Adrenal Gland

ALDH

Epi

Lec. Omeed Akbar Ali

Tikrit University - College of Medicine

Biochemistry Lec. (3)

Overview

- \- INTRODUCTION
- \- Types of adrenal hormone
- \- Formation and function of adrenal hormone
- \- Control of adrenal secretion
- \- Disease of adrenal gland

INTRODUCTION

❖- **Adrenal Gland:** Small, triangular glands loosely attached to the kidneys

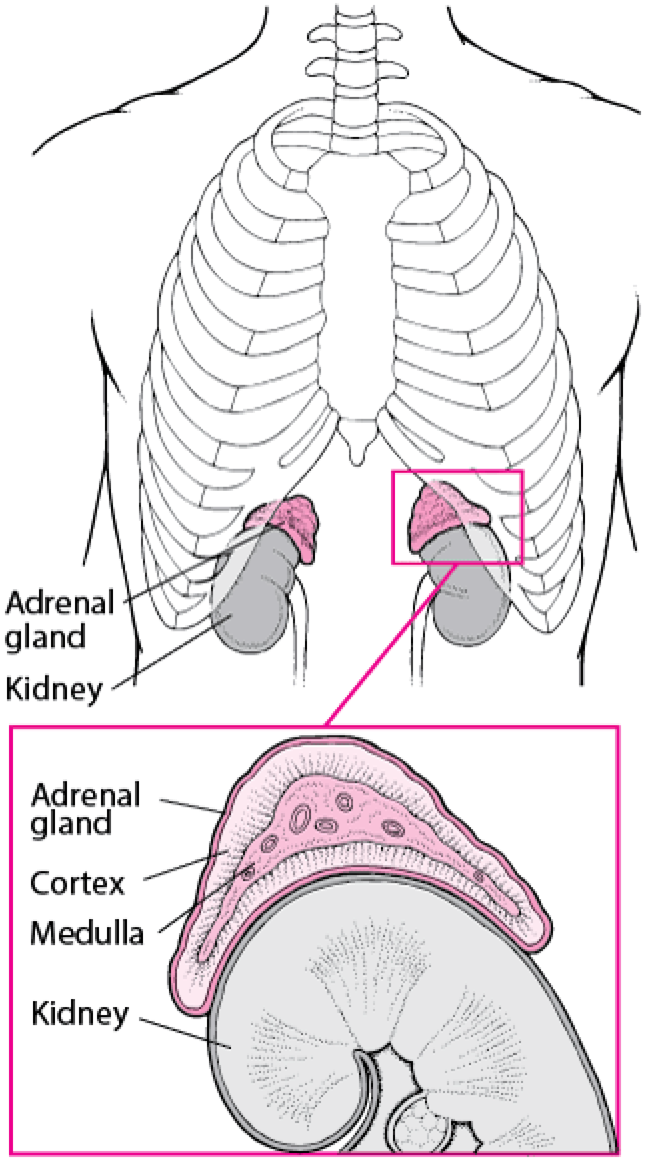
▪- **Divided into two morphologically distinct regions:**

✓- Adrenal Cortex (Outer)

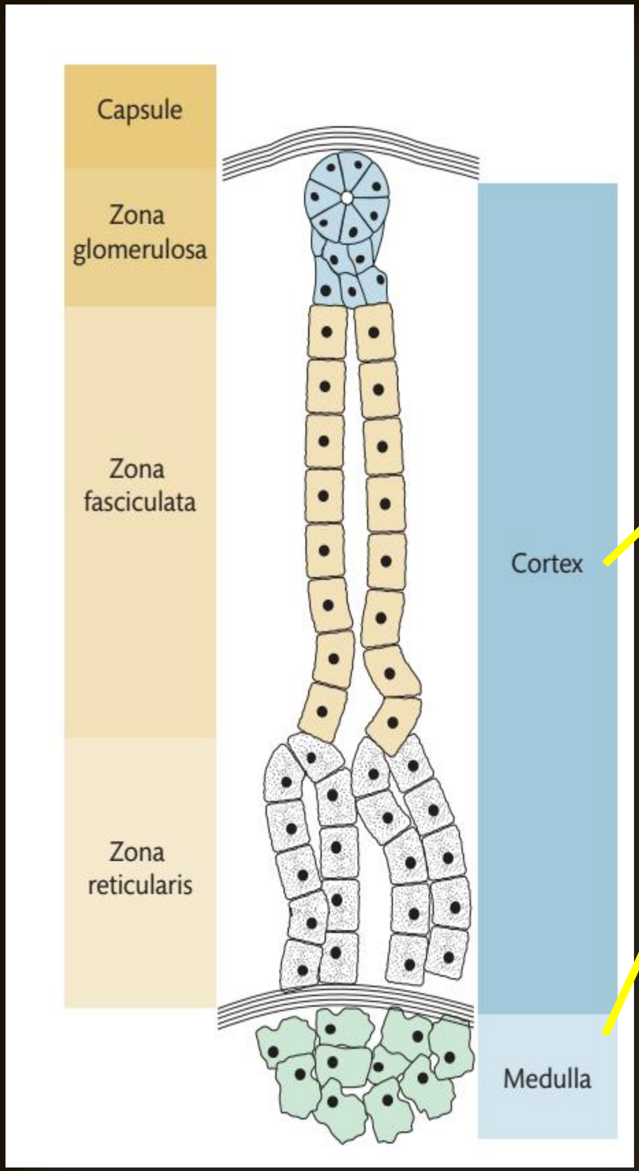
- The adrenal cortex forms about 80–90% of the total gland.

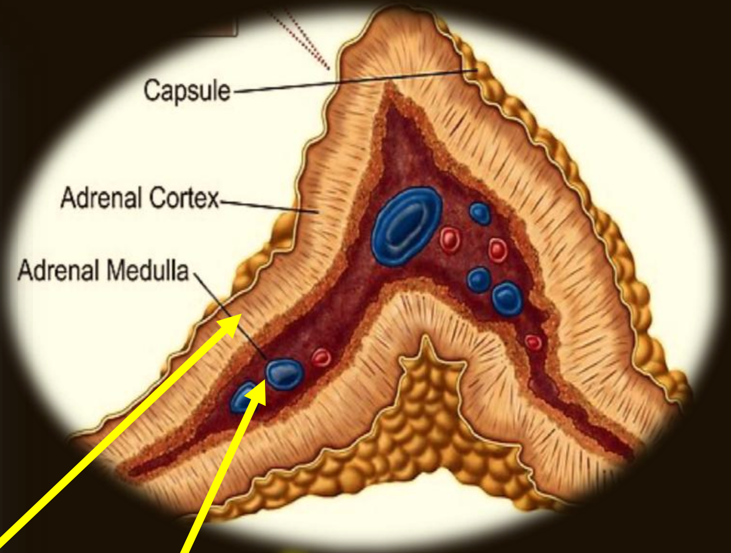
✓- Adrenal Medulla (Inner)

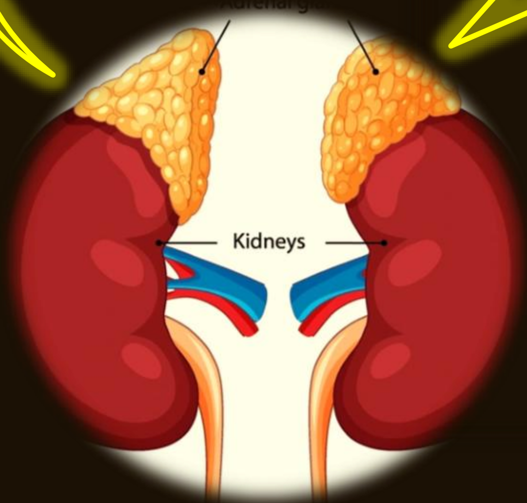
- The adrenal medulla consists of 10–20% of the gland.

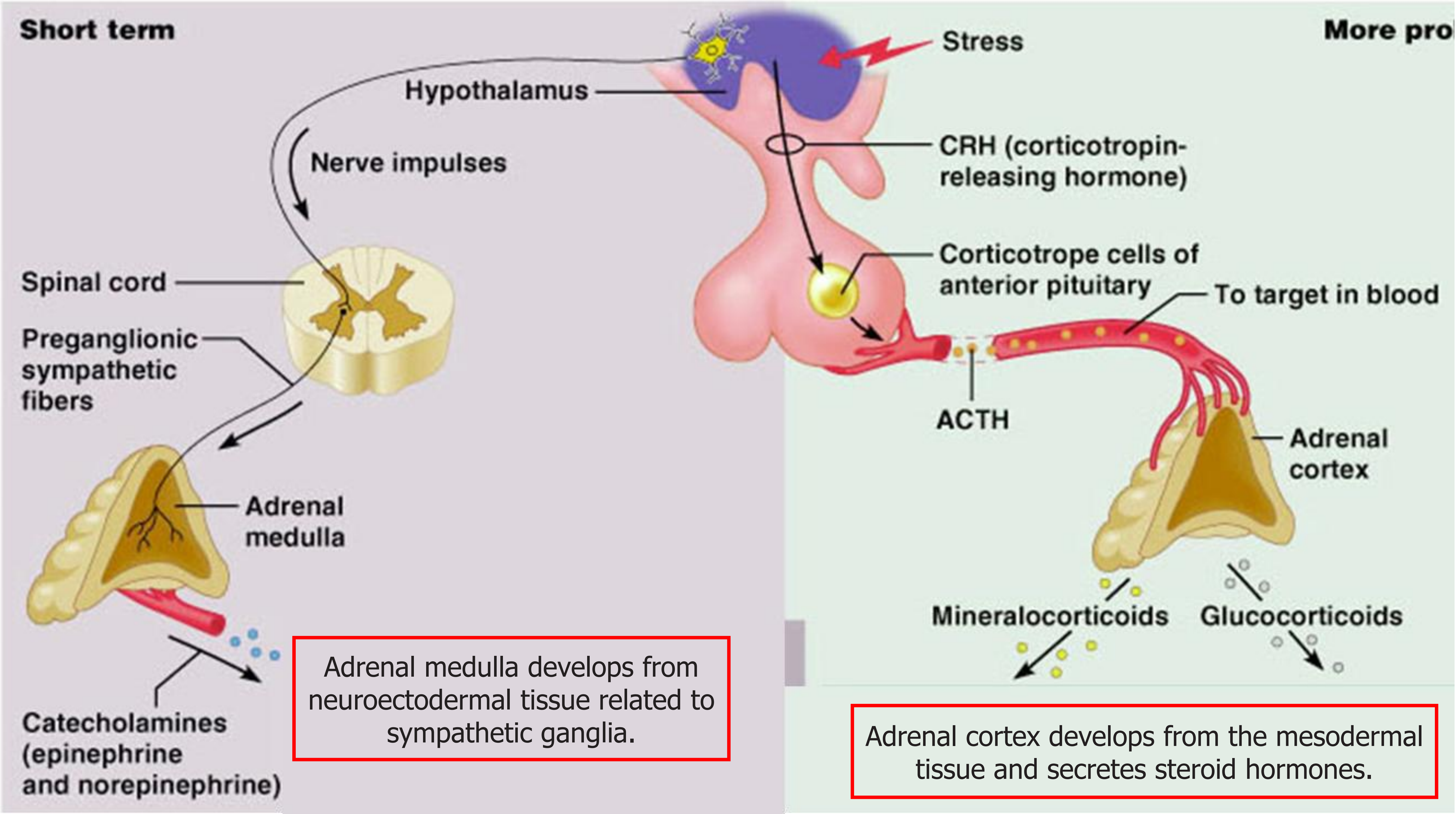


Adrenal Gland





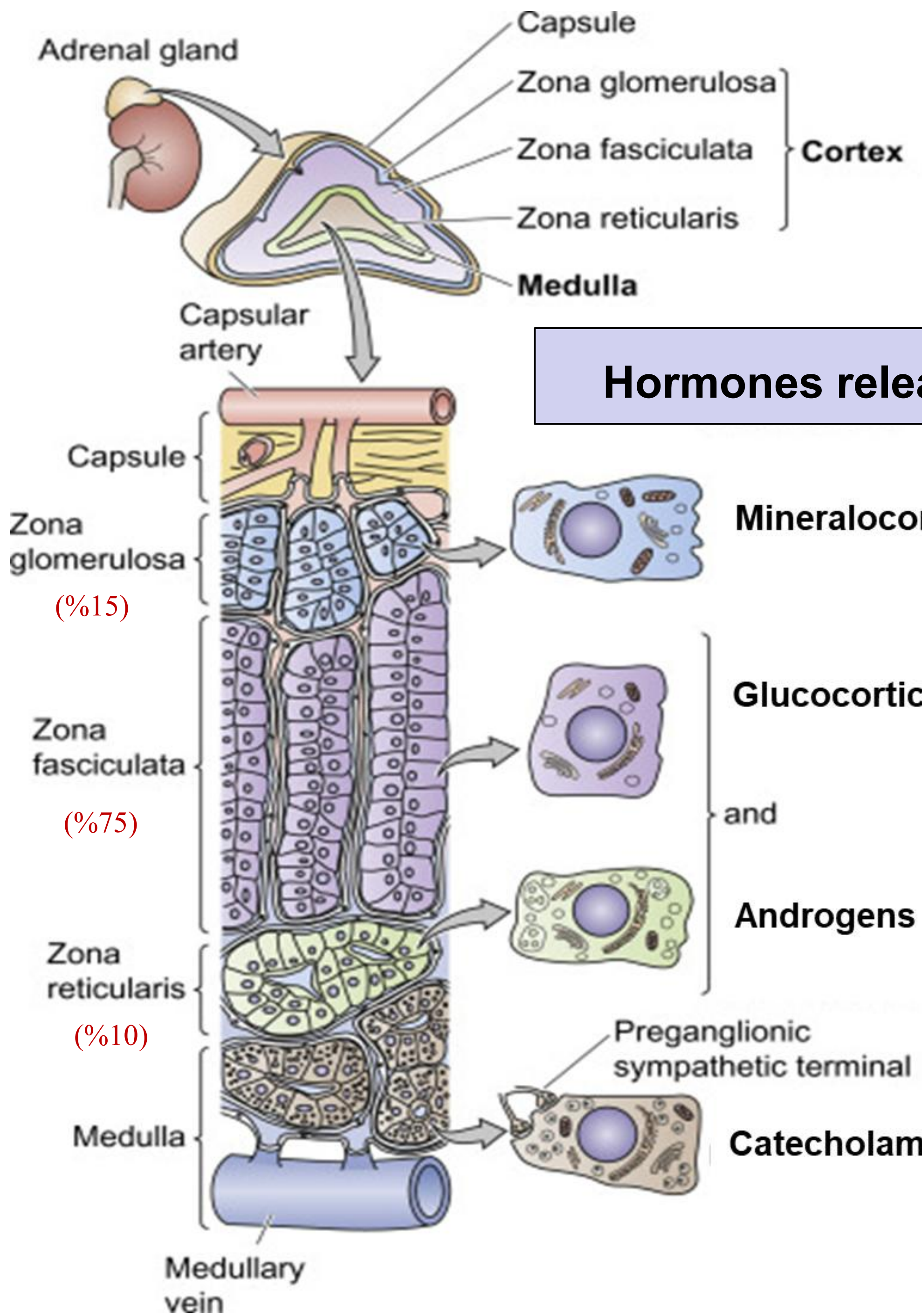




Adrenal medulla develops from neuroectodermal tissue related to sympathetic ganglia.

