

Current evidence for the involvement of sex steroid receptors and sex hormones in benign prostatic hyperplasia

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Abstract: Benign prostatic hyperplasia (BPH) is a pathology that affects 50% of men over 50 years of age and 90% of men develop BPH in their eighth decade of life. In 2018, more than 1 billion men will be affected by this disease worldwide. However, the progression of BPH is highly complex and has been debated and studied for approximately four decades. Recent studies indicate that BPH can originate from the alteration of different hormone synthesis pathways, and that it is also linked to the function of hormone receptors. There is a close relationship between the progression of BPH and sexual hormones, such as progesterone, testosterone, dihydrotestosterone, and estrogen. The focus of this study was to characterize the interactions of these hormones and investigate the direct or indirect role of each sex hormone receptor in the progression of BPH. Although several studies have described the effects of these hormones on BPH, no conclusions have been drawn regarding their role in disease progression. Here, we present a literature review on the sexual receptors possibly involved in the progression of BPH.
Keywords: benign prostatic hyperplasia, testosterone, progesterone, estrogen, dihydrotestosterone

Introduction

Benign prostatic hyperplasia (BPH) is a non-malignant disease characterized by the enlargement of prostatic epithelial and stromal tissues and reduced urinary flow, causing disturbances commonly known as lower urinary tract syndrome.¹

Recent evidences have provided new insights into the mechanisms that govern or generate BPH. In addition, we know that aging is correlated with BPH. BPH currently affects 50% of men over 50 years of age and 90% of men in their eighth decade of life.²⁻⁴ It is estimated that, in 2018, 1 billion new BPH cases will be diagnosed worldwide.⁵

The prostate is a typical androgen-dependent gland and is highly reactive to sex hormones.^{1,6-8} In the 1970s, sex hormones were recognized as potential promoting factors of BPH. Among them, the most studied are testosterone (TT), dihydrotestosterone (DHT), progesterone (PGR), and estrogen.⁹⁻¹¹ However, the influence of each sex hormone on the progression and development of BPH and the pathogenetic role of complex hormone/receptor interactions have not yet been fully clarified.

Androgenic receptors (ARs)

AR is present at high concentrations in the prostate gland¹⁰ in two isoforms, namely AR-A and AR-B.¹² These receptors are encoded by the AR gene, located on the X chromosome at the locus Xq11-Xq12, and comprising eight exons, for a total length of about 90 kb.¹³⁻¹⁵

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The production of AR is particularly important because this protein activates the expression of other genes. The transactivation ability of AR lies in its N-terminal domain, which is encoded by exon 1. In this region, the mutation of two genes CAG and GGC also occurs.¹⁶

An excessive of polymorphisms is present in the CAG repeat, while few repetition polymorphisms are present in GGC.^{17–20} Giovannucci et al²¹ showed that the CAG polymorphism in exon 1 is 25-fold higher than GGC, and that CAG is the main cause of BPH progression. However, Biolchi et al^{18,19} reported that the CAG polymorphism does not directly influence the serum levels of TT or the development of BPH, whereas the GGC polymorphism increases the risk of BPH and prostate cancer.

Thus, AR gene polymorphism may be one of the causes of BPH development and progression. In addition, the binding of sex hormones to AR increases the likelihood of developing BPH. AR not only regulates the expression of hundreds of genes, but it is also involved in androgen binding and mediates the effects of TT and its most active metabolite, DHT.²²

Prostate growth is stimulated by DHT, the active metabolite generated from TT by the enzyme 5- α -reductase.⁶ This enzyme is present in three different isoforms: the type I isoform is ubiquitously expressed but present at low concentrations in the organs of the urogenital system; the type II isoform is enriched in organs of the urogenital system and the hair follicles; the type III isoform is especially abundant in the epidermis and in some organs such as the pancreas.^{23–26}

The inhibition of the TT-to-DHT conversion reduces the levels of intraprostatic DHT^{6,24,25} and prevents the enlargement of the prostatic epithelium, resulting in a 20%–30% decrease in prostate volume after 12 months of treatment.²⁷

