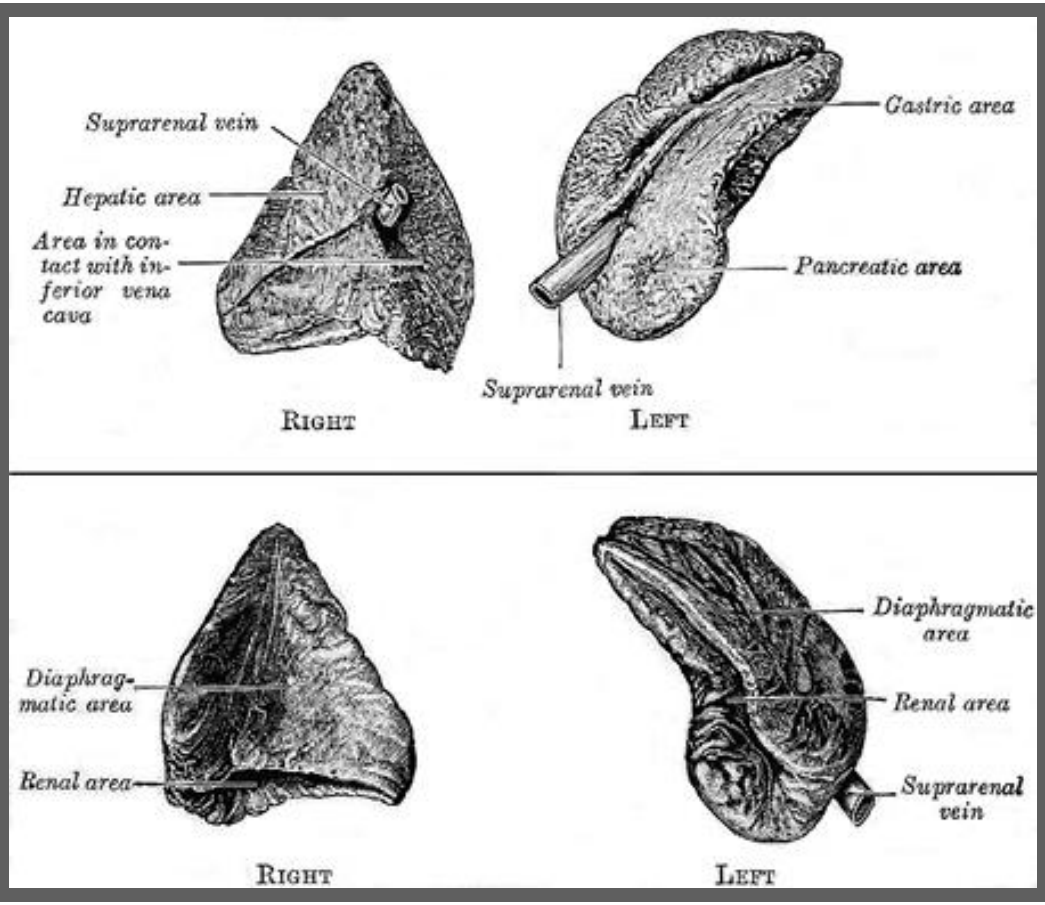
# Adrenal glands (*glandula suprarenalis*)

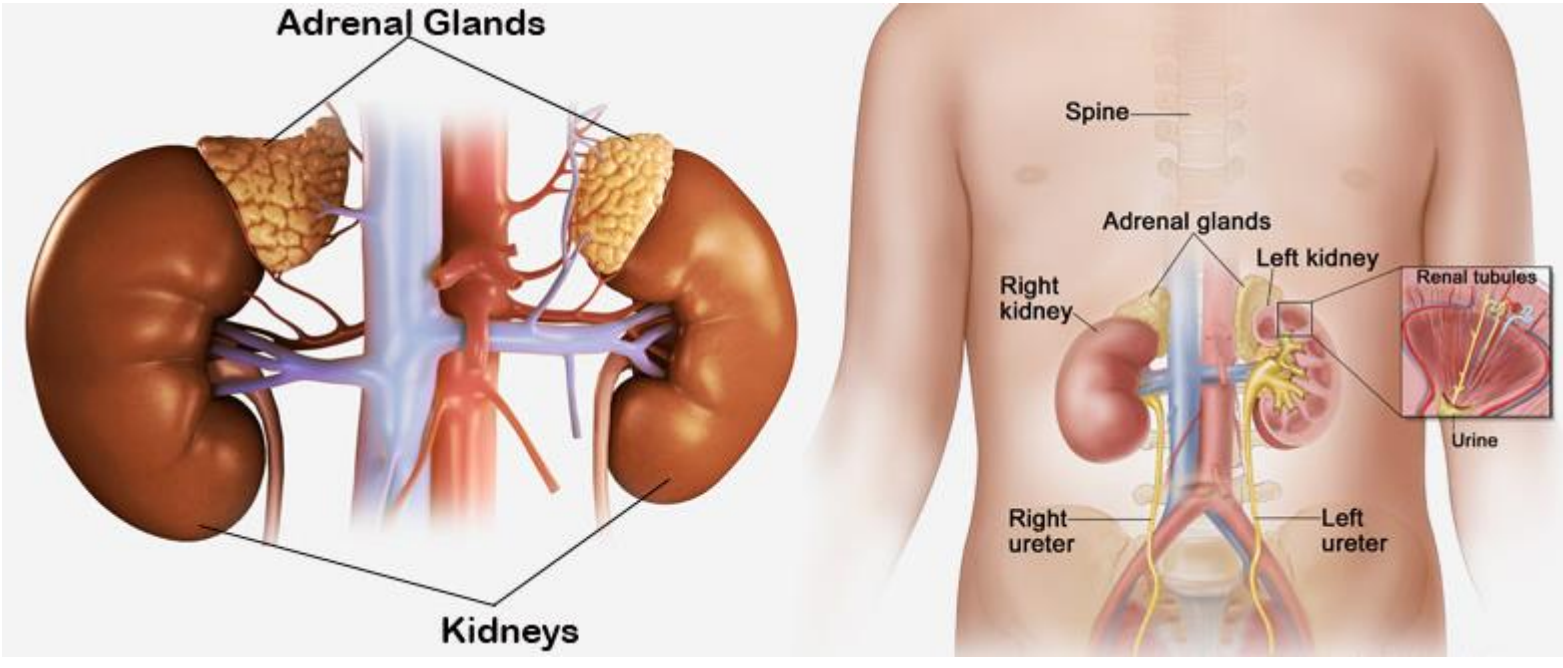


# Adrenal glands

- paired endocrine gland (triangular and crescent-shaped; human approx. 8 g)
- upper pole of the kidneys, common fat sheath (right kidney is lower)
- blood vessels directed through cortex to medulla (glucocorticoids > NA > A)
- fibrous capsula > septa + parenchyma:

**1. Cortex** - mesoderm
- **steroid production**

**2. Medulla** – neuroectoderm, neural crest
- **catecholamine production**



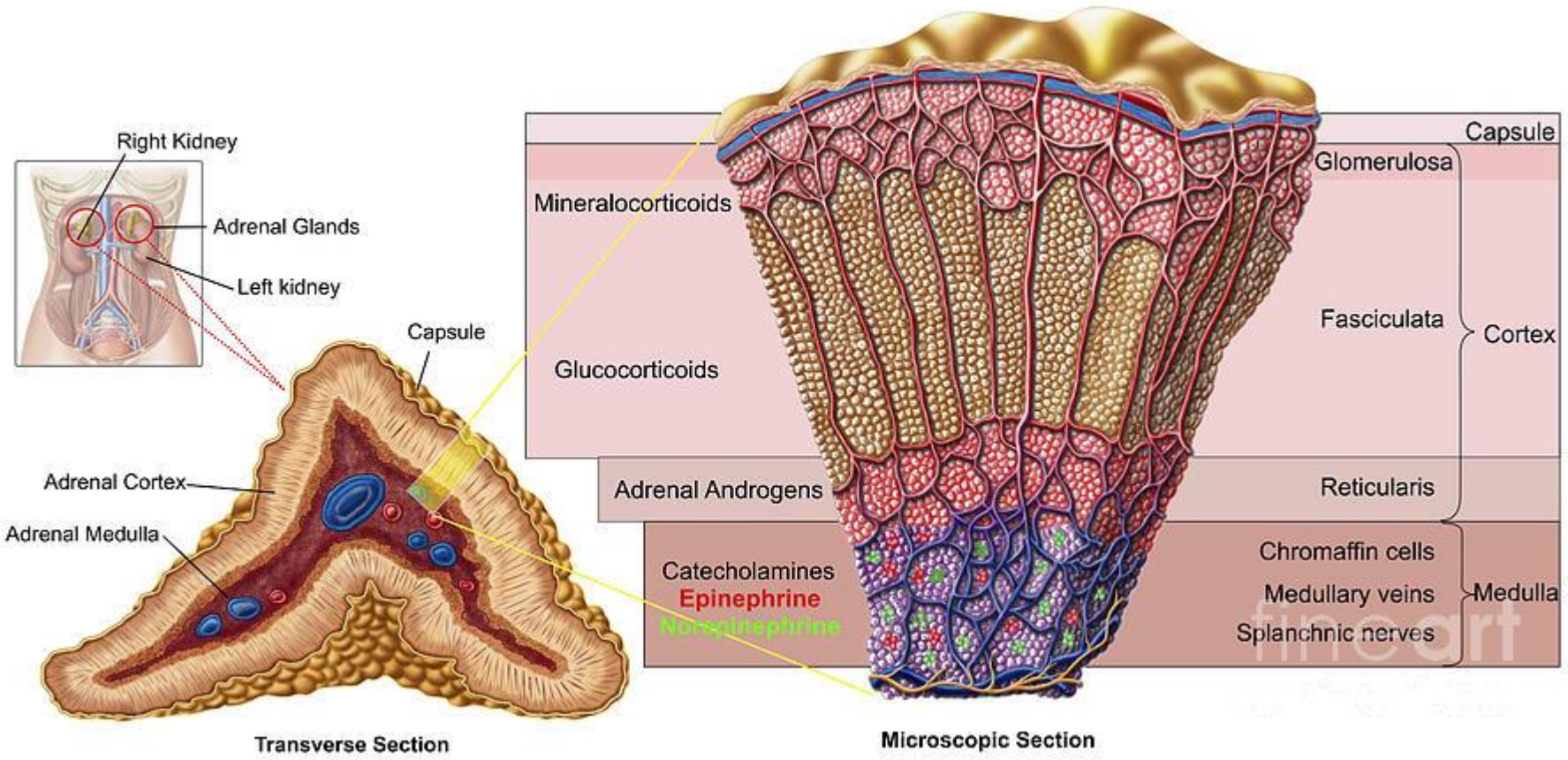
# Adrenal glands - structure of the cortex

- up to 70 % of adrenal volume; rich blood supply:

