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Eavesdropping on brain cell chatter: Novel tools learn how astrocytes listen in on neurons

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This image is an artist's representation of an astrocyte. The light flashes represent changing calcium levels. Credit: Baljit S. Khakh, Ph.D., University of California, Los Angeles.

Everything we do—all of our movements, thoughts and feelings – are the result of neurons talking with one another, and recent studies have suggested that some of the conversations might not be all that private. Brain cells known as astrocytes may be listening in on, or even participating in, some of those discussions. But a new mouse study suggests that astrocytes might only be tuning in part of the time—specifically, when the neurons get really excited about something. This research, published in *Neuron*, was supported by the National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health.

For a long time, researchers thought that the star-shaped astrocytes (the name comes from the Greek word for star) were simply support cells for the neurons.

It turns out that these cells have a number of important jobs, including providing nutrients and signaling molecules to neurons, regulating blood flow, and removing brain chemicals called neurotransmitters from the synapse. The synapse is the point of information transfer between two neurons. At this connection point, neurotransmitters are released from one neuron to affect the electrical properties of the other. Long arms of astrocytes are located next to synapses, where they can keep tabs on the conversations going on between neurons.

In recent years, it has been shown that astrocytes may also play a role in neuronal communication. When neurons release neurotransmitters, levels of calcium change within astrocytes. Calcium is critical for many processes, including release of molecules from the cell, and activation of a host of proteins within the cell. The role of this astrocytic calcium signaling for brain function remains a mystery.

In this study, Baljit S. Khakh, Ph.D., of the University of California, Los Angeles and his colleagues wanted to know when astrocytes responded to neuron activity with changes in their internal calcium levels. Using calcium indicator dyes, the researchers were able to image, for the first time, changes in calcium levels in the entire astrocyte. Previously, it was only possible to look at certain areas of the cell at one time, which provided an incomplete picture of what was happening.

Dr. Khakh said one of the most important outcomes of this work was in the methods that were used. "What our use of these calcium indicators shows is that we can image calcium throughout the entire astrocyte. This provides a new set of tools for the research community to use and to extend these findings," he said.

"There has been intense interest in understanding how astrocytes facilitate communication between neurons, but it is only recently that studies with this level of precision have been possible," said Edmund Talley, Ph.D., program director at NINDS. "Dr. Khakh's study is an example of an exciting basic, or fundamental, research project that could have an important contribution to the shifting field of astrocyte biology," he added.

For these experiments, researchers focused on the mossy fiber pathway, which connects two areas of the hippocampus, the structure involved in learning and memory. "This pathway has a unique architecture and although it has been very well studied, the role of astrocytes in this circuit has not been previously explored. This study provides one of the first really detailed understandings of astrocytes within this particular circuit," said Dr. Khakh.

Dr. Khakh's team activated neurons (getting them to release neurotransmitter by a variety of techniques) and then looked for a response in the neighboring astrocyte. As calcium levels rose, the astrocyte would light up quickly. They discovered that two neurotransmitters, glutamate and GABA, triggered the astrocytes to release calcium from their internal stores. Importantly, the researchers discovered that calcium levels increased through the entire astrocyte only if there was a large burst of neurotransmitter being released.

"We found that astrocytes in the mossy fiber pathway do not listen to the constant, millisecond by millisecond synaptic chatter that neurons engage in. Instead, they listen when neurons get excessively excited during bursts of activation," said Dr. Khakh.

These findings suggest that astrocytes in the mossy fiber system may act as a switch that reacts to large amounts of neuronal activity by raising their levels of calcium. These calcium increases occur over multiple seconds, a relatively long time period compared to that seen in neurons. The spatial extent of the astrocyte calcium increases was also relatively large in comparison to the size of the synapse.

"Astrocytes may be sitting there quietly and when there is excessive activation in the neuronal circuit, they immediately respond with an increase in calcium which we could detect. And the next big question becomes, what they do with that calcium?" said Dr. Khakh.

Dr. Khakh's results in the mossy fiber system differ from those others have described in other brain regions. This raises the intriguing possibility that astrocytes are not all the same and may serve various roles throughout the brain.

"It would be really interesting and important to find that astrocytes function differently in different areas of the brain, in a circuit-specific manner. This study gives a hint that this might be true," said Dr. Talley.

More information: MD Haustein et al. "Conditions and constraints for astrocyte calcium signaling in the hippocampal mossy fiber pathway," *Neuron*, April 16, 2014.