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Review

Integrative neurobiology of energy homeostasis-neurocircuits, signals and mediators

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ABSTRACT

Body weight is tightly controlled in a species-specific range from insects to vertebrates and organisms have developed a complex regulatory network in order to avoid either excessive weight gain or chronic weight loss. Energy homeostasis, a term comprising all processes that aim to maintain stability of the metabolic state, requires a constant communication of the different organs involved; i.e. adipose tissue, skeletal muscle, liver, pancreas and the central nervous system (CNS). A tight hormonal network ensures rapid communication to control initiation and cessation of eating, nutrient processing and partitioning of the available energy within different organs and metabolic pathways. Moreover, recent experiments indicate that many of these homeostatic signals modulate the neural circuitry of food reward and motivation. Disturbances in each individual system can affect the maintenance and regulation of the others, making the analysis of energy homeostasis and its dysregulation highly complex. Though this cross-talk has been intensively studied for many years now, we are far from a complete understanding of how energy balance is maintained and multiple key questions remain unanswered. This review summarizes some of the latest developments in the field and focuses on the effects of leptin, insulin, and nutrient-related signals in the central regulation of feeding behavior. The integrated view, how these signals interact and the definition of functional neurocircuits in control of energy homeostasis, will ultimately help to develop new therapeutic interventions within the current obesity epidemic.

1. Central regulation of energy homeostasis

Metabolic disorders such as obesity and diabetes are rising worldwide and represent a health threat with serious human and monetary consequences [178]. Opposite to what might be expected, obese individuals maintain homeostatic adaptative responses [108]. There is indeed growing evidence that obesity involves the defense of an elevated body weight rather than the absence of regulation [133,198]. In recent years, research on how the body senses the nutrient status and how it defends a set point of energy homeostasis has revealed the complex interaction of neuronal networks integrating homeostatic control mechanisms and hedonic stimuli.

The brain needs to constantly obtain information about the energy status of the periphery to promote the appropriate responses, both in long-term processes (body weight maintenance) and short-term decisions (meal initiation and meal size). Afferent signals that convey information about body fuel stores from the periphery to the CNS include hormones, such as insulin and leptin, as well as nutrient-related signals, such as glucose and free fatty acids. Signals arising from the periphery can be systematically divided into two categories, those that are produced in proportion to the amount of fat in the body (adiposity signals), and those generated during meals to cause satiation (satiety signals) [167,202]. Well-established examples for the first category are insulin and leptin, whereas cholecystokinin (CCK) is the prototypical example contributing to satiation (reviewed in [133,201]).

In times of food abundance and ample fat stores, signals are integrated in key brain areas to promote inhibition of food intake and hepatic glucose production, and to increase energy expenditure and fat stores. In contrast, nutrient deficiency signals transmitted to the CNS result in responses to promote feeding and mobilization of energy stores from adipose tissue and liver [170].

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2. Hypothalamic control of body weight and food intake

The role of the hypothalamus in the regulation of energy homeostasis has been known for as long as 70 years, when it was shown that lesions of the ventromedial hypothalamus lead to hyperphagia and obesity, while lesions of the lateral hypothalamus caused reduced food intake and leanness [5,75]. Later research in the field particularly focused on the mediobasal hypothalamus, and more specifically the arcuate nucleus (ARC), where two neuron populations exert potent effects on food intake, energy expenditure and glucose homeostasis. Agouti-related peptide/neuropeptide Y (AgRP/NPY)–coexpressing neurons act as orexigenic (promoting feeding and inhibiting energy expenditure), while pro-opiomelanocortin (POMC) and cocaine–amphetamine (CART)-coexpressing neurons promote anorexia (reducing food intake and increasing catabolic processes). The opposing effect of both neurons is in part mediated through the same effector neurons by exerting opposite effects on the same signaling mechanism. POMC is the precursor protein of many biologically active peptides. Among them, the melanocyte-stimulating hormones α and β (α- and β-MSH) act on the melanocortin receptors (MC3R and MC4R) to activate anorectic responses [20,54,107]. In contrast, AgRP is a MC3/4-R competitive antagonist of α-MSH and thereby reduces MSH signaling to promote food intake [142]. AgRP has also been proposed to act as an inverse agonist, modulating MC3/4-R independently of the presence of α-MSH, as shown by experiments both *in vitro* and *in vivo* [71,138,188]. Both POMC and AgRP neurons express leptin and insulin receptors and are targeted by the respective hormones to increase POMC mRNA expression and decrease NPY and AgRP mRNA levels [18,93,168,176]. Furthermore, both neuron populations express the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) [74,81] and AgRP neurons inhibit nearby POMC neurons through GABA release [44]. Recently, inactivation of the vesicular GABA transporter specifically in AgRP neurons showed that GABA signaling in this neuron population is necessary for the control of energy balance and that it functions by modulating energy expenditure, at least in part, through POMC inhibition [189].

The melanocortin system and the crucial role of AgRP/NPY and POMC neurons in the regulation of energy homeostasis are well established and their regulation pathways and biological effects have been intensively studied (Fig. 1). Nevertheless, although the basic regulatory principles of the melanocortin pathway have been recognized over the last years, the complexity of the system still yields unexpected results. Thus, in contrast to the predicted important role for NPY and AgRP in energy homeostasis, deletion of *Npy, Agrp* or both genes causes only mild effects in energy balance in mice [52,154]. To directly address the functional role of these neurons and to avoid compensatory effects, we and others selectively removed AgRP/NPY neurons by toxin-mediated ablation, resulting in an acute reduction of feeding when it was induced in adults, but not during the neonatal period [66,120]. POMC neuron removal in similar experiments also had an impact on energy balance and resulted in delayed hyperphagia, obesity and hypocorticolism [66]. Thus, careful interpretation of the results and the combination of different approaches and methodologies is required to unravel functional interactions of neurocircuits in energy homeostasis.

ARC neurons such as POMC and AgRP neurons provide an important first interface in the communication of peripheral organs and the CNS and thus have to be capable of responding to various food-related cues coming from the periphery. In addition to the ARC, other hypothalamic and extra-hypothalamic areas of the brain are now re-emerging or being newly identified as critical modulators of feeding behavior. We comment the main recent advances on these areas as a separate point at the end of this review.

