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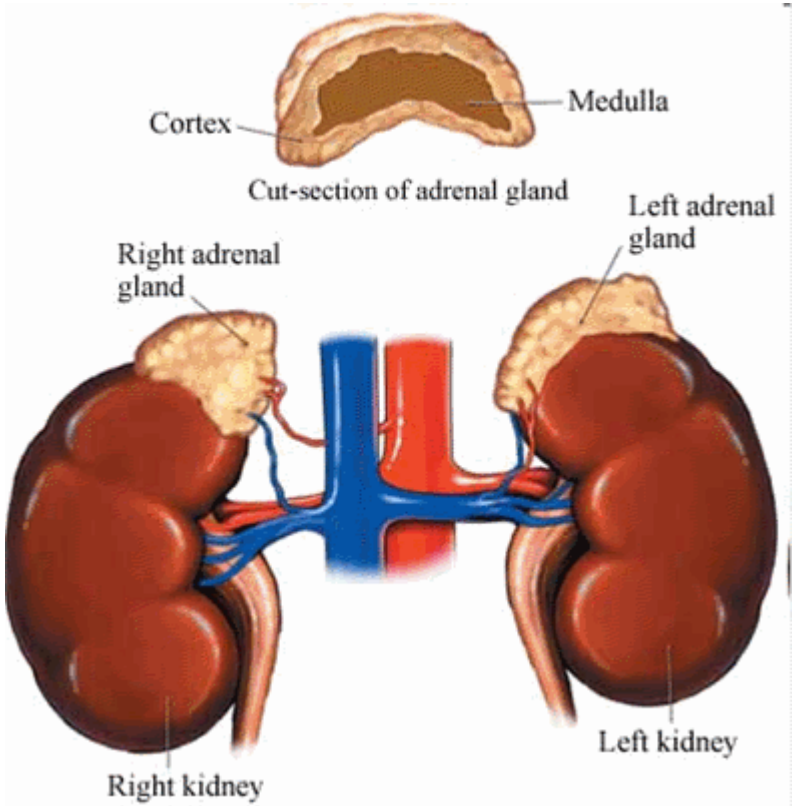
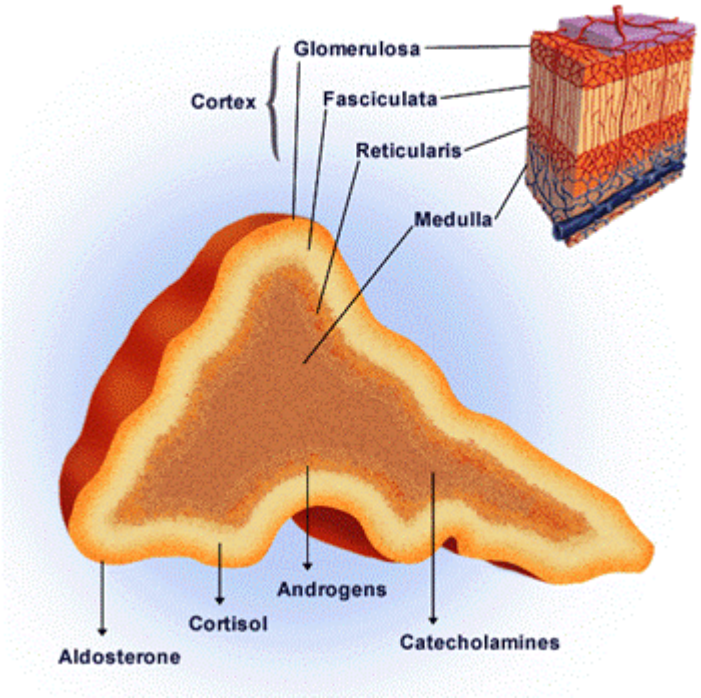
GLUCOCORTICOIDS

Department of Pharmacology MF MU

Suprarenal glands - anatomy





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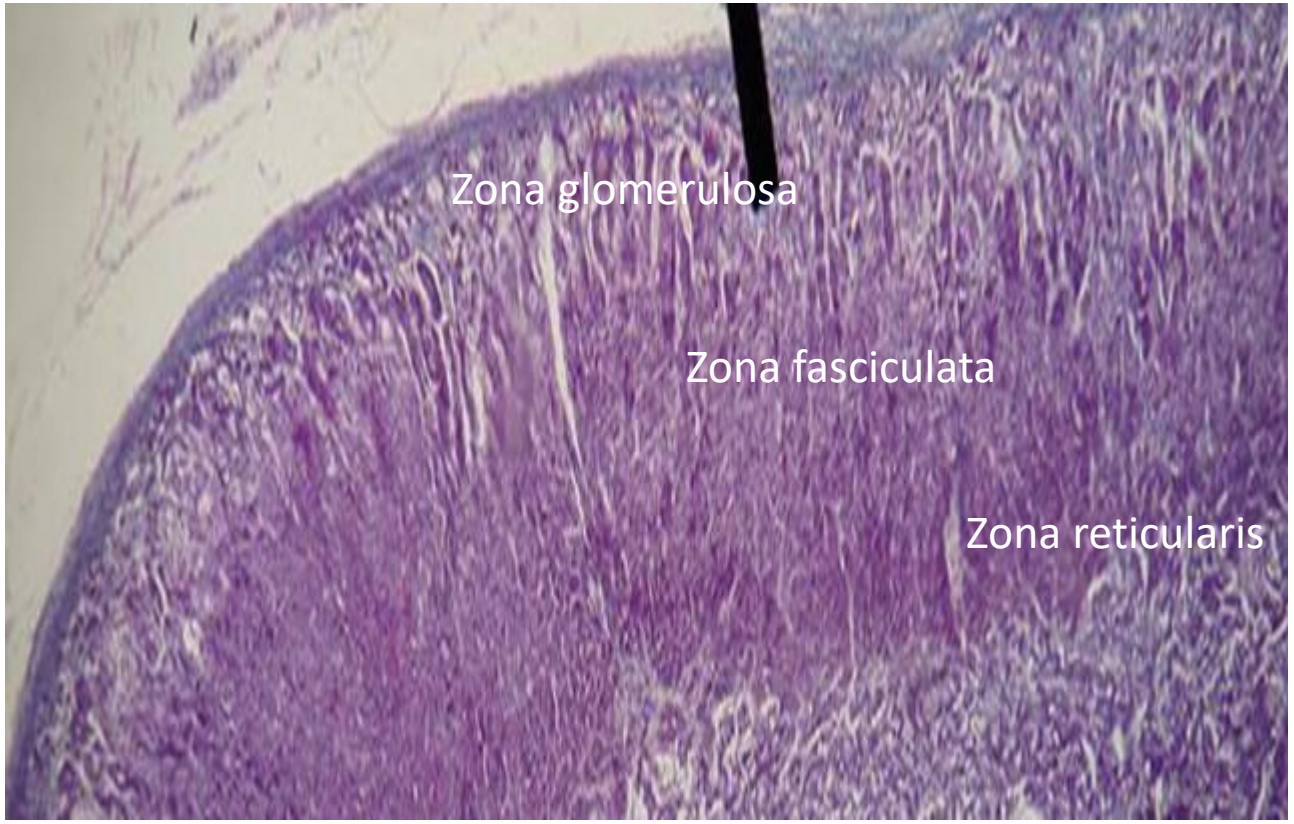
Adrenal cortex - physiology



