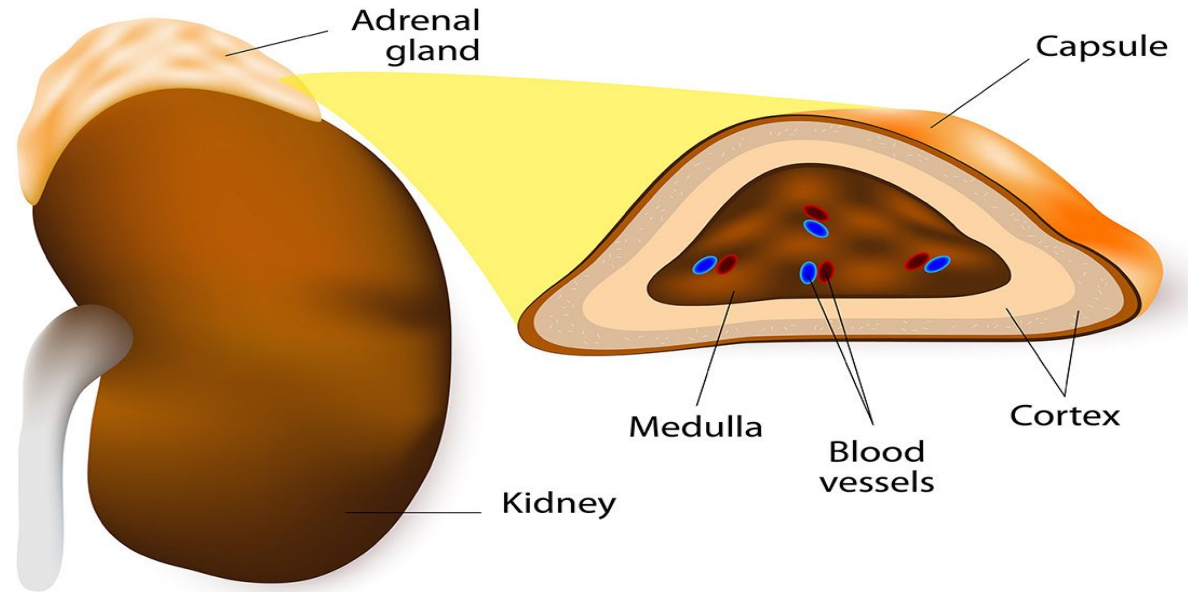


ADRENAL GLAND



PHYSIOLOGY LAB – ADRENAL GLANDS

ROLA ALWAHEIDI, MD

ADRENAL GLAND

- 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 ganglia.



ADRENAL CORTEX

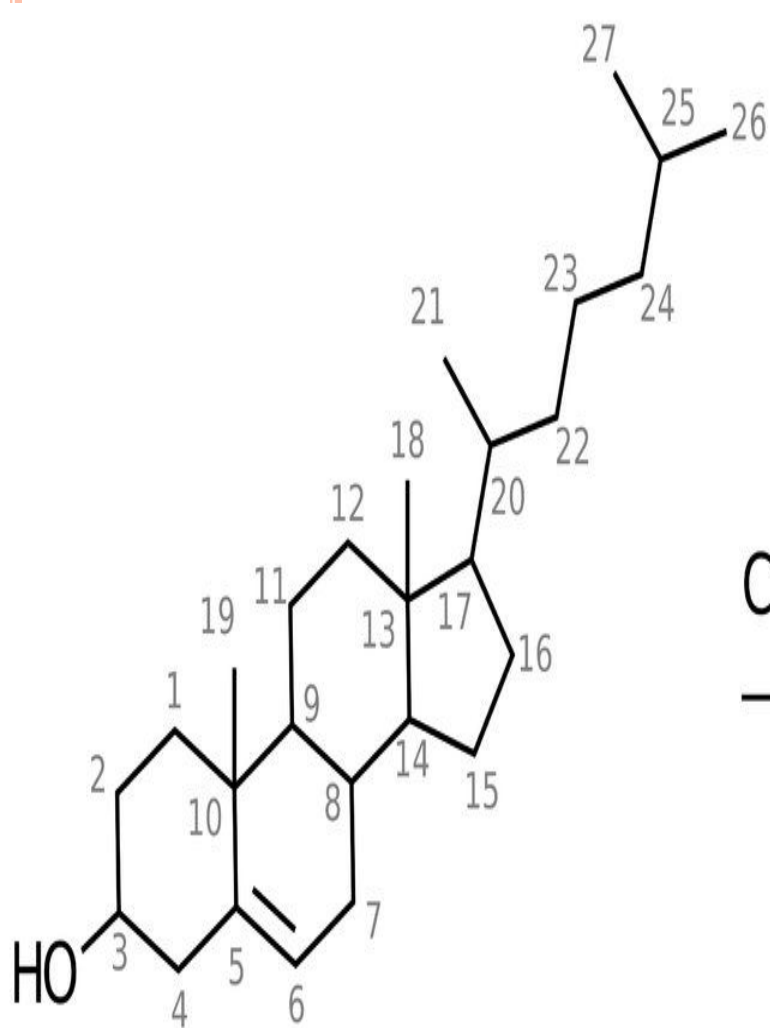
- Synthesizes and releases steroid hormones (corticosteroid).
- Different corticosteroids are produced by each of the three layers:
 - Zona Glomerulosa: Mineralocorticoid.
 - Zona Fasciculata: Glucocorticoid.
 - Zona Reticularis: Androgens.



STEROID HORMONE SYNTHESIS

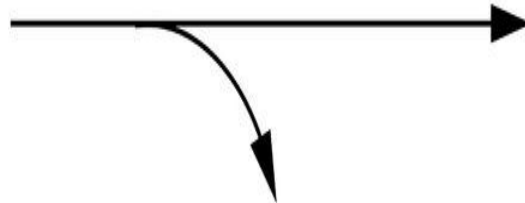
- ❑ Steroids are derivatives of cholesterol.
- ❑ Steroid hormones are synthesized and secreted on demand (not stored).
- ❑ Lipophilic hormones : Diffuse through the lipid plasma membrane of cells, bind to intracellular receptors, and affect transcription. Usually have long-term effects with delayed onset.
- ❑ The first and limiting-step in the synthesis of all steroid hormones is conversion of cholesterol to pregnenolone by the enzyme cholesterol desmolase.



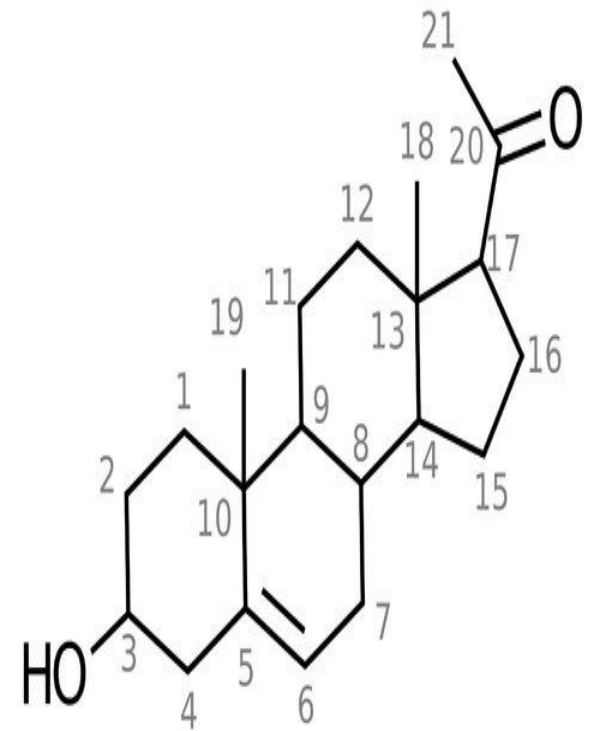


Cholesterol

Cholesterol desmolase



4-Methylpentanal



Pregnenolone

- Newly synthesized hormones are rapidly secreted from the cell.
- Following secretion, all steroids bind to some extent to plasma proteins : corticosteroid binding globulin and albumin.
- **Degradation of hormones**

