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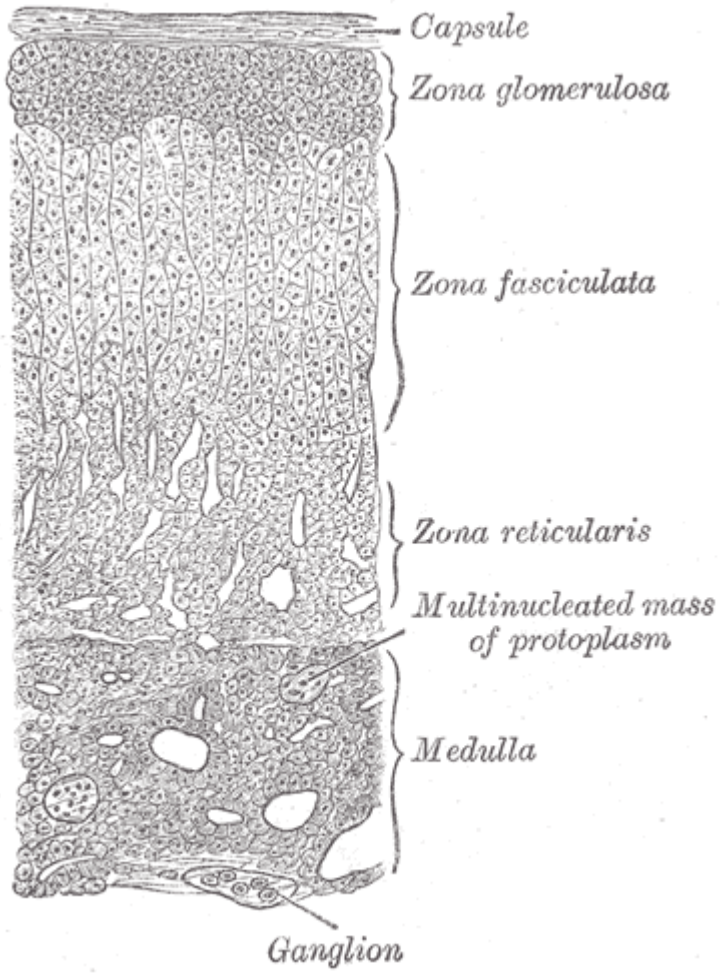
Glucocorticoids

Department of Pharmacology MU

Histology of the adrenal cortex

Three concentric zones comprise 80-90%



Zona glomerulosa

Zona fasiculata

Zona reticularis

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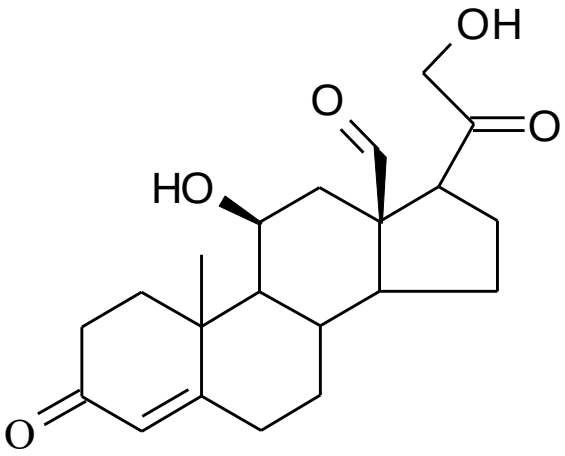
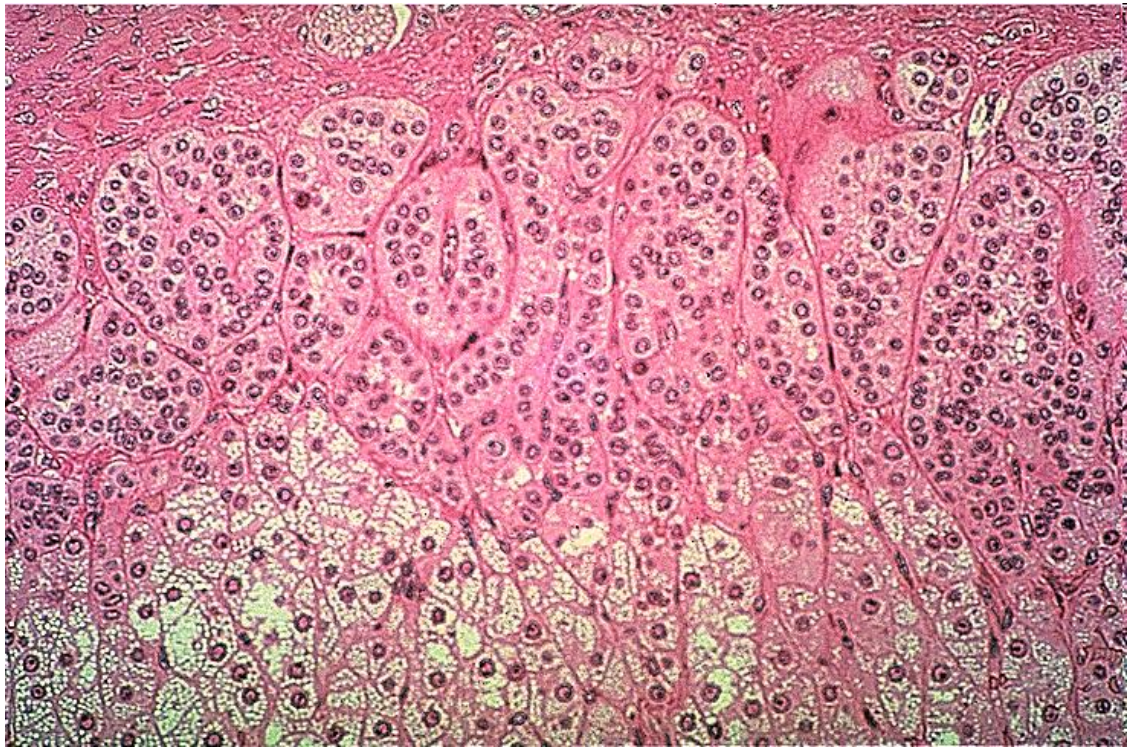
Zona glomerulosa (outer zone)

