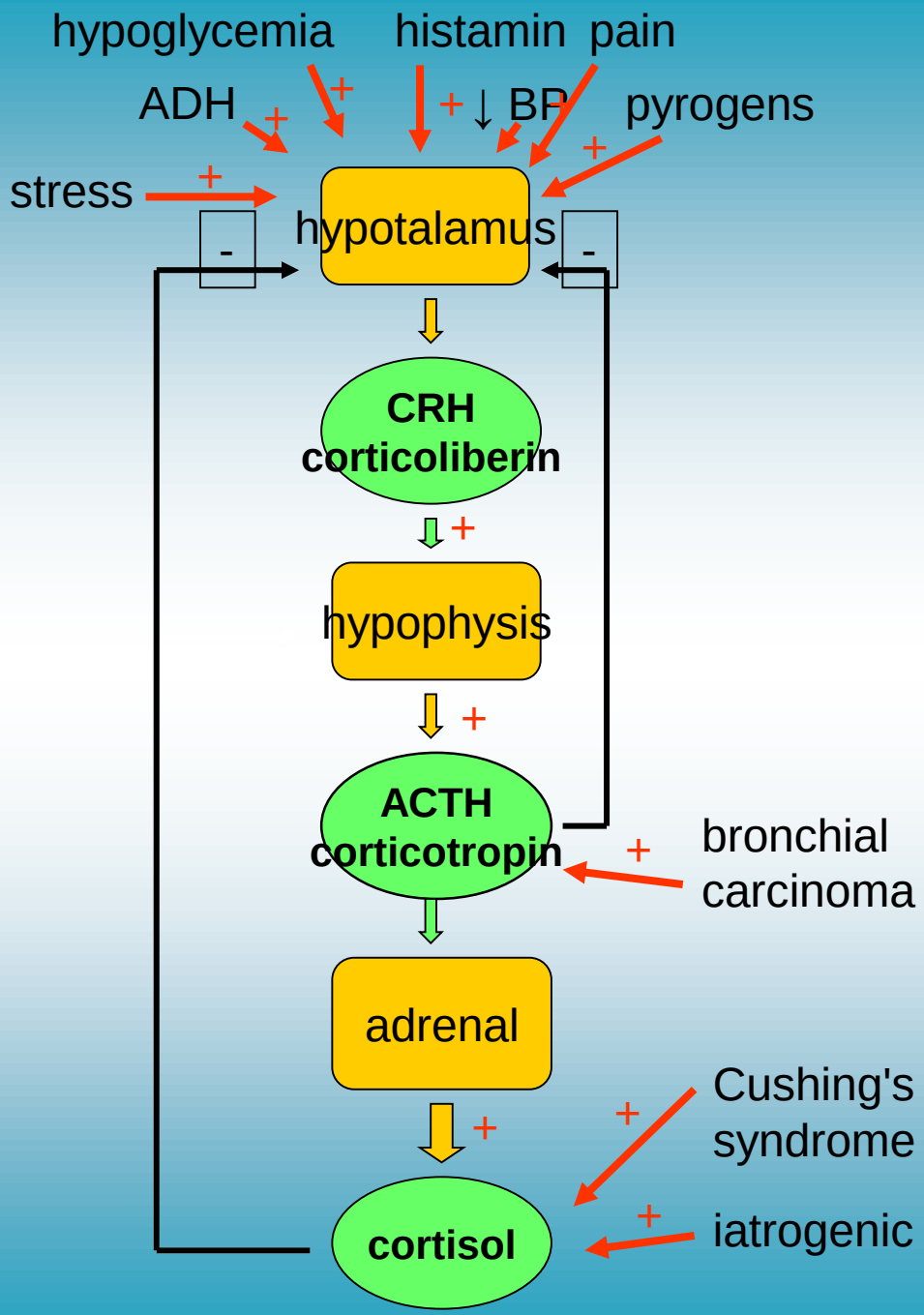
Glucocorticoids


hypoglycemia
histamin
pain
ADH
+
+
+
↓ BP
pyrogens
+
stress
+
hypotalamus
-
-
CRH
corticoliberin
+
hypophysis
+
ACTH
corticotropin
+
bronchial
carcinoma
adrenal
+
Cushing's
syndrome
+
cortisol
+
iatrogenic

Mechanism of glucocorticoid action on cellular level

After entering the cell they bind to specific receptors in cytoplasm causing change of conformation = activation of receptors

Complexes of corticoid + receptor are transported to cell nucleus and bind to DNA elements.

The result is increased transcription of genes either inducing or inhibiting synthesis of other proteins

- GLC receptors are present in all tissues!!!
- Proteins called **lipocortins** are able to suppress phospholipase A

Endogenous secretion:

Quiescent : 25 - 30 mg /24

In stress: 10-fold

Not stored – rate of synth. = rate of release

Maximal: 6-8 A.M.

