Testicular Steroidogenesis

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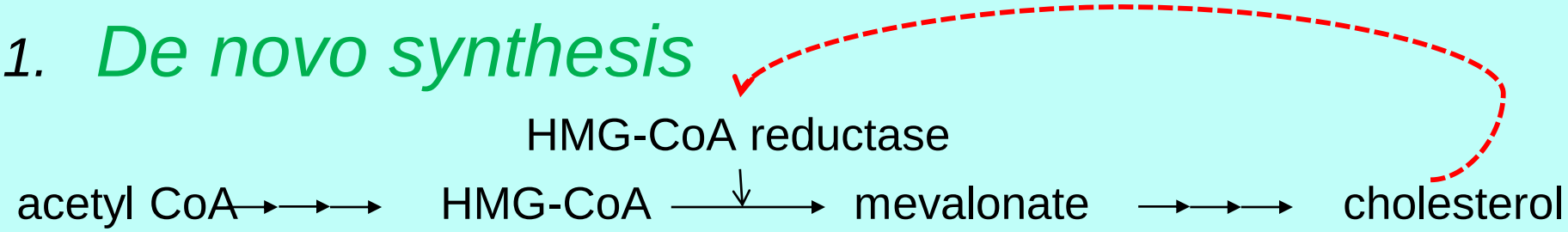
Biosynthesis of steroid hormones

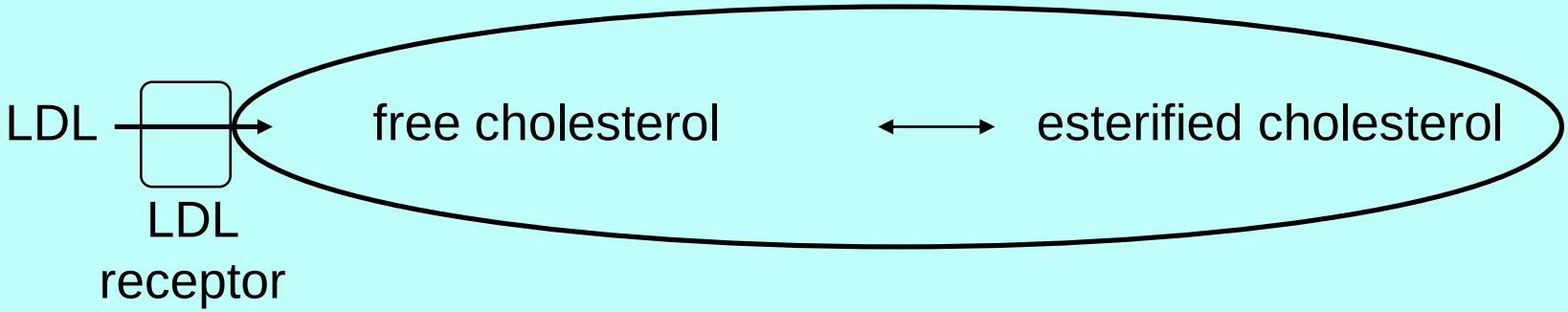
- Synthesized from the enzymatic modification of cholesterol
- Cause genetic expression of various proteins