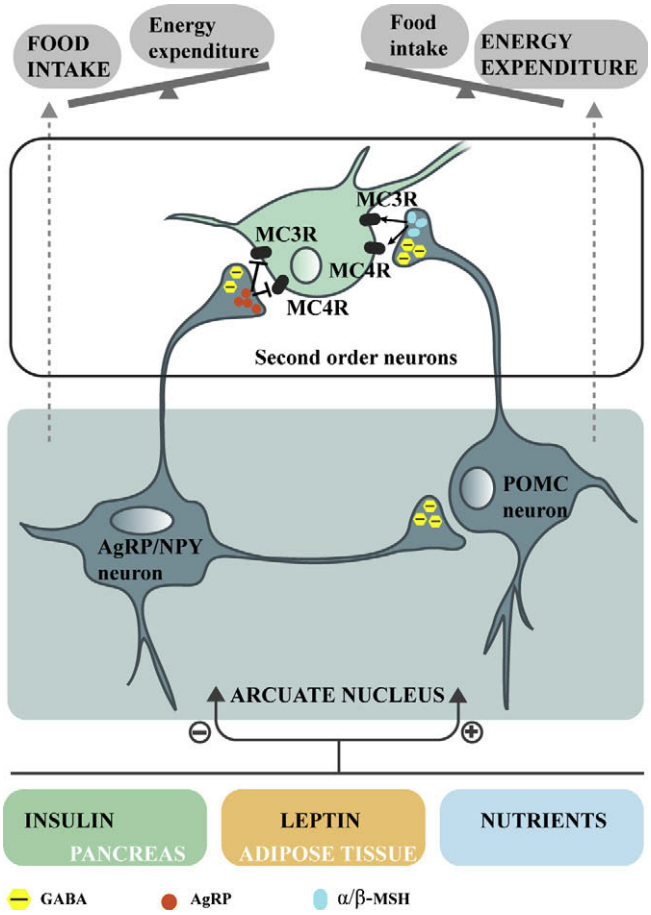

Fig. 1. Regulation of energy homeostasis by POMC and AgRP neurons through the melanocortin system. POMC and AgRP localize in the ARC, close to the blood brain barrier, where they have access to various humoral signals. Both neuron populations exert potent effects on energy balance mediated by their characteristic neuropeptides, which allow the modulation of second order neurons. α- and β-MSH act on the MC3R and MC4R to ultimately reduce food intake and increase energy expenditure. AgRP acts as a MC3R and MC4R antagonist and therefore promotes the opposite responses. GABAergic inhibition has been described from both POMC and AgRP neurons to effector neurons as well as from AgRP neurons to POMC neurons. Abbreviations; GABA: gamma-aminobutyric acid, AgRP: agouti-related peptide, α/β-MSH: alpha and beta melanocyte-stimulating hormone.

3. Insulin action in control of glucose homeostasis and body weight

The pancreatic hormone insulin, first identified in the 1920s, was soon established as a key regulator of glucose homeostasis, as well as a modulator of food intake [157]. Because of its size, insulin was long thought not to be able to cross the blood brain barrier and therefore considered to act exclusively in the periphery. However, careful analysis demonstrated that insulin levels in the brain are proportional to serum insulin concentrations [123,203]. Although insulin is not a major regulator of glucose use by the brain [169] its receptor is widely expressed in many brain areas [72,192], and neuronal insulin signaling is required both for glucose homeostasis and body weight control [32,94,150]. Thus, insulin-deficient mice are hyperphagic (although they are not obese because the absence of insulin promotes lipolysis in adipose tissue) [176] and administration of insulin directly to the brain reverses the phenotype. Moreover, administration of antibodies against insulin in the brain increases body weight and food intake [128,183] and inactivation of the insulin receptor in neurons results in mild diet-sensitive obesity [32].

3.1. Insulin signaling pathways

Upon insulin binding to its receptor (a membrane-bound tyrosine kinase), insulin receptor substrate (IRS) proteins are recruited and tyrosine phosphorylated. IRS proteins in turn activate the enzyme phosphatidylinositol-3-OH-kinase (PI3 K), which generates phosphatydylinositol-3,4,5-triphosphate (PIP3) from phosphatydylinositol-4,5-biphosphate (PIP2) [9]. Subsequently, PIP3 activates several enzymes: the 3-phosphoinositide dependent protein kinase 1 (PDK1), Akt (also known as protein kinase B), and members of the atypical PKC family [3,95,125]. Akt activation results in the phosphorylation of the forkhead-O transcription factor (FOXO), which is then released from the promoter of target genes to relocalize from the nucleus to the cytoplasm [21,31]. Regulation of FOXO activity by insulin affects transcription of neurotransmitters in a manner specific to each neuron-subpopulation, promoting POMC expression in POMC neurons and inhibiting AgRP expression in AgRP neurons [16,92].

Besides its FOXO-dependent transcriptional regulation of insulin target genes, PI3 K signaling can regulate cell excitability via stimulation of ATP-sensitive potassium (K_{ATP}) channels in the brain [14,121,174]. Spanswick et al. initially proposed a role for K_{ATP} channels in insulin signaling in unidentified neurons within the hypothalamus [180], and it has subsequently been shown that activation of PI3 K promotes POMC and AgRP hyperpolarization [99,151].

3.2. Central insulin action and hepatic glucose production

It is only recently that the effects of central insulin action in control of hepatic glucose production captured investigators interest, when it was observed that insulin signaling in the hypothalamus is essential for inhibition of hepatic glucose production (HGP) in rats [141]. Here, insulin action on hypothalamic K_{ATP} channels is necessary to decrease glucose-6-phosphate (G6P) and phosphoenolpyruvate carboxykinase (PEPCK) expression in the liver [153]. Furthermore, Inoue et al. demonstrated that insulin-mediated HGP suppression involves hepatic IL-6 production and the tyrosine phosphorylation of signal transducer and activator of transcription 3 (STAT3) in hepatocytes [86]. Concomitantly, we were able to demonstrate the pivotal role of insulin action on AgRP neurons in this context. Mice with a selective inactivation of the IR in AgRP neurons failed to efficiently suppress hepatic glucose production during euglycemic–hyperinsulinemic clamps [99]. Consistent with the finding of Inoue et al., these mice exhibited downregulation of IL-6 and increased expression of G6P in the liver, revealing a role for AgRP-neuron dependent control of autonomic, hepatic innervation, in the control of peripheral glucose metabolism [99,160].

