Endocrine Physiology

The Adrenal Gland
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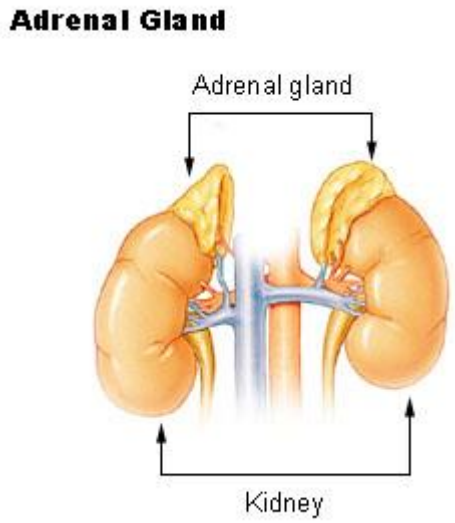


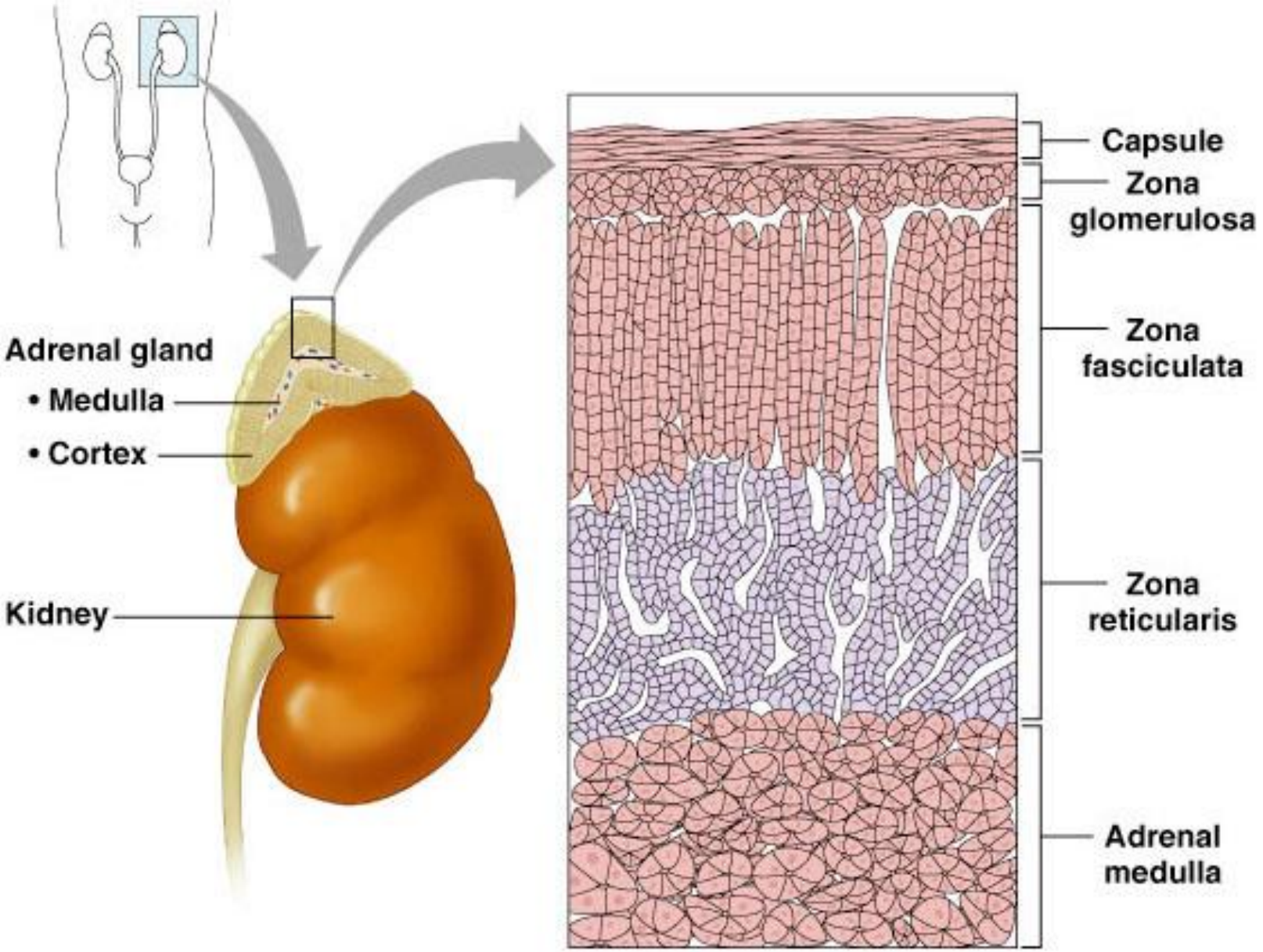
Adrenal (Suprarenal) Glands

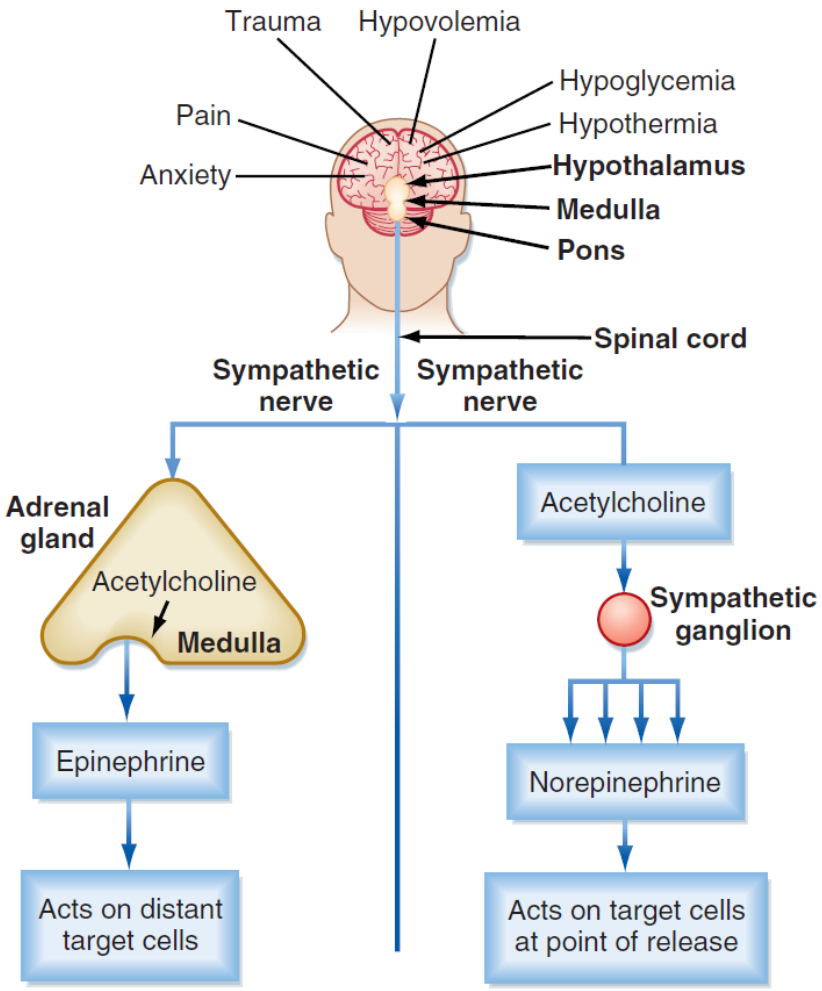
- Adrenal glands – paired, pyramid-shaped organs atop the kidneys
- Weigh 4-10 g.
- Structurally and functionally, they are two glands in one
  - **Adrenal cortex** (80-90%)– glandular tissue derived from embryonic mesoderm
