Endocrine Physiology

The Adrenal Gland
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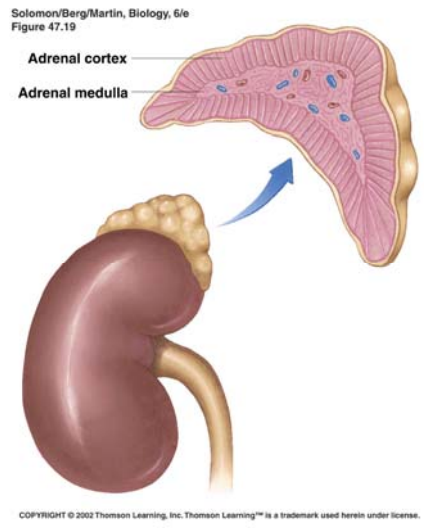


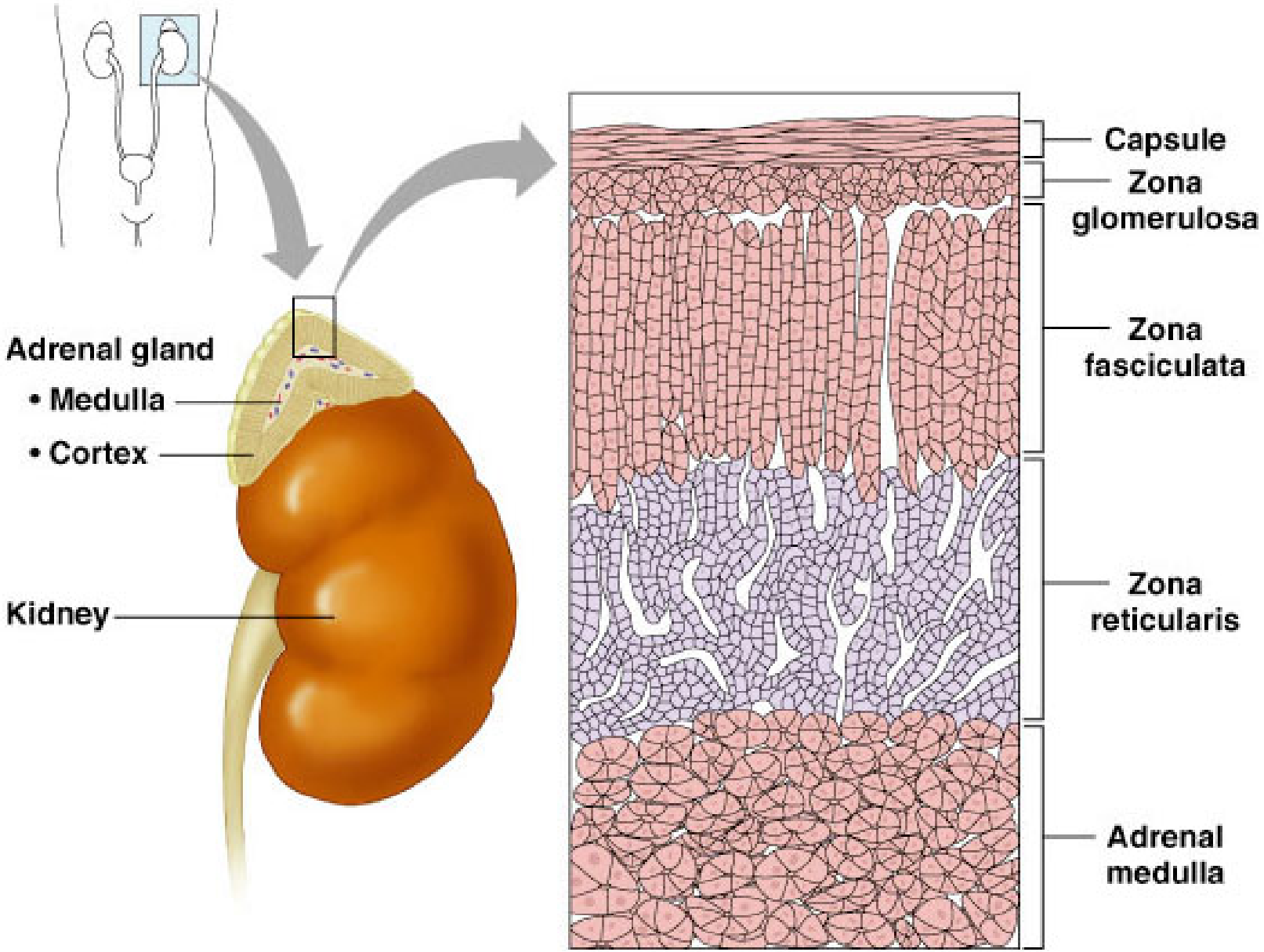
Adrenal (Suprarenal) Glands

- Adrenal glands – paired, pyramid-shaped organs atop the kidneys
- Weigh 6-10 g.
- Structurally and functionally, they are two glands in one
  - **Adrenal cortex** (80-90%)– glandular tissue derived from embryonic mesoderm
  - **Adrenal medulla** (10-20%)– formed from neural ectoderm, can be considered a modified sympathetic ganglion

