

Sensing the fuels: glucose and lipid signaling in the CNS controlling energy homeostasis

Sabine D. Jordan · A. Christine Könner ·
Jens C. Brüning

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Abstract The central nervous system (CNS) is capable of gathering information on the body's nutritional state and it implements appropriate behavioral and metabolic responses to changes in fuel availability. This feedback signaling of peripheral tissues ensures the maintenance of energy homeostasis. The hypothalamus is a primary site of convergence and integration for these nutrient-related feedback signals, which include central and peripheral neuronal inputs as well as hormonal signals. Increasing evidence indicates that glucose and lipids are detected by specialized fuel-sensing neurons that are integrated in these hypothalamic neuronal circuits. The purpose of this review is to outline the current understanding of fuel-sensing mechanisms in the hypothalamus, to integrate the recent findings in this field, and to address the potential role of dysregulation in these pathways in the development of obesity and type 2 diabetes mellitus.

Keywords Hypothalamus · Glucose · Fatty acids · Metabolism · Energy homeostasis · Obesity · Type 2 diabetes mellitus

Introduction

Precise control of energy intake, storage, and expenditure is indispensable in keeping body weight and blood glucose concentrations within physiological ranges. Dysregulation of these homeostatic processes is associated with the development of obesity and type 2 diabetes mellitus; however, the exact underlying mechanisms leading to these diseases are still not fully elucidated.

Communication of the body's nutritional state by feedback signaling of peripheral organs to the CNS and the appropriate behavioral and metabolic responses initiated by the brain are pivotal processes in maintaining energy homeostasis. The hypothalamus, and in particular the arcuate nucleus (the most external hypothalamic nucleus), are located close to the median eminence, a site characterized by a discontinuous blood–brain barrier, allowing for direct access of circulating hormones and nutrients to the CNS [1]. Thus, the hypothalamus is a potential primary site of convergence and integration for nutrient-related signals, which include central and peripheral neuronal inputs as well as hormonal signals [2]. Besides fuel-communicating hormones such as insulin and leptin, increasing evidence indicates that glucose and lipids are detected by specialized fuel-sensing neurons that are incorporated in critical hypothalamic neuronal circuits. Hence, circulating nutrients cooperate with hormones, such as insulin, leptin, and ghrelin, to regulate the activity of distinct neuron populations that control food intake, energy expenditure, and glucose homeostasis. Thus, this review aims to provide an

S. D. Jordan · A. C. Könner · J. C. Brüning (✉)
Department of Mouse Genetics and Metabolism,
Institute for Genetics and Cologne Excellence Cluster
on Cellular Stress Responses in Aging Associated Diseases
(CECAD), University of Cologne, Zùlpicher Straße 47,
50674 Cologne, Germany
e-mail: jens.brueining@uni-koeln.de

S. D. Jordan · A. C. Könner · J. C. Brüning
Center of Molecular Medicine Cologne (CMMC),
University of Cologne, Cologne, Germany

A. C. Könner · J. C. Brüning
2nd Department for Internal Medicine,
University Hospital Cologne, Cologne, Germany

J. C. Brüning
Max Planck Institute for the Biology of Aging,
Cologne, Germany

updated view of the pathways of glucose and lipid sensing in the hypothalamus and to delineate the contribution of impaired neuronal nutrient sensing to the etiology of obesity and type 2 diabetes mellitus.

Central glucose sensing

Glucose sensing in the hypothalamus

The earliest demonstration that the brain is involved in the control of blood glucose levels was provided by Claude Bernard, who showed that hypothalamic lesions induce hyperglycemia in dogs [3]. In 1953, John Mayer proposed that cells located in the hypothalamus could be specialized to monitor variations in blood glucose concentrations and further postulated that these cells translate these variations in glucose concentrations in electrical or chemical signals that control feeding behavior [4]. About 10 years later, two groups indeed demonstrated the presence of such specialized glucose-sensing neurons by electrophysiological analysis of hypothalamic slides. Anand et al. and Oomura et al. independently identified hypothalamic neurons that are able to modulate their firing activity in response to changes in extracellular glucose concentrations [5, 6].

Essentially two different types of glucose-responsive neurons can monitor changes in blood glucose levels: glucose-excited (GE) neurons, whose firing rate is increased by elevation of extracellular glucose concentrations, and glucose-inhibited (GI) neurons, which are activated when glucose concentrations decrease [7]. Both types of neurons are widely distributed throughout the brain but highly represented in hypothalamic nuclei, which are involved in the control of energy homeostasis. GE neurons are most abundant in the ventromedial nucleus (VMN), the arcuate nucleus (ARC), and the paraventricular nucleus (PVN), whereas GI neurons are mostly located in the lateral hypothalamus (LH), the median ARC, and the PVN [8]. In the ARC, the presence of GE and GI neurons responsive to glucose over either a low range (0–5 mM) or a high range (5–20 mM) of glucose concentrations has been described, the latter are referred to as HGE (high glucose excited) or HGI (high glucose inhibited) neurons, respectively [9, 10].

GE and GI neurons are also present in the brain stem, in particular in the area postrema (AP), the nucleus of solitary tract (NTS), and the dorsal motor nucleus of the vagus (DMNX) [11]. The NTS represents a critical node of convergence that integrates various signals from the periphery and relays them to the hypothalamus. Neurons in the NTS are sensitive to small variations in blood glucose concentrations and may regulate the activity of hypothalamic neurons since they project widely into hypothalamic

nuclei implicated in the control of blood glucose levels and food intake [12].

Neuronal circuits of the ARC are among the best-studied systems in the central regulation of energy homeostasis. Key players are two functionally opposing neuron populations, the agouti-related peptide/neuropeptide Y (AgRP/NPY)-expressing and the proopiomelanocortin and cocaine- and amphetamine-related transcript (POMC/CART)-expressing neurons [13, 14]. The anorectic POMC/CART neurons express POMC as a precursor peptide, which, dependent on the cell-type specific expression pattern of prohormone convertases, is processed to different bioactive products [15]. Among these are the melanocyte-stimulating hormones (α -, β -, and γ -MSH). α -MSH and β -MSH reduce food intake and increase energy expenditure both in animals and in humans [16–18]. α -MSH and β -MSH act on melanocortin receptor (MC-R) types 3 and 4, which are expressed in the ARC, the PVN, LH, VMN, and dorsomedial hypothalamus [19, 20]. The second key neuron population in the ARC is formed by the orexigenic AgRP/NPY neurons. NPY is a potent stimulator of food intake and it reduces energy expenditure [21, 22]. AgRP acts as an inverse agonist of the MC3/4-R and prevents the anorectic effect of α -MSH [23]. Besides their regulation by hormones, such as insulin, leptin, and ghrelin, these both types of neurons represent prototypic glucose-sensing neurons. In particular, through electrophysiological recordings of identified, genetically marked neuron populations, it has been demonstrated that increasing extracellular glucose levels inhibit AgRP/NPY neurons and excite POMC neurons [24–27].

