

STEROIDS

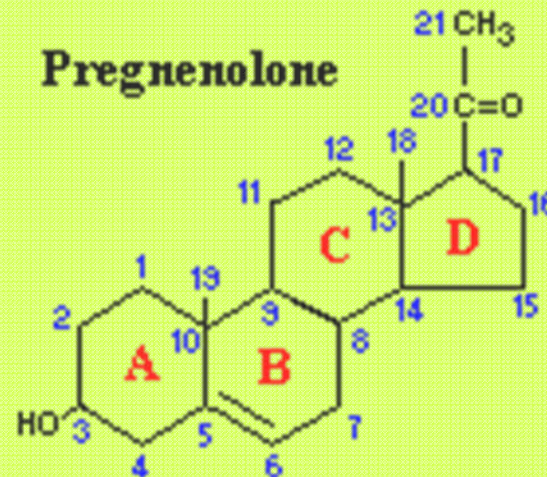
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Steroid Hormones

- Steroid hormones: produced in the adrenal cortex, testis, ovary, and some peripheral tissues (adipose tissue, the brain!)
- All steroid hormones share a typical (but not identical) ring structure.

Steroid hormones

- All steroid hormones are derived from cholesterol and differ only in the ring structure and side chains attached to it.
- All steroid hormones are lipid soluble



Types of steroid hormones

- **Glucocorticoids**; cortisol is the major representative in most mammals
- **Mineralocorticoids**; aldosterone being most prominent
- **Androgens** such as testosterone
- **Estrogens**, including estradiol and estrone
- **Progestogens** (also known as progestins) such as progesterone

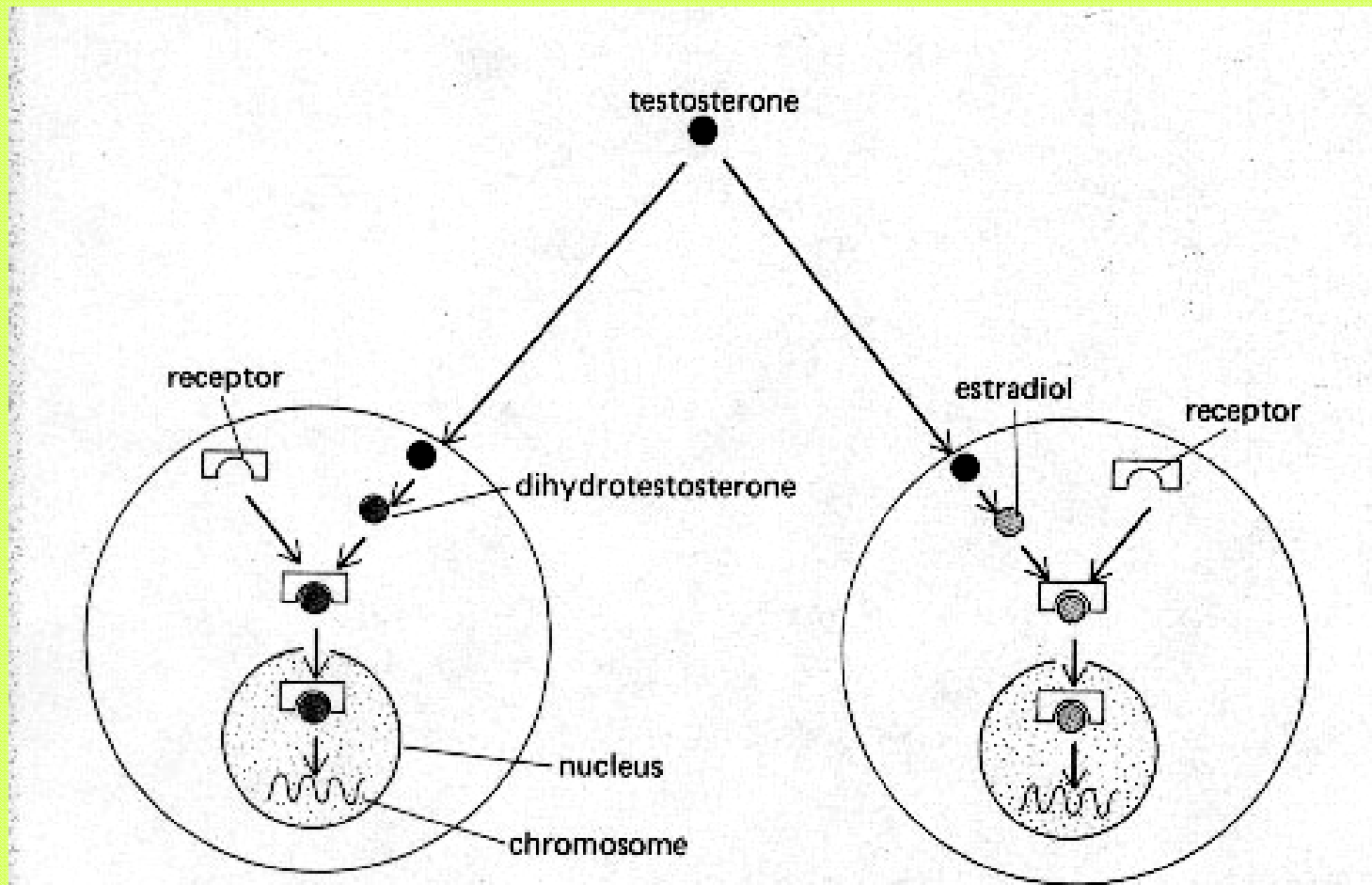
Steroid hormones

- Are not packaged, but synthesized and immediately released
- Are all derived from the same parent compound: Cholesterol
- Enzymes which produce steroid hormones from cholesterol are located in mitochondria and smooth ER
- Steroids are lipid soluble and thus are freely permeable to membranes so are not stored in cells

Steroid hormones

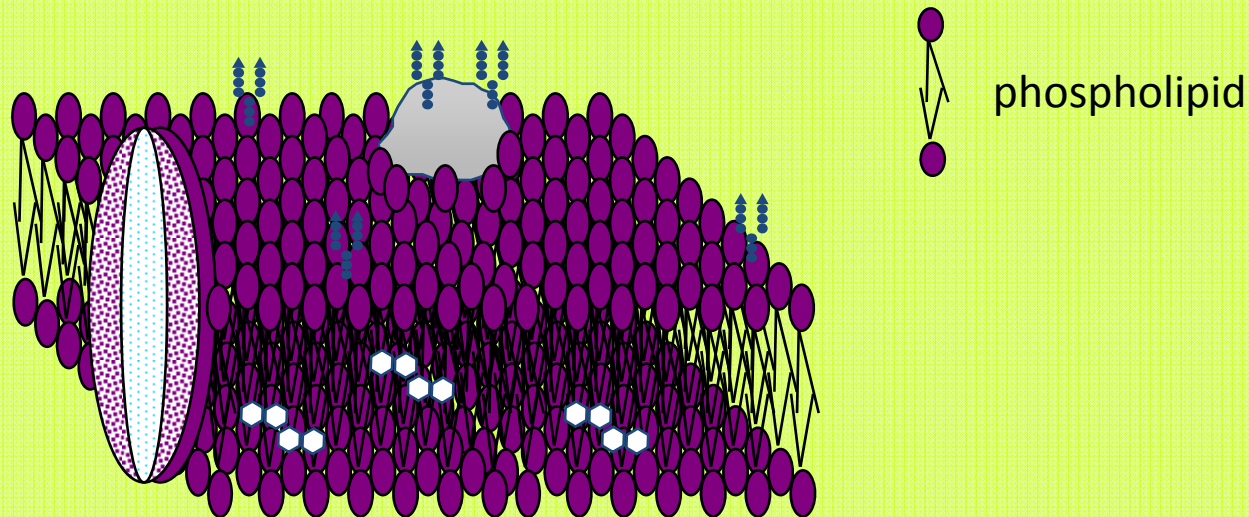
- Steroid hormones are not water soluble so have to be carried in the blood complexed to specific binding globulins.
- Corticosteroid binding globulin carries cortisol
- Sex steroid binding globulin carries testosterone and estradiol
- In some cases a steroid is secreted by one cell and is converted to the active steroid by the target cell: an example is androgen which secreted by the gonad and converted into estrogen in the brain

Steroids can be transformed to active steroid in target cell



Steroid Hormones

- Steroid hormones are nonpolar (no net charge), and can thus diffuse across lipid membranes (such as the plasma membrane). They leave cells shortly after synthesis.



