Study pinpoints role of insulin on glucagon levels

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April 7, 2009 - Researchers at the Joslin Diabetes Center have shown for the first time that insulin plays a key role in suppressing levels of glucagon, a hormone involved in carbohydrate metabolism and regulating blood glucose levels.

The study helps in the understanding of why those with diabetes have high blood glucose levels and could lead to development of a drug aimed at targeting glucagon levels.

"This is a very important finding because until now scientists have only speculated that insulin may be involved in keeping glucagon levels in check," said Rohit N. Kulkarni, M.D., Ph.D., Principal Investigator in the Joslin Section on Cellular and Molecular Physiology and senior author of the study published today in the April issue of *Cell Metabolism*.

Produced by the alpha cells in the pancreas, glucagon acts on the liver to help raise blood glucose when it becomes low. It has the opposite effect on the liver as insulin, which is released from pancreatic beta cells to lower blood glucose when it is high. In a healthy individual, the two counter each other to keep blood glucose levels balanced. In individuals with long-standing type 1 or type 2 diabetes, inappropriate glucagon secretion can increase the chances of hypoglycemia (low blood glucose levels) and can interfere with insulin therapy.

The finding suggests that for people with either type 1 or type 2 diabetes, a therapeutic approach could be developed to target insulin receptors or

proteins in alpha cells in order to suppress glucagon secretion.

In addition, the research may also help in the understanding of why patients with type 1 diabetes in particular, who are required to inject insulin on a regular basis, are at risk for hypoglycemia. It was thought that this increased risk was linked in some way to insulin receptors in the alpha cells, an idea that today's study suggests is in fact the case, Dr. Kulkarni explained.

"This gives us some insight into the cause of hypoglycemia, the most common complication in patients with type 1 diabetes," he said. "Injecting insulin leads to a decrease in blood glucose. If it starts to go too low, glucagon normally kicks in to prevent hypoglycemia. But, what happens in diabetes is the alpha cells become desensitized by repeated insulin injections over many years and they start to behave abnormally. We believe this is linked to insulin receptor function."

In the study, Dr. Kulkarni and his team created a genetically engineered mouse model in which pancreatic alpha cells - those that secrete glucagon - were modified so that they did not contain insulin receptors. The idea was to explore the role of insulin in regulating glucagon secretion.

The modified mice exhibited elevated glucagon levels and also showed impaired glucose tolerance, as is seen in diabetes.

"This is the first genetic model wherein we provide definitive proof that insulin is able to suppress glucagon in mammals," Dr. Kulkarni said. "The next step is to identify the specific proteins in alpha cells that could be targeted to suppress glucagon secretion."

The paper concludes that the findings indicate there is a significant role for insulin signaling in the regulation of alpha cell functioning in both

normal and hypoglycemic conditions and provide direct genetic evidence for a key role for insulin receptors in the modulation of pancreatic alpha cell function.

Source: Joslin Diabetes Center