Neuroscientists' discovery could bring relief to epilepsy sufferers

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Researchers at the University of California, Riverside have made a discovery in the lab that could help drug manufacturers develop new antiepileptic drugs and explore novel strategies for treating seizures associated with epilepsy – a disease affecting about two million Americans.

Neurons, the basic building blocks of the nervous system, are cells that transmit information by electrical and chemical signaling. During epileptic seizures, which generally last from a few seconds to minutes and terminate spontaneously, the concentrations of ions both inside the neuron and the space outside the neuron change due to abnormal ion flow to and from neurons through ion "channels" – tiny gateways that are embedded to the surface of the neuron.

Ordinarily, intracellular (inside the cell) sodium concentration is low compared to extracellular sodium (the reverse is true of potassium). During seizure, however, there is a buildup of intracellular sodium, with sodium ions moving into neurons from the extracellular space, and potassium ions doing the opposite.

To understand exactly how neurons function during epileptic seizures, Maxim Bazhenov, an associate professor of cell biology and neuroscience, and Giri P. Krishnan, a postdoctoral researcher in his lab, developed and used realistic computer simulations in their analyses and found that while there is a progressive and slow increase in intracellular sodium during seizure, it is this accumulation of intracellular sodium that

leads to the termination of the seizure.

"According to our model, sodium concentration reaches a maximum just before the seizure terminates," Bazhenov said. "After seizure initiation, this intracellular sodium buildup is required to terminate the seizure."

The researchers' computational model simulates the cortical network. (The cortex is the outer layer of the cerebrum of the mammalian brain. A sheet of neural tissue, it is often referred to as gray matter.) The model simulates neurons, connections between neurons, variable extracellular and intracellular concentrations for sodium and potassium ions and variable intracellular concentrations for chloride and calcium ions.

Bazhenov explained that conventional antiepileptic drugs are commonly designed to target various sodium channels in order to reduce their activity.

"These drugs essentially slow down the intracellular build-up of sodium, but this only prolongs seizure duration," he said. "This is because seizure duration is affected by the rate of intracellular sodium accumulation – the slower this rate, the longer the seizure duration."

According to Bazhenov, targeting the sodium channels is not the best approach for drugs to take. He explained that even for drugs to increase the activity of the sodium channels (in order to reduce seizure duration) there is an undesirable effect: seizures become more likely.

"The drugs ought to be targeting other ion channels, such as those responsible for the buildup of intracellular chloride," he advises. "According to our model, restricting the chloride increase would lead to a faster termination of seizure and can even make seizures impossible."

Bazhenov and Krishnan's model also shows that the occurrence of seizures depends critically on the activity of ionic "pumps" – structures that are also embedded to the surface of neurons. These pumps help remove the sodium and chloride ions from inside the neurons and critically influence their concentrations in the brain.

More information: Study results appear in the June 15 issue of *The Journal of Neuroscience*.

Provided by University of California - Riverside