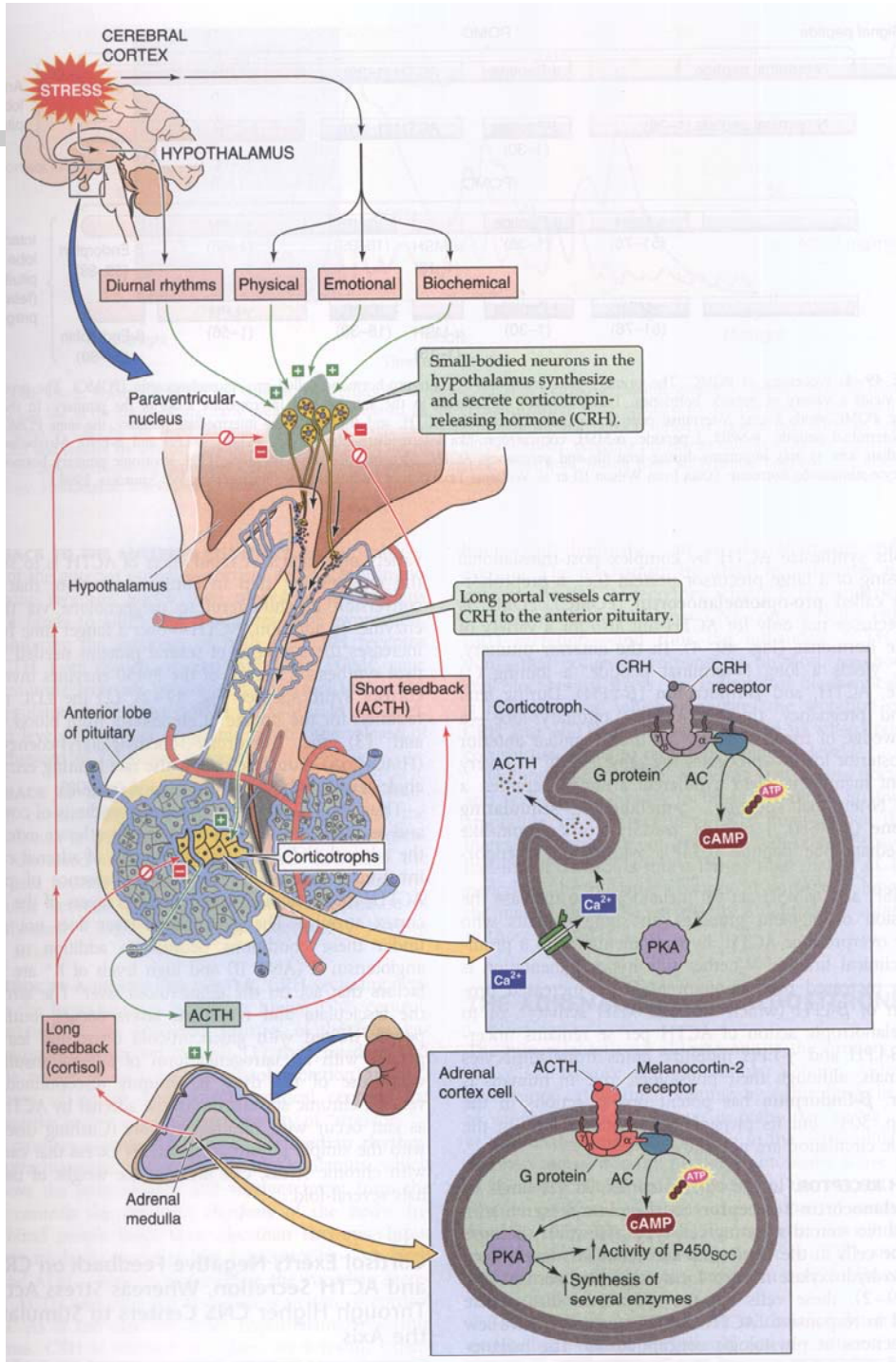
Adrenal Cortex

- Synthesizes and releases steroid hormones (corticosteroids)
- Different corticosteroids are produced in each of the **three layers:**
  - Zona glomerulosa – mineralocorticoids (mainly aldosterone)
  - Zona fasciculata – glucocorticoids +Androgens (mainly cortisol and corticosterone)
  - Zona reticularis – gonadocorticoids + glucocorticoids (mainly dehydroepiandrosterone DHEA)