  - **Adrenal medulla** (10-20%)– formed from neural ectoderm, can be considered a modified sympathetic ganglion

Adrenal Cortex

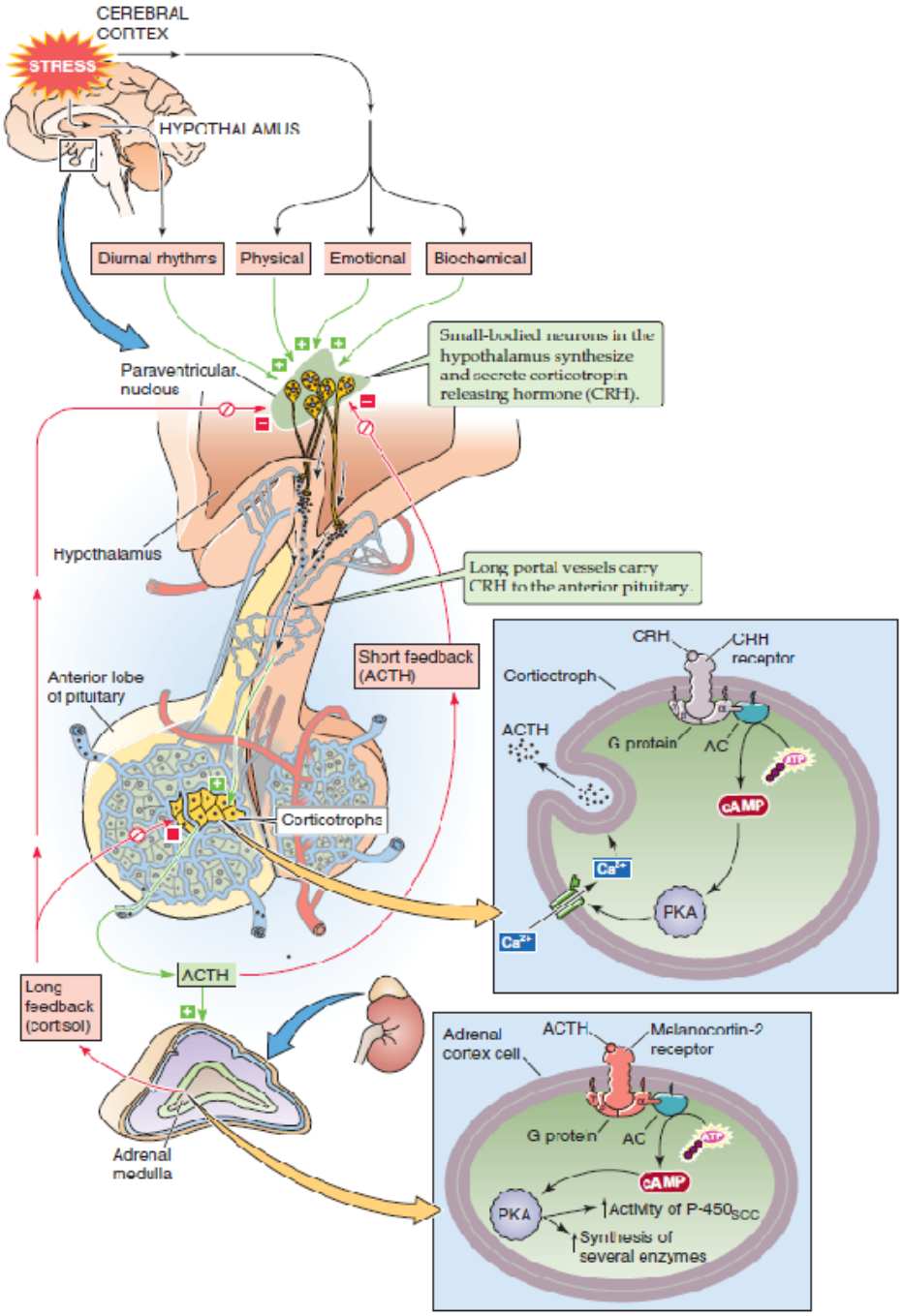
- Synthesizes and releases steroid hormones (corticosteroids)
- Different corticosteroids are produced in each of the **three layers:**
  - Zona glomerulosa – mineralocorticoids (mainly aldosterone)
  - Zona fasciculata – glucocorticoids +Androgens (mainly cortisol and corticosterone)
  - Zona reticularis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

