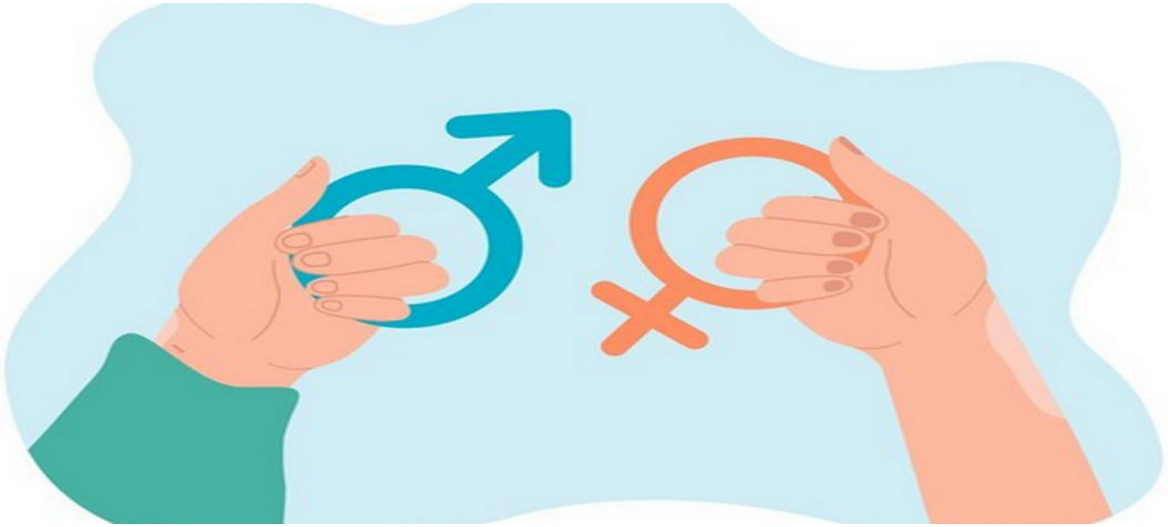
SEX HORMONES



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CONTENTS

1. Classification of sex hormones
2. Site of production of sex hormones
3. Structure of sex hormones
4. Biosynthesis of sex hormones
5. Molecular mechanism of action of sex hormones
6. Physiological effects of sex hormones

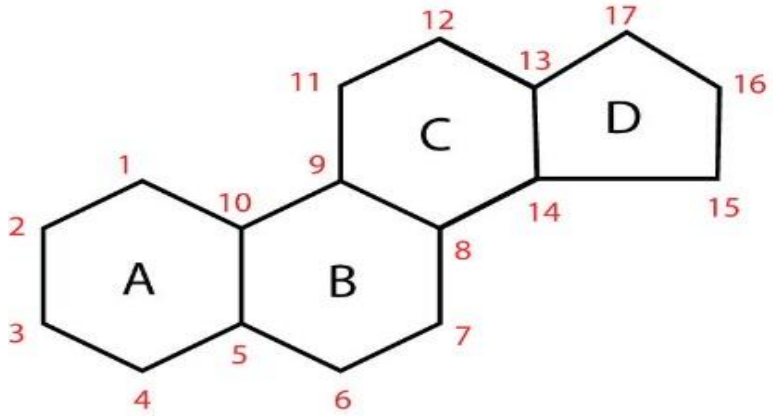
LEARNING OUTCOMES

At the end of this session, the students should be able to:

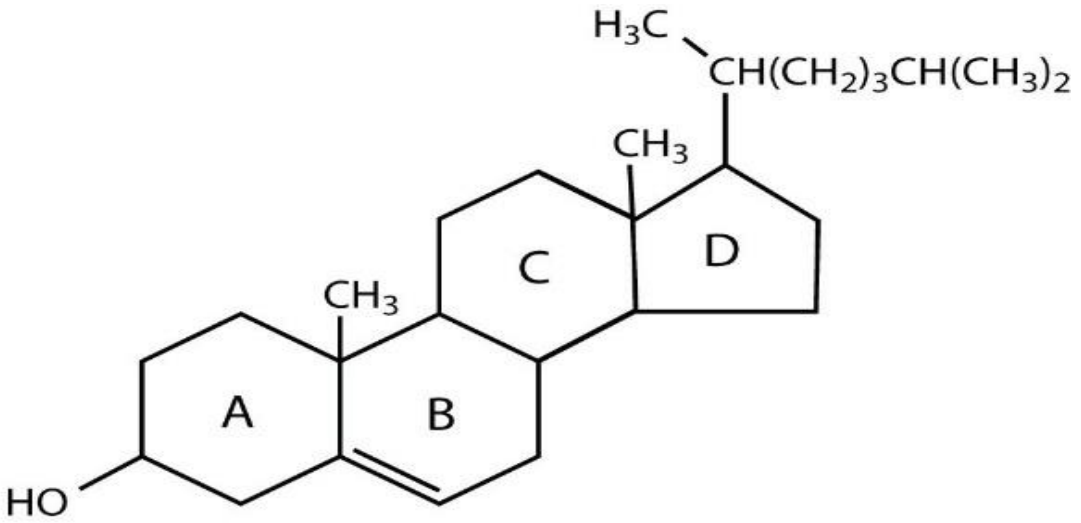
1. Classify the sex hormones
2. Identify the site of production of sex hormones
3. Recognize the structure of sex hormones
4. Recognize the steps of sex hormones biosynthesis
5. Recognize the molecular mechanism of action of sex hormones
6. Mention the physiological effects of sex hormones

SEX HORMONES

- They are **steroid hormones** (containing steroid nucleus).
- They are **derived from cholesterol**.



(a) Steroid skeleton



(b) Cholesterol

- They are **produced** by

  1. Adrenal glands

  2. Gonads (**ovaries** in females

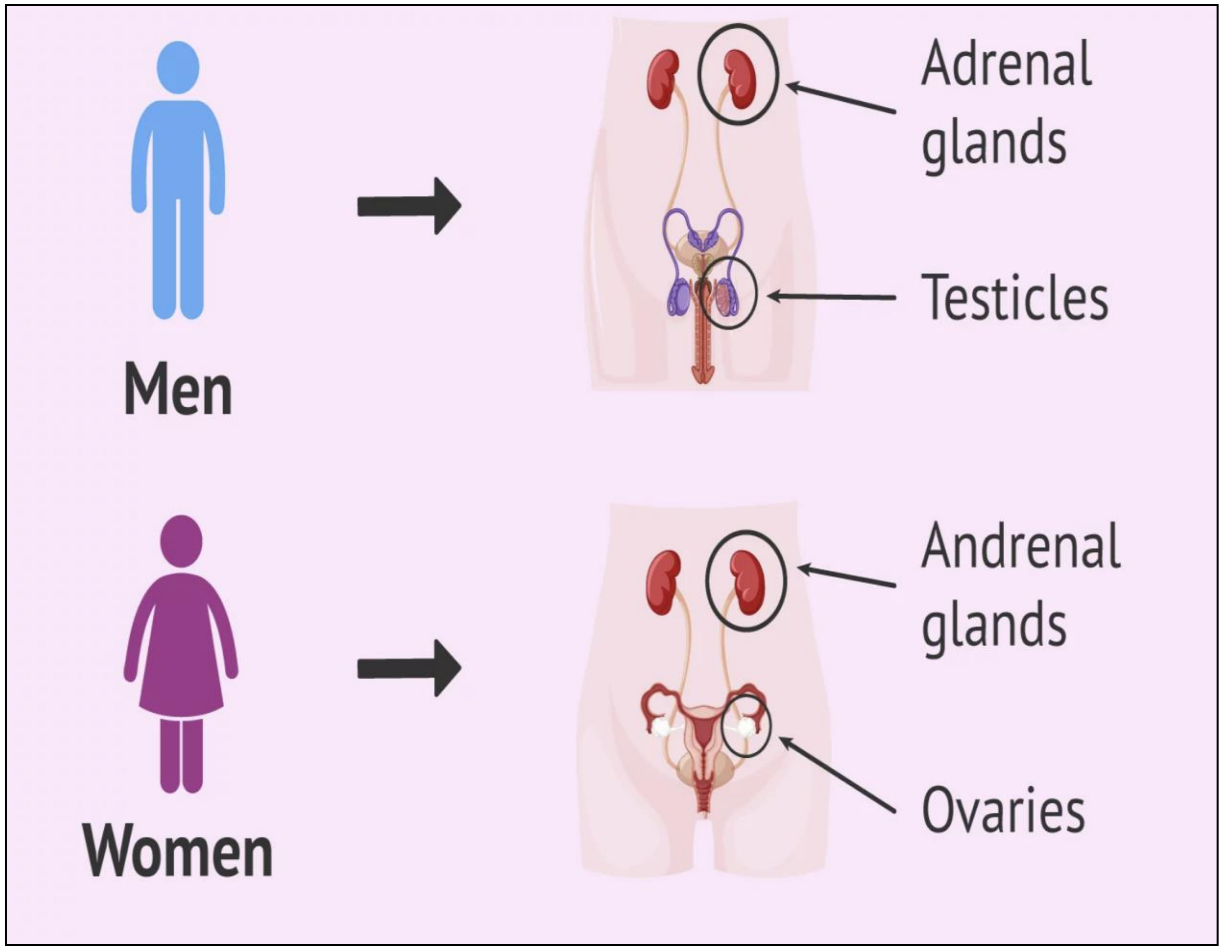
  & **testes** in males).

