Adrenocorticosteroids

&

Adrenocortical antagonists

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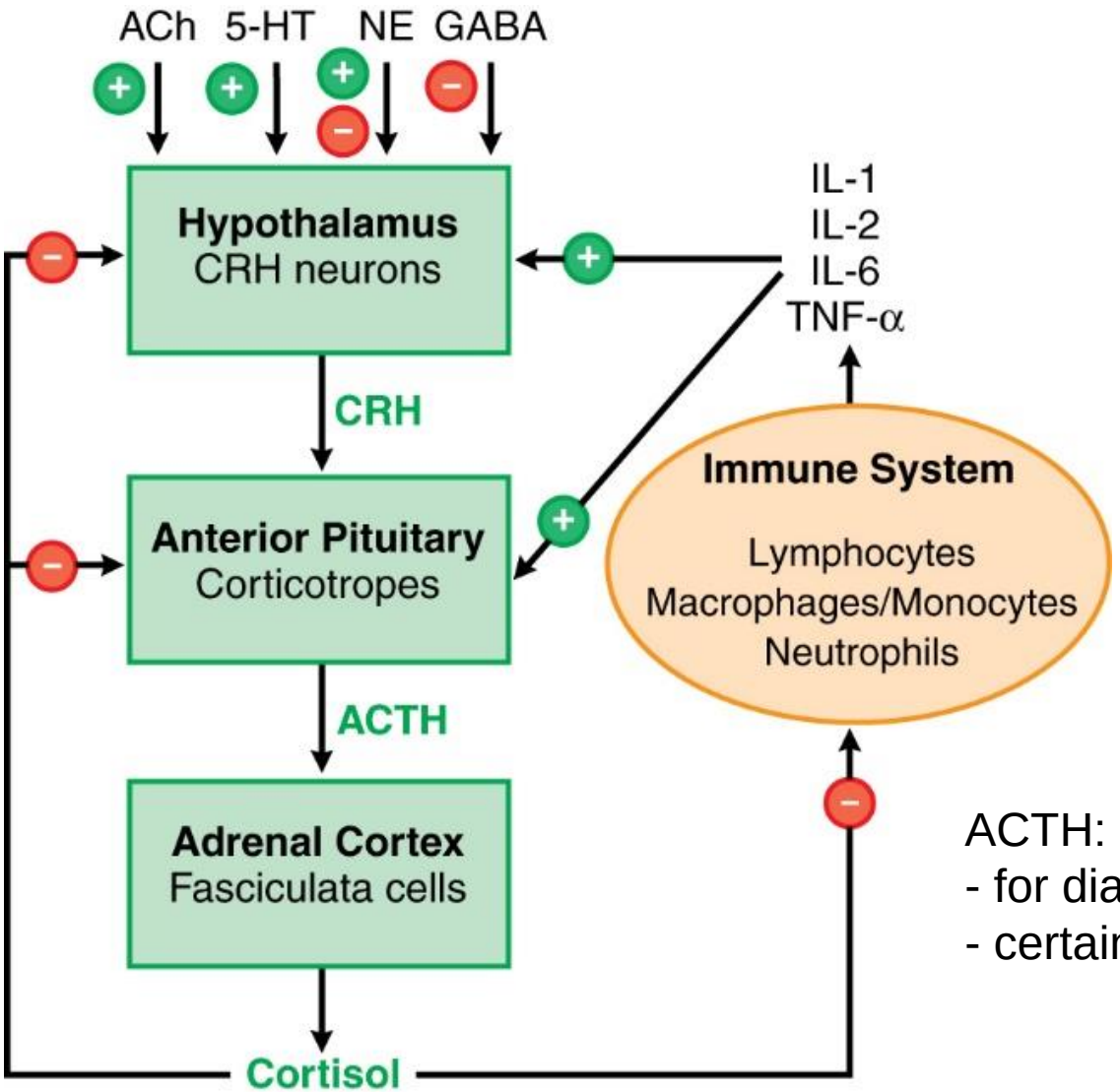
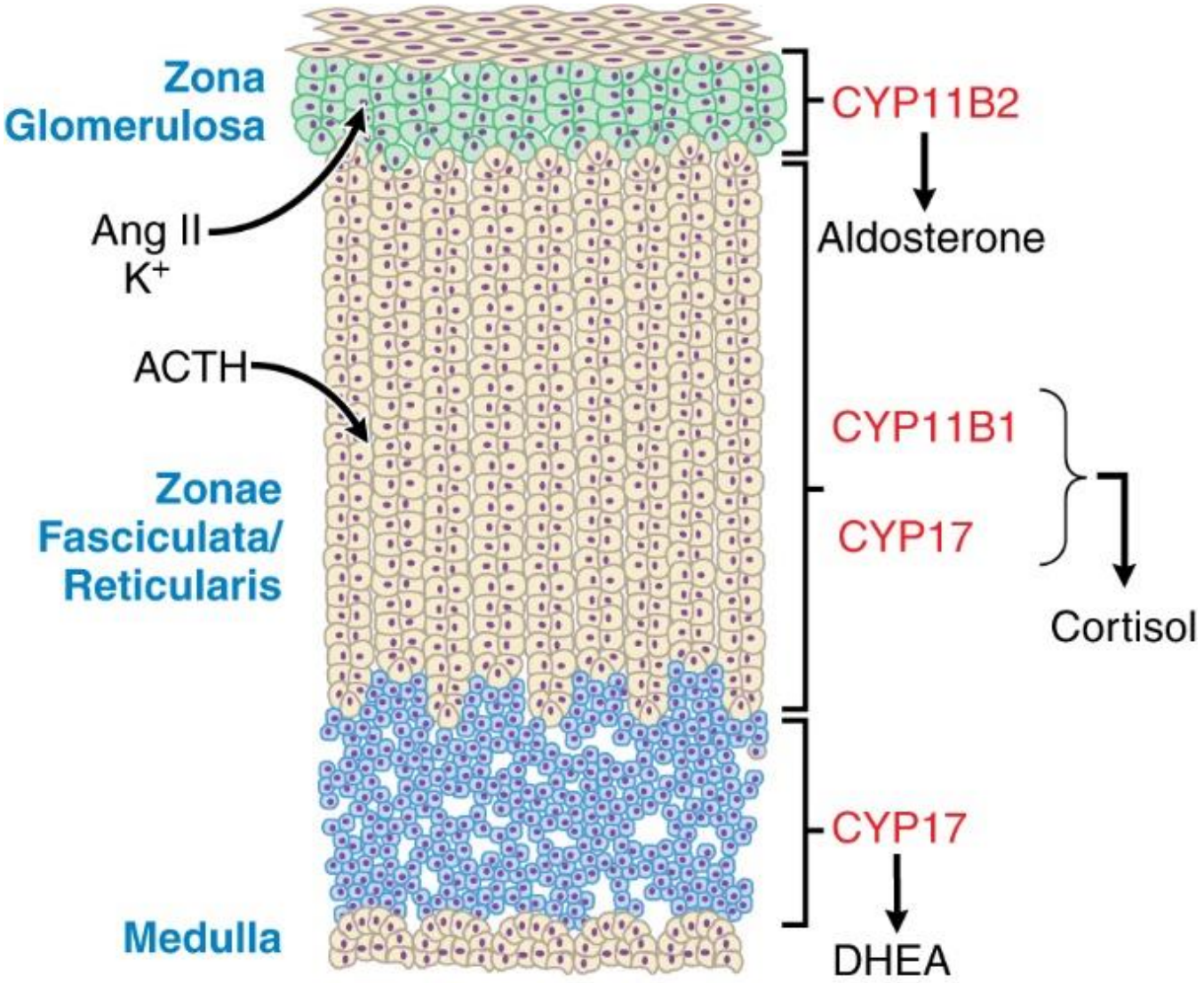
Overview of the hypothalamic-pituitary-adrenal (HPA) axis and the immune inflammatory network



ACTH:
- for diagnostic purposes
- certain epilepsies in childhood

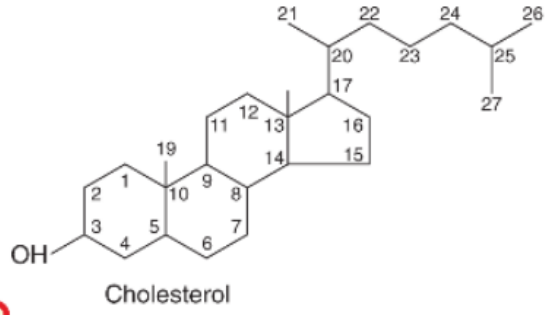
Goodman & Gilman's, 12th Ed.

