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Hypothalamic sensing of fatty acids

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Selective regions of the brain, including the hypothalamus, are capable of gathering information on the body's nutritional status in order to implement appropriate behavioral and metabolic responses to changes in fuel availability. This review focuses on direct metabolic signaling within the hypothalamus. There is growing evidence supporting the idea that fatty acid metabolism within discrete hypothalamic regions can function as a sensor for nutrient availability that can integrate multiple nutritional and hormonal signals.

Energy homeostasis is maintained by multiple mechanisms that gather information on the body's nutritional status and make appropriate behavioral and metabolic responses to changes in fuel availability. Although it is clear that nutrient-stimulated, gut-derived signals are crucial in the moment-to-moment regulation of meal-related feeding behavior[1,2], the hypothalamus is a primary site of convergence and integration for redundant nutrient-related signals[3–20], which include central and peripheral neural inputs as well as hormonal and nutritional signals[3–20].

Opposing theories have been proposed to account for the homeostatic system or systems controlling energy balance. Over the years, the glucostatic[11,21,22] and lipostatic[9,22] hypotheses have attracted the most supporters and detractors. Although these theories were put forth before the discovery of dominant hormonal players such as leptin[23], both have been adapted to incorporate new discoveries. The glucostatic hypothesis[11,21,22] posits that circulating glucose is the main signal of the body's nutritional status; as a corollary, it is increasingly acknowledged to have a role in the modulation of both insulin and leptin biosynthesis and secretion[17,24,25]. The hypothesis was initially supported by evidence that rapid fluctuations in circulating levels of glucose[22,26], glucose administration[6,27,28] and glucose deprivation[29,30] modulate feeding behavior. The lipostatic hypothesis[9,22] initially centered on the role of circulating lipids as the main signal of the body's nutritional status. It later evolved into the adipostat hypothesis, in which lipid storage, rather than circulating lipids, is the main regulatory factor. According to the latter hypothesis, circulating hormones such as leptin and insulin and substrates such as fatty acids and glycerol are proportional to body lipid storage (adiposity) and modulate hypothalamic functions consistent with homeostatic behavioral, neuroendocrine and autonomic responses designed to maintain body adiposity[9,22].

The preponderance of experimental evidence suggests that redundant homeostatic mechanisms are involved in the maintenance of energy balance and that a single theory is not likely to account for the complexity of this regulatory system. Changes in lipid storage generate hormonal and nutritional signals that target CNS regions implicated in the control of energy homeostasis[7,8,16]. On the other hand, the availability of circulating substrates modulates various adipose tissue–related signals[17,31] and may directly influence CNS energy centers.

This review focuses on recent findings related to direct metabolic signaling within the hypothalamus. Specifically, we review the growing evidence supporting the idea that fatty acid metabolism within discrete hypothalamic regions can function as a sensor of nutrient availability that can integrate multiple nutritional and hormonal signals. Although it is likely that complementary nutrient-sensing mechanisms may also operate in other regions within and outside the CNS, based on the currently available experimental evidence, we limit this review to mechanisms responsible for lipid sensing within the hypothalamus.

Cellular metabolism of fatty acids

Plasma long-chain fatty acids (LCFAs) are mostly bound to albumin and cross the blood-brain barrier mainly by simple diffusion in the unbound form. Unbound fatty acids can also be derived from hydrolysis of lipoproteins by lipoprotein lipases within the blood or the cerebral capillary bed. Overall, chylomicrons are likely to be a major circulating source of brain fatty acids after meals, whereas a combination of unbound fatty acids and locally hydrolyzed lipoproteins contribute to the brain fatty acid pool during fasting. A small proportion of fatty acid entry into the brain may also occur through direct uptake of lipoprotein particles mediated by lipoprotein receptors in the luminal surface of the cerebrovascular endothelium[32,33]. Overall, the access of circulating free fatty acids to the CNS is generally proportional to the plasma concentration of fatty acids[34,35], although their concentration in the cerebral spinal fluid is ~6% of the plasma concentration in fasting anesthetized dogs[36] (**Fig. 1a**).

Upon entry into the cell, a fatty acid is rapidly esterified to a fatty acyl–coenzyme A (fatty acyl–CoA). This reaction is catalyzed by the enzyme acyl-CoA synthetase. The size of the intracellular pool of fatty acyl–CoAs is a function of its rate of formation and its rate of use, which takes into account lipid oxidative and synthetic pathways. The transfer of long-chain fatty acyl–CoAs (LC-CoAs) to the mitochondria, where they undergo β-oxidation, requires two membrane-bound carnitine-dependent long-chain acyltransferases (also known as carnitine palmitoyltransferases), CPT1 and CPT2. CPT1 is located on the outer mitochondrial membrane; it catalyzes the formation of long-chain acylcarnitines and is present in two isoforms known as the liver isoform (CPT1-L, encoded by the *CPT1A* gene) and the muscle isoform (CPT1-M, encoded by the *CPT1B* gene; **Fig. 1a**).

Under physiological conditions, cellular fat oxidation is regulated by the availability of malonyl-CoA, a potent inhibitor of CPT1 activity.

