Hypothalamic Lipids and the Regulation of Energy Homeostasis

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Key Words
AMP-activated protein kinase · Acetyl-CoA carboxylase · Fatty acid synthase · Food intake · Hypothalamus · Lipid sensing

Summary
The hypothalamus is a specialised area in the brain that integrates the control of energy homeostasis, regulating both food intake and energy expenditure. The classical theory for hypothalamic feeding control is mainly based on the relationship between peripheral signals and neurotransmitters/neuromodulators in the central nervous system. Thus, hypothalamic neurons respond to peripheral signals, such as hormones and nutrients, by modifying the synthesis of neuropeptides. Despite the well-established role of these hypothalamic networks, increasing evidence indicates that the modulation of lipid metabolism in the hypothalamus plays a critical role in feeding control. In fact, the pharmacologic and genetic targeting of key enzymes from these pathways, such as AMP-activated protein kinase, acetyl-CoA carboxylase, carnitine palmitoyltransferase 1, fatty acid synthase, and malonyl-CoA decarboxylase, has a profound effect on food intake and body weight. Here, we review what is currently known about the relationship between hypothalamic lipid metabolism and whole body energy homeostasis. Defining these novel mechanisms may offer new therapeutic targets for the treatment of obesity and its associated pathologies.

Introduction
Obesity is characterised by excess fat accumulation in the adipose tissue, which causes adverse health problems [1–4]. Currently, the degree of obesity and its related disorders are increasing at a pandemic rate. For this reason, much research effort is concentrated on recognising the molecular mechanisms governing energy balance and food intake.

The central nervous system (CNS) senses the sensory experience of eating as well as the process of ingestion, absorption, metabolism and energy storage. The original theories describing the central control of food intake were based on a ‘Dual Centre Hypothesis’ [5, 6]. In this model, originated from hypothalamic lesioning experiments, feeding was controlled by 2 main hypothalamic areas: the lateral hypothalamic area (LHA) representing the ‘feeding centres’ as opposed to the ventromedial hypothalamic nucleus (VMH) embodying the ‘satiety centres’. Lesions of the LHA reduced food intake and eventually lead to starvation and death. Contrarily, lesions of the VMH resulted in obesity. In spite of our increasing understanding of the hypothalamic regulation of feeding, the main idea remains indisputable, i.e. that anatomically defined hypothalamic areas regulate food intake. These hypothalamic nuclei form interconnected neuronal circuits which react to changes in energy status by altering the expression of specific neuropeptides, resulting in changes in energy intake and expenditure [7–10]. Among them, the arcuate nucleus of the hypothalamus (ARC) is considered as the ‘master hypothalamic centre’ for food intake control. Two distinct neuronal populations in the ARC integrate peripheral nutritional/feeding signals. One set of neurons expresses the orexigenic (feeding-promoting) neuropeptides agouti-related protein (AgRP) and neuropeptide Y (NPY). These neurons project and modulate downstream ‘second order’ neurons located in other hypothalamic nuclei, such as the paraventricular nucleus (PVH).
A second set of ARC neurons expresses the anorexigenic (feeding inhibitors) products of proopiomelanocortin (POMC), the precursor of alpha-melanocyte-stimulating hormone (α-MSH), and the cocaine and amphetamine-regulated transcript (CART). This population of neurons projects more broadly within the CNS, to secondary hypothalamic nuclei such as the dorsomedial nucleus (DMH), the LHA, and the perifornical area (PFA), in addition to the PVH. Dorsal to the ARC lays the VMH which receives projections from AgRP/POMC neurons in the ARC [12–18]. Additionally, the VMH neurons project their axons to the ARC, DMH, LHA as well as brain-stem regions, such as the nucleus of the solitary tract (NTS). Hypothalamic neurons respond to peripheral signals, such as glucose, leptin, ghrelin, adiponectin (Adpn), resistin (RSTN), and insulin, by modifying the expression of key neuropeptides, especially in the ARC but also in other nuclei such as PVH and LHA [7–10, 19–27]. When energy intake exceeds expenditure, the expression of orexigenic neuropeptides, such as AgRP and NPY diminishes, whereas the expression of anorexigenic neuropeptides, such as CART and POMC, rises. Opposite changes occur when energy expenditure exceeds intake [7–10]. Besides the ARC, LHA, and PVH current, evidence has identified the VMH as a key nucleus integrating peripheral signals, such as ghrelin [28, 29] and RSTN [27].