- Sources of Cholesterol for Steroid Synthesis

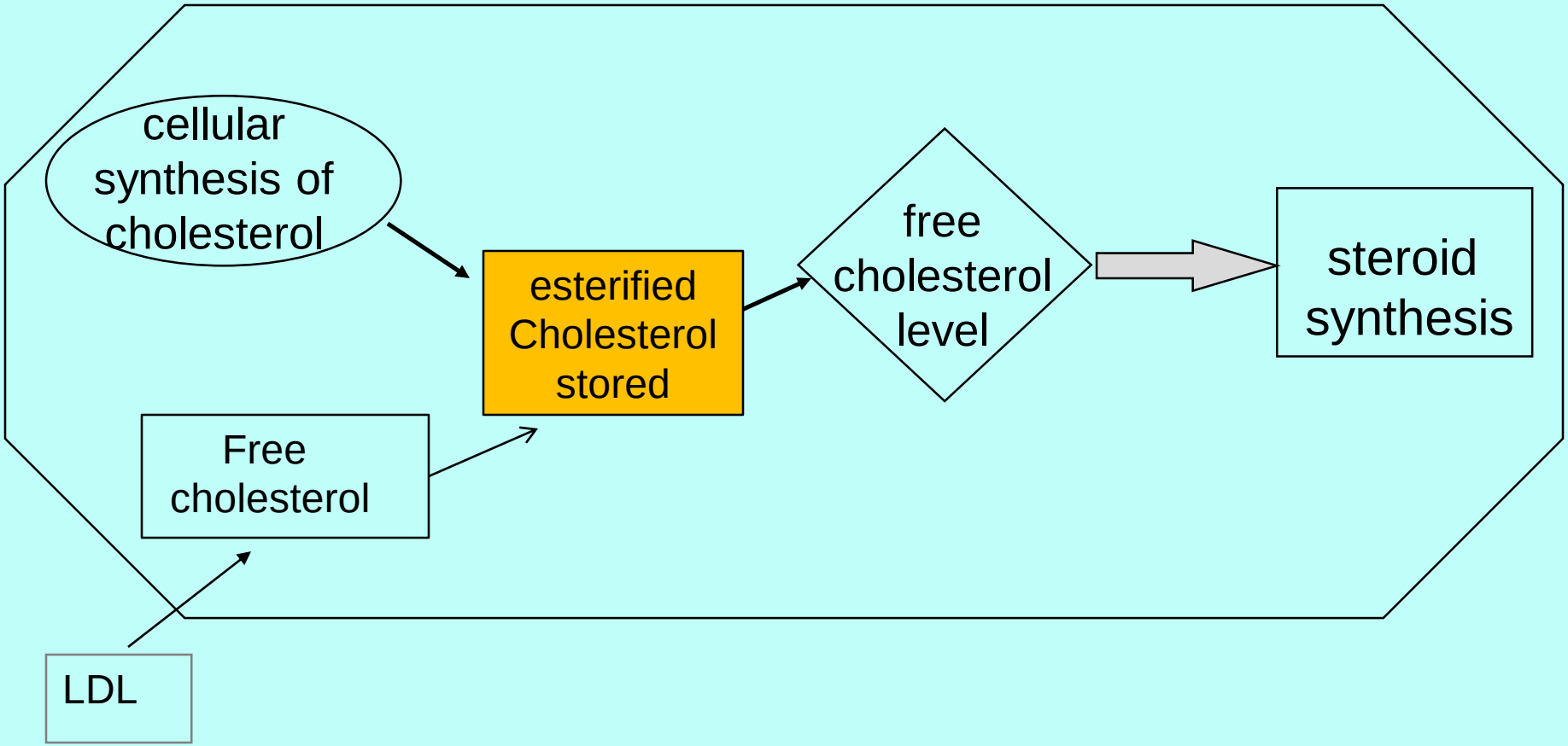
1. *De novo synthesis*



2. *LDL cholesterol*

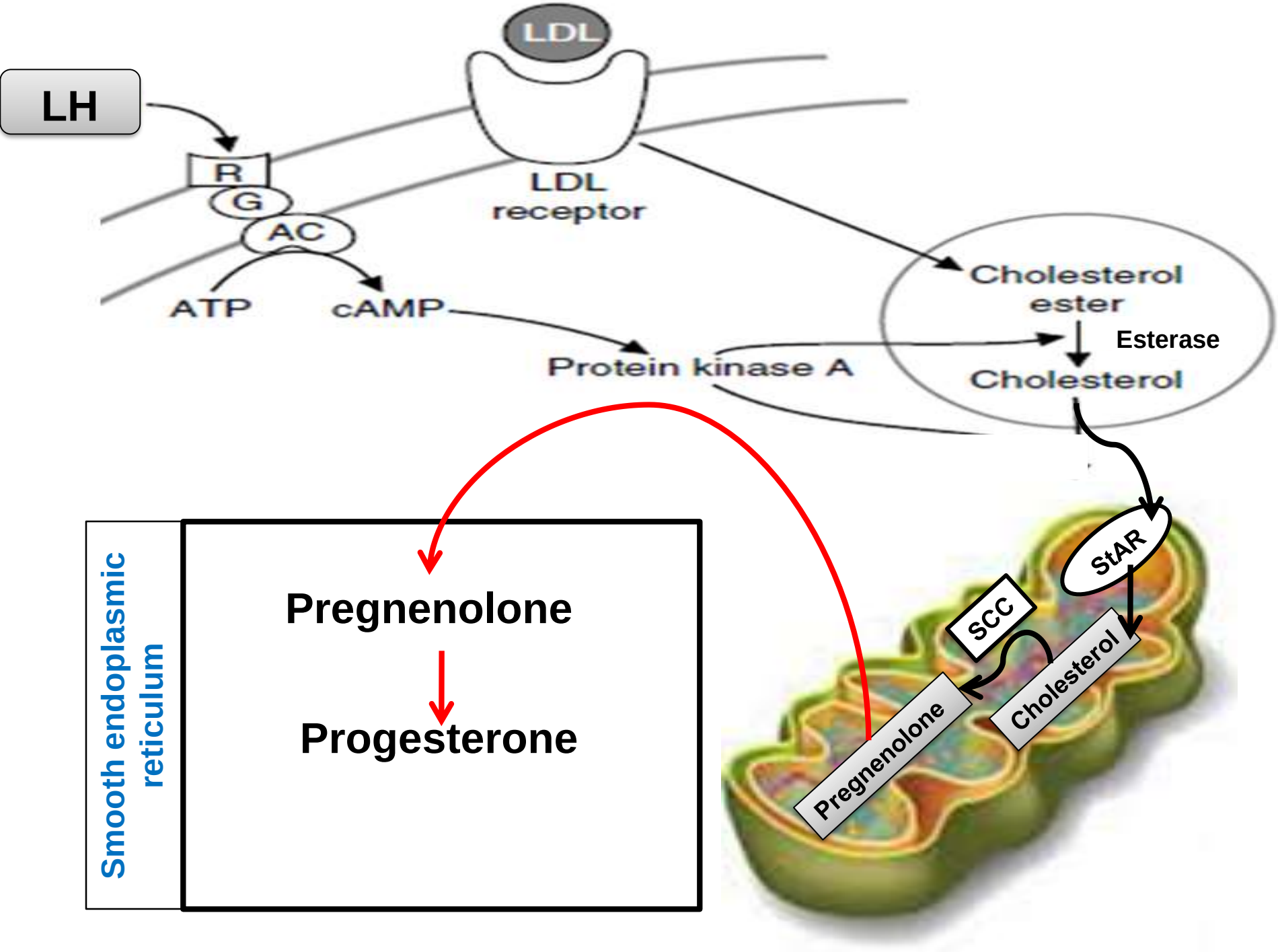


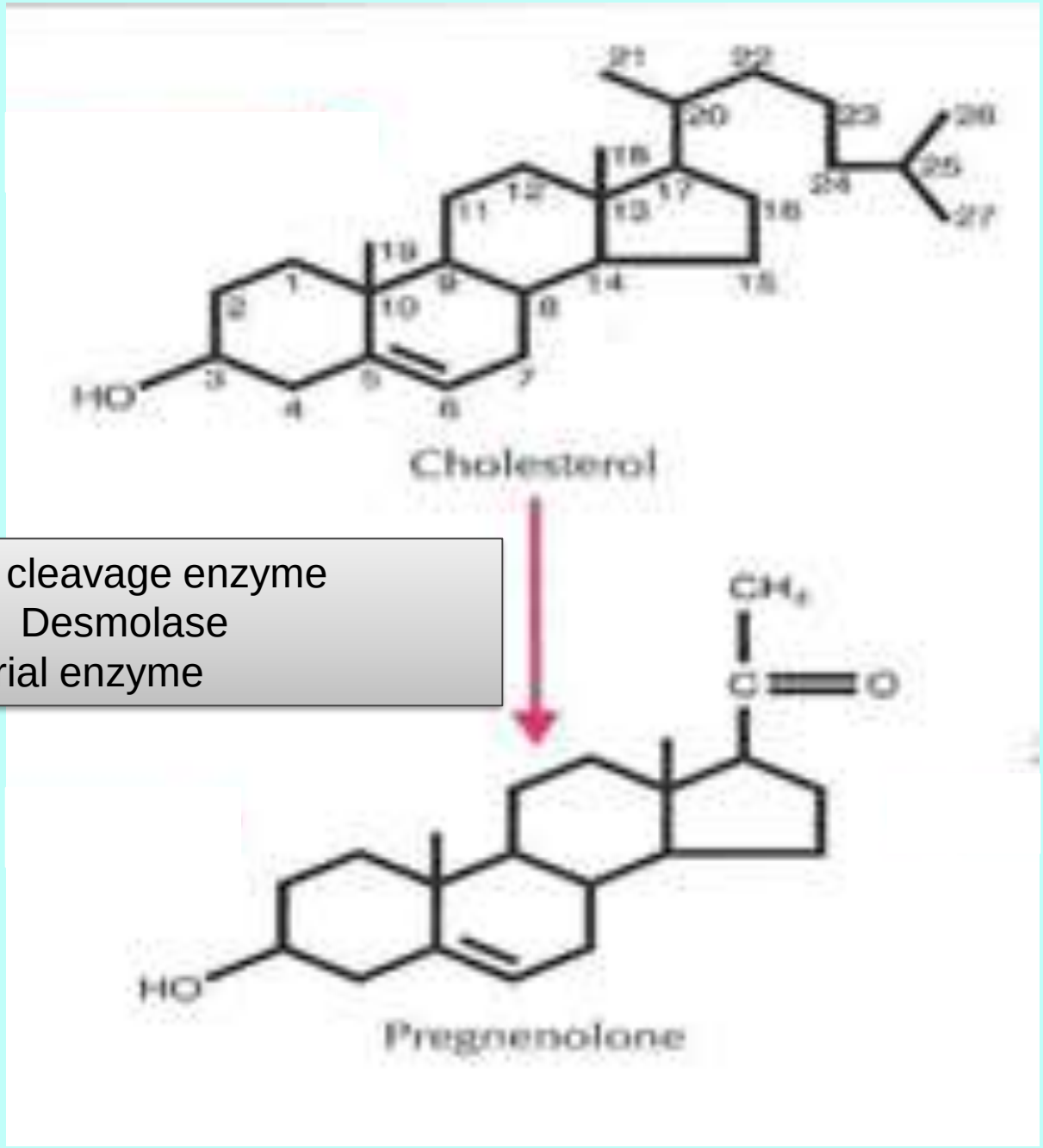
- Much of the cholesterol in the gonads is esterified and stored in cytoplasmic lipid droplets
- The amount of **free** cholesterol in the cell is maintained relatively constant:



Biosynthesis of steroid hormones

- The 1st enzymatic reaction starting from cholesterol occurs in mitochondria
- Transport of free cholesterol from cytosol to mitochondria is the rate-limiting step in this process
- Is carried out by the Steroidogenic Acute Regulatory Protein (StAR)


LH
LDL
R
G
AC
LDL receptor
ATP
cAMP
Protein kinase A
Cholesterol ester
Esterase
Cholesterol
StAR
SCC
Cholesterol
Pregnenolone
Smooth endoplasmic reticulum
Pregnenolone
Progesterone

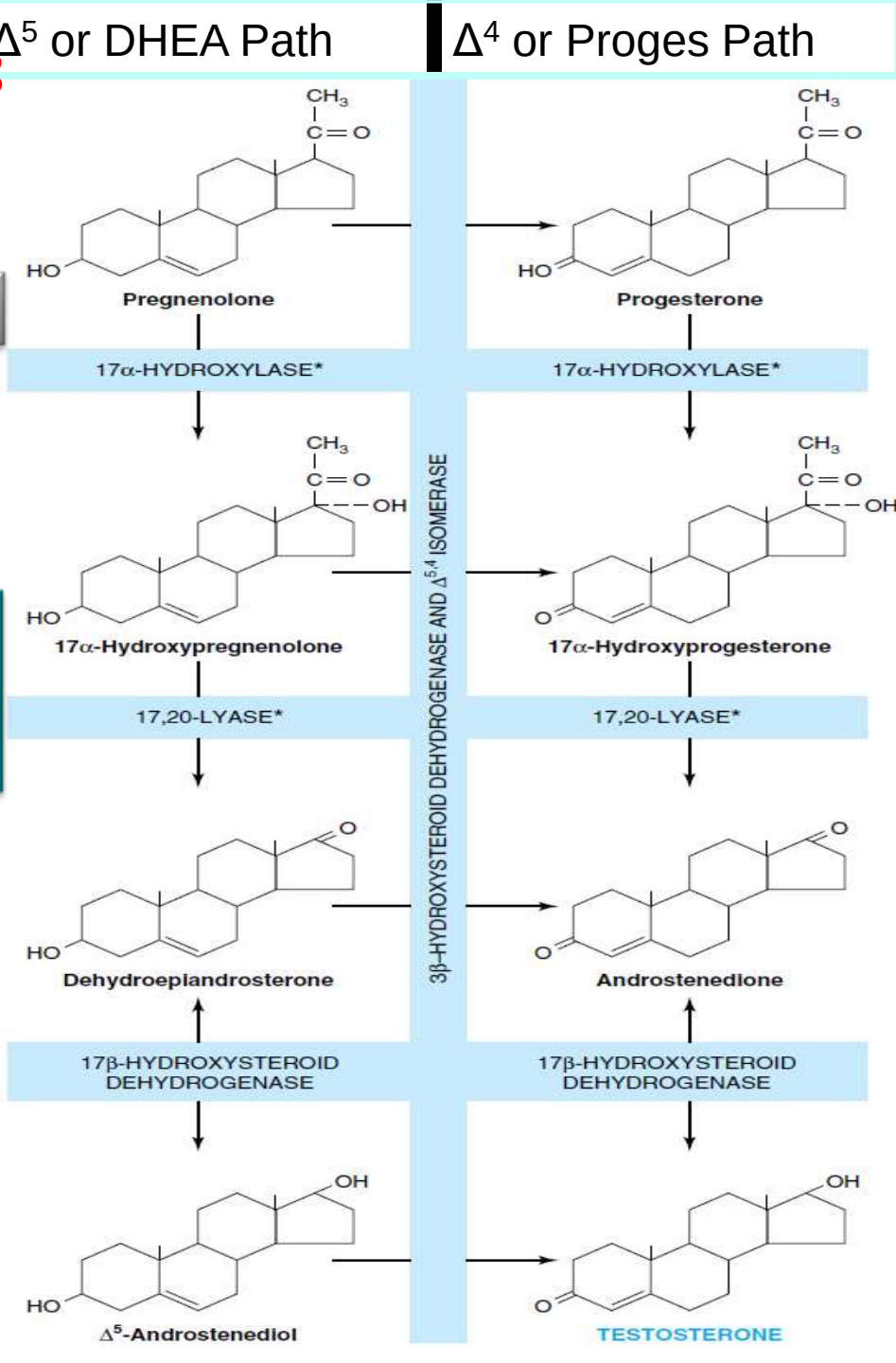

Cholesterol
Side chain cleavage enzyme
Or Desmolase
Mitochondrial enzyme
Pregnenolone

Testicular Steroidogenesis

Two Pathways of testosterone biosynthesis

The 17α-hydroxylase and 17,20-lyase activities reside in a single protein, P450c17.

