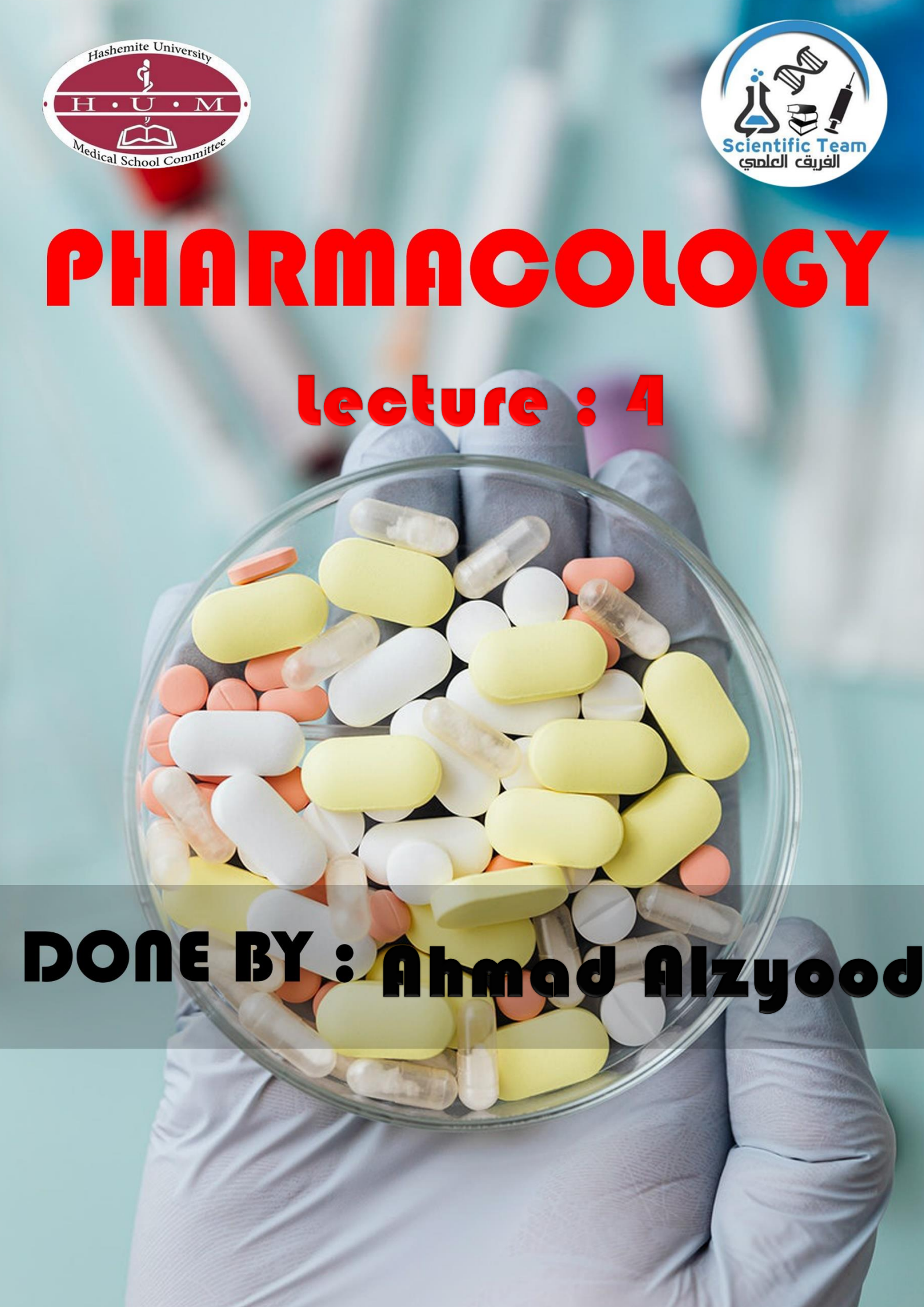
Hashemite University
H · U · M
Medical School Committee

Scientific Team
الفريق العلمي

PHARMACOLOGY

Lecture : 4



DONE BY : Ahmad Alzyood

Male Sex Hormones

MALE SEX HORMONES = ANDROGENS

- The androgens are a group of steroid hormones that have

1- anabolic → increase protein synthesis and muscle development لهيك بستخدموه الي بلعبو كمال اجسام

2- androgenic effects → the development and maintenance of the male sex organs and secondary sex characteristics.

