Genitourinary System Module

Pharmacology

Androgen Therapy

Faculty of Medicine
The Hashemite University

Ola Ebbeni (BDS, MSc, PhD)

Introduction to androgens

- An androgen, or male sex hormone, is defined as a substance capable of developing and maintaining masculine characteristics in reproductive tissues (notably the genital tract, secondary sexual characteristics, and fertility) and contributing to the anabolic status of somatic tissues

- Testosterone together with its potent metabolite, dihydrotestosterone (DHT), are the principal androgens in the circulation of mature male mammals

- In male testosterone is mainly synthesized by Leydig cells in the testes. In females, it is synthesized in smaller amounts, by theca cells in the ovary. In both sexes, it is synthesized by the adrenal gland.

- Other androgen type include:

1. 5α-dihydrotestosterone (DHT): most potent androgen

2. Androstenedione

3. Dehydroepiandrosterone (DHEA): mainly from adrenal gland but also secreted from testes.

Introduction to androgens

Androgens are required for:

1. Normal maturation in the male.
2. Sperm production.
3. Increased synthesis of muscle proteins
4. Increased erythropoiesis
5. Decreased bone resorption.

- Synthetic modifications of the androgen structure are designed to modify solubility and susceptibility to enzymatic breakdown: Have longer half-life
- Can have a separate anabolic or androgenic effect

