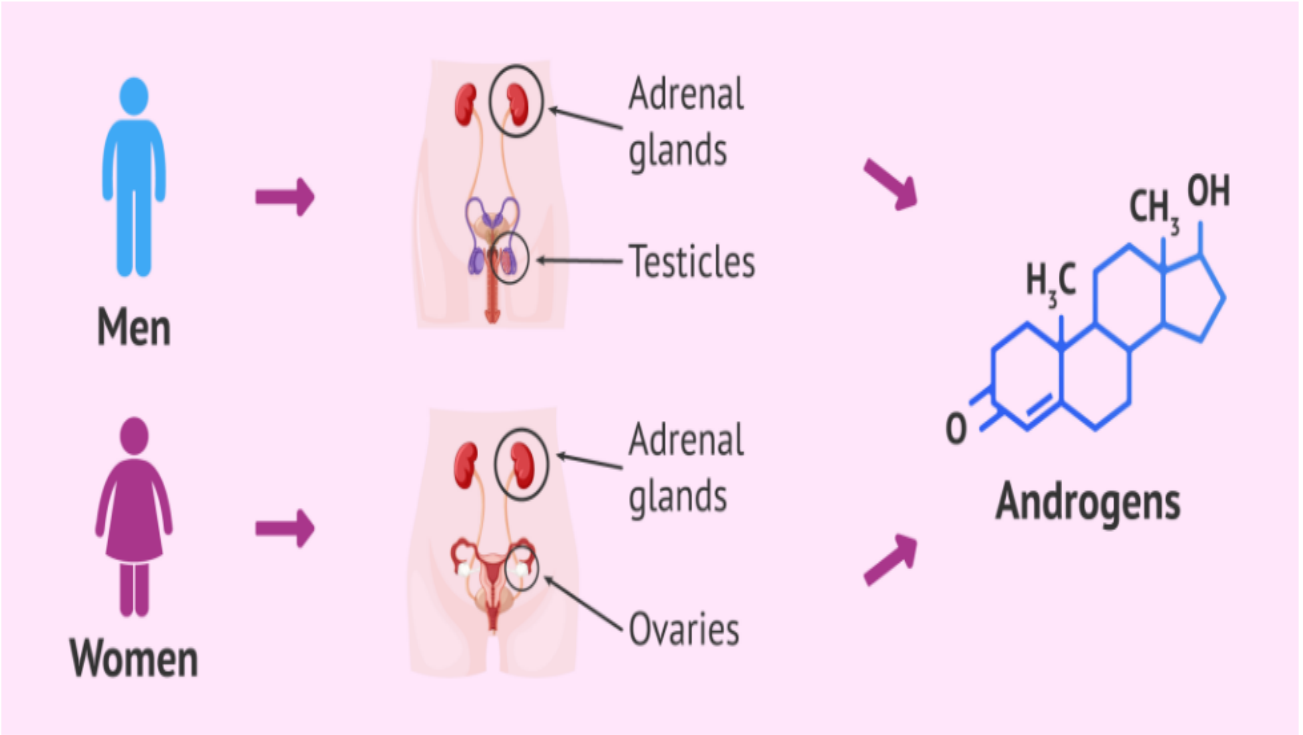
ANDROGENS & THEIR ANTAGONISTS

Dr.Nashwa Abo-Rayah
Associate prof. (clinical &experimental pharmacology)
Mu'tah University- Faculty of Medicine-
JORDAN 2024/2025

Androgens

- **Androgens are the male sex hormones** and include **testosterone**, **androsterone** and **androstenedione**.
- **The main function of these hormones is** to **promote the development of sexual characteristics in male, such as beard and voice tone.**
- **Androgens also intervene in other processes such as :**
- The human metabolism.
- Insulin sensitivity.
- Regulation of the amount and distribution of body fat and muscle tissue.