3.3. Role of central insulin action in adipocyte function

Numerous studies performed through the use of conditional inactivation or selective expression of the insulin receptor in defined tissues and cell types have lead to a better understanding of the integration between peripheral and central insulin action. However, as exemplified by the studies of conventional NPY and AgRP-knockout mice, interpretation of results from gene inactivation can sometimes be affected by the continuous lack of signaling throughout development. Thus, to control for these potentially confounding effects, we recently created mice with an inducible IR deficiency either in the entire body (IR^{wb}) or restricted to peripheral tissues (but not to the brain) of adult mice (IR^{per}) [94]. Our findings showed that, although both models developed similar hyperinsulinemia, hyperglycemia was more affected in IR^{wb} mice. Intriguingly, inactivation of the insulin receptor in the whole body also resulted in a dramatic reduction of white adipose tissue (WAT) concomitant with a severe hypoleptinemia. Restoration of physiological leptin levels in IR^{wb} mice normalized glucose levels, indicating that leptin-evoked STAT3 signaling in the liver represents an important regulator of glucose homeostasis also in this model. Furthermore, when control mice were injected with insulin intracerebroventricularly, WAT mass, adipocyte size and lipoprotein lipase mRNA were significantly elevated. Thus, although direct effects of insulin in adipocytes are well known [98,105], these data unveil a new role for the central insulin action in the control of lipogenesis.

4. Central leptin action in control of glucose and energy homeostasis

The adipocyte-derived hormone leptin is secreted in direct proportion to the amount of stored body fat, meaning that increased fat and weight gain lead to increased circulating leptin concentrations, whereas fasting and leanness inhibit leptin secretion [41]. Animals lacking the hormone (*ob/ob* mice) or its receptor (*db/db* mice or Zucker, *fa/fa* rats) develop hyperphagia and extreme obesity. The obesity resulting from the lack of the hormone is reversed upon leptin administration [37,210]. However, the initial enthusiasm about the therapeutic potential for leptin rapidly declined after the observation that the vast majority of obese animal models, but more important also patients, present with resistance to leptin action [76]. The mechanism(s) underlying this phenomenon are not well understood and finding the causes of leptin resistance remains the focus of attention of many researchers. Interestingly, neuron-specific inactivation of the leptin receptor leads to obesity, and neuron-specific reconstitution of the leptin receptor is sufficient to reverse the obese phenotype of *db/db* mice, supporting the primary role of leptin signaling in the CNS [39,118]. Here, anorectic responses activated by central leptin action are mediated, at least in part, by the melanocortin system [171].

4.1. Leptin signal transduction

In light of leptin resistance underlying the development of obesity in the majority of patients, deciphering the molecular basis of leptin signaling and the mechanisms leading to its improvement represent an important, timely research focus. Six variants of the leptin receptor have been reported so far, although the longest variant (LRb) seems to be the sole true signaling mediator of leptin's effects in energy homeostasis [12]. Leptin receptors belong to the class I cytokine receptors and function through the JAK/STAT, PI3 K and mitogen-activated protein kinase signaling pathways [26]. Leptin binding to the LRb triggers the autophosphorylation of JAK2, which allows the recruitment and phosphorylation of the transcription factor STAT3 [15]. This, in turn, results in the dimerization and nuclear translocation of STAT3, where it binds to specific DNA elements to ultimately modulate target gene transcription. STAT3 binding to AgRP and POMC promoters increases POMC expression and inhibits AgRP expression and therefore promotes anorexia [13]. Furthermore, STAT3 regulates the expression of the suppressor of cytokine signaling (SOCS), which acts as a feedback inhibitor of the pathway [25]. Supporting the critical role for STAT3 in energy homeostasis, mice with either a panneuronal inactivation of STAT3 or with a mutated leptin receptor unable to bind STAT3 rapidly develop massive hyperphagia and obesity that resemble very much to that observed in *ob/ob* or *db/db* mice [13,62]. Nevertheless, the role of STAT3 within the ARC is not that clear, as its inactivation specifically in POMC neurons results only in a slight increase in body weight and altered refeeding responses [207], and mice lacking STAT3 in AgRP neurons have an unex-

pected phenotype of modest weight gain and increased adiposity [64]. Moreover, recent work using a mouse model for the conditional expression of a constitutively active STAT3 in AgRP neurons revealed a novel role for STAT3 in control of energy homeostasis. Here, activation of STAT3 in AgRP neurons resulted in leanness and resistance to diet-induced obesity due to an increased locomotor activity and subsequent increased energy expenditure, since no changes in either AgRP or POMC mRNA expression were observed and food intake did not differ from control mice [130]. These experiments are in line with previous results demonstrating that ARC-specific restoration of leptin receptor promotes locomotor activity [42]. Further defining the neurocircuits involving STAT3 signaling in AgRP neurons in the control locomotor activity may define novel targets for the treatment of positive energy balance.

4.2. PIP3 and K_{ATP} channel as common insulin- and leptin-regulated mediators of glucose and energy metabolism

Leptin can also activate PI3 K through JAK2-mediated tyrosine phosphorylation of IRS proteins, which was first proposed to be a point of convergence for the integration of insulin and leptin signaling [139,140]. However, this is the case only in POMC neurons, where both hormones increase PI3 K signaling [151]. In AgRP neurons, on the contrary, insulin activates PI3 K whereas leptin inhibits it, presumably via presynaptic action [206]. Moreover, the modulation of the electrical activity of these neuron populations also differs between the two hormones. Thus, while insulin hyperpolarizes and silences both POMC and AgRP neurons, leptin depolarizes POMC neurons to increase their firing rate, and hyperpolarizes AgRP neurons to inhibit their electrical activity [44,99,151]. Through the analysis of mice with POMC-neuron restricted overactivation of PIP3 formation and the loss of PDK1 specifically in POMC neurons, we have recently proposed a mechanistic model for the differential modulation of POMC electrical activity via insulin and leptin [16,151] (Fig. 2). Finally, a new perspective for the leptin responses in these hypothalamic populations has been provided by the observation that leptin directly inhibits L-type calcium currents in AgRP neurons through the MAPK signaling, but evokes them in POMC neurons via PI3 K signaling [194].