- **They include**

  1. Androgens (Testosterone)

  2. Estrogens (Estradiol)

  3. Progestogens (Progesterone)



Classification of sex hormones

1. Male sex hormones (androgens):

a) Weak androgens:

1. **Dehydroepiandrosterone** (DHEA) (**The major androgen produced by the adrenal cortex**).
2. **Androstenedione**

b) Strong androgens:

1. **Testosterone**
2. **Dihydrotestosterone** (DHT) (**more potent than testosterone**)

2. Female sex hormones:

a) Progestogens (Progesterone)

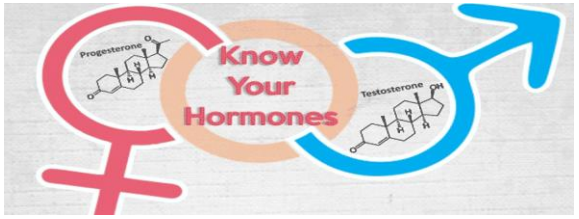
b) Estrogens: include **Estrone** (E1), **Estradiol**(E2), **Estrio**l (E3), **Estetrol** (E4)

Site of production

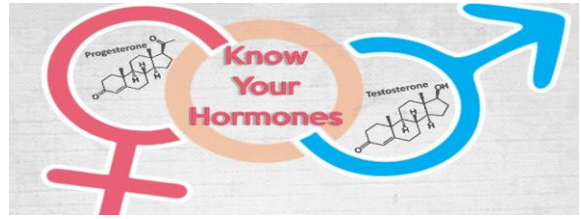
Androgens	Estrogens	Progesterone
Leydig cells of Testes (majority)	**Ovaries (majority)**	**Ovaries (majority)**
Adrenal cortex (lesser amount)	Adrenal cortex (lesser amount)	Adrenal cortex (lesser amount)
Ovaries (in female)	Adipose cells (lesser amount)	Placenta (during pregnancy)

Site of production

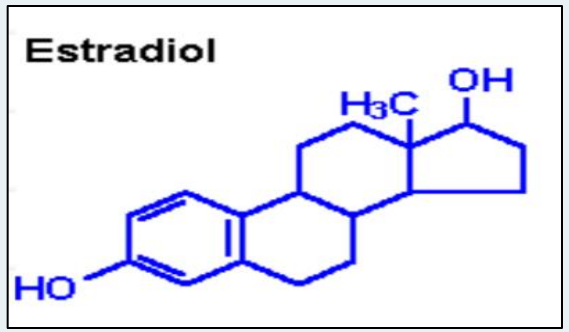
Estrone (E1)	Estradiol (E2)	Estriol (E3)	Estetrol (E4)
✓ produced by women **after menopause** ✓ produced by **ovaries, adrenal gland** and **adipose tissue**	✓ produced by women **before menopause** ✓ produced by **ovaries** ✓ The **most potent** one ✓ It is present in **lower amount** in **males**	✓ produced during **pregnancy** ✓ produced by the **placenta**	✓ produced during **pregnancy** ✓ produced by **the liver in both male** and **female fetuses**

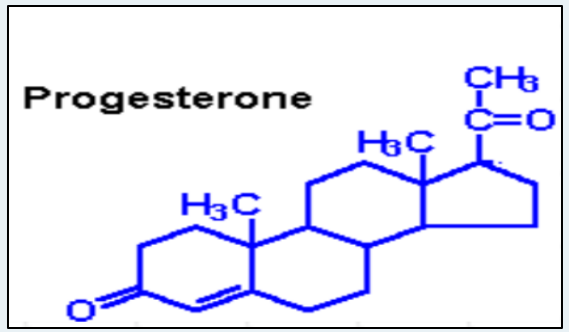


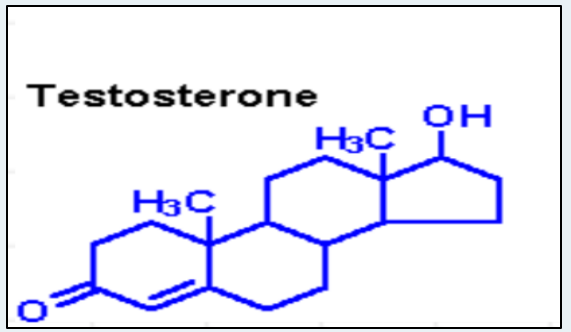
Structure of sex hormone



Estradiol	Progesterone	Testosterone
18 C	**21 C**	**19 C**
Aromatic A ring	**1 Double bond** between C4 and C5	**1 Double bond** between C4 and C5
OH group at C3	**Ketone group** at C3	**Ketone group** at C3
CH3 group at C13	**CH3 group** at C10 & C13	**CH3 group** at C10 & C13
OH group at C17	**CH3CO group** at C17	**OH group** at C17







Biosynthesis of sex hormones

It is controlled by **Hypothalamic-Pituitary-Gonadal axis**

1. Hypothalamus:

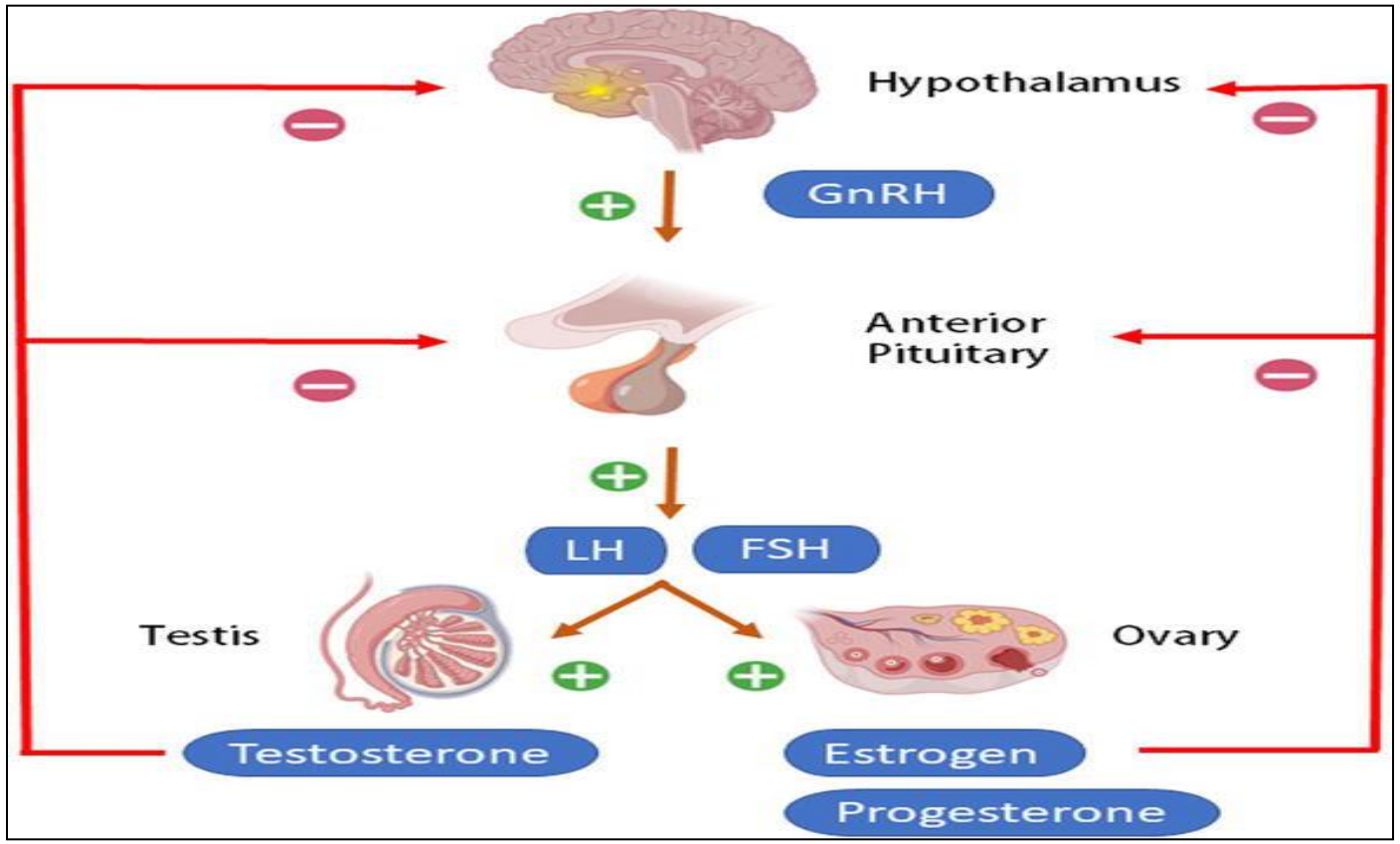
GnRH

2. Anterior Pituitary:

LH - FSH

3. Testis and Ovary:

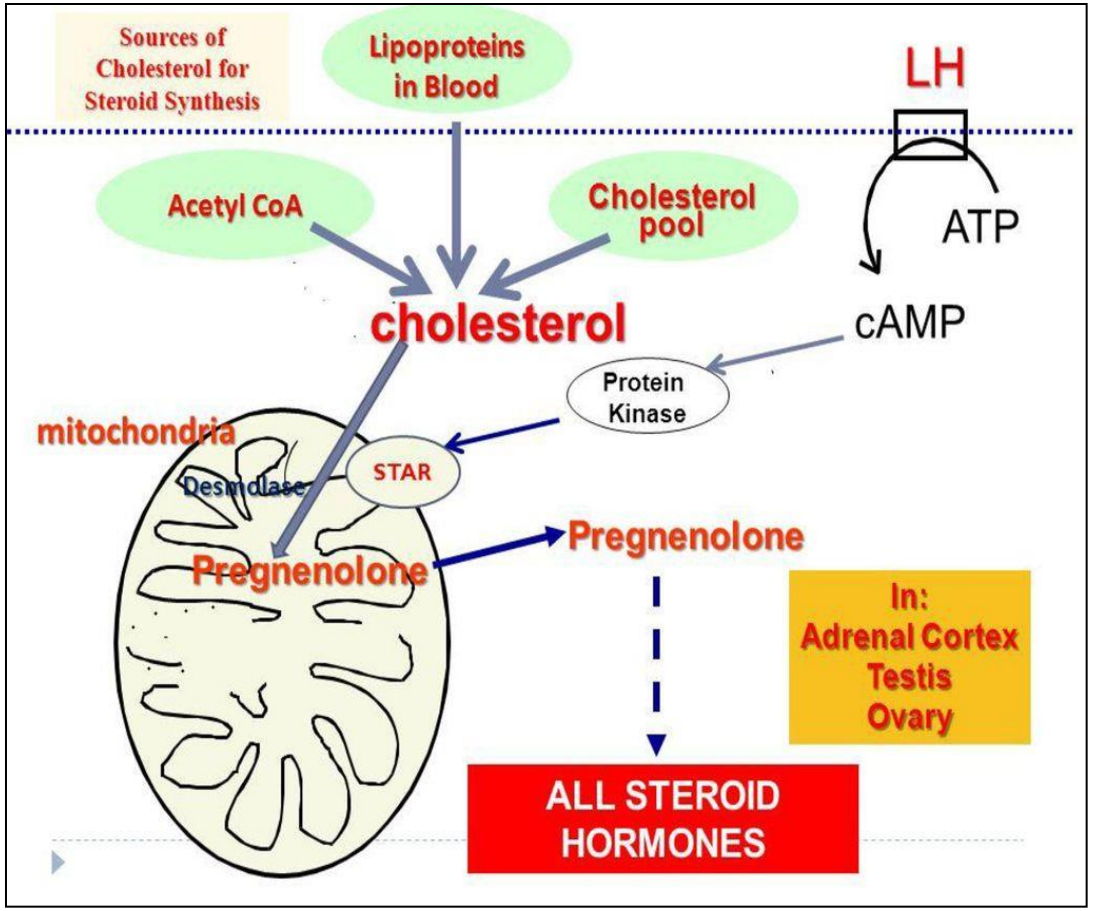
Sex hormones



Biosynthesis of sex hormones

In testis and ovary:

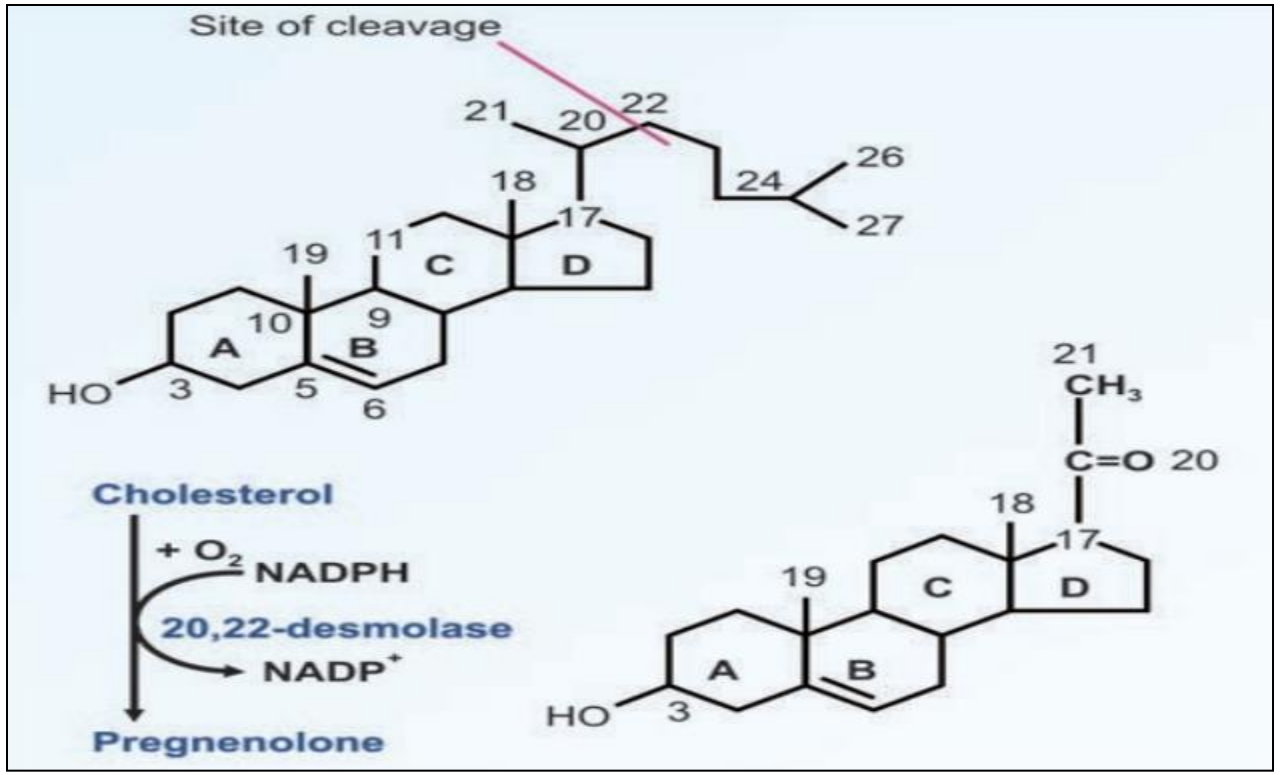
1. LH binds to its target cells and increases the expression of **steroidogenic acute regulatory protein** (**StAR**).
2. StAR promotes the delivery of cholesterol to the inner mitochondrial membrane and initiates steroidogenesis.
3. At the inner mitochondrial membrane, cholesterol is converted into **pregnenolone** by the action of **cytochrome P450 side chain cleavage enzyme (P450scc),** also known as **20, 22-desmolase enzyme,** which is the **rate-limiting step** for synthesis of all steroid hormones.

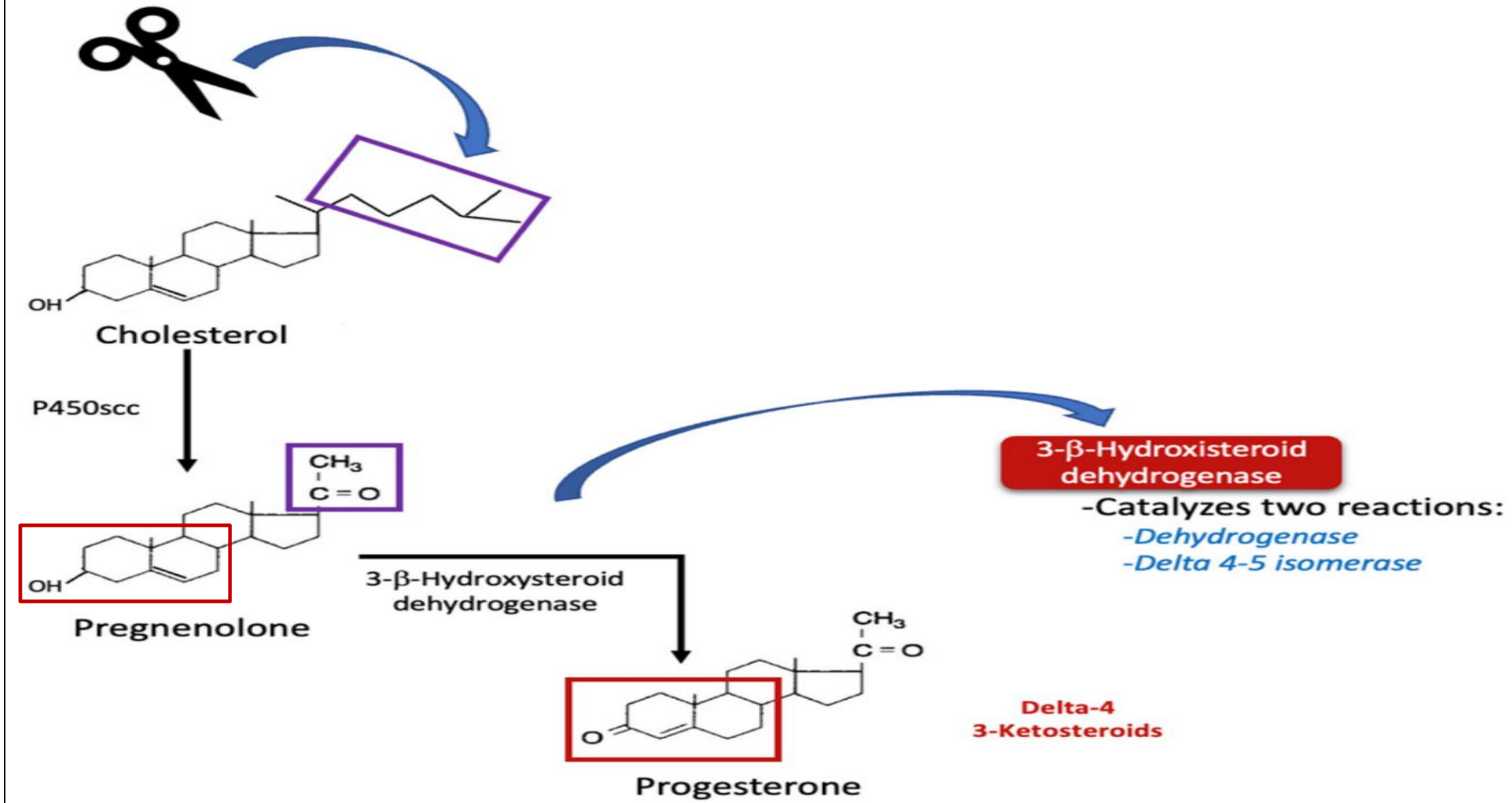


Synthesis of Progesterone

Site: in the **corpus luteum cells**, the **placenta during pregnancy** and the **adrenals**.

Progesterone is the **first steroid hormone** formed from pregnenolone in two steps by action of **3β-hydroxy steroid dehydrogenase** (3β-HSD).

