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Studying altered brain cells sheds light on epilepsy

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Neuroscience researchers have zeroed in on a novel mechanism that helps control the firing of electrical signals among neurons. By isolating the molecular and electrical events that occur when this control is disrupted, the new research sheds light on epileptic seizures and potentially on other prominent diseases involving poorly regulated brain activity.

"By better understanding the detailed events that occur in epilepsy, we are gaining knowledge that could ultimately lead to better treatments for epilepsy, and possibly for other neurological diseases," said neuroscientist Douglas A. Coulter, Ph.D., the corresponding author of the research study, from The Children's Hospital of Philadelphia. "Temporal lobe epilepsy, in particular, often resists current treatments."

Coulter's research group, collaborating with a team led by co-senior author Philip G. Haydon, Ph.D., of Tufts University School of Medicine, published a study online today in the journal *Nature Neuroscience*.

In epilepsy, excessive signaling between neurons, a major type of brain cell that communicates electrical signals across gaps called synapses, can lead to epileptic seizures. However, another class of brain cells called glia can regulate those signals. Among the glia are star-shaped cells called astrocytes—the particular focus of this research.

"This study shows that changes in astrocytes are key to brain dysfunction and opens the potential for novel therapeutic strategies in epilepsy," said

Haydon, the Annetta and Gustav Grisard professor and chair of the department of neuroscience at Tufts.

The researchers focused on an abnormal condition called reactive astrocytosis, known to occur in many neurological diseases. The astrocytes swell to a large size and change expression levels of a number of proteins. The impact of reactive astrocytosis on brain function is difficult to investigate because it usually occurs in the context of brain inflammation and abnormal changes in surrounding cells.

The researchers solved this problem by using a virus to selectively cause reactive astrocytosis without triggering broader inflammation and brain injury, in a mouse model. They were able to focus on how the altered astrocytes affected specific synapses in neurons in the brain's hippocampus.

Studying the neuronal circuitry in brain slices from the mice, the study team found that changes in reactive astrocytes profoundly reduced the inhibitory control over brain signals.

Healthy brain function requires a delicate balance between excitation—the firing of brain signals—and inhibition, which limits those signals. An enzyme called glutamine synthetase is a key actor in a biological cycle that regulates the balance. The current study found that reactive astrocytosis reduces the supply of that enzyme, which in turn decreases inhibition and allows neurons to fire out of control.

"We already know that inhibition is a powerful force in the brain," said Coulter. "In epilepsy, inhibition is not working properly, and uncontrolled signaling leads to epileptic seizures. Because both disrupted inhibition and reactive astrocytosis are known to occur in other neurologic conditions, including many psychiatric disorders, traumatic brain injury, and neurodegenerative disorders such as Parkinson's

disease, our findings may have wide implications."

Significantly, the researchers were able to dampen neuronal excitability in the animals' brain slices by adding glutamine, an amino acid that is depleted as a result of reduced glutamine synthetase activity. Coulter's and Haydon's teams are continuing animal studies to further investigate how this research may contribute to developing better treatments for epilepsy.

More information: "Selective induction of astrocytic gliosis generates deficits in neuronal inhibition," Nature Neuroscience, published online April 25, 2010. dx.doi.org/10.1038/nn.2535

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