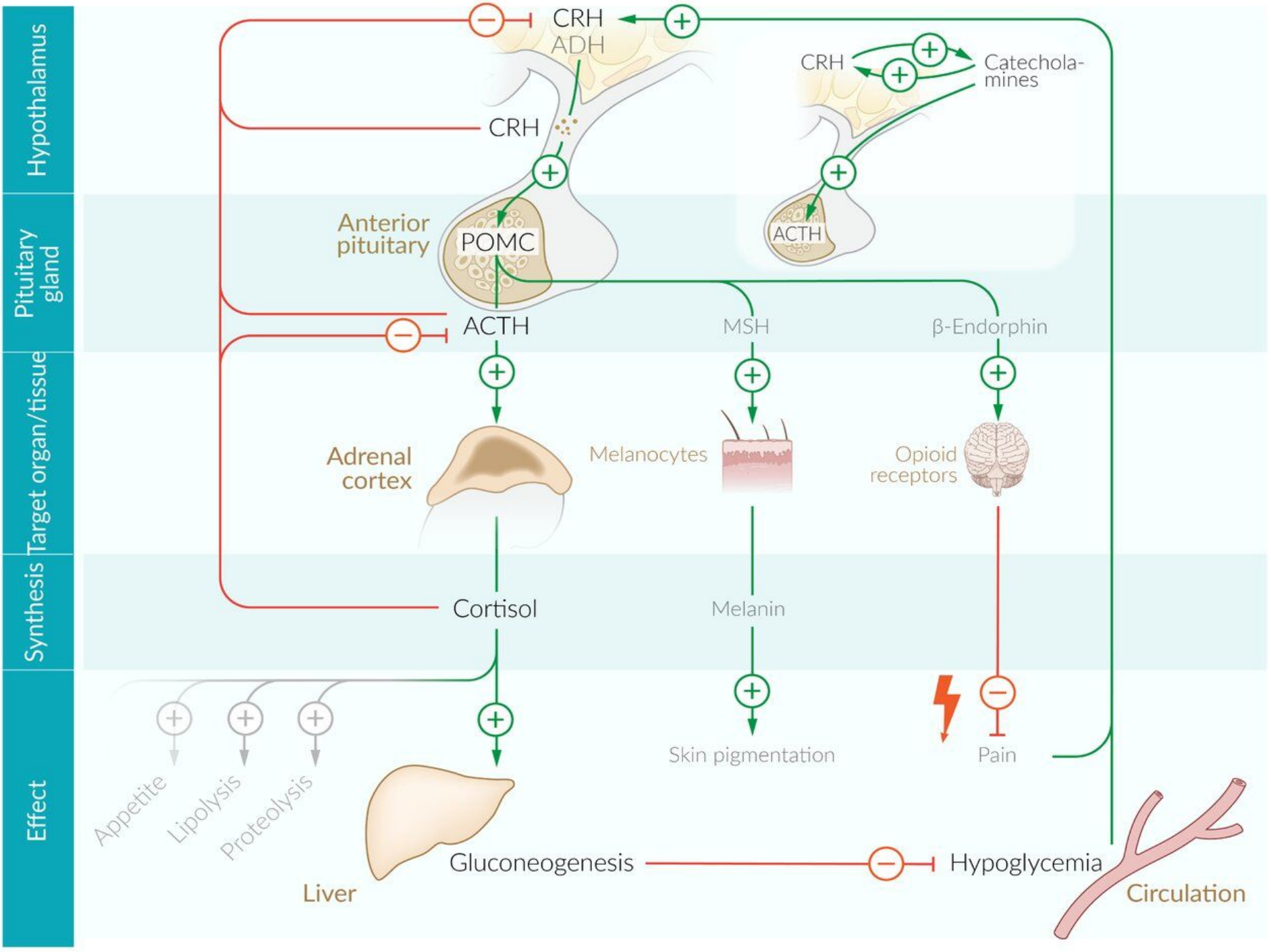
Steroid hormones : inactivation and conjugation in the liver and excretion in bile

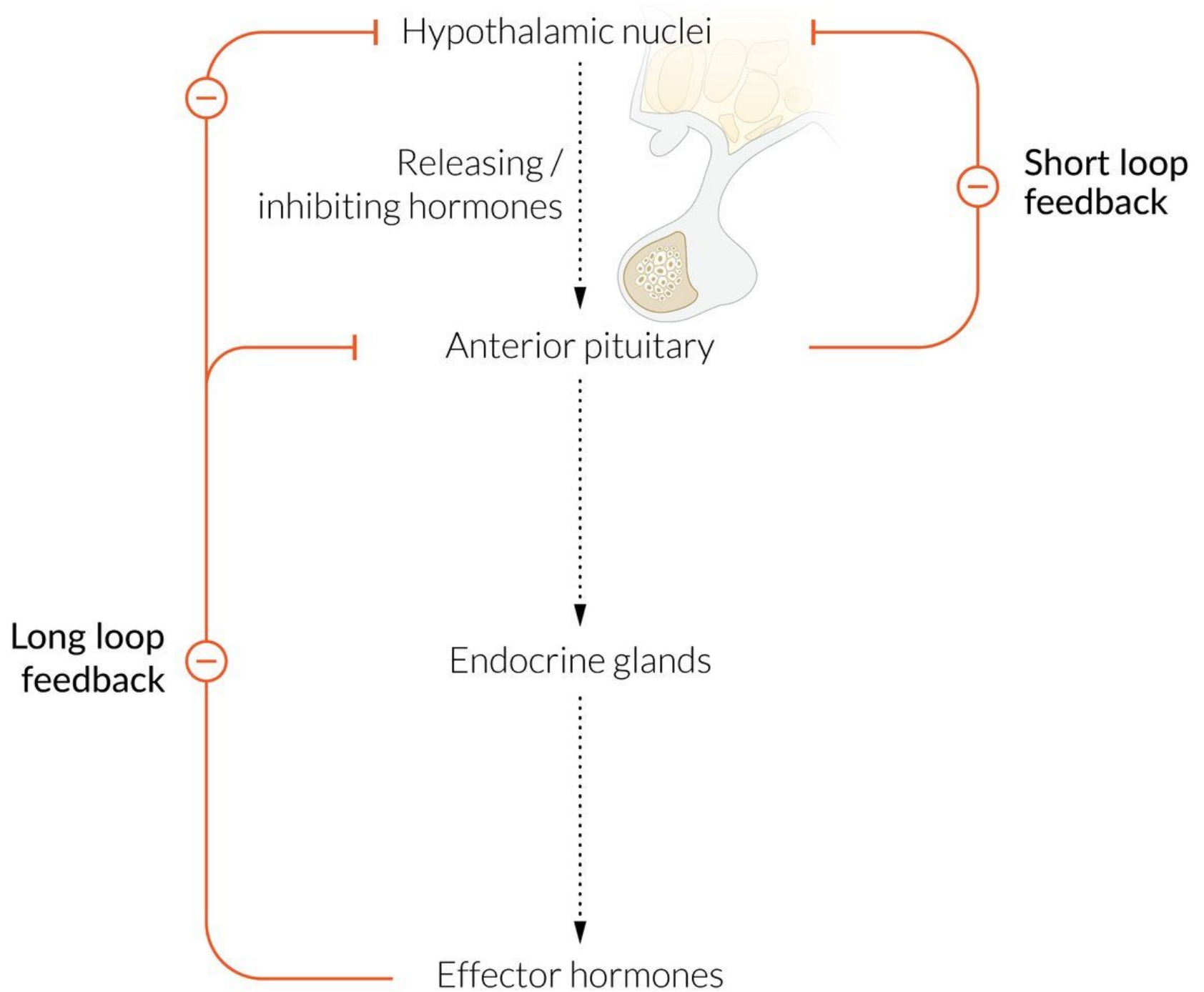


FEEDBACK CONTROL MECHANISMS

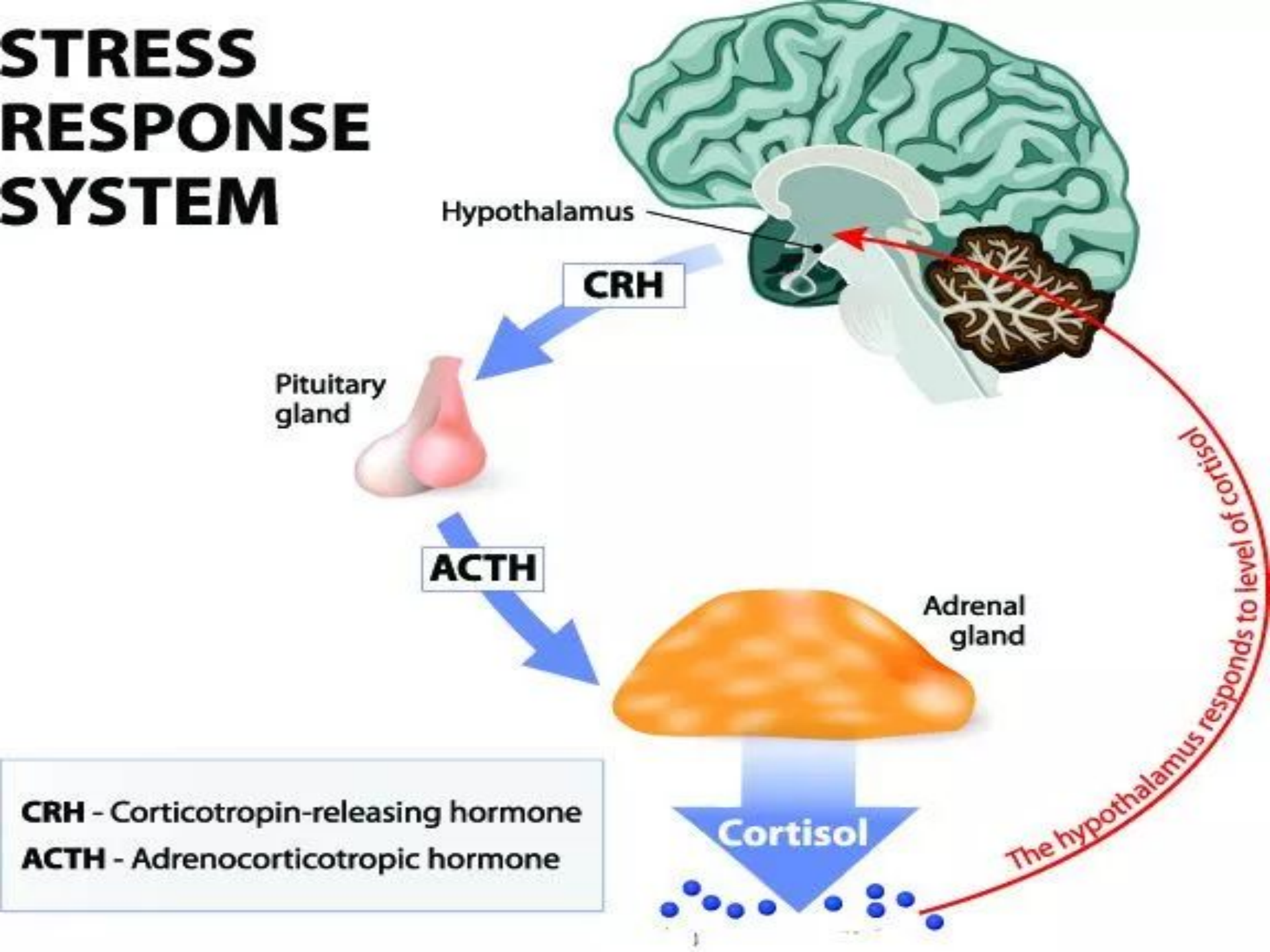
- $\uparrow$ Hypothalamic secretion of CRH $\rightarrow$ $\uparrow$ ACTH secretion from the pituitary $\rightarrow$ $\uparrow$ synthesis of glucocorticoids and androgens from the adrenal cortex
- Mineralocorticoids are secreted as a result of renin-angiotensin-aldosterone system activation.