4.3. Role for central leptin in hepatic glucose production and adipose tissue function

It is well known that leptin action improves insulin sensitivity and regulates glucose homeostasis both via its effects in the CNS and the periphery [42,134,158]. As reported for insulin, leptin's central action also has an impact on hepatic glucose flux, but both hormones likely display different characteristics in such regulation. Although insulin action in the hypothalamus strongly affects glucose homeostasis in the periphery and liver by different means, central administration of leptin does not affect overall hepatic glucose production or blood glucose concentrations, but instead induces a shift in hepatic glucose fluxes by increasing gluconeogenesis and decreasing glycogenolysis [113]. The mechanisms involved are still unknown but it has been proposed that leptin's effects on gluconeogenesis are melanocortin-dependent, whereas changes in glycogenolysis are melanocortin-independent [67]. However, more recent studies on leptin signaling in the mediobasal hypothalamus in a model of induced STAT3 inactivation resulted in a strong reduction of gluconeogenesis after icv injection of leptin that was dependent on STAT3 activation [34]. Further investigations will have to define the overall physiological relevance of central leptin action on peripheral glucose metabolism as well as to identify the leptin-targeted neurons mediating these effects.

In addition to its effects on hepatic glucose homeostasis, we and others have recently shown that central leptin action also affects adipose tissue. We inactivated the PIP3 phosphatase Pten exclusively in leptin receptor-expressing neurons of the CNS and observed that increased PIP3 formation in these neurons results in reduced adiposity and increased energy expenditure due to a partial transdifferentiation of the white adipose tissue (WAT) into brown adipose tissue (BAT) [152]. Moreover, our data also indicate that this phenotype arises from enhanced leptin-stimulated sympathetic nerve activity (SNA). These findings are in line with pharmacological experiments demonstrating leptin-stimulated SNA and BAT-like remodeling of WAT [40], and provide direct evidence connecting leptin impact on PI3 K signaling in the CNS and WAT transdifferentiation. More recently, another group has pointed out to the role of central leptin action in the suppression of WAT lipogenesis mediated by PI3 K, SNA, and the endocannabinoid tone, providing interesting new possibilities for future research on central leptin signaling [33].

5. Synaptic plasticity

Aside from the cell-autonomous regulation of ion channels and their modulation by hormones such as leptin and insulin, feeding circuitries within the hypothalamus can also be regulated by local excitatory and inhibitory synapses, which are modulated according to nutritional states. As an example, fasting increases inhibitory synapses and decreases excitatory inputs on POMC neurons whereas it has the opposite effect on AgRP neurons. Interestingly, leptin-deficient mice present a similar synaptic remodeling [149]. Evidences for the impact of various key metabolic hormones on synaptic plasticity are increasing quickly and involve not only the ARC, but also other hypothalamic and extra-hypothalamic areas, such as the ventral tegmental area (VTA) and the hipoccampus (reviewed in [60,65]). Moreover, some neuronal growth factors such as the ciliary neurotrophic factor (CNTF) and the brain-derived neurotrophic factor (BDNF) also exert dramatic effects on energy homeostasis, and both have been proposed to engage leptin-related pathways [27,88,96,205]. A better understanding of how metabolic and neuronal signals interact with each other should help to prevent not only metabolic diseases, but also a wide range of other neurological alterations associated with diet and nutrient-related factors.

6. Nutrient sensing in the hypothalamus

In addition to hormones, the brain also directly responds to nutrients, such as glucose, fatty acid and amino acids and there is growing evidence that these signals inform the CNS about the energy status to induce profound changes in feeding behavior and energy balance.

6.1. Brain glucose sensing

The importance of central glucose sensing in the regulation of body weight and food intake was proposed more than 50 years ago [126], but the consequences of its alterations have only been subject of study in recent years, and the multiple aspects of glucose metabolism make its analysis extremely complex (reviewed in [111,187]). Two different glucose-responsive neurons have been described within the hypothalamus depending on the effect of altered glucose concentration: glucose-excited (GE) neurons, which increase their firing rate after elevation of glucose concentration and are abundant in the lateral hypothalamus (LH), and glucose-inhibited (GI) neurons, activated by low glucose concentration, which are more abundant in the ventromedial hypothalamus

