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Review

Hypothalamic nutrient sensing in the control of energy homeostasis

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ABSTRACT

The hypothalamus is a center of convergence and integration of multiple nutrient-related signals. It can sense changes in circulating adiposity hormones, gastric hormones and nutrients, and receives neuroanatomical projections from other nutrient sensors, mainly within the brainstem. The hypothalamus also integrates these signals with various cognitive forebrain-descending information and reward/motivation-related signals coming from the midbrain-dopamine system, to coordinate neuroendocrine, behavioral and metabolic effectors of energy balance. Some of the key nutrient-sensing hypothalamic neurons have been identified in the arcuate, the ventro-medial and the lateral nuclei of the hypothalamus, and the molecular mechanisms underlying intracellular integration of nutrient-related signals in these neurons are currently under intensive investigation. However, little is known about the neural pathways downstream from hypothalamic nutrient sensors, and how they drive effectors of energy homeostasis under physiological conditions. This manuscript will review recent progress from molecular, genetic and neurophysiological studies that identify and characterize the critical intracellular signalling pathways and neurocircuits involved in determining hypothalamic nutrient detection, and link these circuits to behavioral and metabolic effectors of energy balance. We will provide a critical analysis of current data to identify ongoing challenges for future research in this field.

Contents

1. Introduction

Obesity has reached epidemic levels worldwide, accounting for multiple comorbidities, including diabetes, cardiovascular disease, hypertension, stroke, and neuropathy. Cellular exposure to excess nutrients in obesity is emerging as a common putative cause for multiple deleterious cellular consequences across diverse cell types, responsible for a variety of metabolic dysfunctions associated with obesity [76,190]. To prevent nutrient excess, the body relies on nutrient sensors that detect nutrient availability and coordinate effectors of energy intake and utilization. Thus, considerable attention is currently turned to the identification and characterization of nutrient sensors and their downstream targets, an integrative approach that may lead to effective treatment strategies for obesity and related metabolic disorders.

The hypothalamus has emerged as one of the body's main concentration of nutrient-sensing elements, and a major center of convergence and integration of multiple nutrient-related signals

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[130]. Within specific hypothalamic nuclei, subsets of neurons with specific neurobiological phenotypes are responsive to glucose, fatty acids, amino acids and other fuel-related stimuli. In these nutrient-sensing neurons, nutrients act as signalling molecules to engage a complex set of neurochemical and neurophysiological responses, thereby regulating energy intake, the release of stored nutrients, and nutrient utilization in most tissues, thus compensating for increased energy availability.

Some of the key nutrient-sensing hypothalamic neurons have been identified in the arcuate (ARC), ventro-medial (VMN) and lateral (LH) nuclei of the hypothalamus, and electrophysiological evidence indicates that they exhibit specific excitatory or inhibitory neurophysiological responses to changes in extracellular nutrient levels [81,143,171,188]. They possess a unique set of transporters, enzymes and ion channels that enable them to detect and process nutrients. Although their neurochemical identity remains to be further elucidated, some data clearly indicate that neurons of the melanocortin system – orexigenic neurons that express both neuropeptide Y (NPY) and agouti-related peptide (AgRP), and anorexigenic neurons that express proopiomelanocortin (POMC), and their projections to neurons expressing melanocortin receptors 3 and 4 (MC3 and 4R) – can directly sense changes in nutrient availability. POMC and NPY/AgRP neurons are located within the ARC, considered as the primary integrative center of the hypothalamus, ideally situated in the vicinity of the 3rd ventricle and the median eminence, an area with a relatively porous blood–brain barrier available to buffer extracellular nutrients and hormones. Anorexigenic POMC neurons depolarize, whereas orexigenic NPY/AgRP hyperpolarize in response to increased nutrient levels [20,56,80,81,135,146]. In the LH, hypothalamic glucose-inhibited neurons have been reported to correspond to a neurochemically diverse group of cells, including wakefulness-promoting hypocretin/orexin neurons [159], while glucose-excited neurons correspond to cells containing melanin-concentrating hormone [28]. The neuropeptide phenotypes of VMN nutrient-sensing neurons remain largely unknown.

Recent findings indicating that (1) hypothalamic nutrient sensing is impaired in animal models of obesity [146], (2) disruption of hypothalamic nutrient sensing induces obesity and dysregulation of glucose homeostasis [74], and (3) restoration of hypothalamic nutrient sensing normalizes food intake, energy balance and glucose homeostasis in overfed rats [151] underscore the relevance of hypothalamic nutrient sensing in the regulation of energy balance and the pathophysiology of obesity and metabolic diseases. This manuscript will review recent progress from molecular, genetic and neurophysiological studies that identify and characterize the critical intracellular signalling pathways, emerging neurocircuits and physiological effectors involved in hypothalamic nutrient sensing, and provide a critical analysis of the available data to identify current challenges for the research in this field.

2. Cellular mechanisms involved in nutrient detection by hypothalamic neurons

Various nutrient-sensing mechanisms and intracellular signal transduction pathways have been implicated in the ability of nutrient-sensing neurons to monitor the amount of available fuel in the body (Fig. 1). The currently broadly diffused model supports a role for nutrient intracellular metabolism in hypothalamic nutrient detection. In this model, ATP production and the associated changes in the ADP/ATP ratio are considered as the main metabolic signals of nutrient availability. This attractive unifying mechanism, which would account for neuronal detection of all 3 macronutrients, is being challenged by several observations underscoring the considerable heterogeneity of nutrient-sensing neurons. Several molecules are currently considered as gatekeepers of neuronal

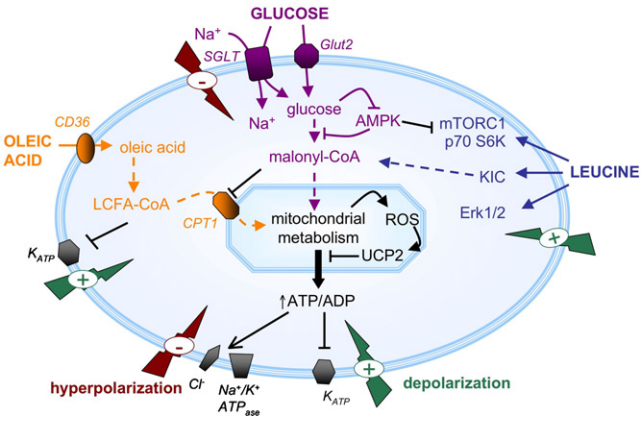

Fig. 1. Intracellular mechanisms involved in hypothalamic neuronal nutrient sensing. In response to changes in extracellular nutrient levels, hypothalamic nutrient-sensing neurons exhibit specific excitatory or inhibitory electrical activity depending on their neurochemical phenotype. This figure depicts the main described mechanisms or working models accounting for hypothalamic nutrient sensing, irrespective of the cell's neurochemical identity. Glucose-induced depolarization is believed to mainly occur through glucose intracellular metabolism, production of ATP and closure of K_{ATP} channels. Glucose-induced hyperpolarization could involve several mechanisms, metabolism-dependent through ATP-induced Na^+/K^+ ATP_{ase} and Cl^- channel activation or mitochondrial ROS production, or metabolism-independent through sodium-glucose cotransport. Oleic acid detection has been shown to involve similar metabolism-dependent mechanisms, as well as oleic acid transport through CD36. Leucine hypothalamic detection involves activation of the mTORC1/p70 S6 kinase pathway, the Erk1/2 pathway, as well as leucine intracellular metabolism, all of which potentially contribute to leucine-induced depolarization.

nutrient-sensing pathways, varying in their association with intracellular ATP levels, but much less is known about the transducers that link these sensors to neuronal electrical or synaptic activity.