producing mineralcorticoids (aldosterone)





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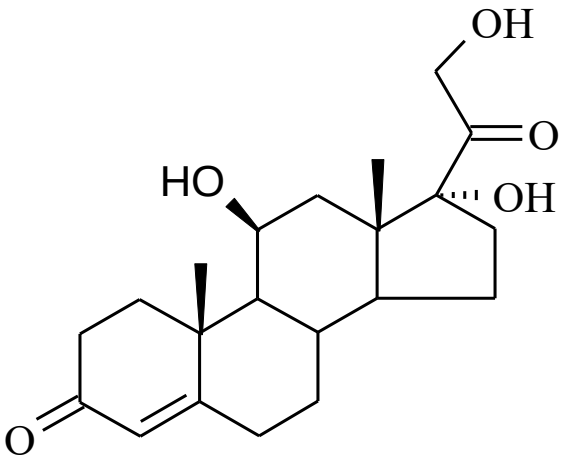
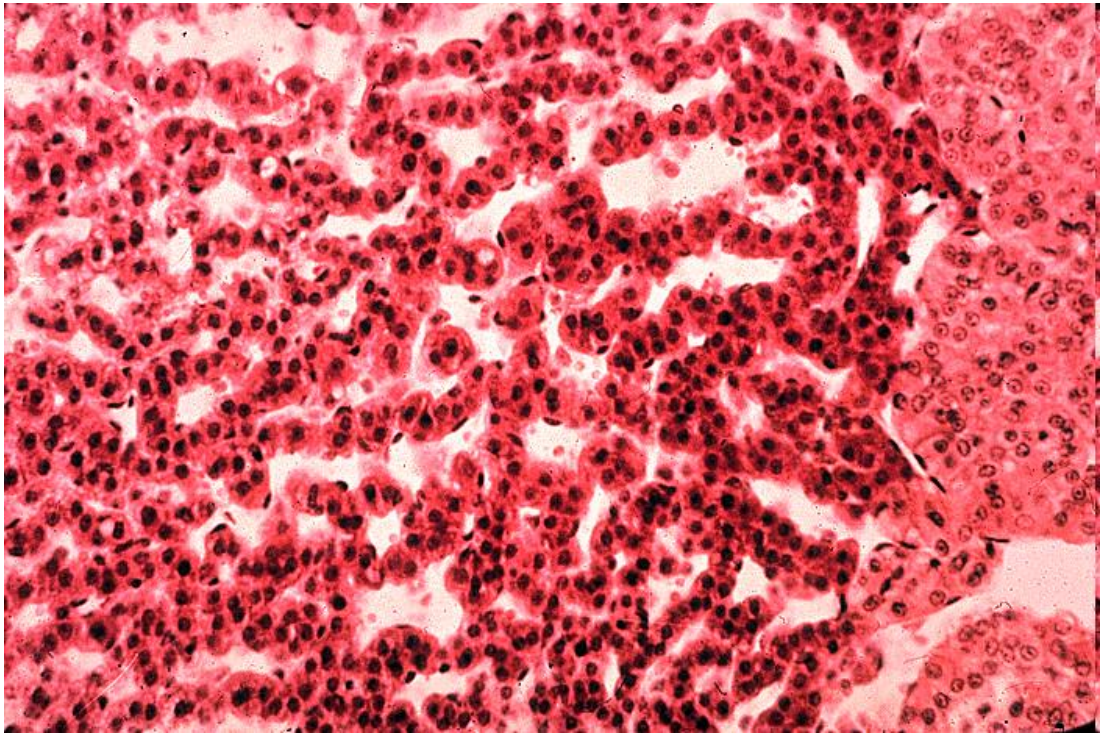
Zona fasiculata (middle zone)

producing glucocorticoids (cortisol)