Δ5 the most used Pathway



Metabolism of Testosterone

- Testosterone is metabolized by two pathways.

1. oxidation at the 17 position
   - occurs in many tissues, including liver
   - produces 17-ketosteroids that are generally inactive or less active than the parent compound
2. Reduction of the A ring double bond
   - Occurs in
     - Prostate
     - External genitelia
     - some areas of the skin

   Produces DHT

- Approximately 400 μg of DHT is produced daily as compared with about 5 mg of testosterone.
- About 50–100 μg of DHT are secreted by the testes.
- The rest is produced peripherally from testosterone in a reaction catalyzed by the NADPH-dependent **5-reductase**

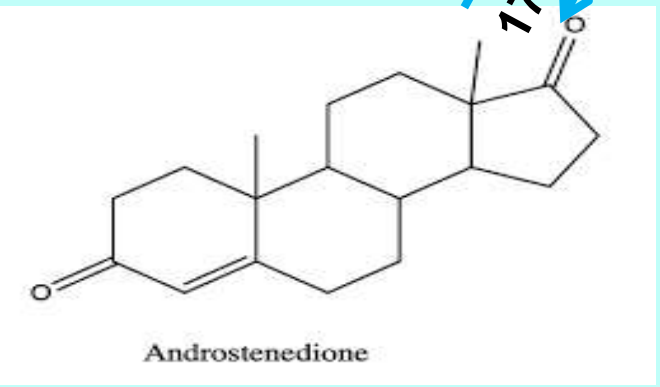
Testes

17-hydroxysteroid DH

Liver

Prostate, ext. genetelia

Some areas of the skin

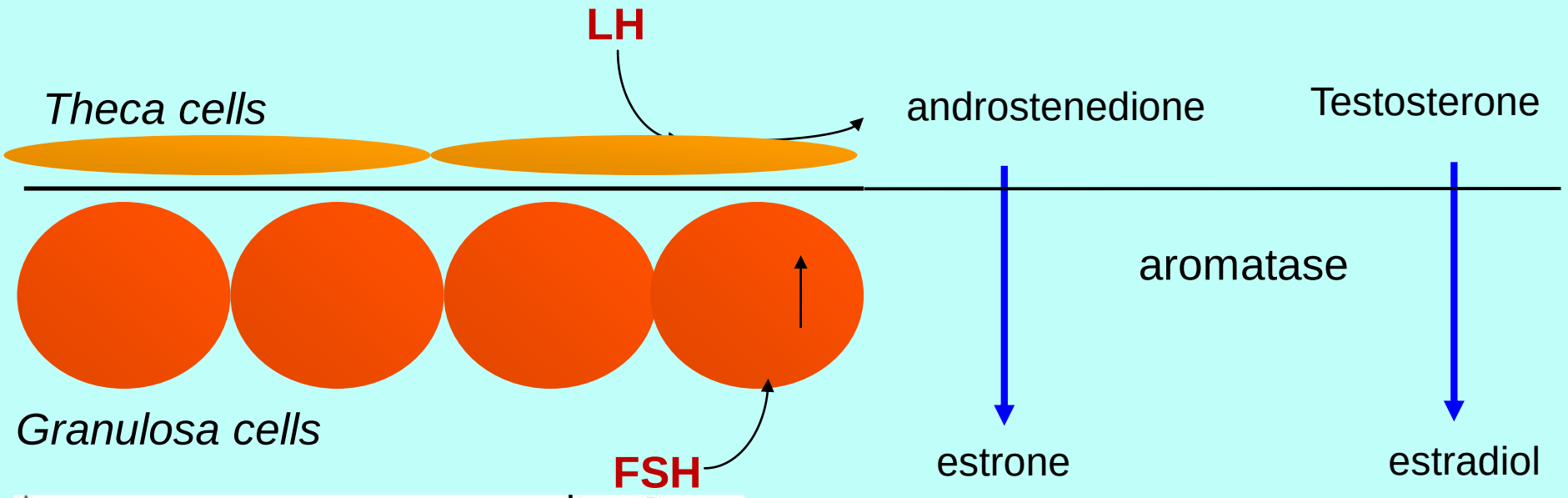


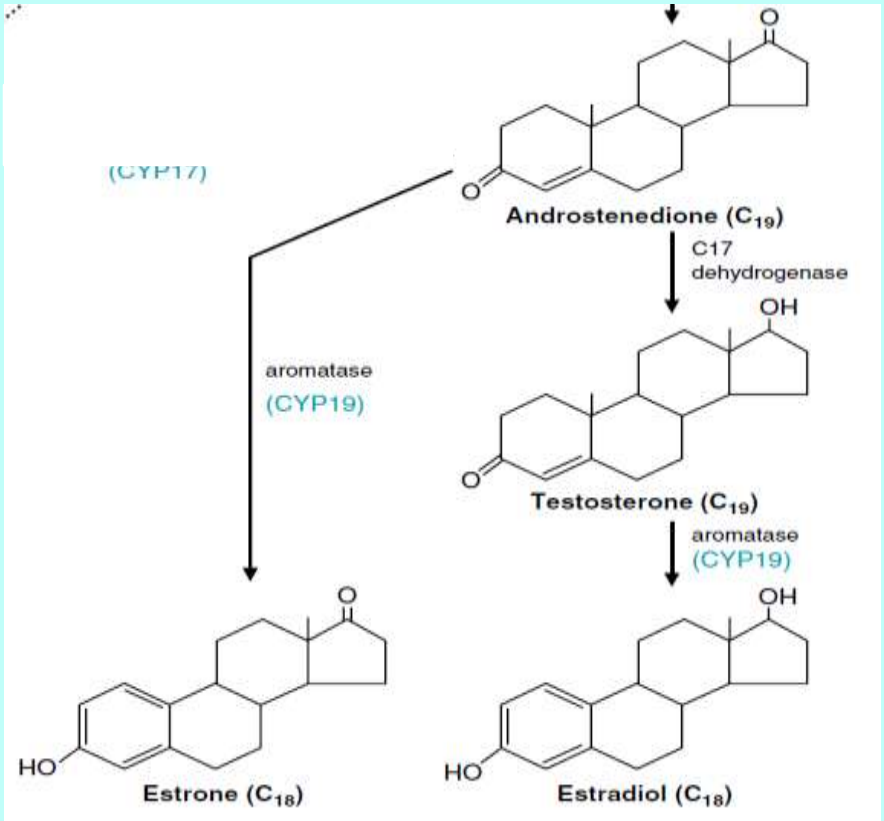
Ovarian Steroidogenesis

- The estrogens are a family of hormones synthesized in a variety of tissues.
- 17β-Estradiol is the primary estrogen of ovarian origin.
- In pregnancy, relatively more estriol is produced, and this comes from the placenta.

Ovarian Steroidogenesis

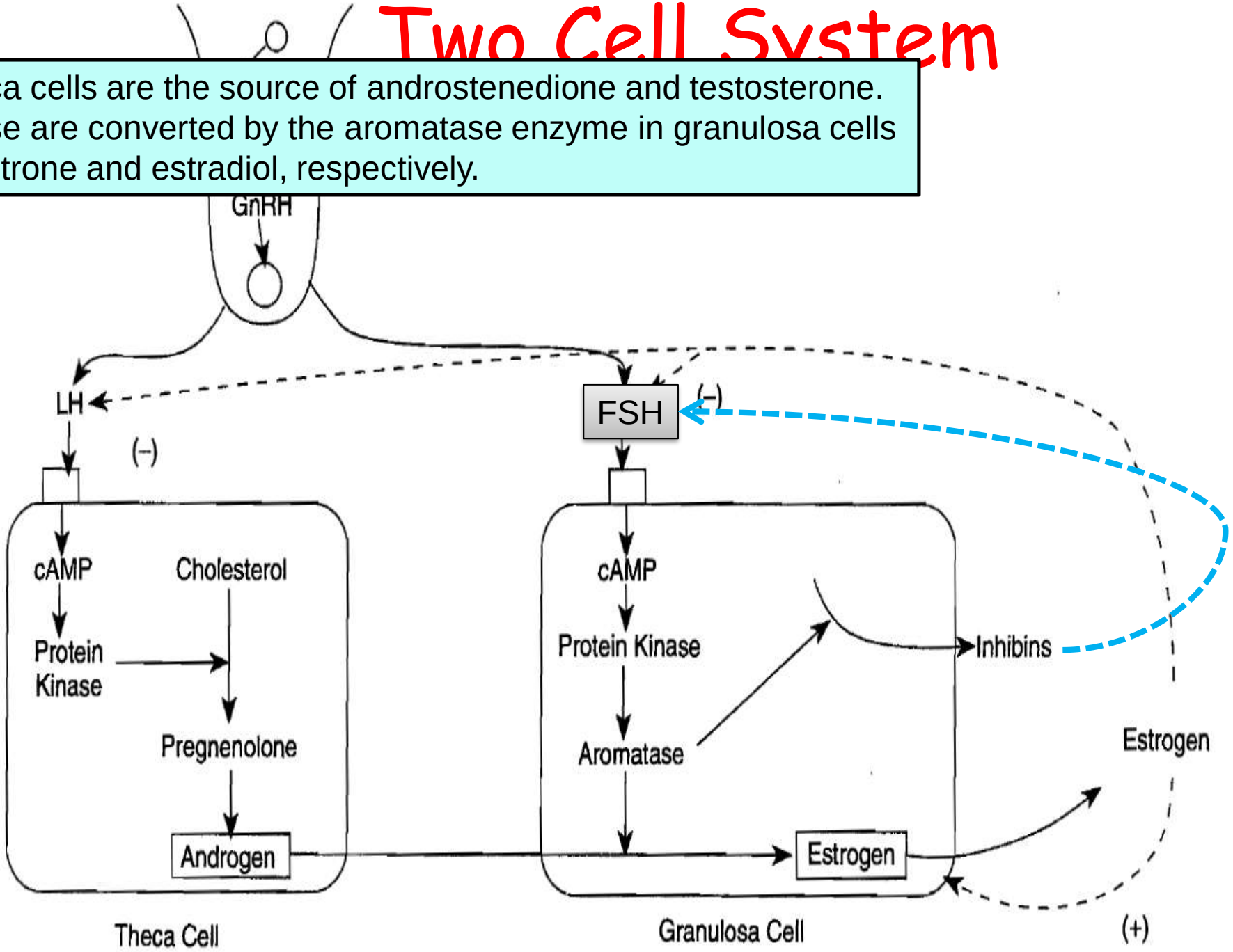
- The general pathway and the subcellular localization of the enzymes involved in the early steps of estradiol synthesis are the same as those involved in androgen biosynthesis