Nutrient sensing through nutrient metabolism and detection of changes in available ATP was first proposed to account for hypothalamic glucose sensing (reviewed in [106,148]). Similarly to glucose sensing in pancreatic β cells [6], hypothalamic glucose sensing would require glucose entry into the cell via the low affinity Glut2 transporter, phosphorylation by glucokinase, processing by the TCA cycle to give rise to intracellular ATP levels, and inhibition of ATP-inhibited K^+ channels (K_{ATP} channels), resulting in calcium influx and cell depolarization [116]. Some pharmacological and genetic evidence, demonstrating the requirement of glucokinase or K_{ATP} channels for glucose-induced hypothalamic neuronal depolarization or hyperpolarization, convincingly support this analogy [84,85,124,146]. However, this model is challenged by several observations showing that (1) intracellular ATP levels do not increase in response to glucose in hypothalamic cells [2], (2) K_{ATP} channels are not required for glucose sensing in the ARC [57] and (3) some but not all glucose-sensing hypothalamic neurons express Glut2, K_{ATP} channels or glucose kinase [85]. In addition, this model is being questioned for glucose-inhibited neurons, although glucose sensing through glucokinase [49] and intracellular metabolism is supported by ATP-mediated activation of the hyperpolarizing Na^+/K^+ ATP_{ase} [143] or ATP-dependent opening of Cl^- channels [56,171]. Recent observations rule out the role of glucokinase, glucose metabolism and ATP production in glucose-inhibited neurons glucosensing properties [66,172], and propose alternative mechanisms. These include electrogenic entry of glucose through sodium-glucose cotransporters (SGLT) [138,199] or non-transporting glucose sensing through sweet taste receptors [156], but further tests are needed to demonstrate their roles in glucose sensing.

Intracellular nutrient metabolism is also believed to be involved in hypothalamic fatty acid sensing (reviewed in [100]). According to this model, increases in the intracellular pool of fatty

acyl-CoA following fatty acid esterification would represent a key signalling component for hypothalamic fatty acid sensing by altering K_{ATP} channel activity [140]. To support this hypothesis, build-up of intracellular fatty-acyl-CoA following genetic or pharmacological inhibition of carnitine palmitoyltransferase 1 (CPT1, fatty-acyl-CoA mitochondrial transporter required for fatty-acyl-CoA β-oxidation) drives behavioral and metabolic effectors of energy balance [139,151]. Further processing of fatty-acyl-CoA in the mitochondria through β-oxidation, leading to ATP production and K_{ATP} channel closure has also been implicated, but neurophysiological data supporting this suggestion is scarce. Patch-clamp recordings have shown that oleic acid can both inhibit and activate arcuate neurons [103,188]. This latter study, together with recent work of Jo et al. [81], confirmed a role for fatty acid intracellular metabolism and K_{ATP} channels in oleic acid-induced depolarization or hyperpolarization of VMN neurons, as well as depolarization of arcuate POMC neurons. Work from Le Foll et al. also indicates that oleic acid metabolism only accounts for part of hypothalamic oleic acid sensing, and implicates the fatty acid transporter CD36 as an alternative sensing mechanism [103]. In spite of these recent advances, well-defined mechanisms linking increased fatty acid availability to neuronal membrane polarization remain elusive.

More recent studies suggest that hypothalamic fatty acid sensing relies on fatty acid-induced activation of novel PKC isoforms (δ, ε and θ), similarly to what has been described in peripheral tissues [47,108]. Conflicting results, showing on one hand that fatty acid-induced activation of PKCδ decreases glucose production [157], and on the other hand that saturated fatty acid-induced PKCθ activation inhibits PI3-kinase signalling and promotes insulin resistance and diet-induced obesity [12], underscore the need for further evaluation of this novel pathway in hypothalamic nutrient sensing to identify potential neurochemical mediators and intracellular mechanisms linking PKCs to neuronal activity.

In line with the view that changes in intracellular ATP levels represent a critical signal for nutrient sensing in hypothalamic neurons, recent data implicate the AMP-activated protein kinase (AMPK), activated in response to an increase in the AMP/ATP ratio, in neuronal nutrient sensing and the regulation of energy balance in the ARC [126]. Electrophysiological evidence, showing that pharmacological AMPK activation or inhibition affects the electrical response of glucose-inhibited neurons to glucose, support this role [133]. Consistently, knockout of the α2 isoform of AMPK abolished glucose-induced excitation of arcuate POMC and NPY/AgRP neurons [36]. However, although recent work proposes that AMPK might drive changes in cytosolic Ca^{2+} [89], the transducers linking AMPK activity to membrane excitability are unknown. Several findings indicate that AMPK might alter neuronal activity by regulating intracellular malonyl-CoA levels: AMPK modulates the activity of acetyl-CoA carboxylase (ACC), the enzyme responsible for malonyl-CoA synthesis from acetyl-CoA, and malonyl-CoA availability regulates fat oxidation through the inhibition of CPT1 activity. Malonyl-CoA is considered as an important component of hypothalamic nutrient sensing through this mechanism (reviewed in [102]) and the intracellular malonyl-CoA pool responds to hypothalamic glucose and fatty acid [191]. Jo et al. recently reported that malonyl-CoA alone does not affect POMC neurons excitability but blunts oleic acid-induced POMC neuron depolarization [81]. However, the mechanisms linking malonyl-CoA availability to neuronal activity remain unknown.

