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Review Article

5α-Reductase Inhibitors in the Treatment of Benign Prostatic Hyperplasia: A Review

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Abstract

Prostate Cancer and Prostatic diseases have become the major causes of concern to elderly men almost in every part of the world. One of the major problems faced by most of the aging men is Benign Prostatic Hyperplasia (BPH). There are varieties of treatments available but no of them have proved to be up to the mark. Most of the synthetic molecules suffer from the drawback of substantial side effects. The enzyme 5α-reductase has been found to be the major factor which plays an important role in the progression of the disease as it is the mediator in the conversion of testosterone to the more harmful dihydrotesterone. The inhibition of this conversion can help prevent BPH. Present review is an effort to list the studies undertaken on 5α-reducatse inhibitors from synthetic and natural origin and the results obtained thereof. This could provide a substantial lead to further research in this area and help in the treatment of BPH.

Keywords: 5α-reductase; Benign Prostatic Hyperplasia; Finasteride; *Ganoderma lucidum*; Prostate disorders; Testosterone

Background

Benign Prostatic Hyperplasia (BPH) has the pathogenesis of an androgen dependent disorder and afflicts a large population of elderly men with chronobiologic progress. BPH does not occur in men castrated prior to puberty, and in a variety of medical conditions whereby testosterone production or function is inhibited, the prostate does not develop normally. In addition, hypogonadal men do not become bald, and hair loss can be induced by testosterone administration to these individuals. Androgens, particularly 5α-Dihydrotestosterone (DHT), are required to maintain the size and function of the prostate in men and are thought to play a major role in the pathogenesis of BPH, prostate cancer, acne and androgenetic alopecia. Because DHT is produced from Testosterone (T) by 5α-reductase (5α-R), this enzyme plays a key role in DHT- mediated effects of BPH and androgenetic alopecia. Androgens are believed to act on the hair follicle via the mesenchyme-derived dermal papilla situated in the middle of the hair follicle bulb. The individuals with autosomal recessive genetic disorder of 5α-R deficiencies do not exhibit androgenetic alopecia, suggesting that DHT is the active androgen in the development of hair loss. The normal growth and secretory activities of the prostate are controlled by androgens, especially by DHT. These observations lead to the development of 5α-R inhibitors like finasteride, which lowers DHT concentration in the prostate without increasing circulating testosterone levels.

The NADPH dependent membrane bound enzyme 5α-R catalyses reduction of the 4-5 double bonds in a variety of steroids. Although the enzyme has both catabolic and anabolic functions, the primary and interesting function is anabolic, i.e. the conversion of T to the more potent androgen 5α-DHT. Studies of 5α-R have been facilitated by the modification of cDNA's coding for the enzyme [1]. Inhibition of 5α-R and limiting DHT production provides a useful approach to androgen deprivation, which may be a useful treatment for 5α-R activity disorders. Any such product that limits local DHT production could be a potential therapeutic agent. Also, an anti-androgen, which specifically blocks 5α-R activities without binding to androgen receptor, would attenuate the action of testosterone.

Types of 5α-Reductase Enzymes

Two isoforms of 5α-R exist, namely type 1 and type 2, which are characterized by distinct molecular genetics, structural and biochemical properties and by different tissue localization. Type 2 isozymes are found predominantly in the prostate, genital skin, seminal vesicles and in the dermal papilla, while type 1 isozymes occur predominantly in non-genital skin, the scalp, the sebaceous gland, the liver and the brain. Type 2 5α-R is expressed in scalp skin for a short period after birth. Both isozymes are expressed at a much lower level in other peripheral tissues, including skeletal muscle and pituitary. Due to the tissue specific expression of 5α-R, prostatic DHT concentration is much higher than prostatic testosterone concentration [2].

Moreover, other important information on the role of the two 5α-R isozymes in the pathogenesis of DHT-related disorders comes from the clinical evidences of 5α-R 2 deficiency. Male pseudohermophroditism, in which total or partial deficiency of 5α-R 2 has been found, demonstrates that the type 2 isozymes are essential for differentiation of male external genitalia during fetal life. In these individuals, the prostate remains undeveloped, facial and body hair growth patterns are more feminine in character, and temporal regression of the hairline is significantly reduced, sebum production rate is instead unchanged with respect to normal individuals indicating that 5α-R 2 is involved in prostate diseases and to some extent in AGA but probably not in acne [3]. For this reason, the development of isozymes specific inhibitors became an important pharmacological target for the treatment of DHT related pathologies.