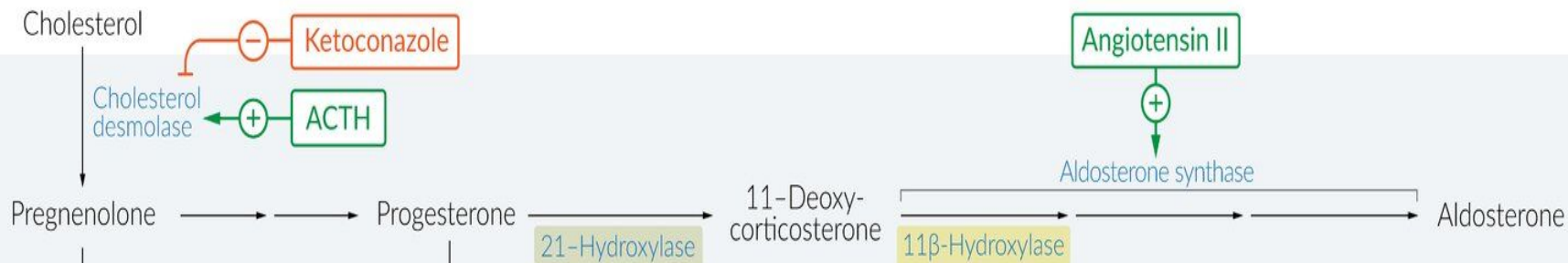


STRESS RESPONSE SYSTEM



Features	Aldosterone	Cortisol	Dehydroepiandrosterone (DHEA)
Hormone class	Mineralocorticoid	Glucocorticoid	Androgen
Production site	Zona glomerulosa	Zona fasciculata	Zona reticularis
Function	Blood pressure regulation: influences renal sodium and water reabsorption and potassium excretion Electrolyte homeostasis - See "Mineralocorticoids."	Mobilization of energy reserves Immunosuppression Antiinflammatory - See "Cortisol."	Substrate in estrogen and testosterone synthesis - See "Androgens."
Regulation of secretion	Renin-angiotensin-aldosterone system (RAAS)	CRH → ↑ secretion of ACTH in the pituitary gland → ↑ secretion of glucocorticoids and androgens in the adrenal cortex	
Associated disorders	- Primary hyperaldosteronism - Adrenal insufficiency - Congenital adrenal hyperplasia	- Cushing syndrome - Adrenal insufficiency - Congenital adrenal hyperplasia	- Adrenal insufficiency - Congenital adrenal hyperplasia

