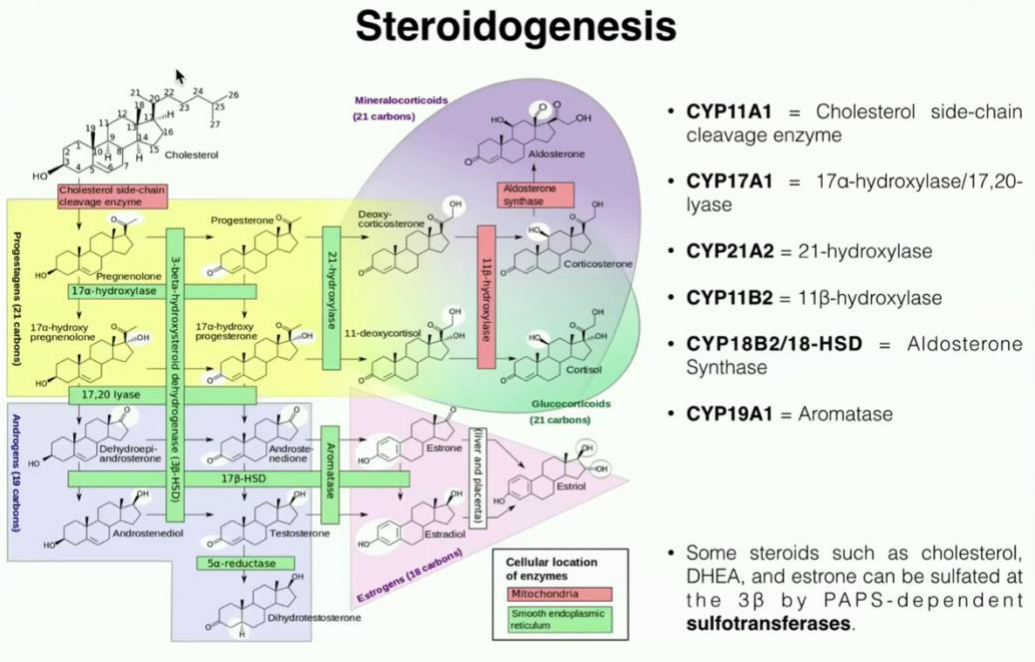
Biochemistry – Lecture 4

Steroidogenesis is the process by which certain cells synthesize steroid hormones—such as aldosterone, estradiol, and testosterone—from the parent molecule, CHOLESTEROL.

- Cholesterol has a variety of functions such as:
  - Stabilizing cell membranes across a wide range of temperatures.
  - Synthesis of bile acids, which aids in the emulsification of fats.
  - Conversion into steroids (the most important function), as illustrated in the steroidogenesis pathway.



- According to this diagram, steroids are categorized into several classes:
  1. Progestogens
  2. Androgens – masculinizing hormones
  3. Estrogens – feminizing hormones
  4. Glucocorticoids (corticosteroids)
  5. Mineralocorticoids – the primary one is aldosterone

- Some of these enzymes (in the diagram) are located in different cellular compartments:
  - Mitochondrial enzymes: the ones in red.
  - Microsomal enzymes: the ones in green (embedded in the membrane of smooth endoplasmic reticulum).
- Pay attention to the numbering system of the parent cholesterol; as some enzymes are named based on it. For example, they act on:
  - Certain carbon atoms
  - Hydroxyl groups

- For example, the enzyme (21-hyroxylase) indicates which atom it acts upon (C#21).

P450 Enzymes and Gene Names

Many enzymes in steroidogenesis belong to the P450 family and are referred to by their gene name.

- Example: Cholesterol side-chain cleavage enzyme is a P450 enzyme encoded by CYP11A1.

Conversion of Cholesterol to Pregnenolone

The cholesterol tail (carbons 22–27) is removed as isocaproaldehyde (not shown in the diagram).

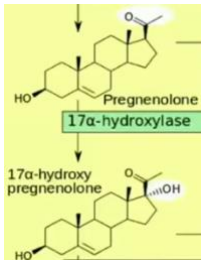
- This reaction is catalyzed by the mitochondrial enzyme CYP11A1.
- The product is pregnenolone, a ketone molecule.

For this reason, some sources call pregnenolone the "parent steroid", as it is the first steroid formed after tail removal.

