

Current Therapies to Treat Androgen-Dependent Diseases

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Despite pharmaceutical science's progress over the past 50 years, the prostate's specific function is still poorly understood. It is believed to be an essential organ for male fertility and protect the urinary tract from infection, yet it is a frequent infection and inflammation site.

On the other hand, the prostate is also the organ in which most benign diseases occur in men. More than 50% of those with approximately 50 years suffer from benign prostatic hyperplasia. This condition shows an abnormal enlargement of the prostate, leading to 25% of men who suffer from surgery. Likewise, the prostate is considered the predominant cancer site in man, since of the 90,000 cases diagnosed each year in the USA, approximately 26,000 patients die from this disease.

Although countless research groups and pharmaceutical companies have directed all their knowledge and effort to the early detection of prostate cancer, most patients present with scattered metastasis, leading to inevitable death at the end of their diagnosis. In Mexico, prostate cancer is the cause of death of around 72.2 per 100,000 elderly inhabitants (Ministry of Health).

There are potentially curative treatments for the early stages of prostate cancer, however, attempts to eradicate the metastasis have not been successful. Surgery and radiation are standard treatment methods that can affect the patient's quality of life because they produce side effects such as incontinence, intestinal damage, and sexual impotence, in addition to those of radiation. Although surgery represents the most accepted treatment to combat it, antiandrogen therapy is an alternative therapy that is currently gaining importance. Because this disease depends on androgens, exists an excellent variety of antiandrogens; those of most significant therapeutic interest belong to the steroidal series since they are homologous to the natural compounds from which they come progesterone derivatives standing out.

The main pharmacological activity of the drugs currently on the market is as follows:

1. The Inhibition of LHRH (Luteinizing Hormone-Releasing Hormone) production. This hormone stimulates the pituitary gland's anterior lobe to produce the luteinizing hormone, which enables the Leydig cells in the testes to produce androgens.
2. The blocking of the conversion of testosterone (T) to dihydrotestosterone (DHT) through inhibitors of the enzyme 5 α -reductase that catalyzes this reduction. DHT is an androgen almost 100 times more potent than T, and it causes benign prostatic hyperplasia and prostate cancer.
3. The drug competition for the androgen receptor binding site. The antiandrogens compete with the T or DHT for the androgen receptor's binding place (AR). These compounds form a complex with the AR that blocking cellular response to androgens.

These antiandrogens' mechanism of action, capable of controlling androgen-dependent diseases, could be understood by delving into men's reproductive functions' physiological and biochemical aspects.

The sexual characteristics in male mammals depend on two steroidal hormones, which are: T and DHT. Both hormones bind to a typical receptor known as the androgen receptor found in target cells' cytoplasm. The androgen-receptor complex is transported to the nucleus and binds the androgen response elements present in DNA. In the presence of androgen, the receptor undergoes a conformational change that allows it to interact as a dimer with DNA, activating specific genes. AR function is to increase or decrease the transduction to functional proteins. The coactivators or corepressors molecules regulate this function. Coactivators have histone acetylase activity and act as binding factors between steroid receptors and components that initiate transcription of the genetic message, resulting in protein production and subsequent cell function alteration. At the same time, the corepressors repress transcriptional activity.

The knowledge that DHT is a more potent androgen than T and a different role than T itself led to discovering the enzyme 5 α -reductase, present in androgen-dependent tissues. The regular activity of the enzyme 5 α -reductase (EC 1.3.99.5) results in T to DHT reduction. T has anabolic effects and maintains spermatogenesis in humans, while DHT mediates actions such as increased facial and body hair, prostate growth, and increased secretion from the sebaceous glands. The human 5 α -reductase abnormal activity increase levels of DHT in peripheral tissues. This abnormal activity is implicated in benign prostatic hypertrophy, prostate cancer, acne, and baldness pattern in the male. Therefore, both 5 α -reductase and DHT play an essential role in both the physiology and pathology of androgen-dependent diseases.

Medical therapy to cure prostate diseases is based on the androgen receptor's competitive binding. Several AR antagonists exist in the market, such as Cyproterone Acetate and non-steroidal anti-androgens flutamide and bicalutamide, to improve androgen-dependent illnesses. Besides the 5-Reductase inhibitors, finasteride and dutasteride had demonstrated effectiveness also in improving these afflictions. Dutasteride is a dual inhibitor for types 1 and 2 of the 5 α -reductase enzyme. Even though there is a wide variety of drugs with antiandrogenic effects today, their use is restricted because they produce various adverse effects.

Antiandrogenic compounds and 5 α -reductase inhibitors have different action mechanisms, and some show very severe side effects and high costs that reduce their clinical usefulness. Among the harmful effects are hormonal abnormalities such as Loss of libido, impotence, semen, and cell atrophy abnormalities.

It is currently a concern for scientists to improve therapies to improve these afflictions. Therefore, the synthesis of novel steroids derived from pregnane and dehydroepiandrosterone with therapeutic potential lower the costs of those currently on the market and produce fewer side effects. Scientific literature reports the detailed synthesis and biological activity for these steroids derivatives.

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