The adrenal cortex contains three anatomically and functionally distinct compartments



Goodman & Gilman's, 12th Ed.

Major pathways in adrenocortical hormone biosynthesis



Cholesterol

Green boxes - intermediates

Blue boxes – circulating hormones

ACTH
Angio II

Amino-
glutethimide

Cholesterol → Pregnenolone → 17-α-OH → 17α-OH-pregnenolone → Dehydroepi-androsterone

Trilostane ⊖ 3-β-dehyd → Progesterone

3-β-dehyd → 17α-OH-progesterone

3-β-dehyd → Androstenedione

17-α-OH → Progesterone → 17α-OH-progesterone → Androstenedione

21-β-OH → 11-β-OH → Corticosterone

Metyrapone ⊖ 21-β-OH → 11-β-OH → Hydrocortisone (Cortisol)

Testosterone

17-α-OH → Corticosterone → Hydrocortisone (Cortisol)

Aldosterone ← Corticosterone

Angio II ⊕ → Aldosterone

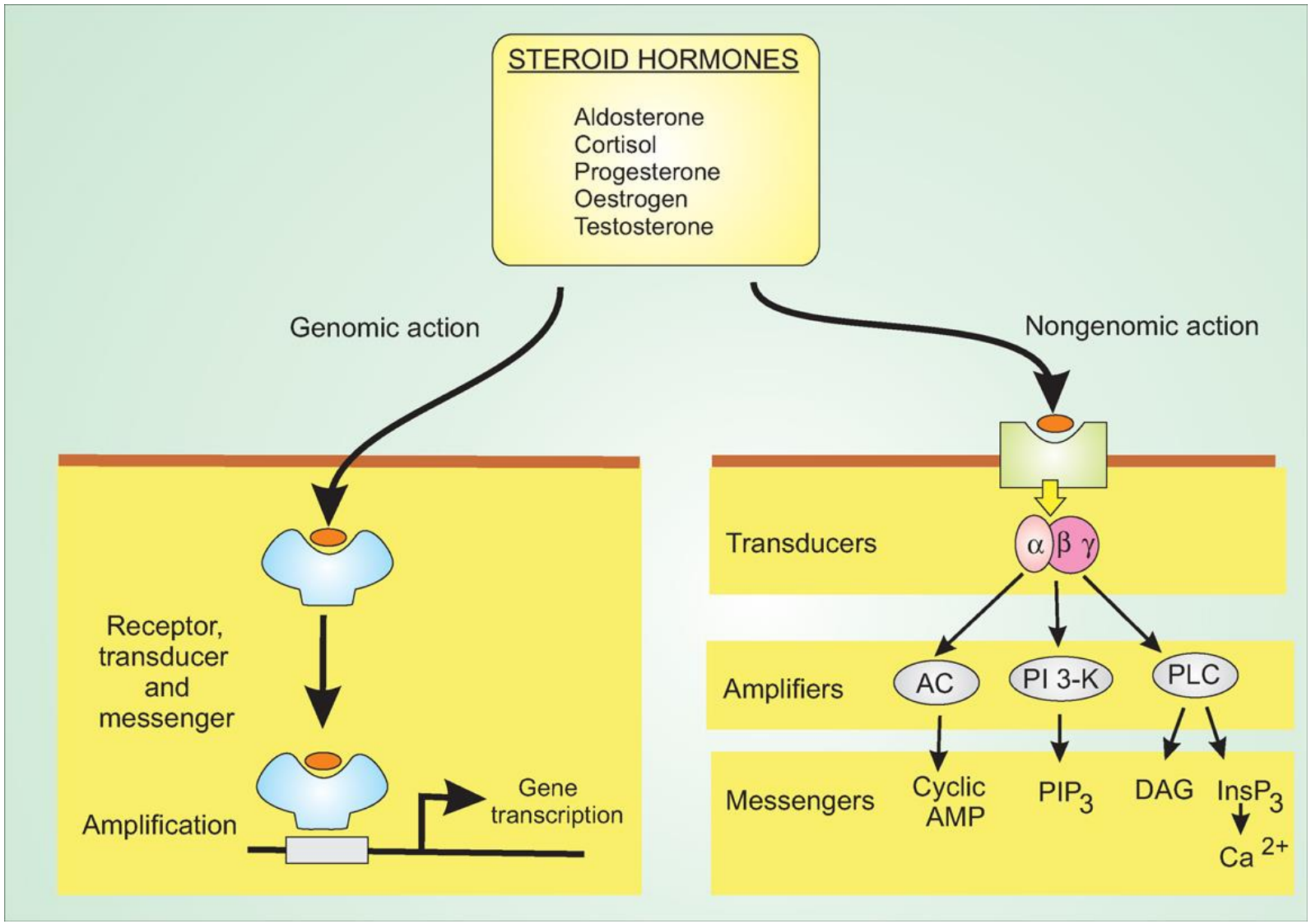
Carbenoxolone ⊖ 11-β-dehyd → Cortisone

Oestradiol
Oestriol
Oestrone

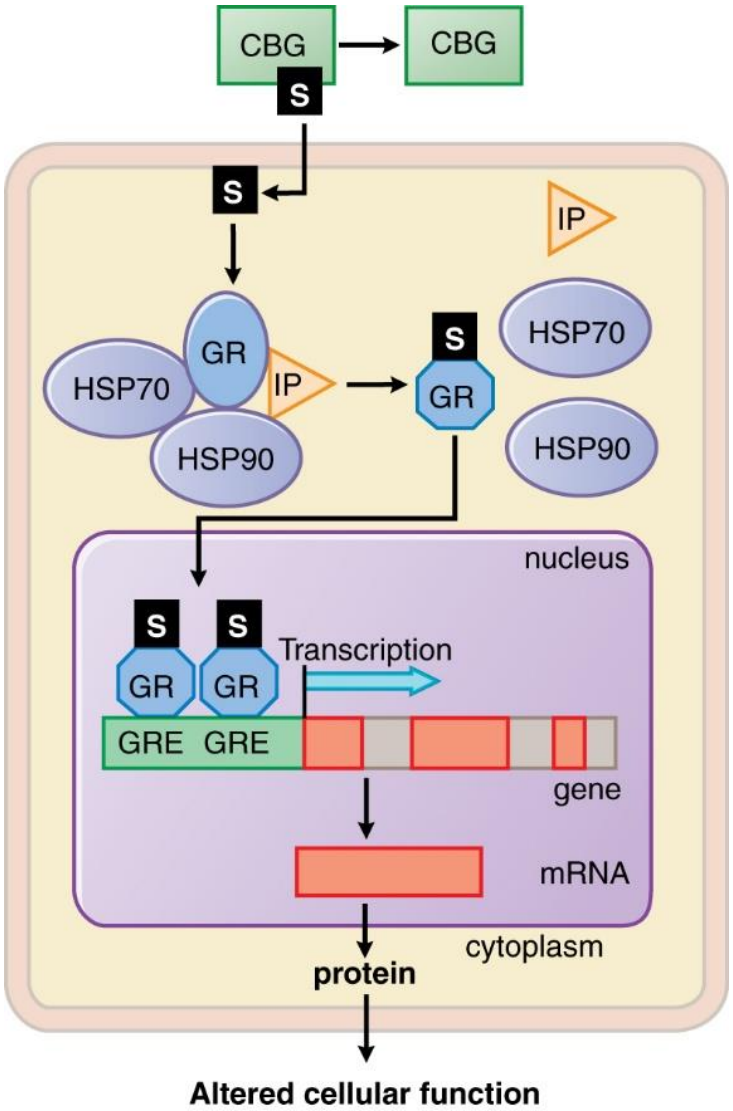
Mineralocorticoids **Glucocorticoids** **Sex hormones**

Rang & Dales's, 8th Ed.