Adrenal Cortex

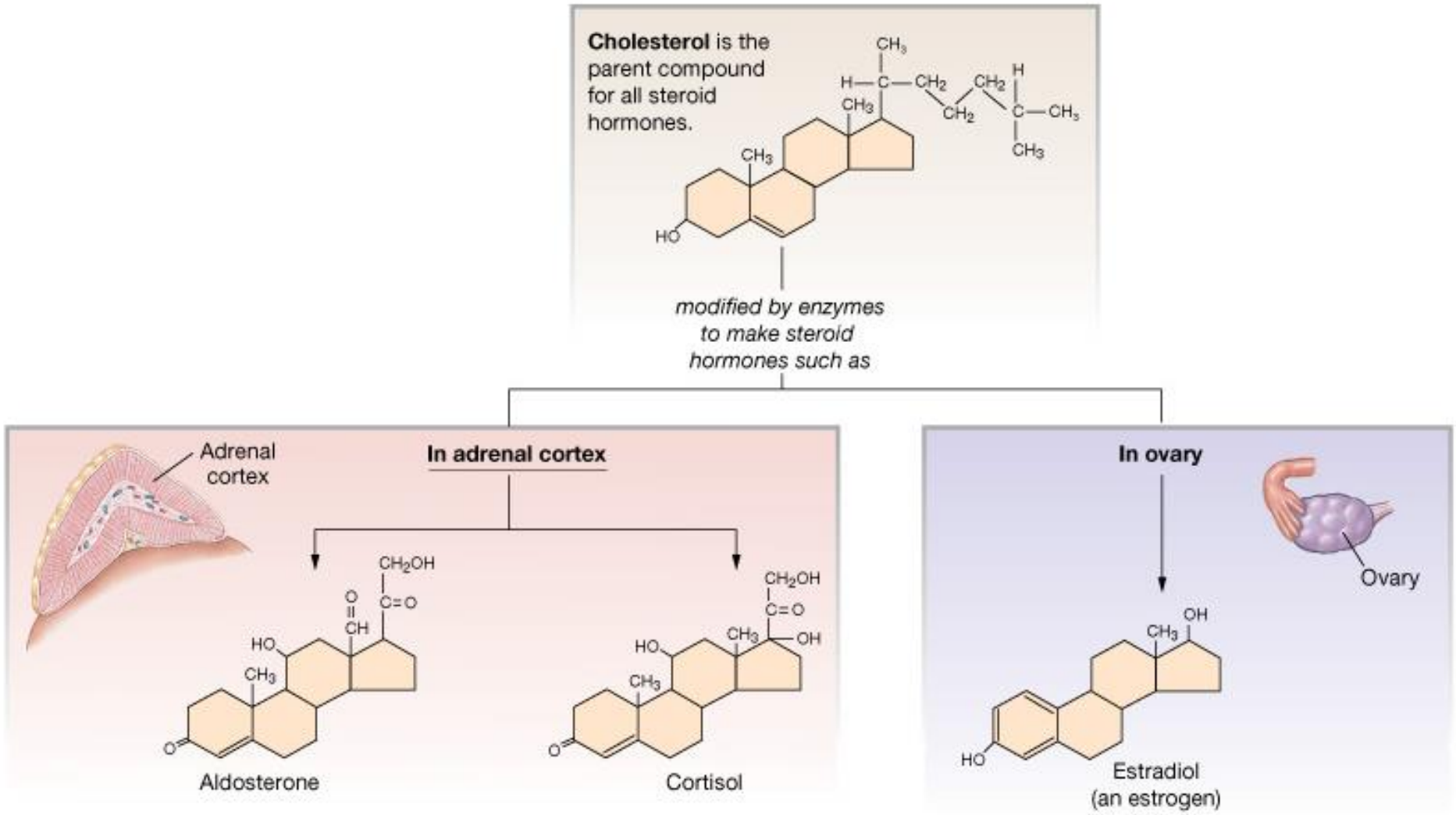



Trauma
Hypovolemia
Hypoglycemia
Pain
Hypothermia
Anxiety
Hypothalamus
Medulla
Pons
Spinal cord
Sympathetic nerve
Sympathetic nerve
Adrenal gland
Acetylcholine
Medulla
Epinephrine
Acts on distant target cells
Acetylcholine
Sympathetic ganglion
Norepinephrine
Acts on target cells at point of release

