Synthesis of Steroid Hormones

Overview of Steroids

Peptide Hormone *vs*. Steroid Hormone Synthesis

The Role of Cholesterol

Adrenal Steroids

Steroids from the Testis

Ovarian Steroids

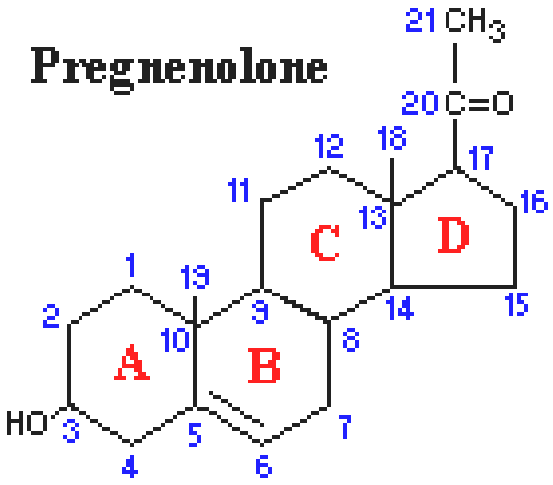
Cortisol

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 a progestins) such as progesterone

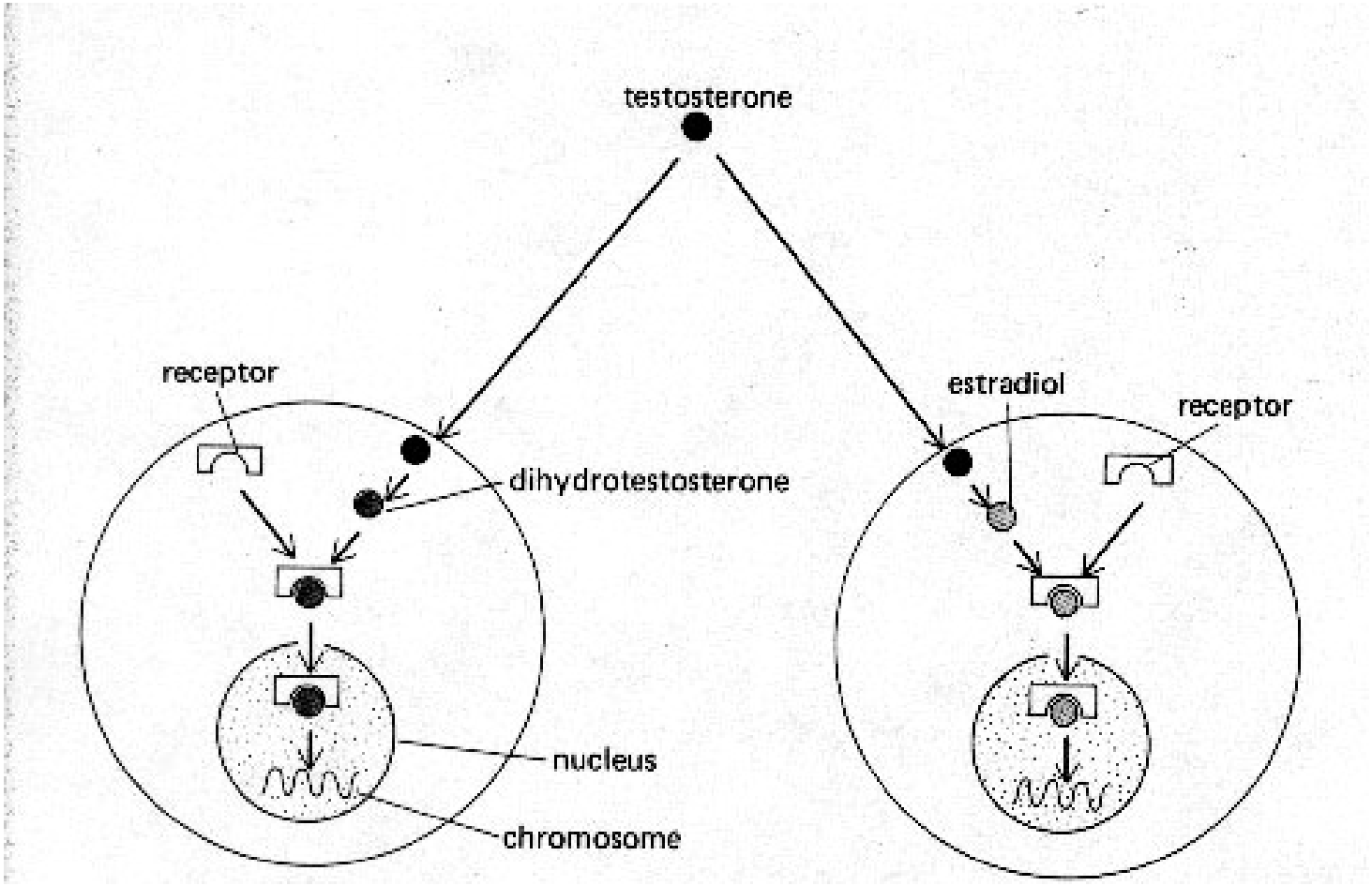
Steroid hormones

- 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

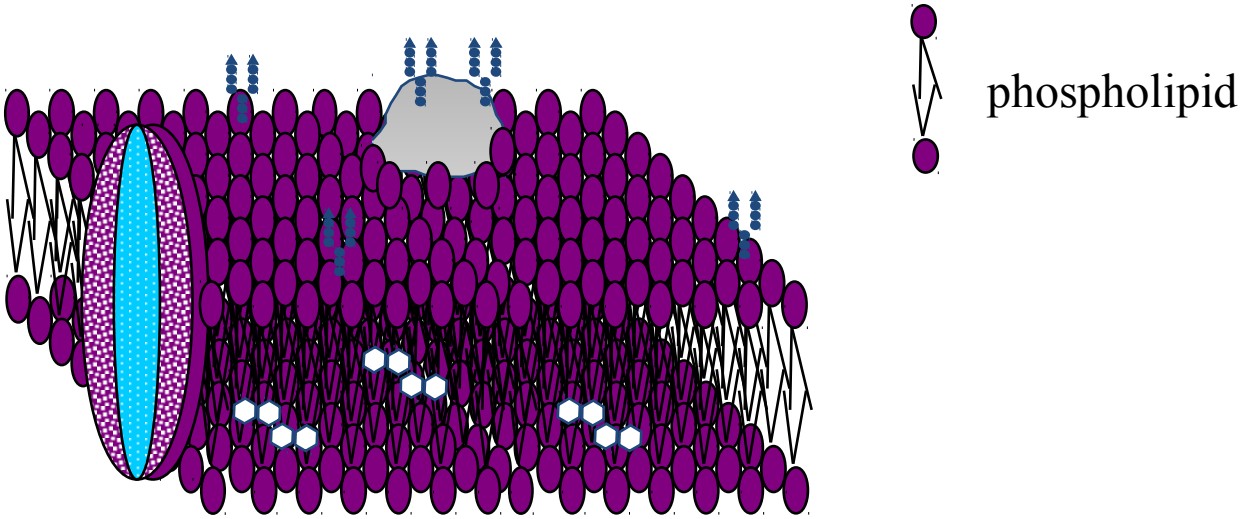
- Steroid hormones are not water soluble so have to be carried in the blood complexed to specific binding globulins.
- Corticosteroid binding globulin carries cortisol
- Sex steroid binding globulin carries testosterone and estradiol
- In some cases a steroid is secreted by one cell and is converted 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?