Another metabolism-dependent but ATP-independent mechanism suggested to contribute to hypothalamic nutrient sensing relies on mitochondrial production of reactive oxygen species (ROS) by electron leakage during intracellular glucose and fatty acid metabolism. This hypothesis is mainly supported by the observation that quenching ROS production prevents glucose-induced electrical activation of arcuate neurons [105], glucose-induced hyperpolarization of 50% of glucose-inhibited neurons in the VMN [103] and oleic acid-induced inhibition or activation of 10–20% of VMN neurons [103]. This sensing mechanism has been related to hypertriglyceridemia-induced anorexia [11] and might be particularly relevant in conditions of nutrient excess, since electrical effects have been demonstrated at supraphysiological glucose levels, and disappear at physiological glucose levels [103]. ROS-induced activation of UCP2 has been linked to ROS-induced changes in neuronal activity [5], and UCP2 inhibition depolarizes glucose-excited neurons through a mechanism requiring ATP-induced closure of K_{ATP} channels [146]. In addition, increased UCP2 activity in diet-induced obesity induces loss of glucose sensing in POMC glucose-excited neurons [146].

Finally, recent data demonstrate that ARC neurons can also sense changes in amino acid availability, and implicate this sensing in the regulation of energy balance. Leucine administration into the mediobasal hypothalamus (MBH) reduces food intake, both through a rapid reduction in meal size and a longer term reduction in meal number, leading to a reduction in body weight gain [20]. These behavioral effects are supported by electrophysiological data demonstrating that increased leucine availability depolarizes POMC neurons, and by studies showing that ARC administration of leucine induces c-Fos expression in POMC neurons in vivo [20]. The first molecular candidate suggested in neuronal amino acid sensing was the mammalian target of rapamycin complex 1 (mTORC1), as pharmacological evidence revealed that mTORC1 inhibition blunted intra-cerebroventricular (icv) leucine-induced anorexia and body weight loss [42]. Our work demonstrating that bidirectional genetic manipulations of MBH p70 S6K1 activity, a major effector of mTORC1, affect behavioral and metabolic determinants of energy balance, provides further support for the role of the mTORC1/p70 S6 kinase 1 pathway in MBH nutrient sensing [21]. MBH $Erk_{1/2}$, whose activation is critical to MBH leucine's effects on food intake and body weight [20], has also been identified as another important transducer of MBH amino acid sensing.

Interestingly, amino acid intracellular metabolism has been implicated in MBH amino acid sensing. MBH administration of both α-ketoisocaproic acid, the product of leucine transamination, and α-chloroisocaproic acid, a selective activator of leucine irreversible decarboxylation, each decrease food intake and body weight gain, indicating that endogenous MBH leucine metabolism generates a signal that contributes to the regulation of energy balance. The final product of leucine catabolism is acetyl-CoA, precursor of malonyl-CoA. Thus, amino acid availability could represent yet another input into the intracellular malonyl-CoA pool, suggesting a synthetic framework for understanding the roles of MBH glucose, fatty acid and amino acid sensing in the control of energy homeostasis.

Taken together, these data support an important role for intracellular intermediates of macronutrient metabolism, used by nutrient-sensing neurons to mediate the negative feedback control of energy balance. Several interesting emerging concepts remain to be investigated:

(1) The nutrient-sensing properties of glucose-, fatty acid-, and maybe amino acid-sensitive neurons are plastic. As an example, glucose responsiveness of glucose-sensing neurons varies according to previous hypoglycemic events [86], and both glucose- and oleic acid-induced neuronal activity are affected by metabolic state in obese rodents [40,81], as well as by various genetic and environmental factors, such as diet composition and maternal obesity [104].
(2) Other nutrient-related signals, such as insulin and leptin, have been reported to alter glucose and oleic acid-sensing properties of hypothalamic nutrient-sensitive neurons [43,81,136,173,174]. Hypothalamic detection of these adiposity hormones plays a critical role in the regulation of energy

balance, and their intracellular signalling pathways share multiple components with nutrient-sensing pathways, such as K_{ATP} channels [149], AMPK [126], or p70 S6 kinase 1 [21]. In addition, some hypothalamic neurons are excited by both glucose and fatty acids [103,188]. How metabolic, hormonal, genetic and environmental signals interact and are integrated at the cellular levels remains to be determined, and this represents a major challenge in the field.

(3) Hypothalamic astrocytes can also detect changes in nutrient availability and interact with hypothalamic neurons to generate a response to these signals. This hypothesis has been substantiated by the demonstration that hypothalamic glia responds to increases in extracellular glucose levels through an increase in glycolytic ATP production, which induces lactate release from astrocytes [2,147]; lactate enters hypothalamic neurons and depolarizes them through K_{ATP} channel closure [172], and hypothalamic lactate sensing has been shown to regulate food intake and hepatic glucose production [92,97]. Astrocytes are also likely to be involved in oleic acid and amino acid sensing, since astrocytes readily take up and utilize fatty acid as a major source of energy [53], and selectively express the mitochondrial isoform of the branched-chain amino acid transferase, allowing them to participate to an astrocyte/neuron nitrogen shuttle operating in parallel with the glutamate/glutamine cycle [79]. This role of hypothalamic glial cells in hypothalamic nutrient sensing has been under evaluated thus far and requires increased attention.

Ultimately, formal proof of the physiological relevance of hypothalamic nutrient sensing may require the demonstration that these nutrient-sensing neurons directly respond to acute postprandial changes in nutrient availability.

3. Neurocircuits activated by hypothalamic nutrient sensing in the regulation of energy balance

Recent advances, mainly achieved during the neurochemical and neurophysiological characterizations of the circuit activated by the adipostatic hormone leptin, have begun to provide a good description of the anatomy of the neural pathways mediating the control of energy balance [51,193]. Several brain areas identified as part of the circuit activated by leptin are also consistently activated following food consumption. These include the ARC, LH, VMN, paraventricular (PVH) and dorso-medial (DMH) hypothalamus, and the dorsal vagal complex of the caudal brainstem (DVC), including the nucleus of the solitary tract of the caudal brainstem (NTS), the dorsal motor vagal nucleus (DMX), and the area postrema [82], suggesting a role for various hypothalamic/brainstem circuits as interneuronal transduction pathways downstream hypothalamic nutrient detection (Fig. 2). However, in spite of the progress in identifying the intracellular mechanisms involved in hypothalamic nutrient sensing, and the growing number of characterized circuits that appear to be reasonable candidates linking hypothalamic nutrient-sensing neurons to effector pathways of energy homeostasis, the neuronal events following nutrient detection by first-order hypothalamic neurons remain poorly characterized.