Adrenal cortex develops from the mesodermal tissue and secretes steroid hormones.

Types of Adrenal Hormone



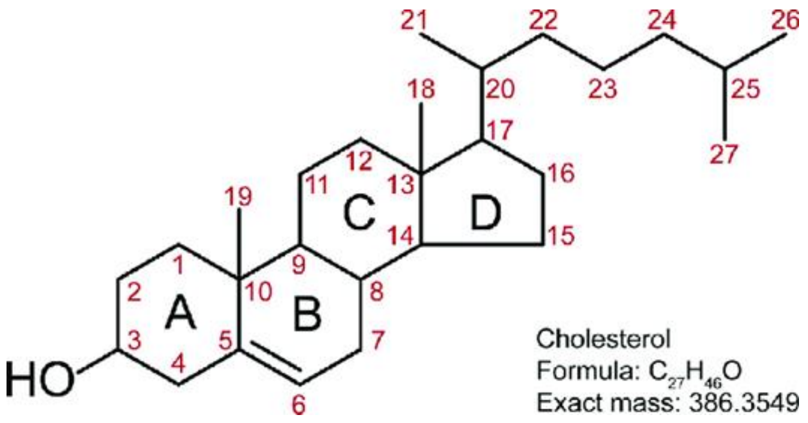
Hormones released	Major hormone	Functions of hormone
Mineralocorticoids	Aldosterone	▪ Regulation of mineral balance (Sodium & Potassium balance)
Glucocorticoids	Cortisol Corticosterone Cortisone	▪ Regulation of glucose metabolism ▪ Immunosuppressant
Androgens	Dehydroepiandrosterone (DHEA)	▪ Stimulate Masculinization
Catecholamines	Adrenaline Noradrenaline	▪ Increase Heart Rate ▪ Contract Blood Vessels ▪ Dilate Air Passages

Synthesis of Adrenal Steroid Hormone

- **Steroid hormones** are made from **derivatives of cholesterol** in the **mitochondria** and **smooth endoplasmic reticulum of endocrine cells.**
  - ✓ -Approximately 80 % of the cholesterol used for steroid synthesis is provided by **low density lipoproteins (LDL)** in the circulating plasma**.**

- Cholesterol is from the lipid droplets in cortical cells **(cholesterol esters in LDL).**

- \- Each layer produces steroid hormones from the precursor cholesterol. However, the **specific steroid hormone** produced differs in each layer because of **zonal specific enzymes.**



Synthesis of Adrenal Steroid Hormone

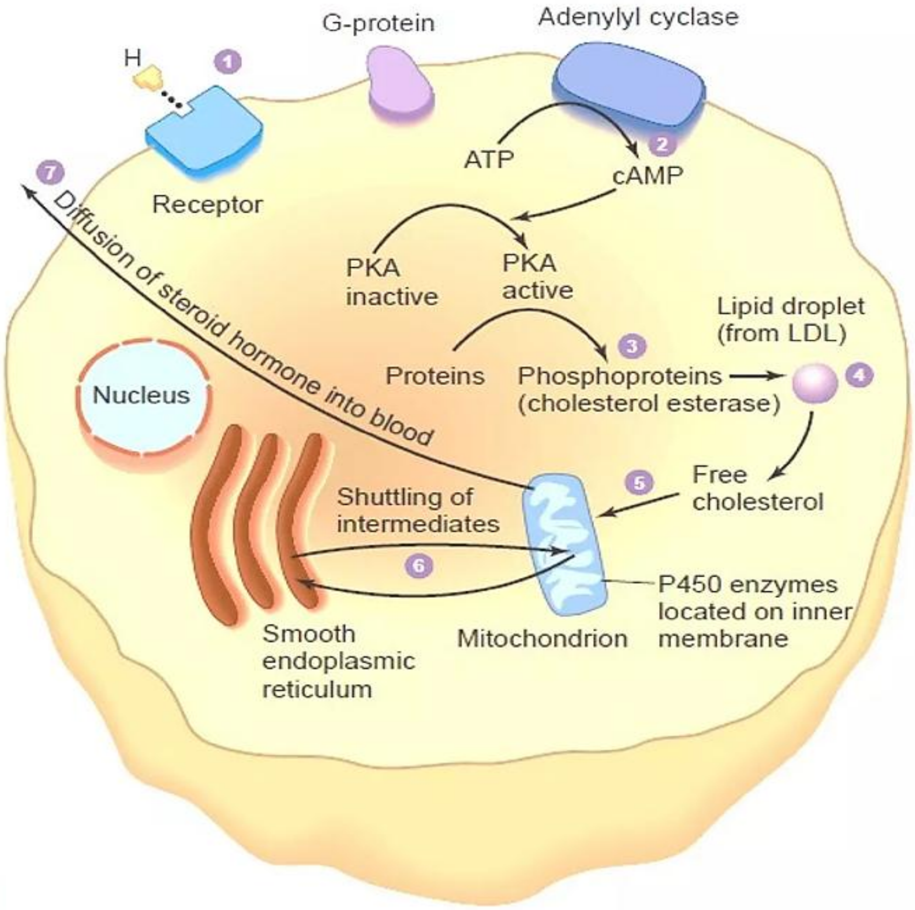
- \- **Cholesterol** and **cholesterol esters** are taken up into the cells of the adrenal cortex.

- \- Cholesterol is released by hydrolysis of the esters.

- \- A **transport protein** is necessary for the initial mitochondrial uptake of cholesterol and is called **steroidogenic acute regulatory protein** (StAR).

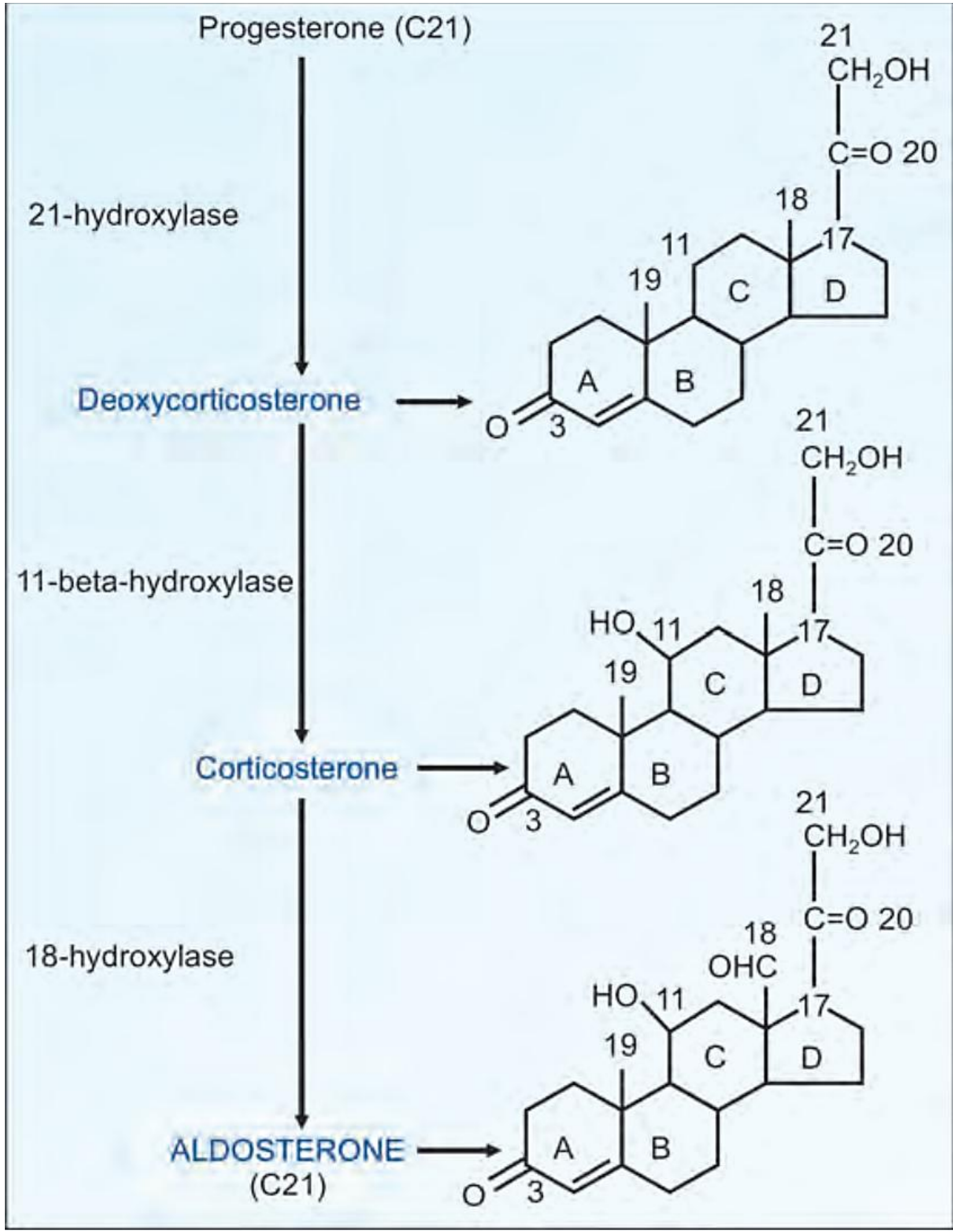
- \- **In the mitochondria cholesterol** is converted to **pregnenolone** by the enzyme **cholesterol dismolase** (also known as cholesterol **side chain cleavage** (SCC) enzyme).
  - ✓- Two hydroxylations at C-20 and C-22 precede cleavage of the C-20 to C-22 carbon bond leaving a carbonyl group at C20.
  - ✓- The steroid hydroxylation steps involve an enzyme based on a cytochrome P450.

- **In the endoplasmic reticulum**, **pregnenolone** is oxidized to **progesterone** through the action of 3β-hydroxysteroid dehydrogenase.



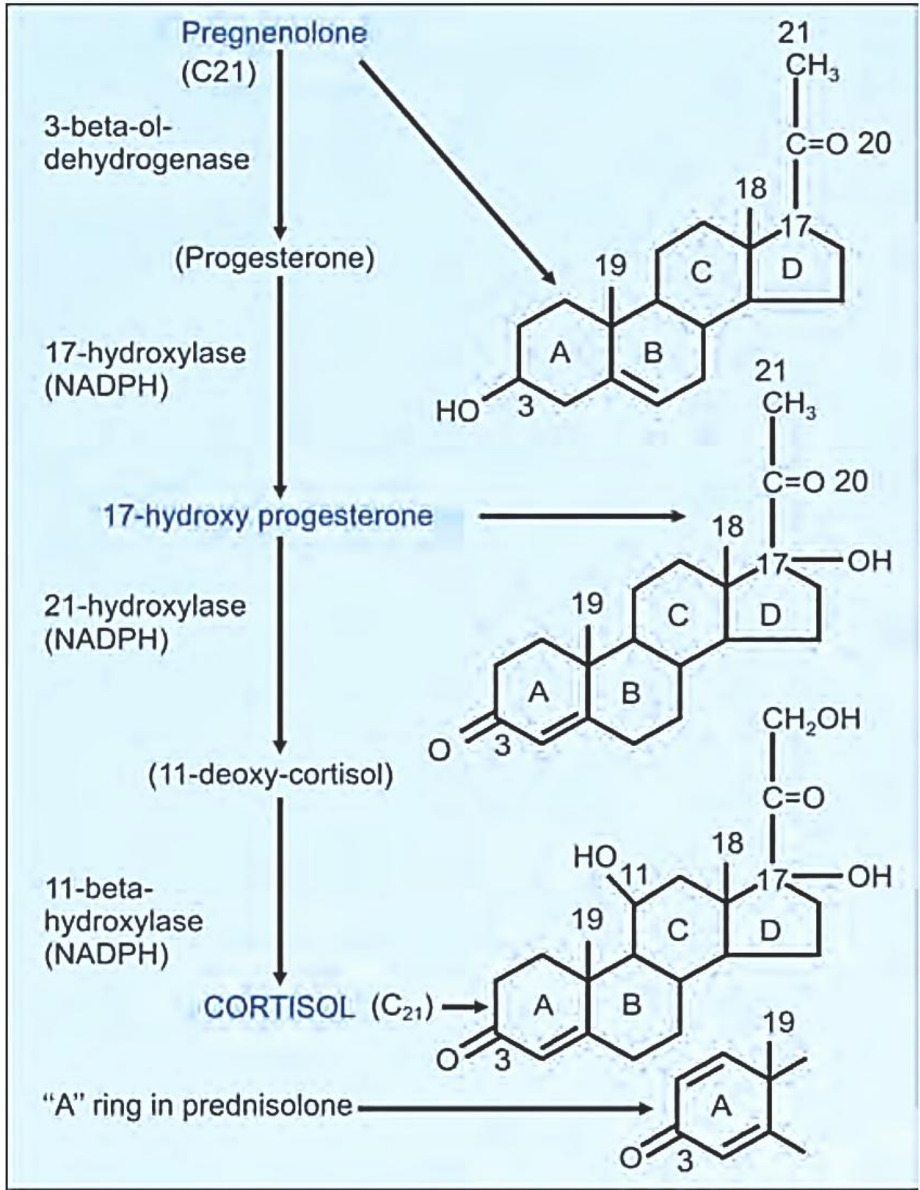
Aldosterone synthesis pathways

- Aldosterone is produced from **cholesterol** in the **zona glomerulosa** by the sequential action of **four enzyme systems**.
- **- The first steps to pregnenolone have been described.**
- **- CYP11B2 or aldosterone synthase has three activities that are only expressed in the zona glomerulosa;**
- - This enzyme **catalyses hydroxylations** at **C-11** and then **C-18** before oxidizing the **C-18** hydroxyl to an aldehyde.
- - The intermediates from **deoxycorticosterone** are **corticosterone** and **18-hydroxycorticosterone**.
- - CYP11B1 and CYP11B2 are located in the mitochondria of the glomerulosa cells respectively.

