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Fat degrading enzyme implicated in type 2 diabetes

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Investigators at Karolinska Institutet have identified a potential therapeutic target for treatment of obesity-associated metabolic diseases such as type 2 diabetes and nonalcoholic hepatic steatosis. The work, performed in collaboration with scientists at the University of California, Berkeley and Danderyd Hospital, is published in *Cell Reports*.

The researchers utilized advanced biochemical techniques to map activities of an enzyme family in liver biopsies from obese and lean individuals. The results reveal that obese individuals only have half the activity of a protein called carboxylesterase 2 compared to their lean counterparts.

Carboxylesterase 2 is best known for its role in breaking down foreign substances, such as drugs, within the body. However, in follow-up experiments the investigators found that carboxylesterase 2 not only decreased with obesity but was an important regulator of the devastating effects of fat on metabolic health. Remarkably, restoring levels of carboxylesterase 2 in obese mice for only one week largely reversed obesity-induced disturbances in glucose metabolism and the deposition of fat within the liver.

Ability to breakdown diacylglycerol

Carboxylesterase 2 may have such profound health promoting effects because of its ability to breakdown diacylglycerol, a lipid intermediate

known to have deleterious effects on glucose metabolism. This also appears to be the case in humans where individuals with higher carboxylesterase 2 activity had significantly lower levels of diacylglycerols and markers of improved glucose metabolism.

"As effective therapies for metabolic disease are presently limited, developing therapies that restore activity of carboxylesterase 2 in obesity may have a profound public health impact. Moreover, given its known role in drug metabolism, decreased activity of carboxylesterase 2 may inform proper dosing in the context of obesity", says Juleen Zierath, professor at the Department of Molecular Medicine and Surgery, Karolinska Institutet, who has led the investigation together with post-doctoral researcher Max Ruby.

More information: Maxwell A. Ruby et al. Human Carboxylesterase 2 Reverses Obesity-Induced Diacylglycerol Accumulation and Glucose Intolerance, *Cell Reports* (2017). DOI: 10.1016/j.celrep.2016.12.070

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