The ARC is considered as a primary nutrient-sensing center of the hypothalamus. Within the ARC, POMC and NPY/AgRP nutrient-sensing neurons represent the starting point of the best-characterized circuit involved in hypothalamic nutrient sensing, the melanocortin system (reviewed in [41]). POMC neurons of the ARC produce α-melanocyte stimulating hormone (α-MSH), an anorectic peptide that acts on melanocortin receptors 3 and 4 (MC3R and MC4R), whereas NPY/AgRP neurons inhibit POMC neurons through GABA release, and antagonize their action through

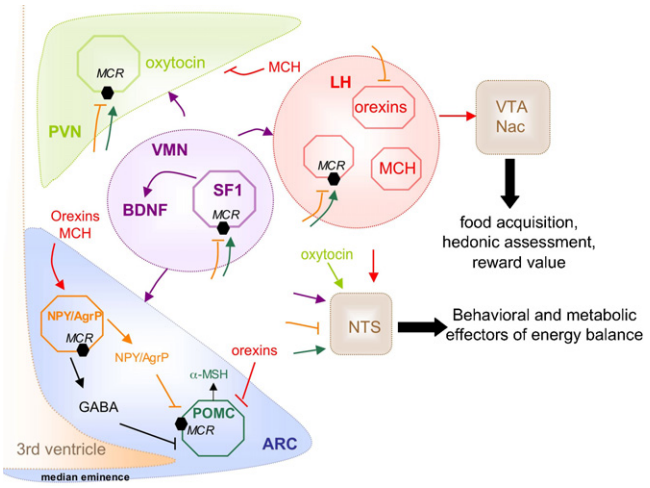

Fig. 2. Neurocircuits activated by hypothalamic nutrient sensing. The melanocortin system is the best-characterized circuit activated by hypothalamic nutrient sensing. Anorexigenic POMC neurons and orexigenic NPY/AgRP neurons of the ARC project to various nuclei involved in nutrient-driven circuits, including hypothalamic nuclei PVN, VMN and LH. In turn, the ARC receives input from the VMN and the LH; these two nuclei are inter-connected and both project to the PVN, an important hypothalamic integration center. Orexins and MCH neurons of the LH interact with the hypothalamic melanocortin system and integrate melanocortinergic information with sensory inputs and reward/motivation-related information, further processed by the ventral tegmental area (VTA) and the nucleus accumbens shell (Nac) to determine food acquisition, hedonic assessment and reward value. The NTS receives projections from the ARC, PVN, VMN and LH, and integrates this forebrain-descending nutrient and adiposity-related information with gut-derived satiety signals to regulate multiple behavioral and metabolic effectors of energy homeostasis.

AgRP, a high-affinity endogenous antagonist of MC3/4R. Arcuate NPY and POMC neurons are also targets for locally released AgRP and α-MSH from arcuate NPY and POMC neurons, as suggested by data showing that (1) arcuate POMC neurons express MC4R (Blouet, unpublished data), (2) arcuate NPY neurons express MC3/4R [131] and (3) MC3/4R agonists depolarize whereas AgRP hyperpolarizes arcuate POMC neurons [169], adding further complexity to the arcuate melanocortin system. Neurons expressing MC3/4R are abundant in many hypothalamic sites, including the LH, VMN, PVH and DMH hypothalamus, as well as in anterior hypothalamic regions, the NTS and the spinal cord [132]. Likewise, NPY receptors are widely expressed throughout the central nervous system. In the hypothalamus, NPY receptors Y1, Y2 and Y5 are densely expressed in the ARC, the PVH and the VMN [145].

The PVH, an important hypothalamic nucleus in the integration of autonomic and neuroendocrine information [144], is one of the regions more densely innervated by POMC and NPY/AgRP neurons [9,41]. While its role in the regulation of pituitary hormone secretion through the release of several neuroendocrine factors (oxytocin, thyrotrophin-releasing hormone or corticotropin-releasing hormone) is well characterized [87], less is known about the PVH integration of melanocortin signals in the regulation of energy balance. Data from neurophysiological studies demonstrates that: (1) individual neurons within the PVH are capable of detection and integration of melanocortin signals, (2) NPY and melanocortins are functional antagonists of each other within the PVH in the regulation of feeding behavior, and (3) melanocortin administration within the PVH regulates both feeding behavior and energy expenditure [44]. PVH oxytocin fibers, activated by food consumption during a meal [82], innervate the NTS [18,163] which integrates gut-derived satiety signals with descending input from the forebrain to limit meal size [15,128]. In vivo PVH electrical stimulation releases oxytocin within the NTS [101], and PVH oxytocinergic activation of meal size regulating NTS neurons

has been implicated in the melanocortinergic control of feeding [19,94,111,117]. The importance of this circuitry in hypothalamic nutrient sensing was not supported until now. In our recent work, we described the contribution of this functional neuroanatomical forebrain–hindbrain circuit in MBH nutrient sensing and the control food intake [20]. Using a combination of electrophysiological, immunohistochemical and pharmacological approaches, we showed that MBH leucine-induced activation of arcuate POMC neurons engages a forebrain–hindbrain circuit involving activation of arcuate melanocortin signalling, PVN oxytocin neurons, and NTS neurons to reduce food intake by a specific reduction in meal size.

The ARC also directly innervates several brainstem nuclei, including the NTS. Activation of brainstem MC4R has been shown to affect NTS neuronal electrical activity and reduce meal size [67,189], which may occur through presynaptic modulation of vagal glutamatergic synaptic transmission, and enhancement of vagal afferent satiation signals from the gastrointestinal tract [186]. However, the demonstration of a role for direct ARC to NTS melanocortinergic projections in hypothalamic nutrient-sensing circuits requires further experimentation.

Interestingly, the activities of AMPK and $Erk_{1/2,}$ intracellular effectors of ARC nutrient sensing, have been shown to be altered in response to glucose, leptin or leucine outside the ARC, in the PVN and the NTS [20,71,126], suggesting that second-order neurons may use similar intracellular effector pathways as first-order neurons to transduce the information. This suggestion has been confirmed in the case of $Erk_{1/2}$, activated in PVN oxytocin neurons and in the NTS in response to ARC leucine administration [20]. Reports proposing that PVN $Erk_{1/2}$ signalling is coupled to PVN or NTS MCR [46,178] suggest that PVN and NTS $Erk_{1/2}$ activation is secondary to ARC activation of melanocortin signalling. Together with data supporting a role for NTS $Erk_{1/2}$ as a molecular integrator of converging gut satiety signals and forebrain adiposity signals [178,179], these data extend the integrative role of $Erk_{1/2}$ in the control of food intake to include the feeding inhibitory consequences of MBH nutrient sensing, and strongly support the role of hypothalamic $Erk_{1/2}$ as an important regulator and effector of feeding processes that has the potential to mediate both acute and long-term changes in neuronal functioning.