AgRP/NPY and POMC neurons extend broad projections to various brain regions including the LH that harbors two other populations of glucose-sensing neurons, the orexin-expressing and the melanin-concentrating hormone (MCH) neurons. Orexin neurons are inhibited and MCH neurons are excited by glucose, in addition both populations receive inputs from AgRP/NPY and POMC neurons [28–30].

Molecular mechanisms of glucose sensing

Since GE neurons increase their firing activity when extracellular glucose rises, they share similarity to pancreatic β -cells [31–33]. Glucose signaling in β -cells requires glucose uptake by the low-affinity glucose transporter type 2 (GLUT2), glucose phosphorylation by glucokinase, the rate-limiting enzyme of glycolysis, and subsequent metabolism of glucose to increase intracellular ATP concentration [34]. This in turn leads to closure of ATP-sensitive potassium (K_{ATP}) channels [35], membrane depolarization, and the entry of Ca^{2+} , which triggers insulin secretion. Thus, many studies have evaluated the

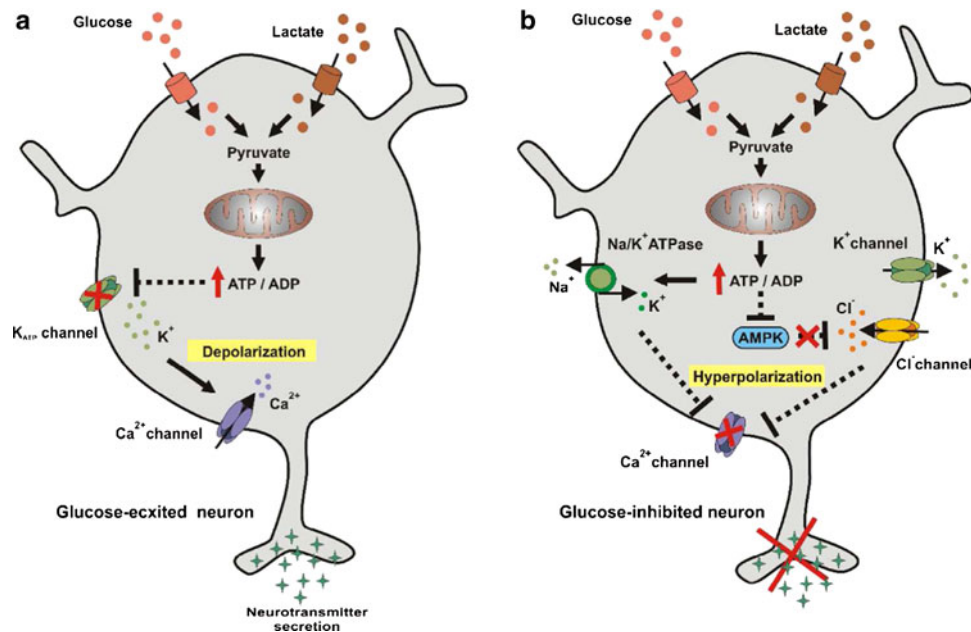


Fig. 1 Potential mechanisms of glucose sensing in hypothalamic neurons. **a** An increase in extracellular glucose and/or lactate raises the ATP/ADP ratio in GE neurons, which leads to the closure of K_{ATP} channels and thus plasma membrane depolarization. Subsequent Ca^{2+} entry through voltage-gated channels finally increases neuronal activity and neurotransmitter secretion. **b** In GI neurons, suppression

of neurotransmitter secretion at elevated glucose might be caused by an ATP-mediated increase in Na^+-K^+ -ATPase activity and/or inhibition of AMPK, which in turn opens Cl^- or other ion channels. In other GI neurons, glucose-induced hyperpolarization might be due to K^+ channels opened by an ATP- and AMPK-independent mechanism

role of GLUT2, glucokinase, and the K_{ATP} channel subunits SUR1, SUR2, and Kir6.2 in central glucose sensing.

GLUT2 is expressed in hypothalamic nuclei where glucose-sensitive neurons are present [36–39]. In transgenic mice, central GLUT2 has been shown to be involved in the counter-regulatory response to hypoglycemia [40].

In the pancreatic β -cell, glucokinase is the critical regulator of glycolytic production of ATP and K_{ATP} channel activity [41]. The pancreatic form of glucokinase is also present in brain areas involved in glucose sensing and in about 70% of GE neurons glucokinase mRNA is detectable [37, 42–44]. Indeed, glucokinase has been shown to regulate the ability of GE neurons to sense glucose [32, 37, 42, 45]. In addition, the selective down-regulation of glucokinase in primary VMH neuronal cultures led to selective loss of glucose sensing [46].

K_{ATP} channels play a fundamental role since they link changes in glucose metabolism to electrical activity [47] and expression has been demonstrated throughout the brain, including hypothalamic regions involved in glucose sensing [48–51]. Using single-cell RT-PCR to analyze glucose-sensing neurons, investigators have shown the expression of the K_{ATP} channel subunits SUR1 and Kir6.2 in the hypothalamus [37]. In addition, electrophysiological studies have demonstrated that pharmacological inhibition or activation of K_{ATP} channels can alter the response of GE neurons to changes in ambient glucose *in vitro* and *in vivo*

[32, 48, 52–57]. In line with a role in glucose sensing, the expression of a mutated version of the K_{ATP} subunit Kir6.2 (resulting in dramatically reduced ATP sensitivity) specifically in POMC neurons blunted glucose sensing. Interestingly, obesity-induced POMC glucose insensitivity is mediated by the mitochondrial protein uncoupling protein 2 (UCP2), which impairs glucose-stimulated ATP production and thus K_{ATP} channel closure, while its genetic deletion or pharmacological inhibition reversed the phenotype [58].

Taken together, there is considerable evidence that similar to pancreatic β -cells, an increase in extracellular glucose raises ATP levels in GE neurons, which leads to the closure of K_{ATP} channels [49, 53, 57, 59, 60], and thus plasma membrane depolarization. Subsequent Ca^{2+} entry through voltage-gated channels finally increases neuronal activity and neurotransmitter secretion [61, 62] (Fig. 1a).

There is however also indication that neuronal glucose sensing could be independent of K_{ATP} channels [9], glucokinase [63], or GLUT2 [37]. For instance, the activation of an ARC GE neuron population by glucose seems to depend on the glucose-regulated activity of transient response potential (TRP) channels [9]. Moreover, a recent study identified the heterodimeric G-protein-coupled sweet receptor T1R2/T1R3 as a candidate membrane-bound brain glucose sensor that allows neurons to change firing rates independently of intracellular glucose metabolism [64].

