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Permissive Role of Estrogens in Prostate Diseases

José Locia Espinoza and Luz Irene Pascual Mathey

Abstract

Estrogens are steroid hormones that act through their receptors (ER) $\alpha$ and $\beta$. They are involved mainly in female physiology but, in males, influence the homeostasis of some tissues like the prostate. In this organ, estrogens promote or limit cell proliferation depending on the activated receptor, with implications for the pathophysiology of benign prostatic hyperplasia (BPH) and prostate cancer (PCa). ER$\alpha$ promotes proliferation while ER $\beta$ is a protective factor against proliferative diseases. However, in the advanced stages of PCa, ER$\beta$ has a permissive role in prostate cells, increasing patient mortality. These effects are mediated by activating androgen-independent signaling pathways that promote proliferation. Another essential aspect of ER actions is the regulation of its expression. Steroid hormones participate in this process, but some non-steroid factors, like environment and epigenetic marks, influence the prostate's physiopathology. Knowledge of these and other aspects of estrogenic action in the prostate will contribute to developing strategies for treating and preventing BPH and PCa. For this reason, this chapter will review the main aspects of estrogens' permissive role in prostate diseases.

Keywords: Estrogen receptors, permissive role, prostate physiology

1. Introduction

Estrogens are steroid hormones that have a very well-characterized morphogenic role since they participate in the development of the ovary, uterus, mammary gland, prostate, lungs, and brain, among others [1]. The primary estrogen identified is Estradiol (E2), to which most of the actions of estrogens are attributed, which act through binding to specific receptors, the ER [2]. It has been shown that the diverse functions in which estrogens intervene depend on the adequate balance in the signaling of their ER (ER$\alpha$ and ER$\beta$). Although the actions of estrogens have been well characterized in female physiology, it has a central role in the maintenance of male sexual function and the development of prostate diseases [3]. Concerning the above, estrogenic stimulation can cause the activation of different intracellular signaling pathways that can influence the development of the prostate gland both in the embryonic stage and in adulthood and intervene in the development of pathologies [2, 4]. Therefore, this review will address the role of estrogens and their receptors in prostate pathophysiology.
2. Estrogens: essential hormones in female and male physiology

Estrogens are steroid hormones that bind to specific receptors, the nuclear receptor (ER) superfamily, ligand-inducible transcription factors that can bind to DNA at sites called estrogen response elements (EREs), activating different responses. Estrogens are generally recognized for stimulating cell proliferation, apoptosis, and differentiation. Although its presence has been reported in both men and women, there are three main estrogens in women, 17β-estradiol (E2) and its two metabolites (estrone and estriol), which, despite their high affinity to ER, it exerts less potent effects [1].

E2 is the most abundant; its primary source is the ovary, although it is also produced in smaller quantities in other tissues, such as the adrenal glands and adipose tissue. Estrogens are considered mainly feminizing hormones due to their effects on the female’s reproductive functions; however, recently, they have also been shown to play an essential role in men, finding elevated levels of this hormone in rete testis fluid and semen where one of the most studied estrogenic effects being the negative feedback they exert on Testosterone (T) secretion [3, 4]; the production of this hormone is controlled at the hypothalamus by the Gonadotropin Releasing Hormone (GnRH), which binds to gonadotroph cells in the pituitary gland, stimulating the release of Luteinizing Hormone (LH). In addition, this hormone is released through the hypophyseal portal system, joining to their receptors in the Leydig cells located at the seminiferous tubules in the testis, where they promote the synthesis of T. So, the inhibition process that estrogen exerts on the T implies a negative feedback mechanism on the secretion of LH at the pituitary gland, causing the consequently lower secretion of T by the testicular Leydig cells [4, 5].

About their role, estrogens have been shown to participate with androgens in the maintenance of sexual behavior and testicular developmental processes. But the most critical estrogenic effect is possibly the control of the reabsorption of fluids at the epididymis, a process that causes an increase in the number of sperm in the semen and, therefore, an increase in the probability of fertilization occurring. Another vital tissue for estrogen action in men is the prostate gland, whose development and estrogenic activities influence function by controlling androgen production through ER activation. Here, the primary source of estrogen is the testis, in which Leydig cells T is transformed into E2 through an aromatization reaction catalyzed by enzymes of the cytochrome p-450 (CYP450) complex called aromatases. The E2 thus obtained is poured into the systemic circulation and reaches the target tissues, where it can be metabolized and interact in a specific way by joining the ER and intervening in direct and indirect actions [4].

