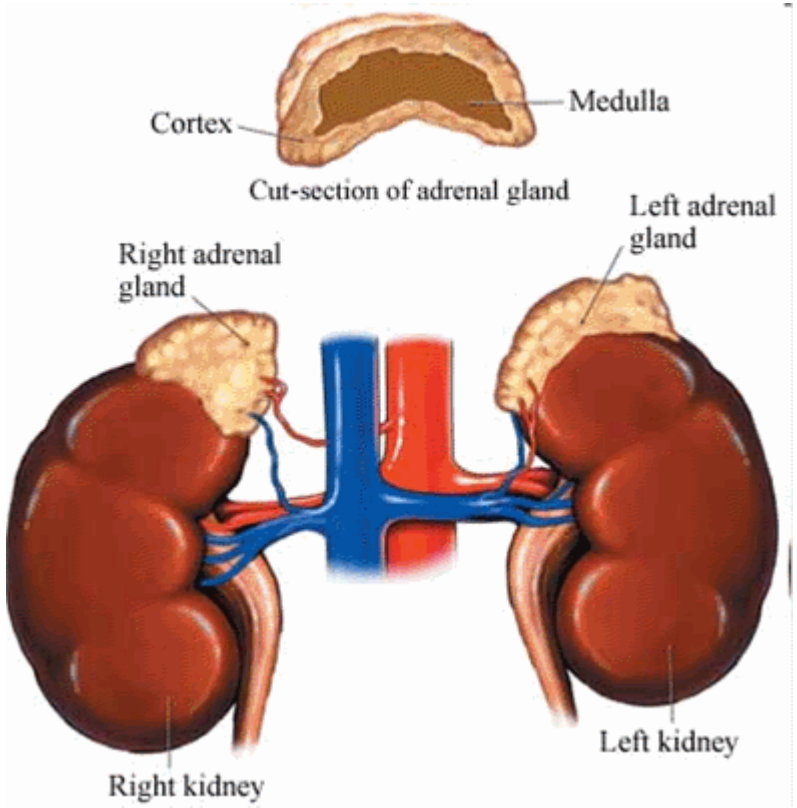
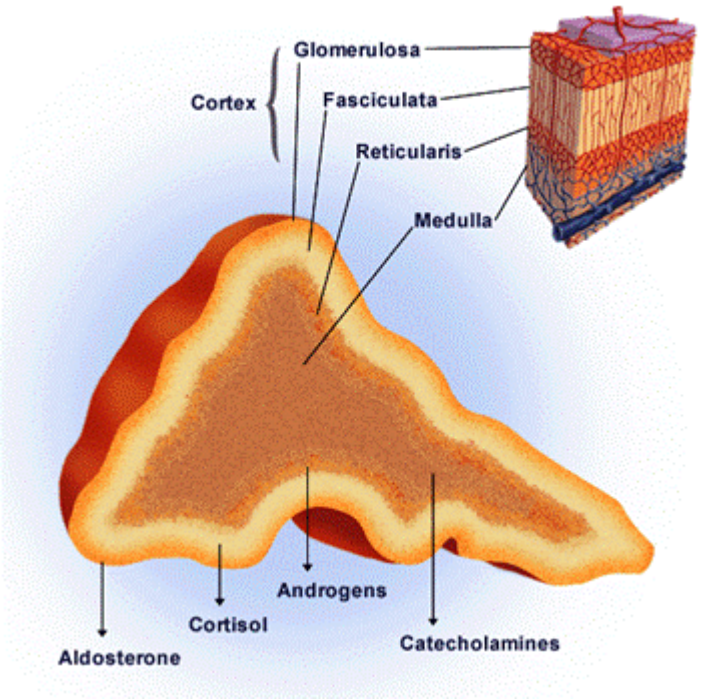
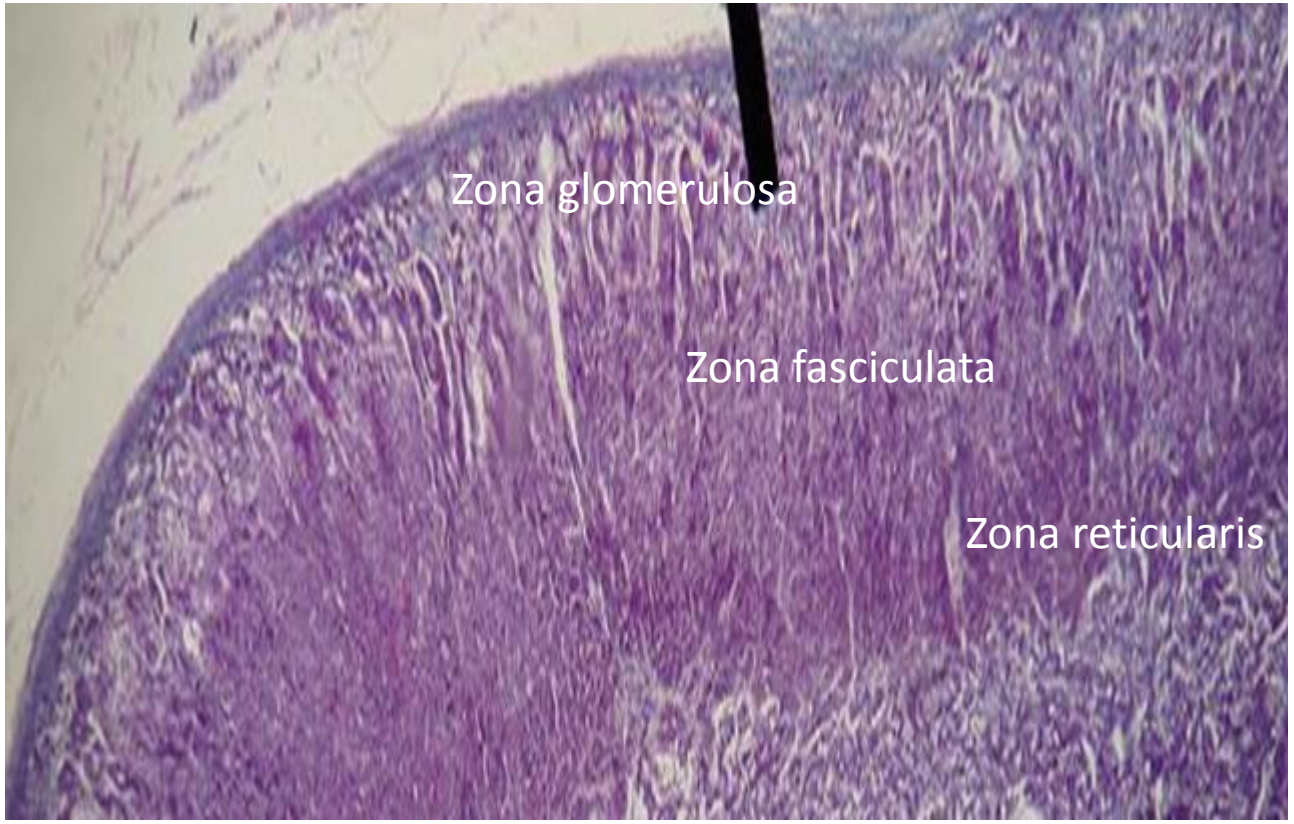
Glucocorticoids

