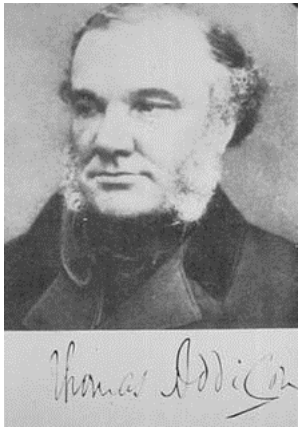
Pharmacology of adrenal steroids

History

- 1849 – Addison's disease
- 1856 – Adrenal glands essential for life
- 1930 – Cortex > medulla
- 1932 – Cushing's syndrome
- 1949 – Hench et al (Steroids in rheumatoid arthritis)
- 1952 – Aldosterone (Simpson and Tait)



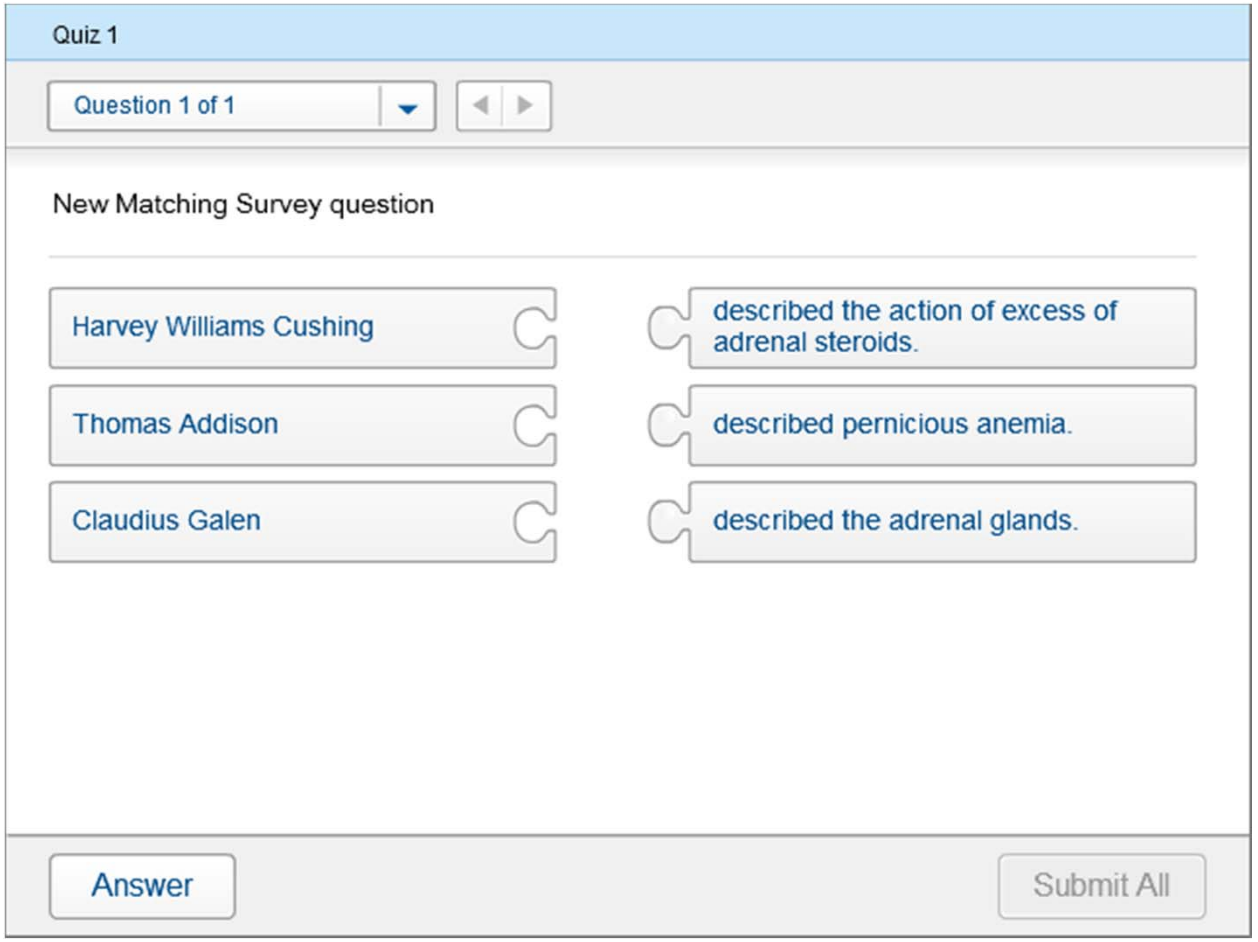
Thomas Addison (1793-1860)

Harvey Williams Cushing (1869-1939)

Notable Addisonian patients:

JFK
Charles Dickens
Osama bin Laden

Quiz



Click the **Quiz** button to edit this quiz

Layers of adrenal cortex

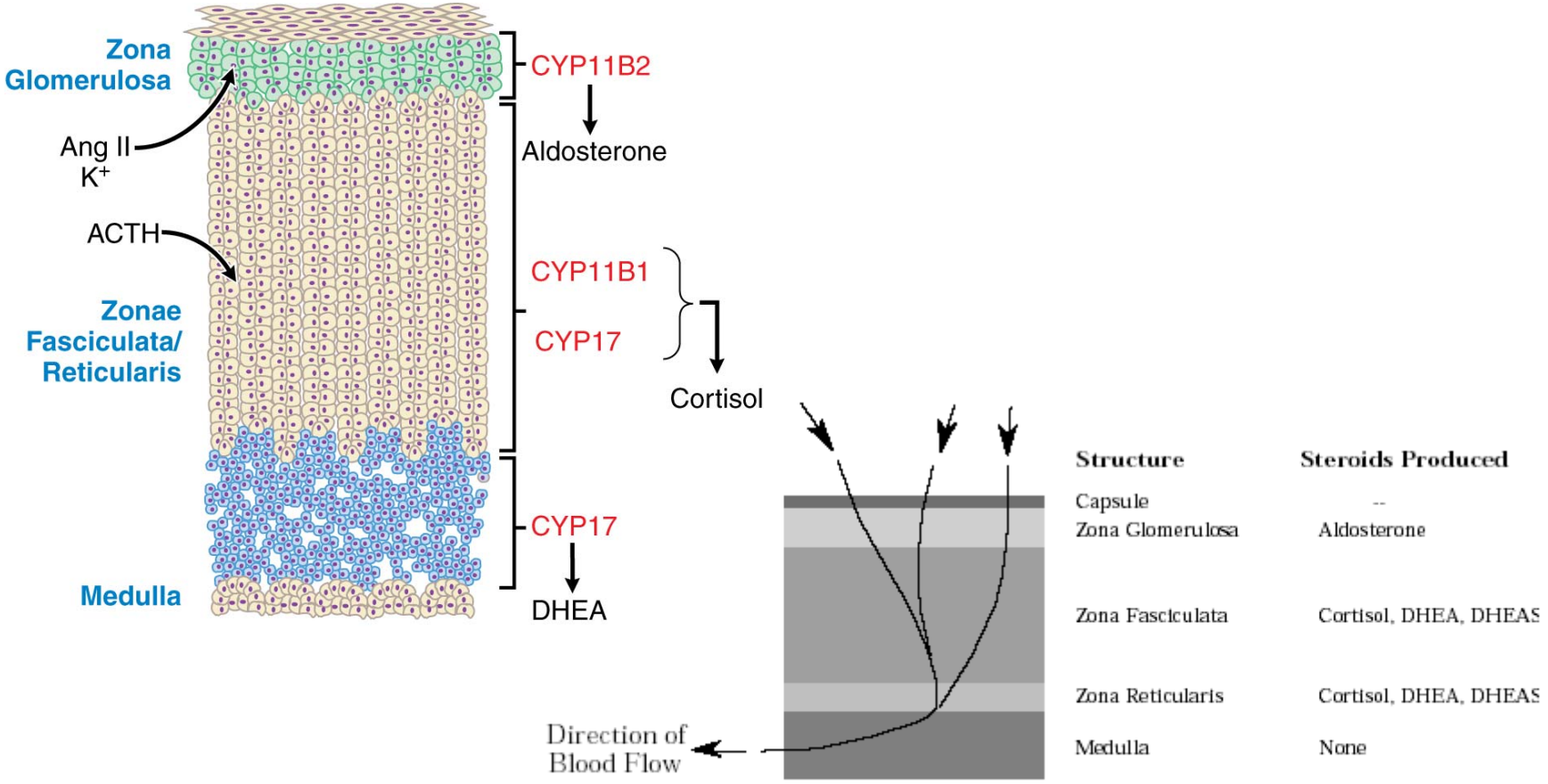
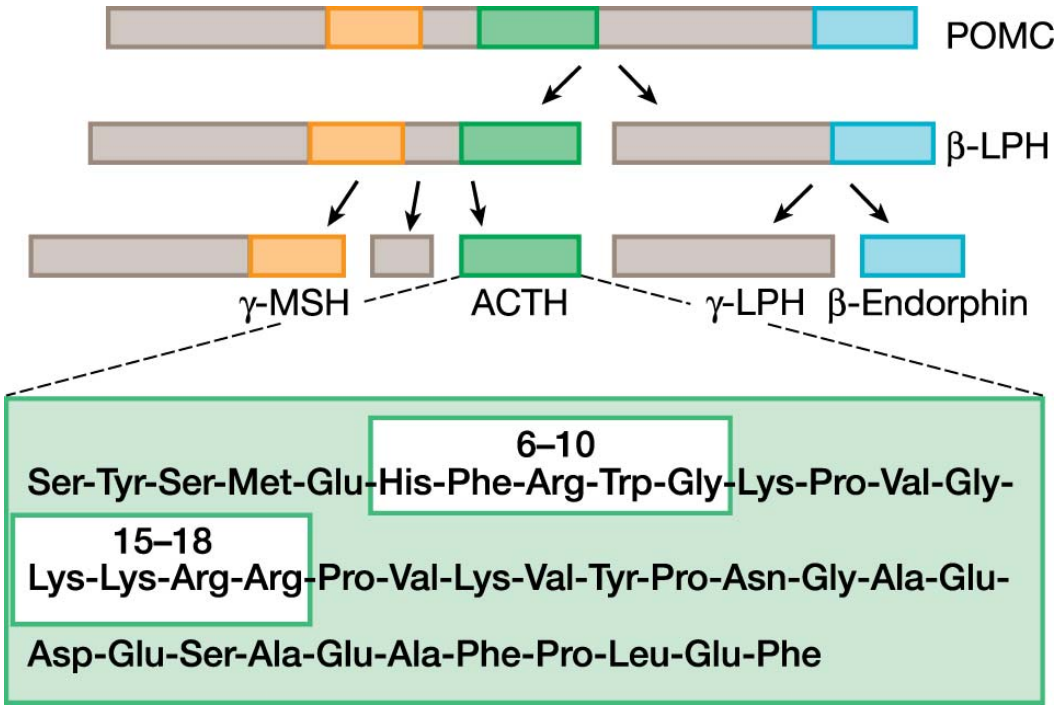
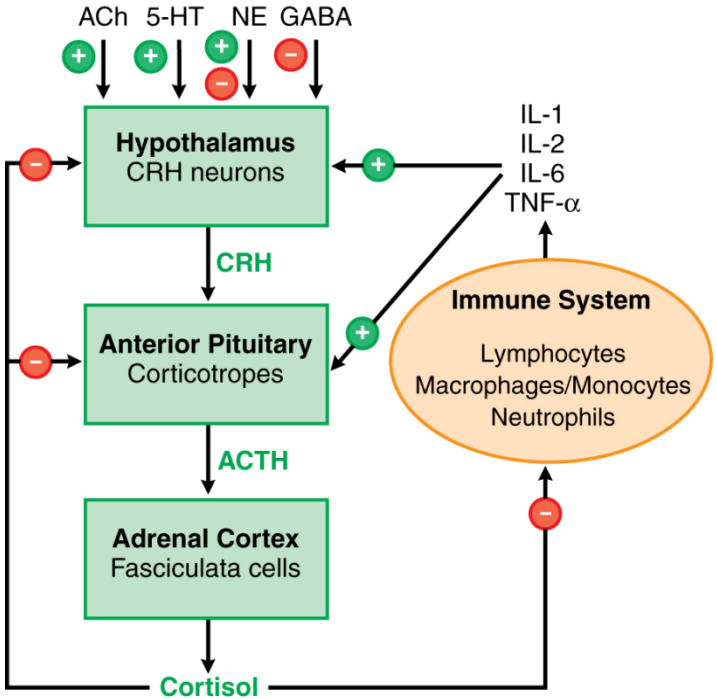


