Burning fat not so sweet

One way to get lean may be to selectively burn fat instead of glucose. That's the thinking behind efforts to develop drugs against molecules that regulate the type of fuel the body burns. But new experiments in mice by Kyle Hoehn *et al.*[1] call this assumption into question. The researchers bumped up fat burning by genetically or pharmacologically manipulating enzymes that control it. These manipulations did not make mice fed a high-fat diet resistant to weight gain and did not shield them from insulin resistance. Do the findings shut the door on approaches to increase fatty acid oxidation, or do they raise more questions? We asked the experts.

Debbie Muoio:

There is no disputing that lipid oxidation confers a metabolic advantage during starvation and exercise, but the role of fuel selection *per se* in combating metabolic disease remains elusive. The new report clearly challenges the widely held theory that it is healthier to burn fat than glucose. A genetically engineered shift to fat catabolism was offset by diminished glucose oxidation and a reciprocal rise in *de novo* lipogenesis. Thus, fat-burning mice were equally susceptible to weight gain and glucose intolerance. These results conflict with human studies reporting a positive association between a high respiratory quotient (indicative of carbohydrate oxidation) and disease risk. The discrepancies might stem from confounding factors that are difficult to control in human studies; alternatively, the mouse models might not mimic human physiology. Although further work is necessary, the new findings offer provocative evidence that "a calorie is a calorie."

Associate Professor of Medicine, Stedman Center, Duke University, Durham, North Carolina, USA.

Antonio Vidal-Puig:

The main conclusions extracted from the experimental design are that the primary function of fatty acid oxidation is to provide energy, which is not a primary regulator of energy expenditure and energy balance—and that fatty acid and carbohydrate oxidation are integrated components of an efficient allostatic mechanism designed to maintain appropriate bioenergetic supply under anabolic and catabolic conditions. From this physiological role, it cannot be inferred that strategies aiming at increasing fatty acid oxidation will not facilitate weight loss and improve insulin sensitivity in obese individuals, particularly when they are on a diet—or recapitulate the beneficial effects of exercise by modifying body composition, insulin sensitivity and resistance to weight gain. Future experiments, such as bumping up fatty acid oxidation in obese mouse models, could help clarify the open questions.

Professor of Molecular Nutrition and Metabolism, University of Cambridge, Cambridge, UK.

K. Sreekumaran Nair:

Mitochondrial ATP synthesis through beta oxidation is a relatively less efficient way to generate ATP than by glucose oxidation and, therefore, theoretically causes fat loss. That notion is not supported by Hoehn *et al.*[1]. The researchers increased fatty acid oxidation by acutely derepressing an enzyme that transports fatty acids into mitochondria, carnitine palmitoyltransferase (CPT-1). One way they did this was with an activator of AMP-activated protein kinase (AMPK). They did not observe an increase in energy expenditure or fat loss. Perhaps different conclusions may have been reached with more chronic activator application—which, in addition to derepressing CPT-1, may induce mitochondrial biogenesis and increase the expression of many mitochondrial proteins, including those that regulate uncoupling.

The two key factors that determine cellular energy requirements are ATP hydrolysis by thermodynamically unfavorable reactions and, within mitochondria, uncoupling of oxidative phosphorylation (a mechanism to generate heat). However, drugs targeting these two reactions alone may not cause fat loss unless targeted to lower energy intake, either pharmacologically or through reduced food intake. Increased fuel oxidation may also increase oxidative damage unless the antioxidant buffer system is simultaneously enhanced.

Professor of Medicine, Mayo Clinic, Rochester, Minnesota, USA.

Eric Ravussin:

Hoehn *et al.*[1] challenge the common belief that pharmacological or genetic strategies to enhance fat oxidation may be ineffective for the treatment of obesity and type 2 diabetes. It is, however, too early for 'big pharma' or biotech companies to discard their compounds increasing fat oxidation in preclinical or clinical studies.

Hoehn *et al.*[1] find no benefit from quelling the activity of acetyl-CoA carboxylase-2 (ACC-2), an enzyme downstream of AMPK that regulates fat oxidation through CPT-1. But, despite this elegant study, much evidence points in a different direction, suggesting that decreasing the activity of ACC-2 and therefore increasing fat oxidation confers a protective effect against diet-induced obesity in rodents. Furthermore, studies in humans have clearly shown that individuals with impaired fat oxidation have a greater propensity for weight gain.

It is only when inhibitors of ACC-2 or activators of AMPK are administered to humans that we will definitely know whether directly 'melting the fat' is a viable strategy for the treatment of obesity and diabetes.

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COMPETING INTERESTS STATEMENT

The author declares competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturemedicine/.

1. Hoehn, K.L. *et al. Cell Metab.* **11**, 70–76 (2010).