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Minireview: Malonyl CoA, AMP-Activated Protein Kinase, and Adiposity

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An increasing body of evidence has linked AMP-activated protein kinase (AMPK) and malonyl coenzyme A (CoA) to the regulation of energy balance. Thus, factors that activate AMPK and decrease the concentration of malonyl CoA in peripheral tissues, such as exercise, decrease triglyceride accumulation in the adipocyte and other cells. The data reviewed here suggest that this is related to the fact that these factors concurrently increase fatty acid oxidation, decrease the esterification of fatty acids to form glycerolipids, and, by mechanisms still unknown, increase energy expenditure. Malonyl CoA contributes to these events because it is an allosteric inhibitor of carnitine palmitoyltransferase, the enzyme that controls the transfer of long-chain fatty acyl CoA from the cytosol to the mitochondria, where they are oxidized. AMPK activation in turn increases fatty acid oxidation (by effects on enzymes that govern malonyl CoA synthesis and possibly its degradation) and inhibits triglyceride synthesis. It also increases the expression of uncoupling proteins and the transcriptional regulator peroxisome proliferator-activated receptor γ coactivator-1α (PGC1α), which could possibly increase energy expenditure. Recent studies suggest that the ability of leptin, adiponectin, 5′-aminoimidazole 4-carboxamide riboside (AICAR), adrenergic agonists, and metformin to diminish adiposity may be mediated, at least in part, by AMPK activation in peripheral tissues. In addition, preliminary studies suggest that malonyl CoA and AMPK take part in fuel-sensing and signaling mechanisms in the hypothalamus that could regulate food intake and energy expenditure. (*Endocrinology* 144: 5166–5171, 2003)

OBESITY ORIGINATES WHEN for a period of time energy intake exceeds energy expenditure and the caloric excess accumulates as triglyceride in adipose tissue (1). Although a remarkable body of research in the past 10 yr has implicated such factors as leptin and its receptor and various neuropeptides in the pathophysiology of obesity (2, 3), at a molecular level the reason some individuals accumulate fat beyond what is healthy for them remains an enigma. In this brief review, we will examine the hypothesis that a contributory factor could be dysregulation of the malonyl CoA-AMP-activated protein kinase (AMPK) fuel-sensing and signaling network.

Malonyl CoA, AMPK, and Obesity: Theoretical Considerations

Obesity and fuel partitioning

A number of lines of evidence have suggested that obesity is a disorder of fuel partitioning. First, humans and experimental animals are generally able to adjust rates of glucose and amino acid oxidation to the quantity of these nutrients in their diet, whereas they are often less able to adjust fat oxidation to its dietary content (1). Second, and perhaps even more compelling, preobese or formerly obese individuals of normal weight have been shown to have a higher respiratory quotient (RQ) than control nonobese people, indicating that they have a lower rate of fat oxidation (4–6) (Fig. 1). Furthermore, as obesity develops or redevelops in these individuals, their RQ decreases to control values or below, suggesting that an increase in fatty acid oxidation occurs as their triglyceride stores expand. Thus, an obese individual achieves a normal balance of fat and carbohydrate oxidation, but only after increasing his or her endogenous lipid stores. One factor that could modulate these events is the ambient concentration of free fatty acids (plasma and intracellular), which is generally elevated in obese compared with lean individuals. Another is the concentration of malonyl CoA.

Malonyl CoA regulates fatty acid oxidation in response to changes in cellular fuel availability and energy expenditure

Malonyl CoA is both an intermediate in the *de novo* synthesis of long-chain fatty acids and an inhibitor of carnitine palmitoyltransferase (CPT1), the enzyme that controls the transfer of long-chain fatty acyl CoA into mitochondria (7) (Fig. 2). By virtue of the latter action, malonyl CoA has been shown to regulate intracellular fatty acid oxidation in a variety of tissues including liver (7), muscle (8, 9), the pancreatic β-cell (10), and endothelium (11), and it very likely performs a similar role in the adipocyte (12) and the central nervous system.

A remarkable feature of malonyl CoA, first worked out in skeletal muscle, is that its concentration changes in response to alterations in cellular fuel availability and energy expenditure. Thus, it was shown by Saha *et al.* (13) that incubation of rat muscle with glucose and insulin (fuel surfeit) and denervation (inactivity) both lead to an increase in the con-

Abbreviations: ACC, Acetyl CoA carboxylase; AICAR, 5′-aminoimidazole 4-carboxamide riboside; AMPK, AMP-activated protein kinase; CoA, coenzyme A; CPT, carnitine palmitoyltransferase; DGAT, acyl CoA:diacylglycerol transferase; GPAT, glycerol 3-phosphate acyltransferase; MCD, malonyl CoA decarboxylase; mGPAT, mitochondrial isoform of GPAT; RQ, respiratory quotient; UCP, uncoupling protein.