Mechanism of Androgen Action in BPH

Androgens (Testosterone and related hormones) are considered to play a permissive role in BPH. This means that androgens have to be present for BPH to occur, but do not necessarily directly cause the condition. This is supported by the fact that castrated boys do not develop BPH when they age, unlike intact men. Additionally, administering exogenous testosterone is not associated with a significant increase in the risk of BPH symptoms. Dihydrotestosterone (DHT) is a critical mediator of prostatic growth. DHT is synthesized in the prostate from circulating testosterone. DHT is localized principally in the stromal cells. Once synthesized, DHT can act in an autocrine fashion on the stromal cells or in paracrine fashion by diffusing into nearby epithelial cell. In both of these cell types DHT bind to nuclear and androgen receptors and signals the transcription of growth factors that are mitogenic to the epithelial and stromal cells. The importance of DHT in causing nodular hyperplasia is supported by clinical observations in which an inhibitor of 5α-R is given to men with this condition. Therapy with 5α-R inhibitor markedly reduces the DHT content of the prostate and in turn reduces prostate volume and in many cases, BPH symptoms [4].

5α-Reductase Inhibitors

The inhibitors of 5α-reductase isozymes (Type 1 and Type 2) can be schematically divided into three groups according to their substrate specificity.

1. Pure or preferential inhibitor of 5α-R type 1, e.g. *Angelica koreana* methanolic extract. The 5α-R type 1 inhibitors seem to be ideal drugs for treatment of acne and hirsutism.
2. Pure or preferential inhibitor of 5α-R type 2, e.g. Finasteride, a selective 5α-R type 2 inhibitor, used in the treatment of AGA and BPH, and
3. Dual inhibitors or non-selective inhibitors e.g. Dutasteride, reduces the scalp DHT in bald men to a greater extent than Finasteride.

Most of the 5α-R inhibitors are steroidal derivatives or compounds with steroid like structure, e.g. Finasteride, 4-azasteroid etc. The steroidal inhibitors have the possibility of an affinity for androgen receptors and expected to produce undesirable effects such as impotence, impairment of muscle growth etc. On the other hand, fewer naturally occurring non-steroidal 5α-R inhibitors have also been reported, e.g., unsaturated fatty acids, etc.

Synthetic Drugs as 5α-Reductase Inhibitors

Mellin, et al. (1993) [5] found that 4-azasteroids are efficient inhibitors of human skin 5α-R and offer a good treatment for acne, hirsutism and AGA [5]. Giudici, et al. (1996) [6] reported FCE 28260 as a highly potent inhibitor of human recombinant 5α R type 2 and 1 isozymes; it was more potent than finasteride on both isozymes [6]. Igarashi, et al. (1999) [7] found a new series of phenoxybenzoic acid derivatives as potent human prostatic 5α-R inhibitors [7]. Igarashi, et al. (2000) [8] presented a series of indole derivatives that showed potent inhibitory activities for human prostatic 5α-R [8]. Cabeza, et al. (2001a) [9] synthesized two new steroidal compounds from 16-dehydropregnenolone acetate, and reported their 5α-R inhibitory activity [9]. Cabeza, et al. (2001b) [10] reported 5α-R inhibitory activities of 4 new progesterone derivatives. P-substituted benzoyloxy compounds were found highly potent [10]. Ramirez et al. (2002) [11] determined the 5α-R inhibitory activity of several new 16- methyl pregnane derivatives *in vitro* [11]. Cabeza, et al. (2002) [12] reported that 16-bromosubstituted trienediones, 16-methyl substituted dienediones, and 16-methyl substituted trienediones inhibit the activity of 5α-R and exhibit a very high affinity for the androgen receptor [12]. Pérez-Ornelas, et al. (2005) [13] reported the *in vitro* and *in vivo* 5α-R inhibitory activity of several new 3-substituted pregna-4, 16-dehydro-pregnenolone acetate [13]. Festuccia, et al. (2005) [14] reported the inhibition of 5α-R type 1 and 5α-R type 2 by MK386 and MK906 respectively. They suggested that these might have therapeutic potential to reduce the growth of prostate through the inhibition of autocrine or paracrine mechanism involving stromal cell compartment [14].

