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Scientists show biological mechanism can trigger epileptic seizures

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Scientists have discovered the first direct evidence that a biological mechanism long suspected in epilepsy is capable of triggering the brain seizures – opening the door for studies to seek improved treatments or even preventative therapies.

Researchers at Cincinnati Children's Hospital Medical Center report Sept. 19 in *Neuron* that molecular disruptions in small neurons called granule cells – located in the dentate gyrus region of the brain – caused brain seizures in mice similar to those seen in human temporal lobe epilepsy.

The dentate gyrus is in the hippocampus of the temporal lobe, and temporal lobe epilepsy is one of the most common forms of the disorder.

"Epilepsy is one of those rare disorders where we have no real preventative therapies, and current treatments after diagnosis can have significant side effects," said Steven Danzer, PhD, principal investigator on the study and a neuroscientist in the Department of Anesthesia at Cincinnati Children's. "Establishing which cells and mechanisms are responsible for the seizures allows us to begin working on ways to control or eliminate the problem therapeutically, and in a more precise manner."

Epilepsy can develop from a wide range of causes, including birth defects in children that disrupt normal brain development. It can also surface in children and adults who suffer serious brain injuries. These

individuals can have high risk of developing some form of epilepsy, depending on the location and severity of their injury, Danzer said.

Technical advances in genetically altering laboratory mice to mimic human disease made it possible for the scientists to generate animals with a specific molecular disruption in dentate gyrus granule cells (DGCs). DGCs are one of only two populations of neural cells that continue to form in significant numbers in the mature brain – the other being olfactory neurons. This is beneficial considering the hippocampus is responsible for learning and memory, and the dentate gyrus acts as a gate for excitatory signals in the brain that can lead to seizures if not properly regulated.

The presence of abnormal DGCs in epilepsy has been observed for decades, although evidence linking them to seizures was lacking until the current study. Danzer and his colleagues were able to delete a gene called PTEN from mouse DGCs that formed after birth. This caused hyper-activation of a molecular pathway called mTOR (mammalian target of rapamycin), which regulates cell growth and is also linked to tumor formation and cancer when hyper-activated under certain circumstances.

In tests by Danzer and his colleagues, hyper-activation of mTOR caused mice to develop abnormal neural connections among their DGCs – similar to that observed in human temporal lobe epilepsy – and the animals experienced seizures. Abnormal neural connections and seizures occurred even in mice that had the PTEN gene deleted in less than 10 percent of their total DGC population, strengthening the link between biological disruption of DGCs and seizures.

When researchers treated epileptic mice with a drug that blocks the mTOR pathway – rapamycin – the seizures stopped, solidifying the link to the PTEN-mTOR pathway. Rapamycin has been tested successfully at Cincinnati Children's in the treatment of a disease called tuberous

sclerosis, in which benign but still dangerous tumors can form around critical organs. Interestingly, people with tuberous sclerosis are also at risk for developing epilepsy, Danzer said. Newer mTOR inhibitors are also being tested at Cincinnati Children's for the treatment of epilepsy.

Danzer is following up the current study by trying to eliminate abnormal DGCs from the brains of mice that already have epilepsy and to see if this will stop the seizures. Researchers are attempting this by treating mice systemically with diphtheria toxin.

Although diphtheria toxin is not normally toxic to mouse cells, in their experiments the researchers will add a molecule to abnormal mouse DGCs that binds with the toxin. In theory, this should allow the toxin to kill off abnormal DGCs. If treatment stops the seizures, it would further verify the connection between abnormal DGCs and the onset of epilepsy, Danzer said. This would also allow researchers to begin laboratory testing of prospective therapeutic strategies for treatment and prevention.

Mutations involving PTEN and the mTOR pathway have also been identified in other neurological conditions, such as autism and schizophrenia. Danzer said findings in the current study will likely attract the interest of researchers studying these diseases and others involving abnormal granule neurons generated after birth.

"The profound impact of disrupting this pathway in just a small number of granule cells suggests the dentate may be a critical target for mTOR pathway mutations in other neurological diseases," Danzer said. "We believe neuroscientists will be surprised by the huge neurological impact of granule cell disruption and interested in the demonstration of a potentially novel disease mechanism."

Provided by Cincinnati Children's Hospital Medical Center