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.

Adrenal medulla - physiology

A-cells – adrenaline - 80 % catecholamines secreted to the blood.
Adrenalin secretion based on n

Nerve impulse →physical and psychological stress (crisis situation) →alarm reaction → adaptation stage → ↑ glucosis, lactate, free fatty acids concentration, → exhaustion stage.

N-cells – noradrenaline – causes contraction of blood vessels (except heart vessels), thereby ↑ blood pressure.

STRESS - physiology

1) Adrenal medulla activation makes changes leaded to **organism survival** in exceptional conditions
2) Cells produced hormons – colored by chrome colors = chromafine = **feochromocytes**
3) Source material for adrenal medulla hormones synthesis = dopamine, noradrenaline and adrenaline = **tyrosine,** created from phenylalanine
4) STRESS – organism reaction to burden – mental (fear, anger), physical (cold, hot), traumatic, exertion – hypoglycaemia, hypoxia

A – **ALARM STAGE** - Acetylcholine is released from presynaptic nerve fibres terms → starts **catecholamines secretion** from feochromocytes

B - ↑ BP, **glycogenolysis** (glycogen breakdown in livers and muscles to glucose = energy source) → hyperglycaemia, **lipolysis** (fatty acids release from fat cells, fatty acids = energy source) = glucose and fatty acids preparation to muscular work „to struggle, to escape".