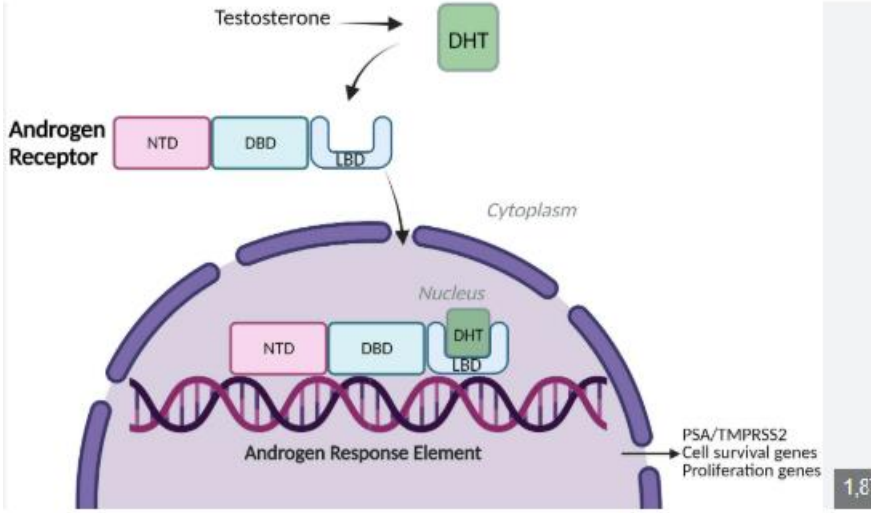
Testosterone

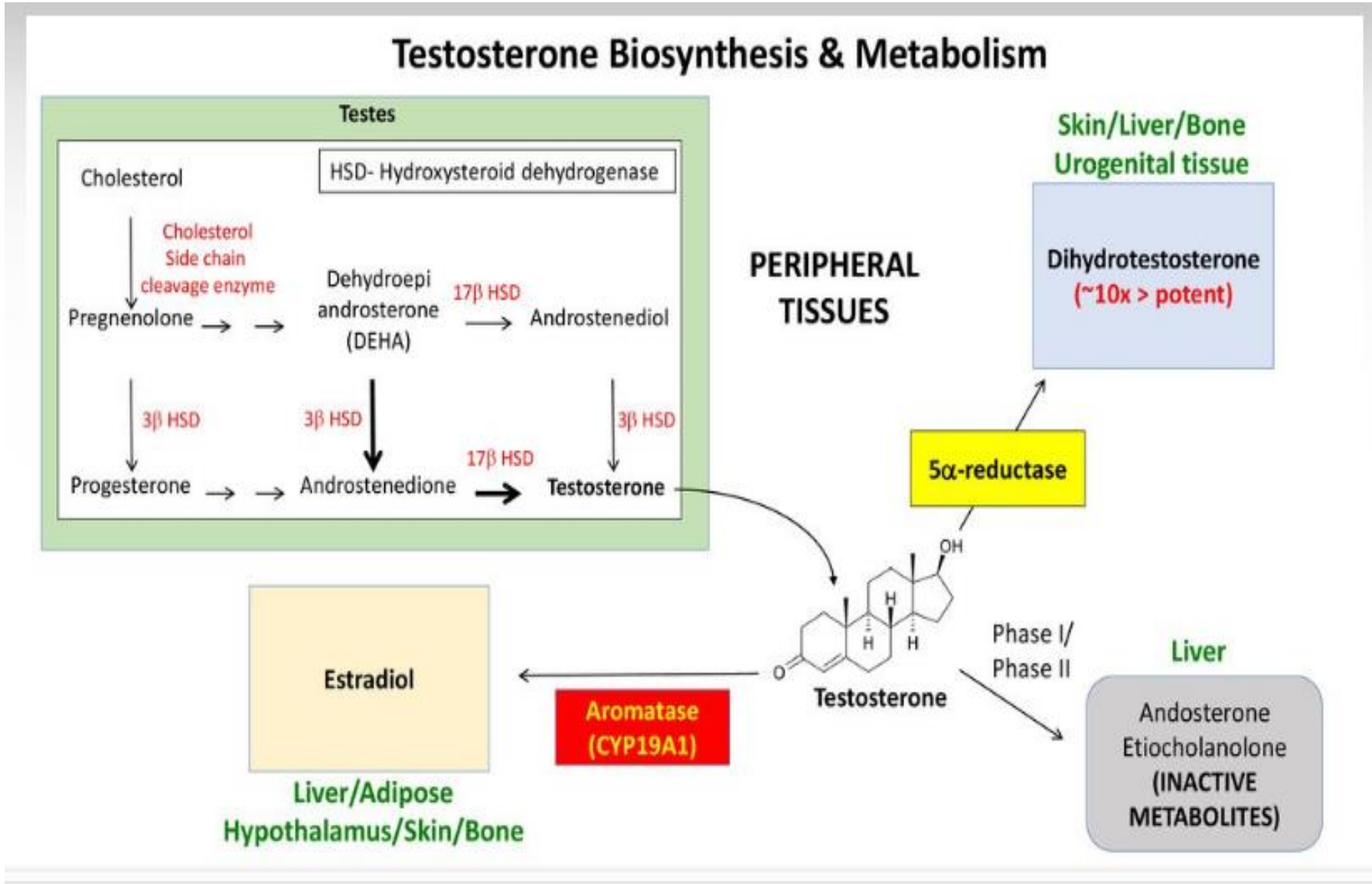
- **Testosterone** is the **main androgen produced in testis** by interstitial cells of Leydig under influence of (LH).

