic nerve activity in the BAT, whereas low doses of insulin decrease it.^{52,53} Food consumption or dietary composition also affects BAT thermogenesis. Although the mechanism of postprandial thermogenesis is unclear, norepinephrine turnover in the BAT is increased after a meal.⁵⁴ Glucose administration increases thermogenesis, whereas fasting or food restriction inhibits thermogenesis. Low-protein diet and high-fat diet increase BAT activity.⁵⁵

Peripheral signals modulating energy metabolism

Adiposity signals. Adiposity signals refer to the peripheral signals that circulate in proportion to the total amount of stored fat and inform the brain about the stored energy state. They modulate energy balance through the regulation of food intake and energy expenditure.^{2,56} Insulin is a hormone that was first identified as an adiposity signal.^{5,57} Insulin is secreted by β -cells in response to energy flux. Plasma insulin concentrations increase in proportion to the amount of stored fat.⁵⁸ When insulin is administered directly into the central nervous system, it induces a dose-dependent reduction in food intake

and body weight.^{59,60} Thus, insulin is thought to signal adiposity to the brain. In hypothalamic neurons, insulin activates the insulin receptor substrate-2 (IRS2)–phosphatidylinositol 3-kinase (PI3K) signaling pathway. Neuronal deletion of insulin receptor and IRS2 results in increased food intake and susceptibility to diet-induced obesity.^{61,62}

The adipose tissue-derived hormone leptin was discovered by positional cloning of the obesity locus (*ob*) in 1994.⁶³ Leptin is now considered a representative adiposity signal.⁶⁴ The receptors activated by leptin are highly expressed in several regions of brain, including the hypothalamus.⁶⁵ Genetic deficiency in leptin or the long-form leptin receptor (*LepRb*) is associated with hyperphagia, hypoactivity and obesity.⁶⁶ Of several brain regions, the ARC is an important area that mediates leptin actions. Injection of leptin directly into the ARC reduces food intake and body weight.⁶⁷ Leptin also stimulates locomotion through signaling in POMC neurons.³⁷ Consistently, ICV administration of leptin in leptin-deficient (*ob/ob*) mice attenuates obesity.⁶⁶ In hypothalamic neurons, leptin provokes several signaling cascades such as the Janus kinase–STAT pathway, IRS–PI3K signaling, the mammalian target of rapamycin–S6 kinase signaling, AMP-activated protein kinase (AMPK) signaling and ERK signaling.⁶⁸ Of those, STAT3 signaling represents hypothalamic leptin signaling and is frequently used as a marker of leptin signaling activity.

Nutrient signals. Nutrients such as glucose, fatty acids and amino acids provide information on nutrient availability to the brain. Glucose signals the presence of an energy supply to the brain, whereas hypoglycemia signals an energy deficit.⁶⁹ Thus, central administration of glucose and long-chain fatty acids decreases food intake.⁷⁰ In contrast, ICV administration of the glucose anti-metabolite 2-deoxy-D-glucose increases food intake.⁷¹ The malonyl-CoA content in hypothalamic neurons has been suggested to be a fuel gauge.^{56,72} Administration of the fatty acid synthase inhibitor C75 induces accumulation of malonyl-CoA in hypothalamic neurons, leading to decreased food intake and body weight.⁷³ Long-chain fatty acyl-CoA (LCFA-CoA) content in hypothalamic neurons also acts as a cellular nutrient sensor. An increased hypothalamic LCFA-CoA level due to ICV long-chain fatty acid (LCFA) administration leads to decreased food intake.⁷⁰ Hypothalamic inhibition of carnitine palmitoyltransferase-1 inhibits food intake by elevating LCFA-CoA content in hypothalamic neurons.⁷⁴

Gastrointestinal signals. Hormones secreted by the gut in response to a meal provide information on energy intake. Cholecystokinin, peptide YY and GLP-1 released from the gut induce satiety by acting on the vagus nerve or in the brain.⁷⁵ For example, GLP-1 is secreted from intestinal L-cells after a meal. GLP-1 receptors are prevalent in vagus nerve terminals,⁷⁶ as well as in the central nucleus of the amygdala, the PVN and ARC of the hypothalamus, and the caudal brain stem.⁷⁷ Both central and peripheral administration of GLP-1 promotes satiety.^{78,79} In contrast, ghrelin is secreted by the stomach during a fast and promotes food intake.⁸⁰