Figure 1. Cartoon of Adrenal Morphology.

POMC pathway



HPA axis


ACh
5-HT
NE
GABA
Hypothalamus
CRH neurons
CRH
Anterior Pituitary
Corticotropes
ACTH
Adrenal Cortex
Fasciculata cells
Cortisol
IL-1
IL-2
IL-6
TNF-α
Immune System
Lymphocytes
Macrophages/Monocytes
Neutrophils

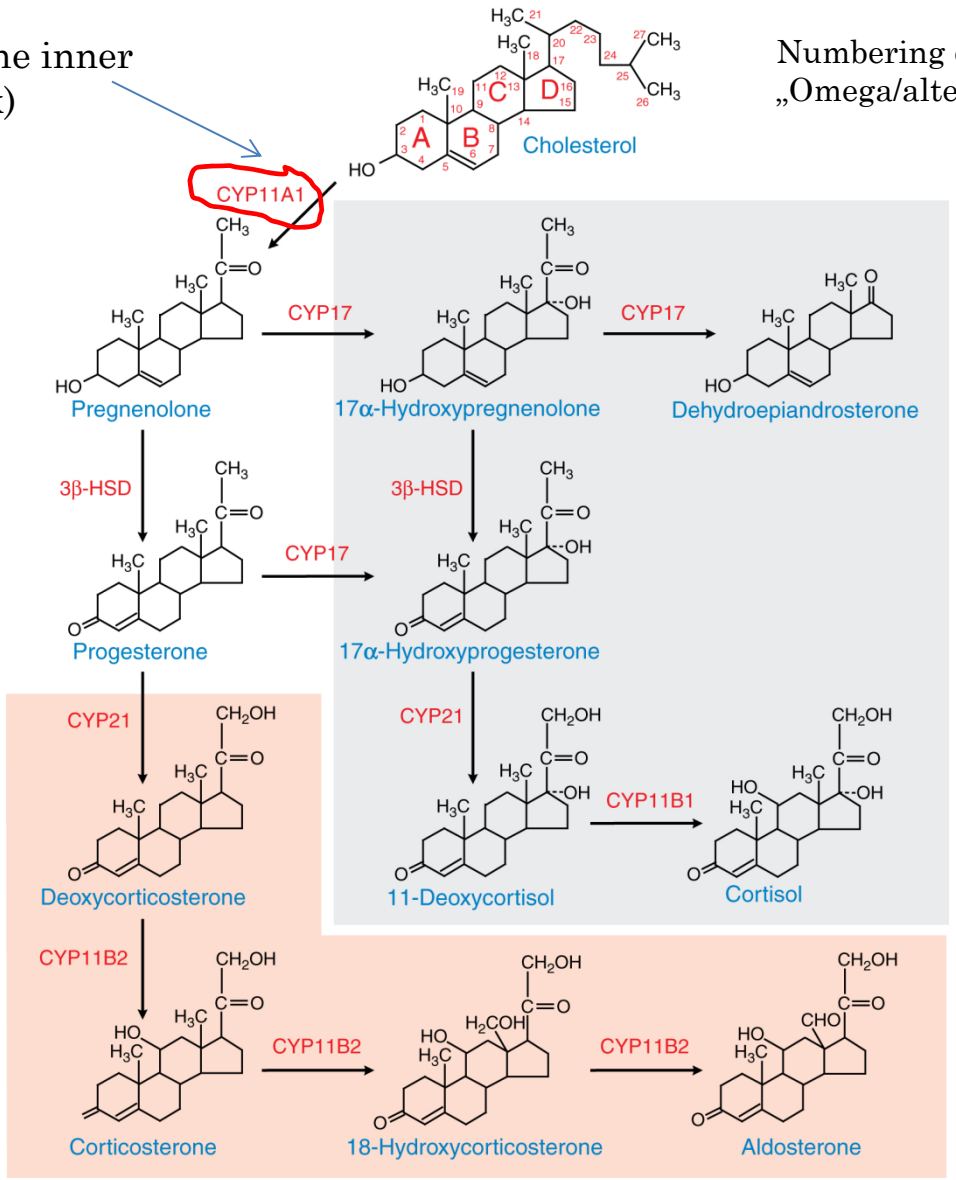
Pathways of corticosteroid biosynthesis

$P450_{SCC}$ (located in the inner mitochondrial matrix)

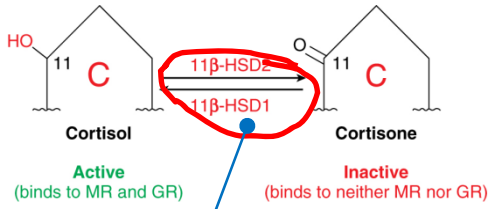
Numbering of steroid ring:
„Omega/alternating current”

Sources of cholesterol for steroidogenesis:

1. circulating cholesterol esters taken via the LDL receptor pathway.
2. Cholesterol esterase activation.
3. Increased de novo cholesterol biosynthesis.



