

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

HORMONES

Definition

- A substance produced in an endocrine gland, secreted into the blood & delivered to a target cell in a separate tissue of the body where it has a specific physiological effect.
- Now includes compounds having ***autocrine*** or ***paracrine*** actions.
- Most hormones are either peptides / compounds from amino acids. Rest are derivatives of cholesterol / one of its precursors (***steroid hormones***)

Steroid Hormones

Steroid hormones are derived from ***cholesterol***

- Synthesized in the tissues from acetyl Co A, extracted from the ***intracellular cholesterol ester pools***
- Or taken up by the cell in the form of cholesterol containing ***lipoproteins*** , ***internalized by a plasma membrane receptor mediated response***

MALE GONADAL HORMONES

- ✦ The male sex hormones /androgen are responsible for normal male sexual development which includes
 - Masculinization of the internal & external genital tracts
 - The development of male secondary sexual characteristics (such as beard growth)
 - Fertility & the anabolic character of somatic tissue (such as male type skeletal shape and size and heavier muscle bulk)

- Over 95% of circulating testosterone, the principal androgen in the blood is synthesized in *testes in males* & in *ovary in females*
- The remainder is produced in *adrenal cortex of both sexes*
- Plasma testosterone level — 300 – 1000 ng/dl♂
(Free/bound) 30 – 70 ng/dl♀

Testes

- ◆ Testes are made up of convoluted seminiferous tubules
- ◆ The walls of seminiferous tubules are lined by
 - **Primitive germ cells** (spermatogenesis)
 - **Sertoli cells**
 - Androgen – binding protein (ABP)
 - Inhibin
 - MIS (Mullarian Inhibitory Substances)
- ◆ Between the tubules are *nests of cells* containing lipid granules, the interstitial cells of **Leydig** which secrete **testosterone** into the blood stream.