Signals from other organs. Interleukin-6 (IL-6) is synthesized and released from contracting skeletal muscle during exercise. The elevation in the plasma IL-6 concentration during exercise correlates with exercise intensity and duration and the muscle mass recruited.⁸¹ IL-6 enters the brain across the blood–brain barrier. IL-6 may mobilize fat from storage sites to provide energy to the muscle. ICV administration of IL-6 stimulates energy expenditure, and mice lacking IL-6 develop mature-onset obesity.⁸²

Hormones secreted from the endocrine pancreas are also involved in energy homeostasis. Insulin and amylin are co-secreted by β -cells. Like insulin, amylin acts as a satiety signal and reduces food intake via amylin receptors in the area postrema. Other brain sites mediating amylin action include the NTS and the lateral parabrachial nucleus.⁸³ Amylin also acts as an adiposity signal because amylin levels are well correlated with body fat content. Glucagon, a counter-regulatory hormone to insulin, is secreted from α -cells. Glucagon reduces meal size by acting on the vagus nerves and stimulates energy expenditure through central and peripheral mechanisms.⁸⁴ Pancreatic polypeptide is also secreted from the endocrine pancreas. Pancreatic polypeptide regulates gastric motility, pancreatic exocrine secretion and food intake. Systemic administration of pancreatic polypeptide reduces food intake and weight gain.⁸⁵ The anorectic effect of pancreatic polypeptide is mediated by Y4 receptors in the dorsal vagal complex.⁸⁶

BRAIN REGULATION OF GLUCOSE METABOLISM

The earliest demonstration of the role of the brain in glucose homeostasis was provided by the physiologist Claude Bernard in 1854. Dr Bernard demonstrated that a puncture in the floor of the fourth ventricle of the rabbit brain resulted in glycosuria.⁸⁷ In the past few decades, the concept of central regulation of glucose metabolism has been further established by the subsequent discovery of glucose-sensing neurons in the hypothalamus^{88,89} and the demonstration of their roles in maintaining normal glucose levels.⁹⁰ A specialized neuronal population in the brain senses hormones (insulin and leptin) and nutrients (glucose and fatty acids) to regulate glucose homeostasis. The major sites of convergence of these metabolic signals are the hypothalamus and brain stem (Figure 2).

Neuronal populations controlling glucose metabolism

Brain regions related to the control of glucose metabolism contain neurons whose excitability changes with alterations in glucose concentrations in the extracellular fluid. These glucose-sensing neurons are found in the hypothalamic nuclei and brain stem, which are also important areas in the control of energy balance. Glucose-sensing neurons are subgrouped into two types. Glucose-excited neurons are excited when extracellular glucose levels increase. In contrast, glucose-inhibited neurons are activated by a fall in extracellular glucose concentrations.⁹¹ Glucose-excited neurons are mostly located in the VMH, the ARC and the PVN,⁹² whereas glucose-inhibited neurons are distributed in the LH, ARC and

