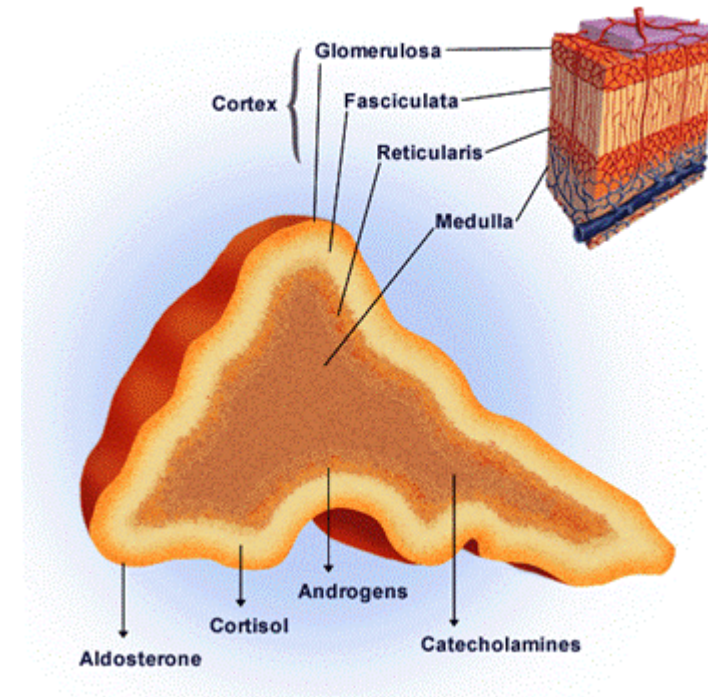
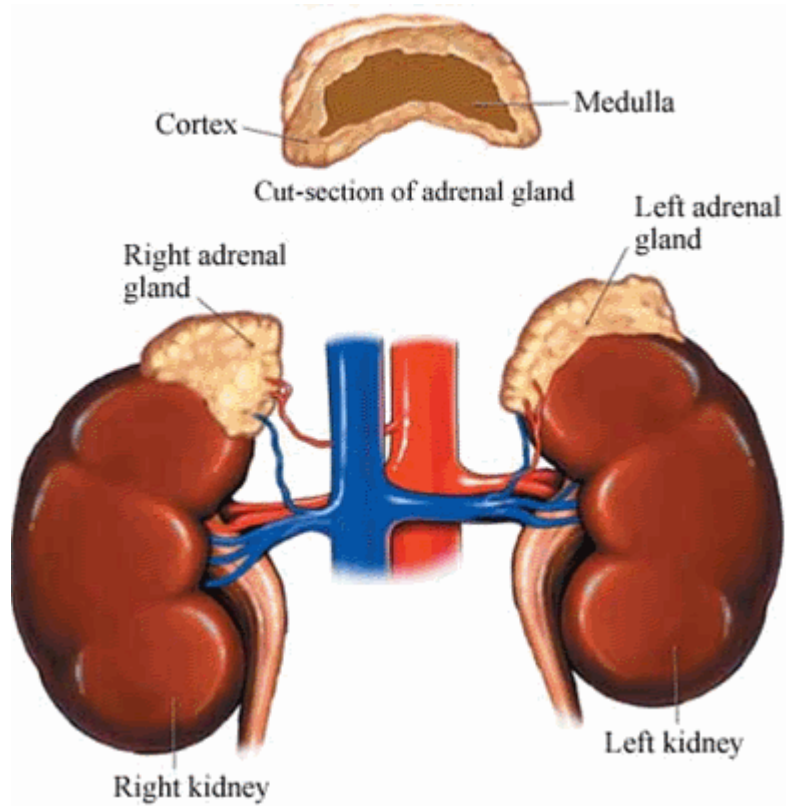




