Mechanisms of action of estrogens and their physiological effects

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Introduction

Estrogens exert a wide range of biological effects through complex mechanisms of action that extend beyond reproductive regulation. Their influence spans the cardiovascular, skeletal, dermal, immune, and central nervous systems (Table 1), mediated by both genomic pathways (through direct or indirect modulation of gene transcription) and non-genomic pathways (through rapid, membrane-initiated signalling).

Estrogen responses are influenced by the distribution and function of the two receptors, estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ), which can act in either a complementary or opposing manner, depending on the cellular context. In addition to receptor binding, pharmacokinetic factors such as half-life, metabolism, SHBG binding, and hepatic effects also play a crucial role in shaping estrogen activity (see Section 4). Moreover, variability in estrogen action has been observed both among individuals and across populations, reflecting differences in receptor distribution and tissue responsiveness. These variations influence not only the efficacy but also the safety of estrogen-containing therapies, underscoring the potential value of tailoring hormonal contraception to individual profiles.

This section outlines the modes of action of estrogens, including receptor-mediated signalling pathways, and their physiological roles across different tissues. Special attention is given to key estrogens used in contraception: ethinylestradiol (EE),17β-estradiol (E2), and estetrol (E4) (Table 2), each with distinct pharmacological and safety profiles.

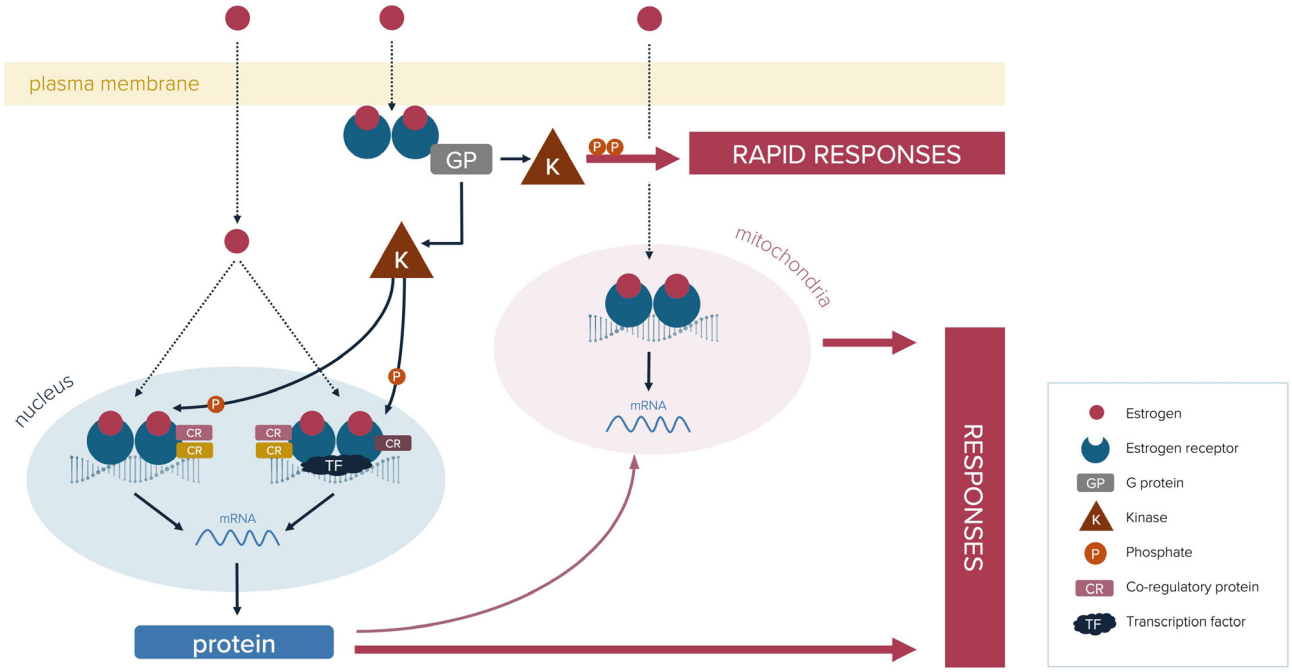
Table 1. Tissue-specific effects of estrogens