Steroid stimuli operate through *genomic* or *non-genomic* mechanisms



Intracellular mechanism of action of the glucocorticoid receptor



The S-GR complex also interacts w/other transcription factors like NF-κB, AP1 → involved in anti-inflammatory & immunosupressive effects

CBG, corticosteroid-binding globulin; GR, glucocorticoid receptor; S, steroid hormone; HSP90, the 90-kd heat-shock protein; HSP70, the 70-kd heat-shock protein; IP, the 56-kd immunophilin; GRE, glucocorticoid-response elements; introns (gray); exons (red).

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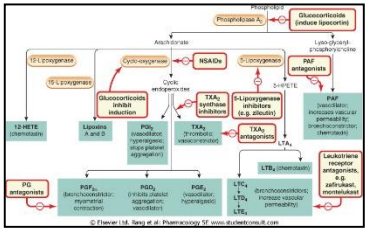
Glucocorticoid receptor actions

Gene activation:

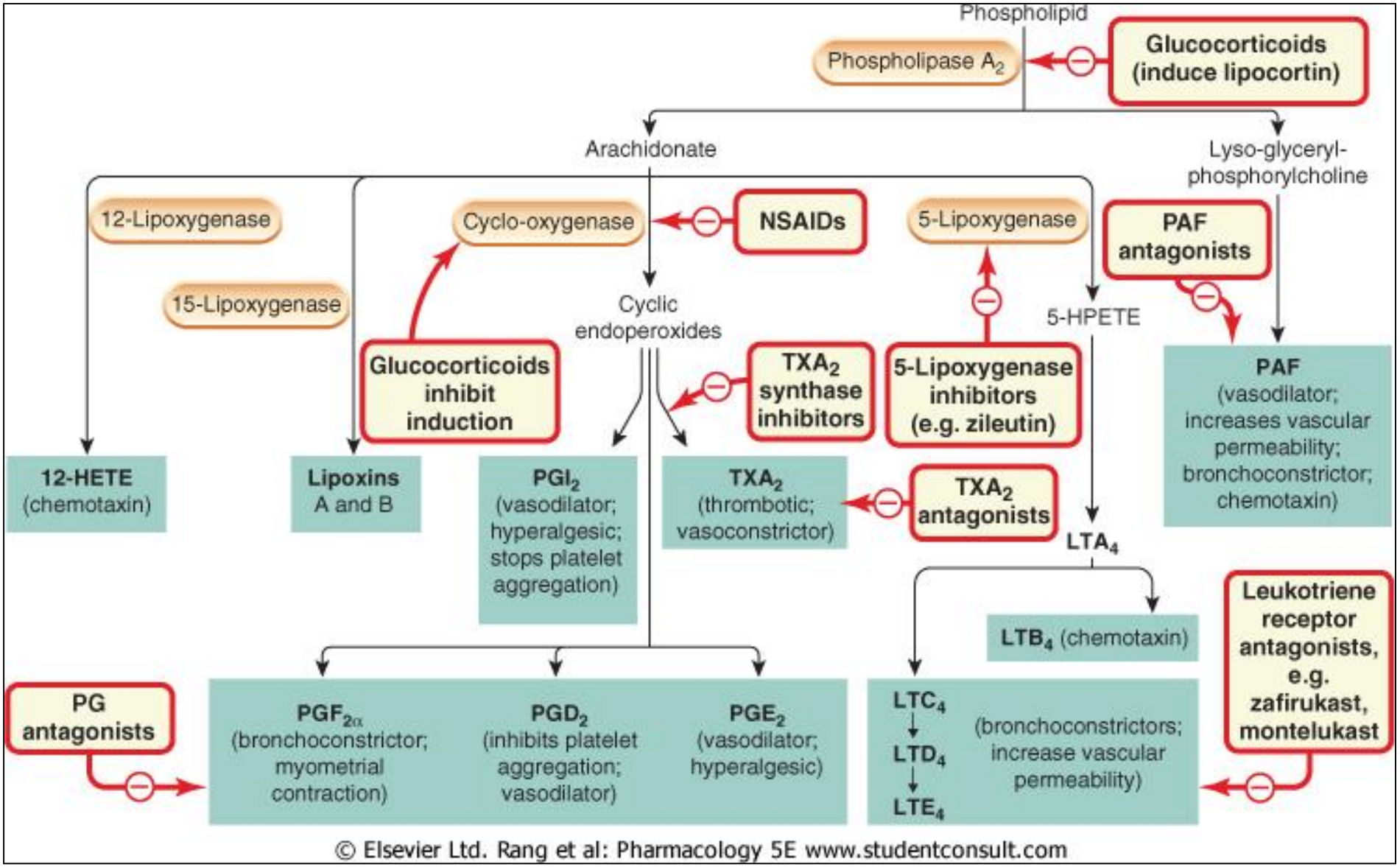


- annexin-1 (lipocortin-1) → PLA2 ↓
- enzymes of *gluconeogenesis* and *amino acid metabolisms* (cAMP dependent protein kinase)
- adrenergic receptors on vascular & bronchial smooth muscle („permissive effect”: e.g. β_2 agonist effect in bronchial asthma)

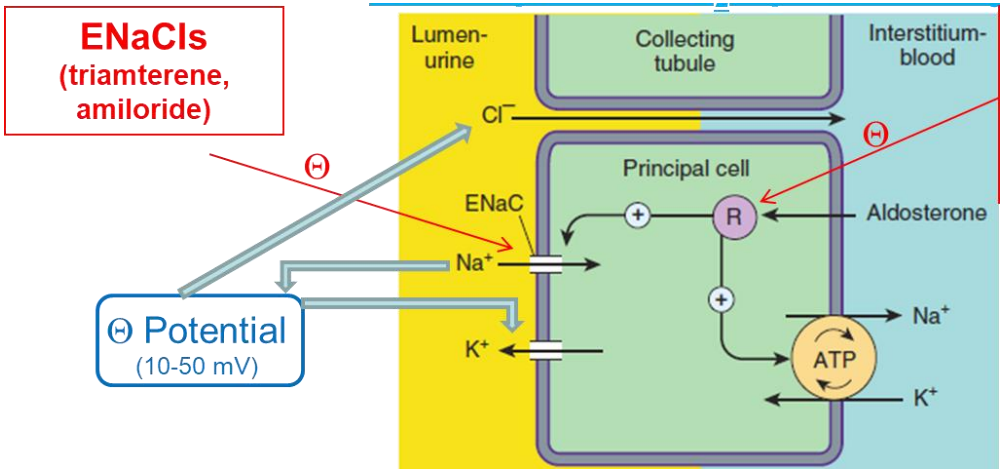
Gene repression:

- COX-2
- NOS
- Cytokines
- Interleukins
- Cell adhesion molecules

10-20 % of expressed genes are regulated by glucocorticoids!



Mineralocorticoid receptor actions



Genomic:

- Na^+/K^+-ATP-ase transcription ↑
- ENa channel activity ↑
- expression of profibrotic molecules (e.g. TGF-β) ↑
- NADPH oxidase expression ↑; ROS ↑ - proinflammatory effect

Non-genomic:

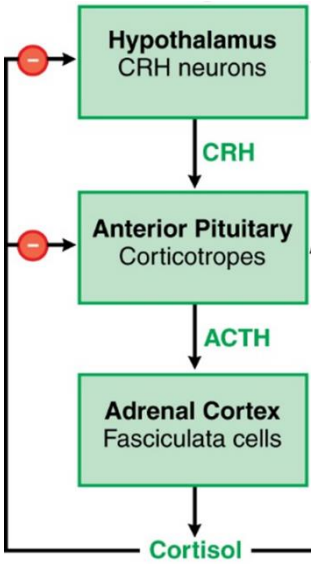
- proinflammatory effects (via EGFR & ERK1/ERK2)

Glucocorticoid effects I.

Metabolic actions:

- *Carbohydrates*: glucose uptake & utilisation ↓, gluconeogenesis ↑
  - hyperglycaemic tendency (→ insulin ↑ → glycogen ↑)
- *Proteins*: catabolism ↑, anabolism ↓
- *Lipids*: redistribution of fat (Cushing type), triglycerides ↑, LDL/HDL ↑

Glucocorticoid effects II.