The VMN is another critical hypothalamic nutrient-sensing region, but the neurochemical identities of VMN nutrient-sensing neurons are not well established. In parallel with directly sensing nutrients, the VMN also: (1) receives input from the ARC, including melanocortinergic projections, and (2) sends projections to the ARC, including direct glutamatergic projection to ARC POMC neurons [177]. Furthermore, MC3/4R agonists inhibit glutamatergic excitatory VMN neurons [61]. The VMN also projects to many other hypothalamic and extra-hypothalamic areas, including the PVH, LH, DMH and the NTS [32,121,164]. Recent progress implicates steroidogenic factor 1 (SF-1) neurons of the VMN in the regulation of energy balance [17,88,204]. VMN SF-1 neurons express MC4R and release brain-derived neurotrophic factor (BDNF), a modulator of ingestive behavior [119,184,187]. In turn, melanocortinergic tone regulates BDNF expression [196]. Loss of function mutations in BDNF receptor result in hyperphagia and morbid obesity in human and rodents [114,201]. Conversely, peripheral or central BDNF administration reduce body weight and food intake in mice, supporting a role for BDNF as an important anorexigenic signal downstream of the melanocortin system [196]. Although some evidence indicates that this circuit responds to changes in the nutritional state or icv glucose [177,184], its relevance in hypothalamic nutrient sensing remains to be confirmed.

Last, the LH is the third hypothalamic region where nutrient-sensing neurons have been clearly identified. In addition to detecting available nutrients, LH neurons receive and integrate sensory inputs and reward/motivation-related information, and widely project to several areas in the hindbrain, cortex, limbic system, thalamus and spinal cord, which enables them to engage both behavioral and autonomic output systems [13]. Two specific distinct groups of LH peptidergic neurons, containing melanin-concentrating hormone (MCH) and orexins, have been suggested to play significant roles in energy balance [160], at least in part through interactions with the melanocortin system. Indeed, ARC NPY/AgRP cells are surrounded by nerve terminals containing orexins [134], orexins exert direct excitatory actions on ARC NPY/AgRP neurons [185] and indirect inhibitory actions on ARC POMC neurons [115]. These data support the suggestion that LH orexinergic modulation of the ARC melanocortin system accounts for the anorexigenic properties of orexins observed following ARC orexin injections [134]. In turn, LH orexin neurons are in close apposition to ARC NPY-containing nerve terminals [25] and NPY robustly inhibits orexin neurons [60], indicating a decrease in orexin cell activity when ARC NPY neurons are active. However, the functional significance of this neurophysiological negative feedback loop is unclear. Orexin A fibers also innervate sympathetic premotor neurons of the caudal raphe nuclei, and this circuit has been implicated in the regulation of thermogenesis, cardiovascular and gastrointestinal functions [14].

LH MCH neurons are also believed to modulate ARC melanocortinergic activity: ARC MCH injections increase ARC AgRP release, decrease ARC α-MSH release, and increase food intake [1]. PVN and DMN MCH injections also depress feeding behavior [1], and several pharmacological and genetic studies support a role for MCH in the control of energy balance and glucose homeostasis [112,165]. Recent evidence indicates that MCH is specifically involved in the control of energy expenditure though projections to the NTS [207]. Again, the relevance of MCH- and orexin-driven circuits in hypothalamic nutrient sensing has not been directly addressed so far. In addition, through their projections to the nucleus accumbens shell and ventral tegmental area, both MCH and orexins are involved in the hedonic control of feeding behavior [63,206], but the potential role of LH nutrient sensing as a modulator of these neural pathways remains unexplored.

Thus, how the information arising from hypothalamic nutrient sensing is processed through candidate hypothalamic/brainstem circuits to regulate behavioral and metabolic effectors of energy balance remains poorly understood. In spite of the relative lack of characterization of the neuronal circuits driven by hypothalamic nutrient detection, the downstream behavioral and metabolic effectors important for energy balance are well identified.

4. Behavioral and metabolic effectors of energy balance regulated by hypothalamic nutrient sensing

Several complimentary approaches have been used to demonstrate links between hypothalamic nutrient detection and the regulation of behavioral and metabolic effectors of energy homeostasis, including (1) 3rd icv or hypothalamic parenchymal nutrient administration, (2) pharmacological or genetic manipulation of the activity of hypothalamic intracellular effectors involved in nutrient detection, and (3) interventions interfering with circuits involved in relaying nutrient-related information from hypothalamic nutrient sensors to effectors of energy balance. These approaches have been valuable in identifying the effectors of energy homeostasis regulated by hypothalamic nutrient sensing, including food intake, pancreatic hormone secretion, hepatic glucose production, adipose tissue metabolism and energy expenditure (thermogenesis, adipose tissue metabolism, substrate utilization and locomotor activity) (Fig. 3), and support a role for severe impairments of hypothalamic nutrient-sensing pathways in the onset and

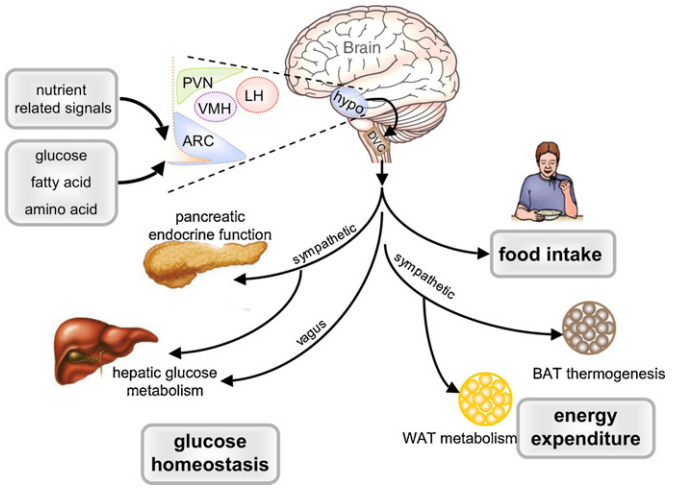

Fig. 3. Behavioral and metabolic effectors of energy balance regulated by hypothalamic nutrient sensing. Hypothalamic nutrient detection activates neurocircuits involved in the regulation of feeding behavior, glucose homeostasis, adipose tissue metabolism and energy expenditure. Neurons in the DVC integrate forebrain-descending nutrient- and adiposity-related information with gut satiety signals to regulate feeding behavior. Descending hypothalamic projections terminate on DVC and adjacent caudal brainstem nuclei to determine autonomic outflow to several effectors of energy balance, including liver, pancreas and brown and white adipose tissues. Hypothalamic nutrient detection also regulates locomotor activity through mechanisms that remain to be identified.

maintenance of metabolic dysfunction. However, recent results underscore the need to develop more physiologically relevant strategies to directly assess (1) the consequences of changes in levels of circulating nutrients during feeding/fasting transitions on hypothalamic nutrient-sensing pathways and their downstream functional effectors, and (2) whether interfering with hypothalamic nutrient-sensing pathways could delay or prevent the onset of obesity or type 2 diabetes. This latter aspect of the field is currently under intensive investigation, in efforts to identify new therapeutic targets aimed at preventing the development of metabolic diseases.

