Steroid hormones

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glucocorticoids-mineralocorticoids-sexualsteroids

- zona glomerulosa

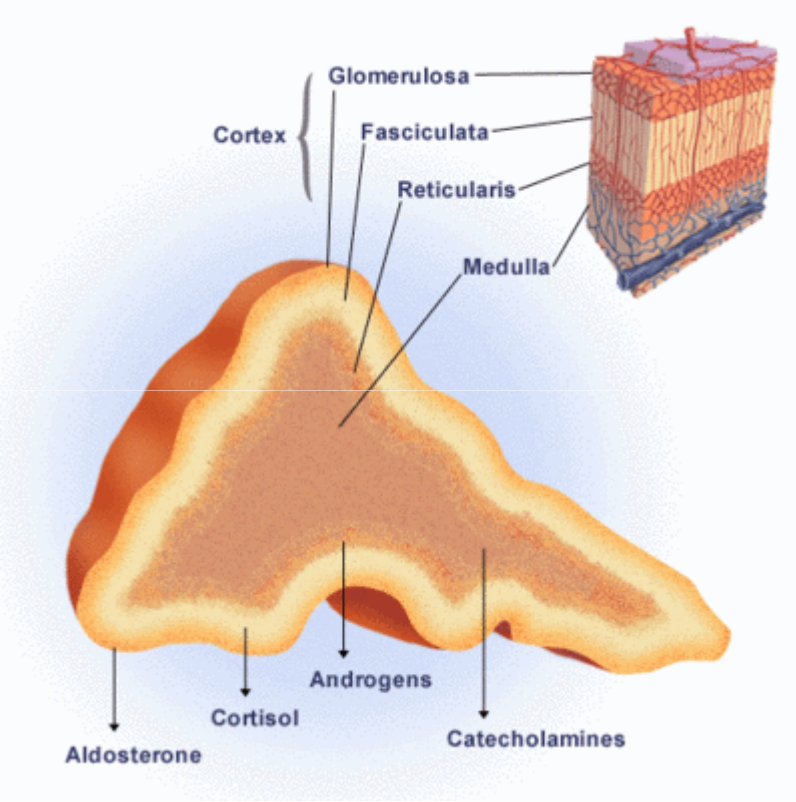
  mineralocorticoids – aldosterone
  tr.o.synth.:RAS, hypoxia, hyponatremia

- zona fasciculata

  glucocorticoids – cortisol/hydrocortison
  trigger of synthesis: stress, CRH, ACTH