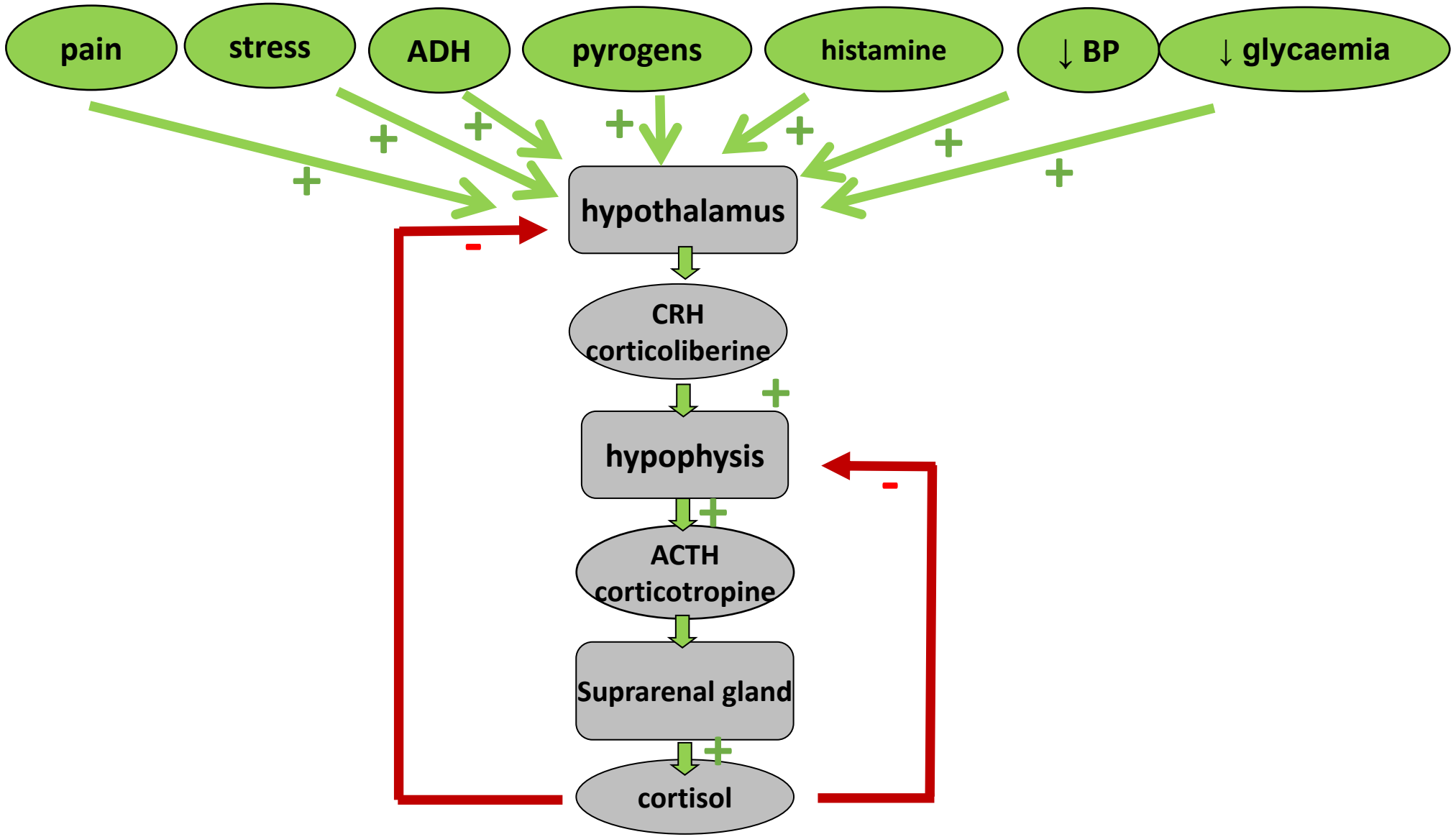
C – parallel **activation of system CRH – ACTH – cortisol** - ↑ cortisol secretion

D - **ADAPTATION STAGE** – Cortizol – encourages **gluconeogenesis** = glucose synthesis (also after exhaustion of glycogen from non-sugar substrates – amino acids, glycerol and lactate) and lipolysis (see above) = additional „secure of fuel" for energy expenditure