- **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.

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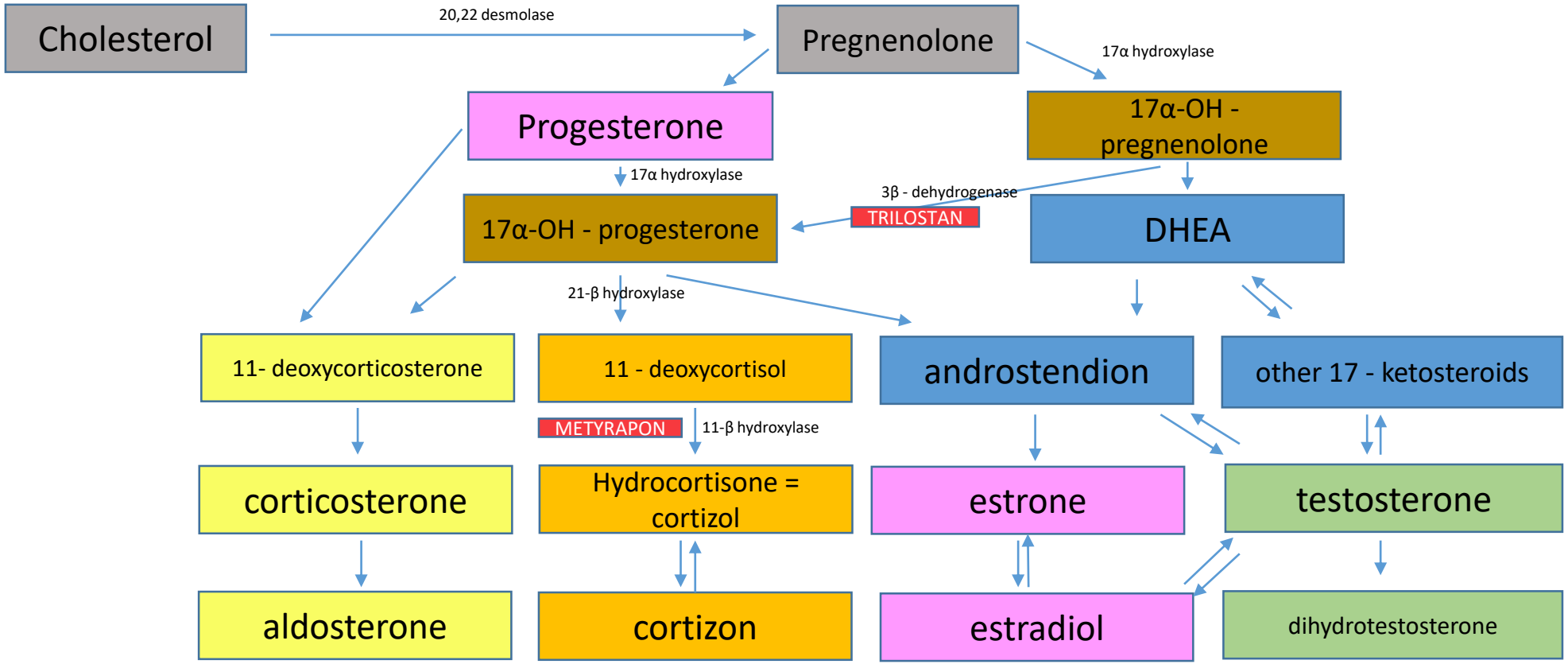
Steroid hormones biosynthesis - biochemistry