Polar substances are water soluble (dissolve in water),
nonpolar substances are lipid soluble.

Functions of Steroid Hormones

- Steroid hormones play important roles in:
 - carbohydrate regulation (glucocorticoids)
 - mineral balance (mineralocorticoids)
 - reproductive functions (gonadal steroids)
- Steroids also play roles in inflammatory responses, stress responses, bone metabolism, cardiovascular fitness, behavior, cognition, and mood.

How does the synthesis of steroids differ from that of peptide hormones?

- While peptide hormones are encoded by specific genes, steroid hormones are synthesized from the enzymatic modification of cholesterol.
- Thus, there is no gene which encodes aldosterone, for example.
- ***As a result:***
 - There are far fewer different types of steroid hormones than peptide hormones.
 - Steroid structures are the same from species to species
 - The regulation of steroidogenesis involves control of the enzymes which modify cholesterol into the steroid hormone of interest.

The Role of Cholesterol in Steroid Synthesis

- The *first enzymatic step* in the production of ANY steroid hormone begins with enzymatic modification of cholesterol

Sources of Cholesterol for Steroid Synthesis

- Cholesterol can be made within the cell from acetyl CoA (*de novo synthesis*).
- This is a multistep process, involving many enzymatic reactions.
- A key rate-limiting enzyme is HMG-CoA reductase.
- There is negative feedback regulation of HMG-CoA reductase activity by cholesterol, so that high intracellular cholesterol inhibits *de novo* synthesis.



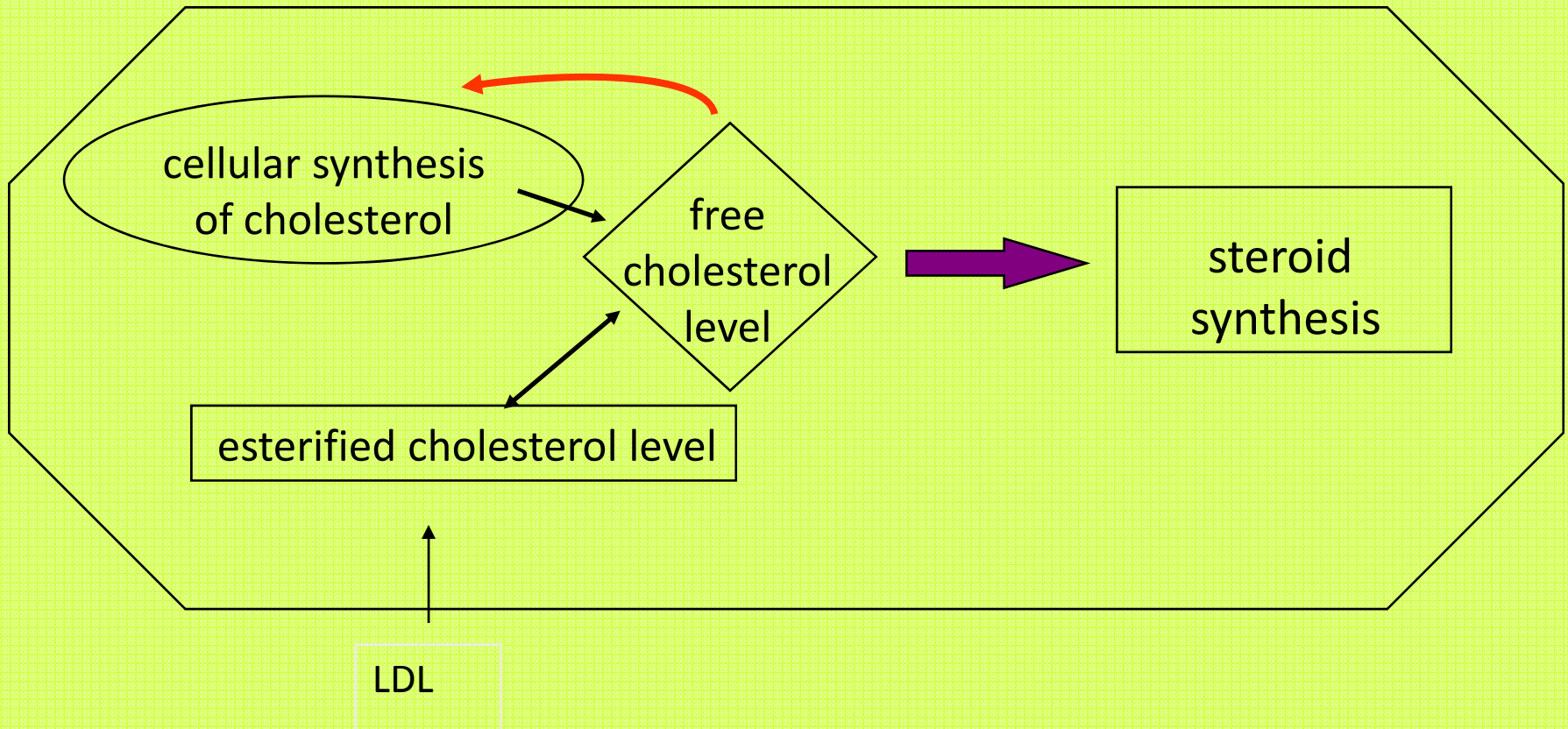
Sources of Cholesterol for Steroid Synthesis

- Cholesterol is also taken up by the cell in the form of low density lipoprotein (LDL).
 - LDL is a complex composed of cholesterol, phospholipids, triglycerides, and proteins (proteins and phospholipids make LDL soluble in blood).
 - LDL is taken into cells via LDL receptors, and broken down into esterified cholesterol, and then free cholesterol:



Source of Cholesterol for Steroid Synthesis

- The amount of **free** cholesterol in the cell is maintained relatively constant:



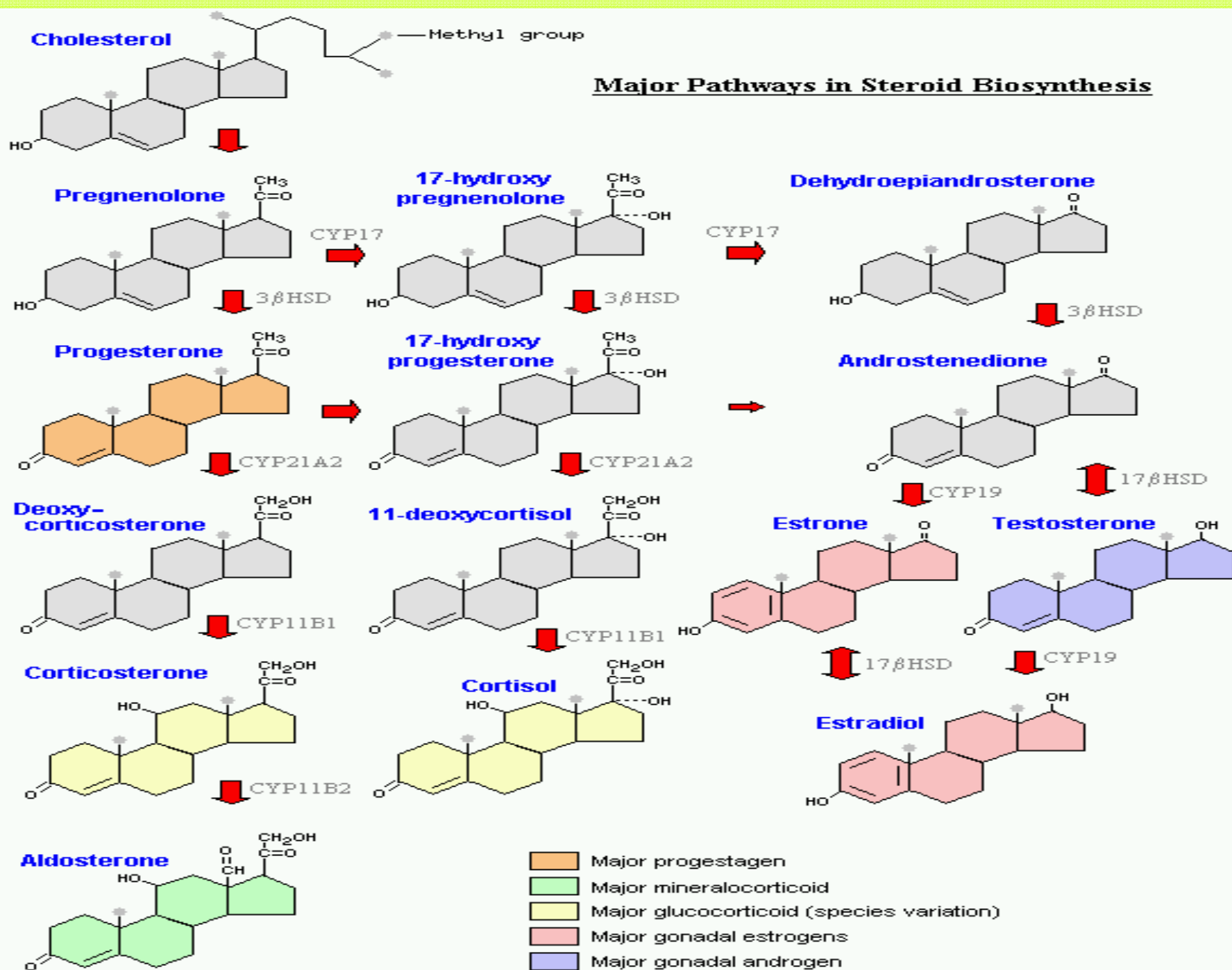
Cellular Localization of Cholesterol Metabolism for Steroid Production

- The first *enzymatic* step in steroid synthesis is the conversion of cholesterol into pregnenolone.
- The enzyme that catalyzes this reaction is located in the inner mitochondrial membrane.

Steroidogenic Enzymes

Common name	"Old" name	Current name
Side-chain cleavage enzyme; desmolase	P450 _{SCC}	CYP11A1
3 beta-hydroxysteroid dehydrogenase	3 beta-HSD	3 beta-HSD
17 alpha-hydroxylase/17,20 lyase	P450 _{C17}	CYP17
21-hydroxylase	P450 _{C21}	CYP21A2
11 beta-hydroxylase	P450 _{C11}	CYP11B1
Aldosterone synthase	P450 _{C11AS}	CYP11B2
Aromatase	P450 _{aro}	CYP19

Major Pathways in Steroid Biosynthesis



Steroid hormone synthesis

All steroid hormones are derived from cholesterol. A series of enzymatic steps in the mitochondria and ER of steroidogenic tissues convert cholesterol into all of the other steroid hormones and intermediates.

The rate-limiting step in this process is the transport of free cholesterol from the cytoplasm into mitochondria. This step is carried out by the **Steroidogenic Acute Regulatory Protein (StAR)**

Steroid hormone synthesis

- The cholesterol precursor comes from cholesterol synthesized within the cell from acetate, from cholesterol ester stores in intracellular lipid droplets or from uptake of cholesterol-containing low density lipoproteins.
- Lipoproteins taken up from plasma are most important when steroidogenic cells are chronically stimulated.

Extracellular lipoprotein

LH

ATP

acetate

Cholesterol pool

cholesterol

cAMP

PKA+

STAR

SCC

3 β HSD

Pregnenolone

3 β HSD

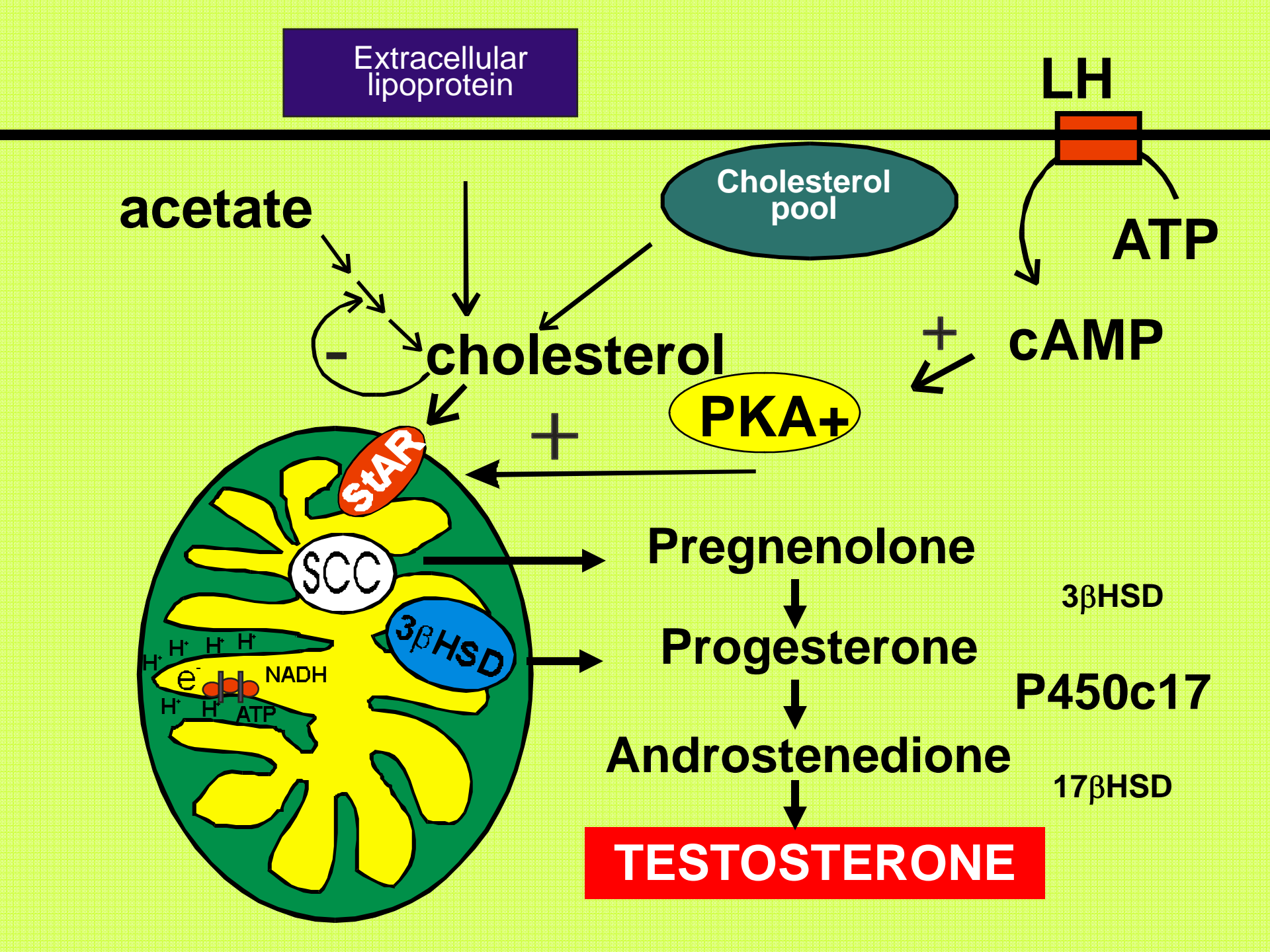
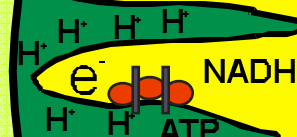
Progesterone

