Gene oppositely controlled by dietary protein, sugar

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Researchers have discovered a gene in flies whose activity rises and falls depending upon the amount of protein and sugar in the insects' diets. The findings, reported in the April issue of Cell Metabolism, might shed light on the way the insects' bodies—and perhaps those of humans too—handle dietary extremes, including high-protein, low-carb diets like the Atkins, according to the researchers. These findings are also yielding new clues about the links between diet and life span.

The gene, which the researchers call tobi (short for target of brain insulin), encodes an evolutionarily conserved a-glucosidase enzyme that converts stored glycogen into glucose.

" This gene is activated by high protein and repressed by sugar," said Michael Pankratz of Forschungszentrum Karlsruhe in Germany, who is now at the Fritz Lipmann Institute. "The question is: Why would the body need such a mechanism for releasing glucose under specific dietary conditions?"

High-protein diets might hold one answer, Pankratz said. For instance, when people consume high-protein, low-carb diets, insulin is released, stimulating cells to take in sugar from the bloodstream. (Most people associate insulin with sugar, he said, but indeed insulin is also released in response to the amino acid building blocks of proteins.) Given that little to no sugar is coming in, this can lead to hypoglycemia, or low blood sugar. The body therefore needs a second mechanism to release glucose from glycogen. "We think this is what's happening [in the flies]," he

said. “It’s a sensitive mechanism for dealing with extreme dietary conditions.”

In mammals, one of the most important systems for controlling metabolism consists of the antagonistic actions of insulin and glucagon, the researchers explained. Upon high sugar intake, insulin is secreted by cells in the pancreas to maintain steady blood sugar levels. When blood glucose is low, glucagon is secreted by other pancreatic cells, causing the release of glucose from glycogen breakdown. The antagonism between insulin and glucagon is not strict, the researchers noted, since amino acids boost both insulin and glucagon secretion.

Earlier studies also identified insulin- and glucagon-like peptides in Drosophila fruit flies, but questions remained about how those signals act.

In the new study, by analyzing changes in gene activity in flies lacking insulin-producing cells, the researchers were led to tobi. They further found that tobi levels increased when flies consumed a protein-rich yeast paste and decreased when the insects ate a sugary concoction. That pattern of tobi expression is reminiscent of the hormone glucagon in mammals, the researchers noted, suggesting that the gene may be controlled by an analogous hormone.

Earlier studies had shown that flies lacking insulin-producing cells (which also express lower tobi levels) live longer. Indeed, the researchers found that this was true—but only in flies fed the high-protein diet.

Exactly what role tobi might play in life span will be a subject of further study, Pankratz said.

“The current study indicates that proteins may have a greater effect than sugars on insulin signaling, and evidence is growing that quality and not

only quantity of calories taken in has an influence on life span," the researchers said. "Therefore, teasing apart the relative contributions of dietary proteins and sugars in insulin signaling should prove insightful."

"What is novel and exciting in the work of [Pankratz and colleagues] is the combination of gene regulation studies, endocrinology, and physiology in a model genetic organism whose genome and gene regulatory linkages can be readily compared to the human genome," wrote Eric Rulifson of the University of California, San Francisco, in an accompanying commentary. "Given the accumulating parallels between the islet-like cells of Drosophila and the pancreatic islets of mammals, it would not be surprising if this homeostatic mechanism, and possibly others yet to be found, is evolutionarily conserved between flies and humans."

Source: Cell Press