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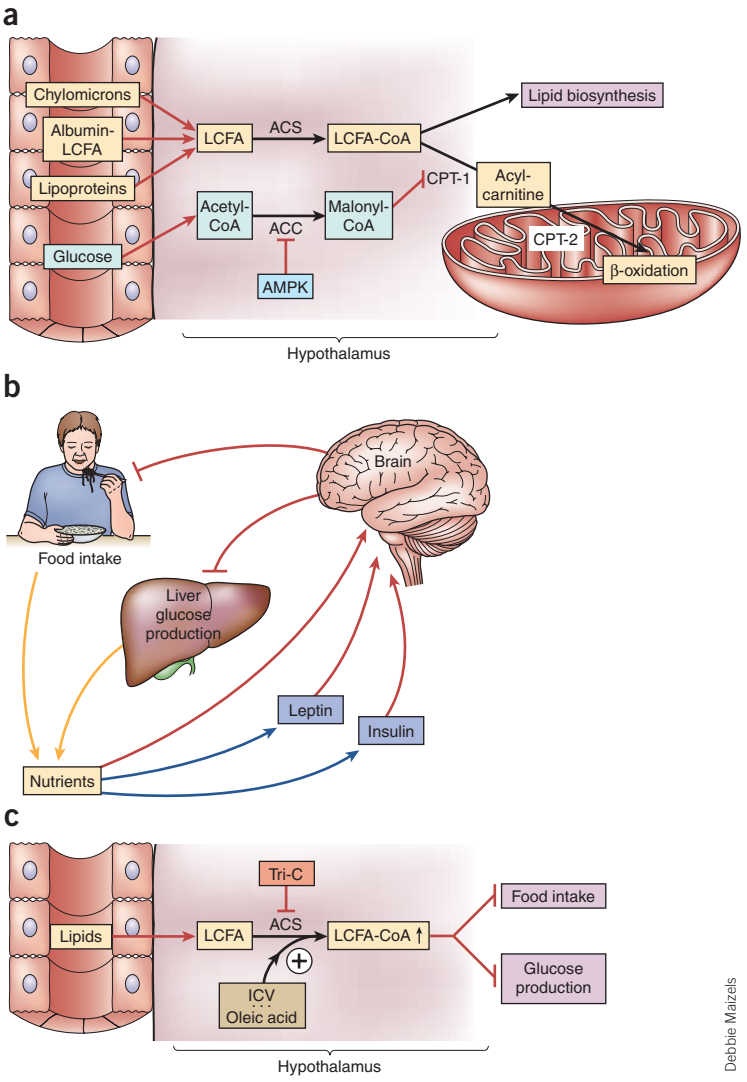

Figure 1 Delivery and metabolism of fatty acids in the hypothalamus. (**a**) Hypothalamic uptake and metabolism of fatty acids. Long-chain fatty acids (LCFAs) are bound to albumin in plasma and cross the blood-brain barrier mainly by simple diffusion in the unbound form. Unbound fatty acids can also be derived from chylomicrons or other circulating lipoproteins. Upon entry into the cell, acyl-CoA synthetases (ACSs) rapidly esterify LCFAs to fatty acyl–CoAs (LCFA-CoAs). The size of the intracellular pool of fatty acyl–CoAs is determined by its rate of formation and use, including lipid oxidative and biosynthetic pathways. Transfer of LCFA-CoAs to the mitochondria, where they undergo β-oxidation, requires two membrane-bound carnitine-dependent long-chain acyltransferases, CPT1 and CPT2. Mitochondrial fat oxidation is regulated by the availability of malonyl-CoA, a potent inhibitor of CPT1 activity. Malonyl-CoA is largely derived from glycolysis end product acetyl-CoA; thus this biochemical pathway is ideally positioned to monitor cellular availability of both carbohydrates and lipids. The formation of malonyl-CoA from acetyl-CoA is catalyzed by the enzyme acetyl-CoA carboxylase (ACC), which is allosterically inhibited through phosphorylation by AMP-activated protein kinase (AMPK). (**b**) Hypothesized negative feedback mechanisms regulating circulating nutrients. There are two main sources of circulating nutrients: food intake, and production of glucose and lipids by the liver. Increased availability of macronutrients such as glucose and lipids activates sensing pathways in the brain, either directly through metabolic signals, or indirectly, through stimulation of insulin and leptin biosynthesis and secretion. The activation of brain efferent pathways in turn suppresses food intake and hepatic output of glucose and lipids. (**c**) Circulating LCFAs signal the body's nutritional status to hypothalamic energy centers. Physiological elevations in the circulating levels of LCFAs can induce a doubling of the LCFA-CoA pool within discrete regions of the hypothalamus, and may therefore generate a metabolic signal of energy surfeit. This increase can be prevented by intrahypothalamic infusion of triascin C (Tri-C), a pharmacological inhibitor of ACS. The esterification of LCFA to LCFA-CoA is also an obligatory step for the hypothalamic effects of LCFA on liver glucose production. The intracerebroventricular (i.c.v.) administration of the LCFA oleic acid is *per se* sufficient to inhibit food intake and liver glucose production, without affecting circulating LCFA concentrations.

Because malonyl-CoA is largely derived from the glycolysis of glucosyl-derived units[37,38], this biochemical pathway is ideally positioned to monitor cellular availability of both carbohydrates and lipids. The formation of malonyl-CoA from acetyl-CoA is catalyzed by the enzyme acetyl-CoA carboxylase (ACC), which is allosterically inhibited by phosphorylation. AMP-activated protein kinase (AMPK) is the main kinase responsible for the phosphorylation and consequent inactivation of ACC. Thus, in addition to the availability and esterification of fatty acids, changes in glucose use through glycolysis and changes in the activity of key enzymes such as AMPK and ACC contribute to the regulation of the intracellular pool of LC-CoAs (**Fig. 1a**).

LCFAs signal energy 'surfeit' in the hypothalamus

Circulating nutrients can be derived from either exogenous (such as food intake) or endogenous (liver glucose production) sources. Central neural circuits concomitantly modulate both exogenous and endogenous sources of energy, in keeping with a negative feedback system that monitors and regulates the input of nutrients in the circulation[13]. The hypothesis advanced in this section is that circulating lipids such as LCFAs regulate feeding behavior and glucose production by generating an increase in the cellular LCFA-CoA pool in the hypothalamus. In turn, LCFA-CoAs signal an energy 'surfeit' within the hypothalamus, which activates neural pathways designed to curtail both food intake and liver glucose production (**Fig. 1b**). Consistent with this hypothesis, intravenous infusion of a lipid emulsion is sufficient to suppress food intake in baboons[28]. Thus, circulating lipids (triglyceride, glycerol and LCFA) seem to generate a signal of nutrient surfeit. This signal is independent of measurable changes in plasma insulin and does not require gastrointestinal nutrient absorption[28,39–41].

