ANDROGENS & THEIR ANTAGONISTS

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Testosterone

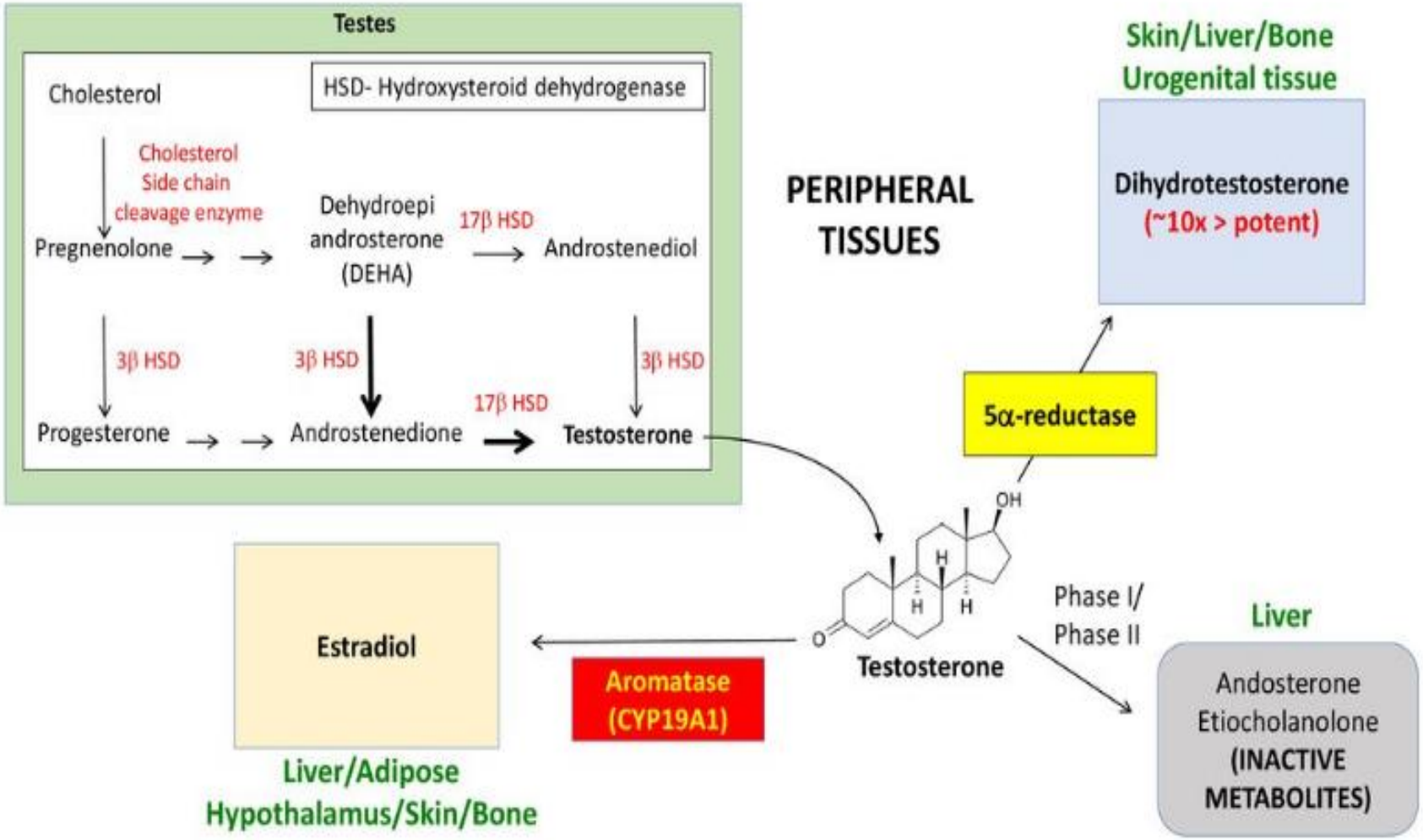
- **Testosterone** is the main androgen produced in testis by interstitial cells of Leydig under influence of (LH).