# GLUCOCORTICOIDS

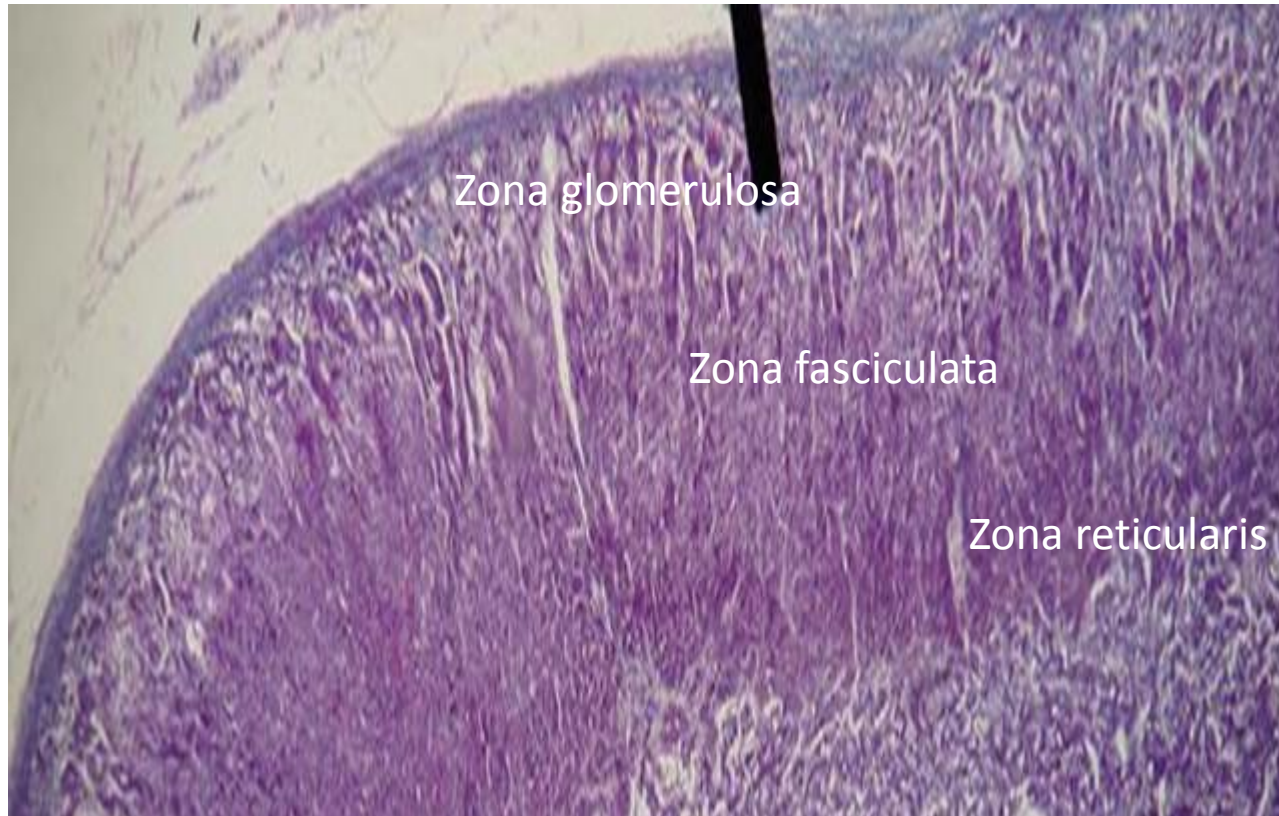


# Suprarenal glands - anatomy



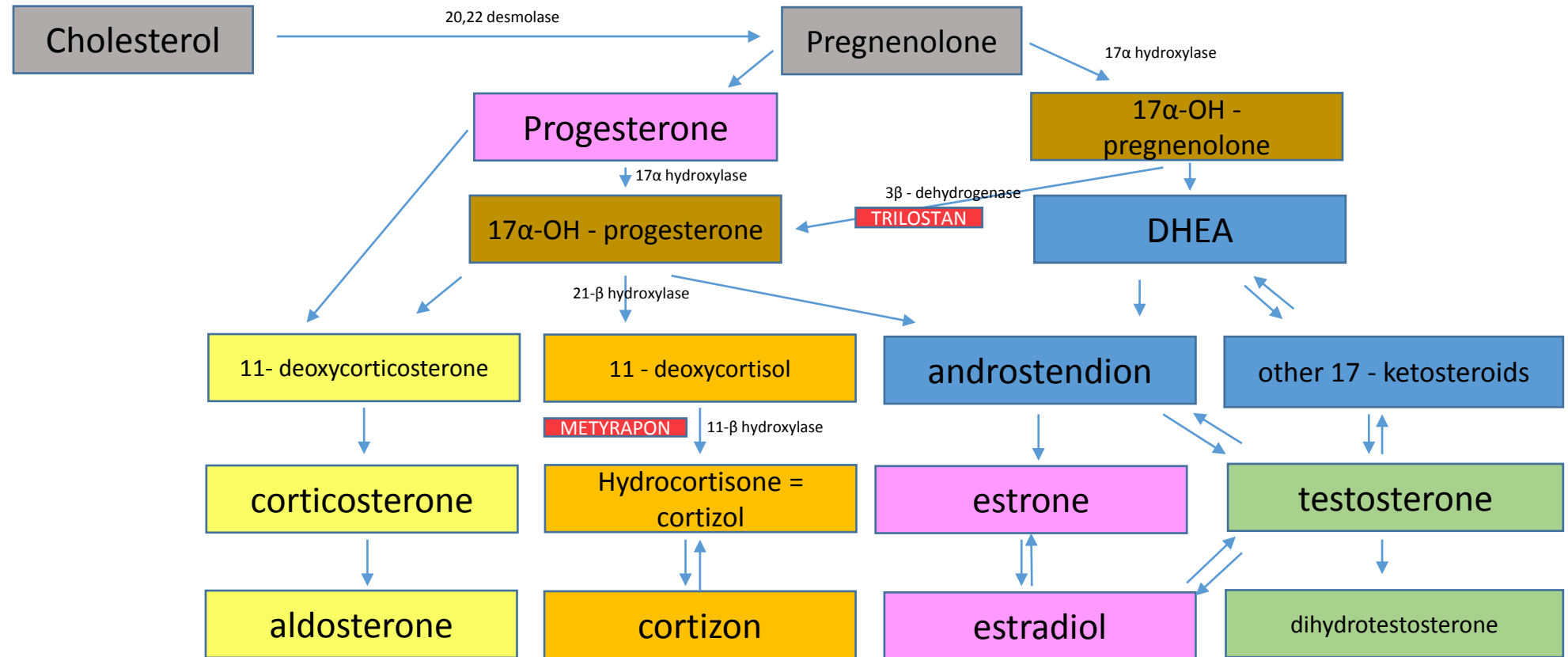


# Adrenal cortex - physiology



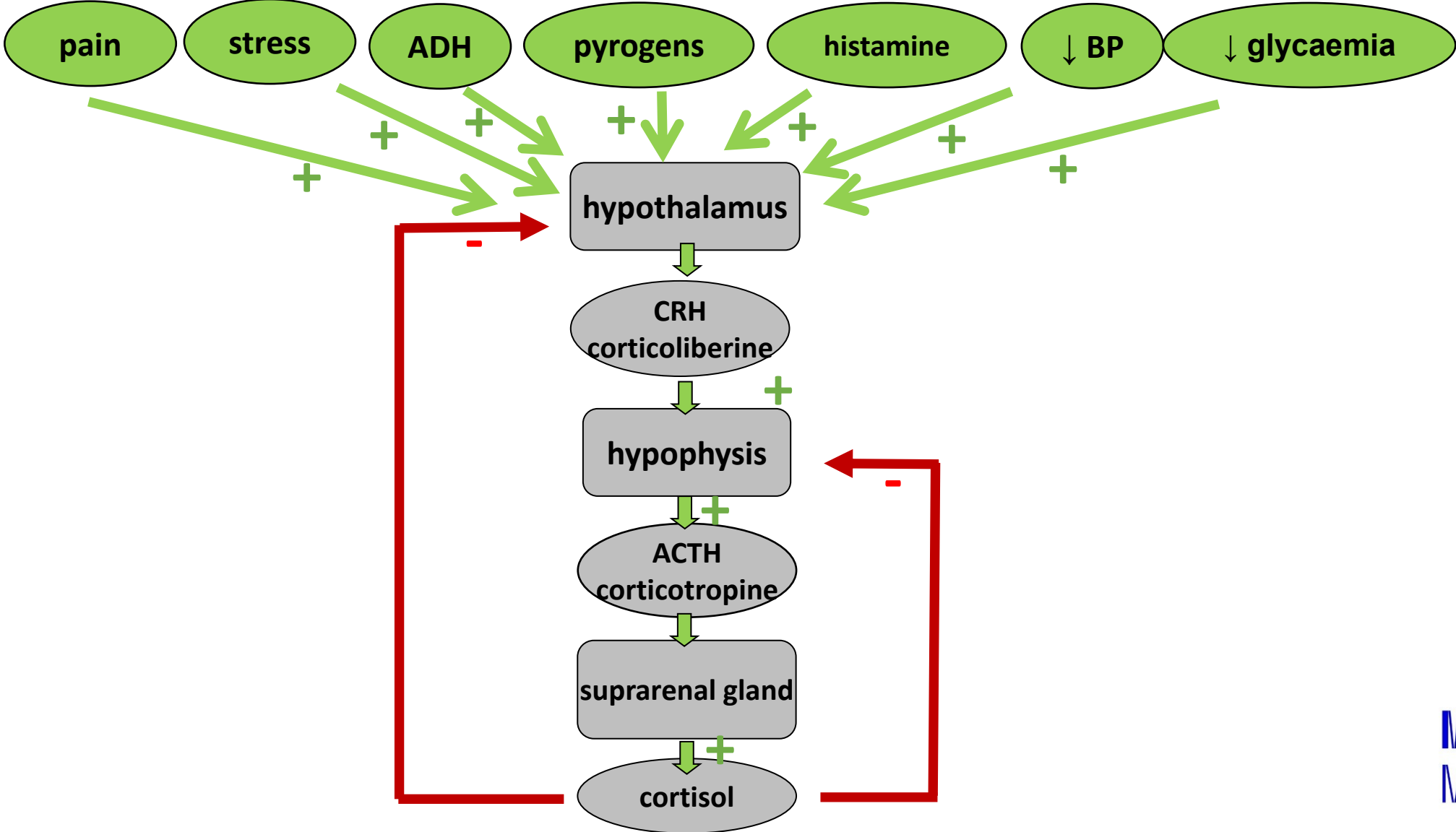
- **Zona glomerulosa – mineralocorticoids production - aldosteron** 10 – 15% of tissue, controlled by ATII a  $K^+$ .
- **Zona fasciculata** 75% of tissue, controlled by ACTH, „stock“ of cholesterol, its releasing and transformation to **cortizol = main human glucocorticoid**.
- **Zona reticularis** 10 – 15 % of tissue – androgens, gestagens, cortisol production.

# Steroid hormones biosynthesis - biochemistry

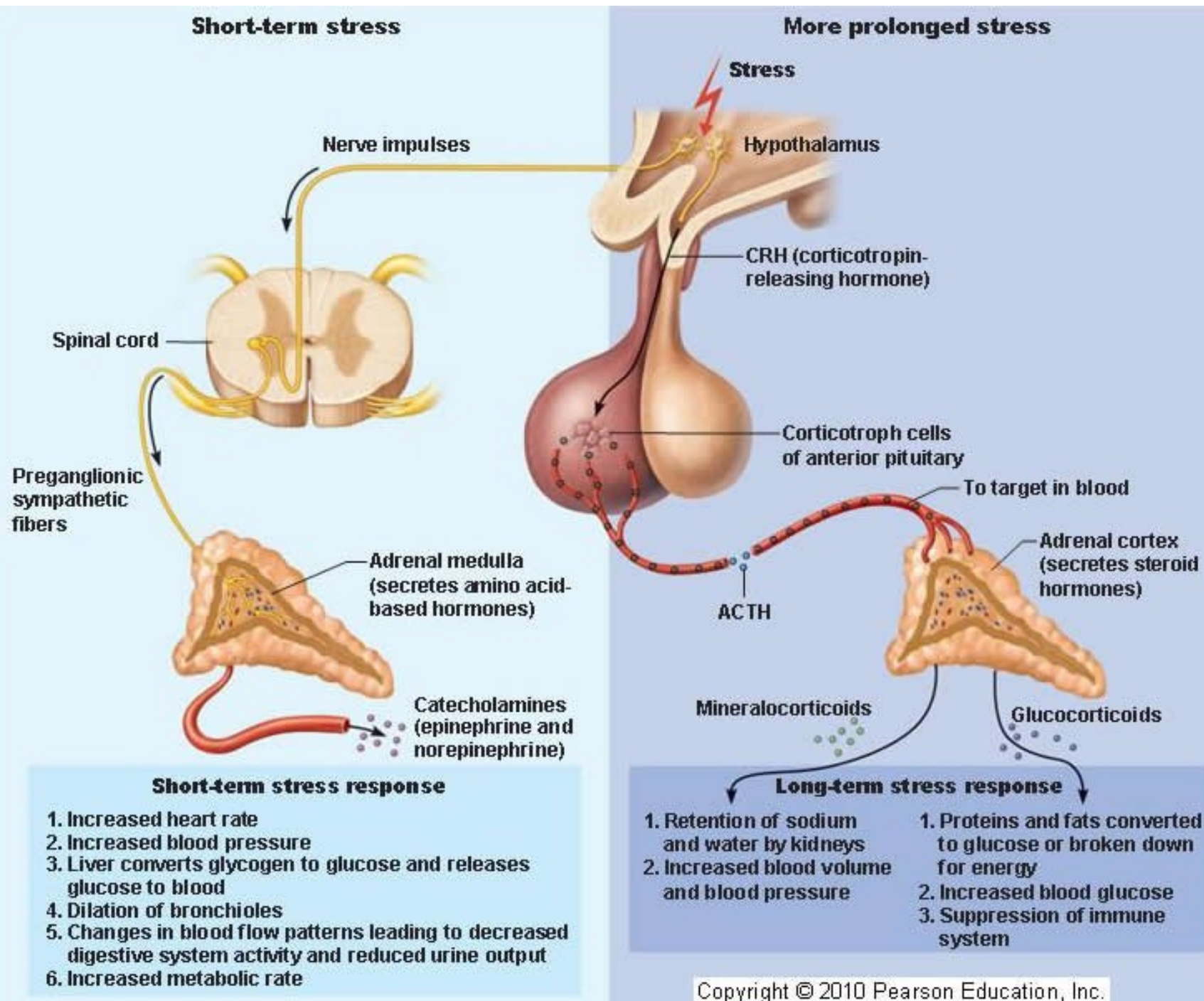


- Precurzors
- Mineralocorticoids
- Glucocorticoids
- Estrogens
- Androgens
- Intermediate products
- 17 ketosteroids

