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BPH and Prostate Diseases
Review

Understanding the role of estrogen in the development of benign prostatic hyperplasia

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Abstract
Introduction: Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate that affects ageing men. As the number of men affected by this condition will only continue to grow with the aging population, finding new strategies and new therapeutic options for its treatment is crucial. Androgenic hormones have been known to play an important role in the development of BPH and they have been a target in its medical treatment. Estrogens have also been implicated in BPH but in contrast to androgens, the functions of estrogens in the prostate are still obscure.
Objective: This review aims to highlight the roles of estrogen in the development of BPH.
Methods: Authors reviewed the literature covering the past forty years to highlight the roles of estrogen in the prostate and BPH. Data from authors' experimental work in this field was also referenced.
Results: The effects of estrogen in the prostate are mediated by estrogen receptors alpha and beta (ERα and ERβ). These two receptors have different expression and functions in the prostate, thereby presenting a window of opportunity to selectively target them for therapeutic purposes in BPH. The actions of estrogens, as mediated by estrogen receptors, appear to contribute to the development of BPH in men through an intricate molecular process that is yet to be fully elucidated. Although surgery remains the gold standard in the treatment of BPH, understanding the elusive role of estrogen in BPH, in addition to the established role of androgens, would enhance the current therapeutic options and perhaps lead to the development of new therapies. There are indications that phytoestrogens might be beneficial in the management of BPH.

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Conclusion: This review highlights the roles of estrogen as well as the therapeutic use of phytoestrogens in the prevention and management of BPH.

Introduction

Benign prostatic hyperplasia (BPH), also referred to as benign prostatic hypertrophy, is a non-malignant enlargement of the prostate gland affecting aging men [1]. BPH is the most common condition affecting men and is present in 50% of men aged above 60 years of age, while over 80% of men above 80 years show histological evidence of BPH, [2–4], the incidence and symptom severity of which is known to be affected by race and ethnicity [5].

The prostate is an accessory reproductive organ in the male that functions in sperm transport and nourishment. Although there is a considerable diversity in morphology across species, the human prostate, which is a sex hormone dependent organ, is ovoid shaped and located at the neck of the bladder. The human prostate consists of both glandular and fibromuscular tissues and is made up of three histological zones which are central, peripheral and transition zones with clinically significant BPH occurring mainly in the transition zone of the prostate [6,7]. The transition zone, which is located in the periurethral area of the prostate gland, accounts for approximately 5% of total prostate volume although the factor responsible for proliferation within this zone is currently unknown [7].

BPH is characterized by stroma and epithelia hyperplasia of the prostate gland, especially at the transition zone, and can cause narrowing of the urethra as it passes through the prostate causing bladder outlet obstruction. BPH and bladder outlet obstruction cause a cluster of urinary difficulties ranging from storage to voiding such as nucturia and increased urinary frequency [8–10]. These urinary voiding problems are generally referred to as lower urinary tract symptoms (LUTS) [10]. LUTS significantly affects quality of life as a significant number of men reaching 80 years are said to require surgical intervention [11].

Androgenic hormones have been known to play an important role in the development of BPH [9] and they have been a target in its medical treatment. However, androgens might not be the only significant hormone in BPH since estrogen is also a metabolite of testosterone. Consequently, the induction of BPH that is attributed to androgens might also be due to estrogens. This review highlights the roles of estrogen in the prostate as well as the potential therapeutic use of phytoestrogens in the management of BPH.

Etiology of BPH

Many theories have been postulated to explain how BPH develops. This includes embryonic reawakening, androgens, estrogens, aging and inflammation [12,13]. Although aging and hormonal alterations appear to be the two main factors responsible for the development of BPH [9], data has also shown prostate growth rate to be higher in BPH patients with metabolic conditions such as insulin resistance syndrome, abdominal obesity, hypertension, hyperglycemia and reduced level of high density lipoprotein [14]. Age has been proved to play a role in the progressive development of pathologic and clinical BPH as virtually all men present with histological BPH as they grow [1,11]. However, the precise etiology of BPH has not been absolutely unraveled.

Pathological BPH develops when there is hyperplasia in epithelia and stromal growth that coalesces into microscopic and macroscopic nodules in the prostate gland. It is a phase in the development of benign prostate hypertrophy that involves the microscopic stage which in turn leads to the macroscopic stage and neither of these produces symptomatic clinical dysuria. Although all men will eventually develop microscopic stage of BPH with advancement in age, only about half of the men having microscopic benign prostatic hyperplasia are likely to develop macroscopic enlargement of the prostate gland. It is possible though that all the BPH nodules might possibly be initiated by different molecular mechanisms giving room for multiple theories to explain the distinct types of BPH. A hormonal theory involving dysregulation of stroma-epithelial interaction is believed to be responsible for BPH development although the pathogenesis is not yet absolutely clear [9].