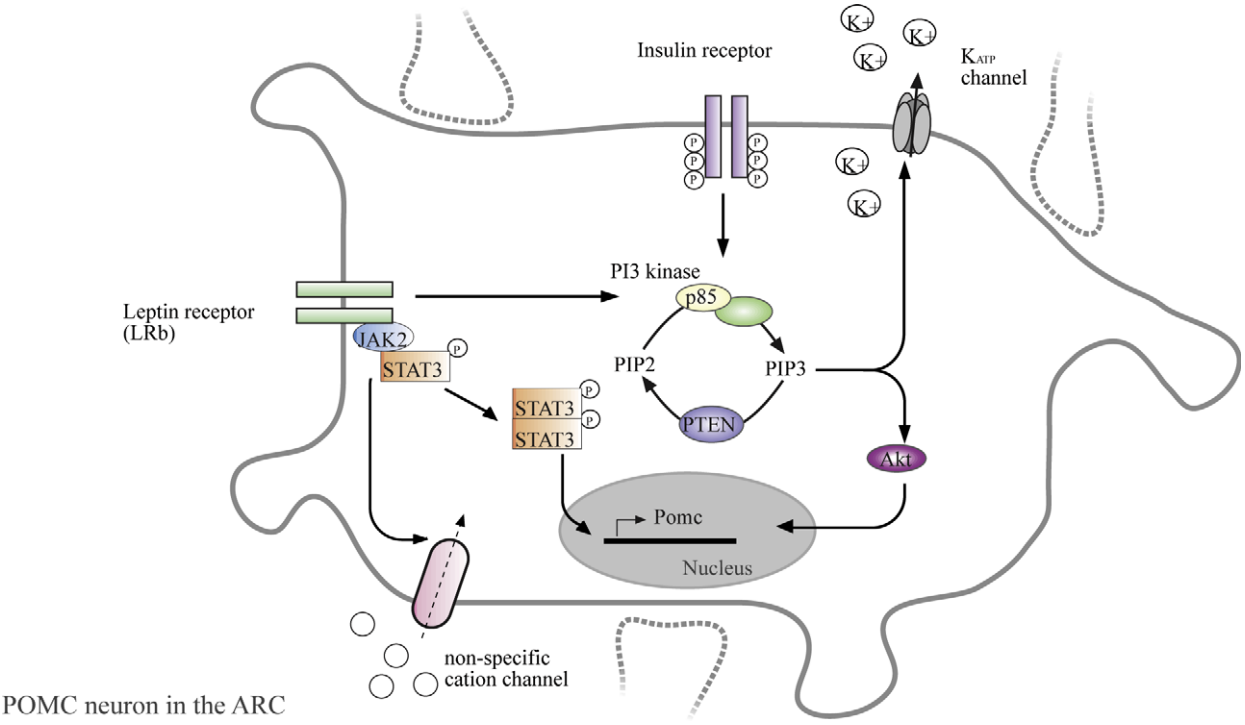

Fig. 2. Mechanisms of insulin and leptin action on POMC neurons in the hypothalamus. Insulin-mediated activation of PI3 kinase (p85: regulatory subunit; p110: catalytic subunit) generates PIP3. PIP3 activates ATP-sensitive potassium (K_{ATP}) channels, thereby producing an outward flow of K^+ ions. Activation of the leptin receptor (LRb) produces relatively weak stimulation of PI3 kinase via IRS proteins but strong STAT3 phosphorylation via activation of JAK2. Furthermore, leptin causes depolarization and increased firing in POMC neurons, most likely via the modulation of non-specific cation channels. Abbreviations: α-MSH: alpha melanocyte-stimulating hormone; Akt: protein kinase B; ARC: arcuate nucleus; JAK2: janus kinase 2; PIP2: phosphatidylinositol 3,4-diphosphate; POMC: proopiomelanocortin; PTEN: phosphatase and tensin homolog; STAT3: signal transducer and activator of transcription 3.

(VMH) [143]. In the ARC, POMC neurons act as GE and AgRP neurons as GI [84,135]. According to the predicted role for K_{ATP} channels in brain 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, while its genetic deletion or pharmacological inhibition reverse the phenotype [146]. In addition, several studies indicate a critical role in brain glucose sensing for glucose transporter 2 (GLUT) and the enzyme glucokinase (GCK), which are expressed in many neuron types (reviewed in [187]). Finally, high glucose levels can reduce the AMP-activated protein kinase (AMPK) activity in both POMC and AgRP neurons to modulate energy homeostasis independently of insulin and leptin signaling [38].

6.2. Hypothalamic sensing of fatty acids

The brain does not use fatty acids as a major fuel source but instead it derives most of its ATP from the oxidation of glucose in the fed state [179]. Inspite of this, levels of fatty acids and, more specifically, of long-chain fatty acids (LCFA) in the brain are intimately involved in energy homeostasis. It was initially shown that central administration of oleic acid reduces food intake and body weight and there is now growing evidence that fatty acid metabolism within distinct hypothalamic regions can function as a sensor for nutrient availability [102,116,117].

Plasma LCFAs are mostly bound to albumin and cross the blood–brain barrier mainly by simple diffusion in the unbound state, so that access of circulating free fatty acids to the CNS is proportional to the plasma concentration of fatty acids [131,156]. Upon entry into the cell, LCFA are rapidly esterified to fatty acyl-coenzyme A (LCFA-CoAs) in a process catalyzed by the enzyme acyl-CoA synthetase (ACS). The transfer of LCFA-CoA to the mitochondria, where they undergo β oxidation, requires the carnitine palmytoyl transferase (CPT1) family of proteins. Under physiological conditions, cellular fat oxidation is regulated by the availability of malonyl-CoA, a potent inhibitor of CPT1 activity. The formation of malonyl-CoA from acetyl-CoA is catalyzed by the enzyme acetyl-CoA carboxylase (ACC), which is inhibited by AMPK-mediated phosphorylation. In addition to its role as a CPT1 inhibitor, malonyl-CoA is the substrate for the enzyme fatty acid synthase (FAS), which generates newly synthesized LCFAs destined for lipid biosynthesis. Pharmacological and genetic evidence have demonstrated that altered levels and activities of many of the enzymes involved in these pathways modulate feeding (reviewed in [102,116]; Fig. 3). The current model proposes that signals leading to the accumulation of malonyl-CoA serve to communicate nutrient excess, thereby promoting reduction of food intake and glucose production [103]. Accordingly, glucose injection and refeeding increase malonyl-CoA concentrations, whereas fasting produces the opposite effect. Since many key metabolic hormones affect the hypothalamic sensing of fatty acids, its integrative role for different homeostatic signals could be of extreme importance [61,115,199]. Nevertheless, the mechanisms that act after malonyl-CoA accumulation in the hypothalamus remain controversial. Although it has been proposed that fatty acid transport into the mitochondria is a critical step in the regulation of fatty acid metabolism, Wolfgang et al. recently described that even though the brain-specific isoform of CPT1 (CPT1c) binds malonyl-CoA, it lacks the carnitine acyltransferase activity necessary to mediate fatty acid transport [200]. Nevertheless, these researchers only investigated the mitochondrial fraction, while others place CPT1c mainly in the endoplasmic reticulum, where it seems to retain its catalytic activity [175]. Moreover, the effects of increased fatty acid levels

