Rewiring the brain to fight epilepsy

August 1 2018, by Lawrence Goodman

Suzanne Paradis. Credit: Mike Lovett

Researchers in the lab of Associate Professor of Biology Suzanne Paradis have discovered a novel treatment for reducing seizure activity in the brains of rodents, a discovery they hope might one day help people living with epilepsy.

An estimated 2.2 million Americans suffer from epilepsy and 20 to 30 percent of these individuals live with seizures that do not respond to current medications.

The research was published this spring in the journal *Epilepsia*. The first author was Daniel Acker, Ph.D. '18, a former graduate student in Paradis' lab now at Insight Data Science. The other authors were Irene Wong '17 and Mihwa Kang.

Paradis's lab researches synapses, the connections between brain cells. Most synapses are excitatory—they facilitate the passage of signals from one brain cell to another. Others though are inhibitory, thwarting transmission.

During an epileptic seizure, the balance between excitation and inhibition goes out of whack, favoring excitation. The result is a kind of power surge where excessive electrical activity causes uncontrolled convulsions, unconsciousness or a temporary loss of awareness.

Several years ago, Paradis and her collaborators pinpointed a protein, Semaphorin 4-D (Sema4D), that stimulates production of inhibitory synapses. In brain tissue taken from mice, the researchers showed that bathing the cells in Semaphorin 4-D increases the number of inhibitory synapses, ameliorating the hyperexcitability, or signal overload, associated with epileptic seizures. These changes happened surprisingly quickly, within minutes.

In the latest research, the Paradis group worked with mice with symptoms resembling those found in epileptic humans. They applied an infusion of Sema4D into the animals' brains. The mice experienced a reduction in the severity of their seizures.

The scientists also observed an increase in the number of inhibitory

synapses in the brains of these animals, leading them to conclude that Sema4D treatment increases the brain's overall resistance to seizures by increasing the number of inhibitory synapses.

"Our idea is simple and has high impact potential," Paradis said. "On command, we instruct neurons to assemble more inhibitory synapses in the brain, thus suppressing seizures. This approach could also be beneficial in preventing the establishment of epilepsy, halting its progression or suppressing hyperexcitability during a seizure event."

In the future, if Sema4D treatment were to work in humans, Paradis envisions that Sema4D could be used in combination with current anti-epileptic drugs, such as benzodiazepines, that work by increasing the function of existing inhibitory synapses.

Paradis will focus next on finding a mechanism, perhaps a drug or gene therapy, to deliver Sema4D to the right target in the brain. Though it's still unknown if the approach will succeed in humans, Acker said, "the excitement is that the general approach works."

More information: Daniel W. M. Acker et al. Semaphorin 4D promotes inhibitory synapse formation and suppresses seizures in vivo, *Epilepsia* (2018). DOI: 10.1111/epi.14429

Provided by Brandeis University

provided for information purposes only.