Pharmacokinetics

- Bound to CBG (cortisol binding globulin) and albumin
- Intensively metabolised
- Metabolites excerted in 72 h
- Synthetic ones have longer t_{half}
- (prednison – prednisolon)

Effects (terapeutic):

- anti-inflammatory
- antialergic and immunosupresive
- antiproliferative

- Substitution (therapeutic)

Physiological effects of Glucocorticoids

1. Influences on intermediary metabolism
2. Permissive Action and circulatory effects
3. Effects on Water Metabolism
4. Effects on the bones and muscles
5. Anti-inflammatory, anti-immune effects
6. Effects on the Central Nervous System
7. Developmental effects

Glucocorticoids Influences Intermediary Metabolism

Sacharides: ↓ Glu uptake and utilisation

↑ gluconeogenesis (from AA, FA)

↑ glycemia

BUT !

in general – fat redistribution and deposition, ↑glycerol,

FA in blood

Proteins: ↑ catabolism, atrophy

Glucocorticoids Influences Intermediary Metabolism

Fat: permisive action on lipolytic hromones

fat redistribution (Cushing sy.)

- ↓ fction of fibroblasts, osteoblasts,

  ↑ osteoclasts activity,

  (= osteoporosis)

- defective collagen metabolism, impaired fibrous tissues synthesis

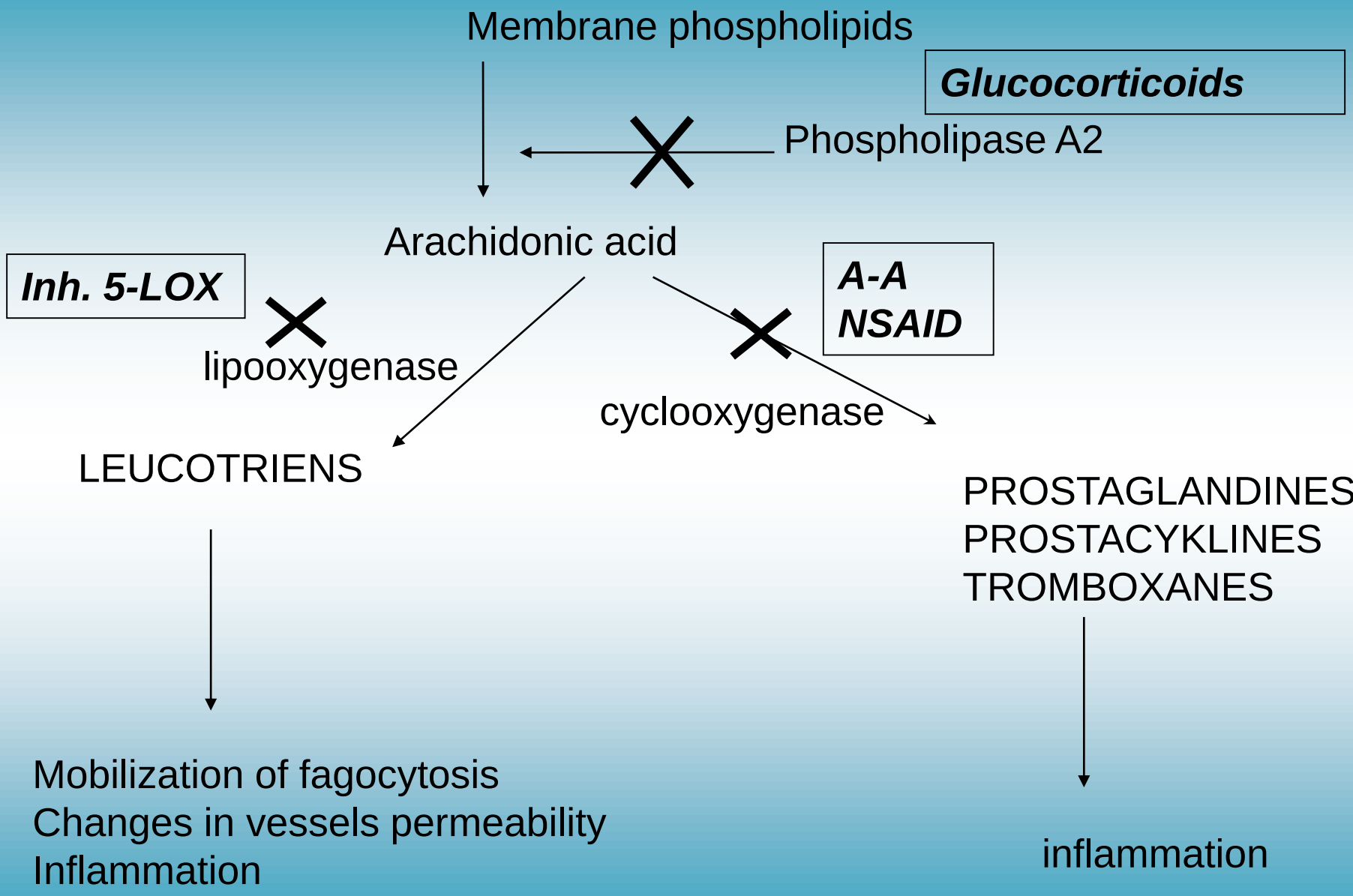
Permissive Action

Cortisol must be present for an effect to occur, although cortisol does not produce the effect by itself.

Permissive Action

Permissive effects on different tissues

- inhibit fibroblasts (connective tissue loss)
- negative calcium balance (osteoporosis)
- negative nitrogen balance (catabolism)
- CNS: euphoria, behavioral changes, psychosis
- GI: increase stomach acid and pepsin production
- cardiovascular effects (increase in heart rate)
- uptake of fat by fat cells
- gluconeogenesis
- insulin release and glycogen deposition


Membrane phospholipids
Glucocorticoids
Phospholipase A2
Arachidonic acid
Inh. 5-LOX
lipooxygenase
A-A
NSAID
cyclooxygenase
LEUCOTRIENS
PROSTAGLANDINES
PROSTACYKLINES
TROMBOXANES
Mobilization of fagocytosis
Changes in vessels permeability
Inflammation
inflammation

Antiinflammatory and imunosupresive effect

- Impairment of migration and functions of leucocytes
- AA cascade inhibition, ↓production of prostaglandins, IgG, influx and activity of neutrofils and macrophages
- Inhibition of transcription of genes of adhesion factors

Antiinflammatory and immunosuppressant effect

- ↓ release of HIS from basophiles
- ↓ blood vessels proliferation…
- ↓ function of fibroblasts
- ↓ activity of osteoblasts
- ↑ osteoclasts (= osteoporosis)

