The metabolic benefit of 17α-Estradiol is not through insulin receptors on POMC neurons

R Sathiaseelan, S Mann, A Helt, S Mondal Ph.D., M Stout Ph D
Nutritional Sciences Laboratory, OUHSC, Oklahoma City, OK-73117

Background: The World Health Organization estimates that there will be a 22% increase in the population who are over 60 years old by 2050, which will result in an increased prevalence of many age-related chronic diseases. Recent studies have reported that there is a strong relationship between the hallmarks of aging and obesity, with obesity increasing in elderly populations for the first time. Aging is also linked to an increase in systemic insulin resistance, which is exacerbated by obesity. Our lab and others previously demonstrated that the dietary administration of 17α-estradiol (17α-E2), a non-feminizing and naturally present estrogen has beneficial effects on median lifespan, food intake, adiposity, liver lipid accumulation, metabolic homeostasis, insulin sensitivity, and cytokines; this implicates 17α-E2 as a potential therapeutic for improving numerous aspects of comorbid disease in elderly obese populations. Despite this potential, how 17α-estradiol elicits its beneficial metabolic action is not yet fully understood and this has been the major obstacle for the use of 17α-estradiol as a clinical tool. Work from our lab found that 17α-E2 acts through pro-opiomelanocortin (POMC) appetite-regulating neurons in the hypothalamus, which respond to insulin and induce satiety. However, it is unclear whether 17α-E2 is acting directly on POMC neurons or indirectly through improvements in insulin sensitivity to induce reductions in food intake and adiposity. Discovering this mechanism of action could provide useful potential therapeutic targets for metabolic disorders in elderly obese people.

Purpose: The purpose of this study was to use an insulin-resistant model to determine whether 17α-estradiol (17α-E2) exerts its action via insulin signaling in POMC neurons in the hypothalamus.

Methods: Mice lacking the insulin receptors on POMC neurons (POMC-IR KO) and wild type (WT) mice, were pre-fattened via a 45% high-fat diet (HFD) for about 6 months. Baseline measures were taken, including body mass, daily calorie intake, body composition (lean and fat mass), fasting blood glucose, and fasting insulin, before randomizing the groups. The mice were then treated with either HFD or HFD+17α-E2 (14.4ppm). Daily body mass and food intake were measured for 28 days, and body composition was measured weekly until 10 weeks of treatment. Fasting blood glucose and insulin were measured after 5 weeks of treatment. Glucose tolerance testing (GTT) was assessed at 8-week post-treatment. Mice were sacrificed 10-week post-treatment and tissue weights were analyzed.

Results: When compared to wild type mice with 17α-estradiol, POMC-IR KO mice treated with 17α-E2 demonstrated no significant differences in the percent change in the body mass (-5.91% ± 1.34; NS), fat mass (14.6g ± 1.41; NS), fasting glucose, fasting insulin, glucose tolerance, and insulin sensitivity. There were no significant improvements between Wild type and POMC-IR KO mice treated with high-fat diet.

Discussions/conclusions: The beneficial food intake, adiposity, and metabolic effects of 17α-E2 are not mediated via insulin signaling in POMC neurons. 17α-estradiol may be acting through some other mechanism, such as estrogen receptor α, on POMC neurons or multiple neuronal populations in the brain. However, determining molecular targets of 17α-E2 and their physiological role in curtailing disease conditions needs to be studied in detail.

Relevance to Allied Health: Findings from this study will move the field one step closer to understanding some of the unknown mechanisms responsible for the beneficial effects of 17α-E2. This would pave the way for the use of 17α-estradiol as a clinical treatment for varieties of disease conditions associated with allied health disciplines.