Blocked brain enzyme decreases appetite and promotes weight loss

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Imagine being able to tone down appetite and promote weight loss, while improving the body's ability to handle blood sugar levels. That's just what Tony Means, PhD, and his team at the Duke University Medical Center were able to do when they blocked a brain enzyme, CaMKK2, in mice.

"We believe we have identified an important drug development target that could potentially turn into a metabolic triple play: appetite control, weight loss and blood sugar management," said Means, who is the Nanaline H. Duke Professor and Chairman of Pharmacology and Cancer Biology.

For many years, scientists have been identifying and testing every step of the appetite stimulation and suppression pathways in search of a target. Such research is considered critical to finding ways for people to better control their weight and minimize their risk of developing diabetes, heart disease and other health conditions.

Activation of the enzyme CaMKK2 is just one step in the appetite stimulation pathway located in the hypothalamus section of the brain. An empty stomach releases the hormone ghrelin, which launches a cascade of signals that ultimately results in increased appetite.

Means and colleagues believed that CaMKK2 in the ghrelin pathway might be a likely candidate for study, because it activates AMPK, an enzyme that stimulates animals to eat and gain weight. They tested their theory in several ways, the results of which are published in the May issue of Cell Metabolism. The work was funded by NIH grants, as well as by the Australian Research Council, National Heart Foundation, and the National Health and Medical Research Council of Australia.

First they blocked CaMKK2 in mice with a specialized molecule inhibitor and then measured food intake. These mice ate significantly less food than untreated mice during the six days in which they were evaluated, and also lost body weight, which led the scientists to think they might be on to something.

Next they studied a group of mice that normally do not make CaMKK2 and found that the molecule inhibitor did not change feeding behavior or reduce weight. "The fact that blocking CaMKK2 worked in normal mice to make them eat less and lose weight, but not in mice missing the enzyme, provides compelling evidence that CaMKK2 signaling is a requirement for appetite control," Means said.

They also studied both normal mice and mice missing CaMKK2 to learn how these types responded to low-fat and high-fat diets. After nearly 30 weeks on the specific diets, the normal mice on the high-fat diet became diabetic – they were unable to respond to insulin and weren't able to manage blood sugar levels well. In contrast, the normal mice on a low-fat diet stayed healthy.

In mice missing CaMKK2, the scientists found that they stayed healthy regardless of whether they were on a low-fat or high-fat diet. The CAMKK2-negative mice apparently were protected from changes that lead to diabetes in a high-fat diet.

"Remarkably, we find that blocking CaMKK2 in the brain prevents the deposits of fat in liver and skeletal muscle that are characteristic of obese, diabetic patients," Means said. "We find this very exciting and are trying to understand the mechanism responsible for this protective effect, as well as to identify more potent drugs to inhibit CaMKK2."

Source: Duke University Medical Center

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