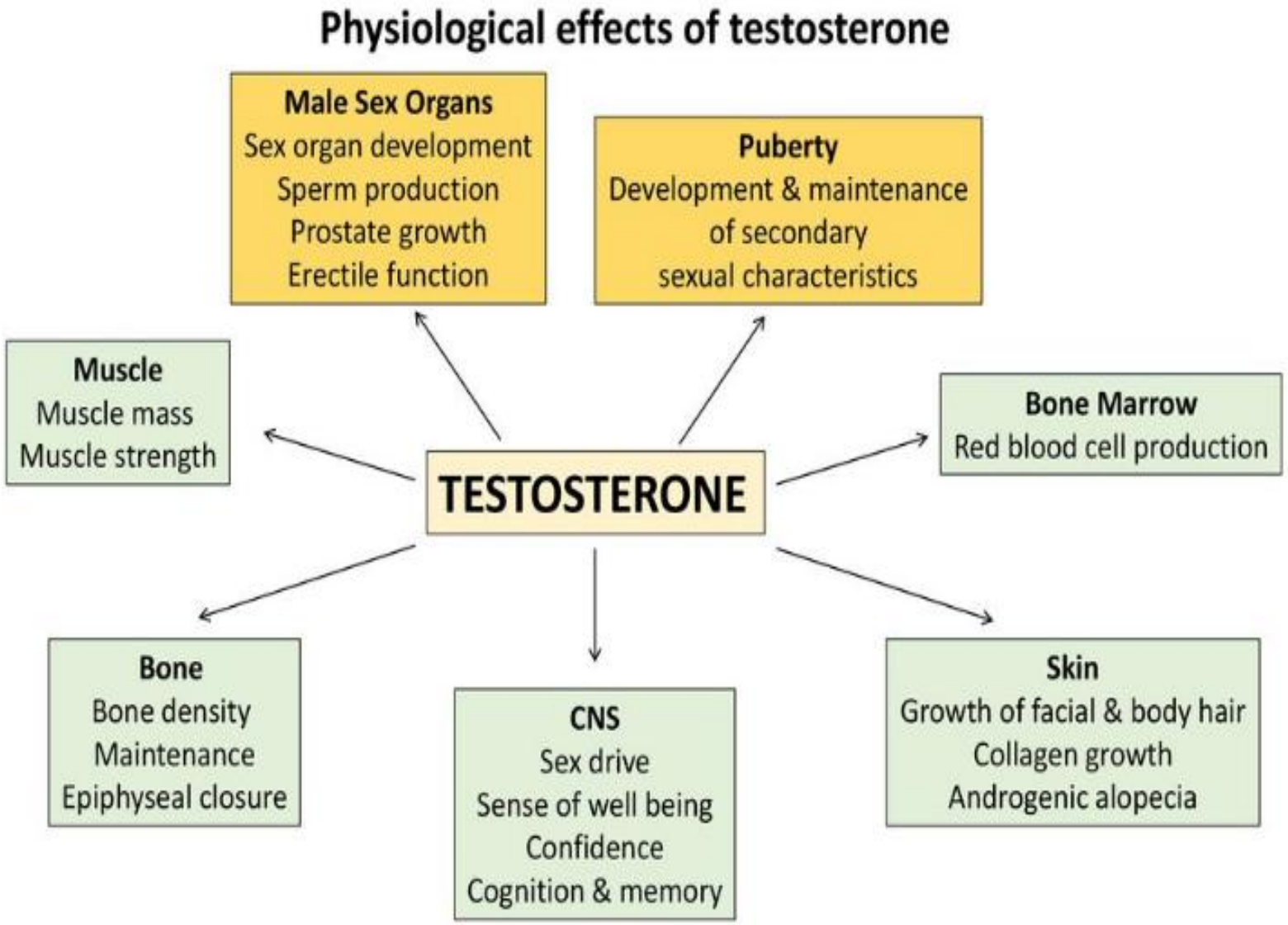
- There are **specific androgen receptors (AR)** in cytoplasm of target cell.