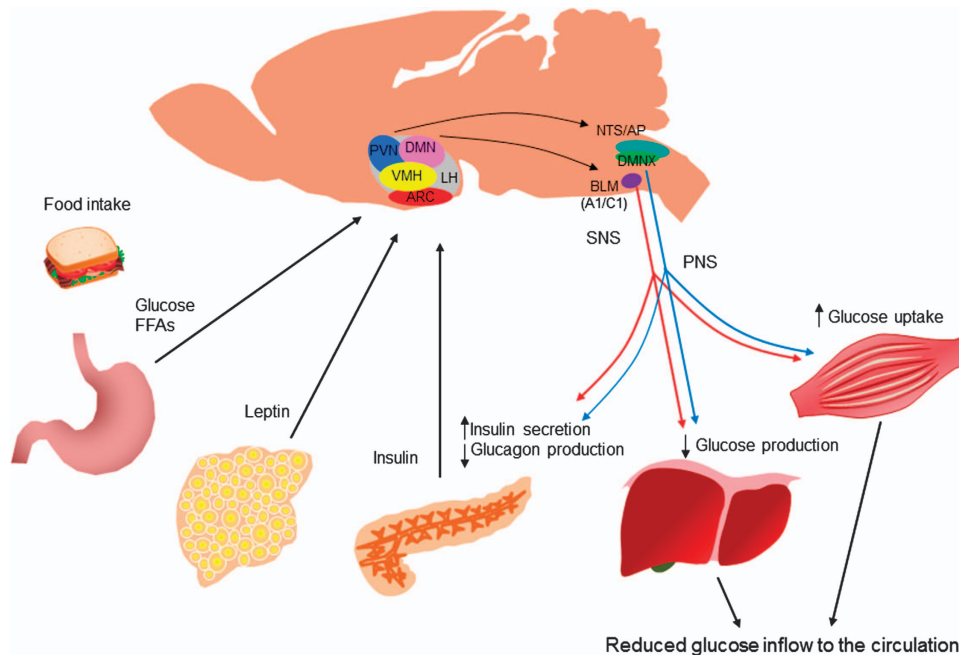


Figure 2 Brain regulation of glucose homeostasis. The brain senses peripheral metabolic signals through hormones (insulin, leptin and so on) and nutrients (glucose, free fatty acids and so on) to regulate glucose metabolism. The sites of the convergence of these metabolic signals are the hypothalamus and brain stem. The autonomic nervous system intervenes in the brain and peripheral metabolic organs to modulate pancreatic insulin/glucagon secretion, hepatic glucose production and skeletal muscle glucose uptake. AP, area postrema; ARC, arcuate nucleus; BLM, basolateral medulla; DMN, dorsomedial nucleus; DMNX, dorsal motor nucleus of the vagus; FFA, free fatty acids; LH, lateral hypothalamus; NTS, nucleus of the solitary tract; PNS, parasympathetic nervous system; PVN, paraventricular nucleus; SNS, sympathetic nervous system; VMH, ventromedial hypothalamus.

PVN.^{89,91} Both types of neurons are also located in the dorsal vagal complex in the brain stem, which encompasses the NTS, area postrema and the dorsal motor nucleus of the vagus.^{93–95}

Peripheral signals affecting brain regulation of glucose metabolism

Insulin. During the past decade, the brain has been recognized to be a site of insulin action with regard to glucose homeostasis. Obici *et al.*⁹⁶ showed that insulin acts on the brain to modulate hepatic glucose metabolism. They showed, by injecting insulin receptor antisense oligonucleotides into the cerebroventricle, that inhibition of central insulin action impaired insulin-mediated suppression of hepatic glucose production (HGP) during hyperinsulinemic clamp studies in rats. They also demonstrated that infusion of insulin into the cerebroventricle suppressed HGP, irrespective of circulating insulin levels. Moreover, central administration of insulin antibodies or inhibitors of the downstream signaling of insulin diminished the ability of insulin to inhibit glucose production.⁹⁷ The hypothalamic insulin signaling pathway was investigated in subsequent studies. Overexpression of the insulin signaling molecules IRS2 and Akt in the hypothalamus enhances the glucose-lowering effect of insulin in streptozotocin-induced diabetic rats.⁹⁸ These data support a role for hypothalamic insulin actions in controlling glucose metabolism in peripheral organs.

The ATP-sensitive potassium (K_{ATP}) channel mediates insulin actions in hypothalamic neurons.⁹⁹ Activation of

neuronal K_{ATP} channels by ICV injection of a K_{ATP} channel activator (diazoxide) lowers glucose production,¹⁰⁰ whereas infusion of a K_{ATP} blocker (sulfonylurea) negates the glucose production-lowering effect of centrally and peripherally administered insulin.^{96,100} Moreover, mice lacking the sulfonylurea receptor subunit SUR1 of the K_{ATP} channel show a diminished response to central insulin action.¹⁰⁰ Vagal efferent fibers constitute the brain–liver axis of insulin actions because hepatic vagotomy blocks central insulin actions.¹⁰⁰ Interestingly, ICV infusion of insulin increases hepatic IL-6 expression, which leads to the activation of hepatic STAT3 signaling.¹⁰¹ Activated STAT3 inhibits FoxO1 activity and gluconeogenic gene expression in the liver. Collectively, central insulin actions are mediated via neuronal K_{ATP} channel–vagus nerve–hepatic IL6/STAT3 signaling, although the detailed mechanisms involved remain to be determined.

Leptin. Leptin has an important role in the control of glucose metabolism. A lack of leptin (*ob/ob* mice) or its functional receptor (*db/db* mice) leads not only to obesity, but also metabolic derangement, including insulin resistance and diabetes.¹⁰² Leptin treatment of *ob/ob* mice improves glucose homeostasis.^{103,104} Notably, acute leptin treatment via both systemic and central routes in *ob/ob* mice restores glucose metabolism independently of changes in food intake and adiposity.^{105,106} Consistently, leptin-treated *ob/ob* mice display a marked reduction in serum glucose and insulin concentrations.¹⁰⁷ Leptin treatment in lipodystrophy mice

improves insulin resistance and hyperglycemia independently of food intake.^{108,109} Thus, leptin regulates glucose homeostasis independently of its anorectic effects.