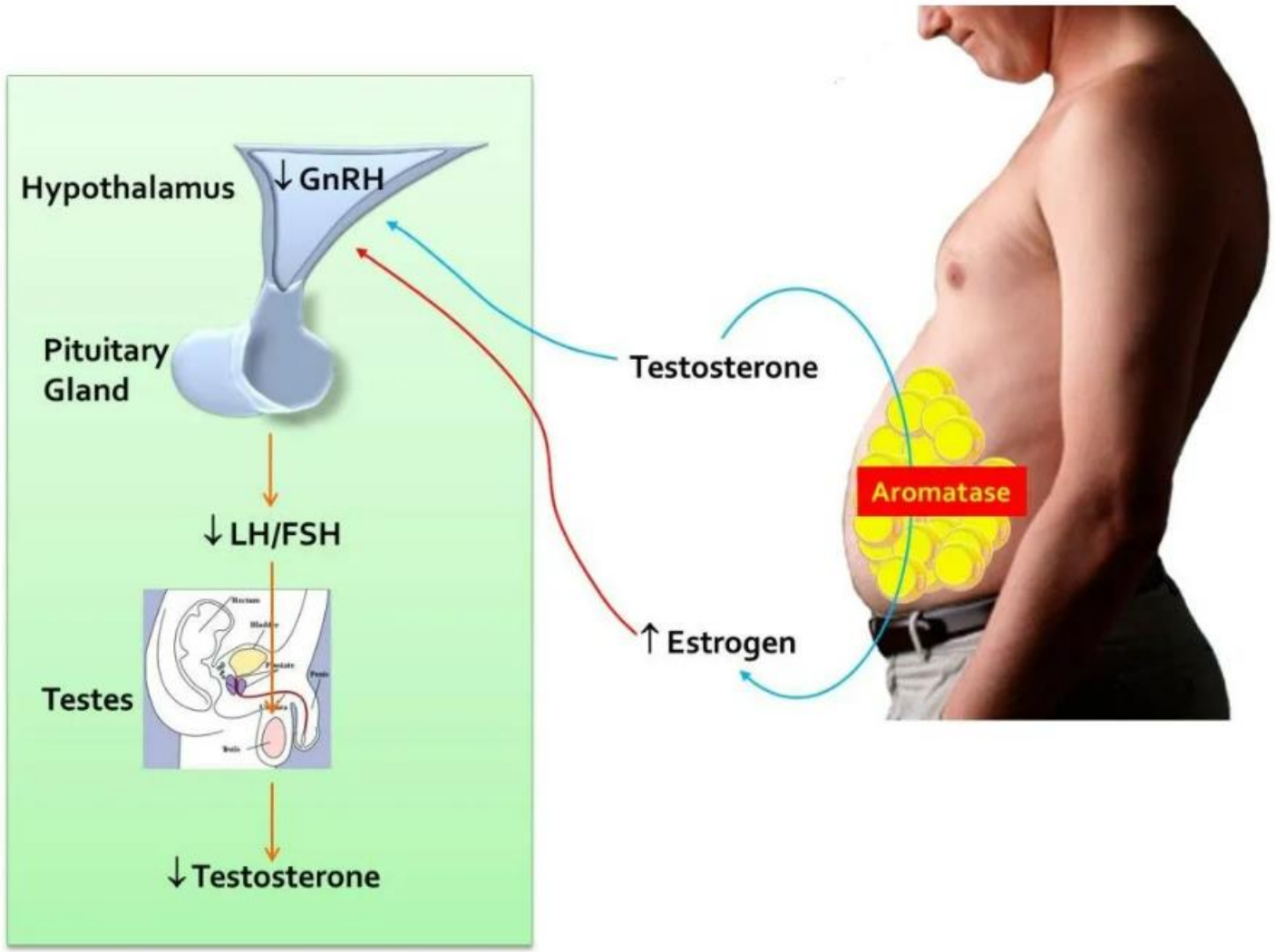
- There are **specific androgen receptors (AR)** in **cytoplasm of target cell.**

