



Sheet# 3

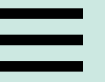
PASSION ACADEMIC TEAM

YU - MEDICINE

Endocrine system

Lec. Title : File No.2/Lec.3
Written By : Roqaya Mahmoud

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Hormones Are Synthesized & Modified for Full Activity in a Variety of Ways

Some hormones are synthesized in final form and secreted immediately.

Synthesized in final form and stored in the producing cells.

Synthesized from precursor molecules in the producing cell, then are processed and secreted upon a physiologic cue

Converted to active forms from precursor molecules in the periphery

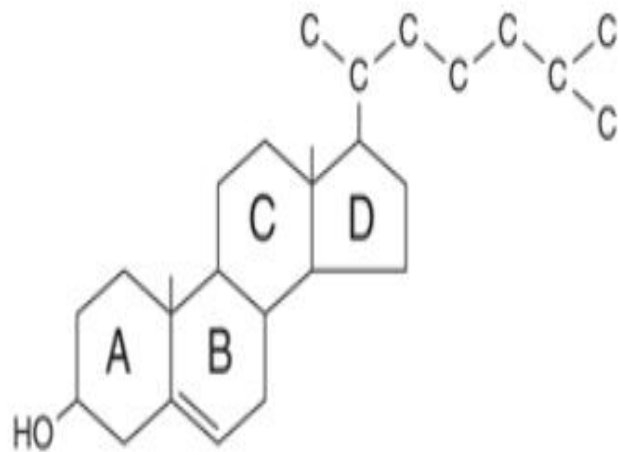
• Regarding to the previous slide:

1. Some hormones are synthesized in final form and secreted immediately upon the action or the response or the triggering of the cell in order to produce these hormones .So,they are already active.
 2. Synthesized in final form and stored in the producing cells until they receive another signal from another kind of tissue.
- ❖ These above two types of hormone share the activity.So,they are already formed ,active and waiting signal but the first one is secreted immediately.
3. Precursor molecules mean that they inactive.(they are synthesized in inactive form and wait the signal in order to be processed and then released to the cells.
 4. Converted to active forms from precursor molecules in the periphery (they need further activation at the site of action)

MANY HORMONES ARE MADE FROM CHOLESTEROL

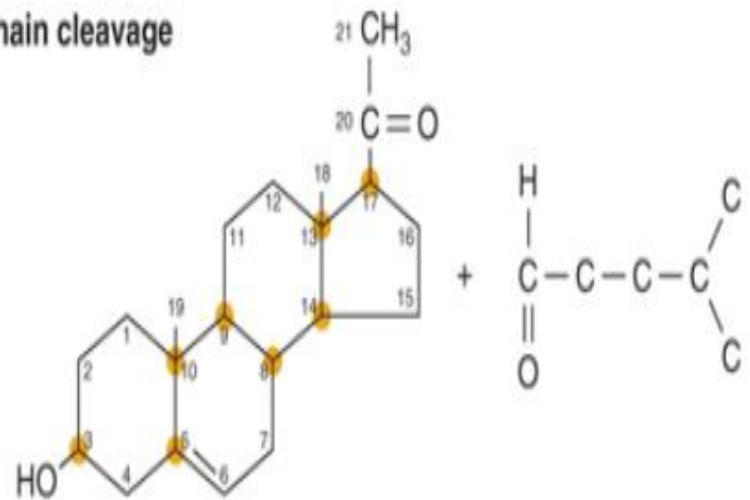
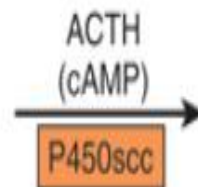
Adrenal Steroidogenesis

- Synthesized from cholesterol
- Upon stimulation of the adrenal by ACTH, an esterase is activated
- Mitochondrial, **cytochrome P450 side chain cleavage enzyme (P450_{scc}) converts cholesterol to pregnenolone.**
- An ACTH-dependent **steroidogenic acute regulatory (StAR) protein is essential for the transport of cholesterol to P450_{scc} in the inner mitochondrial membrane.**



Cholesterol

Cholesterol side chain cleavage



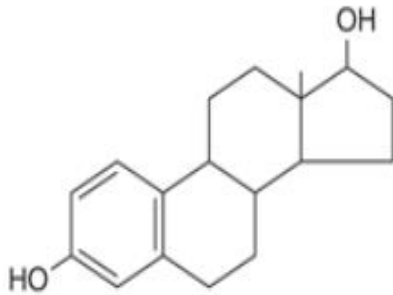
Pregnenolone + isocaproaldehyde

- Regarding to the previous slides:
 - Steroidogenesis means that you are going to synthesize steroids or steroid hormones from the cholesterol by modification.
 - We have adrenal steroidogenesis and gonadal steroidogenesis (testes and ovaries)
 - Cholesterol itself is synthesized from acetyl coA which can be generated from either degradation of fatty acids or metabolism of glucose which is the oxidation process of glucose.
 - you have to remember the anatomy of the adrenal gland because it has different tissues that are responsible for synthesis of different types of steroid hormones.
 - ACTH in general is required in order to stimulate adrenal gland (the target cell)
 - There is need for estrase activity which means that you are going to release the fatty acids from cholesterol in order to generate the free cholesterol that is going to be processed to synthesis other precursors.

- The most important thing to remember the location of enzymes that we need in steroidogenesis. So, the enzymes either mitochondrial or endoplasmic (related to smooth reticulum enzymes).
- There is a complex required in the mitochondria which is called cytochrome (we call it complex because it contains SCC)
- Pregnenolone is the second main molecule (after cholesterol) that is going to be converted to other types of steroid hormones .
- ❖ **Regarding to the picture :**
- **(the cholesterol structure):**
- Hydroxyl group play important role in function and structure as well can be esterified in order to have cholesterol ester .
- The most important thing in metabolism of steroidogenesis is the hydrocarbon chain (the side chain) that is linked to cholesterol molecule and as you see, the first step in the formation of other types of steroids is the cleavage of this side chain in order to generate pregnenolone (this cleavage is catalyzed by p450SCC that is activated by ACTH).

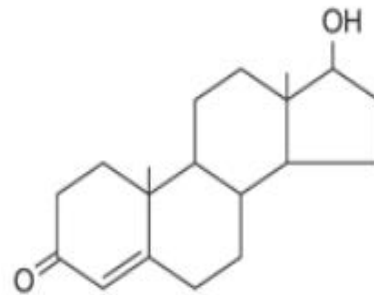
Basic steroid hormone structures

Basic steroid hormone structures



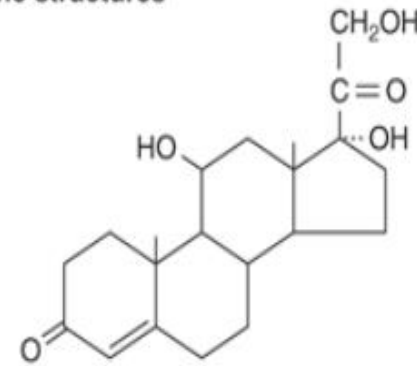
17β-D-Estradiol

Estrane group (C18)



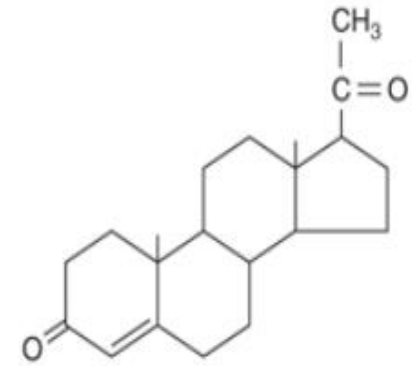
Testosterone

Androstane group (C19)



Cortisol

Pregnane group (C21)



Progesterone

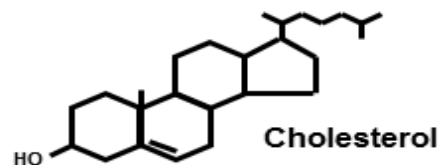
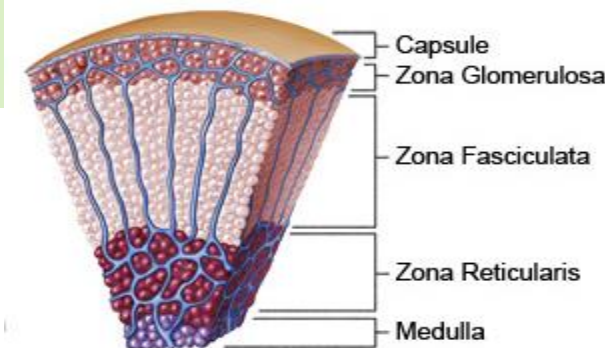
Source: Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA: *Harper's Illustrated Biochemistry, 28th Edition*: <http://www.accessmedicine.com>

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All mammalian steroid hormones are formed from cholesterol via pregnenolone through a series of reactions that occur in either the **mitochondria** or **endoplasmic reticulum** of the producing cell.