This dramatic reduction reflects the high proportion of AR, accounting for ~90% of all prostate sex receptors. The reduction of the intraprostatic TT levels decreases the conversion into DHT, and, thus, the hormone-receptor binding.^{28–33} The impaired binding of androgens to their receptors prevents the translocation of AR from the cytoplasm to the nucleus of the prostate cells, making activation of specific pathways theoretically impossible.³⁴

In addition, patients with BPH present an extremely high DHT plasma concentration, compared to age-matched healthy subjects.³⁵ Also of note is the reported decline in the level of TT in BPH patients,³⁰ reinforcing the theory that DHT is largely responsible for the growth and proliferation of prostatic components. However, the reason for the DHT increase is not clear, as both serum and intraprostatic levels of TT are reduced with age.

A possible explanation for the increased serum and intraprostatic DHT levels observed in patients with BPH may reside in the conversion of 5- α -androstenedione to DHT by 17 β -hydroxysteroid dehydrogenases (17 β -HSDs). 17 β -HSDs belong to a family of enzymes that catalyze the reduction of stereospecific oxides of alcohols or carbonyls using NAD(P)H or NAD(P⁺) as cofactors. HSDs include five primordial subtypes: 3 α -, 3 β -, 11 β -, 17 β -, and 20 α -HSDs.³⁶

Fundamentally, 17 β -HSDs catalyze the synthesis of estrone (E1), estradiol (E2), 5-androstene-3 β , 17 β -diol, TT, and DHT. They also convert inactive or low-activity steroid hormones into more potent hormones, and vice versa. 17 β -HSDs are key regulators in humans. 17 β -HSDs comprise eight isoforms, each responsible for catalyzing the synthesis of a steroid or androgen (Figure 1).^{12,36–38}

Estrogen receptors (ERs)

In the 1970s, a direct link between prostate enlargement and the increase in intraprostatic estrogen was hypothesized.³⁹ Moreover, a crucial role of estrogen in the development of BPH has been described. However, the importance of AR and in the progression of BPH is indisputable.⁴⁰

We currently know that, in men, 75%–90% of the circulating estrogen is produced in adipose tissue, brain, bone, and other tissues. Estrogen synthesis is mainly controlled by the enzyme aromatase, which converts androstenedione to E1 and TT to E2. Aromatase is a member of the CYP/CYP450 superfamily.^{7,41}

Aromatase is expressed in the gonad gland of both sexes. Approximately 10%–25% of TT is converted in the testicles, generating E2. This maintains the levels of E2 required for normal spermatogenesis, sperm maturation, and sperm motility. In addition, 17 β -HSD converts the excess of E2 into E1 (Figure 2).^{12,42}

The hormones E1 and E2 exhibit high affinity and specificity for an intranuclear protein in target cells, termed ER. After binding of the hormone to ER, the latter undergoes a conformational change, allowing it to bind to chromatin with high affinity and, consequently, modulate the transcription of target genes. ER consists of an N-terminal hypervariable domain that contributes to the transactivation of a central domain responsible for a specific binding to DNA. In addition, ER activates the dimerization and nuclear localization of the C-terminal domain involved in ligand binding and ligand-dependent transactivation, ultimately inducing cell mitosis.^{41,43,44}

There are two types of ER, ER α and ER β , encoded by *ESR1* and *ESR2*, respectively.^{7,41,44} In the prostate, ER α is expressed in a few stromal cells, whereas ER β is highly expressed in the epithelium and some stromal cells.⁴⁵

