Hormonal Control of Male Reproduction

Male Reproductive Physiology

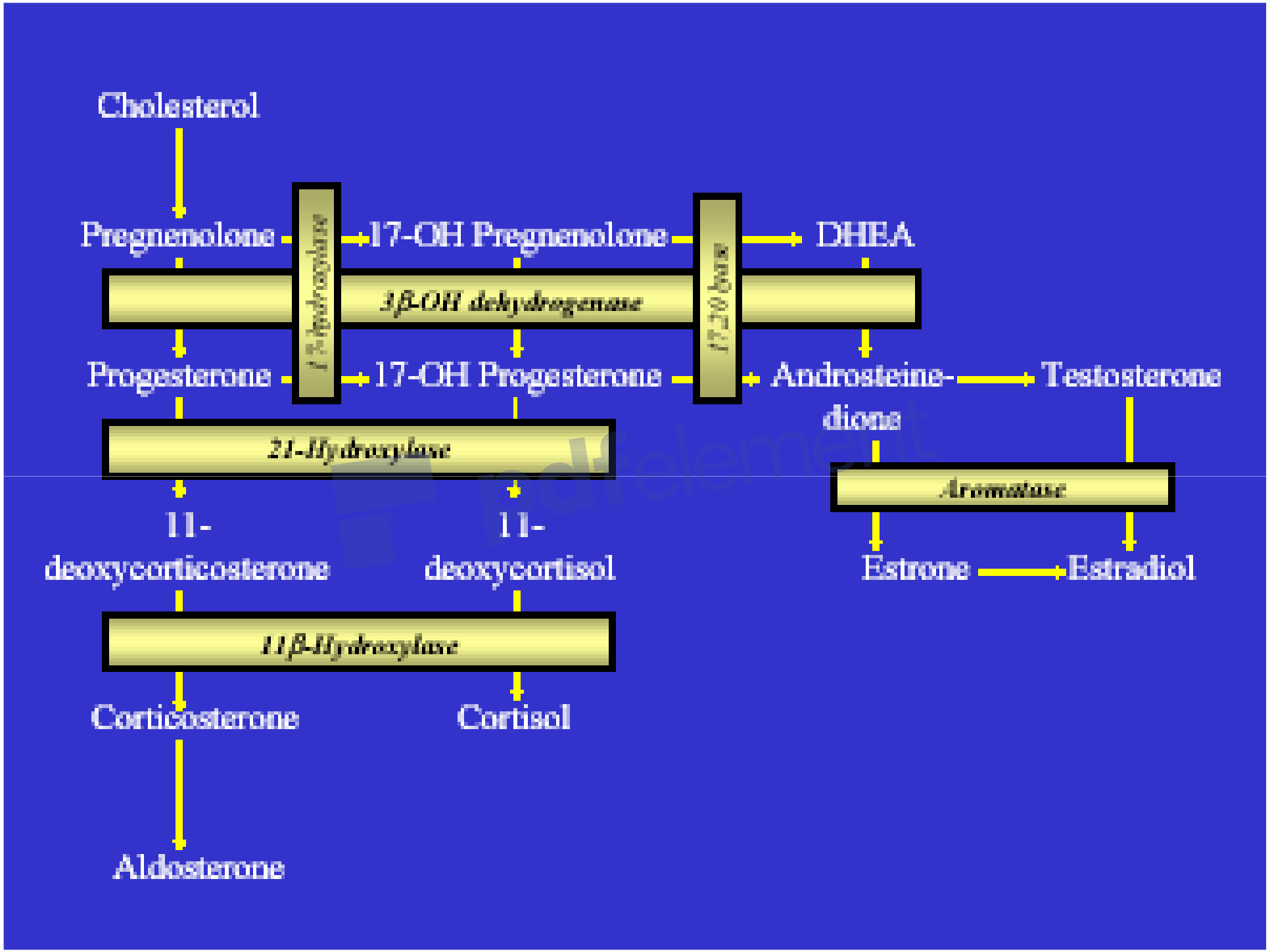
- Pituitary-Hypothalamic control of Functions
- Functions of Luteinizing Hormone
- Functions of Folicle-Stimulating Hormone
- Functions of Sertoli Cells
- Functions of Leydig Cells
- Hormonal Production Rates
- Actions of Androgens