Precurzors

Intermediate products

Mineralocorticoids

Glucocorticoids

Estrogens

Androgens

17 ketosteroids

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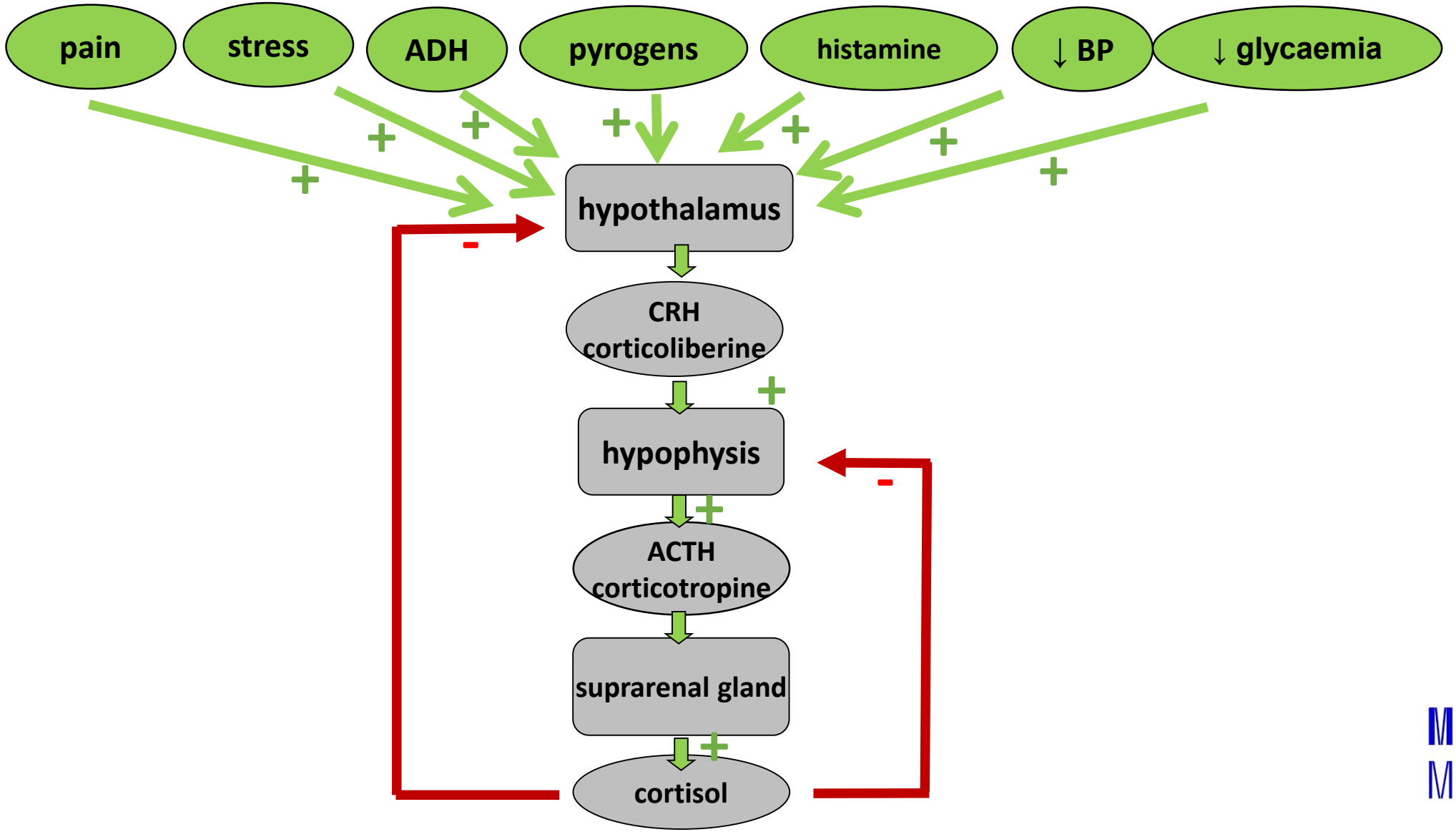
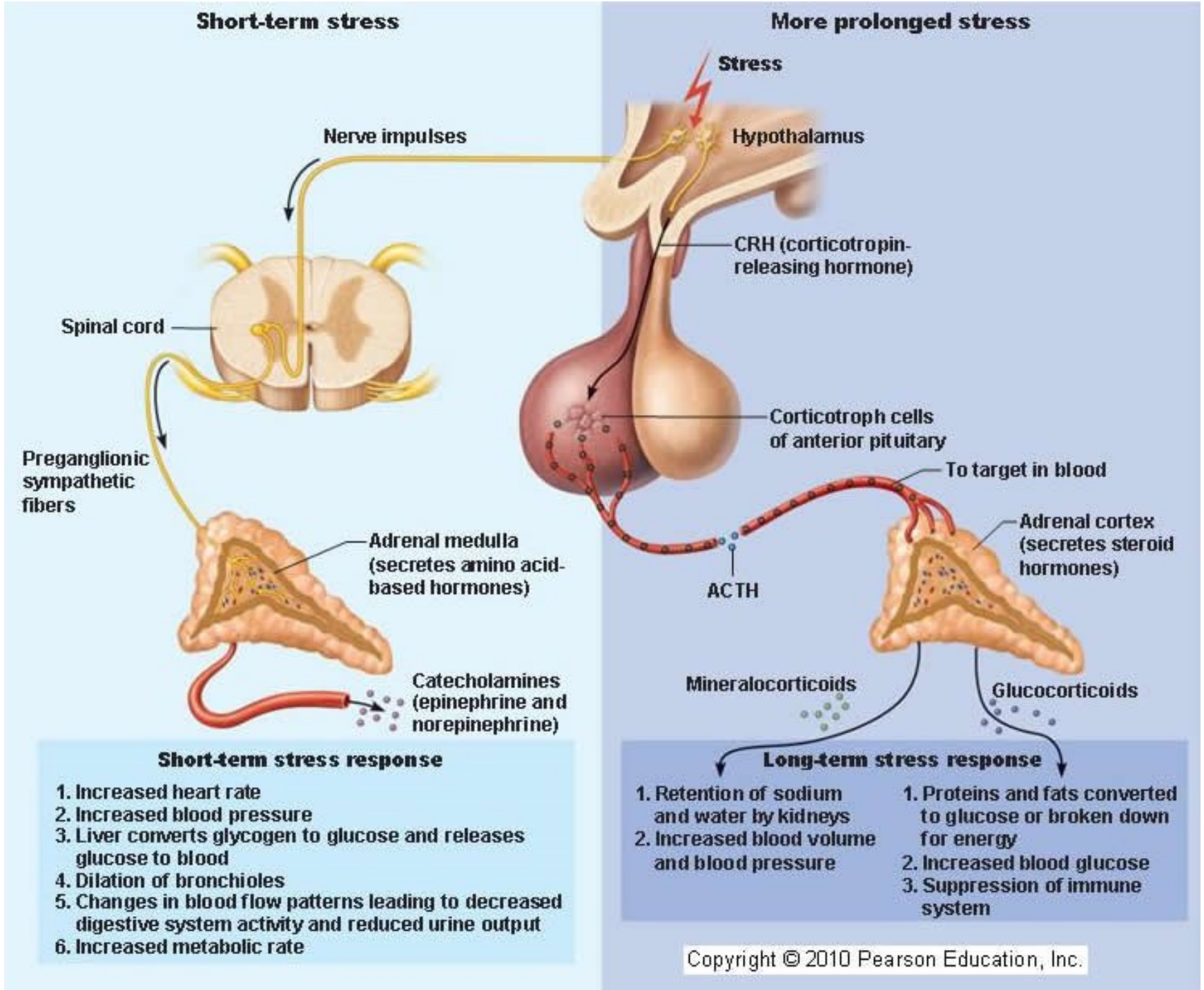
Glucocorticoids - regulation