Hydroxylases, Oxygen, NADPH, Dehydrogenases, isomerase, Lyase

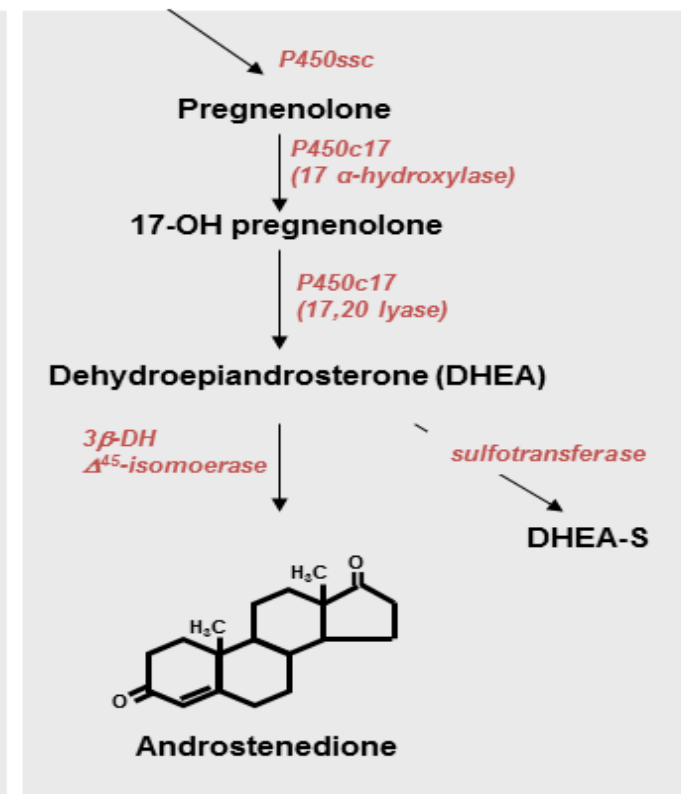
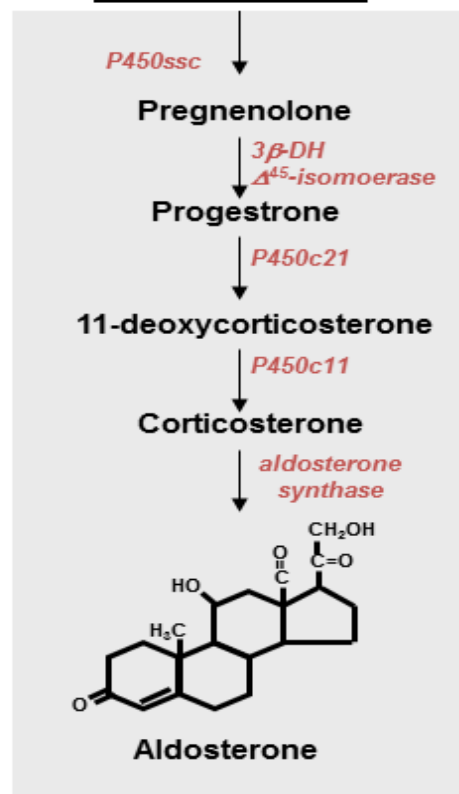
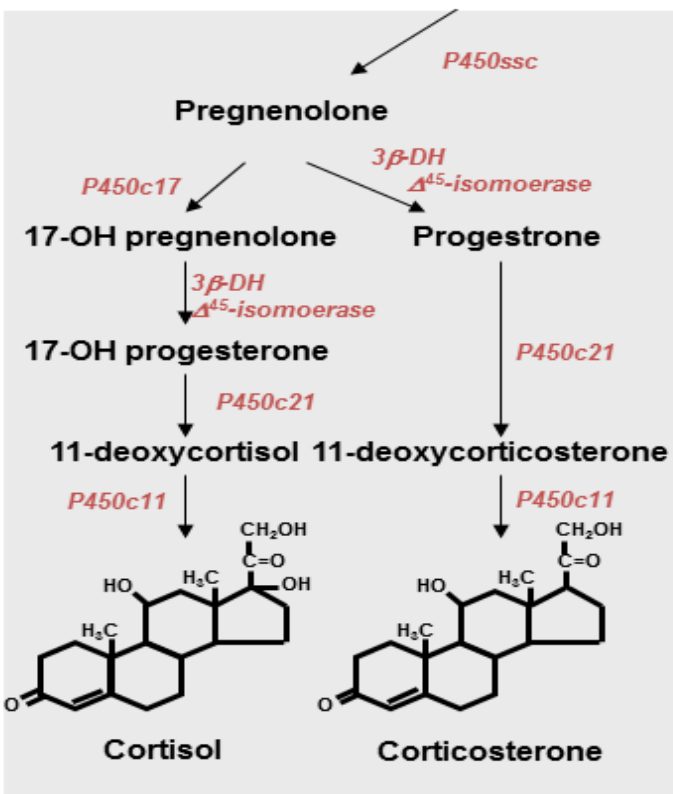
Microscopic Section



Zona fasciculata

Zona glomerulosa

Zona reticularis



- Regarding to the previous slides:

- Basically to understand what we are going to talk about ,we have to imagine what are these molecules that we are going to synthesize:

1. The estradiol is one of the most important estrogens
2. Testosterone which is an androgen
3. Glucocorticoid hormone like cortisol
4. Progesterone as a family of progesterone molecules

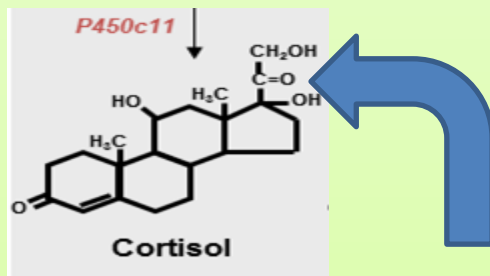
- ❖ We should remember the structure of adrenal gland that consist of zona fasciculate ,zona glomerulosa and zona reticularis.

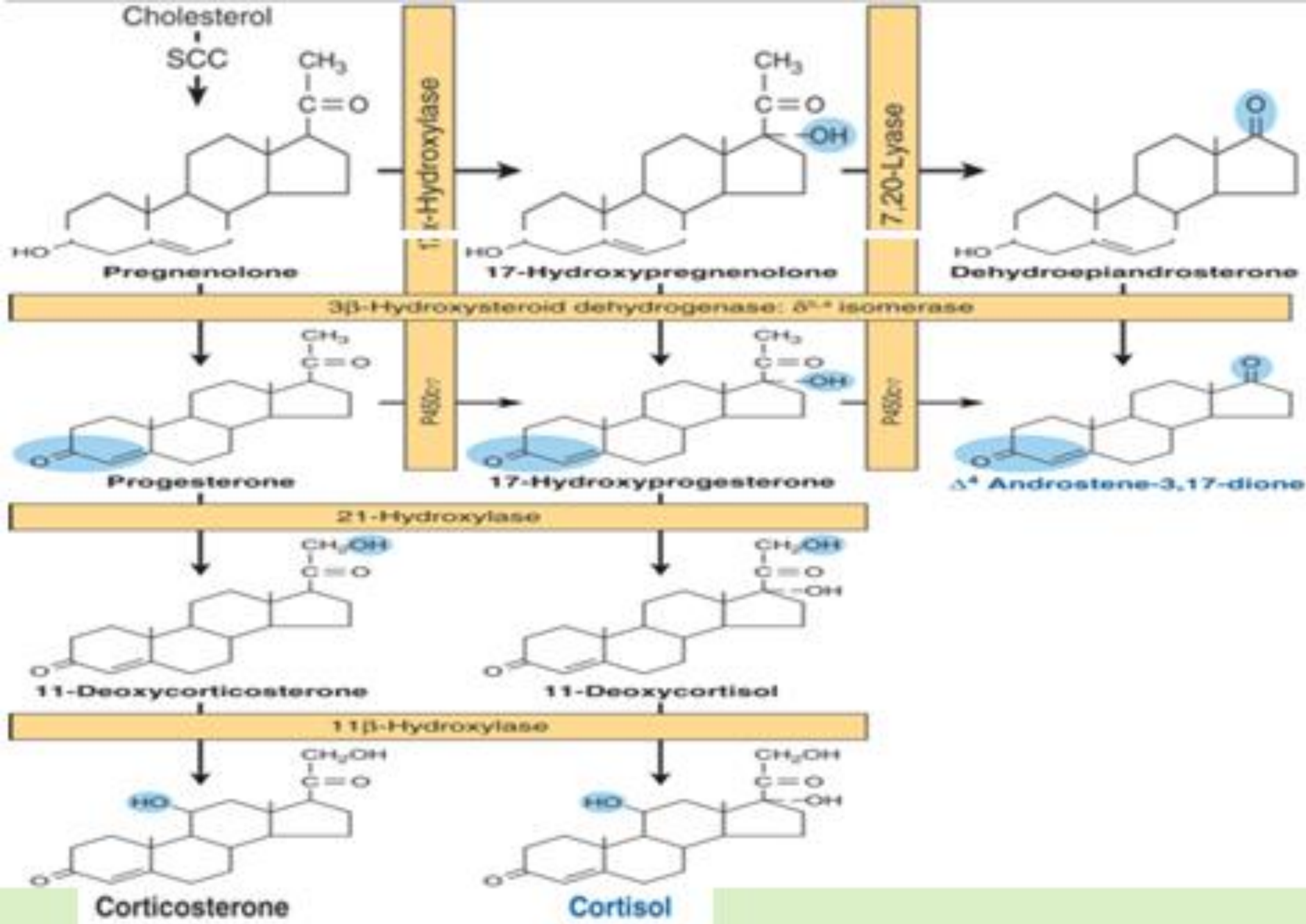
- **it is not important to memorize every specific enzyme in slide 5**