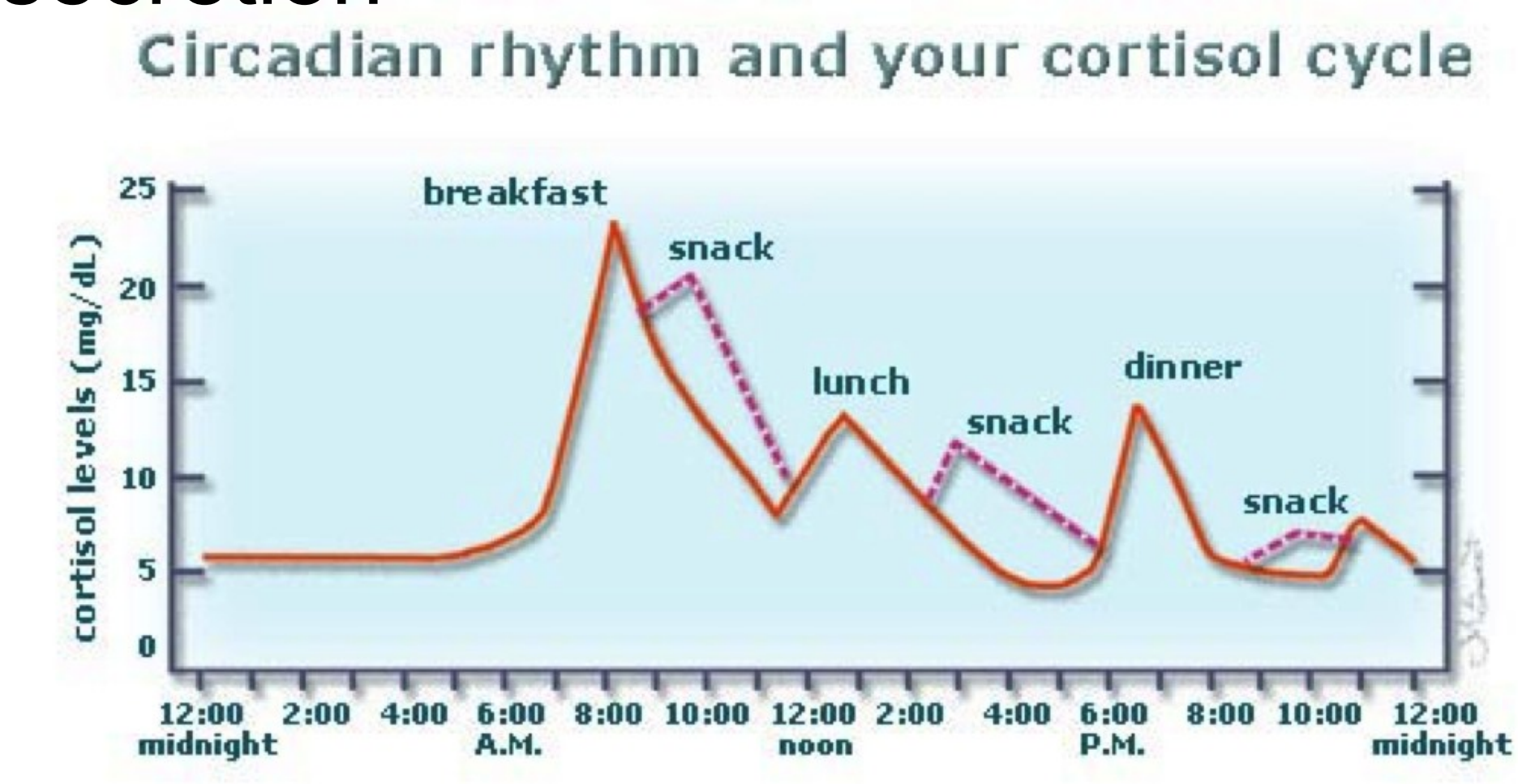
E– **EXHAUSTION STAGE** – during long and heavy stress – depletion of cortisol, disruption of its secretion, (supra renal cortex damage) – organism collapse → hypotension, shock, heart failure.

NT – neurotransmitters, ANS – autonomic nervous system, S – sympathetic, PS – parasympathetic, BP – blood pressure