Regulatory actions:

- *Hypothalamus & anterior pituitary gland*: negative feedback →
  → release of endogenous glucocorticoids ↓
- *Cardiovascular system*: vasodilatation ↓, plasma exudation ↓
- *Musculoskeletal*: activity of osteoblast ↓, of osteoclast ↑
- *Negative Ca^{2+} balance*: Ca^{2+} absorption ↓, Ca^{2+} elimination ↑
- *Inflammation & immunity*:
  - acute inflammation: influx & activity of leukocytes ↓
  - chronic inflammation: activity of mononuclear cells ↓, angiogenesis ↓, fibrosis ↓
  - in blood: neutrophils ↑; eosino-/basophils/monocytes/lymphocytes ↓
  - lymphoid tissues: clonal expansion of T/B cells ↓, cytokine-secreting T action ↓

  Mediators:
  - production and action of cytokines ↓ (ILs, TNF-α, GM-CSF)
  - generation of eicosanoids ↓
  - generation of IgG ↓
  - complement components in the blood ↓
  - release of anti-inflammatory factors ↑ (e.g. IL-10 & annexin-1)

Overall effects: activity of the innate & acquired immune systems ↓,
healing & protective aspects of inflammation ↓

Pharmacokinetics of the glucocorticoids

- Good p.o. absorption
- Transport in blood by:
  - 90 % - corticosteroid-binding globulin (CBG)/α_2 globulin
  - 5-10 % - free
  - ~5 % - albumin (large capacity, low affinity → practically considered as free)
- $T_{1/2}$: 60-90 min
- Metabolism:
  - ~ 80 % in the liver
  - 20 % in the kidney & other MR containing tissue (e.g., colon, salivary glands)
  - 1 % unchanged → urine

Clinical uses of glucocorticoids

- *Replacement therapy* (adrenocortical insufficiency, Addison's disease)
- Diagnostic purposes (dexamethasone supression test; Cushing's disease/syndrome)
- *Stimulation of lung maturation in foetus* (delivery before week 34)
- *Anti-inflammatory/immunosupressive therapy*:
  - in asthma
  - topically in inflammatory conditions of skin, eye, ear, nose (e.g. eczema, allergic conjunctivitis or rhinitis)
  - hypersensitivity states (e.g. severe allergic reactions)
  - in diseases with autoimmune & inflammatory components (e.g. RA & other 'connective tissue' diseases, IBD, some forms of haemolytic anaemia, idiopathic thrombocytopenic purpura)
  - to prevent graft-versus-host reaction (organ or bone marrow transplantation)
- *In neoplastic diseases*:
  - in combination with cytotoxic drugs (e.g. Hodgkin's disease, acute lymphocytic leukaemia)
  - to reduce cerebral oedema (metastatic or primary brain tumours; dexamethasone)
- *Nausea & vomiting* (in chemotherapy & general anesthesia)

Some therapeutic indications for the use of glucocorticoids in nonadrenal disorders

Disorder	Examples
Allergic reactions	Angioneurotic edema, asthma, bee stings, contact dermatitis, drug reactions, allergic rhinitis, serum sickness, urticaria
Collagen-vascular disorders	Giant cell arteritis, lupus erythematosus, mixed connective tissue syndromes, polymyositis, polymyalgia rheumatica, rheumatoid arthritis, temporal arteritis
Eye diseases	Acute uveitis, allergic conjunctivitis, choroiditis, optic neuritis
Gastrointestinal diseases	Inflammatory bowel disease, nontropical sprue, subacute hepatic necrosis
Hematologic disorders	Acquired hemolytic anemia, acute allergic purpura, leukemia, lymphoma, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, multiple myeloma
Systemic inflammation	Acute respiratory distress syndrome (sustained therapy with moderate dosage accelerates recovery and decreases mortality)
Infections	Acute respiratory distress syndrome, sepsis

BG Katzung, 12th Ed.

Some therapeutic indications for the use of glucocorticoids in nonadrenal disorders

Inflammatory conditions of bones and joints	Arthritis, bursitis, tenosynovitis
Neurologic disorders	Cerebral edema (large doses of dexamethasone are given to patients following brain surgery to minimize cerebral edema in the postoperative period), multiple sclerosis
Organ transplants	Prevention and treatment of rejection (immunosuppression)
Pulmonary diseases	Aspiration pneumonia, bronchial asthma, prevention of infant respiratory distress syndrome, sarcoidosis
Renal disorders	Nephrotic syndrome
Skin diseases	Atopic dermatitis, dermatoses, lichen simplex chronicus (localized neurodermatitis), mycosis fungoides, pemphigus, seborrheic dermatitis, xerosis
Thyroid diseases	Malignant exophthalmos, subacute thyroiditis
Miscellaneous	Hypercalcemia, mountain sickness

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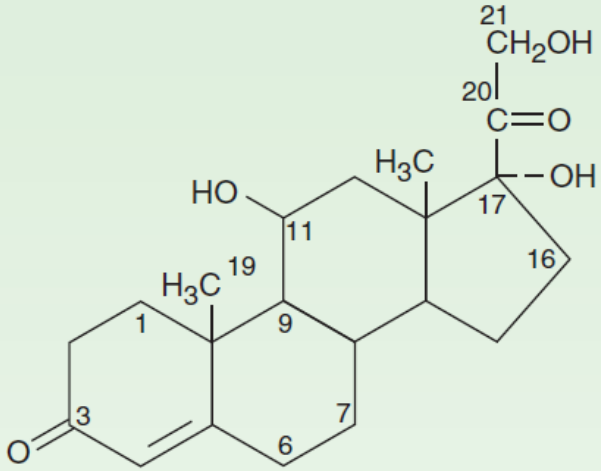
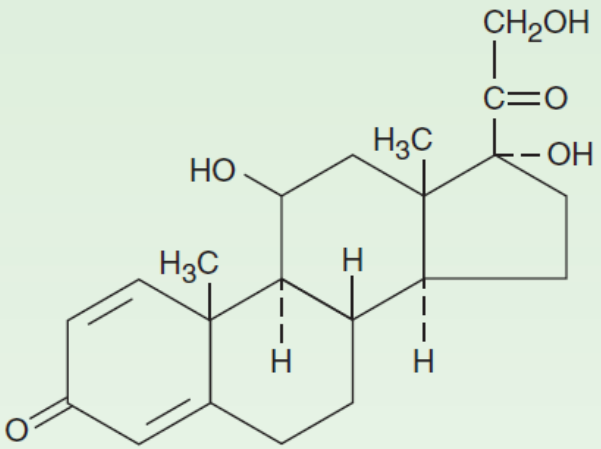
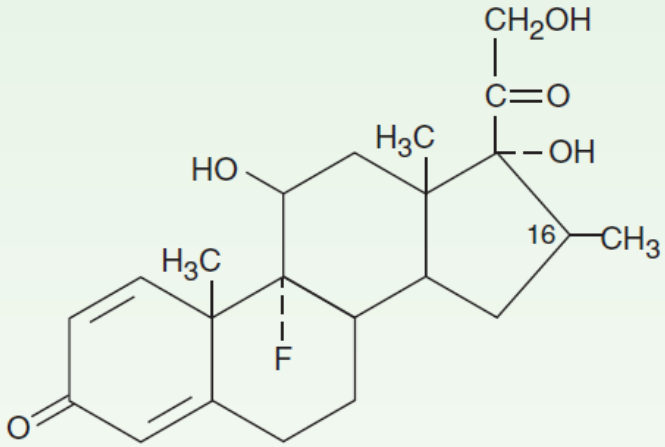
Chemical structures of several glucocorticoids



Cortisol (hydrocortisone)