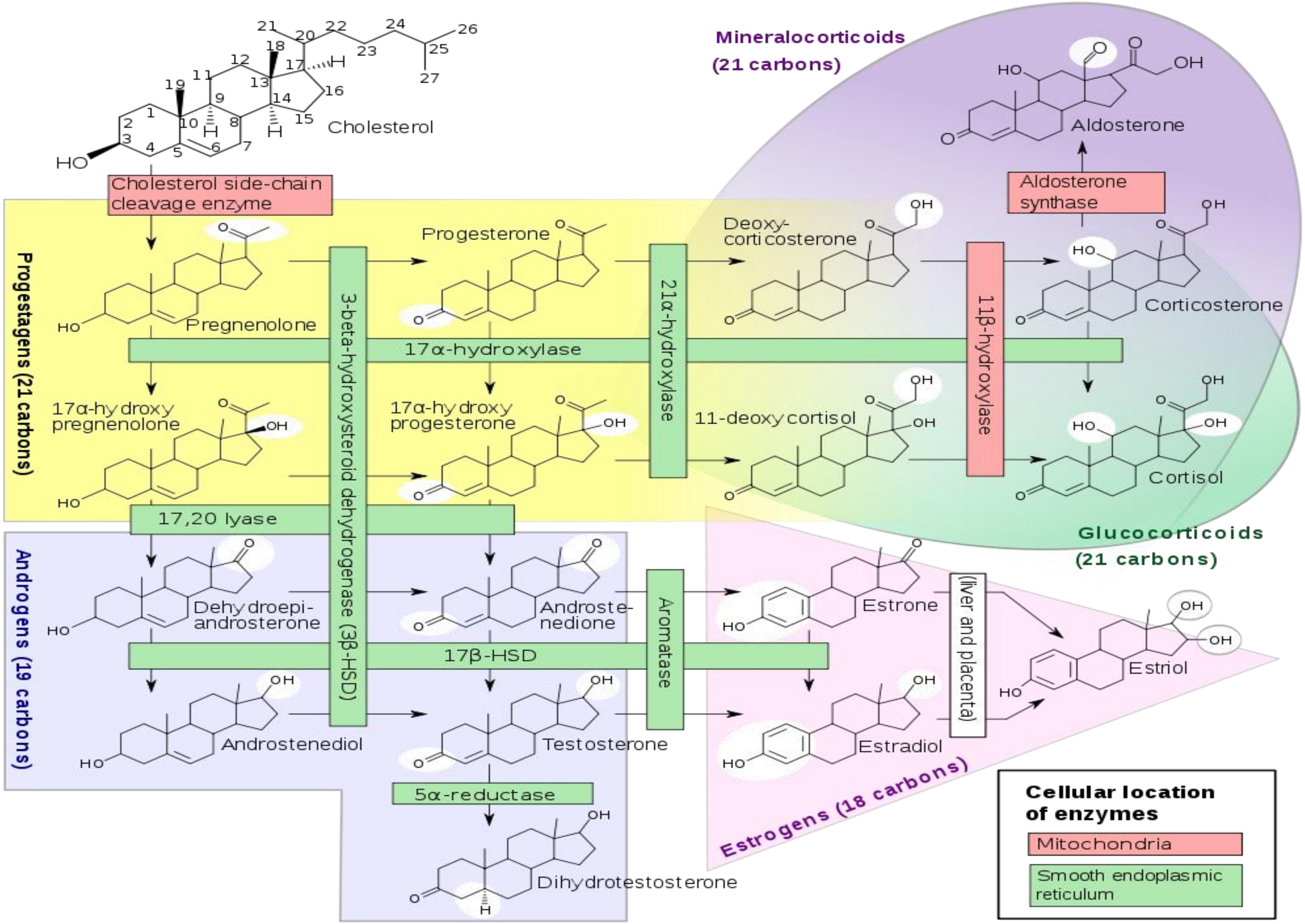


Cortisol synthesis pathways

- ✓- Cortisol is produced from cholesterol in the **zona fasciculata** by the sequential action of five enzyme systems.
- ✓- **The first steps to pregnenolone have been described.**
- ✓- Three **hydroxylation reactions** involving positions 17, 21, and 11 then follow.
- ✓- In the adrenal cortex **3β-hydroxy steroid dehydrogenase** acts to convert 17-hydroxypregnenolone to 17-hydroxyprogesterone which is further **converted to cortisol.**



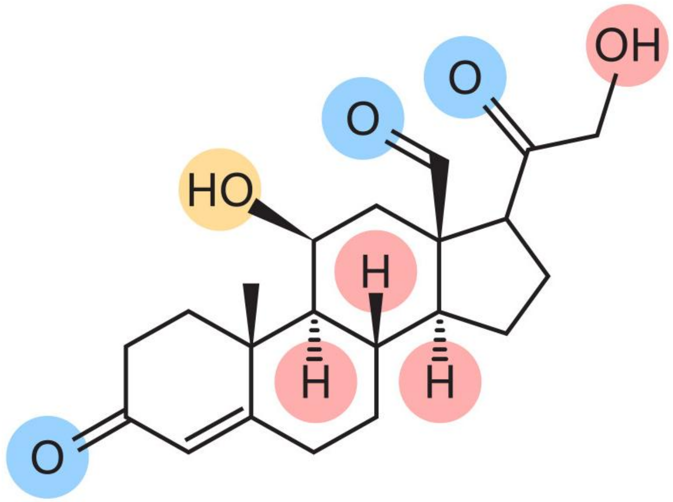
Steroidogenesis



A- Adrenal Cortex : Aldosterone Hormone

Aldosterone Hormones is a steroid hormone synthesized in the **zona glomerulosa** of the adrenal cortex responsible for electrolyte (**sodium**, **chloride**, and **potassium**) and fluid balance in the body. Therefore, Aldosterone is known a **mineralocorticoid** hormone.

- Half_ life of mineralocorticoids is ***20* minutes**



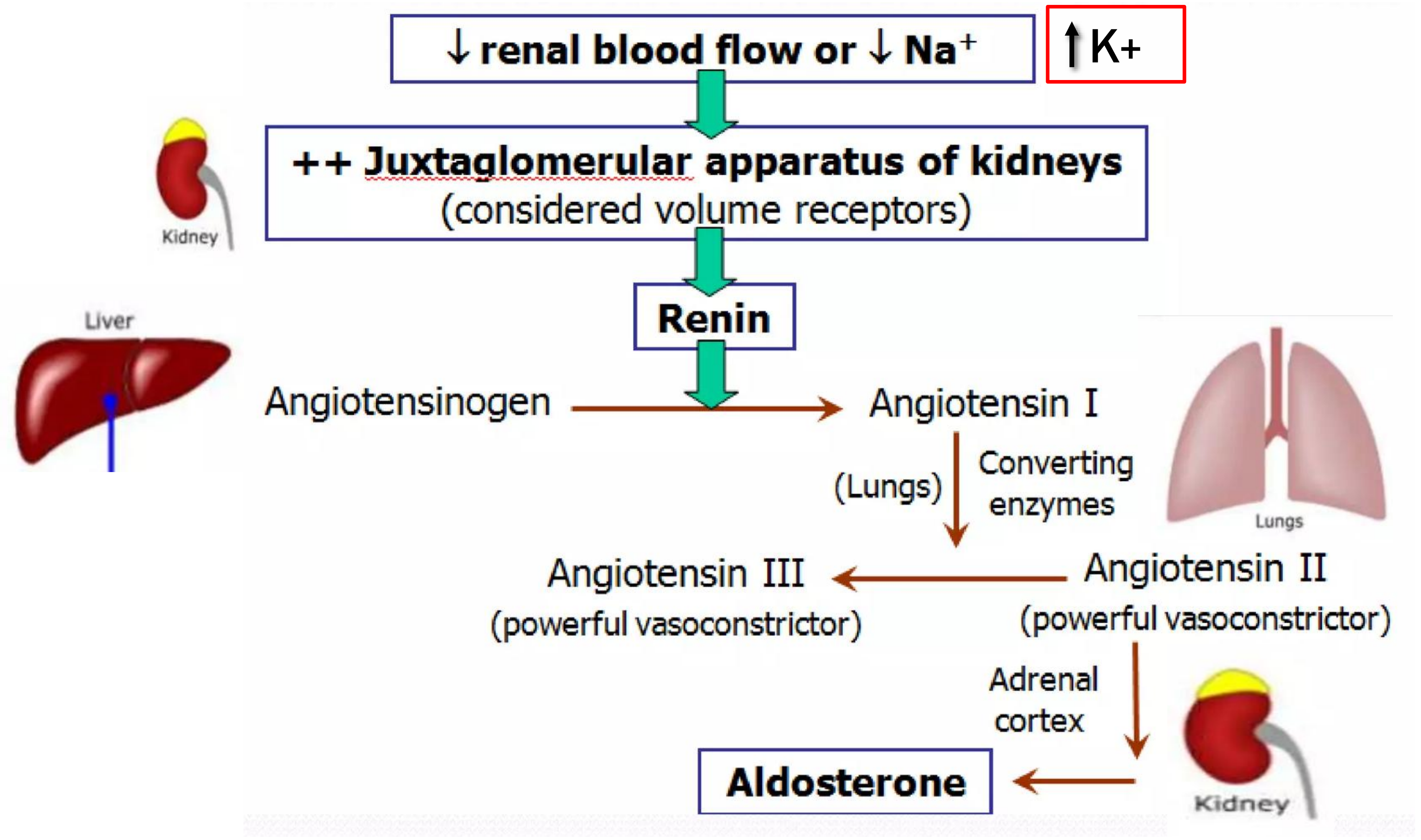
Regulator of Aldosterone Synthesis

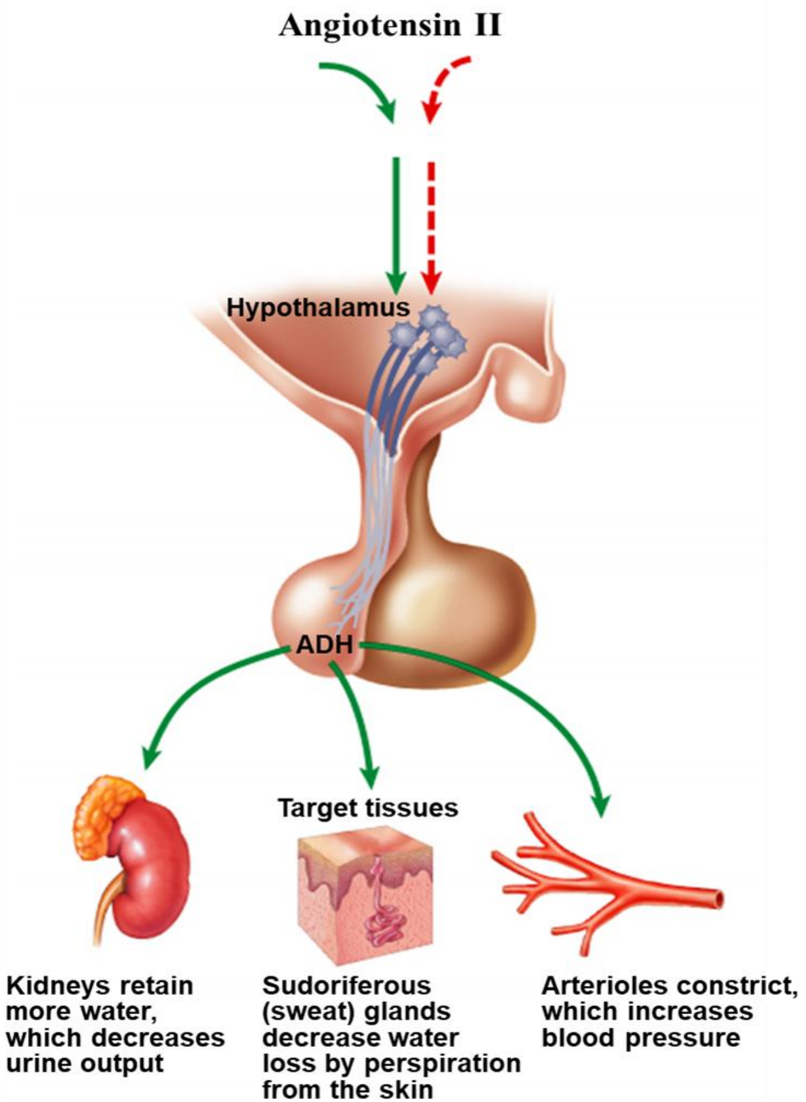
- **The 2 primary regulators of aldosterone are :**

