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Insulin-releasing switch discovered

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Johns Hopkins researchers believe they have uncovered the molecular switch for the secretion of insulin — the hormone that regulates blood sugar — providing for the first time an explanation of this process. In a report published online March 1 in *Cell Metabolism*, the researchers say the work solves a longtime mystery and may lead to better treatments for type 2 diabetes, the most common form of the disease.

"Before our discovery, the mechanism behind how exactly the insulin-producing beta cells in the islet of Langerhans of the pancreas fail in type 2 diabetes was incompletely understood, making it difficult to design new and better therapies, says Mehboob Hussain, M.D., associate professor of pediatrics, medicine and biological chemistry. "Our research cracks open a decades-long mystery."

After a meal, the pancreas produces insulin to move glucose from the blood into cells for fuel. People with type 2 diabetes either don't secrete enough insulin or their cells are resistant to its effects.

In a study designed to figure out more precisely how the pancreas releases insulin, Hussain's group looked at how other cells in the body release chemicals. One particular protein, Snapin, found in nerve cells, caught their eye because it's used by nerve cells to release chemicals necessary for cell communication. Snapin also is found in the insulin-secreting pancreatic beta cells.

To test the role of Snapin, researchers engineered a change to the Snapin gene in mice to keep Snapin permanently "on" in the pancreas.

Researchers removed the pancreas cells and grew them in a dish for a day, then added glucose to the cells and took samples to measure how much insulin was released.

When the scientists compared that measurement to what was released by pancreas cells in normal mice, they found that normal mice released about 2.8 billionths of a gram of insulin per cell, whereas the cells from "Snapin-on" mice released 7.3 billionths of a gram of insulin per cell — about three times the normal amount.

"We were surprised to find that the Snapin-on mice didn't have more or bigger pancreas cells, they just made more insulin naturally," says Hussain. "This means all our insulin-secreting cells have this amazing reserve of insulin that we didn't really know existed and a switch that controls it."

To see if permanently turning off Snapin would reduce insulin release and further demonstrate that Snapin controls the process, the researchers first grew normal mouse pancreas cells in a dish, and treated them with a chemical that stopped them from making the Snapin protein. They again bathed the cells in glucose and measured how much insulin was released by the cells. Normal cells released 5.8 billionths of a gram of insulin, whereas cells with no Snapin only released 1.1 billionths of a gram of insulin — about 80 percent less.

"These results convinced us that Snapin is indeed the switch that releases insulin from the pancreas," says Hussain.

Normally, according to Hussain, when we ingest glucose, the pancreatic beta cells release an initial burst of insulin almost immediately, then gradually release more insulin about 15 minutes later. However, people with type 2 diabetes and mice engineered to react metabolically like people with type 2 diabetes don't release this initial spurt of insulin when

fed glucose, but still have the later gradual insulin release.

"We knew how important the first burst of insulin is for controlling our blood sugar, but we did not know what really went wrong in our beta cells in people with type 2 diabetes," says Hussain. "We have drugs that restore the first burst of insulin and yet we did not completely understand how they work."

Hussain then questioned whether Snapin could be used to fix the defects in cells from a diabetic animal.

Since the cells with Snapin on made too much insulin, researchers wanted to see if they could use this to restore these mice's ability to secrete the initial burst of insulin. After growing pancreatic beta cells from type 2 diabetes mice in a dish and engineering them to make the Snapin-on protein, the researchers fed the cells glucose and found that they did indeed regain the ability to release that initial insulin burst.

"While keeping Snapin on in these mouse cells corrects the problem in this animal model of type 2 diabetes, we're still a long way from knowing if the same mechanism will work in people, but this gives us an encouraging start," says Hussain.

More information: *Cell Metabolism*: www.cell.com/cell-metabolism/

Provided by Johns Hopkins Medical Institutions

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