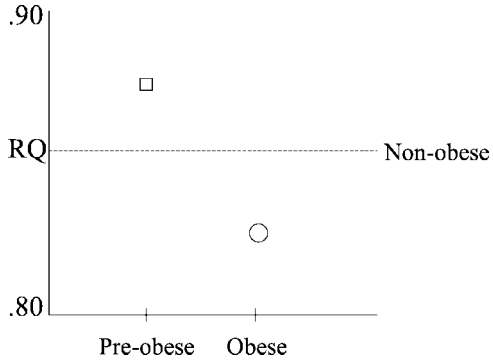

FIG. 1. RQ and obesity status. Preobese and formerly obese individuals have a higher RQ than do nonobese control subjects (4–6). As they gain or regain weight, their RQ diminishes to values equal to or lower than those of control subjects. Presumably, this is a consequence of the greater availability of lipid fuel as cellular triglyceride stores expand; however, this remains to be proven. Values in the figure are calculated from the studies in Refs. 4–6.

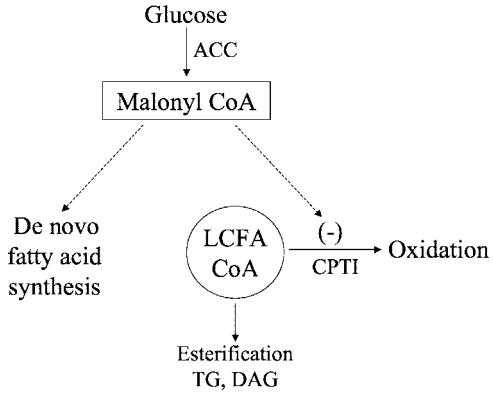

FIG. 2. Malonyl CoA and fatty acid partitioning. Malonyl CoA is an inhibitor of CPT1, the enzyme that controls the transfer of long-chain fatty acyl (LCFA) CoA molecules from the cytosol into mitochondria where they are oxidized. When malonyl CoA levels are elevated (see Fig. 3), CPT1 is inhibited, and the esterification of LCFA to form triglycerides (TG) and diacylglycerol (DAG) is favored.

centration of malonyl CoA, in keeping with the decreased need to generate ATP from fatty acid oxidation in these situations, whereas incubation in a medium devoid of glucose (fuel deprivation) and muscle contraction (increased energy expenditure) have the opposite effect.

Acetyl CoA carboxylase and its regulation by citrate and AMPK in skeletal muscle

Central players in the regulation of malonyl CoA in muscle and other tissues include: acetyl CoA carboxylase (ACC), the rate-limiting enzyme in malonyl CoA synthesis; cytosolic citrate, an allosteric activator of ACC and the precursor of its substrate, cytosolic acetyl CoA; and AMPK, an enzyme activated by decreases in the energy state of a cell, as reflected by increases in the AMP/ATP and creatine to creatine phosphate ratios (9, 14–16). Activated AMPK phosphorylates ACC at Ser 79 and inhibits its activation by citrate. As presently conceived (Fig. 3), muscle contraction regulates ACC solely by activating AMPK. In contrast, a surfeit of glucose increases the concentration of malonyl CoA both by increasing the cytosolic concentration of citrate (17) and by decreasing the activity of AMPK (18), and glucose deprivation decreases the concentration of malonyl CoA by causing changes in citrate concentration (13) and AMPK activity in the opposite direction (18). Not shown in the scheme depicted in Fig. 3 is that AMPK activation during muscle contraction (19) and voluntary exercise (12) also leads to the phosphorylation and activation of malonyl CoA decarboxylase (MCD), a major enzyme responsible for malonyl CoA degradation according to some investigators (12, 20), but not all (21). If so Mother Nature appears to have gone to considerable lengths to ensure that malonyl CoA levels decrease when AMPK is activated in exercising muscle.