P450c17

Androstenedione

17 β HSD

TESTOSTERONE



**Functions of Hormones
Derived from Cholesterol**

Product	Functions
Progesterone	prepares uterus lining for implantation of ovum
Glucocorticoids (cortisol) (produced in adrenal cortex) (catabolic steroid)	promote gluconeogenesis; favor breakdown of fat and protein (fuel mobilization); anti-inflammatory
Mineralocorticoids (aldosterone) (produced in adrenal glands)	maintains blood volume and blood pressure by increasing sodium reabsorption by kidney

**Functions of Hormones
Derived from Cholesterol**

Product	Functions
Androgens (strongest = testosterone) (produced in testes primarily but weak androgens in adrenal cortex) (anabolic steroid)	development of male secondary sex characteristics; prevents bone resorption
Estrogen (produced in ovaries primarily but also in adipose cells of males and females)	development of female secondary sex characteristics; prevents bone resorption
Vitamin D (not a steroid hormone) (produced in the skin in response to UV light and processed to active form in kidney)	intestinal calcium absorption; promotes bone formation; prevents phosphate loss by kidneys

*activated to turn
on pathways*

Cholesterol



Pregnenolone



Progesterone

Progesterone



11-Deoxy-
cortisone



Aldosterone

21-hydroxylase

Progesterone



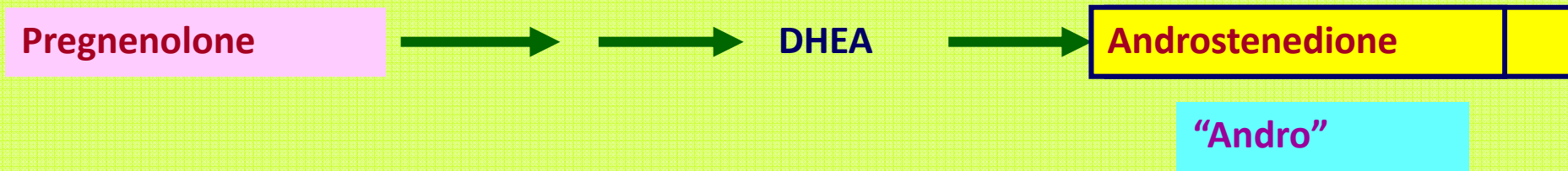
11-Deoxy-
cortisol



Cortisol

21-hydroxylase

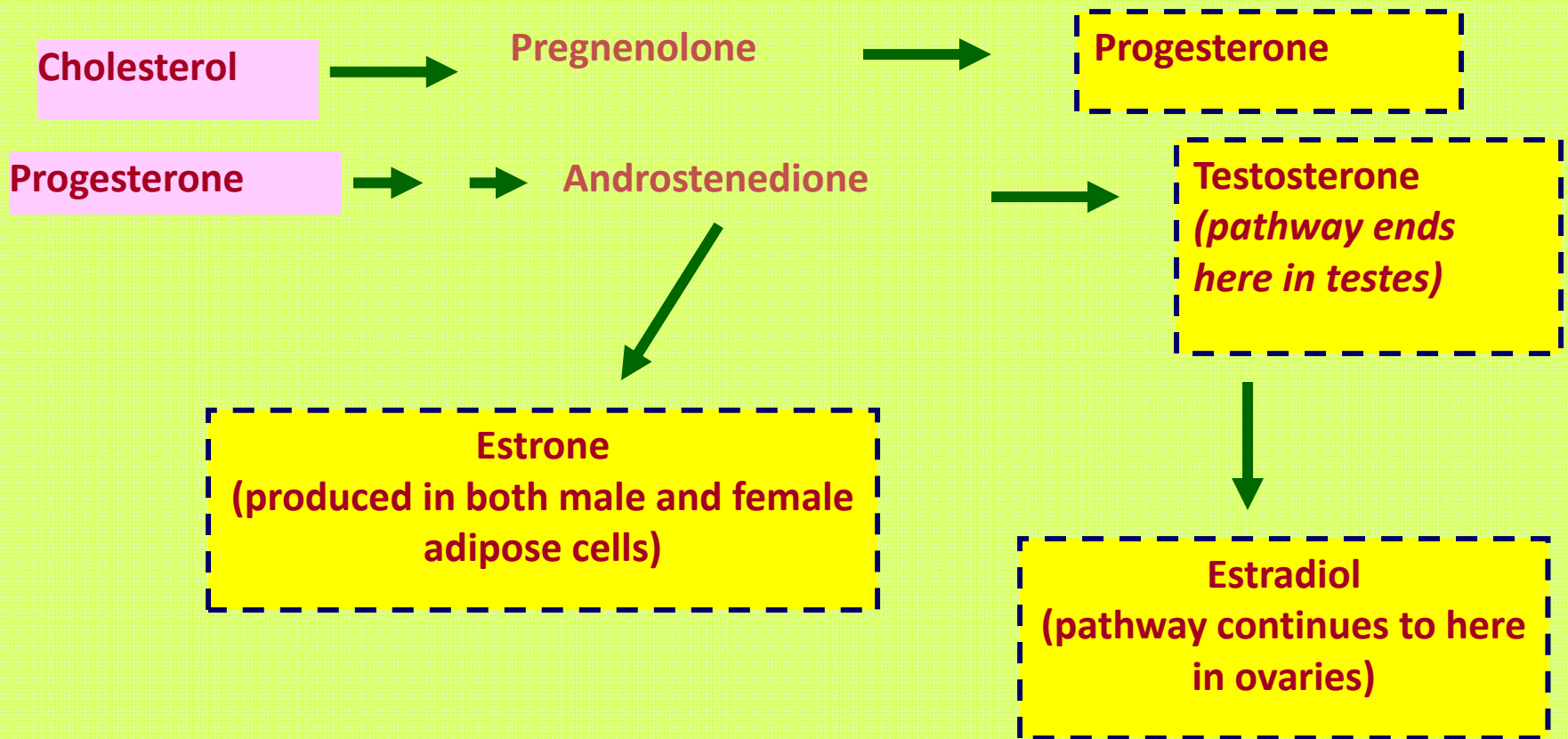
General pathways for the synthesis of aldosterone and cortisol in the adrenal cortex



Pathway for formation of androgens in the adrenal cortex.