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
ACTH
Long feedback (cortisol)
Adrenal medulla
CRH
CRH receptor
Corticotroph
ACTH
G protein
AC
ATP
cAMP
Ca2+
PKA
Adrenal cortex cell
ACTH
Melanocortin-2 receptor
G protein
AC
ATP
cAMP
PKA
↑Activity of P-450SCC
↑Synthesis of several enzymes

Steroid Hormones: Structure



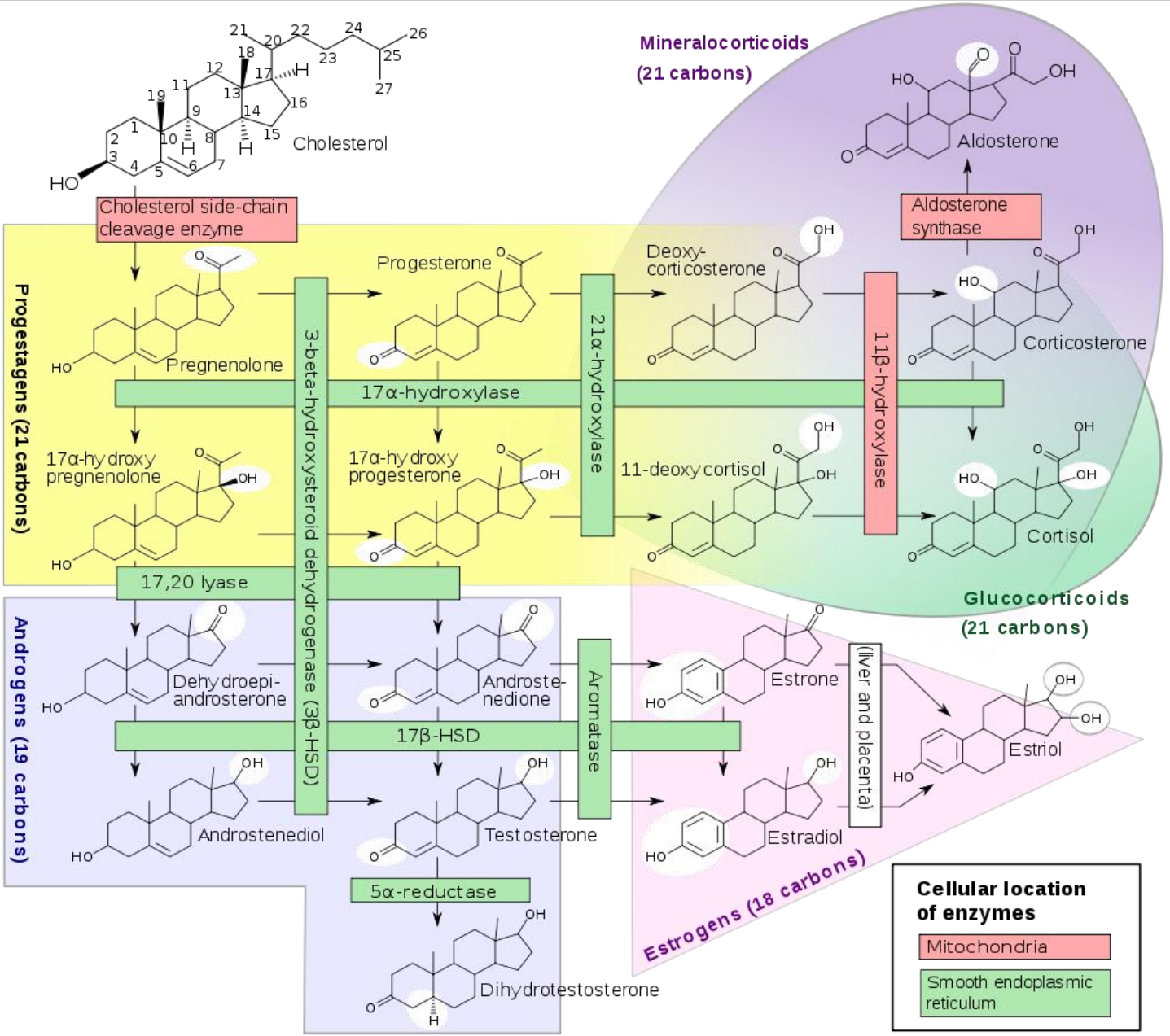
Steroid Hormones Synthesis

- 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
- Steroidogenic Acute regulatory protein **(StAR protein)** transfers cholesterol to the inner membrane of the mitochondria (mutation causes accumulation of cholesterol in the cytoplasm).

Steroid Hormones Synthesis (Cont.)

- Steroid hormones are synthesized and secreted on demand (not stored)
- The first 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