Tissue/system	Main effects	Mode of Action (MOA)
Reproductive system	Regulation of the menstrual cycle, ovulation, and pregnancy maintenance.	Estrogens influence the secretion of gonadotropin-releasing hormones by the hypothalamus, thereby modulating the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the pituitary gland. These gonadotrophins are important for menstrual cycles; FSH supports the maturation of ovarian follicles, while an LH surge triggers ovulation. The combination of a progestin with an estrogen in COCs lowers the LH and FSH production, thereby inhibiting follicle maturation and preventing ovulation. Additionally, they affect the endometrium lining, preventing implantation of the embryo, and change the mucus at the cervix to become less permeable to sperm.
Bone	Prevents bone resorption by inhibiting osteoclast activity.	The bone is constantly being remodelled by osteoblasts (bone formation) and osteoclasts (bone reabsorption). Estrogens protect the bone by repressing pro-osteoclastic cytokines and inducing apoptosis in bone-resorbing osteoclasts [1]. Both ERα and ERβ receptors play a role in the estrogen activity on bone and may interact (partially compensate or antagonise each other) in different bone cell types [1].
Cardiovascular & Metabolism	Enhances nitric oxide production, improves lipid and glucose metabolism, prevents atherosclerosis, and improves endothelial function.	Estrogens affect metabolic activity, resulting in a positive effect on lipoproteins by lowering low-density lipoprotein cholesterol and increasing high-density lipoprotein. Estrogens affect glucose metabolism, facilitating insulin secretion and regulating glucose availability to tissues [2]. These effects could depend on the equilibrium between ERα and ERβ in the metabolic network. Estrogens also enhance nitric oxide production, resulting in vascular relaxation and a decrease in blood pressure [3]. In addition, estrogens promote endothelial healing and exert anti-atherosclerotic effects, with clinical benefit influenced by the timing of exposure. Estrogens generally have neutral to favourable effects on blood pressure, lipid parameters, and glucose metabolism (See Sections 8 and 9).
Central nervous system	Modulates mood, cognition, and libido; provides neuroprotection; reduces vasomotor symptoms (hot flushes).	While the exact MOA of estrogens on mood, cognition, and memory is still being investigated, there is growing evidence that serotonergic pathways play a role [4]. Estrogens may also exert neuroprotective effects by reducing p-Tau and β-amyloid expression, potentially contributing to a lower risk of dementia [4]. Relief of vasomotor symptoms (hot flushes) is mediated through ERα and ERβ signalling in hypothalamic thermoregulatory circuits [5-7].
Skin	Maintains collagen, elasticity, and hydration.	ERs are present in skin cells and regulate the skin collagen content, elasticity and hydration [8].

Table 2. Key estrogens used in combined hormonal contraception

Estrogen	Description
Ethinylestradiol (EE)	Potent synthetic estrogen; strong hepatic effects; associated with higher thromboembolic risk.
17β-estradiol (E2)	Natural, body-identical estrogen; balanced affinity for ERα and ERβ.
Estetrol (E4)	Natural foetal estrogen; selective nuclear ERα activity; minimal hepatic impact on metabolism and coagulation.

Figure 1. Integrated estrogen (E)-ERE signalling pathways (adapted from [10]).



Estrogen-bound Estrogen receptors (EREs) at the plasma membrane activate G-proteins (GP) and downstream kinases (K), leading to rapid cellular responses and post-translational modifications of nuclear factors. In the nucleus, E–ERE complexes regulate gene expression through both estrogen response element (ERE)-dependent and ERE-independent (tethered) pathways. In mitochondria, E–ERE complexes modulate mitochondrial DNA transcription, increase antioxidant enzymes such as manganese superoxide dismutase, and influence apoptosis. These pathways integrate to mediate both rapid and long-term actions of estrogen.
CR: co-regulatory proteins (co-activators, co-repressors), GP: G-protein, K: kinases (e.g., ERK/MAPK, PI3K/AKT cascades), P: phosphates, TF: transcription factors, mRNA: messenger ribonucleic acid

Estrogen receptors and physiological effects

Estrogens exert their biological effects through two distinct nuclear receptors, estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ), which mediate both genomic and non-genomic pathways of action [9,10]. The genomic mechanisms can be divided into direct and indirect modes of gene regulation [9,10].

Genomic mechanisms

Direct gene signalling

In the direct genomic pathway, estrogens cross the plasma membrane and bind to intracellular ERs located in the nucleus or cytoplasm. Ligand binding induces receptor conformational changes, dimerisation, and subsequent binding to estrogen response elements (EREs) on DNA, initiating transcription of various genes involved in cell growth, differentiation, and reproductive functions [9,11-13]. Notably, the G protein-coupled estrogen receptor, initially proposed as an estrogen receptor, is no longer regarded as a true ER [13,14].

Indirect gene signalling

In addition to direct DNA binding, ERs may also regulate gene expression indirectly. In this pathway, ER complexes interact with other transcription factors (e.g., AP-1, Sp1, NF-κB), thereby modulating transcriptional activity without directly engaging with DNA [9,13].

