Leucing Weight with a Futile Cycle

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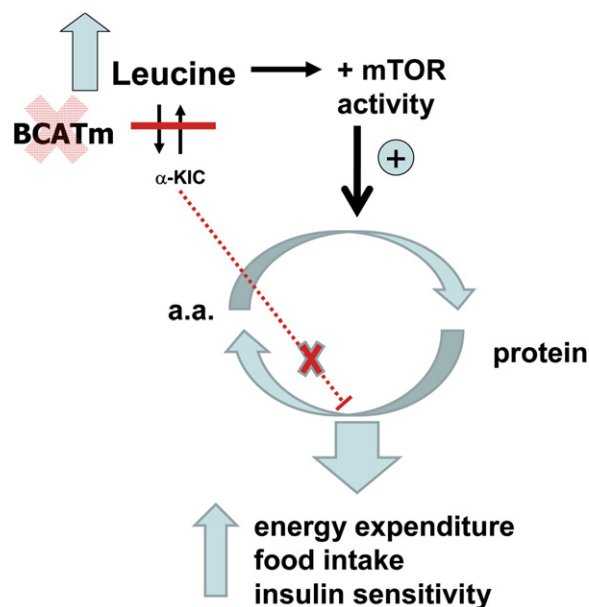DOI 10.1016/j.cmet.2007.08.009

The essential amino acid leucine serves as a signal that activates protein synthesis. A new study by She et al. (2007) in this issue of *Cell Metabolism* shows that raising circulating leucine by blocking leucine breakdown drives a futile cycle of protein synthesis and degradation that contributes to higher-energy expenditure, resistance to dietary obesity, and improved insulin sensitivity.

In the continuing search for the magic combination of nutrients that will facilitate weight loss or prevent obesity, high-protein diets have broad popularity. However, there is scant evidence for a long-term effect of dietary protein on body composition (Astrup, 2005; Lejeune et al., 2006). This is because elaborate, but as yet poorly understood mechanisms, regulate the intake and utilization of dietary protein, and their component amino acids, for energy and protein synthesis. The branched-chain amino acids (BCAA) are essential in the diet, meaning that they cannot be made by mammals. BCAA differ from other essential amino acids in that they are primarily metabolized in peripheral tissues, mainly muscle, but not by the liver. Thus, circulating BCAA rise after a protein meal, and this serves as a signal to activate protein synthesis via activation of mTOR kinase and its downstream targets (Marshall, 2006). Leucine may also act in the hypothalamus, via mTOR, to suppress food intake (Cota et al., 2006). To assess the long-term consequences of elevated leucine signaling, She et al. (2007) engineered a mouse lacking mitochondrial branched chain aminotransferase (BCATm), the first enzyme in the catabolism of BCAA.

BCAA metabolism begins with transamination by BCATm, a mitochondrial enzyme present in most tissues, to produce the α-ketoacids. $BCATm^{-/-}$ mice ate less food when provided with regular chow that included relatively high levels of BCAA. Therefore, She et al. took advantage of the ability of rodents to select diets based on amino acid composition. When provided with two diets, one

Figure 1. Deletion of BCATm Initiates an Energy-Wasting Futile Cycle
Deletion of BCATm prevents the first step in BCAA catabolism, increasing circulating leucine (and other BCAA), which results in a futile and energy-consuming cycle of increased protein synthesis and breakdown. While in wild-type mice, leucine breakdown produces α-ketoisocaproate (KIC) that is thought to simultaneously slow protein breakdown, this inhibition does not occur in the BCATm null mice. The mice show increased food intake for their body size yet remain lean due to increased energy expenditure. They are also insulin sensitive and resistant to becoming obese on high-fat diet.

normal and one devoid of BCAA, the $BCATm^{-/-}$ mice selected more of the BCAA-free diet but ate similar amounts of protein and total calories. Thus, they were consuming 20%–30% more food relative to their smaller body size. The mice appeared healthy and despite their higher caloric intake maintained a lower body weight and were half as fat as controls. When challenged with a high-fat diet that caused obesity in controls, the BCAT null mice remained lean. Measurements of oxygen consumption revealed an increased metabolic rate (~20%–30% over 24 hr) in the $BCATm^{-/-}$ mice, so they could eat more without gaining further weight, the dieter's dream.