Short-term stress
More prolonged stress
Stress
Nerve impulses
Hypothalamus
CRH (corticotropin-releasing hormone)
Spinal cord
Corticotroph cells of anterior pituitary
Preganglionic sympathetic fibers
To target in blood
Adrenal cortex (secretes steroid hormones)
Adrenal medulla (secretes amino acid-based hormones)
ACTH
Catecholamines (epinephrine and norepinephrine)
Mineralocorticoids
Glucocorticoids
Short-term stress response
1. Increased heart rate
2. Increased blood pressure
3. Liver converts glycogen to glucose and releases glucose to blood
4. Dilation of bronchioles
5. Changes in blood flow patterns leading to decreased digestive system activity and reduced urine output
6. Increased metabolic rate
Long-term stress response
1. Retention of sodium and water by kidneys
2. Increased blood volume and blood pressure
1. Proteins and fats converted to glucose or broken down for energy
2. Increased blood glucose
3. Suppression of immune system
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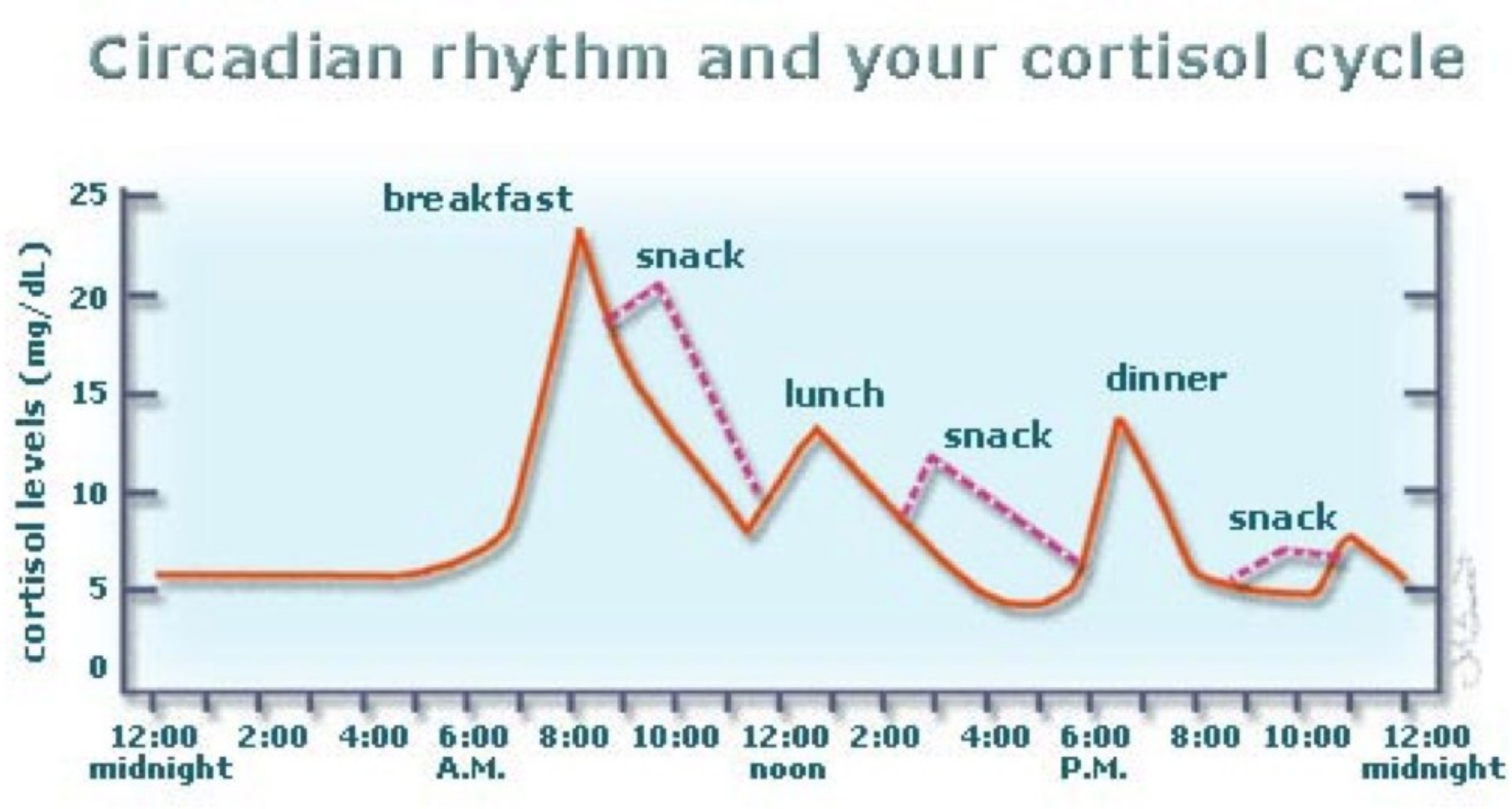
Endogenous and exogenous cortisol secretion



Resting – 20 – 25 mg/24 hours

Stress: 10 times higher

Maximum: 6 – 8 hours a.m.