***zona glomerulosa*** (15 %) - oval groups of cylindrical cells, many capillaries

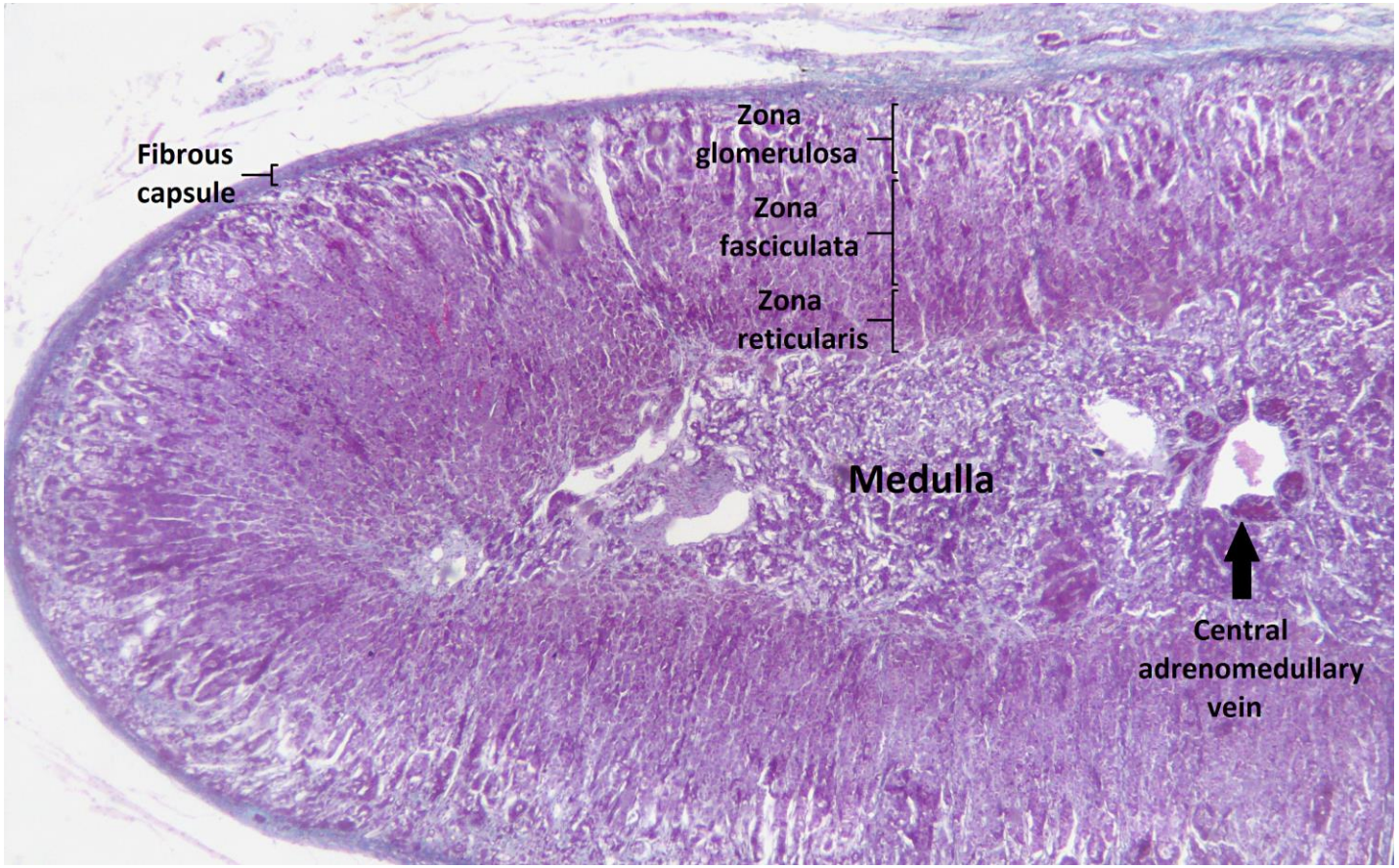
***zona fasciculata*** (75 %) - polyhedral cells arranged radially

***zona reticularis*** (10 %) - smaller cells with lipofuscin in the cytoplasm



# Adrenal glands - structure of the medulla

- irregularly shaped cells grouped around blood vessels (sinusoids)
- chromaffin cells – granules stained with chromium and silver salts
- **A-cells** producing epinephrine / adrenaline
- **NA-cells** producing norepinephrine / noradrenaline



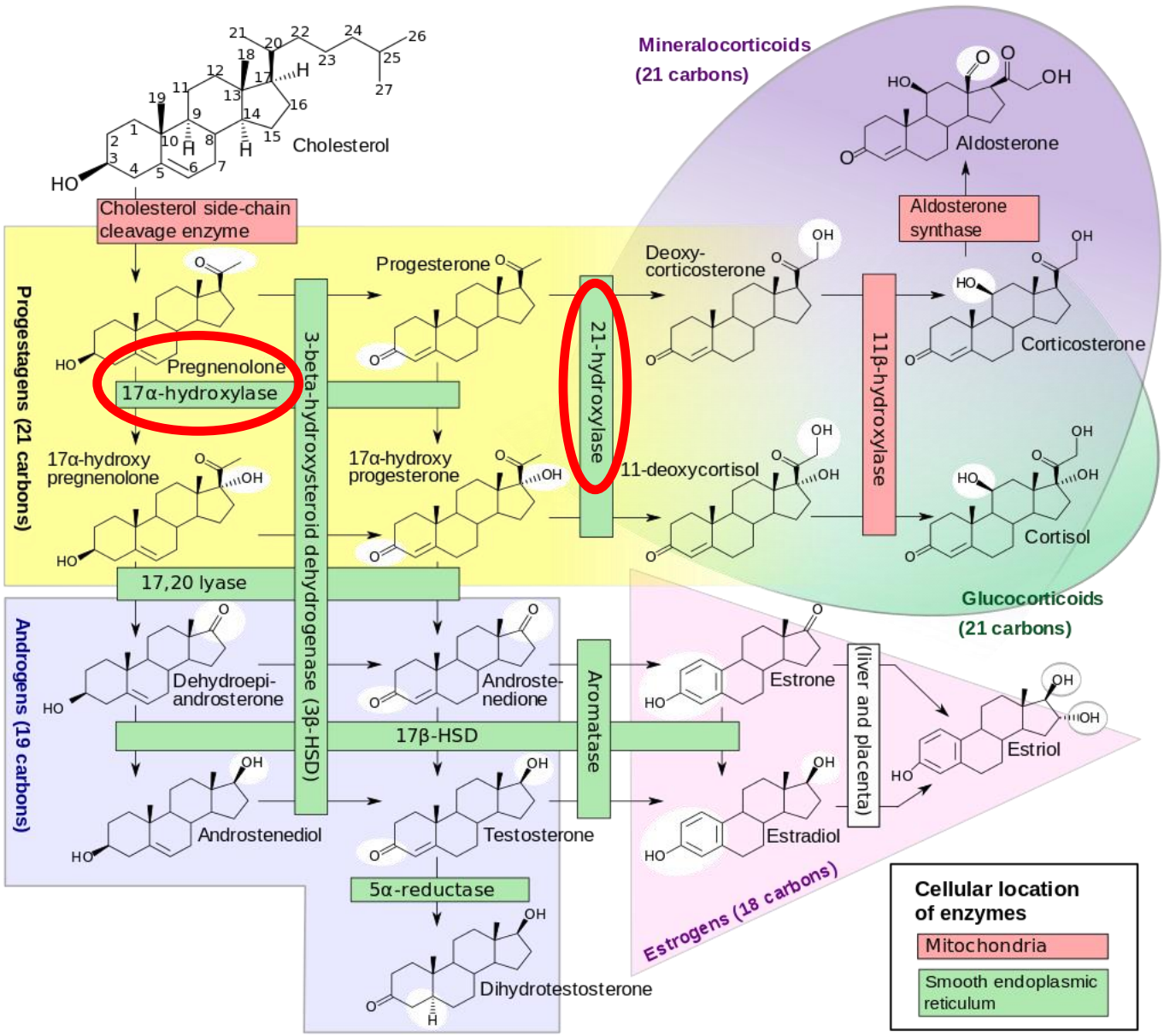
# Synthesis of steroid hormones in the adrenal glands

- cholesterol converted to pregnenolone
- stored only in small quantities (*de novo* synthesis)
- **ACTH receptor**
- **enzymes:**

*21-hydroxylase* (mineralocorticoids)

*17-hydroxylase* (glucocorticoids)

*11-hydroxylase*



# Disorders of steroid hormone synthesis in the adrenal glands

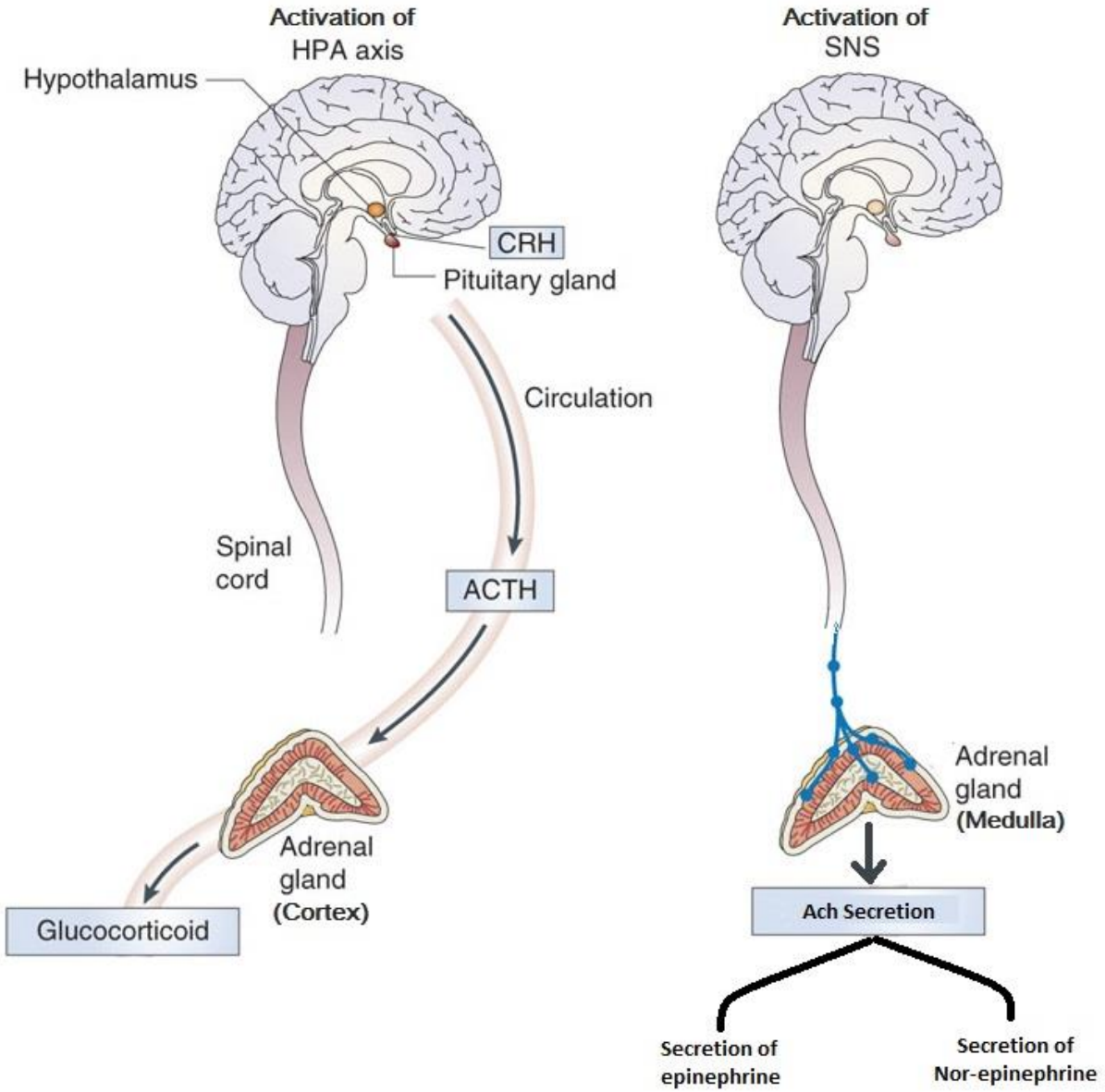
- deficiency of cholesterol or transport protein StAR (transfers cholesterol to the mitochondria
- defects of enzymes catalyzing specific steps of biosynthesis (most often lack of 21-hydroxylase)
- a disorder of the partial step of synthesis usually leads to a reduction in the production of hormones in the pathway behind the defect, but also to an increase in the concentration of precursor steroids, including their hormonal activity