3. RE: proteins responsible for the direct and indirect actions of estrogens

Two primary ER (α and β) have been identified. However, the first ER to be discovered in the 1950s was ERα, while ERβ was found almost four decades later, in 1996 [1]. These transcription factors are classified within class II of the superfamily of nuclear receptors for steroid hormones. They have a tertiary structure that includes six functionally distinct domains designated with the letters “A” to “F”; an N-terminal domain (“A/B” domains); a DNA-binding domain “C,” which is the part of the receptor that binds to DNA (DNA-Binding Domain, DBD); a “D” domain, which acts as a hinge region; the “E” corresponds to the Ligand Binding Domain (LBD) and is the
site of recognition and binding to the specific hormone and other related molecules; as well as a C-terminal “F” domain, whose function, although poorly understood, is believed to be involved in the conformational stability of receptors [4, 6].

It has been shown that, in the absence of a ligand, the ER remains inactive since they are bound to chaperone proteins (HSP, Heath Shock Proteins), which are responsible for maintaining the receptors in a conformation that hides their nuclear localization signal (NLS). Thus, the binding of the receptor with the corresponding hormone generates conformational changes whose consequence is the release of HSP and the appearance of nuclear localization signals; This enables the translocation of the ERs to the nucleus and the activation of the transcription of target genes by interaction with their response elements (ERE). Concerning the above, it is known that EREs are palindromic sequences with the structure 5'-GGTCAnnnTGACC-3', where “n” represents any nucleotide. Genes with an ERE in their structure are called “estrogen-responsive” [4].

However, some genes, even lacking these sequences, can be transcribed by estrogenic signaling activated by indirect mechanisms, which will be discussed later. In this type of signaling, ERs interact with other transcription factors such as Jun, Fos, AP-1, and SP-1, causing their activation and subsequent translocation to the nucleus, where they bind with their response elements and induce gene expression. The interaction with other transcription factors is different depending on the type of ER involved, which has been proposed as an explanation for the fact that the activation of ER by identical ligands can cause other effects depending on the tissue and cellular context. These signaling mechanisms are believed to explain the actions in which ERs are involved [4, 6].

4. ERα and ERβ: receptors involved in the balance of the estrogenic effect

The discovery of estrogen receptors was made after almost four decades. This finding also required tremendous advances in the field of genetic engineering. Since the first estrogen receptor (ERα) was discovered, it was believed that this was the only one responsible for the estrogenic effects, an idea that was modified when the first transgenic mice were designed (known as “ERKO mice” < Estrogen Receptor Knock Out>) and observed that they continued to show a response to estrogenic stimulation, despite having ERα silenced. In this sense, when a patient who did not express ERα was reported in 1994, speculation began about the existence of more than one type of ER. Confirmed this assumption in 1996, the year in which the discovery of a second molecule capable of being activated by binding to its ligand (E2) and other estrogens is evidenced. Identified this new ER in rat prostate and ovary and, from then on, the first ER was named ERα, while the second is known as ERβ [1].

Both receptors are expressed on different chromosomes and show determining structural characteristics; ERα is approximately 600 amino acids long and has a molecular weight of 67KDa, while ERβ is around 500 amino acids long and weighs 55KDa, sharing about 47% amino acid sequence homology [4, 5]. Similarly, of the different domains that have been identified, the “C” domain (DBD) is the one with the most significant similarity concerning both receptors (>95%), which explains, in part, the high affinity that both receptors have for DNA [1, 6].

Specifically, although it has been reported that both receptors similarly bind to their ligands, the evidence indicates that the affinity for E2 is similar with both receptors (α and β). However, they show significant differences in binding to other
natural or synthetic steroids. For example, it has been demonstrated that ERβ shows a high affinity for endogenous steroids and certain phytoestrogens (e.g., genistein). In addition to the above, it has been reported that estrogen receptors can activate different intracellular signaling pathways, which leads to their involvement in such diverse biological effects [6].