Exogenous corticoids usage – endogenous secretion downturn

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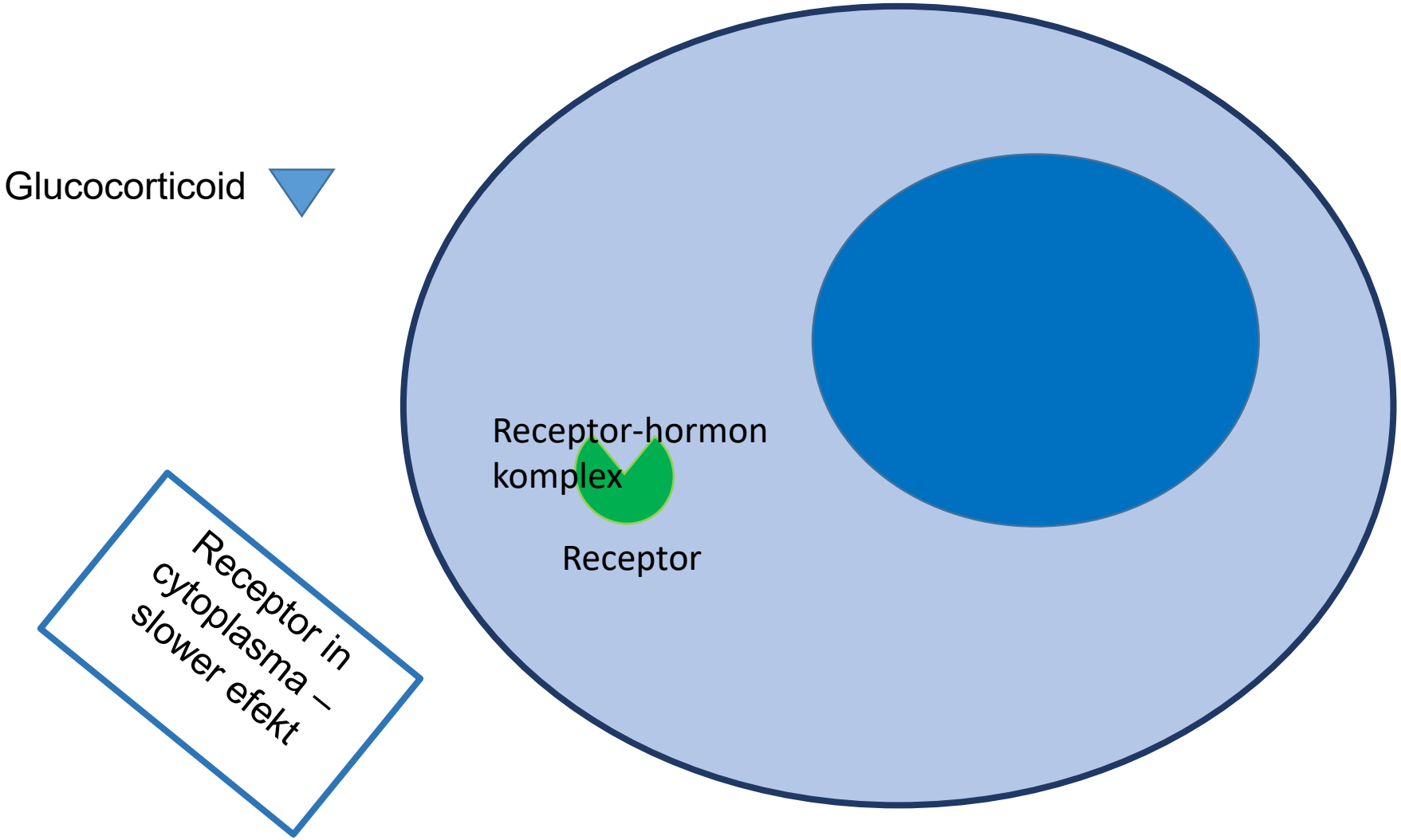
Mechanism of action in cellular level → **Specific**



