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Scientists to study novel mechanisms of epileptic seizures to identify targets for therapy

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Ten percent of Americans experience a seizure in their lifetime, with three million diagnosed with epilepsy, a chronic neurological disorder. Anticonvulsant medications can mitigate the hyperactivity of neurons that leads to seizures, but not without severe side effects, including cognitive impairment.

Now, researchers Todd Fiacco, Ph.D., and Devin Binder, M.D., Ph.D., at the University of California, Riverside will spend the next five years studying the causes of neuronal hyperexcitability with the goal of developing more effective treatments for brain disorders like epilepsy. The researchers will share a National Institutes of Health (NIH) grant totaling more than $1.7 million awarded to them as co-principal investigators of the project.

Besides improving our understanding of how brain cells communicate with each other, the research has the potential to lead to treatments for brain disorders and diseases such as epilepsy, stroke and Alzheimer's disease.

"We're very excited about the opportunity to work together on this project," said Binder, a clinician and an associate professor of biomedical sciences in the School of Medicine. "We've collaborated over the past two years, generating a lot of supporting data for this research."

As a neurosurgeon, Binder has worked with a number of epilepsy patients, an experience that led him to study animal models of seizures in his lab at UC Riverside.

"The patients I've worked with suffer terrible side effects from antiepileptic drugs," he said. "Without new treatments, impaired cognition is the trade-off for preventing severe seizures."

Part of the problem is how researchers have traditionally thought of disorders like epilepsy. Aside from triggering seizures, the hyperactivity of neurons can lead to cell death; as a result, anticonvulsants are prescribed to reduce neuronal activity across the brain, which leads to side effects. The cause of the neuronal hyperexcitability is still unknown, but Fiacco and Binder are gathering evidence to suggest that it may involve expansive star-shaped glial cells found in the brain called astrocytes.

"A single astrocyte surrounds many thousands of synapses in the brain," said Fiacco, an assistant professor of cell biology and neuroscience. "By manipulating astrocytes, you have another tool for controlling neuronal activity."

This is exactly what Fiacco has been doing since arriving at UCR in 2008. In his lab, he exploits a process called "astrocytic swelling" to manipulate astrocytes.

Fiacco explained that in order to maintain a balanced osmolarity, astrocytes take up water via channels unique to them called aquaporin 4. This can lead to selective swelling of astrocytes during bouts of elevated neuronal activity. One result of this swelling is the release of neurotransmitters like glutamate through volume-regulated anion channels (VRACs) that are critical for cell volume regulation. Glutamate, being the most common excitatory neurotransmitter in the

brain, will then bind to receptors on neurons and elevate neuronal activity. Being able to selectively manipulate astrocytes while recording neuronal activity is a key challenge in the NIH-funded project.

"Astrocytic swelling could be a novel target for antiepileptic treatment," Binder said. "Hypertonic saline treatment will shrink astrocytes and could be a quick and specific method for preventing massive seizure activity. Pharmacological agents could also be used to block VRACs from releasing glutamate. Thanks to Dr. Fiacco's work, we can quantify the effects of these treatments on isolated brain tissue *in vitro*."

In vitro work is critical for establishing grounds to test these treatments *in vivo* with live animals. That's where Binder's lab comes in. His work with mouse models of epilepsy will allow him to test the effects of manipulating astrocytic swelling on seizure thresholds.

"We also plan to measure astrocytic swelling before and during a seizure *in vivo* with modern imaging techniques like two-photon microscopy," he said. "That's where the strength of this project lies: being able to study the relationship of astrocytic swelling on neuronal excitability not only at the behavioral level *in vivo*, but also at the cellular level *in vitro*."

Both Binder and Fiacco agree that this collaboration never could have happened without UCR's Center for Glial Neuronal Interactions (CGNI), of which they are members.

"It's the center's monthly meetings that fostered our collaboration," Fiacco said.

Fiacco and Binder will be assisted by graduate students and laboratory technicians in the research project. Results will be presented at various venues including CGNI meetings, the annual CGNI research symposium at UCR, and national and international research conferences.

Provided by University of California - Riverside