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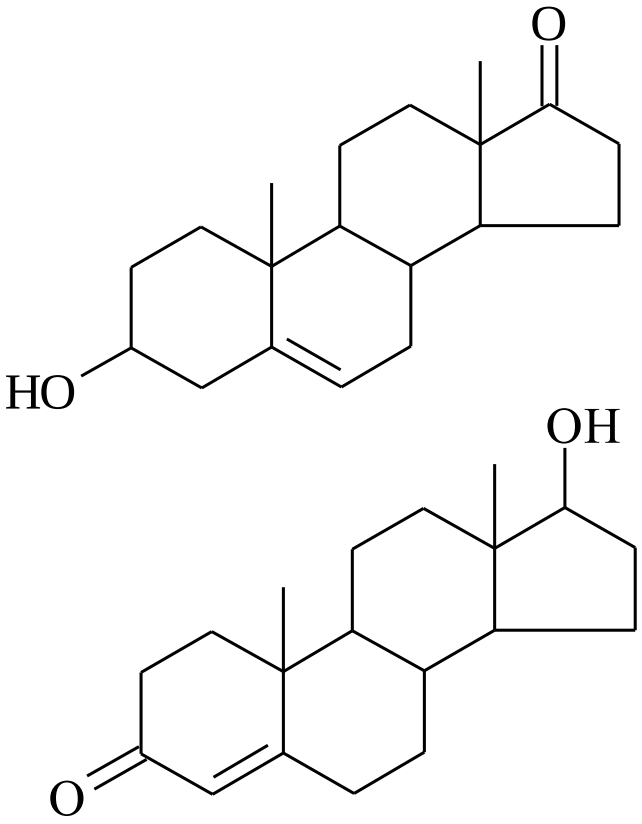
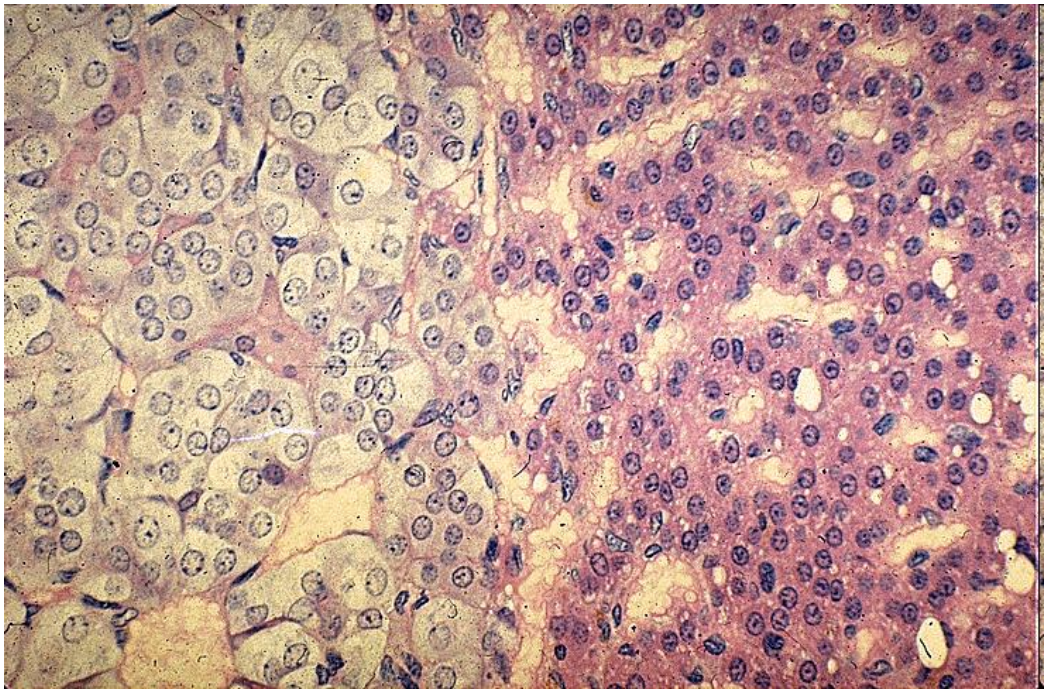
Zona reticularis (inner zone)

producing sex steroids
(dehydroepiandrosterone (DHEA) : androgens)