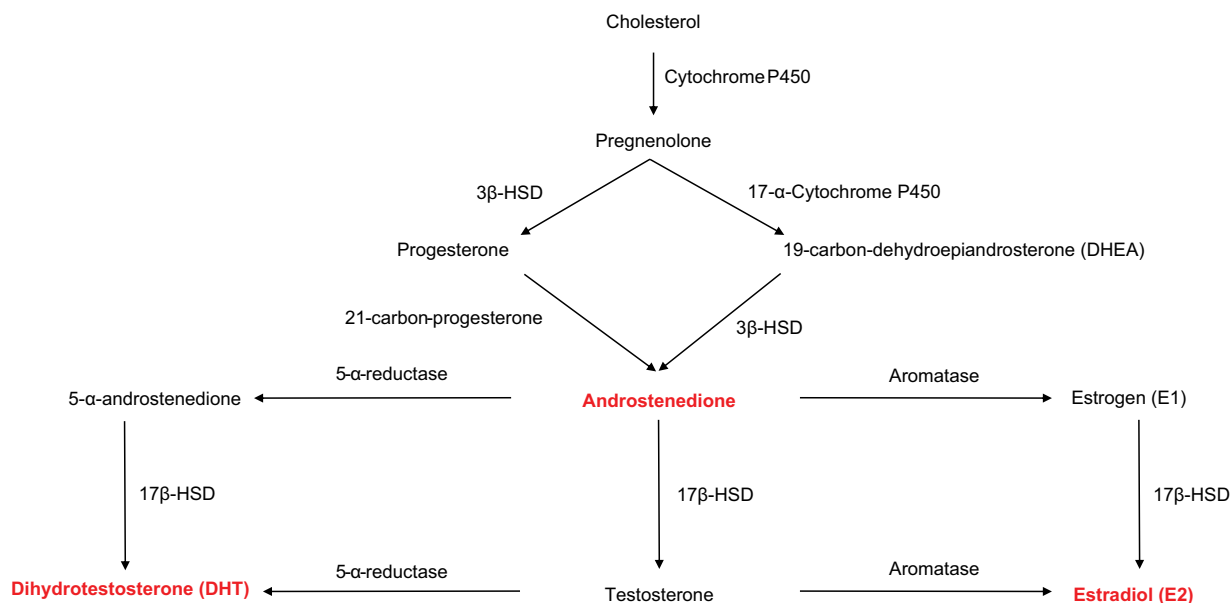


Figure 1 Schematic drawing of the reaction cascade leading to the synthesis of testosterone, dihydrotestosterone, and estradiol from cholesterol. **Abbreviations:** 3β-HSD, 3β-hydroxysteroid dehydrogenases; 5-α-reductase, 5-alpha-reductase; 17β-HSD, 17β-hydroxysteroid dehydrogenases.