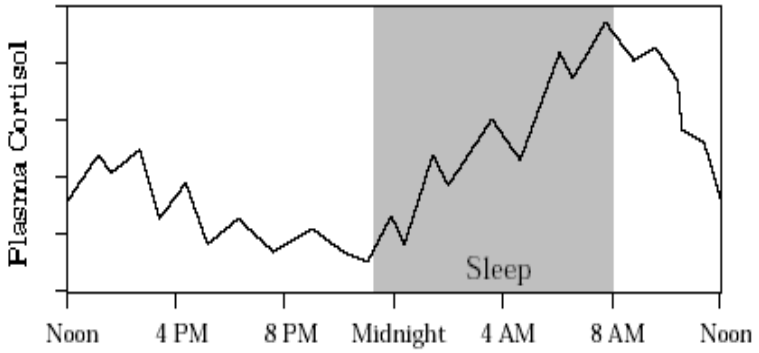
Grey:
Zona reticularis



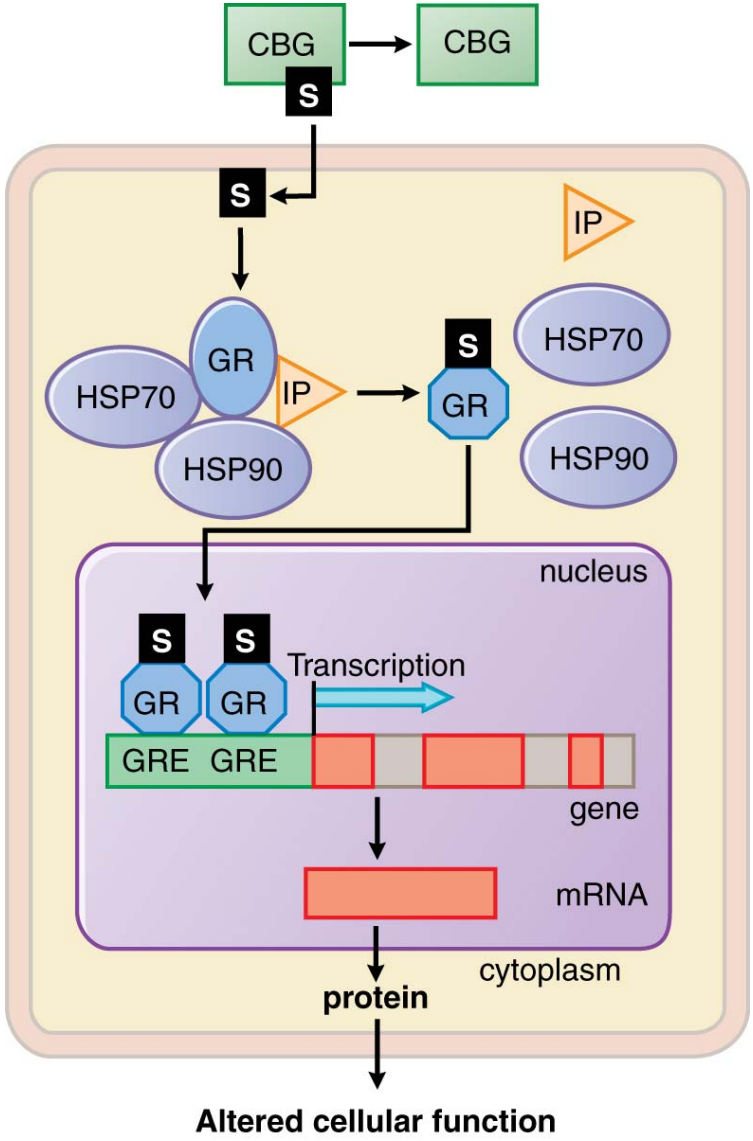
Enzyme defect
Glycyrrhizic acid
(Licorice)
(severe hypokalemia and hypertension)

Orange:
Zona glomerulosa

Basal secretions		
Group	**Hormone**	**Daily secretions**
Glucocorticoids	• Cortisol • Corticosterone	5 – 30 mg 2 – 5 mg
Mineralocorticoids	• Aldosterone • 11-deoxycorticosterone	5 – 150 mcg Trace
Sex Hormones •Androgen •Progestogen •Oestrogen	• DHEA • Progesterone • Oestradiol	15 – 30 mg 0.4 – 0.8 mg Trace

