Adrenocortical hormones
2023

Functions of cortisol

1. Effects on carbohydrate metabolism
- ▶ stimulation of gluconeogenesis
- ▶ promote the storage of carbohydrate as glycogen
- ▶ decreased glucose utilization by cells

2. Effects on protein metabolism
- ▶ decreased amino acid transport into hepatic tissues
- ▶ decreased protein synthesis and increased protein catabolism in the cells
- ▶ Increased liver and plasma proteins level

3. Effects on fat metabolism
- ▶ mobilization of fatty acids from adipose tissue
- ▶ redistribution of fat to the upper trunk and face, with a concomitant loss of fat in the extremities
- ▶ increased oxidation of fatty acids in the cells

Other effects of cortisol

1. Role in stressful situations
- ▶ mobilization of amino acids and fats from their cellular stores

2. Anti—inflammatory effects
3. Inhibition of inflammatory response to allergens
4. Decreases the number of eosinophils and lymphocytes in the blood

Factors that increase cortisol release: trauma, infection, intense heat and cold, surgery, injection of norepinephrine and other sympathomimetic drugs, debilitating diseases

Glucocorticoids - mechanism of action

GENOMIC mechanism: glucocorticoids as lipid soluble substances easily diffuse through the cell membrane. Once inside the cell they bind with protein receptor in the cytoplasm, and the hormone-receptor complex then interacts with specific regulatory DNA sequences, called glucocorticoid response elements, to induce or repress gene transcription.

TRANSACTIVATION – stimulation of transcription of many genes: lipocortin-1, rec.β2 , antagonis of IL-1 receptor

TRANSREPRESSION - inhibition of transcription of many genes: cytokines, enzymes (induced NO synthase, induced COX 2); receptors (NK1, bradykinin) and proteins (endothelin 1)

NON-GENOMIC:
- ▶ interaction with GPCR
- ▶ effect on cell membrane ion transport
- ▶ potentiation of catecholamine action
- ▶ activation of kinase signaling pathways

Non-genomic mechanism of action determines the use of glucocrticosteroids in situations where we expect their rapid effect.

Non-genomic effect is manifested primarily at high dosage

Glucocrticoids

- ❑ Short to medium acting glucocorticoids:
- hydrocortisone (cortisol)
- cortisone
- prednisone
- prednisolone
- methyloprednisolone
- ❑ Intermediate-acting glucocorticoids:
- triamcinolone
- ❑ Long-acting glucocorticoids:
- dexamethasone
- betamethasone

Glucocorticoids effects

- ▶ Cellular effects:
- increased stabilization of lysosomal membrane
- inhibition of migration of leukocyte
- inhibition of macrophages' phagocytosis
- ▶ Metabolic effects (hyperglycemia, hyperlipidemia, hypocalcemia, elevated glucagon, steroid-induced diabetes)
- ▶ Electrolyte and water balance – increased duresis, GFR, sodium retention and potassium excretion
- ▶ Endocrine effects - ↓ ACTH secretion (inhibition of hypothalamic- pituitary-adrenal axis), ↑ GH secretion in acromegaly, ↓ GH secretion in children (prolonged administration)
- ▶ Cardiovascular system - ↑ epinephrine synthesis, sodium retention – hypertension
- ▶ Musculoskeletal system – hypokaliemia, catabolic effect on protein metabolism – weakness, ↑ PTH sensitivity (↑ osteoclast activity – osteoporosis)
- ▶ Hematologic effects – redistribution of blood cells and ↓ lymphocytes, monocytes, and eosinophils, T-lymphocytes apoptosis
- ▶ Antiinflammatory effects – inhibit recruitment of neutrophils and monocytes, induce lipocortin 1 (inhibitor of phospholipase A2), stabilize lysosomes (decrese the release of hydrolytic enzymes and histamine)
- ▶ Immune system – high doses inhibit immunoglobulin synthesis, kill B lymphocytes and decrease production of components of the complement system
- ▶ Other effects – increased intraocular pressure, redistribution of subcutaneous fat

Signs of acute INFLAMMATION

- ▶ Redness - due tu vasodilation by effects mediated by histamine, bradykinine, prostaglandins
- ▶ Hotness – due to increased blood flow
- ▶ Swelling – due to increased vascular permability by the released mediators and increased exudate in the inflammed area
- ▶ Pain – due to irritation of nerve ending by inflammation and the pressure of the swelling on the nerve ending and also from chemical mediators like substance P and bradykinin