Hormonal control of male reproductive function

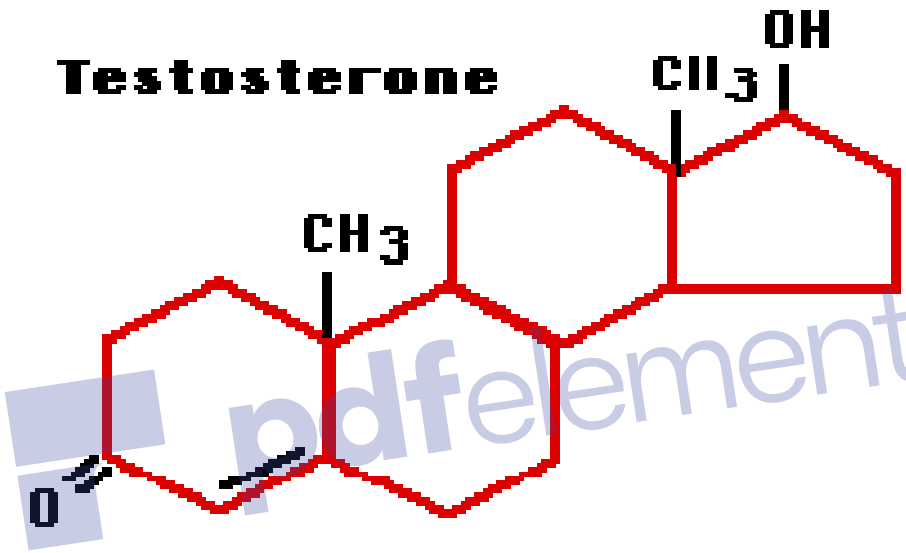
1. Hypothalamic GnRH stimulates the anterior pituitary to secrete FSH and LH, which then act on the testes: FSH on the Sertoli cells to stimulate spermatogenesis and inhibin secretion, and LH on the Leydig cells to stimulate testosterone secretion.
2. Testosterone acting locally on the Sertoli cells, is essential for maintaining spermatogenesis.
3. Testosterone exerts a negative-feedback inhibition on both the hypothalamus and the anterior pituitary to reduce LH secretion. Inhibins exerts a negative feedback inhibition on FSH secretion.
4. Testosterone maintains the accessory reproductive organs and male secondary sex characteristics and stimulates growth of muscle and bone. In many of its target cells it must first undergo transformation to dihydrotestosterone or to estrogen.

Testosterone: Biosynthesis

- Testosterone, the principal hormone of the testis, is a C19 steroid with an –OH group in the 17 position.
- It is synthesized from cholesterol in the **Leydig cells** and is also formed **androstenedione** secreted by the adrenal cortex.
- In the Leydig cells **17a-hydroxylase** is present. **Pregnenolone** is therefore hydroxylated in the 17 position and then subjected to side chain cleavage to form **dehydroepiandrosterone**.
- Dehydroepiandrosterone and androstenedione are then converted to testosterone.
- The secretion of testosterone is under the control of LH, and the mechanism by which LH stimulates the Leydig cells involves increased formation of cAMP via the serpentine LH recepter and Gs.
- Cyclic AMP increases the formation of cholesterol to pregnenolone via the activation of protein kinase A.


Cholesterol
Pregnenolone
17-OH Pregnenolone
DHEA
3β-OH dehydrogenase
17-hydroxylase
17,20 lyase
Progesterone
17-OH Progesterone
Androsteine-dione
Testosterone
21-Hydroxylase
Aromatase
11-deoxycorticosterone
11-deoxycortisol
Estrone
Estradiol
11β-Hydroxylase
Corticosterone
Cortisol
Aldosterone

Testosterone: Secretion



- The testosterone secretion rate is 4- mg/day (13.9-31.33 μmol/day) in normal adult males. Small amounts of testosterone are also secreted in female from adrenal.