- Testosterone

- It is the most important androgen

- It is synthesized by Leydig cells in the testes

- Smaller amounts are synthesized by the ovary of the female and by the adrenal gland in both sexes.

So the sources of Testosterone are:

1- testes in males
2- ovary in females
3- adrenal gland in both

Note: Gonads means primary sex organs (testes in males and ovaries in female)

- Its secretion by is controlled by gonadotropin-releasing hormone (GnRH) from

the hypothalamus → stimulates the anterior pituitary gland → secrete:

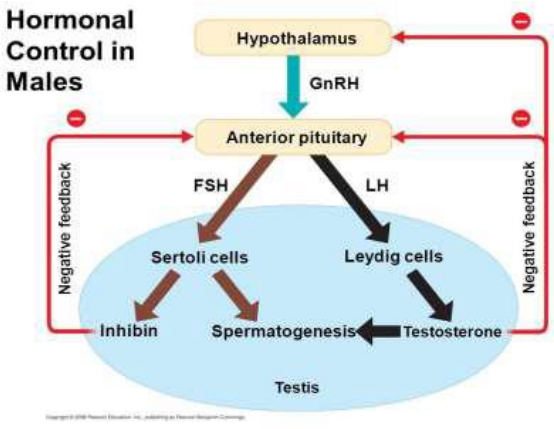
1. FSH→ necessary for spermatogenesis

2. LH → stimulates steroidogenesis (testosterone) in the Leydig cells.

- Testosterone or its active metabolite dihydrotestosterone (DHT)

→ a negative feedback on trophic hormones
→regulates testosterone production.

اي هرمون زي ال thyroid hormone لما بزداد بالدم بيعمل تثبيط للمركز سواء hypothalamus or pituitary



gland

- Mechanism of action: like any lipophilic hormone

- It binds to a specific intracellular androgen receptors in a target cell →the hormone-receptor complex → binds to DNA and affects **gene expression.**

- In muscle and liver: **testosterone** is the active ligand.

- In the prostate, seminal vesicles, epididymis, and skin:

testosterone is converted by 5-α reductase enzyme to **dihydrotestosterone (DHT),** which binds to the receptor.

- In the brain, liver, and adipose tissue: testosterone is biotransformed by cytochrome P450 aromatase enzyme to **estradiol**.

كل صيغة مهم اعرف بتشتغل بأي عضو عشان اعرف أتعامل مع الحالات الي بكون سببها مثلا DHTاو التستوستيرون نفسه والانزيمات مهم اعرفها ورح تفهمو كمان شوي بالإستخدامات

- Actions:

A. Androgenic:

1. Male sex organs development (penile & scrotal development)

2. 2ry sex characters (hair growth, thickening of vocal cords) خشونة الصوت وتوزيع الشعر

3. Testosterone + FSH → spermatogenesis

4. ↑ libido in males & females.

5. Large doses for prolonged time → feedback inhibition of gonads → testicular atrophy.
لهيك الي بياخذوه كثير زي الي بلعبو بالجيم بصير معهم عقم بعد بفتره

B. Anabolic:

1. ↑ protein synthesis

2. ↑ bone density and closure of epiphyseal ends of long bone. بمعنى بوقف نمو العظام

لهيك البالغين لما بزداد الهرمون بوقف عندهم الطول او الاطفال الي بياخذو الهرمون مبكرا بسبب مرض او غيره

3. ↑ muscle development.