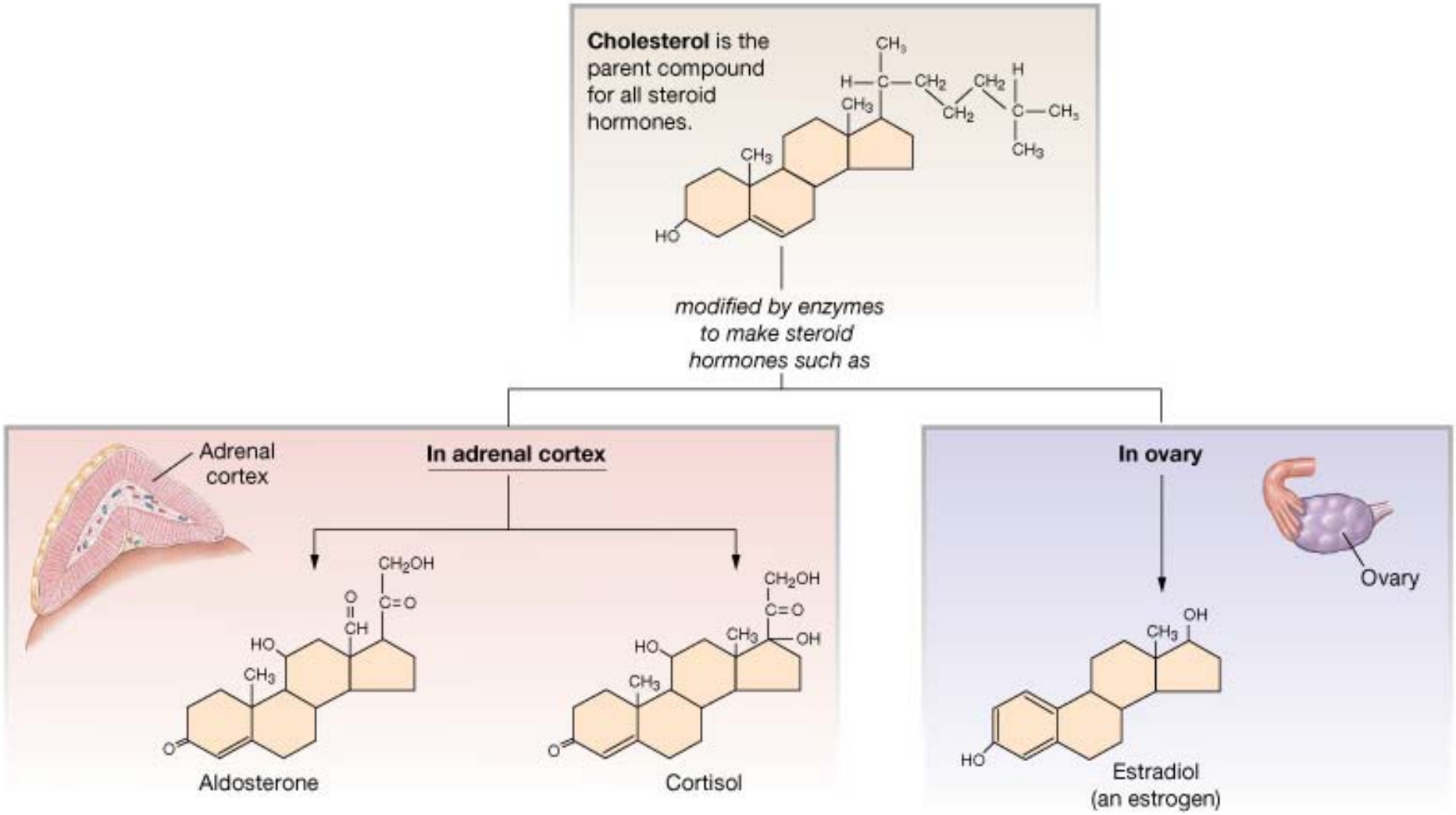
Adrenal Cortex



HPA Axis


CEREBRAL CORTEX
STRESS
HYPOTHALAMUS
Diurnal rhythms
Physical
Emotional
Biochemical
Small-bodied neurons in the hypothalamus synthesize and secrete corticotropin-releasing hormone (CRH).
Paraventricular nucleus
Hypothalamus
Long portal vessels carry CRH to the anterior pituitary.
Short feedback (ACTH)
Anterior lobe of pituitary
Corticotrophs
CRH
CRH receptor
Corticotroph
ACTH
G protein
AC
ATP
cAMP
Ca^{2+}
PKA
Ca^{2+}
ACTH
Long feedback (cortisol)
