SOUTHWESTERN NEWS

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UT SOUTHWESTERN TEAM ISOLATES KEY PROTEIN IN TRANSFORMING EXCESS GLUCOSE INTO FAT

DALLAS – July 31, 2001 – A biochemistry team from the Department of Veterans Affairs and UT Southwestern Medical Center at Dallas has identified a glucose-sensitive protein that translates excessively high-carbohydrate intake into body fat, especially when combined with a sedentary lifestyle.

"Once upon a time, we thought hormones directed this long-term control of metabolism. Turns out, diet also plays a major role," said Dr. Kosaku "Ko" Uyeda, a UT Southwestern professor of biochemistry and research career scientist at the Dallas Veterans Affairs Medical Center.

Uyeda and his UT Southwestern colleagues reported in today's issue of the *Proceedings of the National Academy of Sciences* that they isolated the glucose-sensitive protein, dubbed the carbohydrate response element-binding protein (ChREBP), that triggers the long-term process of transforming excess dietary carbohydrates into fat. They used rat livers in their study, but the results are believed to reflect the human body's functions.

When people eat desserts, pasta, potatoes or other sugar- and starch-laden foods beyond the body's energy and nutritional needs, these carbohydrates become a flood of glucose, and the liver converts the surplus glucose to fat, Uyeda said.

At some point, the glucose reaches a level that signals the ChRE-binding protein to start a chain-reaction along a series of genes that, in turn, activate the synthesis of a dozen enzymes that catalyze the transformation of the excess glucose into fat to be stored in the body, he said.

"Eventually, from this line of ongoing research, it should be feasible to design a drug that will inhibit the protein's response to excess glucose and may enable us to eat all the carbohydrates we want, without getting fat," Uyeda said. "The drug would be able to slow the conversion of carbohydrates to fat, perhaps matching the body's needs. Hopefully, the body

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would be able to excrete or burn the excess glucose."

Identifying the protein itself was a breakthrough, but Uyeda said the lab work also revealed how this protein factor binds to a specific gene's DNA and how hormones and glucose control the gene's biological activity.

"Several proteins bind to the glucose-response site in the DNA. However, all but one appear to have no direct response to glucose," he said. "The newly identified protein appears to be the main factor. It may be the universal factor in activating other genes to respond to the glucose signal."

Uyeda and his team worked continuous laboratory shifts for about four years to track down, isolate, identify and confirm this specialized, but illusive, protein from among many similar proteins and enzymes that operate in the liver. Three scientists at San Francisco-based Genentech also assisted on the project.

After isolating the protein in rats' livers, the researchers turned to Genentech to enlist one of only two mass-spectrometer labs in the nation that could analyze the protein substances at microscopic levels, Uyeda said. His team then had to run a number of tests on the protein in the liver cells to confirm its glucose-driven response at the biochemical and genetic levels, he said.

The study is an ongoing part of Uyeda's work of more than 30 years. His current goal is to explain how the body transforms and stores carbohydrates as fat.

Other UT Southwestern colleagues in the project were biochemists Drs. Hiromi Yamashita, Makoto Takenoshita and Masaharu Sakurai, all of whom have returned to Japan, and Richard Bruick, a current research fellow in biochemistry.

The VA and the National Institutes of Health funded the study.

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