LH
Theca cells
androstenedione
Testosterone
aromatase
Granulosa cells
FSH
estrone
estradiol


(CYP17)
Androstenedione (C_{19})
C17
dehydrogenase
OH
aromatase
(CYP19)
Testosterone (C_{19})
aromatase
(CYP19)
HO
Estrone (C_{18})
HO
Estradiol (C_{18})

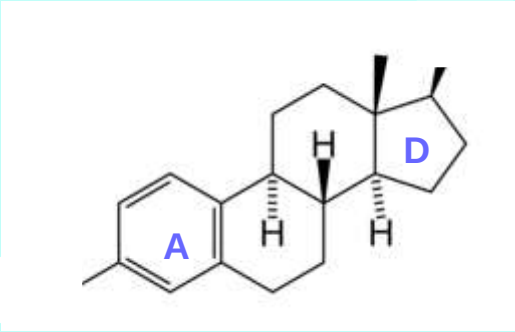
Two Cell System

Theca cells are the source of androstenedione and testosterone. These are converted by the aromatase enzyme in granulosa cells to estrone and estradiol, respectively.

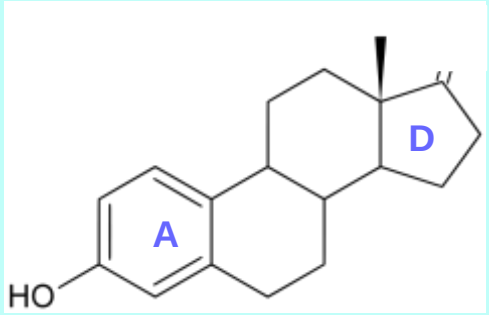


Estrogens

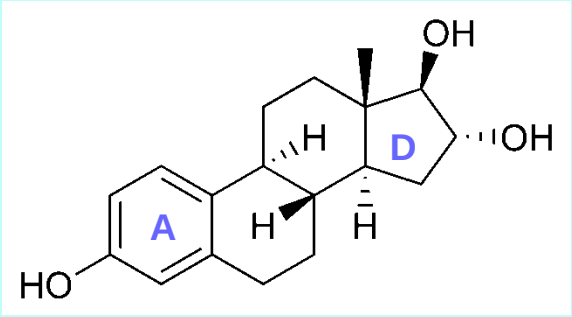
- 18 carbon containing steroids with:
  - a phenolic ring A
  - a hydroxyl group at C3
  - At C-17
    - either a hydroxyl group **(estradiol)**
    - or a ketone group **(estrone)**
  - A 3rd OH group at C-16 **(estriol)**