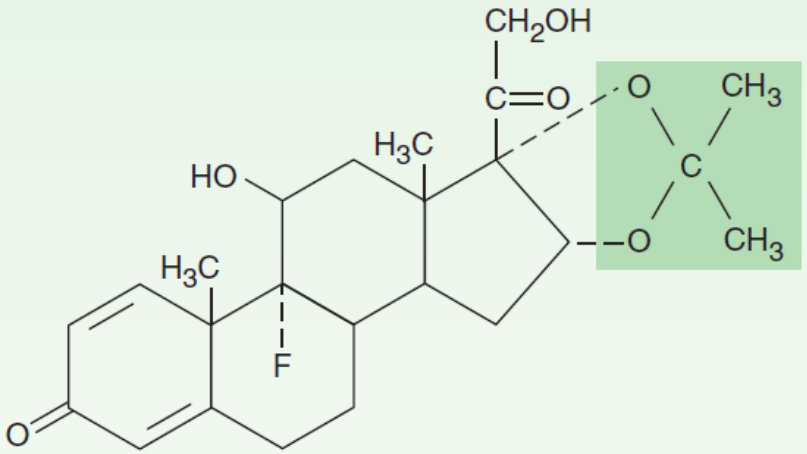


Prednisolone



Betamethasone ~ Dexamethasone

(16 -CH_3: beta ~ alpha)



Triamcinolone (acetonide moiety shaded)

(Increased surface activity → dermatology)

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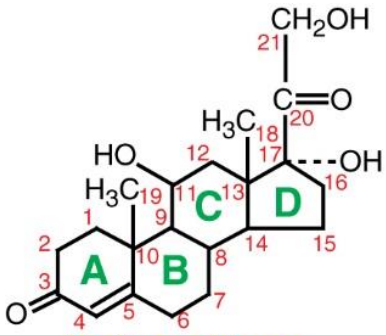
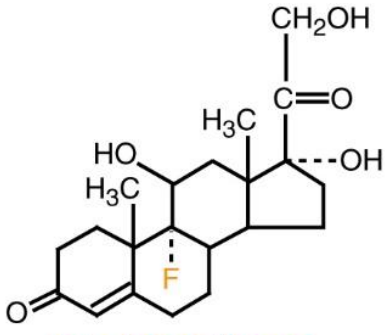
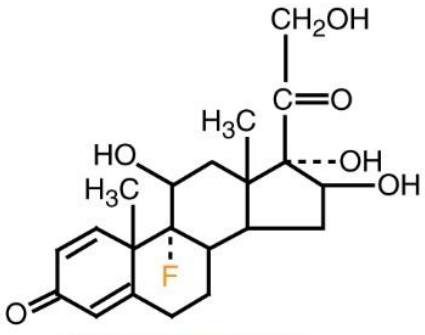
Structure and nomenclature of corticosteroid products and selected synthetic derivatives



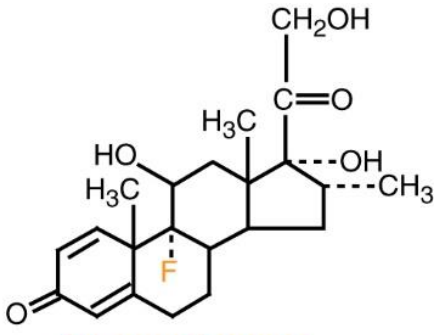
Hydrocortisone
(Cortisol)



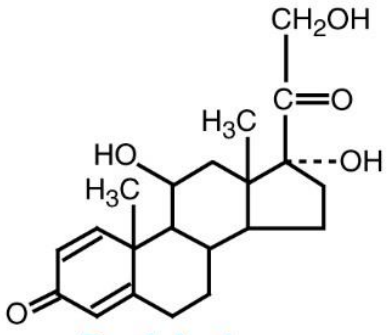
Fludrocortisone



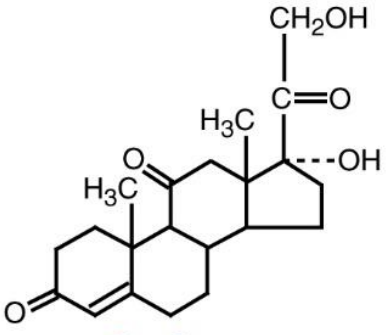
Triamcinolone



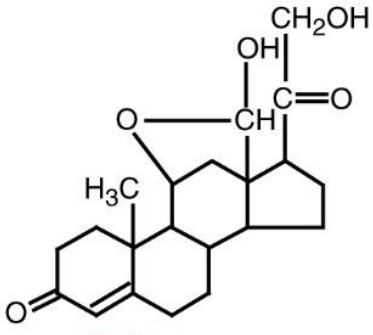
Dexamethasone



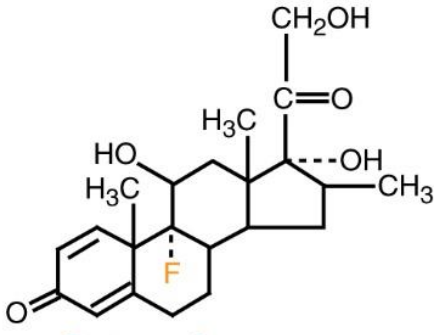
Prednisolone



Cortisone



Aldosterone,
hemiacetal derivative



Betamethasone

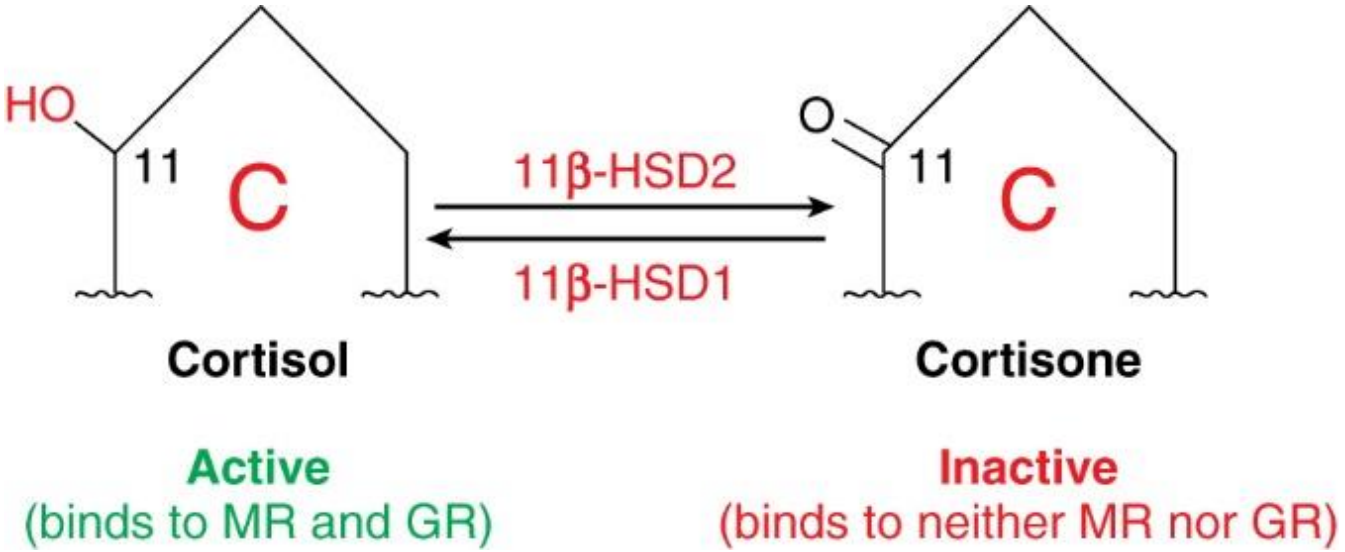
Goodman & Gilman's, 12th Ed.

