The Role of Hypothalamic Malonyl-CoA in Energy Homeostasis*

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Energy balance is monitored by hypothalamic neurons that respond to peripheral hormonal and afferent neural signals that sense energy status. Recent physiologic, pharmacologic, and genetic evidence has implicated malonyl-CoA, an intermediate in fatty acid synthesis, as a regulatory component of this energy-sensing system. The level of malonyl-CoA in the hypothalamus is dynamically regulated by fasting and feeding, which alter subsequent feeding behavior. Fatty acid synthase (FAS) inhibitors, administered systemically or intracerebroventricularly to lean or obese mice, increase hypothalamic malonyl-CoA leading to the suppression of food intake. Conversely, lowering malonyl-CoA with an acetyl-CoA carboxylase (ACC) inhibitor or by the ectopic expression of malonyl-CoA decarboxylase in the hypothalamus increases food intake and reverses inhibition by FAS inhibitors. Physiologically, the level of hypothalamic malonyl-CoA appears to be determined through phosphorylation/dephosphorylation of ACC by AMP kinase in response to changes in the AMP/ATP ratio, an indicator of energy status. Recent evidence suggests that the brain-specific carnitine-palmitoyl-CoA transferase-1 (CPT1c) may be a regulated target of malonyl-CoA that relays the “malonyl-CoA signal” in hypothalamic neurons that express the orexigenic and anorexigenic neuropeptides that regulate food intake and peripheral energy expenditure. Together these findings support a role for malonyl-CoA as an intermediary in the control of energy homeostasis.

During the past several decades there has been a striking increase in the incidence of obesity and Type 2 diabetes, particularly in children. The etiology of obesity and the metabolic syndrome, a multifaceted obesity-associated disease, involves interactions between environmental and genetic variables. The prevalence of obesity and the potential for therapeutic intervention has generated renewed interest in the underlying metabolic basis of this disease.

Recent advances in the regulation of energy metabolism implicate the central nervous system (CNS), particularly the ancient hypothalamic nuclei that regulate energy homeostasis (1, 2). Endocrine molecules have now been identified that act directly on the brain to alter appetite and peripheral energy expenditure. This was most vividly illustrated by the discovery of the adipocyte-specific hormone leptin (3). Leptin is secreted by adipocytes in proportion to adipose tissue mass and affects both feeding behavior and energy expenditure. The inability to produce functional leptin (4) or its signaling intermediates (5, 6) causes extreme obesity in rodents and humans. Endocrine control of energy homeostasis is one means by which the CNS maintains appropriate body weight. However, recently another novel hypothalamic regulatory mechanism was identified whereby an intermediate in a key energy storage pathway, i.e. malonyl-CoA, serves as a modulator of food intake and energy expenditure. This mechanism was revealed by the observation that inhibitors of fatty acid synthase (FAS) suppress food intake and cause profound weight loss when administered either systemically or centrally to obese or lean mice (7).

Hypothalamic Malonyl-CoA Concentration Is Dynamically Regulated

The initial committed step of de novo fatty acid synthesis, the carboxylation of acetyl-CoA to form malonyl-CoA catalyzed by acetyl-CoA carboxylase (ACC), is situated at the branch point of a metabolic crossroad for acetyl-CoA (Fig. 1). Because this reaction limits the rate of subsequent steps catalyzed by FAS, the ACC-catalyzed step is an ideal site at which to exert regulation. Short-term control by ACC occurs largely through phosphorylation/inhibition by 5'-AMP kinase (AMPK) and by feed-forward allosteric activation by citrate produced by ATP: citrate lyase (8). In some cell types, notably heart and skeletal myocytes, that express little or no FAS, malonyl-CoA is decarboxylated by malonyl-CoA decarboxylase (9). In lipogenic tissues and in hypothalamic neurons malonyl-CoA serves as the basic chain-elongating substrate for the formation of C16 and C18 saturated fatty acids catalyzed by FAS. Malonyl-CoA also acts as an allosteric inhibitor of fatty acid oxidation by suppressing the translocation of fatty acids into mitochondria catalyzed by carnitine palmitoyltransferase-1 (CPT1), the first step in this process (Fig. 2). Thus, in lipogenic tissues this mechanism ensures that fatty acid synthesis and oxidation do not occur concurrently.