Glucocorticoids - regulation



Endogenous and exogenous cortisol secretion



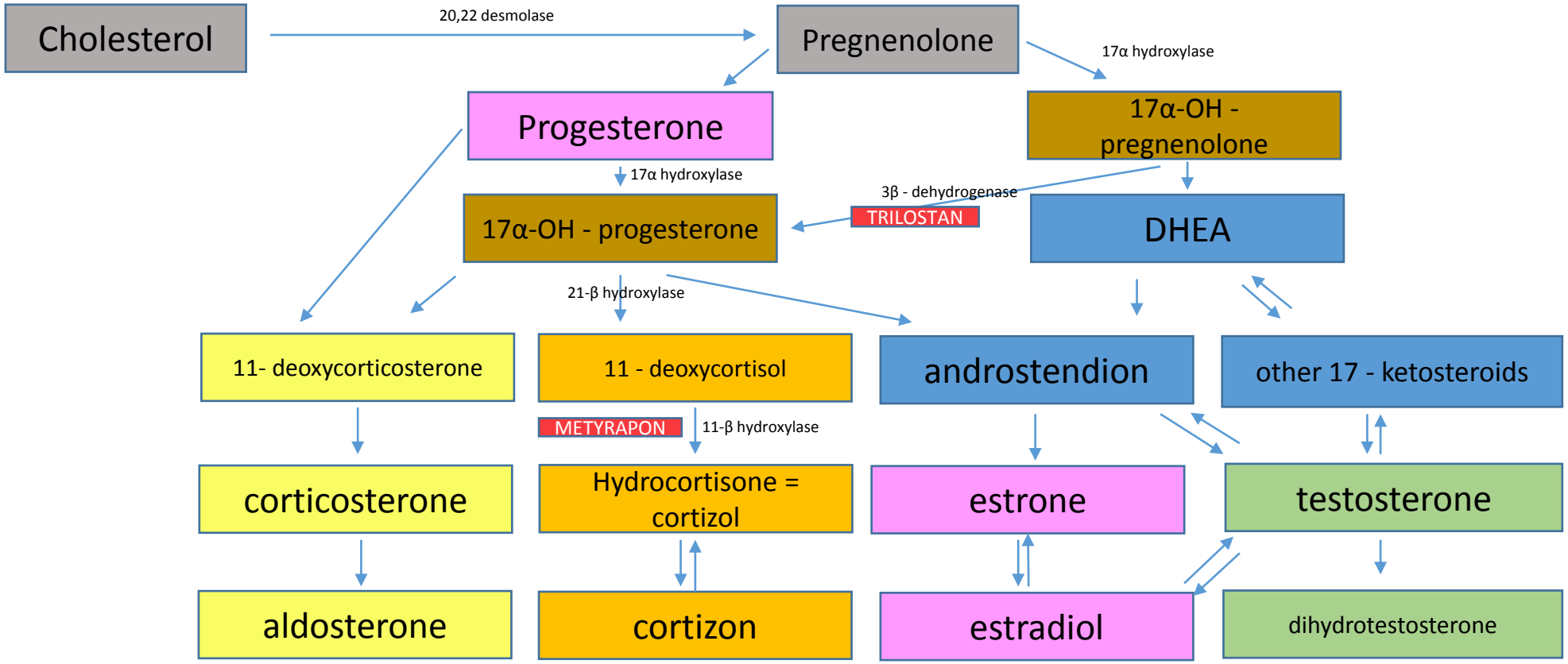
Resting – 20 – 25 mg/24 hours

Stress: 10 times higher

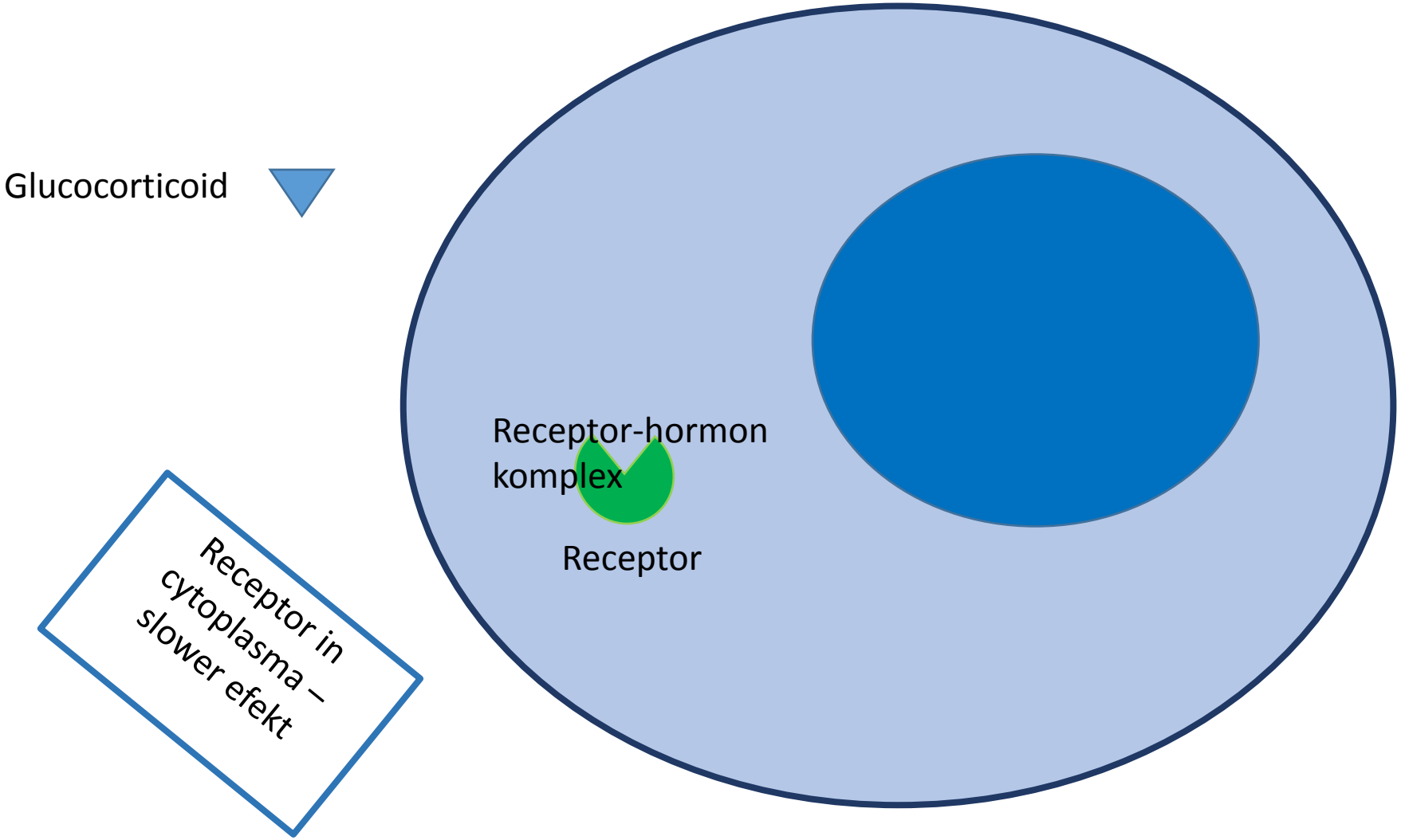
Maximum: 6 – 8 hours a.m.