Circulating LCFAs can signal the body's nutritional status to hypothalamic energy centers. The intracerebroventricular (i.c.v.) administration of the LCFA oleic acid alone is sufficient to inhibit food intake and liver glucose production in the presence of similar circulating LCFA concentrations[13,42]. The i.c.v. oleic acid also inhibits the expression

Table 1 Effects of central lipid sensing on hypothalamic neuropeptides, food intake and glucose production

Reference	NPY	AgRP	POMC	Food intake	Glucose production
I.c.v. oleic acid					
13	↓	n.a.	n.a.	↓	↓
42	↓	↓	↔	↓	↓
I.c.v. CPT-1 inhibitor					
15	↓	↓	↔	↓	↓
Medial hypothalamus DN-AMPK					
48	↓	↓	↔	↓	n.a.
I.c.v./i.p. FAS inhibitor (C75)					
10	↓	n.a.	n.a.	↓	n.a.
53	n.a.	n.a.	n.a.	↓	n.a.
57	↓	↓	↑	↓	n.a.
58	↓	↓	↑	↓	n.a.
I.c.v./i.p. FAS inhibitor (cerulenin)					
54	↔	↔	↔	↓	n.a.

↓decreased, ↑ increased, ↔ no change compared with appropriate controls. DN, dominant-negative.

of the orexigenic peptides neuropeptide Y (NPY) and agouti-related protein (AgRP) in the hypothalamus (**Table 1**) and glucose-6-phosphatase expression in the liver[13,42]. Notably, the potent effect of i.c.v. oleic acid on the liver cannot be reproduced by i.c.v. administration of the medium-chain fatty acid octanoic acid, which does not require CPT1 for entry into mitochondria for β-oxidation[13].

In light of these findings, we asked whether a physiological elevation of circulating levels of LCFAs could generate a measurable increase in the LCFA-CoA pool within discrete regions of the hypothalamus and therefore generate a metabolic signal of energy surfeit. A sustained two- to threefold elevation in circulating LCFA levels is indeed sufficient to double LCFA-CoA concentrations within the mediobasal hypothalamus. Furthermore, this increase is prevented by intrahypothalamic infusion of triascin C, a pharmacological inhibitor of LCFA-CoA synthetase[43]. The esterification of LCFA to LCFA-CoA is a required step for the hypothalamic effects of LCFA on liver metabolism, as the intrahypothalamic infusion of triascin C also negates the ability of circulating LCFA to restrain hepatic glucose production[43] (**Fig. 1c**). These data demonstrate that changes in the levels of circulating fatty acids can significantly modulate the hypothalamic pool of LCFA-CoAs. Taken together with the potent anorectic effects of central administration of oleic acid, this finding suggest that an increase in the hypothalamic levels of LCFA-CoAs may also be important in the inhibition of food intake during systemic increases in lipid availability[28] (**Fig. 1c**). On the basis of these studies, it seems plausible that the cellular accumulation of hypothalamic LCFA-CoA, rather than the influx of fatty acids into the mitochondria for β-oxidation, is the first hypothalamic signal leading to inhibition of food intake and glucose production.

Inhibiting hypothalamic lipid oxidation curtails feeding

If the lipid-generated signal of energy surfeit is indeed the cellular accumulation of esterified LCFAs within the hypothalamus, it should be possible to elicit similar metabolic and behavioral effects either by increasing LCFA availability or by decreasing cellular use of esterified LCFAs. Under genetic or pharmacological inhibition of hypothalamic CPT1 (**Fig. 2a**), the concentration of hypothalamic LCFA-CoAs increases roughly twofold, whereas the expression of the orexigenic peptides NPY and AgRP decreases[15] (**Table 1**). Cellular accumulation of LCFA-CoA also leads to marked inhibition of food intake and liver glucose production[15]. As inhibition of hypothalamic CPT1 activity alone increases cellular accumulation of esterified LCFAs while curtailing their β-oxidation[13], these data provide strong support for the idea that the availability of LCFA-CoAs is a key component of hypothalamic lipid sensing.

It remains to be determined which regions and neuronal populations within the hypothalamus are required for the anorectic and metabolic effects of LCFA-CoA. Both genetic and pharmacological inhibition of CPT1 lead to increased levels of esterified LCFA in the arcuate nuclei, but not in other hypothalamic regions[15], and inhibition of fatty acid

