

OBESITY

Celastrol identified as a leptin sensitizer and potential novel treatment for obesity

Finding an effective drug treatment for obesity has proved difficult. Now, new findings published in *Cell* suggest that treatment with celastrol (a compound found in the roots of the *Tripterygium wilfordii* plant [commonly known as thunder god vine]) leads to reduced appetite and dramatic weight loss in

hyperleptinaemic diet-induced obese (DIO) mice, but not in mice that lack leptin action.

Previous work has shown that endoplasmic reticulum (ER) stress in the brain leads to leptin resistance and consequently obesity. However, agents that effectively target this pathway have, until now, not been found. To search for such compounds, Umut Ozcan and colleagues generated a gene expression signature using microarray data obtained from analyses of various interventions that relieved ER stress. This signature was then compared with an existing database of the gene-expression profiles derived from human cell lines treated with thousands of small molecules. The method identified celastrol as a candidate for increasing leptin sensitivity and reversing obesity.

Ozcan and co-workers then treated wild-type mice, hyperleptinaemic DIO mice, leptin-deficient (*ob/ob*) and

leptin-receptor-deficient (*db/db*) mice with celastrol or a control substance. Leptin sensitivity was increased in the treated DIO mice, which resulted in suppressed food intake and a body fat percentage that was up to 45% less than that of the control mice. The effects of celastrol in the *ob/ob* and *db/db* mice were minimal; no effect was observed in wild-type lean mice. “These results show that celastrol is a true leptin sensitizer,” explains Ozcan. Celastrol was equally effective when administered orally and intraperitoneally.

The researchers now plan to carry out experiments to identify celastrol’s mechanism of action. “In addition, we are taking steps to complete the toxicology studies required to take celastrol to human clinical trials,” states Ozcan.

Claire Greenhill

Original article Liu, J. et al. Treatment of obesity with celastrol. *Cell* 161, 999–1011 (2015)



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CORRECTION

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Nat. Rev. Endocrinol. advance online publication 9 June 2015; doi:10.1038/nrendo.2015.94

In the original article that was published online, leptin was spelled incorrectly. This error has now been corrected for the print, HTML and PDF versions of the article.