Estrogen targets fat mass and glucose metabolism by acting in the brain

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Currently, about 66% of adults are overweight, and approximately ~33% of adults are clinically obese. Excess weight is a risk factor for numerous conditions, including cardiovascular disease, diabetes, dyslipidemia, hypertension, stroke, cancer, adverse reproductive outcomes, osteoarthritis, and premature death (2, 10). Obesity is associated with a systemic state of inflammation and leads to increased adipose tissue infiltration with macrophages and increased inflammatory activation of these cells (9, 10). Adipose tissue expression of tumor necrosis factor-α, interleukin-6, leptin, monocyte chemoattractant protein-1, and plasminogen activator inhibitor 1 is elevated in human obesity and in mouse models of obesity and may contribute to atherosclerosis and insulin resistance (2, 4, 7).

Estrogens (principally 17β-estradiol, or E2) are important regulators of human reproduction, secondary sexual characteristics, bone maintenance, cognition, and cardiovascular function. More recently, E2 has been implicated in the regulation of food intake, energy expenditure, body composition, and glucose metabolism (1, 3, 8). These metabolic roles for E2 hold particular significance for postmenopausal women who experience rapid and significant declines in serum E2 levels in the menopause. Notably, mice that are null for the estrogen receptor-α, and mice or humans that do not produce E2 secondary to loss of aromatase expression, develop obesity and insulin resistance (8).

Both central and peripheral effects of E2 have been proposed to influence metabolism and body fat distribution. By mechanisms that remain incompletely understood, E2 regulates appetite, body fat deposition, energy expenditure, GLUT4 expression in adipose and muscle tissues, pancreatic secretion of insulin, and hepatic sensitivity to insulin (3, 8). The relative contribution of central vs. peripheral effects of E2 with respect to metabolism has remained unknown. In this issue of *Am J Physiol Endocrinol Metab*, Dr. Yonezawa and colleagues endeavor to distinguish the central from peripheral effects of E2 with respect to metabolism and influence body fat distribution. By mechanisms that remain incompletely understood, E2 regulates appetite, body fat deposition, energy expenditure, GLUT4 expression in adipose and muscle tissues, pancreatic secretion of insulin, and hepatic sensitivity to insulin (3, 8). The relative contribution of central vs. peripheral effects of E2 with respect to metabolism has remained unknown. In this issue of *Am J Physiol Endocrinol Metab*, Dr. Yonezawa and colleagues endeavor to distinguish the central from peripheral effects of E2 with respect to metabolism and influence body fat distribution.

Using oophorectomized (OVX), E2-deficient, female mice on an obesogenic diet, the team administered E2 centrally or peripherally and focused on three treatment groups: 1) OVX control mice, 2) intracerebroventricular (ICV) E2 at a dose low enough that there was no effect on the peripheral E2 levels nor any uterotrophic effects of hormone administration, and 3) E2 subcutaneously, which restored systemic levels of E2 and demonstrated the expected uterotrophic effects of hormone replacement.

Control mice on the high-fat diet became obese, adding both subcutaneous and visceral fat, and these mice developed glucose intolerance and insulin resistance. Both centrally and peripherally administered E2 corrected glucose intolerance and insulin resistance in obese mice. Both routes of E2 delivery reduced visceral and subcutaneous fat mass (and visceral adipocyte size), with associated reductions in CD11+ macrophage cell numbers in the perigonadal fat depots.

Some differences were observed between peripherally and centrally administered E2; whereas the peripheral E2 was associated with decreased mRNA expression of *Tnfa, Lpl*, and *Fasn* relative to control mice, central E2 was associated with increased expression of *Lipe* relative to control mice. Both routes of E2 delivered similarly reduced hepatic mRNA expression of *G6pc* and *Pepck*, whereas centrally delivered E2 elevated core body temperature, energy expenditure, and the mRNA expression of uncoupling proteins in brown adipose tissue. The significant observation from these studies is that centrally administered E2 (absent any direct hormone effects in the periphery) was sufficient to enhance energy expenditure, reduce body fat, and improve glucose metabolism in obese mice. In addition, the data distinguish some features of the estrogen response that are more likely to depend on peripheral hormone exposure since these effects were not observed with centrally delivered E2.

The E2 response is mediated in large part by the estrogen receptors-α (ERα/NR3A1) and -β (ERβ/NR3A2), ligand-activated and DNA sequence-specific transcription factors. ERα regulate transcription of target genes through direct binding as homo- or heterodimers to cognate recognition sites, known as estrogen response elements (EREs) or by modulating the activity of other DNA-bound transcription factors at alternative DNA sequences. Furthermore, E2/ER effects can involve rapid plasma membrane and cytosolic effects (dubbed “nongenomic” or “nonclassical” E2 effects); these responses may or may not be mediated by the classical receptors and their various isoforms present outside the nucleus. Reports of a G protein-coupled receptor (GPER1/GPR30) that binds to E2 and activates intracellular second messenger systems remain controversial; most likely, the GPER participates in selected E2 responses but is not a receptor for E2 and is not required for many of the traditional cellular responses to E2 (5, 6).

The work by Dr. Yonezawa and colleagues should be interpreted with certain caveats. 1) Although E2-ICV was shown not to affect peripheral E2 levels or uterine weight/morphology, the reverse can not be assumed; peripherally administered E2 was likely to engender central responses in treated mice, and net metabolic effects in these mice likely included combined central and peripheral responses to hormone. 2) E2 concentrations could not be measured in mouse brains, so whether E2-ICV produced physiological or supra-physiological E2 concentrations remains unknown. 3) Measured mRNA expression changes between groups were, in many cases, modest in magnitude. 4) Both central and peripheral hormone treatments resulted in modest weight loss possibly influencing measured outcomes independent of direct E2 signaling cascades. And 5) effects of E2 on mice may not
extend to humans, most notably with respect to effects on brown adipose tissue.

Future studies will be required to determine the ERs and ER isoforms most relevant to central vs. peripheral responses to E2. The relevance of de novo synthesis of E2 in the central nervous system remains unclear but appears unable to compensate for loss of ovarian function in mice or women. The roles of centrally administered E2 in male metabolism, or in males and females with normal peripheral levels of E2 (i.e., ovaries intact), or for the prevention (not treatment) of obesity, were not addressed in this study. Meanwhile, the findings in this report indicate significant and favorable metabolic effects of centrally administered E2 in obese female rodents that model the E2-deficient menopause. Whether central nervous system-specific delivery of E2 (or a selective ER modulator) would be sufficient to confer metabolic benefit to postmenopausal women, treat hot flashes, maintain bone, and improve cognitive processes, all while avoiding adverse peripheral effects of hormone replacement, remains the “holy grail” in hormone replacement therapy.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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