Androgenic hormones

Androgenic hormones include testosterone, dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), androstenedione and 5α-androstenedione. Androgens are synthesized from cholesterol. Testosterone is the main circulating androgen in men and it's important for the development of accessory sex organs and secondary sexual characteristics. About 90% of testosterone production is by the testes while the rest comes from the adrenal glands. Circulating testosterone is mostly bound to sex hormone binding globulin (SHGB). DHT, the most potent androgen in men, is metabolized from testosterone through the activity of 5α-reductase enzyme. DHT plays a crucial role in the differentiation and growth of the prostate gland during fetal development as well as in the development of male external genitalia and secondary sexual characteristics [15]. In the prostate, testosterone is converted to DHT by the membrane bound NADPH-dependent enzyme, type II 5α-reductase. Although the pathogenesis of BPH is not completely understood, the presence of androgens appears to be permissive in the development of BPH [9]. Inhibition of the production or actions of DHT can result in the inhibition of the growth of the prostate gland. There is substantial clinical evidence that androgen and DHT play a key role in the development of BPH [2,16,17].

Estrogen and their roles in BPH

Androgens might not be the only significant hormone in the development of BPH since estrogens, some of which could be synthesized from testosterone, can also influence normal prostate gland functions and may well potentiate pathological growth [18]. Estrogens within circulation can either be endogenous or exogenous. Endogenous estrogens are mostly produced by the gonads and they include: estrogen (E1), estradiol-17β (E2) and estriol (E3). Estrogen (E1) is produced from testosterone through the activity of aromatase enzyme although it is a weak estrogen with minimal influence on estrogenic pathways within the prostate. Estradiol-17β is formed from aromatization of testosterone mainly in fat and muscles while up to 20% is produced from the Leydig cells in the testis. Such local production of estradiol-17β has been implicated in BPH [19].

Estrogen plays an important role during prostate development and studies have shown that excessive estrogenization during prostatic development may contribute to the high incidence of BPH currently observed in the aging male population. Neonatal exposure to estrogen interrupts normal prostate development. Serum and intraprostatic estradiol levels tend to increase in men with age despite decreasing levels of estrogen and testosterone and patients with larger volumes of BPH tend to have high levels of serum estradiol [20–23]. Adipose tissues express aromatase enzyme, which converts testosterone to estrogen. Adiposity tends to increase with aging. Conversely, testosterone production by the testes tends to decrease with aging. Thus, aging results in a significant increase in the relative level of estrogen compared to testosterone. The estrogen-dominant status in men after middle age may therefore be the most significant factor in the induction and progression of BPH [20]. In addition, estrogen action in the prostate may be independent of serum levels of estrogen since estrogen is produced locally within the prostate via conversion of testosterone to 17β-estradiol by aromatase enzyme expressed within the prostate stroma [24].

Estrogen effects on the prostate gland may also be indirectly mediated through alterations in other serum hormones. Estrogens stimulate the pituitary release of prolactin and prolactin induces prostate enlargement and decreased apoptosis [25]. Also, estradiol inhibits luteinizing hormone secretion and production of androgens by the testis. Besides these indirect effects, many of the estrogenic effects on the prostate are directly mediated through prostatic expression of estrogen receptors [26,27].

Estrogen receptors

Estrogen receptors (ERs) are members of the steroid hormone nuclear receptor superfamily found ubiquitously throughout the animal kingdom. These ligand-activated transcription factors mediate the actions of estrogens and are classified as estrogen receptor alpha (ERα) and estrogens receptor beta (ERβ) [28]. The human ERα gene, located on chromosome 6, encodes 595 amino acids with a molecular weight of 66 kDa while ERβ gene, located on chromosome 14, encodes 530 amino acids with a molecular weight of 54 kDa. ERs are composed of 6 functional modules; an N-terminal (NTD) also called A/B domain, a DNA-binding (C) domain, a hinge (D) region, ligand-binding (E) domain and a C-terminal F domain [29].

The A/B domain of ERs accommodates the AF-1 (activation function-1) domain and specifies the cell and promoter-specific activity of the receptor as well as co-receptor protein interactions. The A/B domain accounts for the greatest structural disparity with only about 30% homology between the two ERs while ERα is about 90 nucleotides longer than ERβ. The C domain functions in the recognition and binding of the receptors to *cis*-acting enhancer DNA sequences or estrogen response elements (ERE) located within regulatory regions of target genes. The C domain is the most highly conserved region with about 95% homology between the two ERs hence, the similarity in affinity for the same EREs by ERα and ERβ. The D domain, with about 30% homology, harbors a nuclear localization signal that influences cellular compartmentalization of the receptor. The E domain is a highly structured, multifunctional region that serves to specifically bind estrogens and provide for ligand-dependent transcriptional activity. Also harbored within the E domain is a strong receptor dimerization interface with about 60% homology in the primary sequence of the E region of two ERs. The F domain, which has about 20% homology, encodes the AF-2 (activation function-2) domain and functions in receptor stability and co-activator recruitment [28–31].

