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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 ERα and ERβ, 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 ERα 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[1] and Deborah J Clegg[2]

[1]Department of Nutrition, University of North Carolina, Greensboro, Greensboro, NC, USA; [2]Department of Internal Medicine, Touchstone Diabetes Center, University of Texas Southwestern Medical Center, Dallas, TX, USA

E-mail: deborah.clegg@utsouthwestern.edu

DISCLOSURE

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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.

We recently completed a microarray analysis to identify changes in gene expression in response to a brief (5 days) and moderate (<10% weight loss) reduction in food intake (Guarnieri *et al*, 2012). Analysis was conducted on RNA from four brain regions: ventral tegmental area, prefrontal cortex, hypothalamus and nucleus accumbens. Stress responsive genes were prominent in the list of genes that change after restriction, and corticosterone was shown to be necessary and sufficient for many of these changes. There were some surprises in these results that deserve emphasis: (1) the gene changes occurred rapidly (within the first 24 h of restriction) before any weight loss was apparent and (2) the expression changes detected were not restricted to one region, and usually were seen in 2–4 of the regions surveyed. This fast and universal response was not something that was anticipated, but is reasonable if a systemic factor such as corticosterone is the key signal. Finally, the changes seen were implicated in increased food motivation that occurred after restriction.

Previously published work supports the role of stress response in mediating effects of caloric restriction. Work from the Bale lab has shown that a longer (21 days) caloric restriction leads to stress pathway activation, including corticosterone as well as corticotropin-releasing factor (CRF) in the bed nucleus of the stria terminalis (Pankevich *et al*, 2010). Restriction increased stress responses as well as binge eating. Interestingly, the changes in CRF did not reverse upon re-feeding, and subsequent analysis showed that the CRF regulatory sequences also maintained altered methylation patterns. Moreover, withdrawal from high-fat food produced similar adaptions in gene expression and chromatin state.

Other work with animals exposed to high-fat diet also supports a role for chromatin changes and transcriptional adaptation within dopamine circuits. Reyes and colleagues (Vucetic *et al*, 2011) have shown specific gene changes in the nucleus accumbens following long-term high-fat-diet exposure. Specifically, decreases in mu-opioid receptor expression correlated with increased methylation and MECP2 binding in the proximal regulatory regions. Moreover, H3K9 methylation was increased and acetylation was reduced, which is consistent with an inactive chromatin state.

In sum, changes in metabolic state can have specific and significant effects on the transcription profile of the brain. These changes are mediated by alterations in chromatin and, most importantly, are likely to have a role in behavioral adaptation to different food environments.

Defining these molecular responses will help us to understand how intake and weight control is influenced by previous metabolic experience. These pathways are targets for potential therapeutics that can reverse or otherwise modulate this plasticity and help with weight loss. Moreover, as with drugs of abuse, stress is a common cause for loss of control over eating. The above work suggests that the brain might interpret stress hormones as a state of hunger, and should inspire stress response attenuation as a potential therapeutic strategy for obesity.

Douglas J Guarnieri[1] and Ralph J DiLeone[1]

[1]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA
E-mail: ralph.dileone@yale.edu

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Neurobiological Correlates of the Familial Risk for Stimulant Drug Dependence

Stimulants such as cocaine and amphetamines are popular recreational drugs, which are thought to be used by up to 52 million individuals worldwide (UNODC, 2010). However, despite their high addictive liability, not everyone who uses these drugs develops dependence, though the risk for dependence is significantly increased for people with a family history of addiction. This familial aggregation of drug and alcohol dependence suggests that either genetic factors, a shared family environment, or an interaction of genes and environment underlie the increased risk for addiction in some people. The concept of endophentoypes may offer a useful tool to better understand how a pre-existing vulnerability to addiction might be inherited. *Endophenotypes* have been described as neurobiological correlates of a disorder, which are thought to be genetically determined and stable over time (Gottesman and Gould, 2003). In other words, abnormalities in brain systems underlying the clinical symptoms of stimulant dependence may not only be observed in individuals who are dependent on stimulant drugs, but also in their non-dependent first-degree relatives. Key symptoms of stimulant dependence, such as the inability to stop using the drug and the loss of control over drug intake, may be underpinned by a general lack of self-control, which may have predated drug-taking.

We assessed a wide range of cognitive and emotional functions as well as personality traits that have previously been associated with drug dependence in three groups of volunteers: 50