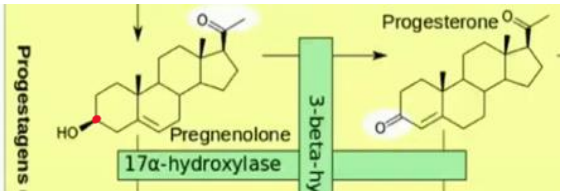
Pathways from Pregnenolone

Pregnenolone can follow two main pathways:

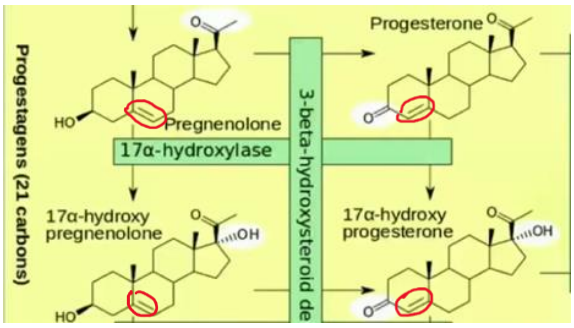
- Hydroxylation at C-17
  - Pregnenolone can be converted into 17α-hydroxypregnenolone.
    - This hydroxylation occurs at the 17 position on the five-membered ring and is catalyzed by 17α-hydroxylase.
    - Both pregnenolone and 17α-hydroxypregnenolone can serve as precursors for corticosteroid synthesis.



  - The enzyme 3β-hydroxysteroid dehydrogenase (3β-HSD) oxidizes the hydroxyl group at the 3 position (hence the name 3β), converting it into a ketone.

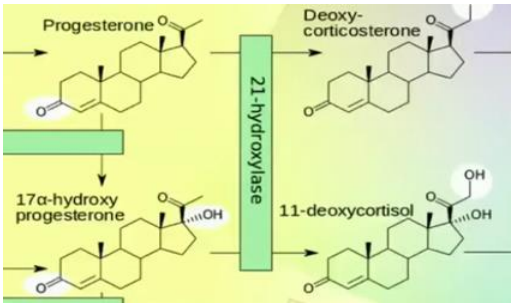


- During this reaction, there is also an isomerization of the double bond: it shifts from positions 5–6 to positions 4–5.
- This oxidation and isomerization occur for both pregnenolone and 17α-hydroxypregnenolone.



- So:
  - Pregnenolone → Progesterone/Progestin (a functional mammalian hormone; which can act independently or as a precursor of aldosterone).
  - 17α-hydroxypregnenolone → 17α-hydroxyprogesterone (precursor of cortisol).

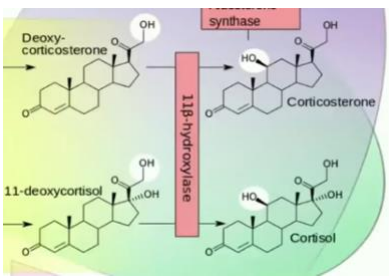
- The next enzyme in this pathway—whether starting from progesterone or 17α-hydroxyprogesterone—is 21-hydroxylase, a P450 enzyme typically encoded by CYP21A2 (there is also another isoform). Carbon #21 is hydroxylated as follows:
  - Progesterone → Deoxycorticosterone
  - 17α-hydroxyprogesterone → 11-deoxycortisol



NOTES:

- Both 3β-hydroxysteroid dehydrogenase (3β-HSD) and 21-hydroxylase are microsomal enzymes.
- Deoxycorticosterone and 11-deoxycortisol are hydrophobic molecules and must be transported into the mitochondria, mostly via simple diffusion.

- The next enzyme is a mitochondrial enzyme, which is why these molecules must enter the mitochondria. This enzyme, 11β-hydroxylase, hydroxylates the 11 position (as shown in the diagram).
  - Deoxycorticosterone is hydroxylated to form corticosterone.
  - 11-deoxycortisol is hydroxylated to form cortisol.



Cortisol is the main glucocorticoid in humans and acts as the primary chronic stress hormone. It can function independently in various physiological processes.