- zona reticularis

  sexual steroids - DHEA, DHEAS



Adrenal steroids/hormones

agonists

Glucocorticoids

•cortizol (hydrocortizon)
short duration of action

•prednisolon
intermediate duration of action

•dexamethson, betamethason
long duration of action

Mineralocorticoids

•aldosteron
physiologic

•fludrocortison
synthetic

antagonists

Synthesis inhibitors

•aminogluthetimide
sedatohypnotic drug

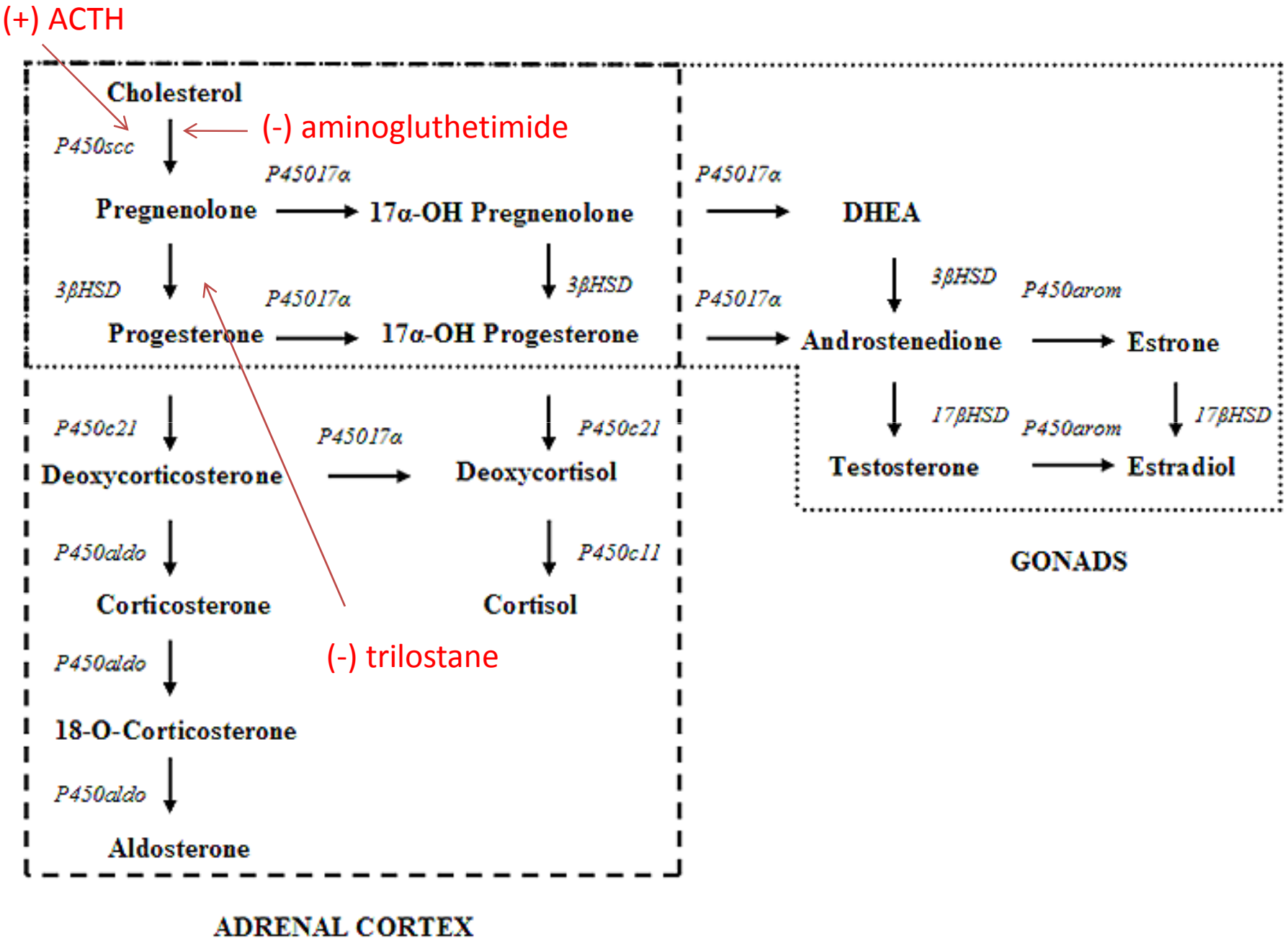
•ketoconazol
antimycotic drug

Receptor antagonists

•spironolactone
diuretics

•mifepristone
prog.R antagonist
RU-486
abortus artef.

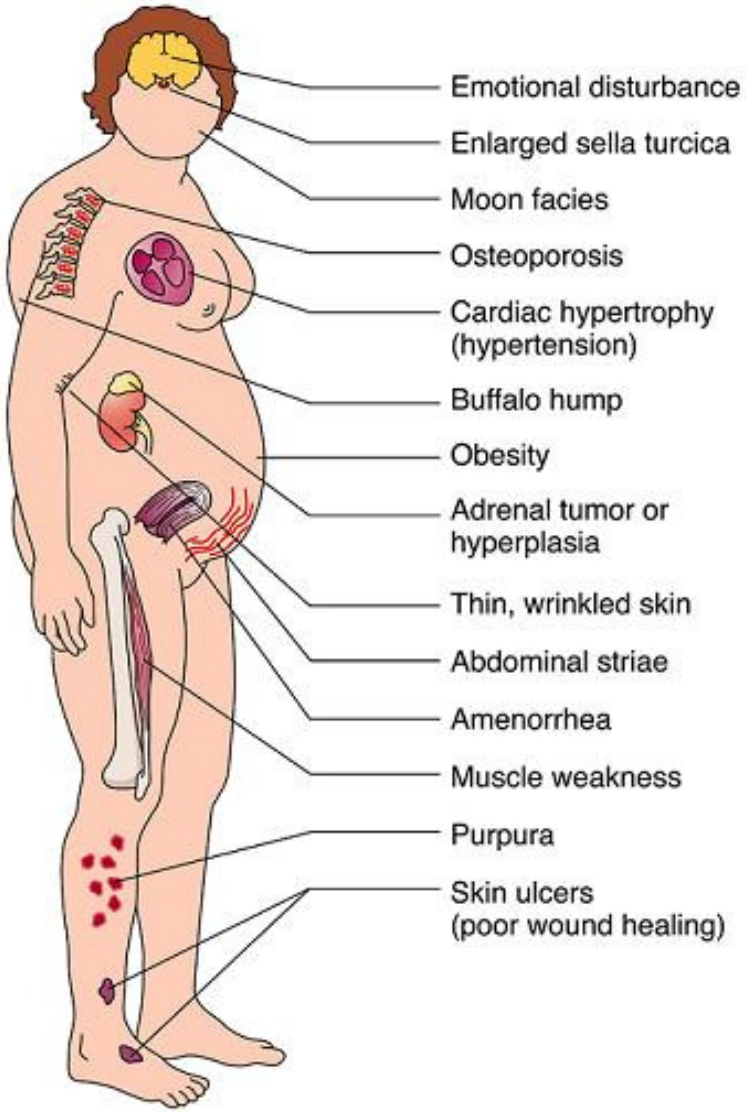
Biosynthesis of steroid hormones



Glucocorticoids-Mineralocorticoids

- Patholgical states of adrenal cortex
  - Cushing's syndrome
    - cortisol ↑
    - central, peripheral, iatrogen, exogenous
  - Conn's syndrome
    - primer hyperaldosteronism
  - Addison's syndrome
    - insufficient activity of adrenal cortex
    - ↓ cortisol, ↓ aldosterone

