MedicalXpress

New drug could help maintain long-term weight loss

July 26 2012

A new drug could aid in losing weight and keeping it off. The drug, described in the journal *Cell Metabolism* on July 26, increases sensitivity to the hormone leptin, a natural appetite suppressant found in the body. Although so far the new drug has only been tested on mice, the findings have implications for the development of new treatments for obesity in humans.

"By sensitizing the body to naturally occurring leptin, the new drug could not only promote weight loss, but also help maintain it," says senior study author George Kunos of the National Institute on Alcohol Abuse and Alcoholism. "This finding bodes well for the development of a new class of compounds for the treatment of obesity and its metabolic consequences."

Although leptin is an appetite suppressant, leptin supplements alone have not been effective at reducing body weight in humans. It's thought that this is because of desensitization to the hormone; leptin is still there, but our bodies can no longer respond to it. While it is not entirely clear how this desensitization occurs, cannabinoid receptors, which mediate the feelings of hunger produced by marijuana and naturally occurring cannabinoids in the body, are thought to be involved. So blocking these receptors, rather than providing excess leptin, could be more effective at long-term weight loss. Knowing that marijuana use causes the munchies, scientists had developed anti-obesity drugs that target cannabinoid receptor type 1 (CB1R). One CB1R-binding drug called rimonabant was sold in Europe beginning in 2006, but it was taken off the market a few

years later due to serious psychiatric side effects, including anxiety, depression and thoughts of suicide.

To minimize these side effects, Kunos and his team previously developed a CB1R-targeting drug that did not enter the brain as easily as rimonabant. However, the drug was not as effective at reducing weight and improving metabolic health, possibly because of its specific mode of action. In the new study, Kunos tested a new compound, JD5037, that targets CB1R without penetrating the brain. JD5037suppressed the appetite of obese mice, caused weight loss, and even improved metabolic health, in part by resensitizing mice to the appetite-suppressing hormone leptin. Importantly, the mice did not show signs of anxiety or other behavioral side effects.

"Obesity is a growing public health problem, and there is a strong need for new types of medications to treat obesity and its serous metabolic complications, including diabetes and fatty liver disease," says Kunos.

More information: Tam et al.: "Peripheral Cannabinoid-1 Receptor Inverse Agonism Reduces Obesity by Reversing Leptin Resistance." dx.doi.org/10.1016/j.cmet.2012.07.002

Provided by Cell Press