5. Ligand-dependent and ligand-independent signaling pathways activated by ERs

In general, it is known that ERs can use at least four different pathways at the cellular level. The first three pathways are ligand-dependent, and the fourth is ligand-independent. In the first “the classic route,” it is known that the ligand-receptor interaction can cause ER heterodimerization, a configuration in which they can bind directly to the EREs sequences in DNA through specific binding, regulating gene expression. A second route consists of the interaction of the heterodimer after the activation of the ligand, with specific proteins, i.e., with transcription factors such as Fos/Jun, by interacting with DNA, promoting gene activation indirectly [1, 6].

In the third pathway (called the “non-genomic” type), the ligand activates the receptor to activate other transmembrane and cytoplasmic proteins, within which another receptor may be included, as well as various proteins that act as second messengers. This interaction, yet not fully elucidated, results in the opening of ion channels and the flow of ions, as well as the generation of rapid responses, including the activation of nitric oxide (NO), which has been suggested to be responsible for the physiological effects attributed to this signaling route. Finally, the fourth pathway (ligand-independent) involves crosstalk mechanisms, in which ERs are activated by other signaling pathways, such as the growth factor signaling pathway. In this case, the binding of the growth factor to its receptor promotes the activation of kinases, which, in turn, cause the phosphorylation of the ERs and their subsequent dimerization and binding to the EREs elements in the DNA [1, 6].

6. Participation of ERs in the proliferation and morphogenesis of the prostate

The different mechanisms of intracellular communication carried out by the interaction of estrogens with their ER allow them to act in several tissues, intervening in multiple functions, such as cell morphogenesis, proliferation, and differentiation. As already mentioned, it was considered that the main effects of estrogens were focused on female physiology. However, the literature had shown that the administration of environmental estrogens (xenoestrogens) from synthetic sources (e.g., bisphenol A or BPA, methoxychlor, and atrazine); pharmaceuticals (e.g., diethylstilbestrol or DES, and Ethinyl estradiol) or natural (e.g., genistein, and daidzein), caused “in utero” abnormalities in the urogenital tract of both males and females, with similar results being obtained when these drugs were administered at different stages of development. In addition, some studies reported other alterations in male physiology, including low semen quality, testicular neoplasia, and prostate diseases [1, 3].

In the prostate gland, both receptors have been demonstrated in epithelial cells, which control and regulate epithelial proliferation. In this sense, it has been suggested that while ERα promotes cell proliferation, ERβ limits it, so several studies
have considered ERβ as a protective factor against the development of prostate diseases, while ERα could act as a promoter by being overexpressed in cancer cells; In this sense, it has been reported that the expression of ERβ is elevated in healthy tissue, while its expression decreases in damaged tissue, while the expression of ERα increases. Although the mechanisms that regulate the expression of these receptors in both conditions are unknown, it is suggested that ERβ could reduce cell proliferation by inhibiting the expression of genes involved in DNA replication and the cell cycle. In this sense, the cyclin D1 gene has been suggested as a factor that controls the transition between the G1 and S phases of the cell cycle. Another inhibition mechanism could be through direct interaction with its promoter regions or through the indirect mechanisms in which ERβ interacts with other transcription factors (AP1 and SP1, for example), stimulating or repressing the expression of their target genes. The previous is possible because some genes whose expression is controlled by ERβ activation lack EREs in their promoters. Finally, another process in which ERβ could intervene to regulate prostate cell proliferation in carcinomatous and normal cells is the expression of androgen receptors (AR), explained later in this chapter [4].

7. Estrogens and their participation in the physiology of the prostate

Development, proliferation, and function of the prostate gland depend on androgens (mainly through its primary metabolite, Dihydrotestosterone <DHT>), which require binding to its receptor (RA) for the transcription of target genes; however, it has been recognized that the prostate is sensitive to other hormones, such as steroids, which have a central role in growth, homeostasis, and in the generation of prostatic diseases [3, 7]. In this sense, it has been established that men exposed to high concentrations of xenoestrogens, whether of natural or synthetic origin, during fetal life or at some other stage of development, such exposure has a significant impact on the development of the prostate gland, so it has been shown that although estrogens can modulate epithelial morphogenesis and differentiation during prostate development, this exposure can also influence the outcome of diseases, including the benign prostatic hyperplasia (BPH) and Prostatic Cancer (PCa) [3].

