PERSPECTIVES: CELL BIOLOGY

Chewing the Fat—ACC and Energy Balance

Neil Ruderman and Jeffrey S. Flier

Recent progress in understanding how energy balance and body weight are regulated has been marked by the discovery of hormones, such as leptin, and the neural pathways operating downstream of these hormones that bring about physiological changes (*1*). These burgeoning discoveries have diverted attention away from more traditional studies of the intracellular metabolic machinery that controls the synthesis and oxidation of lipid fuels. One component of this metabolic machinery, malonyl coenzyme A (CoA), is a critical participant in the regulation of lipid fuel metabolism as it has effects on both fatty acid oxidation in the mitochondria and the synthesis of various lipids. Disturbances in malonyl CoA regulation leading to alterations in signal transduction may contribute to insulin resistance (*2*) and obesity (*2*, *3*), although as yet the evidence for this is indirect. On page 2613 of this issue, Abu-Elheiga *et al.* (*4*) now show that malonyl CoA in certain key tissues (such as, heart and skeletal muscle) is a crucial regulator of fat metabolism and energy balance.

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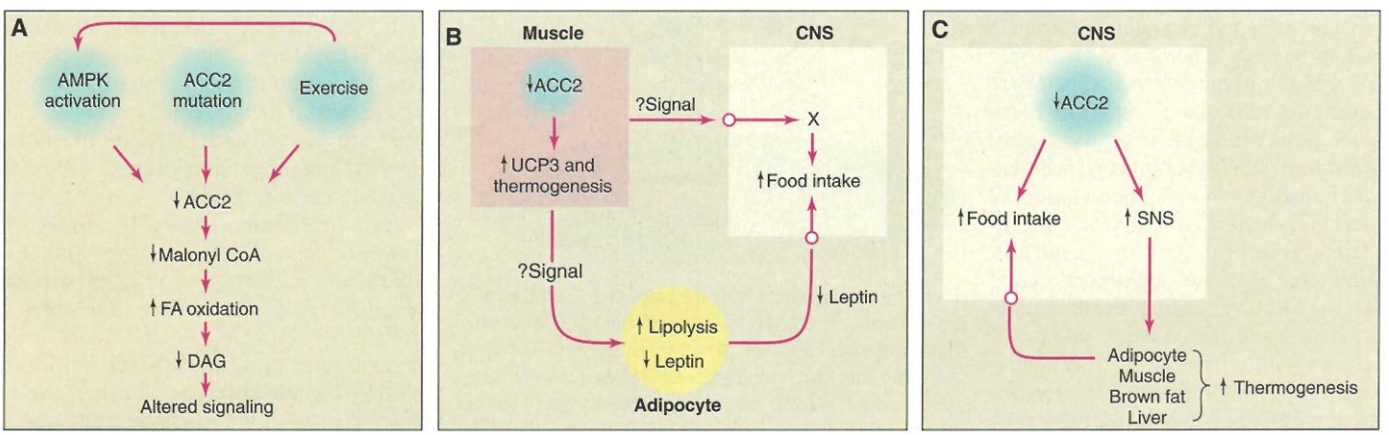
Malonyl CoA—synthesized by the enzyme acetyl CoA carboxylase (ACC)—has two principal tasks in the cell. It provides acetyl groups that are incorporated into fatty acids during their synthesis and it inhibits the enzyme carnitine palmitoyltransferase, which controls transfer of long-chain fatty acyl CoA molecules to the mitochondria, where they are oxidized to provide energy (*5*). Increasing the fuel supply of muscle cells by treating them with glucose and insulin increases the concentration of malonyl CoA and diminishes fatty acid oxidation by increasing the activity of ACC2 (also called ACCβ), the predominant ACC isoform in cardiac and skeletal muscle. Conversely, exercise lowers the concentration of malonyl CoA by activating an AMP-activated protein kinase (AMPK), which phosphorylates and inhibits ACC2 (*2*).