Glucocorticoids and inflammation

- Cytokines and chemokines - suppress pro-inflammatory cytokines (IL-1β, IFN-alpha), induce anti-inflammatory cytokines (Il-10, TGF-β), suppress chemokines that affect cellular migration MCP-1, IL-8
- Inflammatory enzymes – suppress cystolic cPLA 2, COX2 and iNOS (genomic mechanism)
- Cell migration and adhesion molecule – reduce reqruitment of immune cells to the site of inflammation
- Cell proliferation – inhibit T-cells growth factor production (IL-2) - ↓ T cells proliferation
- Apoptosis :

  - apoptotic effect : inhibit NF-κB, apoptosis of T helper cells in patients with autoimmune desease, increase the rate of apoptosis in eosinophilic granulocytes, decrease the rate of apoptosis of neutrophiles (limited efficacy of long-term therapy in COPD)
  - antiapoptotic effect: induce receptors for antiapoptotic signals and intracellular antiapoptotic factors (c-IAP2)

Glucocorticoids – immunosupressive action

- inhibit the differentiation and antigen presentation of macrophages and dendritic cells – supress the initiation of an immune response
- Inhibit proinflammatory cytokines production of IL-1, IL-2, IL-6, IL-12, IFN-γ, TNF-alpha leading to supression of activated T cells
- apoptosis of T cells
- down-regulation of adhesion molecules and chemokines receptors that are up-regulated in acute rejection

Glucocorticoids and cerebral edema

- Steroids reduce or prevent oedema by:

- stabilization of cerebral endothelium, leading to a decrease in plasma filtration
- increase in lysosomal activity of cerebral capillaries
- inhibition of release of potentially toxic substances such as free radicals, fatty acids, prostaglandins
- increase in local and global cerebral glucose use, leading to improved neuronal function

Dexamethasone – i.v.

Steroids in PONV (prevention)

- decreased production of inflammatory mediators which are known to act on the CTZ area as well as improve the blood –brain barrier function
- act synergistically with 5-HT3 receptors antagonists

Dexamethasone – single dose i.v.

Pharmacokinetics

- Absorption – well absorbed after oral administration (bioavailibility 60%-100%)
- Protein binding – moderate

- Distribution – liver, intestines, kidneys, skin, muscles
- Metabolism – in the liver
- Elimination - urine

Pharmacological effects refer to doses higher than replacement doses
Replacement therapy:
- primary and secondary adrenal insufficiency
- adrenalectomy
- adrenogenital syndrome with salt-lossing

Hydrocortisone 30-50 mg/24h
Stress – dose ↑2-3x , diarrhea – i.m. or i.v.

Adrenal crisis – develops in patients who have been taking glucocorticosteroids or have a systemic disease associated with adrenal insufficiency (metastatic cancer, AIDS or tuberculosis).

Symptoms:
- hypotension
- fever
- abdominal pain
- shock (unresponsive to vasopressors and volume replacement)

Treatment:
- 50-100 mg hydrocortisone i.v., i.m.
- sodium chloride
- glucose

Non-adrenal applications:
- leukemia and lymphomas
- connective tissue desease
- autoimmune diseases (e.g. rheumatic disease)
- allergic dermatosis
- ulcerative colitis
- lung diseases – asthma, sarcoidosis, COPD
- organs transplant
- stimulation of fetal lung maturation

Acute indications:
- severe anaphilactic reactions
- edema of the glottis
- brain edema (in the course of cancer, trauma, neurosurgical procedure)
- severe hypoglycemic coma
- asthma attack
- thyroid crisis
- transfusion reactions
- hypercalcemia
- to accelerate fetus lung maturation

- cytostatic induced vomiting (in combination with other anti-emetic drugs)

Glucocorticoid chronic therapy (non-replacement)

- ▶ Low dose (≤ 7,5 mg prednisone equivalent /day) – is consider to be safe even after prolonged therapy (50% receptor saturation)
- ▶ Medium dose (> 7,5 – 40 mg prednisone equivalent /day) (50-100% receptor saturation)
- ▶ High dose (> 40 mg but ≤ 100 mg prednisone equivalent /day) (100 % receptor saturation)
- ▶ Very high dose (> 100 mg prednisone equivalent /day)
- ▶ Puls therapy (> 250 mg prednisone equivalent /day for one or a few days), usually i.v. Very high dose and puls therapy are assumed to enhance clinical effects by additional non-genomic mechanisms.
- ▶ **Emergency treatment**
- antirejection therapy in patients with kidney transplants - methylprednisolone i.v. pulse therapy – 1000 mg per day for 3-5 days or 7 days
- acute CNS diseases – dexamethasone
- ▶ **Non-emergency treatment**
- SLE – pulse therapy with methylprednisolone
- primary glomerulonephritis – methylprednisolone pulses (1000 mg for 3 days every 2 months)
- multiple myeloma – very high dose of methylprednisolone

