Finasteride: A Patient Case Exploring the Downstream Effects of a 5α-Reductase Inhibitor

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Abstract

Benign Prostatic Hyperplasia (BPH) is the most common prostate issue for men that are over the age of 50. It affects as many as 75% of men by age 70.[1] A proposed mechanism for the development of BPH is stimulation by dihydrotestosterone (DHT) causing enlargement of the prostate. [2] BPH is commonly treated with finasteride as a first line treatment. Finasteride works on a molecular level as a 5-alpha-reductase inhibitor (5α-RI), which inhibits the human steroid hormone of testosterone from converting into DHT. [3] While finasteride has no noticeable drug interactions, two side effects of this medication are hypotension and decreased sexual drive.

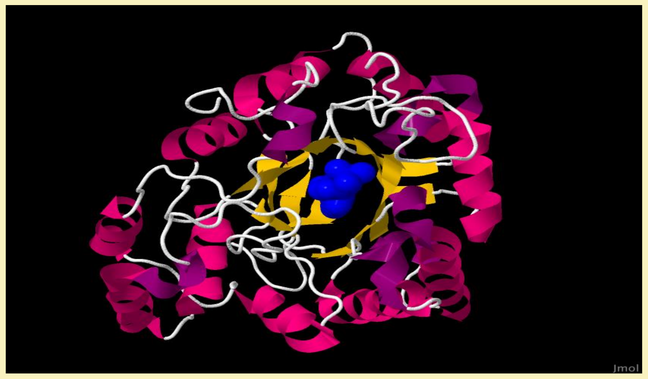


Figure 1. Finasteride (blue) is shown in the binding pocket of 5-β-reductase.

Introduction

In the case we examined, a 57 year old male who was recently diagnosed with BPH. He was taking finasteride and Viagra and had a new prescription for doxazosin to help with both his hypertension and BPH. Finasteride inhibits the enzyme 5α-R, preventing the modification of testosterone to a more potent androgen called DHT. DHT causes prostate growth in older men. It has been shown that men accumulate higher levels of DHT in their prostate as they age. By inhibiting the production of DHT in older men, the effect of DHT on the prostate is diminished or even reversed.

Finasteride, in combination with doxazosin and Viagra (which is also a known vasodilator and may cause a decrease in blood pressure) can potentially increase the hypotensive effect that these medications may exert. Other common side effects of finasteride are impotence and reduced sex drive. The patient is taking an erectile dysfunction medication and the indication may be a result of these side effects. The focus of our research was to describe the therapeutic pharmacology of finasteride and highlight critical drug-receptor interactions which lead to its pharmacologic mechanism of action and resulting side effects.

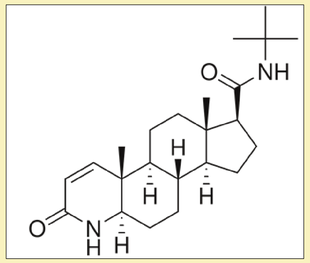


Figure 2. Chemical structure of finasteride.

Molecular Story

Treatment of BPH with finasteride occurs via a manipulation of the hormonal mechanism that pathologically accelerates prostate growth. In androgen synthesis, 5α-R is a key enzyme involved directly in the conversion of testosterone to DHT. The conversion enzyme 5α-R has three isozymes identified as 5α-R1, 2, 3. The 5α-R2 enzyme is shown to be responsible for a majority of DHT synthesis, as opposed to the other isozymes.[4]

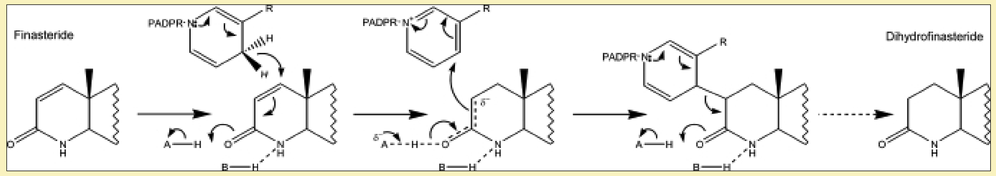


Figure 3. Mechanism-based inactivation of 5α-reductase type 2 by finasteride showing a hydride reaction occurring between finasteride and NADPH that results in a covalent bond between finasteride and the cofactor. [R = -C(=O)-NH2; PADPR = 2'-phosphoadenosine-5''-diphosphoribose; A-H = TYR58.7][4].

Finasteride reduces intraprostatic and serum DHT, reducing the growth rate, halting growth completely, or even reducing the size of the prostate.[2] The downstream effect of 5α-R inhibition by finasteride results in altered gene expression resulting in a reduction of the expression and thus the number of androgen receptors in prostate epithelial cells. The reduction of androgen receptor expression is also correlated with prostatic epithelial cell atrophy which may be contributory to BPH relief, specifically a decrease in size.