Inhibit all types of inflammation regardless of localisation or ethiology !

Antiinflammatory and imunosupresive effect

Acute effects of cortisol

- It stabilizes the lysosomal membranes (proteolytic enzymes)
- It inhibits the production of inflammatory proteins (IL, TNF, etc.)
- It decreases the permeability of capillaries
- It depresses the phagocytosis
- It prevents capillary dilation

Antiinflammatory and imunosupresive effect

Chronic effects of cortisol

-It decreases the collagen synthesis

-It decreases the activity of fibroblasts

Anti-immune and Antiallergic Effects of Glucocorticoids

Anti-immune responses of cortisol

- suppresses the B lymphocytes
- suppresses synthesis of interleukin-1 and interleukin-2
- stimulates synthesis of lipocortins that inhibit the generation of proinflammatory eicosanoids

Antiallergic effects of cortisol

- decreases the histamine release
- decreases the number of eosinophils
- decreases the permeability of capillaries
- prevents capillary dilation

Regulatory effects

negative feedback to hypothalamus and adenohypophysis (anterior pituitary)

- decr. secretion of endogenous glucocorticoids

vascular

decr. in vascular permeability, decr. oedema, decr. NO production

on cellular level:

in acute inflammation: ↓ Leu migration and activity

in chronic inflammation: vascular proliferation, fibrotic changes

in lymphoid tissue: ↓ B and T lymphocytes

Adverse effects (after pharmaclogical intervence!)

1) ↓ Immune responses

recurrent infects, ulcer dissease, mycotic infects…

2) Decrease in endogenous corticoid production (supresion of axis hypothalamus –pituitary – adrenal glands)

--- acute insuficiency in sudden glucocorticoid withdrawal

3) Osteoporosis

4) Mineralocorticoid action – water retention, salts

↑blood pressure, Na, Cl

↓ K^+, NO production

Adverse effects (after pharmaclogical intervence!)

5) Steroid diabetes mellitus

6) Muscle atrophy

7) Psychotrophic effect: euphoria/ depression/psychosis

8) ↑ gastric secretion of HCl

9) Cartillage impairment, striae, reduced wound healing

9) others: increased clottin, ↑trombocytes, erys

glaucoma, increased intracranial pressure

Iatrogenic Cushing sy.

Sudden weight gain
Central obesity
Hypertension
Proximal muscle weakness
Diabetes mellitus
Decreased libido or impotence
Depression or psychosis
Osteopoenia or osteoporosis

Easy bruising
Hyperlipidemia
Menstrual disorders
Violaceous striae wider than 1 cm
Recurrent infections
Acne
Hirsutism...