Recognition that malonyl-CoA in the CNS plays a central role in the control of food intake and energy expenditure began with the observation that potent pharmacologic inhibitors of FAS (C75 and cerulenin)3 suppress food intake causing substantial weight loss (primarily fat (10)) in obese as well as lean mice (7). The reduction of food intake is rapid (<2 h) and dose-dependent and occurs either by intraperitoneal or intracerebroventricular (icv) administration of the inhibitors, icv delivery of C75 being effective at much lower levels consistent with a CNS site of action (7, 11). Intracerebroventricular C75 rapidly

* This minireview will be reprinted in the 2006 Minireview Compendium, which will be available in January, 2007.

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2 The abbreviations used are: CNS, central nervous system; FAS, fatty acid synthase; ACC, acetyl-CoA carboxylase; AMPK, 5'-AMP kinase; CPT1, carnitine palmitoyltransferase-1; icv, intracerebroventricular; MCD, malonyl-CoA decarboxylase; PPAR, peroxisome proliferator-activated receptor; KO, knock-out.

3 C75 refers to 3-carboxy-4-octyl-2-methylenebutyrolactone and cerulenin refers to (2S,3R)-2,3-epoxy-4-oxo-7E,10E-dodecadienamide.
Minireview: Malonyl-CoA and Energy Homeostasis

Malonyl-CoA is a key molecule in energy metabolism. It is synthesized by acetyl-CoA carboxylase (ACC) and is subsequently used in the synthesis of fatty acids. In the hypothalamus, malonyl-CoA plays a crucial role in the regulation of food intake and energy expenditure.

Increased hypothalamic malonyl-CoA concentration is associated with decreased food intake. This is achieved through the activation of metabolic pathways that reduce the availability of fatty acids, leading to a decrease in the synthesis of neurotransmitters that stimulate appetite.

The hypothalamus expresses ACC and fatty acid synthase (FAS), which are involved in the synthesis of fatty acids. ACC is regulated by multiple mechanisms, including feed-forward activation by citrate and phosphorylation/inactivation by AMPK. Malonyl-CoA can either be decarboxylated by ACC or undergo reductive chain elongation to form long-chain fatty acids catalyzed by FAS.

Translocation of long-chain fatty acyl-CoAs into mitochondria is initiated by acyl transfer to carnitine (to produce a fatty acylcarnitine derivative) catalyzed by CPT1. Once in the mitochondrial matrix, the acyl-CoA can then undergo β-oxidation. Malonyl-CoA is a potent allosteric inhibitor of the CPT1-catalyzed reaction that controls entry of fatty acids into the mitochondria and thereby fatty acid oxidation. It should be noted that the reaction catalyzed by CPT1c has not yet been characterized.

Regulation of Hypothalamic Malonyl-CoA Concentration by Acetyl-CoA Carboxylase and 5′-AMP Kinase

Recent evidence suggests that the wide fluctuations of hypothalamic malonyl-CoA during feeding and fasting cycles described above are caused by changes in the phosphorylation state and activity of ACC mediated by AMPK (8, 16, 17). Changes in the activity of hypothalamic AMPK are consistent with their predicted effect on the level of malonyl-CoA and food intake (18, 19). Both the liver and muscle isofoms of ACC, i.e. ACC1 and ACC2, are known to be phosphorylated and thereby inhibited by AMPK. Moreover, both isofoms are found in hypothalamic neurons. ACC2 and CPT1b are anchored to the outer mitochondrial membrane and are expressed in tissues, e.g. muscle, where malonyl-CoA regulates the CPT1b-mediated translocation of fatty acids into mitochondria.