The hypothalamus is a key site of action of leptin-mediated control of glucose metabolism. ICV administration of leptin in the lipodystrophy mice model corrects insulin resistance and improves impaired insulin signaling in the liver. In contrast, peripheral injection of the same dose of leptin did not have a similar effect.¹¹⁰ Acute ICV injection of leptin suppresses glycogenolysis and reduces hepatic insulin resistance induced by high-fat feeding.¹¹¹ Restoration of leptin signaling in the unilateral ARC by viral gene therapy in leptin receptor-null mice markedly improves hyperinsulinemia and normalizes blood glucose levels, with a mild decrease in body weight and food intake. These data demonstrate that leptin signaling in the ARC is critical for the maintenance of glucose homeostasis.¹¹²

Leptin-mediated regulation of glucose metabolism is mediated by hypothalamic STAT3 and PI3K signaling pathways. As in *db/db* mice, *s/s* mice with a mutated leptin receptor, which are unable to activate STAT3, exhibit severe hepatic insulin resistance.¹¹³ Blockade of leptin-induced STAT3 activation in the hypothalamus abolishes the suppressive effect of leptin on HGP, confirming the importance of leptin-induced STAT3 signaling.¹¹³ Conversely, hypothalamic deletion of suppressor of cytokine signaling 3, a negative regulator of STAT3 signaling, enhances leptin sensitivity and improves glucose metabolism.¹¹⁴ On the other hand, reconstitution of leptin receptors in the ARC of leptin-receptor-deficient *fa^k/fa^k* rats improves insulin sensitivity, which is attenuated by ICV infusion of PI3K inhibitor. Consistently, ARC expression of constitutively active Aktin *fa^k/fa^k* rats mimics the effect of restored hypothalamic leptin signaling.¹¹⁵ These findings indicate that PI3K–Akt signaling mediates leptin actions on glucose homeostasis.

Glucose. Glucose sensing in the hypothalamus is important in glucose homeostasis. Injection of 2-deoxy-D-glucose into the VMH increases plasma glucose levels by elevating plasma glucagon and catecholamine levels.¹¹⁶ Conversely, intra-VMH glucose infusion suppresses counter-regulatory hormonal responses to hypoglycemia.⁹⁰ The brain stem is also involved in glucoprivic feeding and counter-regulatory hormone secretion during hypoglycemia. Injection of another glucose anti-metabolite, 5-thio-D-glucose, into the NTS and the basolateral medulla, which contain A1/C1 catecholaminergic neurons projecting to the hypothalamic PVN and ARC, induces feeding and glucose responses, as seen in hypoglycemia.¹¹⁷ Similarly, destruction of hindbrain catecholaminergic neurons by immunotoxins blocks 2-deoxy-D-glucose-induced feeding and blood glucose responses.¹¹⁸

The glucose-sensing mechanisms in hypothalamic neurons are similar to those in pancreatic β -cells.¹¹⁹ Glucose signaling in glucose-excited neurons requires glucose uptake via the type 2 glucose transporter, which is followed by glucose phosphorylation by glucokinase, intramitochondrial glucose oxidation, and

an increased cellular ATP/ADP ratio. This leads to the closure of ATP-sensitive K_{ATP} channels, depolarization of the membrane potential, and influx of Ca^{2+} through voltage-dependent calcium channels, which stimulate neuronal activity and neurotransmitter release.¹²⁰ The role of hypothalamic type 2 glucose transporter, glucokinase and K_{ATP} channels in sensing hypoglycemia and counter-regulatory hormone responses has been demonstrated.^{121–126} How glucose inhibits neuronal activity in glucose-inhibited neurons is unclear. One possibility is that glucose increases the ATP/ADP ratio, which stimulates the Na^+/K^+ -ATPase pump and triggers hyperpolarizing currents.¹²⁷ Alternatively, glucose-induced activation of ATP-dependent Cl^- channels may induce hyperpolarization of the plasma membrane.^{91,128}

