Enzyme Crucial to Insulin Resistance Found in Brain

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Stephen Benoit, PhD

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The discovery is a major step in obesity and metabolic research because insulin plays a significant role in areas of the brain that control food intake, body weight and glucose regulation.

The researchers detail their findings in the September issue of the Journal of Clinical Investigation, the publication of the American Society of Clinical Investigation, an honor society of physician-

scientists. The article is available online at www.jci.org .

Stephen Benoit, PhD, an associate professor in the psychiatry department at UC, participated in the study, which also included scientists from the University of Texas Southwestern Medical Center, the University of Paris and Vanderbilt University. UC research assistants William Abplanalp and Christopher Kemp also participated in the study.

Using animal models, the research team found that the enzyme PKC-theta was expressed in the hypothalamus, a region of the brain that controls body weight and glucose regulation. Exposure of the central nervous system to the fatty acid palmitic acid activated hypothalamic PKC-theta in the hypothalamus. In turn, this activation impaired the function of insulin as well as the hormone leptin, which is released by fat cells and also plays a key role in energy intake and expenditure.

“So when the PKC-theta enzyme is active—for instance, when a diet high in fat is consumed—it’s turning off insulin signaling prematurely,” says Benoit. “And that signaling cascade is important to ultimately controlling food intake and body weight.

“If you remove insulin and leptin signaling from the hypothalamus, an animal can become obese or diabetic—it lacks the ability to sense the correct metabolic environment. In other words, it doesn’t know that it’s full and needs to stop eating.”

Humans commonly ingest palmitic acid through the diet, Benoit says, particularly in dairy products and meat.

The findings have important implications for nutritional counseling and drug discovery, Benoit says.

“Depending on how selectively PKC-theta is expressed in the brain, the

idea of inhibiting its activity represents an interesting potential new drug target," he says.

In addition, Benoit says, the findings will help provide insight into why rapid change in the regulation system occurs in response to a high-fat diet—even something as brief as a weekend binge of hamburgers, ice cream and other fatty foods.

"We know that diets that are high in fat can cause insulin resistance very rapidly," he says. "And even if one withdraws the high-fat diet later, the impairment can remain. So understanding how that may happen in the central nervous system may have some insight for our understanding of the impact of even brief periods of certain kinds of foods."

Provided by University of Cincinnati (news : web)