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Fat cells send message that aids insulin secretion

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The body's fat cells help the pancreas do its job of secreting insulin, according to research at Washington University School of Medicine in St. Louis. This previously unrecognized process ultimately could lead to new methods to improve glucose metabolism in type 2 diabetic or insulin-resistant people.

In a study using laboratory mice, published in the November 7, 2007 issue of *Cell Metabolism*, scientists at the School of Medicine report that fat cells release a protein that aids insulin secretion from pancreatic beta cells, which are the sole source of insulin. The protein is an enzyme that the pancreatic cells themselves produce in only minimal amounts. The enzyme works to enhance glucose-stimulated insulin secretion from pancreatic beta cells.

Insulin helps the body process blood sugar (glucose), and those with type 2 diabetes have a deficiency of insulin or a resistance to its effects. More than 7 million people in the U.S. are living with a diagnosis of type 2 diabetes and many more are undiagnosed.

The researchers assert that the enzyme secreted by fat cells, called Nampt, is an important component of the insulin-secretion pathway. "We think this secretion process allows fat cells to communicate with the pancreas and aid its function," says senior author Shin-ichiro Imai, M.D., Ph.D., assistant professor of medicine and of molecular biology and pharmacology. "I suspect this process could be critical for compensating pancreatic beta cell function in the face of increasing insulin resistance."

The association of type 2 diabetes and insulin resistance with obesity suggests there may be limits to the ability of the process to enhance pancreatic function, according to Imai. "It may be that in some obese individuals a threshold has been reached so that this mechanism no longer provides adequate compensation," he says. "But there may be ways to overcome this threshold."

Interestingly, in 2004 Nampt provoked excitement in the scientific community because it was reported to be a newly discovered fat-derived hormone that worked very much like insulin. That study named the enzyme visfatin. The scientists who made this assertion have since retracted their claim.

In the new study, the Washington University researchers contend that Nampt is not an insulin-like hormone. Instead, their investigation shows it's an enzyme that modulates pancreatic function.

"Our work marks a conceptual breakthrough," Imai says. "Nampt synthesizes a compound in the bloodstream, and when that compound reaches the pancreas it stimulates insulin secretion. This is a surprising mechanism by which a circulating metabolite modulates pancreatic function."

Imai says he believes it's possible that the compound produced by Nampt, called NMN for short, could be used to raise insulin secretion from pancreatic cells and thus help improve the way the body handles sugar. Imai and his group are collaborating with clinical researchers at the University to find out how much NMN is in the blood of normal and diabetic or obese patients. They also hope to initiate clinical trials to test NMN as a therapeutic agent in patients with type 2 diabetes or insulin resistance.

Nampt is actually a widespread enzyme and catalyzes such a

fundamental process that most cells of the body have an internal form of it. But, studying mice, the researchers saw that Nampt could be secreted from cells — but only from fat cells. And because Nampt levels are low in pancreatic cells, the pancreas depends on the enzyme secreted from fat and its product, NMN, in the blood.

When pancreatic beta cells absorb enough NMN, it stimulates them to secrete insulin. In the bloodstreams of laboratory mice, NMN was measured at a concentration shown to be sufficient to enhance insulin secretion from pancreatic beta cells. No one had previously known that NMN circulated in the bloodstream.

Mice engineered to have just one instead of two copies of the Nampt gene had a mildly impaired ability to metabolize glucose and had a defect in insulin secretion. The researchers showed that NMN restored normal insulin secretion in these mice.

In conjunction with the Office of Technology Management at the University, Imai has patented the use of Nampt and NMN for the prevention and treatment of metabolic complications, such as type 2 diabetes.

Next, the researchers will try to identify the factors that cause secretion of Nampt from fat cells and the mechanisms by which NMN enhances insulin secretion in the pancreas.

Source: Washington University