Testis H&E

Leydig cells

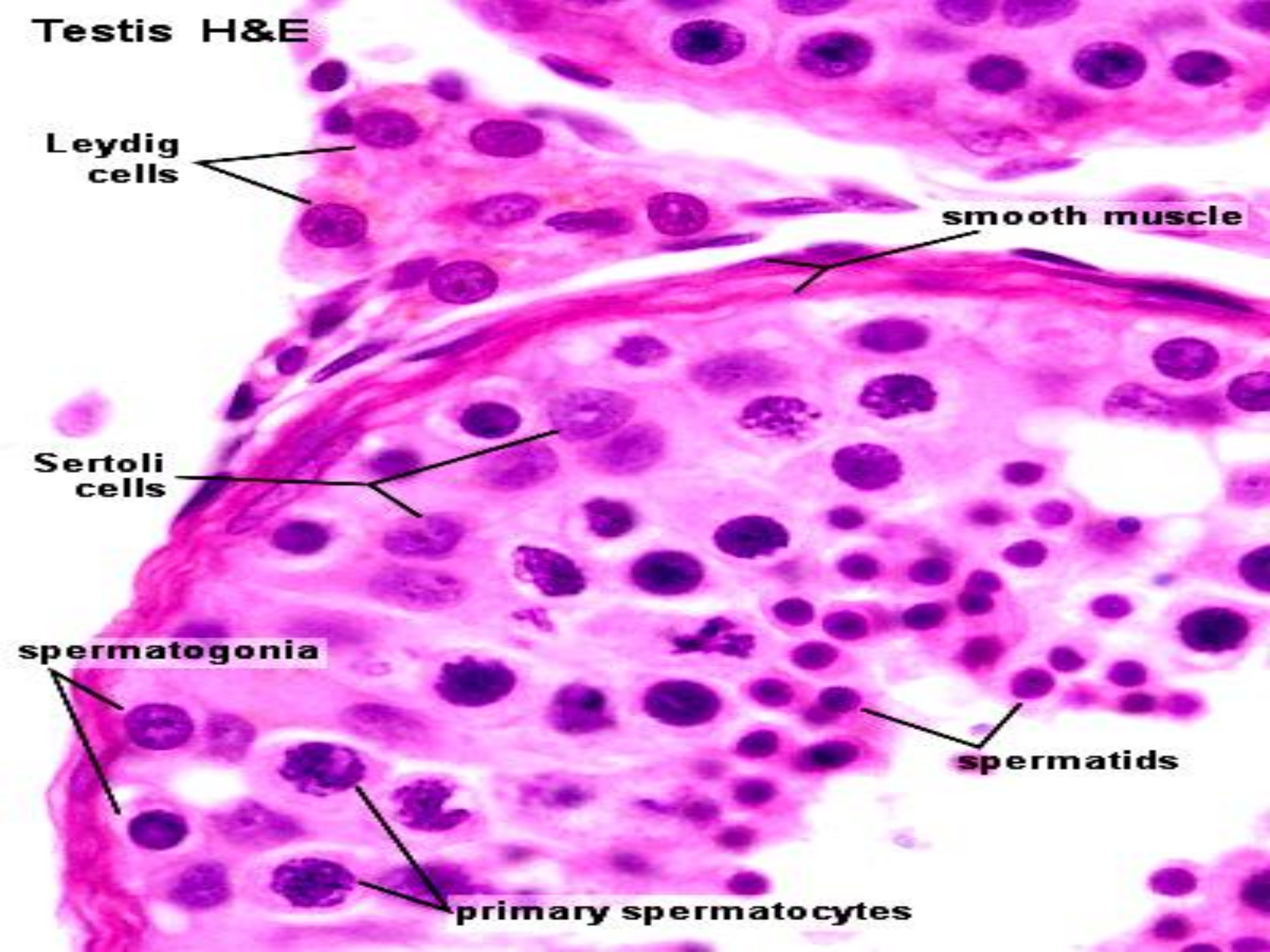
smooth muscle

Sertoli cells

spermatogonia

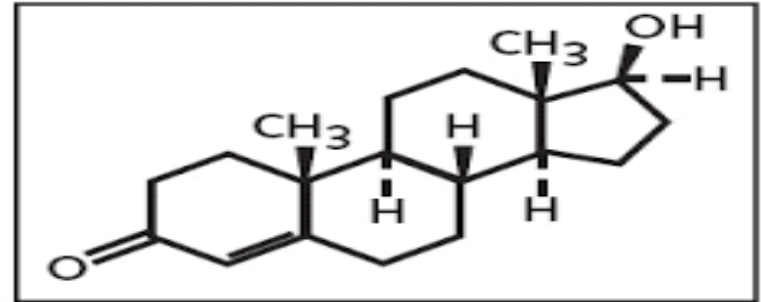
spermatids

primary spermatocytes



Structure and synthesis of testosterone

- Testosterone - principal hormone of the testes **C₁₉** steroid with – OH group at the **17** carbon position