AMPK functions as a ‘fuel gauge’ that monitors cellular energy status and provokes adaptive responses to maintain cellular energy levels.^{129,130} ICV administration of glucose suppresses feeding via inhibition of hypothalamic AMPK activity.^{131,132} Hypothalamic AMPK activation is critical for feeding and counter-regulatory responses to hypoglycemia.¹³¹ Intra-VMH administration of AICAR (5-aminoimidazole-4-carboxamide ribonucleotide), a chemical AMPK activator, increases HGP without changing the plasma levels of counter-regulatory hormones.¹³³ AMPK activation in the VMH restores reduced counter-regulatory responses induced by repeated hypoglycemia.¹³⁴ Consistent with these findings, inhibition of hypothalamic AMPK activity attenuates the counter-regulatory response during hypoglycemia.¹³⁵

Fatty acids. LCFA signals nutrient availability to the brain and modulates peripheral glucose metabolism.⁷⁰ ICV administration of oleic acid suppresses HGP during basal insulin clamping. ICV administration of K_{ATP} channel blocker attenuates the inhibitory effect of oleic acid on glucose production, indicating an involvement of brain K_{ATP} channels in this process.⁷⁰ Increased LCFA-CoA levels in hypothalamic neurons suppresses endogenous glucose production.⁷⁴ Pharmacological inhibition of hypothalamic esterification of fatty acids or surgical resection of the hepatic branch of the vagus nerve increases HGP.¹³⁶ Therefore, hypothalamic lipid sensing regulates glucose homeostasis via a mechanism involving the esterification of LCFAs to LCFA-CoAs, intact K_{ATP} channels and vagal outflow to the liver.

Effector pathways in the brain control of glucose metabolism

To the liver. In rodents, direct action of insulin on the liver is necessary, but is insufficient to inhibit HGP, unless the indirect brain pathway is not fully functional. Restoration of insulin receptor expression in either the liver or brain of insulin receptor-null mice does not completely restore the ability of insulin to inhibit HGP.¹³⁷ In contrast, restoration of insulin receptor expression in both the brain and liver normalizes insulin actions on HGP.¹³⁸ Whether neuronal control of HGP is unique to rodents remains uncertain. ICV insulin infusion in the dog augments hepatic glucose uptake and glycogen synthesis without altering HGP,¹³⁹ indicating that the

regulation of gluconeogenesis by brain insulin signaling may differ among species. The basal HGP rate per weight is almost 5–10 times higher in rodents than in dogs and humans.¹⁴⁰ Dogs and humans maintain hepatic glycogen storage even after a 42-h fasting.^{141,142} In contrast, hepatic glycogen content is significantly depleted in rodents after a relatively short fast, which may be due to higher metabolic rates.¹⁴³ Therefore, the contribution of the gluconeogenic pathway to HGP may be greater in rodents than in animals with a larger body size.¹³⁹ Thus, changes in gluconeogenesis may be more easily detected in rodents.

To the skeletal muscle. Electrical stimulation of VMH neurons and local injection of leptin into the VMH increases glucose uptake in the skeletal muscle of rats independently of circulating insulin levels.^{144,145} These effects appear to be mediated by the sympathetic nervous system as they are abolished by blockade of the sympathetic nervous system.^{146,147} Consistently, central infusion of leptin improves glucose tolerance and enhances insulin-stimulated Akt phosphorylation in skeletal muscle.^{148,149} Activated Akt leads to translocation of the glucose transporter GLUT4 from its sequestered cytoplasmic location to the cell membrane, facilitating glucose uptake¹⁵⁰.

In the skeletal muscle, AMPK activation is induced by muscle contraction and adrenergic agonist and mediates insulin-independent glucose uptake.¹⁵¹ Leptin activates skeletal muscle AMPK through the hypothalamus and sympathetic

nervous system.¹⁵² Therefore, leptin may promote glucose uptake to the skeletal muscle through the sympathetic nervous system–muscle AMPK signaling pathway. On the other hand, orexin-producing neurons in the LH are activated by sweet foods. Orexin regulates skeletal muscle glucose uptake through VMH neurons expressing orexin receptors and the sympathetic nervous system.¹⁵³