Table 32.2 Comparison of the main corticosteroid agents used for systemic therapy (using hydrocortisone as a standard)

Compound	Relative affinity for receptor[a]	Approximate relative potency in clinical use		Duration of action after oral dose[b]	Comments
		Anti-inflammatory	Sodium retaining		
Hydrocortisone (Cortisol)	1	1	1	Short (8-12h)	Drug of choice for replacement therapy (cortisol)
Cortisone	Prodrug	0.8	0.8	Short	Cheap; inactive until converted to hydrocortisone; not used as anti-inflammatory because of mineralocorticoid effects
Deflazacort	Prodrug	3	?	Short	Must be converted by plasma esterases into active metabolite Similar utility to prednisolone
Prednisolone	2.2	4	0.8	Intermediate (12-36h)	Drug of choice for systemic anti-inflammatory and immunosuppressive effects
Prednisone	Prodrug	4	0.8	Intermediate	Inactive until converted to prednisolone
Methylprednisolone	11.9	5	Minimal	Intermediate	Anti-inflammatory and immunosuppressive
Triamcinolone	1.9	5	None	Intermediate	Relatively more toxic than others
Dexamethasone	7.1	27	Minimal	Long (36-72h)	Anti-inflammatory and immunosuppressive, used especially where water retention is undesirable (e.g. cerebral oedema); drug of choice for suppression of adrenocorticotrophic hormone production
Betamethasone	5.4	27	Negligible	Long	Anti-inflammatory and immunosuppressive, used especially when water retention is undesirable
Fludrocortisone	3.5	15	150	Short	Drug of choice for mineralocorticoid effects
Aldosterone	0.38	None	500	–	Endogenous mineralocorticoid

Rang & Dales's, 8th Ed.

Receptor-independent mechanism by which 11β-hydroxysteroid dehydrogenase confers specificity of corticosteroid action



This **inactivation** allows specific responses to aldosterone in sites such as the **distal nephron, colon, sweat glands, salivary glands, placenta**. 11β-HSD1 catalyzes the **reverse reaction**, which converts inactive cortisone to active cortisol in such tissues as **liver**, **fat, CNS, placenta**.
HSD - hydroxysteroid-dehydrogenase;

Goodman & Gilman's, 12th Ed.

Topical administration

Advantage: systemic side effects ↓

- Bronchial asthma: aerosol (beclomethasone, fluticasone, mometasone, budesonide, flunisolide)
- Allergic rhinitis: nasal spray (beclomethasone, triamcinolone, budesonide, flunisolide)
- Ophtalmology: OGT
- Dermatology: ointment, solution (flumetazone, triamcinolone, fluocinolone w/ *acetonide moiety* → topical activity ↑)
- IBD: suppository, enema
- Joint diseases: intra-articular
- Timed-release tablet (phsiology-like cortisol levels; high morning, low evening)

In urgent acute cases – i.v.

(dexamethasone, methylprednisolone)

e.g.:

- Anaphylactic shock (w/ epinephrine)
- Asthma beonciale
- Thyreotoxic crisis
- Brain oedema
- Hepatic coma

Unwanted effects of the glucocorticoids
(< 2 weeks therapy)

Serious side effects are **unusual**. Can be:

- insomnia, hypomania
- peptic ulcer
- Acute pancreatitis (rare; only at high dose)

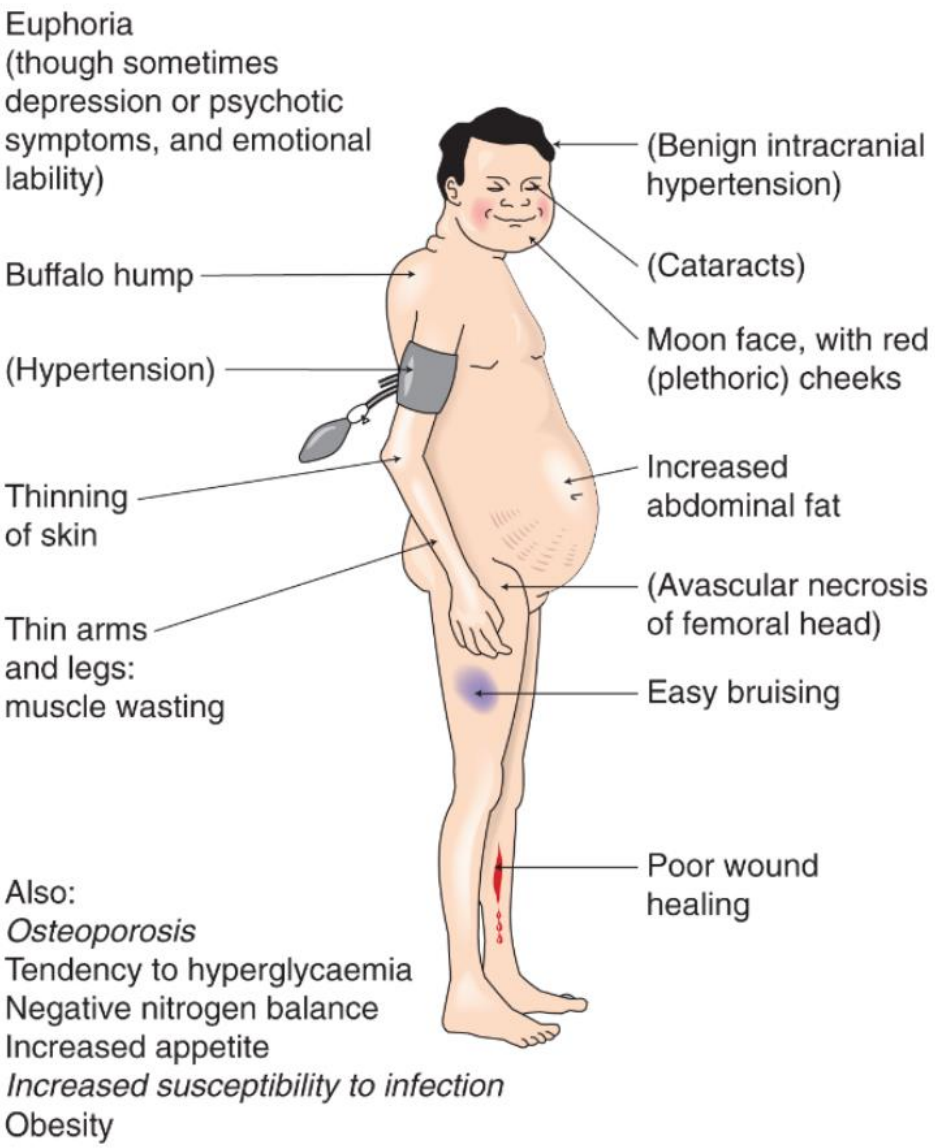
Comorbidities → enhanced risk
- e.g. hypertension, hyperglycemia, peptic ulcer, psychiatric problems

Unwanted effects of the glucocorticoids
(> 2 weeks therapy)

- *Response to infection or injury* ↓ (wound healing ↓, peptic ulceration, oral candidiasis)
- *Iatrogenic Cushing's syndrome*
- *Suppression of endogenous glucocorticoid synthesis*
- *Hypokalemia, hypernatremia, edema, hypertension*
- *Osteoporosis*
- *Aseptic necrosis of femoral head*
- *Hyperglycaemia, insulin ↑, weight gain, DM*
- *Muscle wasting, myopathy*
- *Inhibition of growth in children* (if > 6 months treatment)
- *CNS effects*: hypomania, psychosis (at very large dosis), long term: depression
- *Other* effects: glaucoma (in genetically predisposed persons), incidence of cataracts ↑, intracranial pressure ↑

Patients should be on high protein and K^+ enriched diet w/ low Na^+, and vit D & Ca^{2+} supplementation!

Cushing's syndrome
(italicised effects are particularly common)



Rang & Dales's, 8th Ed.