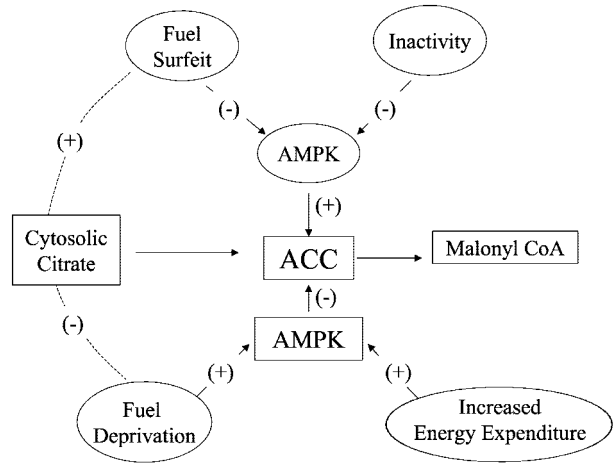

FIG. 3. Positive and negative regulation of ACC in skeletal muscle. Changes in fuel availability and energy expenditure in the muscle cell lead to alterations in the cytosolic concentration of citrate, an allosteric activator of ACC and the activity of AMPK, which phosphorylates and inhibits ACC. This in turn alters the concentration of malonyl CoA and the rate of fatty acid oxidation. Recent studies indicate that the adipocyte-derived hormones, leptin and adiponectin, and most likely α- and β-adrenergic agonists can affect this mechanism by activating AMPK. How they do so remains to be determined.

Changes in tissues other than muscle and additional effects of AMPK activation on lipid metabolism

A malonyl CoA fuel-sensing and signaling mechanism that is regulated by AMPK has been demonstrated in muscle (13), the pancreatic β-cell (10), and endothelium (11), and it is almost certainly present in adipose tissue (12), glucose-sensing cells in the central nervous system (22–25) (see below), liver, and elsewhere (14). Differences exist in these tissues with respect to the isoforms of ACC and AMPK present, whether AMPK also regulates ACC at a transcriptional level, and the principal fate of malonyl CoA once formed (*i.e.* use for fatty acid synthesis *vs.* degradation by malonyl CoA decarboxylase); however, the regulation of malonyl CoA concentration appears to be similar. Thus, in each of these cells evidence for regulation of malonyl CoA by AMPK has been found, and where studied (*e.g.* pancreatic β-cell), changes in cell citrate in response to glucose have been observed (10, 14, 26). Of particular note is the study of Park *et al.* (12) in which they observed that voluntary exercise leads to activation of AMPK and MCD and an acute decrease in ACC activity (indicative of its phosphorylation) in liver and adipose tissue as well as muscle. In addition, they found

that the activity of glycerol 3-phosphate acyltransferase (GPAT), the first committed step in the synthesis of triglyceride and diacylglycerol, was diminished in liver and adipose tissue. Similar changes were observed in rats administered a small dose of the AMPK activator 5′-aminoimidazole 4-carboxamide riboside (AICAR) 2 h previously, strongly suggesting that the effects of exercise were AMPK mediated. These findings are noteworthy because they indicate that AMPK activation during exercise very likely inhibits triglyceride synthesis at the same time it activates fatty acid oxidation (Fig. 4). They also suggest that the effects of exercise on cell signaling and presumably other events extend to adipose tissue and liver and possibly other organs, in addition to muscle.

Direct Evidence Linking Malonyl CoA and AMPK to Obesity

Chronic AICAR administration and adiposity

Studies by Winder *et al.* (27) provided the first direct evidence that AMPK activation can diminish adiposity. They administered the AMPK activator AICAR (1000 mg/kg body weight) to rats on 5 consecutive days (Monday to Friday) of each week over a 28-d period. On this regimen, food intake was diminished; therefore, they added a pair-fed control group. At the end of the study, body weight was identical in the AICAR-treated and pair-fed rats; however, the mass of the epididymal and retroperitoneal fat pads was diminished by more than 30%. A potential confounding factor was that the mass of the liver was increased by nearly 40%. Saha *et al.* (20) repeated this study using a smaller dose of AICAR (250 mg/kg·d), administered to rats on Monday, Wednesday, and Friday of each week for either 4 or 15 wk. Food intake was diminished on the day the rats were injected with AICAR. On subsequent days, the rats ate more; however, overall food intake was still somewhat lower in the treatment group. As in the Winder study, adipose tissue mass was diminished by 30–40%; however, no hepatomegaly was observed. These investigators also observed decreases in hepatic and muscle triglyceride content, indicating that ectopic lipid deposition was diminished. In yet another study (28), a more modest decrease in intraabdominal adiposity of 15%, compared with pair-fed animals, was observed in fatty rats (fa/fa) treated with 500 mg/kg of AICAR administered daily. Once again, AICAR caused a slight decrease in food intake. Collectively, these studies suggest that the decrease in adiposity caused by AICAR is attributable, at least in part, to an increase in energy expenditure. To our knowledge, this possibility has not been directly tested; however, AICAR and muscle contraction have both been shown to increase the expression of the uncoupling proteins UCP3 (29–31) and UCP2 (31), and the transcription factor PGC1 (32) in rat skeletal muscle. Where studied, these changes were associated with increases in the activities of the mitochondrial enzymes, citrate synthase and 3-hydroxyacyl CoA dehydrogenase, both of which are known to increase in proportion to mitochondrial volume and density (30). It is not known whether AMPK activation causes changes in uncoupling potential or otherwise alters mitochondrial function in liver and adipose tissue. Finally, as discussed in the minireview in this series by Hardie (16), AICAR can have actions not attributable to AMPK activation. Thus, it remains to be determined whether all of its effects in the studies described here are AMPK mediated.