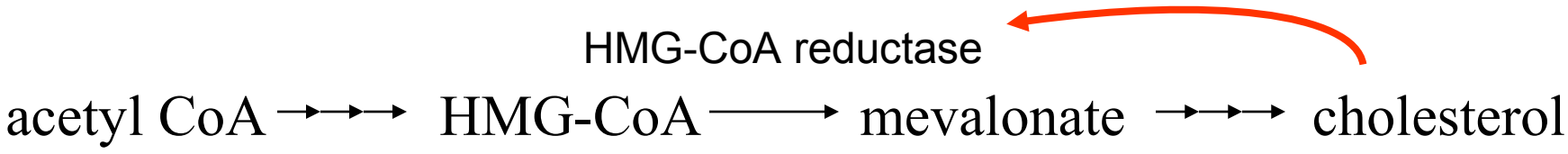
- While peptide hormones are encoded by specific genes, steroid hormones are synthesized from the enzymatic modification of cholesterol.
- Thus, there is no gene which encodes aldosterone, for example.
- ***As a result*:**
  - There are far fewer different types of steroid hormones than peptide hormones.
  - 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.

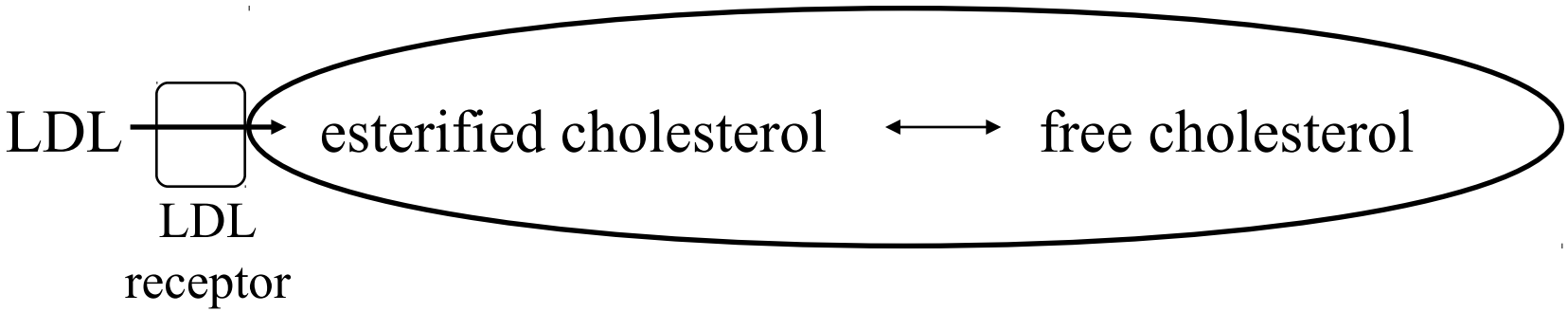


Sources of Cholesterol for Steroid Synthesis

- Cholesterol is also taken up by the cell in the form of low density lipoprotein (LDL).

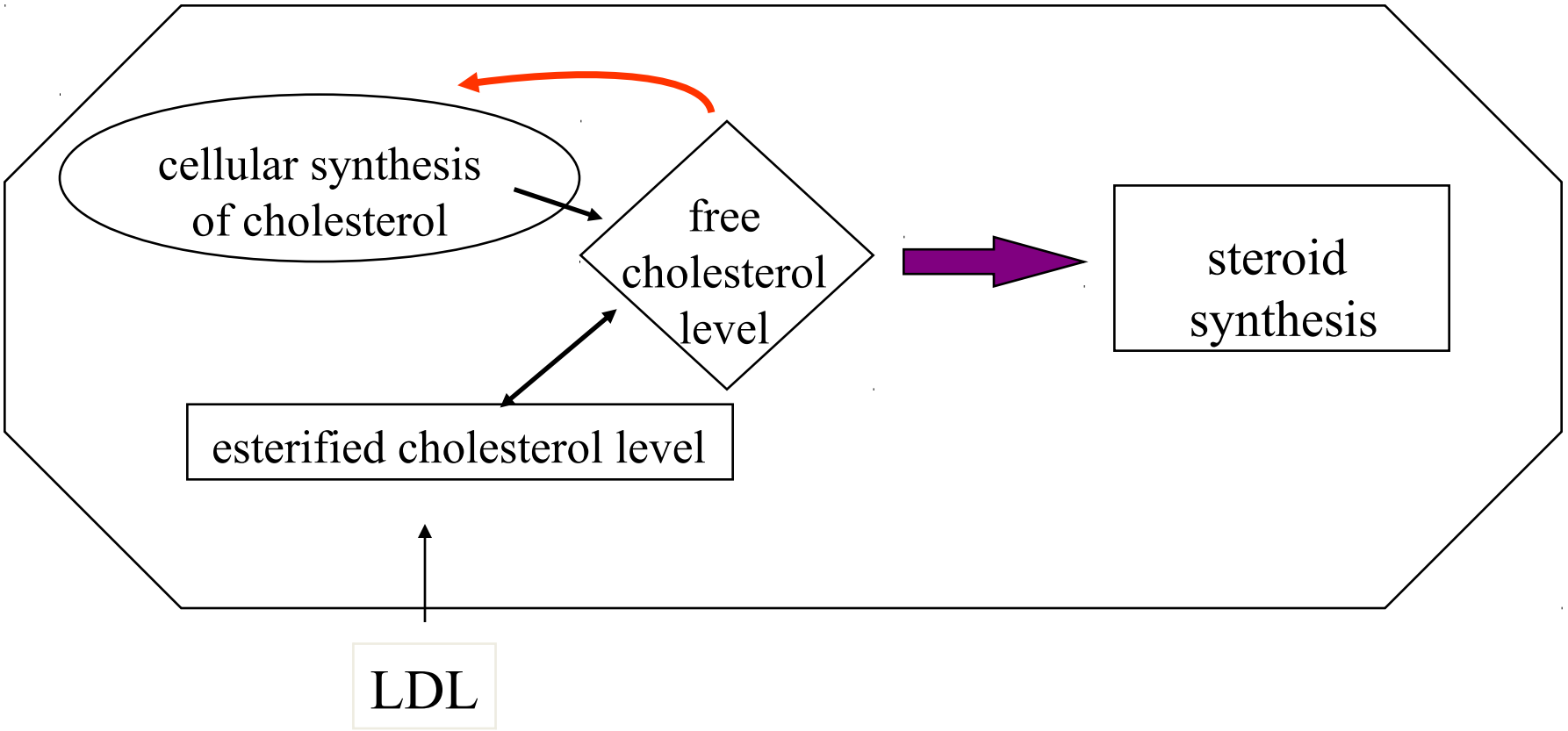
  - LDL is a complex composed of cholesterol, phospholipids, triglycerides, and proteins (proteins and phospholipids make LDL soluble in blood).