Dosage

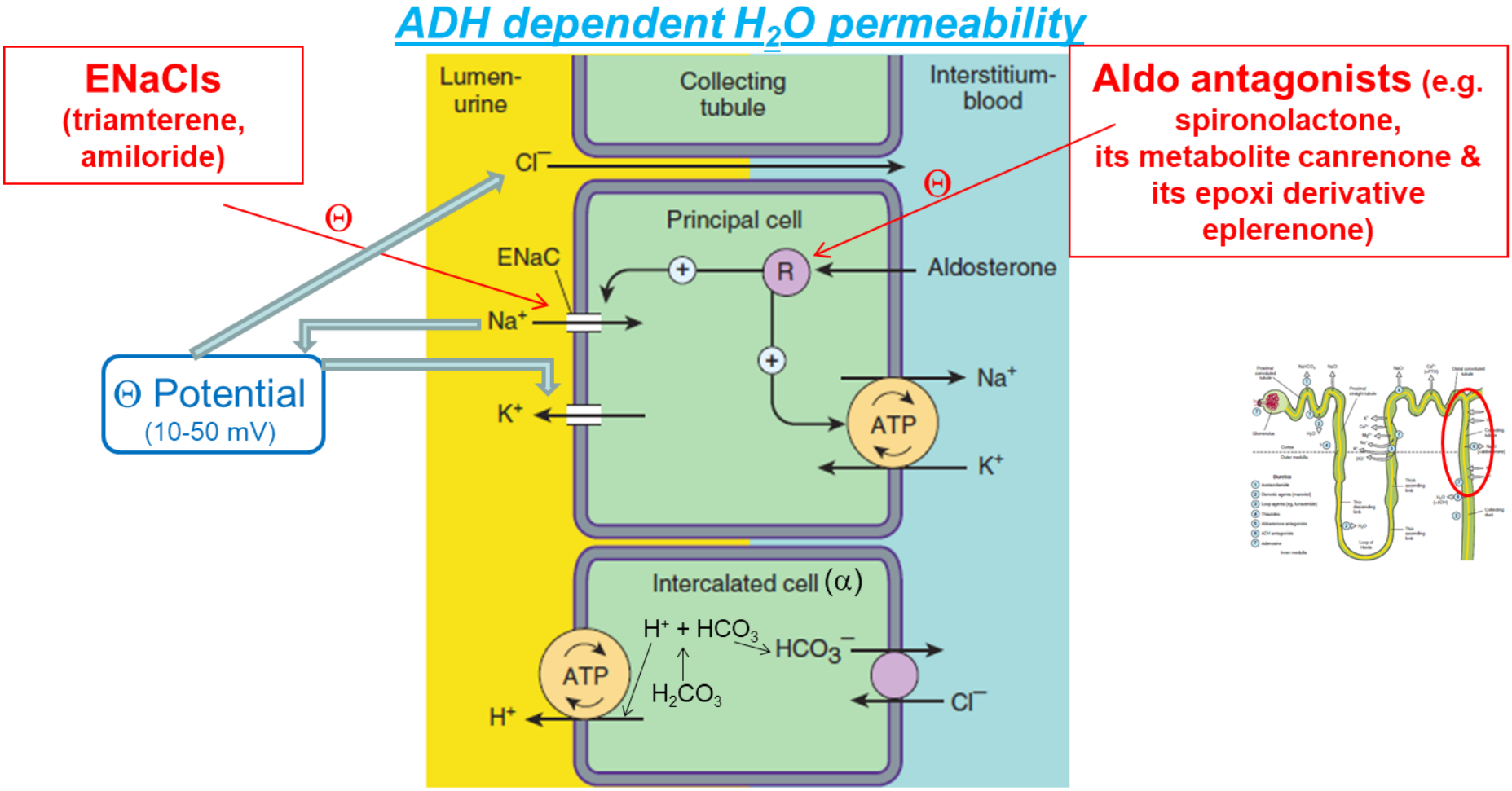
Driven by *seriousness* of the disease, *duration* of therapy.

Keep dosage as low as possible – titrate!

- Higher dose for inital effect, lower dose for maintanance – in many cases
- To supress ACTH: small, frequent p.o. doses or slowly absorbed p.e. preparation
- Inflammatory & allergic disorders: same quantity in a few doses
- Severe autoimmun diseases: high, divided dose, gradual reduction later on
- If large dose required: synthetic w/ minimal mineralocorticoid action
- If large dose for long period required: try alternate-day administration (side effects ↓ sometimes)
- **Slow, gradual cessation, otherwise *disease symptoms* may *reappear* or even intensify or serious *adrenal insufficiency* may appear**

Mineralocorticoid effects

- Na^+ reabsorption ↑
- K^+ & H^+ excretion ↑ (collecting tubule & duct)



Clinical uses of mineralocorticoids

- Replacement therapy in adrenal hypofunction (fludrocortisone)
  But! e.g. in Chrousos syndrome [genetic GR inactivation]: synthetic glucocorticoid w/o inherent MR activity

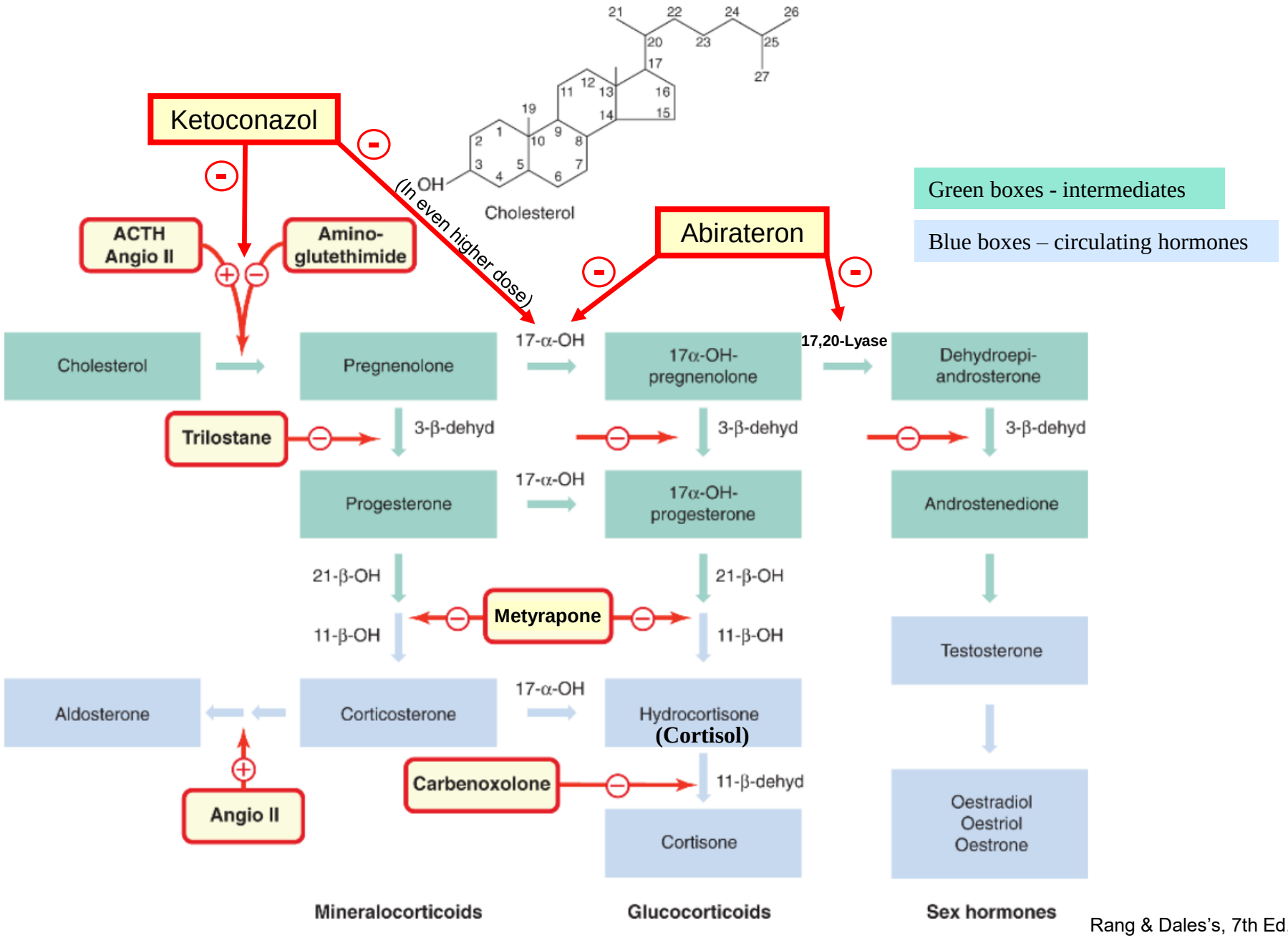
Clinical uses of mineralocorticoid antagonists

- Spironolactone: K^+- sparing diuretic (also an androgen- & progesteron R antagonist), primary aldosteronism (adrenal adenoma)
- Eplerenon: hypertension, heart failure (**no** gynecomastia and libido ↓)