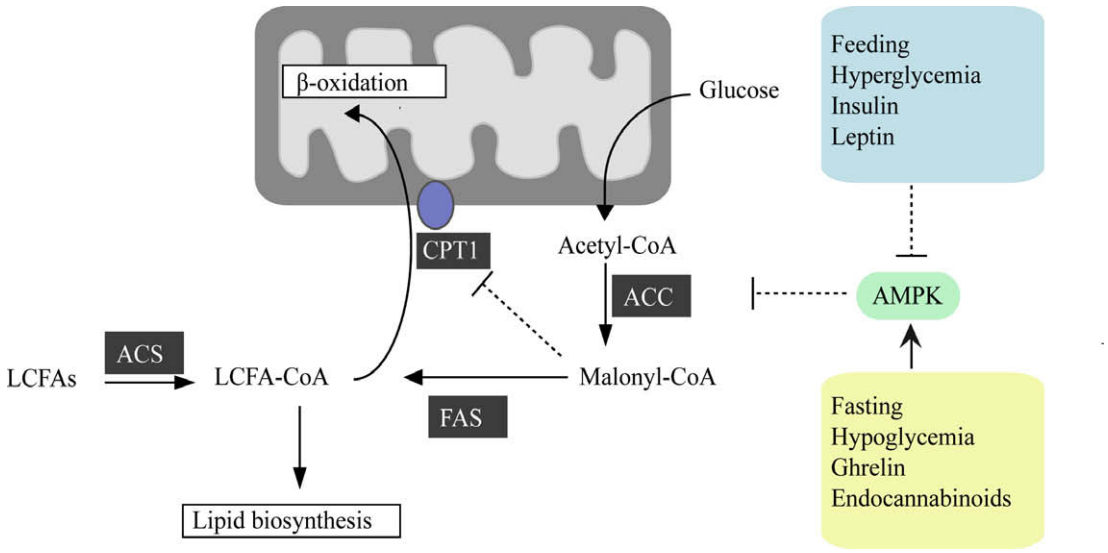

Fig. 3. Hypothalamic sensing of fatty acids. Many hormones and other homeostatic signals can modulate fatty acid metabolism in the hypothalamus as part of their signaling mechanisms to affect energy balance. One of the identified critical steps is the accumulation of malonyl-CoA, which promotes anoretic responses. LCFA: long-chain fatty acid, ACS: acyl-CoA synthase, CPT1: carnitine palmytoyl transferase FAS: fatty acid synthase ACC: acetyl-CoA carboxylase, AMPK: AMP-activated protein kinase.

differ from one hypothalamic region to another and seem to be highly diet-sensitive, as shown by the fact that high fat diet blunts the observed homeostatic responses.

6.3. Sensing fuel levels by AMPK and mTOR

Until now, two fuel-sensing protein kinases functioning as main regulators of body weight and food intake in the hypothalamus have been identified. On one hand, AMPK is activated by ATP depletion, nutrient and hormonal signals generated under energy deficiency conditions and it modulates peripheral responses to restore energy homeostasis (for an extense review we refer to [100,208]). As mentioned earlier, AMPK is a key modulator of fatty acid metabolism and therefore, of malonyl-CoA levels.

On the other hand, the serine–threonine kinase mammalian target of rapamycin (mTOR) is activated by states of positive energy balance, particularly increases in ATP. mTOR has a critical role in the regulation of protein synthesis and cell growth, two processes highly sensitive to nutrient availability. mTOR activity is regulated by hormones and nutrients, particularly branched-chain aminoacids (BCAAs), like L-Leucine [204]. Both protein kinases are expressed in POMC and AgRP neurons in the ARC, where they respond to insulin, leptin and nutrient levels and exert potent effects on feeding and energy balance [43,132]. Furthermore, AMPK activation leads to inhibition of mTOR signaling. The particularities in their signaling cascades and the complementary sensitivity of these kinases to the AMP/ATP ratio and fuel status thus suggest that AMPK and mTOR constitute a robust mechanism for the integration of numerous metabolic signals.

6.4. Role for ROS/mitochondrial respiration in hypothalamic nutrient sensing

Since the products resulting from glucose and fatty acid metabolism enter as a final step the electron transport chain as a final step to generate ATP, it is reasonable to consider that reactive oxygen species (ROS) production, which are naturally produced during mitochondrial respiration, could affect nutrient sensing by the brain. Mostly studied in the context of oxidative stress and its pathological consequences, the implication of ROS under a physiological conditions in different signaling pathways has been unveiled only of late and an increasing number of studies suggest a role for ROS in neuronal function [7,8,59,161]. Even more interesting from a metabolic point of view is the very recently proposed role for ROS signaling in lipid and glucose sensing by the hypothalamus [17,109]. More recently, ROS production has been involved in hypothalamic control of energy homeostasis by the gut-derived hormone ghrelin in AgRP/NPY neurons. The proposed mechanism involves ghrelin-mediated AMPK activation followed by ACC inhibition and consequent CPT1 activation. LCFA-CoA transported into the mitochondria then undergoes β-oxidation and ROS levels increase as a result of mitochondrial respiration, which in turn leads to upregulation of UCP2. UCP2 presumably acts to reduce ROS concentration, thus allowing the long-term maintenance of the signaling pathway. Interestingly, both ROS concentration and UCP2 interact to modulate ghrelin's effects, since $ucp2^{-/-}$ mice fail to manifest mitochondrial changes, upregulate AgRP expression or activate AgRP neurons upon ghrelin administration and this effect can be reversed by antioxidant administration [6,80]. The investigators also observed that POMC neurons maintain constantly high ROS levels to favor satiety, whereas AgRP neurons seem to buffer their production for regulatory purposes while promoting orexigenic responses. Nevertheless, other studies done in the periphery argue against this mechanism [80,104]. Since accurate ROS analysis critically depends on appropriate detection (and quantification) methods [68,196], involvement of ROS in regulation of energy homeostasis in the CNS, although extremely interesting, needs to be carefully addressed and investigated, partially awaiting novel approaches to directly modulate and monitor ROS function.