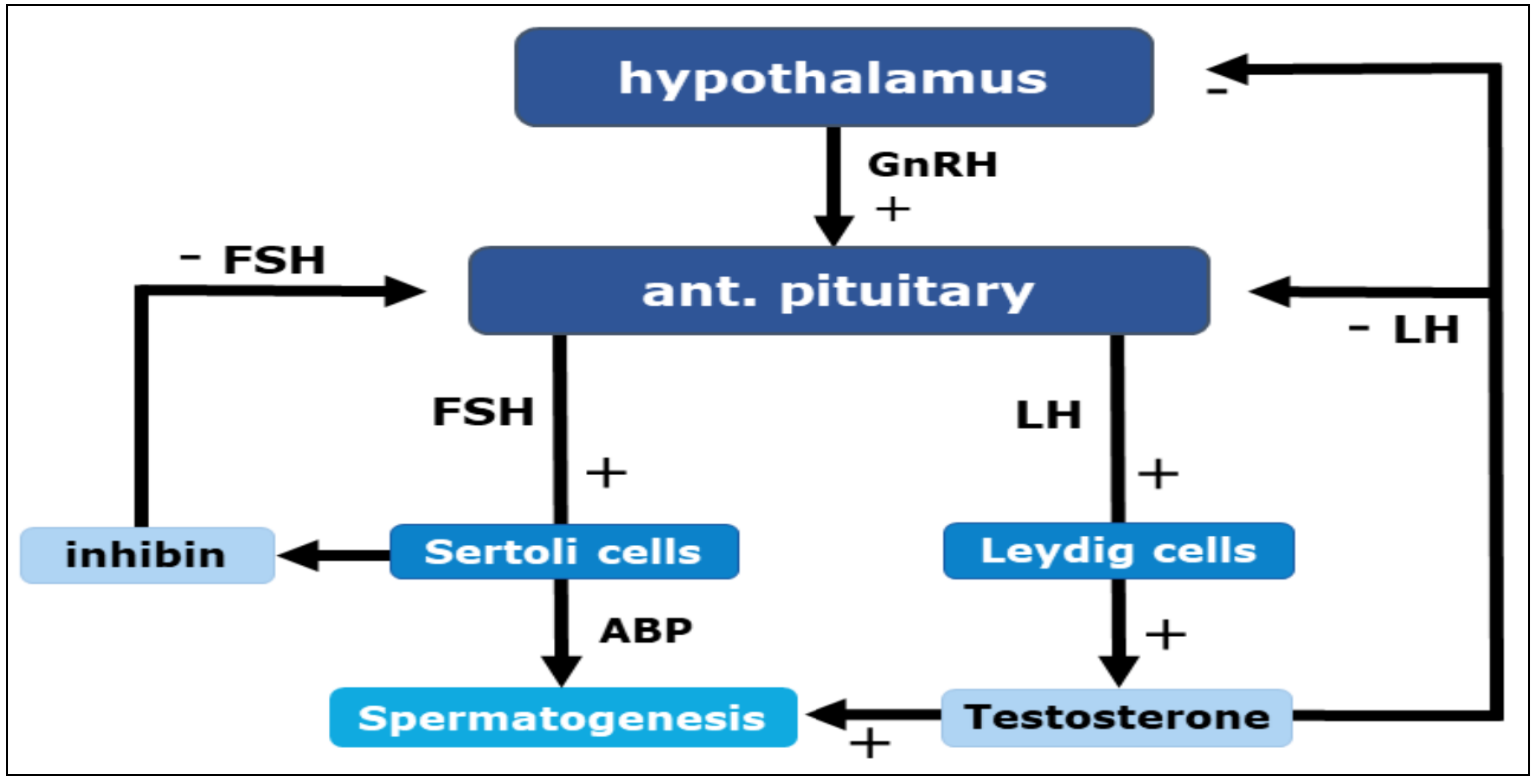



OH
Cholesterol
P450scc
CH3
C = O
OH
Pregnenolone
3-β-Hydroxysteroid dehydrogenase
3-β-Hydroxisteroid dehydrogenase
-Catalyzes two reactions:
-Dehydrogenase
-Delta 4-5 isomerase
CH3
C = O
O
Progesterone
Delta-4
3-Ketosteroids

Synthesis of Androgens

- **LH** stimulates the interstitial **Leydig cells** to produce **testosterone**.

- **FSH** stimulates **Sertoli cells** located within the seminiferous tubules resulting in **Spermatogenesis**.



Steps of androgens synthesis :

A. Leydig cells in testes:

1.LH initiates the production of **pregnenolone**.

2. Then, pregnenolone is converted to testosterone by 2 pathways;

I.Dehydroepiandrosterone (DHEA) (or Δ5) pathway:

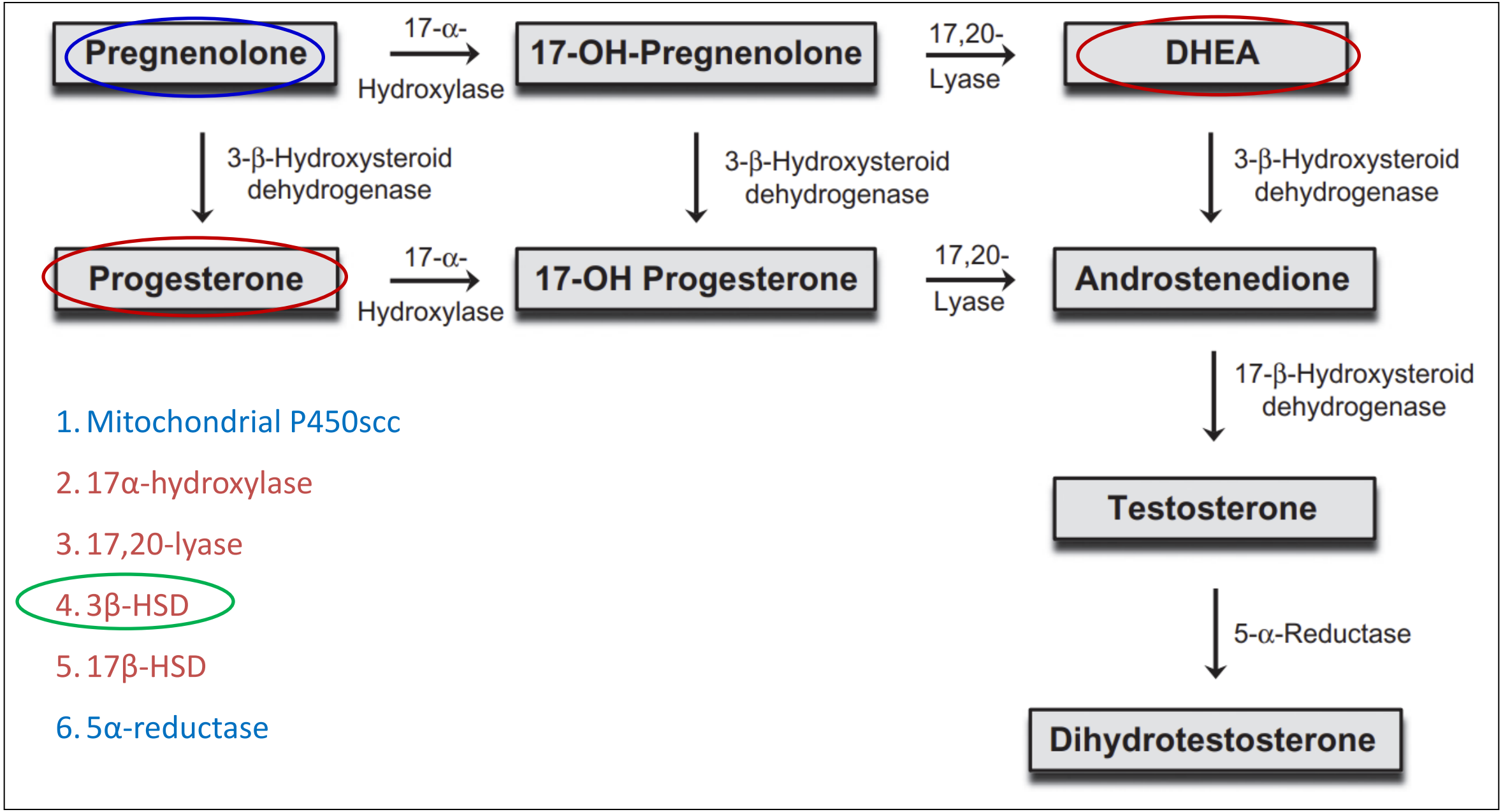
1.Pregnenolone → 17-OH-Pregnenolone → DHEA in a two-step process mediated by **17α-hydroxylase** and **17,20-lyase**.

2.DHEA → androstenedione → testosterone by **3β-HSD** and **17β-HSD**.

II. Progesterone (or Δ4) pathway:

1.Pregnenolone → Progesterone by **3β-HSD** .

2.Progesterone → 17-OH-Progesterone → androstenedione → testosterone by **17α-hydroxylase, 17,20-lyase** and **17β-HSD** respectively.



1. Mitochondrial P450scc
2. 17α-hydroxylase
3. 17,20-lyase
4. 3β-HSD
5. 17β-HSD
6. 5α-reductase

Q: Enumerate 3 fates of testosterone is peripheral tissues?

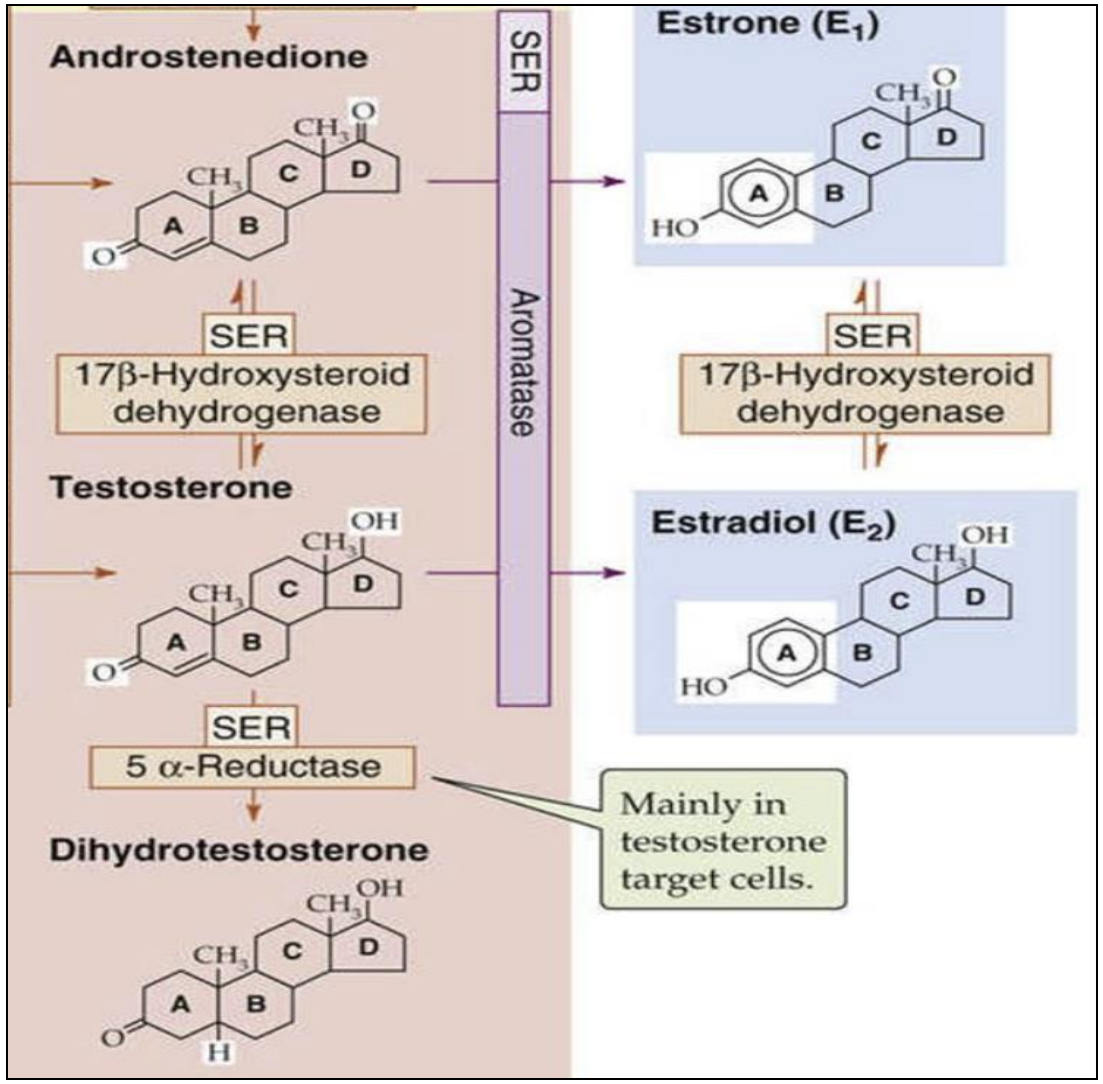
B. In the peripheral tissues:

Testosterone is converted to

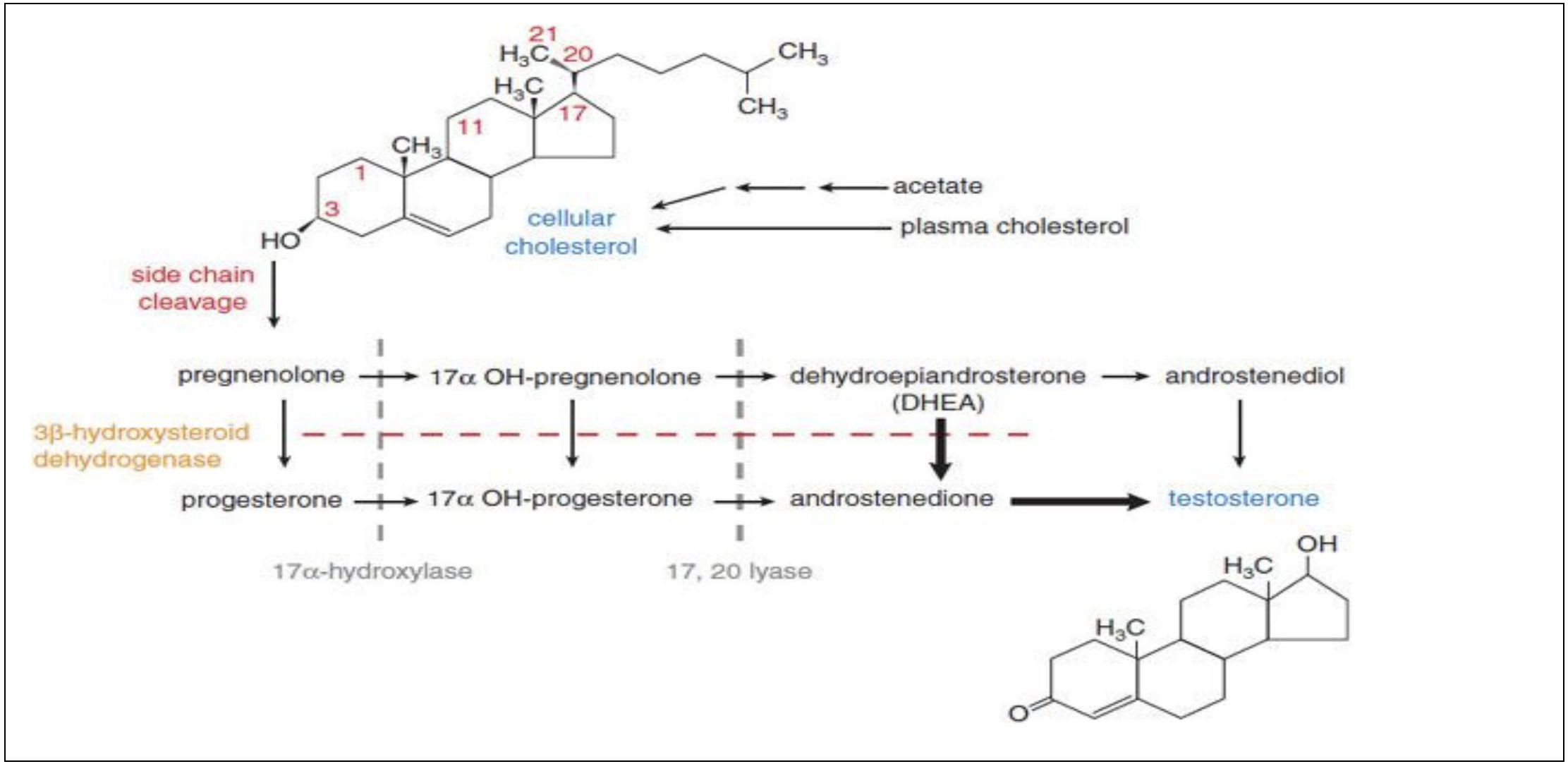
a. **Dihydrotestosterone** (**DHT**) by the **NADPH-dependent 5α-reductase** which is more potent than testosterone.

b. **Estradiol** by **aromatase**.

c. **17-ketosteroids** (e.g., Androstenedione) via oxidation by **17β-HSD**.

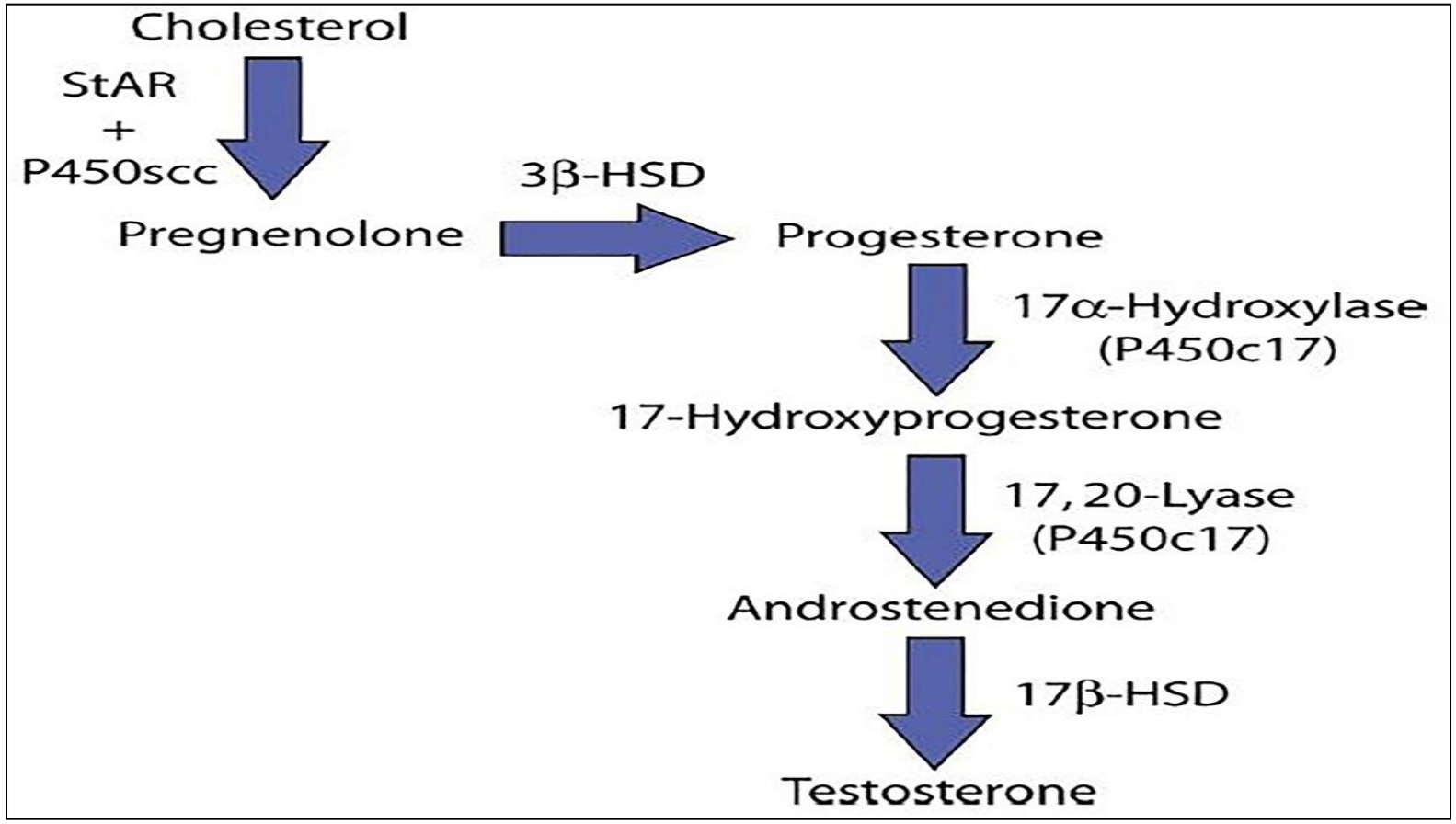


Q: Describe how testosterone is synthesized from cholesterol?



Q: Mention steps of testosterone synthesis via progesterone pathway?

Don't forget to start from cholesterol



Synthesis of Estrogen in females

Site: occurs in the theca and granulosa cells of the ovaries

Steps:

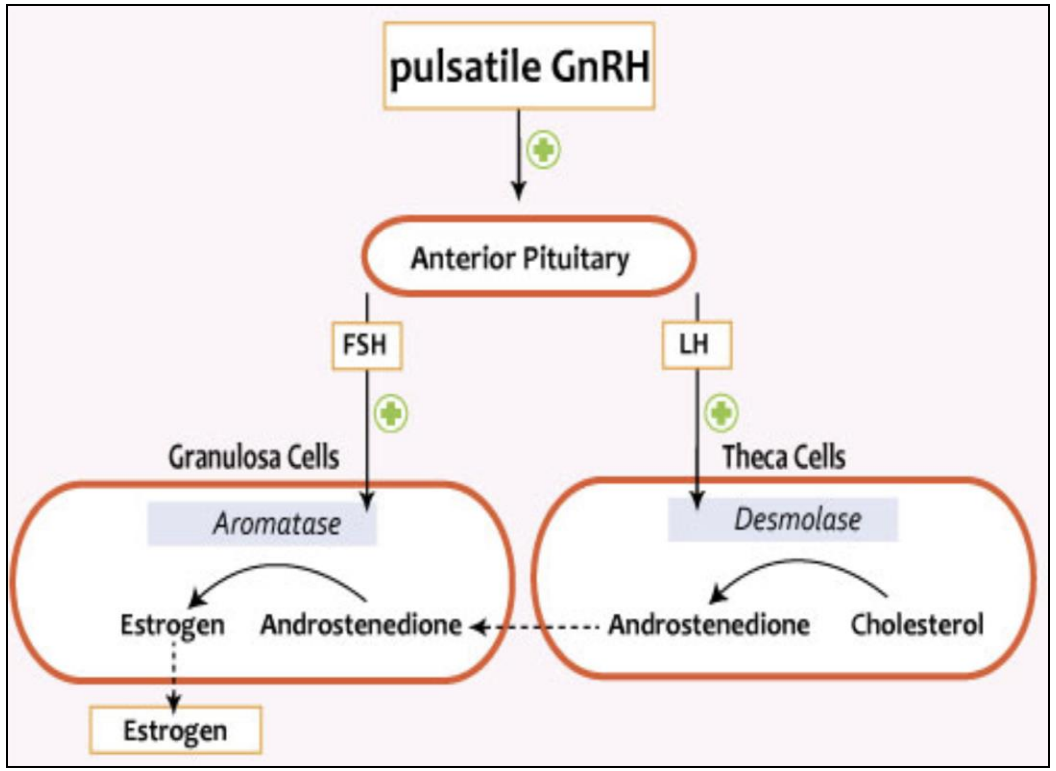
1.In the follicular phase, **LH** primes the **ovarian theca cells** to convert cholesterol to androstenedione.