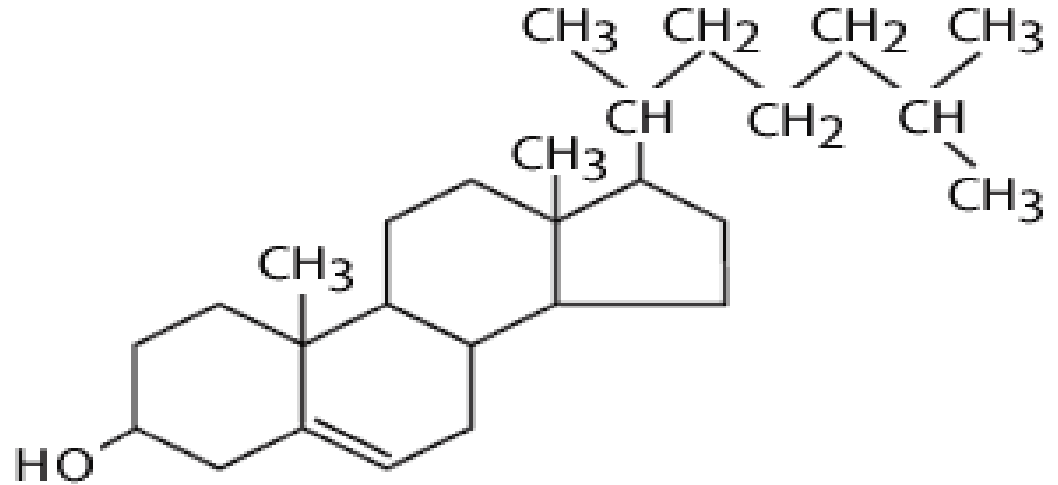


C₁₉H₂₈O₂

M.W.: 288.42

- It is synthesized from
 - **Cholesterol** in **Leydig cells**
 - From **Androstenedione** secreted by **adrenal cortex**
- The biosynthesis involves shortening the hydrocarbon chain of **cholesterol & hydroxylation of the steroid nucleus**