Steroidogenesis



Genetic Defects in Adrenal Steroidogenesis

- **Congenital adrenal hyperplasia**

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

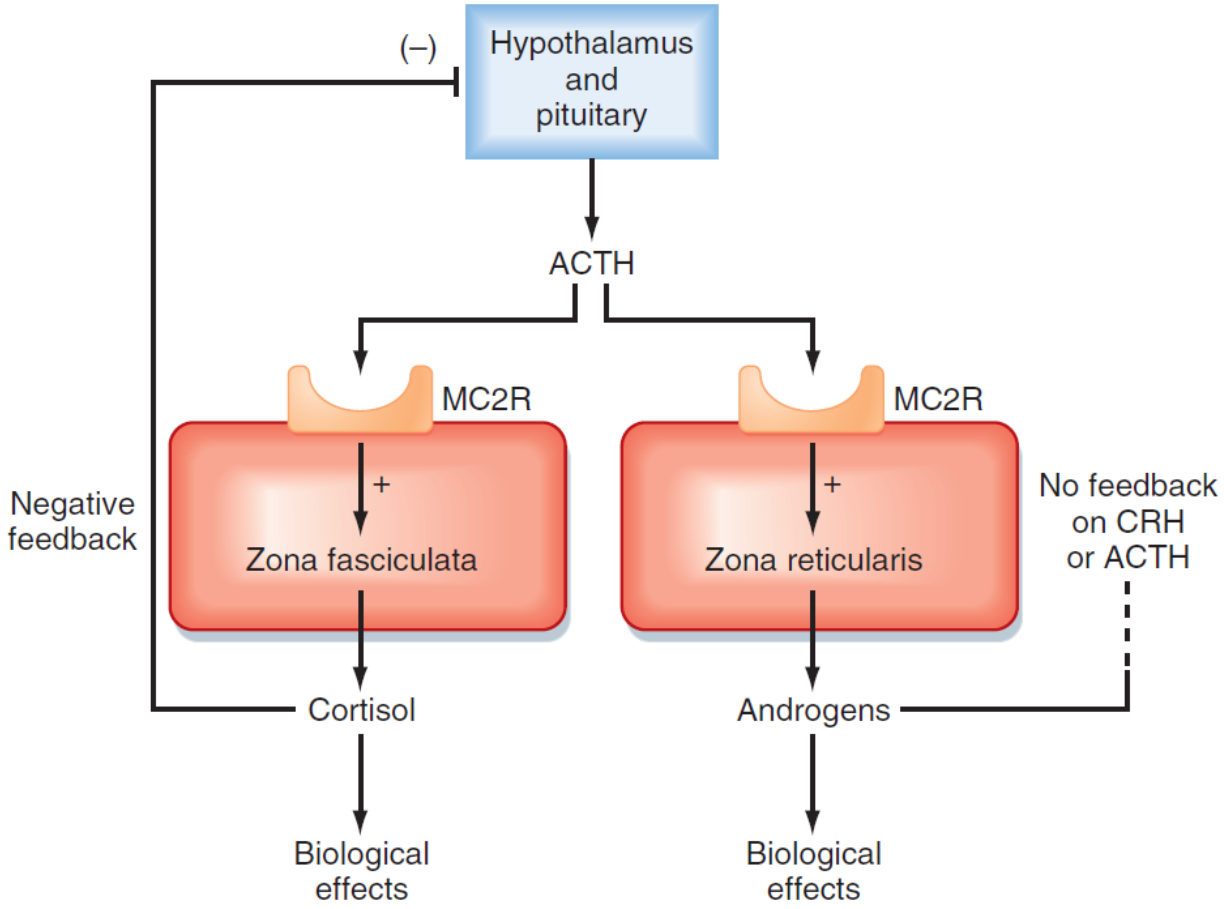
- 21-hydroxylase (P450c21) deficiency:

cortisol, corticosterone, and aldosterone deficiency

*ACTH ⇧ ⟶ Adrenal hypertrophy and high amounts of androgen

* **Virilization** of female (masculanization)

Loophole in the Negative Feedback



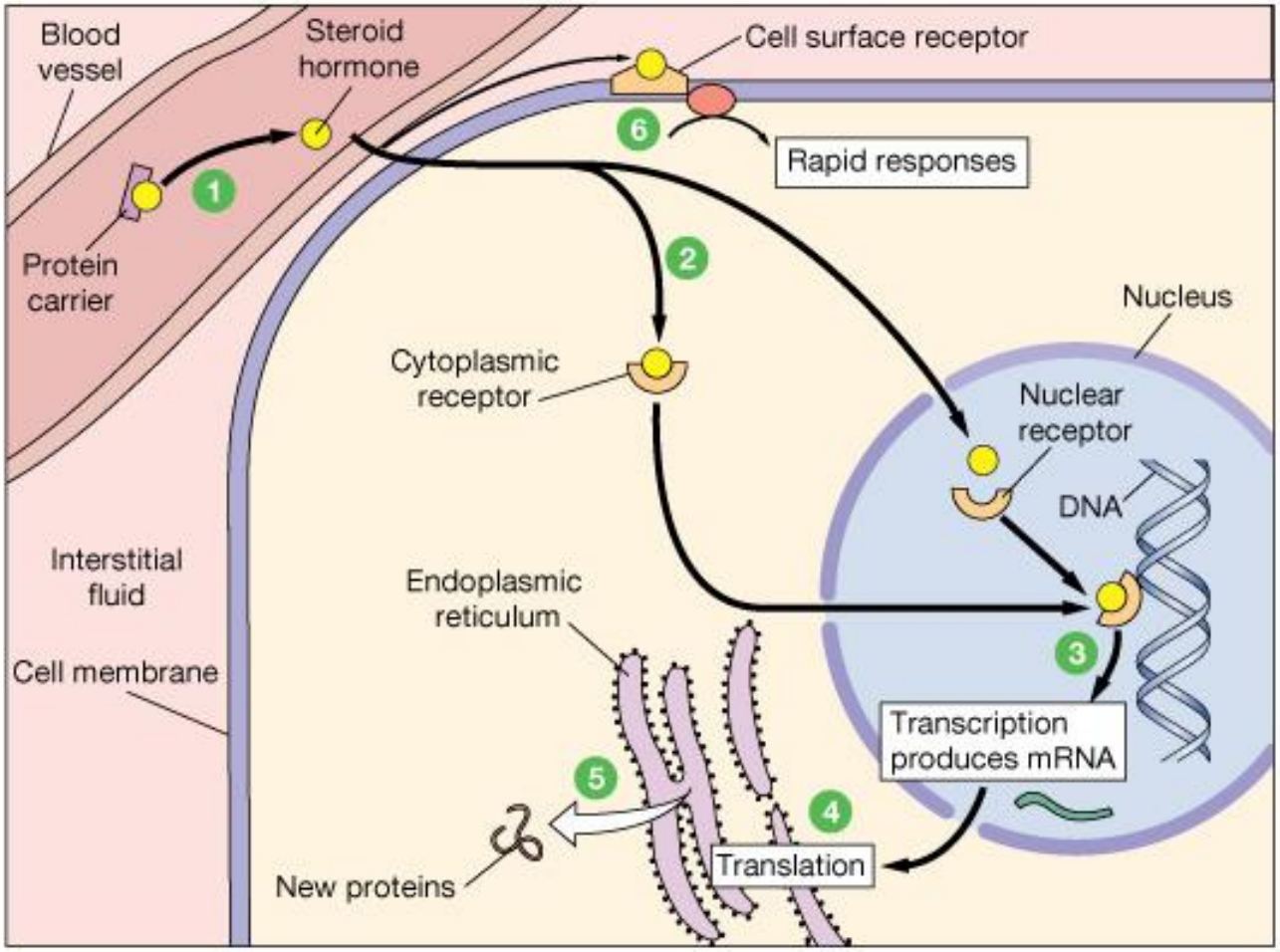
Minerlaocorticoid vs. Glucocorticoid Potency