We need to know the basic concepts of metabolism in each of these zones as well as the major process of the metabolic pathway like the hydroxylases that require O₂ and NADPH as reducing agent, dehydrogenases, lyase, isomerase.

- all the zones share in the first step which is catalyzed by SCC to generate pregnenolone .

Pay attention that the portion below that is pointed by blue arrow exist in aldosterone and glucocorticoid but not in androstenedion. there is a kind of major modification to make different families ,that's why we classify the metabolism close to each other depending on the similarity of the molecules. So, fasciculate zone share glomerulosa zone in the synthesis of similar structure and generation of glucocorticoid hormones as well as mineralocorticoid hormones. Reticularis zone is responsible for generation of estrogens. DHEA_S is the active form of DHEA.

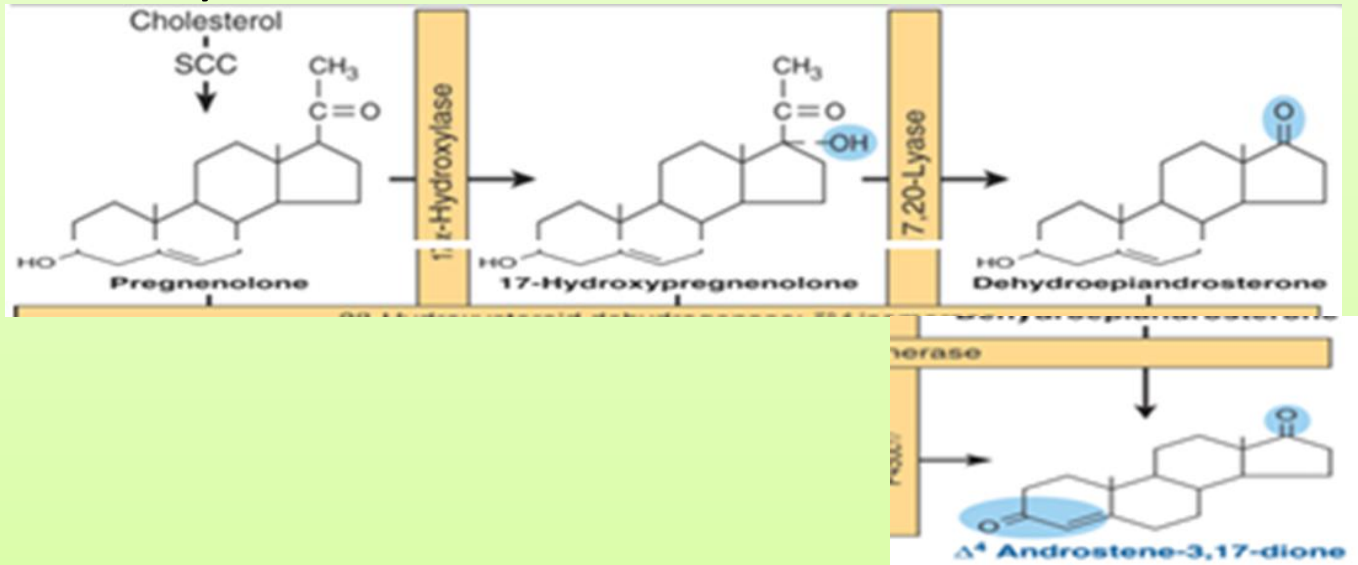




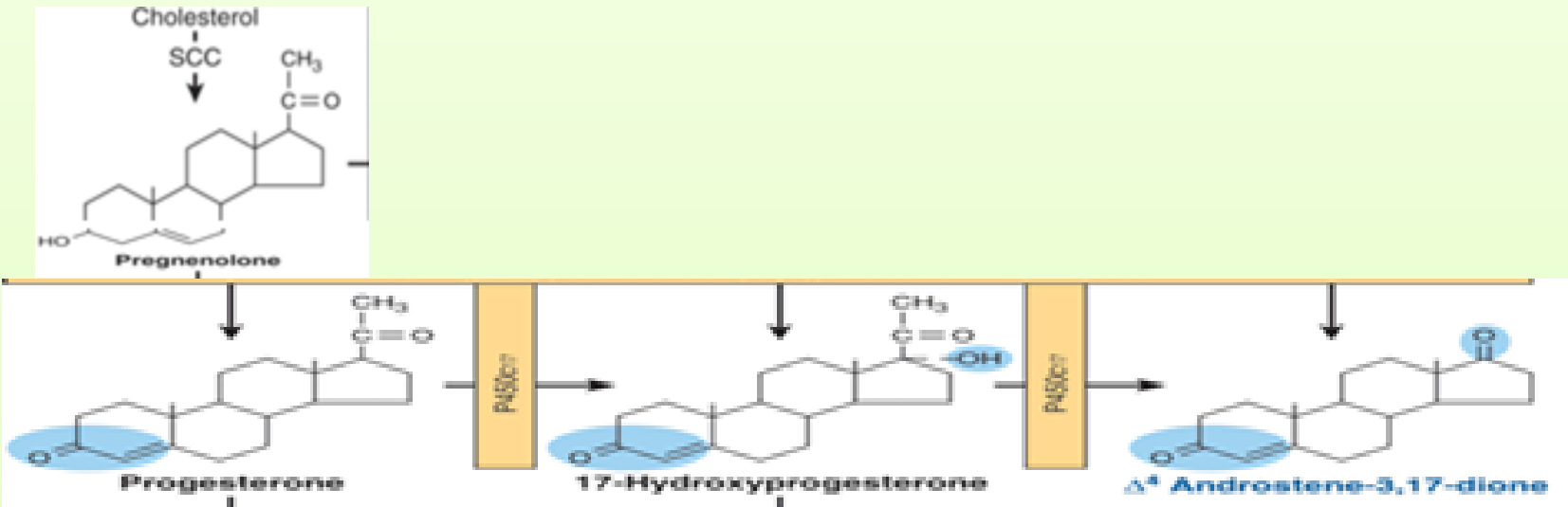
- Regarding to the previous slide:

- Dissecting the metabolic pathway that we describe before in order to know the similarities and the sharing pathways between these molecules in order to form steroid hormones. So, basically we start with cholesterol again and we have the major step which is the cleavage of the side chain to generate pregnenolone. Then, we have two pathways :

1) **hydroxylation** at position number 17 for example in this case and generation of the **Dehydroepiandrosterone** and then **Androstene** hormone. So, these steps are generated by CYP450 that has both hydroxylase and lyase activities in order to remove the rest of side chain.

