Feature Review

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# Estrogens and the control of energy homeostasis: a brain perspective

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**Despite their prominent roles in the control of reproduction, estrogens pervade many other bodily functions. Key metabolic pathways display marked sexual differences, and estrogens are potent modulators of energy balance, as evidenced in extreme conditions of estrogen deficiency characterized by hyperphagia and decreased energy expenditure, and leading to obesity. Compelling evidence has recently demonstrated that, in addition to their peripheral effects, the actions of estrogens on energy homeostasis are exerted at central levels, to regulate almost every key aspect of metabolic homeostasis, from feeding to energy expenditure, to glucose and lipid metabolism. We review herein the state-of-the-art of the role of estrogens in the regulation of energy balance, with a focus on their central effects and modes of action.**

## Estrogens and metabolism in the obesity era

Obesity is defined as a state where excess fat accumulation in the adipose tissue causes adverse health problems [1]. While obesity itself results in mechanical and psychological problems, probably the major concern is its association with insulin resistance, type 2 diabetes mellitus, fatty liver, and a range of other disorders generally known as the metabolic syndrome [1,2], as well as sleep apnea, musculoskeletal and cardiovascular disorders, and several types of cancer [2,3]. Thus, controlling obesity should have a beneficial knock-on effect on all these complications. For this reason, much effort is being placed on identifying the basic molecular mechanisms that regulate energy balance.

Obesity is ultimately the result of a positive energy balance between energy acquisition and energy expenditure. Gaining a deeper understanding of the major homeostatic modifiers of energy balance, and how they might contribute to the metabolic complications of obesity, is warranted. Accordingly, extensive research in this area has led to the recognition of the major metabolic roles of numerous neuropeptides and transmitters, as well as multiple peripheral hormones [4–6]. Of the latter, considerable attention has been paid recently to elucidating the functions of signals from metabolic tissues, such as the pancreas, adipose tissue, and even the gut [7,8]. However, other 'classical' endocrine organs, such as the adrenals, thyroid and gonads, have been long known to secrete hormones that have key roles in the control of metabolism and energy balance. Yet, as a whole, these systems have received less interest in recent metabolic research.

This is probably the case of sex steroids in general, and estrogens in particular. Ovarian hormones, including estrogens, such as 17β-estradiol (E2), are pleotropic regulators of numerous cellular functions [9]. For obvious reasons, most efforts to characterize the physiological roles of estrogens have been devoted to elucidate their effects and mechanisms of action in the control of reproductive maturation and function [10]. As summarized in the following sections, estrogens do not only control different aspects of female fertility, but also operate in multiple tissues controlling a wide spectrum of key physiological functions, from cognition and neuroprotection to cellular metabolism [9,11]. Considering that estrogens are produced in various organs, in addition to the ovary, and that their levels fluctuate physiologically during a lifetime and in different pathological conditions, it has become clear that estrogens are key modifiers of the energy balance equation [9,12,13]. As such, they are likely endowed with prominent roles in defining relevant aspects of energy homeostasis, such as sexual dimorphisms and dynamic changes along development and different states of gonadal function, with a potential major impact on the development of obesity and its comorbidities. However, our knowledge of the effects and major sites of actions of estrogen in the control of whole-body metabolism, body weight, and energy expenditure remains incomplete. In this review, we provide an overview of the state-of-the-art of these key facets of estrogen actions, with special emphasis on how estrogens act centrally, mainly at the hypothalamus, to regulate energy homeostasis.

## Estrogens: modes of action, secretory profiles, and regulatory mechanisms

Estrogens are evolutionarily conserved hormones, produced in all vertebrate and some invertebrate species.

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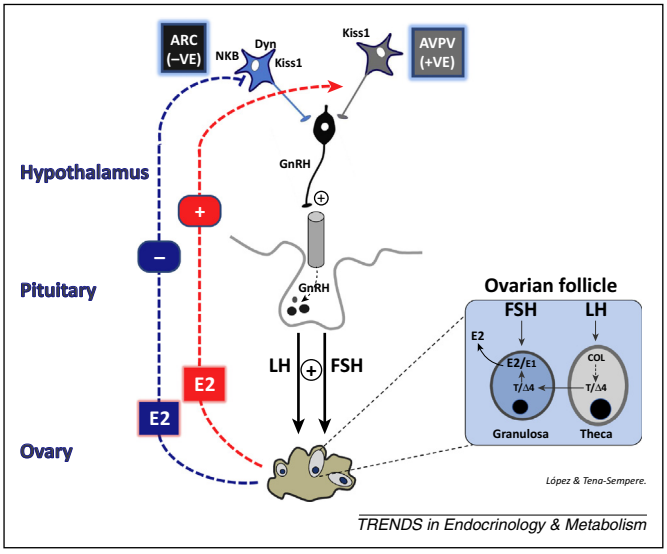


**Figure 1**. Schematic presentation of the major elements of the hypothalamic–pituitary–ovarian (HPO) axis. In addition to the hypothalamic gonadotrophin-releasing hormones (GnRH), pituitary gonadotropins [luteinizing hormone (LH) and follicle-stimulating hormone (FSH)] and ovarian estrogens, the contribution of the populations of kisspeptin 1 (Kiss1) neurons, located in the arcuate nucleus ARC and anteroventral periventricular nucleus (AVPV), in mediating the negative (–VE) and positive (+VE) feedback effects of 17β-estradiol (E2) is depicted. In the inset, details of the two-cell model for estrogen synthesis in the ovarian follicles are also displayed. Pituitary LH acting on theca cells stimulates the synthesis of androgens, testosterone (T) and androstenedione (Δ4). Theca-born androgens diffuse into the neighboring granulosa cells, where they are converted into estrogens, mainly E2, by the action of the enzyme, aromatase.

