

## Estrogen and Leptin Regulation of Endocrinological Features of Anorexia Nervosa

Anorexia nervosa (AN) is an eating disorder characterized by profound weight loss, osteoporosis, amenorrhea, and low leptin levels. Leptin is a hormone secreted from adipocytes in direct proportion to body adiposity and low levels of leptin, or hypoleptinemia, is a key endocrinological feature of AN. AN is more prevalent in women, and is characterized by severely reduced estradiol levels. Estrogens are critical regulators of reproduction and metabolism that act by binding to estrogen receptors (ERs). ERs are members of the nuclear receptor superfamily and they regulate target genes by binding to estrogen response elements (EREs). There is an ERE on the long form of the leptin receptor (OB-Rb), which allows estrogen to modulate OB-Rb expression (Machinal *et al*, 1999). This review will focus on the possible therapeutic benefits of combining estrogens and leptin therapy for AN patients. We propose that combination therapy would decrease the effective dose of each drug and this in turn would reduce the anorexic side effects reported at higher doses.

*ESR1* and *ESR2* are genes that code for estrogen receptors ER $\alpha$  and ER $\beta$ , respectively (Osterlund and Hurd, 2001), and are highly expressed in hypothalamic regions that regulate body weight and reproduction. ERs and OB-Rbs are colocalized in specific hypothalamic neurons and as estrogen levels increase, leptin transport across the blood-brain barrier is enhanced. In addition, knockdown of ER $\alpha$  from hypothalamic steroidogenic factor-1 and pro-opiomelanocortin neurons increases food intake, or reduces energy expenditure, or influences reproduction (Xu *et al*, 2011).

In healthy females, leptin regulates the minute-to-minute oscillations in the

levels of luteinizing hormone (LH) and estradiol, the most potent estrogen (Licinio *et al*, 1998). In women with AN, leptin administration increases pulsatile LH, resulting in an enlargement of the ovaries, increased number and sizes of follicles, and elevated plasma estradiol levels (Welt *et al*, 2004). Therefore, leptin may be necessary for the resolution of amenorrhea in AN. In addition, leptin through OB-Rb reduces food intake by activating transcription factors such as phosphorylated STAT3 (pSTAT3) (Munzberg *et al*, 2005). Estrogens potentiate leptin-induced pSTAT3 activation in the hypothalamus. Leptin is one of the few treatments for AN patients (Welt *et al*, 2004); however, at high doses leptin increases weight loss.

There are no standardized medications approved for the treatment of AN by the Food and Drug Administration; however, research has focused on the potential therapeutic actions of leptin, as leptin may promote restoration of menstrual cycles and prevent osteoporosis. Estrogen is also given as a treatment for AN; however, sudden introduction of sex steroids to hypo-estrogenic girls can be followed by reductions in food intake and heightened manifestations of AN (Kauli *et al*, 1982). Therefore, our hypothesis is that combinatorial treatment with very low levels of estrogens and leptin will decrease the effective dose of each hormone because of the enhanced activation of intracellular cascades, and at the same time this would reduce the anorexic side effects reported at higher doses. To our knowledge, estrogenic enhancement of leptin function has not previously been tested with respect to AN.

Lynda M Brown<sup>1</sup> and Deborah J Clegg<sup>2</sup>

<sup>1</sup>Department of Nutrition, University of North Carolina, Greensboro, Greensboro, NC, USA; <sup>2</sup>Department of Internal Medicine, Touchstone Diabetes Center, University of Texas Southwestern Medical Center, Dallas, TX, USA

E-mail: deborah.clegg@utsouthwestern.edu

### DISCLOSURE

The authors declare no conflict of interest.

- Kauli R, Gurewitz R, Galazer A, Prager-Lewin R, Gil-Ag I, Laron Z (1982). Effect of anorexia nervosa on gonadotrophin secretion in a patient with gonadal dysgenesis. *Acta Endocrinol* **100**: 363–368.
- Licinio J, Negrao AB, Mantzoros C, Kaklamani V, Wong ML, Bongiorno PB *et al* (1998). Synchronicity of frequently sampled, 24-h concentrations of circulating leptin, luteinizing hormone, and estradiol in healthy women. *Proc Natl Acad Sci USA* **95**: 2541–2546.
- Machinal F, Dieudonne MN, Leneuve MC, Pecquery R, Giudicelli Y (1999). *In vivo* and *in vitro* ob gene expression and leptin secretion in rat adipocytes: evidence for a regional specific regulation by sex steroid hormones. *Endocrinology* **140**: 1567–1574.
- Munzberg H, Bjornholm M, Bates SH, Myers MG Jr (2005). Leptin receptor action and mechanisms of leptin resistance. *Cell Mol Life Sci* **62**: 642–652.
- Osterlund MK, Hurd YL (2001). Estrogen receptors in the human forebrain and the relation to neuropsychiatric disorders. *Prog Neurobiol* **64**: 251–267.
- Welt CK, Chan JL, Bullen J, Murphy R, Smith P, DePaoli AM *et al* (2004). Recombinant human leptin in women with hypothalamic amenorrhea. *N Engl J Med* **351**: 987–997.
- Xu Y, Nedungadi TP, Zhu L, Sobhani N, Irani BG, Davis KE *et al* (2011). Distinct hypothalamic neurons mediate estrogenic effects on energy homeostasis and reproduction. *Cell Metab* **14**: 453–465.

*Neuropsychopharmacology Reviews* (2013) **38**, 237; doi:10.1038/npp.2012.176

## Transcriptional Plasticity in the Brain following Metabolic Challenge

Assessment of gene expression is a good place to start a quest for mechanisms of neural plasticity (McClung and Nestler, 2008). Of course, these mRNA and subsequent protein-level changes must eventually lead to synaptic alterations in order to have a role in neural adaptation. Nonetheless, the efficiency of large-scale transcription studies makes it a powerful initial approach. Although this strategy has been used extensively within the field of drug addiction (Robison and Nestler, 2011), few studies have systematically evaluated brain transcriptional adaptation in response to metabolic challenge.