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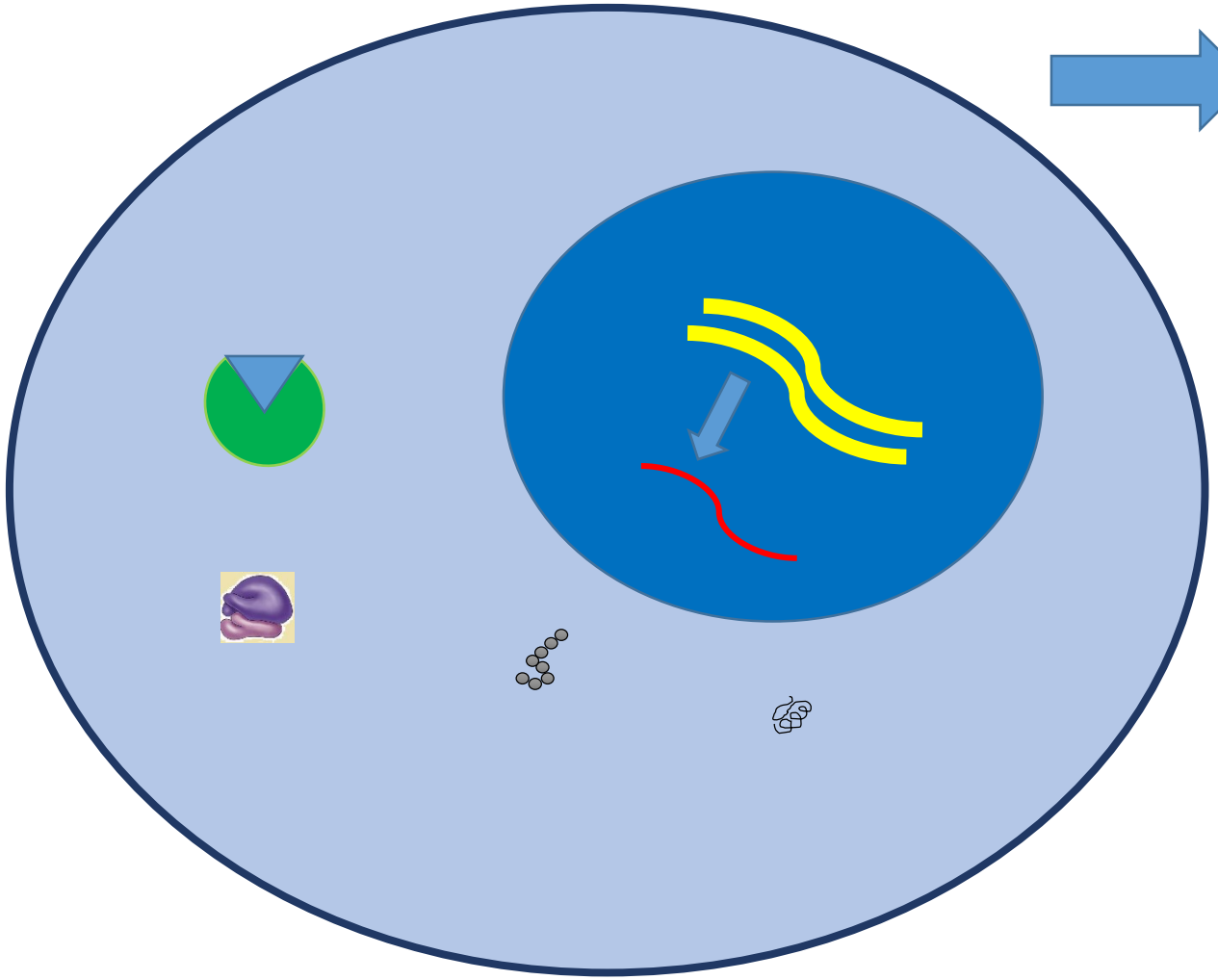
Mechanism of action in cellular level → **Specific**



→ Change of proteosynthesis

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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)

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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

↑ <u>gluconeogenesis</u>
(glucose formation from non sugar residues)

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

↑ glycaemia

↑ of insulin secretion

Connective tissue
muscle atrophy

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

↑ storage of glycogen in the liver

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

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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

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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

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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

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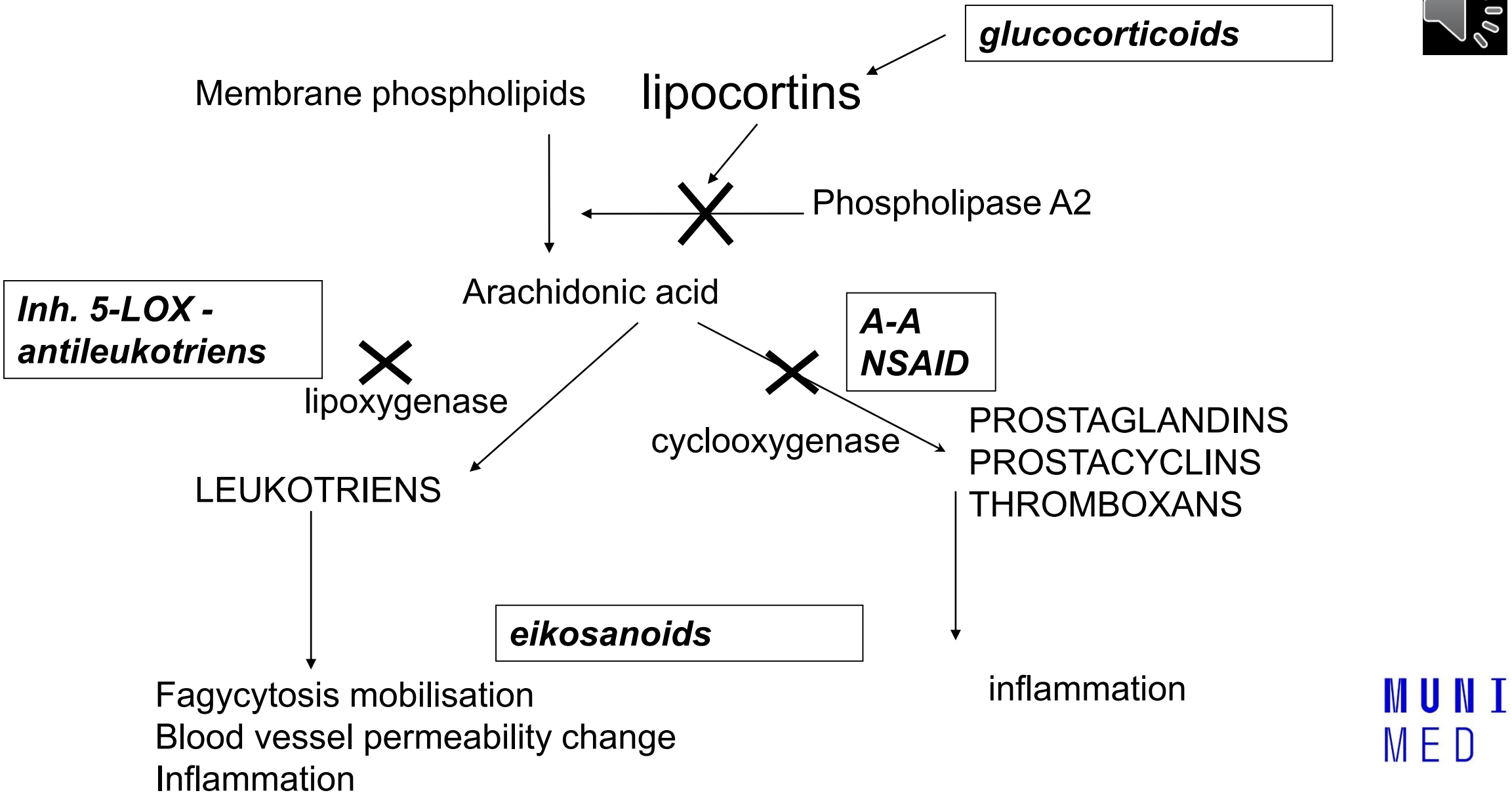
Anti-inflammatory – cascade inhibition of AA



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….)

