Scientists discover leptin can also aid type 1 diabetics

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Terminally ill rodents with type 1 diabetes have been restored to full health with a single injection of a substance other than insulin by scientists at UT Southwestern Medical Center.

Since the discovery of insulin in 1922, type 1 diabetes (insulin-dependent diabetes) in humans has been treated by injecting insulin to lower high blood sugar levels and prevent diabetic coma. New findings by UT Southwestern researchers, which appear online and in a future issue of the *Proceedings of the National Academy of Sciences*, suggest that insulin isn't the only agent that is effective. Leptin, a hormone produced by the body's fat cells, also lowers blood glucose levels and maintains them in a normal range for extended periods, they found.

"The fact that these animals don't die and are restored to normal health despite a total lack of insulin is hard for many researchers and clinicians to believe," said Dr. Roger Unger, professor of internal medicine and senior author of the study. "Many scientists, including us, thought it would be a waste of time to give leptin in the absence of insulin. We've been brainwashed into thinking that insulin is the only substance that can correct the consequences of insulin deficiency."

The mechanism of leptin's glucose-lowering action appears to involve the suppression of glucagon, a hormone produced by the pancreas that raises glucose levels. Normally, glucagon is released when the glucose, or sugar, level in the blood is low. In insulin deficiency, however, glucagon levels are inappropriately high and cause the liver to release excessive

amounts of glucose into the bloodstream. This action is opposed by insulin, which tells the body's cells to remove sugar from the bloodstream.

In type 1 diabetes, which affects about 1 million people in the U.S., the pancreatic islet cells that produce insulin are destroyed. Type 1 diabetics must take insulin multiple times a day to metabolize blood glucose and regiment their diets. In comparison, patients with non-insulin dependent, or type 2, diabetes make insulin, but their bodies don't respond well to it. Type 2 diabetes affects between 18 million and 20 million people in this country.

In the current study, researchers tested for the first time whether a single injection of the leptin gene given to insulin-deficient mice and rats on the verge of death from diabetic coma could reverse the severe condition and prevent the animals from dying. The animals that received the leptin gene began producing excessive amounts of leptin, which reversed all the measurable consequences of type 1 diabetes including weight loss, hyperglycemia and ketoacidosis, a potentially fatal condition that develops when the body doesn't have enough insulin to meet basic metabolic requirements. Much of the effect was mediated by complete suppression of the high glucagon levels, said Dr. Xinxin Yu, assistant instructor of internal medicine and lead author of the study.

"These animals were actually dying," Dr. Yu said. "But if we gave them the leptin gene, within two weeks, the terminally ill rodents were restored to full health without any other treatment."

Dr. Unger said it's too premature to know whether leptin might someday replace insulin as a treatment for diabetic patients, but this study demonstrates that leptin could at least handle some of insulin's job requirements and do it for longer periods of time. Injected insulin is biologically active for only three to four hours.

"My hope is that you could give leptin for one type of action – glucagon's suppression, for example – and insulin for another. Or perhaps give a substance other than insulin entirely," Dr. Unger said. "What would be a tremendous advance would be the ability to give an oral agent that suppresses glucagon without injections."

Dr. Yu said the research team hypothesizes that leptin combats diabetes not only be suppressing glucagon's action on the liver, but also by boosting the insulin-like actions of IGF-1 (insulin-like growth factor-1), a hormone that promotes growth and mimics insulin.

"One of the things that happens when a child gets type 1 diabetes is their growth is stunted until they're given insulin," Dr. Unger said. "The same is true with these mice. However, we found that if you take a diabetic rat that's not receiving insulin and make it hyperleptinemic, it almost catches up growthwise."

While the treated animals' blood glucose levels inched back up over time, their hyperglycemia (high blood sugar) consistently remained well below the elevated pre-treatment levels. The untreated rodents, on the other hand, died within two or three days. The researchers tracked the treated rodents for 25 weeks.

The next step is to study other potential glucagon suppressants and begin leptin clinical trials within the next year.

Source: UT Southwestern Medical Center

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