Testosterone: Transport & Metabolism

- Ninety-eight percent (98%) of the testosterone in plasma is bound to proteins: 65% is bound to a β-globulin called gonadal steroid-binding globulin (GBG) or sex steroid-binding globulin, and 33% to albumin.
- GBG also also binds estradiol. The plasma testesterone level is 300-1000 ng/dL (10.4-34.7 nmol/L) in adult male and 30-70 ng/dL (1.04-2.43 nmol/L) in female. It declines some what with age in males.
- A small amount of circulation testosterone is converted to estradiol, but most of the testosterone is converted to 17-ketosteroids, principally androsterone and its isomer etiocholanolone and excreated in the urine.
- About $^{2}/3$ of the urinary 17-ketosteroids are of adrenal origin, and $^{1}/3$ are of testicular origin. Etiocholanolone hase no androgenic activity, and testosterone it shelf is not a 17-ketosteroid.

Testosterone: Action

- In addition to their actions during development, testosterone has some other functions.

1. Testosterone and other androgens exert an inhibitory feed-back effect on pituitary LH secretion.

2. Develop and maintain the male secondary sex characteristics.

3. Exert an important protein-anabolic, growth promoting effect and along with FSH, maintain spermatogenesis.

Secondary sex characteristics

- **External genitalia :** Penis increases in length & 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, voice becomes deeper.
- **Hair growth :** Beard appears. Hairline on scalp recedes an terolaterally. Pubic hair grows with male pattern. Hair appears in axilles, on chest, and around anus, general body hair increases.
- **Mental:** More aggressive, active attitude. Interest in opposite sex develops.
- **Body conformation:** Shoulder broaden, muscles enlarge.
- **Skin:** Sebaceous gland secretion thickens and increases.

Mechanism of Action 1

- Testosterone binds to an intracellular receptor, and the receptor-steroid complex then binds to DNA in the nucleus, facilitating transcription of various genes.
- In addition, testosterone is converted to **dihydrotestosterone (DHT)** by **5α-reductase** in some target cells, and DHT binds to the same intracellular receptor as testosterone (more stable).
- DHT formation is a way of amplifyng the action of testosterone in target tissues.
- There are two 5α-reductases in humans, encoded by different genes. Type 1 5α-reductases is present in skin through out the body and is the dominant enzyme in the in the scalp. Type 2 5α-reductases is present in genital skin, the prostate, and other genital tissues.

Mechanism of Action 2

- Testosterone-receptor complex are responsible for the maturation of Wolffian duct structure and consequently for the formation of male internal genitalia during development, but DHT-receptor complex are needed to form male external genitalia.
- DHT-receptor complexes are also primarily responsible for enlargement of the prostate and probably of the penis at the time of puberty, as well as for the facial hair, the ace, and the temporal recession of the hairline.
- On the other hand, the increase in muscle mass and the development of male sex drive and libido depend primarily on testosterone rather than DHT.

Mechanism of Action 3

- **Congenital 5α-reductase deficiency**, in which the gene for type 2 5α-reductaseis mutated, produces male **pseudohermaphroditism**.
- Individuals with this syndrome are born with male internal genitalia including testes, but they have female external genitalia and are usually raised as girls.
- When they reach puberty, LH secretion and circulating testosterone levels are increased and they develop male body contours and male libido (enlargement of clitorises).
- This enlargement probably occurs because with the high LH, there is enough testosterone to overcome the need for DHT amplification in the genitalia.
- 5α-reductase-inhibiting drugs are now being used clinically to treat benign prostetic hyperplasia, and finasteride, the most extensively used drug, has its greatest effect on type 2 5α-reductase.

Control of the testes 1

- In a normal adult man, the GnRH secreting neuroendocrine cells fire a brief burst of action potentials approximately every 2h, secreting GnRH at these times.
- The GnRH reaching the anterior pituitary during each periodic pulse triggers the release from the anterior pituitary of both LH and FSH.
- Systemic plasma concentrations of FSH and LH also show rhythmical episodic changes rapid increases during the pulse followed by slow decrease over the next 10 min or so as the hormones are slowly removed from e plasma.
- There is a clear separation of the actions of FSH and LH within the testes.
- FSH acts on the Sertoli cells to stimulate the production of paracrine agents that stimulate spermatogenesis and other Sertoli cell functions.

