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Researchers discover that gene switches on during development of epilepsy

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A discovery made by researchers at Wake Forest University School of Medicine while studying mice may help explain how some people without a genetic predisposition to epilepsy can develop the disorder.

In a study published this month in the *Journal of Neuroscience*, senior researcher Dwayne W. Godwin, Ph.D., a professor of neurobiology and anatomy, and colleagues, report discovering that a gene, already known to predispose people who inherit an active form of it to certain forms of epilepsy, can actually be "switched on" in animals that do not appear to have inherited the active form, and therefore a genetic predisposition, to the condition. The gene codes a calcium channel in the brain that underlies seizures, so the finding may reveal a mechanism by which epilepsy develops in those with no apparent genetic predisposition to it.

"Epilepsy is a terrible disorder that affects millions of kids and adults all over the world," Godwin said. "There are many different forms of epilepsy with different symptoms. We don't know why some people acquire epilepsy - the cause isn't always clear from the person's genetic makeup. We do know that in some forms of epilepsy, once someone has a seizure they tend to have more. Our findings from this study suggest that something about the brain changes that can lead to this increased tendency to have a seizure. Our study shows that an important change occurs in calcium channels that help to transmit this abnormal activity throughout the brain."

Calcium channels come in a variety of forms throughout the body and

are responsible for several key functions, depending on their placement and quantity. The calcium channels in the brain are normally embedded within the membrane of brain cells, where they allow passage of calcium ions into the cell and are responsible for the electrical activity of the brain. The passage of calcium ions into cells determines how excitable the cells are, and how easily abnormal activity spreads through the brain.

If, as in epilepsy, a particular channel shows up where it is not supposed to or appears in too many or too few numbers, the function that channel is responsible for can become abnormal. Researchers know that during epileptic seizures, these calcium channels in the brain, responsible for generating electrical brain rhythms, become highly active.

For the study, researchers used a mouse model to observe changes in tissue from regions of the brain that are involved in seizures, the hippocampus and the thalamus. They measured these changes at different time intervals as the mice developed epilepsy. The researchers found that after an initial seizure, more of this particular kind of calcium channel begins to be expressed where it wasn't before, and the presence of the channel caused brain activity to become increasingly abnormal and epileptic.

"Calcium channels underlie valuable functions," Godwin said. "But in the wrong place, at the wrong time, or in the wrong amount, their presence can be disruptive. In the context of brain circuits, the brain cells that have too many copies of the channel get over excited and respond abnormally."

While the hippocampus is usually targeted in studies of epilepsy, the new channels were being made in a region of the brain called the thalamus. The thalamus is connected to the hippocampus and is involved in the spread of seizures throughout the brain.

"Certain kinds of channels are normal and expected in the thalamus, but after an initial seizure more copies of a channel that isn't normally found in this brain region begin to appear," explained graduate student John Graef, the first author on the study. "The brain activity then becomes dominated by the new copies of this channel. It helps explain how seizures can develop and spread."

The particular gene that codes for the misplaced channel has been called a "susceptibility gene" within the research community because it shows up in the genetic makeup of some individuals with epilepsy. In other individuals, there is no genetic indication that they are capable of making extra copies of the channel.

"What we've shown is that this gene can be switched on in individuals who don't appear to have inherited the susceptibility," Godwin said.

The good news is that certain drugs can inhibit calcium channels, so, if researchers can determine that the over-expression of this calcium channel is solely responsible for seizure activity, future studies could look into the possibility of selectively inhibiting the channel with drugs, or even nutritional changes. Godwin explained that this study provided vital information but that more work needs to be done to translate the findings to human patients.

Source: Wake Forest University Baptist Medical Center (news : web)

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