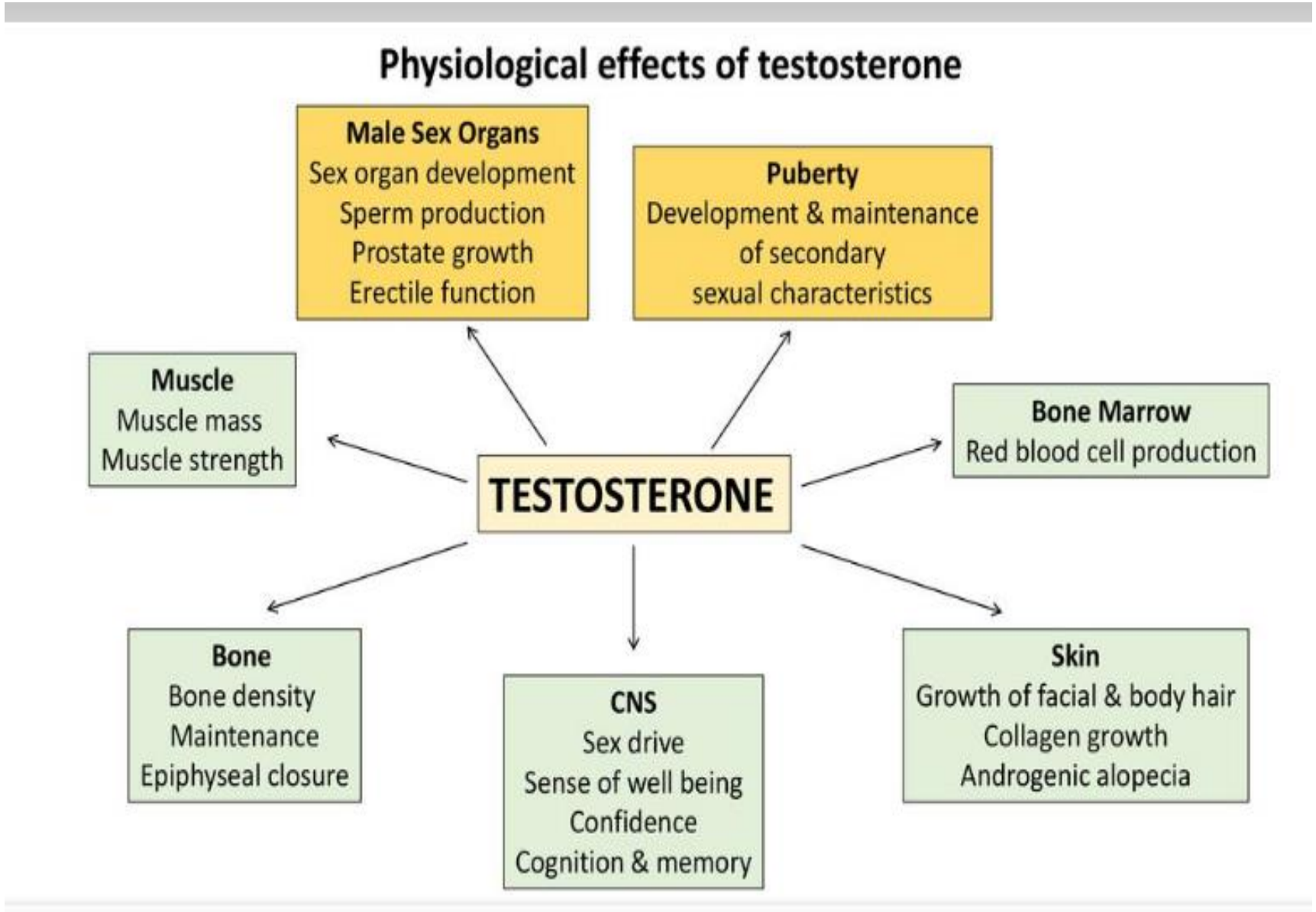
•**Androgen receptor**: **ligand-dependent nuclear transcription factor** and member of the **steroid hormone nuclear receptor family.**

•Testosterone has **androgenic** and **anabolic** activity.