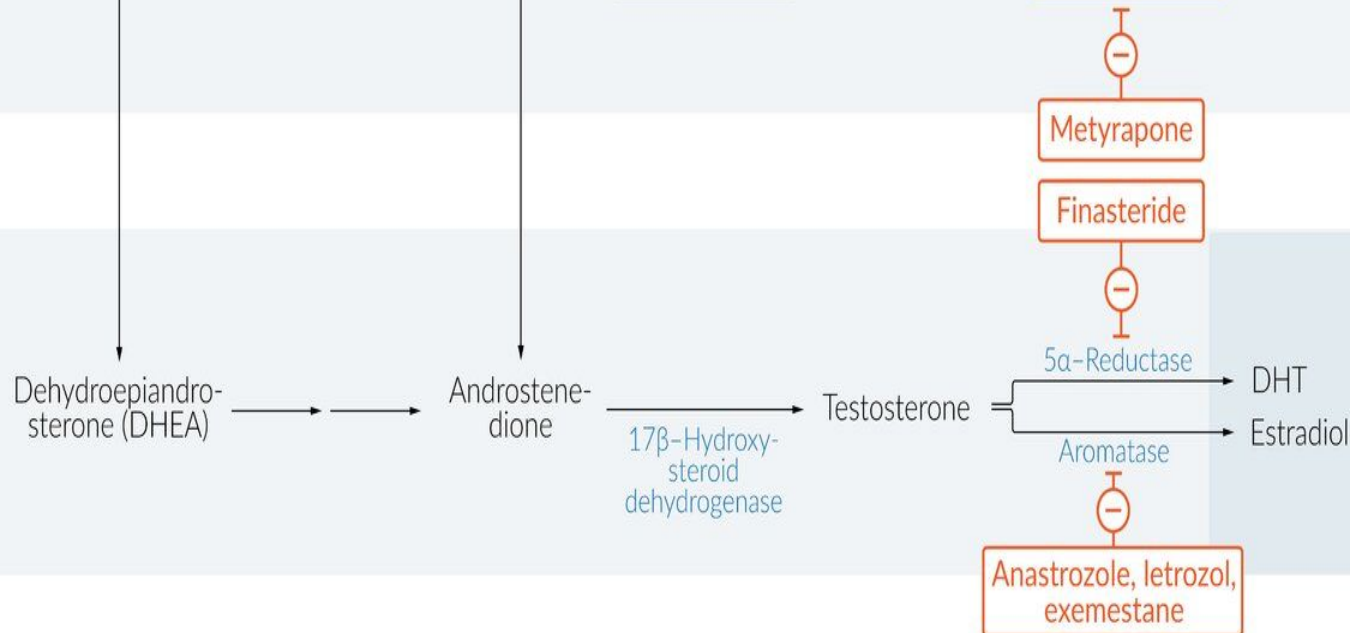
Mineralcorticoids



Glucocorticoids



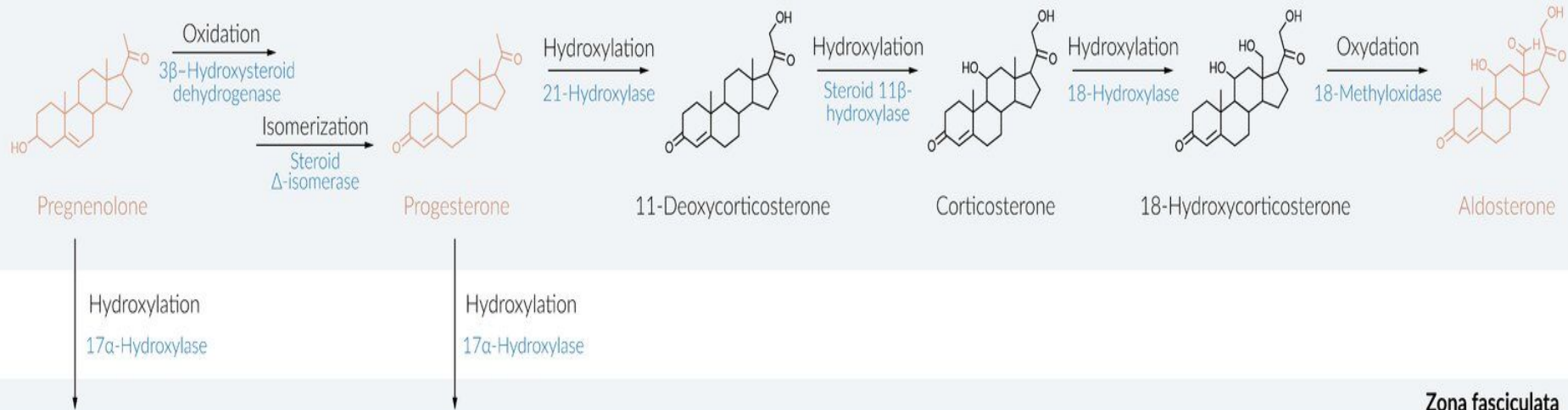
Androgens



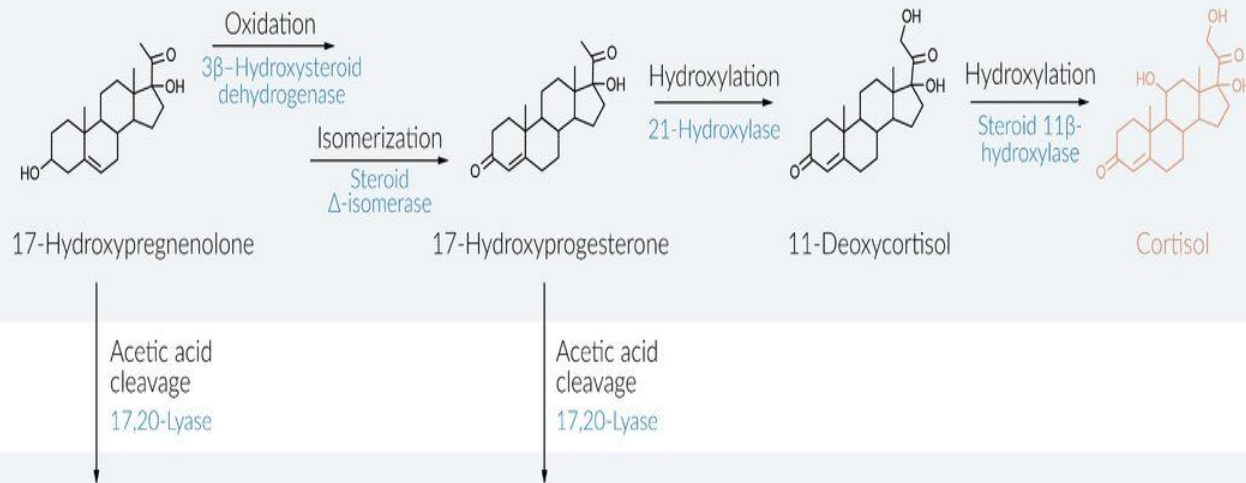
Congenital adrenal enzyme deficiencies:

- 17α-Hydroxylase
- 21-Hydroxylase
- 11β-Hydroxylase

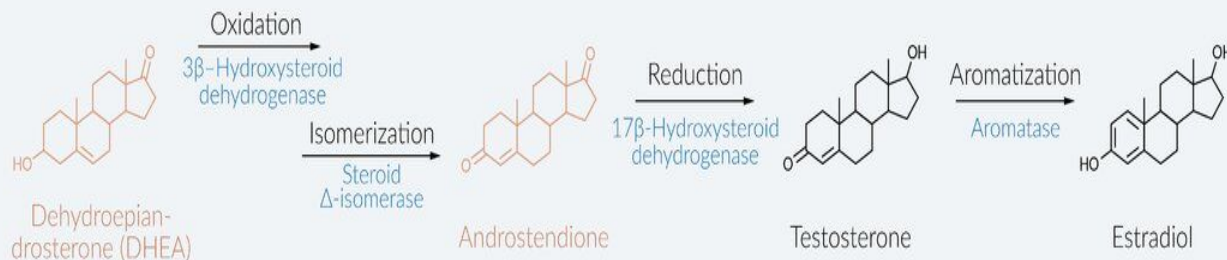
Zona glomerulosa



Zona fasciculata



Zona reticularis



MINERALOCORTICOID

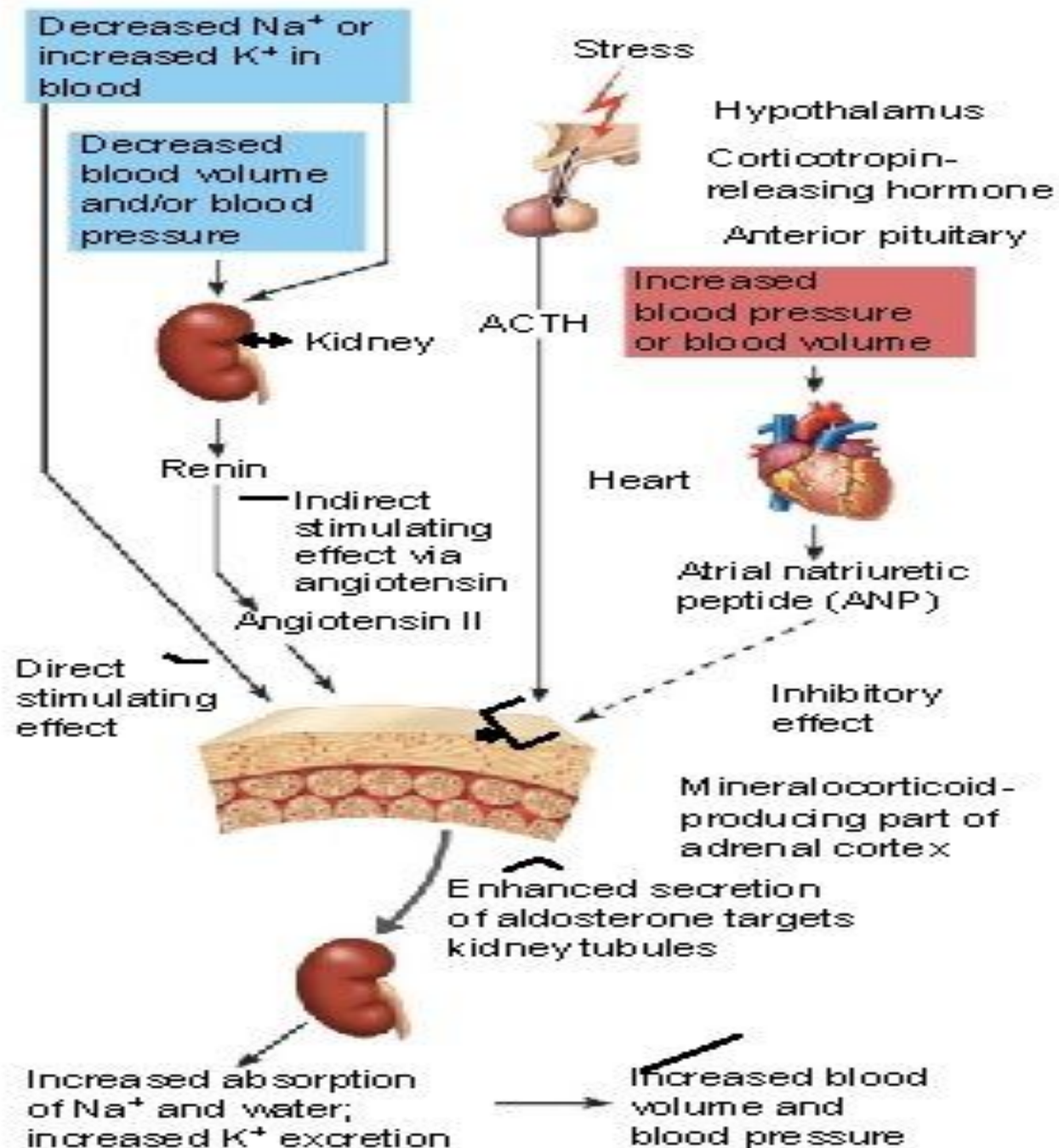
- ❑ Synthesized in zona glomerulosa.
- ❑ Regulate the electrolyte concentration of extracellular fluids.
- ❑ **Aldosterone** is the most important mineralocorticoid
 - maintains Na balance by reducing excretion of sodium from the body.
 - stimulates reabsorption of the Na by kidneys and K excretion.



THE FOUR MECHANISMS OF ALDOSTERONE SECRETION

- ❑ Renin angiotensin aldosterone system RAAS
- ❑ Plasma concentration of NA and K – directly influences the zona glomerulosa
- ❑ ACTH – causes small increase in aldosterone synthesis during stress
- ❑ Atrial natriuretic peptide (ANP) – inhibits activity of zona glomerulosa





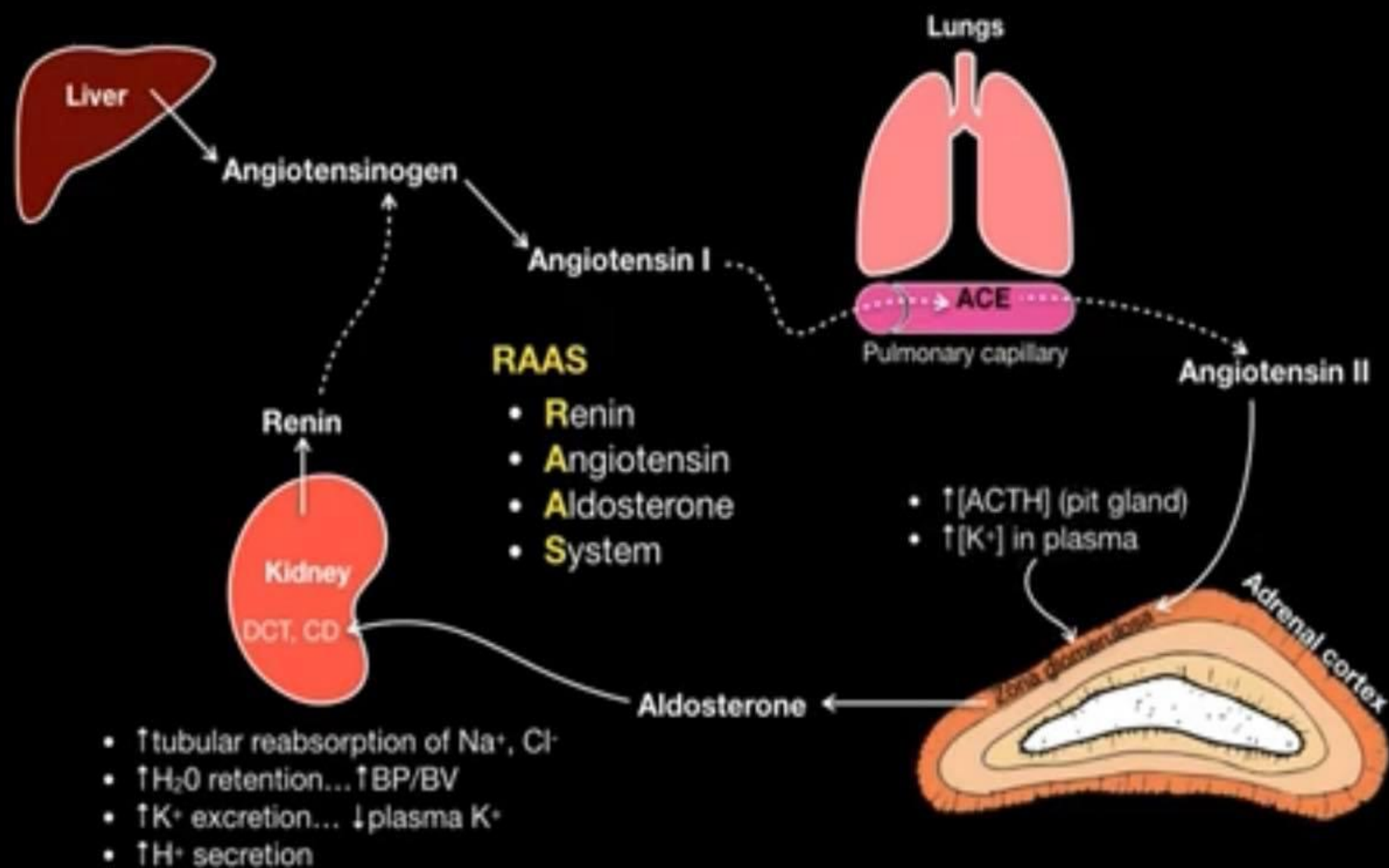
RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS)

