

Review

Sensing the fat: Fatty acid metabolism in the hypothalamus and the melanocortin system

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Abstract

Recent evidence has demonstrated that circulating long chain fatty acids act as nutrient abundance signals in the hypothalamus. Moreover, pharmacological inhibition of fatty acid synthase (FAS) results in profound decrease in food intake and body weight in rodents. These anorectic actions are mediated by the modulation of hypothalamic neuropeptide systems, such as melanocortins. In this review, we summarize what is known about lipid sensing and fatty acid metabolism in the hypothalamus. Understanding these molecular mechanisms could provide new pharmacological targets for the treatment of obesity and appetite disorders, as well as novel concepts in the nutritional design.
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1. Introduction

The hypothalamus is a specialized area in the central nervous system (CNS) that integrates the control of energy homeostasis. Discrete nuclei within the hypothalamus respond to changes in energy status by altering the expression of specific neuropeptides, which cause changes in energy intake and expenditure [11,18,42].

Among the hypothalamic neuropeptide systems regulating feeding, melanocortins play a prominent role [5,7,10,18]. The central melanocortin system modulates energy homeostasis through the anorectic actions of the agonist alpha-melanocyte-stimulating hormone (α -MSH), which is a proopiomelanocortin (POMC) cleavage product, and the endogenous orexigenic antagonist agouti-related protein (AGRP). Both peptides act on the melanocortin-3 and -4 receptors (MC3R and MC4R) [7,10,18]. In the hypothalamus, POMC is expressed only in the ventrolateral part of the arcuate nucleus (ARC) where it is co-expressed with cocaine and amphetamine-regulated transcript (CART). AGRP is

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expressed in the ventromedial part of the ARC, where it is co-expressed with neuropeptide Y (NPY) [7,10,18].

Despite considerable progress in identifying the central melanocortin circuits involved in feeding regulation [8–10,39], the signaling mechanism by which energy status is initially monitored by AGRP and POMC neurons is not completely understood. It is well established that circulating hormones, such as insulin [21,34], leptin [1], ghrelin [9,31,46], peptide YY [2], glucocorticoids [43], and estrogens [12,56] act on melanocortin AGRP and POMC neurons and provide information about energy homeostasis from the periphery.

Recent evidence suggests that circulating macronutrients modulate AGRP and POMC neurons. It is well known that glucose regulates AGRP [13,47] and POMC neurons [16]. Additionally, current data suggest that melanocortin neuropeptides may respond to circulating lipids [30,33]. Furthermore, the lipogenesis and fatty acid oxidation pathways are emerging as a key component of the network of signals regulating food intake [20,26,35].

In this review, we will summarize the current knowledge about lipid sensing and fatty acid metabolism in the hypothalamus paying special attention to the melanocortin system.

2. Lipid sensing in the hypothalamus

More than 40 years ago, the Lipostatic Theory of energy balance regulation proposed that circulating factors, generated in proportion to body fat stores, acted as signals to the brain, eliciting changes in energy intake and expenditure [3]. The discovery of leptin and its receptors [53,60] provided a molecular basis for this theory. Circulating nutrients, from food intake or hepatic production, could indirectly regulate hypothalamic feeding-mechanisms through modulation of leptin levels. Thus, increased plasmatic levels of glucose and lipids stimulate leptin secretion [35,58], and consequently regulate the expression of hypothalamic neuropeptides. Therefore, leptin provides a functional link between adipose tissue and the hypothalamus [11,18,42].

Circulating lipids have been largely proposed as signaling molecules informing about metabolic status [3]; nevertheless, this interaction has been very recently demonstrated. A couple of years ago, it was shown that intracerebroventricular (ICV) administration of long chain fatty acids (LCFAs), specifically oleic acid (OA), inhibited food intake [30,33]. Furthermore, the effect of OA was not reproduced by medium chain fatty acids (MCFAs). These effects of OA are mainly exerted on the ARC; AGRP and NPY mRNA expression was decreased after OA treatment [30,33], indicating that the anorectic action of LCFAs is mediated by an inhibition of these orexigenic neuropeptides. Conversely, POMC expression was not affected by OA treatment [30] suggesting that POMC actions do not mediate LCFAs anorectic effects.