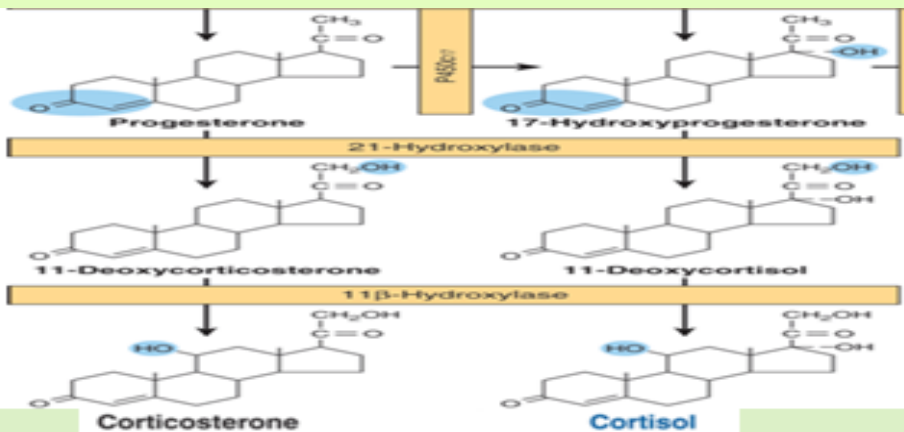


2) The second direction is the generation of progesterone that can be converted to **17_hydroxyprogesterone** and then to **Androstene**.



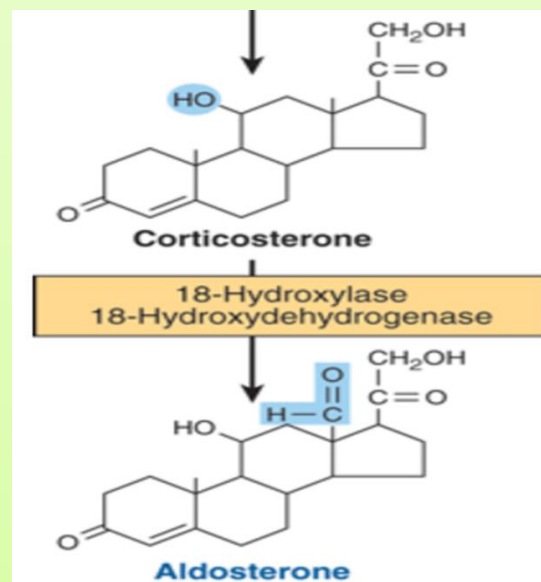
- So, at the end we have two pathway to generate the same molecule.

➤ Progesterone and 17_hydroxyprogesterone can be converted by hydroxylase at position 21 to generate at the end corticosteroid and cortisol respectively.

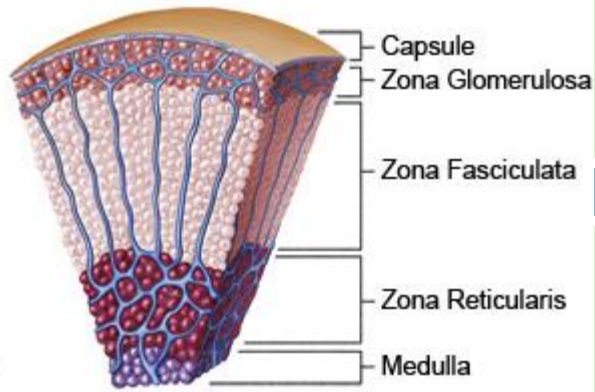


- you should know that we have two pathways to synthesis these hormones depending on the activity of CYP450 and availability of the enzymes. So, hydroxylase, lyase, oxidase are required to synthesis these hormones and these enzymes are localized in complex CYP450. This complex exist in mitochondria at the beginning of steps and the rest of steps it is located in endoplasmic reticulum. Corticosterone (glucocorticoid) can be converted to Aldosterone(mineralocorticoid) in zona glomerulosa by hydroxylation .

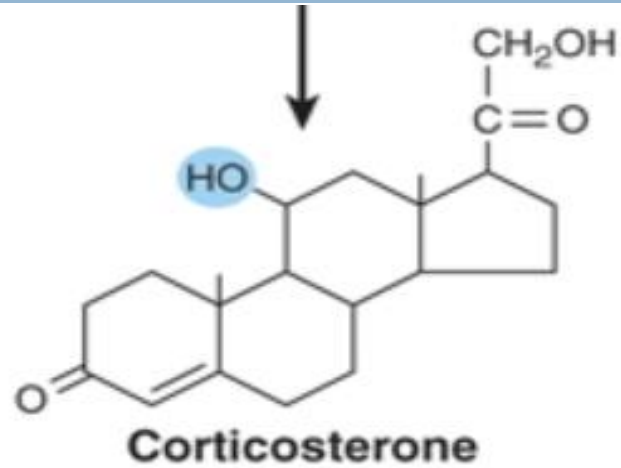
➤ Aldosterone is responsible for regulation of water release by renal system.



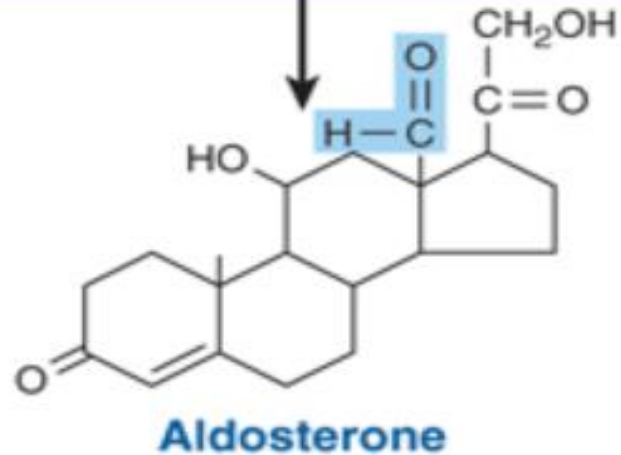
Microscopic Section



Zona glomerulosa cells



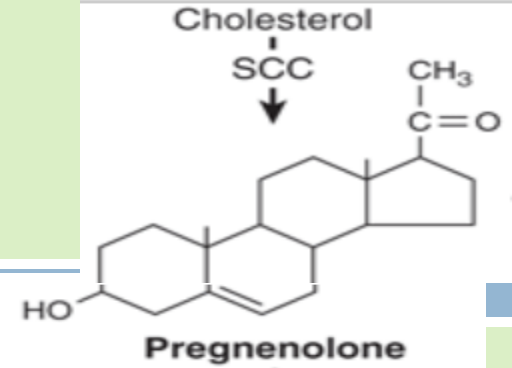
18-Hydroxylase
18-Hydroxydehydrogenase



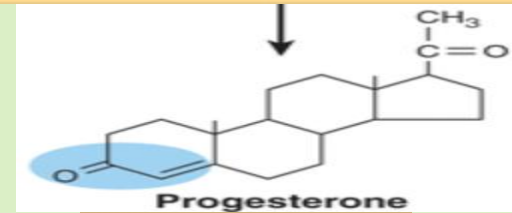
MINERALOCORTICOID SYNTHESIS

- ❖ Synthesis of aldosterone follows the mineralocorticoid pathway and occurs in the zona glomerulosa.
- Just revision and focusing on aldosterone synthesis to understand clearly.