Exogenous corticoids usage – endogenous secretion downturn

Steroid hormones biosynthesis - biochemistry



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



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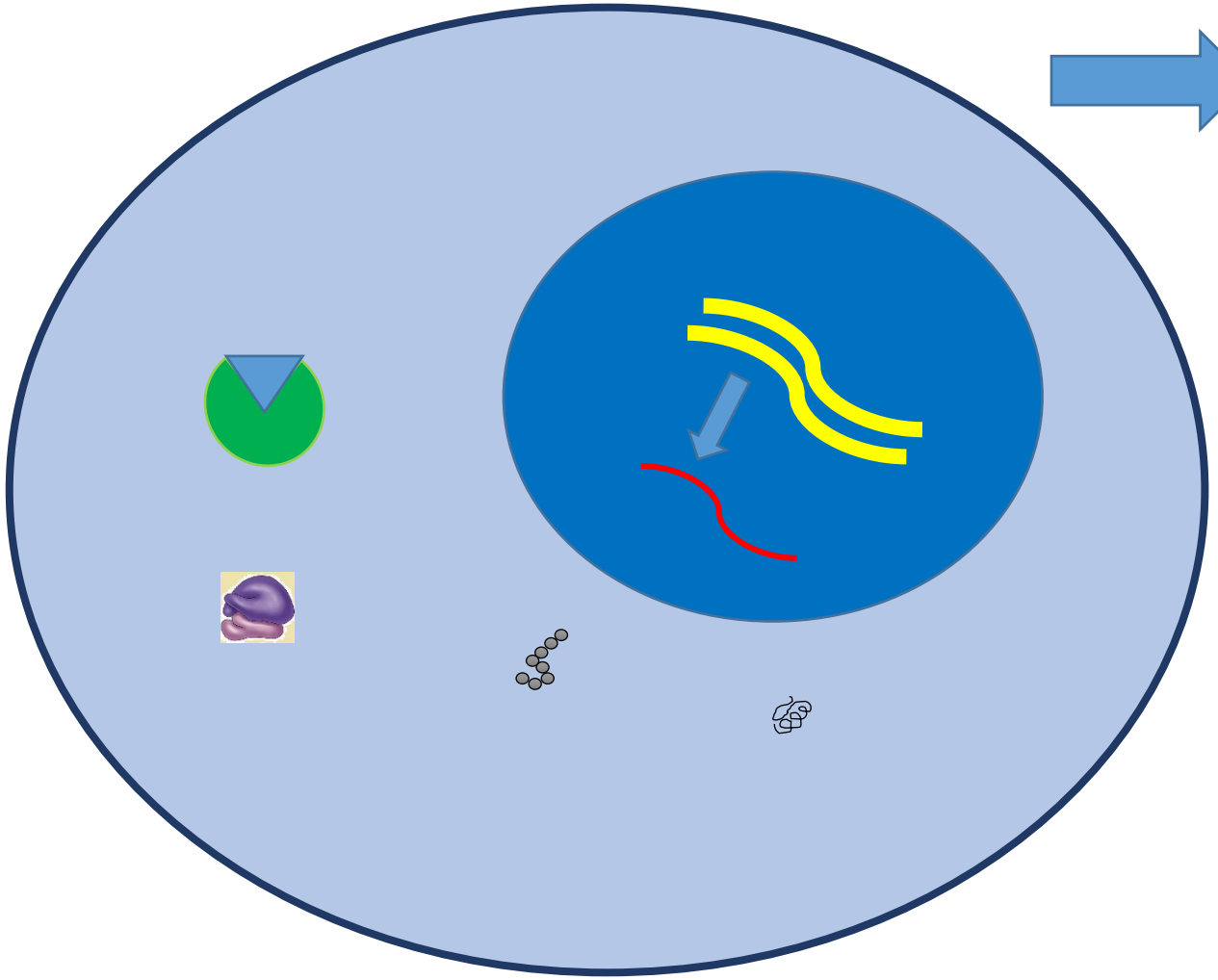