Although this provides a metabolic rationale for the participation of AMPK and its activators in controlling the level of malonyl-CoA in the hypothalamus through phosphorylation of ACC, the evidence to date is circumstantial and incomplete. However, several lines of evidence are compatible with this concept. First, conditions that lead to the activation of AMPK in the hypothalamus and cells in culture lead to the phosphorylation/inactivation of ACC (20). Second, leptin, an anorexigenic hormone, reduces AMPK activity in the arcuate nucleus and paraventricular nucleus of the hypothalamus (18), which would be expected to cause activation of ACC and thereby increase

Increases the concentration of malonyl-CoA in the hypothalamus (11). Concomitant with the rise in malonyl-CoA, neurons in the arcuate nucleus are activated (as assessed by c-Fos expression (12)) followed by down-regulation of key orexigenic (neuropeptide Y (NPY) and Agouti-related peptide (AgRP)) and up-regulation of anorexigenic (α-melanocyte-stimulating hormone (αMSH) and cocaine-amphetamine-regulated transcript (CART)) neuropeptides in the hypothalamus (7, 11, 13). The arcuate nucleus is a major site at which feeding behavior is initiated in the CNS (1, 2). It should be noted that a subset of hypothalamic neurons express ACC and FAS (12) and that FAS is highly expressed in NPY/AgRP neurons of the arcuate nucleus (14).

Within 2 h after icv injection of C75, hypothalamic malonyl-CoA concentration (quantified by a recycling assay4) increases by ≥4-fold and food intake is rapidly and almost completely suppressed. However, prior injection of an ACC inhibitor, which blocks malonyl-CoA formation, blunts the C75-induced rise in hypothalamic [malonyl-CoA] and prevents the suppression of food intake (11). These findings demonstrate that a pharmacologic blockade of the FAS-catalyzed reaction in the CNS causes the accumulation of malonyl-CoA, which alters feeding behavior. Nutritional/physiological perturbations also markedly alter hypothalamic malonyl-CoA concentration and food intake (11). Thus, in the fasted state that produces hunger, hypothalamic malonyl-CoA concentration is low (0.1–0.2 μM), whereas re-feeding after fasting that produces satiation causes malonyl-CoA levels to rise to 1–1.4 μM (11). It should be noted that the KD of malonyl-CoA (～0.3 μM (38)) for CPT1c, a postulated regulated target of malonyl-CoA (see below), lies within the dynamic range of the hypothalamic malonyl-CoA concentration (0.1–1.4 μM). The KD of CPT1c for malonyl-CoA is similar to that of muscle CPT1b, i.e. 0.15 μM, but lower than that of the liver CPT1a (7–15 μM) (15).

4 The methods used before the present studies for the analysis of malonyl-CoA in rodent hypothalami were not sufficiently sensitive to quantify this metabolite in the small amount of rodent hypothalamic tissue (～10 mg/brain) available. A rapid more sensitive recycling assay was developed to circumvent this limitation (11).
Malonyl-CoA concentration. Finally, the central administration of 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR), an activator of AMPK, lowers hypothalamic malonyl-CoA and stimulates food intake (11, 19, 21). Likewise, AICAR activates the phosphorylation/inhibition of ACC and lowers malonyl-CoA concentration in a hypothalamic cell line in cell culture (21). The quantification of AMP and ATP in the hypothalamus under these conditions has not been reported, most likely because the turnover of ATP and AMP is rapid relative to the time required to dissect the hypothalamus for analysis. Nevertheless, these findings have led to the speculation that during fasting the [AMP]/[ATP] ratio increases in neurons in critical hypothalamic nuclei leading to the activation of AMPK, inactivation of ACC, and a decrease in [malonyl-CoA]. Based on this evidence we propose a model that incorporates these events and leads to changes in feeding behavior and energy expenditure (Fig. 1). This model, although incomplete, is supported by a growing body of pharmacologic and genetic evidence that implicates malonyl-CoA as a central regulator in the signaling pathway.