7. Regulation of energy homeostasis beyond the ARC

7.1. Ventromedial hypothalamus

The early finding that electrolytic lesions of the ventromedial hypothalamus (VMH) result in hyperphagia and obesity led to the designation of the VMH as the brain's "satiety center" [30,75]. Chemical lesions and pharmacological studies further supported the hypothesis that the VMH plays a primary role in feeding behavior [10,186]. Both insulin and leptin receptors are expressed in the VMH [51,72,129] and recent studies have indicated an important role for VMH neurons in mediating leptin's effect on

energy control [23]. While animals with a selective leptin receptor knockout in POMC neurons display only mild obesity and unaltered food intake [11], selective deletion of the leptin receptor in neurons expressing steroidogenic factor-1 (SF-1) in the VMH results in obese and hyperphagic mice [47]. SF-1 is an orphan member of the nuclear hormone receptor family, involved in the development and function of the endocrine system [101]. Thus, SF-1 knockout mice are obese and lack gonads and adrenal glands and have impaired function of pituitary gonadotropes [85,119,122,145]. Moreover, SF-1 is an important transcription factor for the development of the VMH, as SF-1 knockout mice show marked alterations in the VMH structure [173]. Notably, mice lacking the leptin receptor on both SF-1 and POMC neurons have a body weight phenotype that is approximately the sum of that observed with loss of the leptin receptor in either set of neurons alone, suggesting that the role of the VMH in mediating an antiobesity effect is independent of the ARC [47] .

Microlesion studies demonstrated afferent projections from the ARC to the VMH [209] and VMH neurons express MC4R, as well as NPY Y1, Y2, and Y5 receptors, further supporting that POMC and NPY arcuate neurons project to the VMH [29,70,114]. NPY administration in the VMH results in increased feeding [29], and responsiveness of VMH neurons to α-MSH is decreased in food-deprived rats or rats treated with AgRP [112]. On the other hand, by using laser-scanning photostimulation, Sternson et al. found that POMC neurons receive a strong excitatory input from the medial VMH that is diminished by fasting [181].

The anorexigenic neuropeptide BDNF is expressed at high levels in the VMH, where its expression is regulated by nutritional state and by MC4R signaling [205]. Furthermore, mice expressing lower levels of the BDNF receptor TrkB develop hyperphagia and excessive weight gain on a high fat diet [205]. Finally, leptin administration induced BDNF expression in the VMH [97], suggesting a role for BDNF in leptin signaling.

The VMH contains both glucose-excited and glucose-inhibited neurons [111,160]. Consistent with this, studies by Tong et al. demonstrated a role for glutamatergic neurons in the VMH in the counter-regulatory response to insulin-induced hypoglycemia. Mice lacking the glutamate synaptic vesicular transporter VGLUT, which is required for synaptic release of glutamate, specifically in SF-1 neurons exhibited increased body weight and a defective counter-regulatory response to hypoglycemia [190]. Thus, glutamate release from VMH neurons is an essential component in this system. Furthermore, recent studies indicated a role for AMPK within the VMH in the detection of acute hypoglycemia and initiation of the glucose counter-regulatory response [127].

7.2. Lateral Hypothalamus

Based on initial findings that experimental destruction of the LH is followed by reduced feeding, drinking and body weight [4,5,45,185], the LH has long been considered to be involved in control of feeding behavior [19]. Subsequently, electrical stimulation studies in the LH demonstrated an induction of food intake [45]. Furthermore, activity of neurons in the LH region is regulated during natural feeding behavior [91] as well as during hypo- and hyper-glycemia [77]. Two subsets of neurons have been identified in the LH: one group expressing the neuropeptide orexin/hypocretin [106,163] and the other expressing the neuropeptide melanin-concentrating hormone (MCH) [24,177]. Both act as orexigenic peptides that stimulate feeding after icv injection [159,163]. Mice lacking either the peptide or its key receptors display altered metabolic alterations [124,164,172,195]. Both neuron populations are connected with POMC and NPY neurons of the ARC, indicating a possible regulatory interaction with the melanocortin system [49,50,82,155,163,191]. Orexin mRNA levels increase by fasting and hypoglycemia [163] and orexin expressing neurons are rapidly activated by fasting [48]. MCH mRNA levels increase upon fasting and expression levels are elevated in obese mutants [155].

Furthermore, recent research highlighted a role for the LH in connecting the basic homeostatic with higher brain functions [28,69,73,182]. Overriding of the homeostatic control systems by the cognitive, rewarding, social and emotional aspects of palatable food is thought to play a major role in the regulation of food intake. Consistent with a role for the LH in this system, LH neurons project to reward-associated brain regions, including the nucleus accumbens (NAc) and ventral tegmental area (VTA) [53,148].

7.3. Food reward and the midbrain dopamine system

Dopaminergic neurons are located in their majority in the ventroanterior midbrain (VTA and substantia nigra), with projections to the dorsal striatum (caudate nucleus and putamen), the ventral striatum with the NAc and areas of the neocortex (mainly the prefrontal cortex), the hippocampus, and the amygdala. Projections from the VTA to the NAc are well characterized regarding their role in drug addiction and the rewarding aspects of food and sex [90,197]. Dopamine is involved in movement, goal-directed behavior, cognition, attention and reward, and the essential role of intact dopaminergic signaling for maintenance of normal feeding behavior has been demonstrated in mice with selective inactivation of the tyrosine hydroxylase gene, the rate-limiting enzyme in dopamine biosynthesis. These mice become hypophagic and die of starvation at 3–4 weeks of age [211]. Moreover, they fail to eat in response to acute glucoprivation, central administered peptide YY (PYY) [78], or leptin deficiency [184].

Food and water are naturally rewarding and motivating substances that activate dopamine neurons and thereby facilitate goal-directed behavior, which results in the adquisition of food and water [137,144,165,166]. Accordingly, the brain regions activated by a food reward stimulus (e.g. highly palatable food, sucrose pellets) are the same regions responsive to drugs of abuse and involved in the development of drug addiction [83,136]. Moreover, dysregulation of neuronal circuits implicated in drug reward is known to be involved in the development of obesity. Along this line, dopamine D2 receptor availability is decreased in obese individuals in proportion to their body mass index [193] and treatment of leptin-deficient mice with dopamine D1/D2 receptor agonists normalizes the phenotype of hyperphagia, body weight gain, hyperglycemia and hyperlipidemia [22]. Notably, chronic food restriction and maintenance of low body weight increase the self-administration and motor-activating effects of abused drugs [35,36,46]. Consistently, performance of an animal in tasks with food as a rewarding substance is enhanced by food restriction or deprivation, states in which insulin and leptin levels are low [2,89,110,162].

