Testosterone

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Sex Hormones

- Male sex hormones
  - Masculinizing hormones (Androgens)
    - Testosterone
    - Dihydro Testosterone
  - Androgen Precursors
    - Dehroepiandrosterone (DHEA)
    - Androstenedione
- Female sex hormones
  - Feminizing hormones
    - Estrogen
    - Progesterone

Sex Hormones

- **Androgen:**
  - Any steroid that controls the development and maintenance of masculine characteristics

- **Testosterone:**
  - A natural male androgen of testicular origin, controlled by the luteinizing hormone (LH)

Synthesis of Androgens

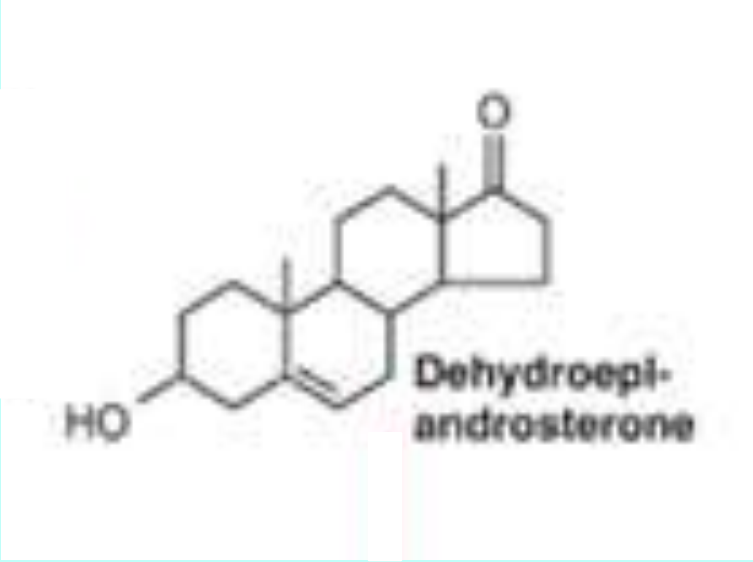
- Sites
  - Adrenal cortex
  - Testes
- Substrate in all Sites
  - Cholesterol

Testicular synthesis of androgens

- Leydig cells
  - Found in
    - Interstitial tissues of Testes
  - Intracellular Site
    - Smooth Endoplasmic Reticulum
    - Mitochondria

***Adrenal Androgens

- Have a keto group at position 17 and therefore are called 17-ketosteroids.
- The major secreted form is dehydro-epi-andro-sterone (DHEA)



***Adrenal Androgens

- Although adrenal androgen is the precursor of the potent androgen testosterone, normally little is produced in the adrenals because the enzymes necessary for the conversion are not present.
- For the same reason, estradiol secretion by the adrenal is small.

Testosterone

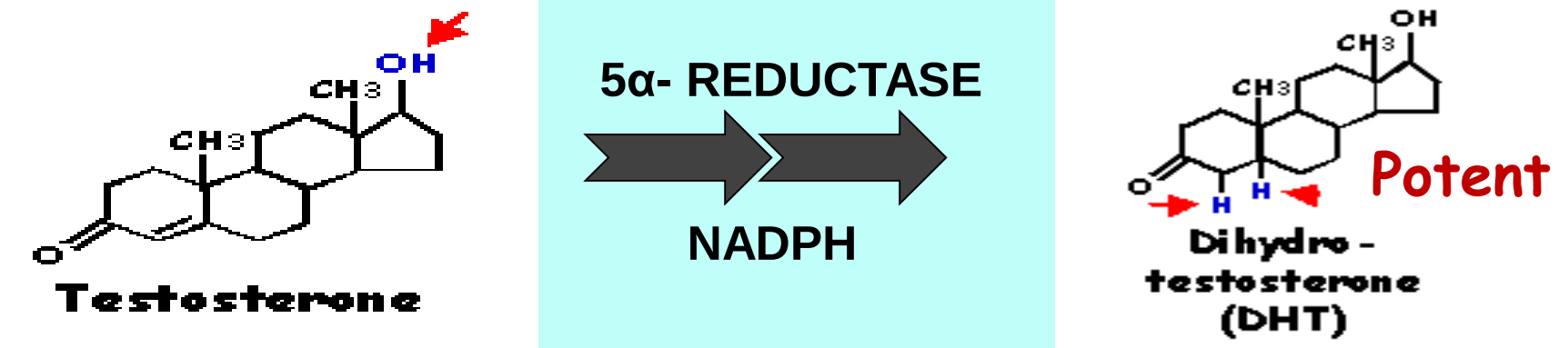
- Circulation
  - 65 % bound to a Globulin called ***SHBG***
  - 33 % is loosely bound to Albumin
  - 2 % is freely circulating ***Free T*** ***(f T)***
- BIOAVAILABLE ***T***
  - free + albumin bound
- TOTAL ***T***
- Normal levels
  - 300—1200 ng / 100 ml

Excretion of Testosterone

- A small amount of circulating testosterone is converted to estradiol, but most of the testosterone is converted to 17-ketosteroids, principally androsterone and its isomer etiocholanolone, and excreted in the urine.
- About two thirds of the urinary 17-ketosteroids are of adrenal origin, and one third are of testicular origin.
- Although most of the 17- ketosteroids are weak androgens (they have 20% or less the potency of testosterone),