Lowering Hypothalamic Malonyl-CoA Concentration Leads to Increased Food Intake and Weight Gain

Based on the findings described above it is evident that increasing hypothalamic malonyl-CoA is sufficient to reduce food intake and cause weight loss. However, is a decrease of malonyl-CoA in the CNS sufficient to increase appetite and produce obesity? Two recent reports have addressed this question directly using viral vectors to overexpress malonyl-CoA decarboxylase (MCD) to lower malonyl-CoA in the hypothalamus of rodents. MCD is normally expressed in muscle where it acts as a regulatory enzyme to decarboxylate malonyl-CoA to form acetyl-CoA. When overexpressed in target tissues, it can lower malonyl-CoA concentration (22).

The delivery of a viral MCD expression vector into the ventral medial hypothalamus of mice by bilateral stereotactic injection decreases food intake, increases body weight gain, and reverses the C75-mediated suppression of food intake (21). Similarly, rats expressing a viral MCD vector in the medial basal hypothalamus exhibited increased food intake, increased rate of body weight gain, and became obese over a period of ~15 weeks (23). These findings provide further compelling evidence that hypothalamic malonyl-CoA plays a central role in energy homeostasis and functions physiologically to modulate food intake.

Raising Hypothalamic Malonyl-CoA Concentration Is Closely Correlated with Increased Peripheral Energy Expenditure

In addition to its effect on feeding behavior, raising hypothalamic malonyl-CoA concentration with an FAS inhibitor also increases peripheral energy expenditure (24, 25). This effect was first observed in longitudinal pair-feeding studies, which showed that C75-treated obese mice lose more body weight than controls limited to the same food/caloric intake (10). Consistent with this apparent rise in energy expenditure, C75-treated obese mice exhibit both an increase in oxygen consumption as indicated by indirect calorimetry (26) and increased rates of whole body and skeletal muscle fatty acid oxidation, *i.e.* the oxidation of [14C]oleic acid to 14CO2 (24). Comprising the largest tissue mass in the body and the greatest consumer of fatty acids, skeletal muscle is the major contributor to whole body energy expenditure.

The inhibition of FAS by the icv administration of C75 rapidly up-regulates hypothalamic malonyl-CoA (11), which initiates a cascade of events leading to a rapid (~2 h) increase of fatty acid oxidation both *in vivo* and in skeletal muscle explants (24, 25). This increase of fatty acid oxidation is the result of phosphorylation/inactivation of ACC2 in muscle, which lowers malonyl-CoA (24). Lowering muscle malonyl-CoA, an allosteric inhibitor of muscle-specific CPT1b, facilitates the translocation of fatty acids into mitochondria (9) and thus oxidation (Fig. 2). These events are closely correlated with increased expression of PPARα, a transcriptional activator of fatty acid oxidizing enzymes, and of UCP3, the thermogenic mitochondrial uncoupling protein of skeletal muscle (27). Phentolamine, an α-adrenergic blocking agent, prevents these effects suggesting that central FAS inhibition mediates its peripheral effects through the sympathetic nervous system (24). Concomitant with the up-regulation of UCP3 and PPARα is a marked increase in the expression of PGC1α, a transcriptional co-activator of the UCP3 and PPARα genes. Also associated with these changes are increases in the expression of the enzymes of fatty acid oxidation, the tricarboxylic acid cycle, and oxidative phosphorylation, as well as mitochondrial biogenesis (25). Treatment with C75 (by intraperitoneal or intracerebroventricular administration) for 3 days leads to an increase in the number of mitochondria in both white and red skeletal muscle.

The responses of lean and obese mice to repeated administration of FAS inhibitors differ markedly (10). C75 lowers food intake and adiposity of both lean and obese mice during the initial phase of treatment. However, lean mice become resistant to the repetitive administration of FAS inhibitors after ~2 days and then exhibit no further reduction of food intake or body weight with food intake returning to pretreatment levels. Resistance to the FAS inhibitor in obese mice occurs only after body fat mass is reduced to that of lean controls (27, 28). These findings indicate that C75 acts through a signaling system with a negative regulatory component.

