Study shows orexin neurons can track how fast blood glucose changes

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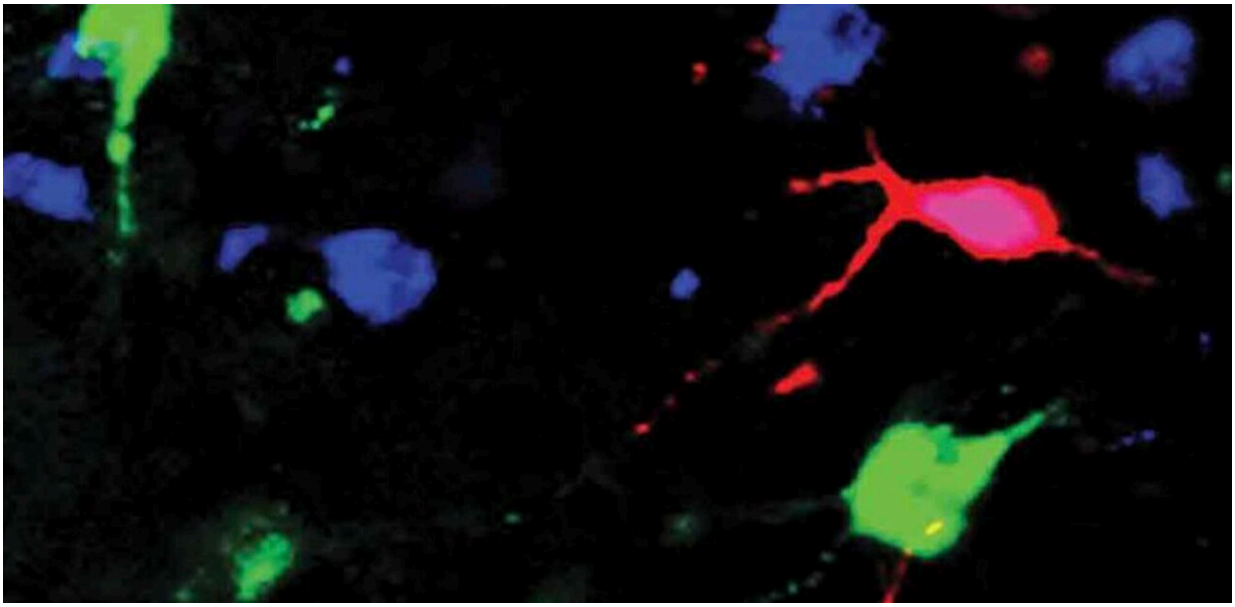

Static images of orexin cells. Credit: Viskaitis et al.

The concentration of glucose in the blood of humans continuously changes in response to what they eat and the activities they engage in. While many studies have investigated changes in blood glucose, the role of different neurons in tracking and predicting these changes remains poorly understood.

Researchers at ETH Zürich recently carried out a study investigating the

potential role of a specific type of neuron, called orexin neurons, in tracking blood glucose levels. Their findings, published in *Nature Neuroscience*, suggest that orexin neurons in the mouse brain are responsible for tracking how fast blood glucose levels are changing.

"In the 2000s, a lot of scientific effort went into identifying the so-called 'glucose-sensing neurons,' since these cells may alter our brain function based on what is happening minute-to-minute inside our body," Denis Burdakov, co-author of the paper, told Medical Xpress. "With the huge 'diabesity [diabetes + obesity] epidemic' happening in some countries, like the U.K. and U.S., this was also important because sugar was implicated."

Between 2005 and 2011, Burdakov's research lab (then at the University of Cambridge) contributed to the identification and characterization of glucose-sensing in orexin neurons. These are specialized neurons that have been found to sense glucose and produce the neurotransmitter orexin/hypocretin.

Orexin/hypocretin is a chemical "messenger" that contributes to the regulation of various physiological processes, including arousal, wakefulness and appetite. Orexin-producing neurons, identified about three decades ago, are only found in the hypothalamus, yet they innervate the entire central nervous system in humans and other mammals.

"Orexin neurons are so important for our arousal and consciousness that without this small cluster of cells our normal consciousness is lost (as in narcolepsy—which is a disorder caused by loss of orexin cells or orexin in humans)," Burdakov said.