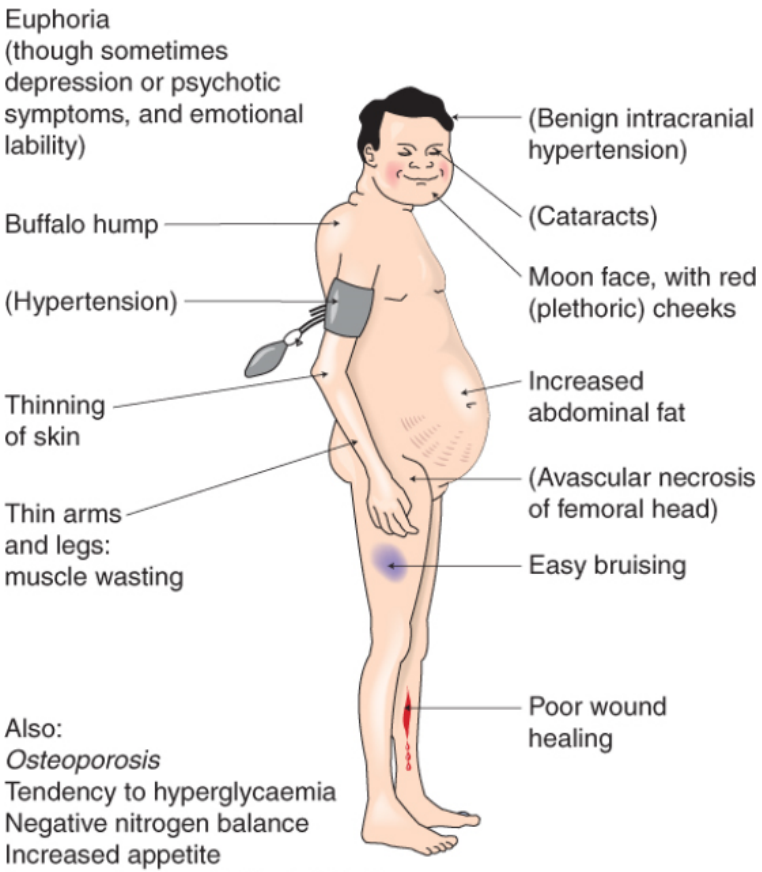


Glucocorticoid receptor ic. action



- GRE: GGTACAnnnTGTTCT

Cushing's syndrome



Pharmacological actions of glucocorticoids

Metabolic effects

1. Carbohydrates
2. Proteins
3. Lipids

Regulatory actions

1. Electrolyte & water
2. CVS
3. Skeletal muscle
4. CNS
5. GI
6. Blood
7. Anti-inflammatory
8. Immunosuppressant
9. Respiratory system
10. Growth & Cell Division
11. Calcium metabolism

Effect on carbohydrate and protein metabolism

- Negative nitrogen balance & hyperglycaemia
  - Gluconeogenesis ↑
    - Hepatic actions
    - Peripheral actions (mobilize AA & glucose and glycogen)
  - Peripheral utilization of glucose ↓
  - Glycogen deposition in the liver ↑
  - Increased protein catabolism and reduced anabolism

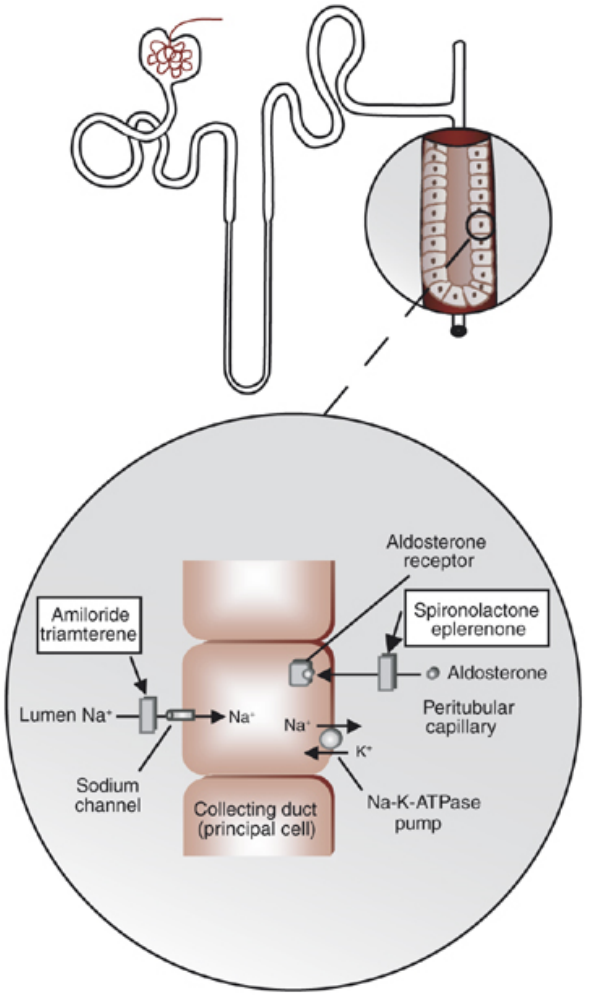
Protects glucose-dependent tissues (brain, heart) from starvation!

Effects on lipid metabolism

- **Redistribution** (centralization) of fat
  - Lean extremities
  - Moon face
  - Buffalo hump
- **Permissive** facilitation of
  - GH,
  - β-adrenergic receptor agonists
    → lipolysis induction and FFA elevation in plasma
- Promote adipokinetic agents activity (glucagon, growth hormone, adrenaline, thyroxine)

Electrolyte and water balance

- Distal tubules, collecting ducts
  - Na^+ retention
  - Loss of K^+ and H^+ → hypertony



Hypoaldosteronism: Addison's disease
Primary aldosteronism:
Pseudohypoladosteronism: Gordon's sy.
Pseudoaldosteronism: Liddle's sy.

Actions on CVS

- Maintain tone of arterioles
- Myocardial contractility
- Restrict capillary permeability
- Development of cardiac fibrosis (hyperaldosteronism)
- Na^+ sensitizes blood vessels to the action of catecholamines & angiotensin
  - Glucocorticoids increase the expression of adrenergic receptors in vascular wall
- →→ HYPERTENSION (atherosclerosis, cerebral hemorrhage, stroke, hypertensive cardiomyopathy)

Actions on skeletal muscles

- Permissive concentrations are required for normal function
  - Addison's disease (weakness and fatigue)
  - **Excessive amounts** also impair muscle function (skeletal muscle wasting → *steroid myopathy*)

Jaimee Addison

Actions on CNS

- Direct effects:
  - Mood
  - Behaviour
  - Brain excitability
- Indirect effects:
  - maintain glucose, circulation and electrolyte balance

Addison's disease: apathy, depression, irritability

Chr. glucocorticoid administration:
mood elevation, euphoria, insomnia, increased motor activity, anxiety and depression, psychosis.