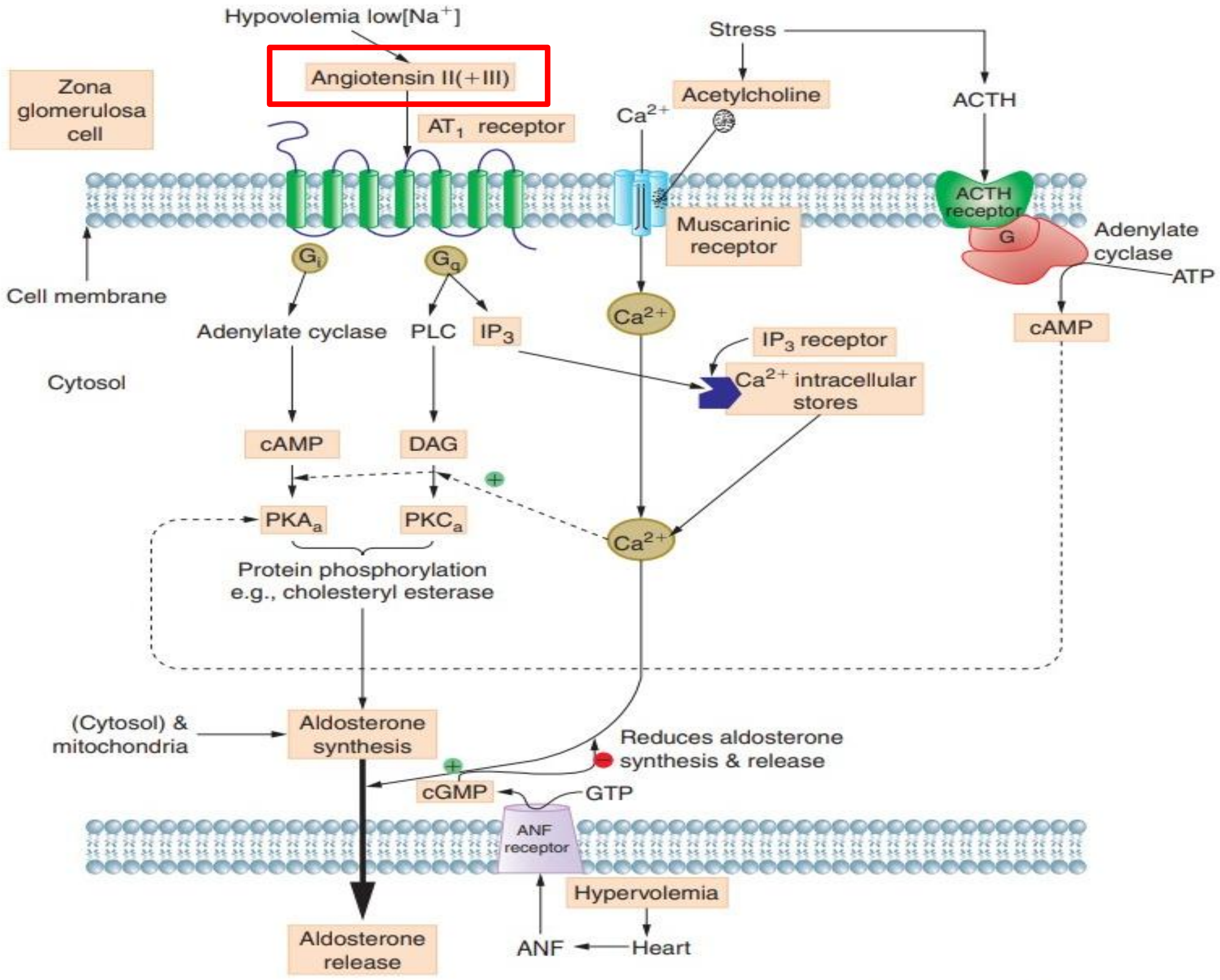
(1) The renin-angiotensin-aldosterone system (RAAS)

(2) Potassium levels

Renin-angiotensin-aldosterone System



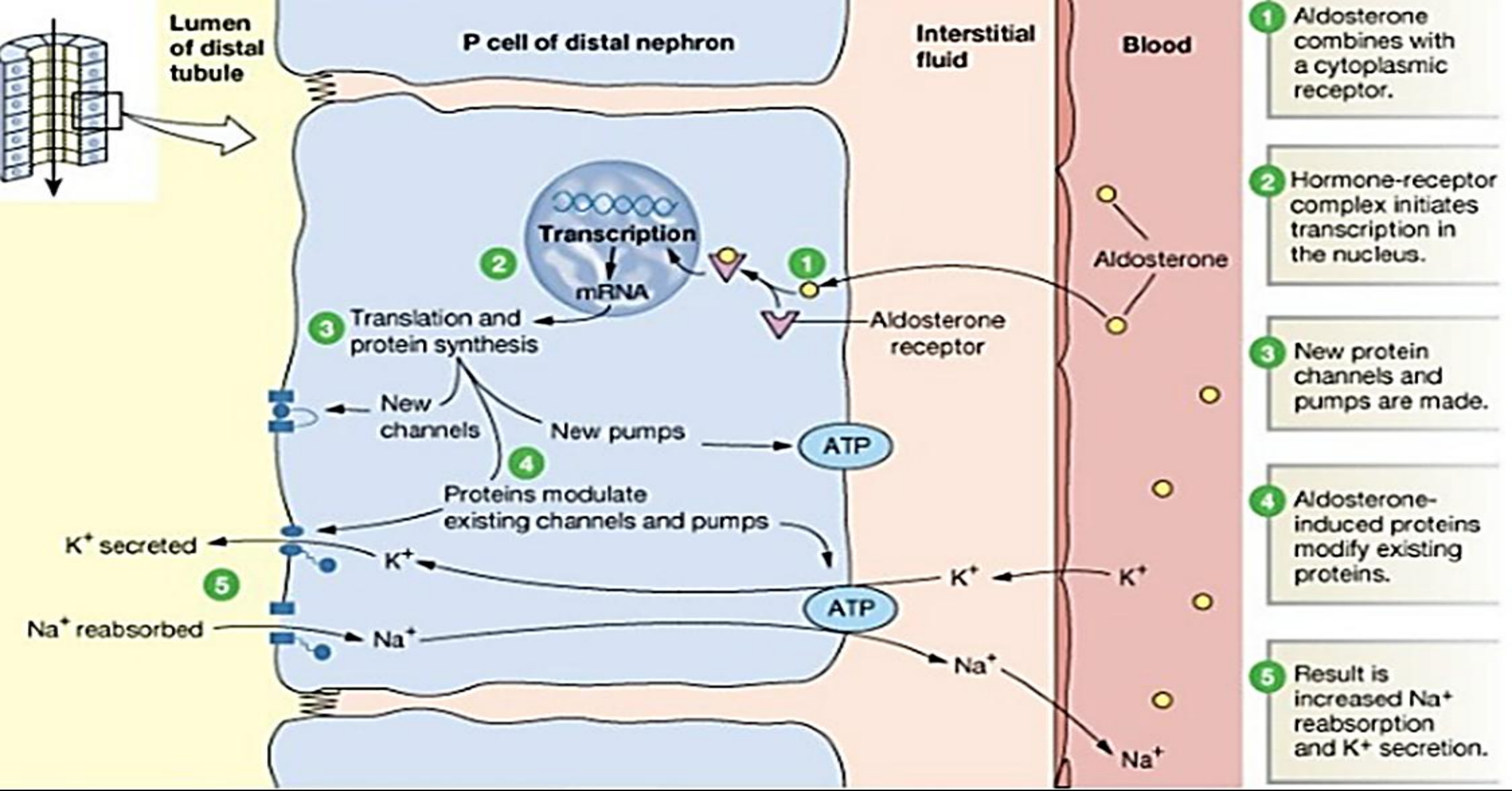




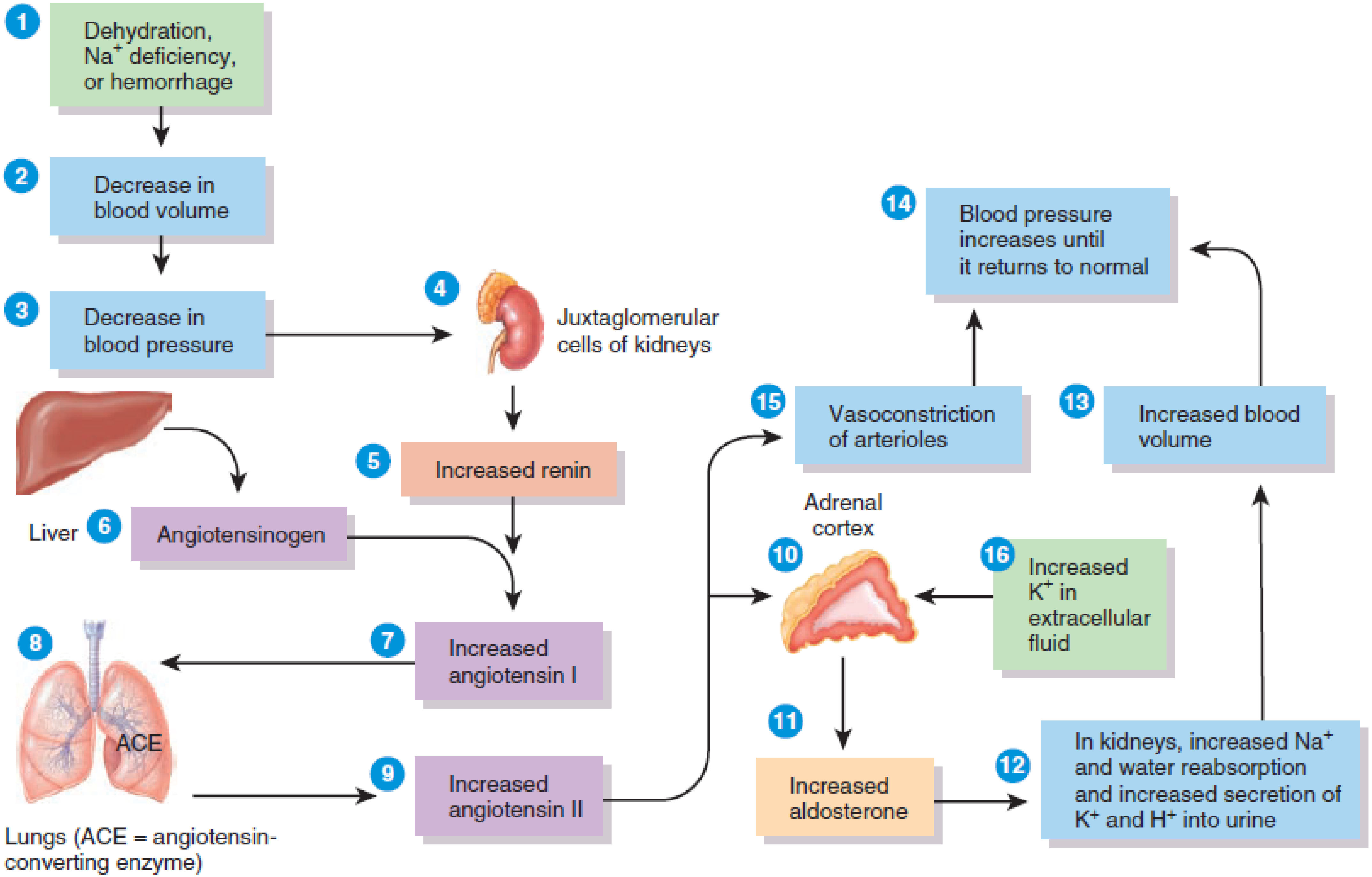
Hypovolemia low[Na+]
Angiotensin II(+III)
AT1 receptor
Zona glomerulosa cell
Stress
Acetylcholine
ACTH
Ca2+
ACTH receptor
G
Muscarinic receptor
Adenylate cyclase
ATP
Cell membrane
Gi
Gq
Adenylate cyclase
PLC
IP3
Ca2+
cAMP
IP3 receptor
Ca2+ intracellular stores
Cytosol
cAMP
DAG
PKAa
PKCa
Ca2+
Protein phosphorylation e.g., cholesteryl esterase
(Cytosol) & mitochondria
Aldosterone synthesis
Reduces aldosterone synthesis & release
cGMP
GTP
ANF receptor
Hypervolemia
Aldosterone release
ANF
Heart

TRANSPORT

- In the plasma, **40%** aldosterone circulates in free form and **60%** in bound form.
- Aldosterone is weakly bound to the specific **aldosterone-binding globulin** to **transcortin** and to **albumin**.



Lumen of distal tubule
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⁺
Na⁺ reabsorbed
Na⁺
1 Aldosterone combines with a cytoplasmic receptor.
2 Hormone-receptor complex initiates transcription in the nucleus.
3 New protein channels and pumps are made.
4 Aldosterone-induced proteins modify existing proteins.
5 Result is increased Na⁺ reabsorption and K⁺ secretion.



1
Dehydration, Na^+ deficiency, or hemorrhage
2
Decrease in blood volume
3
Decrease in blood pressure
4
Juxtaglomerular cells of kidneys
5
Increased renin
Liver
6
Angiotensinogen
7
Increased angiotensin I
8
ACE
Lungs (ACE = angiotensin-converting enzyme)
9
Increased angiotensin II
10
Adrenal cortex
11
Increased aldosterone
12
In kidneys, increased Na^+ and water reabsorption and increased secretion of K^+ and H^+ into urine
13
Increased blood volume
14
Blood pressure increases until it returns to normal
15
Vasoconstriction of arterioles
16
Increased K^+ in extracellular fluid

