Model for brain signaling flawed, new study finds

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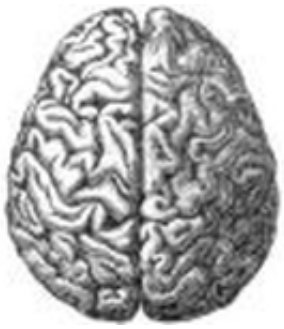

A new study out today in the journal *Science* turns two decades of understanding about how brain cells communicate on its head. The study demonstrates that the tripartite synapse – a model long accepted by the scientific community and one in which multiple cells collaborate to move signals in the central nervous system – does not exist in the adult brain.

"Our findings demonstrate that the tripartite synaptic model is incorrect," said Maiken Nedergaard, M.D., D.M.Sc., lead author of the study and co-director of the University of Rochester Medical Center (URMC) Center for Translational Neuromedicine. "This concept does not represent the process for transmitting signals between neurons in the brain beyond the developmental stage."

The central nervous system is home to many different cells. While neurons tend to garner the most attention, it is only recently that the function of the brain's other cells have been fully appreciated. Glial cells known as astrocytes, for example, had long been considered mainly the "glue" that helps hold all the other cells in the central nervous system in place. Scientists now understand that that these cells are essential to maintaining a healthy environment in the brain by helping carry out functions such as removing waste.

"Neurons are like a racing car," said Nedergaard. "While the driver gets all the credit, there are often 20 people behind the scenes that are optimizing his or her success."

However, when it comes to moving signals between neurons in the brain it turns out that the scientists may have vastly exaggerated the role of the astrocyte.

Neurons are connected to each other via axons or "arms" that extend from the cell's main body. Communication between neighboring neurons takes place where axons meet other nerve cells – called a synaptic juncture – when an electrical charge causes chemicals called neurotransmitters or glutamate to be released by one cell and "read" by receptors on the surface of the opposite. The two cells do not actually touch, so the chemicals messages must pass through a gap in the synaptic juncture. The space around this gap is insulated by astrocytes.

Under the tripartite synapse model, both astrocytes and neurons were believed to play a role in the "conversation" between cells. This understanding was largely based on animal models which showed active receptors and neurotransmission between not only the nerve cells but also the nearby astrocytes.

Specifically, a key neurotransmission receptor called metabotropic

glutamate receptor 5 (mGluR5) was observed to be present and active in astrocytes at the synaptic juncture. It was also observed that when the mGluR5 receptor was activated, the astrocytes would release chemical transmitters that were in turn read by the nerve cells. These findings led to the conclusion that astrocytes must in some manner modulate the signaling process between brain cells.

While this model has held sway for decades, scientists have long been frustrated by their inability to influence this process by targeting it with drugs.

"If this concept was correct, it should have given rise to a clinical trial by now," said Nedergaard. "It has not, which tells us that with so many labs work on this for 20 years that there must be something wrong."

One of the barriers to understanding precise mechanics of passing signals from one neuron to another has been the inability to observe this process in the adult brain. The tripartite synapse model was based – in part – by examining the activity in the brains of very young rodents. Adult rodents could not be similarly studied because the synapses in the brain would die before they could be fully analyzed. This ultimately led to the presumption that the signaling process that was witnessed in the young brain carried over to adulthood.

Collaborating with researchers at the University of Rochester's Institute of Optics, Nedergaard and her team developed a new 2-photon microscope that enables researchers to observe glia activity in the living brain. Using both this method and by analyzing the gene and protein expression in the brain the researchers discovered that the mGluR5 largely disappear in the glial cells of adult mice meaning that these cells do not directly respond to synaptic neuronal signalling, thus calling into question the concepts that drive most of ongoing research in the field.

"The process of neuron-glial transmission as conceived by the tripartite synapse model appears to just be a simplistic signaling pathway that 'teaches' the synapse how to behave," said Nedergaard. "Once the brain matures, it goes away."

More information: "Glutamate-Dependent Neuroglial Calcium Signaling Differs Between Young and Adult Brain," by W. Sun et al., *Science*, 2013.

Provided by University of Rochester Medical Center

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