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

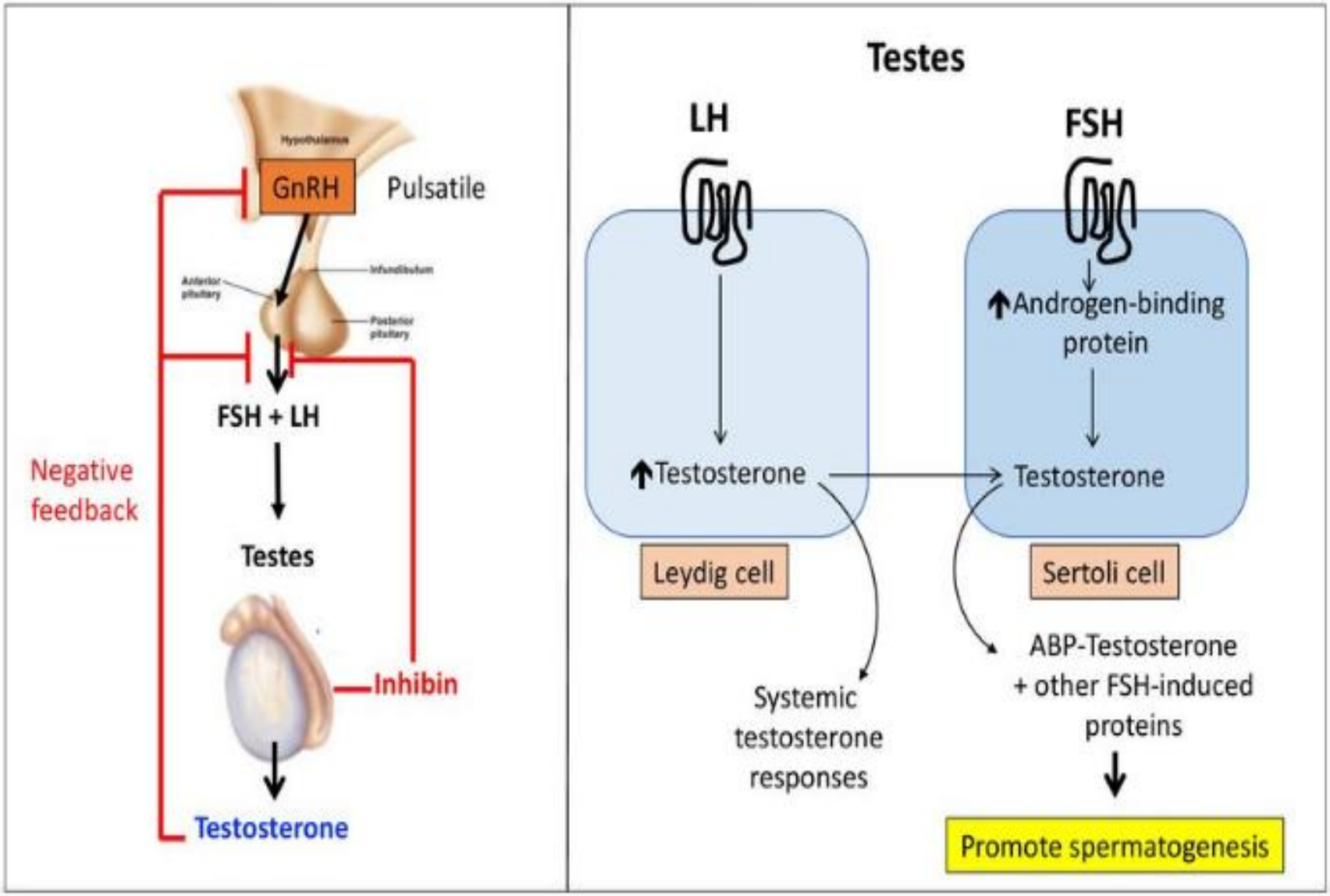
•Testosterone has **androgenic** and **anabolic** activity???