- Cholesterol is converted to **progesterone** in the first **two** steps

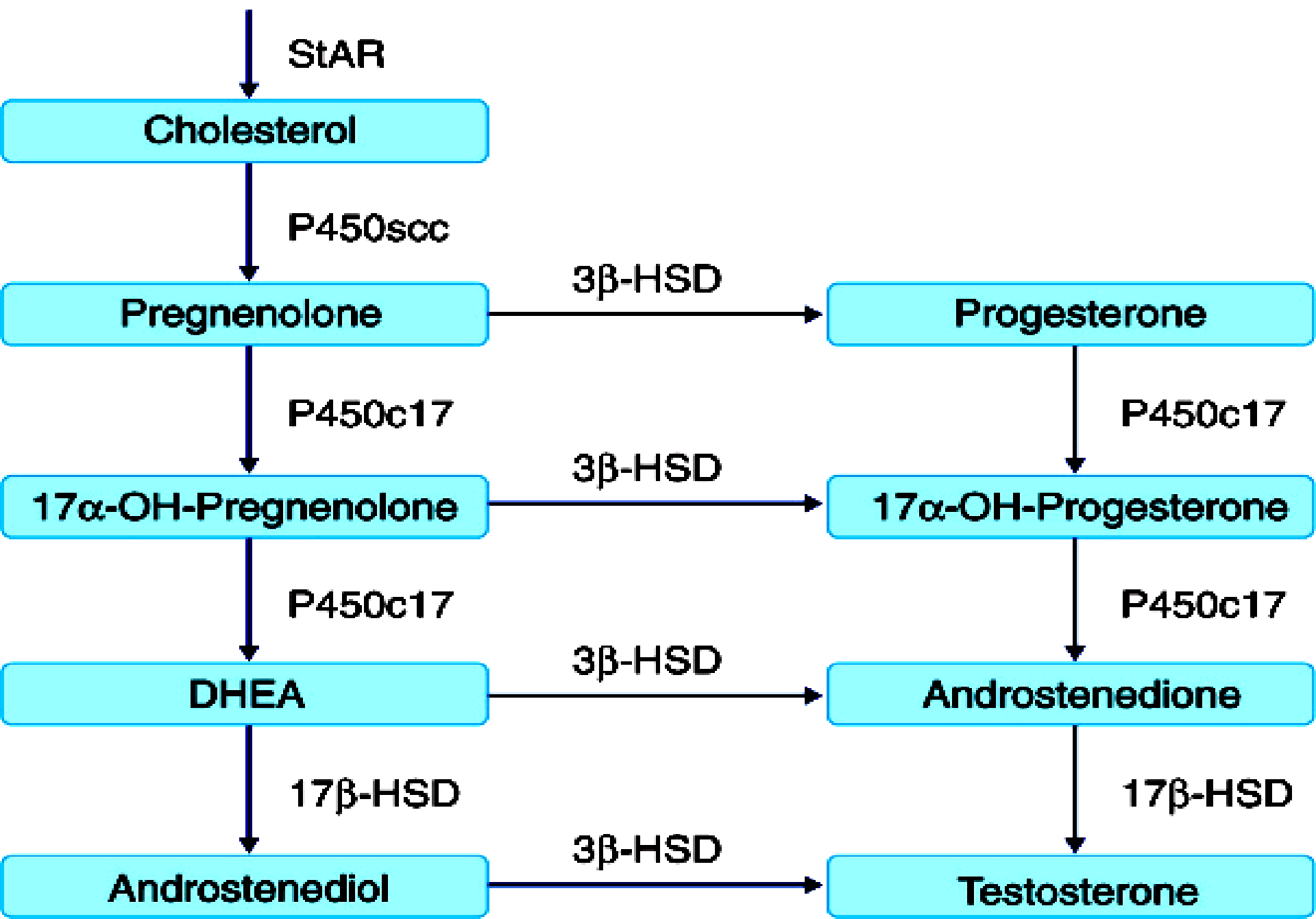


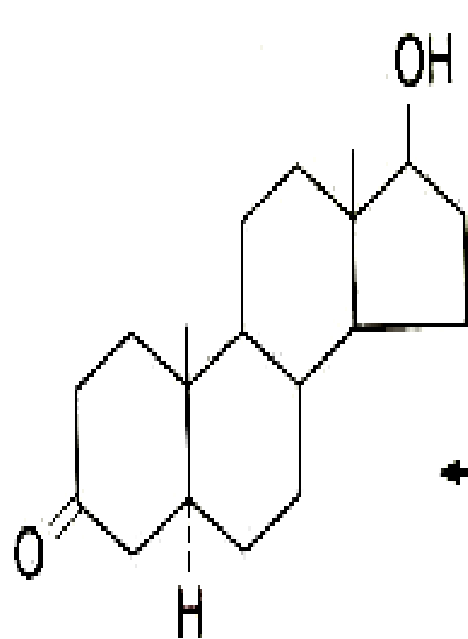
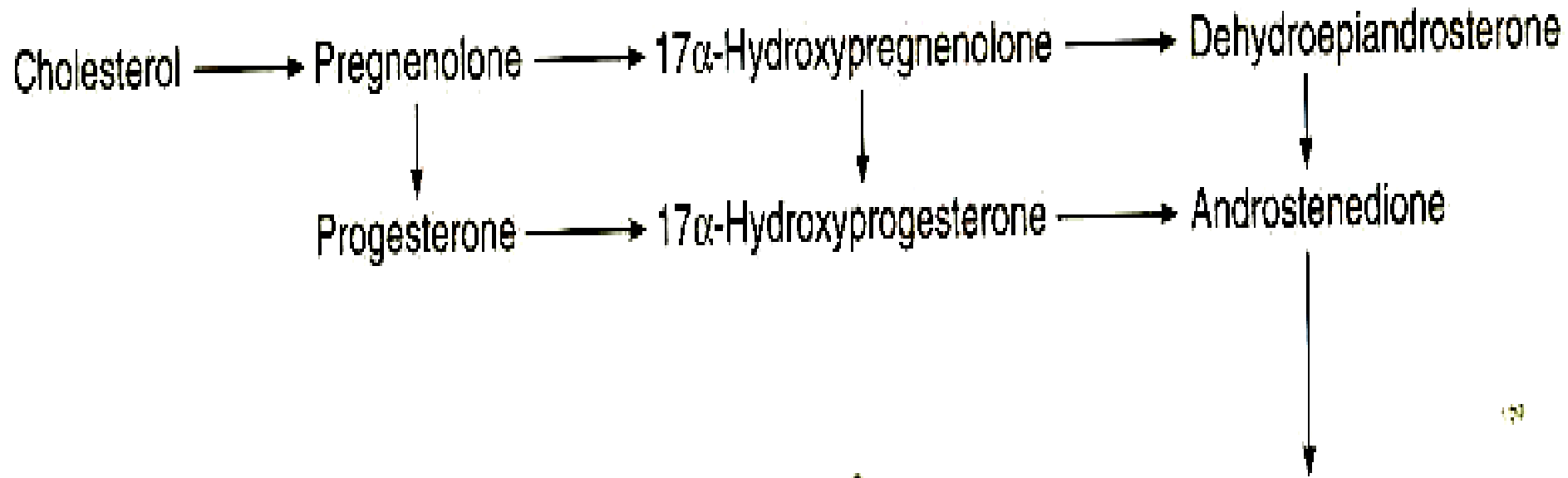
- **Cytochrome P450 side chain cleavage enzymes** (in the mitochondrial inner membrane) removes **6** carbons from side chain of cholesterol forming **pregnenolone 21 C**
- **Initial & rate limiting reaction.**

