

# Researchers identify a role for glucose-sensing neurons in type 2 diabetes

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In cases of Type 2 diabetes, the body's cells fail to appropriately regulate blood glucose levels. Research has suggested that this results from two simultaneous problems: the improper functioning of pancreatic beta cells and the impairment of insulin's actions on target tissues, including the liver, fat and muscles.

But now, research led by scientists at Beth Israel Deaconess Medical Center (BIDMC) and Oregon Health & Science University has identified a third abnormality that could play an important role in the development of obesity-induced Type 2 diabetes. Reported in the journal *Nature*, which appears in its Advance Online format today, the study describes a previously unrecognized role for glucose-sensing neurons in the onset of the disease – in other words, an important component of Type 2 diabetes may indeed be “in your head.”

“For many years we’ve known that subpopulations of neurons in the brain become ‘excited’ by glucose,” explains Bradford Lowell, MD, PhD, an investigator in the Division of Endocrinology, Diabetes and Metabolism at BIDMC and Professor of Medicine at Harvard Medical School (HMS). “But we haven’t understood exactly how or why this is significant. With this study, we show that these neurons sense increases in glucose and then initiate responses aimed at returning blood-glucose levels to normal. This is the first demonstration that glucose-sensing by neurons plays an important role in responding to rising blood glucose levels.” This finding, adds Lowell, who served as the study’s co-senior author together with Michael Cowley, PhD, of the Division of

Neuroscience, Oregon Health & Science University, could potentially lead to novel treatments for Type 2 diabetes.

Knowing that the pro-opiomelanocortin (POMC) neurons regulate body weight in both mice and humans, co-lead authors Laura Parton, PhD, Chian Ping Ye, PhD, Roberto Coppari, PhD, and Pablo Enriori, PhD, decided to study the electrical properties of these cells in an animal model.

“New advances in genetic techniques have allowed us to express green fluorescent proteins [GFP] specifically in one cell type,” explains Parton, a member of the Lowell laboratory at BIDMC and Postdoctoral Research Fellow at HMS. “The advantage of expressing a fluorescent marker specifically in one type of neuron is the ability to identify and distinguish these cells from the many hundreds of other cell types that are present in the brain.”

As predicted, the electrophysiology experiments demonstrated that POMC neurons became electrically excited by a rise in glucose, similar to what would occur after eating a meal. The authors then went on to disrupt glucose-sensing abilities specifically in the POMC neurons – and confirmed that these neurons play a critically important role in regulating blood-glucose levels in mice. And, as is the case in pancreatic beta cells, the glucose-sensing ability of POMC neurons was shown to be defective in the mice with obesity-induced Type 2 diabetes.

“What is apparently happening,” says Parton, “is that an increase in the activity of the mitochondrial uncoupling protein 2 (UCP2), is behind the loss of glucose-sensing ability in the POMC neurons. Increased activity of UCP2 is known to cause loss of glucose-sensing and defective insulin secretion by pancreatic beta cells and this study now shows that a similar phenomenon also occurs in neurons.”

“These new findings add to our understanding of Type 2 diabetes at a critically important time,” adds Lowell. “The incidence of the disease has risen to epidemic proportions, and obesity is a big risk factor for the disease. The discovery that defects in glucose-sensing by the brain may also be contributing to Type 2 diabetes could help lead to new therapeutic strategies for this widespread problem.”

Source: Beth Israel Deaconess Medical Center

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