ERα is localized in the prostate stroma while ERβ is present in both epithelia and stroma [32]. These receptors bind endogenous estrogens in prostate tissue and regulate prostate gene expression. ERα promotes inflammation and hyperplasia while ERβ serves to exert antiproliferative and proapoptotic effect in the prostate [33]. Due to the difference in the homology between ERα and ERβ, their binding affinities for certain ligands also differ. This results in a situation where some estrogen receptor ligands selectively modulate estrogen action in the prostate. This class of compounds is collectively referred to as selective estrogen modulators (SERMs). Phytoestrogens have also been observed to selectively target ERs [34].

Phytoestrogens

The demand for complementary and alternative therapies, including an interest in the use of phytotherapy has increased in recent times [35]. This is especially important as some of the medications currently in use for the treatment of BPH have undesirable adverse effects [36,37]. Phytoestrogens, which are naturally occurring compounds from plants that mimic estrogens, have been known to be used in the treatment and prevention of BPH. The major classes of phytoestrogens include isoflavones, lignans and coumestans [35,38–40]. Isoflavones are perhaps the most researched class of phytoestrogens. They are polyphenolic compounds which are naturally found conjugated to sugar molecules as biologically inactive glycosides. Upon the breakdown of isoflavone glycoside conjugates, the sugar molecules are released resulting in biologically active isoflavone aglycones such as genistein, daidzein, and glycitein. Isoflavones are most abundant in legumes like soybeans, as well as in grains, nuts wine and berries [41]. Lignans are constituents of plant cell walls and found in many fiber-rich foods and fruits such as wheat, barley, rice, linseed, cherries, apples, pears and garlic [35,40,42]. Coumestans are phenolic phytoestrogens with coumesterol being the major constituent of this group. Coumestans are known for a variety of biological activities and they can be found in alfalfa, clover and the sprout of beans [40].

The consumption of plants such as soy, red clover, African plum tree, pumpkin seed and saw palmetto for health benefits, partic-

ularly in ameliorating the symptoms of BPH is well documented [43–46]. Several experimental animal studies have shown the benefits of phytoestrogen in the treatment of BPH [18,34,47–50]. For example, the ethanolic extract of *Echinops echinatus* was shown to confer considerable improvement on the prostatic histoarchitecture of testosterone-induced prostatic hyperplasia in rats [2]. Also, the aqueous extract of bitter leaf (*Vernonia amygdalina*) has been shown to ameliorate testosterone-induced BPH in an experimental animal model [50,51]. Red maca (*Lepidium meyenii*), a cruciferous plant from the highland of Peru, was likewise shown to have reduced the ventral prostate size in normal and testosterone-treated rats [47]. The possible mechanisms of action of phytoestrogens may be related to their structural similarity to estrogens and their ability to act as weak agonist or antagonists of estrogen. They could also act as anti-androgens by competing for androgen receptors and by regulating the activity of 17-hydroxysteroid dehydrogenase, an enzyme that is involved in the metabolism of testosterone [35].

Clinical management of BPH with saw palmetto is very popular [52–55]. Though saw palmetto extract has been shown to be beneficial in the treatment of LUTS that is associated BPH [56], the outcome of clinical trials has not convincingly proved its efficacy compared with placebo [57]. Perhaps this is due to different formulations of saw palmetto extract used in these studies and inherent flaws in the research designs of some of the studies. Hence, it would be necessary to conduct vigorous research and clinical trials to prove the effectiveness or otherwise of saw palmetto extract in the treatment of BPH. Meanwhile, the current status of saw palmetto extract in the treatment of BPH is that it is safe and could be effective, particularly in improving nocturia and other self-reported symptoms [58].

Conclusion

BPH is a non-malignant enlargement of the prostate that affects a significant population of men above 50 years with substantial effect on quality of life. The actions of estrogens, as mediated by estrogen receptors, appear to contribute to the development of BPH in men through an intricate molecular process that is yet to be fully elucidated. Although surgery remains the gold standard in the treatment of BPH, understanding the elusive role of estrogen in BPH, in addition to the established role of androgens, would enhance the current therapeutic options and perhaps lead to the development of new therapies. Therapeutic use of phytoestrogens could be further explored to better harness phytoestrogens in the prevention and management of BPH.

Authors' contribution

A. Ajayi conceived the work, authored and edited the manuscript. K. Abraham authored and edited the manuscript.

Conflict of interest

Authors declare no conflict of interest.

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