4.1. Hypothalamic nutrient sensing and the regulation of feeding behavior

Food intake is a primary behavioral effector that has been identified as a target of hypothalamic sensing of all three macronutrient species, as demonstrated both by studies considering the effect of nutrient infusions, and by approaches using pharmacological or genetic tools to affect the hypothalamic activity of nutrient-driven intracellular effectors.

Systemic and central hypoglycemia induces meal initiation [30,50,123,127]. Conversely, acute 3rd icv glucose infusion decreases food intake [33,96]. Central genetic deletion of the glucose transporter Glut2 induces hyperphagia, and blunts 3rd icv glucose-induced anorexia and 2-desoxyglucose-induced (2-DG) feeding [8]. Likewise, adenoviral mediated bidirectional modulations of MBH AMPK activity, an important glucose sensor, reciprocally affect feeding behavior [126]. Results from these studies, together with other similar work manipulating intercellular intermediates of hypothalamic glucose sensing [105,191], support a role for hypothalamic glucose detection in determining energy intake. However, recent findings question the physiological relevance of hypothalamic glucose sensing in the regulation of feeding. Indeed, spontaneous meals are preceded by a drop in circulating glucose levels which is not accompanied by a fall in ARC and VMN glucose levels [50], making it unclear whether acute changes of glucose within the physiological range play a primary role in normal meal initiation or termination. In addition, in spite of the role of glucokinase in glucose-induced depolarization or hyperpolarization of VMH neurons [84], both acute and chronic alterations in VMH glucokinase activity in adult mice failed to affect food intake and body weight [50]. These data argue against a role for VMH glucose sensing, at least through glucose intracellular metabolism, in the regulation of feeding behavior. The divergent metabolic phenotypes of AgRP- and POMC-specific AMPK-null mice, the former developing an age-dependent anorexic and lean phenotype while the latter become hyperphagic and obese [36], further obscure the physiological role of hypothalamic glucose sensing in the regulation of food intake. These paradoxical data suggest that targeted genetic deletions can lead to multiple, alternative compensatory functions of central pathways regulating energy balance, thereby limiting the interpretation of the data resulting from this experimental approach.

Central fatty acid detection has also been implicated in the regulation of feeding behavior. 3rd icv oleic acid administration inhibits food intake [140], and genetic or pharmacological manipulations of effectors involved in hypothalamic fatty acid sensing also affect feeding behavior. This was first suggested by experiments showing that central administration of the fatty acid synthase inhibitor C75 rapidly reduces food intake and body weight in lean and obese animals [95,110]. More recently, centrally administered C75 has been shown to reduce meal frequency and hypothalamic AgRP expression [3], decrease gastrointestinal motility [107], and inhibit gastric ghrelin secretion [77]. Although the pharmacological and neuronal specificity of the metabolic consequences of central C75 administration remains of concern, both because C75 induces widespread neuronal activation when applied into the ventricle [62,125] and because it may induce visceral malaise [37], results from other studies have confirmed the role of hypothalamic fatty acid metabolism in the regulation of feeding behavior. Acute inhibition or chronic deletion of hypothalamic CPT1 activity is sufficient to reduce food intake [139,192] and overexpression of mediobasal-hypothalamic malonyl-CoA decarboxylase (MCD), leading to a drop in the intracellular pool of long-chain fatty acyl-CoA, increases food intake and body weight gain [74]. However, circulating fatty acid levels do not increase following food ingestion, and are elevated in the fasted state as a consequence of lipolysis. Local processing of meal-related triglycerides at the level of the hypothalamus could provide fatty acids and related metabolites to nutrient-sensing neurons during the postprandial state, which could account for this paradox. Clearly, further data are needed to confirm the physiological relevance of hypothalamic fatty acid sensing in the regulation of feeding behavior.

Last, 3rd icv leucine administration decreases food intake, and this effect is blunted by rapamycin, a pharmacological mTORC1 inhibitor [42]. Our recent findings identified the MBH as a specific neuroanatomical site involved in central leucine sensing and the regulation of feeding behavior. MBH leucine microinjection rapidly reduces meal size, and decreases meal number over the longer term [20]. Bidirectional genetic manipulations of MBH p70 S6K1 activity, an important amino acid sensor activated in the hypothalamus in response to a meal or to a hypothalamic leucine injection, affect food intake specifically through changes in meal size, a critical index of satiety processes [21]. Because our results also indicate that blocking NTS oxytocinergic input blunts the hypothalamic leucine-induced reduction in meal size [20], these data link MBH leucine detection to the activation of NTS satiety effector neurons implicated in the integrative control of ingestion.

The hypothalamic melanocortin system is a critical feeding regulatory circuit driven by hypothalamic nutrient sensing, as suggested by data from studies showing that (1) glucose, oleic acid and leucine directly affect the electrical activity of neurons of

the melanocortin system [20,56,81,135], (2) 3rd icv glucose-, oleic acid- or leucine-anorexia is associated with a reduction in NPY and/or AgRP hypothalamic expression [33,42,129,140], (3) central 2-DG induces c-Fos immunoreactivity in NPY neurons and NPY is required for central 2-DG orexigenic effect [73,166] and (4) MBH leucine administration activates c-Fos immunoreactivity in ARC POMC neurons [20]. Thus, findings evidencing a role for melanocortin signalling in the regulation of food intake indirectly support a role for hypothalamic nutrient sensing in determining this behavior. POMC-null mice are hyperphagic and obese [200], PVH melanocortin administration decreases food intake [44] and centrally administered melanocortin receptor agonists reduce spontaneous and scheduled meal size [7]. MC4R-null mice are obese, due to the combined effects of increased food intake and decreased energy expenditure [34,78,176], and PVH-specific restoration of MC4R expression in MC4R-null mice restores normal feeding [10]. Conversely, central administration of NPY increases food intake [155]. The role of NPY/AgRP neurons in the regulation of feeding behavior has been questioned following the metabolic characterization of NPY-null mice, AgRP/NPY double knock-out mice, or mice overexpressing NPY, each of which have normal food intake and body weight [52,153,175]. In contrast, induced selective ablation of NPY or AgRP neurons in adult mice results in acute reduction of feeding [68,113]. These results suggest that chronic lack of NPY during development may lead to compensatory changes that normalize regulation of food intake and energy expenditure in the absence of NPY.

