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Anti-inflammatory drug counters obesity in mice

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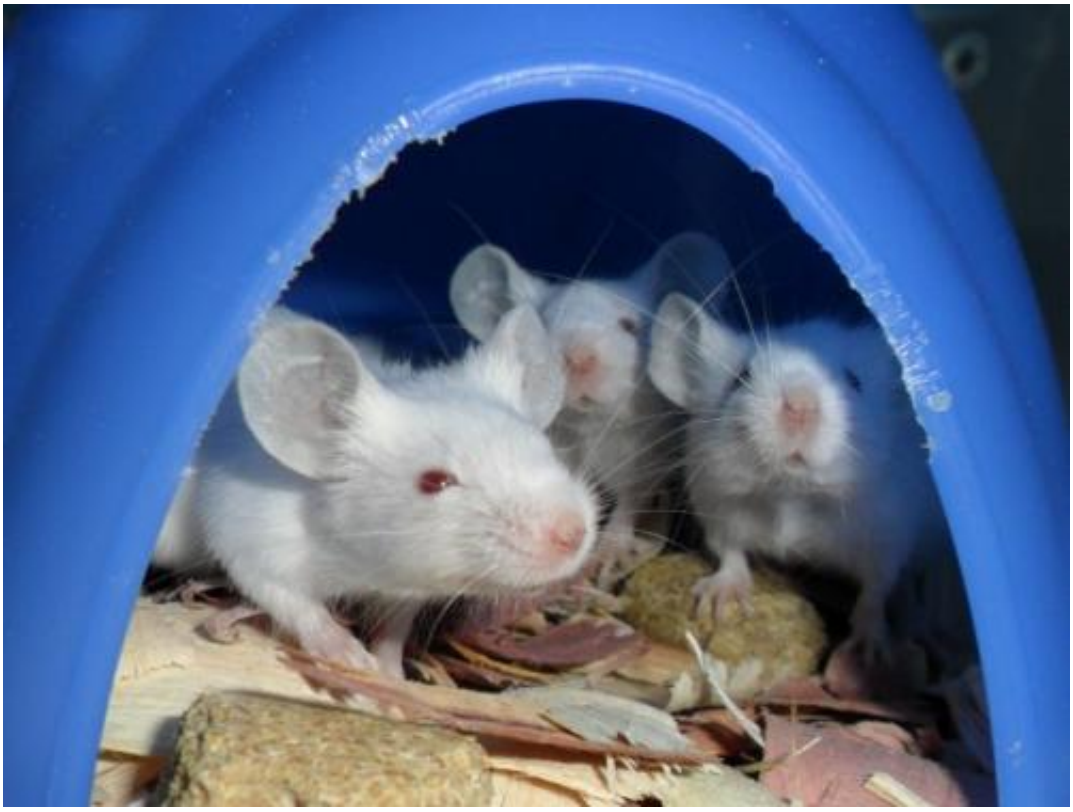

Credit: Martha Sexton/public domain

Obesity represents a global health problem with limited options available for its prevention or treatment. The finding that a key regulator of energy expenditure and body weight is controlled by a drug-targeted inflammatory enzyme opens new possibilities for pharmacologically modulating body weight. This is the conclusion of a study led by

Toshihiro Nakajima of Tokyo Medical University in Japan, reported in *The EMBO Journal*.

Energy spending in human cells is controlled by organelles called mitochondria, which are the major sites for burning of nutrients such as fatty acids. Mitochondria therefore play key roles in the fat cells that form white adipose tissue, an excess of which characterizes obesity. Earlier research has shown that mitochondrial biogenesis and fatty acid breakdown is regulated by hormone receptors known as peroxisome proliferator-activated receptors (PPARs). Pharmacological activators of PPARs have been tried as promising clinical treatments for obesity, but such trials have been hindered by undesirable side effects.

Nakajima's team had been studying a gene called Synoviolin, which is causally linked to the inflammatory condition of rheumatoid arthritis. In previous work, they developed a chemical compound, LS-102, that inhibits the enzyme encoded by the Synoviolin gene and suppresses rheumatoid arthritis in mouse disease models. Given the close associations of inflammation and metabolic diseases, including obesity and diabetes, the authors now tested the role of the Synoviolin gene in mouse models for such disorders. Loss of Synoviolin led to decreased white fat tissue and reduced body weight, which was traced to mitochondrial up-regulation. Importantly, the authors could show that loss or inhibition of SYVN1, the enzyme encoded by the Synoviolin gene, led to stabilization of an endogenous cellular PPAR activator, thus turning on PPAR-dependent energy control pathways. Therefore, treatment with the LS-102 inhibitor may provide an alternative to the side effect-troubled chemical PPAR activators for treating obese patients.

"Obesity is a known risk factor for other chronic disorders," says Nakajima. "Our findings indicate that Synoviolin may be a key for understanding the common features of obesity and chronic inflammatory

disease such as rheumatoid arthritis."

More information: The E3 ligase synoviolin controls body weight and mitochondrial biogenesis through negative regulation of PGC-1β Fujita H, Yagishita N, Aratani S, Saito-Fujita T, Morota S, Yamano Y, Hansson MJ, Inazu M, Kokuba H, Sudo K, Sato E, Kawahara K, Nakajima F, Hasegawa D, Higuchi I, Sato T, Araya N, Usui C, Nishioka K, Nakatani Y, Maruyama I, Usui M, Hara N, Uchino H, Elmer E, Nishioka K, Nakajima T: dx.doi.org/10.15252/embj.201489897

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