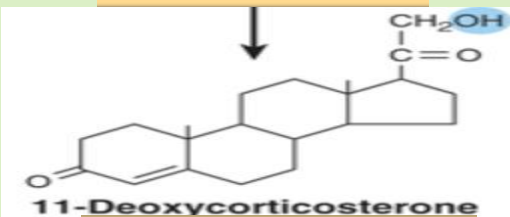
(aldosterone synthase)



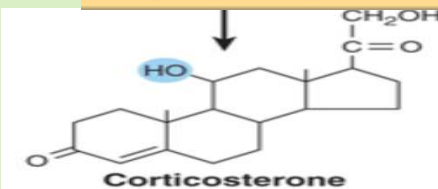
3 β -Hydroxysteroid dehydrogenase: $\delta^{5,4}$ isomerase



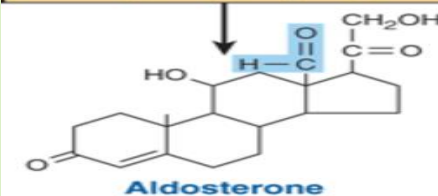
21-Hydroxylase



11 β -Hydroxylase

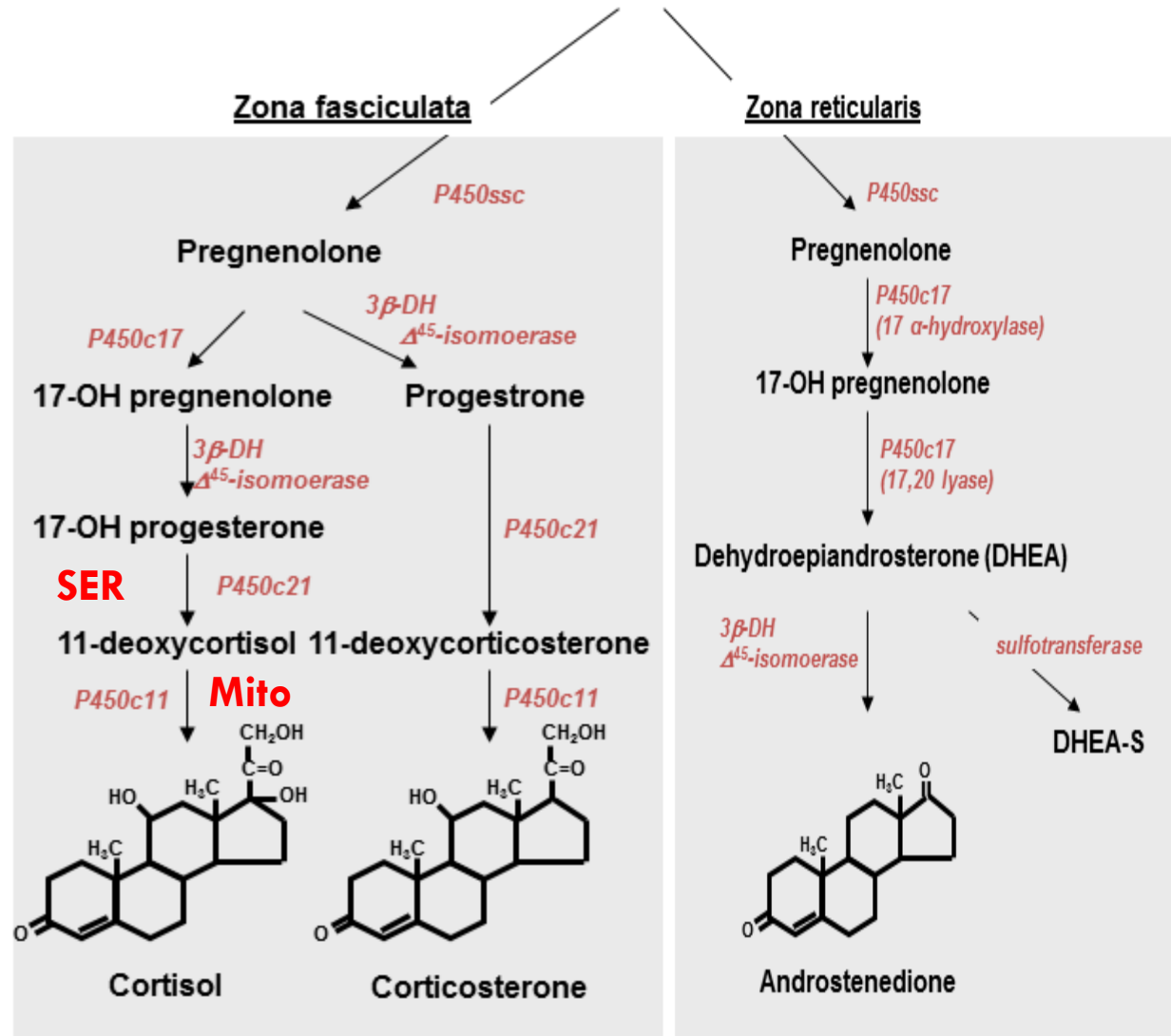
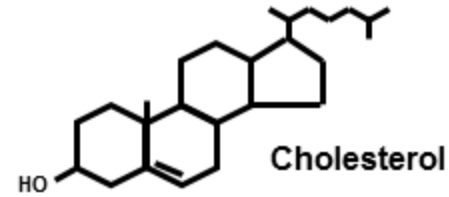


18-Hydroxylase
18-Hydroxydehydrogenase

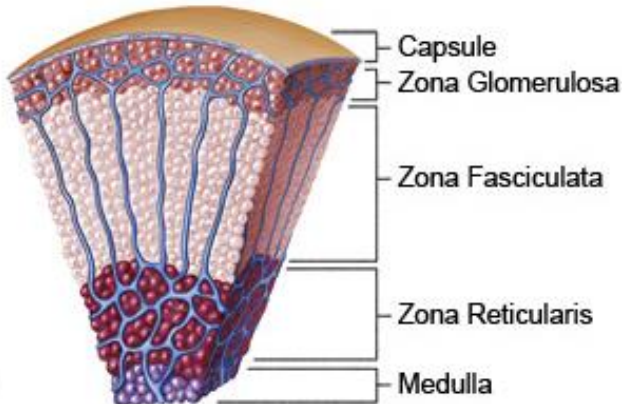


GLUCOCORTICOID SYNTHESIS

Cortisol synthesis requires three hydroxylases located in the **fasciculata** and **reticularis** zones of the adrenal cortex



Microscopic Section



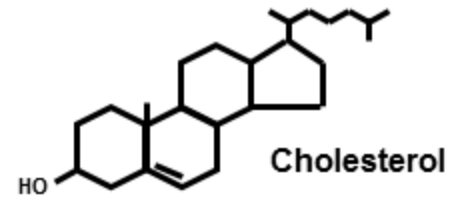
- Regarding to the previous slide:
 - Glucocorticoids has similar structure except the branching. The glucocorticoids synthesis is performed in fasciculated and reticularis zones and each zone has special kind of enzymes that are responsible to production of certain hormones.
 - Very important thing to remember that the final and the first steps in generation of glucocorticoids are performed by mitochondrial enzymes and the middle steps are performed by smooth ER enzymes. So, we start and up with mitochondrial enzymes.

ANDROGEN SYNTHESIS

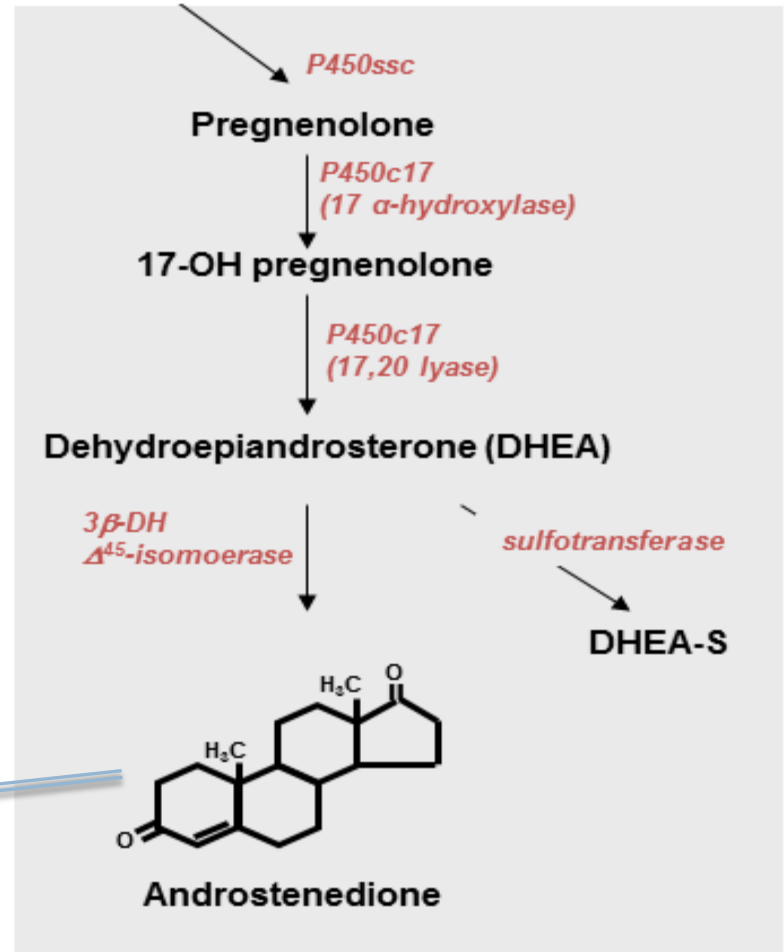
The major androgen or androgen precursor produced by the adrenal cortex is dehydroepiandrosterone

(DHEA). (DHEA is activated by sulfotransferase).

