Drug prevents seizure progression in model of epilepsy

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Carnegie Mellon University researchers have identified a new anticonvulsant compound that has the potential to stop the development of epilepsy. The findings are published in the March issue of the journal *Epilepsia*.

The research discovery builds on previous work identifying a specific molecular target whose
increased activity is associated with seizure disorders, a potassium channel known as the BK channel.

"We have found a new anticonvulsant compound that eliminates seizures in a model of epilepsy," said Alison Barth, associate professor of biological sciences at Carnegie Mellon's Mellon College of Science. "The drug works by inhibiting ion channels whose role in epilepsy was only recently discovered. Understanding how these channels work in seizure disorders, and being able to target them with a simple treatment, represents a significant advance in our ability to understand and treat epilepsy."

Epilepsy is a neurological disorder marked by abnormal electrical activity in the brain that leads to recurring seizures. A person who has a first seizure is statistically much more likely to have a second, and with each subsequent seizure, the chance of having another seizure grows. A person is often diagnosed with epilepsy after having two or more seizures that have no other apparent cause.

In prior studies, Barth and colleagues were the first to link BK channels, ion channels that allow
electrically charged potassium ions to move out of cells, to sporadic epilepsy. Previous studies had shown that these channels were genetically altered in a few rare individuals who suffer from the disease, but Barth and colleagues demonstrated that seizures themselves could lead to the same alterations in BK channel function. Potassium ions move through the channels, starting and stopping the electrical impulses that allow neurons to communicate with one another. The Carnegie Mellon researchers found that after a first seizure, BK channel function was markedly enhanced. As a result, the neurons became overly excitable and were firing with more speed, intensity and spontaneity, leading Barth to believe that the abnormal increased activity of the channels might play a role in causing subsequent seizures and the emergence of
epilepsy.

In the current study, Barth tested this theory by blocking the ion channels using a BK-channel
antagonist called paxilline. Using an experimental model for epilepsy, Barth asked whether paxilline could reduce or prevent experimentally induced seizures, as it could normalize aberrant brain activity induced by previous seizures. Remarkably, Barth and colleagues Jesse Sheehan and Brett Benedetti discovered that the compound was effective at completely blocking subsequent seizures.

"The drug is orally available, and works in the low nanomolar range," said Barth, noting that these characteristics, which mean the drug is effective in low concentrations and can be taken as a pill, make it an especially promising compound for treatment in epilepsy patients. While most anticonvulsants currently used to treat epilepsy work to directly inhibit the activity of neurotransmitters that causes seizures, few compounds interact with specific ion channels, especially potassium

channels.

The researchers believe that targeting the BK channels and the abnormal brain activity that they induce might one day be used as a way to prevent the progression of seizure disorders over time, thus attacking the root cause of epilepsy.

According to Barth, the next steps will be to further investigate paxilline to see whether it is an effective anticonvulsant treatment for multiple types of seizures. The investigators continue to look at how BK channels are regulated by seizures to better understand the development of epilepsy.

Source: Carnegie Mellon University (news : web)