Actions on GI

- Promote and aggravate peptic ulcers
- Increase HCl and pepsin secretion
- Reduce immune response to H. pylori
- Inhibits COX → PGE_2↓

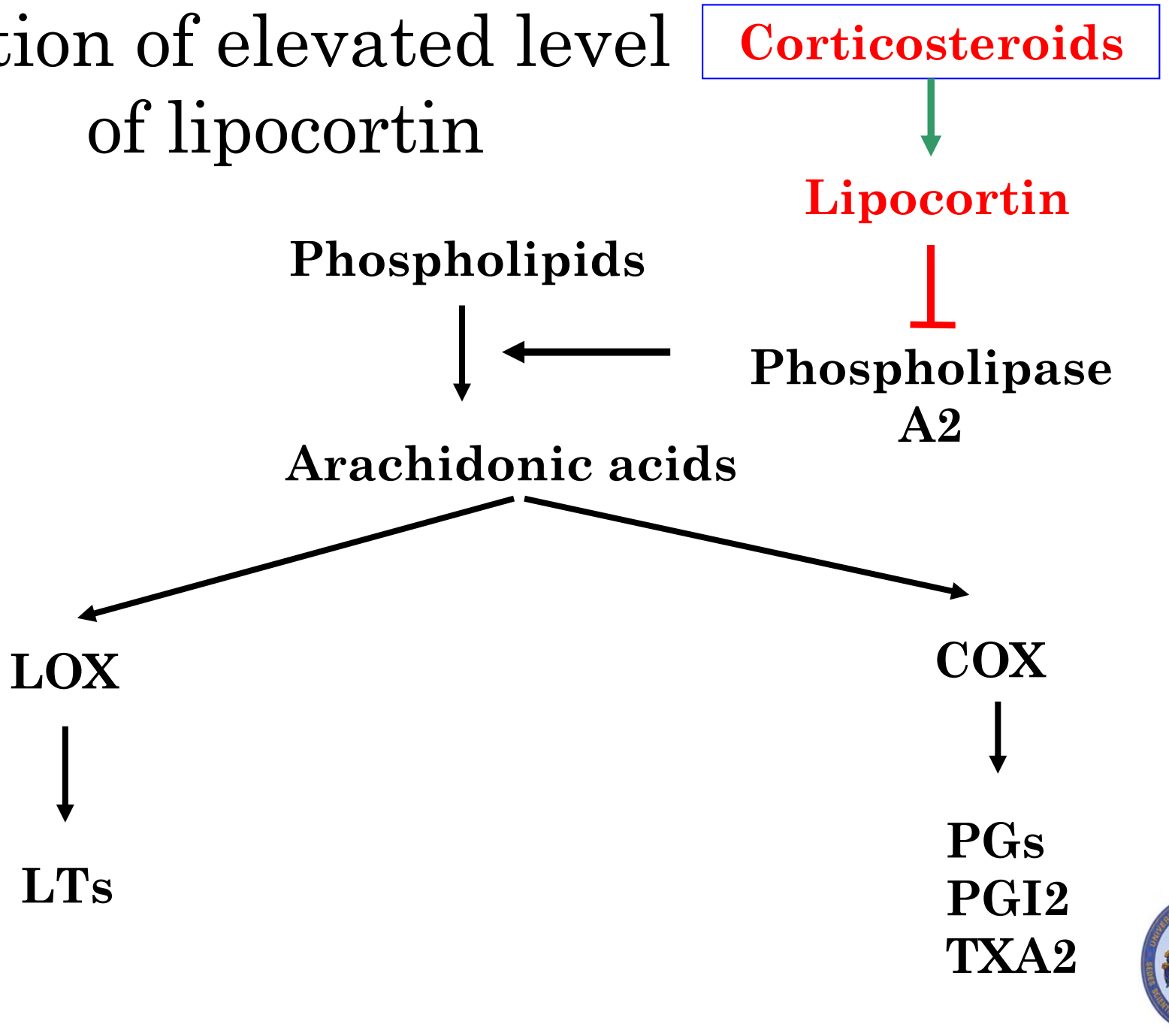
Actions on formed elements of blood

- RBCs
  - Hb & RBC content ↑
- WBCs
  - Lymphocytes, eosinophils, monocytes, basophils ↓
  - Polymorphonuclear cells ↑

Anti-inflammatory effect

- ***Reduction*** in:
  - Recruitment of WBCs, monocyte-macrophage
  - Chemotactic substances
  - ELAM-1 & ICAM-1 in endothelial cells
  - TNF from phagocytic cells
  - IL1 from monocyte-macrophage
  - Formation of Plasminogen Activator (PA)
  - Fibroblastic activity
  - Expression of cyclooxygenase-2
- ***Elevation*** in:
  - Lipocortin

Action of elevated level of lipocortin



Antiallergic and immunosuppressive effects

- Suppresses all types of hypersensitivity and allergic reactions. Can reduce the inflammation in response to radiant, mechanical, chemical, infectious and immunological stimuli. Do not cure the disease!!!
- In transplant rejection:
  - antigen expression from grafted tissues ↓
  - delay revascularization
  - sensitization of T lymphocytes ↓

Effects on growth and cell division

- Delay the process of wound healing
- Retard the growth of children
  - Inhibits cell division or synthesis of DNA

Effect on Ca^{++} homeostasis

- Renal excretion ↑
- Intestinal absorption ↓
- Loss of calcium from spongy bones (ribs, vertebrae etc.)