Unwanted effects of the mineralocorticoids

- Edema
- Blood pressure ↑
- Hypokalemia (weakness, tetany), metabolic alkalosis
- Pro-inflammatory effect

Target sites of adrenocortical hormone synthesis inhibitors



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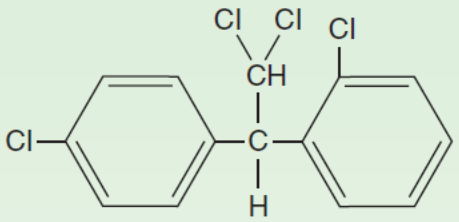
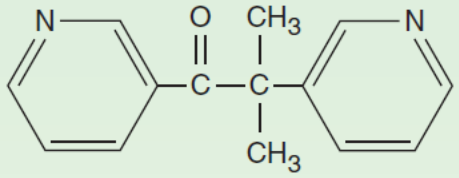
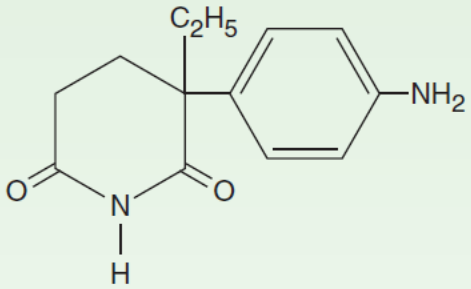
Some adrenocortical antagonists



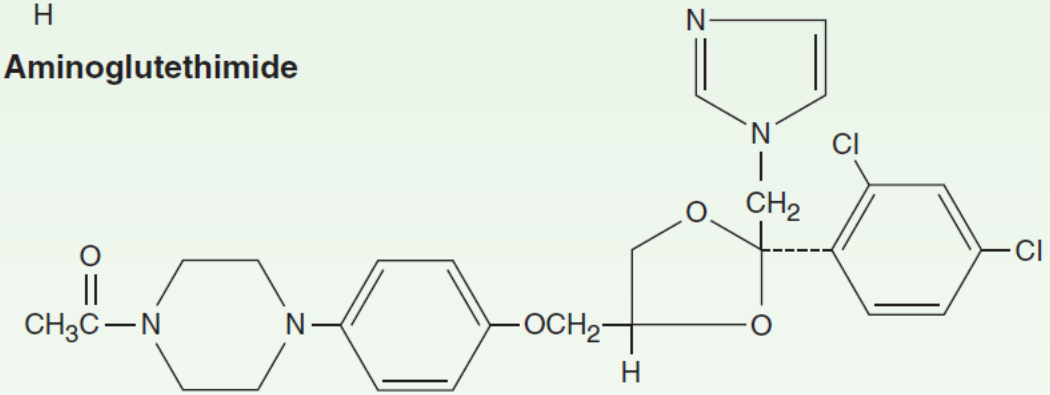
Mitotane



Metyrapone



Aminoglutethimide



Ketoconazole

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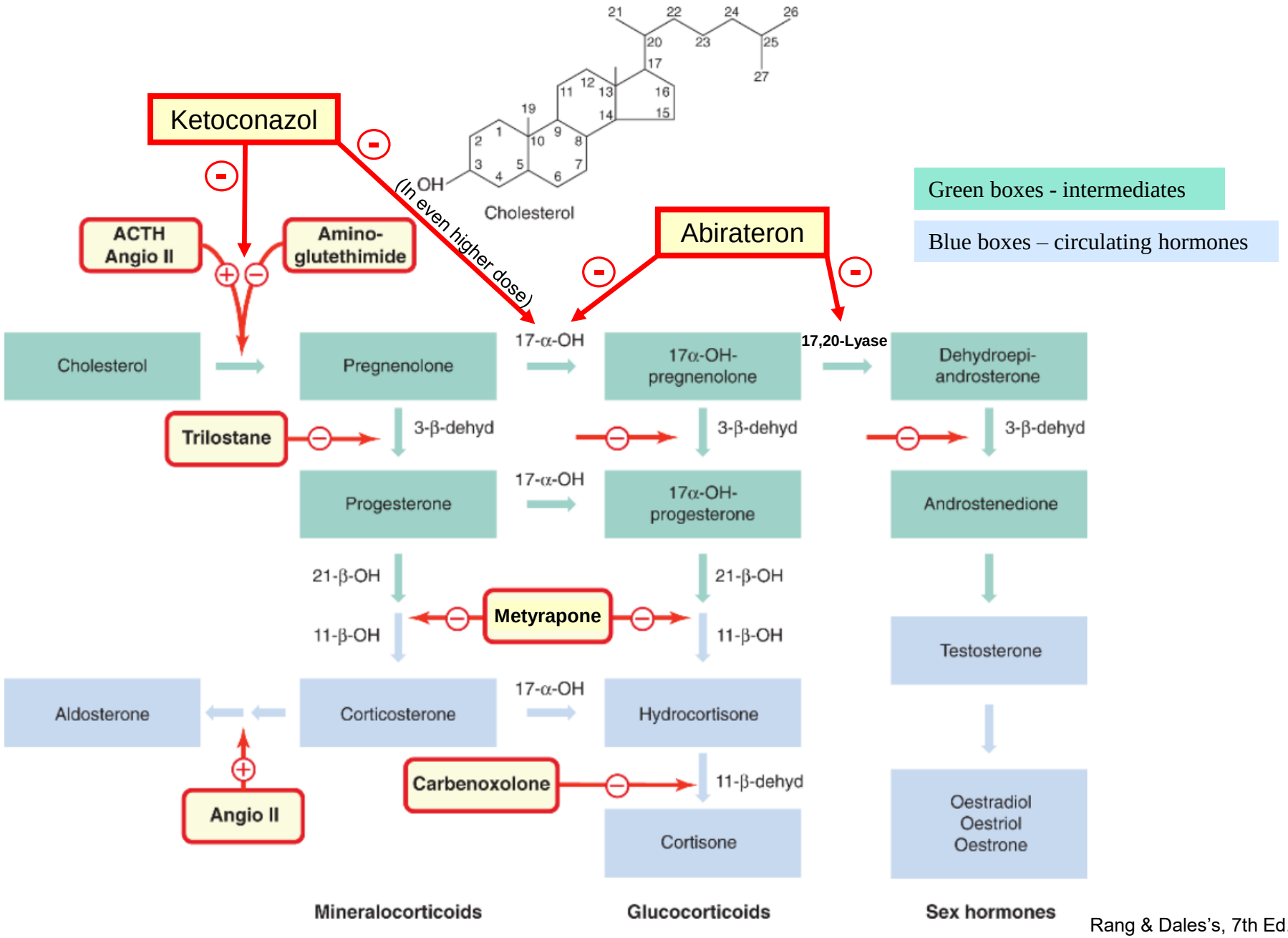
Adrenocortical antagonists & synthesis inhibitors

ACTH producing tumors & tumors of the adrenal gland
first line therapy: surgery, irradiation

- **Pasireotide** (somatostatin analog w/ SSTR5 selectivity): Cushing caused by ACTH producing *hypophysis adenoma*
- **Metyrapone** (inhibitor of 11 β-hydroxylase): also for diagnostic purposes; fairly quick action (some days)
- **Ketoconazole** (antifungal drug): in *Cushing* syndrome (liver toxicity)
- **Mitotane** (derivative of insecticide DDT): p.o. in *adrenal carcinoma* (cytotoxic for adrenal cortex → tumor mass ↓); fairly toxic
- **Aminogluthetimide**:
  - in conjunction with ketoconazole or metyrapone in *Cushing* syndrome *due to adrenocortical cancer* not responding to mitotane
  - in conjunction *with dexamethasone or hydrocortisone to reduce estrogen in breast cancer*
- **Trilostane**: comparable to aminogluthetimide
- **Etomidate** (inhibitor of 11 β-hydroxylase; i.v. anesthetic): in *severe, life-threatening Cushing* syndrome (quickest action)
- **Mifepristone** (SPRM): „chemical abortion”; w/ antiprogesteron & antiglucocorticoid activity → for *inoperable ectopic ACTH tumors* or *adrenal carcinoma*

Target sites of adrenocortical antagonists



Rang & Dales's, 7th Ed.