Regulation of Body Composition and Bioenergetics by Estrogens

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KEYWORDS

• Menopause • Adiposity • Body composition • Estradiol • Estrogen receptor
• Energy expenditure • Energy intake • Ovariectomy

KEY POINTS

- Consistent evidence from basic and preclinical research indicates that the disruption of estradiol (E_2) signaling accelerates abdominal fat accumulation.
- Treatment of ovariectomized animals with E_2 prevents fat accumulation, thereby isolating E_2 as the regulatory ovarian factor, and transgenic studies indicate that these effects are mediated primarily through estrogen receptor alpha.
- The major system-level mechanism for excess fat accumulation in response to the loss of E_2 in animals is a decrease in energy expenditure, which occurs as a result of reductions in spontaneous physical activity and resting metabolic rate.
- Clinical evidence for the regulation of body composition by E_2 is less consistent, but the suppression of ovarian function does promote fat gain.
- If the loss of ovarian estrogens triggers a decline in physical activity and increase in abdominal adiposity in women, as it does in laboratory animals, this could increase risk for diabetes and cardiovascular disease in postmenopausal women.

INTRODUCTION

There is growing evidence that estradiol (E_2) is an important regulator of body composition and bioenergetics. The wide distribution of estrogen receptors (ERs) and their involvement in genomic and nongenomic signaling pathways[1] suggests that the

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loss of E_2 at menopause is likely to have pronounced effects on numerous factors other than reproduction.[2] ER expression in the brain, adipose tissue, and skeletal muscle shows the potential role of E_2 in body-weight regulation and other metabolic processes. Further, the presence of mitochondrial ERs[3] suggests a role of E_2 in the regulation of cellular bioenergetics. This article discusses findings from basic, preclinical, and clinical studies that provide insight on the role of E_2 and ER signaling in the regulation of energy storage (ie, fat accrual), regional fat distribution, and energy balance (ie, energy expenditure and intake).

BASIC RESEARCH

Estrogens have many physiologic effects that were long thought to be caused by a single receptor, ERα.[4] However, the discovery of a second receptor, ERβ,[5] and the recognition that ERs are present not only in the nucleus but also in the plasma membrane,[6] have advanced the understanding of the metabolic actions of estrogens.

The systemic actions of estrogens are mediated through ER signaling. This signaling can occur through nuclear ERs and the consequent transcription of multiple genes,[7] or through membrane-bound ERs that mediate rapid, nongenomic effects of estrogens.[8] E_2 binds to ERα and ERβ with equal affinity.[9] However, ERα and ERβ have distinct and sometimes opposing actions, indicating that the ratio of ERα to ERβ may be an important determinant of tissue-specific responses to E_2.[10–12] Both ER subtypes seem to be present in most, if not all, body tissues, but in varying proportions.[13–15] Knowledge regarding the effects of ER signaling has been advanced through the use of transgenic mice that have deletions of ERα and/or ERβ throughout the body,[16,17] in specific cells or tissues,[18–20] or at the molecular level (nuclear vs membrane).[21–23]

Regulation of Adiposity by Estradiol

The importance of ER signaling in the regulation of adiposity was highlighted by the discovery of Heine and colleagues[24] that a whole-body knockout of ERα (αERKO) resulted in increased fat accrual in both females and males compared with wild-type (WT) mice. By 90 days of age, the parametrial and inguinal fat pads were 2-fold larger in female αERKO mice than in controls as a result of increased adipocyte size and number. The αERKO mice were also more insulin resistant and glucose intolerant than WT mice, consistent with the excess adiposity. Subsequent studies confirmed that the deletion of ERα increases adiposity in female mice.[21–23]

The excess fat mass in αERKO mice suggests that ERα plays a protective role against fat accumulation. However, another possibility is that removal of ERα promotes fat accumulation through increased ERβ signaling. One strategy that has been used to test this possibility is to ovariectomize αERKO (αERKO-OVX) mice to reduce circulating E_2, thereby diminishing ERβ signaling.[25] The increase in fat mass that occurred in αERKO-sham mice was attenuated in αERKO-OVX mice. Further, when αERKO-OVX mice were treated with E_2, thereby increasing ERβ signaling, fat mass increased to the level of αERKO-sham mice.[25] The deletion of ERβ in mice (ie, βERKO) does not result in excess fat mass[26] or body mass[27] compared with WT mice, providing additional evidence that the increased fat accumulation in αERKO mice is mediated, at least in part, through increased ERβ signaling. However, ERα also plays a protective role against fat accumulation. When ERα signaling was reduced in βERKO mice through ovariectomy (OVX), there was an excess gain in body mass and adiposity.[27] In addition, when both ERα and ERβ are absent (ie, double knockout; DERKO), the αERKO phenotype of increased adiposity dominates.[26]