- Hormone system that regulates blood pressure, electrolyte homeostasis, and fluid balance
- **Feedback mechanism**
 - A stimulus triggers renin secretion.
 - Renin promotes the conversion of angiotensinogen (produced in the liver) to angiotensin I (AT I).
 - AT I is turned into angiotensin II via angiotensin-converting enzyme (highest concentration in the lungs where it is produced by vascular endothelial cells).
 - Angiotensin II causes vasoconstriction and triggers the secretion of aldosterone.



- **Aldosterone**

- Stimulation, Function, Inhibition

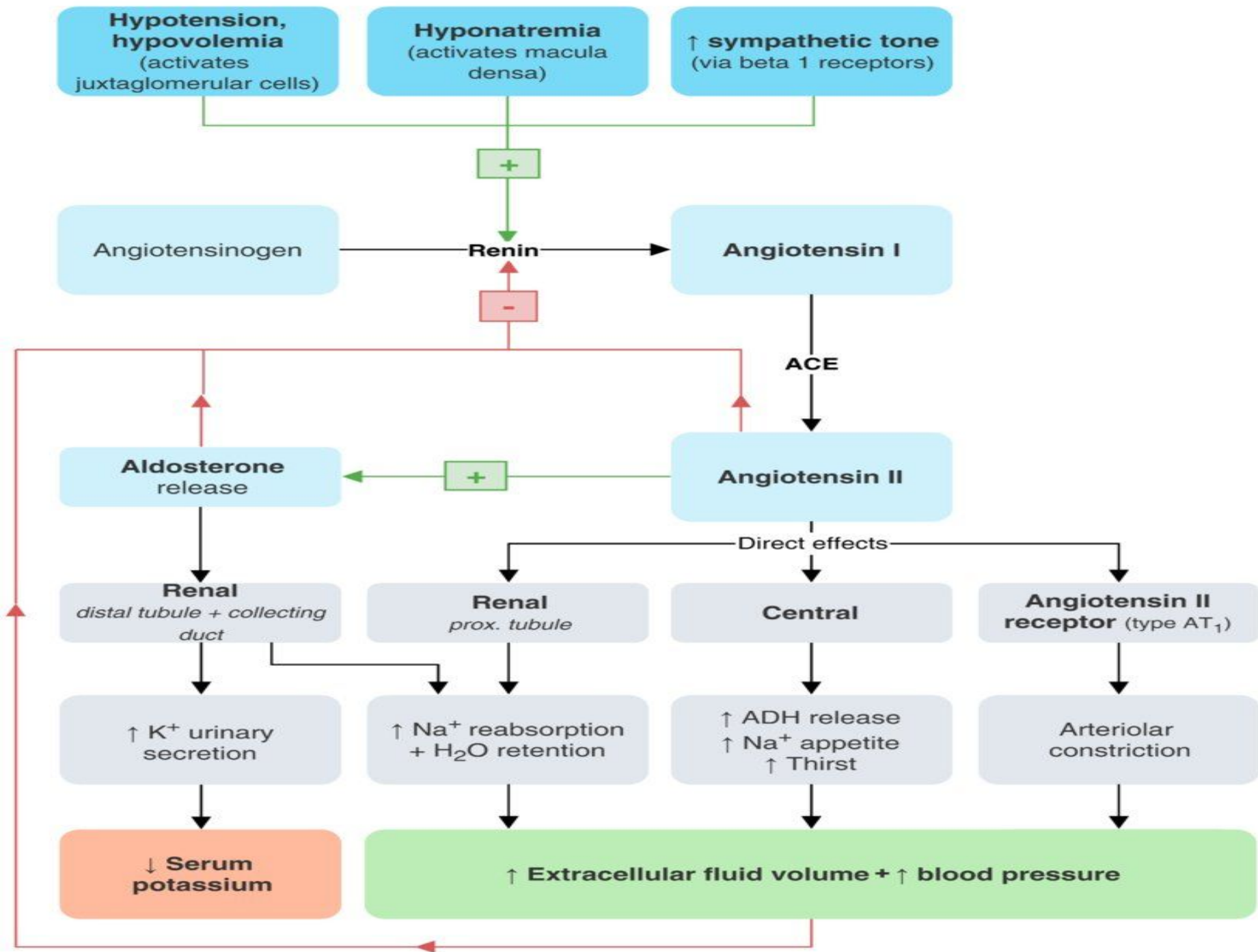


□ Regulation of secretion Positive feedback

- ↓ **Renal perfusion** (e.g., due to hypotension, stimulation of β_1 receptors in the kidney) triggers renin release.
- ↑ **Serum potassium concentration** → stimulation of zona glomerulosa cells → ↑ secretion of aldosterone

□ Negative feedback: ↑ systemic arterial blood pressure → ANP release from atrial myocytes → inhibition of renin release → vasodilation, natriuresis, and ↑ diuresis





MINERALOCORTICOID FUNCTION

- ❑ **Mechanism of action:** aldosterone binds to intracellular mineralocorticoid receptors in the distal tubule and collecting duct of the kidney, inducing protein synthesis and following changes:
 - ↑ Na⁺/K⁺-ATPase in the basolateral membrane
→ transportation of Na⁺ out and K⁺ into the tubule cells
 - ↑ Apical H⁺-ATPase → H⁺ excretion
 - ↑ Na⁺ channels (ENaC; epithelial sodium channel)
→ ↑ **Na⁺ reabsorption**
 - ↑ K⁺ channels (ROMK; renal outer medullary potassium channel) in the luminal membrane
→ ↑ **K⁺ excretion**