  - 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:

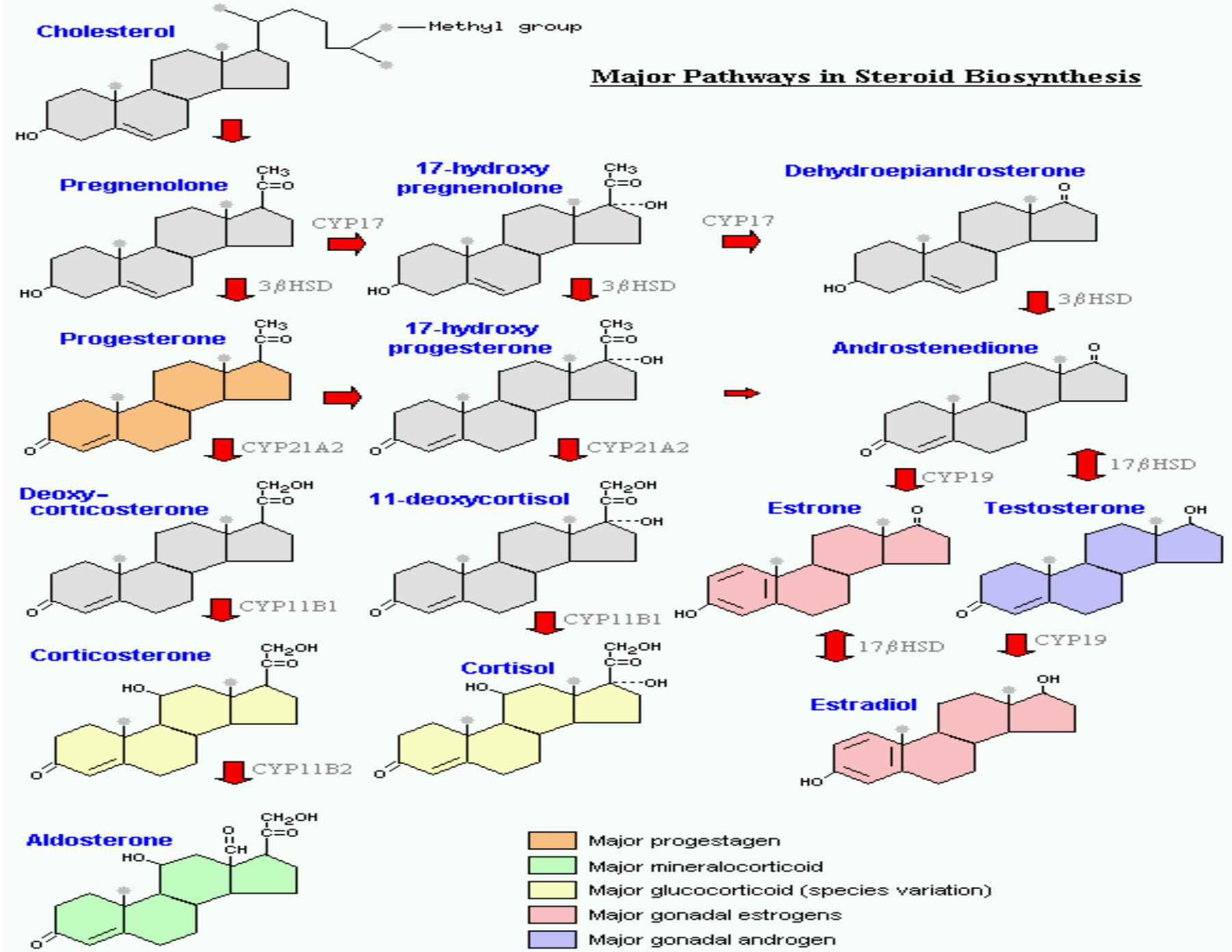


Cellular Localization of Cholesterol Metabolism for Steroid Production

- 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


Cholesterol
Methyl group
Major Pathways in Steroid Biosynthesis
Pregnenolone
CYP17
17-hydroxy pregnenolone
CYP17
Dehydroepiandrosterone
3βHSD
3βHSD
3βHSD
Progesterone
17-hydroxy progesterone
Androstenedione
CYP21A2
CYP21A2
17βHSD
CYP19
Deoxy-corticosterone
11-deoxycortisol
Estrone
Testosterone
CYP11B1
CYP11B1
17βHSD
CYP19
Corticosterone
Cortisol
Estradiol
CYP11B2
Aldosterone
Major progestagen
Major mineralocorticoid
Major glucocorticoid (species variation)
Major gonadal estrogens
Major gonadal androgen

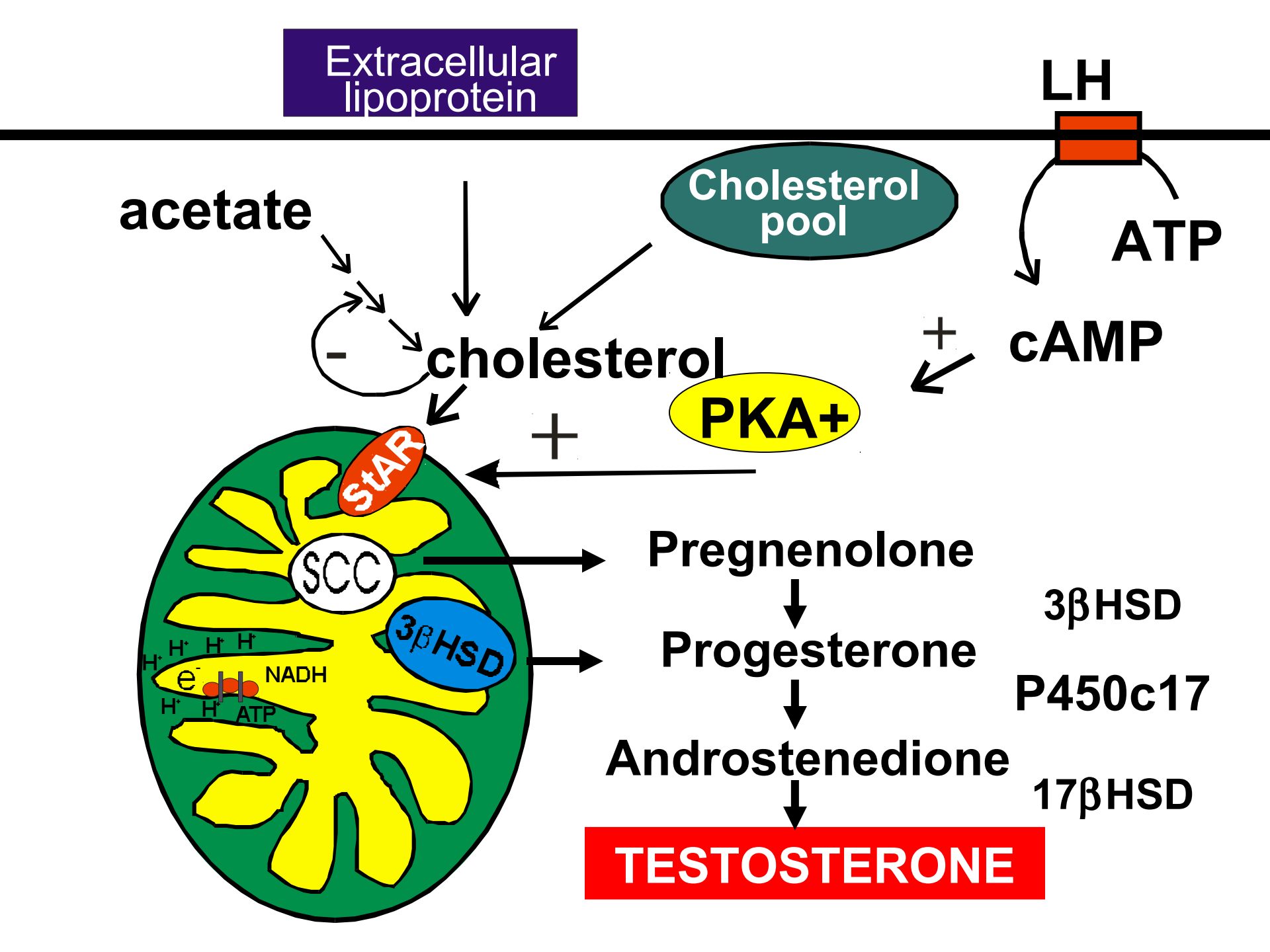
Steroid hormone synthesis

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.