•Cholesterol →Pregnenolone →DHEA →Androstenedione

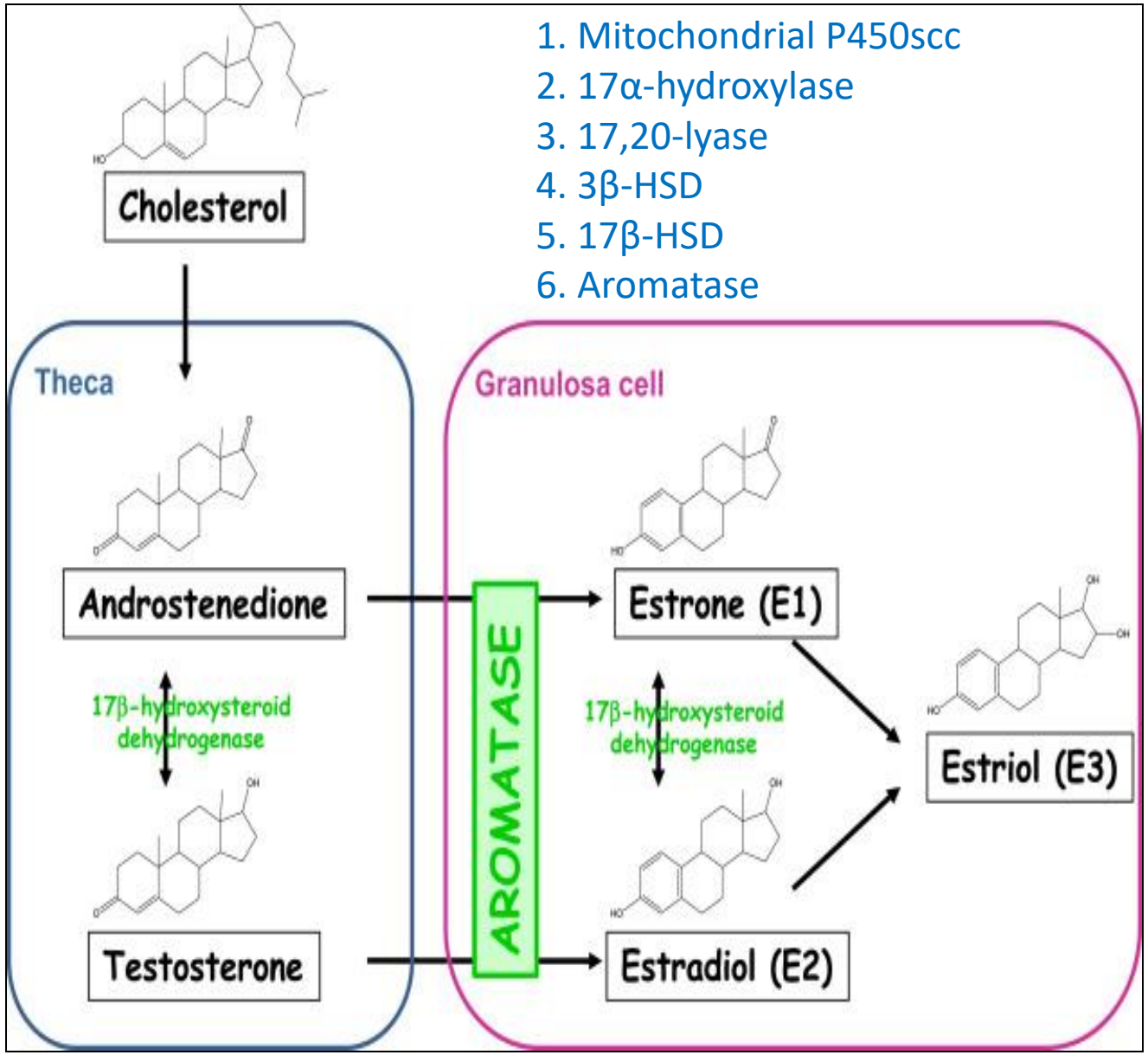
2. Then, **androstenedione** diffuses to **the granulosa cells** and is converted to **estrone** by **aromatase**, which is then converted to **estradiol** by **17β-HSD**. The activity of aromatase and 17β-HSD has been stimulated by **FSH**.

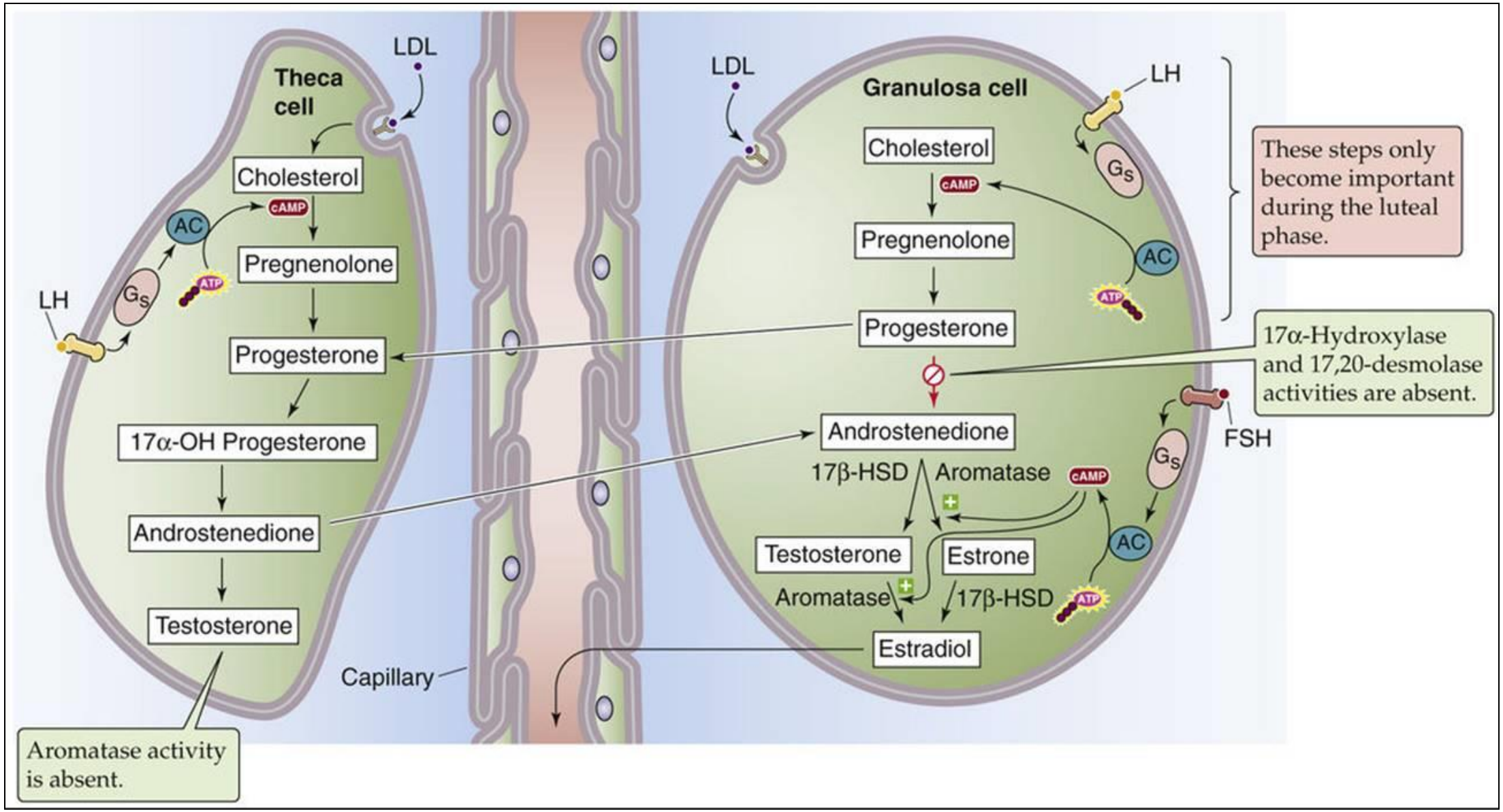
•Androstenedione→ estrone → 17β estradiol

3. In **peripheral tissues** such as bone, **aromatase** enzyme **converts testosterone to estrogen** to help mature the epiphyses.