The physiological relevance of these data is intriguing; since circulating fatty acids can access the brain [29,38],

it is likely that the anorectic action of LCFAs, but not MCFAs, could play an important role in the regulation of energy balance by acting as a “nutrient abundance” signal on AGRP/NPY neurons. In this sense, it is very interesting to note that the anorectic response to OA was nutritionally regulated, being suppressed by short-term overfeeding [30]. This effect was related to the lack of hypothalamic responses to LCFAs in overfed animals, which did not show changes either in AGRP or NPY after OA treatment [30]. In view of these data, it is tempting to speculate that in hyperphagic and obese states there may be desensitization of the AGRP and NPY responses to circulating fatty acids, which contributes to body weight gain. Further work will be necessary to address these issues.

3. Fatty acid synthesis pathway in the hypothalamus

In situations where total energy intake exceeds energy expenditure, fatty acids and triacylglycerols are synthesized and triacylglycerols are deposited in adipose tissue. Fatty acid synthesis is catalyzed by acetyl coenzyme A carboxylase (ACC) and fatty acid synthase (FAS) in the cytoplasm [51,57,59] (Fig. 1). Under lipogenic conditions, excess glucose in the cell is first converted to pyruvate via glycolysis in the cytoplasm. Pyruvate is converted to acetyl coenzyme A (acetyl-CoA) and transported as citrate from mitochondria into cytoplasm. ATP citrate lyase (ACL) then converts citrate back to acetyl-CoA. ACC catalyzes the carboxylation of acetyl-CoA to malonyl-CoA in an ATP-dependent manner. Acetyl-CoA and malonyl-CoA are then used as the substrates for the production of palmitate by the seven-enzymatic reactions catalyzed by FAS. The fatty acids thus produced, along with those transported into the cell, are then used for the synthesis of triacylglycerol. The synthesis step of malonyl-CoA is a reversible regulated mechanism and malonyl-CoA decarboxylase (MCD) converts malonyl-CoA back to acetyl-CoA [51,57,59].

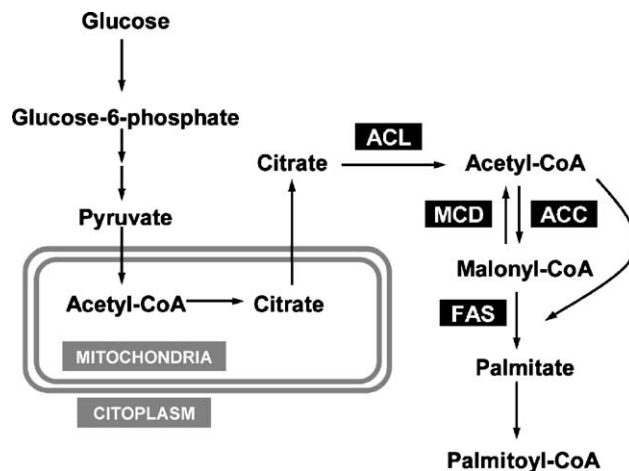


Fig. 1. Fatty acid synthesis pathway. ACC: acetyl-CoA carboxylase; ACL: ATP citrate lyase; FAS: fatty acid synthase; MCD: malonyl-CoA decarboxylase.

Recent reports demonstrate that the enzymes regulating fatty acid synthesis are present in hypothalamic neurons that regulate feeding. Thus, FAS, ACC, and MCD mRNA and protein expression is detected at very high levels in the arcuate (ARC), dorsomedial (DMN), and ventromedial (VMN) hypothalamic nuclei in rodents and humans [20,50]. Double-labeling studies have shown that FAS mRNA co-localizes with neuropeptide Y (NPY) mRNA in ARC neurons. Thus, since AGRP and NPY are co-expressed in the ARC [11,18,42,45], FAS co-localizes with AGRP as well. There are no available data about POMC and FAS co-expression in the ventrolateral ARC. These data suggest that modulation of fatty acid synthesis may act on hypothalamic pathways regulating feeding. Moreover, the direct co-localization of FAS and AGRP/NPY in ARC neurons provides the anatomical basis for a possible mechanism whereby FAS modulation could influence AGRP and NPY production.

