Study finds targeting mitochondria shows promise in treating obesity

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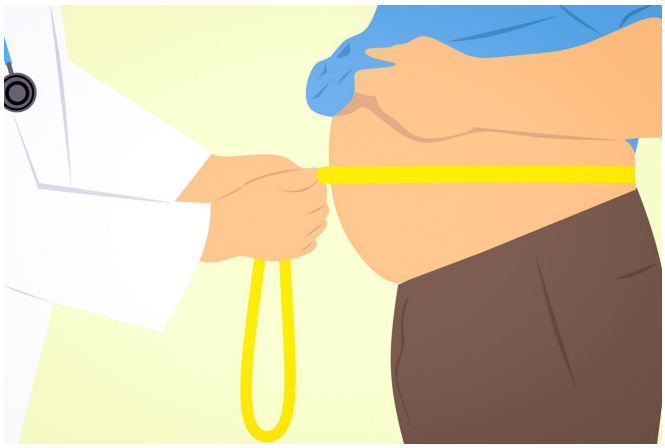

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A team of University of California, Irvine, scientists have discovered a novel pharmacological approach to attenuate the mitochondrial dysfunction that drives diet-induced obesity. The results of their study were published recently in the journal, *EMBO Molecular Medicine*.

Consuming a high-fat diet can lead to obesity and metabolic disorders such as diabetes and fatty liver. Palmitate, a fat abundant in a Western diet, triggers metabolic dysfunction by causing excessive mitochondrial fission within cells. Mitochondria play a crucial role in a cell's energy production, but also coordinate cell stress responses. Too much mitochondrial fission impairs their function, undermining metabolism and increasing toxic by-products associated with insulin resistance in some tissue types.

"Elegant genetic studies in mice show that maintaining mitochondrial networks in a fused state can overcome high fat diet-induced obesity. Our study uses a small molecule to re-shape mitochondria in multiple tissues simultaneously, reversing obesity and correcting metabolic disease even though mice continue to consume the unhealthy diet," said senior author Aimee Edinger, UCI Chancellor's Fellow and professor of developmental & cell biology.

In their new study, Professor Edinger and her team utilized their patented water-soluble, orally bioavailable, synthetic sphingolipid SH-BC-893 to inhibit endolysosomal trafficking proteins required for mitochondrial fission. The study was conducted using *in vitro* experiments and a high-fat diet-induced obesity mouse model. The researchers observed that SH-BC-893 prevented mitochondrial dysfunction in the liver, brain, and white adipose tissue of mice consuming a Western diet. As a result, circulating levels of critical metabolic hormones, leptin and adiponectin, were normalized leading to weight loss, improved glucose handling, and reversal of fatty liver disease despite continued access to high-fat food.

"Imbalances in the hormones leptin and adiponectin that accompany obesity create an uphill battle for people trying to lose weight. Having too much leptin can increase appetite while too little adiponectin activity is linked to many metabolic diseases. How or why is not really clear, but the state of the mitochondria may be an important link between these hormones and obesity," said Elizabeth Selwan, a former graduate student researcher in UCI's Department of Developmental and Cell Biology and co-lead author of the study.

The study's findings suggest that SH-BC-893 could be a promising therapy for managing diet-induced obesity. The authors found the drug to be safe and effective in the mouse model and plan on further investigating the compound for possible use in human patients.

"This compound works through a novel mode of action—if it is safe and effective in humans, it would offer a new weight loss strategy that could also be combined with other treatments," said Professor

Edinger.

More information: Vaishali Jayashankar et al, Drug?like sphingolipid SH?BC?893 opposes ceramide?induced mitochondrial fission and corrects diet?induced obesity, *EMBO Molecular Medicine* (2021). DOI: 10.15252/emmm.202013086

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