In GI neurons, the mechanism linking a decrease in glucose concentrations to increased firing activity is less clear (Fig. 1b). An early study proposed that suppression of firing activity at elevated glucose levels might be controlled by the increase in the ATP-to-ADP ratio, which leads to an increase in $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity [8, 65]. A further study indicated that the opening of plasma membrane Cl^- channels at elevated glucose concentrations leads to cell hyperpolarization and inhibition of VMN and ARC GI neurons [27, 54, 63]. For GI orexin neurons, it has been shown that tandem-pore K^+ channels could mediate their inhibition by glucose [66], however a recent study demonstrated that glucose inhibition persists in orexin neurons lacking tandem-pore K^+ channels [67]. Orexin neurons further exhibit carbohydrate selectivity and can operate independently of glucose metabolism [68]. Moreover, a distinct group of orexin neurons exhibits only transient inhibitory responses to sustained rises in glucose levels due to time-dependent recovery from inhibition via adaptive closure of leak-like K^+ channels, presumably the same channels as those activated by glucose [69]. This adaptive glucose sensing allows orexin cell firing to maintain sensitivity to small fluctuations in glucose levels despite large background levels of glucose.

Changes in AMP-activated protein kinase (AMPK) activity are likely to mediate some effects of glucose on VMN and ARC GI neurons [26, 70]. AMPK is activated in response to a rise in intracellular AMP levels, which increase under conditions of cellular stress or energy deficiency, such as hypoxia, ischemia, and glucose deprivation [71, 72]. Activated AMPK acts to switch off energy-consuming anabolic processes and switch on energy producing catabolic processes [73] and has therefore been suggested as an important glucose sensor. As shown in cell lines and ex vivo hypothalamic tissue, AMPK activity is stimulated by low glucose levels and AMPK activation increases orexigenic AgRP expression [74]. This study also demonstrated that small changes in hypothalamic glucose levels in the physiological range of 1–5 mM altered cellular ATP levels sufficiently to induce AMPK activation and gene expression. Recently, the cAMP response element binding protein (CREB) co-activator CRTC2 was identified as a new hypothalamic AMPK target, linking hypothalamic glucose sensing with cAMP response element (CRE) gene expression [75]. Mechanistically, it is possible that AMPK activation in GI neurons leads to the phosphorylation and thereby inactivation of plasma membrane Cl^- and/or other ion channels [54], leading to depolarization, and activation of the neuron. Consistently, studies of Murphy et al. [76] suggest that in VMH GI neurons activated AMPK phosphorylates neuronal nitric oxide synthase (nNOS) leading to nitric oxide production, which in turn amplifies AMPK

activation and thereby closure of the Cl^- channel cystic fibrosis transmembrane regulator (CFTR).

Since glucokinase mRNA is expressed in about 40% of GI neurons it may also hold a regulatory role in these neurons [42, 46], although it seems that AMPK activity plays a predominant role in GI neuronal glucose sensing.

Glucose-sensing neurons do not perform their function in isolation. They are surrounded and provided with metabolic fuels by glia cells. Astrocytes readily take up and store glucose as glycogen, which is hydrolyzed to release lactate into the extracellular space when glucose is scarce. Extracellular lactate is taken up by neurons and converted to pyruvate, which is then oxidized in mitochondria to provide ATP [37, 77, 78]. By this mechanism, lactate is able to trigger K_{ATP} channel closure [79, 80] and thereby reverse the inhibition of GE activity, which occurs at low ambient glucose levels [63]. Importantly, levels of the lactate/monocarboxylate transporters, which are very low in pancreatic β -cells [81, 82], appear to be relatively high in the hypothalamus [78, 79]. The role of astrocytes in central glucose sensing is further supported by the already-mentioned finding that re-expression of GLUT2 in astrocytes was sufficient to rescue the phenotype of mice lacking central GLUT2 [40]. However, it is conceivable that depending on substrate availability, one or more glucose-sensing pathways are used by different neuronal populations.

Physiological functions regulated by central glucose sensing

Food intake

The role of glucose in the regulation of feeding has early been postulated [4, 83]. It has been shown that initiation of feeding is preceded by a drop in blood glucose concentration [84] and if this is prevented by glucose infusion, then initiation of feeding is suppressed [85]. In addition, intrahypothalamic infusion of glucose leads to a decrease in food intake and body weight [86–88]. Induction of cellular glucoprivation by central administration of 2-deoxy-D-glucose (2-DG), a glucose analogue able to inhibit glucose metabolism, however, induces food intake [89, 90]. In particular, brain stem areas such as the DMNX and NTS appear to be the primary site of glucoprivation detection, since direct injections of 5-thiogluco (5-TG), a 2-DG analogue, into these areas stimulated food intake [89, 91] whereas direct injection of 2-DG into the VMH or LH failed to activate feeding.

As already mentioned, glucose-sensitive neurons of the brain stem project widely into the hypothalamus, in particular the PVN and the ARC. Destruction of these neuronal projections by immunotoxins suppressed the

effect of peripheral 2-DG administration on food intake [92] and on the regulation of NPY and AgRP expression [93]. The pivotal role of AgRP/NPY-expressing neurons in the acute regulation of feeding in adult mammals has been impressively demonstrated by two independent studies using diphtheria-toxin-mediated ablation of this neuron population [13, 94]. However, the extent to which these neurons contribute to glucose-induced inhibition of feeding is still unclear. When Luquet et al. [95] destroyed AgRP/NPY neurons in neonatal mice, they found that feeding responses to glucoprivation were unaffected. The same group previously showed that in contrast to starvation induced upon elimination in adult mice, neonatal destruction of these neurons has minimal effects on feeding in general, which illustrates the impressive plasticity of this circuitry [94]. Thus, it is still possible that glucose-induced inhibition of AgRP/NPY neurons has profound effects on feeding when the brain is allowed to develop normally.

On a molecular level, many of the critical components of glucose sensing have been demonstrated to be involved in the regulation of food intake. For instance, central GLUT2 expression has been linked to feeding regulation by knockdown experiments using antisense oligonucleotides as well as targeted disruption of the *Glut2* gene. Injection of antisense oligonucleotides in the ARC decreased food intake and led to resistance towards the effects of 2-DG on feeding behavior [96]. In the GLUT2-null mice, ad libitum feeding as well as refeeding after a 24 h fast was higher than in controls [97]. Moreover, during the fast-to-refed transition, expression of the orexigenic (NPY, AgRP) and anorexigenic (POMC, CART) neuropeptides was dysregulated in the absence of GLUT2. This was directly attributed to the loss of central glucose sensing, as intracerebroventricular (ICV) glucose in fasted GLUT2-null mice failed to reduce NPY and to increase POMC expression. In parallel in GLUT2 knockdown animals, feeding responses to ICV glucose or 2-DG were also lost. In humans, a genetic variation in GLUT2 is associated with a higher daily intake of sugars [98].

These data indicate that GLUT2 is required for physiological control of feeding by glucose. However, attempts to localize GLUT2 in the brain so far failed to show its expression in POMC or NPY neurons, although it was found to be associated with other hypothalamic and brain stem structures [36–38, 99, 100] and it was further shown to be expressed in astrocytes, endothelial cells, and tanyocytes of the third ventricle [101–103]. Thus, the regulation of orexigenic and anorexigenic peptide expressions by GLUT2-dependent sensors may be controlled indirectly, probably by glucose-sensitive neurons located in other brain regions, such as the brain stem.