During the last 8 years, a bulk of data has demonstrated that in addition to nutrients, hormones, and neuropeptides, basic cellular metabolic pathways play a major role in the regulation of whole body energy homeostasis. The present review summarises the current knowledge about hypothalamic lipid metabolism and energy homeostasis.

**Fatty Acid Metabolism Pathway**

Fatty acids are derived either from the diet or by de novo synthesis. The basic pathway for de novo fatty acid synthesis is summarised in figure 1 [30–32]. The de novo fatty acid biosynthesis pathway comprises 3 key enzymes, acetyl-CoA carboxylase (ACC; EC 6.4.1.2), fatty acid synthase (FAS; EC 2.3.1.85), and malonyl-CoA decarboxylase (MCD; EC 4.1.1.9). ACC catalyses the carboxylation of acetyl-CoA to malonyl-CoA in an ATP-dependent manner. The synthesis step of malonyl-CoA is reversibly regulated by MCD that converts malonyl-CoA back to acetyl-CoA. Both acetyl-CoA and malonyl-CoA are then used as the substrates for the production of palmitate catalysed by fatty acid synthase (FAS). Malonyl-CoA decarboxylase (MCD) converts malonyl-CoA back to acetyl-CoA. Carnitine palmitoyltransferase 1 (CPT1) is the enzyme importing long-chain fatty acyl-CoA into mitochondria for β-oxidation; CPT1 activity is allosterically inhibited by malonyl-CoA. The resulting saturated fatty acid molecule produced by FAS can be further metabolised depending on requirements, desaturated to form unsaturated fatty acids, derived to triglyceride molecules, or channelled to a range of phospholipids and derivatives for membrane and signalling functions.

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The synthesis of palmitate is achieved by the sequential condensation of 7 malonyl-CoA moieties onto a growing carbon chain founded from an acetyl group from acetyl-CoA. The resulting saturated fatty acid molecule produced by FAS can be further metabolised depending on requirements; desaturated to form unsaturated fatty acids, derived to triglyceride molecules for storage, or channelled to a range of phospholipids and derivatives for membrane and signalling functions [30–32].

Malonyl-CoA is an intermediary product in the biosynthesis of fatty acids but also an important regulator of the balance between de novo lipogenesis and fatty acid oxidation. Levels of malonyl-CoA depend on the equilibrium between ACC, FAS, and MCD activities. The activities of ACC and MCD are regulated by phosphorylation via AMP-activated protein kinase (AMPK). Activated (phosphorylated) AMPK phosphorylates and inhibits ACC, whilst activating MCD.
In addition, activated AMPK decreases FAS mRNA expression via a sterol regulatory element binding protein-1 (SREBP-1)-dependent mechanism [28, 29, 34]. Thus, the overall effect of AMPK activation is reducing malonyl-CoA and palmitoyl-CoA. This effect elicits changes in neuropeptide expression, such as agouti-related protein (AgRP), neuropeptide Y (NPY), cocaine and amphetamine-regulated transcript (CART), and proopiomelanocortin (POMC) by still undefined mechanisms (represented as ?) which ultimately regulates feeding. In addition, current evidence has demonstrated that ghrelin-induced carnitine palmitoyltransferase 1 (CPT1) activation promotes the generation of reactive oxygen species (ROS). Fatty acids and ROS increase uncoupling protein 2 (UCP2)-dependent uncoupling activity and UCP2 gene expression which subsequently decreases ROS in a feedback manner, allowing appropriate ghrelin-induced gene transcription. Further work is necessary to demonstrate whether this mechanism (labelled in blue), besides ghrelin, is extensible to other peripheral signals modulating food intake. NrF1 = Nuclear respiratory factor 1.

Fig. 2. Hypothalamic fatty acid metabolism integrates peripheral signals with neuropeptide systems:
Peripheral hormonal and nutrient/ metabolic signals operate on the different components of the fatty acid metabolic pathway, modulating the cytoplasmic pool of malonyl-CoA and palmitoyl-CoA. This effect elicits changes in neuropeptide expression, such as agouti-related protein (AgRP), neuropeptide Y (NPY), cocaine and amphetamine-regulated transcript (CART), and proopiomelanocortin (POMC) by still undefined mechanisms (represented as ?) which ultimately regulates feeding.