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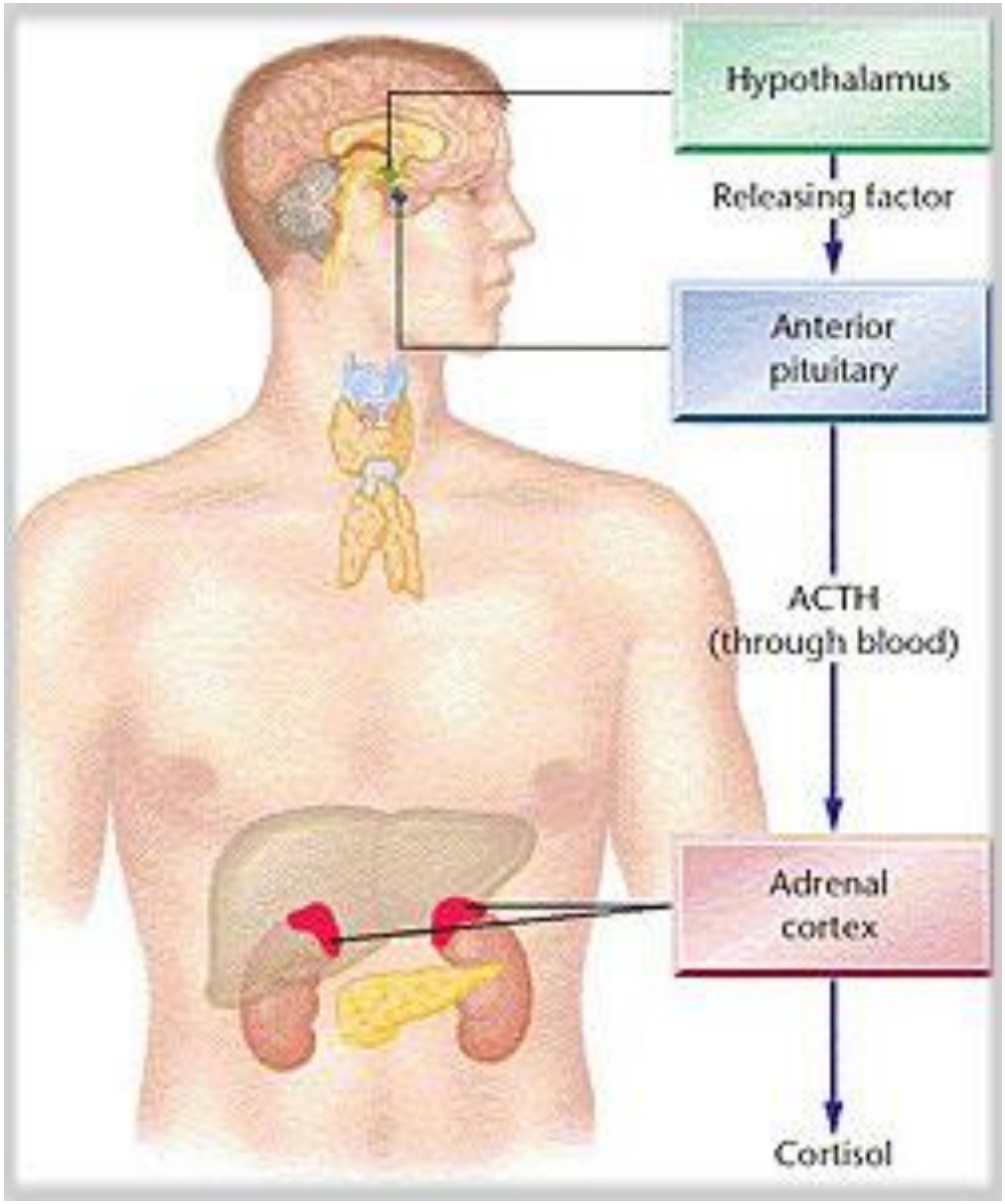
Hypothalamus
Releasing factor
Anterior pituitary
ACTH (through blood)
Adrenal cortex
Cortisol