Adrenal medulla
Adrenal cortex cell
ACTH
Melanocortin-2 receptor
G protein
AC
ATP
cAMP
PKA
↑Activity of $P450_{SCC}$
Synthesis of several enzymes

Steroid Hormones: Structure



Steroid Hormones Synthesis

- Steroids are derivatives of cholesterol
- Cholesterol is from the lipid droplets in cortical cells (**cholesterol esters in LDL**)
- Removed cholesterol is replenished by cholesterol in LDL in blood or synthesized from acetate

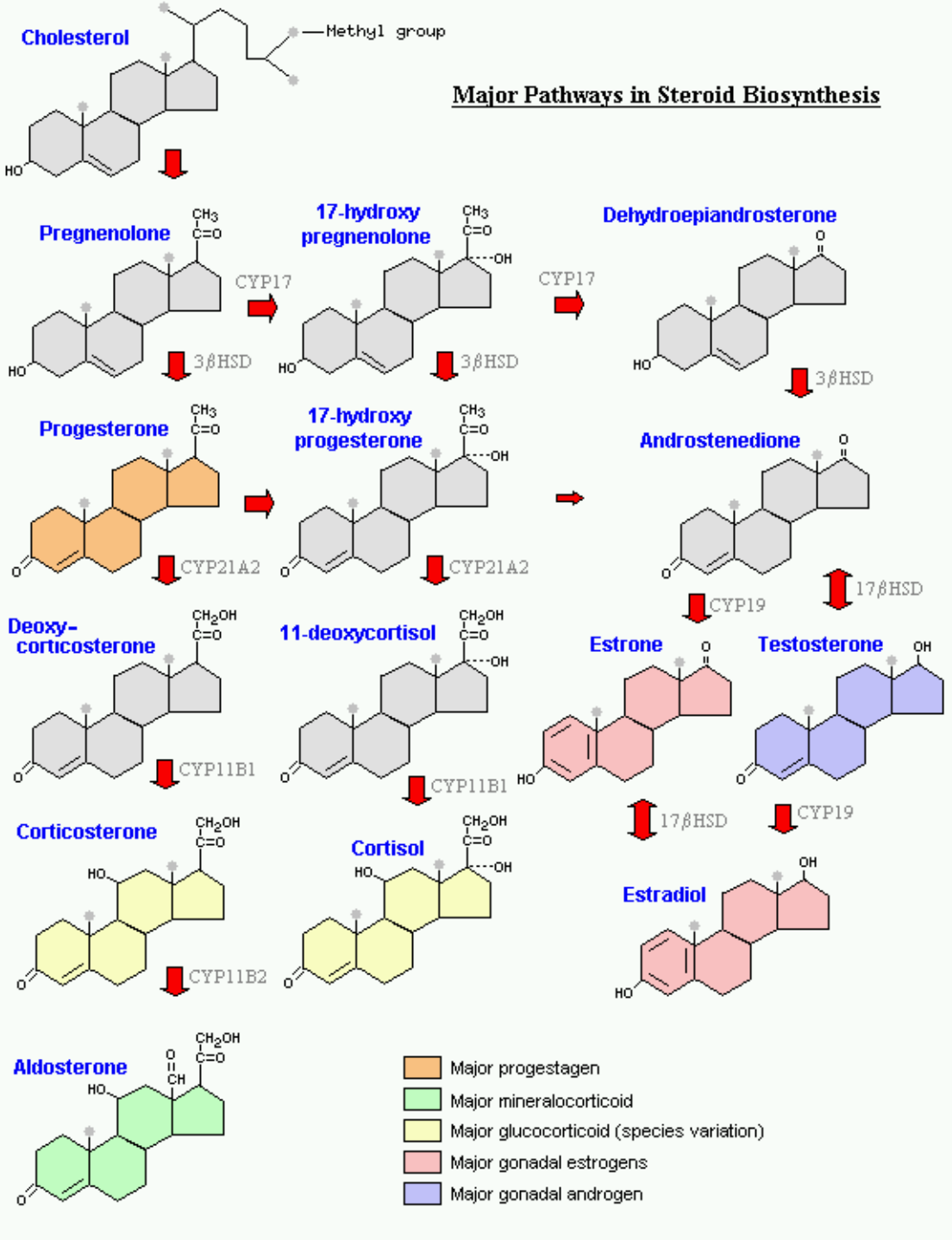
Steroid Hormones Synthesis (Cont.)