Small amounts of testosterone are produced in the adrenal



Zona reticularis



Testicular Steroidogenesis

Testicular androgens are synthesized in the interstitial tissue by the **Leydig cells**.

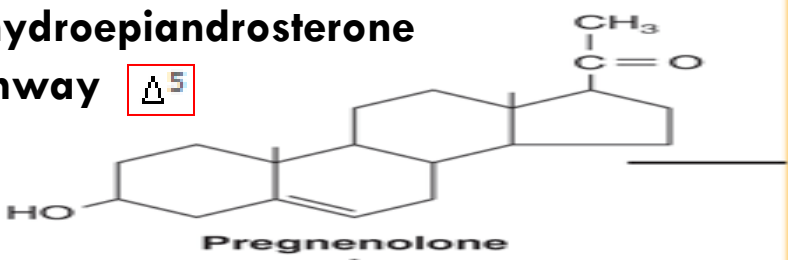
The conversion of cholesterol to pregnenolone is identical in testis, ovary (needs LH), and adrenal (needs ACTH). (ACTH,LH are activating enzymes to the conversion process)

The conversion of pregnenolone to testosterone requires the action of 5 enzyme activities contained in 3 proteins:(means that we have 3 proteins and they have 5 active sites)

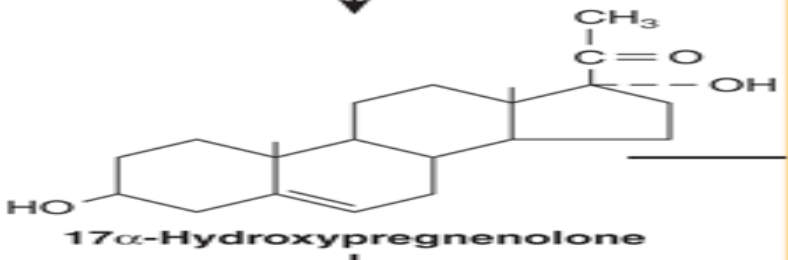
❖ The most important androgene hormone is the testesterone

Dehydroepiandrosterone

Pathway Δ^5



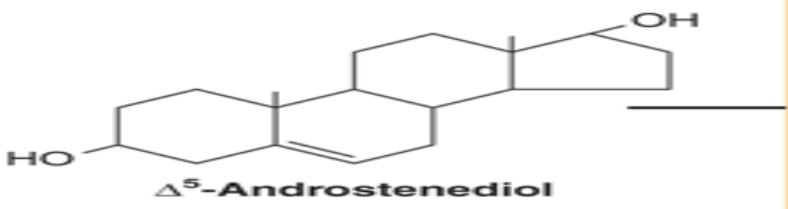
17 α -Hydroxylase*



17,20-Lyase*

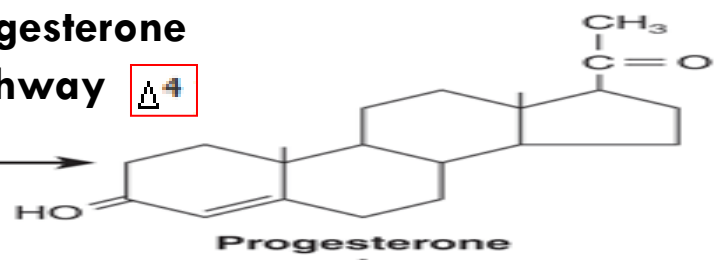


17 β -Hydroxysteroid dehydrogenase

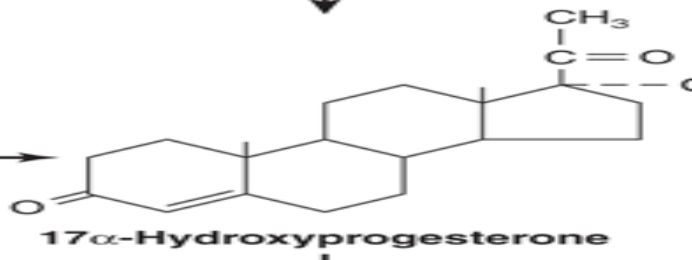


Progesterone

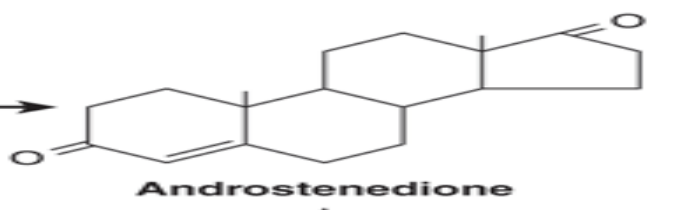
pathway Δ^4



17 α -Hydroxylase*



17,20-Lyase*



17 β -Hydroxysteroid dehydrogenase



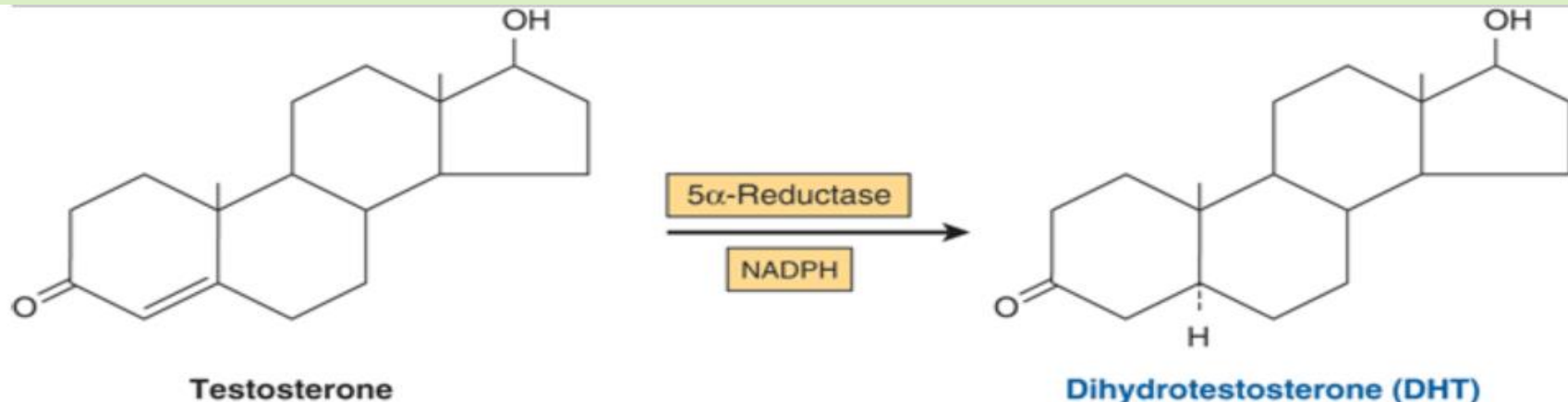
3 β -Hydroxysteroid dehydrogenase and $\Delta^5,4$ isomerase

Dihydrotestosterone Is Formed from Testosterone in Peripheral Tissues

Testosterone is metabolized by two pathways.

1. Oxidation at the 17 position: many tissues, produces less active 17-ketosteroids
2. Reduction of the A ring double bond and the 3-ketone: in target tissues and produces the potent metabolite dihydrotestosterone (DHT). (more important)

*it's activated by reductase .



- Regarding to the previous slide:
 - we have two pathways for testosterone synthesis .one is called **Dehydroepiandrosterone Pathway** or Δ^5 and the other is called **progesterone pathway** or Δ^4 .there is kind of interaction in each step between the two pathways because we have **isomerase** enzyme that convert pregnelone precursors to progesterone precursors.
 - At the end we will have the inactive or less potent as androgen hormone which is testosterone which means that we need further steps for activation to make it effective. The activation process can be performed in testes(source cell)or in target cells.

*less potent means the activity as androgene hormone is not highly effective.

