The 'worm' holds the key to treating epilepsy—new possibilities for rapid drug discovery

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Monica Risley, co-lead author and a Ph.D. student in FAU's Integrative Biology

and Neuroscience program, as well as a student in the new International Max Planck Research School in Brain and Behavior. Credit: Florida Atlantic University

Current methods to control epilepsy, which affects 1 in 26 Americans, are not only inefficient but haven't improved in more than 150 years when the first anticonvulsant drug was developed. Treatment options include invasive surgeries and a combination of antiepileptic drugs that surprisingly don't work in more than 30 percent of patients. Noninvasive treatments are limited for easing symptoms partially due to the complexity of the disorder and lack of knowledge of specific molecular malfunctions. In recent years, fewer and fewer drugs have been introduced into the market most likely due to exhausted screening techniques and less efficient methods for predicting drug effectiveness.

Researchers from Florida Atlantic University, in collaboration with The Scripps Research Institute, have opened up the possibilities for rapid drug screens to treat seizures in the near future by developing the smallest whole-animal electroconvulsive seizure model using a microscopic nematode worm. Electroshock is one of the most common experimental models of acute and chronic seizure in mammals to study epilepsy. The researchers have been able to demonstrate, that just like rodents and even fruit flies, the tiny 1 millimeter C.elegans worm also can undergo an electroconvulsive seizure.

The study, "Modulating Behavior in C.elegans Using Electroshock and Antiepileptic Drugs," just published in *PLOS One*, has led the researchers to build on the current animal models for inducing seizures via electroconvulsion in the genetically modifiable C.elegans that only has 302 brain cells called neurons. C.elegans has been used for decades as a model animal to study the genetic and molecular underpinnings of

neurological disorders through a number of techniques including bio imaging, electrophysiology and behavior.

For the study, researchers treated the worms with several antiepileptic drugs approved for human use, which improved recovery from electroshock seizures worsened by genetic or pharmacological pro-convulsants.

"We were very excited to discover that when we used a typical genetic mutation that was more susceptible to electroconvulsive seizures, we were able to actually rescue these worms by treating them with FDA approved human antiepileptic drugs beforehand," said Monica Risley, co-lead author and a Ph.D. student in FAU's Integrative Biology and Neuroscience program, as well as a student in the new International Max Planck Research School in Brain and Behavior.

Because this new method is rapid, inexpensive and has shown relevance with existing antiepileptic drugs, the C.elegans electroshock assay developed at FAU has the potential to become an efficient screening tool for human seizure therapeutics.

"The fact that we can induce a short seizure, of approximately 1 to 3 minutes long, with the exact timing of an electrical pulse, and that these worms react well to antiepileptic drugs, makes this new assay a perfect model for high-speed drug screens in multi-welled plate readers," said Ken Dawson-Scully, Ph.D., corresponding author and associate professor in the Department of Biological Sciences and associate director of the FAU Brain Institute.

Dawson-Scully notes that the ability to use C.elegans in high speed robotic drug testing facilities like those at Scripps Florida, will enable testing of hundreds of thousands of compounds, even in combinations, using this automated process. "The cost to run high throughput testing

for antiepileptic drug candidates would cost a fraction in time and money compared to the experiments available today," said Dawson-Scully.

More information: Monica G. Risley et al. Modulating Behavior in C. elegans Using Electroshock and Antiepileptic Drugs, *PLOS ONE* (2016). DOI: 10.1371/journal.pone.0163786

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