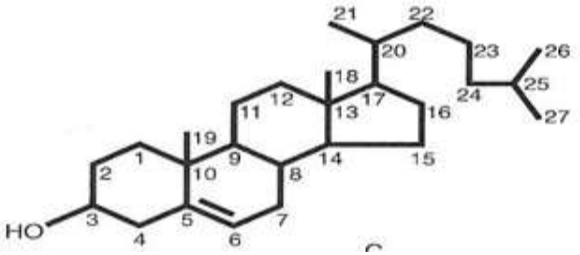
Estradiol



Estrone

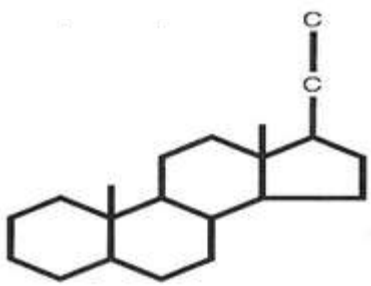


Estriol



Cholesterol (C27)

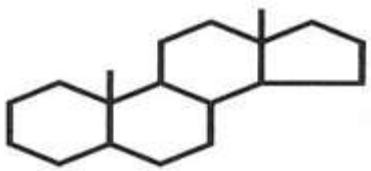
Pregnenolone (C21)



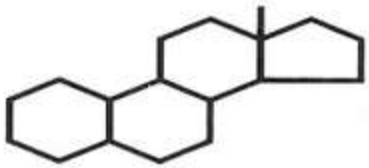
Progestagens (C21)

Glucocorticoids (C21)

Mineralocorticoids (C21)



Androgens (C19)



Estrogens (C18)

Testosterone

Cholesterol → Pregnenolone → Progesterone

17α- hydroxylase

17α-Hydroxypregnenolone → 17α-Hydroxyprogesterone

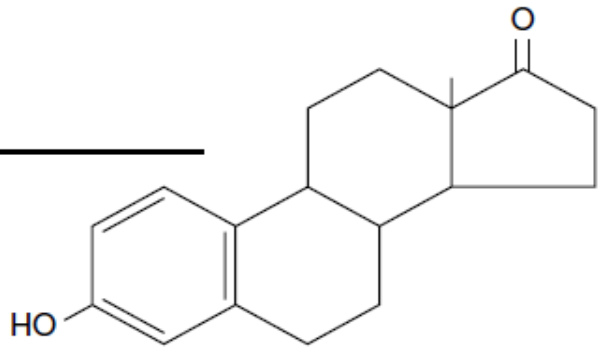
1720 Lyase

Dehydroepiandrosterone → Androstenedione ⇅ Testosterone

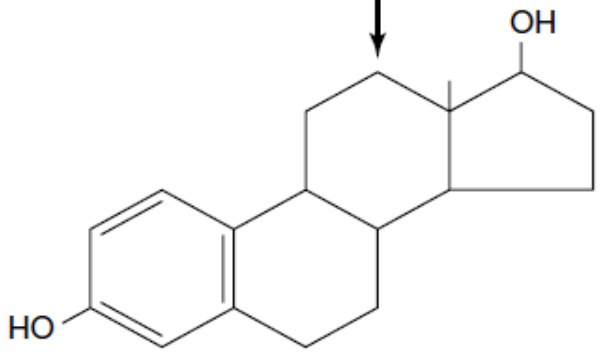
AROMATASE

AROMATASE

Other metabolites



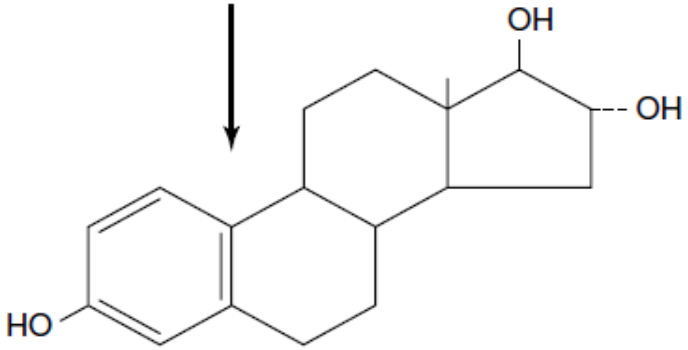
ESTRONE (E_1)



17β-ESTRADIOL (E_2)

16α-Hydroxylase

Other metabolites



Estriol

onal changes in s altered states

pulsatile release of GnRH prevents downregulation of its receptors in anterior pituitary

Chronic release of GnRH causes downregulation of its receptors in anterior pituitary

Condition	Sex steroids	LH	FSH	GnRH
1. Primary hypogonadism	↓	↑	↑	↑
2. Pituitary hypogonadism	↓	↓	↓	↑
3. Postmenopausal women	↓	↑	↑	↑
4. Anabolic steroid therapy (male)	↑	↓	↓	↓
5. Inhibin infusion	--	--	↓	--
6. GnRH infusion (constant rate)	↓	↓	↓	↑
7. GnRH infusion (pusatile)	↑	↑	↑	↑