| Enzym Defect (→ A1–8) | Androgenic Action | Glucocorticoid Action | Mineralcorticoid Action |
|---|---|---|---|
| ❶ 20,22-Desmolase (P450scc, StAR) | ↓ | ↓ | ↓ |
| ❷ 17α-Hydroxylase (P450c17) | ↓ | ↓ | ↑ |
| ❸ 3β-Hydroxydehydrogenase | ↑ (♀) ↓ (♂) | ↓ | ↓ |
| ❹ 17-Reductase | ↓ | – | – |
| ❺ 21β-Hydroxylase (P450c21) | ↑ | ↓ | ↓ |
| ❻ 11β-Hydroxylase (P450c11) | ↑ | ↓ | ↑ |
| ❼ 18-Hydroxylase (P450c11AS) | – | – | ↓ |
| ❽ 18-Methyloxidase (P450c11AS) | – | – | ↓ |

- there may be a loss of feedback; e.g. when the production of glucocorticoids is impaired, the CRH-ACTH axis is not attenuated, it stimulates the adrenal glands, where glucocorticoid precursors accumulate to a greater extent, but glucocorticoids themselves are still missing

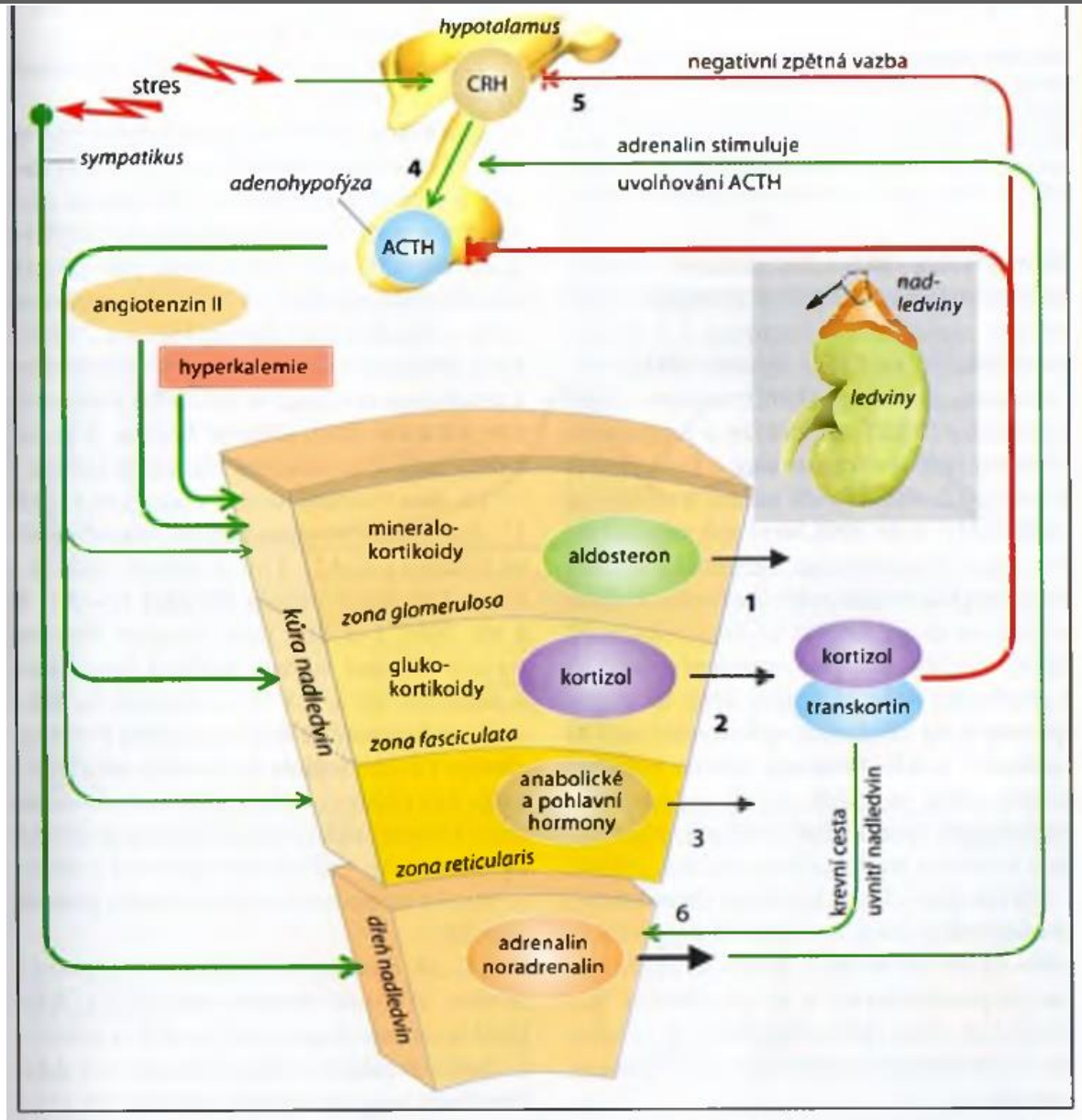
# Regulation of hormone production in the adrenal glands

- **endocrine** (ACTH) > StAR and steroidogenic enzymes > cortical hormones > negative feedback loop
- **renin-angiotensin-aldosterone system** ($K^+$, $Na^+$ concentration)
- **sympathetic** > medullary hormones
- preferentially regulated at the level of synthesis and degradation; stored minimally



# Adrenal hormones

- **mineralocorticoids** (aldosterone)
- **glucocorticoids** (cortisol)
- **androgens**
- **catecholamines** (adrenaline, noradrenaline)



# Mineralocorticoids: aldosterone

- adrenal cortex - *zona glomerulosa*
- **aldosterone**, corticosterone, 11-deoxycorticosterone
- most of aldosterone is transported freely in plasma (0.17 nmol/l) + low amount is bound to protein transporters
- short half-life (20 min)
- cortisol also binds to aldosterone receptors (ineffective at normal concentrations because it is converted to cortisone in target cells)

**Regulation:**

- ACTH stimulation, renin-angiotensin system (when blood volume and blood pressure decrease)
- released at hyperkalemia
- inhibition by atrial natriuretic hormone / peptide (ANP)

**Degradation:**

- conjugated to glucuronic acid in the liver
- bile / fecal excretion, kidney

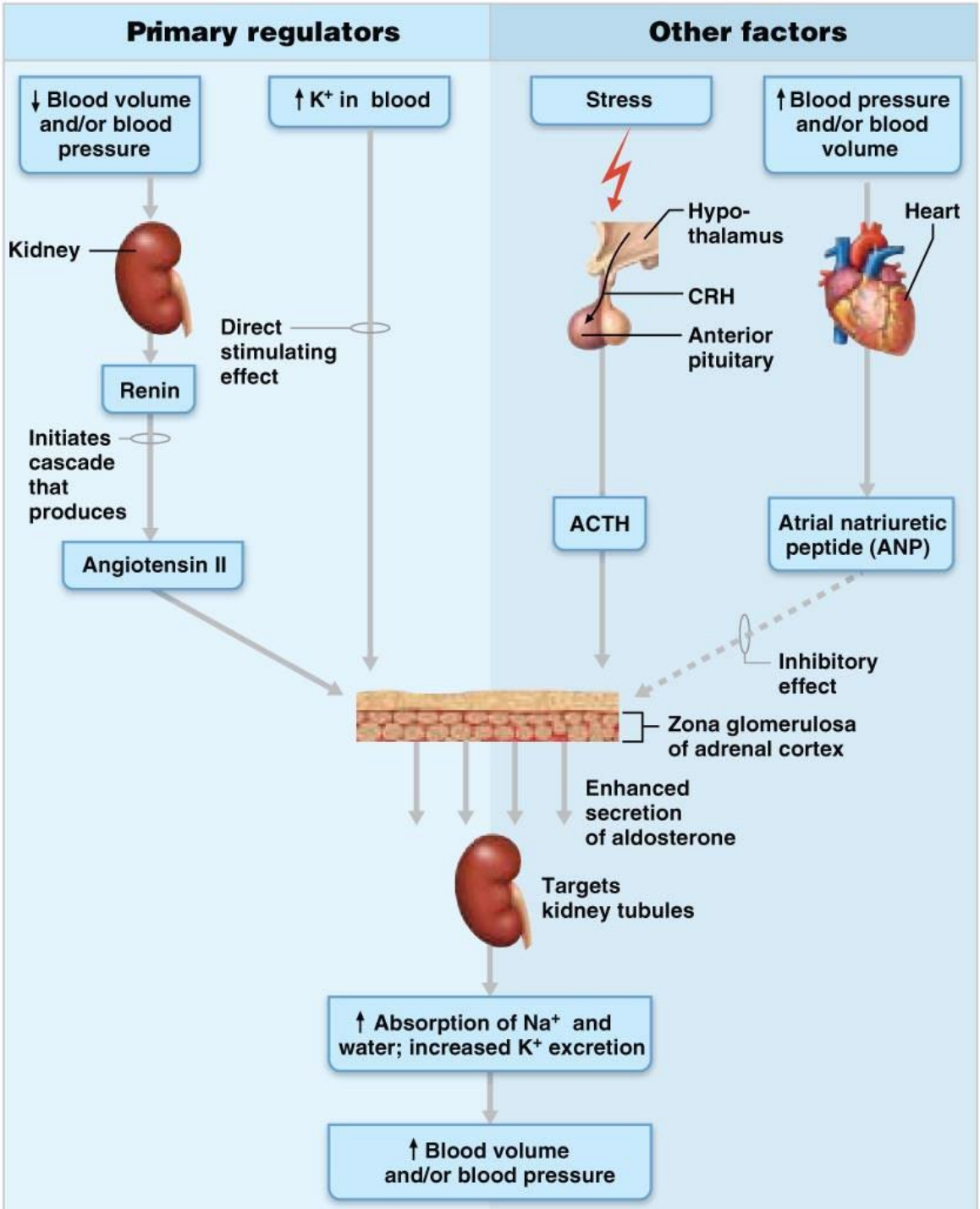
# Mineralocorticoids: activity and action