DihydroTestosterone

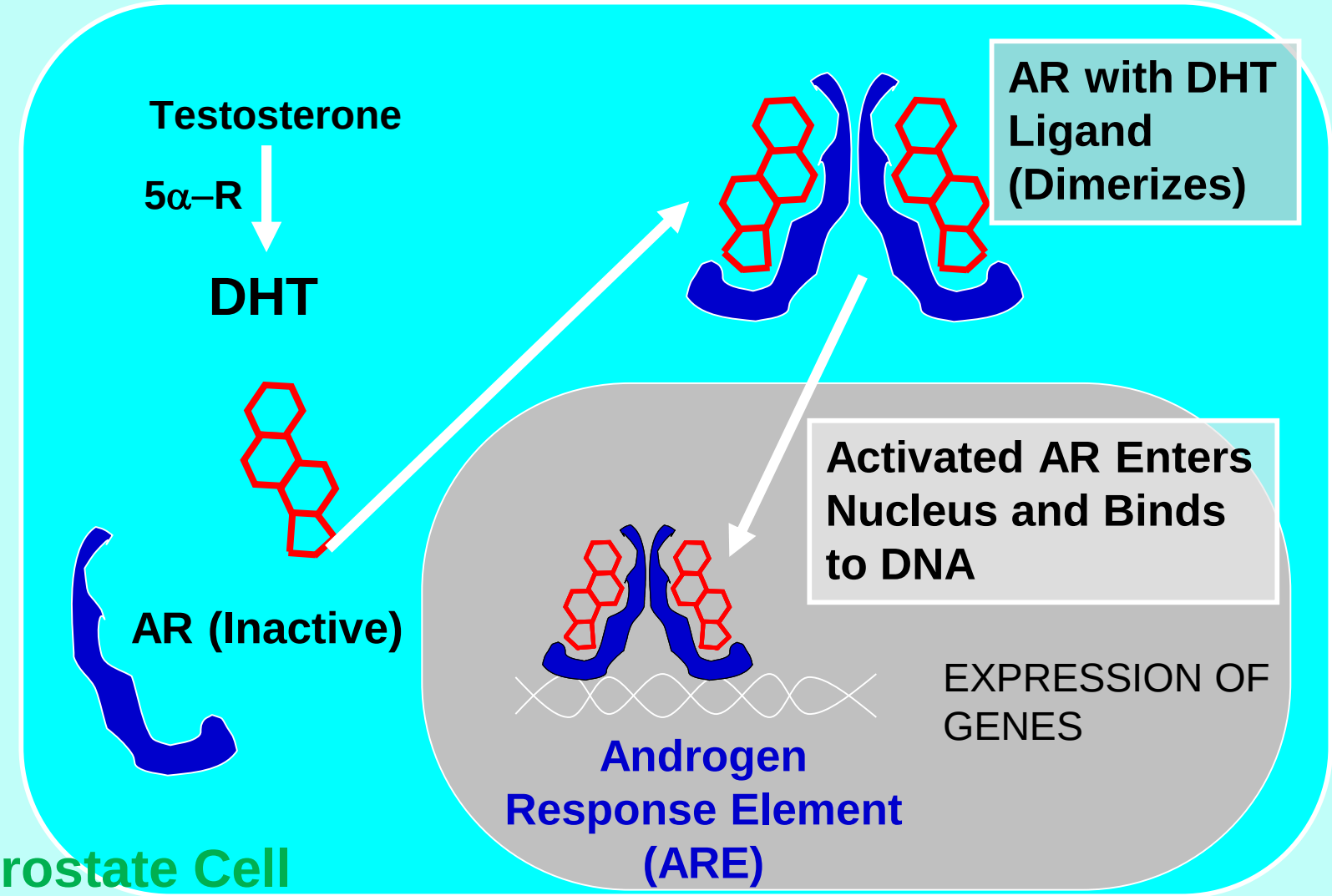
- By
  - Reduction of double bond at C-5 of ring A leads to formation of Dihydrotestosterone



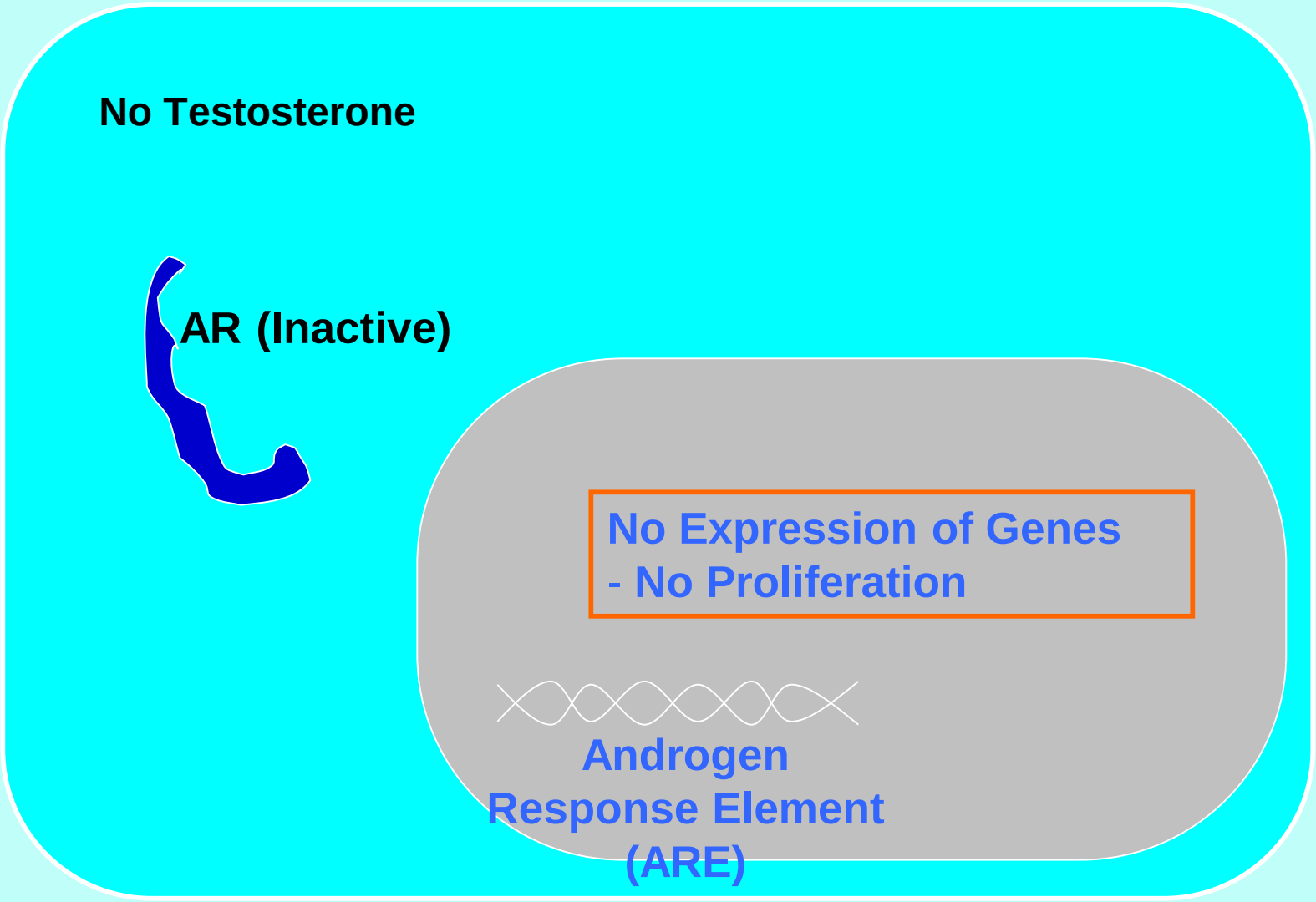
- DHT is acting in classic target tissues
- Classic target organs have
  - Receptor for T
  - 5 α - reductase activity

Mechanism of action of Testosterone

- Classic target cells



When No Androgens are present



Prostate Cell

Metabolic functions of testosterone

- Increase protein synthesis in target organs of the body

- Classic target organs
  - Prostate
  - External genitelia
  - Genital skin

Target organs of Testosterone

- Some target organs have
  - ***NO*** 5 α-reductase activity in their cells
- ***T*** have direct effect
- ½ potency of DHT
- These are
  - Epidydmis > Muscle
  - Vas deference > Bone
  - Seminal vesicals > Brain
  - Spermatogonia

Secondary sexual characters

- Hair distribution
  - Skin has receptors of T
  - Increase protein synthesis
    - Necessary for hair formation
- So leading to
  - Male like hair distribution

- Effect on voice
  - Hypertrophy of laryngeal mucosa
  - & Enlargement of larynx
- Because of
  - ***T*** **receptors**

- Effects on skin
  - Increase thickness
  - Increase secretion of some sebaceous glands sp. on face
- Which result in
- ***Acne***

Secondary sexual characters

External genitalia: Penis increases in length and width. Scrotum becomes pigmented and rugose.