Together, these data support a role for hypothalamic nutrient sensing in the regulation of feeding behavior, but several important caveats remain:

(1) Data directly supporting a role for hypothalamic nutrient detection in the regulation of feeding behavior are mainly those obtained following brain nutrient administration. In the majority of cases, these data were collected following ventricular nutrient administration, which allows widespread brain nutrient exposure and does not restrict the observed effects to the specific consequences of hypothalamic nutrient sensing. In addition, it is impossible to know what extracellular nutrient levels are produced in these studies, and very few data are available to compare the injected doses to actual postprandial extracellular nutrient concentrations at the level of hypothalamic nutrient-sensing neurons. Whether changes in levels of circulating nutrients during feeding/fasting transitions affect hypothalamic nutrient-sensing pathways and their downstream functional effectors remains a matter of debate.
(2) Targeted genetic manipulation, albeit an elegant and powerful strategy that provides a window on the neurochemical specificity of nutrient-sensing pathways, is often associated with compensatory adaptations of central circuits regulating energy balance, which represent a major limitation to the interpretation of the resulting data. This underscores the need to develop new experimental strategies to modulate hypothalamic nutrient-sensing pathways acutely and reversibly in neurochemically defined neuronal populations in adult rodents.
(3) Although we recently showed that hypothalamic administration of a melanocortin antagonist blunts MBH leucine-induced anorexia [20], linkages between hypothalamic nutrient detection, activation of melanocortin signalling, and reductions in food intake require more direct evidence.
(4) The role of other nutrient-driven circuits, such orexin A, MCH or SF1 circuits, in the regulation of feeding behavior remains poorly characterized.

4.2. Hypothalamic nutrient sensing and the regulation of glucose homeostasis

In addition to feeding, central glucose and fatty acid detection has been related to the regulation of glucose homeostasis by affecting endocrine function and endogenous glucose production. Both vagal and sympathetic outflow to the pancreas and the liver have been implicated in this regulation, as discussed below.

Central glucose detection has been primarily implicated in the pancreatic counter-regulatory response to hypoglycemia. Intracarotid glucose infusion activates sympathetic effector areas in the hypothalamus [48], blocks hypoglycemia-induced secretion of counter-regulatory hormones [16,59], and MBH 2-DG administration activates neurohumoral counter-regulatory responses [22]. Furthermore, central pharmacological inhibition of glucokinase, K_{ATP} channels, or AMPK, three intracellular effectors of hypothalamic glucose sensing, blunt hypoglycemia-induced counter-regulatory responses [54,70,122,124,161]. In addition, some data indicate that central fatty acid detection alters pancreatic insulin secretion through alteration of sympathetic nervous activity [38,45,118]. Thus, pancreatic endocrine function seems to emerge as a potential physiological effector of hypothalamic nutrient sensing in the regulation of glucose homeostasis, but supporting data are sparse and lack anatomical and neurochemical specificity. Central glucose detection by LH orexin A neurons has also been implicated in systemic hypoglycemia-induced activation of vagal efferent signalling to the pancreas [194], and 2-DG has been shown to activate AMPK activity specifically in the ARC, VMN and DMN [4], beginning to provide a characterization of the circuits involved in the regulation of pancreatic responses to hypoglycemia secondary to hypothalamic glucose sensing, but further studies are required to identify and characterize the relationships between hypothalamic nutrient sensing, autonomic outflow, and pancreatic function in the control of glucose homeostasis.

Central nutrient detection also modulates glucose homeostasis through its role in the regulation of hepatic glucose production. Hypothalamic autonomic output to the liver regulates circadian plasma glucose rhythm and the hepatic expression of glucose-metabolizing enzymes [29,83]. A link between hypothalamic nutrient sensing and hepatic glucose production was first suggested by studies showing that bidirectional changes in hypothalamic insulin signalling affect hepatic glucose production [141], through activation of PI3-kinase signalling, K_{ATP} channels and efferent vagal nerve outflow to the liver [150]. Conditional knock-out studies confirmed these conclusions and demonstrated that insulin action specifically in AgRP-expressing neurons plays a critical role in controlling hepatic glucose production [93]. Likewise, central leptin signalling modulates hepatic insulin sensitivity and glucose production [27,64]. Because hypothalamic insulin and leptin sensing involve detection mechanisms, intracellular effectors and neural circuits similar to those engaged during hypothalamic nutrient sensing, these data suggest a role for hypothalamic nutrient sensing in the regulation of hepatic glucose production. This suggestion is supported by data from studies showing that 3rd icv administration of glucose or oleic acid [99,140], as well as genetic or pharmacological manipulation of MBH nutrient sensors such as CPT1, MCD, p70 S6 kinase 1 [74,139,142,151], affect hepatic glucose production, and this effect requires the intact hepatic branch of the vagus nerve [98,100,152]. All these manipulations significantly affected the hypothalamic expression of AgRP and NPY, suggesting a role for melanocortin signalling in hypothalamic nutrient detection and the regulation of hepatic glucose output. The first direct support for this role comes from recent work of Parton et al., who showed that K_{ATP} channel-mediated glucose sensing in POMC neurons is required for glucose homeostasis. However, another study reported that

disruption of glucose sensing specifically in POMC or AgRP neurons through AMPK inactivation did not affect glucose tolerance or insulin sensitivity [36]. Thus, the role of melanocortin signalling in hypothalamic nutrient detection and the regulation glucose homeostasis remains unclear. Orexin A signalling has also been implicated in the regulation of hepatic glucose production, as 3rd icv orexin A administration or pharmacological activation of orexin A circuits stimulate hepatic glucose production and induce hyperglycemia, and these effects are blunted by hepatic sympathetic denervation [202]. However, the link to hypothalamic nutrient detection is not established. Interestingly, central nutrient overload has been suggested to impede hypothalamic nutrient sensing and thereby impair the hypothalamic regulation of hepatic glucose production [120,142,205]. These results support a role for deficient hypothalamic nutrient-sensing pathways in pathological situations associated with nutrient excess, such as obesity and diabetes, as a putative cause for metabolic dysfunction.

The role of hypothalamic nutrient detection in the regulation of hepatic glucose production requires further study, both to provide better anatomical and neurochemical characterization of circuits activated downstream from nutrient-sensing neurons, and to identify which circuits are required for the effect of centrally administered nutrients on hepatic glucose production. Significant controversy persists regarding the physiological role of such indirect regulation of hepatic function. Consequently, it is critical to assess the effects of hypothalamic nutrient detection on glucose homeostasis in physiological settings.