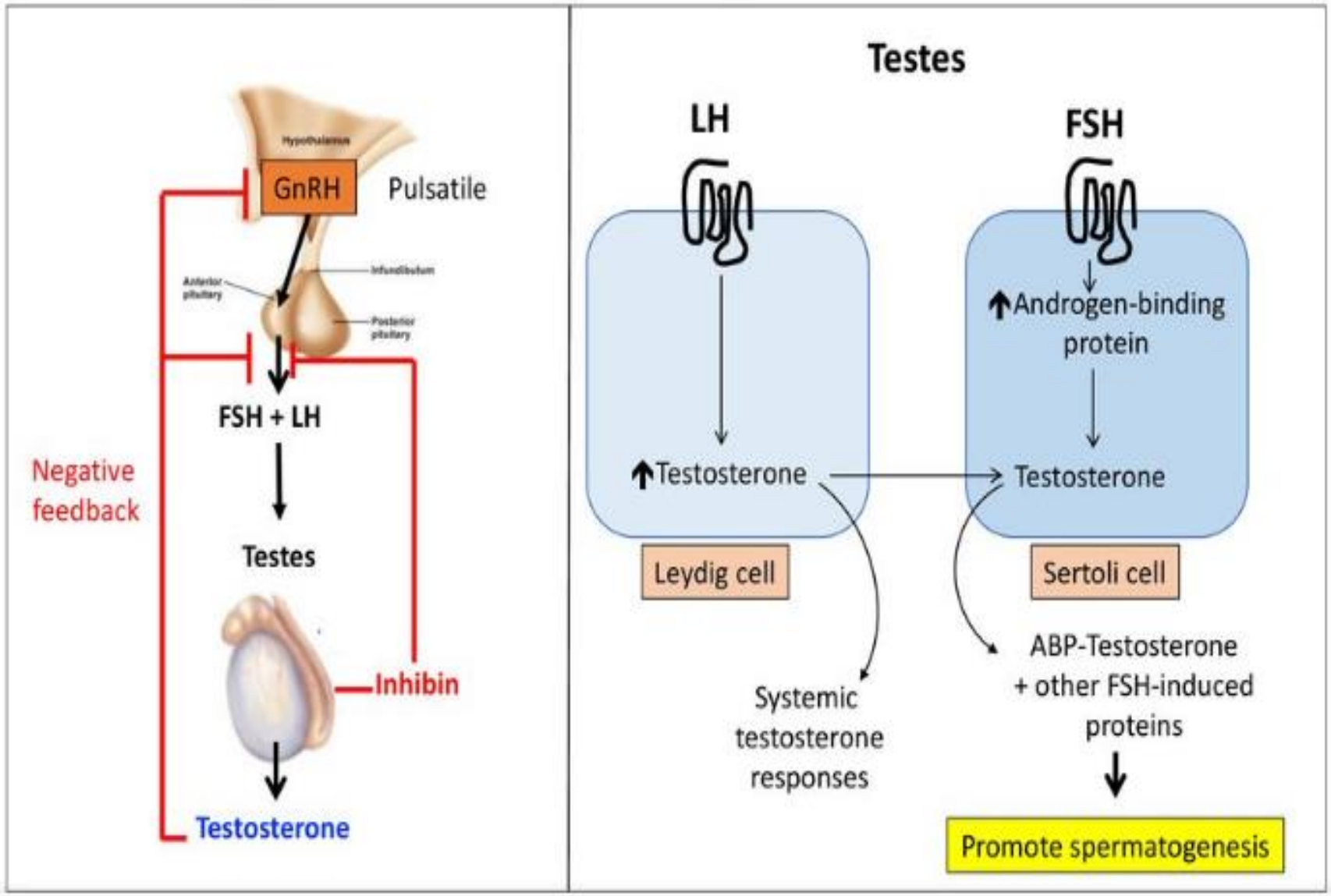


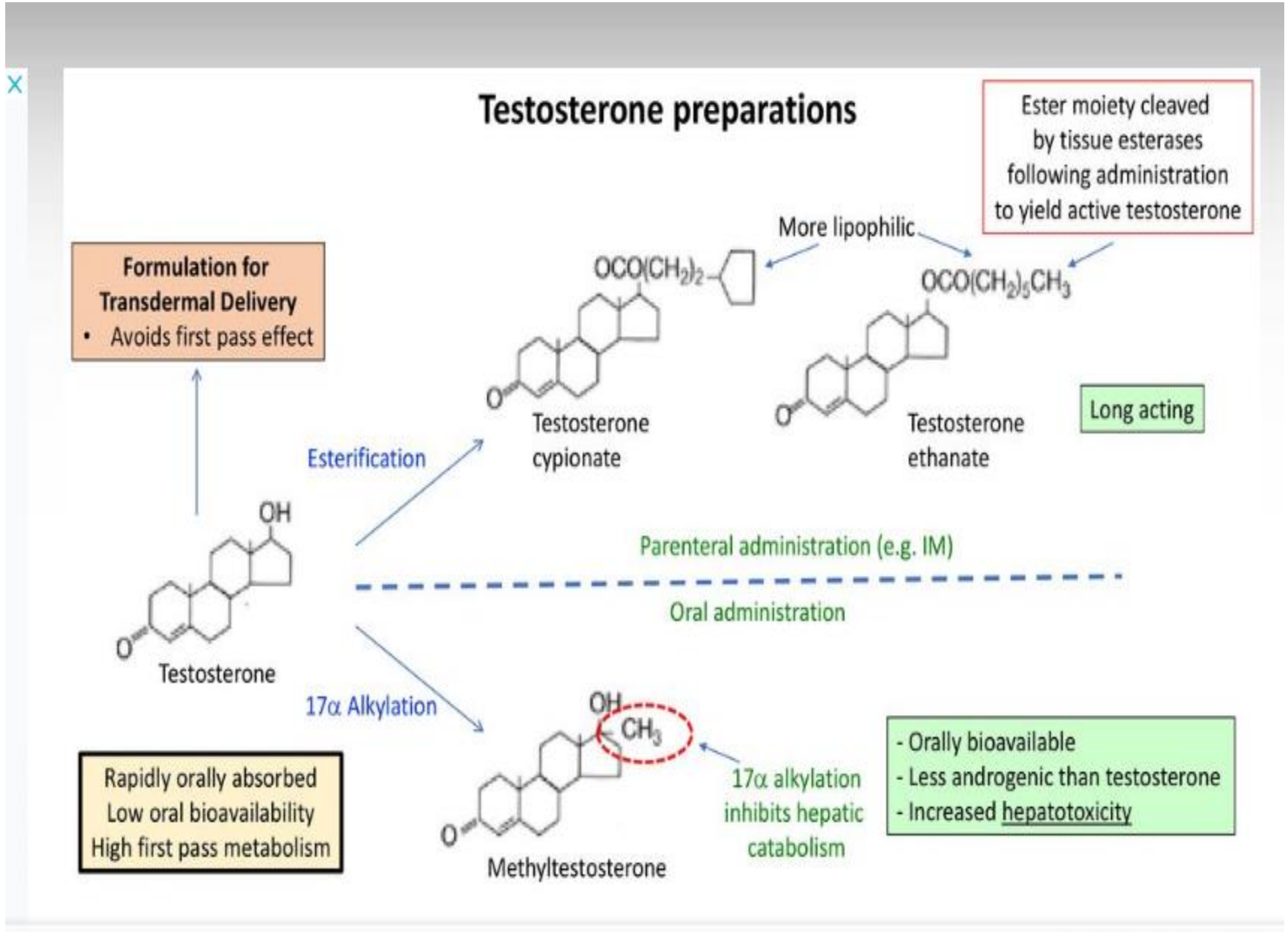

Testosterone Biosynthesis & Metabolism
Testes
Cholesterol
HSD- Hydroxysteroid dehydrogenase
Cholesterol Side chain cleavage enzyme
Pregnenolone
Dehydroepi androsterone (DEHA)
17β HSD
Androstenediol
3β HSD
3β HSD
3β HSD
Progesterone
Androstenedione
17β HSD
Testosterone
PERIPHERAL TISSUES
Skin/Liver/Bone
Urogenital tissue
Dihydrotestosterone
(~10x > potent)
5α-reductase
OH
H
H
H
O
Testosterone
Phase I/ Phase II
Liver
Andosterone
Etiocholanolone
(INACTIVE METABOLITES)
Estradiol
Aromatase (CYP19A1)
Liver/Adipose
Hypothalamus/Skin/Bone


Hypothalamus
↓ GnRH
Pituitary Gland
↓ LH/FSH
Testes
↓ Testosterone
Testosterone
↑ Estrogen
Aromatase


Physiological effects of testosterone
Male Sex Organs
Sex organ development
Sperm production
Prostate growth
Erectile function
Puberty
Development & maintenance
of secondary
sexual characteristics
Muscle
Muscle mass
Muscle strength
TESTOSTERONE
Bone Marrow
Red blood cell production
Bone
Bone density
Maintenance
Epiphyseal closure
CNS
Sex drive
Sense of well being
Confidence
Cognition & memory
Skin
Growth of facial & body hair
Collagen growth
Androgenic alopecia

Regulation of testosterone synthesis & secretion




Testosterone preparations
Ester moiety cleaved by tissue esterases following administration to yield active testosterone
More lipophilic
Formulation for Transdermal Delivery
• Avoids first pass effect
OCO(CH2)2
OCO(CH2)5CH3
Testosterone cypionate
Testosterone ethanate
Long acting
Esterification
OH
Parenteral administration (e.g. IM)
Oral administration
Testosterone
17α Alkylation
OH
CH3
Rapidly orally absorbed
Low oral bioavailability
High first pass metabolism
17α alkylation inhibits hepatic catabolism
- Orally bioavailable
- Less androgenic than testosterone
- Increased hepatotoxicity
Methyltestosterone