Haploinsufficiency for glucokinase in mice gave rise to effects similar to those observed during hypoglycemia, i.e.,

increased food intake and a hypothalamic gene expression profile similar to fasted mice (increased hypothalamic NPY mRNA and reduced hypothalamic POMC mRNA), indicating impaired glucose sensing in these animals [104].

Evidence for a role of K_{ATP} channels in the control of feeding comes from the study of mice with inactivation of the *Kir6.2* gene as well as mice with constitutive active K_{ATP} channels exclusively in POMC neurons. Whereas, *Kir6.2*-null mice display a smaller feeding response to intraperitoneal 2-DG administration than control mice [53], mice expressing a constitutively active *Kir6.2* subunit in POMC cells exhibited normal feeding behavior despite the complete unresponsiveness of these neurons to elevations in extra-cellular glucose concentration [58]. However, studies in POMC cells with constitutive active phosphatidylinositol 3,4,5-triphosphate (PIP3) formation, mimicking insulin-stimulated activation of the PI3 kinase pathway (see below), demonstrated an effect of constitutive active K_{ATP} channels on feeding behavior [105]. In the hypothalamus, PIP3 has been shown to regulate cell excitability by binding to the regulatory subunit of K_{ATP} channels and modulating their activity by at least three different mechanisms: (i) by increasing the probability that K_{ATP} channels are open, which indirectly lowers the ability of ATP to inhibit the channels, (ii) by directly decreasing ATP binding to the channel, and (iii) by modulating the local cytoskeleton in the vicinity of the channels [106–109]. We demonstrated that augmented PIP3-dependent K_{ATP} channel activation leads to electrical silencing of POMC neurons and consequently to hyperphagia [105].

The role of the metabolic sensor AMPK in feeding control was addressed by generating mice lacking AMPK α 2 in either POMC (POMC α 2KO) or AgRP/NPY (AgRP α 2KO) neurons [110]. In both neuron populations, inactivation of AMPK suppressed the glucose-mediated regulation of firing activity, indicating that AMPK function is necessary for glucose sensing in these neuron populations. Absence of this enzyme from POMC neurons led to increased feeding in response to fasting, an imbalance in the expression of hypothalamic orexigenic and anorexigenic peptides, favoring an orexigenic output and body weight gain. Inactivation of AMPK in AgRP/NPY neurons led to a modest reduction of body weight, which developed after 3 months of age. However, this was not associated with detectable differences in feeding or in orexigenic and anorexigenic neuropeptide expressions. The molecular mechanism how AMPK allows POMC and AgRP/NPY neurons to sense glucose and thus alters their neuronal excitation is currently unknown.

Energy expenditure

It has been known for several years that infusions of glucose can both increase general sympathetic activity

(as evidenced by increased plasma norepinephrine levels) [111, 112] and produce an increase in thermogenesis, which is partly due to such sympathetic activation [113]. These effects of glucose were independent of insulin's well-known function as activator of sympathetic activity, since glucose evoked these effects in insulin-deficient animals [112] as well as after direct infusion into the forebrain via the carotid artery (without altering plasma insulin levels) [114, 115]. Such forebrain infusions activate neurons in several hypothalamic areas known to contain glucose-sensing neurons such as those in the PVN [51, 116]. The thermogenic effects of glucose are probably also mediated by hypothalamic glucose-sensing neurons, since intracarotid and direct injections of glucose into the VMH and PVN produce increased activity in the sympathetic efferents to brown adipose tissue [117, 118], and mice lacking AMPK in POMC neurons developed obesity partially caused by reduced resting metabolic rate with concomitant downregulation of brown adipose tissue thermogenic genes [110].

Hepatic glucose production

Similar to what is seen in the central regulation of energy intake and expenditure, the brain also directly responds to changes in fuel availability to maintain glucose homeostasis. In the regulation of blood glucose levels, the liver plays a pivotal role. During times of starvation, breakdown of hepatic glycogen stores (glycogenolysis) and hepatic de novo synthesis of glucose (gluconeogenesis) from precursors such as lactate, gluconeogenic amino acids, and glycerol provide the organism with glucose. On the other hand, when food (and consequently glucose) are available, hepatic glucose production (HGP) needs to be suppressed. Besides being subjected to tight hormonal control [119], these processes are also directly regulated by glucose. In response to changing concentrations of hypothalamic glucose, gluconeogenesis, glycogenolysis, and with it total HGP are significantly reduced [80]. The fact that besides glucose also lactate is able to inhibit glucose production when administered directly into the ARC suggests that mitochondrial oxidation is necessary for the CNS to respond to glucose. The finding that pharmacologically blocking lactate dehydrogenase inhibited both lactate- and glucose-induced decrease in HGP, further supported this notion. In contrast, the activation of pyruvate dehydrogenase mimicked the inhibition of HGP [80]. These findings suggest that the neuronal tricarboxylic acid cycle may function as a biochemical sensor for carbohydrate availability, which in turn modulates HGP. The effects of glucose and lactate seem to depend critically on the activation of K_{ATP} channels. In fact, the suppressive effect of intra-ARC infusions of glucose or lactate on HGP is

blocked by a concomitant infusion of glibenclamide, a K_{ATP} channel blocker [80, 120]. Thus, besides feeding behavior, glucose homeostasis is also linked with K_{ATP} channel function in glucose-sensing neurons. In a more recent study, Kokorovic et al. demonstrated that hypothalamic sensing of circulating lactate levels also regulates glucose production [121]. In the presence of physiologically relevant increases in the levels of plasma lactate (intravenous injection), inhibition of central lactate-sensing mechanisms by lactate dehydrogenase inhibitor oxamate or K_{ATP} channel blocker glibenclamide increased glucose production. Furthermore, direct administration of oxamate into the mediobasal hypothalamus increased glucose production in the presence of a similar elevation of circulating lactate.

Interestingly, central glucose and lactate sensing seems to also affect hepatic lipid metabolism. ICV administration of glucose or lactate was found to lower circulating lipid concentrations and, more importantly, hepatic lipid production [122]. Again, pharmacologically blocking either lactate dehydrogenase or K_{ATP} channel function blunted these effects [122].

Counter-regulatory processes

Glucose sensing in the brain is also implicated in the counter-regulatory response to hypoglycemia. In particular, this involves the activation of glucagon secretion from pancreatic α -cells and catecholamines from adrenal glands [123–125].

