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New links between epilepsy and brain lipids

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In mice that are missing a protein found only in the brain, neural signals "go crazy," leaving the animals with epileptic seizures from a young age, researchers have found. The report in the September 18th *Cell*, a Cell Press publication, details what it is that happens when the protein encoded by plasticity related gene-1 (PRG-1) gets lost, revealing an important fine-tuning mechanism for brain function.

The researchers show that PRG-1's usual calming influence in the brain depends on its proper interaction with a particular class of lipids, known as lipid phosphates, which act as important cellular signals. The team led by Robert Nitsch of Universitätsmedizin Berlin speculates that changes in lipid phosphate signaling and PRG-1 function may be unrecognized causes of epilepsy.

Nitsch and his colleagues were the first to discover the new class of PRG proteins and were particularly intrigued by PRG-1's peculiar pattern of activity; it doesn't show up anywhere in the body or even anywhere else in the brain except on the receiving ends of one type of neuron.

"Most molecules are more or less found in most cells," Nitsch explained. "Some are more confined, but only a very few are confined to particular cell types in particular organs."

In the new study they show that PRG-1 deficient mice develop very severe seizures due to changes in brain activity. Although the neural connections in the animals' brains appeared to be completely normal in their structure, they showed they were far too excitable.

When PRG-1 was restored to individual neurons, activity levels returned to normal. That brain-tempering ability was lost when a portion of PRG-1 that interacts with the lipid known as lysophosphatidic acid (LPA) was altered. Animals lacking both PRG-1 and the LPA receptor didn't have epilepsy either, more evidence that PRG-1 acts via the lipid signal.

LPA has been known to play a role in the brain and there were even some hints it could be involved in epilepsy, but exactly what it does has remained unclear, Nitsch said. LPA is "sticky stuff that goes into membranes," he said, not your everyday signaling molecule.

LPA isn't itself a neurotransmitter, but rather seems to fine-tune the release of glutamate, which is the most prevalent of the chemical brain messengers, he explained. Without glutamate, brain function would simply cease. LPA and its receptor operate on the sending side of neuronal synapses. The new findings show that PRG-1 acts on the receiving side of synapses, taking up LPA from the synapse to control the activity of the sending cell. (Synapses are the small gaps between neurons where cell to cell communication takes place.)

The findings add a new layer to our understanding of how the brain functions.

Our results show that deletion of PRG-1 results in severe hippocampal overexcitability and leads to epileptic discharge in juvenile animals, the researchers wrote. This is due to a specific role of PRG-1 at the excitatory synapse on glutamatergic neurons. These data indicate a scenario for the regulation of glutamatergic transmission controlled by PRG-1, which involves mechanisms mediated by bioactive lipids such as LPA and supplements the classical molecular machinery at the synapse.

Source: Cell Press (news : web)