In the last years substantial evidence has emerged, that peripheral hormonal signals such as insulin and leptin are able to modulate the reward system of the brain (Fig. 4). Both insulin and leptin icv administration has been tested in different behavioral paradigms evaluating aspects of rewarding or motivation. These studies indicate that both insulin and leptin are involved in different aspects of food reward: hedonics, place preference, and the motivation to work for a reward [56]. Indeed, both insulin and leptin receptors, as assessed by double-labeling fluorescence immunohistochemistry, are co-expressed with tyrosine hydroxylase – a marker for dopamine neurons – in the VTA and substantia nigra [55]. Furthermore, insulin and leptin administration into the VTA results in an increased formation of PIP3, the product of the PI3 K, which serves as an indicator for a functional signaling pathway [56]. Moreover, leptin receptor mRNA is expressed in the VTA and in response to peripheral, icv or direct VTA leptin injection, the intracel-

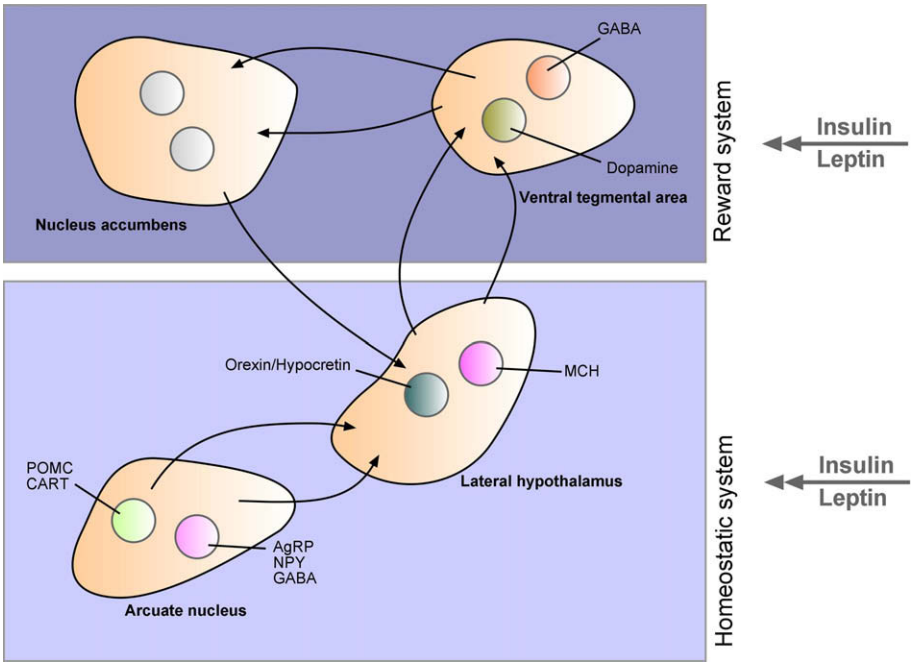

Fig. 4. Integration of neuronal pathways involved in reward and regulation of energy balance. The well-described homeostatic system of the brain consists of POMC/CART-expressing and AgRP/NPY/GABA-expressing neurons in the arcuate nucleus and their projections to second order neurons, e.g. in the lateral hypothalamus. Orexin/Hypocretin and melanin-concentrating hormone (MCH) are neuropeptides secreted by distinct neuronal populations in the lateral hypothalamus. These neurons project to many brain regions (including the ventral tegmental area), and therefore connect the homeostatic with the reward system of the brain. The reward pathway includes dopaminergic neurons in the ventral tegmental area that project to the nucleus accumbens. The VTA also contains GABAergic cells that project to the nucleus accumbens as well. Additionally to their well-known effects on the homeostatic system of the brain, recent studies indicate that insulin and leptin can directly act on the reward system of the brain. Abbreviations: AgRP: agouti-related peptide CART: cocaine and amphetamine related transcript GABA: gamma-aminobutyric acid; MCH: melanin-concentrating hormone; NPY: neuropeptide Y; POMC: proopiomelanocortin.

lular JAK-STAT pathway becomes activated [58,79]. These findings indicate that the respective signaling pathways are indeed activated in dopaminergic cells and further substantiate a role for insulin and leptin in the reward system. Consistent with this, the activation of the JAK-STAT pathway in the VTA mediates leptin's effect on food intake [79]. Moreover, electrophysiology studies revealed that leptin significantly reduces the firing rate of dopaminergic neurons in the VTA [79].

One potential target of insulin action in dopaminergic cells is the dopamine transporter, which mediates extracellular dopamine uptake from the synapses [87]. Insulin signaling through the PI3 K and Akt has been shown to promote cell-surface expression of the DAT *in vitro* [63]. Thus, chronic insulin icv treatment increases DAT mRNA expression in the VTA/substantia nigra, and food deprivation decreases expression and activity of the DAT [57,147]. Other studies have shown that other metabolically important factors, such as the gut hormone ghrelin, also target the VTA and regulate neuronal activity, synapse formation, and dopamine turnover in the NAc [1].

8. Concluding remarks

Many of the historical efforts aiming to define principles controlling energy homeostasis have tried to identify a master regulatory mechanism underlying normal energy balance. Thus, research and scientific debate have focused on theoretically confronting positions: i.e. nutrient sensing (lipostatic vs. glucostatic theories), neuronal regions involved in energy homeostasis (hypothalamus vs. other brain areas), valuation of food as fuel rather than reward (homeostatic vs. hedonic stimuli) and relevance of central vs. peripheral regulation. It is now clear that not one of the positions suffices to explain the regulation of energy homeostasis nor offers an isolated target for the treatment of obesity but rather that all signals contribute to the comprehensiveness of the system. Although this complexity might be perceived as discouraging from a therapeutic point of view, the identification of key integrative sites of functional neurocircuits where all these different signals are integrated should provide unique, putative therapeutic targets.

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