Experimentally, counter-regulation is activated either by insulin-induced hypoglycemia or by injection of 2-DG or 5-TG to induce cellular glucoprivation. In both conditions, afferent neurons located in the abdominal regions relay the information to the brain stem and the hypothalamus, which can also be directly activated by hypoglycemia or the glucoprivic signal. The role of central glucose sensing in the control of counter-regulation can be evidenced by intracarotid glucose infusion, which blocks hypoglycemia-induced secretion of counter-regulatory hormones [126, 127], or by ICV injection of 2-DG, which stimulates glucagon and catecholamine secretion [128]. The involvement of hypothalamic nuclei, in particular the VMH, has been assessed in lesion studies and by pharmacological or genetic interference with glucose detection systems [127]. For instance, glucagon secretion can be induced by direct injection of 2-DG in the VMH [128], or, in contrast, hypoglycemia-induced glucagon secretion can be suppressed by direct VMH injection of glucose [129]. In a series of studies, Chan et al. [130] demonstrated that modulation of the γ -aminobutyric acid (GABA) inhibitory tone in the VMH modifies the magnitude of glucagon and sympathoadrenal responses to hypoglycemia. They could show that during hypoglycemia, K_{ATP} channels are

implicated in the regulation of GABA release in this area of the hypothalamus [131] and that an increased GABAergic tone in the VMH contributes to suppression of counter-regulatory responses after recurrent hypoglycemia [132]. In addition to GABA, the excitatory neurotransmitter glutamate released by VMH neurons has also been linked to the prevention of hypoglycemia. Mice lacking synaptic vesicular transporters for glutamate (VGLUT2) selectively in SF1 neurons (a major subset of VMH neurons) exhibit defective counter-regulatory responses during fasting as well as to insulin- or 2-DG-induced hypoglycemia [133].

Recently, hyperinsulinemic clamp studies in humans could show that the hypothalamus is sensitive to small decrements in systemic glucose levels and that hypothalamic blood flow and presumably neuronal activity, precedes the rise in counter-regulatory hormones seen during hypoglycemia [134].

There is also strong evidence that brain stem nuclei play an important role in the control of glucagon secretion. For instance, when the cerebral aqueduct, which allows circulation of cerebrospinal fluid between the third and fourth ventricle, is obstructed, 5-TG induces a glucoregulatory response only when injected in the fourth but not in the third ventricle [135]. In addition, whereas 5-TG injections in different nuclei of the hypothalamus fail to induce a glucoregulatory response, its injections into the NTS, which projects to different sites of the hypothalamus, induce a strong response [91–93]. Moreover, *c-fos* immunostaining revealed that the activated neurons are present in the NTS [136].

Thus, central glucose-sensing units involved in the physiological control of counter-regulation are present at the brain stem and the hypothalamus. These sites are synaptically connected to form a glucose-monitoring network. The gathered information is integrated to control the counter-regulatory response by activating efferent autonomic nerves that stimulate pancreatic glucagon secretion and the secretion of epinephrine by the adrenals, and at the same time block insulin secretion.

The role of GLUT2 and the K_{ATP} channel in the control of glucagon secretion has been investigated in several studies. Mice with inactivation of the *Glut2* gene, while expressing a transgenic glucose transporter (GLUT1) in their pancreatic β -cells to preserve normal glucose-stimulated insulin secretion (*ripglut1::glut2*-null-mice) [137] display an abnormal increase in random fed plasma glucagon levels. More importantly, ICV 2-DG injections failed to stimulate glucagon secretion in these mutant mice attributing a role of GLUT2-mediated central glucose sensing also in the control of counter-regulatory processes [40]. Furthermore, the analysis of *c-fos*-positive cells in response to intraperitoneal 2-DG injections indicated a decreased number of activated cells in the brain stem, in

particular in the NTS and the DMNX in the *Glut2*-null mice. At the level of the hypothalamus, a reduced stimulation of *c-fos*-positive cells was observed in the PVN but not in the VMH, indicating that the glucose detection mechanisms used to control glucagon secretion might vary between several hypothalamic nuclei.

The involvement of K_{ATP} channel-mediated hypothalamic glucose sensing in the central regulation of glucagon secretion has also been demonstrated. For instance, the counter-regulatory response in a hypoglycemic clamp is blocked upon ICV or direct VMH injection of the K_{ATP} channel inhibitor glibenclamide [55]. Genetic inactivation of K_{ATP} channel by deletion of *Kir6.2* gene also leads to impaired glucagon response, correlated with suppressed glucose-regulated firing activity of VMH neurons [53]. In contrast, the activation of K_{ATP} channels in the VMH amplifies counter-regulatory hormone responses to recurrent hypoglycemia [56].

The above-summarized findings clearly indicate that central glucose sensing is implicated in a variety of important physiological functions. In particular the coordinated crosstalk between different sites of glucose detection allows for the precise control of energy homeostasis and normoglycemia. These studies further demonstrate that there is more than one mechanism to sense either an increase or decrease in blood glucose levels, and that the β -cell model of glucose sensing may have many variations.

Central lipid sensing

Cerebral lipids represent 50% of the brain dry weight, which is the highest organ lipid content after adipose tissue. Since neurons do not use fatty acids as a fuel, it was thought for a long time that they are not able to cross the blood–brain barrier. In recent years, however, it has been demonstrated that cerebral lipids arise from both local synthesis as well as plasma origin. Fatty acids cross the blood–brain barrier mainly by simple diffusion in the unbound form, so that access of circulating free fatty acids to the CNS is proportional to their plasma concentration [138, 139]. However, a small proportion of fatty acid uptake into the brain may also occur through direct uptake of lipoprotein particles mediated by lipoprotein receptors [140, 141]. Upon entry into the cell, fatty acids are rapidly esterified to fatty acyl-coenzyme A (acyl-CoAs) in a process catalyzed by the enzyme acyl-CoA synthetase (ACS). Once integrated to the intracellular acyl-CoA pool, fatty acid fate is diverse and depends on the respective fatty acid. For example, Rapoport et al. [141] reported that 50% of the palmitate taken up by the brain is oxidized, whereas 80% of the arachidonate is incorporated into phospholipids. Furthermore increasing evidence shows that fatty acids are

used in the CNS as cellular messengers that act like glucose to communicate the body's energy status and thus are involved in the control of feeding behavior, HGP, and insulin secretion. Especially the hypothalamus is able to detect and respond to changes in circulating fatty acid concentrations through the involvement of lipid-sensing neurons. Indeed, these neurons use fatty acids and their metabolites as signaling molecules to regulate their membrane potential and action potential frequency in a concentration-dependent manner.

Lipid sensing in the hypothalamus

In 1975, Oomura et al. [142] demonstrated that fatty acids activate neurons of the LH, indicating a role for fatty acids as cellular messengers. Accordingly, a study using *c-fos* immunoreactivity as marker for neuronal activity indicated an activating effect of lipids on neurons located in the LH, whereas neurons in the ARC, DMH, VMH, and PVN were inhibited in response to lipid infusion [143]. Wang et al. [144] demonstrated that distinct neuron populations in the ARC modify their neuronal firing rate in response to fatty acids and that these effects depend on ambient glucose levels.

The molecular mechanisms involved in neuronal lipid sensing are far from being elucidated. However, a body of literature indicates that, in general, fatty acids regulate the conductance of a wide variety of ion channels, which include Cl^- , GABA_A [145], ClC-2 [146], K^+ , $\text{K}^+-\text{Ca}^{2+}$, K_{ATP} [147], and Ca^{2+} channels [148]. Additionally, fatty acids inhibit the $\text{Na}^+-\text{K}^+-\text{ATPase}$ [149]. Addressing hypothalamic lipid-sensing mechanisms, Lam et al. and Pocai et al. evidenced that the central effects of oleic acid on liver metabolism are abolished by genetic or pharmacological inhibition of the K_{ATP} channel [120, 150]. Patch-clamp recordings of oleic acid-inhibited neurons in the ARC further supported a role for K_{ATP} channels in hypothalamic lipid sensing [151]. In contrast, neuronal excitation by oleic acid seems to be mediated by the closure of Cl^- channels [144].