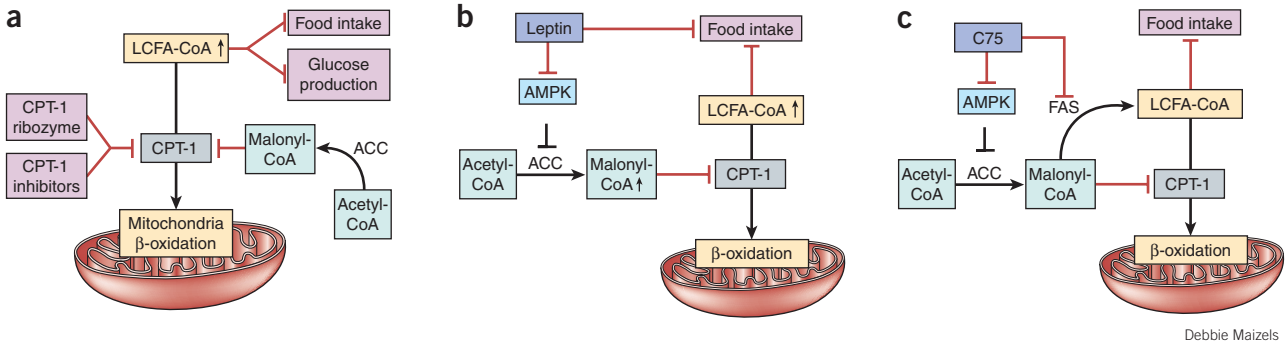

Figure 2 Hypothalamic regulation of LCFA-CoA levels. (**a**) Decreasing the expression or the activity of CPT1 within the medial hypothalamus (by ribozyme knockdown or pharmacological inhibition) is sufficient to increase LCFA-CoA levels and to inhibit food intake and glucose production. An increase in malonyl-CoA (which regulates entry of LFCA-CoA into the oxidative pathway) would be expected to mimic the anorectic and metabolic effects observed with the experimental downregulation of CPT1 activity. (**b**) Bidirectional changes in AMPK activity within hypothalamic nuclei alter feeding behavior in rats. A decrease in AMPK activity inhibits food intake, and enhances ACC activity and the formation of malonyl-CoA. It is likely that this anorectic effect is partly due to inhibition of hypothalamic CPT1 activity. The anorectic hormone leptin inhibits AMPK activity in selective hypothalamic nuclei. Expression of constitutively active AMPK in the medial hypothalamus diminishes the ability of leptin to inhibit food intake, suggesting that the inhibitory effect of leptin on hypothalamic AMPK is a required step in leptin action on food intake. (**c**) Inhibition of fatty acid synthase reduces food intake. Two inhibitors of fatty acid synthase (FAS) activity, cerulenin and C75, reduce food intake and body weight in rodent models. In mice deprived of food, central administration of C75 at anorexic doses also significantly increases the hypothalamic levels of malonyl-CoA, and pharmacological blockade of ACC largely reverses C75's effects on feeding. C75 seems to increase the cellular levels of malonyl-CoA through at least two mechanisms: (i) accumulation of substrate after FAS inhibition and (ii) inhibition of AMPK activity, leading to increased conversion of acetyl-CoA to malonyl-CoA by ACC. Increased levels of malonyl-CoA within the medial hypothalamus may then promote anorexia through their inhibitory action on CPT1.

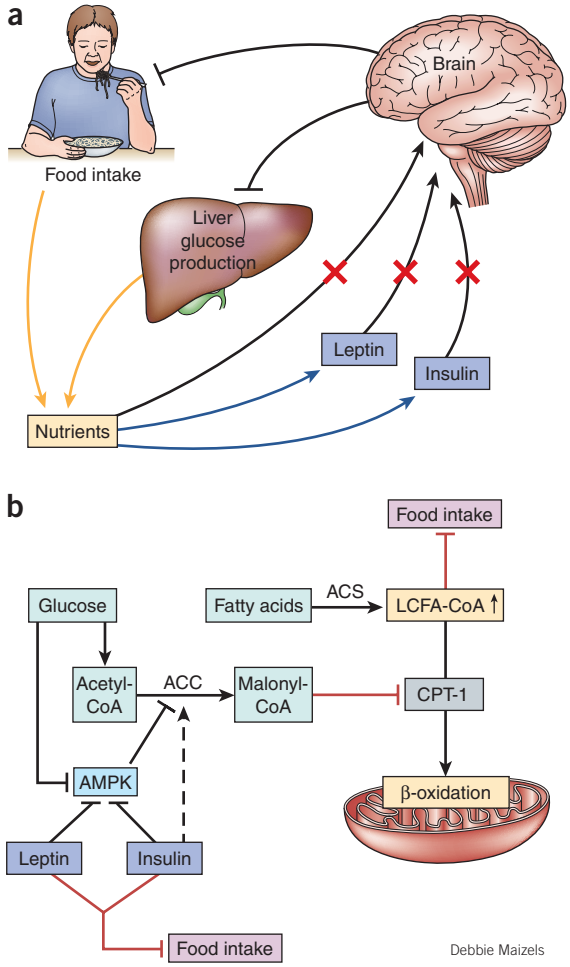

Figure 3 Convergence of nutritional and endocrine signals on hypothalamic LCFA-CoA. (**a**) Hypothalamic sensing of fatty acids and the metabolic adaptation to nutrient abundance. The hypothalamic effects of adiposity hormones such as leptin and insulin, and nutrients such as fatty acids, initiate a negative feedback on energy homeostasis, as shown in **Figure 1b**. We postulate that under conditions of caloric abundance rapid onset of hypothalamic resistance to multiple adiposity and nutritional signals—such as leptin, insulin and fatty acids—contributes to the susceptibility to obesity and insulin resistance in predisposed individuals and animals. (**b**) Convergence of multiple homeostatic signals within the hypothalamus. Elevated levels of LCFA-CoAs are likely to represent a key signal generated in response to increased availability of fatty acids. Additionally, increased availability of glucose could increase levels of malonyl-CoA directly through glycolysis, and indirectly through inhibition of AMPK leading to activation of ACC. In a similar vein, other key modulators of energy balance and feeding behavior such as leptin and insulin have been shown to modulate ACC activity, AMPK activity or both, either within the hypothalamus or in other cell systems. Thus, it is plausible that the sensing of fatty acids integrates multiple hormonal and metabolic homeostatic signals within the hypothalamus.

oxidation in the lateral hypothalamus does not alter food intake[44]. Under physiological conditions, the rate of fat oxidation is controlled by the hypothalamic levels of malonyl-CoA, an increase in which should mimic the anorectic and metabolic effects observed from the experimental downregulation of CPT1 activity[15].

Hypothalamic AMP-activated protein kinase as a fuel sensor

The final enzymatic step in the formation of malonyl-CoA is catalyzed by ACC, which is inhibited by phosphorylation; the main kinase responsible for the phosphorylation of ACC is AMPK. AMPK is a fuel sensor in mammalian cells[45,46], and in skeletal muscle it is activated in response to exercise, hypoxia and prolonged starvation[47].

Hypothalamic AMPK is also implicated in the regulation of food intake[48]. Bidirectional manipulations of AMPK activity within hypothalamic nuclei alone are sufficient to alter feeding behavior in rats[48]. Expression of dominant-negative AMPK in the medial hypothalamus decreases NPY and AgRP expression (**Table 1**) and food intake[48]. Furthermore, the anorectic hormone leptin suppresses[48,49] hypothalamic AMPK activity, whereas the orexigenic hormone ghrelin increases it[49]. Finally, expression of constitutively active AMPK in the medial hypothalamus diminishes the ability of leptin to inhibit food intake[48], suggesting that the inhibition of hypothalamic AMPK by leptin is a required step in leptin action on food intake.

