Steroid Hormone; Androgens

SUBJECT- PHARMACEUTICAL CHEMISTRY-VII (4T2)

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Androgens

- Androgens are a class of steroids characterized by their biological effect on the primary and secondary sex characters of various male animals. In addition androgens possess potent anabolic or growth promoting properties.
- Testosterone is the principal androgenic hormone. It is formed in the testes under the control of anterior lobe of pituitary gland. In a small proportion it is synthesized in the adrenal cortex and ovaries and certain other tissues.
- In women Testosterone is synthesized in small amount by both ovary and adrenal gland.
- In man male reproductive system is under the control of hypothalamus, anterior pituitary and gonads.

- Testosterone and its metabolite, dihydrotestosterone (DHT), are the primary endogenous androgens and play crucial physiologic roles in establishing and maintaining the male phenotype.
- Their actions are essential for the differentiation and growth of male reproductive organs, initiation and regulation of spermatogenesis, and control of male sexual behavior.
- In addition, androgens are important for the development of male characteristics in certain extragenital structures, such as muscle, bone, hair, larynx, skin, lipid tissue, and kidney.
- The other function of Testosterone is anabolic, increasing retention of nitrogen and water. Stimulating skeletal growth, skin becomes more vascular and less fatty.

- Testosterone in therapy is given parentally. Several synthetic analogues of Testosterone have been prepared some of these are androgenic and anabolic, but are active on oral administration. The steroids which have increased anabolic property over the androgenic activity have been referred to as anabolic steroids.
- Testosterone and its esters may be used as replacement therapy in male hypo gonadal disorder and they may be employed with care in adolescent males with delayed puberty.
- In females, the precise physiologic roles of androgens are not completely understood, but the aging-related decline in circulating androgen levels has been linked to symptoms such as decreased libido and sexuality, loss of bone mineral density in postmenopausal women.

- Major differences in endocrine hormones and the anatomy and physiology of the reproductive system and genitourinary tract between males and females make men uniquely susceptible to a variety of disorders, including
  - Aging-related androgen insufficiency (hypogonadism and andropause),
  - Prostate and testicular cancer,
  - Benign prostatic hyperplasia (BPH), and
  - Erectile dysfunction (ED).
- The majority of these disorders and their treatments are associated with the male sex hormones (i.e., androgens), their pharmacologic target (i.e., the androgen receptor [AR]), and the tissues that rely on the androgens.

Prostate problems are common in older men, particularly those age 50 years and older. A man may have prostate problems for a number of reasons, including

- An infection of the prostate (prostatitis),
- A noncancerous enlargement of the prostate (BPH), or prostate cancer, the second most common cancer in men.

Risk of prostate cancer also increases with age. The signs of prostate problems include

- Frequent urge to urinate,
- Blood in the urine,
- Painful or burning urination,
- Difficulty urinating, or inability to urinate.

Aging-related androgen insufficiency (male hypogonadism) is a physiologic condition characterized by the inability of the testes to produce sufficient testosterone to maintain sexual function, muscle strength, bone mineral density, and fertility (spermatogenesis).

Symptoms of aging-related androgen insufficiency may include

- lethargy or decreased energy,
- decreased libido or interest in sex, ED (with loss of erections),
- muscle weakness and aches,
- inability to sleep, hot flashes, night sweats,
- depression, infertility, thinning of bones or bone loss, and cardiovascular disease.

Natural Androgens

Testes of adult male produce 5-12 mg testosterone daily, a part of which is converted in extra glandular tissues to the more active dihydrotestosterone by the enzyme steroid 5α-reductase; cholesterol is the starting material and the same pathway adrenal cortex produces small quantities of dehydroepiandrosterone and androstenedione which are called “weak androgens”.

Anabolic steroids (Synthetic androgens)

Anabolic steroids are synthetic androgens with supposedly higher anabolic and lower androgenic drugs are Nandrolone, Oxymetholone, Stanozolol.

- Methyltestosterone and fluoxymesterone are 17-alkyl substituted derivatives of testosterone which are orally active because of resistance to first pass metabolism, but have submaximal androgenic efficacy and potential to cause cholestatic jaundice.
- Other orally active compounds are testosterone undecanoate which is administered as oily solution to be absorbed through lymphatics bypassing the liver, and mesterolone.
- A number of lipid-soluble esters of testosterone have been produced, suitable for injection in oily vehicle, from which they are absorbed slowly and exert prolonged action after deesterification in the body.