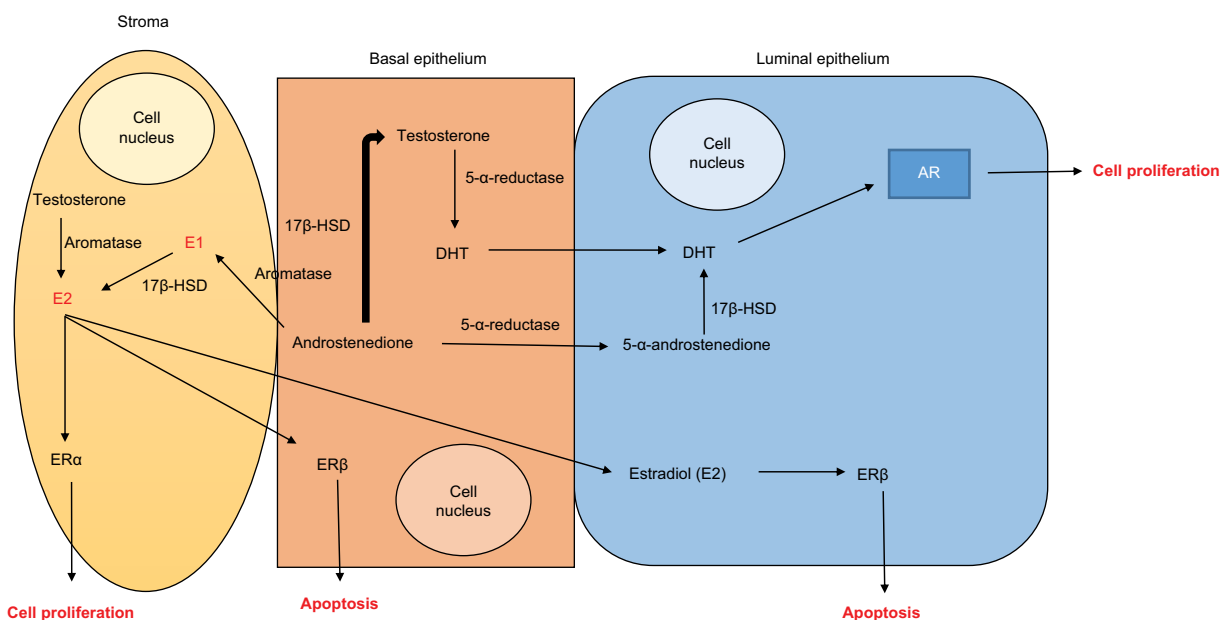


Figure 2 Schematic drawing of the synthesis of the active hormones dihydrotestosterone and estradiol from testosterone and androstenedione and binding of sex hormones with their receptors in the prostatic tissue.

Abbreviations: AR, androgen receptors; DHT, dihydrotestosterone; E1, estrogen; E2, estradiol; ERα, estrogen receptor alpha; ERβ, estrogen receptor beta; 5-α-androstenedione, 5-alpha-androstenedione; 5-α-reductase, 5-alpha-reductase; 17β-HSD, 17β-hydroxysteroid dehydrogenases.

Upon activation, ERα and ERβ translocate from the cytoplasm to the nucleus, where they activate DNA transcription by recruiting cofactors such as specific protein 1 (SP-1), activator protein 1 (AP-1), and nuclear factor κB.^{41,46} In addition, such binding may stimulate further production of E1 and E2, inducing cell proliferation or apoptosis.

During this new transcription tape, SP-1 becomes the predominant mediator of the ER–DNA interaction and stimulates the expression of *ESR2*.⁴¹ In addition, E2 can activate the production of endothelial nitric oxide,⁴⁷ which leads to relaxation of the arterial tunica media via increased blood perfusion of the prostatic tissues.

A number of studies have shown that AP-1 increases the binding of ER α and ER β to DNA.⁴⁸⁻⁵⁰ Moreover, the association of ER α and AP-1 promotes cell proliferation and can promote neoplasias by E2F1 and cyclin D1 co-regulation. Notably, ER β activation by AP-1 only results in cyclin D1 transition and activation.⁴¹

A study conducted in rats reported an alternative ER α -dependent activation mechanism, consisting in direct E2 binding to ER α , at the plasma membrane or in the cytoplasm, forming a complex that functions as a transcriptional activator. This pathway generates a faster DNA transcription response and plays a crucial physiological role.⁵¹

In addition, unlike ER β , which can induce apoptosis, ER α activates the proliferation of prostatic cells.^{44,52} There is a clear difference in the actions of ER α and ER β , as well as in the adverse events possibly caused by estrogen binding to the two receptors. Estrogen binding to ER α is associated with cell proliferation and inflammation of the prostate, whereas estrogen interaction with ER β appears to mediate antiproliferative, anti-inflammatory, and potentially anticarcinogenic effects.⁸ Zhang et al⁵³ reported that patients with BPH exhibit a decreased ER α expression, whereas ER β expression is not affected.

PGR receptors

PGR is a typical female hormone, although it is also synthesized in the adrenal glands and the Leydig cells through the action of 3 β -HSD. Its production occurs through the classical pathway of cholesterol synthesis and can generate TT and estrogen.⁵⁴⁻⁵⁶

PGR binds PR, which belongs to the superfamily of steroid receptors.⁵⁷ Three different human PR isoforms exist, ie, PRa, PRb, and PRc. However, only PRa and PRb are functional.⁵⁸⁻⁶¹

Compared to PRb, PRa contains 164 extra amino acids at its amino terminus.⁶² PRa regulates the transcription of the gene encoding PRb. The two isoforms have been associated with distinct physiological functions and are present in different intracellular concentrations. Moreover, studies have reported that PRa can inhibit the production of PRb.^{63,64}

In 1970, E2 was proposed to bind to PR by virtue of its higher specificity for this receptor, compared to PGR.⁶⁵ Furthermore, Kastner et al⁶⁶ described that PRa expression is controlled by ER α and PRa controls the intracellular concentrations of PRb of both receptors.