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Anti-inflammatory effect

- Decreased histamine release from basophils

- Inhibition of the formation of inflammatory mediators and allergic reactions (cytokines, complement components, kallikrein ...)

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Immunosupressive 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**

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Anti- proliferative effect

Block cell cycle

Induction of differentiation

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

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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

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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 supression)

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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

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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

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Glucocorticoids – adverse events

During the therapy:

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

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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)

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Glucocorticoids – adverse events

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

Supression 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 +

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Glucocorticoids – adverse events

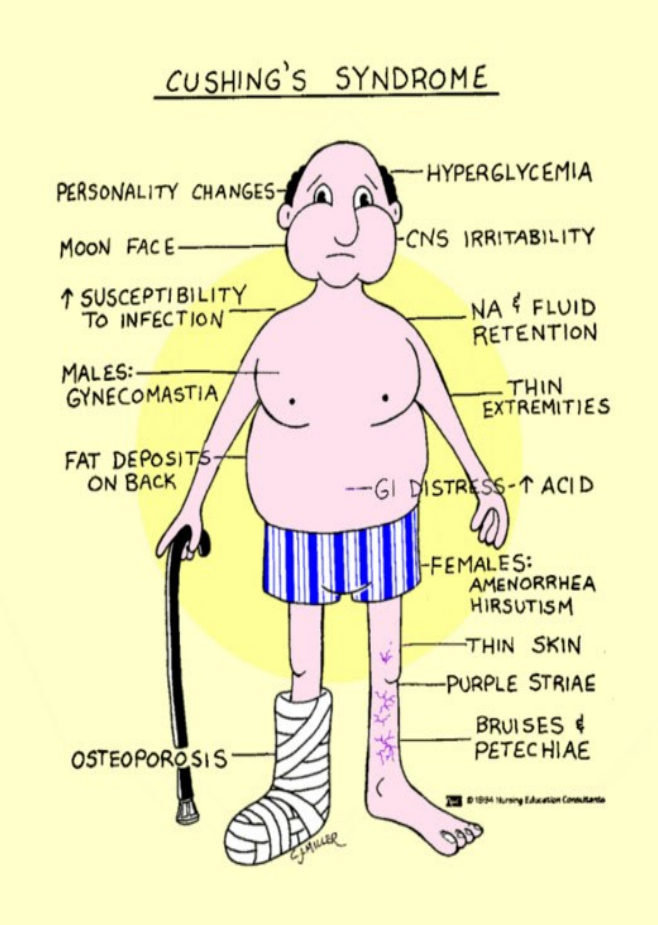
Hyperglycemia, steroidal diabetes

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



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Glucocorticoids – adverse events

Eye
Induction of glaucoma (↑ 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

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Glucocorticoids – interactions

Prednisone reduces the plasma levels of salicylates and oral anticoagulants.

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

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Routes of administration

- p.o.
- i.v.
- i.m.
- s.c.
- inhalatory

- ointment/cream
- eye/nose drops
- intraarticularly

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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)

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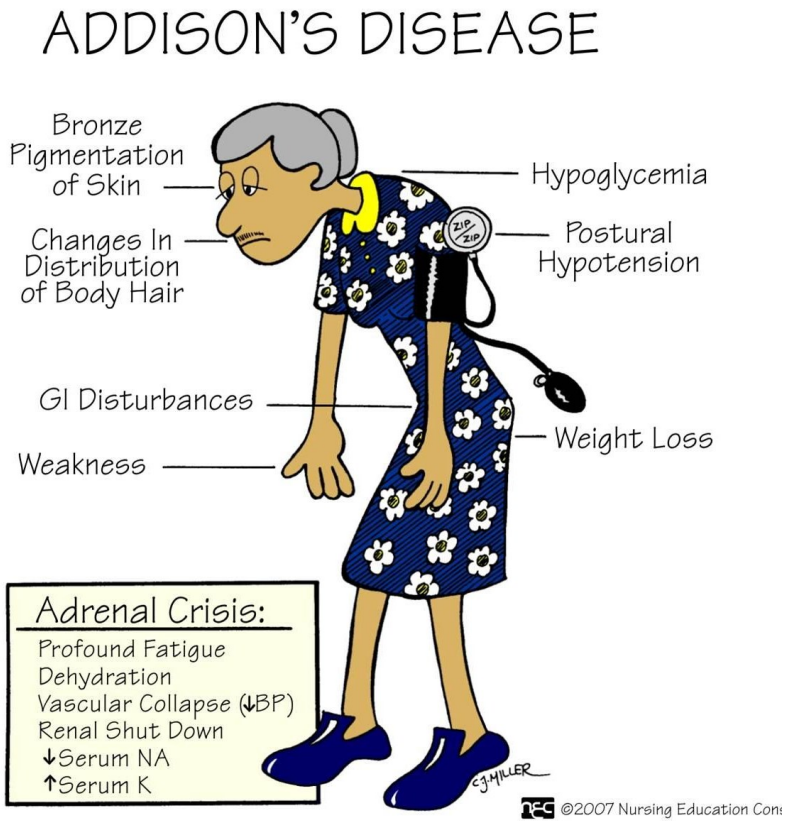
Therapeutic indications

