Glucocorticoids

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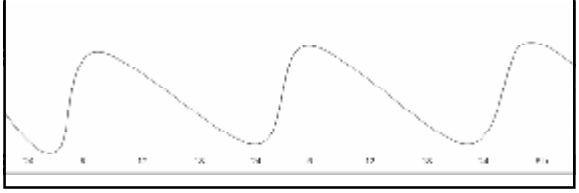
Endogenous cortisol secretion:

- **Basal:** **20 - 30 mg /24 h**
- **In stress:** **up to 10 fold**
- **Maximal:** **4. (6.) - 8. a.m.**



Pharmacokinetics

- Bound to CBH and albumin
- Intensively metabolised
- Reduction of double bond between C4 and C5
- Metabolites excreted in 72 h
- Synthetic slower
- (prednison – prednisolon)

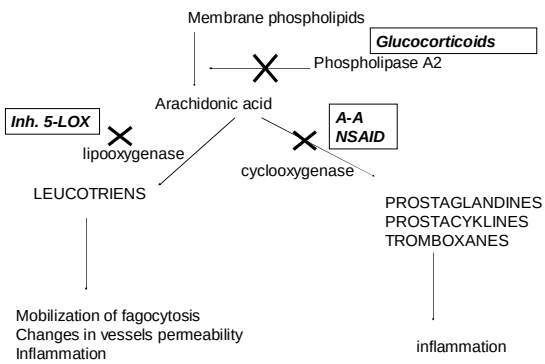
Mechanism of glucocorticoid action on cellular level

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

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

The result is incerased transcription of genes eitzher inducing or inhibiting synthesis of other proteins

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



Antiinflammatory and immunosuppressant effect

- Impaired migration and function of leukocytes
- Inhibition of AA cascade, ↓production of Pg, IgG, influx and activity of neutrophils and macrophages
- Inhibition of adhesive factors synthesis (gene transcription level)

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 !

Antiallergic effect

- decreased release of His from basophiles
- inhibition of leucotriens and PG synthesis
- Increase of β2 receptors density
- antiedematic eff.

Metabolic effects

- **glucose:**
  - **decreased glucose uptake and utilistion in cell**
  - **increase of gluconeogenesis (glucose synthesis from non-sugar sources – aminoacids, fatty acid)**
  - **increase of glycemia ... Insulin...lipogeneze**
- **proteins: increased catabolizms, atrophy**

Metabolic effects

- **fat:**
  - **permissive effect on lipolytic hormones**
  - **fat redistribution (Cushing sy)**
- **connective tissues**
  - **↓ function of fibroblasts, osteoblasts**
  - **↑ osteoclasts (= osteoporosis)**
  - **impair in colagen metabolism, decreased growth of fibrose tissues**

BUT!! generally: body fat deposition, redistribution, ↑glycerole, FA in blood

Ontogenetic effects

Permissive effect on

- organogenesis
- development and maturation of intestinal enzymes
- increased synthesis of surfactant in fetal lungs
- suppressed bone growth

Effects of „pharmacological doses“:

powerful antiinflammatory effect – decrease of

early: erythema, edema, pain, flush
late: healing of the wound, fibrose proliferation

powerful immunosuppressant effect – decrease of

rejection reactions (in organ transplantation)
autoimunne reactions

Ions

- decrease of calcemia
- increased loss of
- retention of natrium and chlorides

"Permissive effects"

catecholamines activity

calorigenic effect, smooth muscle in airways and vessels reactivity

lipolytic effect of catecholamines, ACTH, GH

heart

catecholamines, AT II, inotropic effect,

↑ vessel tonus

kidney

normal excretion of water

maintenance of GF and tubular clearance

"Permissive effects"

- **Low levels of cortisol**

  abnormal vasodilatation

  decreased preload

  decreased of BP

- **High levels of cortisol**

  increase of BP (blood volume + suppressed synthesis of NO)

Regulatory effects

negative feed-back in hypothalamus and adenohypophysis

decreased release of endogenous glucocorticoids

vazotropic

suppression of vasodilatation, edema and NO synthesis

on cellular level

on site of acute inflammation – immunosuppressant eff.

on site of chronic inflammation – suppressed proliferation in connective tissues and angiogenesis

in lymphoid tissue – suppressed B and T lymphocytes expansion

immunology mediators

suppressed synthesis of cytokines and PG

Adverse effects (after pharmacological doses!)

1) suppressed response to infectious agents or tissue damage

even after inhalations !!!

risk of infections, ulcerous disease or mycosis

2) suppression of endogenous glucocorticoids synthesis (axis supression)

acute adrenal insufficiency in sudden stop of therapy by pharmacological doses

prevention: slow withdrawal (at first the evening dose)

long supervision after the end of treatment (> 2 months)

3) osteoporosis (after chronic treatment)

4) mineralocorticoid effects

water and electrolytes retention

↑ BP, loss of K^+

↓ endogenous NO synthesis

Adverse effects (after pharmacological doses!)