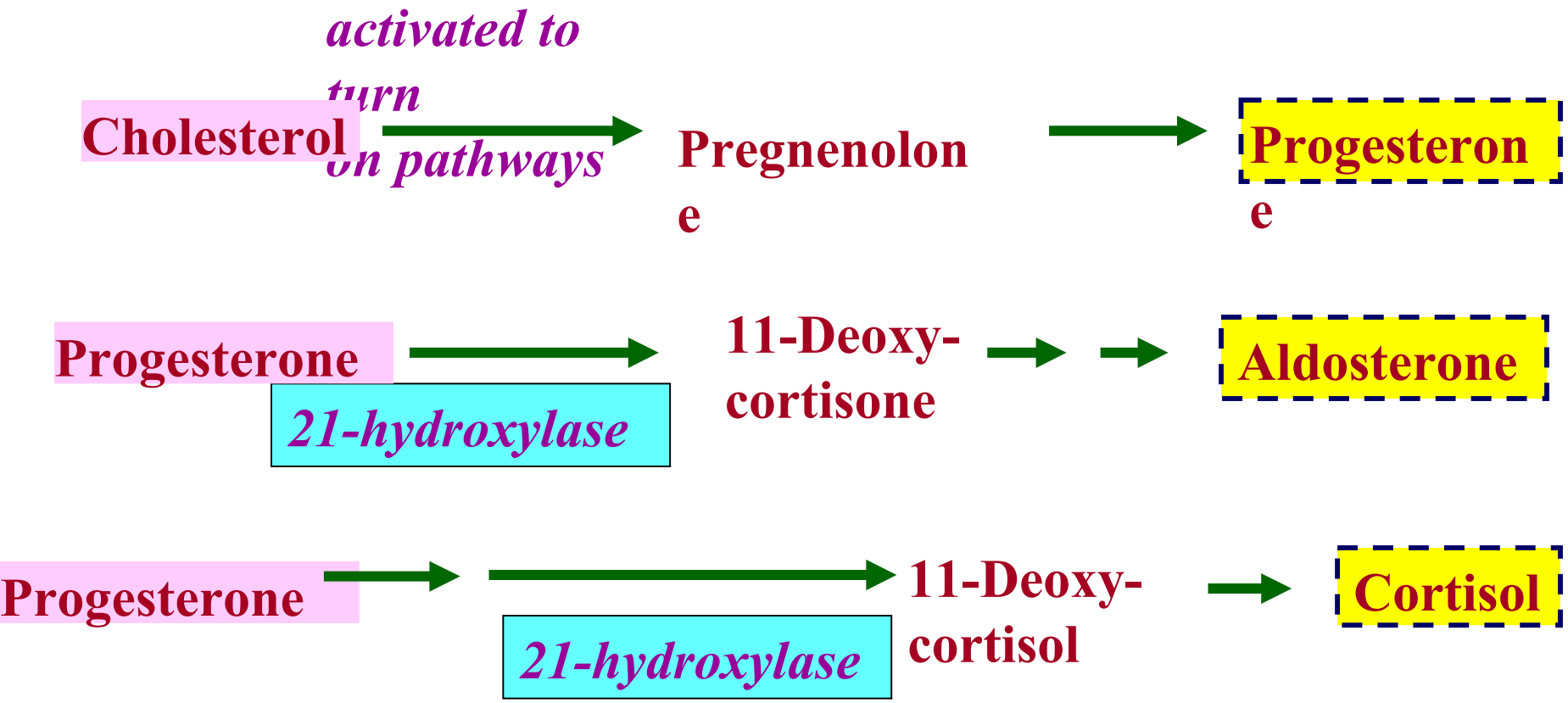

Extracellular lipoprotein
LH
ATP
acetate
Cholesterol pool
cholesterol
cAMP
PKA+
StAR
SCC
3βHSD
NADH
ATP
Pregnenolone
3βHSD
Progesterone
P450c17
Androstenedione
17βHSD
TESTOSTERONE

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

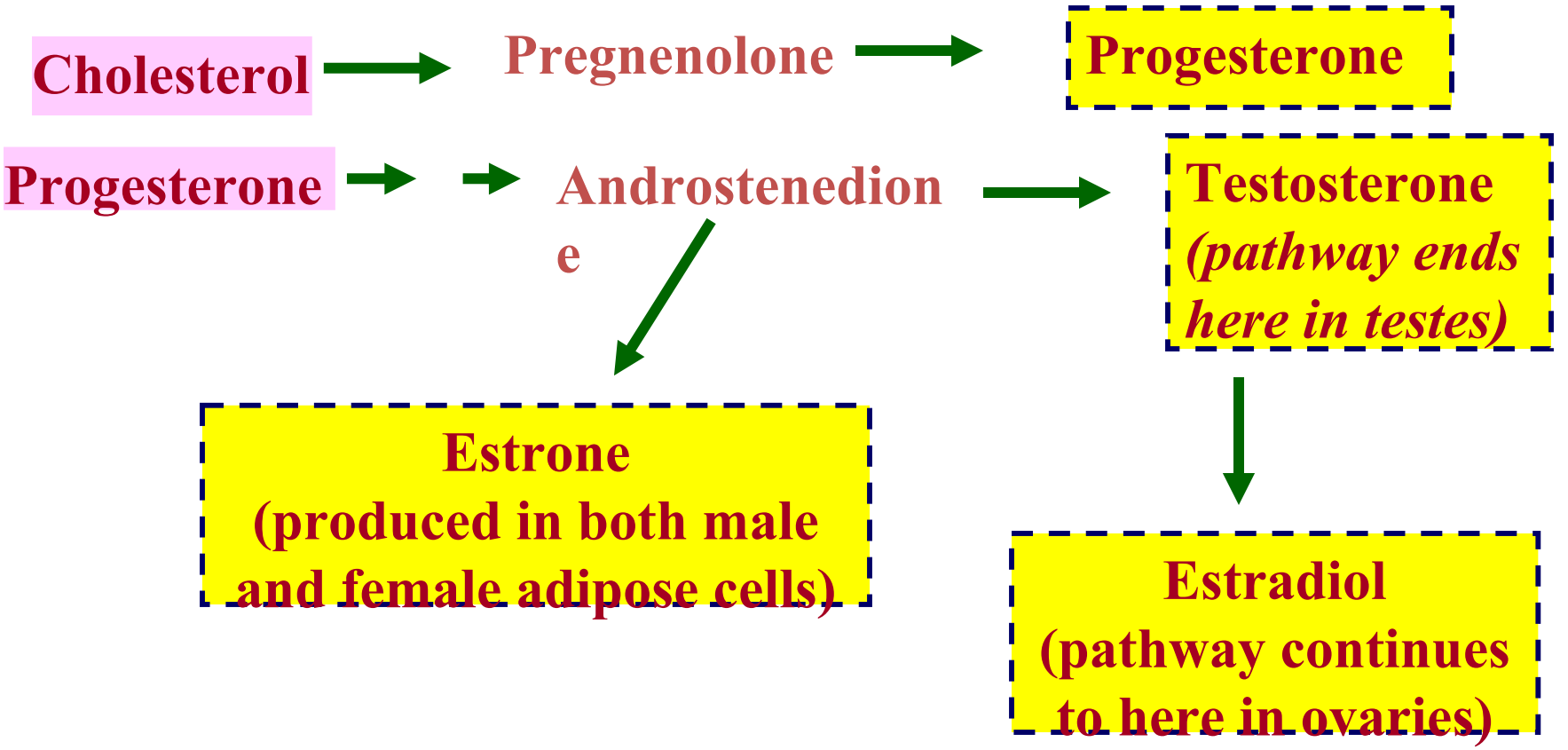


General pathways for the synthesis of aldosterone and cortisol in the adrenal cortex