As expected, the blockade in BCAA metabolism in the BCATm null mice markedly increased circulating BCAA including leucine by >10-fold and increased protein synthesis by ~40% in most tissues. Body and organ weights, however, were not increased, suggesting that protein breakdown was also increased. Increased urinary 3-methyl-histidine excretion (an indicator of skeletal muscle proteolysis) confirmed higher rates of protein degradation. The importance of the increased protein turnover for the elevated energy expenditure was supported by the demonstration that

inhibiting mTOR-mediated protein synthesis with rapamycin partially normalized energy expenditure. Thus, this novel mouse model provides proof of principle that an increase in energy utilization for a "futile" cycle can increase whole-body energy expenditure and regulate body fat over the long term (Figure 1).

In contrast to the 10-fold increased circulating leucine in BCATm deficiency, increasing dietary leucine can only increase levels by less than 2-fold (Zhang et al., 2007). Furthermore, diet-induced increases in leucine simultaneously stimulate protein synthesis and slow protein degradation, resulting in the net accumulation of tissue protein during growth or recovery from stress. This occurs because the product of the leucine metabolism, α-ketoisocaproic acid (KIC), inhibits proteolysis (Mitch et al., 1981). The block in leucine catabolism in the $BCATm^{-/-}$ mice prevents the generation of KIC that would normally inhibit protein breakdown, resulting in a futile cycle. Although circulating KIC concentrations were unchanged in the $BCATm^{-/-}$, it seems likely that levels of KIC within tissues such as skeletal muscle would be decreased. Further research should address this question. Unfortunately for dieters, it appears unlikely that the tactic used by the $BCATm^{-/-}$ mice to avoid weight gain, i.e., a big increase in protein turnover, can be achieved by merely ingesting high-protein diets or leucine supplements.

As with all genetically engineered animal models, the development of $BCATm^{-/-}$ mice raises many more questions than can be answered in an initial report. For example, what happens to the excess BCAA, are they metabolized through an alternative pathway, and if so where, or are they excreted? Also, do they have effects that have not yet been detected? For example, BCAA are transported by the same transporter as tryptophan, so what happens to tryptophan (a precursor of serotonin) availability within tissues such as the brain and what are the consequences? The $BCATm^{-/-}$ mice were also more glucose tolerant and insulin sensitive, even when placed on a high-fat diet. It is unclear whether this results simply from their leanness or whether additional mechanisms are involved. Also, the increased insulin sensitivity may contribute to higher protein synthesis, which remains to be tested.

Elaborate mechanisms normally match energy intake to expenditure so that body weight is regulated with narrow limits (Schwartz and Porte, 2005). At first glance, the hyperphagia of the $BCATm^{-/-}$ mice could be viewed as evidence that high levels of circulating leucine in the periphery may not lead to elevated hypothalamic leucine that is known to inhibit food intake (Cota et al., 2006). However, it seems likely that this pathway was not operative, as, if it had been, the animals may have become even more hyperphagic. The effects of hypothalamic mTOR blockade in the $BCATm^{-/-}$ mice would therefore be revealing.

The mechanism of metabolic inefficiency in the BCATm null mouse stands in contrast to several other mouse models of resistance to dietary obesity (Evans et al., 2004). More commonly, mice increase energy expenditure though induction of uncoupling proteins (UCPs) in brown adipose tissue mitochondria, increasing a proton leak that "wastes" energy as heat. She et al. could not detect any increase in UCP proteins in brown adipose tissue (BAT) or muscle of BCAT null animals. Since adult humans lack brown adipose tissue, it is possible that revving up protein turnover by manipulating BCATm activity through pharmacological means is worth exploring as a treatment for obesity in humans, as She et al. speculate. Additional studies of mechanisms through which leucine signals protein turnover and food intake may offer an additional lifeline for the majority of us who are trying to resist weight gain in our sedentary society.

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