4.3. Hypothalamic nutrient sensing and the regulation of adipose tissue metabolism and energy expenditure

Hypothalamic nutrient sensing may also modulate adipose tissue function mainly via central melanocortinergic circuits. MC3R are primarily implicated in the negative feedback control of metabolism but not feeding [34], whereas MC4R activation determines both feeding behavior and energy expenditure [10,35]. MC3R have also been shown to be required for the expression of anticipatory patterns of activity and wakefulness during periods of limited food availability [180]. Both white (WAT) and brown (BAT) adipose tissues are innervated by the sympathetic nervous system [31,203] and MC4R mRNA is expressed in sympathetic outflow neurons to BAT and WAT [170,172]. Pharmacological or genetic disruption of MCR promotes lipid uptake, triglyceride synthesis, and fat accumulation in WAT [137]. Conversely, 3rd icv administration of a melanocortin agonist increases sympathetic drive to the WAT and BAT, plasma levels of lipolytic products, BAT thermogenesis, and decreases body fat mass in Siberian Hamsters [23]. Similarly, both 3rd icv and 4th icv administration of a melanocortin agonist increases oxygen consumption and BAT thermogenesis in conscious mice, and these effects are blunted by the inhibition of neurons in the rostral raphe pallidus, suggesting that neurons of this brainstem nucleus are a critical relay site in the melanocortinergic regulation of energy expenditure [55]. Interestingly, PVH-specific restoration of MC4R in MC4R-null mice normalizes food intake but does not restore normal energy expenditure [10], suggesting that: (1) the melanocortinergic control of energy expenditure relies on sites outside the PVN and (2) divergent MC4R populations mediate energy expenditure and food intake. Consistently, an intact PVH does not seem to be necessary for food deprivation-induced lipid mobilization [58], and chronic decerebration does not prevent the ability of 4th icv or parenchymal raphe administration of melanocortin receptor agonists to induce thermogenesis in rats [167]. Thus, forebrain melanocortin signalling and/or forebrain-brainstem communication are not required to produce thermogenic responses to central melanocortin agonists. However, the apparent neuroanatomical segregation of melanocortin receptor-expressing neurons important in the regulation of food intake and energy expenditure is challenged by recent observations that local microinjections of an MCR agonist into the PVH, NTS, as well as other sites that drive sympathetic outflow (rostral ventrolateral medulla, parabrachial nucleus and retrochiasmatic area) all induced hyperthermia, tachycardia, hyperactivity, anorexia and body weight loss [168]. Recent data, demonstrating some fat-pad specific patterns of WAT sympathetic drive across different lipid-mobilizing conditions, suggest some heterogeneity in the sympathetic outflow to WAT and BAT [24], but further studies are needed to fully characterize the role of sympathetic tone in the regulation of adipose tissue metabolism.

Other indirect data support a role for hypothalamic nutrient sensing in the regulation of adipose tissue metabolism and energy expenditure. Centrally administered leptin, a known activator of central melanocortin signalling that increases sympathetic neural outflow to several tissues [72,154,162], decreases WAT lipid storage, both through increasing lipolysis [181] and decreasing triglyceride synthesis [109]. More specifically, MBH leptin infusion has been shown to inhibit WAT lipogenesis through a mechanism requiring intact WAT sympathetic innervation [26]. Furthermore, both orexin and MCH receptive neurons have been implicated in the neural control of metabolism. LH orexin signalling is required for fasting-induced increased wakefulness and activity [198] and is involved in the sympathetic regulation of BAT thermogenesis [14]. Chronic 3rd icv MCH administration decreases body temperature and energy expenditure [65], and central MCH agonist administration affects fuel utilization [69].

Lastly, genetic manipulations of hypothalamic intracellular effectors support important linkages between hypothalamic nutrient sensing and the neural control of metabolism. Mice lacking AMPK in POMC neurons develop obesity through a decrease in energy expenditure [36], CPT1c knock-out mice exhibit decreased rates of fatty acid oxidation [192], and bidirectional genetic modulation of MBH p70 S6 kinase 1 activity is sufficient to produce complementary bidirectional changes in adaptive thermogenesis in rats, suggesting that this amino acid sensor regulates sympathetic tone [21]. However, no data directly support a role for hypothalamic nutrient detection in the regulation of adipose tissue function or energy expenditure. In fact, we recently found that MBH leucine administration failed to affect any contributor to energy expenditure in mice [20], in spite of the suggested role of hypothalamic amino acid sensor p70 S6 kinase 1 I the regulation of adaptative thermogenesis [21]. Thus, the links between hypothalamic nutrient sensing and adipose tissue metabolism/energy expenditure need to be more explicitly addressed.

5. Conclusions and future directions

This review of the current literature addressing the role of hypothalamic nutrient sensing in the regulation of energy balance underscores the need for more comprehensive and integrated studies linking hypothalamic nutrient sensors to forebrain/brainstem neuronal circuits that, in turn, drive physiological and behavioral effectors to determine energy homeostasis. Ideally, research designs should pair physiological, pharmacological and genetic manipulations with electrophysiological, behavioral and metabolic observations to develop physiologically relevant models that characterize neuronal circuits and identify specific effectors of energy homeostasis. It will also be important to assess the temporal relationships between hypothalamic nutrient sensing, intra- and extracellular events, and energetically relevant whole body consequences of such sensing, which remain mostly unknown. Adult onset loss- and gain-of-function assessments are preferred, in that they circumvent compensatory developmental changes

that preclude the understanding of the role of the targeted signalling pathway in developmentally normal animals. We have reviewed data suggesting that: (1) the nutrient-sensing properties of nutrient-sensing neurons are plastic, affected by the body's metabolic state and environmental factors such as the diet composition, (2) nutrient excess impairs hypothalamic nutrient sensing and (3) impaired hypothalamic nutrient-sensing pathways contribute to the onset of obesity and insulin resistance. Thus better characterization of the role of hypothalamic nutrient sensing in the onset of metabolic disorders is critical to identify new potential therapeutic targets, and to determine whether interfering with hypothalamic nutrient-sensing pathways could delay or prevent the onset of obesity or type 2 diabetes. In this regard, it will be important to evaluate hypothalamic nutrient sensing in polygenic models of diet-induced obesity and diabetes instead of lean rodents models or monogenic models of obesity.

Emerging properties of hypothalamic nutrient sensors should stimulate new interest, such as the role of fast-acting, small molecule neurotransmitters in the regulation of energy balance. Multiple hypothalamic neuronal subpopulations are GABAergic and glutamatergic [39,75] and a recent study reports that mice lacking the vesicular GABA transporter VGLUT2, required for glutamate synaptic release, specifically in SF1 neurons are hypoglycemic during fasting [182]. Likewise, mice bearing an AgRP-specific deletion of vesicular GABA transporter are lean, resistant to obesity and have an attenuated hyperphagic response to ghrelin [183]. Thus, GABA release from AgRP and SF1 neurons is important in regulating energy balance. Another underexplored area is the function of serotonin signalling in hypothalamic nutrient detection, while its participation in the in hypothalamic regulation of energy balance is supported by several observations [197]. Finally, the role of hypothalamic nutrient detection in the regulation of hypothalamic neurogenesis or neurodegeneration is unknown, although these processes have been implicated in the regulation of energy balance [90,91,158,195]. Progress in this field will be significantly advanced by extending future investigations to include the study of: (1) neuropeptide signals and circuits outside canonical melanocortinergic pathways, (2) putative nutrient-sensing sites outside the MBH, and (3) neuronal and non-neuronal metabolic processes potentially involved in nutrient sensing and the regulation of behavioral and physiological effectors of energy balance.

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