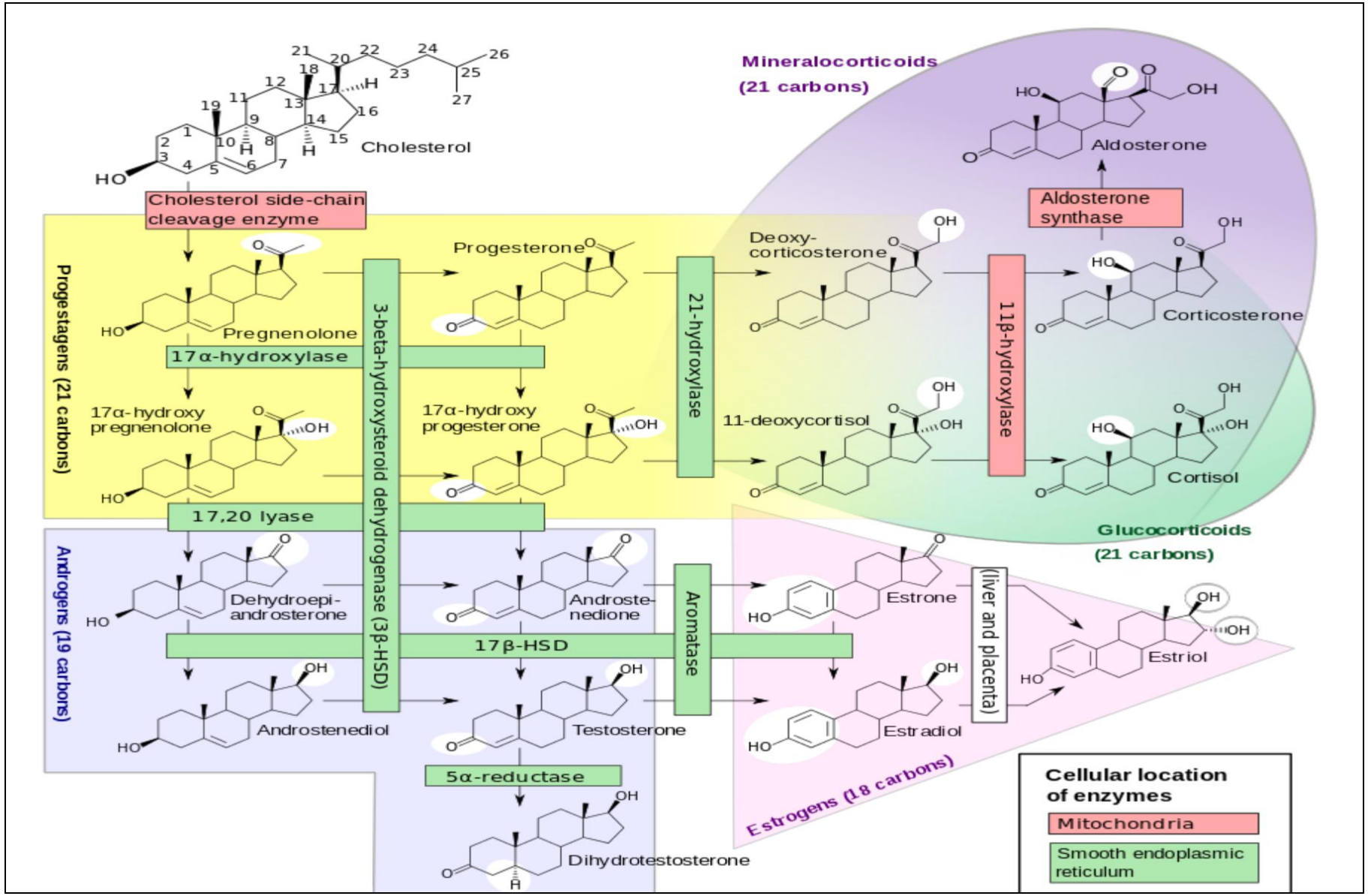


1. Mitochondrial P450scc
2. 17α-hydroxylase
3. 17,20-lyase
4. 3β-HSD
5. 17β-HSD
6. Aromatase




Theca cell
LDL
Cholesterol
cAMP
AC
Pregnenolone
LH
Gs
ATP
Progesterone
17α-OH Progesterone
Androstenedione
Testosterone
Aromatase activity is absent.
Capillary
LDL
Granulosa cell
LH
Cholesterol
cAMP
Gs
Pregnenolone
AC
ATP
Progesterone
These steps only become important during the luteal phase.
17α-Hydroxylase and 17,20-desmolase activities are absent.
Androstenedione
FSH
17β-HSD
Aromatase
cAMP
Gs
Testosterone
Estrone
AC
Aromatase
17β-HSD
ATP
Estradiol

Overall pathway for biosynthesis of sex hormones



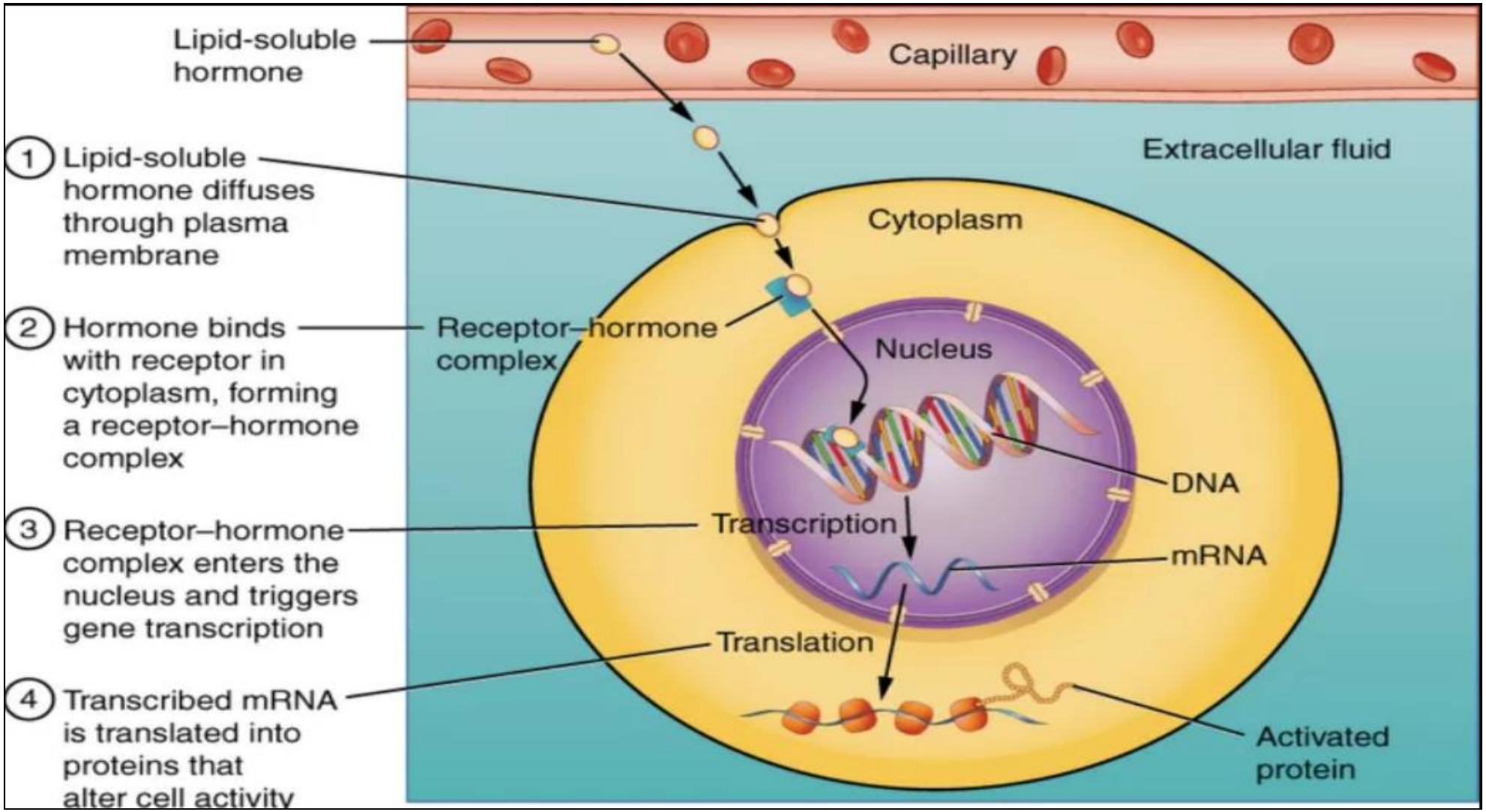
Important notes for MCQs:

- GnRH is a **decapeptide**.
- FSH and LH are **glycoproteins** hormones of **αβ heterodimeric structure**. They have a common α subunit, but unique β subunits.
- Conversion of **cholesterol to pregnenolone** is identical in the adrenal, testis and ovary, but in **adrenal**, the reaction is promoted by **ACTH** rather than LH.
- **Pregnenolone** is a **common precursor** for all the steroid hormones.
- **Testosterone** can be considered **a prohormone** since it is converted outside the testes into **DHT**.
- **Aromatase** can convert androstenedione to estrone and testosterone to estradiol.
- The products of hormone synthesis vary with the menstrual cycle; in the **follicular phase**, **estradiol** is the **main product** during **follicular maturation** whereas in the **luteal phase**, **progesterone** is the **main product** following the ovulation, and the follicle becomes the corpus luteum.

Molecular mechanism of action of sex hormones:

1. Sex hormones are small **lipophilic** molecules that are transported in blood bound to a serum globulin known as **sex steroid binding globulin** (**SSBG**).
2. In **the target cells**, they can cross cell membrane freely to bind to their receptors in the cytoplasm forming hormone-receptor complex.
3. Then, the hormone-receptor complex enters nucleus and binds to specific DNA sequence called **steroid response elements** (**SREs**) located in the promoter of genes.
4. The hormone-receptor complex regulates gene transcription, which leads to formation of mRNA.
5. The mRNA interacts with ribosomes to produce specific proteins that express the effect of sex hormones upon the target cell.

Molecular mechanism of action of sex hormones

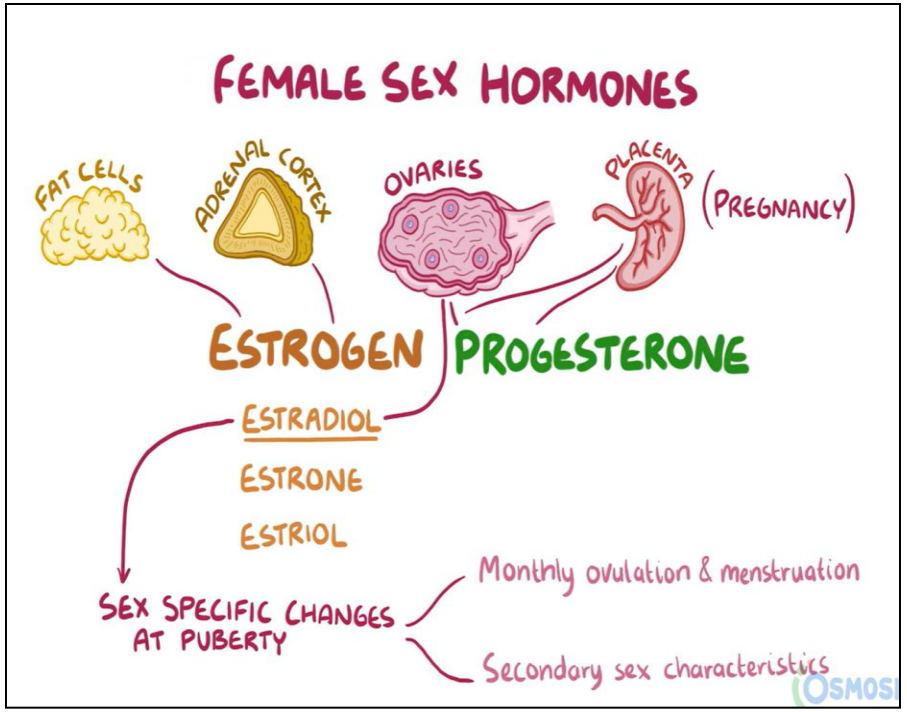


Physiological effects of Estrogens:

1. Development of **female sex organs** and **secondary sex characteristics**.
2. Role in ovulation (follicular phase in the 1st half of menstrual cycle).
3. Role in bone density modulation (male + female).
4. Role in mineral, carbohydrate, protein, and lipid metabolism.