- Steroid hormones are synthesized and secreted on demand (not stored)
- The first and rate-limiting step in the synthesis of all steroid hormones is conversion of cholesterol to pregnenolone by the enzyme cholesterol dismolase (aka cholesterol side chain cleavage (SCC) enzyme
- Newly synthesized steroid hormones are rapidly secreted from the cell
- Following secretion, all steroids bind to some extent to plasma proteins: CBG and albumin

Enzymes in Steroid Biosynthesis

- Side-chain cleavage enzyme; desmolase (P450scc)
- 3 β-hydroxysteroid dehydrogenase (3 β HSD)
- 17 α-hydroxylase/17,20 lyase (P450 c17): Adrenarche

  * not present in glumerulosa cells
- 21-hydroxylase (P450c21)
- 11 beta-hydroxylase (P450c11)
- Aldosterone synthase


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
CYP19
17βHSD
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

Genetic Defects in Adrenal Steroidogenesis

- Congenital adrenal hyperplasia

cortisol ⇩ ⟶ *ACTH* ⇧ ⟶ *Adrenal hyperplasia*

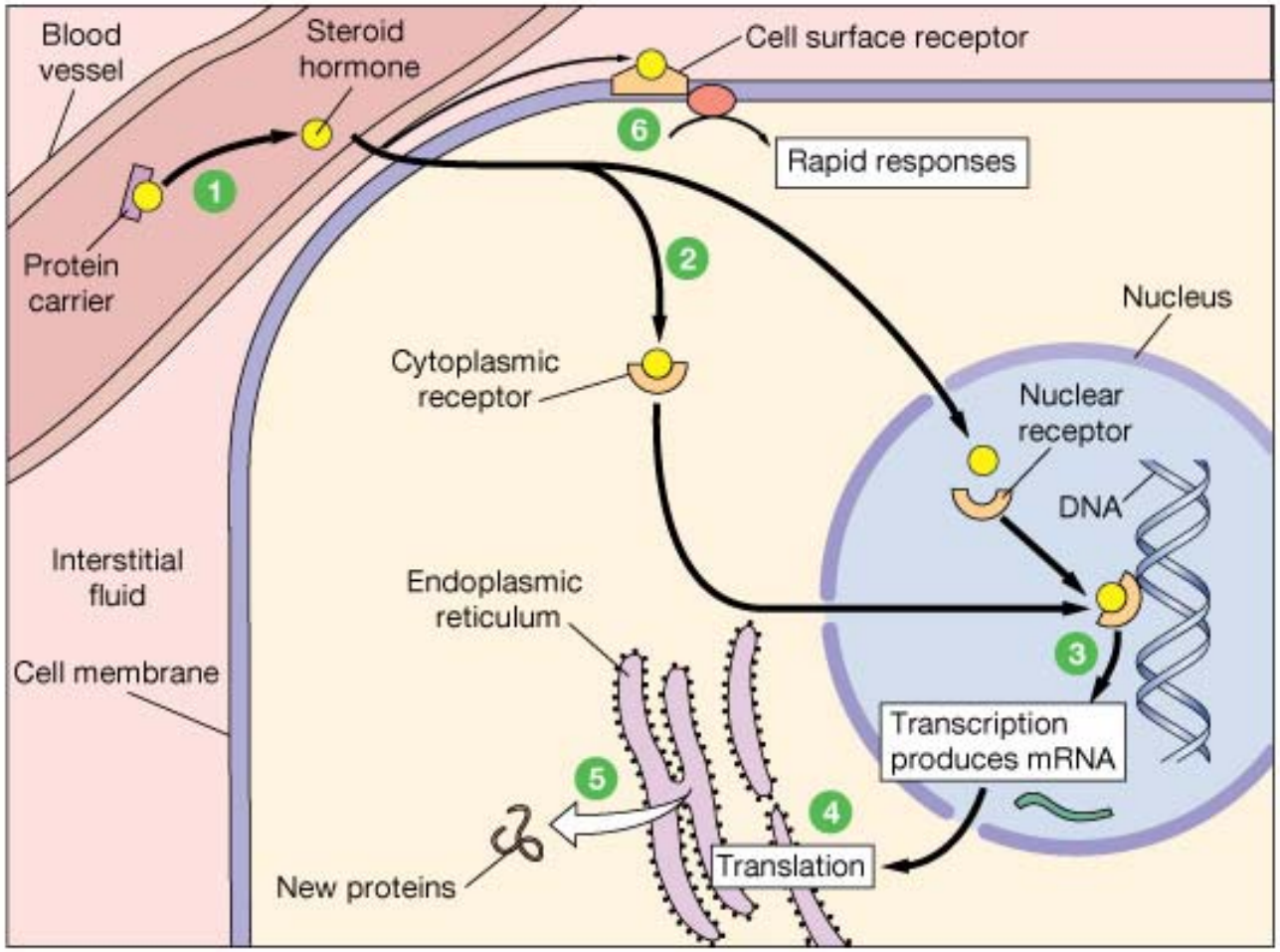
- 21-hydroxylase (P450c21) deficiency:

cortisol, corticosterone, and aldosterone deficiency

*ACTH ⇧ ⟶ Adrenal hypertrophy and high amounts of androgen

* **Virilization** of female (masculanization)

Steroid Hormones: 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.

Mineralocorticoids

- Synthesized in zona glomerulosa
- Regulate the electrolyte concentrations of extracellular fluids
- **Aldosterone** – most important mineralocorticoid
  - Maintains Na^+ balance by reducing excretion of sodium from the body
  - Stimulates reabsorption of Na^+ by the kidneys and K+ excretion