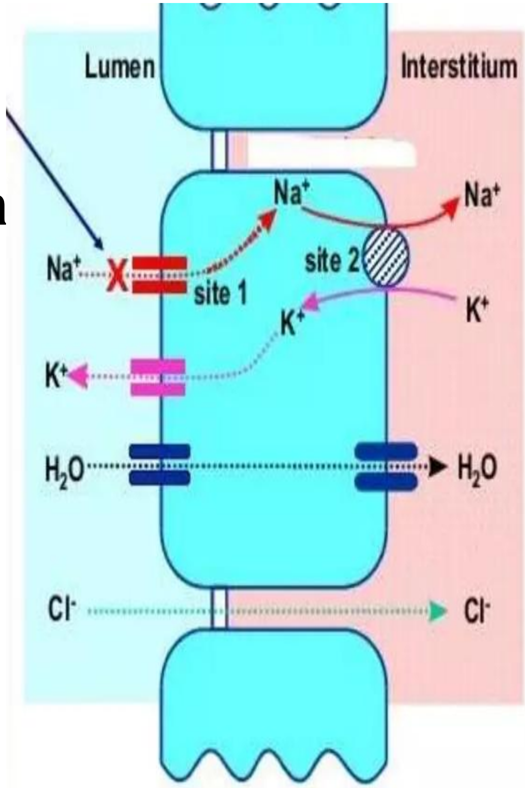
ACTIONS OF ALDOSTERONE

1. Conservation of Na+ & excretion of K+

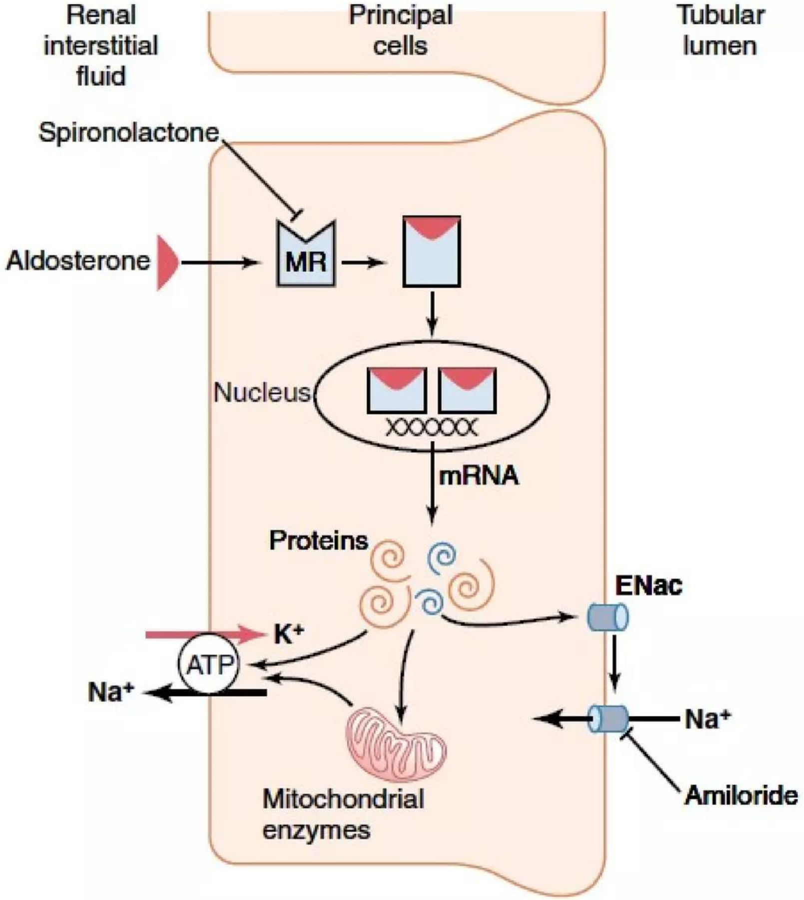
2. Water excretion & ECF Volume Regulation

3. Relationship with Acid – Base balance

4. Secondary effects of excess of aldosterone



Aquaporin-2



1. Effects on Renaltubules

Aldosterone acts on late distal tubules and collecting ducts of kidney and causes following effects:

I. **Sodium reabsorption** from the tubular fluid into the Renal tubular epithelial cells.

II. **Potassium excretion**. In the kidney, the active reabsorption of Na+ occurs in exchange of K+ and H+. Thus, Aldosterone not only causes reabsorption of Na+, but Excretion of K+ as well by renal tubular epithelial cells.

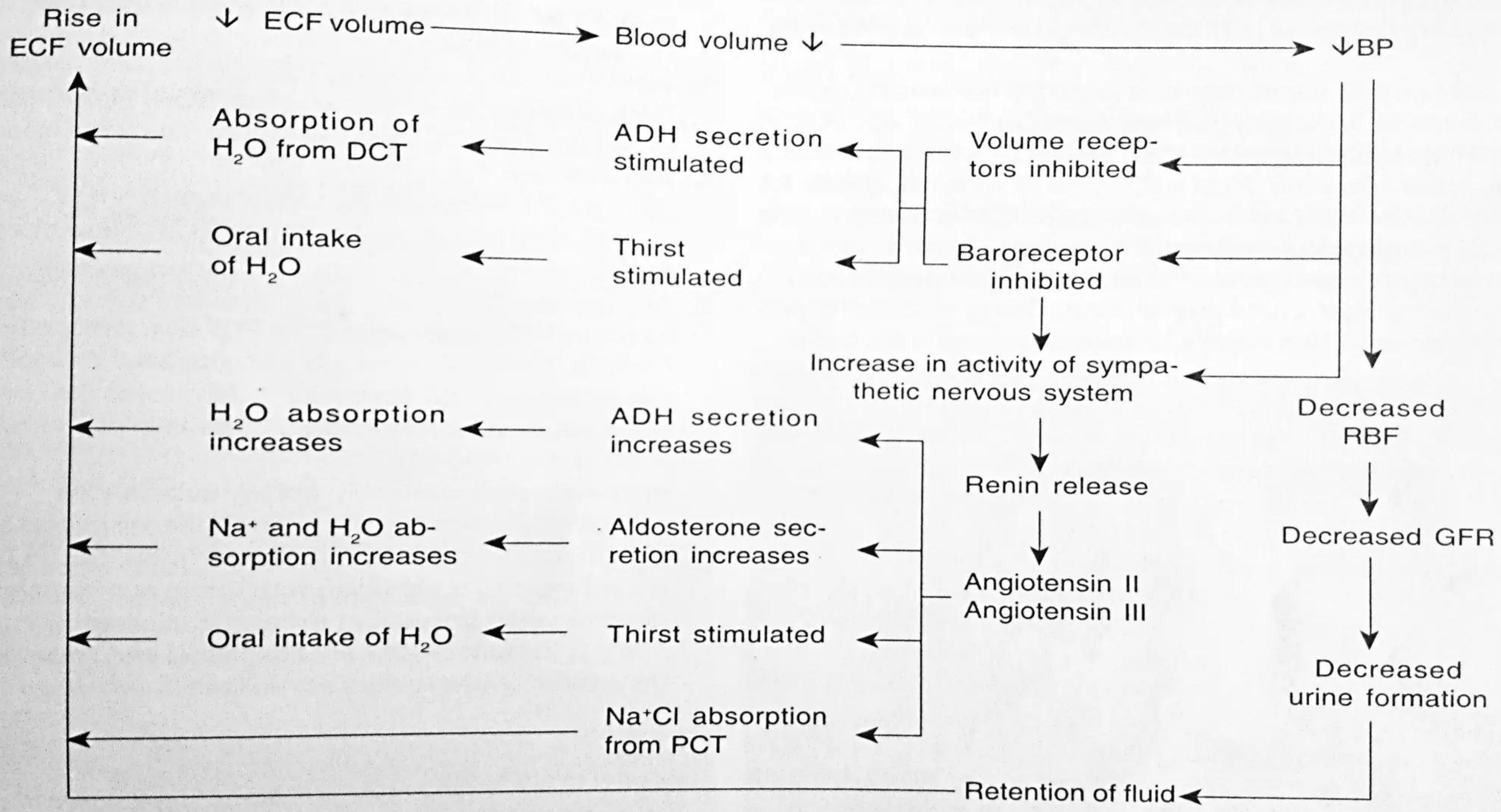
III. **H+ excretion**. Aldosterone also enhances the tubular Secretion of H+ as Na+ is reabsorbed.

IV. **Ammonium and Magnesium excretion** is also increased by aldosterone.

- Excess aldosterone leads to :
    - ↑sed plasma Na+/K+ Conc. Ratio due to ↑ses K+ excretion.
    - Decline in urine Na+/ K+ Conc. Ratio due to ↓ses Na+ and ↑ses K+ excertion.
- Removal of adrenal cortex results in :
    - Na+ & Water loss, but Na+ loss excess then water.
    - Result decreased in ECFV produces hypotension, dehydration, circulatory collapse, finally death.
    - Retention of K+ produces hyperkalemia, dehydration and circulatory collapse.

2. Water excretion & ECF Volume Regulation

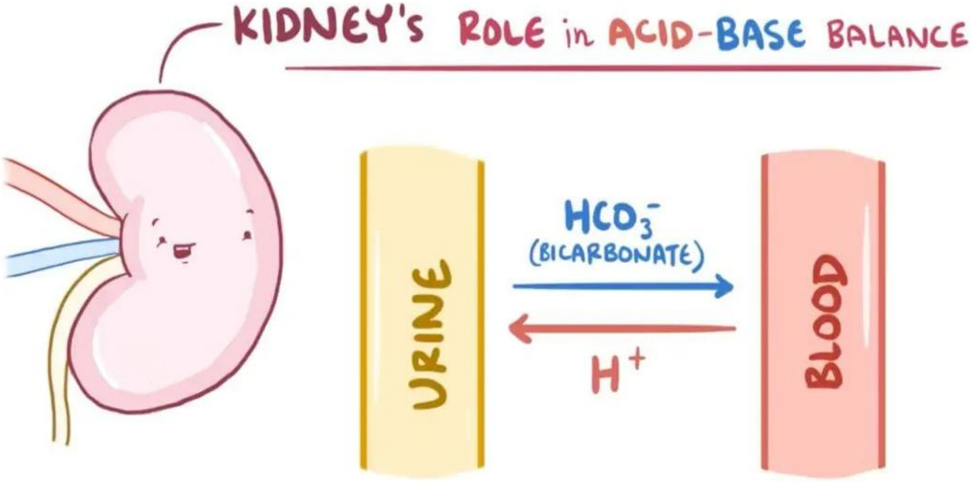
- Aldosterone has no direct effects on GFR, Renal Plasma Flow(RPF) or renin production.
- By stimulating **Na+ reabsorption** it causes **water retention**.
- The result expansion of ECFV then leads to ↑ses in GFR, RPF & ↓ses renin production.
- High circulating aldosterone level is common finding in **cirrhosis** of liver, nephrosis, congestive heart failure, etc.


Rise in ECF volume
↓ ECF volume
Blood volume ↓
↓BP
Absorption of H_2O from DCT
ADH secretion stimulated
Volume receptors inhibited
Oral intake of H_2O
Thirst stimulated
Baroreceptor inhibited
Increase in activity of sympathetic nervous system
H_2O absorption increases
ADH secretion increases
Decreased RBF
Renin release
Na^+ and H_2O absorption increases
Aldosterone secretion increases
Decreased GFR
Angiotensin II
Angiotensin III
Oral intake of H_2O
Thirst stimulated
Decreased urine formation
Na^+Cl absorption from PCT
Retention of fluid

A

3. Relationship with Acid – Base balance

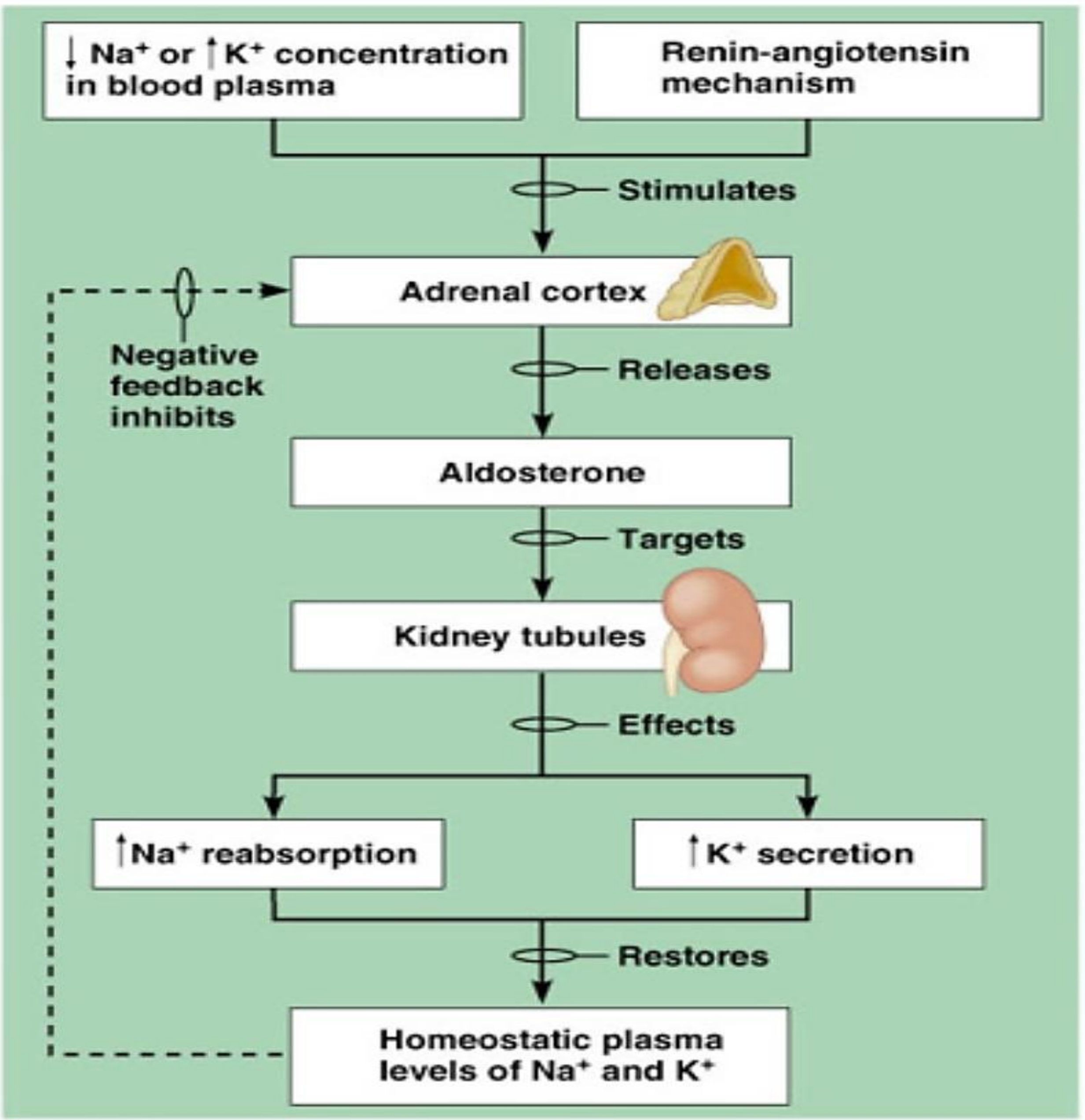
- Secretion of H+ Ion .
- Reabsorption of filtered HCO3- .
- Production of new HCO3-.



4. Secondary effects of excess of aldosterone

- **Increased secretion of K+** in distal convoluted tubule increases its **excretion in urine causing marked hypokalemia**
- Characterized by – muscular weakness, ↑ses H+ secretion – acidic urine etc
- Affects on BP :
  - ✓- **Increase in ECF volume** and the **blood volume** finally leads to increase in blood pressure.