The physiological relevance of lipid sensing is supported by various studies. For instance, intravenous infusion of a lipid emulsion is sufficient to suppress food intake in baboons [152]. This signal is independent of measurable changes in plasma insulin and does not require gastrointestinal nutrient absorption [152–155]. Consistent with the hypothesis that circulating lipids act on hypothalamic energy centers to generate a signal of nutrient surfeit, the group of Rossetti and colleagues demonstrated that ICV administration of the long-chain fatty acid (LCFA) oleic acid inhibits food intake and leads to a decrease in HGP [156, 157]. Interestingly, using the same protocol octanoic acid, a medium-chain fatty acid had no effect, suggesting

that fatty acid action is related to the respective chain length. The authors attributed the anorectic effect of oleic acid to its action on orexigenic ARC neuropeptide expression, i.e., reduction of *AgRP* and *NPY* mRNA expression, whereas *POMC* expression was not affected by oleic acid treatment. In the liver, ICV oleic acid inhibited the expression of glucose-6-phosphatase, the rate-limiting gluconeogenic enzyme [156, 157].

A decrease in food intake and HGP is also obtained by inhibiting hypothalamic carnitine palmitoyltransferase (CPT) 1 [158]. These effects on food intake and HGP were proposed to be caused by the accumulation of intracellular LCFA-CoA due to the inhibition of CPT1-mediated mitochondrial import of LCFA-CoA for β -oxidation. This finding suggests that an increase in intracellular LCFA-CoA concentrations, rather than fatty acids themselves, is the “final” satiety signal that activates neural pathways designed to regulate the input of nutrients in the circulation from either exogenous (food intake) or endogenous sources (HGP) [158–160]. Indeed, a sustained two-to-threefold elevation in circulating long-chain fatty acid levels is sufficient to double LCFA-CoA concentrations within the mediobasal hypothalamus. Furthermore, this increase is prevented by intrahypothalamic infusion of triacsin C, a pharmacological inhibitor of LCFA-CoA synthetase [150]. The inhibition of hypothalamic LCFA-CoA synthetase activity also abolishes the ability of circulating LCFA to suppress HGP, indicating that hypothalamic esterification of LCFA to LCFA-CoA is required for the observed effects of LCFA on liver metabolism [150]. However, it has to be noted that inhibition of CPT1 leads to increased levels of LCFA-CoA in the ARC, but not in other hypothalamic nuclei [158], and inhibition of β -oxidation in the LH does not alter food intake [161].

The role of hypothalamic fatty acid metabolism

Fatty acid metabolism seems crucial to relay the central action of fatty acids on energy homeostasis. Enzymes involved in fatty acid metabolism, such as acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), malonyl-CoA decarboxylase (MCD), and CPT1 are expressed in various brain cell types including hypothalamic neuron populations in the ARC, VMH, and dorsomedial hypothalamus [162]. Furthermore, double-labeling studies have shown that FAS colocalizes with *NPY* (and thus *AgRP*) in ARC neurons [163], indicating that modulation of fatty acid synthesis may act on hypothalamic pathways regulating feeding. Feeding increases the concentration of cytoplasmic malonyl-CoA, which is suggested to be one of the main energy sensors in the hypothalamus. Accumulation of malonyl-CoA derives from an increased flux of glucose into the lipogenic pathway during the fed state, i.e., when

nutrients are abundant. The steady-state level of malonyl-CoA is determined by its rate of synthesis catalyzed by ACC relative to its rate of turnover catalyzed by FAS. The synthesis of malonyl-CoA is the first step of fatty acid synthesis and ACC is the major site of regulation. In addition, malonyl-CoA is a potent inhibitor of CPT1 and thereby β -oxidation. Thus, in times of ample energy supply, when there is a decreased need for fatty acid oxidation, increased malonyl-CoA levels may inhibit β -oxidation and increase fatty acid synthesis and esterification to triglycerides.

Consistent with a role for neuronal FAS in the modulation of feeding, central administration of C75, a potent inhibitor of FAS, increases malonyl-CoA concentrations in the hypothalamus, suppresses food intake and leads to profound weight loss [164, 165]. In mice deprived of food, central administration of C75 at anorexic doses also significantly increases hypothalamic malonyl-CoA levels [166]. Moreover, pharmacological inhibition of ACC, and thereby malonyl-CoA synthesis, largely reverses the effect of C75 on feeding and malonyl-CoA accumulation [164, 166], supporting the idea that malonyl-CoA availability is essential for the hypothalamic control of food intake. In vitro and in vivo studies demonstrate that at least parts of C75's effects are mediated through AMPK [167, 168]. Indeed, ICV administration of 5-aminoimidazole-4-carboxamide-ribonucleoside (AICAR), an AMPK activator, rapidly lowers hypothalamic malonyl-CoA concentrations, increases food intake, and also attenuates C75-induced anorexia [167, 169]. These effects correlate closely with the phosphorylation and thus inactivation of ACC, an established AMPK target.

The anorectic action of FAS inhibition is linked to decreased expression of orexigenic and increased expression of anorexigenic neuropeptides in the ARC, as central administration of C75 blocks fasting-induced up-regulation of AgRP/NPY and down-regulation of POMC/CART expression [164–166, 170]. The molecular mechanisms underlying these effects of FAS inhibition are not completely understood. It has been reported that changes in hypothalamic malonyl-CoA levels correlate with C75's effects on neuropeptide expression [166]. However, it is so far unclear how accumulation of malonyl-CoA is linked to changes in neuropeptide gene expression and whether its effects are direct or indirect via inhibition of CPT1 and the ensuing accumulation of LCFA-CoA. The latter is supported by the anorectic action of both hypothalamic inhibition of CPT1 [158] and central administration of LCFA [156, 157].

Interrelationship between glucose and lipid sensing

It is well known from pancreatic islets that glucose and lipid sensing are interrelated, since elevated fatty acid

concentrations are able to modify the secretory response to glucose [171, 172]. This has been attributed to the intracellular accumulation of various lipid metabolites that interfere with the function of ion channels or other proteins regulating the exocytosis of insulin granules [173]. Moreover, free fatty acids have been demonstrated to decrease the expression of key components of the glucose-signaling pathway such as GLUT2 and glucokinase [174]. There is now also increasing evidence that elevated concentrations of fatty acids may induce ER stress that, under chronic conditions, exerts deleterious effects on pancreatic islet cells [175].