Testosterone Biosynthesis & Metabolism




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
Bone Marrow
Red blood cell production
TESTOSTERONE
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

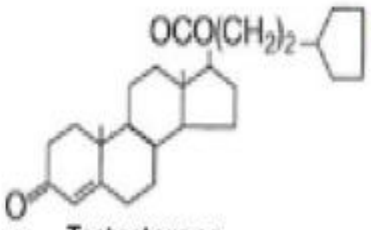


Testosterone preparations

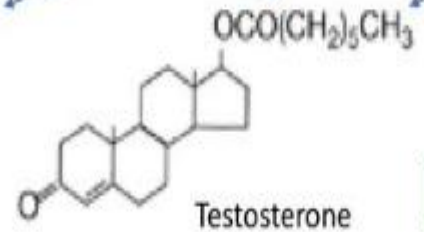
Ester moiety cleaved by tissue esterases following administration to yield active testosterone

Formulation for Transdermal Delivery
- Avoids first pass effect

More lipophilic



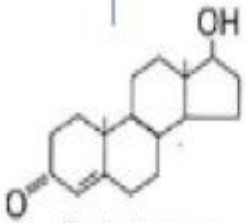
Testosterone cypionate



Testosterone ethanate

Long acting

Esterification

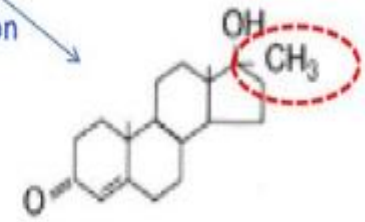


Testosterone

Parenteral administration (e.g. IM)

Oral administration

17α Alkylation



Methyltestosterone

17α alkylation inhibits hepatic catabolism

- Orally bioavailable
- Less androgenic than testosterone
- Increased hepatotoxicity

Rapidly orally absorbed
Low oral bioavailability
High first pass metabolism

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

Treatment: - Testosterone replacement therapy
- adolescents at the time of puberty
- in symptomatic adult men

Note: Treatment of older men with age-related declines in testosterone levels, but no overt hypogonadal symptoms or underlying hypothalamic/pituitary or testicular disease is controversial.

Goal of treatment: - to restore testosterone levels to the normal range
- Serum testosterone levels are monitored for clinical efficacy

Clinical Benefit: - development/maintenance of secondary sexual characteristics
- ↑libido (mediated in part by estradiol)
- ↑muscle strength
- ↑fat-free mass (mediated in part by estradiol)
- ↑bone density (mediated by estradiol)
- improved mood & cognition (+/-)

