Reference

[1] Hoffman NJ, Parker BL, et al. Cell Metab 2015;22(5):922—35.

https://doi.org/10.1016/j.orcp.2016.10.071

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Invited talk: Use of a potent calorie restriction mimetic to selectively recover POMC activity, thereby reversing dietary induced weight gain

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17α-E2 significantly extends lifespan in male mice following late-life administration. We previously showed that this non-feminising, naturally occurring enantiomer of 17β-estradiol (17β-E2) mimics the beneficial effects of calorie restriction, reversing multimorbidity in aged male mice1. Given that 17α-E2 reduced food intake, it was proposed that 17α-E2 might promote weight loss in obese mice through suppressing appetite.

We first assessed the effect of dietary-17α-E2 treatment on body mass, body composition, food intake, activity and energy expenditure in male mice maintained on an obesogenic high fat diet. 17α-E2 initiated weight loss soon following treatment, resulting in an overall reduction in body mass regardless of continued high fat feeding. Reduced body mass was attributed to a loss in total, epigonadal and subcutaneous fat mass and not fat free mass. This was matched by improved glucose clearance and insulin sensitivity. Dietary supplementation with 17α-E2 selectively reduced food intake, without altering physical activity or metabolic rate. We previously proposed that 17α-E2 might selectively modify food intake, acting via hypothalamic proopiomelanocortin (POMC)-expressing neurons. POMC-expressing neurons, located within the arcuate nucleus (ARC) of the hypothalamus, are widely recognised for their capacity to regulate energy homeostasis, and represent the largest and most dominant anorexigenic node of central appetite regulation. Ancillary experiments in mice with selective deletion of ARC POMC neurons found complete loss of 17α-E2 treatment effects on food intake, confirming that 17α-E2 promotes satiety by enhancing the function of anorexigenic feeding circuitry [1].

Collectively, our data show that 17α-E2 acts via hypothalamic POMC-expressing neurons to inhibit food intake. We propose that 17α-E2 may serve as a potent calorie restriction mimetic by enhancing calorie sensing of POMC neurons.

Reference

[1] Stout MB, Steyn FJ, Jurczak MJ, Camporez JG, Zhu Y, Hawse JR, et al. 17α-Estradiol alleviates age-related metabolic and inflammatory dysfunction in male mice without inducing feminization. J Gerontol A Biol Sci Med Sci 2016;24(January), glv309.

https://doi.org/10.1016/j.orcp.2016.10.072