UT SOUTHWESTERN MEDICAL CENTER NEWS

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Brain might be key to leptin's actions against type 1 diabetes, UT Southwestern researchers find

DALLAS – Oct. 20, 2010 – New findings by UT Southwestern Medical Center researchers suggest a novel role for the brain in mediating beneficial actions of the hormone leptin in type 1 diabetes.

"Our findings really pave the way for understanding the mechanism by which leptin therapy improves type 1 diabetes," said Dr. Roberto Coppari, assistant professor of internal medicine at UT Southwestern and senior author of the study involving laboratory mice. "Understanding the mechanism is important, because if we can determine how leptin drives these benefits, then we may be able to develop drugs that eliminate the need for insulin."

The findings are available online and will be published in a future issue of the *Proceedings of the National Academy of Sciences*.

Prior research by Dr. Roger Unger, professor of internal medicine at UT Southwestern, has shown that subcutaneous administration of leptin, a hormone produced by the body's fat cells, can restore terminally ill rodents with type 1 diabetes to full health. The underlying cellular mechanisms that caused that effect, however, have been unclear.

In the current study, the researchers injected leptin continuously into the brains of mice that lacked any naturally produced insulin. Lack of or reduced insulin production is the hallmark of type 1 diabetes in humans.

They found that infusing leptin into the lateral ventricle of the animals' brains reversed the lethal consequences of type 1 diabetes. The results establish the brain as a potentially critical site for mediating the metabolism-improving actions of leptin, Dr. Coppari said.

The team's findings also indicate the smallest amount of leptin required to normalize the animals' food intake, body weight and blood sugar levels.

A human clinical trial currently under way at UT Southwestern aims to determine whether adding leptin to standard insulin therapy might help rein in the tumultuous blood-sugar levels of people with type 1 diabetes.

"It might be that leptin treatment is not going to be effective or well-tolerated or that it

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might cause unwanted effects," Dr. Coppari said. "However, if we understand the mechanisms and how leptin improves type 1 diabetes, then perhaps we can develop alternatives to harness those mechanisms."

The next step, Dr. Coppari said, is to determine which specific nerve cells in the brain are responsible for the anti-type 1 diabetic actions of leptin.

"Living without insulin was once considered impossible, but our results have shown that it is possible when leptin receptor signaling in the brain is enhanced. If we can identify which neurons are responsible for driving the anti-type 1 diabetic actions of leptin, we may eventually develop better therapies for individuals with type 1 diabetes."

Other UT Southwestern researchers involved in the study were Dr. Teppei Fujikawa, lead author and postdoctoral researcher in internal medicine; and Drs. Jen-Chieh Chuang, Giorgio Ramadori and Ichiro Sakata, postdoctoral researchers in internal medicine.

The National Institutes of Health and the American Heart Association funded the study.

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