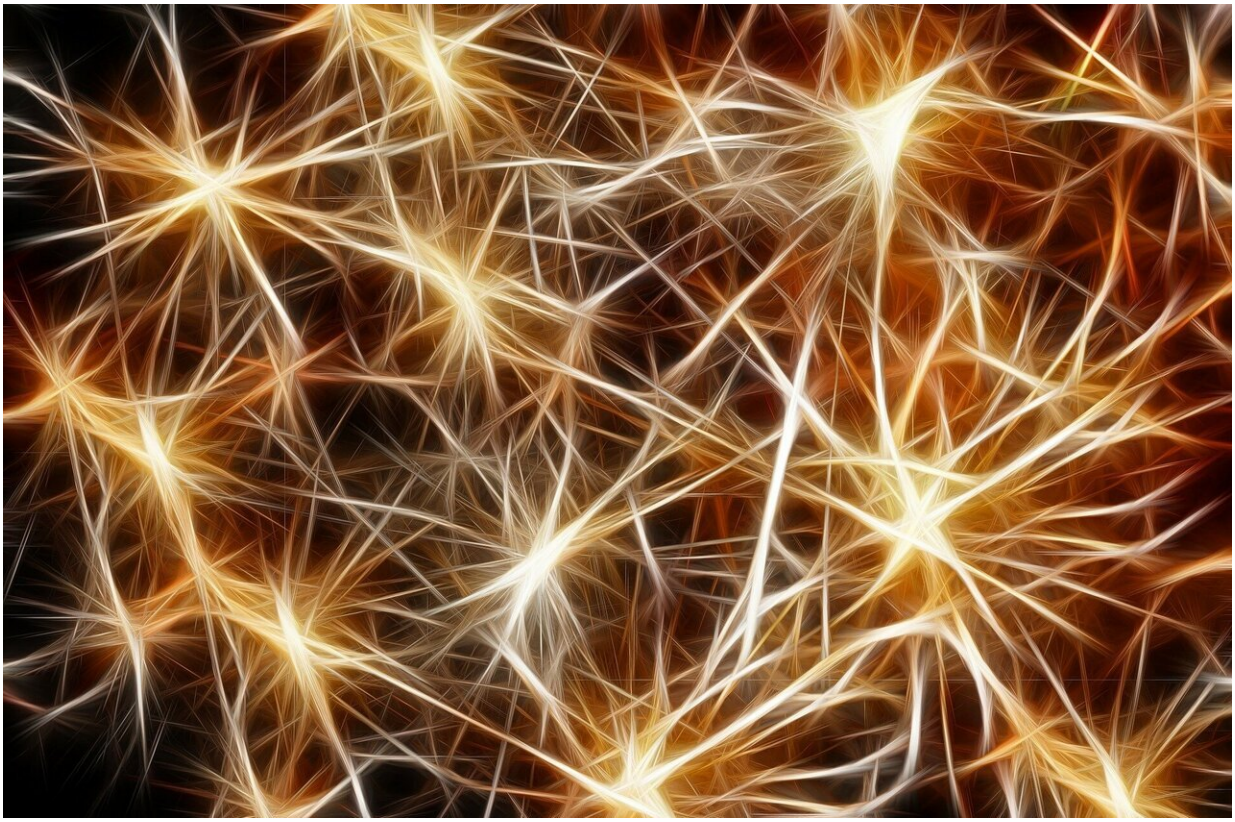
MedicalXpress

Researchers identify unique glucose-sensing neurons that regulate blood sugar

May 1 2020



Credit: CC0 Public Domain

Low blood sugar levels, known as hypoglycemia, can be a life-threatening situation, especially for people with type 1 diabetes who rely on intensive insulin therapy to prevent blood sugar from going too high.

Solutions to this problem may come from a better understanding of the basic mechanisms keeping blood sugar in balance.