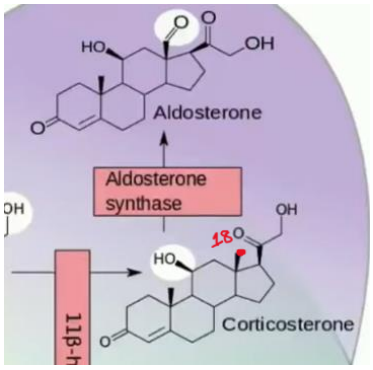
- Corticosterone is also present in humans and has some glucocorticoid activity, but it is considered a minor corticosteroid. In other species, such as mice and rats, corticosterone serves as the primary glucocorticoid, while cortisol is minor. Both are classified as glucocorticoids.

Aldosterone

- Corticosterone can be further processed into aldosterone, the principal mineralocorticoid, which regulates salt and water retention in the kidneys.

Aldosterone synthase, a mitochondrial enzyme, carries out two reactions:

1. Hydroxylation at carbon #18
2. Oxidation of the hydroxyl group to an **aldehyde**, forming aldosterone



Aldosterone synthase (CYP18B2/18-HSD) has two enzymatic activities:

- Hydroxylase activity → CYP18B2
- Oxidase activity → 18-HSD

Minor Degradation Pathways

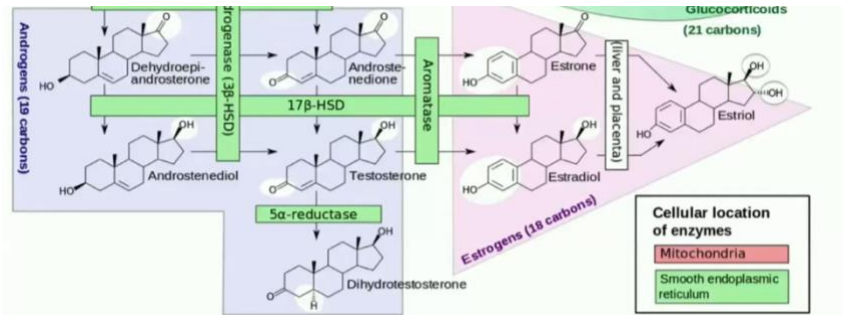
Some minor degradation pathways:

- Aldosterone and cortisol are considered endpoints of the steroidogenesis pathway. These hormones can follow one of two fates:

    1. Act independently at their specific receptors throughout the body.
    2. Be metabolized in the liver for further breakdown and excretion.

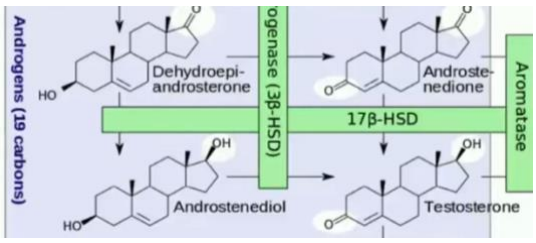
How are androgens and estrogens synthesized?

- To produce androgens, the process begins with the formation of two progestagens, which are hydroxylated derivatives of pregnenolone and progesterone. These are 17α-hydroxypregnenolone and 17α-hydroxyprogesterone, respectively.
- The enzyme 17,20-lyase (which is essentially the same as 17α-hydroxylase) then acts. While it performs the same hydroxylation activity, it can also have a secondary function: on pregnenolone and progesterone, it uses the newly added hydroxyl group to remove the ketone group. This results in the formation of the first two androgens, Dehydroepiandrosterone (DHEA) and Androstenedione.
- These androgens differ from progestagens in that their side chains (tails) have been completely removed—a feature also seen in estrogens. This structural change is a characteristic feature of both of these sex hormones.

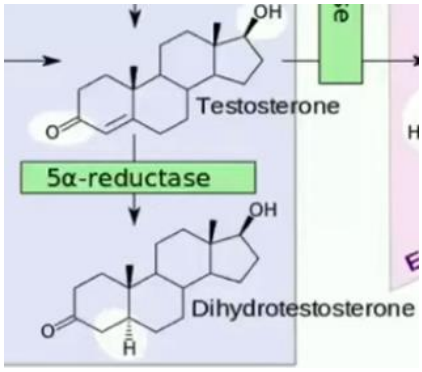


- Another enzyme, 3β-HSD (which we have seen before), can oxidize the 3β-hydroxyl group of DHEA into a ketone. This reaction is accompanied by an isomerization of the double bond from the 5–6 position to the 4–5 position, converting DHEA into Androstenedione. Subsequently, 17β-HSD converts Androstenedione into Testosterone.
- Alternatively, DHEA can first be converted into Androstenediol by 17β-HSD, after which 3β-HSD oxidizes its hydroxyl group to form Testosterone.