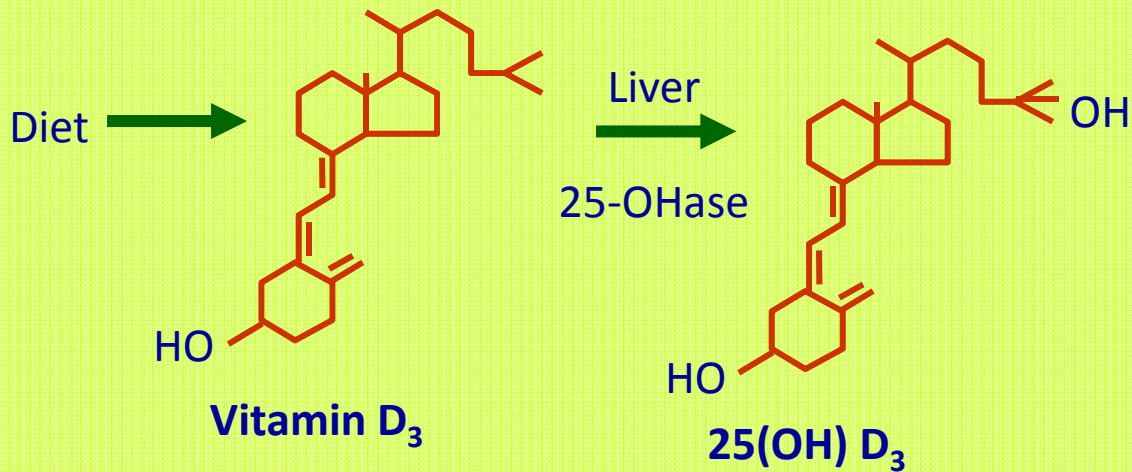
Beware of the hype about taking DHEA

Cortisol made in same cells as androstenedione



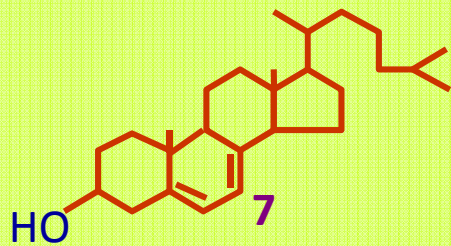
In obese men, overproduction of estrogen in fat cells can cause gynecomastia = excessive male breast development

Pathways for the synthesis of testosterone (testes) and the estrogens estradiol (ovaries) and estrone (adipose cells)

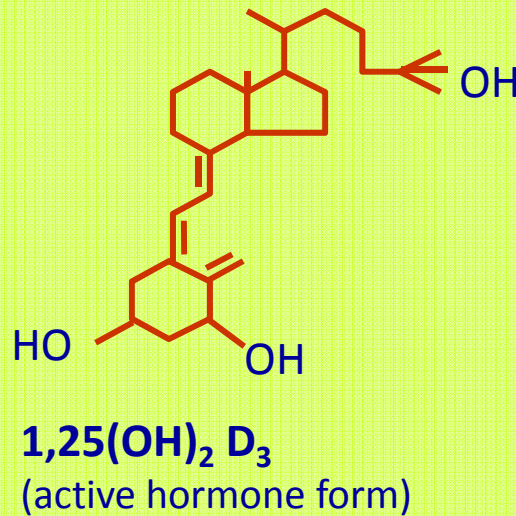


**OHase =
hydroxylase**

UV from
sunlight ↑
Skin



↓
Kidney
1-OHase



**Specific receptors in
intestine, bone, kidney**

**Ca:
Intestinal absorption
Renal reabsorption**

**PO₄:
Intestinal absorption
Renal reabsorption**

Photobiosynthesis of vitamin D₃ and its metabolism

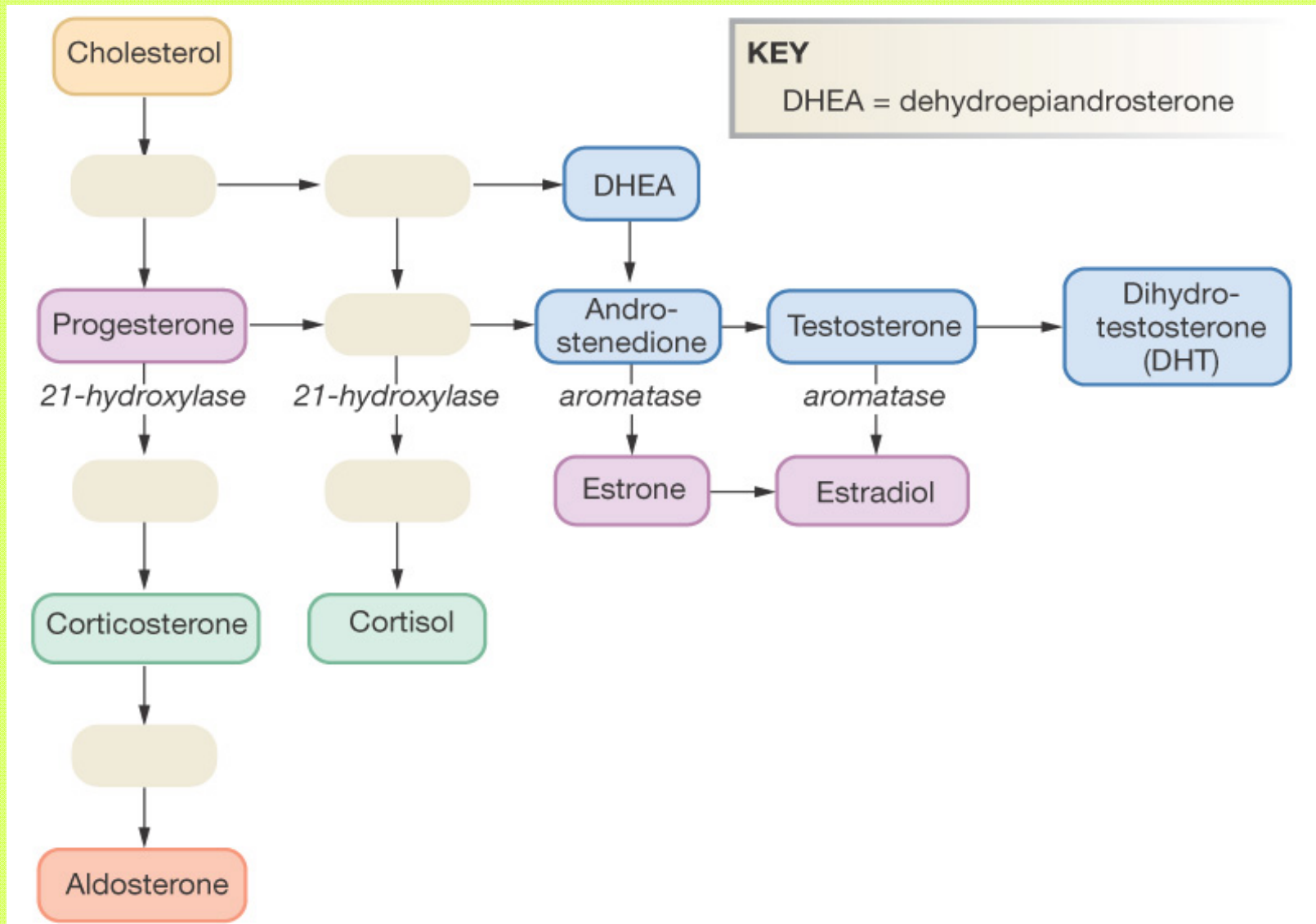
1,25-Dihydroxy Vitamin D3

- 1,25-dihydroxy Vitamin D3 is also derived from cholesterol and is lipid soluble
- Not really a “vitamin” as it can be synthesized *de novo*
- Acts as a true hormone

Adrenal Cortex: Steroid Hormone Production

- Aldosterone, sex hormones, cortisol
- Synthesized from cholesterol—steroid ring

Adrenal Cortex: Steroid Hormone Production



Transport of Cholesterol

- Cholesterol is lipid soluble, and mostly located associated with the external mitochondrial membrane.
- The conversion of cholesterol to steroids occurs in the internal mitochondrial membrane.
- **Now, to see if you have been paying attention...**
- How does cholesterol get from the external membrane to the internal membrane?
- *Answer:* Steroidogenic acute regulatory protein (StAR), which transports cholesterol into the mitochondria, moving it from the outer membrane to the inner membrane.

Adrenal Steroids

- The adrenal glands are located immediately superior to the kidneys.
- There are three classes of adrenal steroids:
 - mineralocorticoids,
 - glucocorticoids, and
 - androgens

Organization of the Adrenal Gland

There is an adrenal cortex and adrenal medulla.

