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A new paradigm for metabolic health: reduced intake of dietary branched-chain amino acids

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Obesity is an increasing problem worldwide. While even a modest reduction in weight can improve the health of overweight and obese people, and reduce the risk of developing associated diseases such as diabetes, cardiovascular disease, and cancer, most people have trouble losing weight by cutting calories.

For many years, so-called "fad" diets have promoted the idea that altering the source of calories (*e.g.* "low fat" or "low carb" diets) can help promote weight loss. While sustainable weight loss with such diets remains elusive for may people, the fundamental premise behind this idea – the concept that not all calories are equivalent – is likely correct. While most such popularized diet plans have focused on the negative health effects of dietary fat or sugar, studies by our laboratory and others have linked low protein diets with both improved metabolic health and a decreased risk of diabetes in humans.

Dietary protein is made up of amino acids, and two years ago we showed that feeding young, healthy mice a diet with low levels of the three amino acids leucine, isoleucine, and valine – collectively known as the branched-chain amino acids, or BCAAs – promotes metabolic health. Since the BCAAs are essential, we can't eliminate these from the diet, but we were able to reduce levels by 2/3rds with no negative effects on mouse health. While these results were somewhat surprising – many humans take BCAA supplements to help build muscle mass – they fit well with other studies showing that blood levels of BCAAs correlate with insulin resistance in both humans and rodents.

In our recent report, we extended these studies to mice that were obese and pre-diabetic due to consumption of a high-fat, high-sugar energy dense "Western" diet. We tested the hypothesis that reducing dietary BCAAs might be able to restore metabolic health to these mice. We discovered that feeding these mice a low BCAA diet rapidly improved their metabolic health, making them as lean as mice that had never eaten a Western diet and restoring their ability to regulate blood sugar.

These metabolic improvements occurred even though the mice could eat as much food as they wanted. Their food consumption actually ramped up as the experiment progressed, but their energy expenditure also increased dramatically, so extra food calories were burned off as heat. While the exact physiological and molecular mechanisms responsible for the metabolic benefits of a low BCAA diet are not yet understood, a hormone called FGF21 produced by the liver may be involved. We are continuing our research into the role of FGF21 and other factors in the response to dietary BCAAs.

One puzzle about our study is that BCAA supplements are routinely taken by many athletes without obvious negative effects on metabolic health – indeed, many health benefits have been attributed to BCAAs. We think that

the effect of dietary BCAAs on health might be modulated by exercise, and that's something we want to explore.

If humans respond to dietary BCAAs in a way that is similar to mice, we think that lowering the amount of BCAAs in the diet – or identifying pharmaceuticals that mimic the effects of a low BCAA diet – could be an effective way to treat or prevent metabolic syndrome. Since the mice in our studies could eat as much as they wanted, reduced-BCAA diets might be easier for people to stick with than diets based on calorie-counting. We are now working to find out if humans respond to a low BCAA diet the same way mice do.