



Getting AMP'ed

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A few months ago I wrote a *Viewpoint* about an enzyme called AMP Kinase (AMPK), which has been getting a lot of attention because of its involvement in fat burning and insulin sensitivity. AMPK is found in many organs, including "energetic" tissues like fat, liver, and muscle. AMPK is an ancient enzyme, meaning that some version of it can be found in organisms as diverse as yeast, worms, plants, and humans.

In lower organisms, AMPK-like proteins act as a sort of 'fuel gauge', detecting when energy levels are low and altering biochemical pathways inside cells to generate more. This general effect also occurs in mammals like us. AMPK activation leads to increased sugar uptake in muscle and the burning of fatty acids in liver, among other things.

These actions would be predicted to have a beneficial effect in obesity and diabetes, by reducing blood sugar levels and by burning triglycerides that can interfere with insulin signaling pathways in muscle and liver. Two of the most popular oral agents for type 2 diabetes, metformin and the thiazolidinediones, stimulate AMPK, which may account for some of their therapeutic actions. As you might imagine, there is enormous interest among pharmaceutical companies to produce newer and more powerful drugs that activate AMPK for use in obesity and diabetes.

Two new studies have just appeared that put a new wrinkle into the AMPK story. These papers show that AMPK is expressed in the areas of the brain that control appetite and food intake. As you might predict from a protein that acts as a sensor for low energy levels, activation of AMPK in the brain (specifically, in parts of the hypothalamus) induces food-seeking behavior. In fact, hormones or proteins that are known to increase hunger, like ghrelin and AGRP, induce AMPK activity. Conversely, agents that diminish appetite, like leptin and MC4 receptor agonists, decrease AMPK activity in the hypothalamus. Furthermore, adding a supercharged version of AMPK to the brain of a mouse causes the animal to eat more and gain weight, while a so-called "dominant negative" enzyme (which not only doesn't work well by itself but also messes up any normal copies of the enzyme that are hanging around) causes mice to eat less and lose weight.

The implication of these studies is that drugs that activate AMPK might have beneficial effects on insulin sensitivity in peripheral tissues like liver and muscle, but paradoxically, this benefit might be negated by increased food intake and body weight. Similarly, drugs that antagonize the effects of AMPK in the brain would be expected to cause people to lose weight, but might also promote insulin resistance in liver and muscle. This conundrum will spur research into *tissue-specific* modulators of AMPK, which might simultaneously reduce AMPK activity in the hypothalamus,

while stimulating the enzyme in muscle and liver. It may be a lot to ask, but hey, a guy can dream....

References

Ulrika Andersson, Karin Filipsson, Caroline R. Abbott, Angela Woods, Kirsty Smith, Stephen R. Bloom, David Carling, and Caroline J. Small. AMP-activated Protein Kinase Plays a Role in the Control of Food Intake. *Journal of Biological Chemistry*, Mar 2004; 279: 12005 - 12008.

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