# Glucocorticoids - regulation

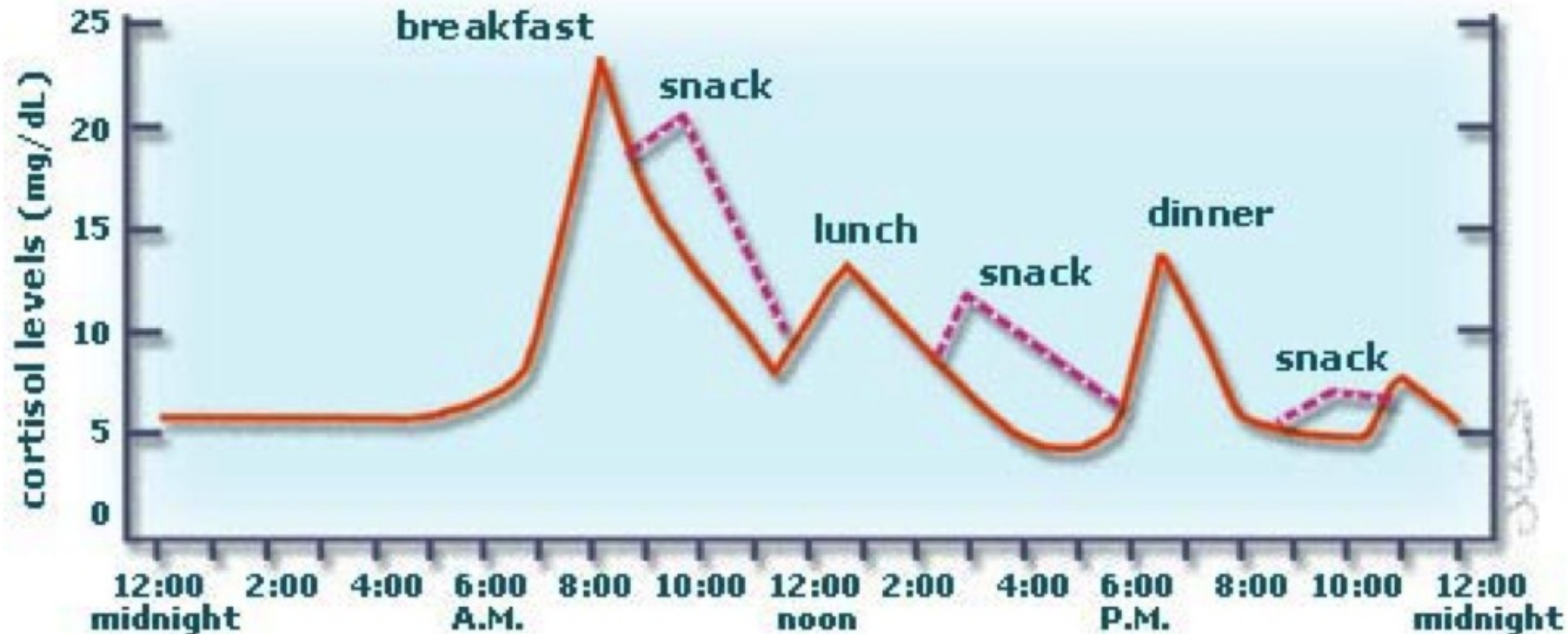






# Endogenous and exogenous cortisol secretion

## Circadian rhythm and your cortisol cycle



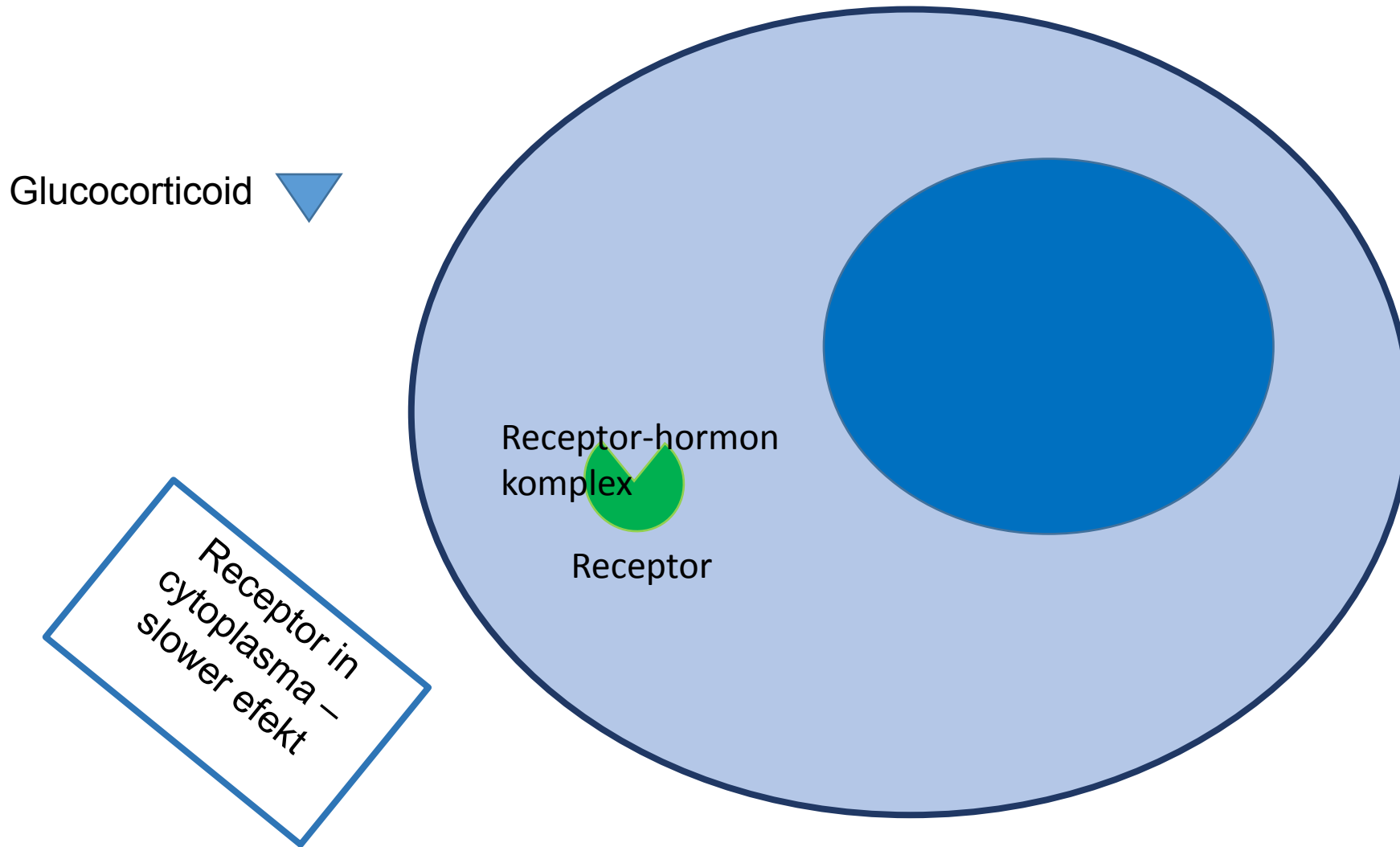
Resting – 20 – 25  
mg/24 hours

Stress: 10 times  
higher

Maximum: 6 – 8  
hours a.m.

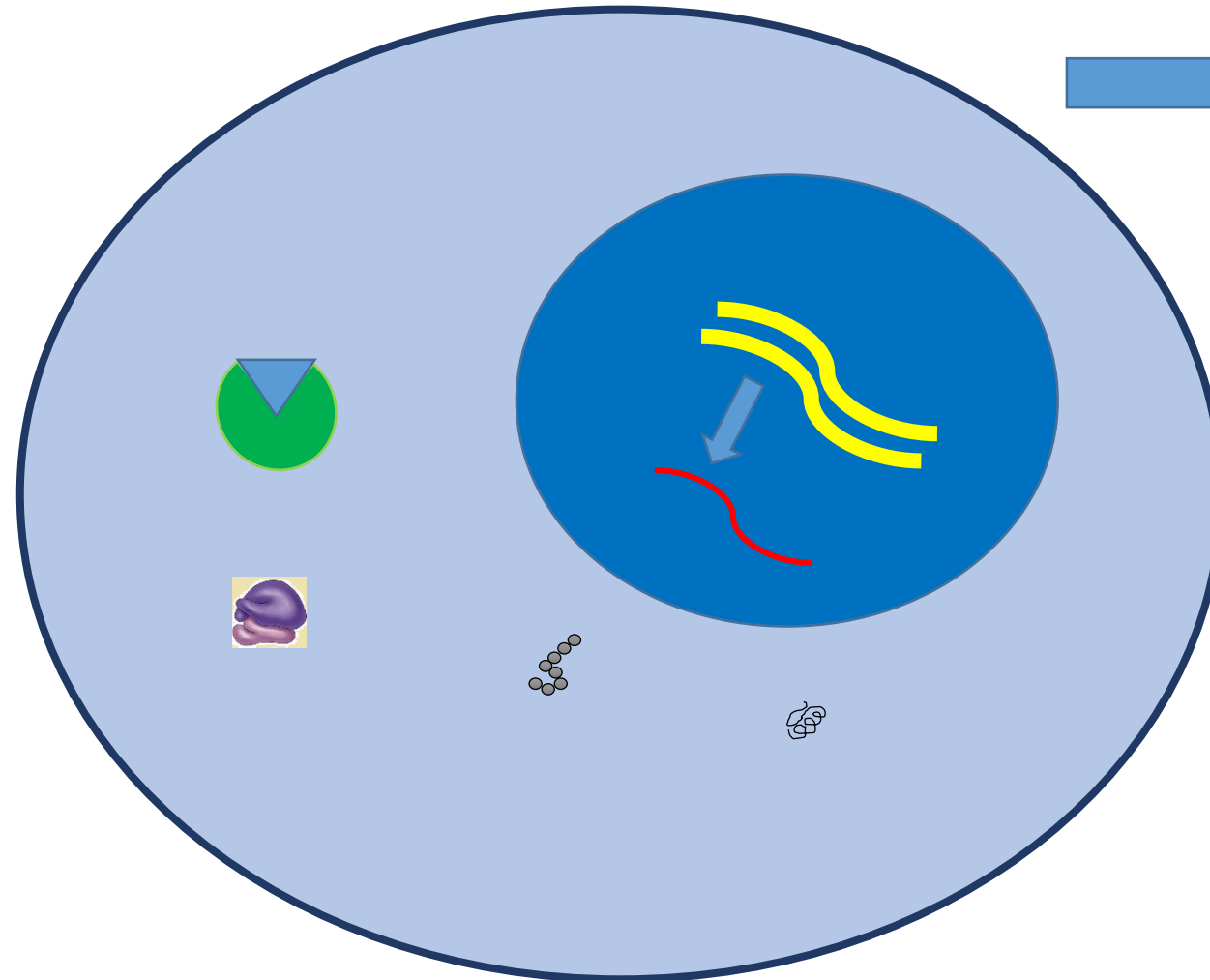
Exogenous corticoids usage – endogenous secretion downturn

# Mechanism of action in cellular level → Specific





Mechanism of action in cellular level → Specific



Change of proteosynthesis



# Glucocorticoids

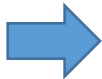
- influence sugar, fat and protein **metabolism**
- have **anti-inflammatory** and **anti-allergic** effect
- have **immunosuppressive** effect (in many branches – in next slides)
- have **antiproliferative** effect
  
- hydrocortisone (cortizol)