TABLE 43.3 **Relative Glucocorticoid and Mineralocorticoid Potency of Natural Corticosteroids and Some Synthetic Analogues in Clinical Use**[a]

	Glucocorticoid	Mineralocorticoid
Corticosterone	0.5	1.5
Prednisone (1.2 double bond)	4	<0.1
6α-Methylprednisone (Medrol)	5	<0.1
9α-Fluoro-16α-hydroxyprednisolone (triamcinolone)	5	<0.1
9α-Fluoro-16α-methylprednisolone (dexamethasone)	30	<0.1
Aldosterone	0.25	500
Deoxycorticosterone	0.01	30
9α-Fluorocortisol	10	500

[a]All values are relative to the glucocorticoid and mineralocorticoid potencies of cortisol, which have each been arbitrarily set at 1.0. Cortisol actually has only 1/500 the potency of the natural mineralocorticoid aldosterone.

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:

Aldosterone

Mineralocorticoids: Aldosterone

- A steroid hormone.
- Essential for life.
- Synthesized in zona glomerulosa
- Responsible for regulating Na^+ reabsorption in the distal tubule and the cortical collecting duct
- It also affects Na+ reabsorption by sweat, salivary and intestinal cells.

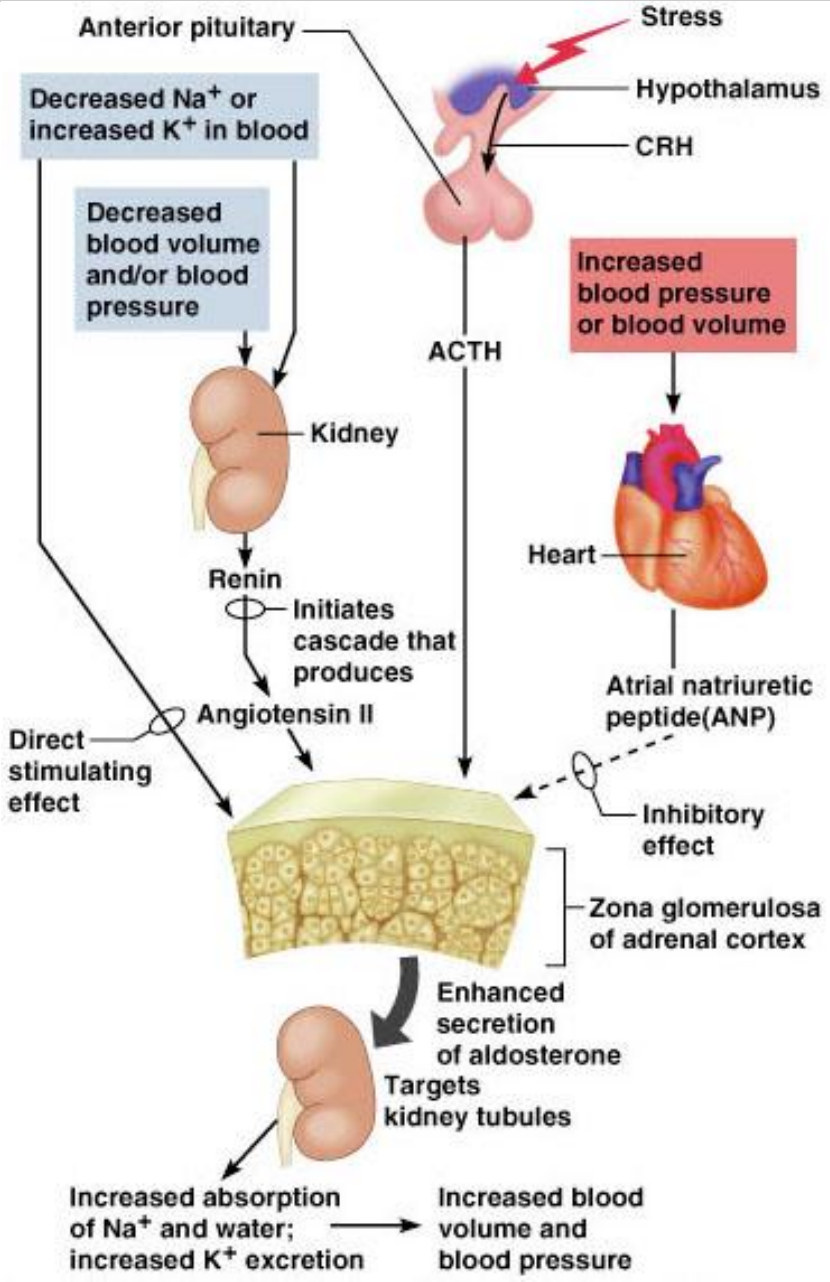
Mineralocorticoids

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