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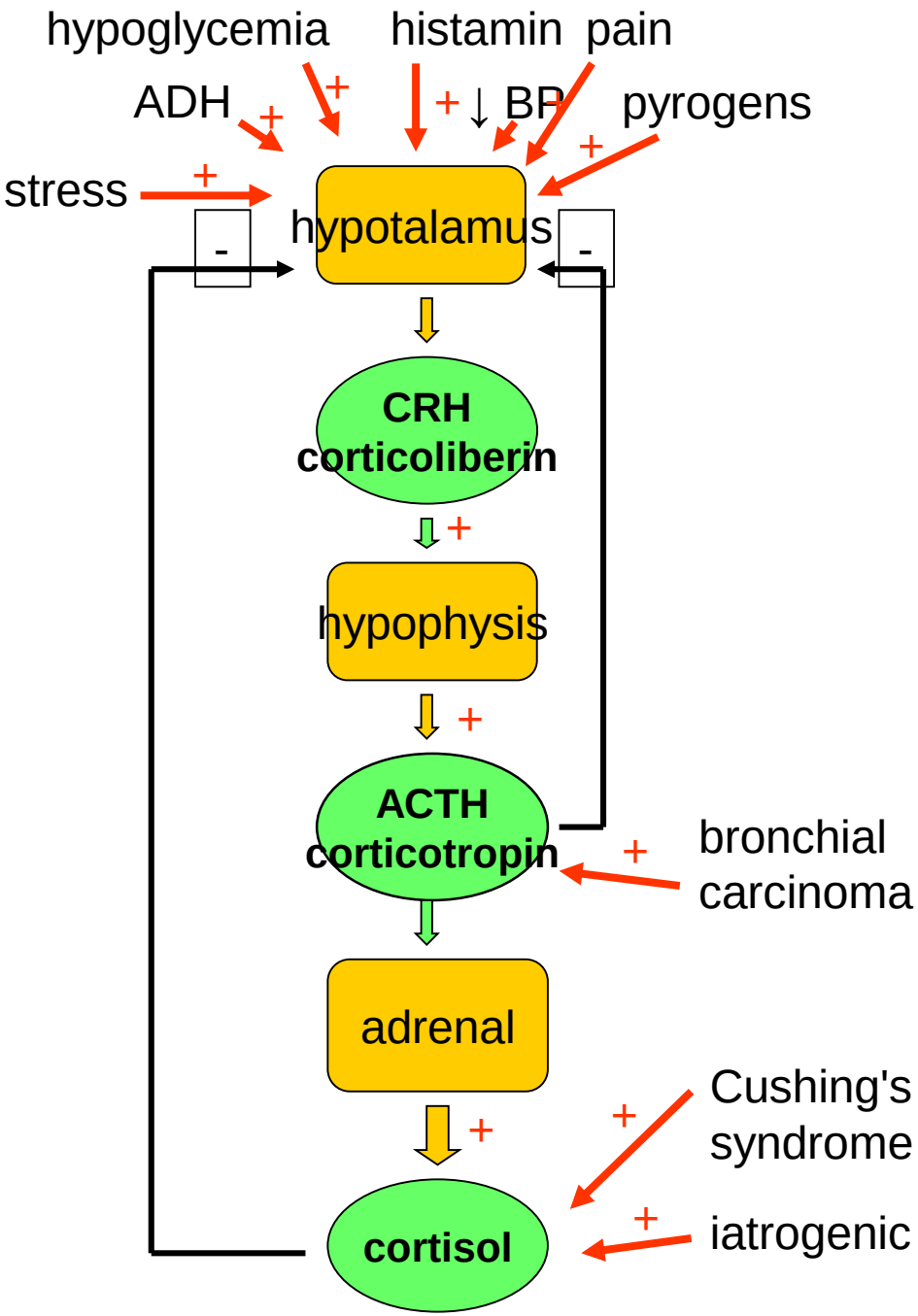
hypoglycemia
histamin
pain
ADH
+
+
+
↓ BP
pyrogens
+
stress
+
hypotalamus
-
-
CRH
corticoliberin
+
hypophysis
+
ACTH
corticotropin
+
bronchial
carcinoma
adrenal
+
Cushing's
syndrome
+
cortisol
+
iatrogenic

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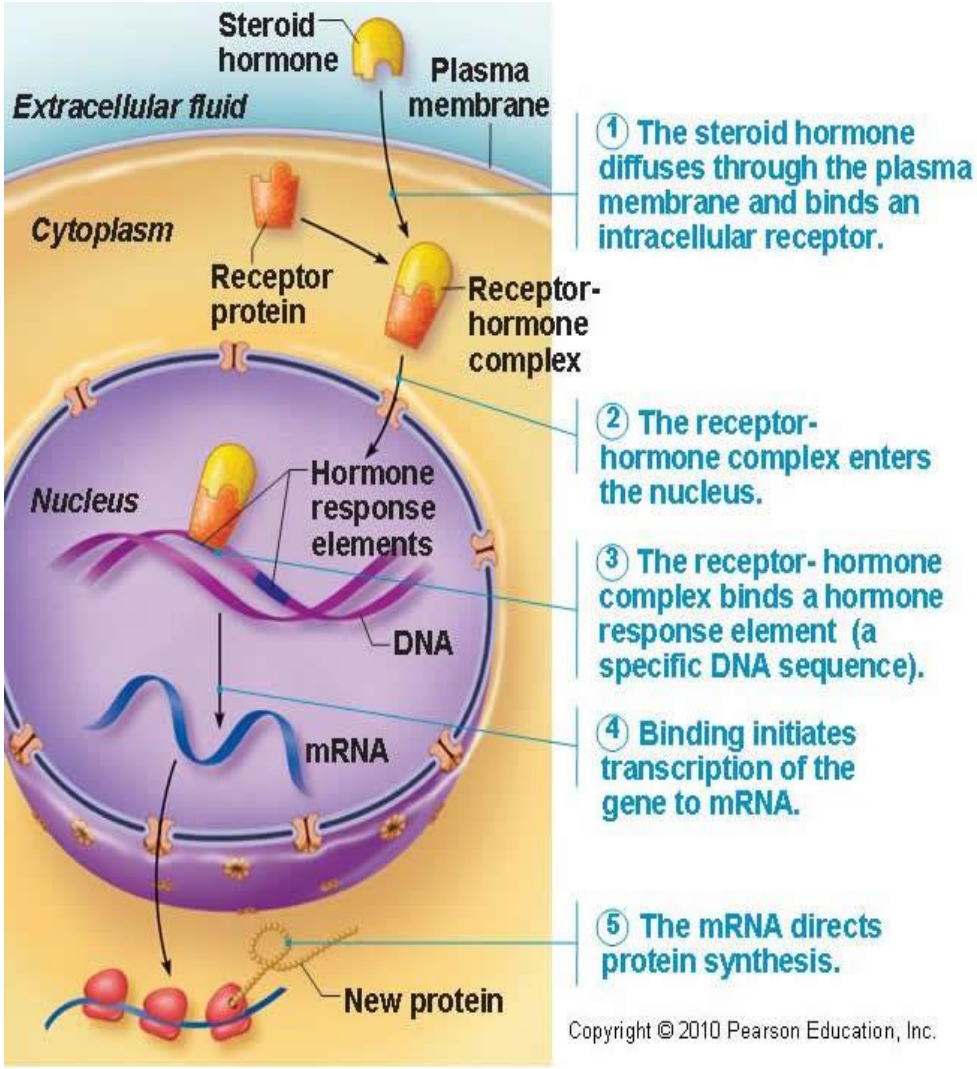
Mechanism of glucocorticoid action on cellular level