Indications

Physiological doses

substitution – adrenocortical insuficiency, congenital adrenal hyperplasia, Addison dissease *(hydrocortisone, fludrocortisone)*

Pharmacological doses

Antiinflammatory and imunosupressive effects

- **asthma (inhaltions)**
- **topic application, in allergy (conjuctivitis, rhinitis)**
- **hypersensitivity in general**
- **anaphylaxis**
- **autoimune diseases (revmatoid arthritis, Crohn disease …)**
- **prevent non-acceptance in transplantations**

Indications

Oncology

Acute Lymphoblastic Leucaemia, hodgkin disease
tumors of brain (antioedematose effect - dexamethasone)
antiemetics

Others

height sickness, nephrotic sy., sclerosis multiplex, subacute thyreoitidis

Review of glucocorticoids

Drug	GC (ant-inflamm.)	MC	Usage, duration of effect
Hydrocortisone (cortisol)	1	1	Substitution, 8 - 12 h
Cortisone	0,8	0,8	Prodrug
Prednisolone	4	0,8	antiinflammatory, imunosupresive
Prednisone	4	0,8	Prodrug
Methylprednisolone	5	minor	antiinflammatory, imunosupresive 12-26 h
Triamcinolone	5	0	12 - 26 h
Dexamethasone	30	minor	antiinflammatory, imunosupresive treatment, esp. where fluids retention is unfavourable
Betamethasone	30	minor	- „ -
Beclomethasone	+	-	local antiinflammatory imunosupresive treatment
Budesonide	+	-	- „ -

Glucocorticoids:

	Glucocorticoid effect	Mineralocorticoid effect
Cortisol	1	1
Cortisone	0,8	0,8
Prednisone	4	0,8
Prednisolone	4	0
Triamcinolon	5-10	0
Betametazon	25	0
Dexametazon	25	0

Glucocorticoids for systemic use

- Approx. 1-5 times more eff. than cortisole
  - methylprednisolone, prednisolone
  - prednisone, hydrocortisone

  short acting
- Approx. 5-15 times more eff. than cortisole
  - triamcinolone
  - paramethasone
  - fluprednisolone

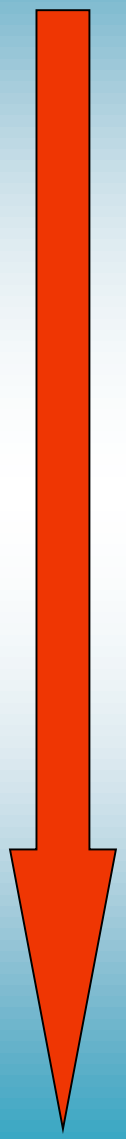
  intermediate
- Approx. 30 times more eff. than cortisole
  - betamethasone
  - dexamethasone

  long - acting

  (more powerfull axis suression)

Topically administered glucocorticoids

- hydrocortisone
- dexamethasone
- prednisolone
- triamcinolone
- flumethasone
- prednikarbat
- bethametason valerate
- fluocinolone
- betamethason adipate
- budesonid
- halcinomide
- clobetasole



Weak action

Very strong acting

Glucocorticoid therapy

1) Very High doses (2 - 4 g methylprednisolone)

   polyutrauma, septic, toxic shock

   30 mg / kg methylprednisolone in short infusion

2) Few –day administration of high dose

   anaphylaxis, status asthmaticus, hypoglycemic coma, acute hypercalcemia, brain oedema, thyreotoxic crisis, snakebite…

   more than 500 mg i.v. / 24 h

3) pulse therapy

1 g metylprednisolone (infusion)

3 - 5x – different intervals

Needs hospitalization

resistent RA, lupus erythemoatodes, myasthenia gravis...

4) prolonged glucocorticoid treatment

in most cases, antiinflammatory, imunosupressive effects

antiallergy effects

CAVE !

To prevent axis supression (hypothalamus- ant. pituitary – adrenal glands)

- Administration up to 10 days
- 6 - 8 A.M.
- Preparations with lower blocking effect

(non-fluorinated derrivatives)

- Pulse therapy

Adverse effects prevention

- lowest effective dose should be administered
- topic administration if possible (inh., rect., intraarticular, s.c.) with low bioavailability
- total dose can be decreased by combination with imunosupresives
- dosing schedule should reflect circadian rhythm – if possible (not in life threating situations)
- avoid sustained release preparations
- stepwise decreasing of doses

  approx. 2.5 mg eq. prednisolone /3 days

Contraindications

- hypertension
- Heart insufficiency /CHF
- Cushing. sy
- Peptic ulcer
- diabetes
- glaucoma
- psychoses
- Viral/bacterial infection
- Vaccination with attenuated vaccine