Abu-Elheiga *et al.* address the question of whether malonyl CoA is a regulator of fat metabolism and energy balance by creating a mouse strain that lacks ACC2 (*4*). ACC1 (also called ACCα), the dominant isoform in liver and adipose tissue, is encoded by a separate gene, and is expressed normally in these mice. The ACC2-deficient mice showed a marked decrease in the concentration of malonyl CoA in skeletal muscle (30-fold) and heart muscle (10-fold) and a substantial increase in fatty acid oxidation in skeletal muscle. Furthermore, fatty acid stores in adipose tissue and liver, two organs in which ACC1 is the dominant isoform, were markedly decreased (in adipose tissue by 50%), despite normal concentrations of malonyl CoA. Fatty acids and glucose in plasma and glycogen in the liver were diminished by 20 to 30%. In addition, the ACC-deficient mice consumed 20 to 30% more food than wild-type mice, yet they maintained or, even more surprisingly, lost body weight, suggesting that they were expending energy at an increased rate. Finally, despite the depletion of their lipid stores, these mice appeared normal morphologically, grew at the expected rate, and bred normally. These findings raise three obvious questions: What accounts for the loss of fatty acid stores in adipose tissue and liver of the ACC-deficient mice? Why do these mice eat more? Why do they lose or at best maintain body weight despite an increase in food intake?



Eat more, weigh less. Increased food intake and heat production in ACC2-deficient mice. **(A)** A decrease in malonyl CoA, induced by lack of ACC2, results in an increase in fatty acid oxidation and decreases in the production of lipid signaling molecules such as diacylglycerol (DAG). **(B)** In skeletal muscle, the lack of ACC2 may possibly increase heat production through an increase in the expression of UCP3. Secondary increases in food intake and the lipolysis of fat cells may reflect production of yet-to-be-identified signaling molecules that enable muscle to communicate with the central nervous system (CNS) and with adipose tissue. **(C)** A decrease in ACC2 in the CNS might contribute to the phenotype of ACC2-deficient mice through its effects on the brain, resulting in increased food intake and energy expenditure. Whether a decrease in leptin contributes to increased food intake in either (B) or (C) is unclear. SNS, sympathetic nervous system.

The authors speculate that the primary event initiating these changes is an increase in fatty acid oxidation in the mitochondria of muscle and liver cells. A decrease in a pool of malonyl CoA would release the block on carnitine palmitoyltransferase activity, increasing the transport of long-chain fatty acids into the mitochondria and promoting their oxidation to produce energy. How might a change in fatty acid oxidation in muscle and liver affect the energy balance of the entire body? The authors propose that increased food intake is caused by a 30% decrease in plasma leptin (a molecule that regulates hunger), which may be secondary to the decrease in fat tissue. However, this explanations does not address how an increase in fatty acid oxidation in muscle and liver signals fat cells (adipocytes)

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to increase the breakdown of fat stores (triglycerides), or why whole-body energy expenditure is enhanced, given that a low concentration of leptin would decrease energy expenditure. Furthermore, it is not clear from the data whether the increase in food intake was an early event, preceding the elevation of plasma leptin, or whether it occurred later, as the authors propose.

Alternatively, the observed changes may reflect a loss of ACC2 activity in tissues other than muscle. Previous work by Abu-Elheiga (*6*) suggests that ACC2 in skeletal muscle is associated with mitochondria and that the malonyl CoA that it generates (versus that produced by ACC1) is an important regulator of carnitine palmitoyltransferase and fatty acid oxidation. Because some ACC2 may be present in cells in which ACC1 is the dominant isoform—such as pancreatic islets, human adipose tissue, and brain—it is possible that fatty acid oxidation and, secondarily, various signaling and downstream events are altered by loss of ACC2 in these or other tissues. Consistent with this notion are recent results suggesting that a pharmacologically induced increase in malonyl CoA in the hypothalamus both decreases the expression of neuropeptide Y and food intake and increases production of heat (thermogenesis) in obese mice (*5*). Thus, loss of ACC2 in hypothalamic neurons that regulate energy balance could alter energy intake and expenditure by modulating the production of malonyl CoA or another key metabolic intermediate. ACC has been detected in select neurons of the brain, notably in the arcuate nucleus of the hypothalamus (*5*), although which ACC isoforms are present in these neurons has not been determined.