- binding to nuclear receptors (mineralocorticoid receptor) and affecting gene expression

**Effects:**

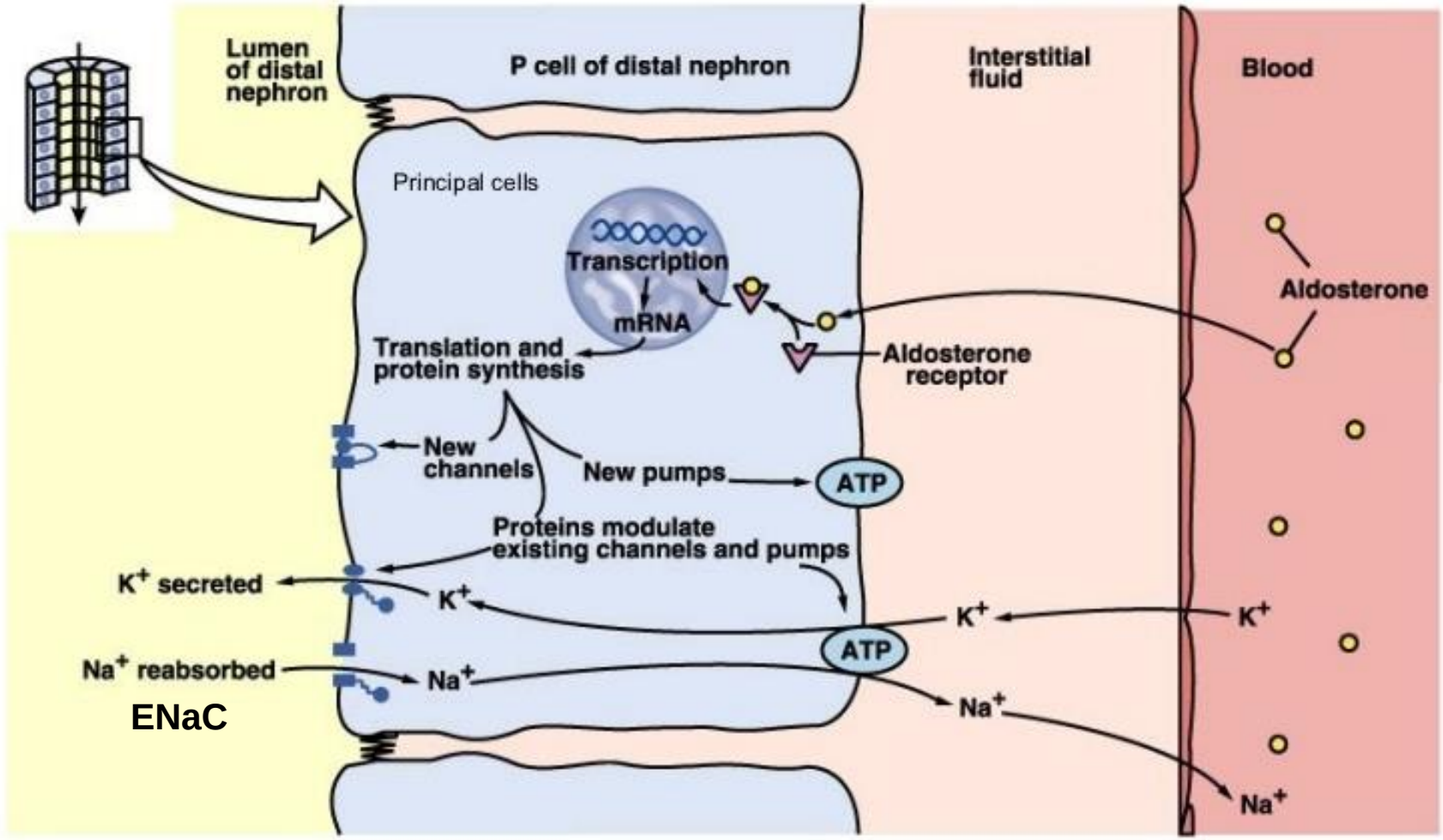
- $Na^+$ uptake in renal tubules > water resorption through osmotic gradient (synergy with ADH x ANP antagonist)
- $K^+$ and $H^+$ excretion in kidneys
- $Na^+$ uptake and $K^+$ excretion in the large intestine
- also targets sweat and salivary glands, gallbladder
- increase the number of **$Na^+/K^+$ ATPases** in cells

**Increase in blood pressure due to retention of $Na^+$ in the body.**



# Mineralocorticoids: activity and action

- genomic (mineralcorticoid receptor) and non-genomic effect (EGFR, ERK1/2)
- epithelial $Na^+$ channels (ENaC)



# Mineralocorticoids: abundance (Cushing disease) deficiency (Addison‘s disease)

**Abundance**

- most often due to increased renin release (see renin-angiotensin-aldosterone system), such as kidney problems or dehydration
- adrenal tumors producing aldosterone (Conn‘s syndrome)
- adrenal defects (mineralocorticosteroid effects of high cortisol concentrations)

- due to increased hypervolemia **hypertension** occurs (in combination with the effects of glucocorticoids abundance may lead to atherosclerosis)
- reduction in potassium concentration (hypokalaemia) leads to increased neuromuscular excitability, cardiac disorders

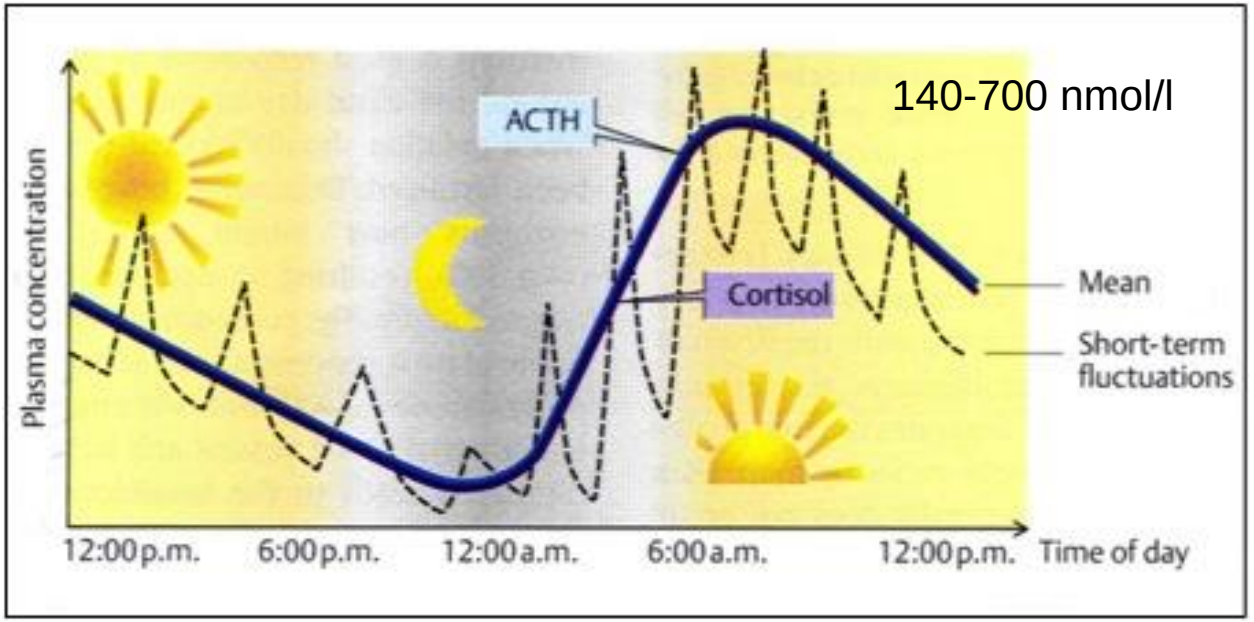
**Deficiency**

- genetic defects, autoimmune inflammation, tumors, after operations, etc.
- hypokalaemia or malfunction of renin-angiotensin system

- high losses of $Na^+$ in kidneys, retention of $Mg^{2+}$ and $H^+$ > hypotonic dehydration, hypovolemia and **decreased blood pressure**
- high concentration of $K^+$, $H^+$ and $Mg^{2+}$ and leads to a reduced neuromuscular irritability and defects in neural conduction
- restricted renal flow causes increased production of renin and angiotensin

# Glucocorticoids: cortisol and corticosterol

- adrenal cortex – mainly *zona fasciculata*
- **cortisol** (hydrocortisone), smaller amount of cortisone
- regulated by CRH-ACTH axis
- negative feedback (cortisol) x stimulation by CRH and adrenaline
- cortisol secretion at 2-3 hour intervals + day/night rhythm (maximum in the morning; opposite to melatonin) + response to **stress** and low blood glucose
- mostly binding and transport by globulin transcortin; small part free in plasma and biologically active
- receptors in almost every tissue > diverse action



# Glucocorticoids: activity and action

- binding to nuclear receptors and changing gene expression
- mediates the adaptation of metabolism, blood circulation, immune system and other tissues to stress
- **catabolic effect** in muscles, bones and adipose tissue x **anabolic effect in liver**
- **increases blood glucose level**