Pathway for formation of androgens in the adrenal cortex.

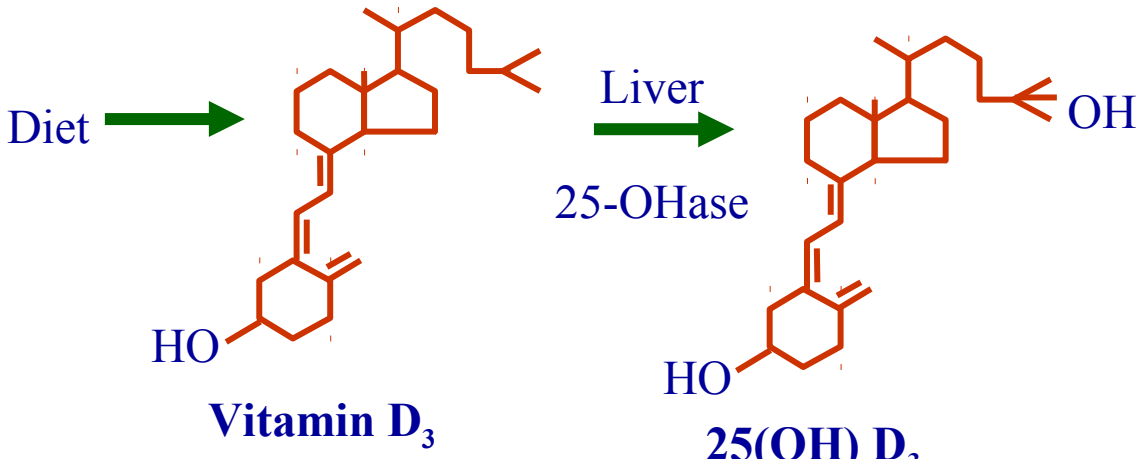
Beware of the hype about taking DHEA

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

Specific receptors in intestine, bone, kidney

Ca:
Intestinal absorption
Renal reabsorption

PO_4:
Intestinal absorption
Renal reabsorption

Photobiosynthesis of vitamin D_3 and its metabolism

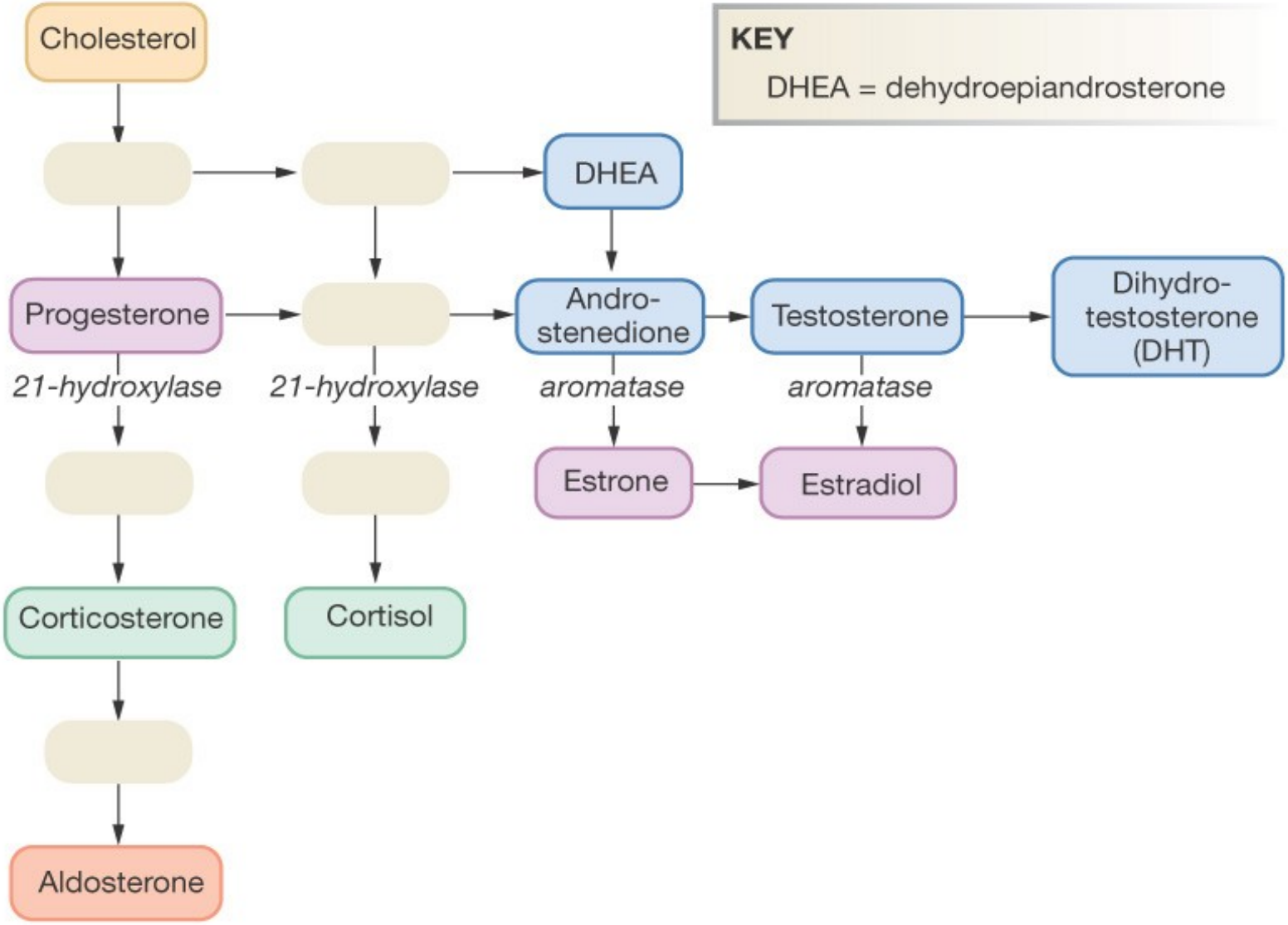
1,25-Dihydroxy Vitamin D3

- 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

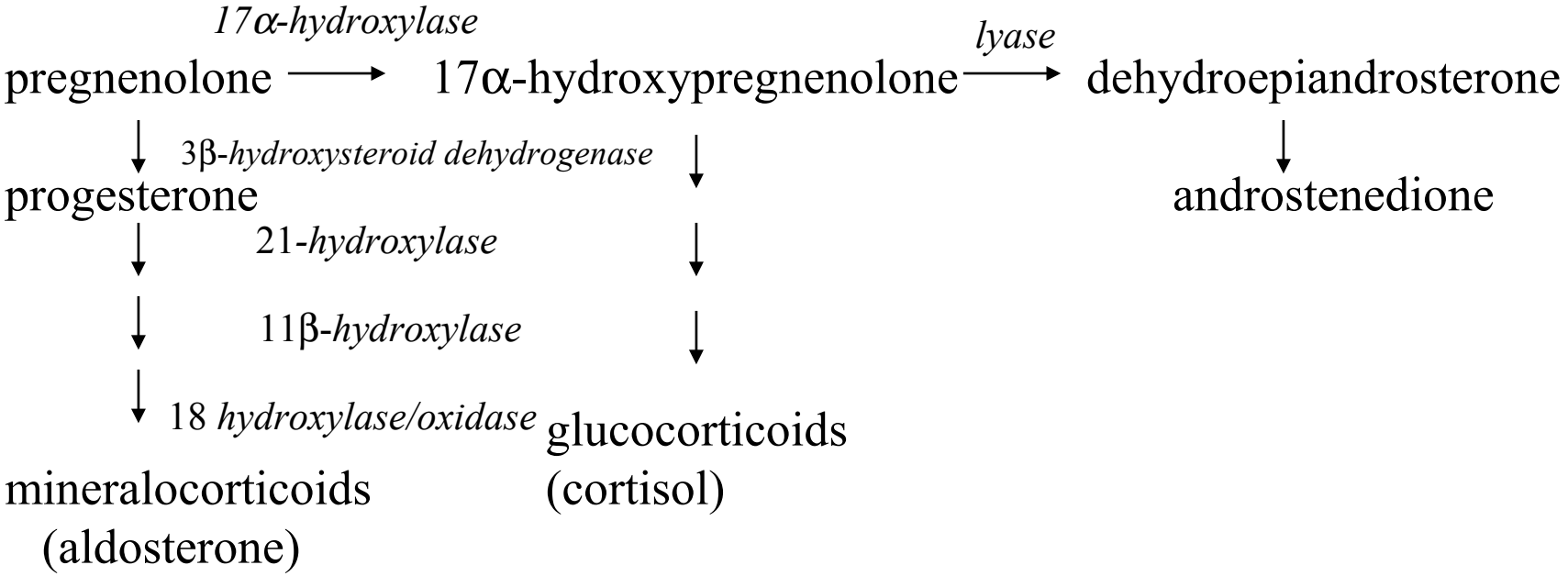
(What's made in the adrenal medulla??)