In mammals, three major forms of estrogens exist: estrone (E1), E2, and estriol (E3) [14]. The major source of estrogens is the ovary, specifically the growing follicles that, during reproductive life, produce predominantly E2, which is endowed with the highest biopotency. Other sources of estrogens are the placenta, responsible to a large extent for the high levels of estrogens during pregnancy, and, at much lower levels, the adrenals and testes [14]. The adipose tissue is also known to synthesize estrogens, although the physiological or pathological roles of such adipose-born estrogens are yet to be fully elucidated [15].

The ovarian synthesis of estrogens occurs in the so-called 'two-cell' model [16] (Figure 1). Synthesis begins at the inner theca cell layer of the growing follicles, which produce androgens, such as androstenedione and testosterone, from cholesterol, under the stimulation of the pituitary gonadotropin, luteinizing hormone (LH), whose receptors are expressed in theca cells (Box 1). These androgens diffuse to the neighboring granulosa cells, which highly express aromatase, the enzyme encoded by the *CYP19* gene responsible for the conversion of androgens into estrogens: androstenedione into E1 and testosterone into E2; E1 can be further converted into E2 by the enzyme, 17-beta hydroxysteroid dehydrogenase (17βHSD), while both E1 and E2 can be precursors for the synthesis of E3 [14]. Granulosa cells selectively express aromatase under the stimulation of the pituitary gonadotropin, follicle-stimulating hormone (FSH) (Box 1), but lack the expression of upper biosynthetic enzymes of the steroidogenic route. Thus, both theca and granulosa cells are needed to drive ovarian estrogen synthesis [16].

Due to their lipophilic nature, estrogens readily diffuse through cellular membranes and operate, to a large extent, via interaction with intracellular receptors. Two classical nuclear receptors for estrogens (ER) have been described: ERα and ERβ [17,18]. The latter was discovered in 1995 as a second receptor for estrogens, which were previously thought to operate via a single ER, later called ERα [19]. Both ERα and ERβ operate as ligand-dependent transcription factors that, upon ligand binding, form dimers to interact with canonical ER response elements (ERE) in the promoter regions of estrogen-regulated genes [17,18]. However, this classical mode of action accounts for just a fraction of the effects of estrogens, whose capacity to modulate gene expression and cellular functions are more pleotropic.

While detailed description of the whole repertoire of mechanisms of actions of estrogens clearly exceeds the scope of this review, it is important to stress that numerous actions of estrogens, while conducted via ERα and ERβ, do not involve classical direct interactions with EREs, but rather the interplay with other transcriptional mediators, which operate at nonERE regions. Such dichotomy of estrogen modes of action, namely ERE versus nonERE signaling pathways, has been elegantly demonstrated by the generation of a nonclassical ER-knock-in mouse model on a global ERα null background, the so-called 'NERKI' mouse [20]. This mouse line is defined by the expression of an ERα mutant that cannot bind to EREs, but maintains its capacity to tether other transcriptional factors and modulate transcriptional activity via nonERE-dependent mechanisms. Notably, key functions of estrogens, such as their capacity to negatively feedback on gonadotropin secretion, seem to be conducted, at least to a large extent, via such a nonERE pathway [21]. Similarly, ERα-mediated effects of estrogens on energy homeostasis appear to be mediated, at least partially, via nonERE pathways, because genetic rescue of nonclassical ERα signaling in a global ERα-knockout (KO) mouse was sufficient to restore, to nearly normal values, major metabolic parameters, including body weight, to nearly normal values [22].

Notably, the above evidence for nonclassical actions of estrogen cannot dissect out the nuclear versus non-nuclear component of such effects, because membrane actions of nuclear ERs have been documented in several settings. In addition, distinct membrane receptors for estrogens have been described, whose nature is not fully elucidated yet. These are likely to include both ion channels, which can be modulated by estrogens, as well as *bona fide* surface receptors, such as the G-protein-coupled receptor, GPR30, now termed GPER1, which seem to conduct, even in an overlapping fashion, some of the rapid effects of estrogens on different cellular systems [23]. Of note, genetic ablation of GPER1 has been shown to recapitulate some of the consequences of estrogen insufficiency (e.g., increased body weight and glucose intolerance), but not others (e.g., increased food intake and decreased locomotor activity) [24]. Admittedly, however, conflicting results on the actual cellular location (membrane versus intracellular) and pharmacology of GPR30/GPER1 have been reported, and considerable controversy persists on the actual physiological roles of some of these nonclassical receptors in mediating estrogen actions [25]. Given their prominent relevance, we focus our attention here on the classical ER-mediated

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