To the pancreas. The autonomic nervous system controls the secretion of insulin and glucagon in the pancreas. Sympathetic and parasympathetic nerve endings are found in pancreatic islets.¹⁵⁴ Moreover, α - and β -cells express neurotransmitter receptors.¹⁵⁵ Both sympathetic and parasympathetic nerve branches can stimulate glucagon secretion. In contrast, parasympathetic branches stimulate insulin secretion, whereas sympathetic branches inhibit it.¹⁵⁶ Neurons in the dorsal motor nucleus of the vagus project nerve terminals to the pancreatic ganglions via the vagus nerve, and thus vagus nerves connect the dorsal motor nucleus of the vagus and endocrine pancreas.¹⁵⁷

Insulin regulates whole-body glucose metabolism by acting on the brain, and modulating insulin and glucagon secretion. ICV administration of insulin increases pancreatic insulin output, demonstrating that pancreatic β -cells are influenced by insulin-sensitive cells of the brain.¹⁵⁸ Moreover, insulin injection into the VMH inhibits glucagon secretion by pancreatic α -cells, indicating that insulin controls glucagon secretion via brain-mediated mechanisms.¹⁵⁹ Taken together,

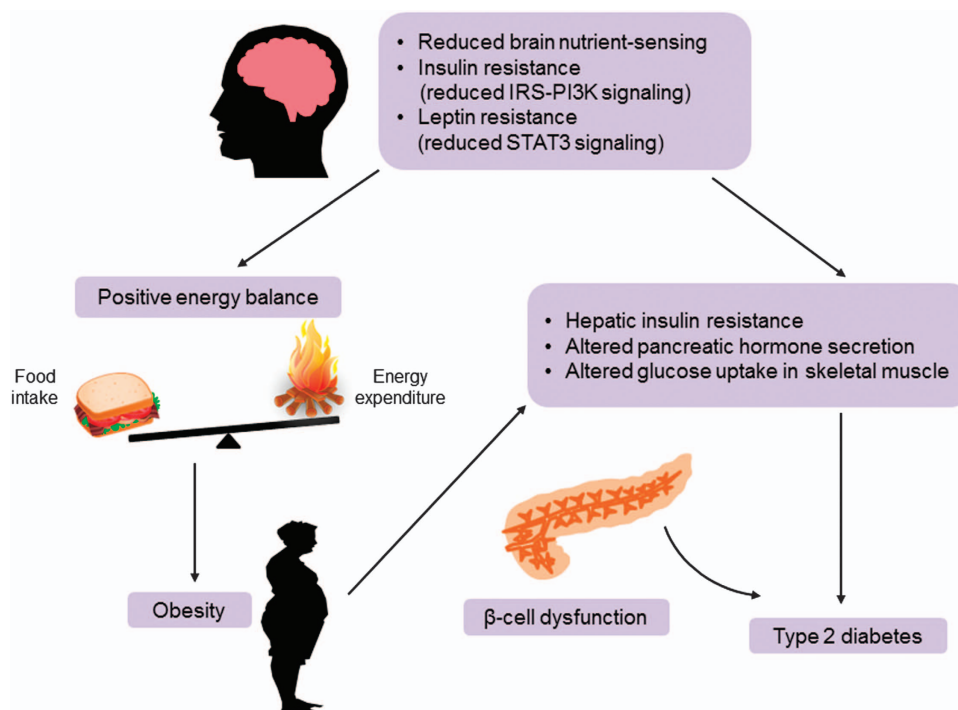


Figure 3 Pathogenesis of obesity and type 2 diabetes due to defective central regulation of energy and glucose homeostasis. Reduced nutrient sensing and impaired insulin and leptin signaling in the hypothalamus may result in a positive energy balance and predispose weight gain, causing insulin resistance in peripheral metabolic organs. Obesity-associated insulin resistance may lead to type 2 diabetes when it is combined with β -cell dysfunction. IRS, insulin receptor substrate; PI3K, phosphatidylinositol 3 kinase; STAT3, signal transducer and activator of transcription 3.

the brain, especially the hypothalamus and brain stem, modulates pancreatic insulin and glucagon secretion via the parasympathetic and sympathetic efferent nerves that innervate pancreatic α - and β -cells.¹⁶⁰

DYSREGULATION OF ENERGY/GLUCOSE METABOLISM IN OBESITY AND DIABETES

In healthy conditions, energy intake matches energy expenditure to maintain normal body weight. Impaired ability of the brain to maintain energy homeostasis may underlie pathological weight gain and obesity (Figure 3). Several defects in the negative-feedback pathway in energy homeostatic mechanisms have been suggested.³ Defects in the secretion of key metabolic hormones such as insulin and leptin may predispose weight gain. Because leptin primarily acts on hypothalamic neurons to regulate the energy balance, leptin transfer to the brain may be critical for its action.⁵ Leptin concentrations in the plasma increase in proportion to body mass index, an indicator of fat mass. However, the increase in leptin concentrations in the cerebrospinal fluid of obese individuals is less than that of plasma leptin concentrations.¹⁶¹ Therefore, reduced leptin transport to the brain may be due to reduced action of leptin in obesity.

