Obesity: will withaferin win the war?

Paul T Pfluger & Matthias H Tschöp

Lee *et al.* show that withaferin A, a steroidal lactone isolated from *Withania somnifera*, can exert profound metabolic benefits in mice, including body-weight loss, reduced hepatic steatosis and improved glucose control.

Over ^the past two decades, we have witnessed considerable efforts by numerous research organizations around the world to discover safe and efficacious weight-lowering drugs that have the potential to combat the continuously expanding obesity and type 2 diabetes pandemic. So far, however, the only therapeutic intervention with curative potential is bariatric surgery, such as gastric bypass. In additon, unimolecular combinatorial peptides aimed at mimicking endogenous signals that occur after gastric-bypass surgery seem to offer some promise, although they are only in the early stages ^of clinical testing[1]. By contrast, small-molecule drugs—often identified by costly high-throughput screens of extensive chemical libraries—have failed to show sufficient weight-lowering efficacy, and several drugs have been either rejected by regulatory authorities or withdrawn from the market because of adverse cardiovascular or psychiatric side effects[1]. In this issue of *Nature Medicine,* Lee and colleagues[2] make a potentially important contribution toward overcoming that challenge by identifying the small molecule withaferin A as a potential candidate for a therapy countering obesity and its metabolic side effects. They show in mice that withaferin A seems to harness endogenous weight-control machinery by restoring the sensitivity of the hypothalamus to leptin ^.

The satiety hormone leptin is secreted by adipocytes in direct proportion to fat mass, and activates anorexigenic circuitry in the hypothalamus of lean individuals, which thereby leads to diminished food intake and subsequent weight loss. Upon high fat intake, ^calorie overconsumption and/or diet-induced obesity (DIO), leptin fails to activate hypothalamic anorexigenic circuitry. This failure is thought by many to result from either cellular or systemic resistance to leptin action in the brain. The subsequent failure to curb appetite leads to chronically higher food consumption and increasing body adiposity.

Recent reports of unimolecular polyagonists of gut-hormone receptors[1] or the plant constituent celastrol[3] offer some hope that overcoming leptin resistance could be a viable weight-loss option. The exact mechanism for this restoration of leptin sensitivity remains unclear, but it might entail improved leptin transport across the blood–brain barrier, altered leptin signaling or attenuated inflammation and/ or endoplasmic reticulum (ER) stress[4]. Lee and colleagues[2] add withaferin A to the list of novel leptin sensitizers by directly building upon their recent work on the ER stress agent celastrol[3]. They carried out microarrays on mouse embryonic fibroblasts undergoing celastrol treatment[2] and compared the ensuing ER stress signatures to a public collection of genome-wide transcriptional expression data derived from cells treated with one of more than 1,000 ^bioactive small molecules. Subsequent connectivity mapping (CMAP) on the basis of biomathematical similarities in

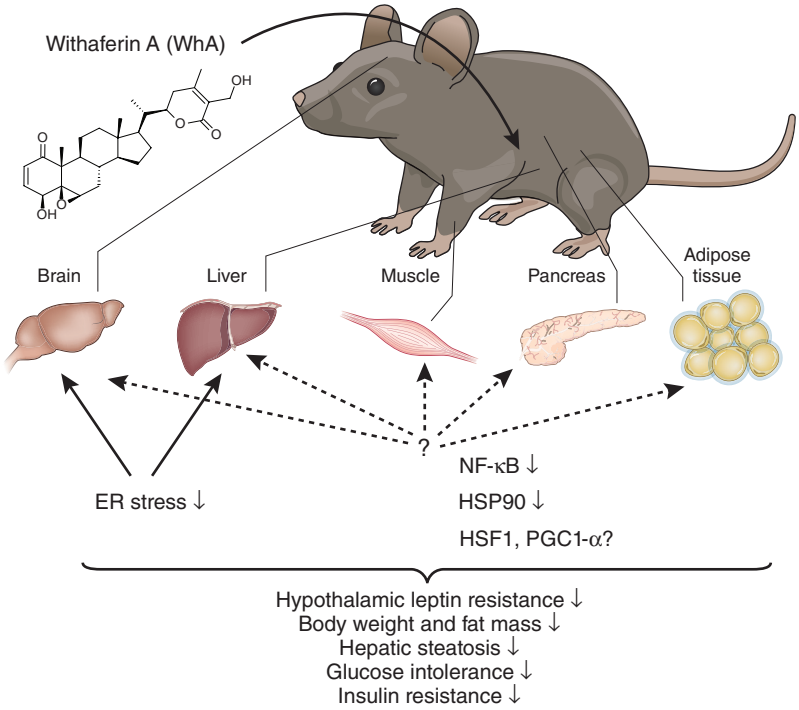

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Figure 1 Structure, molecular targets and physiological effects of withaferin A in mice with DIO. Lee and colleagues[2] show that treatment of mice that have DIO results in the annotated effects through signaling in the hypothalamus. The dotted arrows indicate the potential effects of withaferin A, according to studies *in vitro* and the effects of the related drug celastrol.^

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expression patterns led to the identification of withaferin A as a compound that had similar effects to celasterol.