Marketed 5α-Reductase Inhibitors

There are two 5α-reductase inhibitors approved by the FDA-Dutasteride and Finasteride. Dutasteride inhibits both type 1 and type 2 isoenzymes whereas finasteride inhibits only the type 2 isoenzyme. Clinical effects of 5α-reductase inhibitors include decrease in serum DHT, decrease in serum PSA, decreased risk of symptomatic progression of BPH, reduction in risk of acute urinary retention, reduction in need for surgery for BPH, decreased risk of prostate cancer, and prevention of gross hematuria secondary to BPH [15]. Although various approaches involving attenuation of androgenic stimulation of prostatic growth and the use of 5α-reductase inhibitors such as finasteride, dutasteride and epristeride have been employed, but their use is limited by multiple side effects. Finasteride can cause adverse effects such as gynecomastia, impairment of muscle growth and severe myopathy due to the structural similarity to steroidal hormones. However, the magnitude of therapeutic effect produced by finasteride is relatively small, and a clinically significant benefit is observed in less than half of the treated patients [16]. Sexual adverse effects, such as decreased libido, erectile dysfunction, and decreased ejaculate, have been reported [17]. Thus, it may be rewarding to look into traditional herbal medicines for the management of BPH.

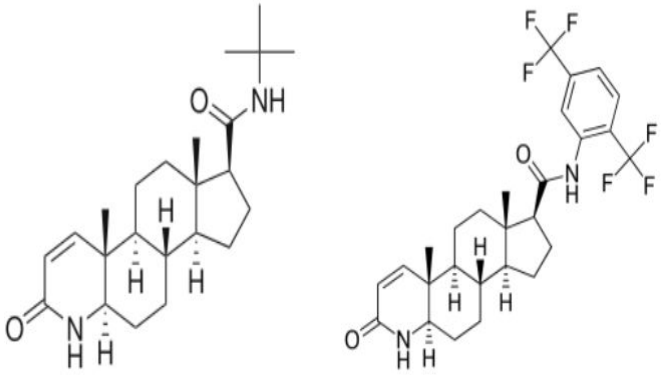

Figure 1: Chemical Structures of Finasteride and Dutasteride.

Herbal Drugs as 5α-Reductase Inhibitors

Komoda (1989) [18] isolated the inhibitors of 5α-R from 50% ethanolic extract of *Populus nigra*. The compounds were identified as pinobanksin, 8, 7-dimethyl quercetin and pinocembrine. Pinocembrine showed most potent activity among them [18]. Liao and Hiipakka (1995) [19] reported that green tea catechins, (-) epigallocatechin-3-gallate and (-) epicatechin-3-gallate are potent inhibitors of 5α-type 1 but not 5α-R type 2 [19]. Lesuisse, et al. (1996) [20] evaluated the inhibition of 5α-R by the aqueous extract of *Epilobium parviflorum*. The active compound was identified as macrocyclic tannin, oenothein B [20]. Liang and Liao (1997) [21] reported that γ-linolenic acid inhibits 5α-R activity *in vitro* and *in vivo*. The effect of γ-linolenic acid was localized and did not affect the androgen dependent growth of testis and prostate, thus can only be useful for androgen dependent skin disorders [21]. Palin et al. (1998) [22] showed the inhibitory action of *Sereona repens* on prostate porcine microsomal 5α-R activities [22]. *Sereona repens* (Permixon®) at a concentration of 10 µg/ml was shown to be an effective inhibitor of both 5α-R type 1 and 2 isozymes without influencing the secretion of PSA by the epithelial cells [23]. Sundaram, et al. (1999) [24] evaluated the 5α-R inhibitory potential of Prostane, a polyherbal formulation consisting of *Tribulus terrestsis, Areca catechu, Pedalium murex, Caesalpinia bonducella* and *Asparagus racemosus* using rat prostate homogenate as an enzyme source [24]. Ishiguro et al. (2000) [25] investigated that the 35% ethanolic extract of aerial parts of *Impatiens balsamina* has inhibitory activity for testosterone 5α-R [25]. Shimizu et al. (2000) [26] reported the potent inhibitory activity of the methanolic extract of heartwood of *Artocarpus incisus* against 5α-R [26]. Chlorophorin and artocarpin showed more potent inhibitory activity than α-linolenic acid. A geranylated chalcone was isolated from leaves of the plant which showed potent 5α-R inhibitory activity [27].