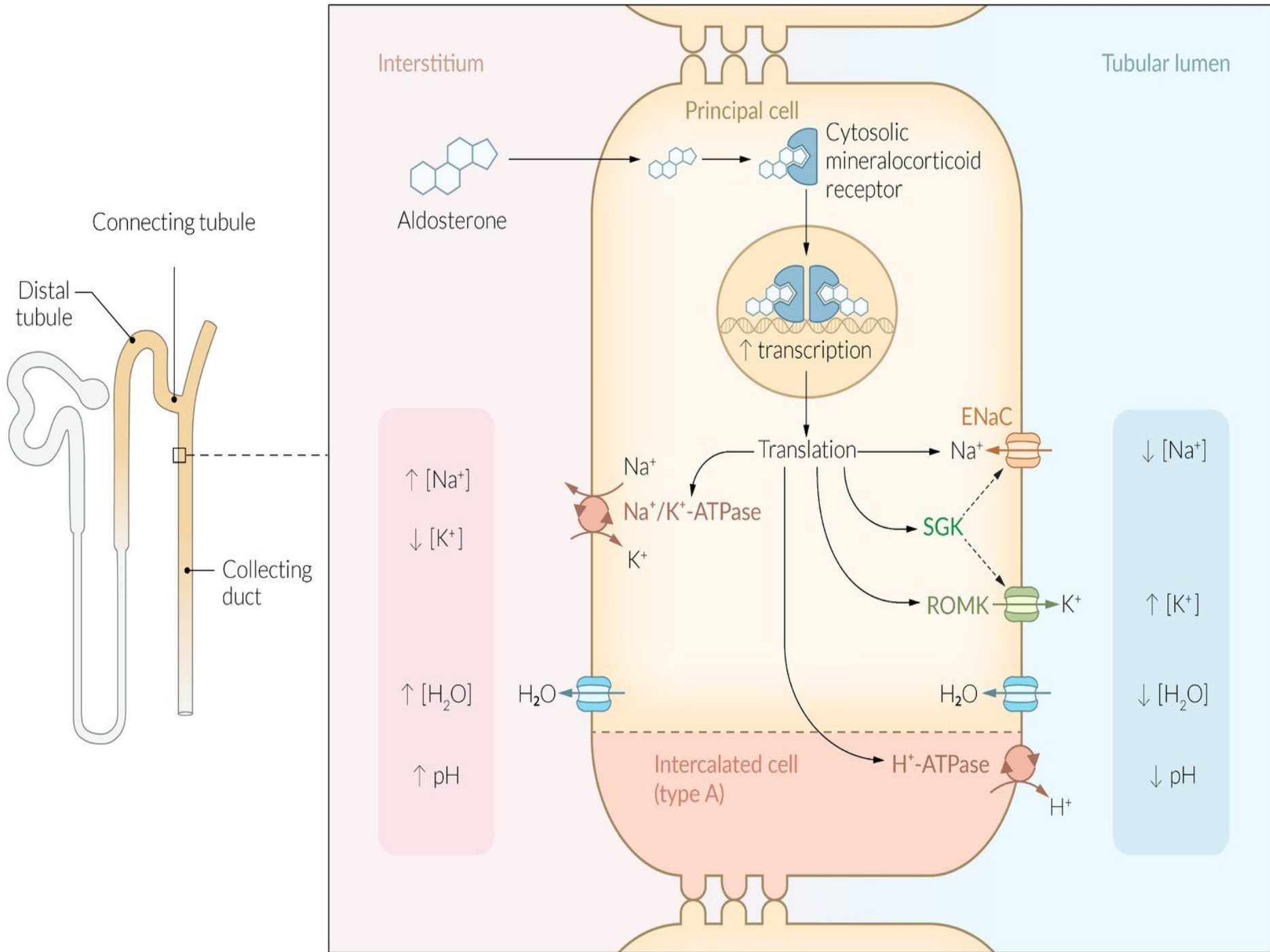


□ Effects

- These aldosterone-induced changes produce a concentration gradient → Na^+ reabsorption → water reabsorption and K^+ secretion into the urine.
- Ultimately, these effects → ↑ **blood pressure**, hypokalemia, and ↑ pH level.

□ Aldosterone stimulates potassium excretion in the collecting duct of the kidney as well as sodium and water retention.





GLUCOCORTICIDS

- Glucocorticoids are steroid hormones.
- They have gained their name because they exhibit important effects that increase blood glucose concentration.
- They have additional effects on protein and fat metabolism that are equally as important to body function as their effects on carbohydrate metabolism.



CORTISOL

- A very potent corticosteroid. Accounts for about 95 percent of all glucocorticoid effect.
- It helps control the body's use of fats, proteins and carbohydrates; suppresses inflammation; regulates blood pressure; increases blood sugar; and can also decrease bone formation.
- This hormone also controls the sleep/wake cycle. It is released during times of stress to help your body get an energy boost and better handle an emergency situation.



HYPOTHALAMIC-PITUITARY GLAND-ADRENAL CORTEX

- ▣ **Feedback mechanism:** a stimulus causes increased secretion of corticotropin-releasing hormone (CRH) → ↑ secretion of adrenocorticotrophic hormone (ACTH) in the pituitary gland → ↑ secretion of glucocorticoids in the adrenal cortex.



▣ Regulation of secretion

- Positive feedback: A number of stimuli can trigger CRH release.
 - ▣ Psychological/physical pain and stress
 - ▣ Pyrogens, epinephrine, histamine
 - ▣ Hypoglycemia
 - ▣ Hypotension
- Negative feedback: Glucocorticoids themselves trigger a negative feedback loop that inhibits the secretion of CRH and ACTH.
- Circadian rhythm
 - ▣ Endogenous biological rhythm influences CRH secretion.
 - ▣ Cortisol levels are highest early in the morning and decrease during the day, until they drop sharply during the night and the early phase of sleep.



Stimuli



Epinephrine



Histamine

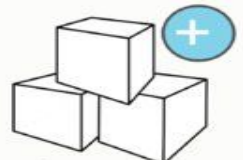


Pain/stress



Pyrogens

Hypothalamus



Glucose



Blood pressure

1

CRH

2

Anterior
pituitary
gland

ACTH

Glucocorticoids

Androgens

Adrenal gland

Releasing
hormone

Target organ

FUNCTIONS

A. Metabolic effects:



1. On carbohydrate metabolism:

- Increased hepatic gluconeogenesis
- Decreased utilization of glucose by the cells.
- Increased blood glucose concentration.

2. On protein metabolism:

- Increased protein catabolism and decreased protein synthesis in most tissues except the liver.
 - In the liver, cortisol increases amino acid uptake and enhances protein synthesis.
- Furthermore, the plasma proteins (produced by the liver) are also increased.

3. On fat metabolism:

- Increased lipolysis promotes mobilization of fatty acids from adipose tissue
- Increased fat mobilization causes increased formation of ketone bodies (Ketogenic effect).



PROTEIN METABOLISM

Decrease in
Cellular
proteins

- ↑Catabolism of all cellular proteins except liver.
- By ↓AA transport into extrahepatic tissues.

Increases
Liver &
Plasma
Proteins

- Paradoxically, there is ↑ AA transport into Liver cells for Gluconeogenesis.
- ↑ Plasma protein formation in the Liver (for transport of cortisol).

B. Anti-inflammatory effects:

Cortisol has two basic anti-inflammatory effects. 🖐️

- 1. It blocks the early stages of the inflammatory process by stabilizing cellular lysosome and*
- 2. If inflammation has already begun, it causes rapid resolution of the inflammation and increased rapidity of healing.*

C. Effect on allergy:

Cortisol block the inflammatory response to allergic reaction.

D. Effect on immunity:

Administration of large doses of cortisol significant atrophy of all lymphoid tissue through out the body, which in turn decrease the output of both T cells & antibodies from the lymphoid tissues. As a result, immunity of the body is decreased.

E. Effect on blood cells:

It decreases eosinophils & lymphocytes





F. Functions of cortisol in resisting stress:

Cortisol resists physical or neurogenic stressful conditions like

- 1. Trauma of almost any type*
- 2. Infection*
- 3. Intense heat or cold*
- 4. Surgery*
- 5. Restraining a person so that he cannot move*
- 6. Almost any debilitating disease*
- 7. Anxiety*

The exact mechanism is not known, but one possibility is that the glucocorticoids cause rapid mobilization of amino acids and fats from their cellular stores, making them immediately available both for energy and for synthesis of other compounds, including glucose, needed by the different tissues of the body. Damaged tissues which are severely protein depleted can use the amino acids to form new proteins that are essential to the lives of the cells.



❑ Glucocorticoid function

❑ **Metabolism:** Cortisol plays an important role in the mobilization of energy reserves.

- ↑ Gluconeogenesis to maintain blood glucose levels
- ↑ Glycogen synthesis to maintain glucose storage
- ↑ Protein catabolism
- ↑ Lipolysis
- ↑ Appetite
- ↑ Insulin resistance

❑ Immune

system: antiinflammatory and immunosuppressive effects

❑ Wound healing: fibroblast inhibition → ↓ collagen synthesis → ↓ wound healing

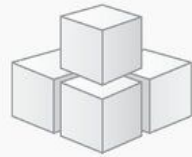
❑ **Blood pressure**: mild mineralocorticoid effect (stimulation of aldosterone receptors in high concentrations) and ↑ potassium excretion → ↑ **blood pressure**



- To remember the effects of cortisol, think “**A BIG FIB**”: increased **A**ppetite, **B**lood pressure, **I**nsulin resistance, **G**lucose production, and decreased **F**ibroblasts, **I**mmunity, and **B**one formation.