Although the mechanism or mechanisms by which the inhibition of hypothalamic AMPK causes decreased expression of orexigenic peptides (NPY and AgRP) and decreased food intake are unknown, it is likely that decreased AMPK activity would increase hypothalamic malonyl-CoA levels by activation of ACC. Consistent with this idea, the increased cellular levels of malonyl-CoA would in turn inhibit CPT1 activity and inhibit food intake through cellular accumulation of LCFA-CoA[13,15]. On the other hand, AMPK could also modulate the transcription of hypothalamic neuropeptides independently of its effects on ACC or malonyl-CoA[48].

A role for ACC in the regulation of feeding behavior is also consistent with the marked hyperphagia of mice lacking acetyl-CoA carboxylase 2 (ref. 50), although a primary increase in energy expenditure may also account for this phenotype through decreased fat mass. Overall, the cellular accumulation of LCFA-CoAs is an anorectic signal that may lie downstream of the leptin-induced inhibition of hypothalamic AMPK, pointing toward a convergence between hypothalamic leptin signaling and lipid sensing in the regulation of food intake (**Fig. 2b**).

Central inhibition of fatty acid synthase reduces feeding

Fatty acid synthase (FAS), as well as other enzymes required for the generation and degradation of malonyl-CoA (ACC and MCD, respectively), are localized to multiple cellular populations in the mouse brain, including the hypothalamus[51]. Furthermore, FAS immunoreactivity colocalizes with NPY immunoreactivity, consistent with a role for neuronal FAS in the modulation of feeding in orexigenic neurons[52].

Two inhibitors of FAS activity, cerulenin and C75, reduce food intake and body weight in rodent models[10,53,54]. Based on divergent results from conditioned taste aversion studies, it remains controversial whether the suppression of feeding by systemic C75 is secondary to visceral malaise, rather than specific to feeding[53]. These concerns are in part fueled by neurophysiological[55] and c-Fos expression studies[51,56] indicating widespread neuronal activation in response to C75. However, the effects of much lower doses of this FAS inhibitor given in a cerebral ventricle elicits more specific effects on feeding behavior and c-Fos activation[51].

In mice deprived of food, central C75 at anorexic doses also significantly increases hypothalamic malonyl-CoA levels[57] and blocks fasting-induced increases in hypothalamic NPY and AGRP expression[10,57,58] (**Table 1**). Furthermore, pharmacological blockade of ACC, an enzyme required for malonyl-CoA synthesis, largely reverses the effects of C75 on feeding and malonyl-CoA accumulation[57], supporting the idea that malonyl-CoA availability is critical to the hypothalamic control of food intake[10]. C75 seems to increase the cellular levels of malonyl-CoA by at least two mechanisms: (i) accumulation of substrate after FAS inhibition

and (ii) inhibition of AMPK activity leading to increased conversion of acetyl-CoA to malonyl-CoA by ACC (**Fig. 2c**). Accordingly, central pharmacological stimulation of AMPK using 5-aminoimidazole-4-carboxamide-ribofuranoside (AICAR) produces small but significant increases in food intake[59] and also attenuates C75-induced anorexia[59]. Paradoxically, however, C75 also increases fatty acid oxidation and CPT1 activity in primary dissociated rat hepatocytes[60] and in primary rat cortical neuronal cultures[61], where the liver isoform of CPT1 predominates[62]. It remains to be established whether the increase in the cellular levels of malonyl-CoA or the apparent direct stimulatory effect of C75 on CPT1 activity prevails within relevant hypothalamic cells *in vivo*.

Metabolic adaptation to nutrient abundance

The development of obesity and type 2 diabetes mellitus is influenced by a complex interaction of environmental and genetic factors[63–65]. Evolutionary pressures may have favored the selection of genes whose products maximize energy storage when food availability is high[66–69]. Thus, we and others have proposed that a rapid, sustained increase in caloric intake initiates a 'tug of war' between peripheral 'anabolic signals'[70] and hypothalamic 'catabolic signals'[10,13–15,20]. Consistent with this hypothesis, the hypothalamic effects of adiposity-influencing hormones such as leptin[23,71–74] and insulin[14,19,75,76] and nutrients such as fatty acids[10,13,15] initiate negative feedback on energy homeostasis that includes restraint on food intake, stimulation of energy expenditure and decreased output of nutrients from endogenous sources (predominantly the liver). The impairment in this hypothalamic response to a sustained increase in food availability can be viewed as an attempt to promote efficient energy storage as an 'adaptive' response to the increased availability of energy sources (**Fig. 3a**). However, genetically predisposed animals and humans may also become susceptible to weight gain and metabolic dysregulation when this negative feedback is disrupted. The rapid onset of leptin resistance in rodent models of voluntary overfeeding provides initial support for this theory[77,78].

We tested a tenet of this theory, demonstrating that a short-term increase in caloric intake rapidly induces resistance to the central effects of the long-chain fatty acid oleic acid on feeding behavior and on glucose production[42] in a rodent strain susceptible to diet-induced obesity and insulin resistance. Indeed, inhibition of food intake caused by central administration of oleic acid is blunted after 3 d of voluntary overfeeding in Sprague-Dawley rats[42]. NPY is also a target of LCFA-CoAs, as central administration of either oleic acid or modulation of hypothalamic lipid metabolism impedes the rise in hypothalamic NPY mRNA induced by fasting[10,13,15]. This facet of hypothalamic lipid sensing may be particularly important in mitigating the rise in hypothalamic NPY levels and the hyperphagia that occurs during fasting, when circulating fatty acids are elevated and plasma leptin and insulin levels are suppressed. Conversely, the lack of inhibition of hypothalamic NPY expression by fatty acids observed in overfed rats can lead to further increase in food intake after fasting. Regarding the biochemical mechanism or mechanisms responsible for the rapid alteration in central lipid sensing, the sustained increase in the cellular levels of LCFA-CoAs during voluntary overfeeding may lead to adaptive changes in lipid metabolism (such as inhibition of ACC leading to decreased formation of malonyl-CoA). In this regard, it is intriguing that the anorectic effects of the FAS inhibitor C75 are preserved in diet-induced and genetic obesity in mice[79]. This may be due to a restoration of adequate levels of malonyl-CoA within the hypothalamus.