Cushing's syndrome



Glucocorticoids/Mineralocorticoids

- mechanism of action (slow acting)
    - effect on i.c. GC receptor (GRα, GRβ) – associated with hsp56, hsp90
        - nuclear receptor superfamily
        - represented in every tissues
        - steroid receptor complex form heterodimers
        - GRE of DNA – modulating transcription
    - cortisol and aldosterone equiactive on mineralocorticoid R
        - kidney, ureter, colon
        - 11-β-OH-dehidrogenase – converts cortisol → cortison (inactive)

Effects of GCs

- anti-inflammatory/immunsuppressive eff.
  - inhibiting the late phase reaction of immune response
    - ↑ lipocortin release – inhibition of PLA2
  - ↓ leukocyte migration
    - ↓ transcription of IL-2 genes, COX-2, cytokines (TNF-α), cell adhesion molecules
    - ↓ histamine release
  - ↓ activation of T-helper cells
  - ↓ wound healing, chronic inflammatory reactions
    - ↓ fibroblast proliferation
    - ↓ collagenase activity
  - ↑ osteoporosis
    - ↓ activity of osteoblast, ↑ activity of osteoclasts
    - ↓ D_3 vitamin mediated osteocalcin gene transcription
  - ↓ generation of nitric oxide

Effects of GC

- metabolic actions
  - hyperglycemia (diabetic effect)
    - ↓ uptake and utilisation of glucose
    - ↑ gluconeogenesis
  - proteolytic effect
    - decrease protein synthesis
  - lypolytic effect
    - permissive effect on cAMP dep. lipase
  - lipogenetic
    - redistribution of adipose tissue
    - N.B.: Cushing's syndrome
  - (-) Ca^{2+} balance
    - ↓Ca^{2+} absorption from GIT
    - ↑ Ca^{2+} excretion in kidney
  - ↑ α-adrenerg R density

Glucocorticoids

- Pharmacokinetic aspects
  - transported by CBG
  - cortisole $t_{1/2}$: 90 min
  - metabolized in liver
  - administration
    - oral, i.v., i.m., topical, aerosol, eyedrop, intranasal

Unwanted effects of GC therapy

- inc.
  - large doses, prolonged administration, sudden withdrawal
- peptic ulcer
- impaired wound healing
- hypertension
- infection (opportunistic) – oral candidiasis
  - suppr. of immune response
- acute adrenal insufficiency
- hyperglycemia, insulin resistance, type II. DM
- muscle atrophia
- osteoporosis
  - (-) Ca^{2+} balance
  - decreased D_3 action
- electrolyte disturbances
  - hypernatremia, hypokalemia,
- avascular necrosis in bones (femur)
- inhibition of growth (children)
- epileptogen effect

Effects of MC

- act on i.c. receptors, modulating DNA transcription
- ↑ Na^+ reabsorption in distal tubules
- K^+ and H^+ efflux into the tubules
- forms
  - physiologic: aldosterone
  - synthetic: fludrocortisone
- applied with GCs in replacement therapy

Therapeutical indications

- Replacement therapy
  - Addison's syndrome
  - Waterhouse-Friedricksen syndr. (AAI c. by Neisseria)
  - congenital adrenal hyperplasia (loss of 21-hydroxilase, 11-β-hydroxilase)
    - progressive Na^+, K^+ excretion,
    - virilisation (DHEA↑, DHEAS↑)
  - post adrenalectomia
  - IRDS profilaxis
    - surfactant synthesis

Therapeutical indications

- Anti.inflammatory, immun-suppressive therapy
  - in asthma
  - topically in various inflammatory conditions of skin, eye, ear, nose (ekzema, rhinitis, allerg. conjunctivitis)
  - hypersensitivity states (severe allergic reactions)
  - autoimmune disease (SLE, Sjögren's syndr., PM/DM, RA, IBD)
  - transplantation (prevent GVH reaction)

Therapeutical indications

- In neoplastic disease
  - combination with cytotoxic drugs (acute leukaemia, Hodking's disease)
  - reducing cerebral oedema in patients with primary or metastatic brain tumors
    - oradexon, dexomethasone

Equivalent doses of GCs

- Methyl-prednisolon – 4mg
- Prednisolon – 5mg
- Cortisole – 20mg
- Dexamethason – 0,75mg