

N-glycan remodeling on glucagon receptor is an effector of nutrient-sensing by HBP

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A possible therapeutic target for control of blood glucose in the treatment of type 2 diabetes and obesity has been identified by Dr. Anita Johswich and her colleagues. Their findings were published in *Journal of Biological Chemistry*, online April 17, 2014.

An imbalance in the competing action of insulin and glucagon is widely viewed as a critical factor in onset of type 2 diabetes, a relentlessly increasing health problem. A delicate balance between two hormones controls [blood glucose](#) levels day and night. After a meal, blood glucose rises, which stimulates insulin release and promotes glucose uptake and metabolism. During periods of fasting the blood glucose drops and is countered by glucagon, which stimulates glucose synthesis (gluconeogenesis) to re-supply levels of circulating glucose.

Dr. Johswich's study began with the intriguing observation that compared to wild type mice, mice deficient in the *Mgat5* gene are leaner, with lower blood glucose and resistance to high calorie diets. Mice lacking the *Mgat5* gene had a minimal response to glucagon which was found to be due to a requirement for the action of *Mgat5* on the liver glucagon receptor. Dr. Johswich is a post-doctoral fellow in the lab of Dr. Jim Dennis at the Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, in Toronto, Canada.

Dr. Johswich and colleagues also found evidence for a positive feedback loop between *Mgat5* and a glucose metabolism-related pathway termed the hexosamine biosynthesis pathway (HBP) that acts to amplify

responses to glucagon. Mgat5 and HBP work together to increase glucagon receptor sensitivity, thereby enhancing [glucose production](#) by the liver.

In a nutrient-rich environment typical of the developed world today, carbohydrate-rich diets and positive feedback to glucagon signaling increases gluconeogenesis leading to chronic hyperglycemia, obesity, and insulin resistance.

The results suggest that selective inhibitors of Mgat5 and/or HBP may represent novel therapeutic approaches to restore normal glucose control in the setting of [type 2 diabetes](#).

"It is extraordinary that almost a century after Banting and Best introduced insulin – and with it, the era of modern medicine – some of the world's best researchers are working on the disease just blocks from the lab where Banting and Best stood 1921," says Dr. Jim Woodgett, Director of Research at the Lunenfeld-Tanenbaum. The American Diabetes Association has named one of the paper's coauthors, Dr. Daniel J. Drucker, the 2014 awardee of the Banting Medal for Scientific Excellence, a top international honour.

More information: The paper is "N-glycan remodeling on glucagon receptor is an effector of nutrient-sensing by the hexosamine biosynthesis pathway," published online on April 17 2014.

Provided by Lunenfeld-Tanenbaum Research Institute

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