Metabolism



↑ Gluconeogenesis



↑ Lipolysis

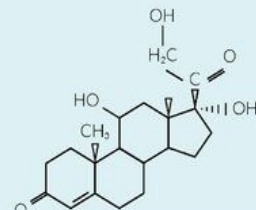


↑ Protein catabolism



↑ Bone resorption

Immunosuppressive



Glucocorticoids

1



+

IkB-gene

2

IkB

NF-kB

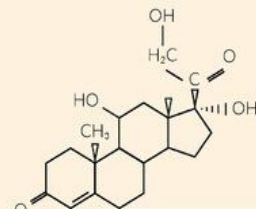
-

NF-kB

+

Proinflammatory factors, e.g.,
IL-1, IL-2, IL-6,
TNF α , COX-2

Catecholamine sensitivity



Glucocorticoids

+



Adrenoceptor

Catecholamines

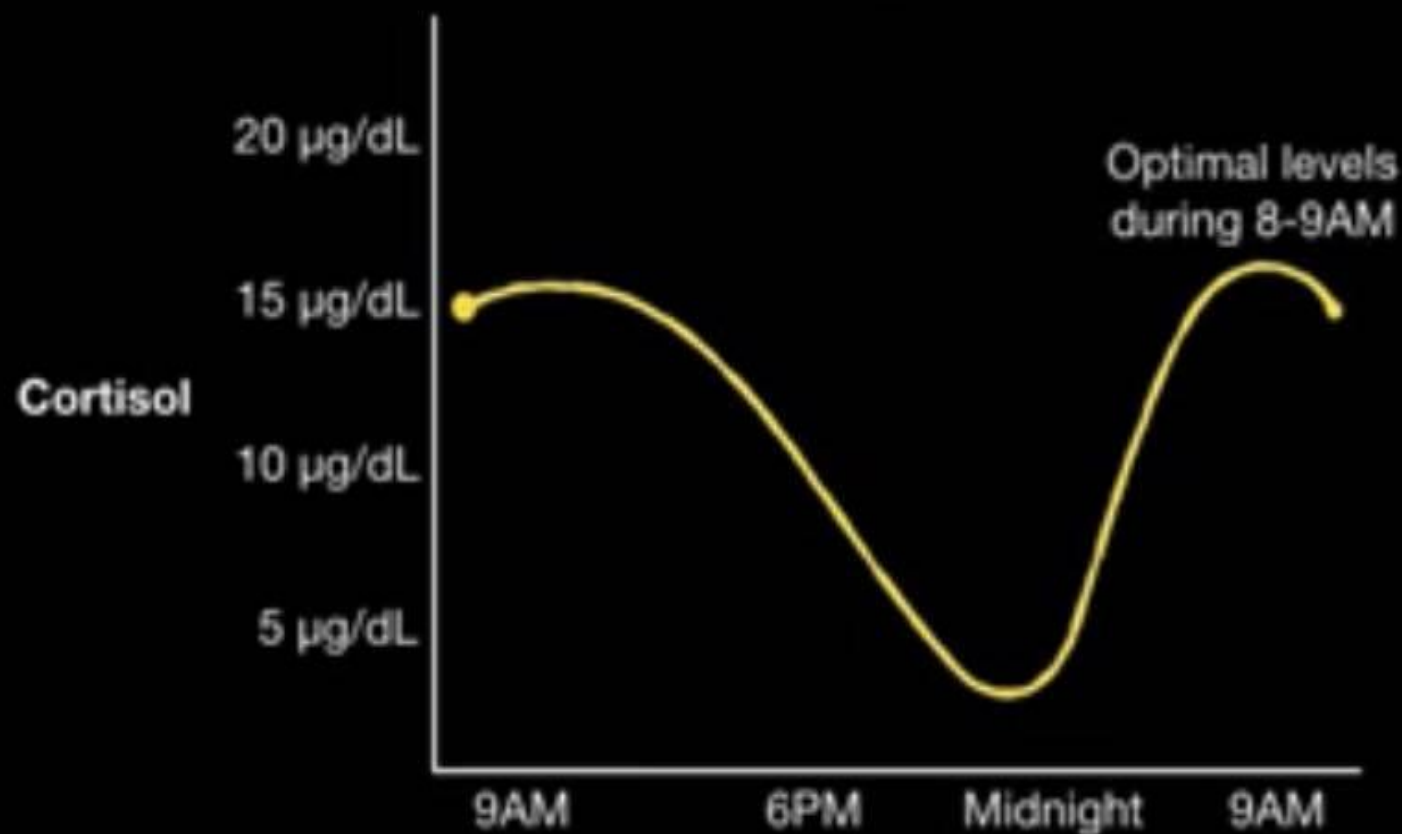
Circadian rhythm of glucocorticoid secretion

- The secretory rates of CRF, ACTH and cortisol are high in the early morning but low in the late evening.*
- This effect results from a 24 hour cyclical alteration in the signals from the hypothalamus that cause cortisol secretion.*



- **Cortisol**
 - Stimulation, Function, Inhibition

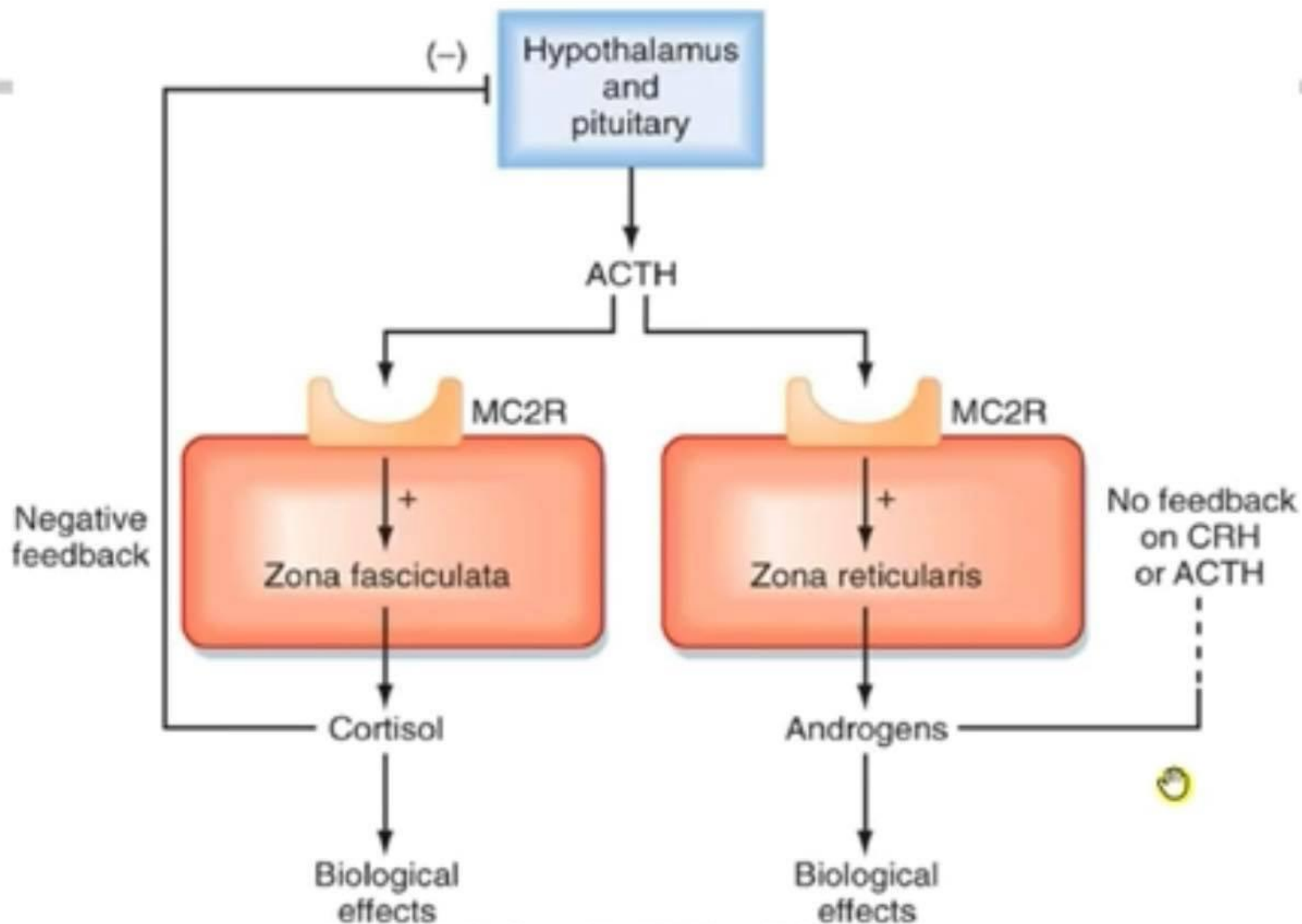
↑ stress; circadian rhythm



ANDROGENS

- Androgens are a group of steroid hormones, that play a role in male traits and reproductive activity. Present in both males and females.
- Androgens secreted by adrenal cortex are:
 - DHEA
 - Androstenedione
 - testosterone
- DHEA is the most active adrenal androgen.
- The androgens in general are responsible for masculine features of the body.





- In normal conditions, the adrenal androgens have insignificant physiologic effects because of low secretion (low amount) both in males and females.
- In congenital adrenal hyperplasia of adrenal cortex or tumor of zona reticularis, an excess amount of androgen is secreted.
- In males, it doesn't produce any special effects because large quantity of androgens are produced by testes also.



- In females , the androgens produce masculine features.
- Some of the androgens are converted into testosterone.
- Testosterone is responsible for the androgenic activity in CAH.



