UT SOUTHWESTERN MEDICAL CENTER NEWS

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EMBARGOED UNTIL 2 P.M. CST THURSDAY, MARCH 24, 2011

UT Southwestern researchers find potential new non-insulin treatment for type 1 diabetes

DALLAS – March 24, 2011 – Researchers at UT Southwestern Medical Center have discovered a hormone pathway that potentially could lead to new ways of treating type 1 diabetes independent of insulin, long thought to be the sole regulator of carbohydrates in the liver. Results of this new study will be published March 25 in *Science*.

Another hormone, fibroblast growth factor 19 (FGF19), has insulin-like characteristics beyond its role in bile acid synthesis. Unlike insulin, however, FGF19 does not cause excess glucose to turn to fat, suggesting that its activation could lead to new treatments for diabetes or obesity.

"The fundamental discovery is that there is a pathway that exists that is required for the body, after a meal, to store glucose in the liver and drive protein synthesis. That pathway is independent of insulin," said Dr. David Mangelsdorf, chairman of pharmacology at UT Southwestern.

Naturally elevating this pathway, therefore, could lead to new diabetes treatments outside of insulin therapy. The standard treatment for type 1 diabetes, which affects about 1 million people in the U.S., involves taking insulin multiple times a day to metabolize blood sugar.

Dr. Mangelsdorf and Dr. Steven Kliewer, professor of molecular biology and pharmacology at UT Southwestern, are co-senior authors of the study. Dr. Kliewer has been studying the hormone FGF19 since he discovered its involvement in metabolism about eight years ago.

Fibroblast growth factors control nutrient metabolism and are released upon bile acid uptake into the small intestine. Bile acids, produced by the liver, break down fats in the body.

Researchers studied mice lacking FGF15 – the rodent FGF19 hormone equivalent. These mice, after eating, could not properly maintain blood concentrations of glucose and normal amounts of liver glycogen. Glycogen is a form of glucose storage found mainly in liver and muscle tissue. The mice were then injected with FGF19 to evaluate its effects on metabolism in the liver.

FGF19 restored glycogen levels in the mice lacking FGF15. When administered to diabetic mice lacking insulin, FGF19 also corrected the loss of glycogen.

"FGF19 does not make fat, and that's one of the effects that separates it from insulin. Insulin

(MORE)

also does not really have a dramatic effect on bile acid synthesis. So, the two pathways are different even though they both function in glycogen and protein synthesis," said Dr. Mangelsdorf, a Howard Hughes Medical Institute investigator at the medical center.

Manipulating FGF19 as an alternative to insulin therapy remains a daunting challenge, however, given some unwelcome side effects. In some studies, he said, activating the hormone in rodents caused the liver to grow and develop cancer.

One promising diabetes treatment route could involve the nuclear bile acid receptor FXR, which Dr. Mangelsdorf said induces expression of FGF19. Modulators of FXR (farnesoid X receptor) have been shown to lower triglycerides and improve cholesterol profiles in preclinical models.

The study's lead author is Serkan Kir, a UT Southwestern graduate student in pharmacology. Also involved in the study were researchers from Yale University School of Medicine; Case Western Reserve University; Van Andel Research Institute; and the Howard Hughes Medical Institute.

The work was supported by the National Institutes of Health, HHMI, the Robert Welch Foundation and the Yale and Case Western Reserve University Mouse Metabolic Phenotyping Centers.

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