Control of the testes 2

- LH acts on the Leydig cells to stimulate testosterone secretion.
- Testosterone acts locally, as a paracrine agents, on permatogenesis by moving from the interstitial spaces into the seminferous tubules.
- Testosterone enters Sertoli cells, and it is via these cells that it facilitates spermatoenesis.
- It must be emphasized that, despite he absence of any direct effect of LH on spermatogenesis, this hormone exerts an essential indirect effect because the testosterone secretion stimulated by LH is required for spermatogenesis.
- Negative feedback: **Castration** (removal of the gonads) results in marked increases in the secretion of both LH and FSH.
- Even though, FSH & LH are produced by a single cell, their secretion rates can be altered to different degrees by negative-feedback inputs.

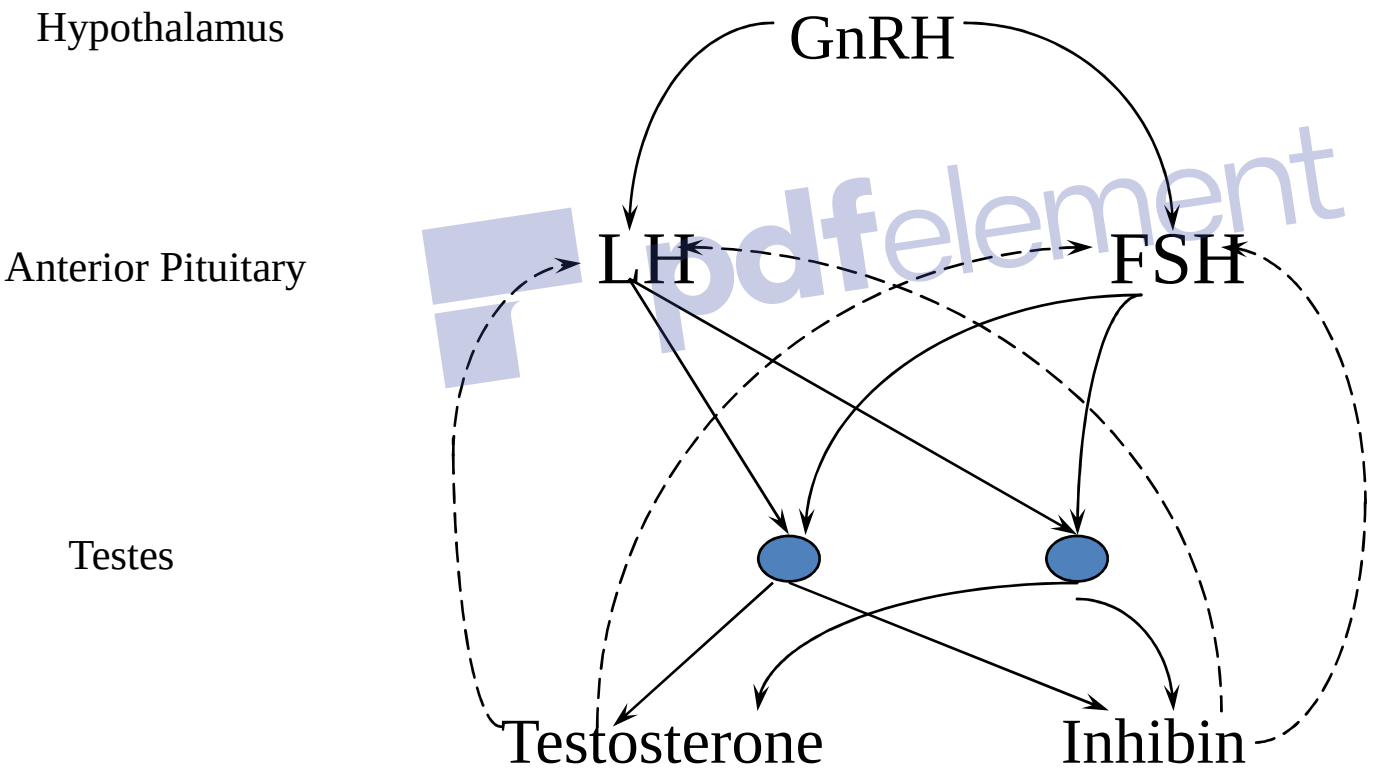
Control of the testes 3

- Testosterone inhibits mainly LH secretion by two ways: (i) it acts on the hypothalamus to decrease the frequency of GnRH bursts, thereby resulting in less GnRH reaching the pituitary over any given period of time. (ii) It acts on the anterior pituitary to cause less LH secretion but not less FSH secretion, in response to any given level of GnRH.
- FSH is tropic to the Sertoli cells, and FHS and androgens maintain the gametogenic function of the testes.