Because of the proclivity for obesity in Western society, a pharmacologic approach for obesity treatment has long been sought. Therapeutic intervention in human obesity to date, however, has been largely unsuccessful, suggesting the need to consider new drug targets for appetite reduction. For the reasons described above, hypothalamic malonyl-CoA would appear to be a viable target. In this connection a recent report described a young patient with a rare MCD deficiency who

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5 It has been reported that C75 directly activates CPT1a, which could account for increased translocation of fatty acids into mitochondria leading to β-oxidation in peripheral tissues (26, 41). However, because the icv delivery of C75 is sufficient to activate peripheral fatty acid oxidation and energy expenditure, this effect is more likely to be initiated indirectly via the CNS and signal transmission to peripheral tissues via the sympathetic nervous system. It should also be noted that recent biochemical studies suggest that C75 undergoes conversion to its CoA thioester derivative before its inhibitory action (42).
refused to eat (29). This scenario predicts an elevated malonyl-CoA level in the CNS because of an impaired breakdown of malonyl-CoA and suggests that this pathway may play a role in human satiety. Thus, small molecules that act by increasing hypothalamic malonyl-CoA offer an alternative strategy worth exploring as obesity drugs (28, 30).

Possible Neuronal Targets of Malonyl-CoA

An important missing link is the downstream molecular mechanism by which malonyl-CoA acts to inhibit food intake and increase energy expenditure; ergo what is the cellular target of malonyl-CoA and how is its signal transmitted? McGarry et al. (31–33) elucidated the role of malonyl-CoA in suppressing hepatic fatty acid oxidation and ketogenesis some 20 years ago. Malonyl-CoA is an allosteric inhibitor of the CPT1 isoforms in the liver (CPT1a) and muscle (CPT1b) and limits the entry of cytosolic fatty acids (as their CoA thioester derivatives) into mitochondria for oxidation (Fig. 2) (34, 35). Thus, when hepatic de novo fatty acid synthesis is activated and malonyl-CoA concentration rises, fatty acid degradation is suppressed. Conversely, during times of energy deficit, fatty acid oxidation is de-repressed as the level of malonyl-CoA falls. In this way, malonyl-CoA serves two roles: 1) as the elongation unit for de novo fatty acid synthesis and 2) as a signaling molecule that controls the rate of mitochondrial fatty acid oxidation. Most tissues utilize both functions to some degree, but certain tissues, e.g. skeletal muscle, rely only on the signaling role of malonyl-CoA.

Muscle possesses unique metabolic characteristics in that, this tissue uses fatty acids as its primary fuel but contains little or no FAS and expresses a specialized mitochondria-bound ACC, i.e. ACC2. The juxtaposition of ACC2 and CPT1b in the outer mitochondrial membrane and the relative dearth of FAS argue for the primary role of malonyl-CoA as a signaling molecule in muscle. Because malonyl-CoA is not used for de novo fatty acid synthesis in muscle, its build-up is prevented through decarboxylation catalyzed by MCD, an enzyme present in abundance in this tissue (33). Thus, the flux of synthesis and turnover of malonyl-CoA mediates the fatty acid oxidative potential of muscle. Therefore, there is a strong precedent for malonyl-CoA as a signaling intermediate.

Neurons possess unique metabolic properties worthy of consideration. In the fed state neurons use glucose as primary fuel, whereas in the fasted state ketones derived from hepatic fatty acid oxidation serve as primary fuel. Although the extent to which peripheral fatty acids are metabolized in the CNS is uncertain, metabolic logic suggests that fatty acids (as their CoA derivatives) probably serve a regulatory role. In this connection it has been reported that the oleate administered by icv injection inhibits food intake (36, 37). The blood-brain barrier in the region of the arcuate nucleus is “leaky” (12), and thus hypothalamic fatty acids could be derived from the blood. If hypothalamic fatty acids are of exogenous origin, it seems unlikely that they would repress food intake because blood levels of fatty acids rise during fasting, a physiological state in which appetite increases rather than decreases. The physiological source of brain fatty acids, however, is not known. Alternatively, hypothalamic fatty acids may be of endogenous origin derived from either phospholipid turnover or de novo biosynthesis. Further research will be necessary to determine the source of fatty acids in the region(s) of the hypothalamus that monitor energy status.