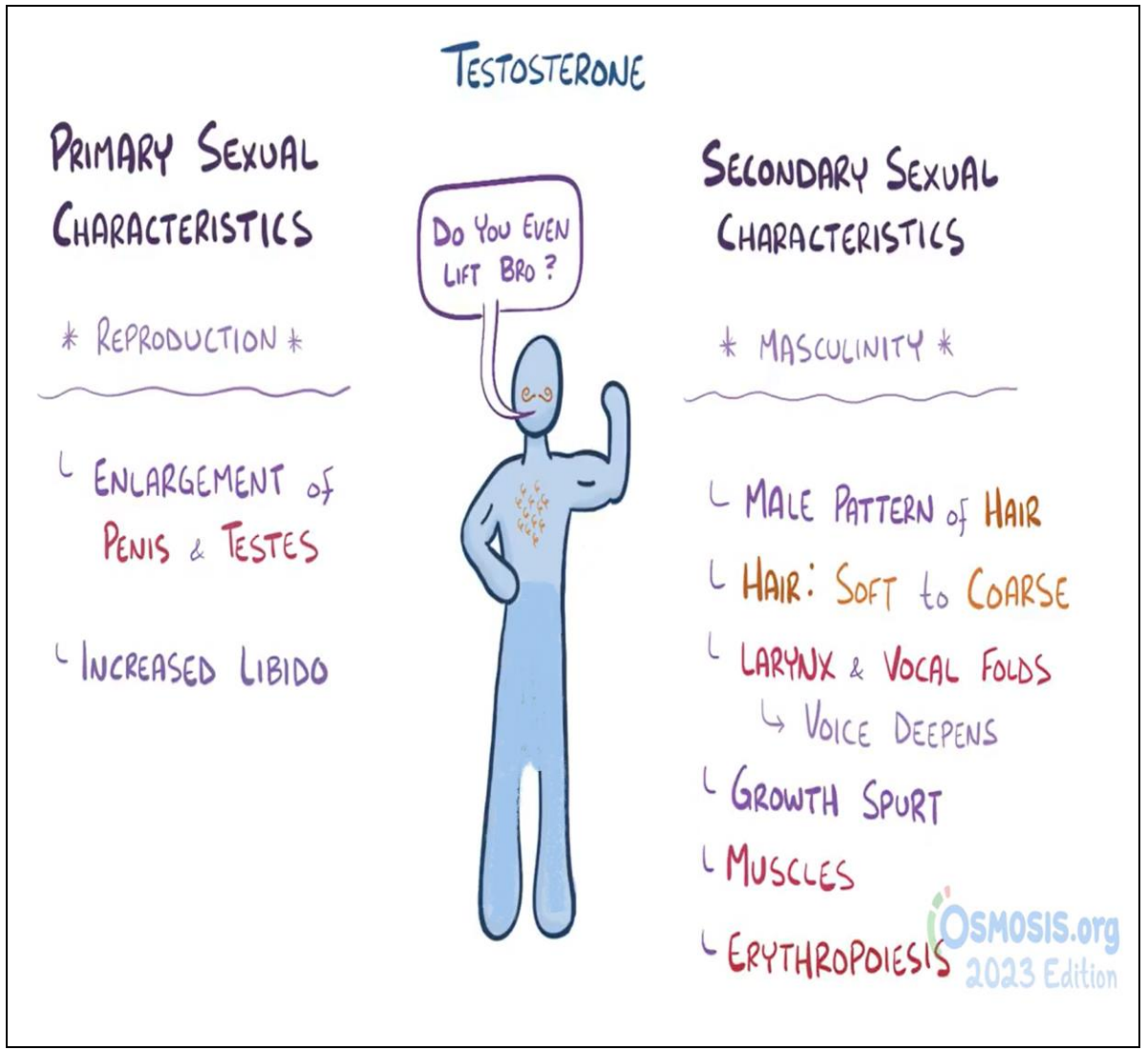
Physiological effects of Progesterone:

1. **Maintenance of Pregnancy**.
2. Ovulation (luteal phase in the 2nd half menstrual cycle).
3. Prevention of spontaneous uterine contractions.

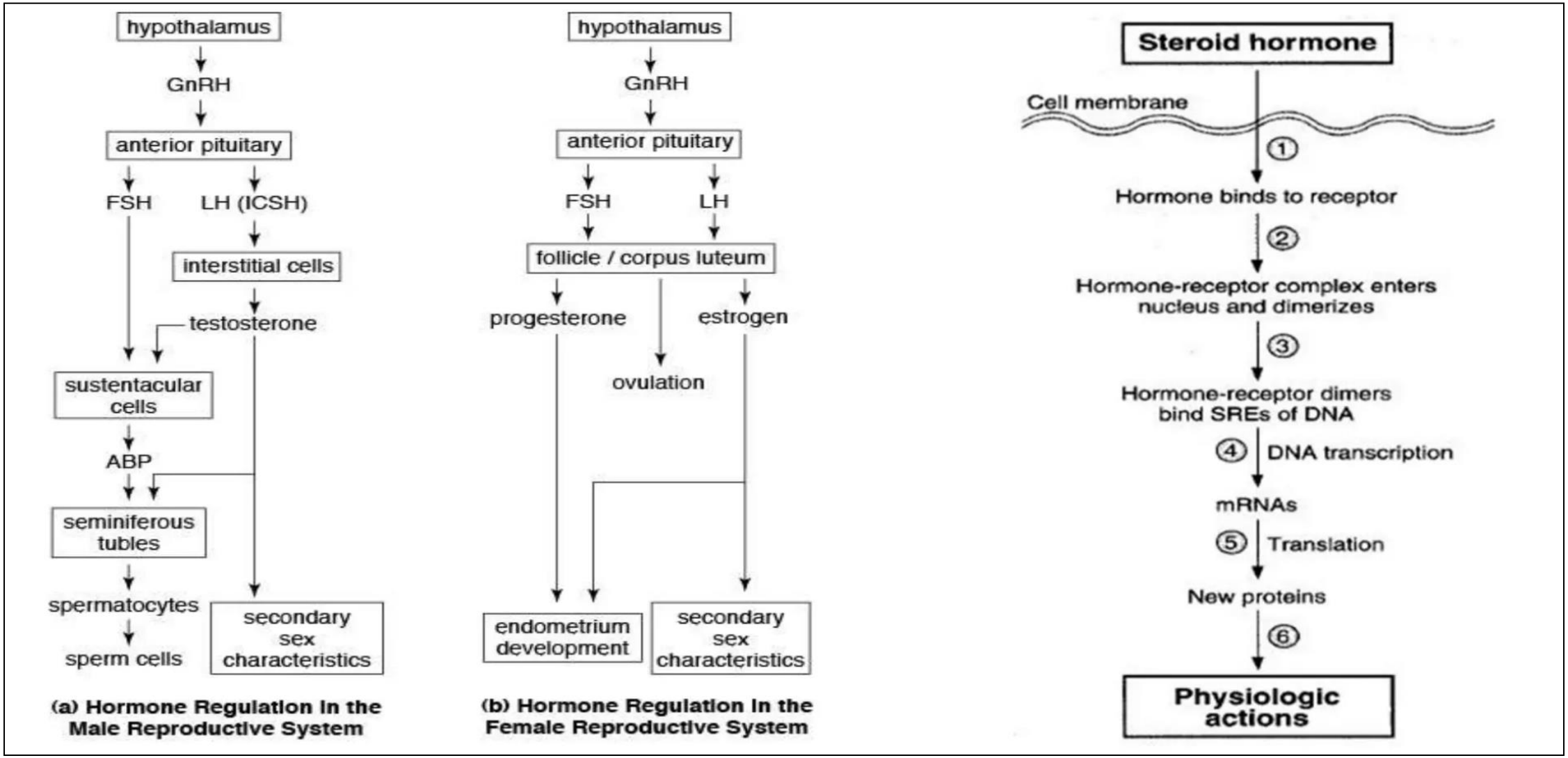


Physiological effects of Androgens:

1. Development of **the male sex organs** and **secondary sex characteristics**.
2. **Spermatogenesis**.
3. Androgens also have an **anabolic effect** producing hypertrophy of prostate, seminal vesicles, skeletal muscles, bone and kidney cells.



Molecular mechanism of action of sex hormones



Question Time

Q1

3-β-Hydroxysteroid dehydrogenase and Δ5,4 isomerase catalyze the conversion of the weak androgen DHEA to:

A. Androstenedione
B. Testosterone
C. Progesterone
D. Dihydrotestosterone
E. Estrone

Q2

In the biosynthesis of testosterone, the rate limiting step is conversion of:

A. Cholesterol to pregnenolone

B. Pregnenolone to progesterone

C. Progesterone to 17 α-hydroxy progesterone

D. 17 α-Hydroxy progesterone to androstenedione

E. Androstenedione to testosterone

Q3

Gonadotropin-releasing hormone (GnRH) is:

A. A pentapeptide
B. A tripeptide
C. A decapeptide
D. An octapeptide
E. A hexapeptide

Q4

One of the following enzymes is not required for synthesis of Estradiol:

A. 17α-hydroxylase

B. 3β-HSD

C. 20, 22-desmolase

D. 5α-reductase

E. Aromatase


THANKS
FOR YOUR
ATTENTION