→ Change of proteosynthesis

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

↑ <u>gluconeogenesis</u>

(glucose formation from non sugar residues)

↑ glycaemia

↑ of insulin secretion

Connective tissue

muscle atrophy

fibroblasts growth stopping

↓osteoblasts, ↑osteoclasts

↓collagen synthesis

↓Ca resorption from intestine, kidneys (osteoporosis)

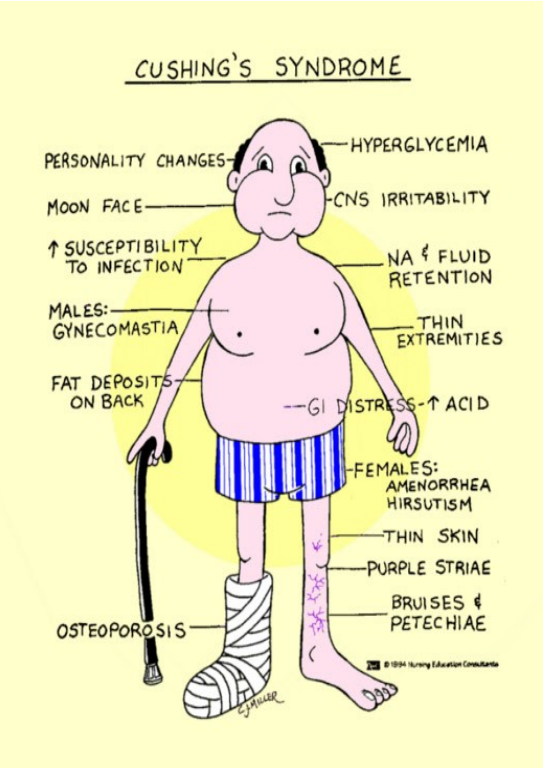
↑ storage of glycogen in the liver

lipogenesis support, lipolysis inhibition

fat deposition, redistribution,

↑glycerol, aminoacids in blood

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



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

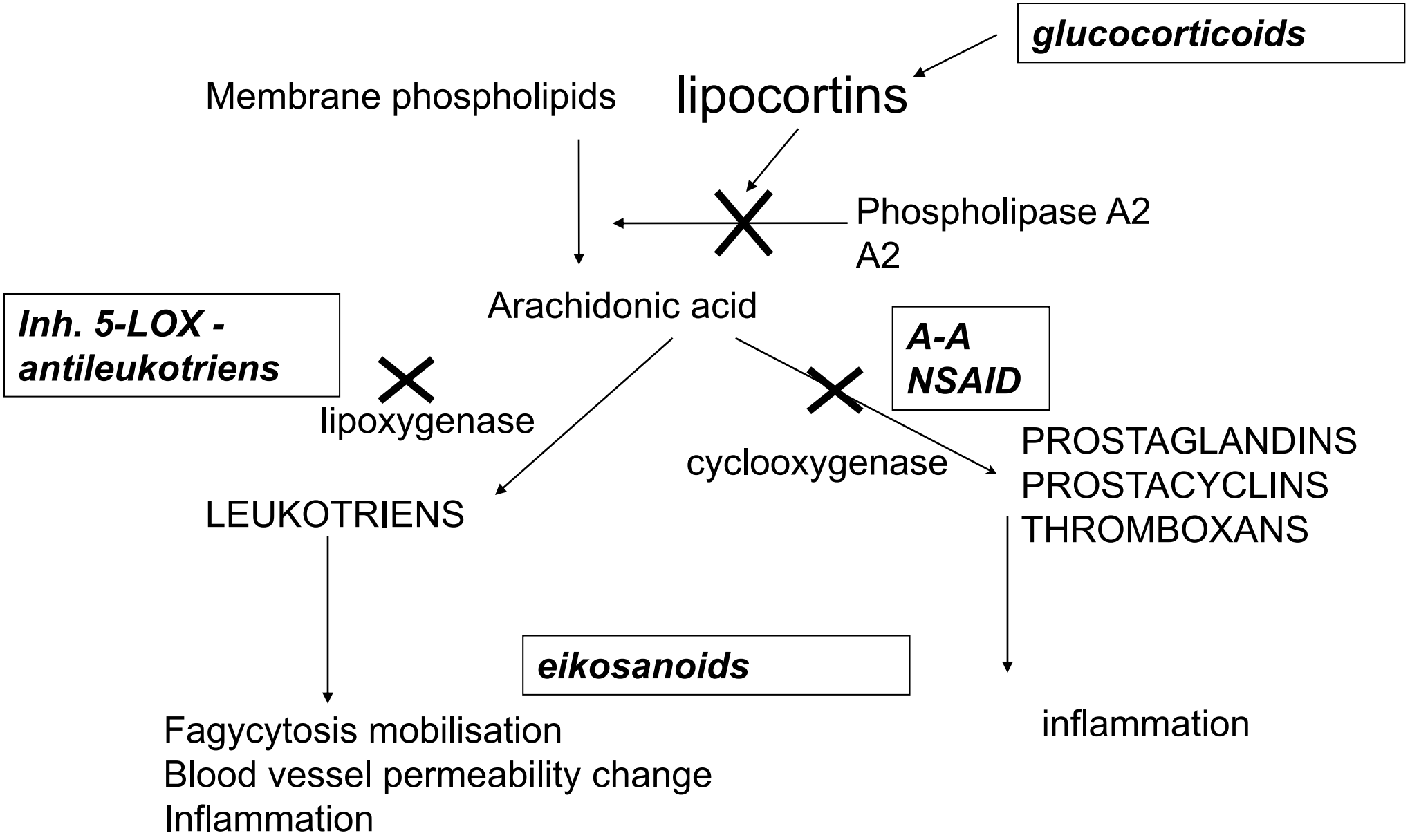
Regulatory effects

- **Negative feedback on the hypothalamus and the anterior lobe of the pituitary gland**
  reduced release of endogenous glucocorticoids

- **Vazotropic** - 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….)

Immunosupressive effect

Inhibition of antigen recognition

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

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

Anti-inflammatory effect

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

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

GCs effects, anti-inflammatory, immunosupressive and other effects

Strong anti-inflammatory and immunosuppressive action

INHIBITION OF ACUTE AND CHRONIC DISEASE, INFLUENCE OF ALL TYPES OF INFLAMMATORY REACTIONS

Inhibition of healing repair processes, prevention of graft rejection

Mineralocorticoid effects: sodium retention, potassium depletion