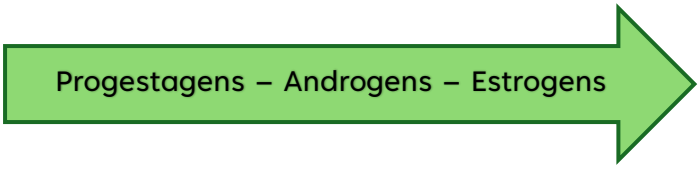
    - In summary, there are two main pathways through which DHEA can be converted into Testosterone.



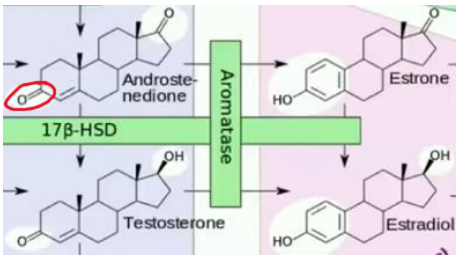
- Among the androgens mentioned, Testosterone is initially the second most potent. The most potent androgen is Dihydrotestosterone (DHT), which is formed from Testosterone by the enzyme 5α-reductase.
- This enzyme uses NADPH to reduce the double bond between positions 4 and 5 of Testosterone. As a result, the double bond is removed, producing Dihydrotestosterone.
- This reduction dramatically increases the androgenic potency of DHT—by roughly 20–100 times—making it an extremely strong androgen. (The reaction can be illustrated as shown below.)



- Both Androstenedione and Testosterone can serve as direct precursors for estrogen synthesis.
- The general pathway to produce estrogens is: first, progestagens are formed, then they are converted into androgens, and finally, these androgens are transformed into estrogens.



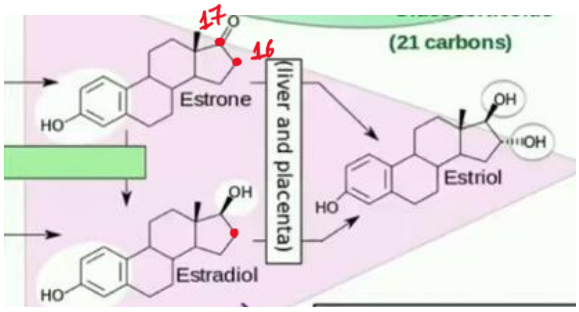
- The enzyme responsible for converting androgens into estrogens is aromatase. During this process, the ketone group (highlighted in red) is reduced to an alcohol, and the A ring of the steroid becomes fully aromatic.
    - A key characteristic of all estrogens is that their A ring is aromatic, which is why the enzyme performing this conversion is named aromatase.



- The aromatase enzyme is encoded by CYP19A1 gene.
    - ❖ Aromatase converts Androstenedione into Estrone which is the least active estrogen.
    - ❖ Aromatase converts Testosterone into Estradiol which is the primary estrogen in all mammalian species.

Both **Estrone** and **Estradiol** can be metabolized in the liver and placenta to produce a molecule called Estriol, which is the 3rd estrogen.

- The process of conversion of estrodiol into estriol is a one-step process which involves the hydroxylation of carbon #16 (in red) of the D five-membered ring.
- While the process of conversion of estrone into esrtiol is a two-step process, first the ketone at the carbon #17 must be reduced by 17β-HSD into alcohol, then hydroxylation as the previous point.



This process is catalyzed by another p450 hydroxylase; 16-hydroxylase enzyme.

NOTES:

- Although cholesterol is the parent steroid, progestagens can also be considered parent compounds, because the synthesis of mineralocorticoids requires the prior formation of glucocorticoids (derived from progestagens). Likewise, the synthesis of estrogens requires androgens, which are also derived from progestagens.

- Some steroids such as cholesterol, DHEA, and estrone can be sulfated at the 3ß by PAPS-dependent sulfotransferases.
    - Sulfation is a good way to inactivate a steroid but it also prepares it for excretion in the urinary system which is actually how these steroids are going to be removed which is a part of phase 2 metabolism in the liver.

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