Negative Feedback



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.

Over production of aldosterone

primary causes, ie. Conn's syndrome

- adenoma, nodular hyperplasia of zona glomerulosa

secondary

- cirrhosis, ascites, nephrotic syndrome

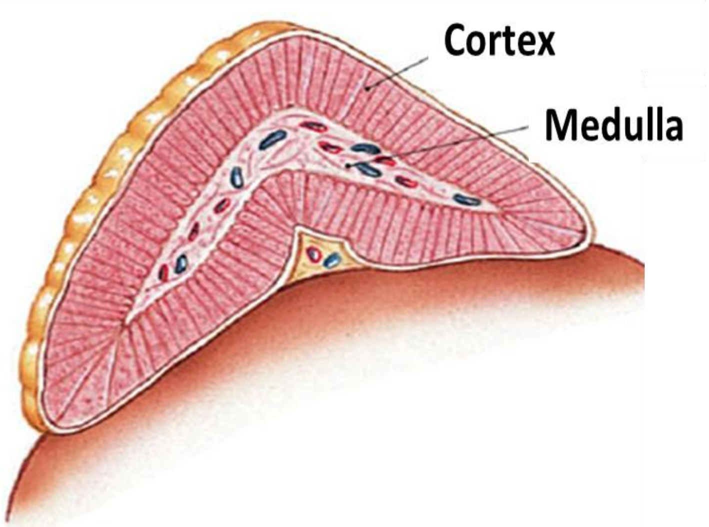
symptoms, signs

- headache, hypokalemia causing muscle weakness, hypernatremia, hypervolemia, nocturnal polyuria, hand cramping

B- Adrenal Medulla

- The adrenal medulla is the **inner part** or core of each adrenal gland**.**

- **Activated** by same stimuli as the **sympathetic nervous system**.
  - ✓- examples :– exercise, cold, stress, hemorrhage, etc.
- Hormones synthesized in adrenal medulla are **catecholamines.**
- **It secretes catecholamines:**
  - ✓ - **Adrenaline** (epinephrine) -- 80% of the secretion.
  - ✓ - **Noradrenaline** (norepinephrine) -- 20 % of the secretion.
  - ✓- Small amount of **dopamine**



❖ Half_ life of catecholamines is ***25* minutes**

Adrenaline (epinephrine)

Adrenaline, also known as **epinephrine**, is a hormone which is involved in regulating visceral functions.

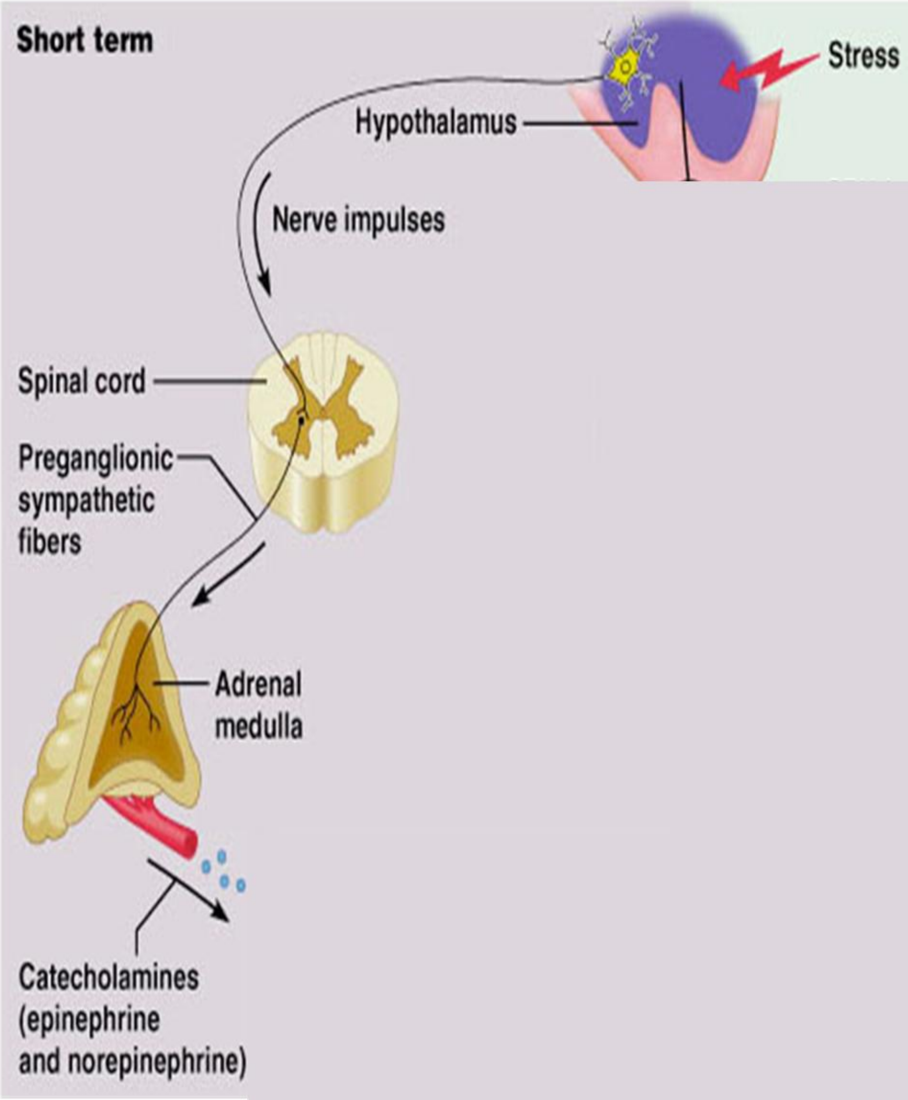
- \- It plays an essential role in the fight-or-flight response, helping to prepare body for **extreme efforts**.
  - ✓- **Extreme efforts** (increase heart rate, increase blood pressure, dilation of bronchioles, elevation in blood glucose, reduced blood flow to skin and digestive organs and increase blood flow to heart and muscles).
- \- It does this by binding to **alpha** (α) and **beta** (β) receptors.

Regulation of Secretion

❖- Adrenaline secretion from the adrenal medulla increases in following conditions.

- **Exercise**
- **Hypoglycemia**
- **Trauma (physical injury)**
- **Anger and anxiety**
- **Pain**
- **Cold.**

✓The main mechanism of secretion in these conditions is sympathetic stimulation.



Synthesis of Adrenaline

Adrenaline is synthesized from the amino acid Phenylalanine and Tyrosine:

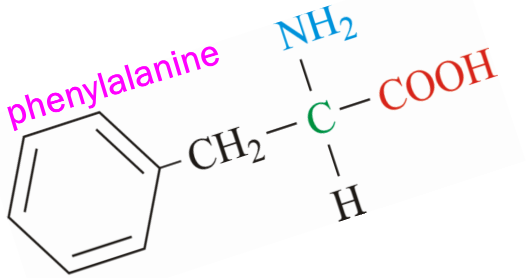
1. Conversion of tyrosine to DOPA is catalyzed with the addition of a hydroxyl group (OH) by **tyrosine hydroxylase.**

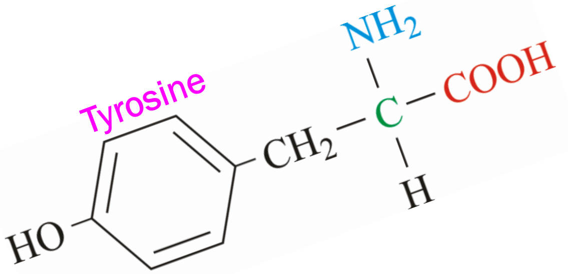
2- Then the removed carboxyl group (COOH) from **DOPA** and converted into **dopamine** by the **DOPA decarboxylase** enzyme.

3- After the removed (COOH) group from DOPA, the **dopamine β-hydroxylase** enzyme adds (OH) group to **dopamine** to formed **noradrenaline.**

4- **Epinephrine** is formed by methylation (CH_3) of **norepinephrine** by **phenylethanolamine-N-methyltransferase** (PNMT).

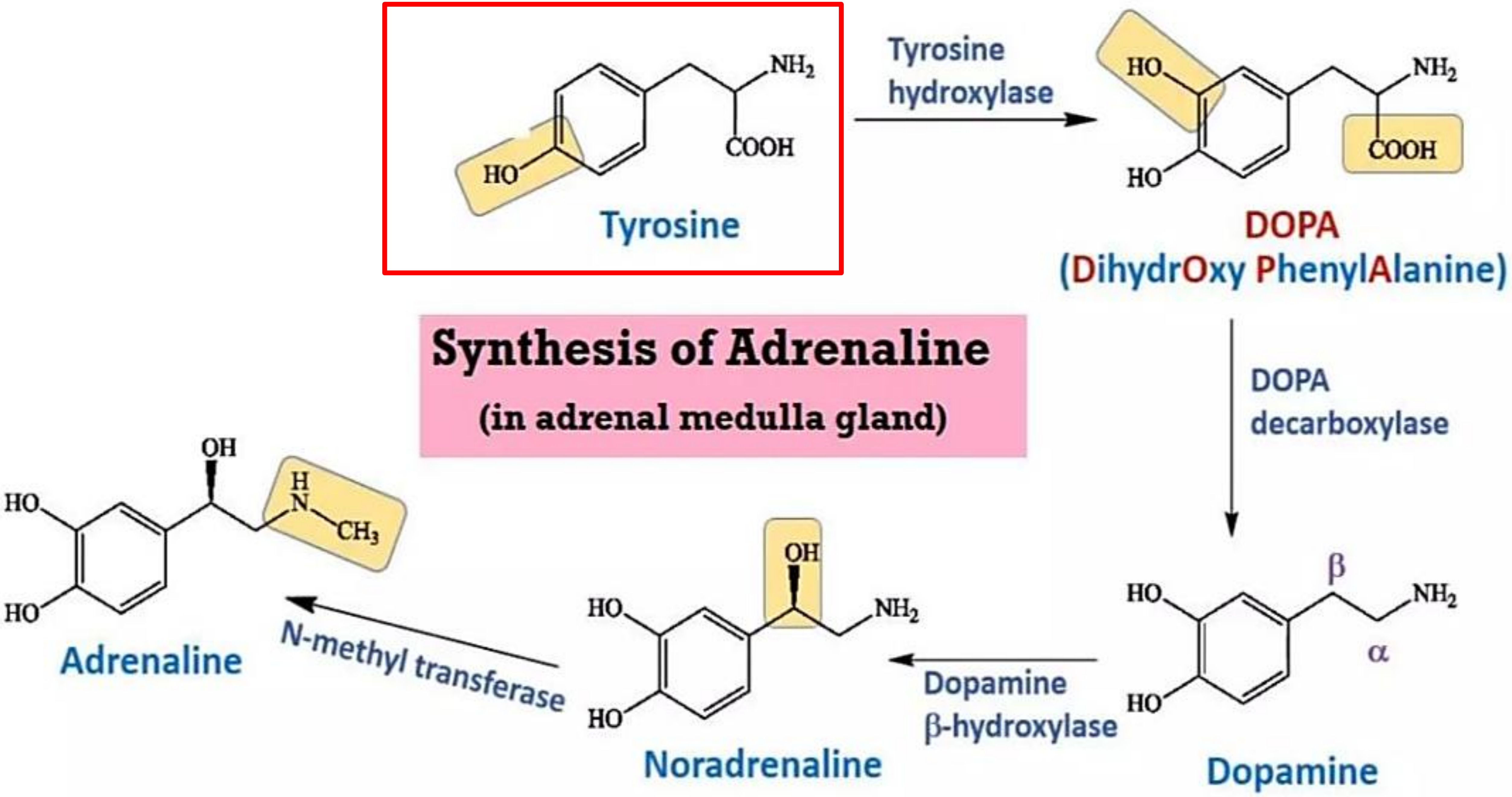
5. After synthesis, the hormones are stored in the **granules of chromaffin cells** before they are secreted.





Synthesis of Adrenaline

(in adrenal medulla gland)



Mechanism of Action

- - Catecholamines act on α and β receptors.

- -There are **three types of β receptors**: β1, β2, and β3, and **two types of α receptors**: α1 and α2.