Blood and lymphatic system: ↓ lymphocytes, ↓ eosinophils in circulation, their redistribution to BM, spleen, LN, ↑ platelets, erythrocytes and HB

Kidneys: glucocorticoids maintain the ability of the kidneys to secrete water, retain glomerular filtration, tubular resorption, prevent the transfer of water to cells and maintain extracellular fluid volume

Heart and vessels: allow for increased sensitivity to the vasoactive effect of catecholamines and ATII, increased myocardial contractility and vascular tone

CNS: mood regulation, strong insomnia

GIT: increased secretion of HCL and pepsin, increased absorption of lipids from the intestine, decreased absorption of Ca

Bone metabolism: osteoporosis (metabolism of Ca, P, collagen synthesis and degradation, osteoblasts / clasts)

Pulmonary surfactant: cortisol - an endocrine stimulant for pulmonary surfactant formation

Systemically administered GCs

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

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)

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

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 osteporosis 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

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 +
- ↑ TK, 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 (↑ 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.

Therapeutic indications

- Diseases of connective tissue, rheumatological diseases and collagenoses (RA, SLE, SS, DM…)
- 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
- Renal Disease
- Immunalternative disease in neurology
- Substitution therapy for secondary adrenocortical insufficiency
- Congenital adrenal hyperplasia