Researchers identify new method for stimulating signaling to improve metabolic health and possibly treat obesity

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Following up on a 2018 study that identified an epigenetic modifier known as histone deacetylase 11 (HDAC11) as a potential therapeutic

target for treating obesity and diabetes, researchers from the University of Colorado School of Medicine have published new research that finds HDAC11 regulates G protein-coupled receptors (GPCRs) called beta-adrenergic receptors (β-ARs).

The details of the study are published in the *Proceedings of the National Academy of Sciences (PNAS)*, the official journal of the National Academy of Sciences.

Lead author of the study, Rushita Bagchi, Ph.D., is now a faculty member at the University of Arkansas for Medical Sciences and was previously a postdoctoral fellow in the laboratory of Timothy McKinsey, Ph.D., professor of medicine in the Division of Cardiology, who is the corresponding author of the article. Both are part of the Consortium for Fibrosis Research & Translation, a program funded by the CU School of Medicine to improve understanding of fibrotic diseases across various organ systems.

The scientists originally studied the biological function of HDAC11, a lysine demyristoylase enzyme, and determined that deleting it in animal models stimulates the formation of brown adipose tissue (BAT). The absence of HDAC11 also triggered "beiging," turning white adipose tissue (WAT) into brown-like adipose tissue. BAT and beige WAT are unique forms of fat that are stimulated in response to cold temperature. BAT and beige WAT produce heat, and in so doing, burn calories. From a therapeutic perspective, there is intense interest in developing drugs that activate BAT or convert normal WAT into beige WAT as a means of triggering weight loss in the context of obesity and diabetes. One approach to doing this is to stimulate β_2- and β_3-ARs. However, drugs targeting these GPCRs have underperformed as anti-obesity therapies in the clinic, perhaps due to the high doses required, which can cause cardiovascular side effects.

"Our new research shows that inhibiting HDAC11 promotes β-AR signaling in fat cells through a previously unrecognized mechanism called lysine myristoylation," McKinsey says. "The findings lay the foundation for developing therapeutics for obesity and diabetes based on enhancing GPCR signaling in adipose tissue by inhibiting HDAC11. Reversible lysine myristoylation is a very unique mechanism that has never been described for the regulation of a GPCR. Given the critical roles of β-ARs in various physiological and pathophysiological processes, we think this work will be of interest to a broad audience, and has great potential for clinical translation."

"Before taking anything like this into the clinic, there's a lot of additional work that needs to be done at the bench," Bagchi adds. "This paper describes only the second myristoylated substrate of HDAC11. There are likely many more proteins that are substrates for HDAC11, and thus, we are at the tip of the iceberg when it comes to understanding the biological consequences and the therapeutic potential of inhibiting this fascinating demyristoylase."

More information: Rushita A. Bagchi et al, Reversible lysine fatty acylation of an anchoring protein mediates adipocyte adrenergic signaling, *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2119678119

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