● The next step, the conversion of pregnenolone to **progesterone** is catalyzed by **3 β -Hydroxysteroid Dehydrogenase. (3 β -HSD)**

● The predominant pathway leading to testosterone synthesis is through **pregnenolone to 17-hydroxypregnenolone to DHEA (dehydroepiandrosterone) & from androstenedione to testosterone**

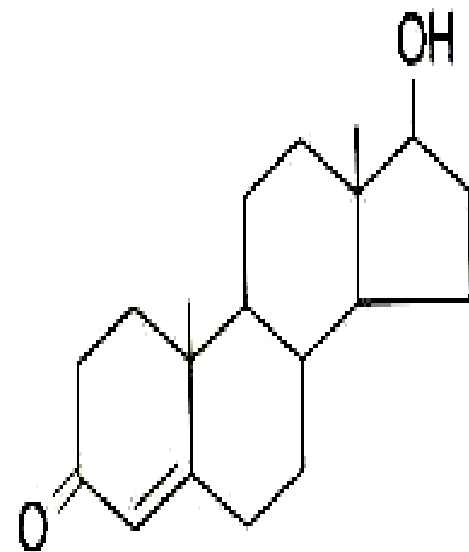
Testosterone Synthesis in the Testis





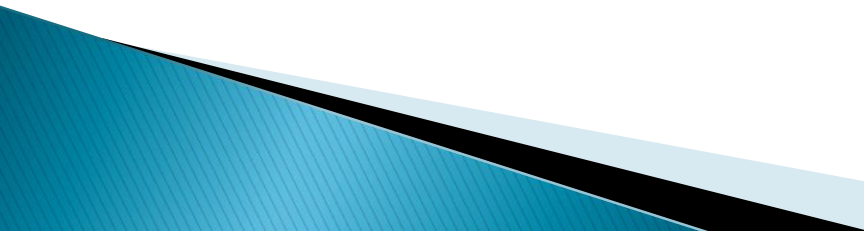
Dihydrotestosterone

In some target tissues
5 α -reductase,
type 1 or type 2



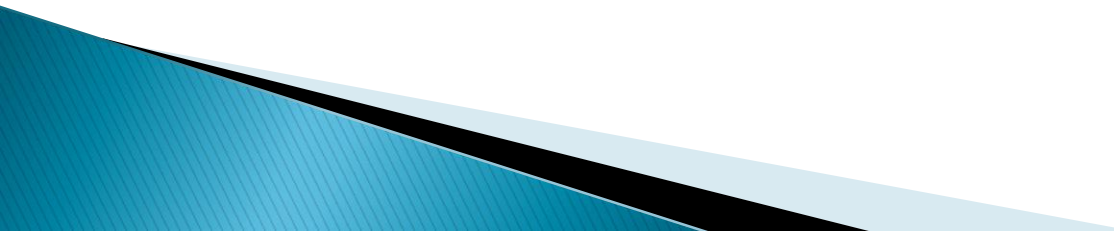
Testosterone

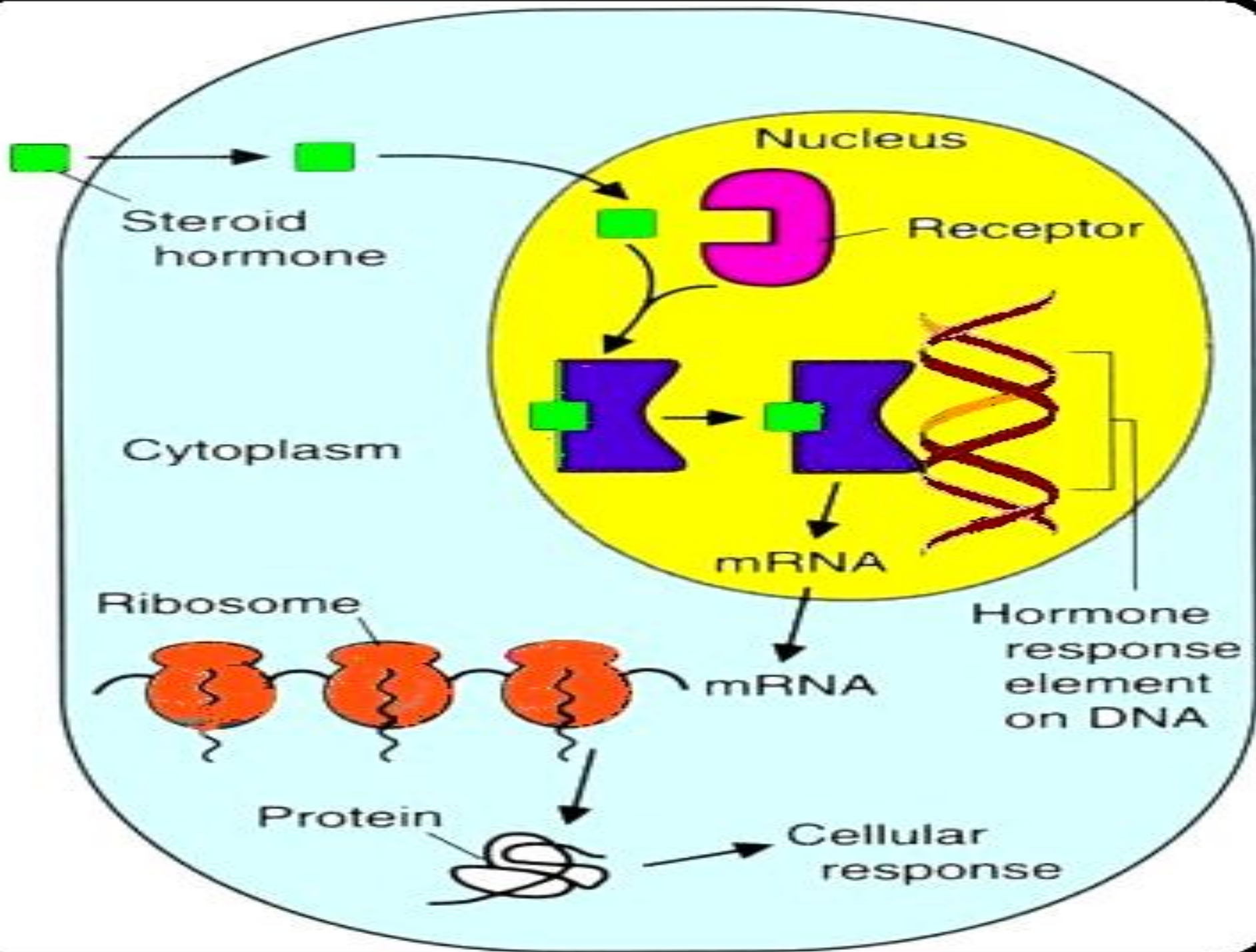
Mechanism of Action

- The steroid hormone receptors are found in cytosol & nucleus
 - Unbound steroid hormone diffuses through the plasma membrane (active process of cellular uptake of hormone may take place)
 - After diffusion into the cell testosterone binds to receptor protein (in ***nucleus***) which contains ***specific binding domains*** .
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- ✿ The hormone binds to an ***inactive & non transformed receptor*** with an *unoccupied ligand binding site*.
- ✿ The inactive receptor are complexed with several ***heat shock proteins(HSP)*** of varying size which cover the ***DNA binding domain*** of the inactive unbound receptor molecule.