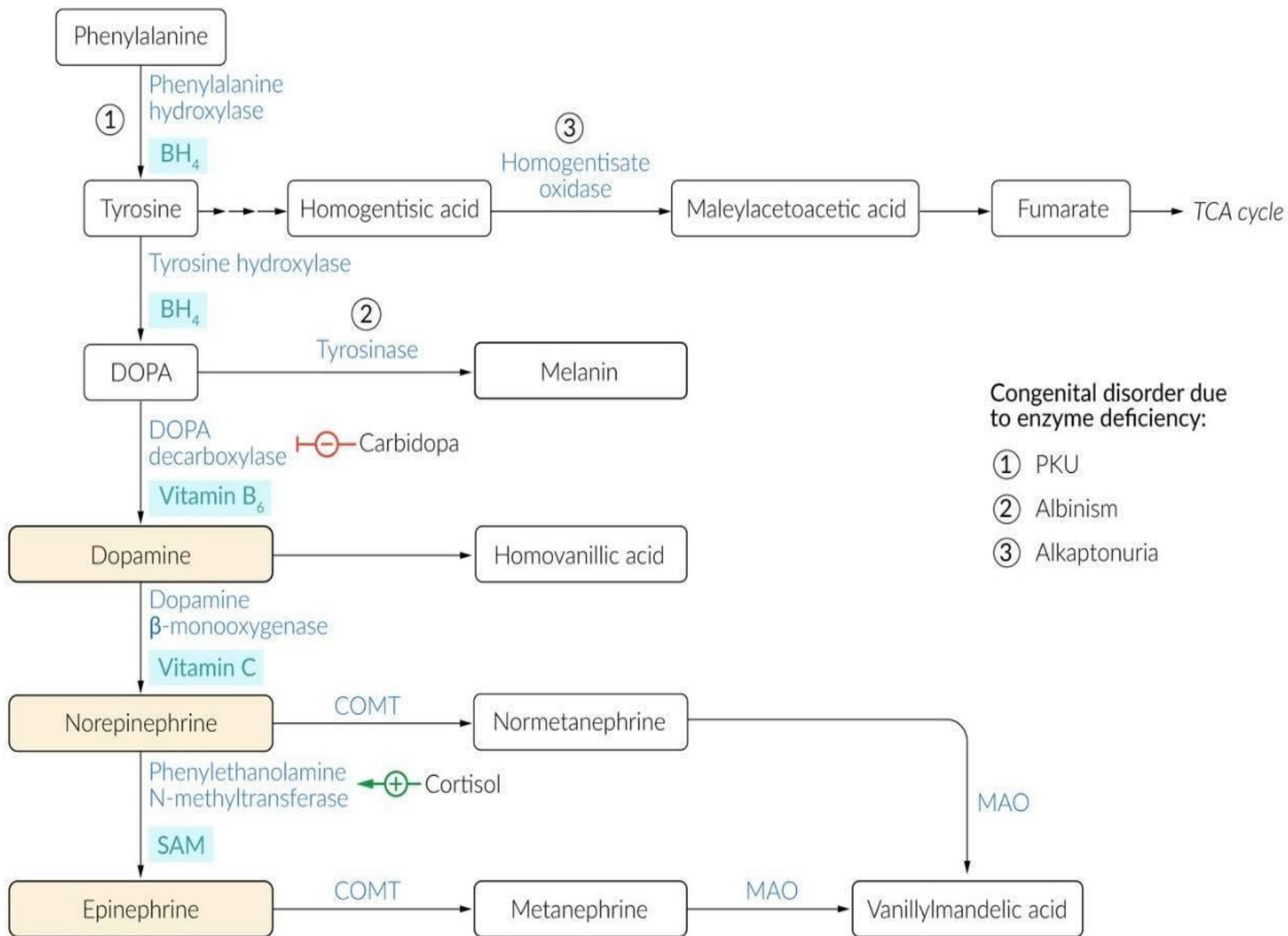
ADRENAL MEDULLA

□ Catecholamine synthesis

Catecholamines (norepinephrine, epinephrine, dopamine) can also be synthesized at sites in the human body other than the adrenal medulla, such as specific regions of the CNS and postganglionic adrenergic neurons.

- Epinephrine has the shortest half-life of the catecholamines.





CATECHOLAMINE FUNCTION

▣ Mechanism:

Catecholamines bind to various adrenergic receptors located on different organs and tissues.

▣ Effects

- Binding triggers tissue-specific responses.
- This leads to sympathetic activation to prepare the human body for a fight-or-flight reaction.



OVERVIEW OF PERIPHERAL ADRENERGIC RECEPTORS

□ α_1 receptor

Signal transduction- stimulation of phospholipase

C: $\text{PIP}_2 \rightarrow \text{IP}_3$ and DAG $\rightarrow \uparrow \text{Ca}^{2+}$

•Vasculature (<u>skin</u> and <u>GI tract</u>)	• $\uparrow$ Contraction of smooth muscles $\rightarrow$ vasoconstriction
--	--

• <u>GI tract</u> • <u>Bladder</u>	• $\uparrow$ Constriction of sphincters
---------------------------------------	---



α_2	•G _i	•Inhibition of <u>adenylate cyclase</u> : ↓ <u>cAMP</u>	• <u>White adipose tissue</u>	•↓ <u>Lipolysis</u>
			• <u>GI tract</u> • <u>Bladder</u>	•↓ Muscular contraction
			• <u>Pancreas</u>	•↓ <u>Insulin</u> secretion



β_1			• <u>Heart</u>	• $\uparrow$ <u>Chronotrope</u> • $\uparrow$ <u>Inotrope</u> • $\uparrow$ <u>Dromotropy</u>
			• <u>Kidney</u>	• $\uparrow$ <u>Renin</u> secretion
			• Vasculature (coronary vessels, <u>skeletal muscles</u>) • <u>Bronchi</u>	• $\downarrow$ Contraction of smooth musculature $\rightarrow$ <u>vasodilation</u> and bronchodilation
β_2	• G_s	• Stimulation of <u>adenylate cyclase</u> : $\uparrow$ <u>cAMP</u>	• <u>Liver</u> • <u>Skeletal muscles</u>	• $\uparrow$ <u>Glycogenolysis</u>
			• <u>White adipose tissue</u>	• $\uparrow$ <u>Lipolysis</u>
			• <u>Pancreas</u>	• $\uparrow$ <u>Insulin</u> secretion
			• <u>Uterus</u>	• <u>Tocolysis</u>
β_3			• <u>Brown adipose tissue</u>	• $\uparrow$ <u>Lipolysis</u>

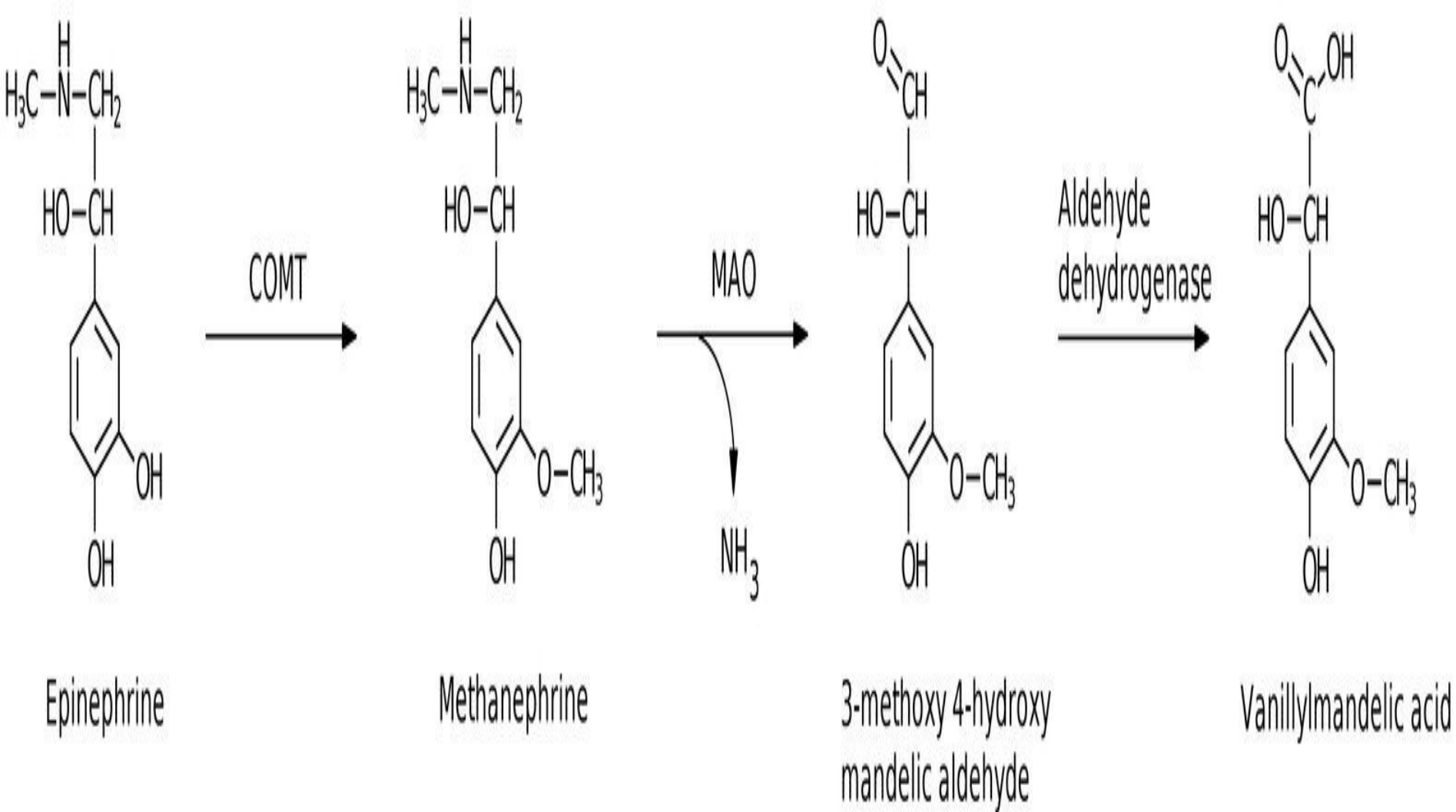
▣ Regulation of secretion

Catecholamine secretion can be triggered by a number of stimuli, such as high-stress situations (e.g., fight-or-flight) or cortisol.



- ❑ Catecholamine degradation
- ❑ Enzymatic degradation occurs via catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO).
- ❑ MAO can be blocked by MAO inhibitors to elevate catecholamine concentration in synaptic cleft.
- ❑ Vanillylmandelic acid (VMA) is an end-stage metabolite. Urinary excretion is elevated in patients with pheochromocytoma and neuroblastoma.





COMT = catechol-O-methyltransferase; cofactor S-adenosylmethionine

MAO = monoamine oxidase; cofactors FAD and copper