Steroids are made in three zones of the adrenal cortex:

mineralocorticoids: zona glomerulosa

glucocorticoids: zona fasciculata

androgens: zona reticularis

(What's made in the adrenal medulla??)

Adrenal Steroidogenesis

- The first **enzymatic** step is the conversion of cholesterol to pregnenolone, which occurs in the mitochondria.
- This reaction is carried out by the enzyme, cytochrome P450 side-chain cleavage (P450_{scc}; also called desmolase, or CYP11A1).
- This is a *rate limiting, nonreversible* step in the initiation of steroid biosynthesis.
- This step occurs in adrenal, ovary, and testis.

Adrenal Steroidogenesis

What determines which pathway is taken?

- Each step of the pathway is regulated by a specific enzyme.
- Different zones of the adrenal cortex have different relative activities of enzymes, resulting in different chemical reactions taking place.
- These enzymes are located in the smooth ER.

In the adrenal, you do NOT have to learn the names of these enzymes. You DO have to understand what hormones are produced, where they are produced, and why they are produced there.

Production of Steroids in the Testis

- The **main** steroid produced in the male is testosterone, from the testis. In addition, the testis makes some androstenedione, dihydrotestosterone, and estradiol.
- In the male, there is peripheral conversion of testosterone to **dihydrotestosterone** (in androgen target tissues, like muscle) and **estradiol** (mostly in adipose tissue).

Organization of the Testis

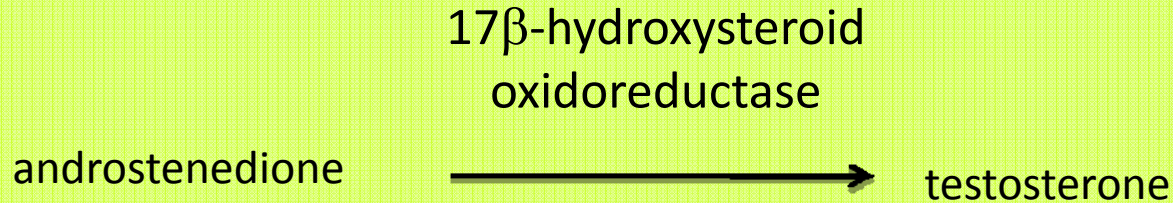
- The testis is organized into two main parts:
 - **seminiferous tubules**: production of sperm cells, location of Sertoli cells (stay tuned...)
 - **interstitial tissue**: outside of the seminiferous tubules; the steroidogenic cell is the **Leydig** cell

Function of Leydig Cells

- Leydig cells: respond to luteinizing hormone (LH) with steroid production (primarily testosterone).
- Leydig cells are unusual in that they rely on *de novo* synthesis of cholesterol more than other cells (50%). Thus, only about 50% of cholesterol used in steroid production is obtained from LDL.

Pathway of Testosterone Production in the Testis

- The production of androgens from cholesterol is identical to that in the adrenal, except that it continues from androstenedione to testosterone.



Testosterone Metabolism

- Testosterone can then be converted (mostly in peripheral tissues) to:
 - DHT (dihydrotestosterone) by 5α -reductase, or to
 - estradiol (E2) by cytochrome P450 aromatase

Important Note

- Since the enzymes/pathways for producing androgens and estrogens are utilized in adrenal, testis, and ovary, you **will** be expected to know the names of these enzymes, and their role (example; know that 3β -HSD converts pregnenolone into progesterone).
- You are NOT responsible for drawing the structures of these steroids. (You should recognize the typical ring structure when you see it, however).
- Also, know that LH stimulates Leydig cell steroidogenesis.

Ovarian Steroidogenesis

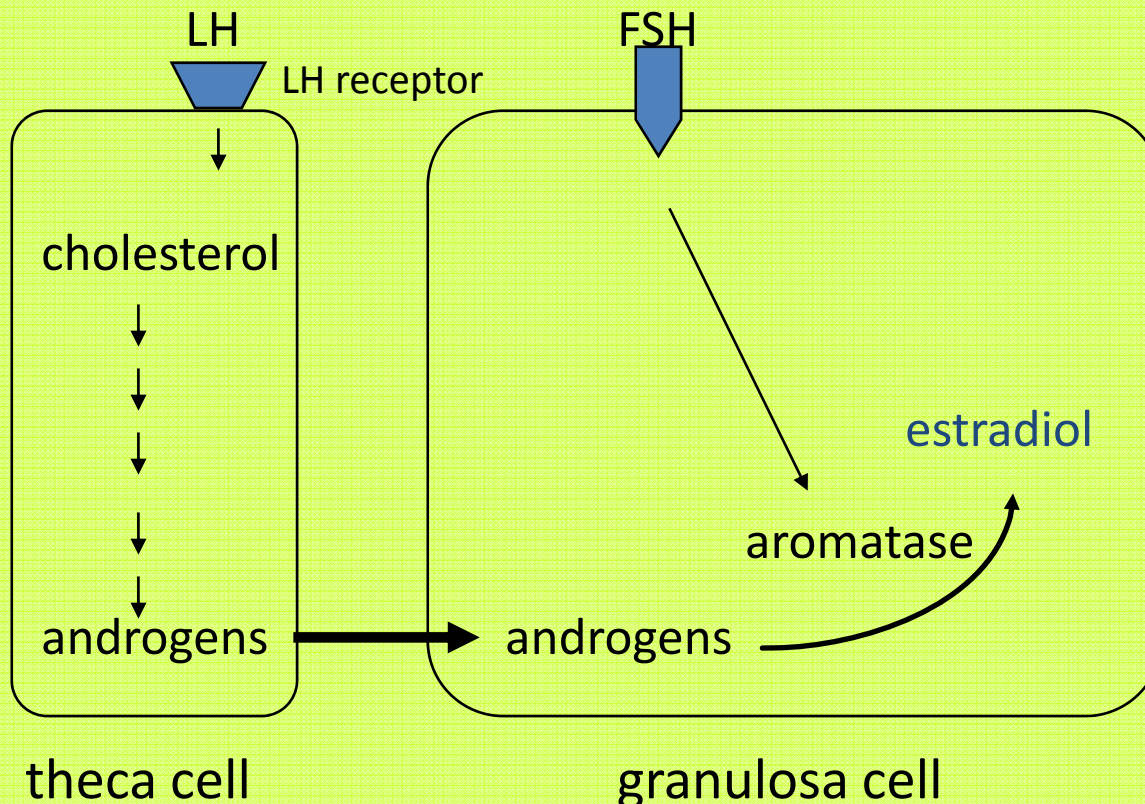
- The ovary produces estrogens (primarily estradiol), progesterone, and androgens.
- It relies largely on LDL as a source of cholesterol for steroid synthesis (compare with testis).
- Ovarian steroids are secreted primarily from ovarian follicles and corpora lutea.

The Puzzle of Estrogen Production in the Ovary

- In the ovary, estradiol is formed from the conversion of testosterone into estradiol by the enzyme *cytochrome P450 aromatase*. This occurs in granulosa cells.
- However, granulosa cells do not have the enzyme 17α -hydroxylase/lyase, and thus cannot convert progesterone into androgens.
- Where do the androgens required for estrogen production in granulosa cells come from?

The Two-Cell Theory of Estrogen Production in the Ovary

- Numerous studies have now shown that the androgens required for aromatization come from the neighboring theca cells:

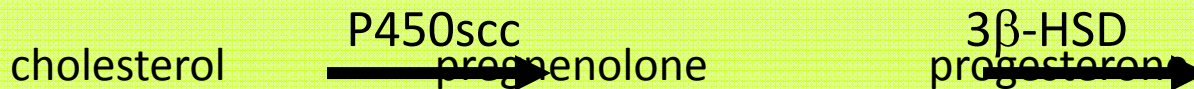


Other Steroid Production in the Ovary

- After ovulation, the corpus luteum produces progesterone and estradiol, to support the uterine endometrium during pregnancy.
- Progesterone is also produced from theca cells and granulosa cells.