Internal genitalia: Seminal vesicles enlarge and secrete and begin to form fructose. Prostate and bulbourethral glands enlarge and secrete.

Voice: Larynx enlarges, vocal cords increase in length and thickness, and voice becomes deeper.

Hair growth: Beard appears. Hairline on scalp recedes anterolaterally. Pubic hair grows with male (triangle with apex up) pattern. Hair appears in axillas, on chest, and around anus; general body hair increases.

Mental: More aggressive, active attitude. Interest in opposite sex develops.

Body conformation: Shoulders broaden, muscles enlarge.

Skin: Sebaceous gland secretion thickens and increases (predisposing to acne).

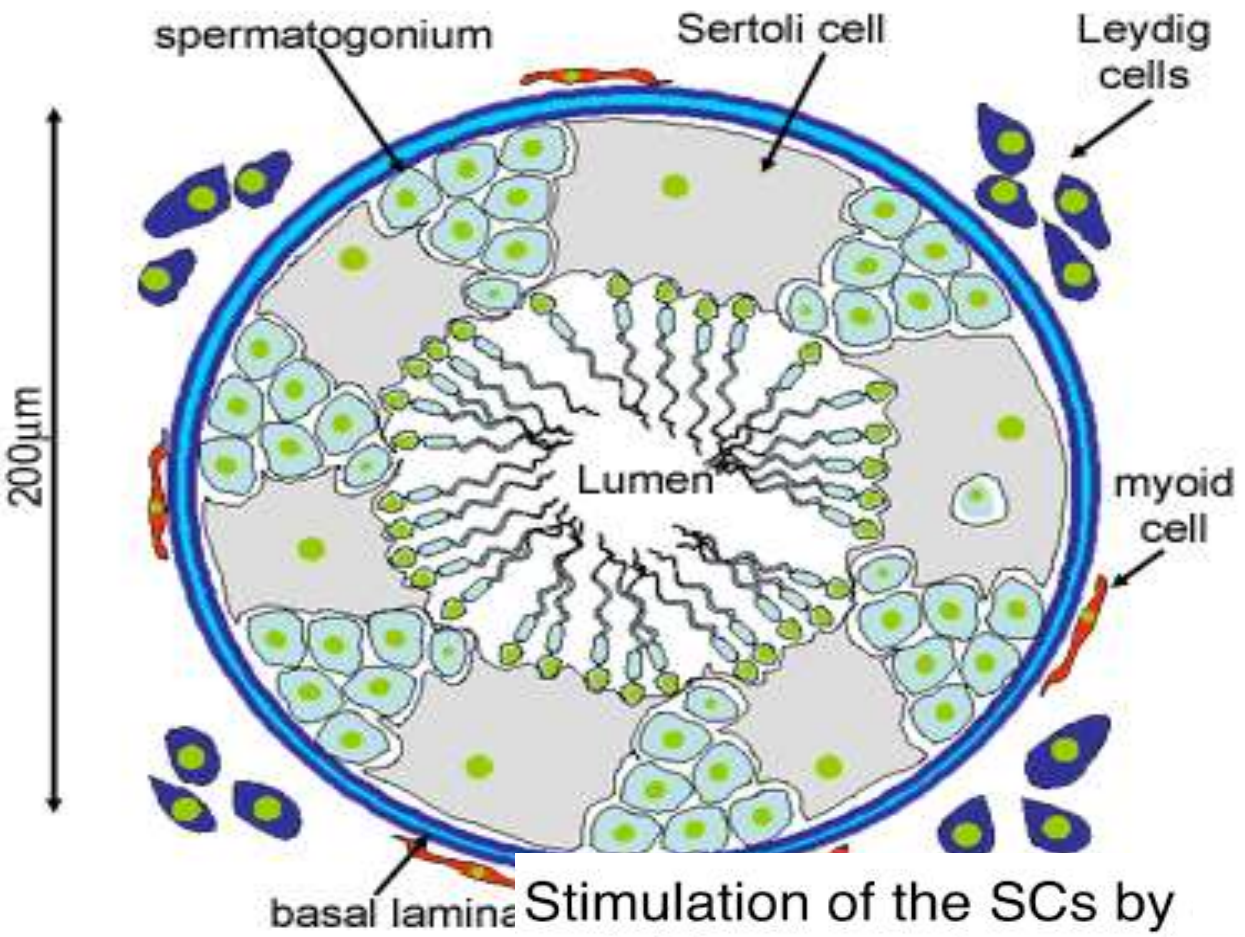
- Effects on muscles
  - A 50 % increase in mass over females
  - Increase formation & storage of creatine in muscle

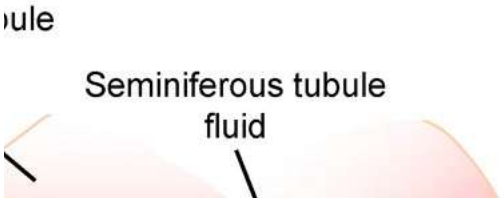
- Effect on bone
  - Increase in bone matrix
    - Because of osteoid tissue formation

- Effect on ***Basal metabolic rate***
  - A 15 % increase because of synthesis of
    - ***Enzymes***
- So activities of all cells increase
  - cause moderate Na+, K+, H2O, Ca2+, SO4–, and PO4– retention;
- Increase the size of the kidneys.