In summary, we postulate that the rapid onset of hypothalamic resistance to multiple adiposity and nutritional signals such as leptin, insulin and fatty acids contributes to the susceptibility to obesity and insulin resistance in predisposed individuals and animals (**Fig. 3a**).

Integration of homeostatic signals in the hypothalamus

To control energy homeostasis, hypothalamic energy centers must gather nutritional information from multiple signals that were initially included within the glucostatic and adipostat/lipostatic hypotheses. How does the hypothalamus convert these diverse signals into a cogent and coordinated response to changes in nutrient availability? We propose that the hypothalamic sensing of fatty acids provides a viable biochemical explanatory framework (**Fig. 3b**).

The well-established biochemical link between cellular carbohydrate and lipid metabolism must be important in modulating the hypothalamic sensing of fatty acids. In fact, the cellular levels of LCFA-CoAs are likely to represent a key signal generated in response to increased availability of fatty acids. Similarly, it is likely that an increase in the availability of carbohydrates would also increase the cellular levels of LCFA-CoAs through increased levels of (glycolytically derived) malonyl-CoA, leading to the inhibition of fatty acid oxidation. Thus, it is likely that this central nutrient-sensing mechanism is able to respond to increased availability of lipids, carbohydrates or both (**Fig. 3b**).

The evidence reviewed here also suggests that the degree of activation of this hypothalamic fuel sensor in response to increased nutrient flux is highly dependent on the activity of key biochemical pathways. In this regard, the enzymatic regulation of the formation and degradation of malonyl-CoA could be critical in either amplifying or curtailing the energy 'surfeit' signal conveyed by the availability of macronutrients. Thus, it is likely that the body's nutritional status is important in determining the amplitude of the signal generated by hypothalamic LCFAs through modulation of their cellular metabolism.

The recent observation that leptin's anorectic action requires inhibition of AMPK activity within the hypothalamus may be also linked to a rapid increase in the cellular malonyl-CoA pool. In a similar vein, other key modulators of energy balance and feeding behavior, such as insulin[80,81] and ghrelin, modulate ACC activity, AMPK activity or both, either within the hypothalamus or in other cell systems. Thus, it is conceivable that the sensing of fatty acids integrates multiple hormonal and metabolic homeostatic signals within the hypothalamus.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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1. Moran, T.H. & Schwartz, G.J. Neurobiology of cholecystokinin. *Crit. Rev. Neurobiol.* **9**, 1–28 (1994).
2. Gibbs, J., Young, R.C. & Smith, G.P. Cholecystokinin decreases food intake in rats. *J. Comp. Physiol. Psychol.* **84**, 488–495 (1973).
3. Ahima, R.S. *et al.* Role of leptin in the neuroendocrine response to fasting. *Nature* **382**, 250–252 (1996).
4. Air, E.L. *et al.* Small molecule insulin mimetics reduce food intake and body weight and prevent development of obesity. *Nat. Med.* **8**, 179–183 (2002).
5. Bruning, J.C. *et al.* Role of brain insulin receptor in control of body weight and reproduction. *Science* **289**, 2122–2125 (2000).
6. Davis, J.D., Wirtshafter, D., Asin, K.E. & Brief, D. Sustained intracerebroventricular infusion of brain fuels reduces body weight and food intake in rats. *Science* **212**, 81–83 (1981).
7. Flier, J.S. Obesity wars: molecular progress confronts an expanding epidemic. *Cell* **116**, 337–350 (2004).
8. Friedman, J.M. Obesity in the new millennium. *Nature* **404**, 632–634 (2000).
9. Kennedy, G.C. The role of a depot fat in the hypothalamic control of food intake in the rat. *Proc. R. Soc. Lond. B* **140**, 578–592 (1953).

