Review
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Understanding the Biological Activity of Endogenous Estrogens: Current Knowledge and Insights

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Abstract

Estrogens represent a class of cholesterol-derived female sex hormones, essential in the regulation of numerous physiological processes. On the basis of their origin, they can be classified into endogenous (synthesized within the body) or exogenous (introduced from external sources) compounds. In humans, four types of endogenous estrogens have been identified, namely estrone, 17-β-estradiol, estriol, and estetrol. Despite their similarities in chemical structures, they have distinct receptor affinities and functional roles at different life stages. This review presents, in addition to an overview of their diverse physiological functions, a discussion of the three estrogen receptors (ERα, ERβ, and GPER1) currently investigated as possible targets in the development of new therapeutic strategies for hormone-dependent breast cancer.

Keywords: *endogenous estrogen; estradiol; estriol; estrone; estetrol*

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1. Introduction

Estrogens are cholesterol-derived female sex hormones implicated in various physiological functions, such as the regulation of the menstrual cycle, regulation of the immune system, brain function, cardiovascular effects, and modulation of bone density [1–9]. Depending on their origin, they are classified as endogenous or exogenous (derivatives of synthetic estrogens, food, and drugs) [7, 10]. As presented in the literature, four endogenous human estrogens have been found: estrone, 17-β-estradiol, estriol, and estetrol [7, 11, 12]. The chemical structures of the four endogenous estrogens are presented in **Figure 1**, while the organs responsible for the synthesis of estrogens in the human body, with the main difference between the sexes being the function of the gonads, are highlighted in **Figure 2**.

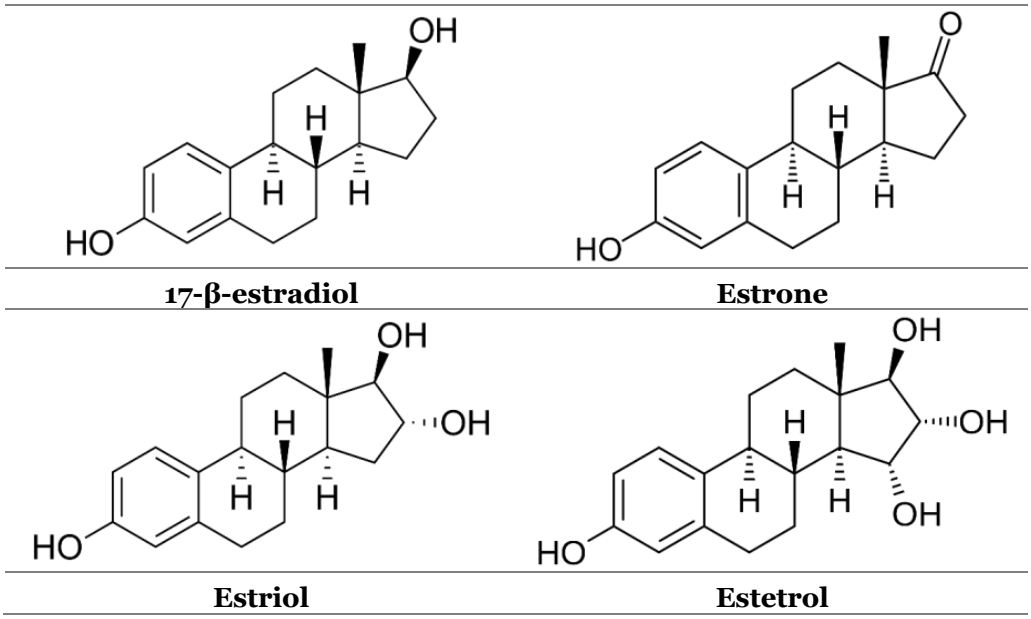

Figure 1. Chemical structures of the four endogenous estrogens.