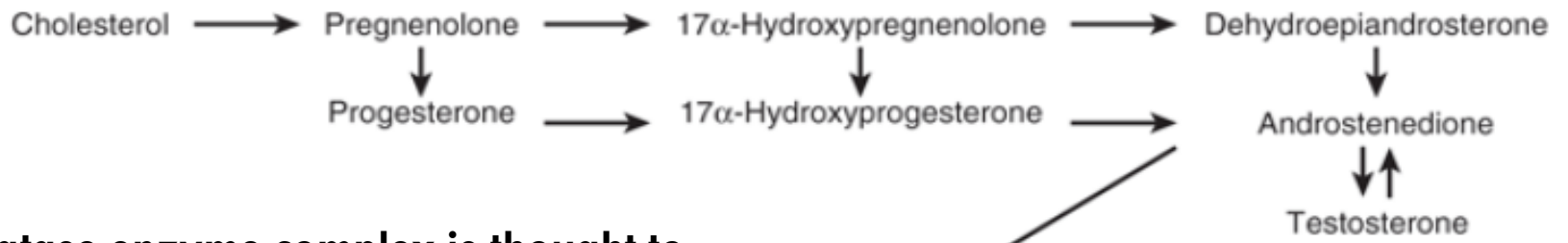
Ovarian Steroidogenesis

The estrogens are a family of hormones synthesized in a variety of tissues.

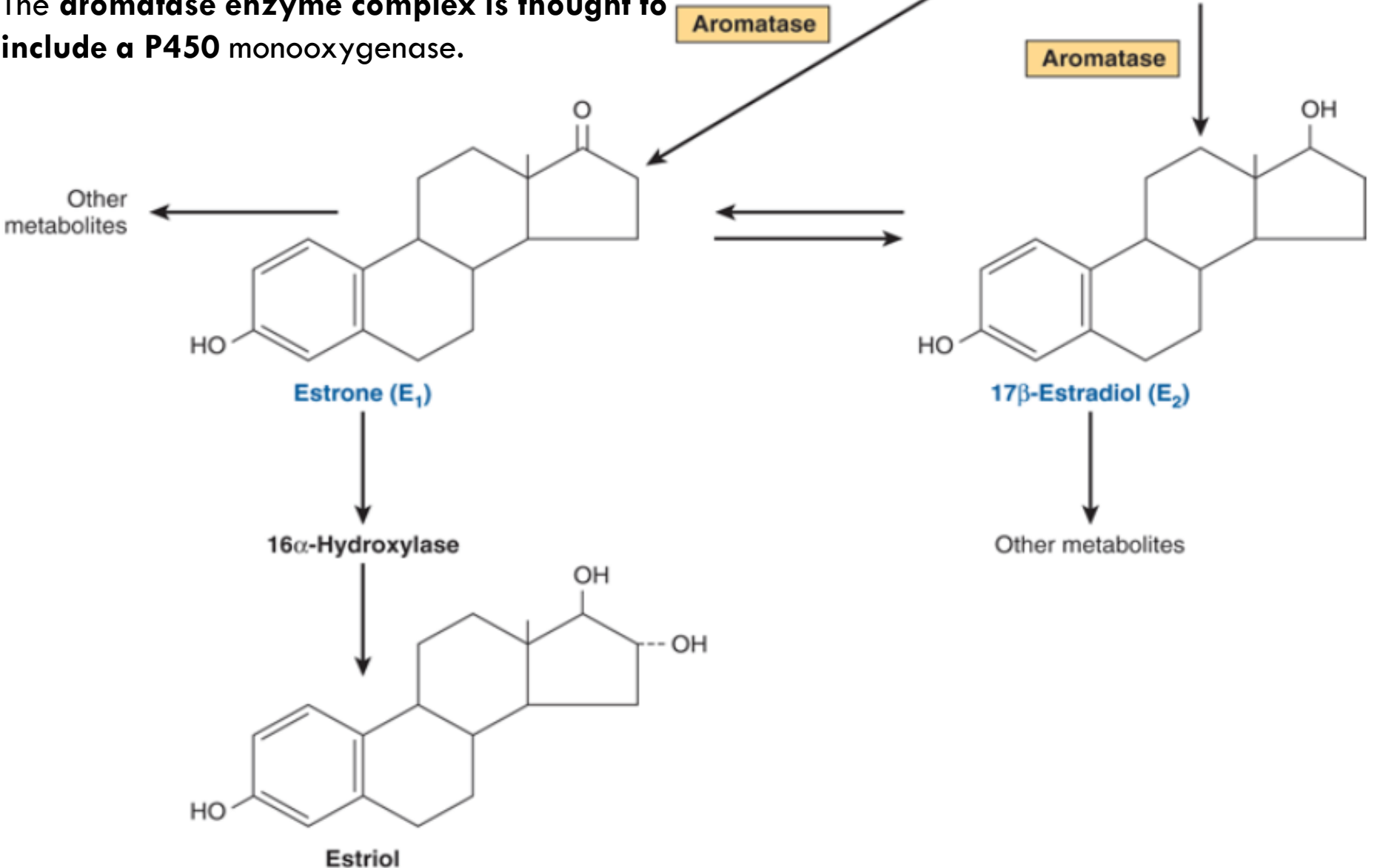
17 Beta-Estradiol is the primary estrogen of ovarian origin.

Theca cells are the source of androstenedione and testosterone.

Granulosa cells convert androstenedione and testosterone to estrone and estradiol



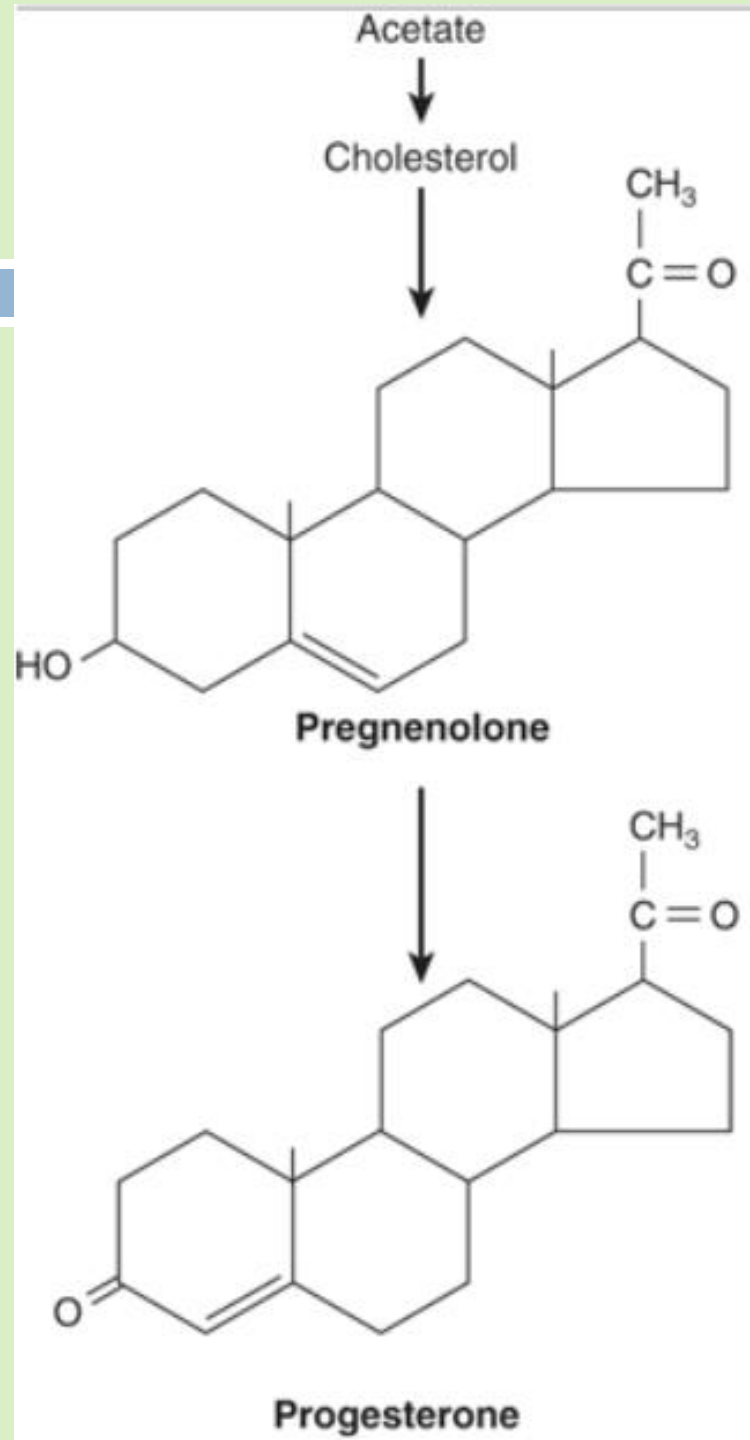
The **aromatase enzyme complex** is thought to include a **P450** monooxygenase.