1. The α1 and α2 receptors have three subtypes each (αA, αB, αC).

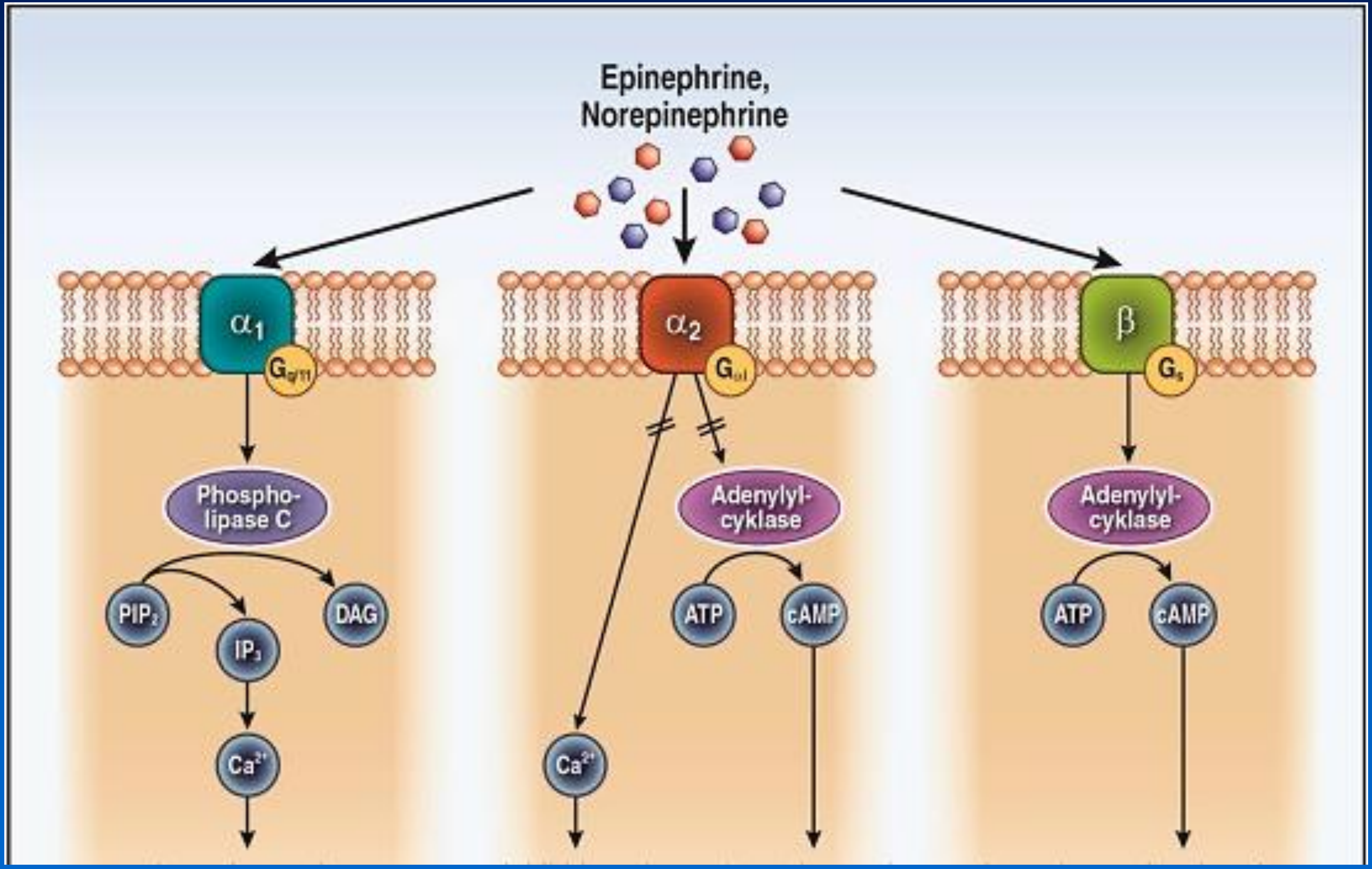
2. Epinephrine and norepinephrine act on both α and β receptors

3. The β1, β2, and β3 receptors are coupled to **adenylyl cyclase**; therefore, catecholamine action through these receptors is mediated by **increase in cAMP** in the cell

4. The α2 receptor is coupled to **inhibitory G protein**; therefore, binding of catecholamines with this receptor decreases cAMP in the cells.

5. The α1 receptor is coupled to **phosphatidylinositol** in the membrane.

Epinephrine Binding to Receptor



Epinephrine Binding to α Receptor

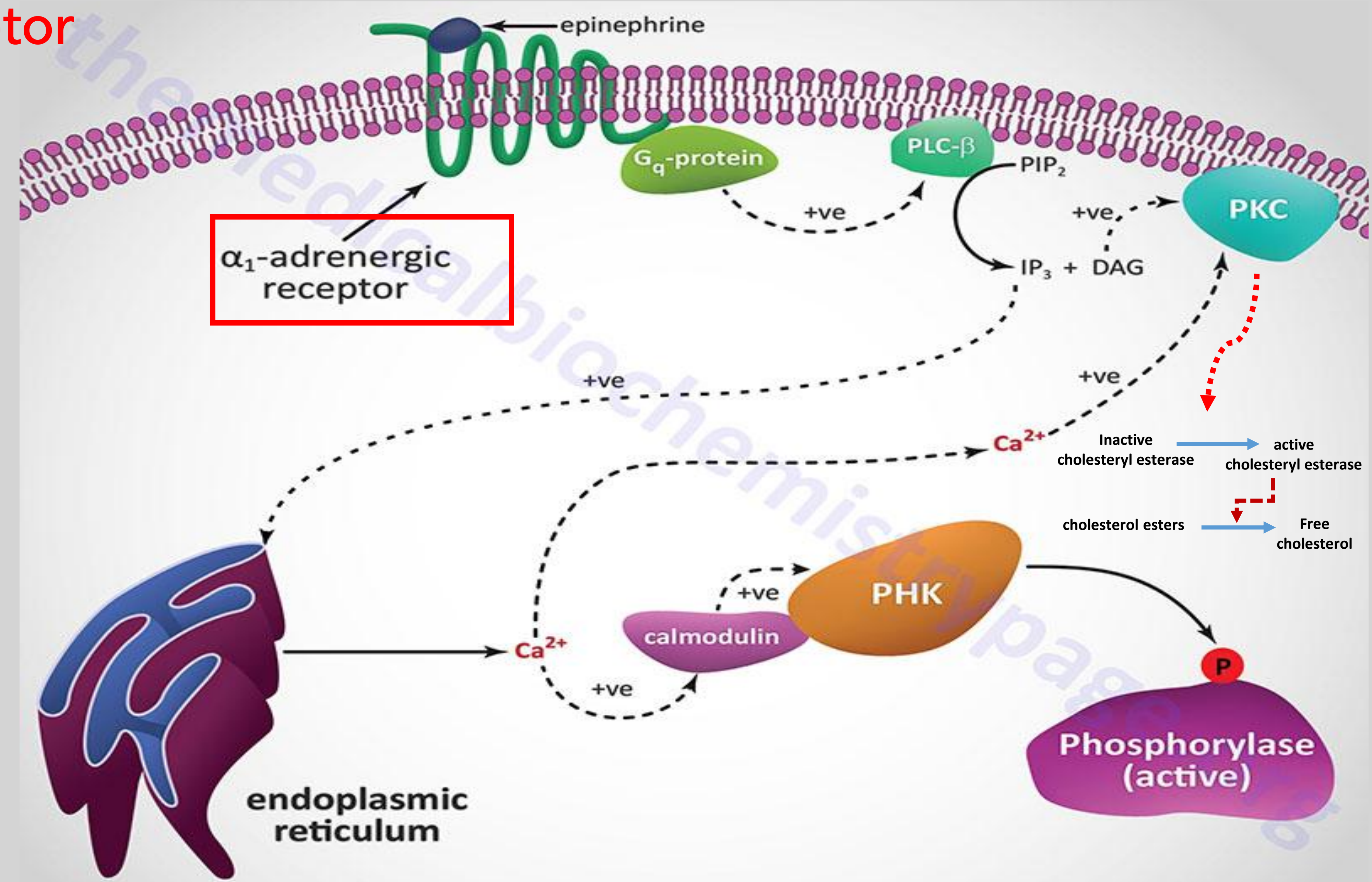
PLC: Phospholipase C

PIP2: Phosphatidyl inositol Bis phosphate

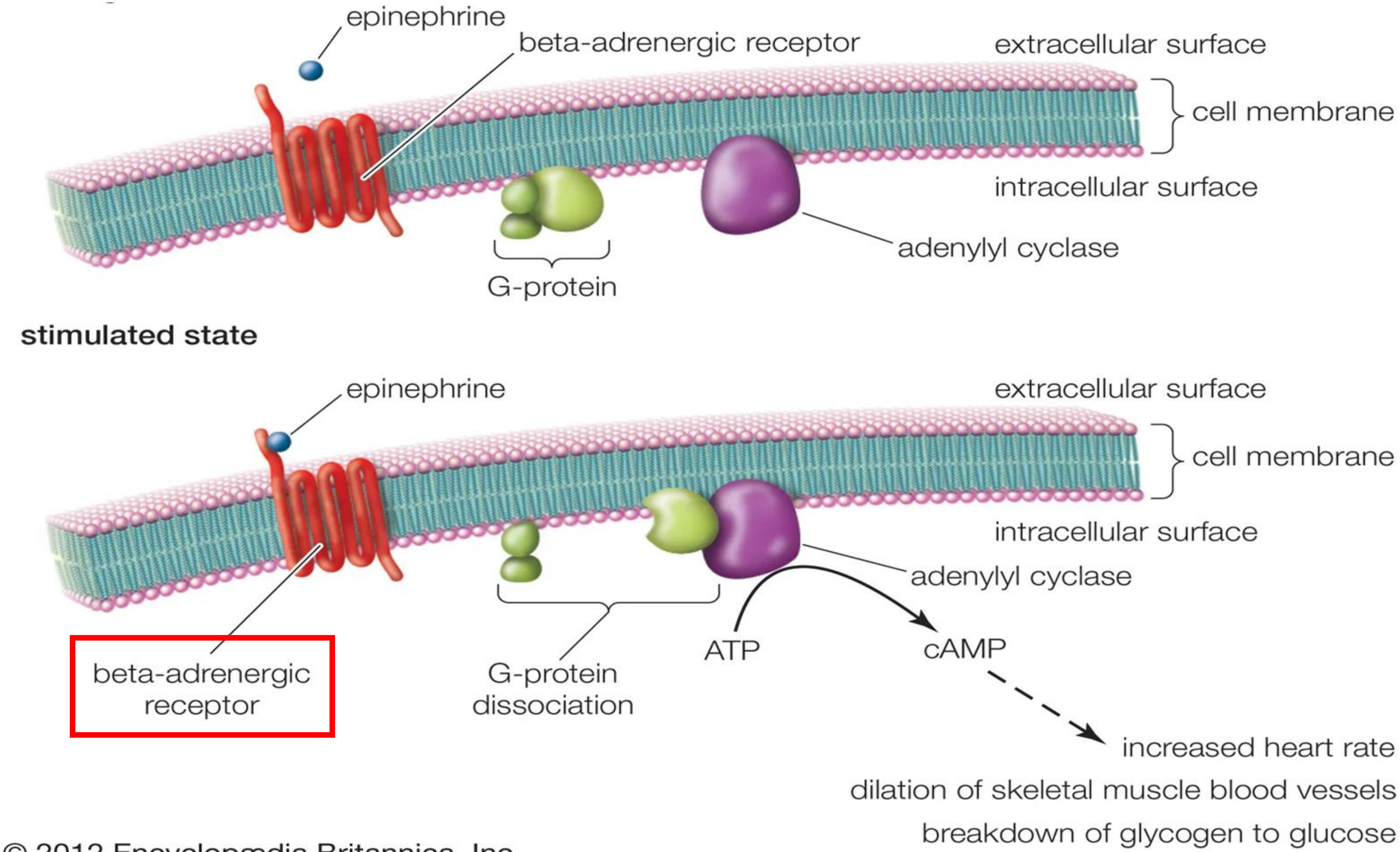
IP3 : inositol Phospholipid

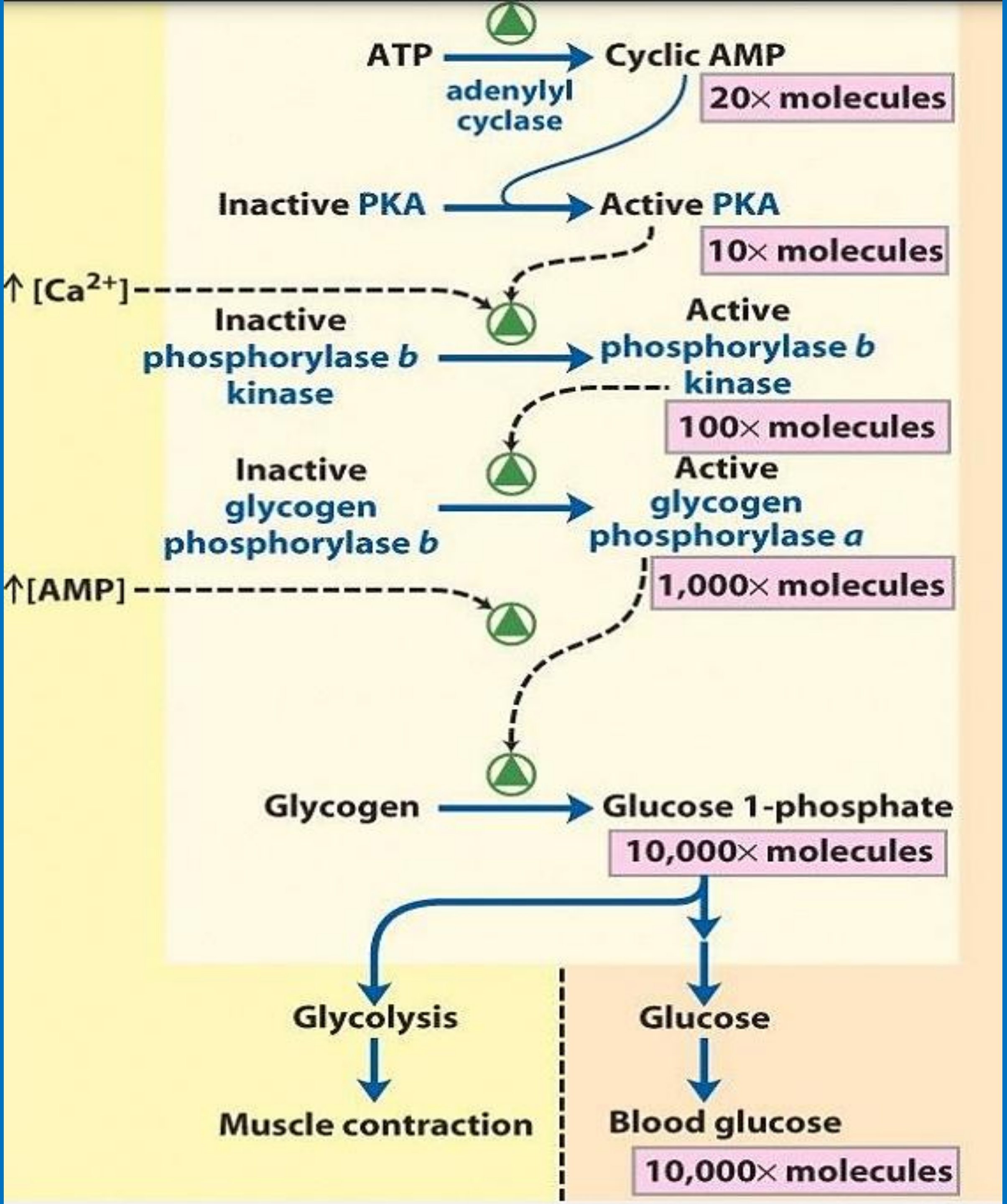
DAG : Di acyl glycerol

PKC : Protein Kinase C



Epinephrine Binding to β Receptor





ATP
adenylyl cyclase
Cyclic AMP
20× molecules
Inactive PKA
Active PKA
10× molecules
↑ [Ca2+]
Inactive phosphorylase b kinase
Active phosphorylase b kinase
100× molecules
Inactive glycogen phosphorylase b
Active glycogen phosphorylase a
1,000× molecules
↑[AMP]
Glycogen
Glucose 1-phosphate
10,000× molecules
Glycolysis
Muscle contraction
Glucose
Blood glucose
10,000× molecules