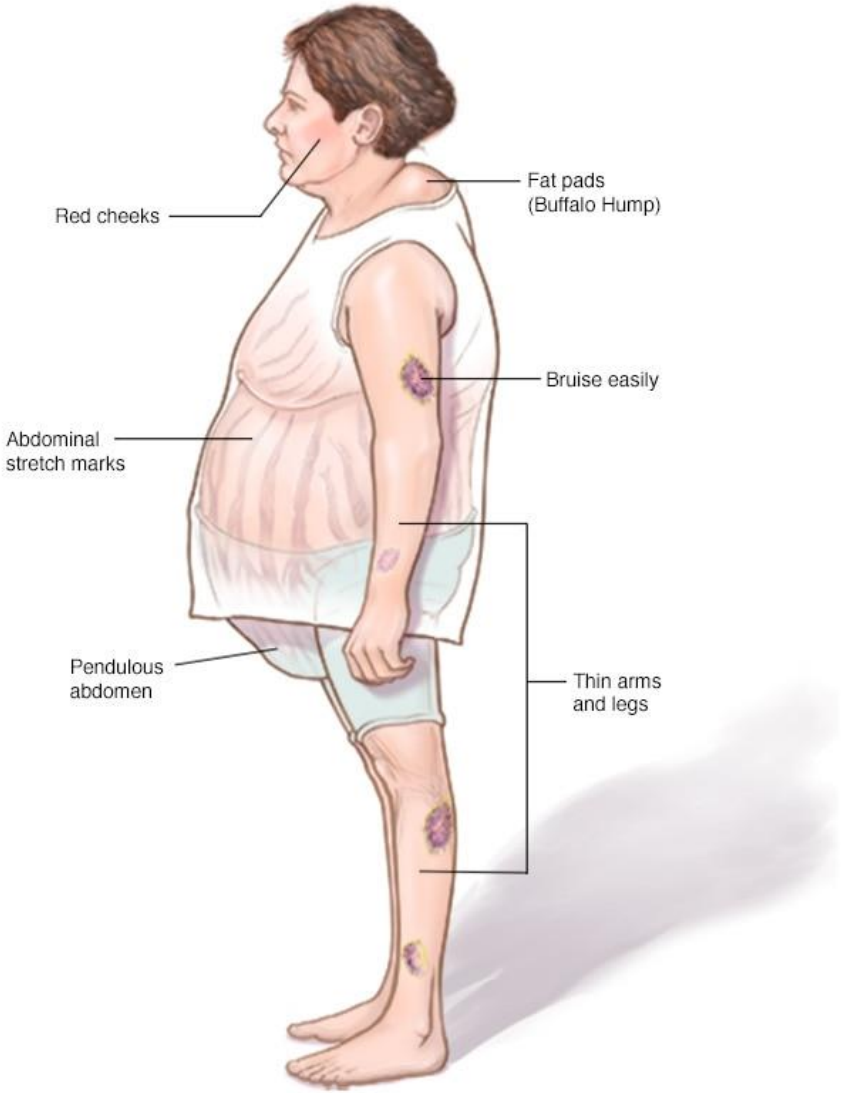
- stimulates protein degradation in liver and lipolysis of adipose tissue (gluconeogenesis)
- glycogen storage (glycogenesis) in liver
- slows down development and growth of bones and muscles (catabolism and decreased protein synthesis, e.g. collagen)
- enhancing the effect of catecholamines > stronger cardiac contraction and vasoconstriction
- suppresses production of lymphokines (IL-12, IFN-α, IFN-γ, TNF-α), reduces leukocyte counts, inhibits histamine release and stabilizes lysosomes > anti-inflammatory and anti-allergic effects (**immunosuppressive effect**)
- weakens the protection of the gastric mucosa (stress)

# Glucocorticoids: abundance (Cushing disease)

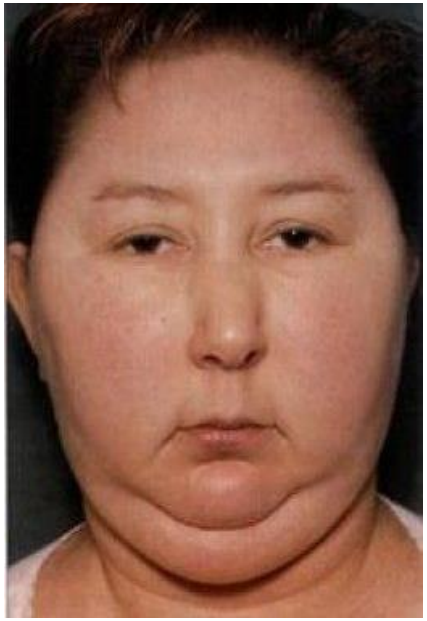
- most commonly the therapeutic administration of glucocorticoids to induce immunosuppression
- tumors
- excessive stimulation of the adrenal glands by the CRH-ACTH axis

- cortisol increases the concentration of glucose in the blood, in extreme cases it causes **steroid diabetes** associated with increased insulin production
- adipose tissue is redistributed by glucocorticoids and insulin > **characteristic obesity** (moon face, buffalo neck)
- loss of muscles, osteoporosis, subcutaneous tissue breakdown (stretch marks), increased vascular damage (purpura), impaired wound healing
- polyglobulinemia and increased blood clotting, higher risk of infection due to immunosuppression
- hypertension, increased risk of atherosclerosis, thrombosis and clogging of blood vessels
- inhibition of mucus production in stomach and increased secretion of hydrochloric acid and pepsin > gastric and duodenal ulcers

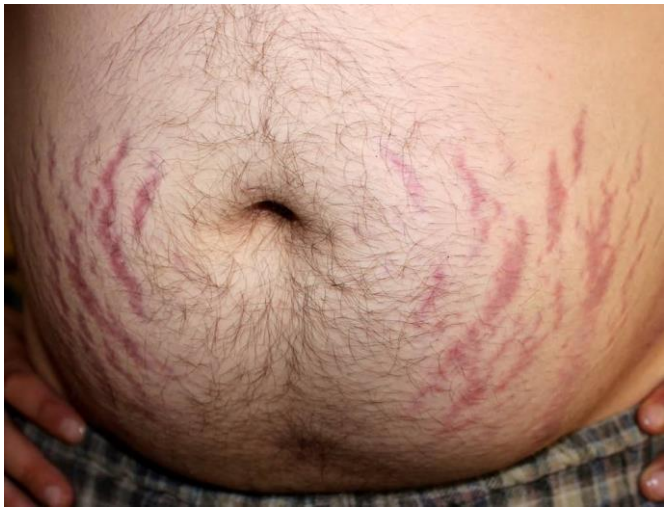
# Glucocorticoids: abundance (Cushing disease)





moon face

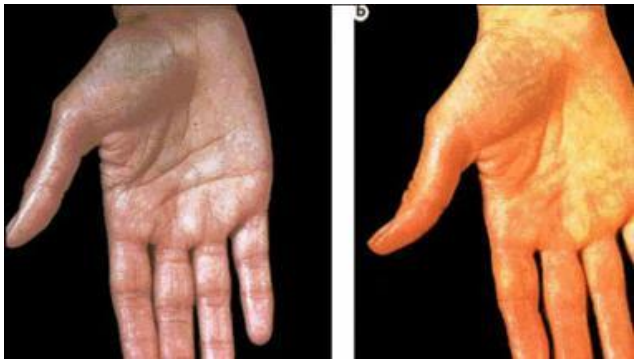


purpuric striae

# Glucocorticoids: deficiency (Addison‘s disease)

- causes are the same as for mineralocorticoids, except for renin-angiotensin stimulation

- decreased gluconeogenesis and increased glycolysis lead to **hypoglycemia**
- as a result of hypoglycemia, the sympathetic nervous system is activated and adrenaline increases lipolysis, protein breakdown, cardiac activity and sweat production > **muscle weakness, tachycardia, sweating**
- stomach and intestinal infections due to lower production of hydrochloric acid, diarrhea and vomiting
- weakening of hematopoiesis (anemia)



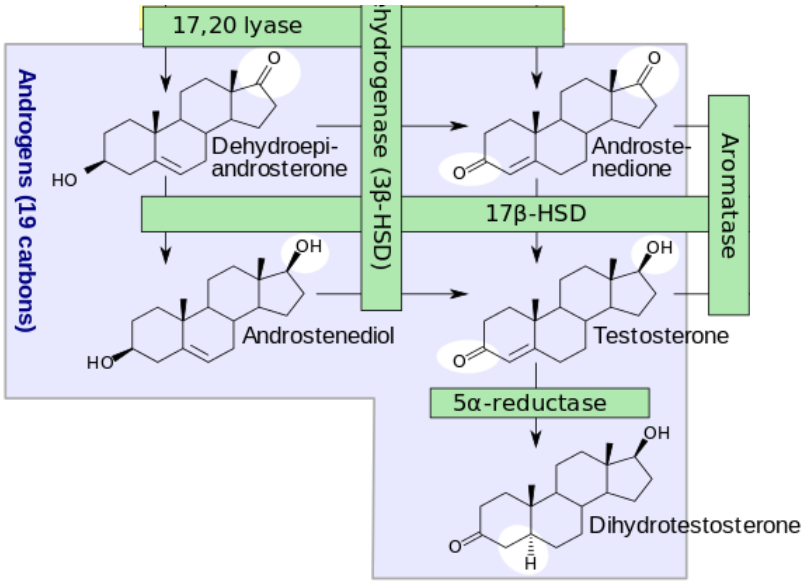
- cortisol deficiency causes failure of **negative feedback loop**, so that a larger amount of ACTH, including its precursor proopiomelanocortin (POMC), is formed in the pituitary gland > production of α-melanotropin (α-MSH) > increased **skin pigmentation** (Addison‘s disease is also referred to as "bronzing")

# Androgens

- adrenal cortex - *zona reticularis*; furthermore, testicles and ovaries
- dehydroepiandrosterone and its sulphate, androstenedione and more
- low production > do not play a significant role in the organism
- **in the adrenal glands, mainly precursors for the production of sex hormones in the gonads are formed**
- androgens transported from arenal glands to other organs (gonads)