"Our older experiments indicated that orexin cells are profoundly silenced by glucose, but that was 'in a dish,' in our experiments in

isolated orexin cells. It since transpired that, in the living brain of a behaving mammal, orexin cells are profoundly controlled by many other things, including direct neural inputs from much of the brain."

While their previous studies gathered interesting insight about orexin, they were primarily carried out on isolated cells examined in petri dishes. Therefore, the role of these cells in the brain of living animals and their connection to blood glucose levels had yet to be examined.

As part of their new study, Burdakov and his colleagues set out to fill this gap in the literature, particularly trying to determine whether physiological changes in blood glucose levels were "perceived" by orexin-producing cells. Moreover, if these cells can in fact detect changes in glucose, the team wished to determine whether they focused on some specific attributes of these changes and if their contribution affects behavior.

"The challenge in our experiment was to measure the real-time activity of live orexin neurons in the brain, together with the concurrently happening glucose level fluctuations in the blood," Burdakov explained.

"This was essential to make any conclusions. To achieve this, we put tiny electrochemical glucose sensors into an artery. At the same time, we used extremely thin glass tubes inserted deep into the brain to watch what orexin cells were doing—we could see that because we gene-targeted a fluorescent activity reporter specifically to orexin cells."

The concentration of glucose in the blood is not only controlled by eating and exercising, it is known to also be regulated by the naturally occurring hormone insulin and the liver, which produce dynamic waves of blood glucose. Burdakov and his colleagues used their sensors introduced in arteries to monitor these wave-like changes in glucose concentration over time.

This allowed them to note at what point in the waves (i.e., at their crest, trough, rise, fall) orexin neurons in the mouse brain became excited or fell silent. In addition, the researchers observed the behavior of the mice, particularly their spontaneous running, to determine whether it was influenced by blood glucose in normal mice and in mice that did not have orexin-producing neurons.

"We found that the biggest modulation of orexin cell activity happened during the rise and fall of blood glucose waves," Burdakov said. "Surprisingly, orexin cells appeared almost blind to absolute levels of blood glucose, but mostly tracked the rises and falls, especially the rate-of-change of glucose during these rises and falls."

The findings gathered by the researchers highlight the potential role of orexin cells in tracking blood glucose levels, particularly their temporal features (i.e., their changes over time). They thus shed new light on the complex neurobiology of blood glucose perception in the brain.

"It is fantastic to work here at the ETH, where we biologists are surrounded by engineers," Burdakov said. "Any engineer will tell you that rate-of-change sensing is really important for rapid, timely control. This is a very basic idea in control engineering, that it is useful to respond to how quickly something is changing, rather than waiting for a big change to occur (by which time it's often too late to do anything).

"Engineering textbooks' name for this is 'derivative-based control,' meaning you emit control signals based on the first temporal derivative of the variable you are tracking."

Essentially, Burdakov and his colleagues showed that brain glucose sensors can emit control signals responding to temporal features of blood glucose (i.e., the rate of change), rather than absolute glucose concentrations. Their paper thus uncovered an innate biological sensing

process that the brain engages in to monitor blood glucose concentrations over time.

"In addition to fundamental implications for understanding how our brains are designed (i.e., 'reverse engineering the brain'), in this case specifically how brain activity syncs up with our body metabolic state, our findings have practical implications for trying to control our brain activity via dietary regimens," Burdakov said.

"We also confirmed that this could be very important for a basic output of the brain, voluntary movement: Mice who lacked orexin neurons could not normally adjust their running behavior to their glucose."

The interesting results gathered by this team of ETH Zürich researchers could soon inspire new experiments focusing on orexin-producing neurons. Collectively, these research efforts uncover important neural processes that support the monitoring of blood glucose–related physiological states.

"We now want to go further in testing whether classic assumptions about brain function still hold when examined with the modern techniques for monitoring temporal physiology of the body," Burdakov added. "We are particularly interested in orexin neurons and how their 'activity algorithms' alter things downstream in our brains, especially circuits linked to cognition and emotion."

More information: Paulius Viskaitis et al, Orexin neurons track temporal features of blood glucose in behaving mice, *Nature Neuroscience* (2024). DOI: 10.1038/s41593-024-01648-w