Mechanism of Androgen Action

- Testosterone, DHT, and other androgens execute their actions predominantly through the AR.
- The AR is mainly expressed in androgen target tissues, such as the prostate, skeletal muscle, liver, and central nervous system, with the highest expression level being observed in the prostate, adrenal gland, and epididymis.
- Testosterone is thought to be largely responsible for initiation of AR action in muscle, bone, brain, and bone marrow, whereas DHT plays a major role in genitalia, prostate, skin, and hair follicles due to their higher expression of 5α-reductase enzymes.
- The AR function is regulated by the binding of androgens, which initiates sequential conformational changes of the receptor that affect receptor– protein interaction and receptor–DNA interactions.

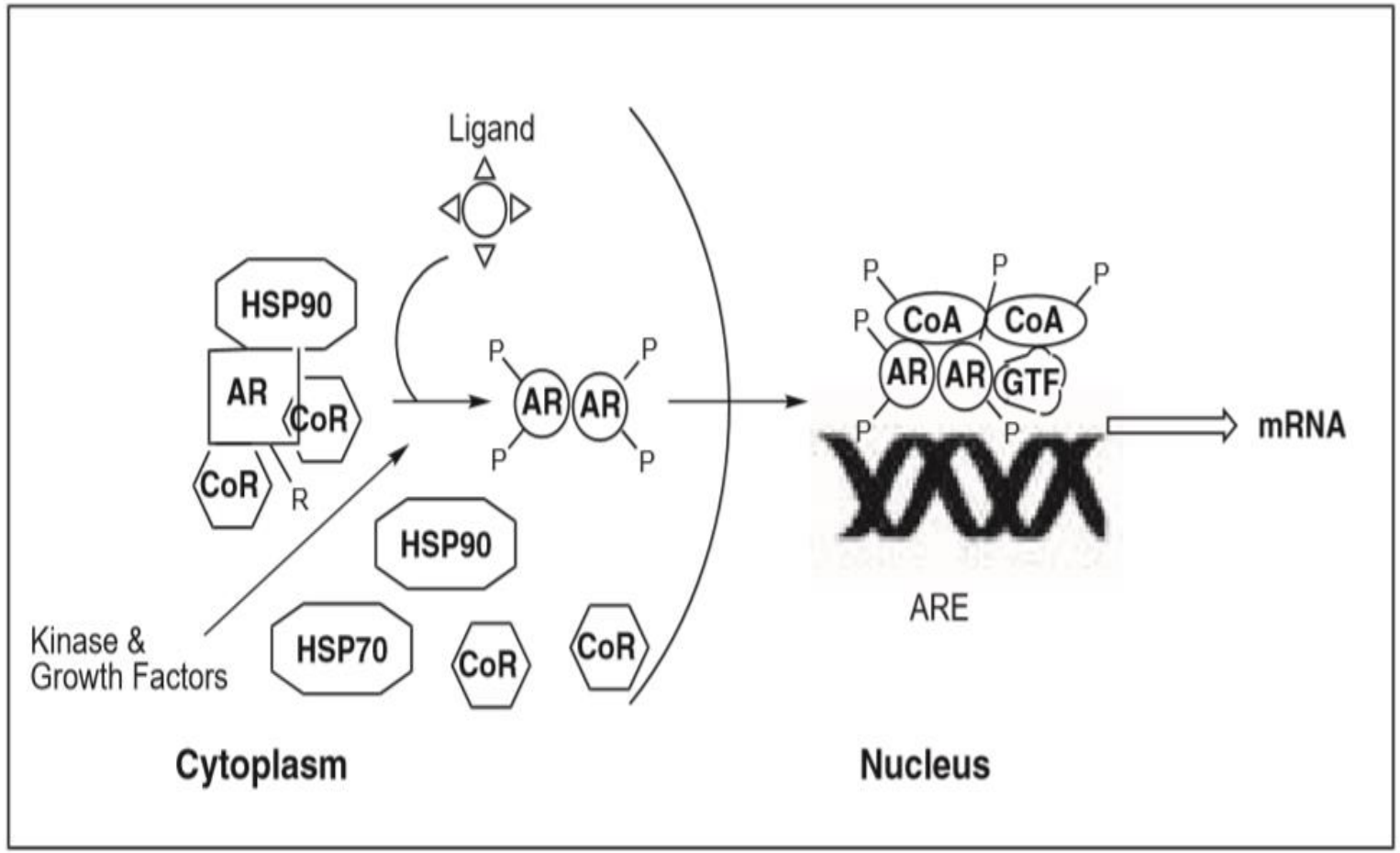

FIGURE 40.8 Mechanism of androgen action. The androgen receptor (AR) is maintained in an inactive complex by heat shock protein (HSP) 70, HSP90, and corepressors (CoR). On ligand binding, it homodimerizes and enters the nucleus. The receptor is basally phosphorylated (P) in the absence of hormone, and hormone binding increases the phosphorylation status of the