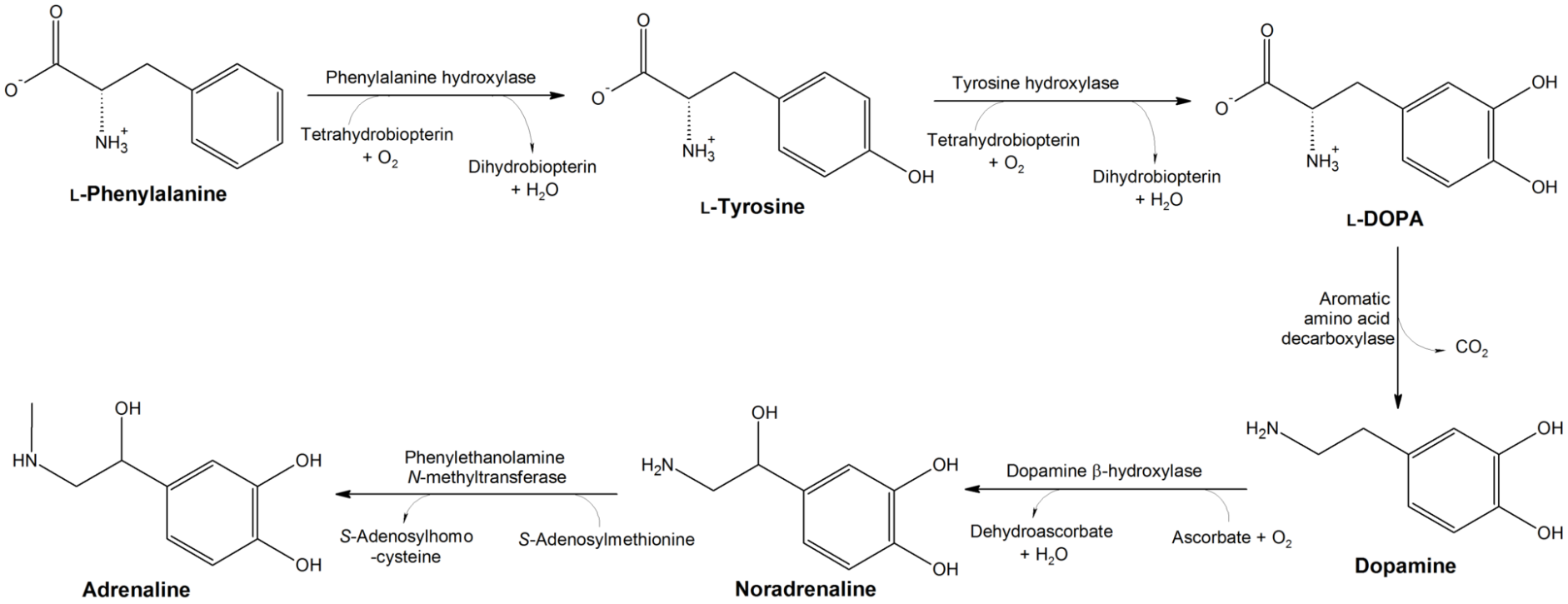
## Dehydroepiandrosterone

- mild masculinisation (in women) and anabolic effects
- premature puberty



# Catecholamines: adrenaline (A) and noradrenaline (NA)

- adrenaline/epinephrine (A), noradrenaline/norep. (NA) derived from tyrosine
- hydroxylation and decarboxylation of tyrosine
- phenylethanolamine-N-methyltransferase (PNMT) methylates NA to form A
- NA converted to A in the cytoplasm
- NA and A stored in vesicles (**chromaffin granules**) > impulse > exocytosis as peptide hormones
- adrenal medullary cells release endocrine A (95 %) and NA (5 %)

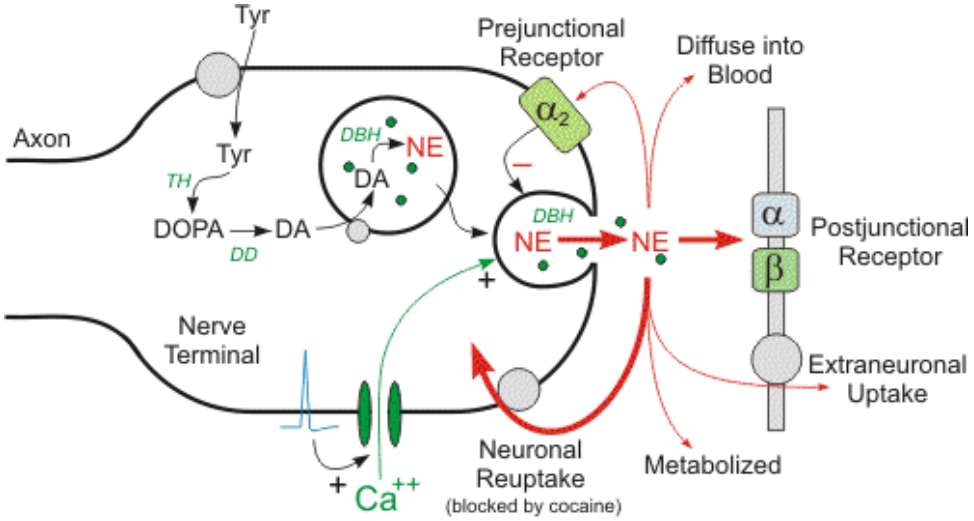


# Catecholamines: regulation

- **sympathetic nerves** stimulate production of hydroxylases in medulla:

stress situation > sympathetic signalling > acetylcholine release in synapses > receptor signal > depolarization > $Ca^{2+}$ influx through voltage-gated channels > exocytosis of chromaffin granules > release of NA into the blood > reaction of cells without direct sympathetic innervation

- stimulated by **ACTH and cortisol** (expression of PNMT)
- reuptake into nerve endings, diffusion from the synaptic cleft,
- half-life app. 2 min: enzymatic degradation, reuptake into synapses, diffusion from synaptic cleft
- **adrenaline is not regulated by negative feedback!**
- NA suppresses dopamine production (negative feedback)



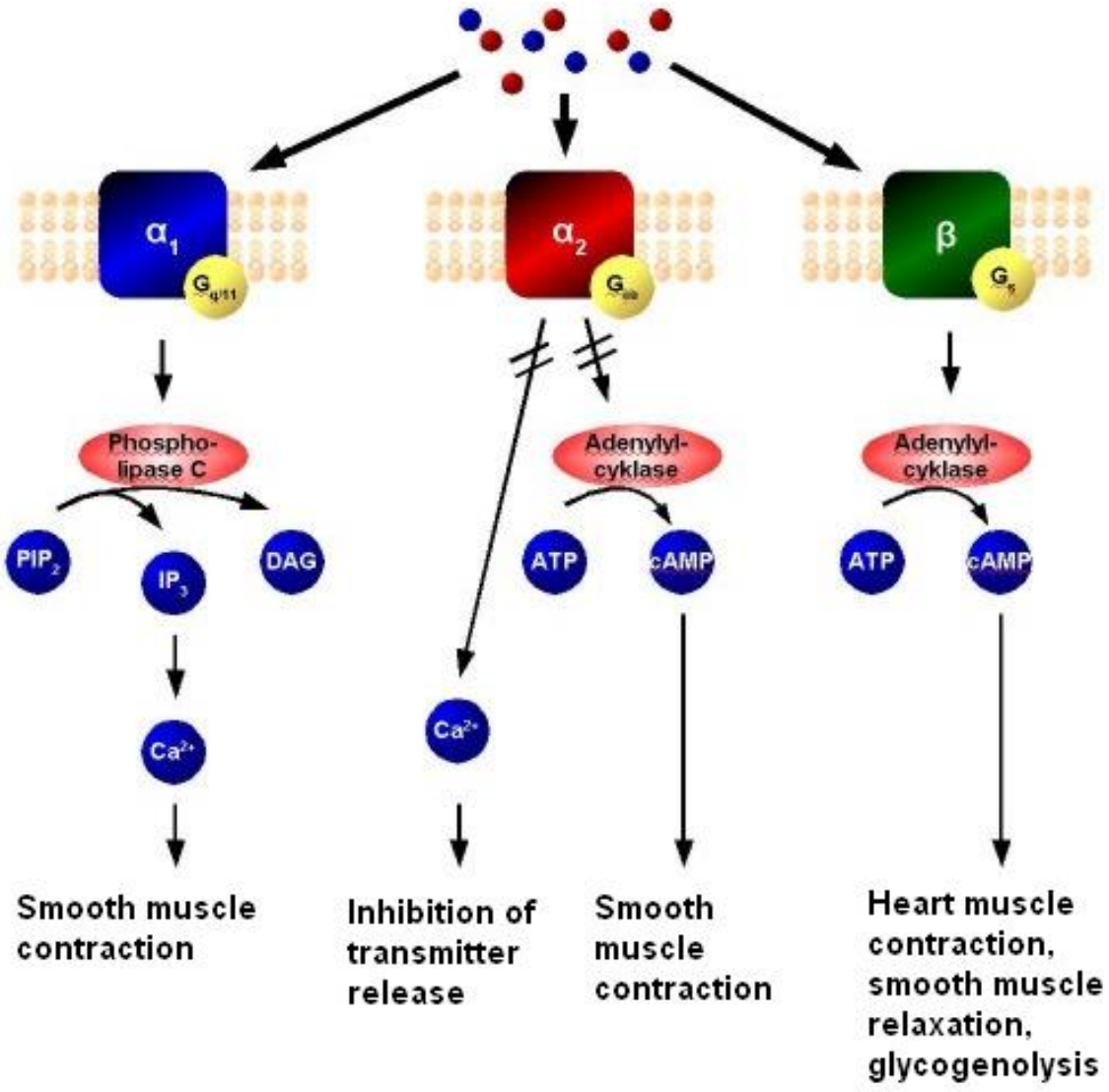
# Catecholamines: activity and action

adrenaline and noradrenaline

G protein-coupled receptors in the membrane of target cells (adrenoreceptors)

intracellular pathway

hormone effect



# Catecholamines: activity and action

- water-soluble hormone (A) and neurotransmitter (NA)
- four main types of adrenergic receptors for NA/A: $\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$ (differences in sensitivity) + $\beta_3$ (lipolysis and oxidation of fatty acids)
- A it binds to all receptors, NA doesn't bind to $\beta_2$
- all receptors act through G proteins

**$\alpha_1$-adrenergic receptors:**

- via PLC > $IP_3$ > ↑$Ca^{2+}$ and DAG > PKC
- ↑ sympathetic activity in the CNS, ↑ secretion in the salivary glands, ↑ **glycogenolysis in the liver**, ↑ **smooth muscle contraction**
- hyperpolarization in intestinal ducts > **inhibition of gastrointestinal motility**

**$\alpha_2$-adrenergic receptors:**

- inhibits adenylate cyclase and production of cAMP
- supports opening of voltage-dependent $K^+$ channels (hyperpolarization)
- **inhibition of exocytosis and secretion** (e.g. salivery glands)

# Catecholamines: activity and action

**$\beta_1$-adrenergic receptors:**

- adenylate cyclase > production of cAMP > PKA > protein phosphorylation
- **increase in blood pressure**
- opening $Ca^{2+}$ channels in heart muscle > ↑ **heart rate transmission**; ↑ **renin release in the kidneys**