# GCs and sugar, fat and protein metabolism



reduced glucose uptake and reduced glucose utilisation in the cell

Proteolysis, tissue  
proteins = aminoacids  
decomposition of tissue proteins  
catabolism



↑ gluconeogenesis  
(glucose formation from non sugar residues)

Fats: ↑ lipolysis, facilitation  
of lipid absorption, fat  
redistribution



↑ glycaemia



↑ of insulin secretion



↑ storage of glycogen in the liver



lipogenesis support, lipolysis inhibition  
fat deposition, redistribution,  
↑ glycerol, aminoacids in blood

Connective tissue  
muscle atrophy  
fibroblasts growth stopping  
↓ osteoblasts, ↑ osteoclasts  
↓ collagen synthesis  
↓ Ca resorption from intestine,  
kidneys (osteoporosis)



# Other effects



**CNS:** Euphoria / psychotic disorder after high doses / depression

**GIT:** Increasing formation of HCl and pepsin in the stomach

**BLOOD:** ↑ Tro, Ery, circul. ↓lymfocytes, ↓eosinofils

**LUNGS:** ↑ formation of pulmonary surfactant

HCl – hydrochloric acid

# GCs and congenital developmental defects

## GK and ions



### **Permissive effect to:**

- Development of organs of the fetus
- Development and maturation of intestinal enzymes
- Increases the synthesis of surfactant in the lungs of the fetus
- Suppresses bone growth

### **Ions**

- Decreased calcemia
- Increased potassium loss
- Sodium and chloride retention

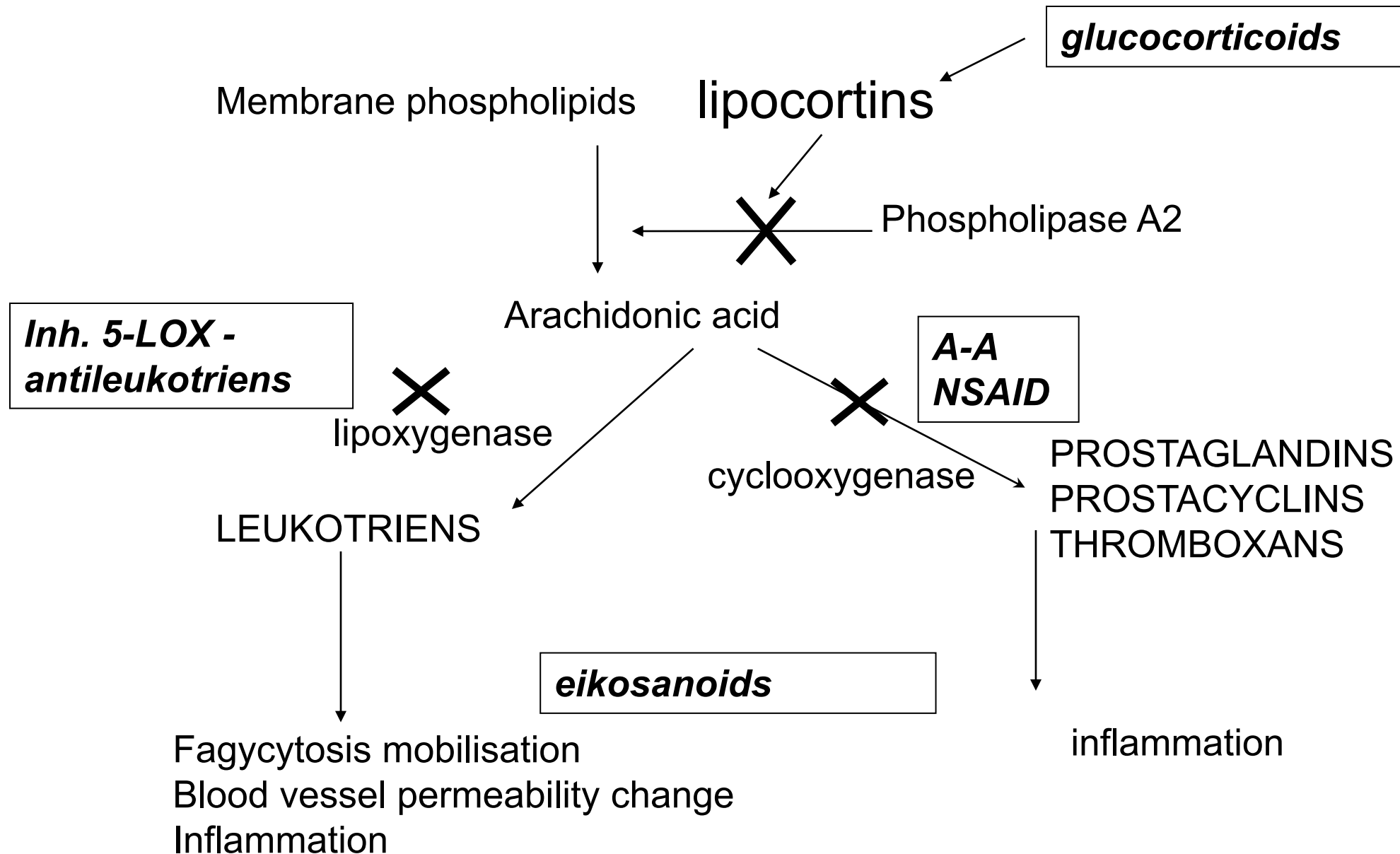


# Regulatory effects



- **Negative feedback on the hypothalamus and the anterior lobe of the pituitary gland**  
reduced release of endogenous glucocorticoids
- **Vasotropic** - GCs - vasoconstriction, decrease of permeability of vessels, suppression of edema
- **At cell level:**
  - in place of acute inflammation: decrease in migration and leucocyte activity
  - in place of chronic inflammation: decrease proliferation of blood vessels and fibrosis
  - In place of lymphoid tissue: decrease B and T lymphocyte expansion
- **Towards the mediators of inflammation and immunological reaction:**  
Decrease of cytokine production and activity, decreased synthesis of PGs

# Anti-inflammatory – cascade inhibition of AA





# Anti-inflammatory effect

- AA cascade inhibition
- Migration and leucocyte function disruption
- Antibody production reduction

**All types of inflammation regardless of origin!**

**(aseptic, viral, bacterial, parasitic....)**

# Anti-inflammatory effect



- Decreased histamine release from basophils
- Inhibition of the formation of inflammatory mediators and allergic reactions (cytokines, complement components, kallikrein ...)