The observation that anorexia resulting from FAS inhibition is dependent on changes in central glucose uptake and/or metabolism [176] supported the idea that nutrient-sensing pathways are also interconnected in the brain. High glucose levels are known to elevate intracellular malonyl-CoA, which in turn inhibits CPT1 and thereby β -oxidation. Increased levels of malonyl-CoA may in turn induce an increase in glucose oxidation as a consequence of decreasing fatty acid oxidation. Thus, the CNS may use the relative ratio of glucose to fatty acid utilization as an index of the overall energy status of the body [176]. Further points of interaction between glucose and lipid metabolism are K_{ATP} channels and AMPK (Fig. 2). Increased glucose oxidation raises intracellular ATP levels, which leads to the closure of K_{ATP} channels. These channels also seem to be affected by intracellular accumulation of LCFA-CoA [120, 150]. Finally, a decrease in glucose concentration activates AMPK, which phosphorylates and thereby inhibits ACC, thus reducing malonyl-CoA formation and increasing β -oxidation.

Electrophysiological evidence for a direct functional interaction of central lipid and glucose sensing in the hypothalamus has been provided by measuring the firing rate of ARC and VMH neurons in response to oleic acid in the presence of different ambient glucose concentrations [144, 177]. These data revealed an interaction between glucose and fatty acids to regulate oleic acid sensing in neurons of these hypothalamic nuclei, implying that subtypes of lipid-sensing neurons are activated or inhibited, depending on the hypo-, normo- or hyperglycemic status. Even more interesting in this context is the proposed role for reactive oxygen species (ROS) signaling in glucose and lipid sensing by AgRP/NPY and POMC neurons [178–180]. ROS production naturally occurs during mitochondrial respiration of products resulting from both glucose and fatty acid metabolism and thus may represent an additional interconnection of neuronal nutrient sensing. This notion is further supported by an increasing number of studies indicating that ROS production is not simply a byproduct of substrate oxidation but, instead, is implicated in the regulation of neuronal function in a substrate-

dependent manner [179–182]. Andrews et al. observed that during positive energy balance, glucose-excited POMC neurons accumulate ROS due to increased glucose utilization. Contrariwise, during negative energy balance, when low glucose levels activate AgRP/NPY neurons, elevated fatty acid oxidation in these cells does not increase intracellular ROS levels. Endogenous buffering of ROS production seems to be indispensable for the function of AgRP/NPY neurons, since uncontrolled ROS formation impairs neuronal firing of these cells. Thus, persistent high ROS levels in active POMC neurons seem to favor satiety during energy surplus, whereas in active AgRP/NPY neurons ROS production needs to be buffered to allow for the appropriate orexigenic responses to energy deficiency [180, 183].

Hormonal modulation of glucose and lipid sensing

Apart from influencing each other, hypothalamic glucose and lipid sensing is controlled by peripheral hormones, such as insulin, leptin, and ghrelin. The central actions of these hormones comprise several sites of convergence with nutrient sensing, as, for instance, in the ARC, they regulate neuronal activity of glucose-excited POMC as well as glucose-inhibited AgRP/NPY neurons [2, 14, 184].

The finding that central applied insulin decreases food intake and body weight led to the proposal that insulin serves as an adiposity signal in the brain, decreasing food intake and increasing energy expenditure [185–187]. Along these lines, mice with brain-specific insulin receptor deletion are mildly obese and display impaired fertility, assigning insulin receptor signaling in the brain a role in regulation of fuel metabolism and reproduction [188]. Importantly, insulin action in the brain not only controls body weight [185, 188–190] but also peripheral glucose and fat metabolism [191–193]. Insulin's central action in controlling food intake and hepatic gluconeogenesis is mediated by the activation of the PI3 kinase and subsequent regulation of K_{ATP} channel activity by its product PIP3 [105, 192, 194]. Thus, K_{ATP} channel activation might represent a mechanism allowing for integration of hormonal and nutrient (glucose)-dependent modulation of glucose and lipid sensing in the hypothalamus (Fig. 2). This notion is supported by the recent finding that insulin attenuates the ability of VMN GE neurons to sense decreased glucose via the activation of PI3 kinase and K_{ATP} channels [195]. These data are consistent with the role of insulin as satiety factor, as in the presence of insulin glucose levels must decline to a greater extent before GE neurons respond.

Similarly, the adipocyte-derived hormone leptin, which is secreted in proportion to the body fat content [196, 197],

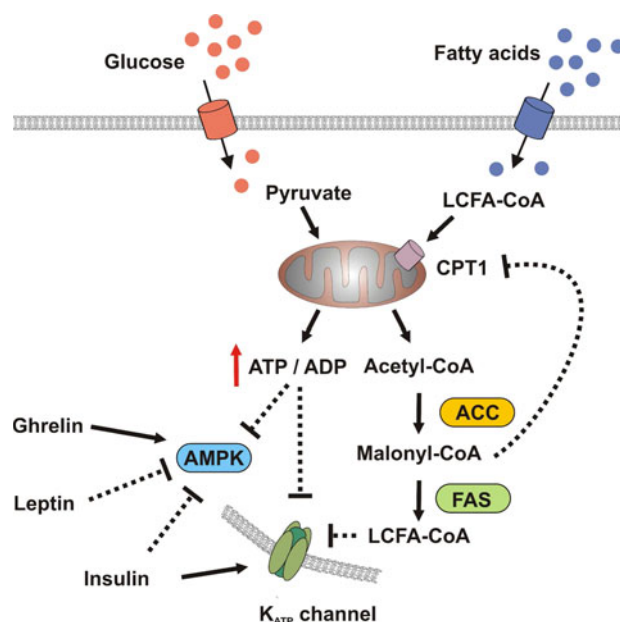


Fig. 2 Crosstalk and hormonal regulation of glucose and lipid sensing. This schematic representation of the interrelationship between glucose and lipid-sensing mechanisms and their modulation by hormones underlines the convergence of these signals on three key players: AMPK, malonyl-CoA, and K_{ATP} channels. *LCFA-CoA* long-chain fatty acyl-CoA, *ACC* acetyl-CoA carboxylase, *FAS* fatty acid synthase, *CPT1* carnitine palmitoyltransferase 1

has provided the prototypic adiposity signal in the control of energy homeostasis [198]. Mice carrying a mutation in the leptin gene (*ob*) exhibit dramatic weight gain (*ob/ob*) [198], and a naturally occurring loss-of-function mutation of the leptin receptor in the CNS and periphery underlies the phenotype of obese and diabetic mice (*db/db*) [199]. Importantly, the phenotype of mice with a neuron-specific deletion of the leptin receptor resembles that of the *db/db* mouse [200], and neuron-specific reconstitution of the leptin receptor is sufficient to reverse the obese phenotype of *db/db* mice [201], indicating that indeed the major role of leptin action to control energy homeostasis is accounted for by its signaling in the CNS. Consistent with this, central application of leptin decreases food intake and body weight in various species, underlining the pivotal role of leptin in the regulation of energy homeostasis via its action in the CNS [202]. Moreover, leptin, via activation of the CNS PI3 kinase pathway, is crucial for the regulation of glucose metabolism and peripheral insulin sensitivity [105, 203–207]. Leptin has been shown to inhibit hypothalamic AMPK activity [208]. Furthermore, expression of a constitutively active AMPK mutant in the hypothalamus blunts leptin's effects on food intake, thus indicating that AMPK serves as a principal mediator of leptin's effects on food intake and fatty-acid metabolism [26, 209, 210]. Since AMPK is also inhibited by insulin [208], regulation of

hypothalamic AMPK activity represents a further site of convergence between hormonal and nutritional control of neuron excitability (Fig. 2).