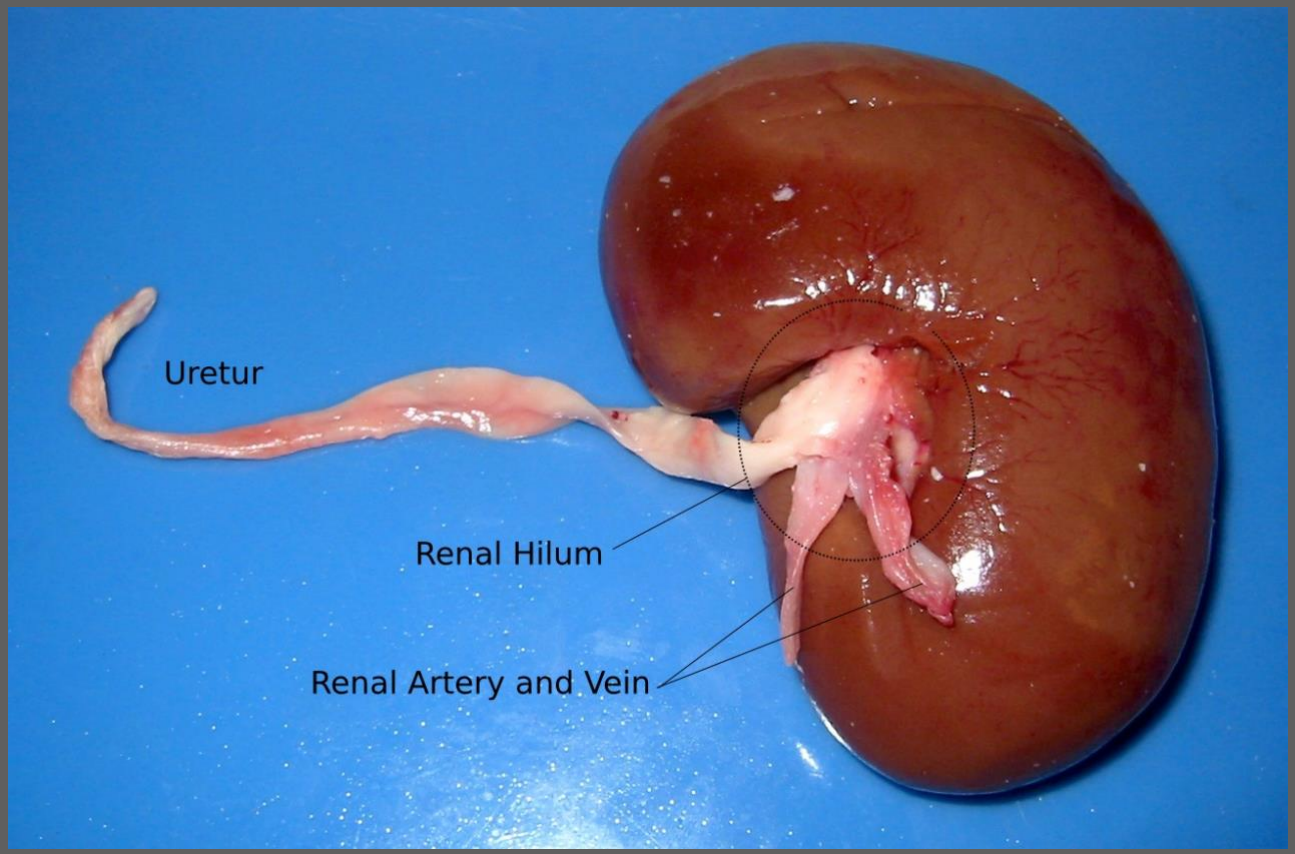
**$\beta_2$-adrenergic receptors:**

- adenylate cyclase > cAMP > decrease of $Ca^{2+}$ concentration (mechanism not yet fully understood)
- **dilatation of bronchioles and blood vessels in muscles**, gastrointestinal relaxation

**Stress reaction (A):**

- energy mobilization (lipolysis, glycogenolysis), ↑ glucose uptake in skeletal muscle, increase in cardiac output and blood flow to organs other than the digestive tract, support of the release of hormones controlling the recovery of energy reserves (ACTH)

# Kidneys (*nephros*)

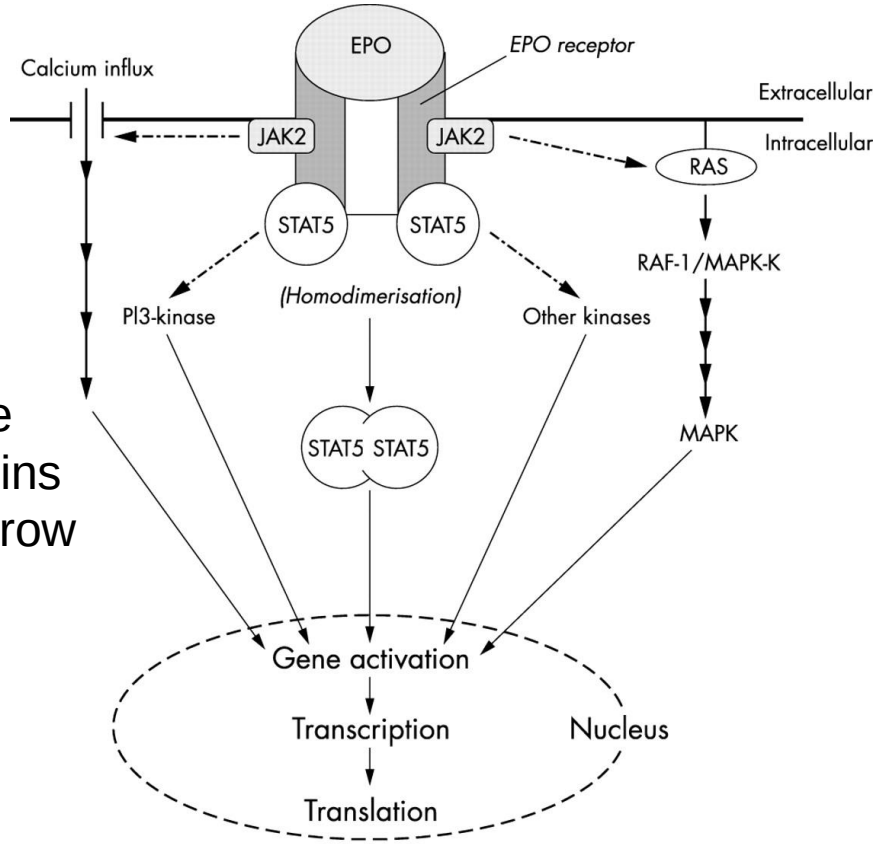


# Renal endocrine function

- **erythropoietin synthesis**
- **calcitriol synthesis** ($Ca^{2+}$ resorption in intestine and kidneys)
- **eicosanoids production** (prostaglandins)
- **renin-angiotensin-aldosterone system**

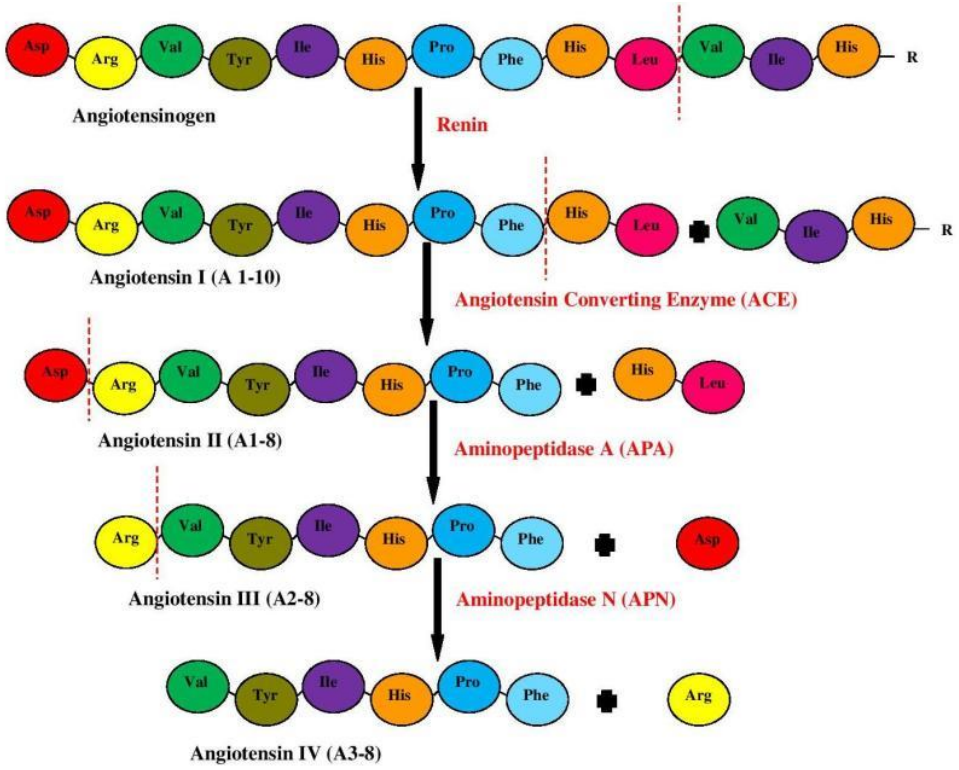
**Erythropoietin:**

- glycoprotein (34 kDa)
- half-life 5 hours
- produced in the kidneys and liver
- released in response to hypoxia
- receptors associated with tyrosine kinase acitivity > phosphorylation of target proteins
- stimulation of erythropoiesis in bone marrow



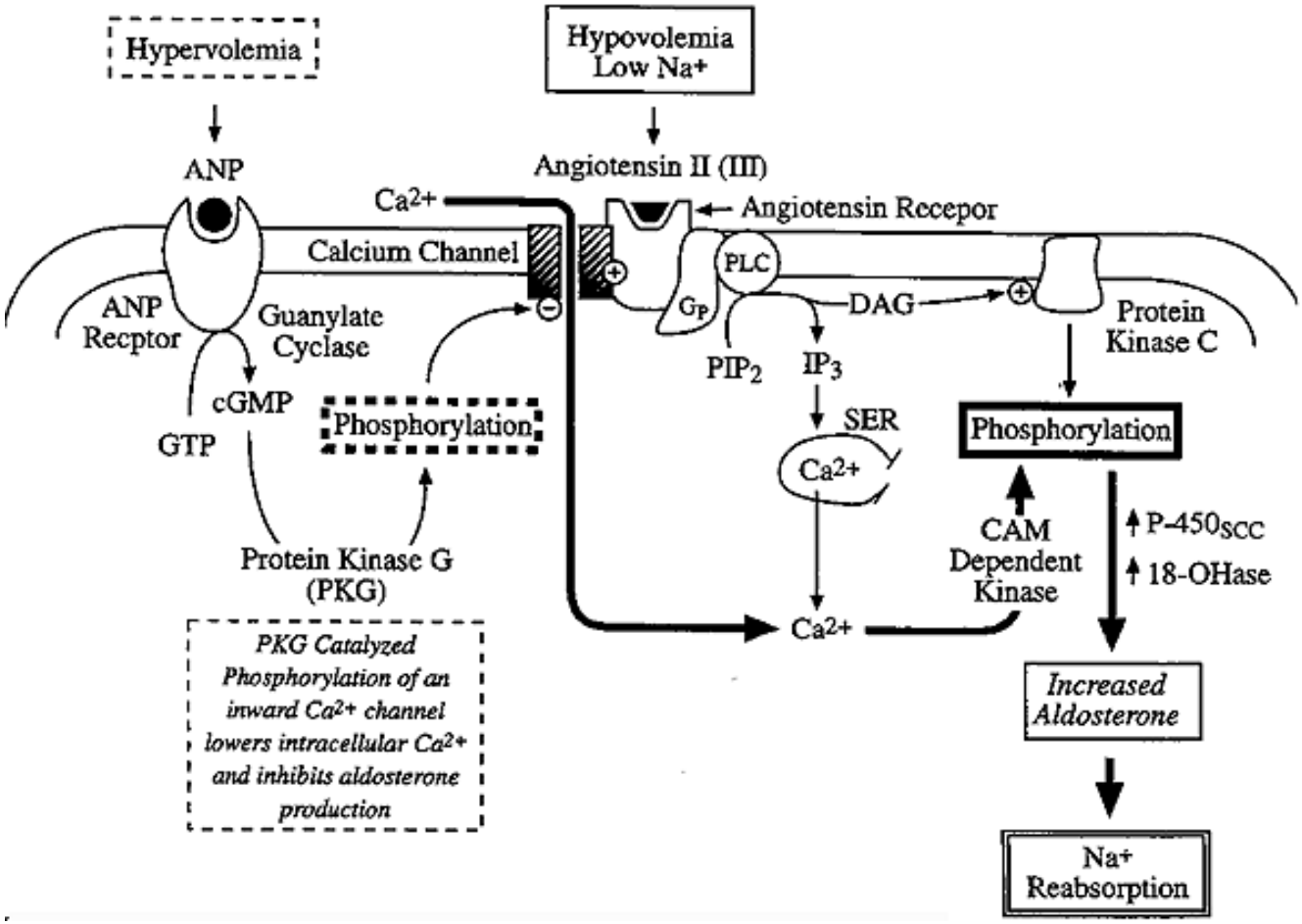
# Renin-angiotensin-aldosterone system (RAAS)