# Immunosuppressive effect

Inhibition of antigen recognition

Inhibition of the effector phase of the immune response (cell lysis)

- **! CAUTION:**
- **Inhibition CELL MEDIATED immunity**
- **ANTIBODY immunity is affected significantly less and in GSc higher doses**



# Anti- proliferative effect



Block cell cycle

Induction of differentiation

GCs - lymphocyte disintegration (acute and chronic lymphocytic leukemia, lymphomas, myelomas)



# Effect and equipotent doses of CSs

Substance	Equip.dose	Anti infl. effect	Mineral. effect
Cortisol	20 mg	1	1
Cortisone	25 mg	0,8	0,8
Prednisone	5 mg	4	0,8
Prednisolone	5 mg	4	0
Methylpredn.	4 mg	5	0
Triamcinolone	4 mg	5-10	0
Dexamethasone	0,75 mg	25	0
Bethametasone	0,6 mg	25	0
Fludrocortisone	-	10	125

# Systemically administered GCs



- 1-4 times efficient than cortisol
  - **prednisolone, prednisone**
  - **hydrocortisone**

Short term acting

- 5-15times efficient than cortisol
  - **methylprednisolone (Solu-Medrol)**
  - **triamcinolone**
  - paramethasone
  - fluprednisolone

Medium term acting

- approx 30times efficient than cortisol
  - bethametasone
  - **dexamethasone**

Long term acting

(stronger axis supressior

# Glucocorticoids therapeutical regimen types

## Short term application of high doses



### **A) single** (2-4 g methylprednisolone)

Polytraumatas, septic, toxic shock

Hydrocortisone 30 mg / kg

### **B) repeated** (methylprednisolone, hydrocortisone, dexamethasone)

Anaphyl. shock, status asthmaticus, hypoglycemic coma ...

Duration up to 48 hours

Exceptionally up to 7 days

# Glucocorticoids therapeutical regimen types



## **C) Pulse therapy**

Short-term infusions for several days

Originally in transplant rejection

Today predominantly in immune-mediated diseases resistant to standard therapy

## **D) Prolonged therapy**

In most branches

Primarily for anti-inflammatory and immunosuppressive effects

Dosage and length depends on the current status of the patient

Strength differences, duration and frequency of adverse effects

No hydrocortisone with respect to mineralocorticoid activity



# Glucocorticoids – adverse events



## **Before therapy start:**

- potential infection elimination
- fasting glycaemia
- diabetes compensation
- preventive application of D vitamine
- anti-ulcer treatment

# Glucocorticoids – adverse events



## **During the therapy:**

- DM monitoring compensation
- monitoring of mental state
- myopathy and osteoporosis prevention (K, Ca, rehab., exercise)
- thromboembolic prevention
- consultation the centre for growth hormone treatment in pediatric medicine

# Glucocorticoids – adverse events prevention



## Prevention

- Application of the lowest effective dose
- If possible local applications
- Combination with other drugs
- Circadian therapy / alternating therapy
- Minimizing the use of depot medication (circadian rhythm disruption, local trophic changes after application)

# Glucocorticoids – adverse events



## **Immunosuppression**

- ↑ susceptibility to infections, activation of latent infections
- Slow wound healing
- Even with local administration

## **Suppression of endogenous glucocorticoid production**

- Acute inadequacy when suddenly discontinuing higher doses
- Prevention = complete therapy by gradual dose reduction

## **Osteoporosis**

- Risk only for chronic therapy
- Densitometric examination

## **Mineralocorticoid effect**

- Water retention and Na +
- ↑ BP, loss of K +

# Glucocorticoids – adverse events



Hyperglycemia, steroidal diabetes

Muscle weakness, myopathy, atrophy

Psychotropic effects

Insomnia, motor agitation, vertigo, euphoria, depression

Psychic habit

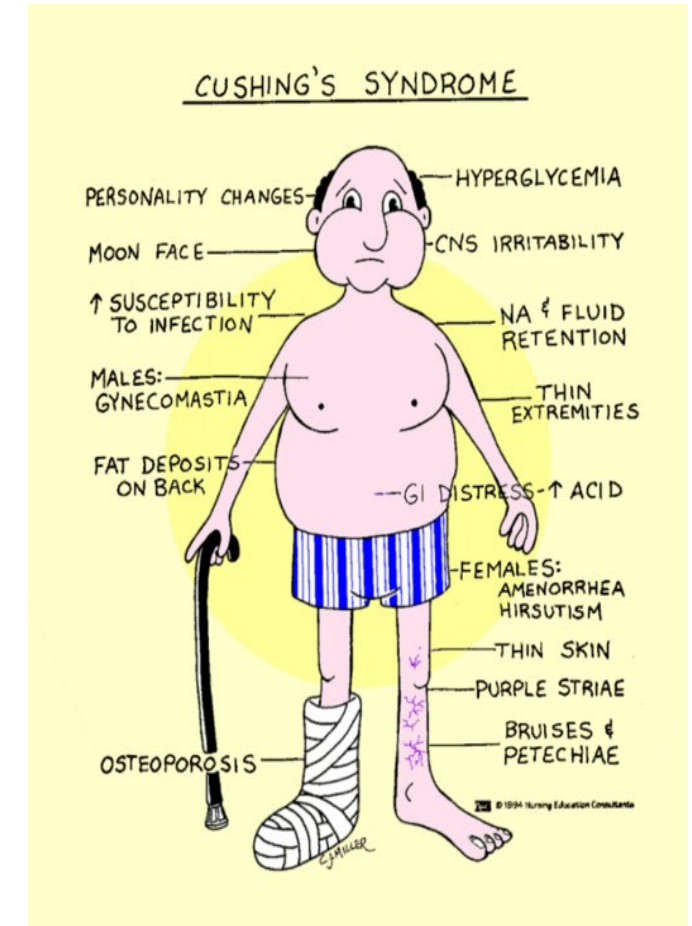
GIT

Exacerbation of gastric ulcer

Intestinal perforation, acute pancreatitis

KVS

- HT, atherosclerosis, cardiomyopathy, ↑ coagulopathy, arrhythmia



# Glucocorticoids – adverse events



## **Eye**

Induction of glaucoma ( $\uparrow$  intraocular pressure)

Corneal ulceration in keratitis herpetica

## **Endocrine**

Growth inhibition in children (therapy longer than 6 months)

Amenorrhea, potency and libido decrease

## **Skin**

Atrophy

Intradermal bleeding

Acne, hirsutism

# Glucocorticoids – interactions



Prednisone reduces the plasma levels of salicylates and oral anticoagulants.