4. Anorectic effects of FAS inhibitors

Feeding increases cytoplasmic malonyl-CoA concentration, both by increasing its precursors and cytoplasmic citrate, which is an allosteric activator of ACC. Increased malonyl-CoA concentration inhibits carnitine palmitoyltransferase-1 (CPT-1, also carnitine acyltransferase 1), which is the enzyme that translocates LCFAs into mitochondria and makes their oxidation possible [28,32,40,41]. Under physiological conditions, the inhibition of CPT-1 activity occurs when animals are fed and thus the levels of malonyl-CoA are increased due to an increased flux of glucose into the lipogenic pathway [15,36,40]. For these reasons, it has been hypothesized that the increased levels of malonyl-CoA might act by signaling the fed state in several cell types [15,35,36,40].

All this evidence suggested that the regulation of FAS could be a mechanism of food intake control and that the increase in malonyl-CoA induced by FAS inhibition may act as central lipid-sensing signal. As predicted, it has been recently demonstrated that peripheral administration of the FAS inhibitor C75 reduces food intake and body weight [6,14,26,27]. This effect was exerted through the CNS since ICV administration also caused marked effects on feeding and body weight [6,14,26]. As expected, the anorectic effect of C75 requires the accumulation of malonyl-CoA in the hypothalamus [15]. In fact, simultaneous inhibition of FAS by C75 and ACC by 5-(tetradecyloxy)-2-furoic acid (TOFA), which prevents malonyl-CoA accumulation, does not result in decreased food consumption [15,26].

The anorectic action of FAS inhibitors is linked to decreased expression of orexigenic and elevated expression of anorexigenic neuropeptides in the ARC. Thus, one single administration of C75 prevents fasting-induced up-regulation of AGRP and NPY and down-regulation of POMC and CART [6,14,26,48]. Of interest, in *ob/ob* mice C75 prevents the normal fasting-induced increase in expression of AGRP and NPY but had no effect on the

expression of CART and POMC [48], suggesting that an intact leptin-signaling system is necessary for the effect of C75 on POMC/CART neurons. Despite these differences, the suppressive effect of C75 on food intake is the same in both *ob/ob* and wildtype lean mice, indicating that the C75 anorectic action is leptin-independent [4,6,22,26,48].

The effect of cerulenin on hypothalamic neuropeptides is more controversial. One report demonstrated that, in contrast to C75, cerulenin did not prevent the effects of fasting on hypothalamic mRNA levels of AGRP, NPY, POMC, and CART [27]. Also, in this study cerulenin was highly effective at reducing body weight in agouti (*A^y*) mice, in which obesity is caused by blockade of the melanocortin receptor, suggesting melanocortin-independence [27]. Conversely, a more recent paper suggests that the actions of cerulenin, as in the case of C75, are mediated by activation of hypothalamic POMC neurons [49]. The reasons for these discrepancies are not clear but they could be related with the doses used and the toxic effects of cerulenin [25,52,55]. Moreover, it is interesting to note that although both cerulenin and C75 inhibit FAS they have alternative actions. Cerulenin is able to block protein acylation [17,24,44] and C75 stimulates CPT-1 [23,54]. Finally, both cerulenin and C75 modulates AMP-activated protein kinase (AMPK) activity [19,23]. The interaction of all these functions could explain the differential effects of both molecules.

The molecular mechanisms of the FAS inhibitors actions on neuropeptides are not completely understood. It has been reported that changes in hypothalamic malonyl-CoA levels correlate with the effects of ICV C75 on the expression of NPY, AGRP, and POMC [15] (Fig. 2). However, it is not known how accumulation of malonyl-CoA is linked to changes in neuropeptide gene expression. Several possible mechanisms have been proposed [15] (Fig. 2): (1) a direct action of malonyl-CoA on the signaling mechanism regulating neuropeptide expression or (2) an indirect action through the inhibition of CPT-1, which would prevent the entry of LCFA-CoAs into the mitochondrion and consequently increase their cytoplasmic levels [28,40,41]. In the cytoplasm, LCFA-CoAs could interact with the signaling pathways that regulate neuropeptide expression. This second hypothesis is supported by the anorectic action of both the inhibition of hypothalamic CPT-1 [32] and the central administration of LCFAs [30,33]. However, further studies will be necessary to address these issues.