10. Loftus, T.M. *et al.* Reduced food intake and body weight in mice treated with fatty acid synthase inhibitors. *Science* **288**, 2379–2381 (2000).
11. Mayer, J. Glucostatic mechanism of regulation of food intake. *N. Engl. J. Med.* **249**, 13–16 (1953).
12. Obici, S. *et al.* Central melanocortin receptors regulate insulin action. *J. Clin. Invest.* **108**, 1079–1085 (2001).
13. Obici, S. *et al.* Central administration of oleic acid inhibits glucose production and food intake. *Diabetes* **51**, 271–275 (2002).
14. Obici, S., Feng, Z., Karkanias, G., Baskin, D.G. & Rossetti, L. Decreasing hypothalamic insulin receptors causes hyperphagia and insulin resistance in rats. *Nat. Neurosci.* **5**, 566–572 (2002).
15. Obici, S., Feng, Z., Arduini, A., Conti, R. & Rossetti, L. Inhibition of hypothalamic carnitine palmitoyltransferase-1 decreases food intake and glucose production. *Nat. Med.* **9**, 756–761 (2003).
16. Schwartz, M.W., Woods, S.C., Porte, D. Jr, Seeley, R.J. & Baskin, D.G. Central nervous system control of food intake. *Nature* **404**, 661–671 (2000).
17. Wang, J., Liu, R., Hawkins, M., Barzilai, N. & Rossetti, L. A nutrient-sensing pathway regulates leptin gene expression in muscle and fat. *Nature* **393**, 684–688 (1998).
18. Wang, J. *et al.* The effect of leptin on *Lep* expression is tissue-specific and nutritionally regulated. *Nat. Med.* **5**, 895–899 (1999).
19. Woods, S.C., Lotter, E.C., McKay, L.D. & Porte, D. Jr. Chronic intracerebroventricular infusion of insulin reduces food intake and body weight of baboons. *Nature* **282**, 503–505 (1979).
20. Woods, S.C., Seeley, R.J., Porte, D. Jr & Schwartz, M.W. Signals that regulate food intake and energy homeostasis. *Science* **280**, 1378–1383 (1998).
21. Mayer, J. Genetic, traumatic and environmental factors in the etiology of obesity. *Physiol. Rev.* **33**, 472–508 (1953).
22. Mayer, J. Regulation of energy intake and the body weight: the glucostatic theory and the lipostatic hypothesis. *Ann. NY Acad. Sci.* **63**, 15–43 (1955).
23. Zhang, Y. *et al.* Positional cloning of the mouse obese gene and its human homologue. *Nature* **372**, 425–432 (1994).
24. MacDonald, M.J. Elusive proximal signals of beta-cells for insulin secretion. *Diabetes* **39**, 1461–1466 (1990).
25. Hedeskov, C.J. Mechanism of glucose-induced insulin secretion. *Physiol. Rev.* **60**, 442–509 (1980).
26. Van Itallie, T.B., Beaudoin, R. & Mayer, J. Arteriovenous glucose differences, metabolic hypoglycemia and food intake in man. *Am. J. Clin. Nutr.* **1**, 208–217 (1953).
27. Walls, E.K. & Koopmans, H.S. Effect of intravenous nutrient infusions on food intake in rats. *Physiol. Behav.* **45**, 1223–1226 (1989).
28. Woods, S.C., Stein, L.J., McKay, L.D. & Porte, D. Jr. Suppression of food intake by intravenous nutrients and insulin in the baboon. *Am. J. Physiol.* **247**, R393–R401 (1984).
29. Kanarek, R.B. & Mayer, J. 2-Deoxy-D-glucose induced feeding: relation to diet palatability. *Pharmacol. Biochem. Behav.* **8**, 615–617 (1978).
30. Smith, G.P. & Epstein, A.N. Increased feeding in response to decreased glucose utilization in the rat and monkey. *Am. J. Physiol.* **217**, 1083–1087 (1969).
31. Saladin, R. *et al.* Transient increase in obese gene expression after food intake or insulin administration. *Nature* **377**, 527–529 (1995).
32. Qi, K., Hall, M. & Deckelbaum, R.J. Long-chain polyunsaturated fatty acid accretion in brain. *Curr. Opin. Clin. Nutr. Metab. Care* **5**, 133–138 (2002).
33. Rapoport, S.I. In vivo fatty acid incorporation into brain phosholipids in relation to plasma availability, signal transduction and membrane remodeling. *J. Mol. Neurosci.* **16**, 243–261 (2001).
34. Rapoport, S.I. In vivo labeling of brain phospholipids by long-chain fatty acids: relation to turnover and function. *Lipids* **31** (Suppl.), S97–S101 (1996).
35. Miller, J.C., Gnaedinger, J.M. & Rapoport, S.I. Utilization of plasma fatty acid in rat brain: distribution of [^{14}C]palmitate between oxidative and synthetic pathways. *J. Neurochem.* **49**, 1507–1514 (1987).
36. Goto, M. & Spitzer, J.J. Fatty acid profiles of various lipids in the cerebrospinal fluid. *Proc. Soc. Exp. Biol. Med.* **136**, 1294–1296 (1971).
37. Ruderman, N.B., Saha, A.K., Vavvas, D., Heydrick, S.J. & Kurowski, T.G. Lipid abnormalities in muscle of insulin-resistant rodents. The malonyl CoA hypothesis. *Ann. NY Acad. Sci.* **827**, 221–230 (1997).
38. McGarry, J.D., Mannaerts, G.P. & Foster, D.W. A possible role for malonyl-CoA in the regulation of hepatic fatty acid oxidation and ketogenesis. *J. Clin. Invest.* **60**, 265–270 (1977).
39. Monnikes, H. *et al.* Pathways of Fos expression in locus ceruleus, dorsal vagal complex, and PVN in response to intestinal lipid. *Am. J. Physiol.* **273**, R2059–R2071 (1997).
40. Matzinger, D. *et al.* The role of long chain fatty acids in regulating food intake and cholecystokinin release in humans. *Gut* **46**, 688–693 (2000).
41. Schwartz, G.J., Whitney, A., Skoglund, C., Castonguay, T.W. & Moran, T.H. Decreased responsiveness to dietary fat in Otsuka Long-Evans Tokushima fatty rats lacking CCK-A receptors. *Am. J. Physiol.* **277**, R1144–R1151 (1999).
42. Morgan, K., Obici, S. & Rossetti, L. Hypothalamic responses to long-chain fatty acids are nutritionally regulated. *J. Biol. Chem.* **279**, 31139–31148 (2004).
43. Lam, T.K. *et al.* Hypothalamic sensing of circulating fatty acids is required for glucose homeostasis. *Nat. Med.* **11**, 320–327 (2005).
44. Beverly, J.L. & Martin, R.J. Influence of fatty acid oxidation in lateral hypothalamus on food intake and body composition. *Am. J. Physiol.* **261**, R339–R343 (1991).
45. Hardie, D.G. & Carling, D. The AMP-activated protein kinase—fuel gauge of the mammalian cell? *Eur. J. Biochem.* **246**, 259–273 (1997).
46. Ruderman, N. & Prentki, M. AMP kinase and malonyl-CoA: targets for therapy of the metabolic syndrome. *Nat. Rev. Drug Discov.* **3**, 340–351 (2004).