Another very intriguing possibility is that the increased food intake and thermogenesis, and decreased adiposity of the ACC-deficient mice are caused by an increase in the expression of uncoupling protein–3 (UCP3), which exists exclusively in muscle (see the figure). UCP3 is a close relative of UCP1, which is found solely in brown fat, and similarly appears to be important for energy balance and lipid metabolism (*7*). Transgenic mice engineered to overexpress UCP3 in skeletal muscle are hyperphagic (that is, they overeat), yet they weigh less than their wild-type littermates (*8*). In addition, these mice show a striking decrease in fat tissue and have low glucose levels, as do the ACC-deficient mice. Intriguingly, activation of AMPK in muscle, whether by exercise or incubation with the AMPK activator 5-amino-imidazole 4-carboxamide riboside (AICAR), increases the expression of UCP3 within 1 to 2 hours (*9*). Because activation of AMPK in these situations is very rapid (seconds to minutes), as is ACC2 inhibition (*2*), it is conceivable that the increase in fatty acid oxidation in these muscles is responsible for increases in UCP3 mRNA and protein. That UCP3 expression in muscle is increased during starvation and other situations in which fatty acid oxidation is elevated is consistent with this notion, although in starvation, the increase in UCP3 is not sufficient to increase whole-body thermogenesis. The status of muscle UCP3 in ACC-deficient mice is eagerly awaited.

Finally, a number of studies provide evidence for cross talk between fat cells and other organs, most notably skeletal muscle and the central nervous system (*10*). Indeed, the discovery that adipocyte-derived molecules—such as leptin, tumor necrosis factor–α, gAcrp30 (*11*), and most recently resistin (*12*)—have systemic metabolic effects has firmly established the adipocyte as an endocrine organ. The results of Abu-Elheiga *et al.* and the findings in mice that overexpress UCP3 suggest that skeletal muscle could act in a similar manner to regulate whole-body energy homeostasis. Studies of altered signaling and gene transcription in muscle cells when fatty acid oxidation is increased or decreased, and an evaluation of whether and how these alterations are communicated to other organs are clearly in order.

The new work demonstrates that mice deficient in ACC2 have major alterations in systemic energy balance, with decreased body fat despite increased food intake. These findings provide important insights into the part played by malonyl CoA, the regulatory molecule produced by ACC2, in fatty acid oxidation in muscle and other cells. They also raise questions about the cellular sites and signal transduction pathways through which ACC2 exerts its newly identified systemic job. Whatever the mechanism, inhibition of ACC2 may be a plausible target for the design of new anti-obesity therapeutics.

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PERSPECTIVES: NEUROSCIENCE

The Song Does Not Remain the Same

Daniel Margoliash

You say tomato and I say to-mah-to. Why? This question may keep songwriters amused but has kept behavioral neurobiologists, who study speech development in humans and song development in birds, feverishly busy for decades. When humans learn to speak or to play an instrument they require guidance from a teacher, followed by a laborious period of trial-and-error imitation and iterative improvement. It is not yet clear how the teacher's instructions are represented in the neuronal circuitry of the brain and how they produce changes in behavior. Vocal learning in songbirds, a lengthy and complex process, is a valuable model for understanding how the human brain learns sequences of behavior from a teacher. But the complexities of song learning in birds have made systematic quantification of the process difficult. This, in turn, has hampered the matching of measures of altered neural activity with the evolving sounds produced by juvenile birds as they mature. On page 2564 of this week's *Science*, Tchernichovski and colleagues (*1*) combine a clever behavioral experiment on juvenile zebra finches with modern signal-analysis techniques to provide the first atomic description of song learning in birds. The results reveal several new and unsuspected features of vocal development.

Juvenile male zebra finches learn their song between 35 and 90 days after hatching (the sensitive period for vocal learning) by imitating the songs of adult male tutors. Zebra finch songs consist of complex sounds (syllables) separated by silent intervals. To obtain a baseline for the untutored vocal material of juvenile zebra finches, the investigators delayed song learning by preventing their exposure to adult males. Then, starting at 43 days of age, the juveniles were allowed to peck at a key, which triggered brief bouts of song from a small loudspeaker inside a model bird placed in the cage. Counterintuitively, limiting juveniles to brief periods of tutor-

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