- When binding of ligand occurs, the heat shock proteins dissociate from the receptor ,exposing the receptor's DNA binding domain.
- The *activated transformed receptor* now binds to DNA. The activated receptor searches for the DNA for a specific high affinity acceptor site (*the steroid-receptor complex response element (SRE)*)

- After binding, trans-activation process stimulate RNA polymerase activity & subsequently transcription occurs.
 - The newly formed mRNAs bind to the ribosomes in the cytosol, where they are translated producing specific proteins.
 - These proteins will alter target cells function according to the command inherent in the hormone-receptor interaction.
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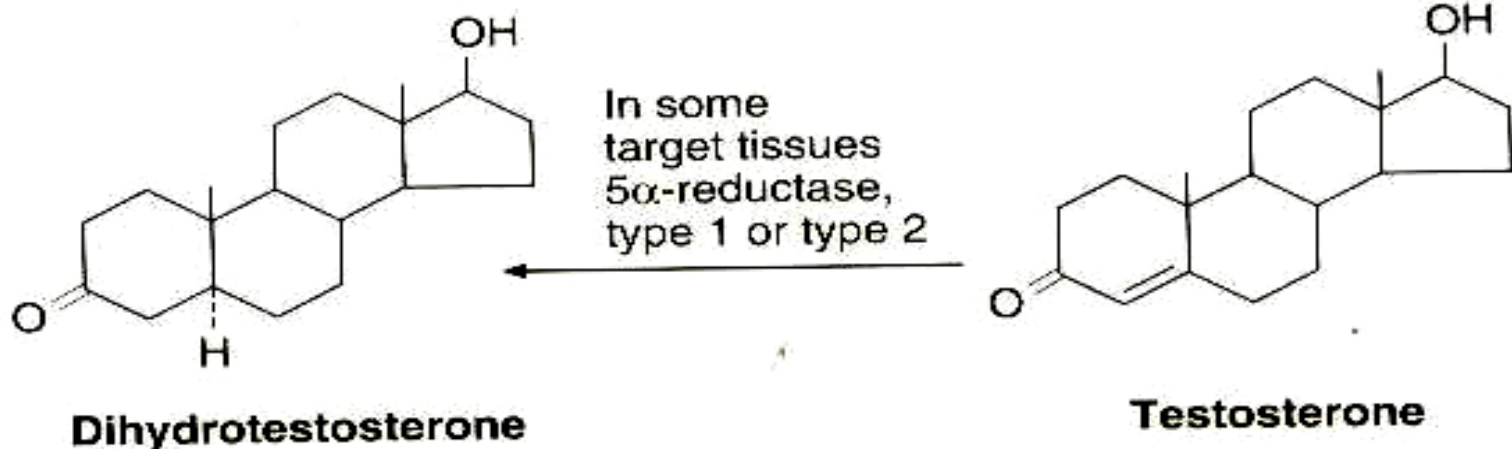


Transport & metabolism

- **98%** of the testosterone in plasma is bound to proteins
 - 65% - bound to a β -globulin called ***Gonadal Steroid – binding Globulin/ GBG***
 - 33% - bound to **albumin**
- **2%** of the total testosterone in blood is an unbound / free form, easily diffusible form

- Free hormone is biologically most active form of total hormone because of its ability to move passively into the cytosol of target cells
- A fraction of the total testosterone is loosely bound to **GBG** & makes up a readily accessible pool for the diffusible free fraction

- ▶ Testosterone can be reduced to **DHT** by the cytoplasmic enzymes **5-alpha reductase** & binds to receptor more strongly than testosterone.
- ▶ In its target cells the double bond in ring A of testosterone is reduced forming the active hormone **Dihydrotestosterone (DHT)**. This conversion is catalyzed by an enzyme called type 2 **5 alpha-reductase**



Testosterone is **metabolized** in **two** pathways

Oxidation at 17 carbon position

- Occurs in many tissues including liver & produces **17-ketosteroids** that are generally inactive / less active than the parent compound.
- Most of the circulating testosterone is converted to 17-ketosteroids, mainly ***androsterone*** & its isomer ***etiocholanolone*** & is excreted in urine.

- About ***two thirds*** of the urinary 17-ketosteroids are of ***adrenal origin*** & ***one third*** are of ***testicular origin***.
- About 0.2% of the circulating testosterone is converted to ***estrogens*** in various tissues containing ***aromatase*** enzyme. These have either androgen / anti androgen like effects depending upon the molecular interconversion.