Non-genomic mechanism

Beyond classical nuclear actions, estrogens can also exert rapid cellular effects through membrane-initiated steroid signalling (MISS). Here, subpopulations of ER-α and/or ER-β are localised to extranuclear membranes where they trigger rapid intracellular responses, such as activation of endothelial nitric oxide synthase, leading to vasodilation in the cardiovascular system and improved blood flow [15]. Increasingly, such extranuclear signalling has also been linked and is associated with regulations in the central nervous system, involving functions such as reproduction, energy homeostasis, and stress [15,16].

Physiological effects of estrogens

In addition to the female reproductive system, estrogen receptors are also found in various other tissues, including the cardiovascular system, brain, bone, liver, fat tissue, colon, and skin (Table 1) [17]. The physiological outcome of estrogen action is influenced not only by the relative expression of ER subtypes in specific tissues, but also by pharmacokinetic and metabolic factors, including duration of action and local estrogen metabolism through sulfation and sulfatase activity (see Section 4). While ERα can be mainly found in the mammary gland, uterus, ovary (theca cells), bone, male reproductive organs (testes and epididymis), prostate (stroma), liver, and adipose tissue, ERβ expression is more restricted in mammalians, and found mainly in the prostate (epithelium), bladder, ovary (granulosa cells), colon, adipose tissue, and immune system. Both types are present in the cardiovascular system and the central nervous system (CNS) [18]. ERα plays a crucial role in the mammary gland and uterus, as well as in maintaining skeletal homeostasis and regulating metabolism. At the same time, ERβ has a more profound effect on the CNS and immune systems and could counteract the ERα-promoted cell hyperproliferation in tissues such as the breast and uterus, although ERβ abundance is low [18].

Key estrogens in COCs and their distinct profiles

In combined oral contraceptives (COCs), estrogens play a central role in the contraceptive mechanism of action by suppressing gonadotropin secretion, stabilising the endometrium, and altering cervical mucus. At the same time, estrogens exert a range of non-contraceptive beneficial effects on the bone, cardiovascular system, central nervous system, and other tissues, as outlined above. Although these actions are mediated through shared ERα and ERβ pathways (Table 3), the choice of estrogen determines potency, receptor selectivity, metabolism, and hepatic impact, thereby shaping both clinical efficacy and safety. A brief description of the three estrogens used or investigated in COCs, ethinylestradiol (EE), 17β-estradiol (E2), and estetrol (E4), is provided below. Their pharmacological and clinical characteristics are discussed in more detail in other sections.

Ethinyl-estradiol

EE is a synthetic derivative of E2. The addition of the ethinyl group results in higher oral bioavailability and slower metabolism compared to E2, making it ideal for once-daily oral administration. EE binds to both ERα and ERβ, but is much more potent than E2, mainly because of its longer half-life. For example, with respect to the stimulation of SHBG and angiotensinogen, EE is approximately 614 times and 331 times more potent than E2, respectively [19]. This high potency, combined with high hepatic exposure, causes pronounced effects on the liver and haemostasis parameters, thereby contributing to an increased risk of venous thromboembolism (VTE) [20].

17β-Estradiol

E2 is the natural female sex hormone produced by the follicles in the ovaries. In oral contraception, E2 is provided either as estradiol valerate or as the micronised form of bio-identical E2. Esterification to

valerate or micronisation of E2 is needed to increase oral bioavailability. After absorption, exogenous E2 is body-identical to endogenous E2. E2 is lipophilic and passes through the cell membrane by passive diffusion and binds to the ERα and ERβ in the nucleus with similar binding affinities.

Estetrol

E4 is a natural body-identical estrogen with a more selective estrogen pharmacological profile compared to other estrogens [13,21-24]. E4 selectively binds to both ERα and ERβ, with a 4 to 5-fold higher binding affinity for ERα [25]. E4 exhibits tissue-specific neutral, or even anti-estrogenic activities [25-28]. The tissue-selectivity of E4 is caused by a specific profile of ERα activation, which uncouples nuclear and membrane activation. In certain cell types, such as endothelial cells and possibly breast cancer cells, E4 exhibits a distinct profile of ERα activation, inducing only ERα nuclear actions while preventing ERα membrane actions [29]. Potentially due to its selective pharmacological profile, E4 has a low estrogenic impact on the liver, with minimal effects on the synthesis of hepatic coagulation factors, SHBG and angiotensinogen synthesis, and lipid parameters [30-32]. Although E4 has markedly lower binding affinity for ERα compared with E2, its long half-life, CYP-independent metabolism, and lack of SHBG binding explain its clinically relevant activity in vivo (see Section 4).