The effect of prednisone is reduced by barbiturates, phenytoin, rifampicin.

# Routes of administration



- p.o.
- i.v.
- i.m.
- s.c.
- inhalatory
  
- ointment/cream
- eye/nose drops
- intraarticularly



# Inhalation GCs in asthma treatment



- The most effective preventative antiasthmatics
- Improve pulmonary function, reduce bronchial hyperreactivity, reduce exacerbations, improve quality of life
- Beclomethasone dipropionate, budesonide, fluticasone propionate
- Inhaled corticosteroids have a better safety profile than oral
- Fixed combination - fluticasone + salmeterol (Seretide Discus)  
- budesonide + formoterol (Symbicort Turbuhaler)



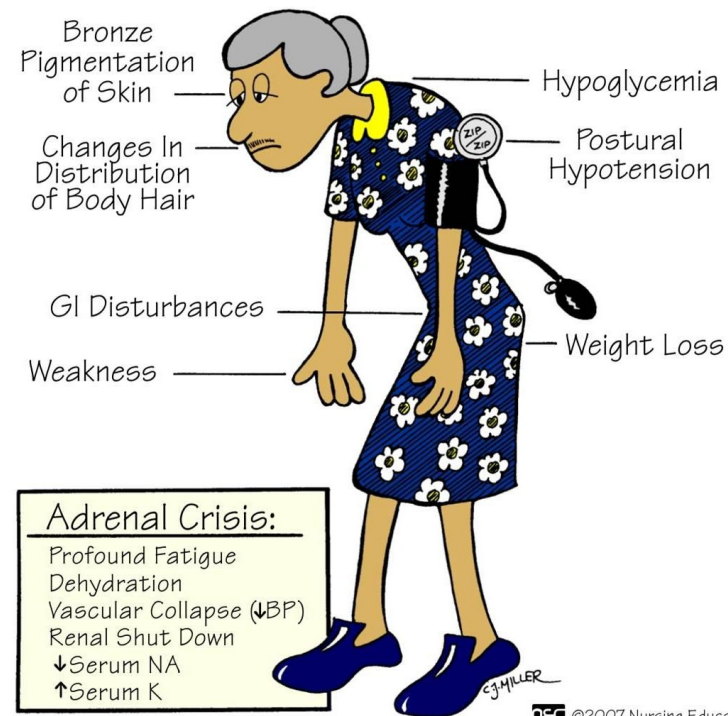


# Therapeutic indications

## PHYSIOLOGICAL (low) DOSES

- insufficiency: cortisol + fludrocortison (mineralokortikoid)
- I: Addison's disease

### ADDISON'S DISEASE



REG ©2007 Nursing Education Con:

# Therapeutic indications



## Higher doses

- Diseases of connective tissue, rheumatological diseases and collagenoses
- Severe forms of allergic reactions
- Non-infectious inflammatory diseases of the eye
- Severe skin disorders
- Haematological diseases
- Malignant diseases
- Conditions after organ transplantation
- Inflammatory gastrointestinal disease
- Non-inflammatory respiratory disorders
- Immunalternative disease in neurology

# Acute rejection in transplant organs



- Sudden deterioration of graft function on immune basis
- It occurs in the first three months
- Diagnosis of rejection - biopsy and histology result
- Therapy:
  - Pulse treatment of corticosteroids 250 - 500 mg of methylprednisolone 3 - 5 days leading to a graft stabilisation in majority of patients
- In case of corticoresistance - antithymocytic globulin



# Corticoids in clinical practice

# Skin diseases

## Eczema dyshidroticum, before therapy

Hand-foot syndrom

Man 35 years old

2 – 3 years of hands eczema

Status of treatment with local corticosteroids for 2 years

Extreme impact on quality of life!





# Skin diseases

## Eczema dyshidroticum, after therapy

Prednison 50 mg / daily – 1 month

Proton pump inhibitors

Effect after 1 week of systemic therapy, but:

Severe AE:

- Sleep disturbances
- Depression
- Hypertension

(repeatedly 160/110)

withadrawal

Next strategy?

Immunosupressants?





# MINERALOCORTICIDS





The main endogenous mineralocorticoid is aldosterone.

Its chief action is to increase  $\text{Na}^+$  reabsorption by the distal tubules in the kidney, with a concomitant increase in excretion of  $\text{K}^+$  and  $\text{H}^+$ .

An excessive secretion of mineralocorticoids: marked  $\text{Na}^+$  and water retention, with increased extracellular fluid volume and sometimes hypokalaemia, alkalosis and hypertension

Decreased secretion: Addison's disease,  $\text{Na}^+$  loss, marked decrease in extracellular fluid volume



## Mechanism of action

Like other steroid hormones, aldosterone acts through specific intracellular receptors of the nuclear receptor family.

Unlike the glucocorticoid receptor, which is present in most cells, the mineralocorticoid receptor is restricted to a few tissues (kidney and the transporting epithelia of the colon and bladder).



**Fludrocortisone** is given orally to produce a mineralocorticoid effect.

increases  $\text{Na}^+$  reabsorption in distal tubules

increases  $\text{K}^+$  and  $\text{H}^+$  efflux into the tubules

acts on intracellular receptors that modulate DNA transcription, causing synthesis of protein mediators

**is used together with a glucocorticoid in replacement therapy**



## Clinical use of mineralocorticoids

The main clinical use of mineralocorticoids is in replacement therapy of patients with Addison's disease.

The most commonly used drug is **fludrocortisone** (p.o.) to supplement the necessary glucocorticoid replacement.