As previously mentioned, these effects are regulated by the expression of ERs. Specifically in the prostate, ERα is expressed mainly in a small portion of adult prostatic stromal cells in humans, dogs, monkeys, and rodents; however, there is evidence reporting its presence in periurethral epithelial cells [6]. Furthermore, its expression is elevated in the uterine stage, declining during adolescence and adulthood, increasing again as the concentration of androgens decreases, playing a fundamental role in the changes in the prostate due to the imbalance between the T and E2 [6].

On the other hand, ERβ has been located mainly in the prostatic epithelium; Although its expression varies during fetal development, its expression increases from week 7, remaining present in low amounts throughout pregnancy, including the postnatal stage. From this period, its levels begin to rise together with the process of cytodifferentiation, reaching high levels in puberty, where it participates in prostatic epithelial differentiation [3, 7, 8].

Although it has been suggested that ER-ligand signaling is not as essential for prostate development, it is crucial for developing pathologies. As already mentioned, early treatment (especially in the prenatal stage) with estrogens or xenoestrogens produces alterations in the development and differentiation of the prostate. Furthermore, these changes occur permanently (chronic inflammation, epithelial hyperplasia,
precancerous lesions, and adenomas), a process called developmental estrogenization or estrogen imprinting, which we will discuss later [7, 9]. Interestingly, it has been shown that these alterations are mediated by the signaling exerted by ERs (α and β), suggesting that the expression of these receptors can carry out antagonistic actions [2].

8. Antagonistic actions between ERβ and ERα in the generation of pathologies in the prostate

The antagonism of ERs in controlling prostate cell proliferation and differentiation has implications for the development, progression, and treatment of cancer in various tissues. There is evidence that ERα promotes while ERβ limits cell proliferation, so some studies suggest that ERβ acts as a protective factor against cancer. In contrast, ERα could be an oncogene overexpressed in carcinomatous cells [10, 11].

Evidence of this has been shown in other types of cancer, such as breast, where an absence of the chromosome that codes for ERβ has been observed, suggesting that this absence is a crucial factor in the proliferative process that accompanies tumor development. Similarly, when comparing ER expression in prostate cancer tissue, an increase in ERα expression and a decrease in ERβ expression have been observed, with a direct relationship between the reduction of this receptor and the increase in the degree of proliferation, as well as PIN (prostatic intraepithelial neoplasia) in localized prostate cancer tissues, which indicates that the absence of this receptor promotes tumor proliferation and possibly the metastatic process, having a high expression in normal epithelial cells, lower in tissue samples with BPH and very low or absent in carcinoma cells [4, 6, 12].

As we have already mentioned, this decreased expression is accompanied by an increase in the expression of ERα [10]. In this sense, it has been shown that the epithelial cells in the periurethral prostatic duct consistently express ERα in BPH tissue. Although the mechanisms accompanying these antagonistic effects are not precisely known, it is suggested that the signaling mediated by the ERβ could reduce cell proliferation by inhibiting the expression of genes involved in DNA replication and the cell cycle. Among the latter is the cyclin D1 gene, a factor that controls the transition between the G1 and S phases of the cell cycle [11].

Moreover, ERβ could inhibit the expression of these genes by directly interacting with their promoter regions and preventing their transcription or through indirect mechanisms in which ERβ interacts with other transcription factors (AP1 and SP1, for example) and causes stimulation/repression of their target genes. The last is possible because some genes whose expression is controlled by ERβ activation lack EREs in their promoter regions. More aggressive PCa have recently been found to be associated with the presence of an acquired chromosomal mutation. In this translocation, the promoter region of the Serine-Protease Transmembrane-2 (SPT2) gene is fused with the coding region of some transcription factors of the Erythroblast Transformation-specific (EST) family. Chromosomes with this fusion (SPT2-EST) are susceptible to the action of ERs. Specifically, activation of ERα has been shown to promote an increase in SPT2-EST gene expression, while activation of ERβ promotes a decrease [4, 10].

Another process in which ERβ intervenes to regulate proliferation in both carcinomatous and normal cells is the expression of ARs; cell proliferation depends mainly on androgens, which require their receptor to exert their effects by activating the target gene transcription [4]. Some studies show that one of the functions of ERβ
is to maintain AR expression at adequate levels to prevent excessive cell proliferation. For example, in βERKO mice, there are higher amounts of AR than in healthy mice, as well as an increase in cell proliferation. Similarly, treating human prostate cancer cell cultures with ERβ-specific ligands results in decreased AR expression [10]. In this context, it is possible to promote an increase in the expression of AR by administering specific agonists of the ERα, which constitutes another evidence of the antagonism between these two receptors in the development of pathologies. In the same way, because the ERβ can act in different stages of development, intervening in processes such as cell differentiation, antiproliferative, anti-inflammatory, and antioxidant actions is a good candidate for developing therapeutic strategies in tumor processes [4, 6].

