Low-glucose sensor in the brain promotes blood glucose balance

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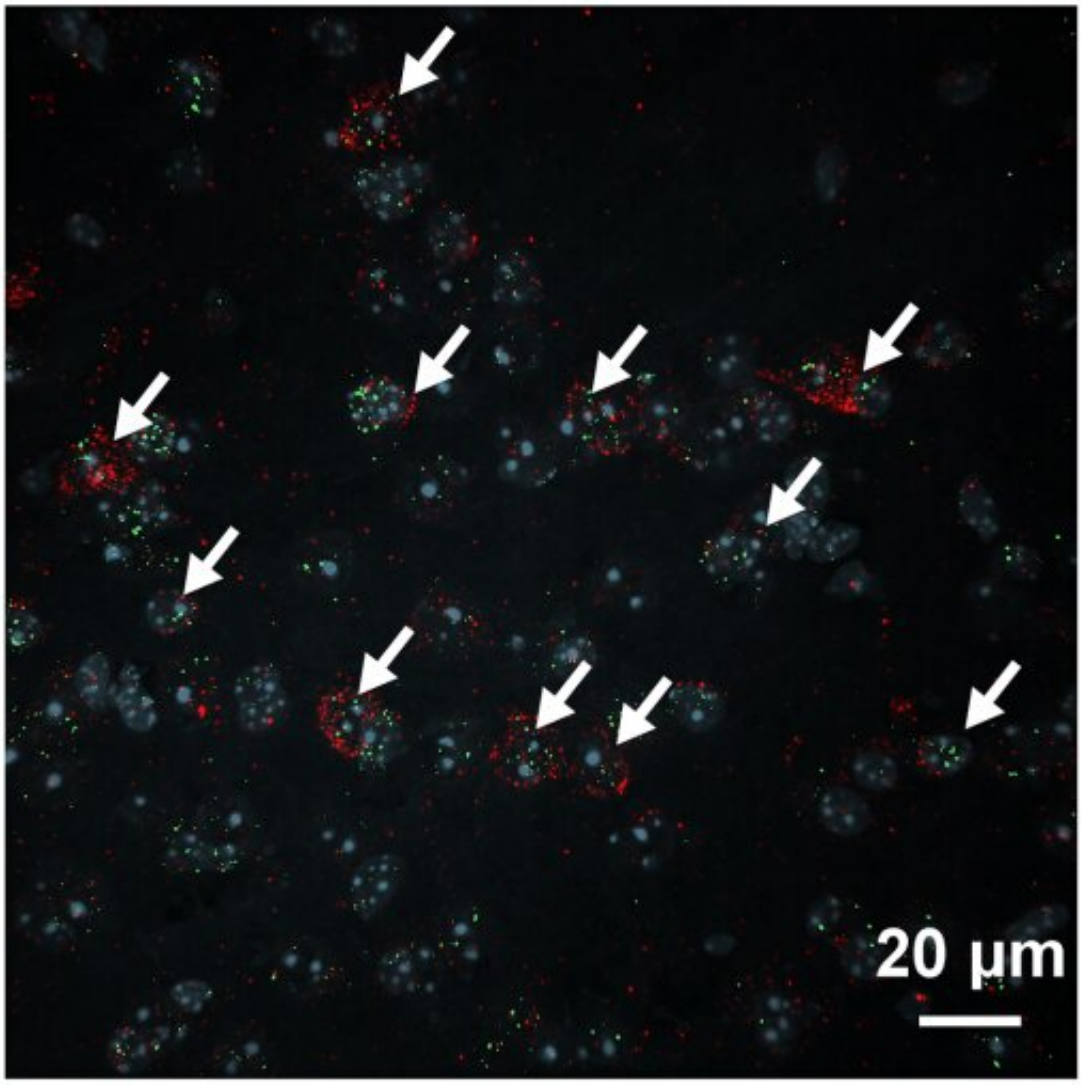

White arrows point at VMH neurons, identified by the expression of both tdTomato (red) and Ano4 (green) mRNAs. Credit: Image courtesy of Longlong (Lucas) Tu/Xu lab.

The body's blood glucose level needs to be maintained in a relatively narrow range. It cannot be too high, as it can lead to diabetes, and it cannot be too low because it can cause fainting or even death.

"There are many glucose-sensing neurons in the brain that are thought to actively participate in detecting small changes of glucose levels in the body and then trigger responses accordingly to return the level to a healthy range," said Dr. Yong Xu, professor of pediatrics—nutrition, molecular and cellular biology, and medicine at Baylor. "But there have been several questions about this for a long time."

Does the brain play a role in blood glucose regulation?

The accepted concept is that blood glucose levels are tightly controlled by hormones secreted in the pancreas, such as insulin and glucagon. So, some scientists have wondered, do glucose-sensing neurons in the brain really play a role in the regulation of whole-body glucose level?

In this study published in the *Journal of Clinical Investigation*, Xu and his colleagues examined the role of a particular group of glucose-sensing neurons in maintaining blood glucose balance in animal models.

"Glucose-sensing neurons can be divided into two groups according to how they respond to glucose fluctuations," Xu explained. "One group is called glucose-excited (GE) neurons and the other is the glucose-inhibited (GI) neurons. In this study, we focused on the second group, the less studied of the two."

GE neurons are activated or excited when the glucose level around them is higher. "This is expected because glucose is a fuel for most cells, including neurons," Xu said. "Having more fuel available would support

increased cell activity."

On the other hand, GI neurons are inhibited when glucose levels are higher and paradoxically, they are activated when glucose levels are lower. "This has been puzzling to researchers, as they were expecting the opposite, less neuronal activity when glucose is low," Xu said. "We wanted to understand the mechanism that triggered GI neuronal activity under low glucose levels and whether this contributed to blood glucose balance."

The researchers focused on GI neurons located in a region called the ventromedial hypothalamic nucleus (VMH) in the mouse brain. Specifically, they studied which ion channels on GI neurons mediated low-glucose sensing. Ion channels are proteins on the surface of neurons that allow charged ions to flow in and out of the cell. This process is necessary for neuronal activation or firing.

"We found that an ion channel called anoctamin 4 (ano4) is required for the activation of GI neurons in response to low glucose," Xu said. "In fact, our data shows that ano4 is a marker defining GI neurons. If a VMH neuron expresses ano4, then it is a GI neuron. If a VMH neuron does not express ano4, it is not a GI neuron."

GI neurons and type 1 diabetes

Next, the researchers investigated the role of GI neurons in the regulation of blood glucose in a mouse model of type 1 diabetes. In this model, insulin-producing pancreatic beta cells are absent. The lack of insulin triggers increased blood sugar levels, the hallmark of diabetes. By genetically eliminating the ano4 gene in the GI neurons located in the VMH in these diabetic mice, the researchers substantially normalized blood sugar levels.

"Our findings suggest that glucose-sensing neurons in the brain are important for whole body glucose regulation. We found that GI neurons have an important function during diabetes, when pancreatic beta cells are not producing insulin to control blood sugar levels," Xu said. "In this case, blood glucose levels can be manipulated quite effectively in the mouse model by knocking out a single gene in GI neurons, a small group of cells in the brain. Next, we want to determine whether pharmacological inhibition of ano4 would also help control blood glucose levels in this model of type 1 diabetes, and in models of type 2 diabetes."

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