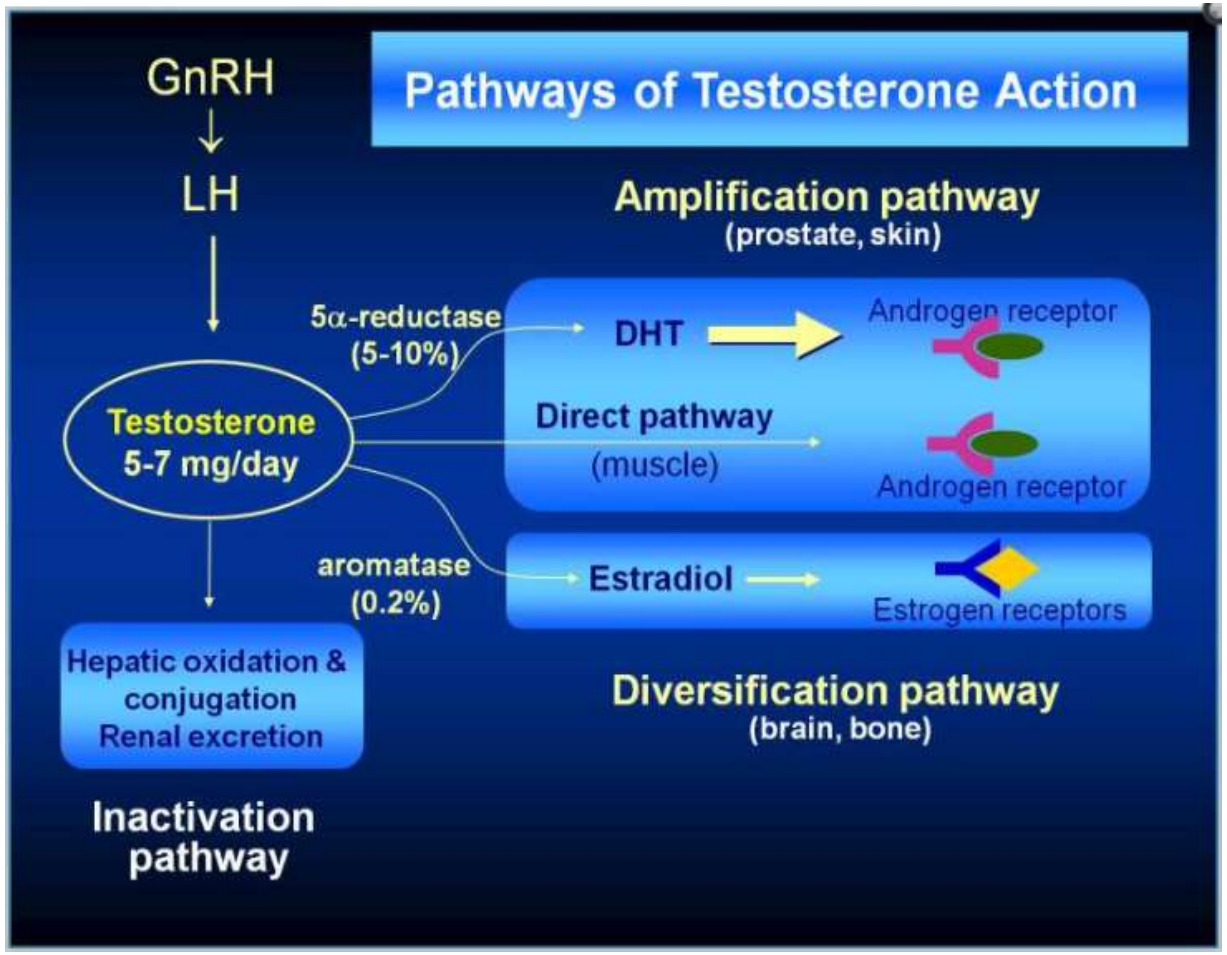
Mechanism of action

- Androgens bind to a specific nuclear receptor in a target cells.
- Testosterone is the active ligand in muscle and liver.
- It must be metabolized to derivatives such as DHT in other tissues (e.g. prostate and skin).
- [Note: Testosterone analogs that cannot be converted to DHT have a greater effect on the skeletal musculature than they do on the reproductive system.

Mechanism of action

In men, most (>95%) testosterone is produced under LH stimulation of Leydig cells. The daily production of testosterone (5-7 mg) is disposed along one of four major pathways. :

1. **The direct pathway:** in skeletal muscle testosterone itself binds to and activates the androgen receptor. In such tissues there is little metabolism of testosterone to biologically active metabolites.
2. **The amplification pathway:** in prostate and hair follicle testosterone is converted by the type 2 5α reductase enzyme into the more potent androgen, DHT.
3. **The diversification pathway** of testosterone action allows testosterone to modulate its biological effects via estrogenic effects. The diversification pathway, characteristic of bone, and



Therapeutic uses:

- Androgenic steroids: for primary hypogonadism caused by testicular dysfunction and secondary hypogonadism due to failure of the hypothalamus or pituitary.

- Anabolic effects: to treat chronic wasting associated with human immunodeficiency virus (HIV) or cancer.

- Endometriosis and fibrocystic breast disease: Danazol, (a mild androgen) [Note: Danazol also possess antiestrogenic activity.] It inhibits release of FSH and LH.

- Unapproved use: Anabolic steroids are used to increase lean body mass, muscle strength, and endurance in athletes and body builders.

Pharmacokinetics

Testosterone:

- ineffective orally because of inactivation by first-pass metabolism.

- Testosterone and its esters demonstrate a 1:1 relative ratio of androgenic to anabolic activity.

- Testosterone derivatives:

• Alkylation of the 17α position of testosterone (less hepatic metabolism) allows oral administration of the hormone, e.g., Fluoxymesterone and Methyltestosterone (associated with more hepatotoxicity)

• Have a longer half-life in the body than naturally occurring androgens.

Side Effects

- **In females:** masculinization, acne, growth of facial hair, deepening of the voice, male pattern baldness, and excessive muscle development. Menstrual irregularities may also occur.

**Testosterone should not be used by pregnant women because of possible virilization of the female fetus.

- **In males:** priapism, impotence, decreased spermatogenesis, and gynecomastia. Cosmetic changes such as acne, baldness.

**Testosterone replacement should not be used in patients actively trying to produce a pregnancy or which preserve their fertility and sperm counts. Testosterone supplementation reduces sperm counts and spermatogenesis.

**Clomiphene citrate (SERM) can effectively increase testosterone levels in symptomatic hypogonadal men who wish to maintain their fertility and sperm counts. Clomiphene increases FSH and LH. it is not effective in those cases where LH and FSH are elevated, characterizing primary hypogonadism.

Side Effects

- **In children:** abnormal sexual maturation and growth disturbances resulting from premature closing of the epiphyseal plates.

- **General effects:** Androgens raise LDL levels while decreasing HDL levels, increasing the LDL:HDL ratio and potentially increasing the risk of premature coronary heart disease. Androgens can also cause fluid retention, which can lead to edema.

- **In athletes:** 1. Can cause premature closing of the epiphysis of the long bones, which stunts growth and interrupts development. 2. High doses taken by young athletes may result in reduction of testicular size, hepatic abnormalities and increased aggression

Antiandrogens

Counter male hormonal action by:

1. interfering with the synthesis of androgens: Finasteride and dutasteride inhibit 5α-reductase, resulting in decreased formation of DHA. These agents are used for the treatment of benign prostatic hyperplasia

2. blocking their receptors: such as flutamide, bicalutamide, enzalutamide , and nilutamide, act as competitive inhibitors of androgens at the target cell and are given orally for the treatment of prostate cancer