Table 3. Receptor binding affinity and activation characteristics of EE, E2, and E4

Characteristics	Ethinylestradiol (EE)	Estradiol (E2)	Estetrol (E4)
ERα IC 50 (nM)	5.6 [33]	11.2 [33]	281.8 [33]
ERβ IC 50 (nM)	15.9 [33]	8.9 [33]	354.8 [33]
Relative binding affinity to ERα	194 % [34] 200% [33]	100 % [33]	1-4% [35] 4% [33]
Relative binding affinity to ERβ	195 %[34] 56% [33]	100% [33]	1-4%[35] 3% [33]
Binding affinity ERα/ERβ	3.6 [33]	1 [33]	4 to 5 [36] 1.3 [33]
Nuclear ERα activation	Yes	Yes [13]	Yes [13,37]
Membrane ERα activation	Yes	Yes [13]	No* [13,37]

*E4 is also able to antagonise the effect of E2 on membrane ERα activation partially [37].
IC 50: half maximal inhibitory concentration. It refers to the concentration of an estrogen needed to inhibit 50% of a reference activity in the assay used. Lower IC 50 values indicate higher relative potency. Reported values depend on assay conditions and should be interpreted comparatively rather than as absolute measures.

Population-level variability in estrogen action

Although estrogen signalling mechanisms are fundamentally conserved across humans, growing evidence indicates that population-level differences in ER polymorphisms, expression, and responsiveness may influence physiology and disease outcomes. Genetic evidence shows that the ERα PvuII genotype is associated with a significantly increased risk of uterine leiomyomas in both Black and White women, underscoring the role of ER variants in estrogen-related disease risk across populations [38]. At the tissue level, studies in South African women have demonstrated that gluteal subcutaneous fat from Black women exhibits higher ERα and lower ERβ expression compared with that of White women, a pattern linked to greater peripheral fat mass and lower central adiposity [39].

In oncology, clinical data show that African American women with ER-positive breast cancers are more likely than European American women to present with weakly ER-positive tumours (1–50% ER staining), highlighting racial variation in estrogen signalling pathways and their implications for treatment response [40]. Complementary evidence from dermatological models suggests that ERα transcript induction in response to E2 occurs earlier or more strongly in skin samples from African American donors compared with those from Caucasian donors, indicating inter-ethnic variability in dermal estrogen responsiveness [41].

In addition, polymorphisms in cytochrome P450 (CYP) enzymes that metabolise ethinyl estradiol and estradiol, but not estetrol, may further contribute to interindividual differences in oestrogen exposure and activity. Although the absence of estetrol metabolism by CYP enzymes results in a lower risk of drug-drug interactions, the relevance of CYP polymorphisms remains to be fully clarified for estradiol or ethinylestradiol-containing oral contraceptive use (see Section 4).

Together, these findings demonstrate that ethnic variability in ER genetics, distribution, and function exists across reproductive, adipose, breast, and skin tissues. While the direct implications for contraceptive efficacy remain uncertain, such data underscore the importance of considering population-level diversity in estrogen action when evaluating the benefits and risks of estrogen-containing therapies. This may be particularly relevant for contraceptive choices involving EE, E2, and E4, which differ in receptor selectivity, metabolism, and hepatic impact.

Conclusion

Estrogens act through a balanced interplay of genomic and non-genomic pathways, with tissue specificity determined by the relative distribution of ERα and ERβ. This underpins both their contraceptive and non-contraceptive actions. Among the estrogens used in COCs, EE is potent but is associated with significant hepatic effects and an increased risk of thromboembolism. E2 provides a body-identical alternative but is limited by its oral pharmacokinetics (See Section 4), whereas E4 offers a distinctive nuclear ERα–selective profile with minimal hepatic impact and potential safety advantages.

Genetic polymorphisms and ethnic variability in ER expression contribute to interindividual and interpopulation variability in estrogen action. Recognition of these differences reinforces the importance of tailoring contraceptive choice to both individual risk factors and the unique pharmacodynamic properties of each estrogen.

Knowledge gaps and future directions

The long-term clinical significance of ERβ's counter-regulatory role remains incompletely understood.

The precise contribution of MISS signalling in different tissues is not yet fully delineated.

Comparative, head-to-head studies of EE, E2, and E4 in diverse populations are still limited.

The impact of genetic polymorphisms and ethnic variability on contraceptive safety and efficacy requires large-scale, multi-ethnic validation.

Key messages

Estrogens act through both genomic and non-genomic mechanisms, enabling rapid and long-term physiological effects.

The differential distribution of ERα and ERβ governs tissue-specific responses.

EE is potent and effective but associated with pronounced hepatic effects and higher VTE risk.

E2 is body-identical and more physiological, though its oral bioavailability is limited.

E4 shows a distinctive tissue-selective profile with minimal hepatic effects, offering potential safety advantages.

Pharmacokinetic factors such as half-life, metabolism, SHBG binding, and hepatic impact critically influence the clinical relevance of estrogen action (see Section 4)

Population-level and individual variability, including CYP polymorphisms, ER variants, and differences in receptor expression, significantly influence estrogen metabolism and response.

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