receptor. The AR binds to the androgen response element (ARE) on the promoter of androgen responsive genes, leading to the recruitment of coactivators (CoA) and general transcription factors (GTF), leading to gene transcription.

Regulation and Production

- Testosterone is secreted by the interstitial (Leyding cell) of the testes under the influence of pulsatile secretion of LH from pituitary FSH is mainly responsible for promotion of spermatogenesis in Sertoli cells. The mediator of feedback relationship with pituitary is uncertain, while relative high concentrations of testosterone inhibit LH secretion.
- Estrogen are more potent inhibitor of Gn secretion even in males and it is believed that the small amount of estradiol produced by testes and that resulting from conversion of testosterone to estradiol play a role in feedback inhibition.
- Inhibin produced by Sertoli cells, has strong FSH inhibiting action and may be mediating the feedback inhibition.
- Testosterone and estradiol act on hypothalamus to reduce GnRH as well act directly on pituitary.

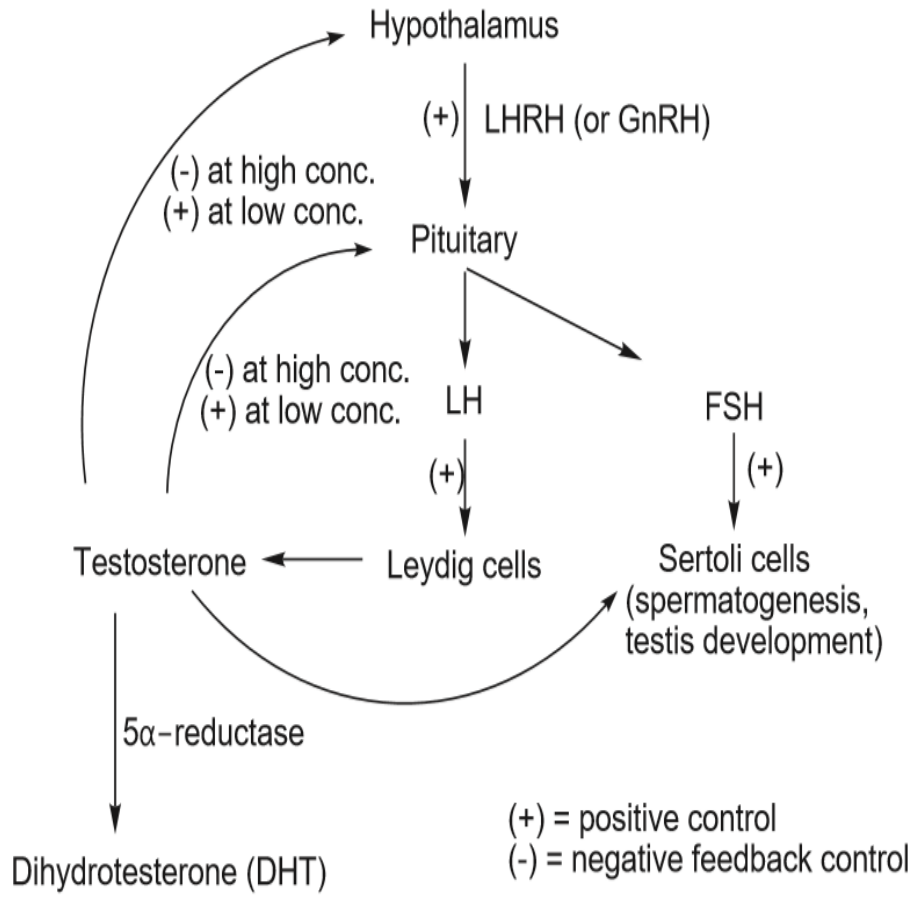

FIGURE 40.2 Hypothalamus-pituitary-testicular axis. (+), positive control; (–), negative feedback control.

