Molecule from trees helps female mice only resist weight gain

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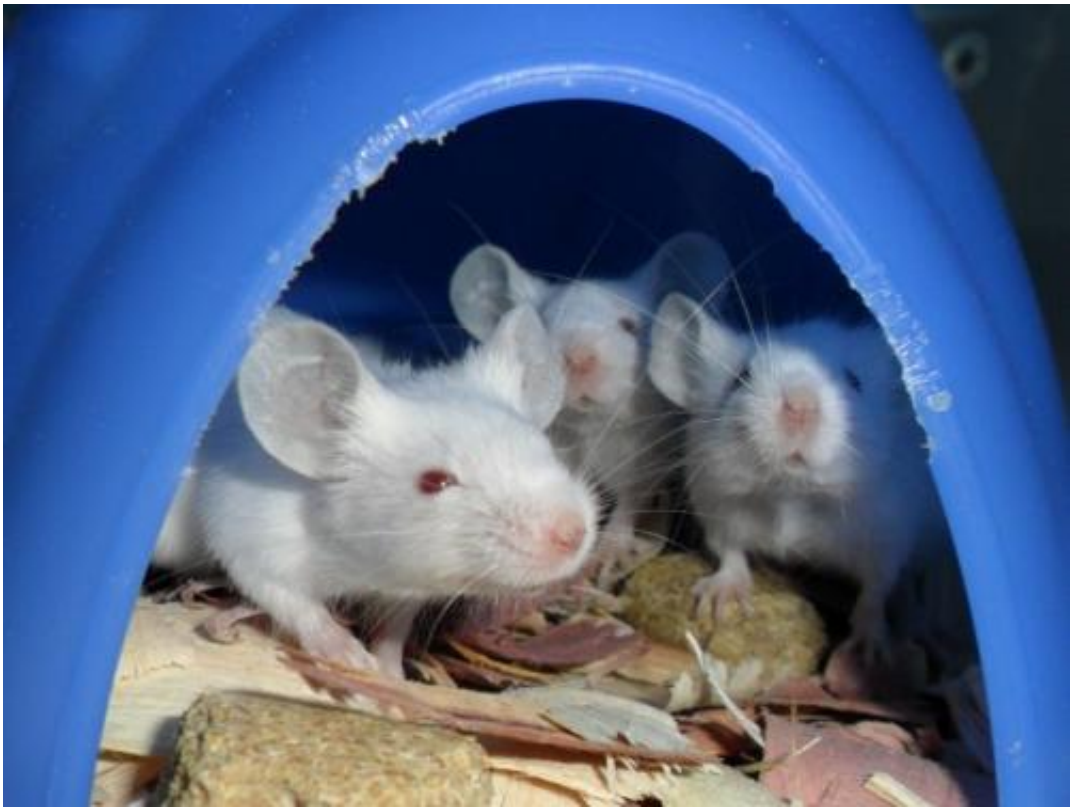

Credit: Martha Sexton/public domain

A molecule found in some plants can combat weight gain induced by a high-fat diet, but only in female mice, not males. 7,8-dihydroxyflavone (7,8-DHF) is thought to mimic the effects of a growth factor induced by exercise.

Emory researchers led by Keqiang Ye, PhD, have shown that female mice treated with 7,8-DHF could consume a high-fat diet without gaining weight. In the mice, 7,8-DHF could increase energy expenditure by acting on muscle cells, without suppressing appetite.

"An equivalent diet pill in humans would allow people to maintain a healthy weight, despite a high-fat diet," says Ye, professor of pathology and laboratory medicine at Emory University School of Medicine. "The pill would burn calories without affecting appetite."

The findings highlight the need to study both sexes while developing drugs for obesity and related conditions. They also reveal a surprising effect of a molecule previously thought to act mainly on brain cells, instead of muscle cells.

The results are scheduled for publication in *Chemistry & Biology*. The first author, Chi Bun Chan, PhD, is now assistant professor of physiology at University of Oklahoma College of Medicine.

Ye's laboratory has been studying brain-derived neurotrophic factor (BDNF) and its receptor TrkB. Previous research has shown that BDNF is secreted after physical exercise. Lack of BDNF is also thought to play a role in neurodegenerative diseases such as Alzheimer's. However, BDNF degrades quickly in the body. Ye and his colleagues discovered 7,8-DHF while looking for ways to activate TrkB with drugs in the absence of BDNF.

7,8-DHF can be found in *Godmania aesculifolia* and primula tree leaves from Central and South America. A 7,8-DHF pro-drug (meaning that it is hydrolyzed in the body to 7,8-DHF) is planned for phase I human clinical trials in Shanghai and Australia, Ye says.

When mice were fed 7,8-DHF along with a high-fat diet, females

maintained their appetites but kept a healthy weight and metabolic profile; males, on the other hand, still developed obesity and diabetes. The mechanisms behind this sex difference are unknown, but interactions between BDNF/TrkB signals and estrogen might play a role, Ye says.

"This drug has been tested in a variety of neurological diseases and exhibits promising efficacy in both male and female animal models," Ye says. "Further investigation is necessary to explore why it selectively burns fat in the female mice."

Ye says another surprise was that 7,8-DHF appears to act on muscle cells and does not suppress appetite. BDNF was previously thought to act on the hypothalamus, part of the brain that controls appetite. In muscle cells , 7,8-DHF appears to activate production of an "uncoupling" protein called UCP1, which was first discovered in brown fat and helps generate heat.

More information: *Chemistry & Biology*, Chan et al.: "Activation of Muscular TrkB by its Small Molecular Agonist 7,8-Dihydroxyflavone Sex-dependently Regulates Energy Metabolism in Diet-induced Obese Mice" www.cell.com/chemistry-biology … 1074-5521(15)00041-1

Provided by Emory University

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