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Research Article

Epilepsy Channel

Ketogenic diet prevents seizures

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"These findings support our hypothesis that a dietary regimen can dramatically affect the expression of genes and the function of neurons within the brain, which enhances the ability of these neurons to withstand the metabolic challenges of epileptic seizures"

By Emory University Health Sciences Center, Although the high-fat, calorie-restricted ketogenic diet (KD) has long been used to prevent childhood epileptic seizures that are unresponsive to drugs, physicians have not really understood exactly why the diet works. New studies by a research team at Emory University School of Medicine show that the diet alters genes involved in energy metabolism in the brain, which in turn helps stabilize the function of neurons exposed to the challenges of epileptic seizures. This knowledge could help scientists identify specific molecular or genetic targets and lead to more effective drug treatments for epilepsy and brain damage.

"These findings support our hypothesis that a dietary regimen can dramatically affect the expression of genes and the function of neurons within the brain, which enhances the ability of these neurons to withstand the metabolic challenges of epileptic seizures," Dr. Dingledine said.

The ketogenic diet causes molecules called ketone bodies to be produced as fat is broken down. Scientists have understood that these molecules somehow cause a change in metabolism leading to a potent anticonvulsant effect. According to some animal studies they also may limit the progression of epilepsy.

The Emory research team studied the link between diet and epileptic seizures on the behavioral, cellular and genetic level. They found, as had others, that in rats fed the KD the resistance to seizures develops slowly, over one to two weeks, in contrast to rats treated with conventional anticonvulsant drugs. On the cellular level, they found that the anticonvulsant effect of the ketogenic diet did not correlate with a rise in plasma ketone levels or with a decrease in plasma glucose. Because longer treatment with the KD was necessary to increase the resistance to seizures, they concluded that changes in gene expression might hold the key to the diet's anticonvulsant effects.

To identify which genes might be involved, the researchers used microarray "gene chips" to examine changes in gene expression for more than 7,000 rat genes simultaneously. They focused on the hippocampus, a region of the brain known to play an important role in many kinds of epilepsies. More than 500 of the genes they examined were correlated with treatment with the KD. The most striking finding was the coordinated up-regulation of genes involved in energy metabolism.

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To explain this genetic effect, the scientists first eliminated the possibility that the KD diet might cause enhanced production of GABA, a chemical messenger in the brain that helps limit seizure activity. They found that GABA levels in the hippocampus were unchanged with the KD.

To test whether energy reserves in hippocampal neurons were enhanced with the KD, they counted the number of energy "factories," or mitochondria, within cells using electron microscopy. They found that KD treatment significantly increased the number of mitochondria per unit area in the hippocampus. This finding, along with the concerted increase in the expression of genes encoding energy metabolic enzymes, led them to conclude that KD treatment enhances energy production in the hippocampus and may lead to improved neuronal stability.

Finally, the researchers tested whether brain tissue affected by the KD would be more resistant to low levels of glucose (an effect of seizures) because of their enhanced energy reserves. They found that synaptic communication in KD-fed rats was more resistant to low glucose levels than in control animals fed a regular diet.

The researchers believe their new knowledge could lead to the development of more effective drug treatments for epilepsy and brain damage.

And because the diet enhances the brain's ability to withstand metabolic challenges, they also believe the ketogenic diet should be studied as a possible treatment for other neurodegenerative disorders such as Alzheimer's or Parkinson's diseases.

- The research will be presented at the annual meeting of the Society for Neuroscience in Washington, D.C. by Kristopher Bough, PhD, a postdoctoral student in the laboratory of Emory pharmacology professor Raymond Dingledine, PhD.

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