Obesity-induced fatty liver disease reversed in mice

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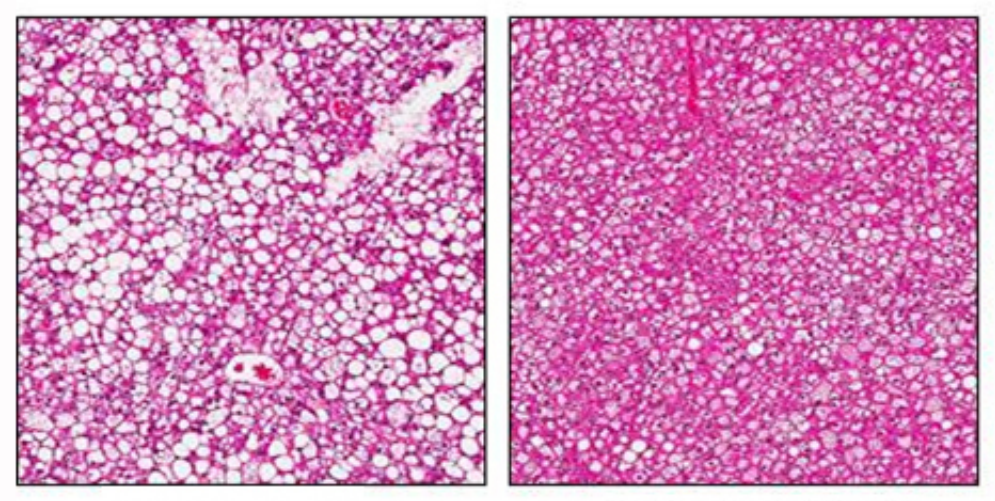

The liver cells (magenta) of untreated obese mice (left) contain many large, white droplets of fat while those of obese mice treated with valproic acid (right) have much less fat accumulation. Credit: Lindsay B. Avery and Namandjé N. Bumpus. Valproic Acid Is a Novel Activator of AMP-Activated Protein Kinase and Decreases Liver Mass, Hepatic Fat Accumulation, and Serum Glucose in Obese Mice. Mol Pharmacol January 2014; 85:1-10.

Johns Hopkins researchers have discovered that valproic acid, a widely prescribed drug for treating epilepsy, has the additional benefits of reducing fat accumulation in the liver and lowering blood sugar levels in the blood of obese mice. A summary of their research appears in this month's issue of the journal *Molecular Pharmacology*.

Fatty liver disease can lead to liver failure and is often caused by obesity and a high-fat diet. Obesity is also associated with the development of type 2 diabetes, which sabotages the body's process for controlling blood sugar levels. A rapidly rising problem in the developed world, obesity currently affects over 90 million Americans.

Studying the ways in which the cytochrome P450 family of enzymes processes valproic acid, the Johns Hopkins biochemists found that it can activate the protein AMPK, which was already known to be a good drug target for treating metabolic disorders like type 2 diabetes and obesity.

The Bumpus laboratory studies how drugs are processed in cells by enzymes of the cytochrome P450 family. Humans have 57 of these enzymes, and several of them work on the drug valproic acid. In the course of their research, Namandjé Bumpus, Ph.D., assistant professor of pharmacology, and postdoctoral fellow Lindsay Avery, Ph.D., found that valproic acid could activate AMPK in mouse and human liver cells in a dose-dependent way.

"It was exciting to find that valproic acid can activate AMPK," Bumpus says. "What's even better is that its byproducts can activate AMPK at much lower doses. That's a desirable quality if you want to eventually use it to treat people."

This is a normal mouse (left) next to an obese mouse (right). Credit: The Jackson Laboratory

Knowing that valproic acid is extensively processed by cytochrome P450 enzymes, the research team added a cytochrome P450 inhibitor to mouse and human liver cells and found that AMPK was no longer activated. This suggested that the byproducts of valproic acid, as opposed to valproic acid itself, were the molecules activating AMPK. To test this theory, they added four chemically modified versions of the drug to the cells and found that the derivatives were able to activate AMPK without valproic acid. In fact, they achieved higher activation of AMPK at one-fortieth the concentration.

To assess the uptake and breakdown of valproic acid in living organisms, they gave the drug to obese mice with high blood sugar levels, fatty livers and rapid weight gain. Treated mice showed decreased blood sugar levels, decreases in the size and the fat accumulation of their livers, and a stabilization of weight—rather than the continued weight gain experienced by untreated mice.

"The improvements seen in the health of these obese mice were very encouraging," says Bumpus. "We hope that we will find similar results in obese people who take valproic acid."

More information: dx.doi.org/10.1124/mol.113.089755

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