Hypothalamic Fatty Acid Metabolism Modulates Feeding: The ‘Malonyl-CoA Hypothesis’
Fatty acid biosynthetic enzymes are constitutively expressed in the brain. Neurons and glial cells need lipid synthesis to maintain their metabolic homeostasis. Importantly, ACC, AMPK, CPT1, FAS, and MCD mRNAs and proteins are highly expressed in hypothalamic nuclei involved in energy homeostasis, such as ARC, DMH, PVH and VMH [28, 29, 36–41]. Despite the fact that anatomical evidence suggested that the fatty acid metabolism was important in hypothalamic neurons, the interest in the role of fatty acid metabolism in energy balance came from the field of oncology [42]. The finding that numerous tumours expressed high levels of FAS raised the possibility that inhibition of this enzyme could be a target for cancer treatment [42]. Interestingly, treatments with FAS inhibitors, such as cerulenin and C75, produced a massive weight loss, which was associated with a marked hypophagic effect [43]. It is noteworthy that the anorectic effect of these drugs, especially C75, is mediated by the accumulation of malonyl-CoA in the hypothalamus, which is sensed as a signal of nutrient abundance (‘malonyl-CoA hypothesis’) [44]. In fact, simultaneous
inhibition of FAS and ACC (by 5-(tetradecyloxy)-2-furoic acid, TOFA) prevents malonyl-CoA accumulation and consequently does not result in decreased food consumption [39, 43, 44]. Conversely, reduction of malonyl-CoA levels by adeno-associated, virus-mediated gene transfer of MCD into the medial basal hypothalamus of rats results in increased food intake and progressive weight gain [45, 46].

The anorectic effect of FAS inhibitors is associated with decreased expression of orexigenic (AgRP and NPY) and elevated expression of anorexigenic (CART, POMC) neuropeptides in the ARC (fig. 2) [43, 47]. Although the molecular mechanisms of the actions of FAS inhibitors on neuropeptides are not fully understood, two possible mechanisms have been proposed. Firstly, malonyl-CoA or a derivative can interact directly with a signalling protein that regulates the expression of neuropeptides. Supporting this idea is the evidence that malonyl-CoA can act directly as a signalling molecule in bacteria. The FapR (also known as FabR) transcription factor in Bacillus subtilis modulates the expression of several genes involved in fatty acid metabolism [48]. Secondly, malonyl-CoA can act indirectly by inhibiting CPT1 and prevent access of LCFA-CoA into the mitochondria. Accumulation of cytoplasmic fatty acyl-CoA thus could interact with signalling proteins that regulate expression of the orexigenic and anorexigenic neuropeptides. Both hypotheses are based on indirect supporting evidence. For instance, pharmacological inhibition or genetic ablation of hypothalamic CPT1 activity reduce food intake [49, 50]. Conversely, increased hypothalamic CPT1 activity in the context of decreased malonyl-CoA levels after ghrelin treatment increases feeding [28]. Altogether, these data suggest that accumulation of fatty acyl-CoA is the mediator in the signalling pathway controlling feeding behaviour.

Despite the relevance of these data, they can appear contradictory in some way: FAS inhibitors are anorectic [39, 43, 44], implying that the activity of FAS (an anabolic enzyme) is usually involved in an orexigenic tone. On the other hand, CPT1 (a catabolic enzyme) is also orexigenic [49, 50]. The explanation for this apparent paradox is found in the malonyl-CoA levels and the integrated nature of metabolism, illustrated by the cooperative regulation of fatty acid synthesis and oxidation. Levels of malonyl-CoA play a key role in this system by acting not only as a substrate for FAS but also as a potent allosteric inhibitor of CPT1, the enzyme importing fatty acyl-CoA into the mitochondria for β-oxidation [30–32]. In summary, inhibition of FAS increases the cytoplasmatic malonyl-CoA content in hypothalamic neurons, which in turn inhibits CPT1 activity, leading to decreased feeding [28, 29, 39, 50].

FAS: A Housekeeping Enzyme with Nucleus-Specific Regulation

While FAS inhibitors displayed a marked anorectic action, it was unclear whether this effect affected the whole hypothalamus or was specific to selected hypothalamic nuclei or sets of neurons. Once more, a pharmacology-based approach answered this question. We have recently reported that tamoxifen (TMX), a widely used drug for the treatment of estrogen receptor-positive breast cancers, displays a very potent FAS inhibitory effect in the liver and in the hypothalamus [39, 51]. Our data demonstrated that TMX-induced anorexia is associated with specific FAS inhibition, increased levels of malonyl-CoA in the hypothalamus and specific changes in CART and POMC in the ARC [39]. However, the most important finding of our study was that TMX inhibited FAS expression in a nucleus-specific pattern restricted to the VMH but not in other hypothalamic nuclei, such as ARC and PVH, or other brain areas, such as the cortex, the thalamus, and the hippocampus [39]. The physiological significance of these observations was further supported by the evidence of changes in hypothalamic FAS in response to fasting and refeeding. In spite of unchanged total levels of FAS mRNA and protein in the fasted state when analysing the entire brain or the whole hypothalamus in mammals [28, 36], our results showed that the nutritional status regulates hypothalamic FAS expression in a nucleus-specific manner, with FAS mRNA levels being downregulated by fasting and upregulated by refeeding, specifically in the VMH [27, 28, 39], which is the same nucleus where FAS was modulated after central or peripheral TMX administration. Overall, these data suggest an important role for FAS in the VMH, which was confirmed by the lean and hypophagic phenotype of FAS knockout mice (FASKO) in the VMH [40].