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

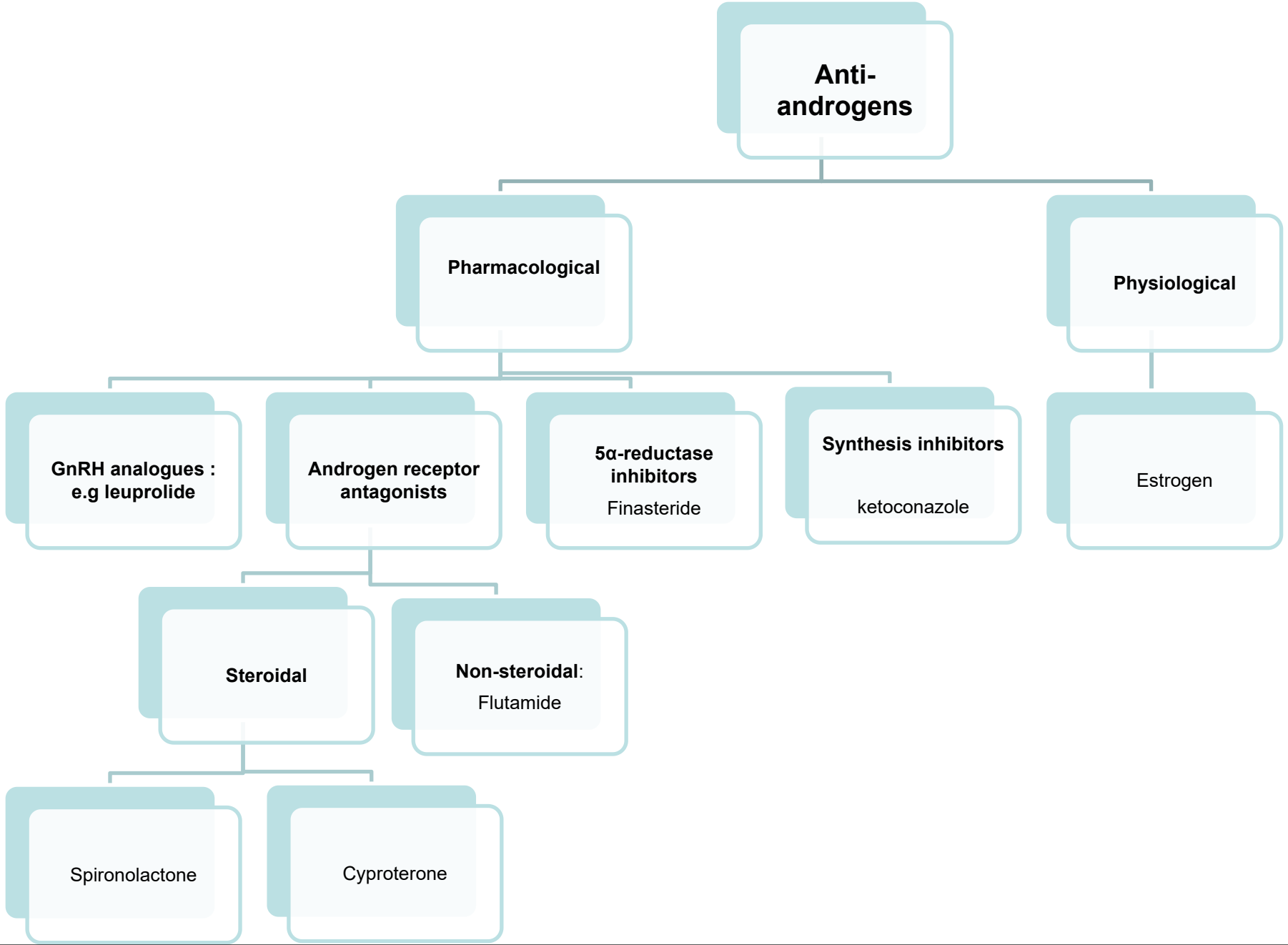
Contraindications:

- 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 – "Doping" refers to the use of banned substances in competitive sports.

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, but 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 during administration of exogenous Gonadotrophins,

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

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 :** block AR and decreasing testosterone synthesis by inhibiting 17α-hydroxylase. **Used for Hirsutism, alopecia, acne**

2. **Cyproterone :** blocks androgen receptors,
   Used for Hirsutism if spironolactone fails.

   Sometimes it is used **in prostate cancer palliation**

Dianette contains an oestrogen and an anti-androgen. Dianette is used to treat 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.

S.E.: loss of libido, impotence, vomiting, gynaecomastia, reversible hepatic dysfunction.

- Bicalutamide has fewer GI side effects;
no liver toxicity

3. Synthesis inhibitors :

Ketoconazole : blocks many CYP450 enzymes in gonads for synthesis of Testosterone. Found to be less effective than anti-androgens in prostate cancer. S.E.: gynaecomastia; 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 :

Benign prostatic hyperplasia in elderly

(20% reduction in prostate size after 1 year of use)

Other uses of finasteride are :

Male pattern of baldness

Hirsutism

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

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

References

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THANK YOU