Testosterone indications and therapeutic uses

Male hypogonadism

Primary	Disease of testes	- Sperm & testosterone < normal - LH & FSH > normal (no negative feedback)
Secondary	Hypothalamus/ Pituitary Disease	- Sperm & Testosterone < normal - LH & FSH < normal

Symptoms:

In utero	- ambiguous sexual organ development - micropenis at birth
Prepubertal	- failure to undergo complete puberty
Adult	- ↓energy & libido - infertility - ↓muscle mass, ↓bone density & ↓sexual hair

Adverse effects:

- Acne
- Increased risk of prostate cancer/benign prostatic hyperplasia
- Worsening of sleep apnea
- Increased cardiovascular disease risk (↓HDL & ↑LDL)
- Increased risk of venous thromboembolic disease
- Erythrocytosis – increase in red cell mass (increased risk of VTE)
- Hepatic dysfunction (- 17α alkylated derivatives)
- Suppression of spermatogenesis
    - inhibition of LH production results in reduction of high level endogenous local testicular testosterone known to be required for sperm production

Contraindications:

- Pre-existing Prostate cancer
- High levels of PSA in men at high risk for prostate cancer
- Untreated sleep apnea

Androgens as performance enhancing drugs

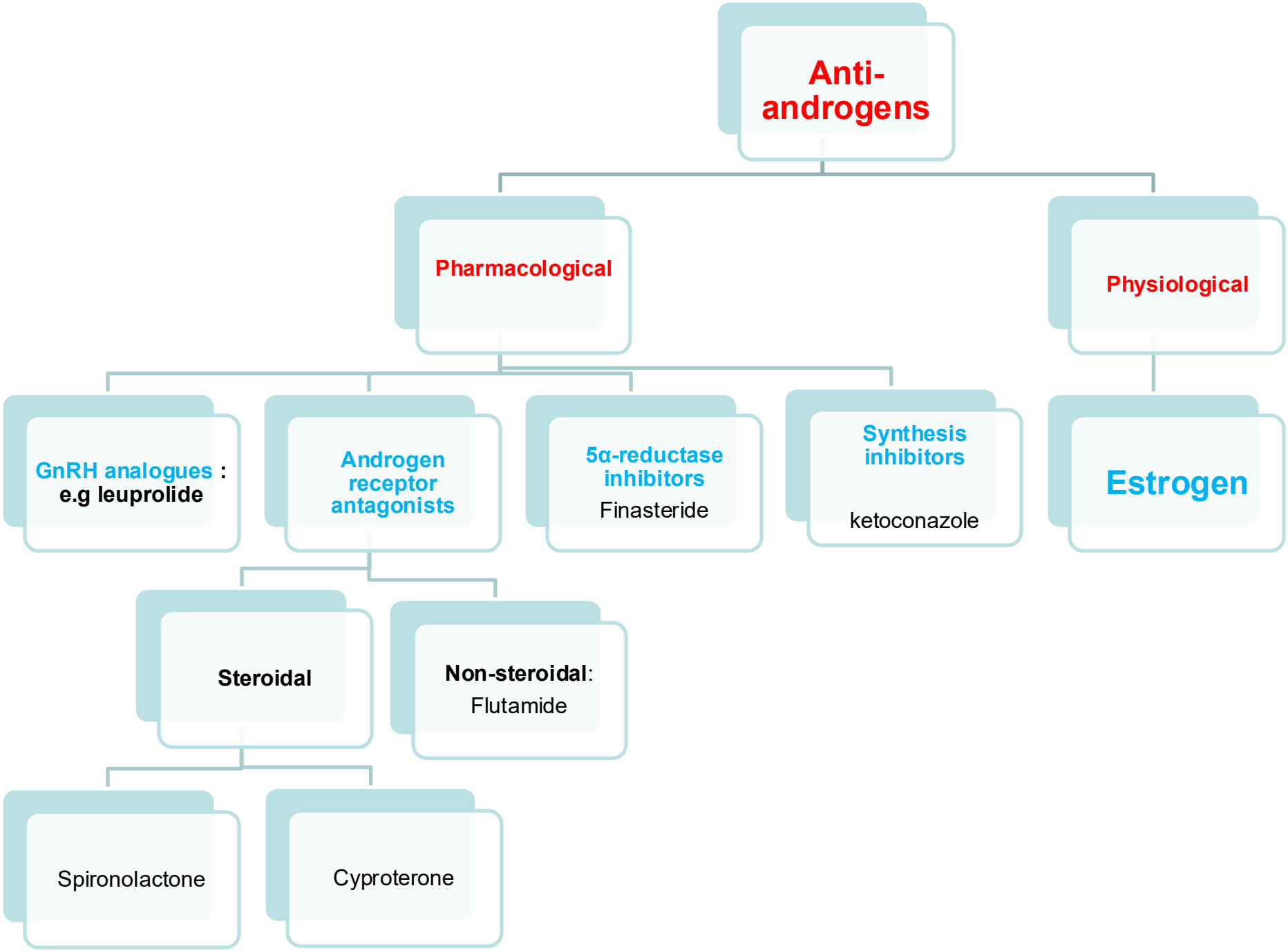
•**Anabolic Androgenic Steroids (AASs)** –(**naturally** occurring or **synthetic**) hormones **increase lean body mass** and **decrease fat mass** and are the most frequently used class of **performance-enhancing drugs**.