PK

- A
  - All are rapidly and completely absorbed (except DOCA)
- D
  - Transcortin 75%
  - Albumin 5%
  - Free form 20%
- M
  - liver enzymes, conjugation
  - $t_{1/2}$ of cortisol is around 1.5 h
- E
  - by urine
  - partly excreted as 17-ketosteroids

Available preparations

- Glucocorticoids
  - Short acting
  - Intermediate acting
  - Long acting
- Mineralocorticoids
- Inhalant steroids
- Topical steroids

Some commonly used natural and synthetic corticosteroids for general use

Agent	Activity[1]			Equivalent Oral Dose (mg)	Forms Available
	Anti-Inflammatory	Topical	Salt-Retaining		
Short- to medium-acting glucocorticoids ($t_{1/2}$ < 12h)					
Hydrocortisone (cortisol)	1	1	1	20	Oral, injectable, topical
Cortisone	0.8	0	0.8	25	Oral
Prednisone	4	0	0.3	5	Oral
Prednisolone	5	4	0.3	5	Oral, injectable
Methylprednisolone	5	5	0	4	Oral, injectable
Meprednisone[2]	5		0	4	Oral, injectable
Intermediate-acting glucocorticoids ($t_{1/2}$=12-36h)					
Triamcinolone	5	5[3]	0	4	Oral, injectable, topical
Paramethasone[2]	10		0	2	Oral, injectable
Fluprednisolone[2]	15	7	0	1.5	Oral
Long-acting glucocorticoids (t1/2 > 36h)					
Betamethasone	25-40	10	0	0.6	Oral, injectable, topical
Dexamethasone	30	10	0	0.75	Oral, injectable, topical
Mineralocorticoids					
Fludrocortisone	10	0	250	2	Oral
Desoxycorticosterone acetate[2]	0	0	20		Injectable, pellets

[1]Potency relative to hydrocortisone.

[2]Outside USA.

[3]Acetonide: Up to 100.

Mineralocorticoid preparations

Drug	Anti-inflammatory	Salt retaining	Preapartions & dose
Fludrocortisone	**10**	**150**	**100 mcg tab.**
DOCA	**0**	**100**	**2.5 mg sublingual**
Aldosterone	**0.3**	**3000**	**Not used clinically**

Inhalant Steroids in the treatment of Bronchial Asthma

Beclomethasone dipropionate	**50,100,200 mcg/md inhaler** **100, 200, 400 mcg Rotacaps**
Fluticasone propionate	**25, 50 mcg/md inhaler** **25,50,125/md MDI** **50, 100, 250 mcg Rotacaps**
Budesonide	**100,200 mcg/md inhaler** **0.25, 0.5 mg/ml respules**

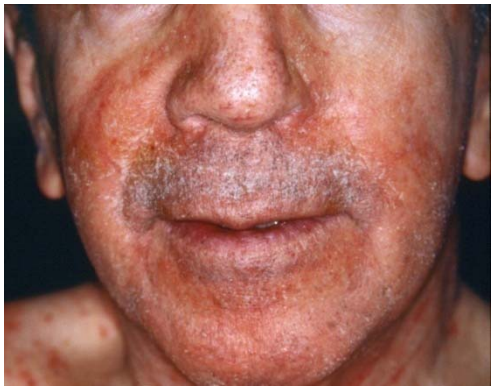
Topical steroid preparations

Drug	Topical preparation	Potency
Beclomethasone dipropionate	0.025 % cream	Potent
Betamethasone benzoate & B. valerate	0.025 % cream, ointment 0.12 % cream, ointment	Potent
Clobetasol propionate	0.05 % cream	Potent
Halcinonide	0.1 cream	Potent
Triamcinolone actonide	0.1 % ointment	Potent
Fluocinolone actonide	0.025% ointment	Moderate
Mometasone	0.1 % cream, ointment	Moderate
Fluticasone	0.05 % cream	Moderate
Hydrocortisone acetate	2.5 % ointment	Moderate
Hydrocortisone acetate	0.1 – 1.0% ointment	Mild

Indications for topical steroids

- Atopic eczema
- Psoriasis of face
- Allergic contact dermatitis
- Primary irritant dermatitis
- Lichen simplex
- Seborrheic dermatitis
- Varicose eczema
- Slow effect on:
  - Psoriasis of palm, sole, elbow and knee
  - Cystic acne
  - Hypertrophied scars
  - Alopecia areata
  - Discoid LE
  - Keloids
  - Lichen planus

Contact dermatitis

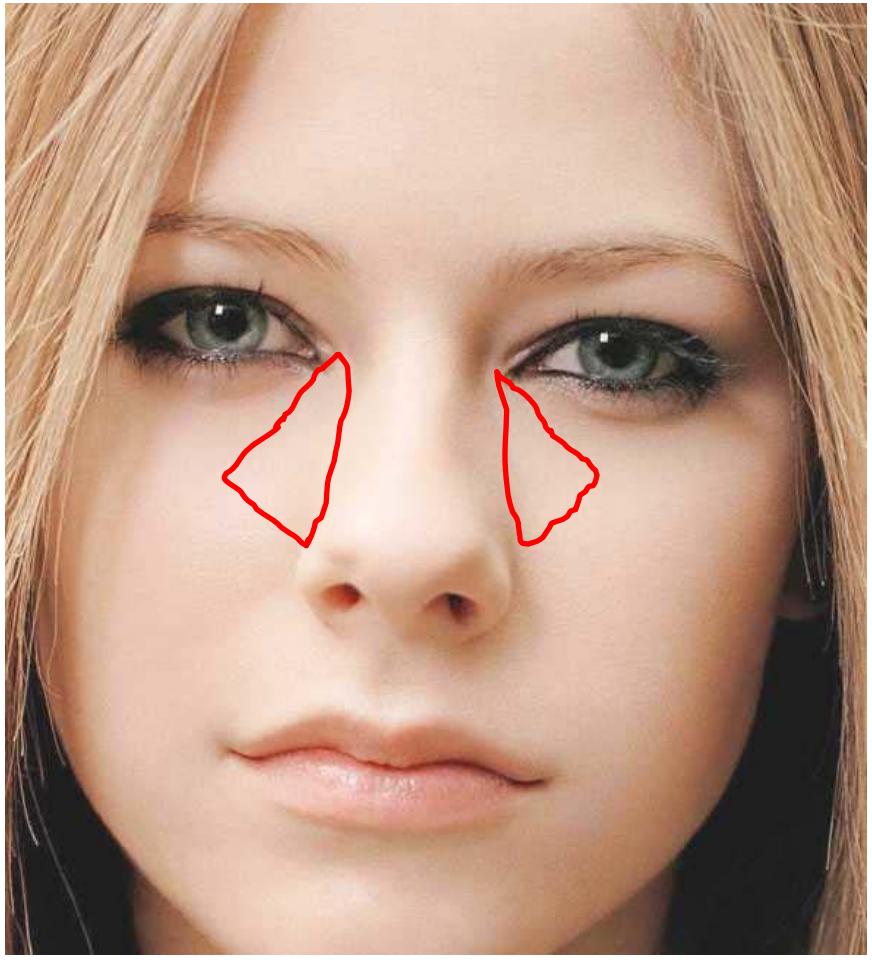


Seborrheic dermatitis of the face. Courtesy of Dirk M. Elston, MD.