- peptidase **renin** (juxtaglomerular cells) secreted when the mean blood pressure in the kidneys falls below 90 mmHg (renal baroreceptors) > increase of plasma concentration
- **angiotensinogen** (453 AA) from liver converted to **angiotensin** (10 AA)
- angiotensin I converted to **angiotensin II** by cleaving 2 AA (**ACE** = angiotensin-converting enzyme from lungs and endothelial cells)
- stimulates the production of **aldosterone** in the adrenal glands



# Renin-angiotensin-aldosterone system (RAAS)

- stimulation of **aldosterone** synthesis in the adrenal glands



# Renin-angiotensin-aldosterone system (RAAS)

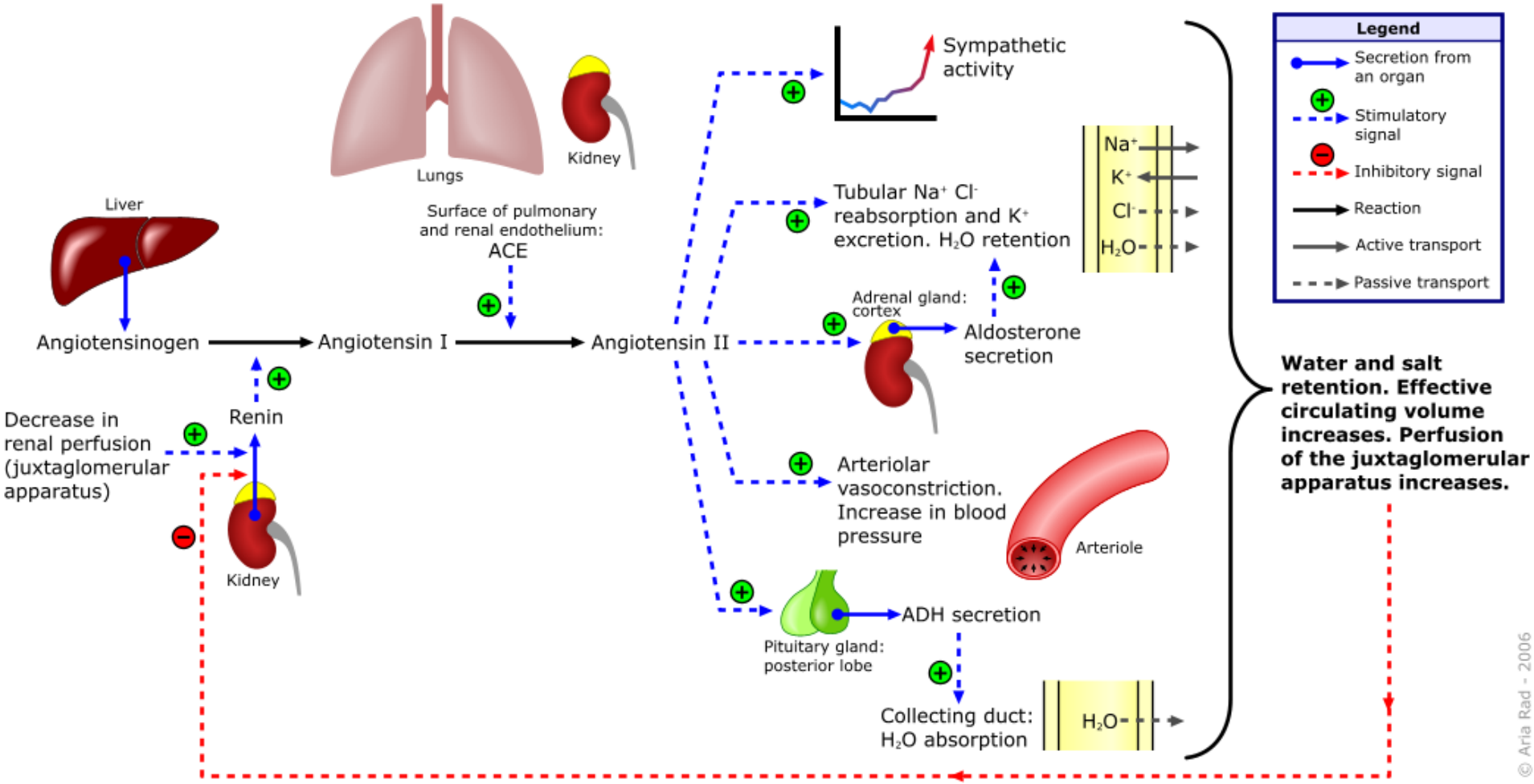
**Regulation:**

- stimulated by acute decrease in plasma volume and blood pressure
- activated by $\alpha_1$-adrenoreceptors > higher mean blood pressure required for renin secretion x $\beta_1$-adrenoreceptors > lower mean blood pressure is sufficient for renin secretion
- prostaglandin-stimulated renin secretion ($PGI_2$, $PGE_2$)
- negative feedback (angiotensin II and aldosterone)

**Action:**

- aldosterone reduces $Na^+$ and water losses
- angiontensin II is strongly vasoactive (vasoconstriction)
- constriction in the renal blood vessels
- hypothalamus > thirst and taste for salty
- angiotensin II increases secretion of aldosterone, vasopressin (ADH) and adrenaline

# Renin-angiotensin-aldosterone system (RAAS)




ACE = angiotensin-converting enzyme

# Summary of the response to stress: mobilization of energy stores and vasoconstriction

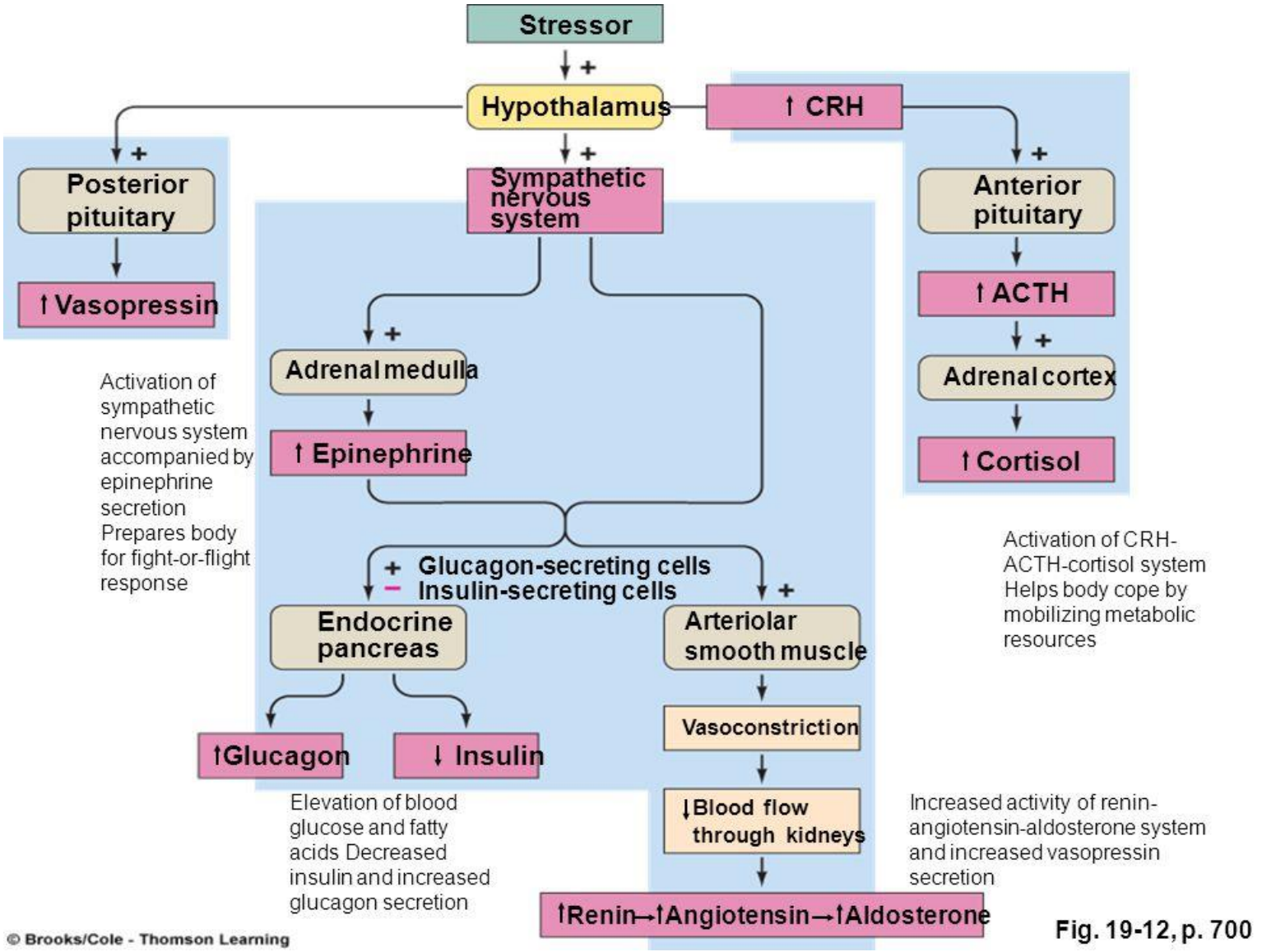





Fig. 19-12, p. 700