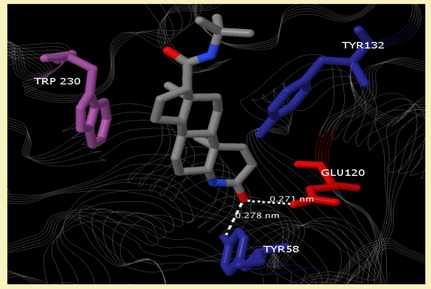
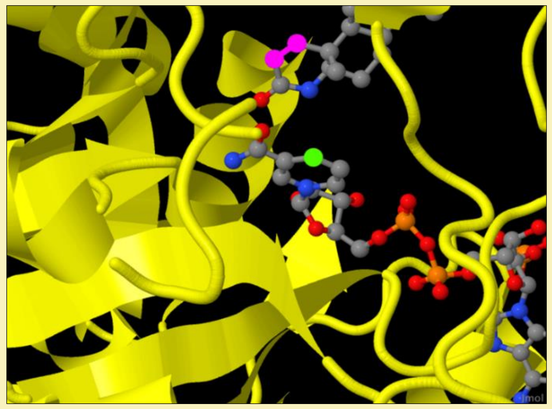


Figure 4: Finasteride in the catalytic tetrad of 5-βR, amino acids glutamate at positon 120 and tyrosine at position 58 form hydrogen bonds with the ketone at the 3 position of finasteride.



Figures 5. Orientation of finasteride and NADPH cofactor binding 5-β-reductase. The hydride of NADPH (shown in green) cofactor is too distant to react with the 1-2 ene (shown in pink) of finasteride. In 5-α-reductase, a hydride reaction between the cofactor and finasteride yields a bisubstrate analogue that binds 5-α-reductase with sub-nanomolar affinity.

The conversion enzyme 5α-R has three isozymes identified as 5α-R1, 2, and 3 with each performing similar functions in different tissues.[4] The 5α-R2 enzyme is shown to be responsible for a majority of DHT synthesis, as opposed to the other isozymes.[4]

Originally, it was thought that finasteride was a competitive inhibitor with affinity for 5-α-reductase type 2, but it has been recently shown that it acts as a mechanism-based inactivator of 5α-R2. [5] This mechanism works by NADPH donating a hydride to the 1,2-ene double bond of finasteride, which then allows NADP+ to covalently bind to dihydrofinasteride at the enzyme active site, forming a NADP+ - dihydrofinasteride complex. [5] It is this bisubstrate that has affinity for 5α-R2. [5] Refer to Figure 3 for a stepwise diagram showing the mechanism-based inactivation of 5α-R2 by finasteride.

The Next Question

After exploring the mechanism of action of finasteride, there are possible areas of improvement in order to decrease side effects. The downstream side effects could potentially be reduced by increasing specificity for 5α-R2 so there are fewer interactions with 5α-R1. The most direct means of improving specificity would be to obtain an x-ray crystallography structure of finasteride in a 5α-R2 enzyme. The binding of finasteride to 5β-R does not result in a reduction reaction, while the binding of finasteride to 5α-R does result in a reduction reaction. As these two enzymes utilize the same cofactor, these differences in reactivity must be due to differences in enzyme structure. As the names of the two enzymes suggest, they both reduce double bonds, but add hydrogens to distinct faces of the steroid skeleton. Obtaining a structure of 5α-R in complex with finasteride and cofactor may elucidate the interaction between finasteride and 5α-R.[5] This would allow for specific investigation of molecular changes that could be made to finasteride in an effort to improve specificity for this enzyme.

Finasteride binds selectively to 5α-R2 significantly reducing the number of adverse side effects seen. One area of improvement may be in reducing the effects of sexual dysfunction including decreased libido, impotence, and ejaculation disorder. These side effects may occur because 5α-R2 inhibits the conversion of testosterone to DHT. A secondary explanation of side effects may be the ability for small amounts of finasteride to cross the blood brain barrier. In keeping the effectiveness of the drug, changing selectivity of binding in the prostate is not a good idea. However, one proposed alteration to the molecular make up of finasteride to reduce these side effects may be to add a more polar group or steric bulk to the amide nitrogen on finasteride. In doing so, it would potentially decrease the drug's ability to cross the blood brain barrier leading to less binding in the hypothalamus, pituitary and cerebral cortex.

Summary

The affinity of finasteride with 5-beta-reductase is a result of the orientation of finasteride in the enzyme active site and H-bond interactions between finasteride and 5-Beta-reductase. Finasteride binds several reductase enzymes, with the significant clinical effects deriving from 5-alpha-reductase enzymes. The side effects of sexual dysfunction, and hypotension must be weighed against the benefit of the medication when determining its use in patients with BPH.

References

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