Regulation of Ovarian Steroidogenesis

- The rate of estradiol production from follicles varies greatly during the menstrual cycle.
- Estradiol production is regulated by the effects of FSH on P450 aromatase.
- Similarly, LH and FSH influence the expression of P450_{scc} in granulosa cells. This increases production of which gonadal steroid?



Cortisol Effects: Body Responses to Stress

- Permissive effect on glucagon
- Memory, learning and mood
- Gluconeogenesis
- Skeletal muscle breakdown
- Lipolysis, calcium balance
- Immune depression
- Circadian rhythms

Cortisol Effects: Body Responses to Stress

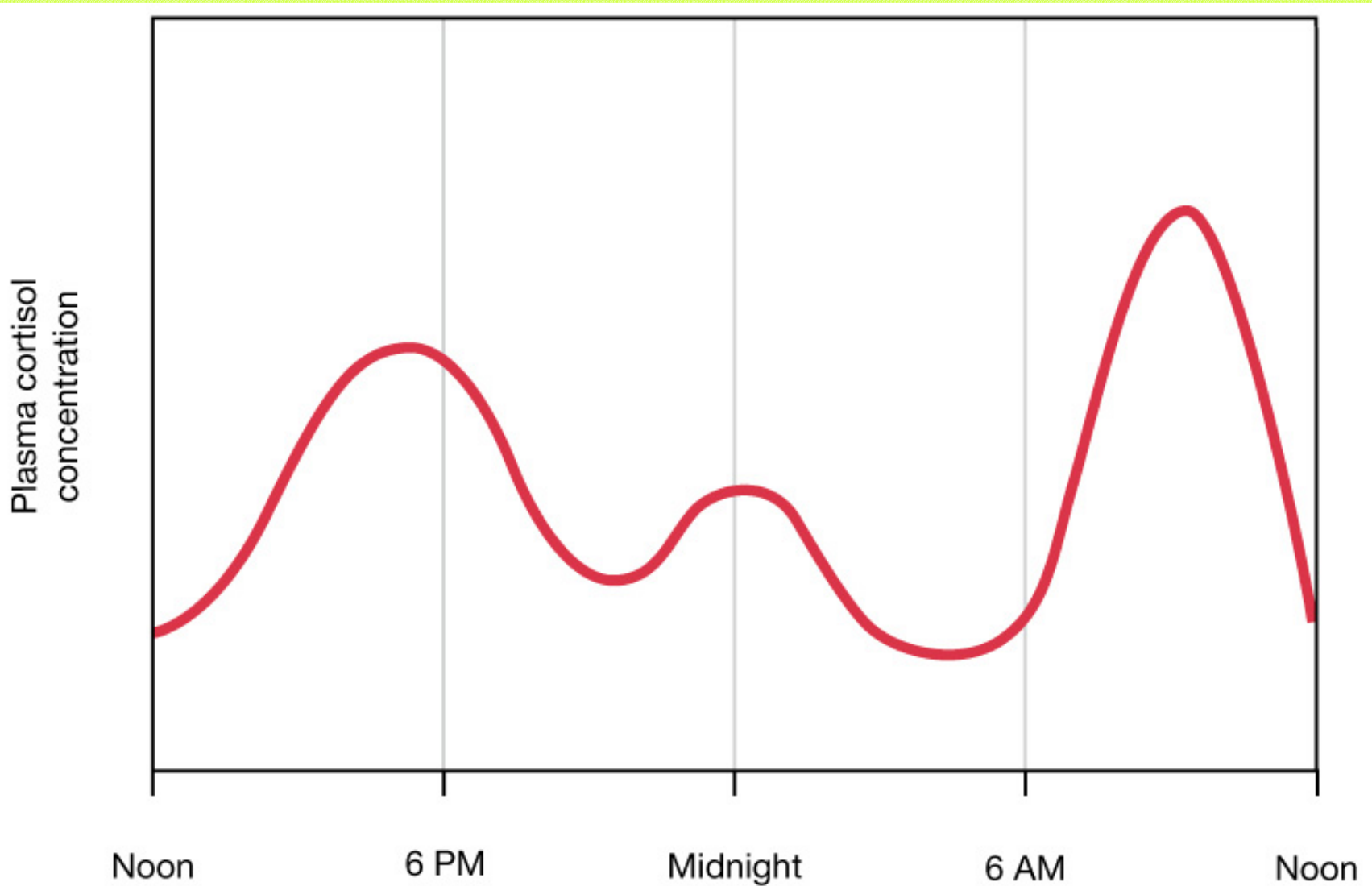


Figure 23-4: Circadian rhythm of cortisol secretion

Control of Cortisol Secretion: Feedback Loops

- External stimuli
- Hypothalamic
- Anterior Pituitary
- Adrenal cortex
- Tissues