- Increase ***RBC*** mass
  - Due to
    - Protein synthesis

Hormonal control of testicular function



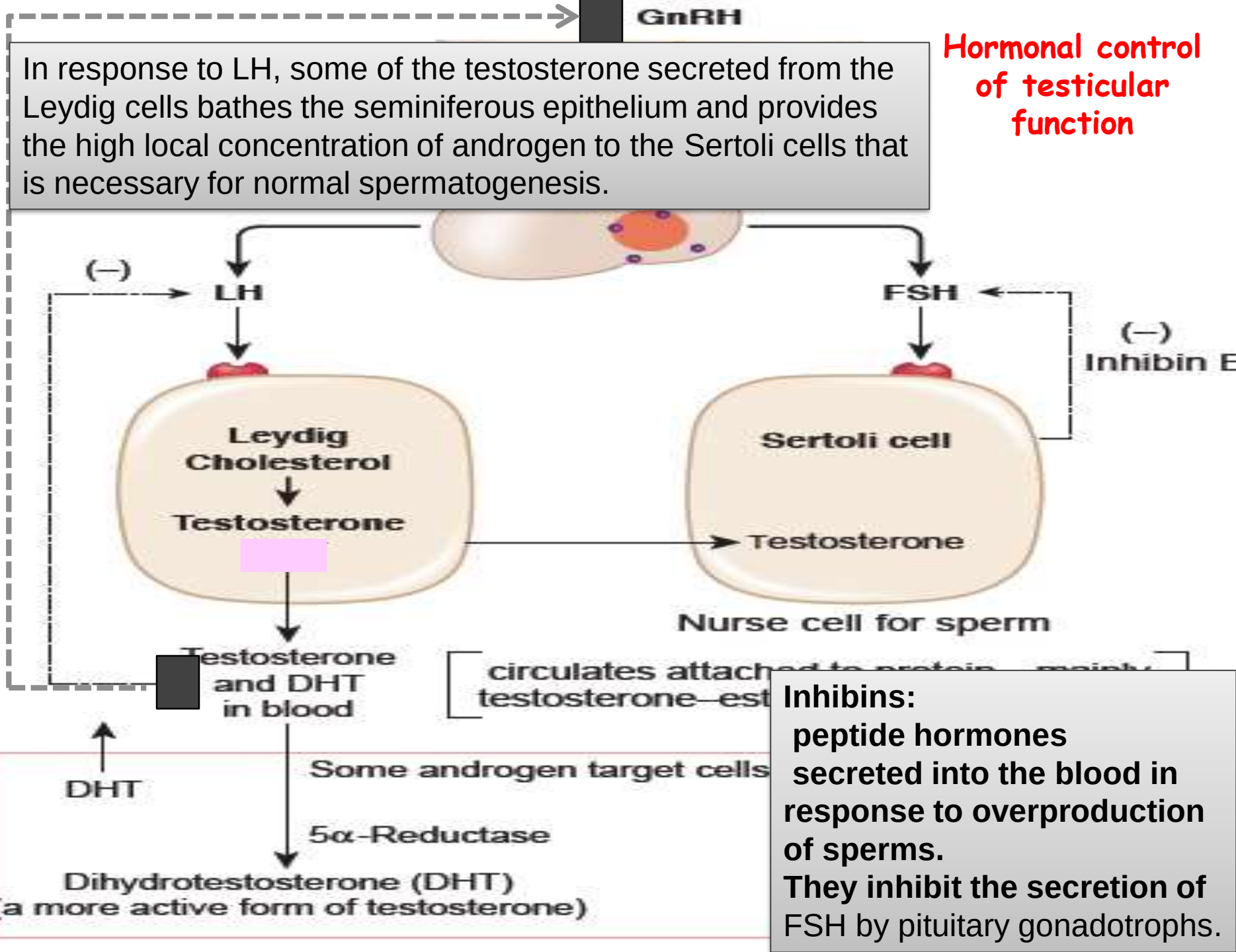


Stimulation of the SCs by FSH helps to maintain spermatogenesis:

- SCs express androgen receptors that are needed for the recognition of testosterone, essential in the progression of spermatogenesis[41].
- SCs express follicle-stimulating hormone (FSH) receptors that are required for the recognition of FSH, essential for maximal sperm production

Hormonal control of testicular function

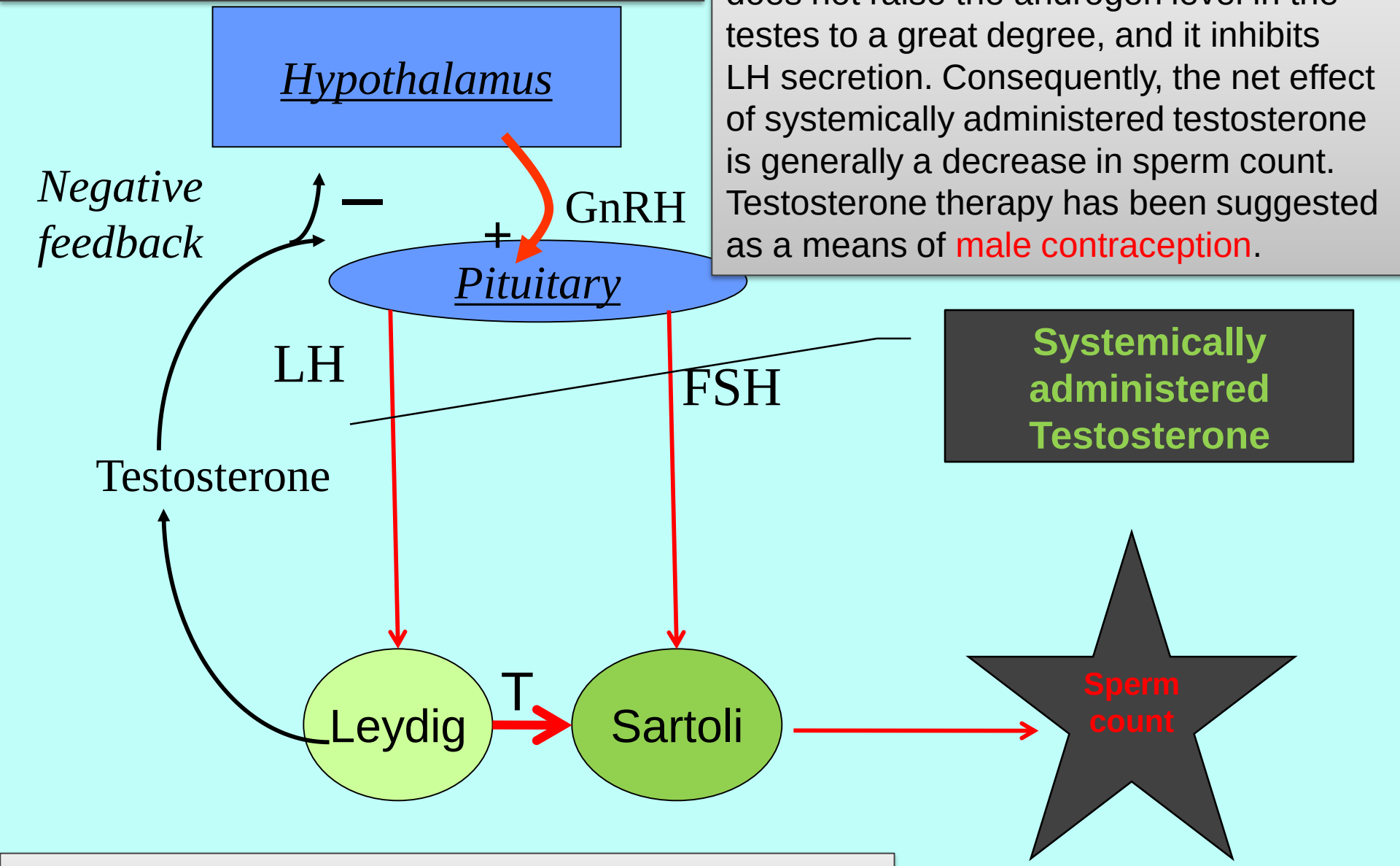
In response to LH, some of the testosterone secreted from the Leydig cells bathes the seminiferous epithelium and provides the high local concentration of androgen to the Sertoli cells that is necessary for normal spermatogenesis.



