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Review

Central effects of estradiol in the regulation of food intake, body weight, and adiposity☆

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ABSTRACT

In recent years, obesity and its associated health disorders and costs have increased. Accumulation of adipose tissue, or fat, in the intra-abdominal adipose depot is associated with an increased risk of developing cardiovascular problems, type-2 diabetes mellitus, certain cancers, and other disorders like the metabolic syndrome. Males and females differ in terms of how and where their body fat is stored, in their hormonal secretions, and in their neural responses to signals regulating weight and body fat distribution. Men and post-menopausal women accumulate more fat in their intra-abdominal depots than pre-menopausal women, resulting in a greater risk of developing complications associated with obesity. The goal of this review is to discuss the current literature on sexual dimorphisms in body weight regulation, adipose tissue accrual and deposition.

Contents

1. Introduction

Gonadal hormones potently control food intake and body weight. In female animals, the activational effects of estradiol acutely and chronically influence body weight homeostasis [1–3]. In rats and mice, estrogen exerts a tonic inhibitory effect on meal

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size and daily food intake throughout the ovarian cycle and a cyclic inhibitory effect during the peri-ovulatory phase [1,3–5]. Removal of estrogen leads to changes in meal size and duration [6,7], hyperphagia, and obesity. Estrogen has similar effects in humans where it modulates peri-ovulatory decreases in daily food intake [8]. Additionally, reductions in estrogen are associated with changes in body weight and fat distribution in humans, which parallel the findings in animals [8]. Estrogen has the ability to control energy balance, food intake, and body fat distribution and this may be mediated through its interaction with orexigenic and anorexigenic hormones. This review aims to explore these interactions and discuss the link between estrogen and obesity.

1.1. Estrogen regulates adiposity

The accumulation of fat in a central distribution (intra-abdominal) has emerged as a risk factor for the metabolic syndrome [9,10] which includes a higher risk of diabetes, hypertriglyceridemia, hypertension, and cardiovascular disease [11]. Estrogen promotes the accumulation of subcutaneous fat [12], and the loss of estrogen with menopause is associated with an increase in central fat [10,13]. The sexual dimorphism in adipose tissue distribution may partially explain the greater risk for the metabolic syndrome in men compared with pre-menopausal women.

1.2. Estrogen regulates adipose tissue distribution

Visceral fat varies inversely with estrogen levels [14]. When estrogen levels become sufficiently low visceral fat accumulation occurs in females, possibly due to direct effects of estrogen, especially since progesterone and androgen receptors (PR and AR), as well as, estrogen receptor (ER) are expressed in adipose tissues [15]. Subcutaneous adipose tissue has higher concentrations of ER and PR; however, visceral adipose tissue has higher concentrations of AR [16]. Additionally, subcutaneous adipose tissue has few androgen receptors, and estrogen down-regulates AR expression in subcutaneous fat [17]. Adipose tissue-specific AR knock-out mice have increased intra-adipose estradiol levels, which leads to increased subcutaneous obesity and hyperleptinemia [18].

Ovariectomized (OVX) rats gain fat, specifically visceral fat with no change of subcutaneous fat [19]. Peripheral or central administration of estradiol to OVX rats restores central leptin sensitivity and changes their body fat distribution to mirror that of intact females; additionally, altering the sex hormone milieu in males with estradiol administration increases sensitivity to central leptin and increases subcutaneous fat deposition [19]. An important implication from these findings is that estrogen regulates body fat distribution, interacts with the integrated adiposity message conveyed to the brain by leptin, and enhances leptin's action in sympathetic activation to the visceral fat, which facilitates fat mobilization in the visceral depot and fat deposition in the subcutaneous depot.

1.3. Estrogen regulates adiposity through estrogen receptors

Estrogen regulates body adiposity and fat distribution through its receptors, ER alpha (ERα) and beta (ERβ) [20,21]. However, only ERα has been reported to have a major influence on energy homeostasis [22]. ERα is necessary for estradiol's genomic actions on body weight regulation [23] while ERβ functions more as a modulator of estrogen actions [24]. Rapid, non-genomic actions of estradiol also have been described and some of them appear to involve ERα [25].

Heine et al. [22] reported that male and female mice with total body deletion of ERα, ERα-knock-out (αERKO) mice, have increased adiposity in both male and female mice, suggesting an important role for this estrogen receptor in the regulation of body weight and adiposity. Recently, site-specific knockdown of ERα expression in the VMH, a brain region critical for body weight regulation, demonstrates the role of VMH ERα activity in the regulation of body weight homeostasis [23]. Knockdown of VMH ERα results in obesity due to an anabolic process, with changes in energy expenditure primarily mediating the weight gain [23]. These data are consistent to previous finding in the αERKO mice where it has been demonstrated that the obesity is primarily due to changes in energy expenditure rather than changes in food intake [22,26] and those mice have increased visceral adiposity (unpublished data). These data suggest that estrogen signaling with critical hypothalamic nuclei is responsible for the regulation of body weight via modulating energy expenditure.

Since ERα is expressed in hypothalamic areas that regulate energy homeostasis [27–33], the absence of ERα expression is consistent with changes in body weight. Furthermore, ERα polymorphisms identified in humans have been associated with increased levels of visceral fat.

A ventral medial nucleus (VMN) specific ERα knockdown in both female mice and rats resulted in phenotypes characteristic of a metabolic syndrome [23]. Microinjections of low doses of estradiol directly into the brain were shown to inhibit food intake [19,34,35]. Taken together, these observations suggest that the binding of estradiol to ERα in the hypothalamus, or elsewhere in the brain, may represent a mechanism by which estradiol regulates food intake, body weight, and possibly body fat distribution.

1.4. Estrogen regulates adiposity by decreasing inflammation

Obesity is a state of chronic inflammation, and inflammatory signaling pathways in obesity are linked to insulin resistance [36–38]. Sex differences where females are protected have been reported in diet-induced obesity, insulin resistance and inflammatory response to a high-fat (HF) diet [39–41]. This may be explained in part by the anti-inflammatory properties of estrogen [42]. Recent studies have shown that estradiol may play a role in reducing the inflammatory response in adipose, cardiovascular, and neural systems [43], in addition to being neuroprotective both *in vivo* and *in vitro* [44,45].

ERα (and in some cases ERβ) is expressed in immune and cytokine-producing cells including macrophages and microglia, and *in vitro* studies have shown estradiol-activated ERα decreases the number of pro-inflammatory cytokines [44,45]. The anti-inflammatory properties of estradiol can be partially explained by the ability of ERs to act as transcriptional repressors by inhibiting the activity of nuclear factor kappa B (NFκB) through protein-protein interactions between agonist-bound ERs and activated NFκB subunits [42,46,47]. Estradiol's inhibitory effect on NFκB function is not fully understood and may be target selective [47–49].

Symptoms of a metabolic syndrome increase when animals are maintained on a HF diet or when females have low ovarian hormone levels. Free fatty acids (FFAs), particularly saturated fatty acids, increase inflammation by activating toll-like receptor 4 (TLR4) [50]. Muscle and liver expression of tumor necrosis factor-alpha (TNFα), interleukin-6 (IL-6), and NFκB also increase with HF diets [50]. Estradiol has been shown to be neuroprotective and to increase the expression of growth factors and proteins involved in apoptosis [51,52].

Estradiol signaling pathways are active in monocytes and macrophages, and ERs are expressed by these cells [45,53]. Therefore, the protective effects of estradiol in neurodegenerative diseases can be mediated by inhibiting the inflammatory response, and consequently, hormone withdrawal can increase inflammation [53].