The Four Mechanisms of Aldosterone Secretion

- **Renin-Angiotensin System (RAS),** hypovolemia
- **Hyperkalemia**: Plasma concentration of 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 and reduces aldosterone

The Four Mechanisms of Aldosterone Secretion



Transport and Metabolism of Aldosterone

- Aldosterone binds to albumin and corticosteroid-binding protein in blood with low affinity and therefore has a biological half-life of about 20 minutes.
- Aldosterone is inactivated by the liver and conjugated to a glucuronic acid or sulfate and secreted in bile or excreted by the kidney.

Actions of Aldosterone

Binds to mineralocorticoid receptor [MR]

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 (basolateral)
- Increases the expression of apical Na channels and Na/Cl cotransporters (NCC)
- Stimulates the secretion of K^+ into the tubular lumen
- Stimulates secretion of H^+ via the H+/ATPase by the intercalated cells of the cortical collecting tubule

Actions of Aldosterone

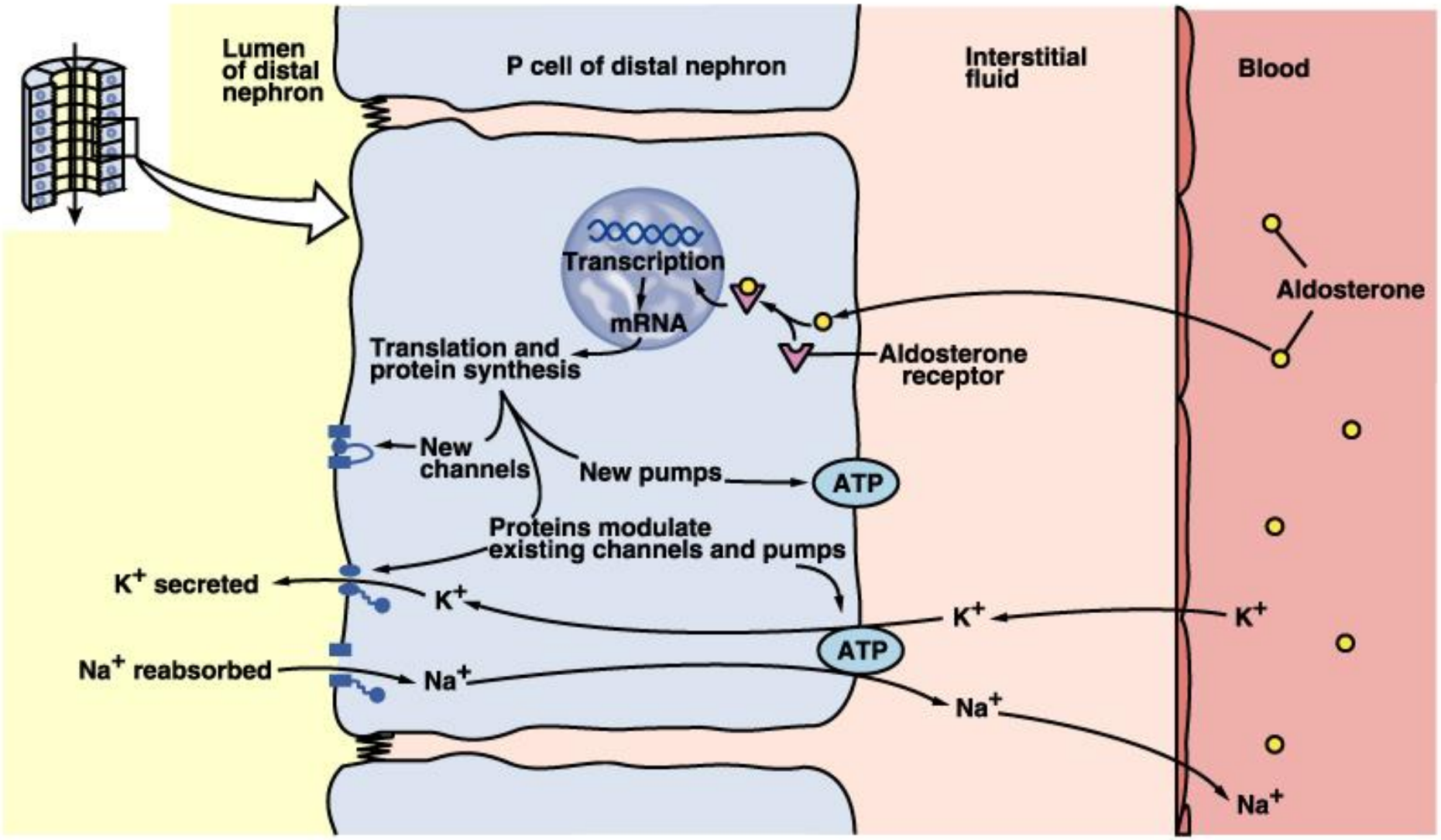
- Aldosterone increases extracellular fluid volume and arterial pressure but has only a small effect on plasma sodium concentration.