Benign prostatic hyperplasia

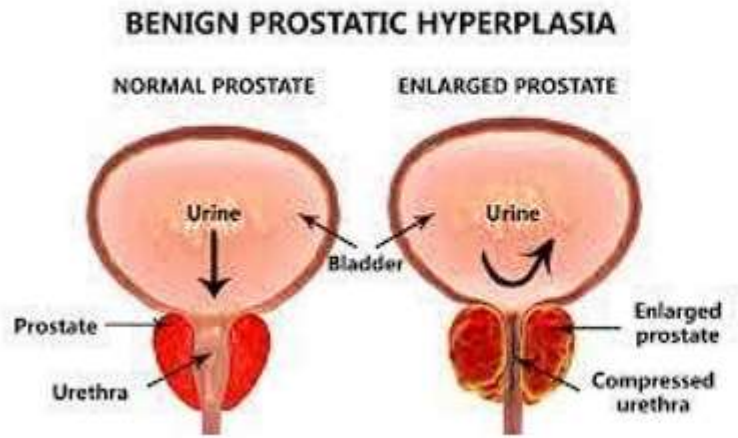
- BPH is a condition typically seen in middle-aged and older men with increasing frequency seen with increasing age. BPH correlates with lower urinary tract symptoms that can cause significant distress, including nocturia, urinary urgency, increased frequency of urination, decreased stream caliber, straining while voiding, and a sensation of incomplete bladder emptying.

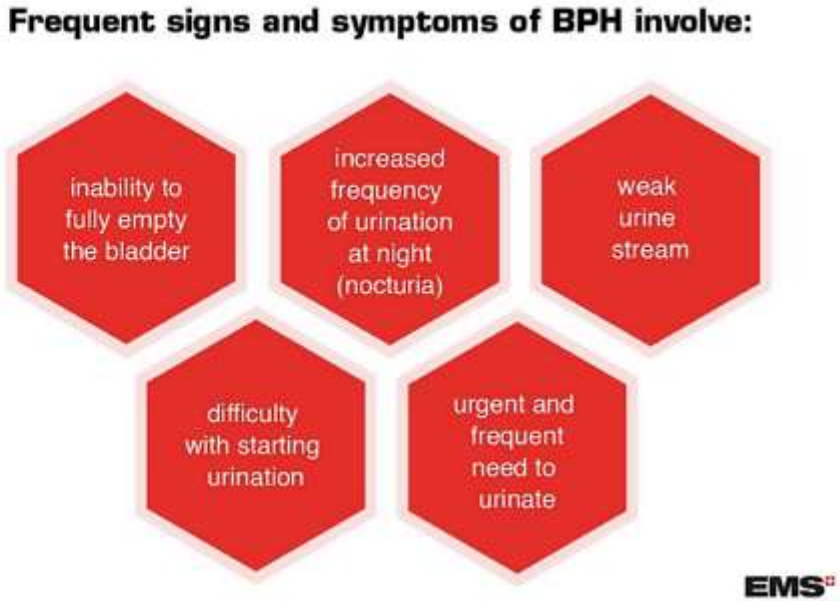
- Three classes of medications are used to treat BPH:

1. α1 -adrenergic antagonists: Relieve symptoms within 7 to 10 days.
2. 5-α reductase inhibitors: may take up to 12 months to relieve symptoms.
3. Tadalafil (Phosphodiesterase-5 inhibitors) is the only PDE-5 inhibitor approved for the treatment of BPH. PDE-5 is present in the prostate and bladder. As such, inhibition of PDE-5 by tadalafil allows for vasodilation and relaxation of the smooth muscle of the prostate and bladder, which thereby improves symptoms of BPH.

Benign prostatic hyperplasia

BPH is nonmalignant enlargement of the prostate, results in lower urinary tract symptoms.





α1-Adrenergic antagonists

- Terazosin, doxazosin, tamsulosin, alfuzosin, and silodosin are selective competitive blockers of the α1 receptor.

- Mechanism of action: the α-blockers cause prostatic smooth muscle relaxation, which leads to improved urine flow.

- **Tamsulosin** and **silodosin** are more selective for the α1A receptor. Because **doxazosin**, **terazosin**, and **alfuzosin** block α1B receptors, these agents decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle. In contrast, tamsulosin and silodosin have less of an effect on blood pressure because they are more selective for the prostate-specific α1A receptor.

- Adverse effects α-Blockers may cause dizziness, nasal congestion, headache, drowsiness, and orthostatic hypotension.

Anti-androgen: 5α-reductase inhibitors

- Including: Finasteride and Dutasteride
- The FDA currently has two approved indications for 5-alpha-reductase inhibitors. These conditions include benign prostate hyperplasia (BPH) and androgenic alopecia (male pattern hair loss).
- Inhibit the enzyme 5-α reductase, preventing conversion of for testosterone to DHT. DHT is an androgen that stimulates prostate growth. By reducing DHT, the prostate shrinks and urine flow improves.
- Since it takes several months for 5-α reductase inhibitors to reduce the prostate size, it is appropriate to use these agents in combination with an α-blocker to provide relief of symptoms.
- Reported side effects: Primarily sexual and include erectile dysfunction, decreased ejaculatory volume, a decrease in libido, as well as gynecomastia.

Therapy for benign prostatic hyperplasia (BPH).