



OBESITY

New leptin sensitizer identified

Withaferin A, a compound isolated from the medicinal plant *Withania somnifera*, reduces body weight in diet-induced obese (DIO) mice and has positive effects on glucose metabolism, according to new research published in *Nature Medicine*.

In previous work, some of the authors of this paper identified celastrol as a leptin sensitizer that could induce weight loss in DIO mice, leading them to hypothesize that molecules with a similar gene expression signature to celastrol would also affect leptin sensitization.

The researchers first established the gene expression signature of celastrol, and then searched the Broad Institute Connectivity Map database for molecules with a similar gene expression signature. Withaferin A was identified as the molecule with a gene expression signature most similar to that of celastrol.

To test the effects of this molecule, DIO mice were administered with either vehicle or withaferin A. Vehicle-treated mice maintained a stable weight, whereas those given withaferin A lost an average of 22.8% of their body weight. Furthermore, mice treated with withaferin A consumed 62% less food than vehicle-treated mice. The mice given withaferin A also had lower circulating levels of leptin than the vehicle-treated mice, which suggests withaferin A increases leptin sensitivity.

Leptin reduces food intake; however, DIO mice do not respond to leptin treatment, as they are leptin resistant. To test whether withaferin A sensitized mice to leptin, mice were treated with vehicle or withaferin A and then saline or leptin. The vehicle plus leptin group did not change their food consumption. However, mice that received

withaferin A plus saline reduced their food intake by 42% compared with the vehicle plus leptin group. In addition, the withaferin A plus leptin group reduced their food intake by 71% compared with the vehicle plus leptin group. These results indicate that withaferin A increases sensitivity to leptin.

Withaferin A treatment was also found to increase responsiveness to insulin in DIO mice. These mice also had lower blood levels of glucose and insulin than vehicle-treated mice.

The researchers conclude that withaferin A is a potent antiobesity agent with antidiabetic effects. They hope that withaferin A will be used to treat patients with obesity in the future.

Claire Greenhill

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ORIGINAL ARTICLE Lee, J. et al. Withaferin A is a leptin sensitizer with strong antidiabetic properties in mice. *Nat. Med.* <http://dx.doi.org/10.1038/nm.4145> (2016)