Inhibins:
peptide hormones
secreted into the blood in response to overproduction of sperms.
They inhibit the secretion of FSH by pituitary gonadotrophs.

The possible use of inhibins as male contraceptives is now being explored.

Systemically administered testosterone does not raise the androgen level in the testes to a great degree, and it inhibits LH secretion. Consequently, the net effect of systemically administered testosterone is generally a decrease in sperm count. Testosterone therapy has been suggested as a means of male contraception.



However, the dose of testosterone needed to suppress spermatogenesis cause sodium and water retention..

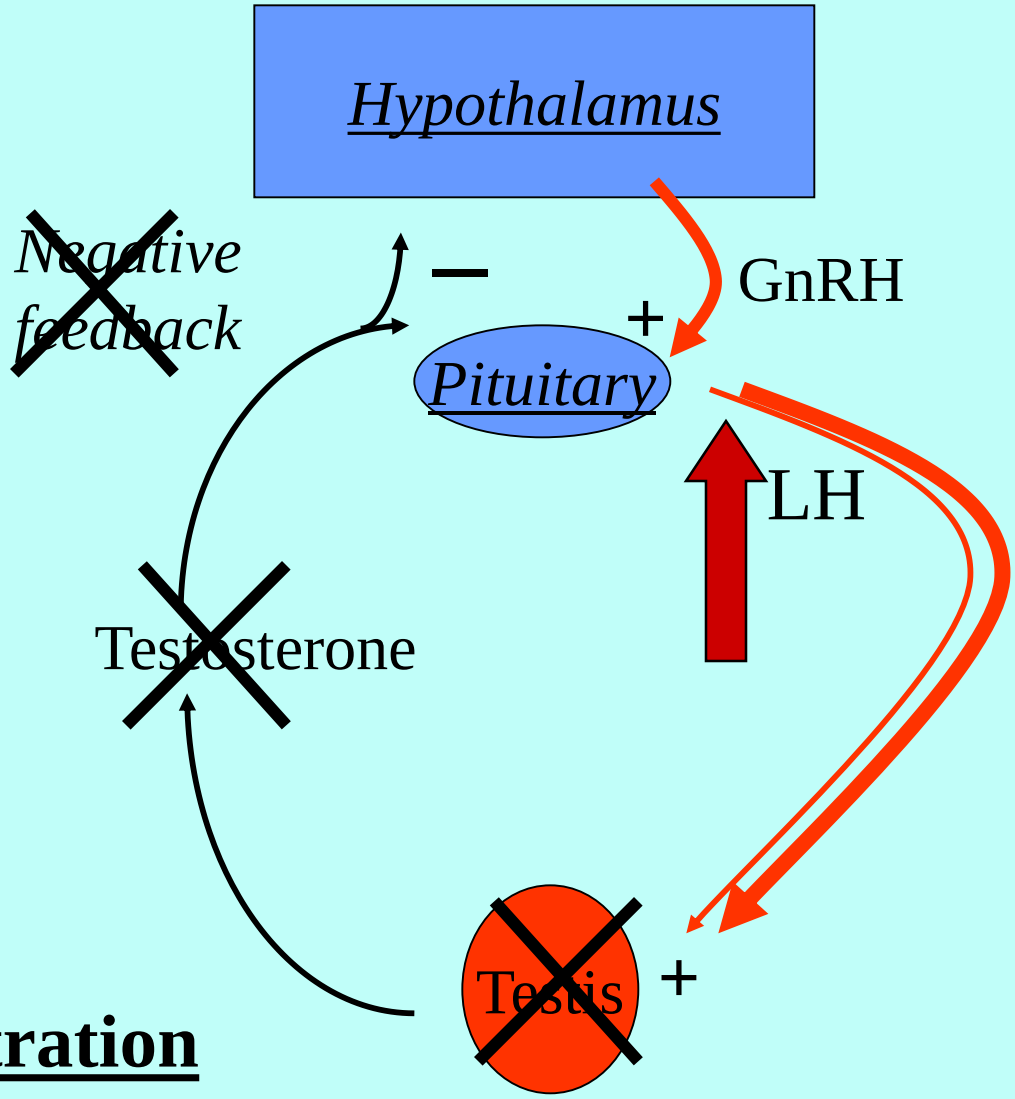
BPH & Prostatic carcinoma

- The cancerous cells are usually stimulated to more rapid growth by testosterone and are inhibited by removal of both testes so that testosterone cannot be formed.
- Prostatic cancer usually can be inhibited by administration of estrogens.