Defective hypothalamic sensing of these hormones favors a positive energy balance because loss of leptin receptors in the hypothalamus leads to obesity in mice.¹³ Rats with diet-induced obesity have reduced expressions of leptin receptors in the hypothalamus.¹⁶² Impaired postreceptor signaling in hypothalamic neurons may also result in pathological weight gain. Disruption of the hypothalamic IRS–PI3K signaling pathway causes resistance to peripheral metabolic signals and leads to obesity.¹⁶³ Likewise, mice with disrupted neuronal STAT3 signaling develop hyperphagia and obesity.¹⁶⁴

In rodents, long-term high-fat feeding reduces the anorectic response and hypothalamic STAT3 activation induced by leptin, which is called leptin resistance.¹⁶⁵ Increased hypothalamic expression of suppressor of cytokine signaling 3 has been suggested to be a mechanism of hypothalamic leptin resistance. Ablation of suppressor of cytokine signaling 3 expression in neurons mitigates high-fat diet-induced weight gain and hyperleptinemia and improves glucose tolerance and insulin sensitivity.¹⁶⁶ Protein-tyrosine phosphatase 1B, a well-known negative regulator of insulin and leptin signaling,^{167,168} has also been suggested to cause leptin and insulin resistance in hypothalamic neurons. Neuronal Protein-tyrosine phosphatase 1B knockout mice are hypersensitive to exogenous leptin and insulin, and display improved glucose tolerance during chronic high-fat feeding.¹⁶⁹ Increased IKK β –NF κ B and endoplasmic stress have been found in the hypothalamus of obese rodents and shown to disrupt hypothalamic leptin and insulin signaling.^{170,171} However, a recent paper has shown, using a leptin receptor antagonist, that endogenous leptin signaling and actions in high-fat diet-fed obese mice treated are comparable to those of chow diet-fed mice, arguing against the concept of leptin resistance.¹⁷² Thus, further studies are needed to clarify the issue of leptin resistance in obese humans and animals.

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia that affects ~9% of adults worldwide.¹⁷³ It results from deficits in pancreatic insulin secretion and insulin signaling/actions in insulin target organs. Experimental evidence suggests that defective metabolic sensing in hypothalamic neurons may lead to dysregulation of glucose homeostasis and diabetes (Figure 3). Hypothalamic insulin–PI3K signaling is markedly impaired in rats with streptozotocin-induced diabetes.⁹⁸ Pharmacological inhibition of hypothalamic PI3K signaling attenuates the glucose-lowering effect of insulin. Conversely, enhanced hypothalamic PI3K signaling via adenoviral gene therapy potentiates insulin-induced glucose lowering.⁹⁸ Notably, central insulin actions are blunted by short-term high-fat diet feeding.¹⁷⁴ Thus, a fat-rich diet may contribute to the development of diabetes by disrupting insulin signaling in the hypothalamus.¹⁷⁴

CONCLUDING REMARKS

This review highlights the role of the brain in the homeostatic regulation of energy and glucose metabolism. The brain detects energy intake by sensing gut hormones released in response to food intake and detecting nutrients in circulating blood. The brain also monitors body energy stores by sensing adiposity-related signals. Information on nutrient availability and stored fat is transferred to specialized neurons in the hypothalamus and brain stem. In the control of the energy balance, outflow pathways from the brain regulate food intake and energy expenditure (thermogenesis or locomotor activity).

The brain also has an important role in the maintenance of glucose homeostasis, which is achieved by the modulation of insulin/glucagon secretion in the endocrine pancreas, HGP, and skeletal muscle glucose uptake. The autonomic nervous system constitutes the outflow pathways from the brain to peripheral metabolic organs. Defective crosstalk between the brain and peripheral metabolic organs observed in the obese condition may lead to type 2 diabetes development and obesity progression. Therefore, better understanding of neural mechanisms involved in the regulation of glucose/energy homeostasis will provide us with the opportunity to develop new therapeutics combating obesity and diabetes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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