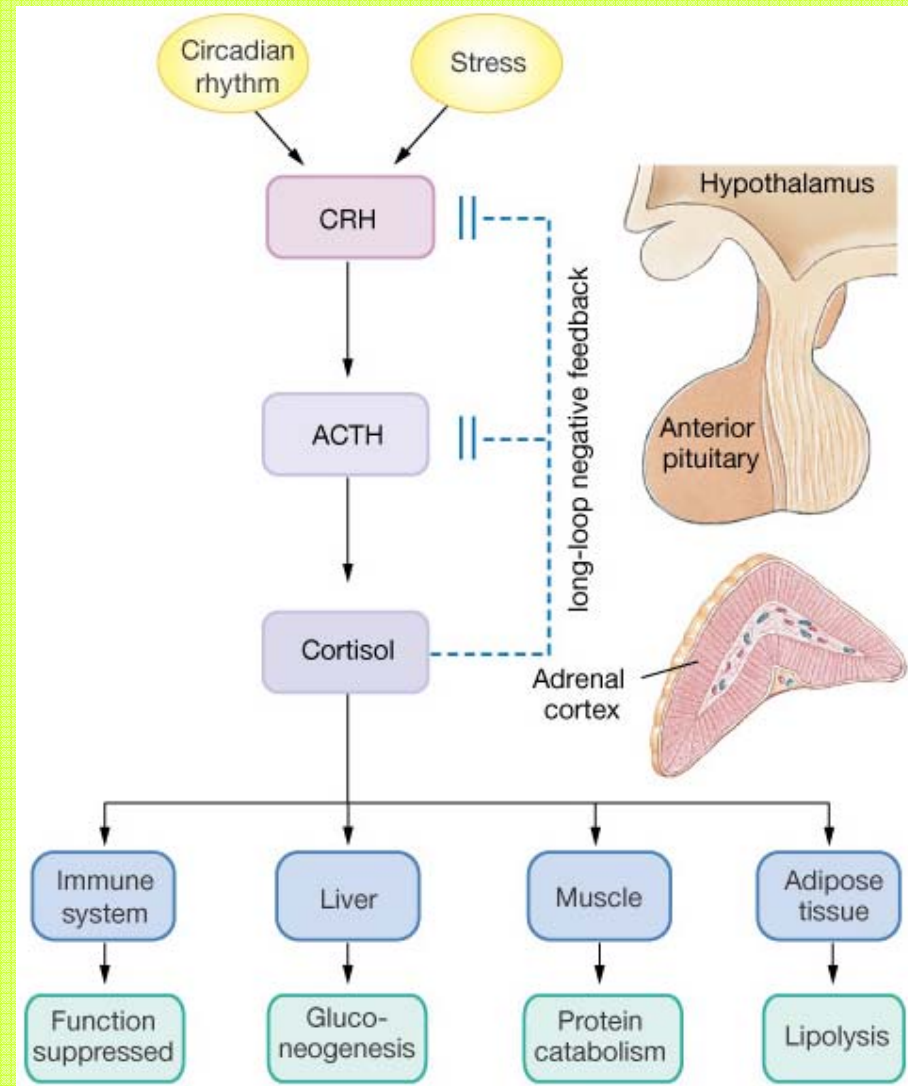


Figure 23-3: The control pathway for cortisol

Cortisol: Role in Diseases and Medication

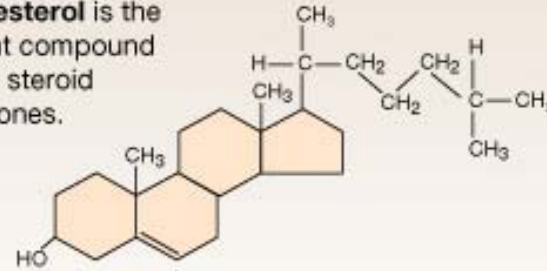
- Use as immunosuppressant
 - Hyperimmune reactions (bee stings)
 - Serious side effects
- Hypercortisolism (Cushing's syndrome)
 - Tumors (pituitary or adrenal)
 - Iatrogenic (physician caused)
- Hypocortisolism (Addison's disease)

Steroid Hormones: Characteristics

- Are made from cholesterol, are lipophilic & can enter target cell
- Are immediately released from cell after synthesis
- Interact with cytoplasmic or nuclear receptors
- Activate DNA for protein synthesis
- Are slower acting and have longer half-life than peptide hormones
- Examples: cortisol, estrogen & testosterone

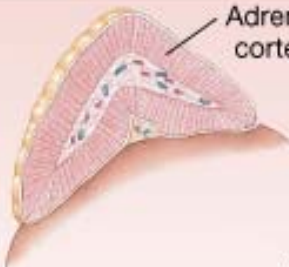
Steroid Hormones: Review the Structure

Cholesterol is the parent compound for all steroid hormones.

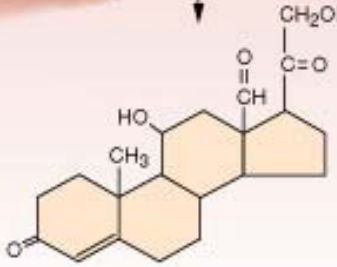


modified by enzymes to make steroid hormones such as

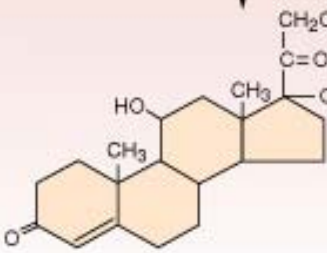
In adrenal cortex



Aldosterone




Cortisol

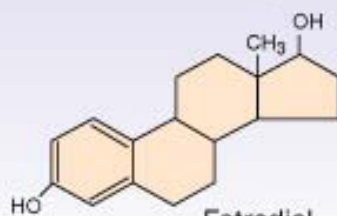


The adrenal cortex produces Aldosterone and Cortisol. Aldosterone has a ketone group at C3, a double bond at C4, and a dihydroxyacetone side chain at C17. Cortisol has a ketone group at C3, a double bond at C4, a hydroxyl group at C11, and a dihydroxyacetone side chain at C17.

In ovary

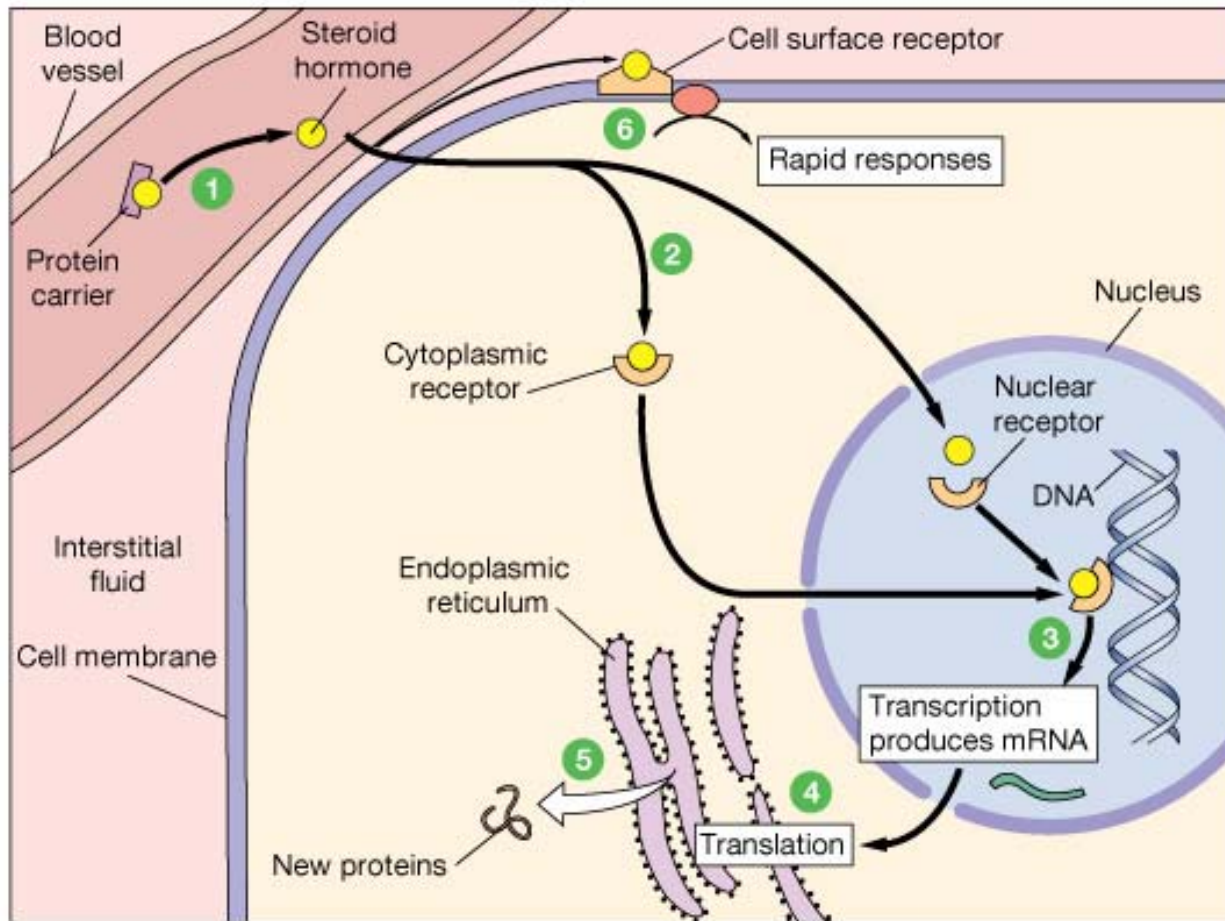


Estradiol (an estrogen)



The ovary produces Estradiol, which has a ketone group at C3, a double bond at C4, and a hydroxyl group at C17.

Steroid Hormones: Molecular Action



- 1 Most hydrophobic steroids are bound to plasma protein carriers. Only unbound hormones can diffuse into the target cell.
- 2 Steroid hormone receptors are in the cytoplasm or nucleus.
- 3 The receptor-hormone complex binds to DNA and activates or represses one or more genes.
- 4 Activated genes create new mRNA that moves back to the cytoplasm.
- 5 Translation produces new proteins for cell processes.
- 6 Some steroid hormones also bind to membrane receptors that use second messenger systems to create rapid cellular responses.

Thank You