Study explains how western diet leads to overeating and obesity

January 11 2017

This is an image of a weight scale. Credit: CDC/Debora Cartagena

More than two in three adults in the United States are considered overweight or obese, with substantial biomedical and clinical evidence suggesting that chronic overconsumption of a "western diet" - foods consisting high levels of sugars and fats - is a major cause of this epidemic.

New research by scientists at the University of California, Riverside now shows that chronic consumption of a western diet leads to overeating and obesity due to elevations in "peripheral endocannabinoid signaling."

The endocannabinoid system is located throughout the mammalian body, including the brain and all peripheral organs, and participates in the control of many physiological functions in the body, including food intake, energy balance, and reward. It is comprised of lipid signaling molecules called endocannabinoids—which can be thought of as the body's own "natural cannabis"—that bind to cannabinoid receptors located on cells throughout the body.

"Our research shows that targeting cannabinoid receptors in the periphery with pharmacological inhibitors that do not reach the brain holds promise as a safe therapeutic approach for the treatment of overeating and diet-induced obesity," said Nicholas V. DiPatrizio, an assistant professor of biomedical sciences in the School of Medicine, who led the research project. "This therapeutic approach to targeting the periphery has substantial advantages over traditional drugs that interact with the brain and cause psychiatric side-effects."

The work describes for the first time that overeating associated with chronic consumption of a western diet is driven by an enhancement in endocannabinoid signals generated in peripheral organs.

Study results appear in the journal *Physiology & Behavior*.

To examine the role for endocannabinoids generated in peripheral organs in controlling the overeating of western diet, DiPatrizio and coauthor Donovan A. Argueta, a bioengineering Ph.D. student in his lab, used a mouse model of western diet-induced obesity (chronic exposure to high levels of sugars and fats).

They found that when compared to mice fed a standard low-fat/low-sugar diet, mice fed a western diet for 60 days rapidly gained body weight and became obese, and displayed "hyperphagia," that is, they consumed significantly more calories, and consumed significantly larger meals at a much higher rate of intake (calories per minute).

"These hyperphagic responses to western diet were met with greatly elevated levels of endocannabinoids in the small intestine and circulation," DiPatrizio said. "Importantly, we found that blocking the actions of the endocannabinoids with pharmacological inhibitors of cannabinoid receptors in the periphery completely normalized food intake and meal patterns in western diet-induced obese mice to levels found in control lean mice fed standard chow."

DiPatrizio and Argueta caution that further research is necessary to identify whether similar mechanisms drive obesity in humans.

"Importantly, however, other research groups have reported elevations in circulating levels of endocannabinoids in obese human subjects, which suggests that this system may also be overactive in human obesity," DiPatrizio said.

He explained that rimonabant, a drug which blocked endocannabinoid signaling at cannabinoid receptors, was on the market in Europe for the treatment of human obesity.

"It worked quite well at reducing body weight and improving metabolic profiles; however, this drug was not restricted to the periphery and thus, led to severe psychiatric side effects and was not given FDA approval in the United States," DiPatrizio said. "Peripherally restricted inhibitors of cannabinoid receptors, such as AM6545 used in our experiments, however, would be devoid of these side effects given that they do not reach the brain."

DiPatrizio and Argueta were surprised to find that inhibiting peripheral endocannabinoid signaling with inhibitors like AM6545 completely normalized intake to that found in lean mice maintained on a standard chow.

"This suggests that these elevations in peripheral endocannabinoid signaling are critical in driving hyperphagia associated with a western diet," said Argueta, the first author of the research paper.

Next, the researchers plan to identify critical upstream and downstream mechanisms of endocannabinoid signaling in western diet-induced obesity, as well as the possible specific dietary constituents in western diet (e.g., sucrose) that drive overeating as a result of elevated peripheral endocannbinoid levels.

"In addition, we aim to translate our work in rodents to similar studies in humans," DiPatrizio said.

More information: Donovan A. Argueta et al, Peripheral endocannabinoid signaling controls hyperphagia in western diet-induced obesity, *Physiology & Behavior* (2017). DOI: 10.1016/j.physbeh.2016.12.044

Provided by University of California - Riverside