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

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

The result is increased transcription of genes either inducing or inhibiting synthesis of other proteins

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



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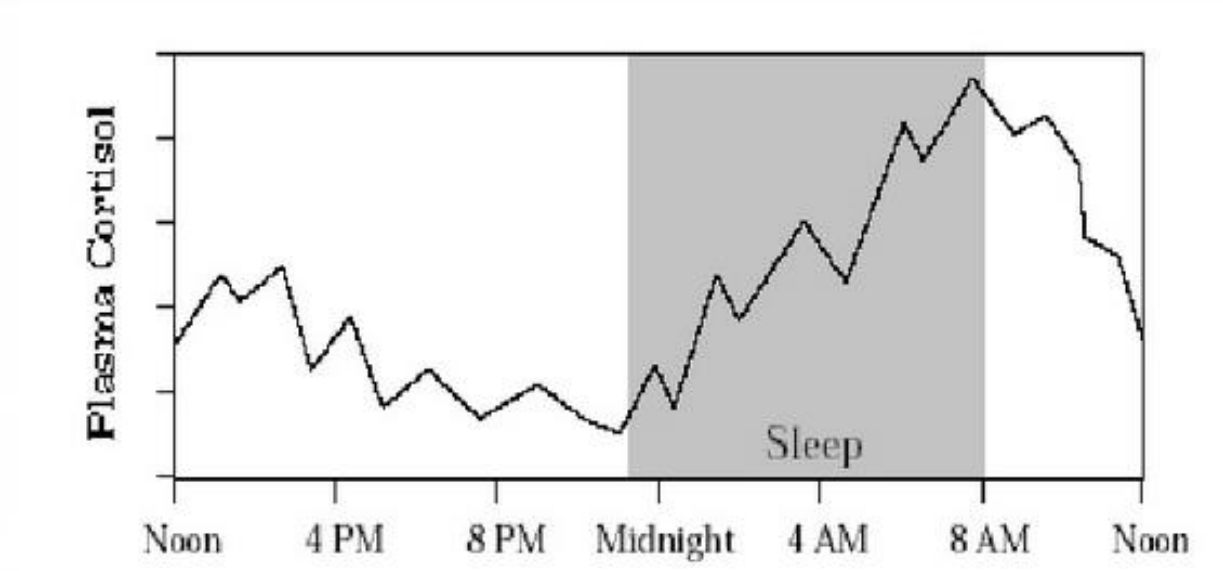
Endogenous secretion:

Quiescent : 25 - 30 mg /24
In stress: 10-fold
Not stored – rate of synth. = rate of release
Maximal: 6-8 A.M.



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Pharmacokinetics

- Bound to CBG and albumin
- Intensively metabolised
- Metabolites excerted in 72 h
- Synthetic ones have longer t_{half}
- (prednison – prednisolon)

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Physiological effects of Glucocorticoids

1. Influences on intermediary metabolism
2. Permissive Action and circulatory effects
3. Effects on Water Metabolism
4. Effects on the bones and muscles
5. Anti-inflammatory, anti-immune effects
6. Effects on the Central Nervous System
7. Developmental effects

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Effects (terapeutic):

- anti-inflammatory
- antialergic and immunosupresive
- antiproliferative

- Substitution (therapeutic)