Prolonged administration of pharmacological doses of systemic corticosteroids or topical preparations (resulting in systemic absorption) may result in hypothalamic-pituitary-adrenal (HPA) suppression and/or manifestations of Cushing's syndrome in some patients. Acute adrenal insufficiency and even death may occur following abrupt discontinuation of prolonged systemic therapy. Withdrawal from prolonged systemic corticosteroid therapy should be gradual. HPA suppression can last for up to 12 months following cessation of systemic therapy.

<u>Hydrocortisone</u>

- synthetic steroid hormone
- chemically indentical to cortisol
- available in rectal, parenteral, oral, topical dosage forms
- used primarily as replacement therapy in adrenocortical defficiency states and for anti-inflammatory effects in disorders of many organs
- topical hydrocortisone – low potency

Pharmacokinetic:

- Absorption – very well from variouse sites
- Protein binding – binds extensively to proteins
- Distribution – kidneys, liver, intestines, skin, muscle
- Metabolism – liver, inactive metabolites
- Elimination – urine

<u>Prednisone</u>

- most commonly-prescribed oral glucocorticoid

- is metabolized in the liver to its active form, prednisolone
- has very little mineralocorticoid activity
- used primarily in allergic, dermatologic, and inflammatory states (e.g. asthma, COPD, SLE, rheumatoid arthritist)
- administered orally

Pharmacokinetic:

- Absorption – very well from GI
- Protein binding – binds extensively to proteins
- Distribution – kidneys, liver, intestines, skin, muscle
- Metabolism – metabolised by the liver to active metabolite - prednisolon
- Elimination – urine

Prednisolone

- active metabolite of prednisone
- because the drug does not get hepatically activated, prednisolone is sometimes used in place of prednisone in patients with severe hepatic disease
- has very little mineralocorticoid activity
- used primarily in allergic, dermatologic, and inflammatory states (e.g. asthma, COPD, SLE, rheumatoid arthritist)
- administered orally, parenterally (i.v., i.m) and ophtalmic

Pharmacokinetic:

- Absorption – very well from GI
- Protein binding – binds to proteins in 70-90%
- Distribution – kidneys, liver, intestines, skin, muscle
- Metabolism – systemic used is metabolised by the liver to sulfate and glucuronide conjugates
- Elimination – urine

Methylprednisolone

- has very little mineralocorticoid activity
- used primarily in allergic, dermatologic, and inflammatory states (e.g. rematoid arthritist, systemic lupus erythematosus, drug-induced hypersensitivity reactions, dermatitis, conjunctivitis)
- administered orally, parenterally (i.v., i.m, intra-articular, intralesional)

Pharmacokinetic:

- Absorption – very well from GI
- Distribution – kidneys, liver, intestines, skin, muscle
- Metabolism –metabolised by the liver (CYP3A4) to inactive metabolites
- Elimination – urine

Dexamethasone

- one of the potent and longest acting corticosteroids
- has very little or no mineralocorticoid activity
- is usually selected for management of cerebral edema because of its superior ability to penetrate the CNS

- is roughly 20 to 30 times more potent than hydrocortisone and 5 to 7 times more potent than prednisone
- used as anti-inflammatory or immunosuppressive agents
- administered orally, parenterally (i.v., i.m, intra-articular) and topically (spray, ophtalmic, intraocular)

Pharmacokinetic:

- Absorption – very well from GI
- Protein binding – binds to proteins very weakly
- Distribution – kidneys, liver, intestines, skin, muscle
- Metabolism –metabolised by the liver to inactive metabolites
- Elimination – urine

Triamcinolone

- has little mineralocorticoid activity
- used as anti-inflammatory or immunosuppressive agents (e.g. severe asthma, local joint inflammation)
- administered orally, parenterally (i.v., i.m, intraarticular, intravitreal) and topically (cream, ointment, spray, ophtalmic, intraocular)
- topical preparations are considered medium or high potency

Pharmacokinetic:

- Absorption – very well from GI
- Protein binding – binds to proteins very weakly
- Distribution – kidneys, liver, intestines, skin, muscle
- Metabolism –metabolised by the liver to 3 metabolites with little or no activiity
- Elimination – urine,