The authors next assessed the weight-lowering effect of withaferin A on mouse models with differential degrees of leptin resistance. In mice with DIO that display reversible leptin resistance[3,4], 3 weeks of withaferin A treatment induced an impressive and apparently non-toxic weight-lowering effect, leading to a 23% reduction of body weight and 35% reduction of fat mass ^, and near complete remission from hepatic steatosis. Withaferin A decreased body weight, showing substantially lower efficacy ^ in lean mice with intact leptin sensitivity and in leptin-receptor-deficient (Lep^{db}) mice that have complete and irreversibe leptin resistance. These data suggest that the effects of withaferin A on body weight and food intake are predominantly, but not exclusively, mediated via the restoration of central leptin sensitivity. By contrast, withaferin A displayed potent antidiabetic actions in both Lep^{db} mice and mice with DIO, which suggests that the glucoregulatory roles of withaferin A are independent from leptin sensitivity and weight loss. The improvements in glucose tolerance and insulin sensitivity induced by withaferin A stand in stark contrast to the actions of celastrol, which showed no antidiabetic efficacy after low-dose treatment of mice with DIO or Lep^{db} mice[3]. However, when administered at ten-fold higher doses, celastrol also decreased body weight, fat mass and insulin resistance in Lep^{db} mice, potentially via the inhibition of inflammatory nuclear factor (NF)-κB signaling[5].

Overall, both celastrol and withaferin A display near identical action profiles on ER stress and leptin sensitivity, as evidenced by distinct hypothalamic ER-stress gene signatures and the activation of signaling pathways and improved efficacy of exogenous leptin *in vivo* toward reducing food intake and body weight in mice with DIO[2,3]. Accordingly, celastrol and withaferin A display high and leptin-dependent drug specificity when administered at low doses[2,3]. However, previous reports that used higher doses of both compounds propose additional mechanisms of action[5–7], and both compounds have indeed been considered as potential cytotoxicants and anticancer agents. In particular, anticarcinogenic activities of withaferin A and celastrol have been ascribed to their inhibition of heat-shock protein 90 (HSP90) and NF-κB signaling[6,7]. Both pathways are also involved in the etiology of hypothalamic inflammation and metabolic dysfunction[8,9], and they might link celastrol and withaferin A action with improved body-weight control and diabetes remission. Further studies are warranted to disentangle their mechanisms of action and the exact site(s) of action, which could entail—in addition to the hypothalamus—other brain areas and several peripheral tissues. In this context, the roles of adipose tissue and skeletal muscle deserve special attention, according to a recent study by Ma *et al.*[10] that suggests increased skeletal muscle nonshivering thermogenesis, subcutaneous adipose-tissue browning and brown-fat thermogenesis as major drivers for celastrol-induced weight loss, which are potentially mediated via heat-shock factor protein 1 (HSF1) and peroxisome proliferator-activated receptor gamma co-activator-1α (PGC-1α, encoded by Ppargc1a) ^.

Whether withaferin A will be effective in humans as a weight-loss and antidiabetic agent must be tested rigorously. Withaferin A is available orally and seems to be a naturally occurring leptin sensitizer capable of inducing impressive levels of weight loss and near complete remission from type 2 diabetes and hepatic steatosis in mice with DIO. A relatively broad spectrum of action, including such prominent pathways as NF-κB signaling or heat-shock proteins, might indicate considerable challenges for long-term safety and translation to humans. Yet a pharmacologically rich action profile could be what is required to achieve efficacy at a level that could alleviate ^the obesity and type 2 diabetes pandemic. Moreover, the CMAP-based drug-discovery approach by Lee *et al.*[2] might yield additional substances of therapeutic value.

COMPETING FINANCIAL INTERESTS ^
The authors declare competing financial interests: details are available in the online version of the paper.

1. Tschöp, M.H. *et al. Cell Metab.* **24**, 51–62 (2016).
2. Lee, J. *et al. Nat. Med.* **22**, XXX–XXX (2016). ^
3. Liu, J., Lee, J., Salazar Hernandez, M.A., Mazitschek, R. & Ozcan, U. *Cell* **161**, 999–1011 (2015).
4. Myers, M.G. Jr. *et al. Cell Metab.* **15**, 150–156 (2012).
5. Kim, J.E. *et al. PLoS One* **8**, e62068 (2013).
6. McKenna, M.K. *et al. Cancer Biol. Ther.* **16**, 1088–1098 (2015).
7. Yang, H. & Dou, Q.P. *Curr. Drug Targets* **11**, 733–744 (2010).
8. Kleinridders, A. *et al. J. Clin. Invest.* **123**, 4667–4680 (2013).
9. Zhang, X. *et al. Cell* **135**, 61–73 (2008).
10. Ma, X. *et al. Cell Metab.* **22**, 695–708 (2015).

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AUTHOR Query_NM4182

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