'UnZIPPING' zinc protects hippocampal neurons

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Zinc ions released at the junction between two neurons (called a synapse) are important signals, but when too much zinc accumulates, cells become dysfunctional or die.

Researchers in the Blue Bird Circle Developmental Neurogenetics Laboratory in the department of neurology at Baylor College of Medicine have discovered that zinc enters cells through specialized protein gates known as ZIP transporters, and removing these ZIP proteins from cells in the hippocampus (an area of the brain that facilitates storing and retrieving memory) significantly protects them from injury. The results are published in the latest issue of *Journal of Neuroscience*.

"These findings pave the way for the development of a new type of neuroprotective medicine for conditions such as seizures, stroke, brain trauma and other neurodegenerative disorders," said Dr. Jeffrey L. Noebels, professor of neurology, neuroscience and molecular and human genetics at BCM as well as director of the Blue Bird Circle Developmental Neurogenetics Laboratory. Many laboratories are looking for such drugs, and this provides an important clue.

Large amounts of synaptic zinc are found in the hippocampus. However, this brain circuit is a common site for epileptic seizures, and hippocampal cells are extremely vulnerable to damage during a prolonged brain "storm," as seizures are sometimes called. Since seizures activate many other molecules that may potentially injure cells and also

are accompanied by a cutoff off of oxygen and glucose to nerves, the contribution of excessive zinc released during the seizure has not been clear.

Zinc finds its way into brain cells through multiple entry sites: ion channels, glutamate receptors, and a family of special uptake transporters known as ZIP proteins. Dr. Jing Qian, assistant professor of neurology at BCM, used optical imaging techniques in brain slices to demonstrate that most zinc enters neurons through two ZIP proteins, ZIP1 and ZIP3. Qian also found that the entry is accelerated by neuronal firing.

When he analyzed cellular damage following prolonged seizures in mice that were genetically engineered to be missing the two ZIP genes, he found that a crucial group of hippocampal neurons are remarkably undamaged following even severe seizures lasting six hours or longer.

"This study is exciting, because for the first time we have shown that reducing zinc entry alone, without removing it from the diet or interfering with its other important functions, is an effective way to protect brain cells from damage due to seizures, and probably a variety of other insults to the brain," said Noebels. "We now believe these ZIP proteins represent new and important molecular targets for the development of drugs that can specifically reduce zinc entry and protect memory circuits in the brain from damage."

More information: http://www.jneurosci.org/

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