(water is also absorbed, ADH is secreted)

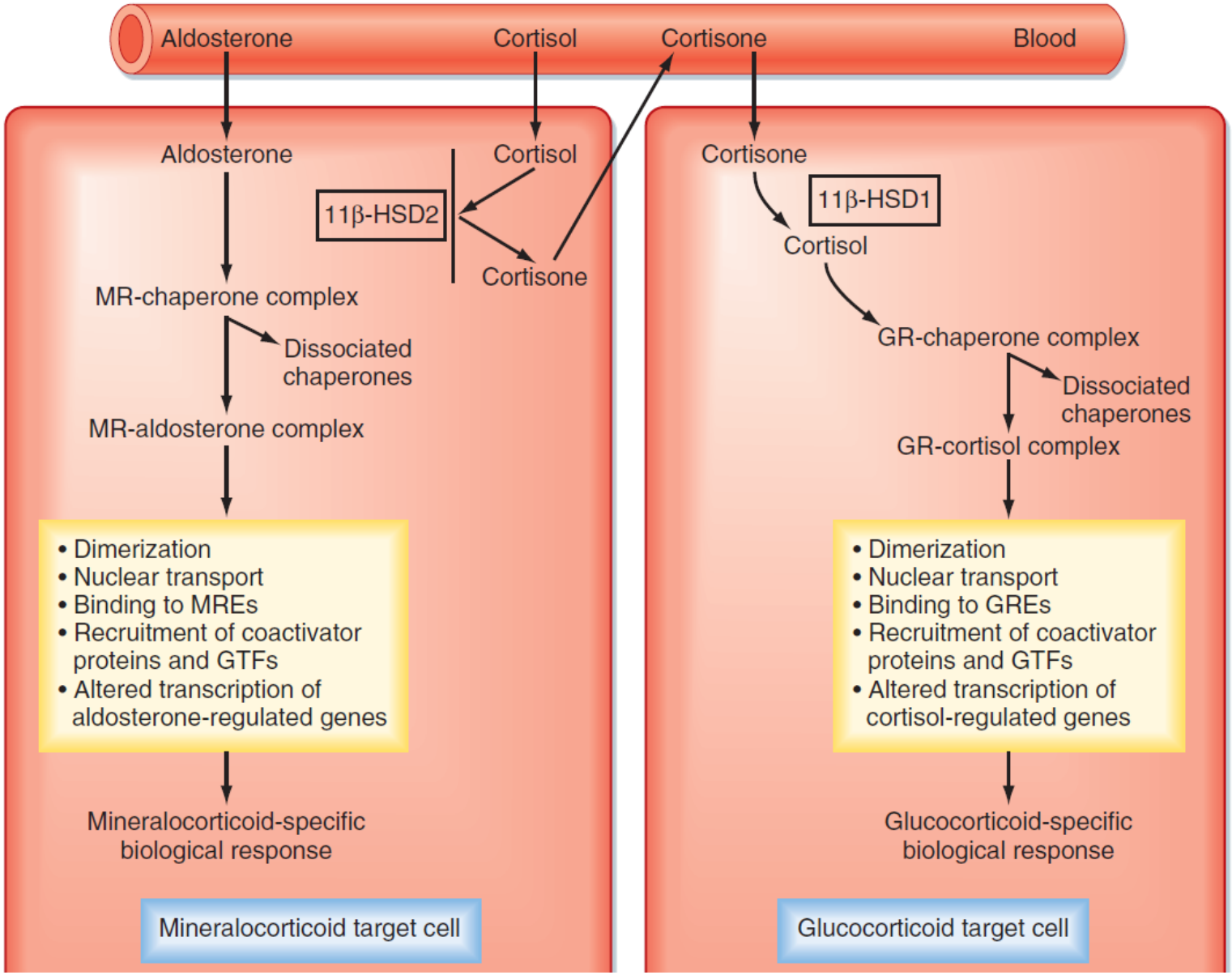
- Excess aldosterone not only causes loss of potassium ions from the extracellular fluid into the urine but also stimulates transport of potassium from the extracellular fluid into most cells of the body.
- Excess Aldosterone Increases Tubular Hydrogen Ion Secretion and Causes Alkalosis.

Actions of Aldosterone

- Aldosterone has the same effects on sweat glands and salivary glands as it has on the renal tubules, reabsorption of Na^+ and Cl^- and excretion of K^+
- Aldosterone also greatly enhances sodium absorption by the intestines, especially in the colon


Lumen of distal nephron
P cell of distal nephron
Interstitial fluid
Blood
Transcription
mRNA
Translation and protein synthesis
Aldosterone receptor
Aldosterone
New channels
New pumps
ATP
Proteins modulate existing channels and pumps
K+ secreted
K+
K+
K+
ATP
Na+ reabsorbed
Na+
Na+
Na+

Mineralocorticoid Receptor and Cortisol



Aldosterone: Role in diseases

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

- Hyperaldosterone 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
  - left ventricular failure, cor pulmonale, cirrhosis, ascites, hyperreninism
- *Apparent mineralocorticoid excess syndrome* (AME) (cortisol binds MR)
- symptoms, signs
  - headache, hypokalemia causing muscle weakness, hypernatremia, hypervolemia, metabolic alkalosis, nocturnal polyuria, hand cramping

Overproduction of aldosterone

- treatment
  - surgical for adenoma
  - Spironolactone, a potassium-sparing diuretic that acts as an aldosterone antagonist.