However, studies in mice lacking a functional AMPK α 2 subunit specifically in either AgRP or POMC neurons suggest differential mechanisms for glucose sensing and leptin/insulin-stimulated pathways, since these neurons were still responsive to both insulin and leptin but not glucose [110]. Conversely, Murphy et al. [211] recently demonstrated that leptin-induced changes in glucose sensing of NPY-expressing GI neurons are mediated by AMPK and concluded that during energy sufficiency, leptin reduces the ability of AgRP/NPY neurons to sense decreased glucose concentrations.

AMPK activity is further regulated by ghrelin, an orexigenic gut hormone, which is released to the circulation upon fasting [212, 213]. In the arcuate nucleus, ghrelin activates AgRP/NPY neurons, thereby mediating its orexigenic effect [214]. In addition to its stimulatory effect on food intake, centrally applied ghrelin, presumably via control of sympathetic innervation, influences adipocyte metabolism [215]. Central ghrelin induces AMPK activity via the activation of Ca²⁺ signaling and subsequent activation of CamKK2 in NPY neurons [216–218]. The following chain of intracellular events seems to contribute to ghrelin's effect on AgRP/NPY neurons. AMPK inhibits ACC activity, thereby eliminating the inhibitory effect of malonyl-CoA on CPT1 activity. CPT1 activation enhances mitochondrial β -oxidation of long-chain fatty acids, which ultimately promotes generation of reactive oxygen species (ROS). Fatty acids and ROS promote UCP2 transcription and activity, which aims to neutralize ROS, thereby enabling continuous CPT1-promoted fatty acid β -oxidation. Moreover, UCP2 can increase NPY/AgRP neuronal activity, thereby increasing inhibitory GABA-ergic input onto POMC neurons, ultimately stimulating food intake [180, 219].

Taken together, these findings clearly point towards a convergence between hypothalamic nutrient sensing and hormone signaling in order to maintain energy homeostasis via the integration of multiple signals.

Fuel sensing in obesity and type 2 diabetes mellitus

Since peripheral nutrient sensing and its dysregulation represent key components of diet-induced obesity and diabetes mellitus, impaired fuel sensing in the CNS, especially the hypothalamus, may also be involved in the development of high-fat-diet-induced obesity and peripheral insulin resistance. In peripheral tissues, sustained exposure to a supply of nutrients that exceeds energy requirements induces insulin resistance via multiple,

convergent mechanisms [220]. Given the diversity of tissues affected by nutrient excess, it is not surprising that resistance to the actions of both insulin and leptin in the CNS represents a hallmark during the development of high-caloric-diet-induced weight gain and peripheral insulin resistance [190]. However, this response has the potential to cause obesity, rather than simply being its consequence, because insulin and leptin are crucial hormonal signals that convey adiposity negative feedback information to the hypothalamus regarding the amount of body fuel stored in the form of fat. When input from these hormones is reduced, this triggers an adaptive increase of food intake that favors body weight gain. Consistently, high-fat-diet-induced obesity reduces the ability of intracerebroventricularly applied insulin, leptin, and LCFA to reduce food intake and glucose production [157, 221–224]. These effects are also present in rats fed a high-fat diet that are calorically and body weight matched to rats on a low-fat diet [222]. Moreover, exposing the animals to a normal chow diet can restore high-fat-feeding-induced leptin resistance in mice, even before body weight has been normalized [225]. Taken together, these data indicate that diet-induced leptin and insulin resistance in the CNS may be caused directly by food components, rather than obesity per se.

Indeed, saturated fatty acids, such as palmitate, which is also increased in the hypothalamus upon high-fat feeding [226], acutely causes leptin resistance in the CNS [227]. Saturated fatty acids represent important candidates for causing diet-induced leptin and insulin resistance, they act as ligands for Toll-like receptor 4 (TLR4) [228], thus activating JNK- and IKK-signaling cascades, both of which inhibit insulin action in peripheral tissues such as skeletal muscle, liver, and adipose tissue [229] as well as in the hypothalamus [230–232]. In the hypothalamus, pro-inflammatory signaling via TLRs not only inhibits neuronal insulin action but can also inhibit leptin signal transduction to further aggravate obesity [227, 233–235]. Consistently, the ability of a high-fat diet to induce obesity and its associated metabolic derangements depends upon neuronal expression of MyD88, a key intracellular mediator of inflammatory signaling [227].

Obesity also correlates with altered hypothalamic glucose sensing, as obese Zucker rats display central glucose hypersensitivity, which has recently been linked to mitochondrial dysfunction leading to changes in redox signaling [236].

A better understanding of the mechanisms by which high-caloric diets and and/or the resulting obesity reduce central sensitivity to peripheral hormonal and nutritional signals may allow for the development of potential novel pharmacological targets for the treatment of obesity and type 2 diabetes mellitus. Nevertheless, many aspects

regarding the extra- and intracellular mechanisms that contribute to CNS nutrient and hormonal resistance are still elusive and further investigations will have to unravel the complex network of the CNS in sensing nutrients and transmitting their effects.

Concluding remarks

The global prevalence of obesity and diabetes mellitus is increasing at an alarming rate and dysregulation of the central control of energy homeostasis has been posited as a causative mechanism of these metabolic diseases. Besides the capability of selective brain regions, especially the hypothalamus, to integrate a variety of neuronal and hormonal signals, increasing evidence indicates that fuel sensing also plays a pivotal role in the central regulation of food intake, energy expenditure, and glucose homeostasis. Recent progress has confirmed the presence of distinct hypothalamic neuron populations that respond to changes in circulating nutrient concentrations by either activating or inhibiting their firing activity. At the molecular level, some proteins required for neuronal fuel sensing have already been identified. Among them, K_{ATP} channels and the well-known fuel sensor AMPK represent critical points of interaction between hypothalamic glucose and lipid sensing. A wide range of data further implicates the modulation of neuronal fuel sensing by a variety of hormones such as insulin, leptin, and ghrelin, leading to an increased degree of complexity in the response of these neurons to changes in whole-body energy level. Beyond the scope of this review is another relative new concept in central nutrient sensing involving the role of amino acids in the regulation of energy homeostasis. Studies have demonstrated that increasing or decreasing the dietary intake of leucine, a branched-chain amino acid, as well as ICV administration of this amino acid affects glucose metabolism and food intake [237, 238]. The latter was attributed to changes in hypothalamic AgRP expression and mechanistically linked to mammalian target of rapamycin (mTOR) [237, 239].

A better understanding of the complex interaction of nutrients, hormones, and neuronal circuitries in the modulation of central behavioral and metabolic output signals might point to novel interventions to prevent or treat obesity and type 2 diabetes mellitus.

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