- FSH also stimulates the secretion of ABP and inhibin. Inhibin feeds back to inhibit FSH. The major inhibiting signal, exerted directly on the anterior pituitary.
- There are 2 inhibins in extracts of testes in men and in antral fluid from ovarian follicles in women. They are formed from 3 polypeptide subunits: a glycosylated α subunit with a MW of 18,000 and 2 nonglycocosylated β subunits, β_A and β_B, aech a MW of 14,000.

Control of the testes 4

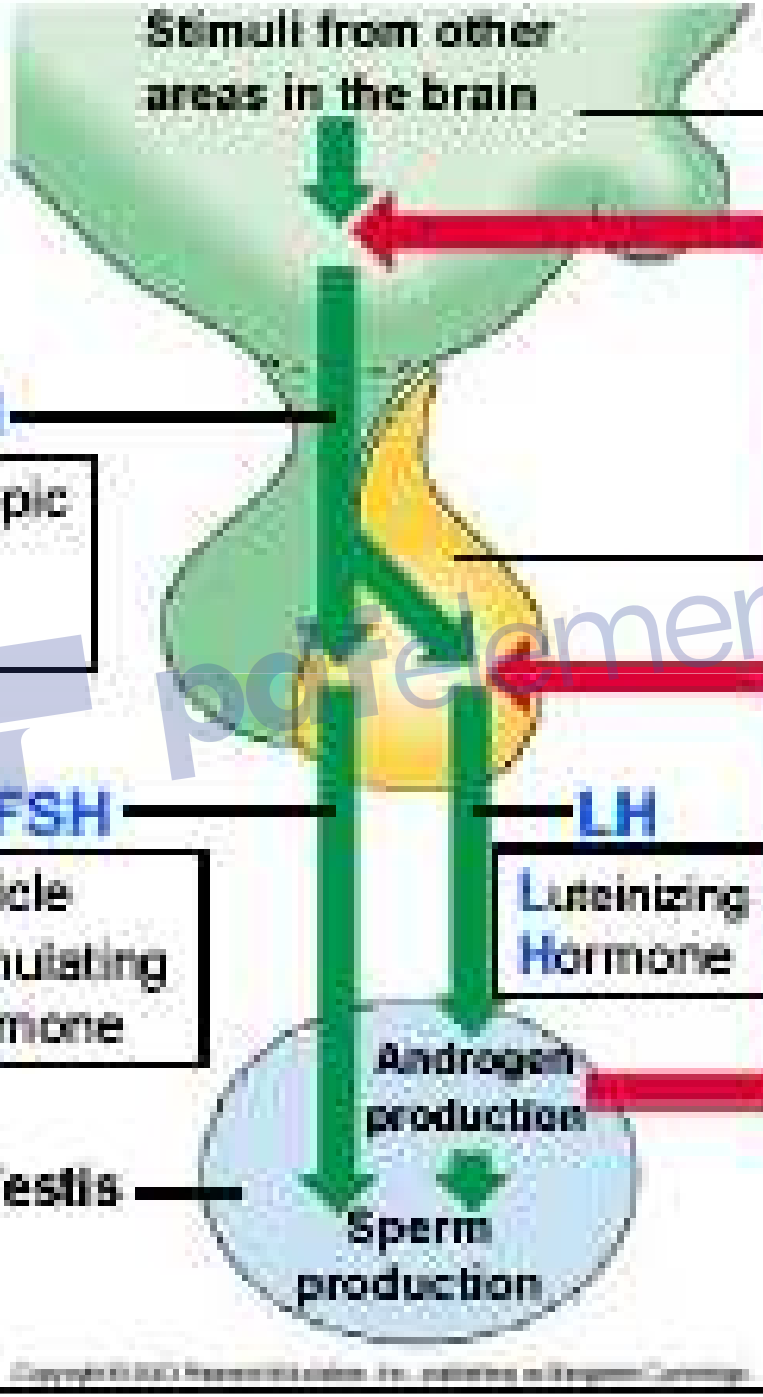
- The subunits are formed from precursors proteins. The α subunit combines with β_A to form a heterodimer and with β_B to form another heterodimer, with the subunits linked by disulfide bonds.
- Both $\alpha\beta_A$ (inhibin A) and $\alpha\beta_B$ (inhibin B) inhibit FSH secretion by a direct action on the pituitary, though it now appears that it is inhibin B that is the FSH-regulating inhibin in adult men and women.
- Inhibins are produced by Sertoli cells in males and granulosa cells in females. The heterodimer β_A β_B and the homodimers β_A β_A are also formed. They stimulate rather than inhibit FSH secretion and consequently are called **activins**. Their function in reproduction is unsettled.
- However, the inhibins and activins are members of the TGFβ (transforming growth factor) super family of dimeric growth factors that also includes MIS.