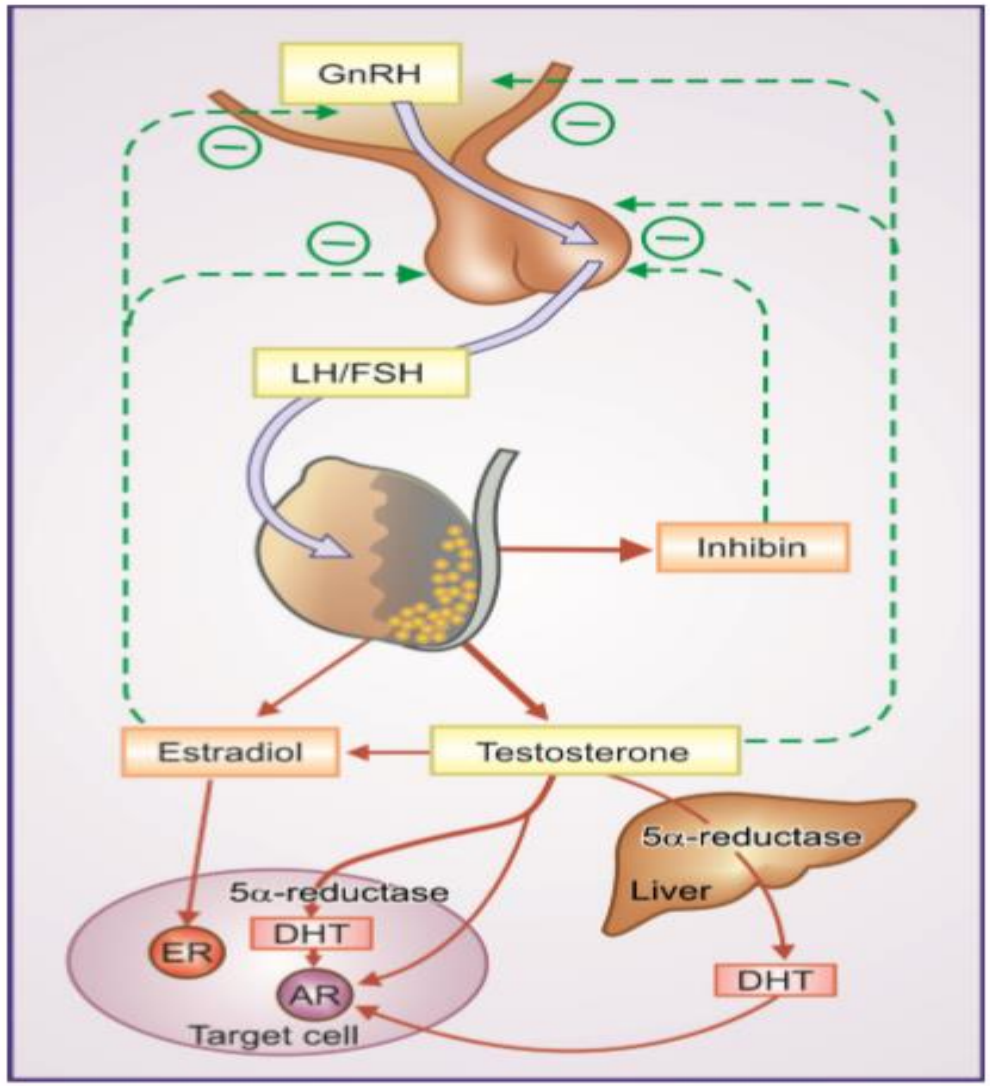

Fig. 21.1: Regulation and production of sex steroids in the male.