4. ↑ Erythropoiesis and coagulation بكون خلايا الدم الحمرا اعلى وعوامل التخثر كمان

- Uses:

A. For its **Androgenic effects**:

1. Replacement therapy in **Male hypogonadism**:

- ❖ The problem in the testis itself: 1ry hypogonadism due to testicular dysfunction→ give testosterone. → Here GnRH is normal or high. (also FSH and LH)
- ❖ 2ry hypogonadism (due to failure of the hypothalamus or pituitary) → low FSH and LH or Low GnRH

هون بكون فحص الخصية تمام وفش مشاكل

2. Adjuvant in the treatment of Cancer breast: ↓release of gonadotropins

(+ anti-estrogen drugs)

بسبب انه هرمون التستوستيرون لما يرتفع بالدم بيعمل تثبيط لل GnRH ؛ لذا يتم استخدامه بالأمراض الي بكون سببها GnRH مثل هذا المرض لانه سببه زيادة الاستروجين بسبب زيادة GnRH بالإناث

B. For its **anabolic effect**

1. Growth stimulant in debilitating conditions e.g. after major surgery.

الامراض المزمنه او العمليات المتعبه للمرضى ؛ يتم استخدام هذا الهرمون .

2. Senile osteoporosis: ↑ protein formation and calcium deposition in bones.

هنا لا يوجد نقص بالمعادن زي الكالسيوم وإنما بسبب السن بصير هشاشة عظام لهيك بنستخدمه

في rickets او osteomalacia ما بنستخدمه لانه الأساس نقص كالسيوم.

3. Aplastic anemia: ↑erythropoietin synthesis

- Preparations: Natural or Non-natural. الاسماء حفظ

1. Natural: **Androsterone and Testosterone** (more active) are In-effective orally due to the extensive 1st pass metabolism in the liver.

- are given IM , SC.

2. Synthetic including:-

- ❖ Esterified preparations: **testosterone propionate** (IM)
- ❖ Conjugated preparations: **methyl-testosterone** (sublingual- oral)

3. Semisynthetic: **Fluoxymesterone** (oral)

- Adverse Effects:

1. In female: Virilization (ظهور علامات الذكورة): masculinization – acne - growth of facial hair deepening of the voice - menstrual irregularities – clitoral enlargement.

→ Contraindicated : pregnant women → virilization of the female fetus . لهيك ممكن يفكروها ذكر

2. In males: Azospermia - ↓ libido – riapism

Riapism: (painful erection for more than 4 hours treated by aspiration of the corpora cavernosa and injection ***of alpha agonist - VC***). It due to severe VD and blockage of venous drainage that may lead to gangrene.

Note: - Azospermia → no sperms in semen.

- Oligospermia → low sperms in semen.

- Behavioral effects: increased aggressiveness, and psychotic symptoms.

3. In children: Short stature due to premature closure of epiphysis

4. Methyl-testosterone causes reversible cholestatic jaundice. (bile duct بيأثر على)

5. Increase incidence of **cancer prostate**

لانه الخلايا السرطانيه تتغذى على هرمون التستوستيرون

CI: cancer prostate

ANTIANDROGENS

A. Inhibitors of testosterone secretion:

- Analogs of GnRH as **Leuprolide** when are given continuously → inhibit LH secretion → inhibit testosterone production.
  Normal secretion of GnRH is not continuously.
- Used to - suppress precocious puberty.

- treat prostate cancer

B. Inhibitors of testosterone synthesis:

- Some antifungal drugs such as **ketoconazole** inhibit **CYPs** → block the synthesis of steroid hormones, including testosterone and cortisol.
- They are **not used** to inhibit androgen synthesis because they may induce adrenal insufficiency and are associated with hepatotoxicity.

- May used in cases of glucocorticoid excess

C. Inhibitors of androgen action:

1) 5-α reductase inhibitors: **Finasteride & Dutasteride**:

- block the conversion of testosterone to dihydrotestosterone, especially in the male external genitalia.