Cell culture studies reported that ER α interacts with SP-1 and AP-1, thereby controlling the expression of PR.^{67,68} However, other studies using the same cell line suggested

that ER α binds to regulatory regions of the PR gene rather than acting directly on the PR synthesis and did not affect the production of the PR isoforms.^{69,70}

Therefore, ER α is associated with the transcription of the PR gene only as a recruiter of transitional co-regulators that are dependent on the PR gene.⁷⁰ These co-regulators alter the chromatin and activate the DNA transition. However, the transcriptional activation of the PR gene isoforms depends primarily on the status of DNA methylation and chromatin as their promoters.⁷¹

Thus, it demonstrates that the synthesis of PR isoforms is much more complex than the ER synthesis, as it encompasses several mechanisms of PR gene regulation.⁶² Some studies have indicated that, in humans and rats with BPH, a higher expression of PGR is associated with an increased proliferation of prostatic stromal cells.^{1,57}

Clinical correlation and the role of AR, ER, and PR in BPH

The role of sex receptors and hormones in the progression and development of BPH has been discussed for decades and pharmacological treatments targeting the hormone-receptor interaction have been developed and described. The most effective and utilized treatment worldwide is based on 5-alpha-reductase enzyme inhibitors.^{3,25,28} However, various studies have reported that this treatment generates changes in the morphology of the corpus cavernosum that are linked to erectile dysfunction, after or during therapy.^{3,72,73}

Despite the availability of effective pharmacological treatments, little is known about the progression of BPH. One hypothesis is that the abnormal expression of AR receptors in the prostate stroma leads to enhanced DHT binding to AR, thereby resulting in increased cell proliferation.¹² However, in patients with BPH, the levels of TT are low, contradicting the theory that TT is responsible for the progression of BPH.

An abnormal expression of AR in the prostate could derive from CAG and GGC repeat polymorphism in the AR gene.^{18,19,21} However, Weng et al⁷⁴ showed that CAG is linked to prostate cancer but not to BPH in Caucasian men.

The observation that serum levels of TT in patients with BPH are reduced generates uncertainty about the biogenesis of intraprostatic DHT. We believe that this phenomenon could be related to the reaction converting androstenedione to α -androstenedione, catalyzed by 5-alpha-reductase, followed by 17 β -HSD-mediated α -androstenedione conversion to DHT. This may explain the presence of intraprostatic DHT in the serum of patients with BPH, even in the absence of high levels of TT.

17 β -HSD is extremely important as it converts androstenedione into TT, α -androstenedione in DHT, and E1 into E2. Thus, this enzyme is considered a potential therapeutic target for BPH. However, the efficacy of 17 β -HSD inhibitors, as well as their possible adverse effects, are still a matter of intense debate, and additional studies are needed to definitively clarify this issue.^{12,20}

Another question that should be addressed is the role of aromatase, which is expressed in the prostate stroma and can convert TT to E2 and androstenedione to E1. Increased aromatase activity in the stroma can affect the local production of precursor estrogens, leading to increased estrogen and disproportionate levels of androgens.¹²

The inhibition of aromatase activity reduces intracellular E2 concentrations, and may allow control of the synthesis ER receptor, representing another potential therapeutic strategy for BPH.¹² However, further studies are needed to determine whether the inhibition of aromatase can reduce prostate cell proliferation in patients with BPH.