Indications for topical glucocorticoids and antimicrobial combinations

- Furunculosis
- Impetigo
- Secondary infected dermatoses
- Otitis externa
- Napkin rash
- Intertriginous eruptions

Dangerous territory for topical steroid application



Possible thrombosis of sinus cavernosus

Side effects of glucocorticoids 1.

- Fluid and electrolyte: Hypokalemic alkalosis, edema and hypertension
- Immune responses: Increased susceptibility to infections (reactivation of tuberculosis)
- Possible risk of peptic ulcers: PG synthesis inhibition and suppressed immune response against Helicobacter pylori.
- Myopathy: weakness. Respiratory muscle in asthma and chronic obstructive pulmonary disease. After discontinuation recovery is slow and incomplete.
- Behavioral changes: Nervousness, insomnia, changes in mood, psychosis.
- Cataracts: The development is related to the dosage and the duration of therapy. Children appear to be at risk. Cessation of therapy does not lead to complete resolution of opacities. Slit-lamp examination to detect glucocorticoid-induced posterior subcapsular cataracts.

Side effects of glucocorticoids 2.

- **Osteoporosis:**
  Inhibits the Ca^{++} absorbtion from the intestine, increase Ca^{++} excretion by the kidney → decreased Ca^{++} level → PTH induction → bone resorption.
  Treatment: 1.5 g of Ca^{++} and 400 IU/day vitamin D.
- **Osteonecrosis:** Aseptic necrosis.
- **Growth retardation**

Side effects of glucocorticoids 3.

- Precipitate diabetes mellitus
- Elevate the TG level in the plasma, LDL/HDL ratio is worsened
- Increase the intraocular pressure: glaucoma!
- Candidiasis: inhalation of steroids for the treatment of asthma, dysphonia/aphonia
- Atrophy: in the case of topical administration
- Withdrawal of therapy: cessation of therapy: iatrogenic acute adrenal insufficiency; withdrawal syndrome: fever, myalgias, arthralgias

Steroid withdrawal

- Less than 1 week: withdrawal in few steps
  - Rapid withdrawal: 50% reduction of dose every day
  - Slow withdrawal: 2.5 – 5 mg prednisolone reduced at an interval of 2-3 days

- Longer period and high dose:
  - Halve the dose weekly until 25 mg prednisolone or equivalent is reached
  - Later reduce by about 1 mg every 3-7 days.

Longer the duration of therapy, slower the withdrawal!
The recovery may take months or up to 2 years!

Contraindications of corticosteroid administration

- Infections
- Peptic ulcer
- Diabetes mellitus
- Hypertension
- Psychosis
- Osteoporosis
- Glaucoma
- Pregnancy

Therapeutic uses of glucocorticoids 1.

- Replacement therapy in acute adrenal insufficiency: water , sodium chloride, glucose, cortisol. CVP should be measured. Iv. bolus of hydrocortisone (100 mg), then infusion of 100 mg/8 hours, then 25mg/6-8 hours im.
- Chronic primary adrenal insufficiency, secondary adrenal insufficiency, congenital adrenal hyperplasia
- Therapeutic uses in nonendocrine disease:
  - Rheumatic disorders (SLE, Wegener's granulomatosis, polyarteritis nodosa, giant cell arteritis (prednison: 1 mg/kg per day)
  - Renal diseases (nephrotic sy., minimal change)
  - Allergic disease (hay fever, serum sickness, urticaria, contact dermatitis, bee stings, drug reactions, angioneurotic edema) methylprednisolon 125 mg/6 hours iv.
  - Bronchial asthma: budesonide
  - Ocular diseases: in ocular inflammatory diseases (anterior uveitis, after glaucoma filtering (decreasing fibroblast infiltration))

Therapeutic uses of glucocorticoids 2.

- Skin diseases: treatment of inflammatory dermatoses. 1% hydrocortisone ointment. 100 mg/day prednison life-saving in pemphigus
- GI diseases: (in the treatment of chronic ulcerative colitis and Crohn's disease)
- Hepatic diseases: controversial
- Malignancies: ALL and lymphoma
- Cerebral edema: parasite and neoplasm induced
- Sarcoidosis: 1 mg/kg /day prednison
- Thrombocytopenia: 0.5 mg/kg prednisone
- Autoimmune destruction of erythrocytes
- Organ transplantation: high doses of prednisone (50-100 mg) in conbination with immunosuppressant agent.
- Stroke and spinal cord injury: after acute spinal cord injury treated within 8 hours of injury (30 mg/kg initially then infusion of 5.4 mg/kg/hour for 23 hours

Glucocorticoid antagonists

- **Mitotane**: structure similar to DDT, used in inoperable adrenal cancer
- **Metyrapone**: inhibit 11 β-hydroxylase
- **Aminoglutethamide**: inhibit conversion of cholesterol to pregnolone, medical adrenelectomy
- **Trilostane**: inhibit conversion of pregnolone to progesterone; used in Cushing's syndrome
- **Ketoconazole**: anti-fungal, inhibit CYP450 enzymes, inhibit steroid synthesis in adrenal cortex and testis; used in Cushing's syndrome and prostate cc.
- **Mifepristone**: glucocorticoid receptor antagonist; anti-progesterone, used in Cushing's syndrome