Hypothalamic AMPK: A Master Cellular Sensor-Regulating Feeding Behaviour

AMPK is a serine/threonine protein kinase composed of a catalytic subunit (α1 or α2) and 2 regulatory subunits (β1 or β2 and γ1 or γ2 or γ3). AMPK is activated by phosphorylation on Thr172 of the α subunit, a process catalysed by LKB1 or Ca+2/calmodulin-dependent protein kinase α or β (CaMKKα or CaMKKβ) [30, 33, 52, 53]. Transforming growth factor-β-activated kinase (TAK1) also activates AMPK [54]. Current data also point out that protein phosphatase 2C (PP2C) inactivates AMPK by dephosphorylation [55]. AMPK is allosterically activated by AMP, which also inhibits PP2C, increasing phosphorylation in Thr172. Whatever the mechanism, activated (phosphorylated) AMPK is a counter-regulatory response to avoid ATP depletion in many tissues to switch off ATP-consuming processes (such as fatty acid synthesis) whilst switching on catabolic processes that produce ATP (such as fatty acid β-oxidation) to restore the AMP:ATP ratio [30, 33, 52, 53].

Similarly to fatty acid metabolism enzymes, AMPK is expressed in several key hypothalamic nuclei, including ARC, LHA, PVH, and VMH [28, 38]. Regulation of hypothalamic...
AMPK is part of the adaptive changes observed during physiological regulation of feeding. Fasting stimulates hypothalamic AMPK, while refeeding inhibits it [27, 28, 33, 38]. Activation of AMPK in the hypothalamus (by using adenoviruses expressing constitutively active AMPK) is sufficient to increase food intake and body weight, whereas repression of hypothalamic AMPK activity (by using adenoviruses expressing dominant negative AMPK) induces anorexia [38]. Alterations in hypothalamic AMPK activity are associated with changes of neuropeptide expression. Overexpression of a dominant negative AMPK in the mediobasal hypothalamus represses mRNA expression of NPY and AgRP in the ARC, whilst conversely, overexpression of constitutively active AMPK increases the fasting-induced increase in expression of NPY and AgRP in the ARC and of MCH in the LHA [38].

Recent data have highlighted the key physiological importance of hypothalamic AMPK in the control of food intake. The effects of fasting and refeeding on hypothalamic AMPK can be linked to alterations in circulating nutrients, hormones, and ARC neuropeptides involved in energy homeostasis (table 1, fig. 2). Activation of AMPK in several hypothalamic nuclei such as VMH, ARC and PVH, appear to play a prominent role in hypoglycaemia sensing [56], mediating counter-regulatory responses [57, 58]. In line with this, central administration of glucose suppresses AMPK activity in the hypothalamus [38]. α-Lipoic acid, a cofactor of mitochondrial enzymes with antioxidant and anorectic properties, also inhibits AMPK activity in the hypothalamus [59]. Lastly, intracerebroventricular (ICV) administration of citrate elicits an anorexigenic response associated with inhibition of AMPK, activation of ACC, and subsequent increase in malonyl-CoA [60]. Anorectic hormones, such as leptin, insulin, glucagon-like peptide-1 (GLP-1), ciliary neurotrophic factor (CNTF), and melanocortin receptor agonists, including melatonin II (MTII), inhibit hypothalamic AMPK [38, 61–63]. On the other hand, orexigenic signals, such as cannabinoids, glucocorticoids, thyroid hormones, adiponectin, ghrelin, and AgRP, activate hypothalamic AMPK [28, 61, 64–67]. It is noteworthy that RSTN, despite its anorectic effect, activates hypothalamic AMPK [27]. So far, it is still unclear whether hypothalamic AMPK is involved in the anorexigenic/orexigenic properties of