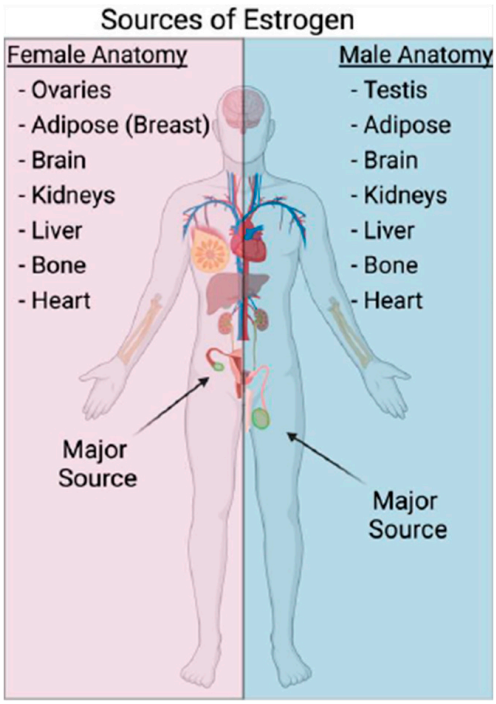

Figure 2. Organs responsible for the synthesis of estrogen in the human body [13].

Usually, the use of the term "estrogen" is associated only with 17-β-estradiol due to its numerous physiological functions, as it is essential in the development of secondary characteristics of the female sex, regulates the menstrual cycle, and promotes endometrial growth from menarche to menopause. It presents the highest affinity for the three estrogen receptors (ERs), namely ERα, ERβ, and G protein-coupled ER 1 (GPER1) [7, 14, 15]. In the case of estrone, a lower affinity for the estrogen receptors is observed, and it is the predominant hormone in the postmenopausal period. Estriol is synthesized mainly during the pregnancy period, presenting an insignificant value in nonpregnant women. Regarding the affinity for estrogen receptors, it is lower than that observed for estrone, namely ERα (14%) and ERβ (21%) [7, 10, 14]. Estetrol is observed only during the fetal period, with a lower affinity for ER [11, 14].

2. Estrogen Receptors (ERs)

ERs were observed for the first time in 1958, when Elwood Jensen indicated that gene transcription may be the result of the binding of estrogen derivatives to specific proteins in the female reproductive tissues [1, 15, 16]. Afterwards, in the year 1985, the first human ER was cloned, namely ERα [17], leading to the identification of a second receptor subtype, ERβ (or ERβ1), by Kuiper et al. in 1996 [18].

In 2012, GPER1, a new membrane receptor coupled with the G protein-coupled membrane receptor, was identified by molecular cloning [7, 19, 20]. The research regarding this type of receptor started in 1997, when the seven-transmembrane receptor named GPR30 was cloned. Subsequently, other studies revealed that 17-β-estradiol can activate the signaling pathways through GPR30 even in breast cancer cells without classical ERs but expressing GPR30 receptors [19, 21]. However, those activated signaling pathways could not be noticed in the cells where GPR30 expression was blocked. Additional studies confirmed the hypothesis, namely the essential role played by GPR30 in the membrane-bound estrogen receptor [7, 22, 23]. In 2007, GPR30 was officially renamed G protein-coupled estrogen receptor 1 (GPER or GPER1). In **Table 1**, the type, subcellular location, structure, and distribution in tissues of ER [20] are presented.

Table 1. Principal properties of each ER [20].

ER	Type	Subcellular localization	Structure	Distribution in tissues
ERα	Nuclear steroid hormone receptor superfamily	Nucleus (ERα66) cell membrane. (ERα36) cytoplasm	DNA binding domain, ligand binding domain, N-terminal domain	Hypothalamus, hippocampus, testes, ovary, endometrium, uterus, prostate, kidney, liver, breast, epididymis, muscle, adipose tissue
ERβ	Nuclear steroid hormone receptor superfamily	Nucleus cytoplasm	DNA binding domain, ligand binding domain, N-terminal domain	Testes, ovary, prostate, vascular endothelium, bladder, colon, adrenal gland, pancreas, muscle, adipose tissue
GPER1	G protein coupled receptor superfamily	Cell membrane	7 transmembrane α-helical regions, 4 extracellular and 4 cytosolic segments	Central and peripheral nervous system, uterus, ovary, mammary glands, testes, pancreas, kidney, liver, adrenal and pituitary glands, cardiovascular system, adipose tissue

Recently, studies have focused on the discovery of new therapeutic molecules with antiestrogenic effects, which may inhibit estrogen synthesis or block the interaction of the estrogen molecule with the estrogen receptor in order to treat hormone-dependent breast cancer.