Removing Androgens

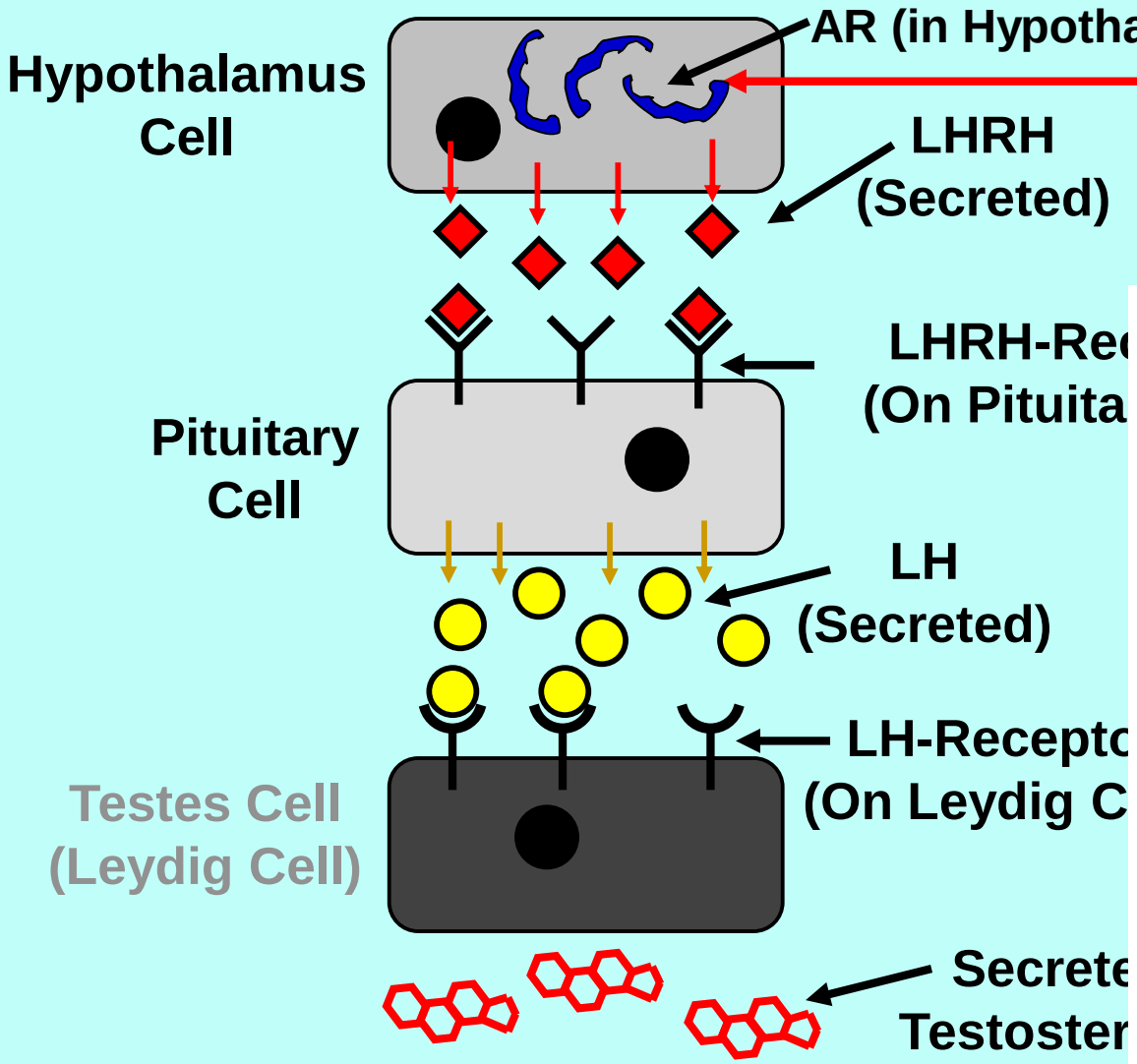
1. Orchiectomy (castration):
   - surgical removal of the testicles.
2. Block testosterone **production**.
3. Block **conversion** to DHT.
4. Block the **effects** of testosterone.

Orchiectomy (castration):



Castration

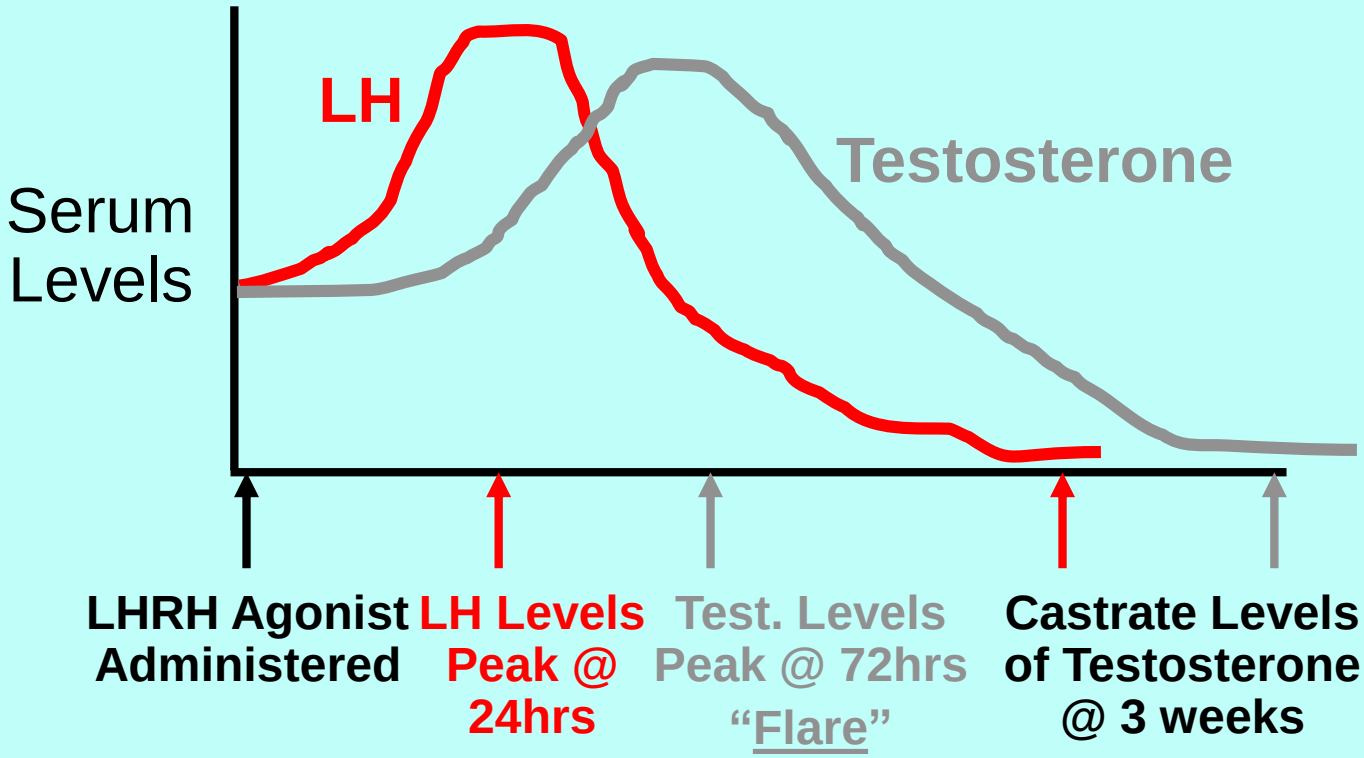
Receptors and Feedback



GnRH—synthesized in preoptic region of hypothalamus and secreted in pulses into hypophyseal portal vessels

- produces pulsatile release of LH and FSH
- pulsatile release of GnRH prevents downregulation of its receptors in anterior pituitary