Effects of Epinephrine

1- Glycogenolysis in liver and skeletal muscle (can lead to hyperglycemia) which increases blood glucose level

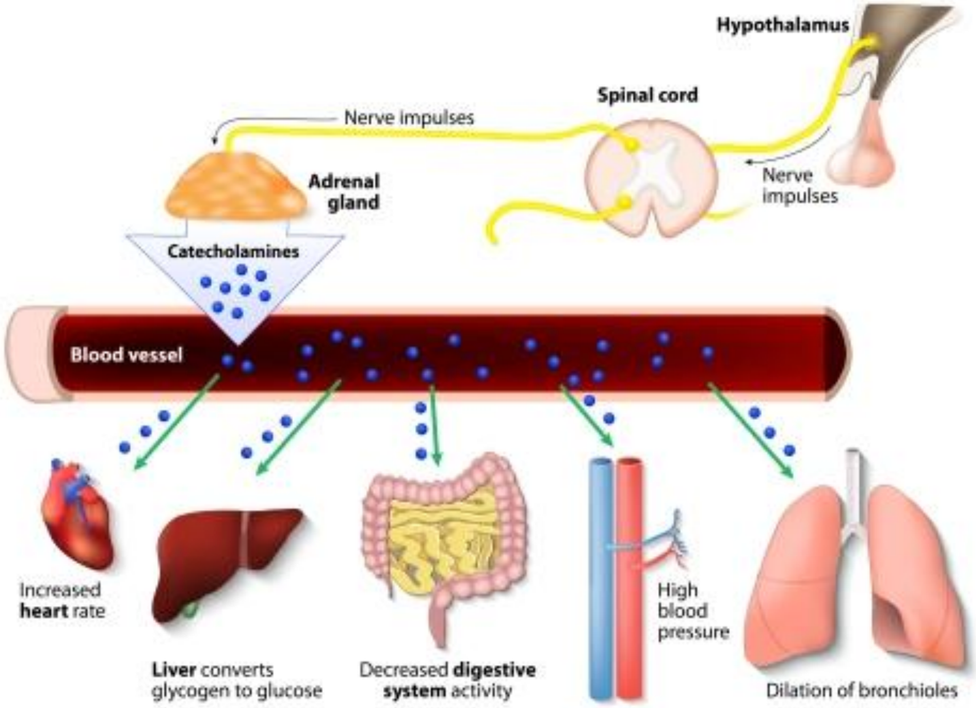
2- Increase heart rate and blood pressure

3- Cause vasoconstriction of blood vessels

4- Mobilization of free fatty acids

5- Increase metabolic rate

6- Increase O_2 consumption



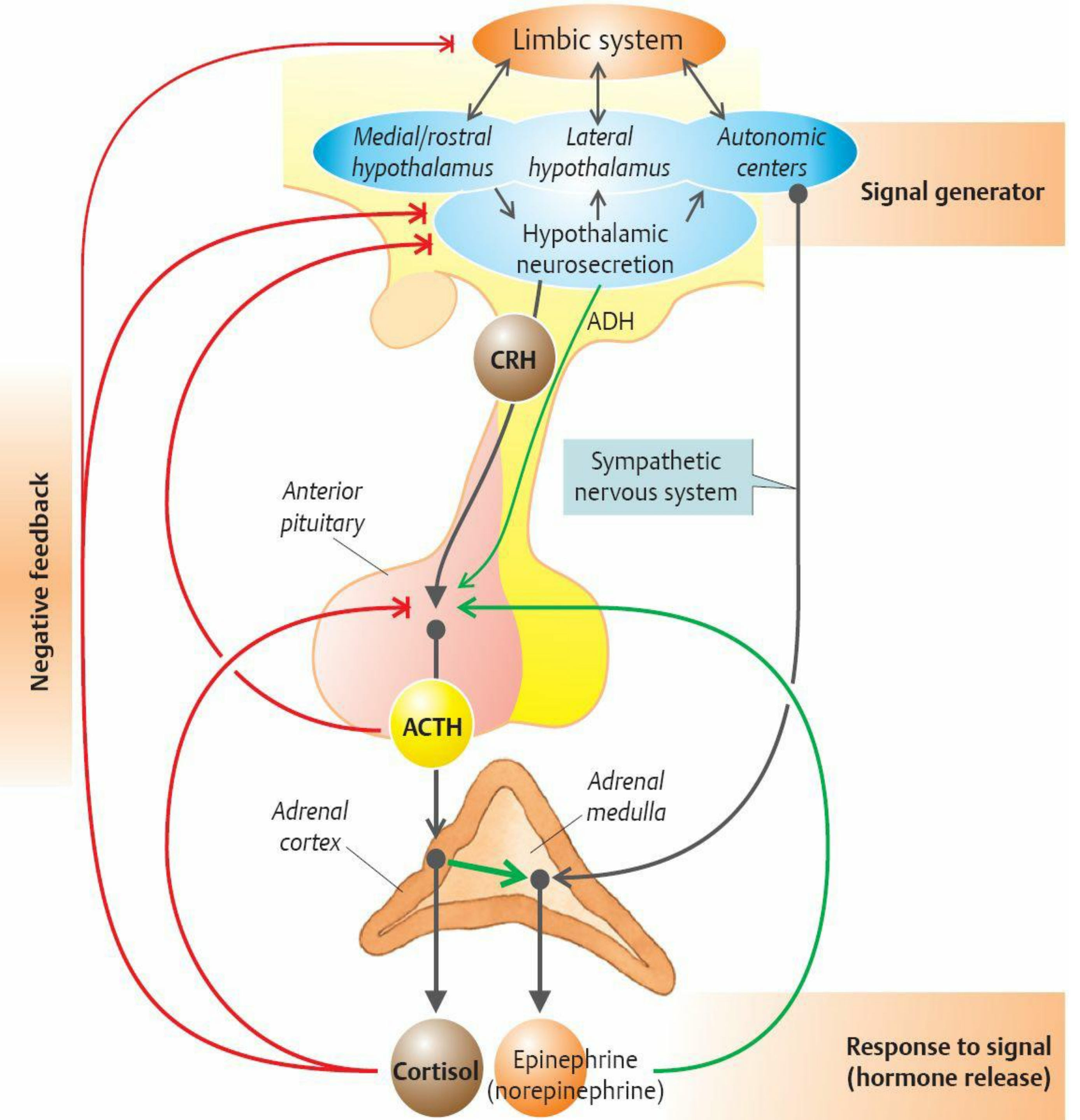
Effects of adrenaline on organs and tissues in the body

ORGAN	EFFECT	RECEPTOR TYPE
Heart	Increase heart rate Increased contractility	$\beta 1$ $\beta 1$
Blood vessels	Vasoconstriction Vasodilation	$\alpha 1$ $\beta 2$
Lungs	Bronchodilation	$\beta 2$
Uterus	Relaxation	$\beta 2$

ORGAN	EFFECT	RECEPTOR
Metabolism	Inhibits pancreatic insulin secretion	α2β2
	Glycogenolysis in liver and muscle	α1β2
	Glycolysis in muscle	α1β2
	Gluconeogenesis	α1β2
	Glucagon secretion in pancreas	α2
	ACTH secretion by pituitary	β
	Lipolysis in adipose tissue	β2β3
	Renin secretion from kidney	β1β2

Control of secretion of adrenal medullary hormones

- Adrenal hormones are released from the medulla in response to signals from the sympathetic nervous system.
- The sympathetic nervous system is activated in response to stress also know as the “fight or flight” response.
- Adrenal medulla hormones stimulate the pituitary gland to produce ACTH.
- ACTH stimulates adrenal cortex to produce cortisol.
- Secretion of cortisol causes negative feedback to Limbic system.

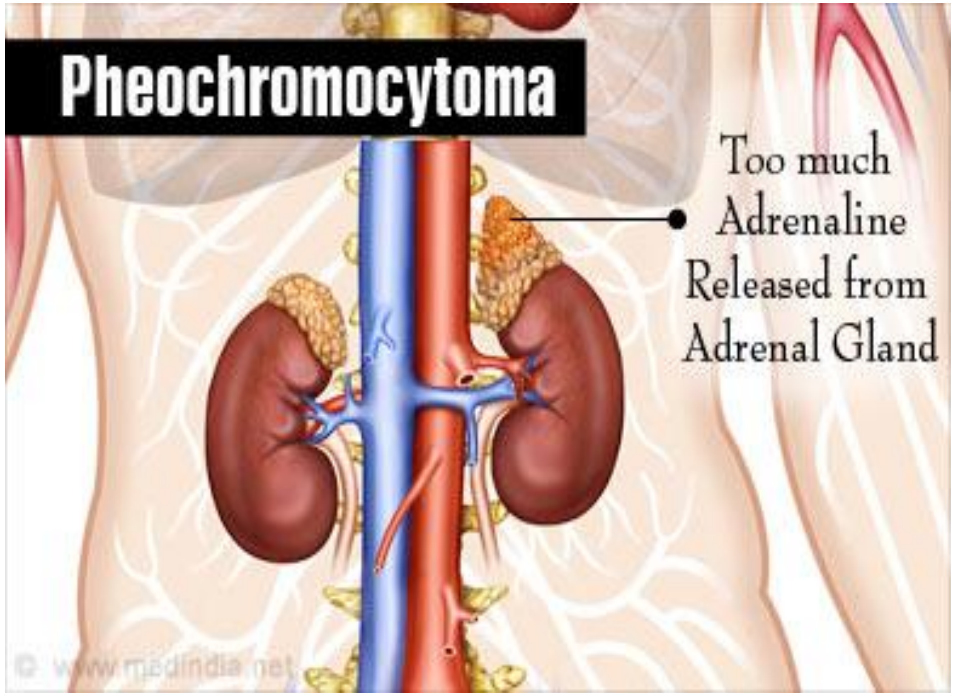


Pheochromocytoma

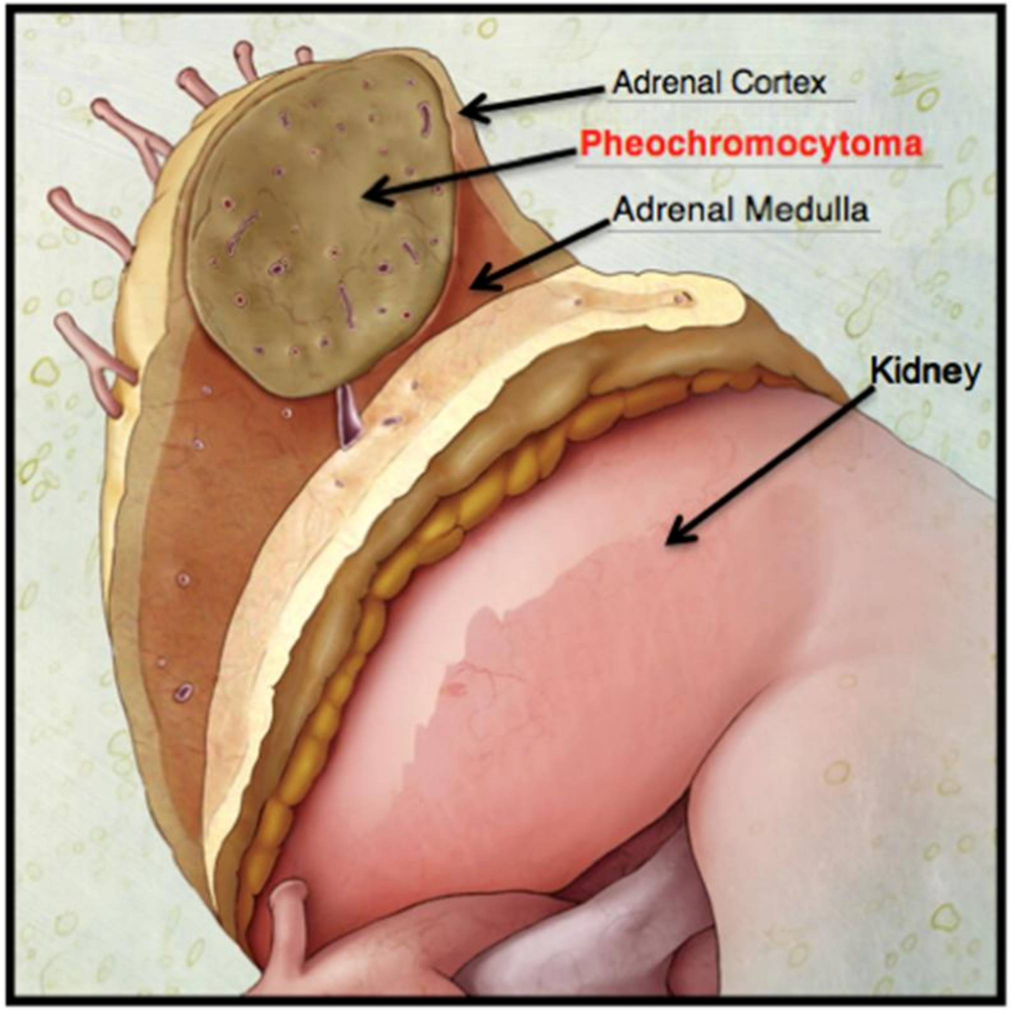
- Pheochromocytoma is a tumor of adrenal medulla .
- It can be life threatening if not recognized & not treated.
- Most often occurs in middle age.

- Symptoms & signs →

- **Pheochromocytoma : 3 most common symptoms**
  - ✓ - Palpitations
  - ✓ - Headache
  - ✓ - Episodic sweating (diaphoresis)



- Pheochromocytoma is derived from chromaffin cells (arise from neural crest).
- Most tumors secrete epinephrine, NE, and dopamine Therefore, the concentration of **epinephrine** and **norepinephrine** is very high and can cause episodic hypertension.
- Diagnosis is established by detecting increased concentration of catecholamines in blood when the patient is in recumbent and at rest. Urinary vanillylmandelic acid, VMA (a breakdown product of norepinephrine).



Thanks For Listening ..