Fatheads: How neurons protect themselves against excess fat

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We're all fatheads. That is, our brain cells are packed with fat molecules, more of them than almost any other cell type. Still, if the brain cells' fat content gets too high, they'll be in trouble. In a recent study in mice, researchers at Johns Hopkins pinpointed an enzyme that keeps neurons' fat levels under control, and may be implicated in human neurological diseases. Their findings are published in the May 2013 issue of *Molecular and Cellular Biology*.

"There are known connections between problems with how the body's cells process fats and neurodegenerative diseases such as Alzheimer's, Parkinson's and amyotrophic lateral sclerosis," says Michael Wolfgang, Ph.D., an assistant professor in the Department of Biological Chemistry at the Johns Hopkins University School of Medicine's Institute for Basic Biomedical Sciences. "Now we've taken a step toward better understanding that connection by identifying an enzyme that lets neurons get rid of excess fat that would otherwise be toxic."

Wolfgang says one clue to the reason for the neurodegeneration/fat-processing connection is that neurons, unlike most cells in the body, seemingly can't break down fats for energy. Instead, brain cells use fats for tasks such as building cell membranes and communicating information. At the same time, he says, they must prevent the buildup of unneeded fats. Neurons' fat-loss strategy is rooted in the fact that a fat molecule attached to a chemical group called coenzyme A will be trapped inside the cell, while the coenzyme A-free version can easily cross the cell membrane and escape. With this in mind, Wolfgang, along

with colleagues Jessica Ellis, Ph.D., and G. William Wong, Ph.D., focused their study on an enzyme, called ACOT7, which is plentiful in the brain and lops coenzyme A off of certain fat molecules.

The team created mice with a non-working gene for ACOT7 and compared them with normal mice. The scientists saw no obvious differences between the two types of mice as long as they had ready access to food, Wolfgang says. But when food was taken away overnight, so that the mice's cells would start to break down their fat stores and release fat molecules into the bloodstream for use as energy, ACOT7's role began to emerge. While the normal fasting mice were merely hungry, the mice lacking ACOT7 had poor coordination, a sign of neurodegeneration. More differences emerged when the researchers dissected the mice; most strikingly, the livers of mice missing ACOT7 were "stark white" with excess fat, Wolfgang says.

Wolfgang cautions that his group's results are not quite a smoking gun for ACOT7's involvement in human neurological disease, but says they add to existing circumstantial evidence pointing in that direction. He notes that a special diet that changes the levels of fats and sugars in the bloodstream – the so-called ketogenic diet – can prevent seizures in epileptics; in addition, one study found that patients with epilepsy have less of the ACOT7 enzyme than healthy people.

"We think ACOT7's purpose is to protect neurons from toxicity and death by allowing excess fat to escape the cells," Ellis says. "Our next step will be to see whether this enzyme does indeed play a role in human neurological disease."

More information: Paper: mcb.asm.org/content/33/9/1869.full