Betamethasone

- has little mineralocorticoid activity
- used as anti-inflammatory or immunosuppressive agents (e.g. cerebral edemas)
- administered orally, parenterally (i.v., i.m, intraarticular, intravitreal) and topically (cream, ointment, spray, ophtalmic, intraocular)
- topical preparations are considered medium or high potency

Pharmacokinetic:

- Absorption – very rapidly from GI
- Protein binding – binds to proteins very weakly
- Distribution – kidneys, liver, intestines, skin, muscle
- Metabolism – in the liver by CYP3A4 to inactive metabolites
- Elimination – urine

Fludrocortisone

- adrenocortical steroid derived from hydrocortisone
- has potent mineralocorticoid activity
- Its sodium-retaining activity is extremely high compared with other adrenocorticoids

Mechanism of action: sodium reabsorption, hydrogen and potassium excretion

Pharmacokinetic:

- Absorption – very well from GI
- Protein binding – binds extensively to the plasma proteins
- Distribution – kidneys, liver, intestines, skin, muscle
- Metabolism – in the liver to inactive metabolites
- Elimination – urine

Use (orally):

- primary and secondary adrenocortical insufficiency in Addison's disease
- neurogenic orthostatic hypotension
- adrenogenital syndrome

Adverse effects:

- hypokalemia
- hypernatremia
- hypertension
- swelling
- tachycardia
- congestive heart failure

<u>Adverse effects – systemic therapy</u>

Adverse effects of glucocrticoids appear more likely after long-term treatment but less frequently after short-term treatment even with high doses.

- adrenal atrophy - Inhibition of hypothalamic – pituitary – adrenal axis
- hypertension, edema
- Immunosupression, increased risk of infection
- weakness, muscular dystrophy
- osteoporosis / growth retardation in children
- hyperglycemia/diabetes
- impaired wound healing
- obesity – deposition of fat tissue in „typical" places: on the neck and face („bull's neck", moon-shaped face) - cortisol inhibits peripheral glucose consumption, stimulates LPL activity. Higher density of glucocorticoid receptors in visceral tissue is assiociated with greater expression of local glucocorticoid effects. This area is characerized by ↑ insulin resistance.
- psychosis
- vomiting, nausea, increased apetite, peptic ulcer
- cataracts, glaucoma
- skin problems

<u>Adverse effect of glucocorticoids used locally</u>

(inhalation, intranasally, on the skin and mucosa)

- oral and sinus fungal infections
- hoarseness
- cough
- allergy
- cataracts
- glaucoma
- skin atrophy
- telangiectasias (spider veins)

- hirsutism
- acne
- skin irritation, thinning
- hypo- and hyperpigmentation
- Inhibition of hypothalamic – pituitary – adrenal axis

Contraindications

- None – if an indication is substitution in adrenal insufficiency
- None – if the indication is acute condition

Absolute contraindications

- systemic fungal and viral infections
- corneal and eyelid herpes
- mental disorders (especially acute psychosis)

Relative contraindications:

- active or latent tuberculosis
- active peptic ulcer
- hypertension
- osteoporosis
- glaucoma
- severe infections
- gastrointestinal diverticula
- epilepsy
- 8 weeks before and 2 weeks after immunoglobulins administartion
- Diabetes

Antagonists of adrenal steroids

Indications:

- ➢ <u>receptor antagonists:</u>
- treatment of inoperable Cushing's Syndrome
- treatment of primary and secondary hyperaldosteronism
- ➢ <u>synthesis antagonists</u>
- in the treatment of adrenal tumor (in case of ineffective surgery)

<u>Agents inhibiting steroids synthesis</u>

- ▶ **Ketoconasole:** an antifungal imidazole derivative, inhibitor of CYP 3A4, CYP11A1 and CYP11B1 – essential for steroids synthesis

- non used for the treatment of mycoses
- doses several times higher than anti-fungal (1000 mg/24h) can lead to desired supression of the adrenal cortex (within a few weeks)

- ▶ **Mitotane:** cytostatic, causes of atrophy of adrenal cortex

- modyfies peripheral metabolism of steroids, as well as directly inhibits adrenal function
- used chronically in the treatment of adrenal cortical cancer – at therapeutic concentrations in plasma it irreversebly damages adrenal fragments

<u>Agent inhibiting steroids receptor</u>

- ▶ **Mifepristone:** derivative of synthetic progestin -norethindrone

- potent antiprogesterone activity
- used as postcoital contraceptive agent