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|↓ = Non-reported data |
all those signals. We have recently reported that in the case of ghrelin, the orexigenic action is mediated via the AMPK-malonyl-CoA-CPT1 axis [28, 29]. In fact, pharmacologic or genetic inhibition of AMPK or CPT1 blunts ghrelin feeding-promoting effects [28]. In this sense, one interesting and unsolved question is whether specific changes in the AMPK-malonyl-CoA-CPT1 axis in the VMH are related to the classical ghrelin action on AgRP/NPY neurons in the ARC [25]. Current data demonstrate that pharmacological or genetic manipulations of the AMPK-malonyl-CoA-CPT1 axis in the VMH induce marked changes in the expression of neuropeptides in the ARC ([68] and our unpublished observations). The molecular/neural mechanism underlying this effect is still unclear, but we speculate that glutamate neurons from the VMH to the ARC may play a critical role in this circuit [69, 70].

Besides its effects on the AMPK-malonyl-CoA-CPT1 axis, ghrelin exerts an interesting action on hypothalamic FAS, decreasing its expression specifically in the VMH, but not in other hypothalamic and extra-hypothalamic brain areas. We speculate that this effect prevents the decrease of hypothalamic malonyl-CoA in this nucleus (secondary to fasting-induced inactivation of ACC by AMPK) from reaching deleteriously low levels in the context of food deprivation, which would increase the level of β-oxidation and thus compromise neuronal viability [29]. Supporting this concept are our data showing that the reduction in FAS levels is not further decreased by prolonged fasting over a period of 48 h [39]. This suggests a tightly controlled low FAS threshold in hypothalamic neurons [29], which is mediated by a mechanism involving the transcriptional regulation of SREBP-1 by AMPK [28, 29].

Interestingly, the effect of ghrelin on AMPK has recently been linked to i) endocannabinoids, demonstrating that an intact cannabinoid signalling pathway is necessary for the orexigenic action of ghrelin and also for its stimulatory effects on AMPK [71] and ii) changes in hypothalamic mitochondrial reactive oxygen species (ROS) and respiration that are dependent on uncoupling protein 2 (UCP2) [68]. This effect is related to ghrelin-induced CPT1 activation [28, 29], which stimulates fatty acid β-oxidation, promoting the generation of ROS. Fatty acids and ROS increase UCP2-dependent uncoupling activity and UCP2 gene expression, which subsequently decreases ROS in a feedback manner, allowing appropriate ghrelin-induced gene transcription [68]. Further work is necessary to demonstrate whether this mechanism, besides ghrelin, is extensive to other peripheral signals modulating food intake.

The integrative role of hypothalamic AMPK in whole body homeostasis is demonstrated by the fact that nutrient- and hormone-induced alterations in hypothalamic AMPK activity correlate with changes of neuropeptide expression, mainly in the ARC, such as AgRP, NPY, CART, and POMC [27, 38, 60, 63, 66–68, 72–75] (table 1, fig. 2), but also in the LHA, such as melanin-concentrating hormone (MHC) [38], and in the PVH, such as corticotrophin-releasing hormone (CRH) [60]. The specific relevance of AMPK in the development of obesity is currently under study, with several data pointing out a major role for this enzyme. Diet-induced obesity (DIO) alters AMPK activity in both hypothalamus and skeletal muscle, with DIO mice displaying resistance to the action of leptin on AMPK [76]. These results suggest that flawed responses of AMPK to leptin might contribute to leptin resistance in obese states. AMPKα2KO mice in POMC neurons (POMCα2KO) fed on standard or high fat diet (HFD), show increased body weight and fat mass [74]. On the contrary, mice with selective ablation of AMPKα2 in AgRP (AgRPα2KO) neurons show an age-dependent lean phenotype [74]. CaMKKβKO mice are protected against HFD-induced obesity, insulin resistance, and glucose intolerance, while exhibiting hypophagia and weight loss [77]. Finally, genetic ablation of AMPK in the VMH blunts the orexigenic effect of ghrelin [28]. Altogether these data indicate that hypothalamic AMPK is a suitable target for the treatment of obesity.

Summary and Future Directions

Complexity and redundancy are clear benefits to guarantee precise regulation of important homeostatic systems. Current anatomical, pharmacological, genetic, and physiological data unequivocally demonstrate that hypothalamic fatty acid metabolism plays a key role in the regulation of food intake. Our challenge for the years to come resides in trying to fully understand the molecular mechanism underlying these effects and subsequently open new avenues for the design and development of suitable drugs for the treatment of obesity and its comorbidities.

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Disclosure

The authors declared no conflict of interest.
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