

Blocking natural, marijuana-like chemical in the brain boosts fat burning

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Stop exercising, eat as much as you want ... and still lose weight? It sounds impossible, but UC Irvine and Italian researchers have found that by blocking a natural, marijuana-like chemical regulating energy metabolism, this can happen, at least in the lab.

To create this hypermetabolic state, UCI pharmacology professor Daniele Piomelli and colleagues engineered neurons in the forebrains of mice to limit production of an endocannabinoid compound called 2-AG. All mammalian brains contain 2-AG, which the researchers believe helps control the activity of forebrain [neural circuits](#) involved in [energy dissipation](#).

As a result, these modified mice ate more and moved less than typical mice but did not gain any weight, even when they were fed a high-fat diet. Additionally, they did not develop any signs of [metabolic syndrome](#), a combination of health problems such as obesity and [high blood pressure](#) that increases the [risk of cardiovascular disease](#) and diabetes.

"We discovered that these mice were resistant to obesity because they burned fat calories much more efficiently than normal mice do," said Piomelli, the Louise Turner Arnold Chair in the Neurosciences. "We had known that endocannabinoids play a critical role in cell [energy regulation](#), but this is the first time we found a target where this occurs."

Specifically, these [mutant mice](#) stayed thin because their brown fat – a type of fat that exists in all mammals to keep them warm – became

hyperactive and was converted into heat at a much more rapid pace than in ordinary mice.

Does this mean that a drug limiting 2-AG levels may one day become a weight-loss panacea? That's more easily said than done, according to Piomelli. For the study, the mice were bred with brain cells manipulated to limit 2-AG production – which can't be done with humans.

"To produce the desired effects, we would need to create a drug that blocks 2-AG production in the brain, something we're not yet able to do," he explained. "So don't cancel that gym membership just yet. But as you hit the treadmill, think about the added health benefits if you could train your brain to make fewer endocannabinoids."

Findings appear in the March issue of *Cell Metabolism*. Nicholas DiPatrizio, Giuseppe Astarita, Kwang-Mook Jung, Jason Clapper, Ana Guijarro, Dean Thongkham and Agnesa Avanesian of UCI; Giuseppe D'Agostino and Sabrina Diano of Yale University; and Andrea Frontini and Saverio Cinti of Marche Polytechnic University in Ancona, Italy, contributed to the study, which received support from the National Institute on Drug Abuse.

About endocannabinoids

Endocannabinoid compounds are created naturally in the body and share a similar chemical structure with THC, the primary psychoactive component of the marijuana plant, Cannabis. Endocannabinoids are distinctive because they link with protein molecule receptors – called cannabinoid receptors – on the surface of cells. For instance, when a person smokes marijuana, the cannabinoid THC activates these receptors. Because the body's natural cannabinoids control a variety of factors – such as pain, mood and appetite – they're attractive targets for drug discovery and development. Piomelli is one of the world's leading

endocannabinoid researchers. His groundbreaking work is showing that this system can be exploited by new treatments to combat anxiety, pain, depression and obesity.

Provided by University of California - Irvine

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