Biosynthesis of Androgens

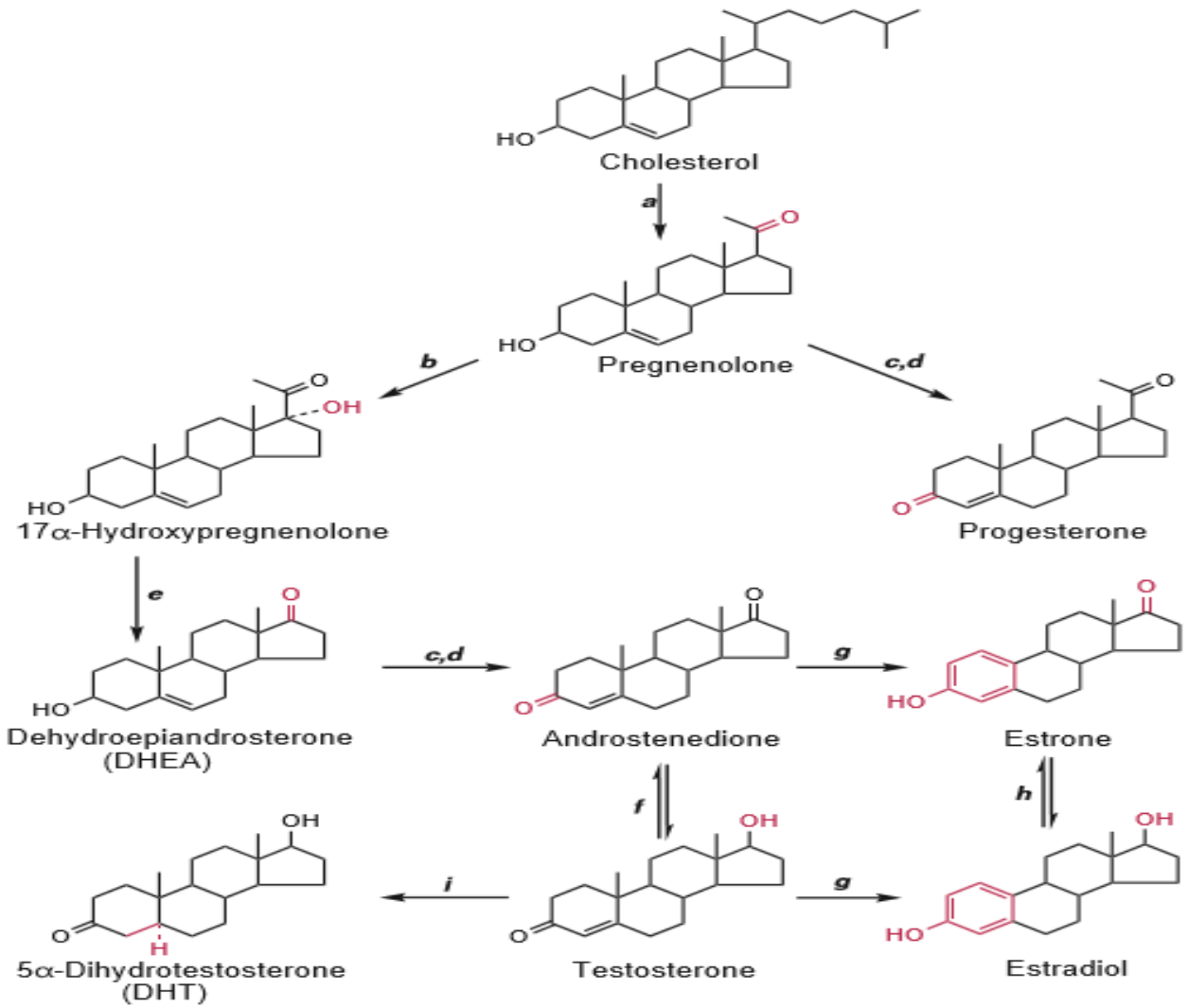

FIGURE 40.3 Biosynthesis of androgens and other sex steroid hormones. The enzymes involved in this biosynthesis are (*a*) side-chain cleavage, (*b*) 17a-hydroxylase, (*c*) 5-ene-3b-hydroxysteroid dehydrogenase, (*d*) 3-oxosteroid-4,5-isomerase, (*e*) 17,20-lyase, (*f*) 17b-hydroxysteroid dehydrogenase, (*g*) aromatase, (*h*) estradiol dehydrogenase, and (*i*) 5a-reductase.

Thank You