SOUTHWESTERN NEWS

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UT Southwestern researchers uncover process for sugar-induced fat formation

DALLAS – Oct. 18, 2004 - Researchers at UT Southwestern Medical Center at Dallas are one step closer to understanding how high carbohydrate diets lead to obesity and diabetes.

Dr. Kosaku Uyeda, professor of biochemistry, has shown that a single protein called carbohydrate response element binding protein (ChREBP), discovered by his research group, activates several genes that cause cells in the liver to turn sugar into fat.

Their work appears in two studies in *Proceedings of the National Academy of Sciences*. The first study, published in an earlier issue, is available online, and the second, also online, will appear in an upcoming issue of *PNAS*.

"Purifying ChREBP from rat livers took two postdoctoral fellows two years of very hard work," said Dr. Uyeda, senior author of both studies and a research scientist at the Veterans Affairs North Texas Health Care System. "With the discovery of this factor, the biochemical mechanism of how carbohydrates are converted to fat has become clearer."

Eating meals high in carbohydrates or sugars leads the body to do several things. Some of the sugars are immediately converted to energy while the rest of the sugars are converted to fat. The sugar-to-fat conversion occurs two ways – an immediate response, where enzymes are mobilized to rapidly convert sugars into fat; and a slower response, in which several different genes are turned on and off, creating more enzymes that can also turn sugar into fat. ChREBP is involved in the slow response.

ChREBP is a type of protein called a transcription factor. Transcription factors work in the cell nucleus to turn genes on and off in response to a signal. In the case of ChREBP, the signal is glucose, a simple sugar formed when carbohydrates are broken down during digestion. Glucose enters the bloodstream and, through transport molecules, enters cells where it is broken down into even smaller pieces. These smaller pieces are diverted from the energy production pathway to build fat for energy storage when glucose consumption exceeds the body's energy needs.

ChREBP is normally expressed in the liver and in fat and muscle. In the first of two studies,

(MORE)

Sugar-induced fat formation – 2

Dr. Uyeda studied mice lacking the gene for ChREBP. Without the gene, mice cannot make the ChREBP protein and do not effectively convert sugar to fat. Even when fed a normal diet, the mice had high levels of glucose in their bloodstreams. Called glucose intolerance, this condition is often seen in patients with diabetes.

The researchers then fed the mutant mice a high-carbohydrate diet. Unable to convert the large excess of sugar into fat, the mice could not create enough energy to survive.

The liver is the primary depot for the sugar to fat conversion. In the second study, Dr. Uyeda and Dr. Bonnie Miller, assistant professor of internal medicine and co-author of the study, collected liver cells from mice lacking the ChREBP gene and compared them to liver cells from normal mice to determine what happened to genes associated with fat formation.

The researchers grew the cells in a high-glucose solution to mimic the high-carbohydrate diet the mice were fed in the previous study. They found that unlike normal liver cells, liver cells from mice lacking ChREBP were unable to turn on fat-formation genes. The researchers then used biochemical assays to show that ChREBP binds directly to the DNA of fat formation genes, turning them on.

"I think one of the most exciting findings of these studies is that a single transcription factor is directly responsible for increasing expression of multiple enzymes for making fatty acids," Dr. Miller said. "This is significant because ChREBP makes sure that glucose is only converted to fat when it is in excess. It coordinates glucose breakdown and energy storage via fat."

Other contributors to the first study were Drs. Katsumi Iizuka and Guosheng Liang, former postdoctoral fellows; Dr. Richard Bruick, assistant professor of biochemistry; and Dr. Jay Horton, associate professor of internal medicine and molecular genetics. Dr. Seiji Ishii, former postdoctoral fellow, and Dr. Iizuka contributed to the second study.

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