It is evident that hypothalamic neurons possess the metabolic machinery for fatty acid synthesis (12, 14) and a dynamic range of malonyl-CoA (see above and Ref. 11) compatible with a role in the regulation of CPT1 (15). Might the downstream target of neuronal malonyl-CoA simply be CPT1 that is subject to inhibition by malonyl-CoA? Evidence shows that pharmacologic inhibition of CPT1 in the CNS of rodents results in a reduction of food intake and a loss of body weight, consistent with a role for CPT1 via this mechanism (38). In our laboratory, however, we have been unable to detect robust expression of CPT1a or CPT1b in hypothalamic neurons compatible with a role in food intake management.

Recently, however, another brain-specific CPT1 was identified based on its high DNA and amino acid sequence similarity to those of CPT1a (70%) and CPT1b (66%) (39). This newly discovered putative CPT1, i.e. CPT1c, is expressed exclusively in the brain, notably in hypothalamic nuclei known to regulate energy homeostasis (39), particularly the arcuate nucleus. Because CPT1c binds malonyl-CoA with an affinity (K_D ≈ 0.3 μM) within the dynamic range of malonyl-CoA in the hypothalamus (0.1–1.4 μM) (see above), we speculate this CPT1 is the target of malonyl-CoA in the pathway that regulates feeding behavior (39, 40). What is not known is the enzymatic role of CPT1c or how it is linked to a downstream regulatory target that controls food intake and/or energy expenditure. In heterologous systems, CPT1c neither catalyzes fatty acyl transfer to carnitine from a diverse group of acyl-CoAs as donor substrates nor supports fatty acid oxidation in cells transfected with a CPT1c expression vector (39, 40). These observations suggest that CPT1c may have a unique activation mechanism or may catalyze an unconventional reaction.

The phenotype of CPT1c KO mice suggests that CPT1c may be a target of malonyl-CoA in the CNS and is consistent with a role in regulating energy homeostasis. KO animals exhibit decreased food intake and lower body weight compared with wild-type littermates when fed a normal or low fat diet (40). Given that malonyl-CoA is an inhibitor of CPT1a and CPT1b and binds to CPT1c, we suggest that malonyl-CoA might inhibit CPT1c. Two recent findings are consistent with a role for CPT1c in mediating the malonyl-CoA-induced signal by a mechanism, as yet undefined, involving hypothalamic fatty acyl-CoA (Fig. 1). CPT1c KO mice exhibit: 1) a large increase/accumulation of fatty acyl-CoAs in the hypothalamus and 2) a reduced whole body fatty acid oxidation rate (16), apparently a consequence of impaired signaling from the CNS to skeletal muscle (see above and Refs. 23 and 25).

Paradoxically, CPT1c KO animals lack resistance to the effect of a high fat diet. CPT1c KO mice are more susceptible to diet-induced obesity and gain substantially more weight than wild-type littermates on a high fat diet (40). Heterozygotes on a high fat diet exhibit an intermediate phenotype suggesting co-

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6 Y. Dai, M. J. Wolfgang, and M. D. Lane, unpublished results.
7 M. J. Wolfgang, G. I. Shulman, and M. D. Lane, unpublished results.
dominant expression.\(^8\) Food intake of KO mice remains lower than wild-type mice on a high fat diet, but peripheral energy expenditure is lower in KO animals. How can this paradox be explained? There are two likely explanations: 1) malonyl-CoA may have another target; and/or 2) fatty acids play a major signaling role in energy expenditure. The answer could lie in the action of fatty acids and fatty acyl-CoAs in the CNS. FAS inhibitors raise hypothalamic malonyl-CoA but also inhibit de novo fatty acid synthesis. CPT1c KO animals possess normal levels of FAS; therefore, only the effects of malonyl-CoA on CPT1c would be inferred. It is evident that further work must be done to clarify the role of fatty acids and the role of CPT1c in the regulatory circuitry that regulates feeding behavior and energy expenditure.

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\(^8\) M. J. Wolfgang and M. D. Lane, unpublished results.