9. Environment, epigenetics, and estrogens; how this influences prostate development

The morphogenic development of the prostate gland depends on the participation of multiple components, including hormones and a wide variety of factors, among which the Homeobox genes stand out, which includes the Hox and NK family genes. Within these genes are Hoxb-13 and Nkx3, whose expression is essential for prostatic epithelial differentiation. Interestingly, it has been shown that steroid hormones can regulate these genes. Specifically, exposure to the xenoestrogen DES has resulted in the downregulation of Hoxb-13 gene expression and suppression or downregulation of the Nkx3 gene. The last is correlated with a loss of prostatic epithelial differentiation and suppression of secretory genes, triggering alterations related to the estrogenization process that occurs in later stages [7, 8]. In addition to the above, embryogenesis requires the presence of proteins expressed at the level of epithelial-mesenchymal tissue cells, as well as the signals exchanged by these tissues. Bmp4 proteins act as inhibitors of proliferation during development; specifically, the Bmp4 mRNA is expressed in mesenchymal tissue during embryonic development, declining in the first days of postnatal development. Interestingly, exposure to estrogens in the prenatal period causes Bmp4 protein levels to remain elevated for a prolonged period after birth (day 15), the direct consequence of which is associated with prolonged suppression of prostatic tissue, which contributes to the development of a hypomorphic phenotype [7, 8].

Similarly, other morphogenic developmental regulators are the Shh and Fgf10 proteins. On the one hand, Shh is a secretory glycoprotein produced by epithelial cells in developing tissues. At the same time, the Fgf10 factor has a central role in stimulating prostatic budding, ductal outgrowth, and branching morphogenesis. As expected, the presence of prenatal estrogens produces an inhibition of both molecules (Shh and Fgf10), which results in an inhibition of branching morphogenesis [7, 8].

Furthermore, in the adult stages of development, other epigenetic factors influence the appearance of prostate alterations; In this sense, reports are indicating that in cancerous tissues, the ERα gene is methylated, which leads to a silencing of this gene, triggering different types of alterations, ranging from the development of BPH to varying degrees of tumor lesions. Therefore, it has been suggested that the risk of PCA is highly associated with polymorphisms in the ERα gene, particularly in populations such as the Japanese and African, which are more susceptible to estrogenic actions [6]. Similarly, it has been reported that the absence/decrease in the expression of the β receptor that occurs as the cancerous proliferative process progresses could be associated with a hypermethylation process, which has been shown to appear in the CpG
islands of the promoter region of the gene that codes for this receptor, causing the silencing of this gene and its transcription. This effect is reversed with demethylase treatment, an epigenetic mark involved in the progression of prostate tumors [13].

10. Conclusions

The prostate is a gland responsive to estrogens, which are involved in the normal development of this organ (morphogenesis) and the development of pathologies. These actions are regulated at different stages of development by the presence/absence of ERs (α and β) and the pathways activated by them, participating both in normal tissue development and in the generation of pathologies.

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Conflict of interest

The author declares no conflict of interest.

Acronyms and abbreviations

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<tr>
<td>ER α/β</td>
<td>estrogen receptors α and β</td>
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<td>BPH</td>
<td>benign prostatic hyperplasia</td>
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<td>PCa</td>
<td>prostate cancer</td>
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<td>E2</td>
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<td>EREs</td>
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<td>DBD</td>
<td>DNA-binding domain</td>
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<td>estrogen receptor knockout mouse</td>
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<td>BPA</td>
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<td>DES</td>
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<td>androgen receptor</td>
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<td>DHT</td>
<td>dihydrotestosterone</td>
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<tr>
<td>PIN</td>
<td>prostatic intraepithelial neoplasia</td>
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<tr>
<td>SPT2</td>
<td>serine-protease transmembrane-2 gen</td>
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<td>EST</td>
<td>erythroblast transformation-specific factor</td>
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References