- Regarding to the previous slides:
 - we have androgens at the beginning and then they are converted into estrogens by specific mechanism in ovarian tissue.
 - estrone can be generated from estradiol or androstenedione by aromatase enzyme . Also, estrone can be converted to estriol which is less potent estrogen hormone.

*estradiol is the active form and estrone is less active form.

Biosynthesis of progesterone in the corpus luteum



Significant amounts of estrogens are produced by the peripheral aromatization of androgens.

- In males, the peripheral aromatization of testosterone to estradiol (E2) accounts for 80% of the production of the latter.
- In females, 50% of the E2 produced during pregnancy comes from the aromatization of androgens.

- Regarding to the previous slide:

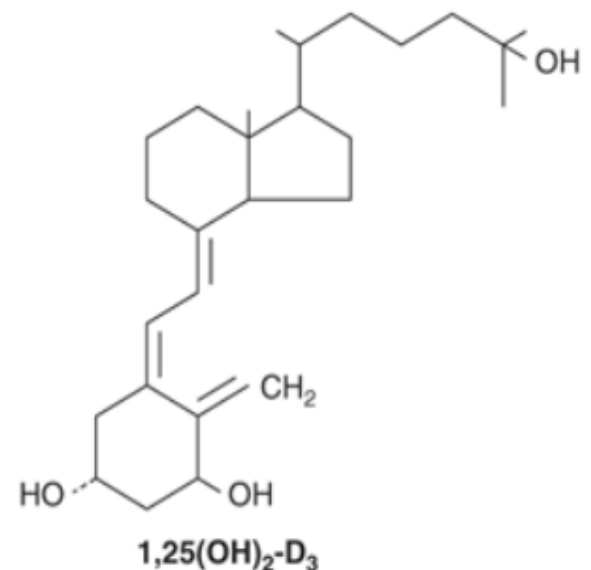
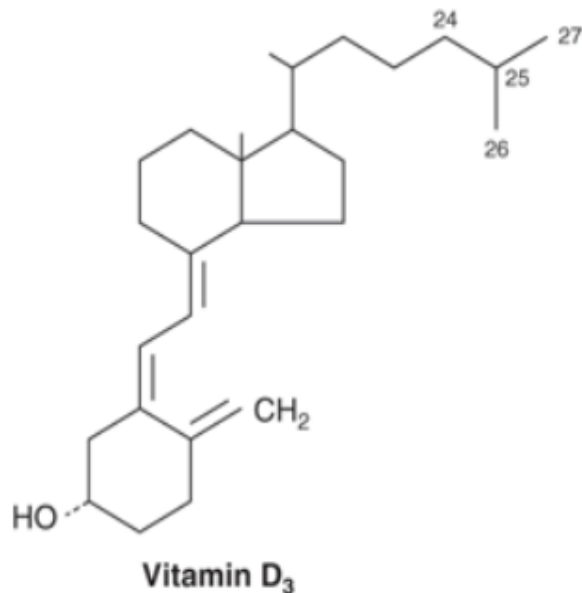
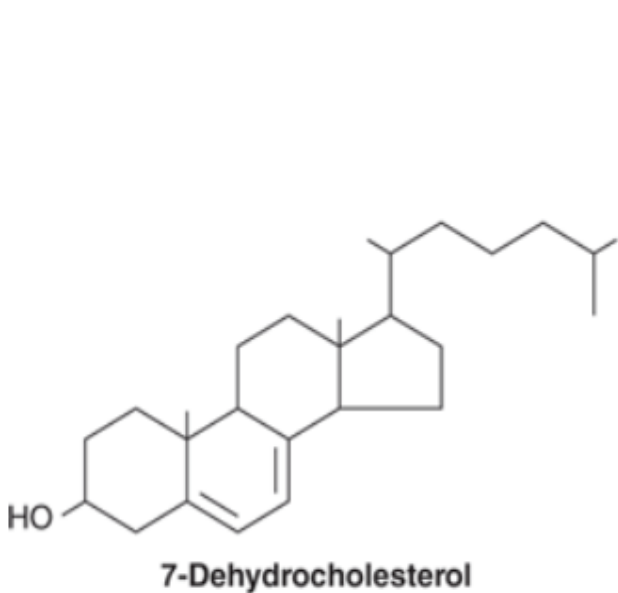
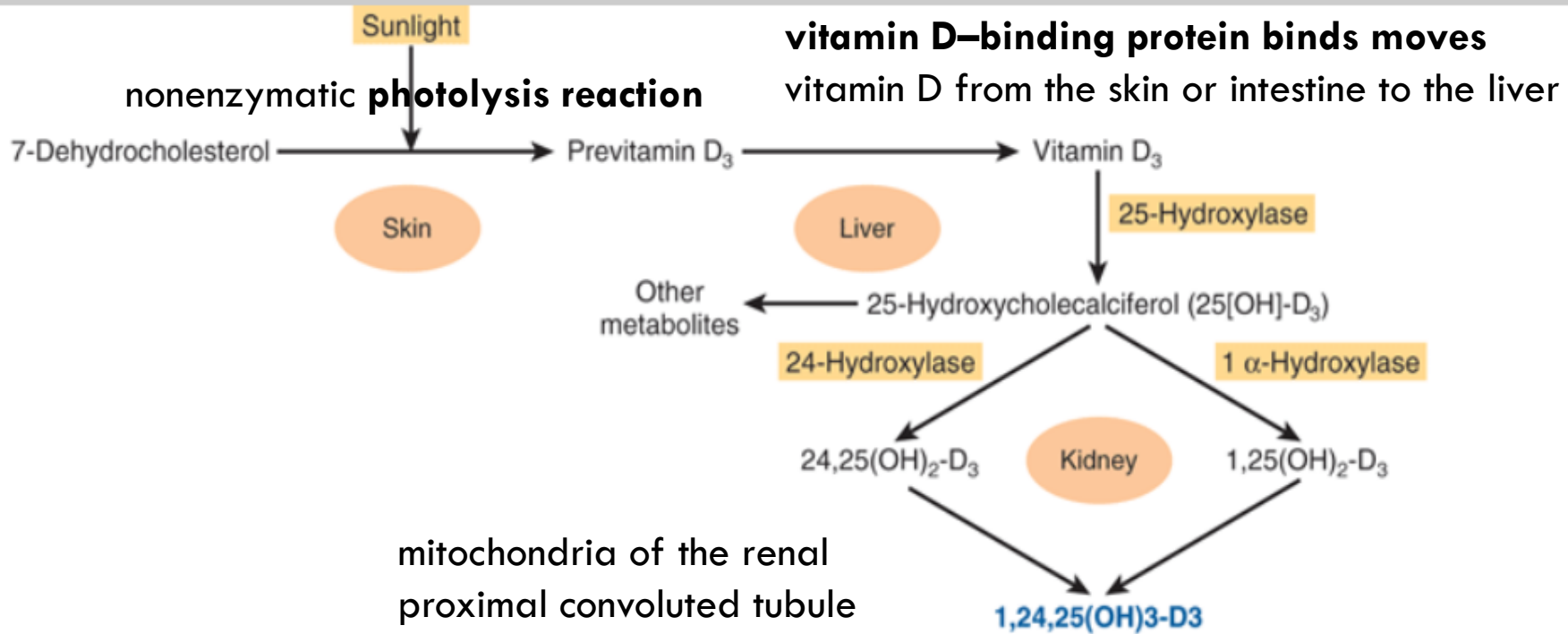
- We talked about the precursors of hormones that will be released upon stimulation but still precursors and need activation at the site of action . there are certain kind of tissues can convert androgens to estrogens rather than the gonadal system itself . So, the peripheral tissues are responsible to aromatization of androgens and it depends on the gender . here the testosterone is the precursor and the end product is estradiol.

1,25(OH)₂ –D₃(Calcitriol) Is Synthesized from a Cholesterol Derivative

Produced by a complex series of enzymatic reactions that involve the plasma transport of precursor molecules to a number of different tissues.

As a precursor, Vitamin D—really not a vitamin.

—•



- vitamin D is water insoluble so it need carrier
- Skin , liver and kidney are responsible for metabolism of vitamin D3 in order to produce the active form and other metabolites with different potent activity of this vitamin.
- $1,25_{(OH)}_2D_3$ is the active form that we need to have the action of vitamin D3.