Lipid enzyme heightens insulin sensitivity, potential therapy to treat Type 2 diabetes

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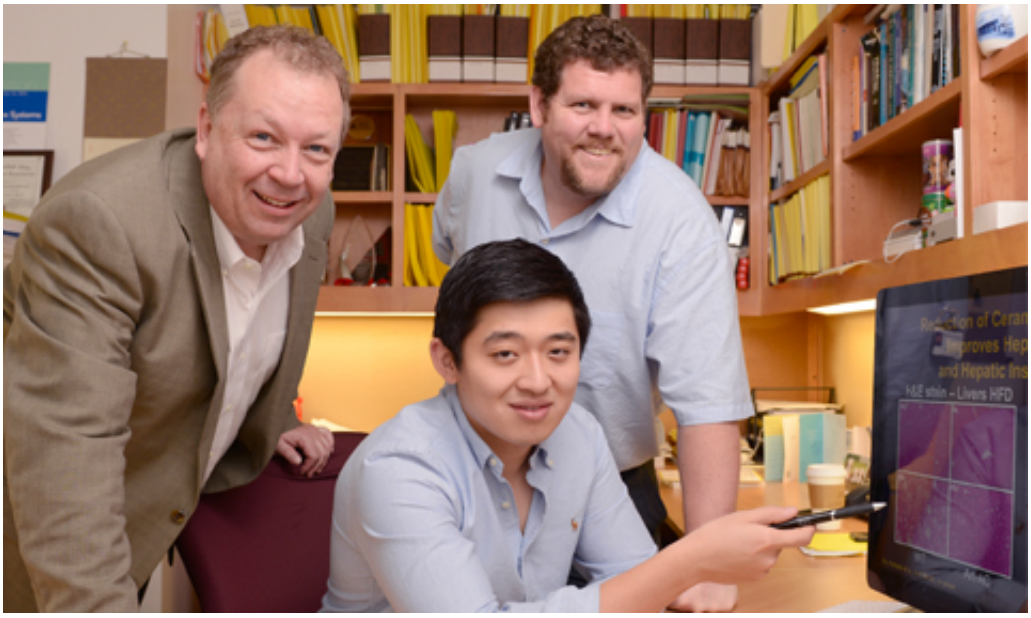

A study led by Dr. Phillip Scherer (l-r), Jonathan Xia, and Dr. William Holland determined that reducing concentrations of the fatty molecule ceramide improves insulin sensitivity, offering potential as a new therapy for diabetes. Credit: UT Southwestern

Reducing high concentrations of a fatty molecule that is commonly found in people with diabetes and nonalcoholic fatty liver disease rapidly improves insulin sensitivity, UT Southwestern Medical Center diabetes researchers have found.

Insulin is a crucial hormone that helps the body convert sugar into

energy, absorb nutrients, and reduce the storage of sugars as fat. Poor insulin sensitivity reduces the effectiveness of these processes and results in diabetes and fatty liver disease. UT Southwestern researchers showed that introducing an enzyme called ceramidase in diabetic mice returned their insulin sensitivity to normal.

"Lowering ceramides may also make people more insulin-sensitive," said study senior author Dr. Philipp Scherer, Director of the Touchstone Center for Diabetes Research at UT Southwestern. "Our findings suggest a new means to potentially treat Type 2 diabetes and nonalcoholic fatty liver disease."

Though no such therapy currently exists, Dr. Scherer said a drug form of the enzyme ceramidase likely could be developed.

The findings are outlined in the journal *Cell Metabolism*.

When more fatty acids are consumed than the body burns off, some excess fat is converted to ceramide. When too much ceramide builds up, the lipid interferes with insulin signaling, resulting in insulin resistance and possibly diabetes or nonalcoholic fatty liver disease.

"It is a nasty lipid at times," said Dr. Scherer, Professor of Internal Medicine and Cell Biology who holds the Gifford O. Touchstone, Jr. and Randolph G. Touchstone Distinguished Chair in Diabetes Research. "If we can lower ceramide, then we believe the body's metabolism will return to normal."

In their new study, the scientists showed that inducing ceramidase in the diabetic mice triggered degradation of ceramide in both fat tissue and the liver. This action then normalized insulin sensitivity and had the same beneficial effect when ceramidase was induced in the liver or fat cells. Excess ceramide was converted into sphingosine, another lipid

byproduct. Both ceramide and sphingosine are energy sources, but the two lipids have contrary metabolic signaling power. Too much ceramide signals insulin resistance and inflammation, while more sphingosine does the opposite.

"This research suggests the existence of a rapidly acting "cross talk" between liver and adipose (fat) tissue in which ceramide and sphingosine critically regulate glucose metabolism and the uptake of lipids by the liver," Dr. Scherer said.

Provided by UT Southwestern Medical Center