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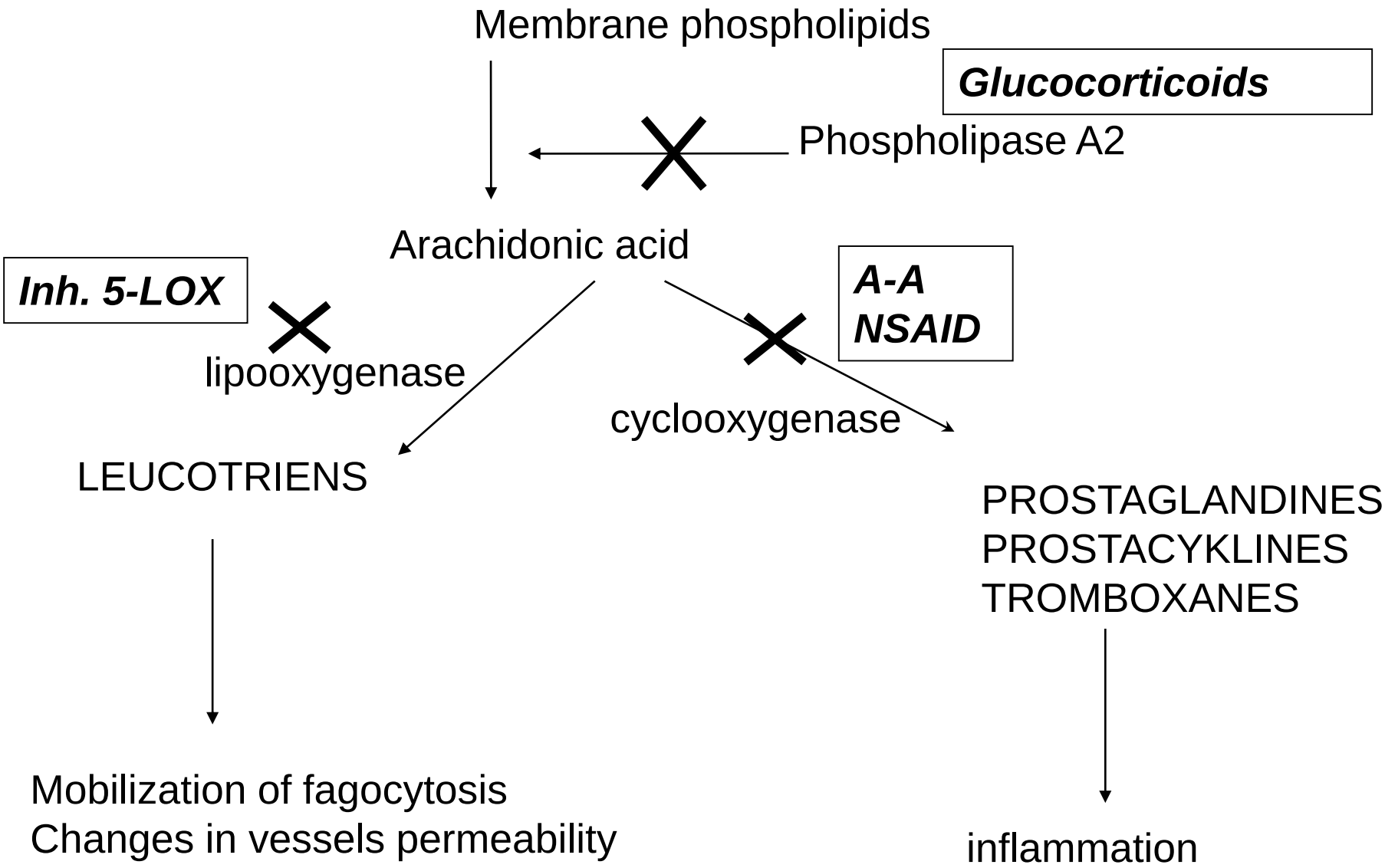
Membrane phospholipids
Glucocorticoids
Phospholipase A2
Arachidonic acid
Inh. 5-LOX
lipooxygenase
A-A
NSAID
cyclooxygenase
LEUCOTRIENS
PROSTAGLANDINES
PROSTACYKLINES
TROMBOXANES
Mobilization of fagocytosis
Changes in vessels permeability
Inflammation
inflammation

Indications

Physiological doses

substitution – adrenocortical insuficiency, congenital adrenal hyperplasia, Addison dissease *(hydrocortisone, fludrocortisone)*

Pharmacological doses

Antiinflammatory and imunosupressive effects

- **astma (inhaltions)**
- **topic application, in allergy (conjuctivitis, rhinitis)**
- **hypersensitivity in general**
- **anaphylaxis**
- **autoimune diseases (revmatoid arthritis, Crohn disease …)**
- **prevent non-acceptance in transplantations**

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Indications

Oncology

Acute Lymphoblastic Leucaemia, hodgkin disease
tumors of brain (antioedematose effect - dexamethasone)
antiemetics

Others

height sickness, nephrotic sy., sclerosis multiplex, subacute thyreoitidis

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Adverse effects (after pharmaclogical intervence!)

1) ↓ Immune responses

recurrent infects, ulcer dissease, mycotic infects…

2) Decrease in endogenous corticoid production (supresion of axis hypothalamus –pituitary – adrenal glands)

--- acute insuficiency in sudden glucocorticoid withdrawal

3) Osteoporosis

4) Mineralocorticoid action – water retention, salts

↑blood pressure, Na, Cl

↓ K^+, NO production

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Adverse effects (after pharmaclogical intervence!)