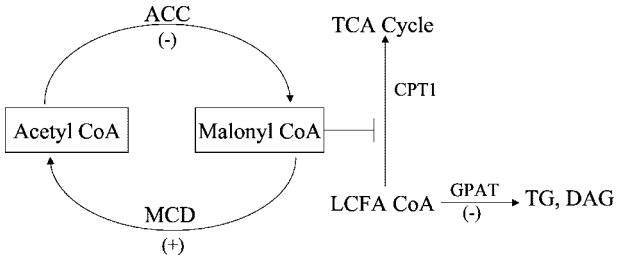

FIG. 4. Concurrent regulation of ACC, MCD, and GPAT by AMPK. Published data indicate that these effects occur *in vivo* in liver, in adipose tissue, and, except for GPAT inhibition, in skeletal muscle after exercise (12). The net effect is to increase the β-oxidation of fatty acids and to decrease their use for the synthesis of esterified lipids such as triglycerides (TG), diacylglycerol (DAG) phospholipids, and ceramide (data not shown). Presumably, inactivity and a sustained increase in glucose use by these tissues in the presence of insulin would initially have opposite effects, thereby favoring glycerolipid synthesis. LCFA, Long-chain fatty acid; TCA, tricarboxylic acid.

Decreased adiposity in mice deficient in ACC2

ACC exists in two isoforms. ACC1 is thought principally to generate the malonyl CoA used for *de novo* fatty acid synthesis, and ACC2, the dominant isoform in cardiac and skeletal muscle, is thought to generate the malonyl CoA that inhibits CPT1 (33). Abu-Elheiga and Wakil and their coworkers (33) have generated a mouse in which 2.5 kb of the ACC2 gene was deleted to diminish its activity. As expected, the concentration of malonyl CoA was markedly diminished, and fatty acid oxidation was increased in heart and skeletal muscle of these mice. In addition, the mass of adipose tissue was significantly diminished, as was the lipid content of liver (which contains both ACC1 and ACC2) and muscle. Intriguingly, the decrease in adipose mass occurred even though the mice ate nearly 80% more food than did control mice in which ACC2 was not mutated (note that ACC1 or ACCα, the major isoform in liver and adipose tissue, was not diminished). Thus, these animals presumably had both an increase in energy expenditure and, possibly, a central or peripheral alteration that increased appetite and/or diminished satiety. Later studies revealed increases in UCP3 mRNA in skeletal muscle and UCP2 mRNA in adipose tissue and heart of these mice (34); however, UCP1 in brown adipose tissue, the uncoupling protein most closely linked to increases in energy expenditure, was unchanged.

Mice lacking GPAT and acyl CoA:diacylglycerol transferase (DGAT)

The mitochondrial isoform of GPAT (mGPAT), which catalyzes the first committed step in glycerolipid synthesis, is subject to nutritional and hormonal regulation (35). As already mentioned, it is inhibited by AMPK (see also Ref. 35) and, in keeping with this, its activity is diminished in both liver and adipose tissue in the rat after exercise (12). Hammond *et al.* (36) have recently reported that mice deficient in mGPAT have reduced body weight and liver triglyceride

content and a 30–35% decrease in the mass of their intraabdominal fat pads that was statistically significant in females.

A similar phenotype has been observed in mice lacking DGAT, the enzyme that catalyzes the final step in the glycerol phosphate pathway leading to triglyceride synthesis. As reported by Smith *et al.* (37), these mice are viable and capable of synthesizing triglyceride; however, they have less adipose tissue than control mice, and they are resistant to diet-induced obesity. Food intake was not decreased in these mice; however, whole body O_2 consumption was increased by 20%, due at least in part to an increase in physical activity. In preliminary studies (Saha, A. K., unpublished observations), we have found that the activity of DGAT, like that of GPAT, is diminished when AMPK is activated.

