New study finds possible clues to epilepsy, autism

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Rice University researchers have found a potential clue to the roots of epilepsy, autism, schizophrenia and other neurological disorders.

While studying the peripheral nerves of the Drosophila, aka the fruit fly, Rice doctoral student Eric Howlett discovered an unanticipated connection between glutamate – an amino acid and neurotransmitter in much of the food we eat – and phosphoinositide 3-kinase (PI3K), an enzyme that, Howlett found, regulates the activity of neurons.

Howlett and his colleagues, graduate student Curtis Chun-Jen Lin, research technician William Lavery and Michael Stern, a professor of biochemistry and cell biology, discovered that negative feedback mediated by PI3K regulates the excitability of neurons, an issue in a number of ailments that include neurofibromatosis, and that a mutation in a glutamate receptor gene common to both the fruit fly and humans has the ability to disrupt that regulatory mechanism.

Howlett found the Drosophila's metabotropic glutamate receptor (DmGluRA) gene, when mutated, increased the excitability of the neuron by preventing PI3K from doing its job.

Published online by the *Public Library of Science Genetics*, the study is the culmination of four years of work that built upon research by Marie-Laure Parmentier and her team at the University of Montpelier, France, to connect glutamate to regulatory functions in the fruit fly.

"As science often goes, we didn't set out with this hypothesis," said Howlett, who began the project on funding obtained by Stern from the Department of Defense to study neurofibromatosis. "This all came about as a control for a completely different experiment, and we said, 'Wow, this is some interesting stuff.'"

What he saw was that the overexpression of PI3K in motor neurons had a dramatic effect. "I noticed under the scope that these nerves were really big, and electrophysiologically, they were really slow. That wasn't what I expected, and it set me on a path of trying to find out what was going on."

Howlett's breakthrough was identifying the negative feedback loop that acts to maintain neuronal excitability at normal levels. "What we found was that glutamate, which is released due to neuronal activity, feeds back onto metabotropic glutamate receptors on the same neurons that released it in the first place. This leads to the activation of PI3K and ultimately to the dampening of the amount of glutamate that is released." Without that regulation, he said, things inside the cell can go terribly wrong.

"He put his heart and soul into this," said Stern of Howlett's exploration of the neuronal chain. "He was working on PI3K because that has a key role in neurofibromatosis. The Department of Defense is very interested in how PI3K is regulated in the nervous system because of its role in tumor formation."

Discovering the negative feedback loop that keeps neurons stable was key, said Stern, but not the end of the investigation. "We know that glutamate activates mGluR and PI3K, but we don't know how," he said. "There are almost certainly a number of intermediates that remain to be identified, and we have several candidates we're looking into.

"We're finding a mechanistic link among these molecules that hadn't

been previously appreciated," Stern said.

"Obviously the next step would be to test whether these same molecules are playing similar roles in mammalian neurons," said Howlett, who will leave Rice in the spring to pursue postdoctoral cancer research at Virginia Commonwealth University. A native Houstonian, he earned his bachelor's in biology at the University of Houston-Clear Lake.

Howlett said mGluRs had already been targeted in possible treatments for schizophrenia, epilepsy and other "excitability" diseases, so it's not a stretch to think his research could lead to even more strategies in treating neurological ailments.

"Actually, all of the molecules involved in our model have been implicated in one way or another with neurological diseases, but no one has been able to link them together into a coherent explanation of the diseases," he said. "Our model provides a novel framework that could really go a long way toward doing that."

Source: Rice University