5) Steroid diabetes mellitus

6) Muscle atrophy

7) Psychotrophic effect: euphoria/ depression/psychosis

8) ↑ gastric secretion of HCl

9) Cartillage impairment, striae, reduced wound healing

9) others: increased clottin, ↑trombocytes, erys glaucoma, increased intracranial pressure

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Iatrogenic Cushing sy.

Sudden weight gain
Central obesity
Hypertension
Proximal muscle weakness
Diabetes mellitus
Decreased libido or impotence
Depression or psychosis
Osteopoenia or osteoporosis

Easy bruising
Hyperlipidemia
Menstrual disorders
Violaceous striae wider than 1 cm
Recurrent infections
Acne
Hirsutism...

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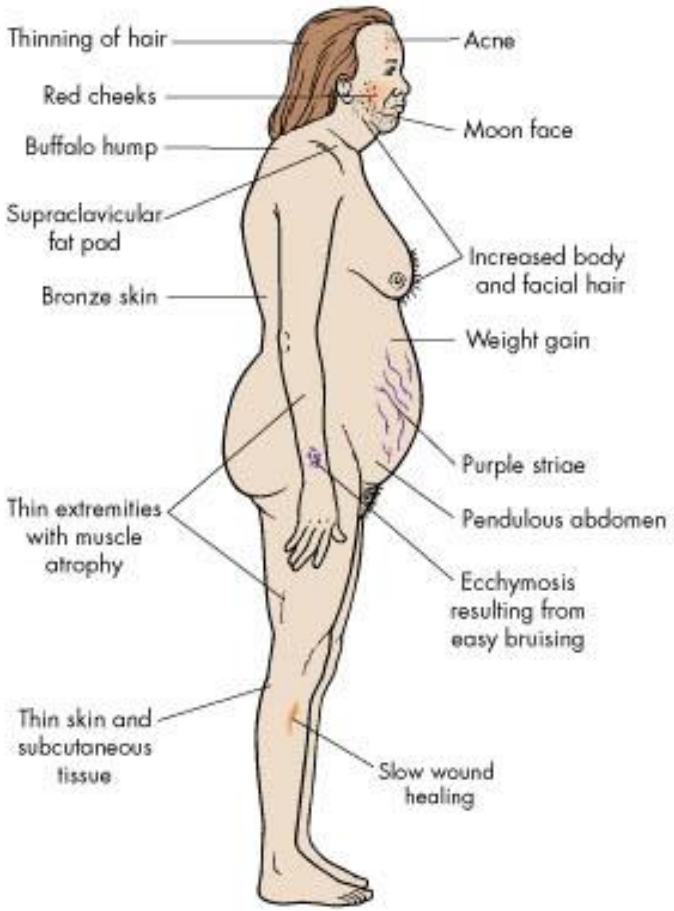

Figure 47-9 Common characteristics of Cushing's syndrome.

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Glucocorticoids:

	Glucocorticoid effect	Mineralocorticoid effect
Cortisol	1	1
Cortisone	0,8	0,8
Prednisone	4	0,8
Prednisolone	4	0
Triamcinolon	5-10	0
Betametazon	25	0
Dexametazon	25	0

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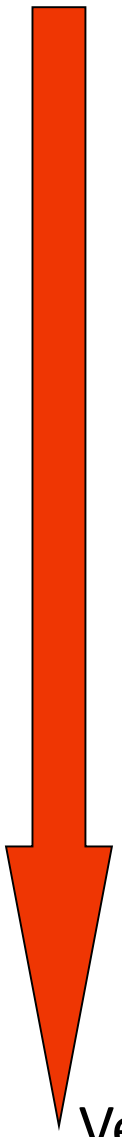
Topically administered glucocorticoids

- hydrocortisone
- dexamethasone
- prednisolone
- triamcinolone
- flumethasone
- prednikarbat
- bethametason valerate
- fluocinolone
- betamethason adipate
- budesonid
- halcinomide
- clobetasole



Weak action

Very strong acting

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CAVE !
To prevent axis supression

(hypothalamus- ant. pituitary – adrenal glands)

- Administration up to 10 days
- 6 - 8 A.M.
- Preparations with lower blocking effect

  (non-fluorinated derrivatives)
- Pulse therapy

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Adverse effects prevention

- lowest effective dose should be administered
- topic administration if possible (inh., rect., intraarticular, s.c.) with low bioavailability
- total dose can be decreased by combination with imunosupresives
- dosing schedule should reflect circadian rhythm – if possible (not in life threating situations)
- avoid sustained release preparations
- stepwise decreasing of doses

approx. 2.5 mg eq. prednisolone /3 days

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Contraindications

- hypertension
- heart insufficiency /CHF
- Cushing. sy
- peptic ulcer
- diabetes
- glaucoma
- psychoses
- viral/bacterial infection
- vaccination with attenuated vaccine

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