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NEWS

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**UCI, French researchers find master switch for adult epilepsy
Study identifies new approach to preventing the chronic neurologic condition**

Irvine, Calif., June 27, 2011 – UC Irvine and French researchers have identified a central switch responsible for the transformation of healthy brain cells into epileptic ones, opening the way to both treat and prevent temporal lobe epilepsy.

Epilepsy affects 1 to 2 percent of the world's population, and TLE is the most common form of the disorder in adults. Among adult neurologic conditions, only migraine headaches are more prevalent. TLE is resistant to treatment in 30 percent of cases.

UCI neurologist and neuroscientist Dr. Tallie Z. Baram and her colleagues found that TLE manifests after a major reorganization of the molecules governing the behavior of neurons, the cells that communicate within the brain. These alterations often stem from prolonged febrile seizures, brain infections or trauma.

“This discovery marks a dramatic change in our understanding of how TLE comes about. Previously, it was believed that neurons died after damaging events and that the remaining neurons reorganized with abnormal connections,” said Baram, the Danette Shepard Chair in Neurological Studies. “However, in both people and model animals, epilepsy can arise without the apparent death of brain cells. The neurons simply seem to behave in a very abnormal way.”

To learn why, Baram's UCI team collaborated with a French group led by Christophe Bernard of the University of Marseille and Inserm. They focused on ion channels, molecules that straddle the boundaries of brain cells and govern how they fire and communicate among themselves.

Specifically, they explored an ion channel called HCN1 – which is suppressed in response to brain seizures, injuries and infections that lead to epilepsy – hoping to find the long-sought mechanism that triggers epileptic activity in previously normal brain cells.

In their study, which [appears online](#) in the Annals of Neurology, the researchers reveal that mechanism: The HCN1 channel gene and about three dozen other important genes are altered by a major cellular repressor called NRSF, which increases after events that give rise to epilepsy.

NRSF proteins work by attaching to the DNA of selected genes and shutting them down, causing neurons to fire abnormally and promoting the development of epilepsy. This was discovered when Baram and her colleagues prevented NRSF from linking to HCN1 and other NRSF-regulated genes, the development of epilepsy was markedly lessened.

This NRSF binding process is an example of epigenetics – enduring changes to gene expression without changes to the DNA sequence. Baram said the study is the first to show the significance of epigenetic mechanisms in the formation of epilepsy. The findings also point to NRSF having a larger role in influencing brain activity.

“NRSF operates like a master switch on many genes affecting neuron function,” said Shawn McClelland, UCI researcher and study co-author. “And if its levels increase, it can provoke changes lasting for years.”

“We’re quite excited about this discovery,” Baram said. “Understanding how previous brain infections, seizures or injuries can interact with the cellular machinery to cause epilepsy is a crucial step toward designing drugs to prevent the process. We don’t want to just treat people with epilepsy. We hope to develop medicines that will prevent epilepsy from occurring – and influence the lives of millions of people around the globe.”

The founder of UCI’s Epilepsy Research Center, Baram is considered the world’s leading investigator of the basic neural mechanisms involved in childhood febrile seizures – those caused by high fever – and how prolonged febrile seizures might lead to the onset of TLE.

Celine Dubé, Cristina Richichi and Qinqin Zha of UCI and Corey Flynn, Antoine Ghestem and Monique Esclapez of the University of Marseille and Inserm – the French national biomedical research agency – also contributed to the study, which received support from the National Institutes of Neurological Disorders and Stroke and the French Institute of Health & Medical Research.

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