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 (P450scc; 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

- Next, pregnenolone can be converted into three different pathways, depending upon whether you want to make mineralcorticoids, glucocorticoids, or androgens:



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

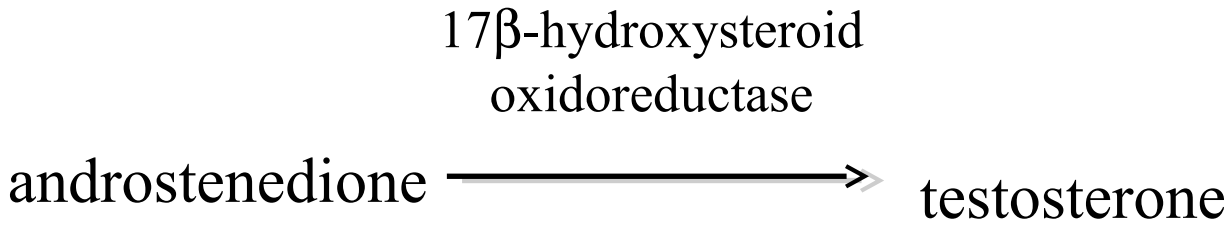
Function of Leydig Cells

- 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.

Ovarian Follicle

- The follicle is the basic functional unit of the ovary.
- It is composed of an oocyte, granulosa cells, and theca cells.

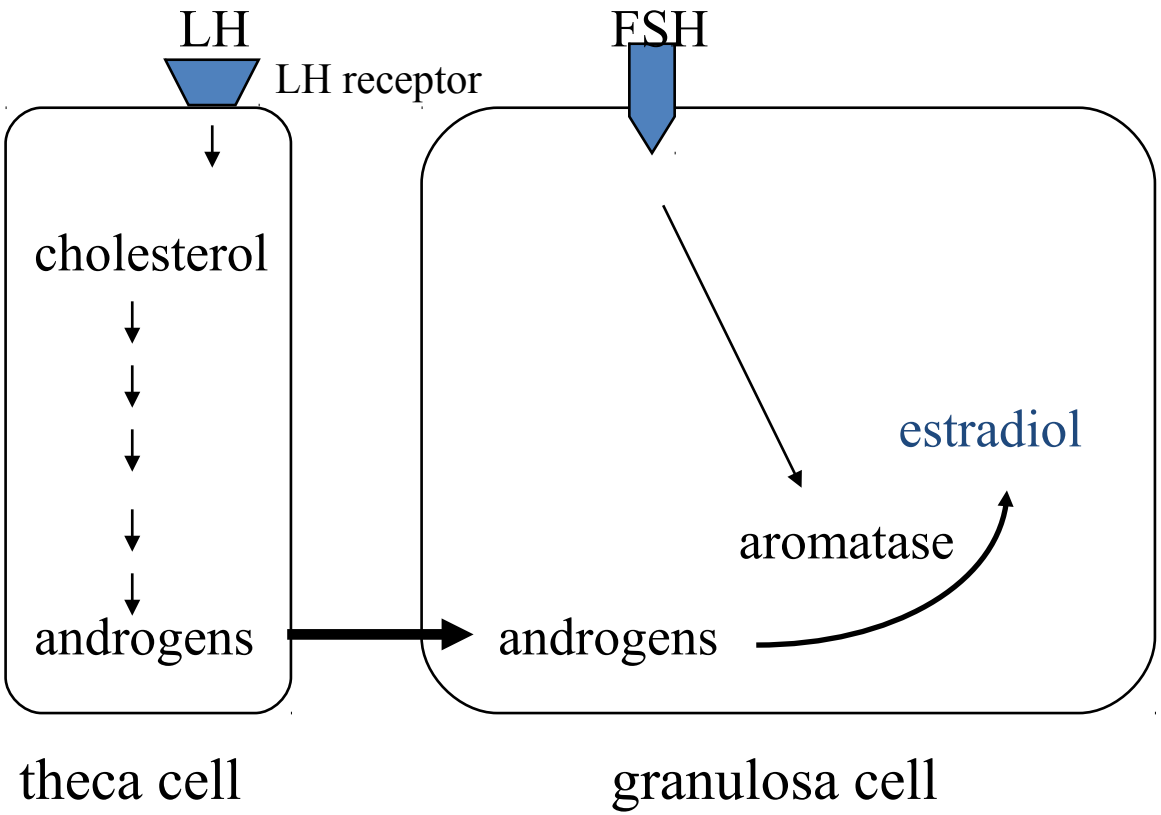
- When the follicle ruptures, it becomes a corpus luteum.