•They can also have **significant adverse effects**, especially when used incorrectly.

•**Long-term**, **non-medical** uses are linked to heart problems, unwanted physical changes, and aggression.

•**Doping**: refers to the **use of banned substances** in competitive sports.

Androgen antagonists (Anti-androgens)


Anti-androgens
Pharmacological
Physiological
GnRH analogues : e.g leuprolide
Androgen receptor antagonists
5α-reductase inhibitors
Finasteride
Synthesis inhibitors
ketoconazole
Estrogen
Steroidal
Non-steroidal: Flutamide
Spironolactone
Cyproterone

Pharmacological antagonists include :

1. GnRH analogues : e.g leuprolide **Higher affinity for GnRH receptor** in pituitary than endogenous GnRH.

- **Administration:** SC or IM **of leuprolide (DEPOT FORM)** every 1-4 months
- At **first it will stimulate, then desensitizes GnRH receptor causing ↓ secretion of FSH & LH, so ↓ testosterone secretion in male or estrogen secretion in female**.

Indications:

1- **palliative treatment of prostate cancer**(androgen-dependent), usually with androgen receptor antagonist

2- **Ovarian hyperstimulation programs for anovulatory infertility:**

- to suppress endogenous Gn production

  but **pure GnRH competitive antagonists** **like Ganirelix are preferred for this suppression since they act Rapidly.**

- **Adverse effects:**

  Prolonged use of GnRH analogues may produce menopausal symptoms, and osteoporosis in females (if used longer than 6 months).

2. Androgen receptor antagonists

a. Steroidal :

1. Spironolactone :

•**Mechanism of action**: block AR and decreasing testosterone synthesis by inhibiting **17α-hydroxylase.**

• **Uses: Hirsutism, alopecia, acne**

2. Cyproterone :

•**Mechanism of action**: **blocks androgen receptors**

•**Uses: 1- Hirsutism** if spironolactone fails.

• 2- Sometimes it is used **in prostate cancer palliation**

• ***Dianette*** contains an **estrogen** and **an anti-androgen**.

•**Uses**: skin conditions such as **acne**, **very oily skin** and **excessive hair growth in females of reproductive age.**

b. Non-steroidal :

- Flutamide :

- Used **for palliation of prostate cancer**.
- Its continued use may lead to **↑ LH secretion** which **↑ testosterone synthesis**, and may thus cause **therapeutic failure.**
- So usually it is **combined with GnRH antagonist** or **replaced by cyproterone**.
- **Adverse effects:**
- loss of libido, impotence, vomiting, gynaecomastia, reversible hepatic dysfunction.

- Bicalutamide

1- Fewer GI side effects

2- No liver toxicity

3. Synthesis inhibitors

Ketoconazole :

- **Mechanism of action:**
- Blocks **many CYP450 enzymes** in **gonads** for synthesis of Testosterone.
- Found to be **less effective than anti-androgens** in prostate cancer.
- **Adverse effects**: gynecomastia- liver toxicity

4. 5α-reductase inhibitors

- **Finasteride :** blocks synthesis of Dihydrotestosterone from testosterone in ***prostate*** and ***hair follicles*** by **inhibiting the enzyme 5α-reductase 2**.

Used orally in :

1- **Benign prostatic hyperplasia in elderly**
(20% reduction in prostate size after 1 year of use)

2- Male pattern of baldness

3- Hirsutism

- **Finasteride Was not found useful in prostate cancer** since **5α-reductase 1** is still intact in other tissues e.g. liver, skin fibroblasts

- **Advantages of finasteride:**

less likely to cause ↓ libido or impotence than androgen receptor antagonist

References

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Katzung *by Anthony Trevor, Bertram Katzung, and Susan Masters . 16th edition McGraw Hill,*

Rang & Dale's Pharmacology: *by Humphrey P. Rang ; James M. Ritter ; Rod Flower Churchill Livingstone; 10th edition*

THANK YOU