Reduction of the A ring double bond

- This pathway is less efficient, occurs primarily in target tissue & produces the potent metabolic **DHT**
- It is the most significant metabolic product of testosterone since in many tissues including prostate external genitalia & some areas of skin this is the active form of the hormone
- About **4%** of the circulating enzyme is converted to DHT which serves as the intracellular mediator of most of testosterone's androgenic action

Testosterone

Androstenedione

17-ketoreductase

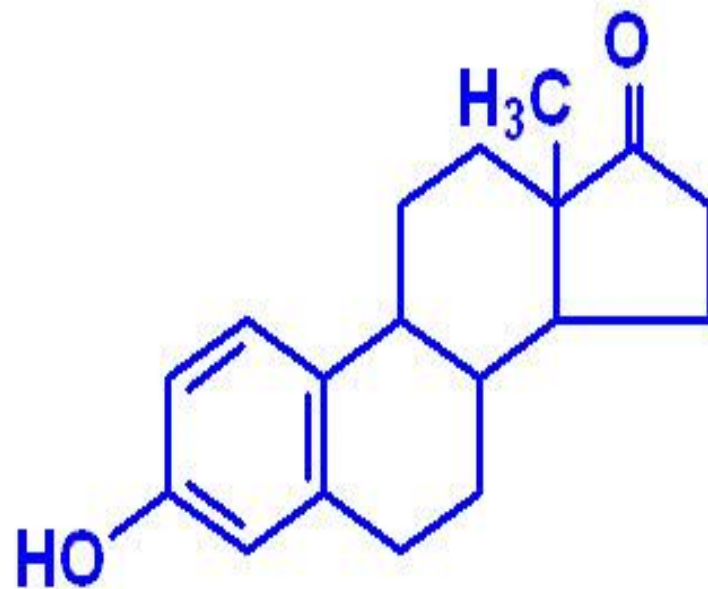
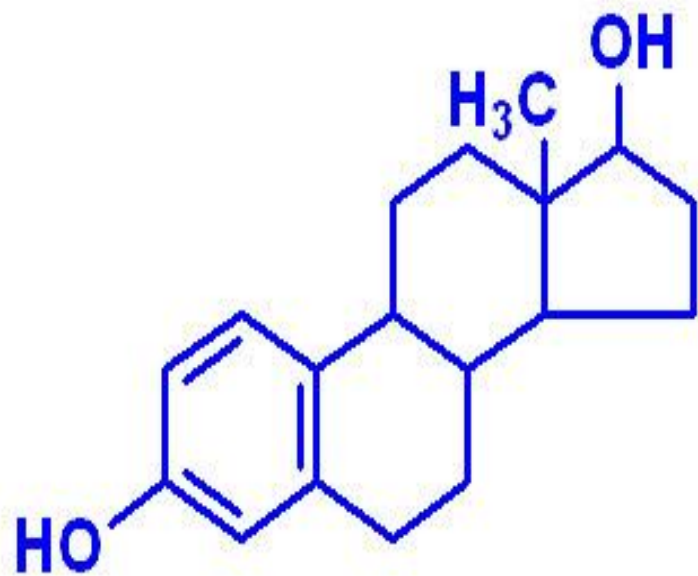
aromatase

aromatase

Estradiol

17-ketoreductase

Estrone



Athletic Use

- Testosterone may be administered to an athlete in order to improve performance & is considered to be a form of **doping** in most sports.



- There are several application methods for testosterone, including intramuscular injections, transdermal gels, patches, & implantable pellets.

- Anabolic steroids (of which testosterone is one) have also been taken to enhance muscle development, strength or endurance by increasing the muscles protein synthesis directly. In result muscle fibers become larger & repair faster than the average person.

- ▶ After a series of scandals and publicity in the 1980s (such as *Ben Johnson's* improved performance at the *1988 summer Olympics*), Prohibitions strengthened by many sports organizations.

