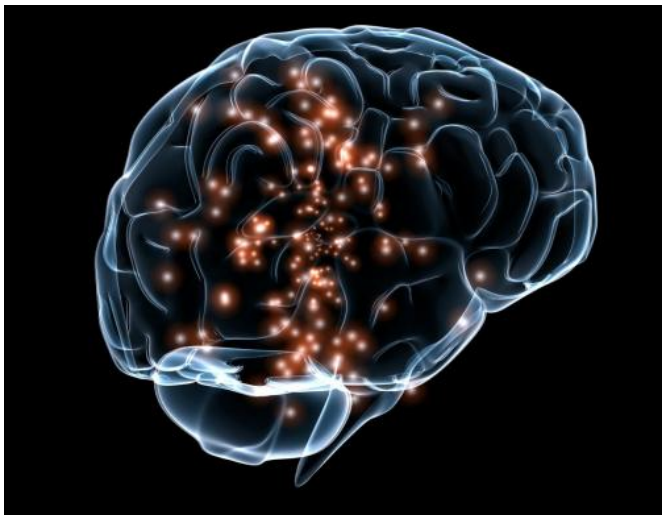
How celastrol sensitizes brains to leptin, curbing hunger and obesity

4 March 2019



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Celastrol's potent anti-obesity effects were widely reported in 2015. Derived from the roots of the thunder god vine, the drug curbed food intake in obese mice by nearly 80 percent, producing up to a 45 percent weight loss. Celastrol increases the brain's sensitivity to leptin, the hormone that signals we've had enough to eat, but until now, no one knew how. In today's *Nature Medicine*, a study led by Umut Ozcan, MD, at Boston Children's Hospital finally solves the mystery.

Ozcan's team initially identified celastrol's effects several years ago, through a screen of more than 1,000 compounds. Ozcan later founded ERX Pharmaceuticals to take celastrol and other leptin sensitizers into clinical development; the company is now testing celastrol in Phase 1 clinical trials.

The new study shows that celastrol works through a pro-inflammatory signaling pathway, by increasing amounts of a receptor called IL1R1. This receptor, which receives signals from the cytokine interleukin 1, is essentially the gatekeeper for celastrol's metabolic actions, the study found.

"If you knock out IL1R1, the leptin-sensitizing and anti-obesity effect of celastrol is completely gone," says Ozcan, the study's senior investigator.

Mice deficient in IL1R1 also lost celastrol's other metabolic benefits, which include curbing insulin resistance/type 2 diabetes.

Inflammation is good?

Scientifically, the finding seems somewhat surprising, but it is in line with Ozcan's previous discoveries. Papers published in *Nature Medicine* (2011) and *Cell* (2017) indicate that the relationship between inflammation and obesity seems to be more complex than previously appreciated. Inflammatory stimuli—cytokines or activation of inflammatory signaling pathways—had been thought to help drive the development of obesity and type 2 diabetes. But Ozcan and his colleagues showed that inflammatory signaling is actually beneficial and required for keeping glucose homeostasis in control. In fact, leptin itself is a pro-inflammatory cytokine.

"Basically, I believe that inflammatory signaling cascades have been wrongly regarded as the scapegoat of obesity and diabetes research," Ozcan says. "On the contrary, our work has shown that it is probably the dysfunction of pro-inflammatory signaling pathways that contributes to the development of obesity and type 2 diabetes. The problem is that the body becomes resistant to cytokine signaling, rather than cytokine action being the problem."

In any event, the researchers believe that it may be possible to make use of cytokine signaling, via ILR1, to alter our metabolism and help us lose weight.

Finding IL1R1

ILR1 was identified through a stepwise approach. The researchers first investigated how celastrol changes gene expression in the hypothalamus, the part of the brain where leptin does its signaling. They created three groups: lean mice, mice made obese by overfeeding and mice that were obese because they lacked functioning leptin receptors.

By analyzing RNA in the hypothalamus from all three groups, Ozcan and colleagues homed in on a group of genes whose up- or down-regulation could plausibly account for celastrol's effects. Ultimately, their search narrowed to genes altered specifically in the overfed obese mice, which still had leptin receptors. IL1R1 rose to the top of the list.

The IL1R1 finding offers new potential options for obesity treatment. Celastrol is producing encouraging weight-loss results so far in the early-stage trials, but should it ultimately fail, there may now be other avenues to explore.

"We will now investigate what upregulates IL1R1," says Ozcan. "It could lead to development of new molecules for the treatment of obesity and associated diseases. This is a new chapter for understanding the regulation of hunger."

More information: IL1R1 is required for celastrol's leptin-sensitization and antiobesity effects, DOI: 10.1038/s41591-019-0358-x , https://www.nature.com/articles/s41591-019-0358-x

Provided by Children's Hospital Boston