Leptin and adiponectin

The classic endogenous antiobesity hormone is leptin, a fat cell-derived protein that both suppresses food intake and increases energy expenditure (38). Leptin also prevents the accumulation of lipid in nonadipose tissues, thereby preventing the functional impairment often referred to as lipotoxicity (39). A link between leptin and AMPK (and presumably malonyl CoA) was first demonstrated by B. Kahn and her co-workers (40), who observed that leptin administered peripherally both acutely (15–30 min) and for a more prolonged period (up to 6 h) increases AMPK activity in skeletal muscle. The acute effect of leptin was attributed to a direct action on skeletal muscle, and the later occurring and more sustained effect to an increase in centrally mediated sympathetic nervous system activity. In keeping with this notion, the late-occurring effect of leptin was inhibited by muscle denervation and by phentolamine, an α-adrenergic antagonist, and it could be reproduced by injecting a smaller amount of leptin into the third ventricle.

A second fat cell-derived hormone that has been linked to AMPK and malonyl CoA is adiponectin, also referred to as ACRP30. A large body of work has shown an inverse relation between low levels of circulating adiponectin and a variety of abnormalities associated with the metabolic syndrome, including insulin resistance, type 2 diabetes, atherosclerosis, and obesity (41–44). In addition, the administration of the globular subunit of adiponectin (g-adiponectin) has been reported to diminish obesity and insulin resistance in obese mice (44). Two recent reports (44, 45) have demonstrated that adiponectin and g-adiponectin activate AMPK and diminish ACC activity in muscle and liver. In addition, g-adiponectin has been shown to activate AMPK in adipose tissue (46).

Pharmacological agents

To date, no pharmacological agents for treating obesity have targeted AMPK or malonyl CoA. On the other hand, two compounds that are widely used in the therapy of type 2 diabetes, metformin (47) and rosiglitazone (48), have been reported to activate AMPK. This effect of metformin has been demonstrated *in vitro* and *in vivo* in skeletal muscle (48–50), and that of rosiglitazone in cultured cells (48) and in a preliminary report in rat liver and adipose tissue *in vivo* (51). Both of these agents have been shown to increase insulin sensitivity, as has AMPK activation by AICAR (52, 53). Neither compound, when used as a monotherapy, causes a striking decrease in adiposity; indeed, thiazolidinediones such as rosiglitazone, increase peripheral adipose mass, even when they cause decreases in ectopic lipid (muscle, liver, pancreatic β-cells) deposition (39).

TABLE 1. Effect of factors that have been reported to diminish adiposity on malonyl CoA concentration, and AMPK activity in peripheral tissue, and whole-body energy expenditure

Factor	Malonyl CoA	AMPK	Energy expenditure
Exercise	−	+	+
AICAR	−	+	+
Leptin	−	+	+
Adiponectin	−	+	ND
ACC2 deficiency	−	ND	+

ND, Not done. +, Increased; −, diminished.

Malonyl CoA, AMPK, and the Hypothalamus

An emerging body of evidence, most of it still preliminary, has raised the possibility that malonyl CoA and AMPK fuel-sensing and signaling mechanisms, similar to those in muscle, exist in the hypothalamus where they play a role in initiating signaling events that regulate food intake. Thus: 1) AMPK activity has been shown to diminish in various hypothalamic nuclei of rodents as a result of refeeding after a fast (23), glucose (23) and insulin administration (24), and the injection of leptin (40), all of which diminish food intake; 2) the concentration of malonyl CoA diminishes with starvation in the hypothalamus (25), in keeping with the increase in AMPK activity; and 3) the central administration of C75, a fatty acid synthase inhibitor that markedly diminishes food intake and decreases body weight in rodents (25, 54), prevents the decrease in malonyl CoA that occurs in the hypothalamus during starvation. Collectively, these studies suggest that factors that increase the concentration of malonyl CoA in specific hypothalamic nuclei diminish food intake, whereas factors that decrease the concentration of malonyl CoA have the opposite effect. Whether the increased food intake observed in ACC2-deficient mice (33) is due to such a decrease in malonyl CoA remains to be determined. It has recently been reported (55) that inhibition of CPT1 in the mouse hypothalamus with ribozyme or pharmacological agents, like an increase in malonyl CoA, diminished food intake. See also the paper by Rossetti (56) in this series.

Concluding Remarks

As reviewed here, dysregulation of the malonyl CoA and AMPK fuel-sensing and signaling mechanisms could account for the alterations in fatty acid partitioning and energy expenditure that predispose to obesity (Fig. 1 and Table 1). As discussed elsewhere (14), it could also provide a biochemical explanation for the thrifty gene hypothesis proposed by Neel (57) to explain the survival value to our hunter-gatherer ancestors of an increased ability to store energy intake as fat. For all of these reasons, it will be of considerable interest to determine whether genetic alterations in components or regulators of the malonyl CoA-AMPK fuel-sensing mechanisms are linked to obesity in different populations.

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