The most important ER is represented by ERα, which is involved in the regulation of approximately 70% of the transcription factors associated with breast cancer. It was observed that the mutations of this receptor, peculiarly in the ligand-binding domain, may be the crucial factor contributing to resistance. In the 1990s, the first mutation for three regions of the ligand-binding domain of the ERα receptors in metastatic breast cancer was discovered, lately confirmed by advanced DNA sequencing techniques. Recent investigations emphasize that the most frequent mutations, predominantly during the metastasis stage, are at Asp538 and Tyr537 in helix 12 of the ligand-binding domain, which occasionally occur in the early stage of the disease. These findings emphasize the need for new ligands with improved effectiveness against resistant ERα mutations to improve therapeutic outcomes [20, 24–26].

Currently, investigated compounds belong to the following pharmacological classes:

- Selective estrogen receptor modulators (SERMs):
  - Triphenylethylenes (Tamoxifen, Clomiphene, Toremifene);
  - Benzothiophenes (Raloxifene);
  - Tetrahydronaphthylenes (Nafoxidine hydrochloride).
- Benzopyran derivatives (Acolbifene, Levormeloxifene);
- Indoles (Bazedoxifene);
- Phytoestrogen-based SERMs;
- Coumarin-based SERMs;
- Selective estrogen receptor downregulators (SERDs);
- Aromatase inhibitors;
- Sulfatase inhibitors.

3. The Physiological Functions of Estrogens

3.1. Gynecological Effects

The gynecological effects of estrogens are observed at the following levels of the female reproductive system [27–30]:

- Breast: The effects on the mammary glands are observed mainly during puberty, where estrogens promote the development of the glands. Also, estrogens stimulate the secretion of breast milk during lactation, alongside the regulation of the growth of the mammary glands.
- Uterus: Studies have demonstrated that these hormones play a crucial role during the follicular phase of the menstrual cycle, determining the proliferation of the endometrial cells and the thickening of the uterine lining to prepare it for pregnancy.
- Vagina: Estrogens can stimulate the proliferation of the epithelial cells in both the vagina and vulva, which maintains the thickness and the health of the mucosal lining. For example, during menopause, the estrogen level decreases, causing the thinning of the vaginal and vulvar epithelium, leading to vulvovaginal atrophy.

3.2. Regulation of the Immune System

Initially studied only for their role in the development of the reproductive system, research indicates that estrogens play a major role in the immune system, presenting strong anti-inflammatory effects, which may improve the outcomes of severe infections, wound healing, and tissue repair. The effectiveness of estrogens in immunity is closely related and influenced by the type of pathogen, inflammatory trigger, hormone concentration, and the number of ERs in each tissue. The main purpose of further studies is represented by hormonal regulation of the immune pathways, in order to observe the individual variations in the treatment responses, which may offer insights into personalized therapeutic interventions for conditions involving immune dysregulation or chronic inflammation [13, 31].

3.3. Brain Function

In the literature, several biological pathways through which the estrogens may influence cognitive function and dementia risk are presented, including the reduction in the accumulation of amyloid beta and enhancement of cholinergic activity (crucial for memory and learning). They also promote axonal growth and dendritic spine formation to support neuronal connectivity and diminish cerebral arteriosclerosis to maintain adequate blood flow to the brain. These mechanisms highlight the potential role played by estrogens in the preservation of cognitive health and the delay of neurodegenerative processes [2, 32]. Estrogens can also modulate the dopamine pathways and mitochondrial functions influencing schizophrenia. For example, hyperprolactinemia associated with low levels of estrogen can be a common symptom of schizophrenia [5].

3.4. Cardiovascular Effects

Epidemiological studies have revealed that premenopausal women have a lower risk for cardiovascular diseases compared to men, while for postmenopausal women, the risk increases significantly, surpassing the male rates. These findings demonstrate the protective role played by estrogens for the cardiovascular system. Oxidative stress is a key factor in cardiovascular diseases such as atherosclerosis, myocardial dysfunction, and heart failure. Modulation of ERs helps to regulate oxidative stress, which may represent a therapeutic option for menopausal women [6, 9].

3.5. Modulation of Bone Density

The effects of estrogens on bone density were highlighted for the first time in the 1940s, when they were found to be associated with osteoporosis, but the mechanism in terms of their physiological role has only been clarified in recent years. Menopause and surgical ovariectomy are now known to cause changes in bone mineral density and structure. Studies where bone-derived serum markers were used to investigate bone metabolism stated that estrogen withdrawal increases the rate of bone turnover with the enhancement of bone resorption [8, 33, 34].

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The authors declare no conflicts of interest.

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