Medical Xpress

Study identifies brain pathway that shuts down seizures

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Researchers at the University of Iowa and the Veterans Affairs Iowa City Health Care System have uncovered a brain pathway that shuts down seizures.

The multidisciplinary team of scientists pieced together information from clinical observations made in the first half of the 20th century with knowledge from modern genetics and molecular biology to show that an acid-activated ion channel in the brain reacts to a drop in pH (increased acid) in a way that shuts down seizure activity.

The link between low pH in the brain and seizure termination was first hinted at nearly 80 years ago when clinical experiments showed that breathing carbon dioxide, which makes brain tissue more acidic, helps stop epileptic seizures. Subsequent studies in the 1950s found that seizures themselves reduce brain pH. However, it was the modern discovery of an acid-activated ion channel (ASIC1a) in the brain that provided the key to the UI discovery, which is reported in *Nature Neuroscience* Advance Online Publication on June 8.

"We found that ASIC1a does not seem to play a role in how a seizure starts, but as the seizure continues and the pH is reduced, ASIC1a appears to play a role in stopping additional seizure activity," said Adam Ziemann, a student in the Medical Scientist Training Program at the UI and co-lead author of the study.

Specifically, the study shows that mice without the ASIC1a gene have more severe and longer seizures than mice with the gene. In addition, chemically blocking ASIC1a increases the severity and duration of seizures in mice with the gene. Conversely, increasing the expression of ASIC1a in mice protects the animals from severe seizures.

The team also showed that reducing the pH in slices of brain tissue expressing ASIC1a reduced seizure activity, but acid had no effect on seizures in tissue without the protein.

When the team measured pH in mouse brains, they showed that seizures lower the pH to levels that can activate ASIC1a channels. They also found that breathing carbon dioxide causes an additional rapid drop in brain pH, and that breathing 10 percent carbon dioxide was sufficient to protect mice with the ASIC1a protein from lethal seizures.

"In seizures, ASIC1a appears to be activating inhibitory neurons," explained John Wemmie, M.D., Ph.D., senior study author and assistant professor of psychiatry in the UI Roy J. and Lucille A. Carver College of Medicine, and a staff physician and researcher at the VA Iowa City Health Care System. "This is the first study to show that ASIC1a activation can have an inhibitory effect."

"One of the most exciting aspects of the work is that it highlights the potent anti-epileptic effects of acid in the brain -- effects that have been recognized for nearly 100 years but until recently have been poorly understood -- and it identifies ASIC1a as a key player in mediating the anti-epileptic effect of low pH," Ziemann said.

"We don't know yet, but presumably there might be examples where the seizures don't stop because of a deficit in this pathway," Wemmie added.

Seizures involve abnormal synchronous firing of groups of neurons, which can cause physical symptoms such as spasms or convulsions and, in the most serious cases, altered control of vital bodily functions, like breathing. Approximately 2 to 4 percent of people will have a seizure at some point in their lives. People who have epilepsy experience repeated seizure activity.

Although the vast majority of seizures are self-limiting and stop by themselves, seizures that don't stop can develop into a life-threatening condition called status epilepticus with a mortality rate of up to 20 percent.

"The discovery helps explain why breathing carbon dioxide stops seizures, which might stimulate the use of carbon dioxide for stopping seizures, Wemmie said. "However, although this work provides insight into how seizures normally stop and might help us learn more about how to terminate those seizures that don't stop, it will take more work to turn the finding into a new therapeutic approach. We will be working with colleagues in neurology and neurosurgery to try and translate the findings to treatments."

Ziemann noted that a particular strength of neuroscience research at the UI is the close interaction between faculty doing cutting-edge human studies and those pursuing basic science.

Source: University of Iowa