Alternatively, two recent reports have demonstrated that C75 regulates feeding by an alternative mechanism based on the modulation of AMPK [19,23]. Through its inhibition of FAS and stimulation of CPT-1 activity, C75 elevates the neuronal ATP levels that inhibit AMPK, which in turn modulates neuropeptide expression (Fig. 2) [19].

Overall, and independently of the molecular mechanism, these data indicate that ARC neuropeptides, and especially melanocortins, are playing a fundamental role in the anorectic actions of FAS inhibition. Finally, this evidence indicates that the melanocortin system is able to sense fatty acids and

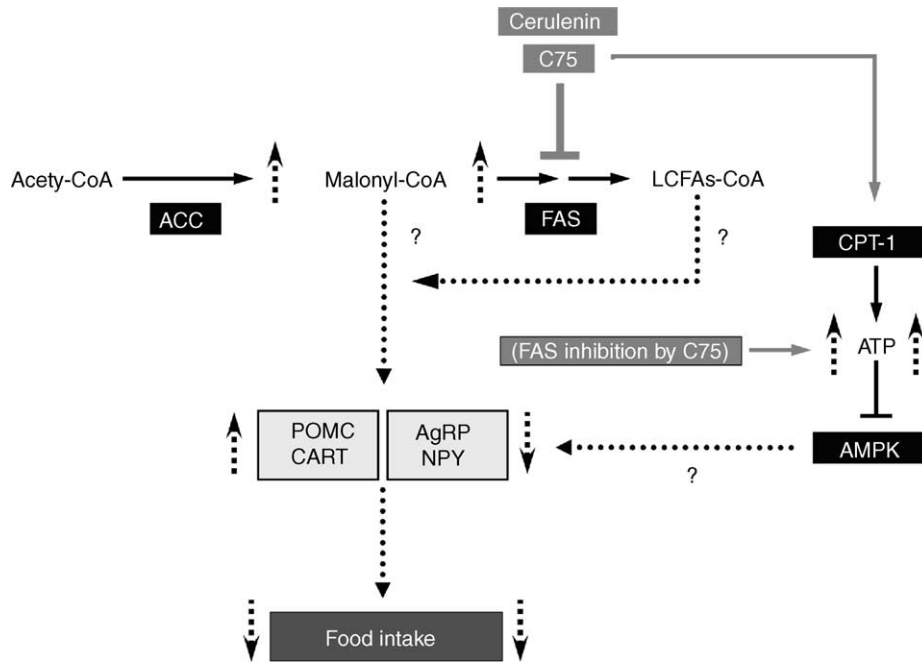


Fig. 2. The figure shows the actions of C75 and cerulenin on hypothalamic neuropeptides. The inhibition of FAS induces an increase in the levels of malonyl-CoA in the hypothalamus. The link between this effect and the neuropeptide changes is unknown (?).

related metabolites. The further study of the effects of FAS inhibition on the melanocortin system will provide a better understanding of the mechanisms underlying feeding control.

5. FAS as pharmacological target in obesity

The results from long-term treatment studies have demonstrated that while lean mice become resistant to repeat C75 administration, obese ob/ob mice do not show this response, showing only slight resistance [4,22]. Moreover, consistent with increased energy expenditure, C75 treatment to ob/ob mice caused greater weight loss than pair-fed controls and increased expression of skeletal muscle uncoupling protein-3 (UCP-3) mRNA [4].

The ability of FAS inhibitors to regulate neuropeptide actions, especially the melanocortin pathway, in a leptin-independent fashion suggests that modulation of FAS/malonyl-CoA actions in the hypothalamus could be a possible pharmacological target against food intake/weight disorders. Thus, drugs that increase the malonyl-CoA levels in the hypothalamus could be used as appetite suppressants and antiobesity treatment. However, taking into account the toxic effects of cerulenin and C75 [25,37,52,55] further work is necessary to design or screen new possible pharmacological agents with therapeutic use.

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