SOUTHWESTERN NEWS

(EMBARGOED FOR 5 P.M. MONDAY, APRIL 28, 1997)

Contact: Susan A. Steeves
(214) 648-3404
or E-mail: ssteev@mednet.swmed.edu

LEPTIN HAS AN ANTIDIABETIC EFFECT

DALLAS — April 29, 1997 — For the first time, the controversial hormone leptin has been directly linked to metabolism that might prevent obesity-caused diabetes, UT Southwestern Medical Center at Dallas scientists reported today.

By inhibiting fat formation and speeding its depletion, leptin should impede development of type II diabetes (non-insulin dependent diabetes mellitus), according to a study published in the April 29 issue of *Proceedings of the National Academy of Sciences*.

UT Southwestern researchers said leptin receptors, which enable the hormone to function in its apparent role of ridding the body of fat, act in both adipose and nonadipose cells in the liver, in skeletal muscle and in the pancreas, the source of insulin. Previously, scientists speculated that leptin acted only through cells in the middle of the brain to decrease appetite and to increase metabolism, but this study raises the possibility of additional pathways.

By inhibiting fat formation in tissues, the hormone lowers glucose in the blood, improves the function of insulin-producing cells and increases tissues' sensitivity to insulin, thereby exerting an antidiabetic effect, said Dr. Michio Shimabukuro, UT Southwestern research fellow and lead scientist on the study.

Type II diabetes most often occurs in obese individuals, and an important part of the treatment is weight loss and a carefully controlled diet.

"The effect of leptin is not only on fat cells but also on all cells that express leptin receptors, including the insulin-secreting cells — the pancreatic islet beta cells," Shimabukuro said. "The leptin receptors are widely distributed throughout the body."

The researchers, working in Gifford Laboratories for Diabetes Research at UT Southwestern and at the Dallas Veterans Affairs Medical Center, tested leptin's effects on hyperleptinemic rats, which have virtually no body fat, on normal rats eating the same diet as the skinny rodents, on obese rats, and on pancreatic islet cells in vitro.

"Our findings show for the first time that if you take tissue out of the body and put it in a

(MORE)

little culture dish, where there obviously is no central nervous system, then add leptin, you will find that leptin has a direct effect on fat degradation," Shimabukuro said.

"These obese rats have fat overload in their insulin-producing pancreatic islet beta cells, which don't function normally," he said. "Leptin action can reverse this and rid the islets of excess fat."

The hormone had no effect, however, on the cells of obese rats because they have defective leptin receptors, which allow fat to form faster and disable the beta cells.

In rodents with normal leptin receptors, fatty acid in cells apparently breaks down and is burned up inside the cell, Shimabukuro said. This explains why there is no increase of fatty acids in the bloodstream or liver nor any increase in ketones, a product of fat metabolism, in the urine of rats that overproduce leptin.

The fat rats, like obese humans, produce insulin but their cells are so fat-laden that the insulin does not control the body's glucose levels. However, when fat is decreased and is normally metabolized, it takes much less insulin to control glucose. People with glucose levels that are too high are diagnosed as having diabetes.

In previous research, UT Southwestern scientists used a virus to insert the leptin gene into rats. This produced hyperleptinemic rodents — animals with virtually no fat. They manufactured 20 times the normal amount of leptin and half the amount of insulin yet did not develop diabetes.

The latest study links the defective leptin receptor to the fat-induced failure of insulin to control glucose and helps explain why obese rats have type II diabetes, Shimabukuro said.

Shimabukuro said the logical conclusion from this research is that if leptin reduces fat, then the cells' resistance to respond to insulin will decrease.

Other researchers involved in this study were UT Southwestern research fellows Dr. Kazunori Koyama, Dr. Guoxun Chen, Dr. May-Yun Wang; research assistant Falguni Trieu; Dr. Young Lee, assistant instructor of internal medicine; Dr. Christopher Newgard, professor of biochemistry and internal medicine and holder of the Gifford O. Touchstone Jr. and Randolph G. Touchstone Distinguished Chair in Diabetes Research; and Dr. Roger Unger, director of Gifford Laboratories and holder of the Touchstone/West Distinguished Chair in Diabetes Research.

The study was supported by grants from the National Institutes of Health, Juvenile Diabetes Foundation and the Department of Veterans Affairs.

###