At Baylor College of Medicine and other institutions, researchers led by Dr. Yong Xu, associate professor of pediatrics-nutrition and of molecular and cellular biology at Baylor, have identified a group of unique glucose-sensing neurons in the brain and how they work together to prevent severe hypoglycemia in mice. Their results appear in the journal *Nature Communications*.

"Glucose-sensing neurons sense fluctuations in blood sugar levels and respond by rapidly decreasing or increasing their firing activities. This response can trigger changes in behavior to increase glucose levels. For instance, the animals may begin eating," Xu said. "Glucose-sensing neurons also can affect the production of hormones such as glucagon that can directly regulate glucose production or uptake by peripheral tissues. It's a feedback system that keeps the balance of blood glucose."

Glucose-sensing neurons are found in several brain regions. Xu and his colleagues focused on neurons located in a small area called the ventrolateral subdivision of the ventromedial hypothalamic nucleus (vlVMH). Many neurons in this region express estrogen receptor-alpha and respond to glucose fluctuations in the blood, but their functions in glucose metabolism had not been specifically investigated.

A unique population of neurons

The researchers found that neurons in the vlVMH nucleus of murine brains had unique characteristics.

First, Xu and his colleagues were surprised that, while in other VMH subdivisions about half of the neurons were glucose-sensing, in the ventrolateral subdivision all the estrogen receptor-alpha neurons were

glucose-sensing. "Just this fact makes this group of neurons quite unique," Xu said.

They also found that, although all the neurons in this area sense glucose, they do not respond to changes in glucose level in the same way. About half of the neurons are 'glucose-excited' - their firing activity increases when they sense high glucose levels and decreases when glucose levels are low. In contrast, the other half of the neurons are glucose-inhibited—they decrease firing when glucose is high and increase it when glucose is low.

"We wondered why these neurons responded in opposite ways to the same glucose challenge," Xu said.

The researchers combined genetic profiling, pharmacological, electrophysiological and CRISPR gene-editing approaches to look into this question. They investigated the ion channels that each type of glucose-sensing neuron uses to respond to glucose levels. Ion channels are large molecules spanning across the cell membranes of neurons. The channels control the traffic of ions—electrically charged atoms or molecules—in and out of neurons, a process that is crucial for regulating neuronal firing activities.

The researchers found that glucose-excited neurons use a KATP ion channel, but the glucose-inhibited neurons used a different ion channel called Ano4. "The KATP ion channel is well known in our field, but the role of Ano4 ion channel in glucose sensing has never been reported. We have identified a new ion channel that is important for glucose-inhibited neurons."

A coordinated effect regulates blood glucose

In addition, Xu and colleagues identified the neuronal circuits that are

involved when glucose-excited and glucose-inhibited neurons respond to low blood glucose levels. They discovered that the circuits were different—glucose-excited neurons project neuronal connections to a brain region that is different from the one reached by glucose-inhibited neurons.

Using optogenetics, a combination of genetic modifications and light to activate specific neuronal circuits, the researchers showed in mice that when glucose-inhibited neurons responded to low glucose levels, they activated a particular circuit, and the result was an increase of blood glucose. On the other hand, when glucose-excited neurons responded to low blood glucose, they inhibited a different circuit, but the result also was an increase in blood glucose levels.

"When the mice were hypoglycemic, these two circuits were regulated in an opposite manner—one was excited while the other was inhibited—but the outcome was the same, bringing blood glucose to normal levels," Xu said. "This forms a perfect feedback system to regulate blood glucose levels."

Interestingly, all the neurons in this important group express estrogen receptor-alpha, a well-known mediator of the ovarian hormone, estrogen. In the future, Xu and colleagues want to investigate whether estrogen plays a role in the glucose-sensing process and whether there are gender differences in the functions of these neurons on glucose balance.

More information: Yanlin He et al, Estrogen receptor-α expressing neurons in the ventrolateral VMH regulate glucose balance, *Nature Communications* (2020). DOI: 10.1038/s41467-020-15982-7

Provided by Baylor College of Medicine