Another “hot topic” is the abnormal overexpression of ER in the prostate stroma and the epithelium of BPH patients. Several studies indicate that ER α and ER β control proliferation and apoptosis in the prostatic tissue.^{12,41,75}

ER α may associate with excessive proliferation, inflammation, and, possibly, carcinogenic effects. In contrast, ER β appears to be responsible for antiproliferative, anti-inflammatory, and anticancer effects. At puberty, the serum levels of testosterone are elevated over time but decreasing levels may correlate with the action of aromatases. By raising the E2-to-TT ratio, aromatase causes an increase in serum estradiol levels.⁷⁶ Men with BPH have higher levels of E2 than patients without BPH^{77,78} and, surprisingly, ER β was found to be linked to prostate cancer.⁷⁶ This reinforces the theory that ER α receptors are responsible for the development of BPH.^{45,76}

Circulating and intraprostatic E2 levels increase with age, eventually activating extracellular signal-regulated kinases 1/2 (ERK1/2), responsible for cell proliferation.⁷⁷ Increased differentiation and proliferation of smooth muscle cells.^{78,79} Cell replication triggers a series of changes in stromal cells, including loss of expression of G protein-coupled receptor 30 (GPR30), a proliferation factor downstream of E2, ER α , and ER β . It is believed that, as a consequence of ERK1/2 activation, an epigenetic inhibitory change occurs in the promoter of the GPR30 gene.^{80,81} With the activation of ERK1/2 and cell differentiation, there is an increase in the expression of TGF β 1, which is responsible for stromal cell growth and differentiation.⁸²

Increased production of ER α is related to high concentrations of E2 and ER α controls the synthesis of PR.^{62,67,68} A study of patients with BPH showed an increase of PR in the prostate stroma, demonstrating that the expression of ER α and PR receptors were tightly linked and were linked to complex mechanisms of receptor synthesis,⁸³ and no PR was found in the prostate stroma of patients with BPH.⁸⁴ Rather than reducing its expression with the ER α demonstrating that PGR may be a promoter of BPH.^{85–87}

A new pharmacological strategy against BPH may be based on the modulation of specific ERs. For instance, the use of ER α antagonists and ER β agonists has been proposed.⁸ Moreover, the inhibition of intraprostatic E2 synthesis can be achieved through modulation of 17 β -HSD, resulting in a decreased rate of E1-to-E2 conversion and reduced prostatic cell proliferation.⁸⁸ In accordance with these findings, ER β agonists have been reported to decrease prostate cancer and BPH in humans.⁵²

However, other studies found higher expression of AR and PR, compared to ER α , in the prostate stroma of animals with BPH. This may indicate that AR and PR play a role in the pathogenesis of BPH, whereas ER α only regulates PR production.^{1,44,53,76,89,90}

In normal prostate and BPH samples, ARs are located in the nuclei of stromal, as well as luminal and basal epithelial cells. TT and DHT bind to ARs, influencing the BPH growth factors. The increased expression of prostatic epithelial AR might contribute to enhanced cell proliferation and is one of the possible causes of BPH.^{91–93}

Androgens play several roles in prostate maintenance. Notably, TT supplementation to castrated animals restored the prostate architecture.⁹⁴

Patients with deficiency of the enzyme 5-alpha-reductase exhibit reduced serum and intraprostatic levels of DHT and normal growth and development of the prostate gland.²⁰ DHT deficiency can be associated with a decline in serum androgen levels and is characterized by numerous clinical symptoms.⁹⁵

Conclusion

E2 has a major influence on the expression of the ER α -encoding gene, *ESR1*. We conclude that ER α controls the synthesis of ER β and has an impact on cell proliferation and apoptosis, thereby affecting the risk of BPH and prostate cancer. In addition, ER α can stimulate the synthesis of PR, exerting proliferative effects on the prostate gland and possibly causing BPH. Thus, alterations in E2 levels may represent a major cause of BPH. However, robust evidence indicates that a major pathogenetic factor for BPH is rep-

resented by ARs. Notably, the binding of DHT to AR can stimulate cellular proliferation factors. The origin of DHT in men with BPH is unclear, as these patients have low serum and intraprostatic levels of TT. We believe that a possible explanation may reside in the 17 β -HSD-mediated conversion of 5- α -androstenedione to DHT. In line with this hypothesis, 17 β -HSD inhibitors interfere with BPH progression. However, additional studies on the role of 17 β -HSD and E2 in the prostate of patients with BPH are necessary to definitively solve this issue.

Disclosure

The authors report no conflicts of interest in this work.

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