47. Kemp, B.E. *et al.* Dealing with energy demand: the AMP-activated protein kinase. *Trends Biochem. Sci.* **24**, 22–25 (1999).
48. Minokoshi, Y. *et al.* AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. *Nature* **428**, 569–574 (2004).
49. Andersson, U. *et al.* AMP-activated protein kinase plays a role in the control of food intake. *J. Biol. Chem.* **279**, 12005–12008 (2004).
50. Abu-Elheiga, L., Matzuk, M.M., Abo-Hashema, K.A. & Wakil, S.J. Continuous fatty acid oxidation and reduced fat storage in mice lacking acetyl-CoA carboxylase 2. *Science* **291**, 2613–2616 (2001).
51. Gao, S. & Lane, M.D. Effect of the anorectic fatty acid synthase inhibitor C75 on neuronal activity in the hypothalamus and brainstem. *Proc. Natl. Acad. Sci. USA* **100**, 5628–5633 (2003).
52. Kim, E.K. *et al.* Expression of FAS within hypothalamic neurons: a model for decreased food intake after C75 treatment. *Am. J. Physiol. Endocrinol. Metab.* **283**, E867–E879 (2002).
53. Clegg, D.J., Wortman, M.D., Benoit, S.C., McOsker, C.C. & Seeley, R.J. Comparison of central and peripheral administration of C75 on food intake, body weight, and conditioned taste aversion. *Diabetes* **51**, 3196–3201 (2002).
54. Makimura, H. *et al.* Cerulenin mimics effects of leptin on metabolic rate, food intake, and body weight independent of the melanocortin system, but unlike leptin, cerulenin fails to block neuroendocrine effects of fasting. *Diabetes* **50**, 733–739 (2001).
55. Takahashi, K.A., Smart, J.L., Liu, H. & Cone, R.D. The anorexigenic fatty acid synthase inhibitor, C75, is a nonspecific neuronal activator. *Endocrinology* **145**, 184–193 (2004).
56. Miller, I., Ronnett, G.V., Moran, T.H. & Aja, S. Anorexigenic C75 alters c-Fos in mouse hypothalamic and hindbrain subnuclei. *Neuroreport* **15**, 925–929 (2004).
57. Hu, Z., Cha, S.H., Chohnan, S. & Lane, M.D. Hypothalamic malonyl-CoA as a mediator of feeding behavior. *Proc. Natl. Acad. Sci. USA* **100**, 12624–12629 (2003).
58. Shimokawa, T., Kumar, M.V. & Lane, M.D. Effect of a fatty acid synthase inhibitor on food intake and expression of hypothalamic neuropeptides. *Proc. Natl. Acad. Sci. USA* **99**, 66–71 (2002).
59. Kim, E.K. *et al.* C75, a fatty acid synthase inhibitor, reduces food intake via hypothalamic AMP-activated protein kinase. *J. Biol. Chem.* **279**, 19970–19976 (2004).
60. Thupari, J.N., Landree, L.E., Ronnett, G.V. & Kuhajda, F.P. C75 increases peripheral energy utilization and fatty acid oxidation in diet-induced obesity. *Proc. Natl. Acad. Sci. USA* **99**, 9498–9502 (2002).
61. Landree, L.E. *et al.* C75, a fatty acid synthase inhibitor, modulates AMP-activated protein kinase to alter neuronal energy metabolism. *J. Biol. Chem.* **279**, 3817–3827 (2004).
62. Lavrentyev, E.N., Matta, S.G. & Cook, G.A. Expression of three carnitine palmitoyltransferase-I isoforms in 10 regions of the rat brain during feeding, fasting, and diabetes. *Biochem. Biophys. Res. Commun.* **315**, 174–178 (2004).
63. Friedman, J.M. A war on obesity, not the obese. *Science* **299**, 856–858 (2003).
64. Hill, J.O. & Peters, J.C. Environmental contributions to the obesity epidemic. *Science* **280**, 1371–1374 (1998).
65. Ravussin, E. & Gautier, J.F. Metabolic predictors of weight gain. *Int. J. Obes. Relat. Metab. Disord.* **23** (Suppl. 1), 37–41 (1999).
66. Wang, J. *et al.* Overfeeding rapidly induces leptin and insulin resistance. *Diabetes* **50**, 2786–2791 (2001).
67. Neel, J.V. The 'thrifty genotype' in 1998. *Nutr. Rev.* **57**, S2–S9 (1999).
68. Coleman, D.L. Obese and diabetes: two mutant genes causing diabetes-obesity syndromes in mice. *Diabetologia* **14**, 141–148 (1978).
69. Coleman, D.L. Obesity genes: beneficial effects in heterozygous mice. *Science* **203**, 663–665 (1979).
70. Kersten, S. Mechanisms of nutritional and hormonal regulation of lipogenesis. *EMBO Rep.* **2**, 282–286 (2001).
71. Cinti, S. *et al.* Immunohistochemical localization of leptin and uncoupling protein in white and brown adipose tissue. *Endocrinology* **138**, 797–804 (1997).
72. Frederich, R.C. *et al.* Leptin levels reflect body lipid content in mice: evidence for diet-induced resistance to leptin action. *Nat. Med.* **1**, 1311–1314 (1995).
73. Schwartz, M.W. *et al.* Specificity of leptin action on elevated blood glucose levels and hypothalamic neuropeptide Y gene expression in *ob/ob* mice. *Diabetes* **45**, 531–535 (1996).
74. Schwartz, M.W., Seeley, R.J., Campfield, L.A., Burn, P. & Baskin, D.G. Identification of targets of leptin action in rat hypothalamus. *J. Clin. Invest.* **98**, 1101–1106 (1996).
75. Brief, D.J. & Davis, J.D. Reduction of food intake and body weight by chronic intraventricular insulin infusion. *Brain Res. Bull.* **12**, 571–575 (1984).
76. Obici, S., Zhang, B.B., Karkanias, G. & Rossetti, L. Hypothalamic insulin signaling is required for inhibition of glucose production. *Nat. Med.* **8**, 1376–1382 (2002).
77. Widdowson, P.S., Upton, R., Buckingham, R., Arch, J. & Williams, G. Inhibition of food response to intracerebroventricular injection of leptin is attenuated in rats with diet-induced obesity. *Diabetes* **46**, 1782–1785 (1997).
78. Halaas, J.L. *et al.* Physiological response to long-term peripheral and central leptin infusion in lean and obese mice. *Proc. Natl. Acad. Sci. USA* **94**, 8878–8883 (1997).
79. Thupari, J.N., Landree, L.E., Ronnett, G.V. & Kuhajda, F.P. C75 increases peripheral energy utilization and fatty acid oxidation in diet-induced obesity. *Proc. Natl. Acad. Sci. USA* **99**, 9498–9502 (2002).
80. Kim, K.H., Lopez-Casillas, F., Bai, D.H., Luo, X. & Pape, M.E. Role of reversible phosphorylation of acetyl-CoA carboxylase in long-chain fatty acid synthesis. *FASEB J.* **3**, 2250–2256 (1989).
81. Witters, L.A. & Kemp, B.E. Insulin activation of acetyl-CoA carboxylase accompanied by inhibition of the 5′-AMP-activated protein kinase. *J. Biol. Chem.* **267**, 2864–2867 (1992).