Fat turns from diabetes foe to potential treatment

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A new weapon in the war against type 2 diabetes is coming in an unexpected form: fat. Researchers have discovered a new class of potentially therapeutic lipids, called fatty-acid esters of hydroxy fatty acids (FAHFAs). These lipids are found at lower levels in people with insulin resistance, a risk factor for type 2 diabetes, compared with those who don't have the condition. Administering FAHFAs to diabetic mice improved their glucose metabolism and insulin secretion, opening a surprising avenue for the development of novel medications for the disease.

The team will describe their approach in one of nearly 11,000 presentations at the 249th National Meeting & Exposition of the American Chemical Society (ACS).

One in ten people in the United States has type 2 diabetes, which is the seventh leading cause of death. Excess weight and body fat increase disease risk. Genes also play a role, but much remains unknown.

"There are some drugs available for treating type 2 diabetes, but there are still gaps in our knowledge about what causes it," says Alan Saghatelian, Ph.D., who is at the Salk Institute for Biological Studies. He co-led the study with Barbara Kahn, M.D. "Our discovery came out of basic research to understand the mechanism underlying type 2 diabetes."

The researchers had been studying insulin resistance, a metabolic defect believed to contribute to the development and progression of type 2

diabetes. Insulin resistance occurs when the body does not respond to the insulin being produced, causing glucose to build up in the blood. It is typically associated with obesity. But Kahn's team at Beth Israel Medical Deaconess Center found that they could create obese mice that were unusually sensitive to insulin.

As it turned out, these mice had levels of a previously undiscovered family of fats, which they named FAHFAs, that was massively elevated —16- to 18-fold. The researchers suspected that these lipids were behind the increased insulin sensitivity. They figured if that were the case, then research on these newly discovered fats could someday lead to a diabetes therapy. In total, the researchers identified 16 different types of FAHFAs in the mice using a technique called mass spectrometry.

To check that their findings weren't limited to rodents, the researchers measured FAHFA levels in the blood samples from human subjects, finding lower levels of these compounds in those with insulin resistance. They also checked various foods and detected FAHFAs in many common items, such as apples, broccoli, beef, chicken and eggs. "We've been eating them for a long time, and they aren't toxic," says Saghatelian, suggesting FAHFAs may be safe to use as a medication.

To test how well FAHFAs could work as a potential therapy, the researchers fed the lipids to insulin- resistant mice, and observed an improvement in inflammation, insulin sensitivity and glucose uptake. Although this experiment suggests that FAHFAs may make good type-2-diabetes drugs, Saghatelian says he's now looking beyond lipids. "These are very cool compounds, but lipids aren't typically used as drugs for several reasons, including that they might not be able to reach effective doses in the relevant tissues," he says. "But the existence of FAHFAs means there is a metabolic pathway for making and breaking down these molecules. Identifying the enzymes involved in those processes may provide a lead toward even better drug targets."

The Saghatelian and Kahn laboratories are currently parsing human tissues for those that show increasing or decreasing levels of FAHFAs. Once identified, the scientists will search the tissue for enzymes involved in FAHFA metabolism. Drugs could potentially be developed that work by either increasing the activity of enzymes that produce FAHFAs or blocking those that destroy FAHFAs.

"As we learn more about type 2 diabetes," says Saghatelian, "we may be able to come up with better therapies that treat the disease with fewer side effects and that are effective in a larger number of people."

More information: Discovery of a class of endogenous mammalian lipids with anti-diabetic and anti-inflammatory effects, 249th National Meeting & Exposition of the American Chemical Society (ACS).

Abstract
Increased adipose tissue lipogenesis is associated with enhanced insulin sensitivity. Mice overexpressing the Glut4 glucose transporter in adipocytes have elevated lipogenesis and increased glucose tolerance despite being obese with elevated circulating fatty acids. Lipidomic analysis of adipose tissue revealed the existence of branched fatty acid esters of hydroxy fatty acids (FAHFAs) that were elevated 16- to 18-fold in these mice. FAHFA isomers differ by the branched ester position on the hydroxy fatty acid (e.g., palmitic-acid-9-hydroxy-stearic-acid, 9-PAHSA). PAHSAs are synthesized in vivo and regulated by fasting and high-fat feeding. PAHSA levels correlate highly with insulin sensitivity and are reduced in adipose tissue and serum of insulin-resistant humans. PAHSA administration in mice lowers ambient glycemia and improves glucose tolerance while stimulating GLP-1 and insulin secretion. PAHSAs also reduce adipose tissue inflammation. In adipocytes, PAHSAs signal through GPR120 to enhance insulin-stimulated glucose uptake. Thus, FAHFAs are endogenous lipids with the potential to treat type 2 diabetes.