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 P450scc 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

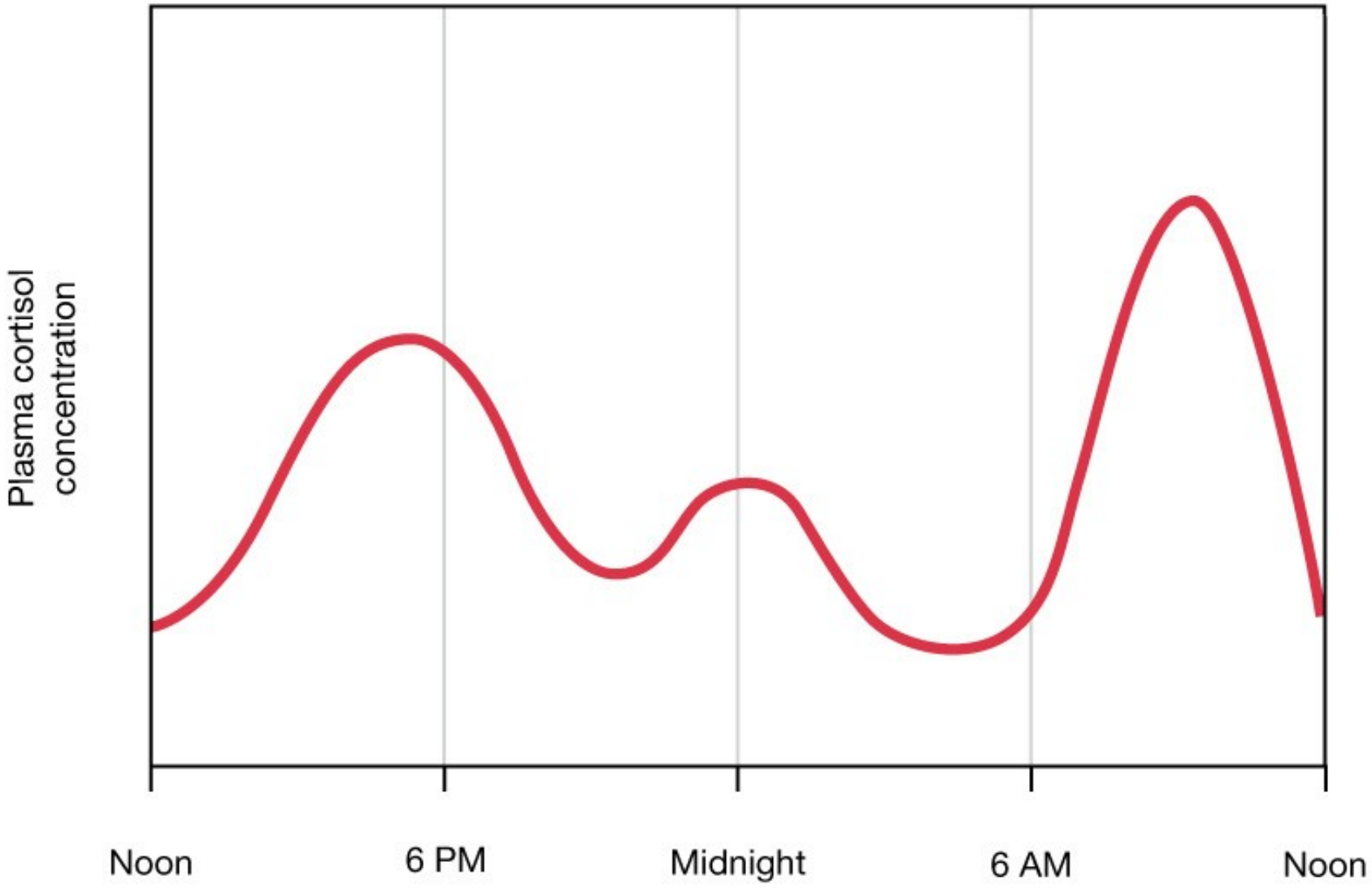


Figure 23-4: Circadian rhythm of cortisol secretion

Control of Cortisol Secretion: Feedback Loops

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

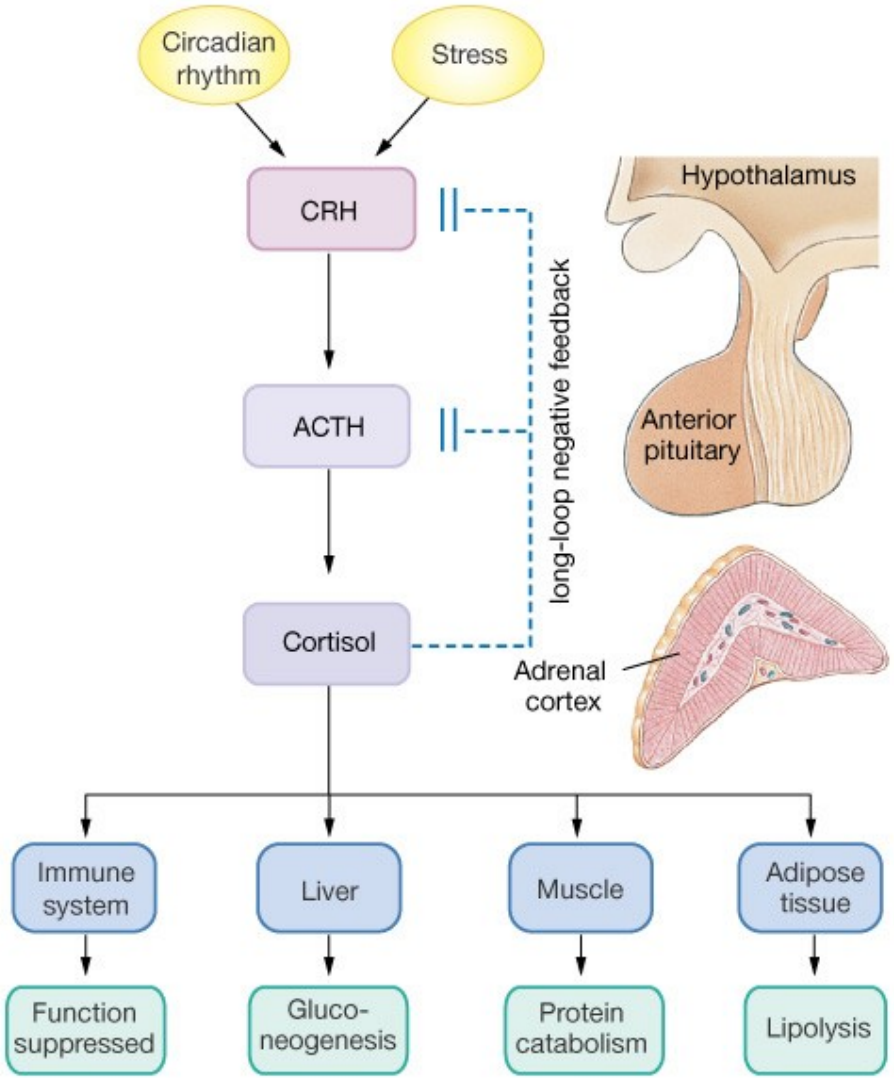