LHRH Agonists

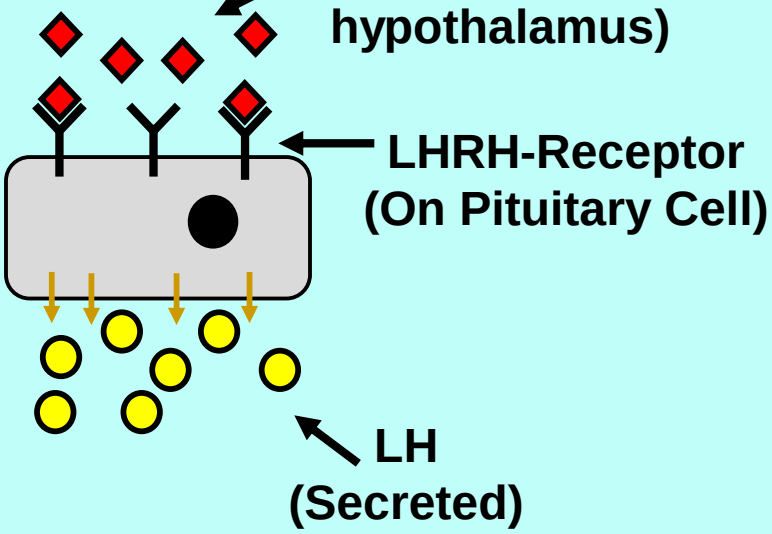


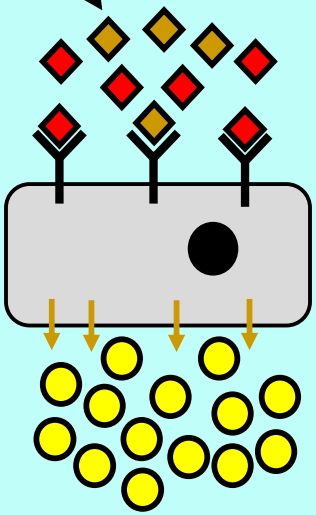
Not to scale.

LHRH Agonists

- An LHRH agonist is a factor that mimi
  function of LHRH.
- Examples: Leuprolide (Lupron), Gose
  (Zoladex), Buserelin (Suprefact), and
  (Synarel).
  - Used to treat:
    - prostate and breast cancer
    - Uterine fibroids
    - Early puberty

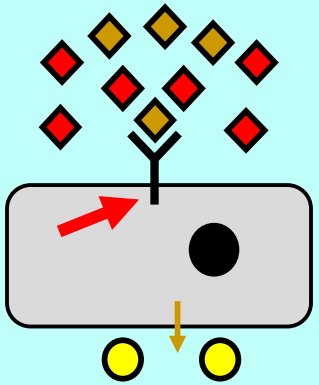
How Do Chronic LHRH Agonists Decrease Testosterone?





Initially:
Secreted Levels of LH Increase (Flare)
which typically lasts for about 1-2 weeks

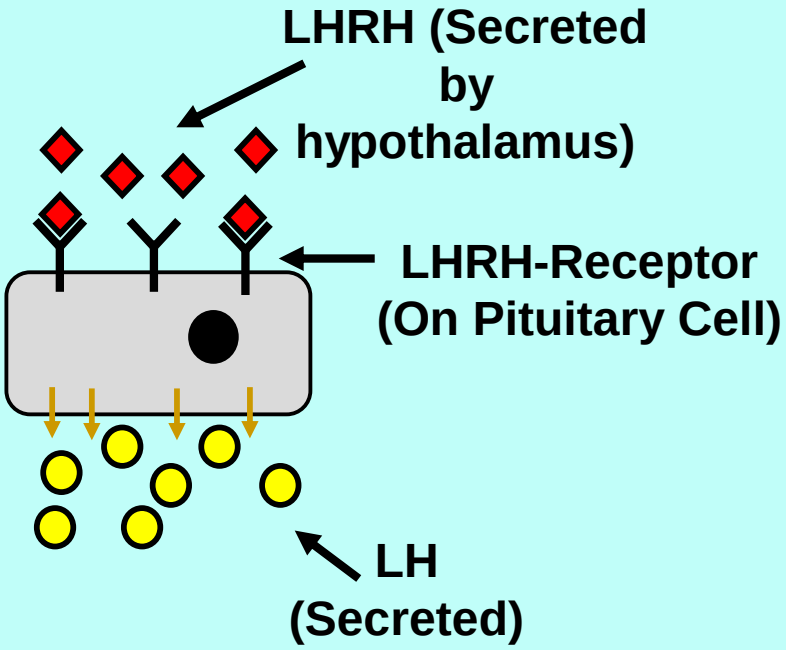
Chronically

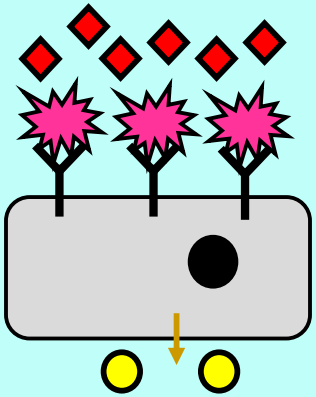


GnRH agonists, decrease testosterone levels in the body through a mechanism known as "down-regulation" or "desensitization" of the pituitary gland.

LHRH Antag

- An LHRH Antagonist is a factor effect of LHRH.
- Examples: Cetrorelix (Cetrotide), Abarelix (Plenaxis), and Orgalutran (Ganirelix).
  - For advanced prostate cancer
- Mechanism: directly inhibit the LHRH-receptor on Pituitary cells, resulting in decreased secretion of LH.