5) steroid diabetes

6) muscle weakness, atrophy

children: retarded growth (therapy > 6 months)

7) psychotropic effects:

euphoria/ depression/psychoses

8) increase of gastric HCl secretion

9) damage of cartilage, impaired wound helaing, development of striae

10) others:

increased hemocoagulation and aggregation

↑ trombocytes, erythrocytes (necessary thrombosis prevention)

glaucoma

increased intracranial pressure

Adverse effects of local application

- **Mouth**
  - mycosis,
  - hoarse voice (rinsing mouth after application!!)
- **Skin:**
  - atrophy
  - teleangiectasia
  - acne
- **Eye**
  - glaucoma
  - cataracta

Indications

Physiological doses = substitution therapy

adrenocortical insufficiency
congenital adrenal hyperplazia
Addison disease (hydrocortison, fludrocortison)

Pharmacological doses

• antiinflammatory and immunosuppressant therapy

asthma (inhalations)
locally on skin, mucouse affections, allergic conjunctivitis, rhinitis
hypersenzitive reactions, anaphylaxis
autoimmune and inflammatory diseases (eg. arthritis rheumatica,
morbus Crohn, morbus Bechterev = spondylartritis
ankylosa)
prevention of rejection reaction

Indications

Pharmacological doses

• oncology

specific tumors - ALL, Hodgkin disease
brain tumors (antiedematous effect - dexametazon)
antiemetic effects

• others

mountain sickness
nephrotic syndrome
sclerosis multiplex
malign exophtalmus
subacute thyreoitis

Dexamethason suppression test

- Cushing. sy. diagnosis
- depression diff. dg.

- 1 mg of dexamethason in 23 h
- In the morning evaluation of cortisol plasma levels
  - normally under 3 ug/l
  - in Cushing more than 5 ug/l

Potency of glucocorticoids

	antiflogistic effect	retention of natrium
cortisol	1	1
cortison	0,8	0,8
prednison	4	0,8
prednisolon	5	0,8
triamcinolon	5-10	0
betamethazon	30	0
dexamethazon	30	0

Overwiev of the most important drugs

Drug	GC (antiinflam)	MC	Uses
Hydrocortison (cortisol)	1	1	substitution therapy, 8 - 12 h
Cortison	0,8	0,8	prodrug
Prednisolon	4	0,8	antiinflammatory,immunosuppressant therapy, 12 - 26 h
Prednison	4	0,8	prodrug
Methylprednisolon	5	minimal	antiinflammatory, immunosuppressant therapy, 12 - 26 h
Triamcinolon	5	0	more AE, 12 - 26 h
Dexamethason	30	minimal	antiinflammatory, immunosuppressant therapy, especially when water retention is unwanted
Betamethazon	30	minimal	- „ -
Beklomethazon	+	-	Local antiinflammatory, immunosuppressant therapy
Budesonid	+	-	- „ -

Systemically administered glucocorticoids

- 1-5x more potent than cortisol (short acting)
  - methylprednisolon, prednisolon
  - prednison, hydrokortison
- 5-15x more potent than cortisol (intermediate acting)
  - triamcinolon
  - paramethason
  - fluprednisolon
- cca 30x more potent than cortisol (long acting (stronger axis supression))
  - betametason
  - dexamethason

Topically administered glucocorticoids

- hydrocortison
- dexamethason
- prednisolon
- triamcinolon
- flumethason
- prednicarbate
- bethametason valerate
- fluocinolon
- betamethason adipate
- budesonid
- halcinomid
- clobetasol

Intensive corticotherapy

- megadoses (2 - 4 g of metylprednisolon)

  polyutraumas, septic or toxic shock

  30 mg / kg methylprednisolon in short infusion

  anaphylactic shock, status asthmaticus, hypoglycemic coma, acute hypercalcemia, brain edema of different etiology, thyreotoxic crisis, snakebite, dangerous stinging of insects, acute spinal cord injuries…

  more than 500 mg i.v. / 24 h

Intensive corticotherapy

- pulse therapy

  1 g methylprednisolon (infusion)

  3 - 5x – alternating intervals (during a day, on different days…)

  Only on hospitalisation

- prolonged treatment

  most of cases

  using antiinflammatory, antiallergic and immunosupressant effects

CAVE ! Axis suppression - prevention

- Application cca in 10 days
- Application in mornings 6 - 8 h a.m.
- Preparations with lower suppressant effect (non-fluorinated derivates)
- Pulse therapy

Substitution therapy

- hydrocortison – minerals
- Individual sufficient dose – basal + situations with incerased demand!!
- Usual basal dose 20 – 30 mg
- If it is not possible to administer perorally, hospitalisation and im or iv application
- In chronic hypotension, adynamia and hypocalemia, add fludrokortizon 0,1 mg/day
- First signs of overdose is swelling of legs and hypertension

One dose administration

• One megadose in polytrauma, inhalation trauma and acidic aspiration

• As soon as possible!!!