- Used in Benign Prostatic Hyperplasia (BPH). Remember DHT is the active form in prostate.

→BPH lead to urethra obstruction and increase the risk of UTI.

2) Androgen receptor (AR) antagonists:

Flutamide - Bicalutamide & Cyproterone:

- Competitive antagonist at androgen receptors.

- Used in

1- Cancer prostate

2- Acne & hirsutism in females. They due to high testosterone in female

Spironolactone: aldosterone antagonist that also is a weak AR antagonist and a weak inhibitor of testosterone synthesis (by inhibiting CYP)

** Common adverse effects of antiandrogens: بشكل عام لكل الادوية

1. Gynecomastia
   Due to high formation of estradiol from testosterone (its receptor or enzymes are blocked) in males.
2. ↓ libido (sexual desire).
3. Erectile dysfunction (impotence): inability to obtain or maintain erection of penis for sexual intercourse.

ANABOLIC STEROIDS

(Stanozolol - Nandrolone)

- Synthetic androgens with high anabolic and low androgenic activities.

- Indications

1. Chronic debilitating diseases, e.g. cancer.

2. Bodybuilding & athletes

3. Osteoporosis

4. Prolonged immobilization.

Adverse effects: as androgens. Negative feedback of them lead to testicular atrophy (in chronic use).

ERECTILE DYSFUNCTION (ED)

Causes of ED: **VC**

1- Cardiovascular diseases. Affect the vessels of penis.

2- DM. affect microvasculature.

3- Psychological (14%).

4- Drugs: e.g **antidepressants, H2-blockers and thiazide diuretics.**

- Treatment:

1. Sildenafil (Viagra):

-Mechanism of action:

It inhibits phosphodiesterase type-5 (PDE5) → ↑ levels of cGMP → vasodilatation → engorgement of the sinusoids and expansion of the corpora cavernosa → erection of the penis.

الطريقة الي تتم فيها عملية الانتصاب هو زيادة cGMP ؛ لذا تقليل تكسيره مهم لتقوية الانتصاب

Side effects: headache (VD), flushing (VD), nasal congestion (VD) & transient color vision disturbance (VD).

Priapism (prolonged VD) may occur.

-Contraindications: with any drug cause VD or Hypotensive patients.

1- With nitrates → severe acute hypotension.

2- Recent stroke, acute myocardial infarction.

→VD of peripheral vessels causes ischemia in heart lead to Angina and MI.

3- blood pressure < 90/50 mmHg.

2-Alprostadil: is PGE1 analog.

PGE1→ powerful vasodilator injected in the corpora.

3-Androgens: effective **only if ED due to testosterone deficiency**

4-papaverine + phentolamine: were used by injection in the corpora.

- Painful priapism and penile fibrosis may occur on repeated injections.

BENIGN PROSTATIC HYPERPLASIA (BPH)

The prostate gland is formed of:

- Capsular & stromal tissue rich in alpha adrenoreceptors.
- Glandular tissue under the influence of androgens.

Both alpha adrenoreceptors and androgens **are targets for drug therapy**.

1. Alpha1-adrenoceptors blockers e.g. prozosin, terazosin

- ↓ prostatic congestion → ↑ the maximal urine flow rate.
- Additional effect → ↓ BP in hypertensive patients. (Benefit)

- Major adverse effect: 1st dose hypotension & postural hypotension

So start with low dose and take the dose before sleep. (sit down when taking the drug)

- Tamsulosin doesn't block vascular α1-adrenoceptors → avoid undesirable side effects of other alpha-blockers. (more selective so used in non-hypertensive patients)

2. Antiandrogen: Finasteride – Dutasteride → AE of these is Erectile dysfunction. Combined with PDE5 inhibitors.

3. Phosphodiesterase type-5 inhibitor: if ED developed due to antiandrogen.

Good luck