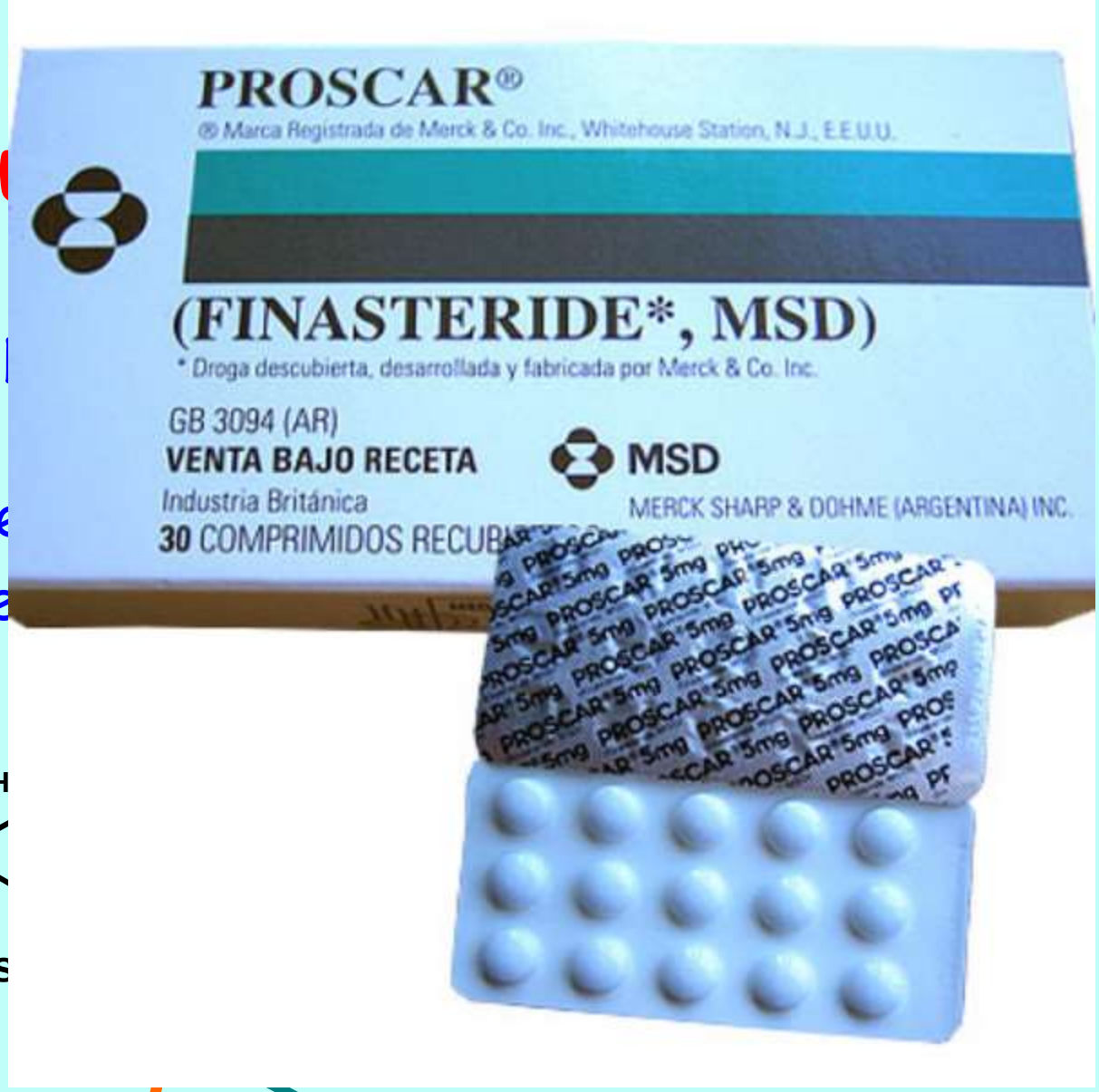


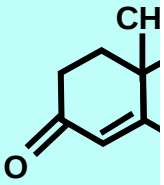


- LHRH-Antagonist prevents LHRH from binding to receptor.
- Decreased LH secretion and thus decreased testosterone production.
- No testosterone "flare"

5α-Redu

- Purpose: Block t
  testosterone to
- Example: Finaste
- Result: decrease





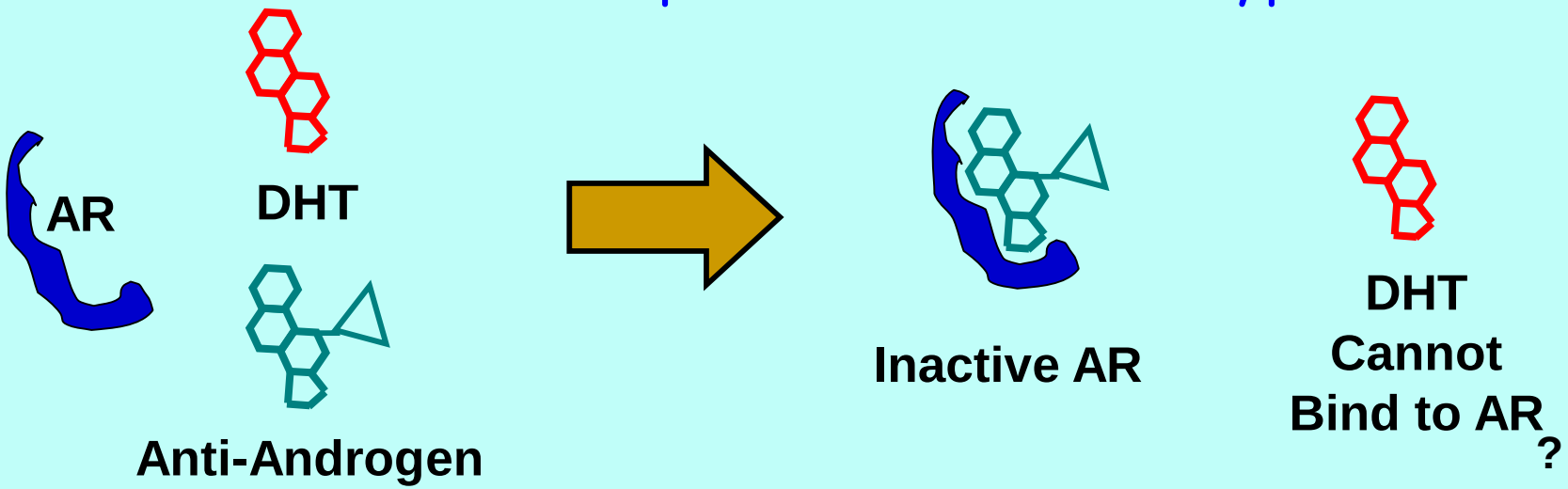
Testos

Converting Enzyme:
5-alpha-Reductase

Finasteride

Anti-Androgens

- Androgen "look-alike" mo
  Androgen Receptor and p
  (competitive inhibition).
- Examples: Cyproterone (
  Chimax) , Bicalutamide (
  (Nilandron).
- Used treatment of androgen dependent conditions:
  - Acne, excessive hair grwth, early puberty, prostate cancer
- Bind and inhibit ARs in prostate as well as hypothalamus.



Hormonal changes in specific altered states

	Sex steroids	LH	FSH
1. Primary hypogonadism	↓	↑	↑
2. Pituitary hypogonadism	↓	↓	↓
3. Postmenopausal women	↓	↑	↑
4. Anabolic steroid therapy (male)*	↑	↓	(↓)
5. Inhibin infusion (male)†	–	–	↓
6. GnRH infusion (constant rate)‡	↓	↓	↓
7. GnRH infusion (pulsatile)	↑	↑	↑