Pituitary-Hypothalamus Control of Male Reproduction



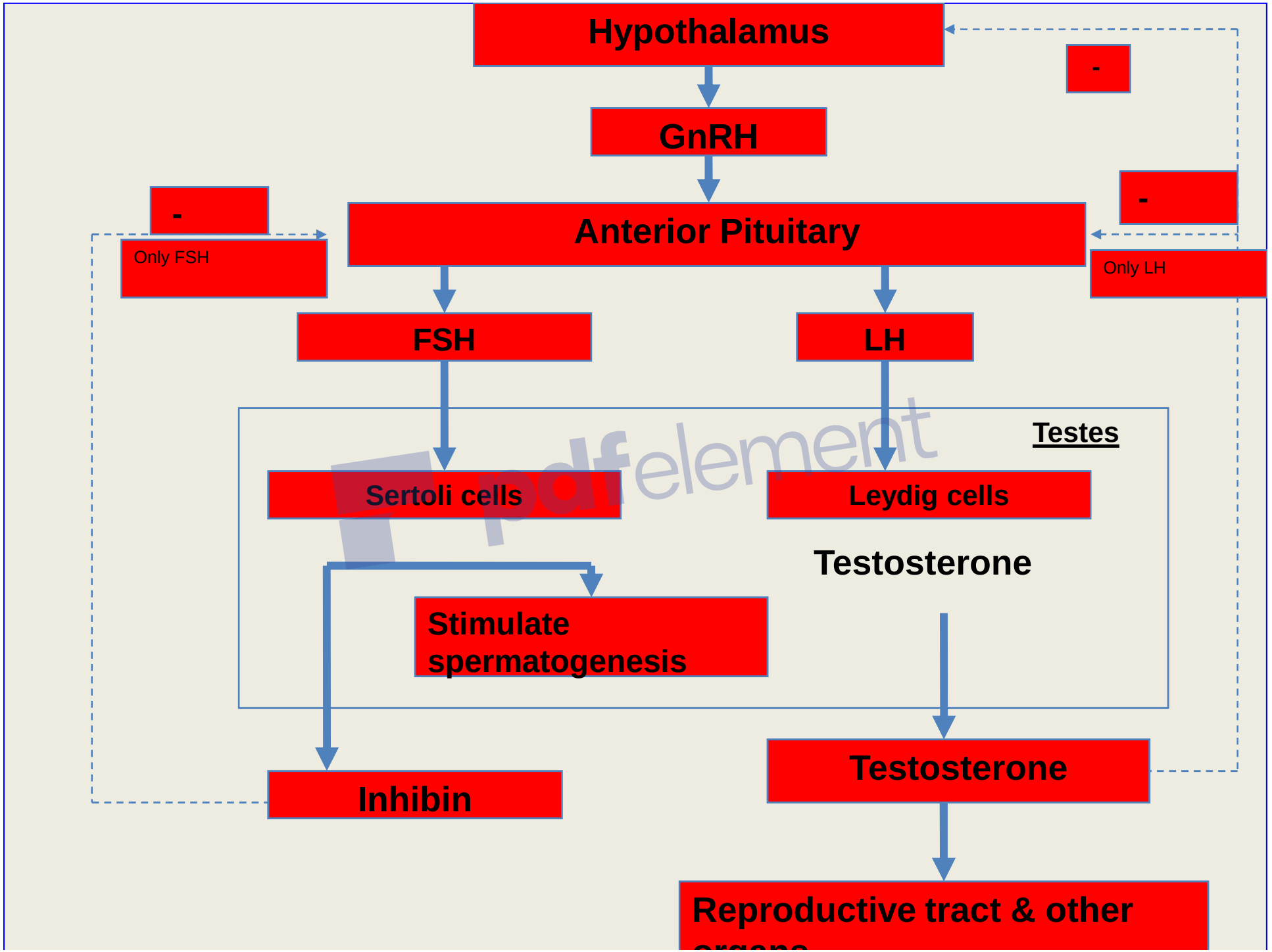
Hormonal Control of the Testes

[Fig. 27.3D, p. 539]



•LH is also known as ICSH

Interstitial Cell Stimulating Hormone


Hypothalamus
-
GnRH
-
Anterior Pituitary
Only FSH
Only LH
FSH
LH
Testes
Sertoli cells
Leydig cells
Testosterone
Stimulate spermatogenesis
Inhibin
Testosterone
Reproductive tract & other

Functions of Luteinizing Hormone in Males

- Stimulation of and Maintenance of Leydig Cells (Interstitial Cells)
- Stimulation of Steroidogenesis through cAMP mediated reactions
- Stimulation of Fetal, Juvenile and Adult Testosterone, Estrogen and DHT production

Functions of FSH in Males

- Stimulation of Sertoli Cells
- Stimulation of Androgen Binding Proteins Formation
- Stimulation of Inhibin Production
- Stimulation of Spermatogenesis

Functions of Leydig Cells

- Production of High Levels of Testosterone (5mg/day in adults)
- Direct Production of Estradiol
- Production of Dihydrotestosterone (DHT)
- Production of dehydroepiandrosterone (DHEA) and androstenedione
- Production of Progesterone and 17α -prog.

Functions of Sertoli Cells

- Support Production of Spermatozoa
- Production of Androgen-Binding Protein Intratesticularly (TeBG)
- Form Blood-Testes Barrier
- Produce Inhibin
- Produce Seminiferous tubule fluid (bathing medium, nutrients, capacitation, motility)

Hormonal Production Rates

- Testosterone — 5 mg/day
  - Primary Testicular Androgen
- Estradiol — 10-15 μg/day
  - Functions in Sperm Production
- Dihydrotestosterone — 50-100 μg/day
  - 2.5X as powerful as Testosterone
- 17α-Hydroxyprogesterone — 1-2 mg/day

Actions of Androgens in Male 1

- Stimulate Development, Growth and Function of Male genitalia
- Stimulate Secondary Sexual Characteristics
  - Stimulate male hair growth and pattern
  - Sebaceous gland secretion (Acne)
  - Bone growth and long bone closure
  - Stimulate and maintain male libido (behavior)

Actions of Androgens in Male 2

- Initiation and Maintenance of Spermatogenesis
- Stim. of Androgen-Binding Globulin Synthesis (synergy with FSH)
- Maintains secretions of sex glands