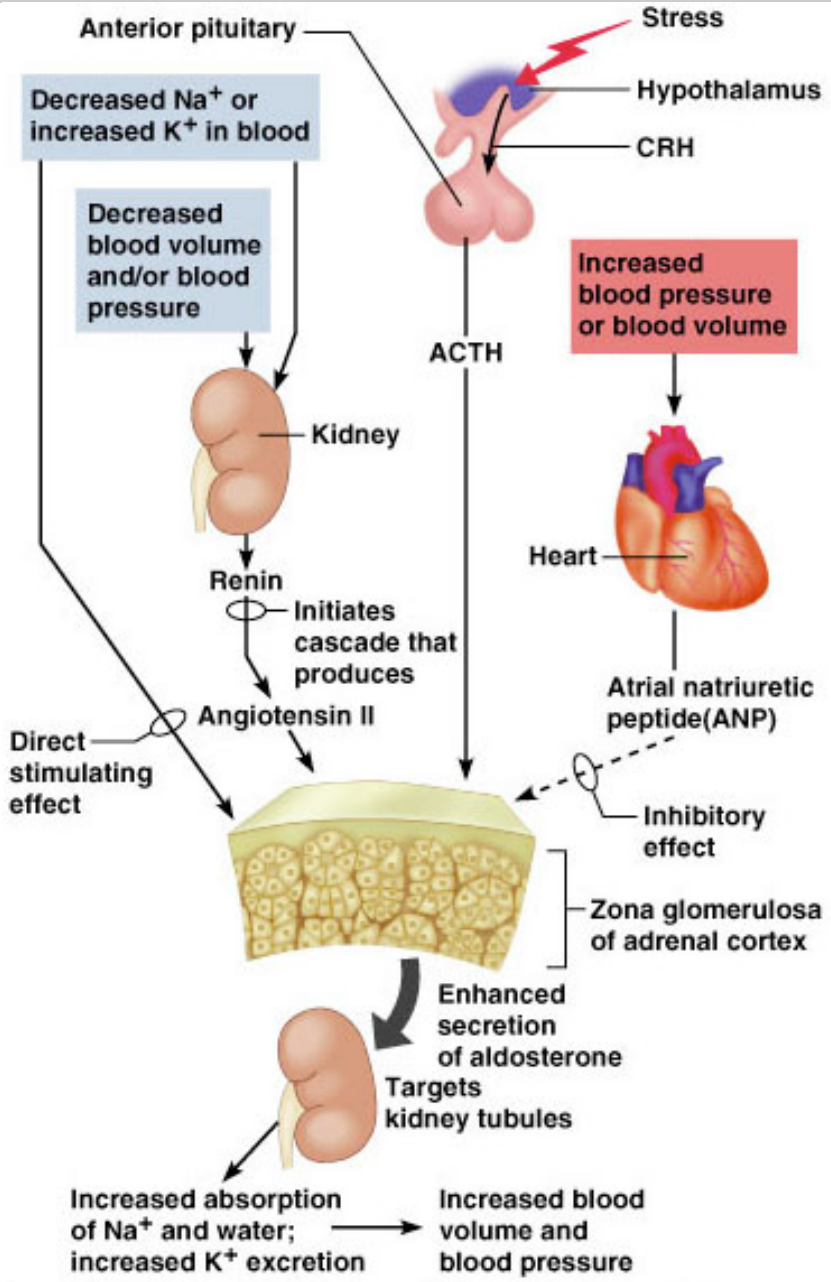
Mineralocorticoids

- Aldosterone secretion is stimulated by:
  - Decreasing blood volume or pressure (renin-angeotensin system) is the major stimulant
  - Low blood Na^+
  - Rising blood levels of K^+
  - ACTH

The Four Mechanisms of Aldosterone Secretion

- Renin-angiotensin mechanism – kidneys release renin, which is converted into **angiotensin II** that in turn stimulates aldosterone release
- Plasma concentration of sodium and potassium – directly influences the zona glomerulosa cells
- ACTH – causes small increases of aldosterone during stress
- Atrial natriuretic peptide (ANP) – inhibits activity of the zona glomerulosa

The Four Mechanisms of Aldosterone Secretion



Actions of Aldosterone

Stimulates sodium reabsorption by distal tubule and collecting duct of the nephron and promotes potassium and hydrogen ion excretion

- Increases transcription of Na/K pump
- Increases the expression of apical Na channels and an Na/K/Cl cotransporter

- Expands ECF volume

Aldosterone: Role in diseases

- Complete failure to secrete aldosterone leads to death (dehydration, low blood volume).

- Hyperalsdosterone states: Contribute to hypertension associated with increased blood volume.

Overproduction of aldosterone

- primary causes, ie. Conn's syndrome
  - adenoma, nodular hyperplasia of zona glomerulosa
- secondary
  - cirrhosis, ascites, nephrotic syndrome
- symptoms, signs
  - headache, hypokalemia causing muscle weakness, hypernatremia, hypervolemia, nocturnal polyuria, hand cramping

Overproduction of aldosterone

- treatment
  - surgical for adenoma
  - medical for hyperplasia with Spironolactone