Shimizu, et al. (2000) [28] reported potent 5α-R inhibitory activity of the acetone extract of *Boehmeria nipononivea*. The active components were α-linolenic, linolenic, palmitic, elaidic, oleic and stearic acid [28]. Matsuda, et al. (2001) [29] showed *in vitro* testosterone 5α-R inhibitory activity of myricanone, myricanol and myricetin isolated from the aqueous ethanolic extract of *Myricae cortex* (bark of *Myrica rubra*) [29]. Matsuda, et al. (2001) [30] reported the testosterone 5α-R inhibitory activity of the diethyl ether extract of rhizomes of *Amenorrhena asphodeloides* [30]. Liao, et al. (2001) [31] reported that certain unsaturated aliphatic fatty acids such as myristoleic acid and other natural compounds alizarin and curcumin are effective 5α-R inhibitors [31]. Seo et al. (2002) [32] isolated a prenylated coumarin, osthenol and a sesquiterpene bisabolangelone from the root of *Angelica koreana* and reported their 5α-R type 1 inhibitory effect in LNCaP cells [32]. Hiipakka et al. (2002) [33] reported that several polyphenolic compounds are potent inhibitors of type 1 and 2 5α-R. Myricetin, querectin, baicalein and fisetin were potent inhibitors type 1 5α-R. Biochanin A, diadzein, genistein and kaempferol were much better inhibitors of type 2 than the type 1 isozyme [33]. Matsuda et al. (2002) [34] reported that the aqueous ethanolic extract of spores of *Lygodium japonicum* showed *in vitro* testosterone 5α-R inhibiting activity [34]. Kim, et al. (2003) [35] evaluated the activity against 5α-R, of four diarylheptanoids from the acetone extract of the rhizomes of *Alpinia officinarium* [35]. Park, et al. (2003) [36] reported that torilin isolated from the methanolic extract of the fruits of *Torilis japonica*, showed potent inhibition against 5α-reductase activity *in vitro* along with demonstrated the inhibitory activity of *Thujae occidentalis* semen extract for 5α-R type 2 isozymes [36].

Liu, et al. (2006) [37] reported that triterpenoids isolated from ethanolic extract of *Ganoderma lucidum* inhibited 5α-R

activity. The presence of the C-3 carbonyl group and of the C-26 α, β-unsaturated carbonyl group was characteristic of almost all inhibitors isolated from *G. lucidum* [37]. *Ganoderma lucidum* has been reported to inhibit testosterone induced prostatic hyperplasia in rats and mechanism of action has been attributed to its activity to inhibit 5α-reductase enzyme [38-40]. Liu, et al. (2007) [41] identified the active principles *in vivo* as triterpenoids and hence suggested that the triterpenoid fraction of *Ganoderma lucidum* can be effective in the treatment of BPH [41]. Further varieties of herbs with proven antiandrogenic activity have been evaluated for their 5α-reductase inhibitory potential and *Ganoderma lucidum* was found to be the most potent among the eleven herbs included in the study [42]. Previously studies have been done on *Benincasa hispida* [43], *Echinops echinatus* [44], *Urtica dioica* [45] and *Sphaeranthus indicus* [46] wherein all the tested herbs have been found to be potent inhibitors of 5α-reductase and had shown their effectiveness in the treatment and management of BPH in rat models. Furthermore, these herbs have shown their effectiveness on human prostate cancer cell lines (PC3 and DU145) proving their potential to be future candidates for cancer research, especially for prostate cancer [47, 48].

Conclusion

The main aim of this review was to shortlist all the drugs useful in the treatment of Benign Prostatic hyperplasia which have 5α-reductase inhibitory activity. Targeting this enzyme for the treatment of BPH is a very important strategy which has proved successful in the research cited in this review and further research in this area may lead to the discovery of some very potent combinations for the treatment of BPH. Molecular level mechanistic studies are a need of the hour for finding a sure remedy of this disease. It can be said that the findings in this area should have a positive impact on the ongoing research on Prostate Cancer too.

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