PHYSIOLOGICAL (low) DOSES

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



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

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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

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Corticoids in clinical practice

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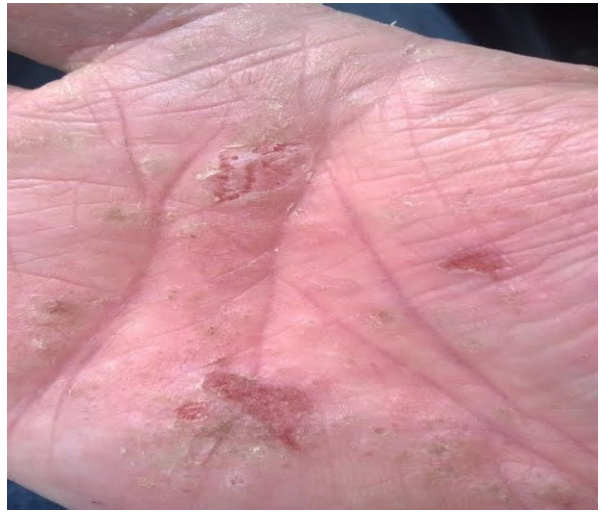
Skin diseases
Eczema dyshidroticum, before therapy



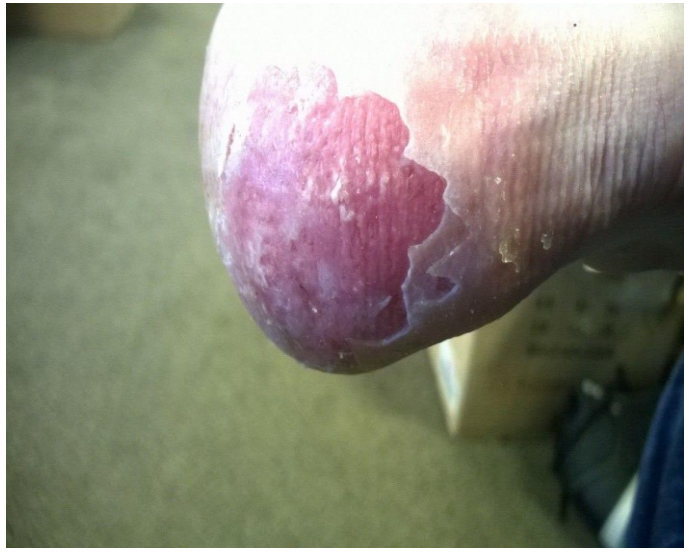
Hand-foot syndrom

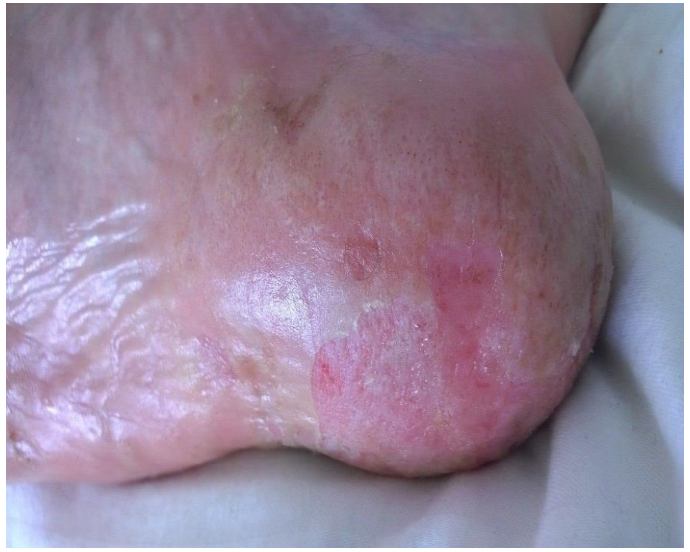
Man 35 years old

2 – 3 years of hands eczema

Status of treatment with local corticosteroids for 2 years

Extreme impact on quality of life!





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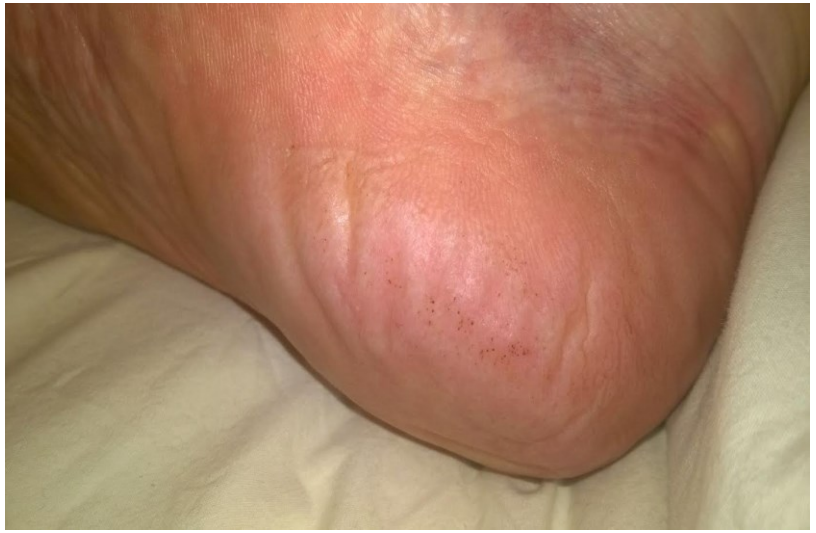
Skin diseases
Eczema dyshidroticum, after therapy



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?

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MINERALOCORTICOIDS

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The main endogenous mineralocorticoid is aldosterone.

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

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

Decreased secretion: Addison's disease, Na^+ loss, marked decrease in extracellular fluid volume

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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).

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Fludrocortisone is given orally to produce a mineralocorticoid effect.

increases Na+ reabsorption in distal tubules

increases K+ and 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

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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.

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