Figure 23-3: The control pathway for cortisol

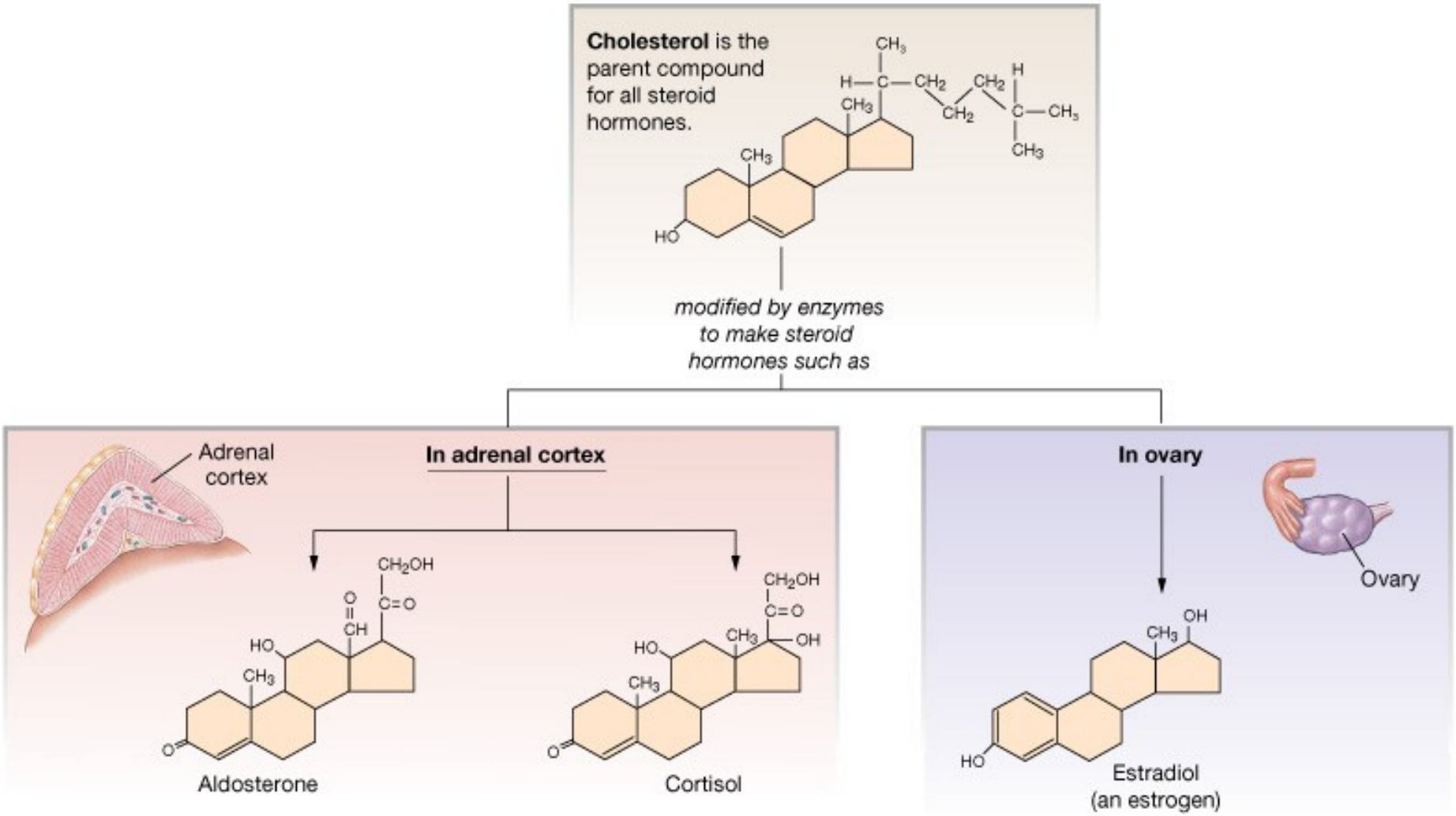
Cortisol: Role in Diseases and Medication

- 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)

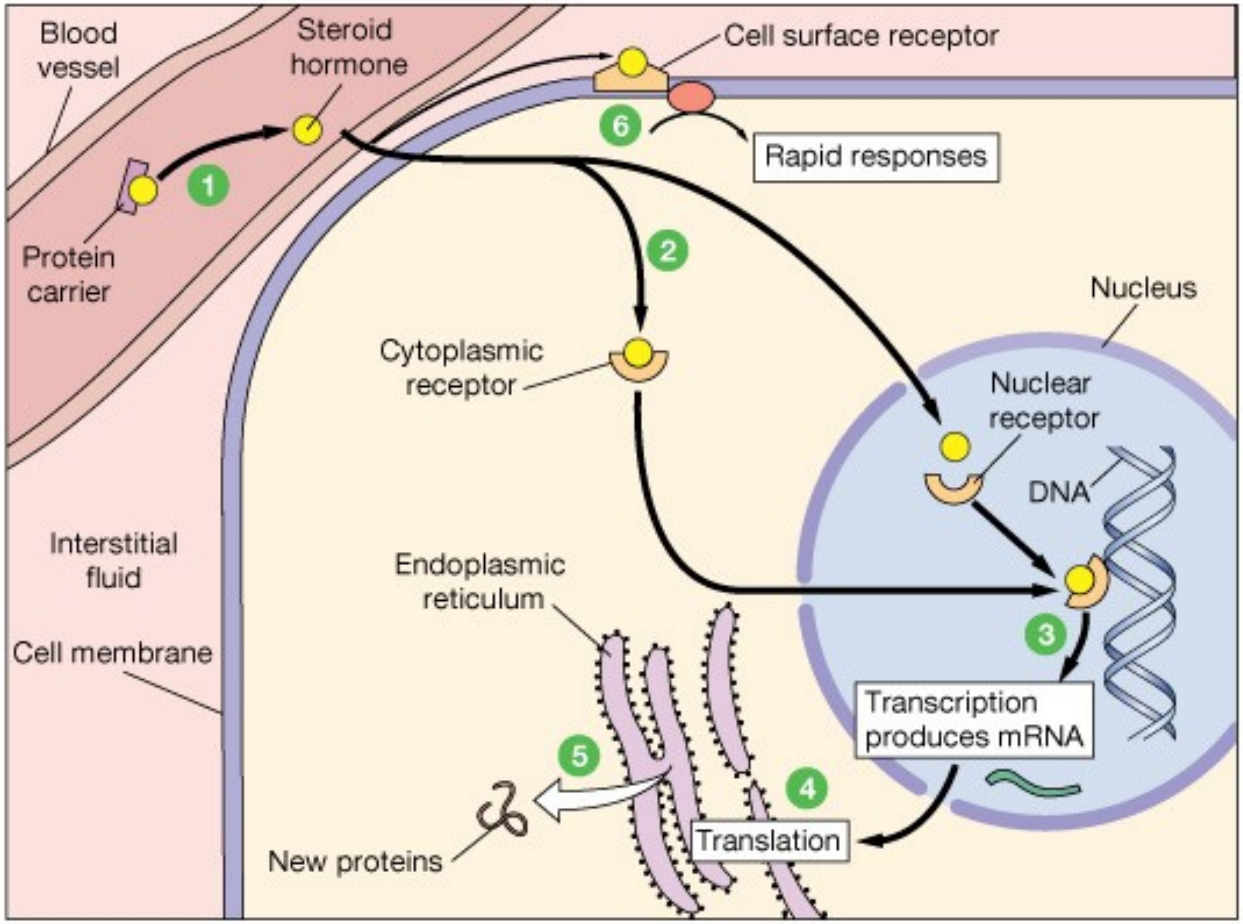
Steroid Hormones: Characteristics

- 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



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.