• Short infusion of prednisolon 30 mg/kg (for an adult 3-4 ampules, each 1000 mg)

Short term therapy

Max 48 h, can be ended abruptly

Indications -

hypocortical crisis
anaphylaxis
status astmaticus
Quincke edema
hypoglycemic coma
acute hypercalcemia
brain edema
tyreotoxic crisis
biting or stinging by dangerous snakes or insects
spinal cord injury etc.

Complications –

dysrytmia (hypocalemia)
hyperglycemia or ketoacidosis
hemorrhagic stomach ulcerations
latent infections including mycoses
fluid retention or cardial insuff.,
thrombembolia
myorelaxation or weakness
corticoid psychosis
acute pancreatitis
bone infarction

Short term therapy

• **Injection preparations**

- **Hydrocortison** – natriumretention
- **Prednison and prednisolon** - weak natriumretention
- **Dexametason, betametason** – no natriumretention, best for brain edema, psychotropic effects, the biggest axis suppression
- **Metylprednisolon** has best penetration to alveolobronchial tree
- **Triamcinolon** – smallest effect on BP and psychic, the highest incidence of myopathy

Pulse therapy

• rejection of transplantates

• immunologically conditioned diseases woth no answer to standard therapy (resistant RA, lupus erythemoatodes, myasthenia gravis...)

• some hematologic malignities (ultimum refigium)

• always on hospitalisation

Prolonged treatment

• most of medical specialisations

• All synthetic corticoids are suitable (not hydrocortison)

• Tablets are manufactured in equipotent power

• Long-acting more suppress axis

Prolonged treatment

• before starting the therapy check:

- All infections
- Rtg of chest to negate TBC (elderly people, foreigners)
- Fasting glycema, ev compensate diabetics
- Ophtalmology check (elderly - glaucoma, catarakta, infections)
- Preventively substitute vit D, postmenopauzal women can get hormonal substitution, men - androgens, others – bisphosphonates
- People with risk of osteoporosis can be send to densitometry
- Watch out for gsatriculcers in people with anamnesis
- Recommend corticoids with meals
- Contraindication of vaccination!!!

Prolonged treatment

- in course of therapy watch for:
  - Glycemia
  - Depression, psychosis
  - In abdominal distress fibroscopy of stomach and duodenum, amylase
  - Osteoporosis, fractures
  - Recommend physical exercise
  - Lipidogram
  - Cardial insufficiency, potassium
  - Hypertension
  - Prevention of thrombembolic disease
  - In children somatotropin may be indicated

Prolonged treatment

- when stopping the therapy avoid:
  - Adrenal insuff.
  - Exacerbation of the original condition
  - Detraction syndrome – can be caused by sudden drop of corticoid levels (eve if you just decrease substitution doses) – musce pain and joint, nausea, anorexia, loss of body weight, hypotension
  - Syndrome of benign intracranial hypertension
  - Psychic addiction to corticoid therapy

Stopping the therapy- rules

- what does not suppress the axis yet? – 7,5 mg of prednison
- still on therapy check endogenous secretion by taking plasma levels before the morning dose
- patients with long-acting corticoids (triamcinolon, dexametason, betametason) should be switched to short-acting (prednison)
- Dose of prednison should be decrased by 2,5 to 5 mg each 7 days, when we reach dose of 5 mg, check endogenous production
- At this point wait until endogenous production is restored

AE prevention

- administer the lowest dose possible
- whenever possible, administer locally (inh., rect., intraarticular, s.c.) with low absorption
- the total dose can be sometimes decreased by co-administration with immunosuppressants
- respect circadian rhythm whenever possible (increased risk of exacerbation)
- avoid depot preparations
- decrease the dose slowly

  cca 2,5 mg ekv. of prednisolon /3 days

Glucocorticoid antagonists

metyrapon – inh. hydroxylation on C11
trilostan – inh. 3 beta dehydrogenase
aminoglutethimid – inh. aromatase
ketokonazol – i-CYP
mitotan similar MoA as metyrapon

Contraindications

- hypertension
- cardial insuff.
- developed Cushing. sy
- peptic ulcers
- diabetes
- glaucoma
- psychoses
- bacterial infections
- after vaccination with living vaccine