Corticosteroids

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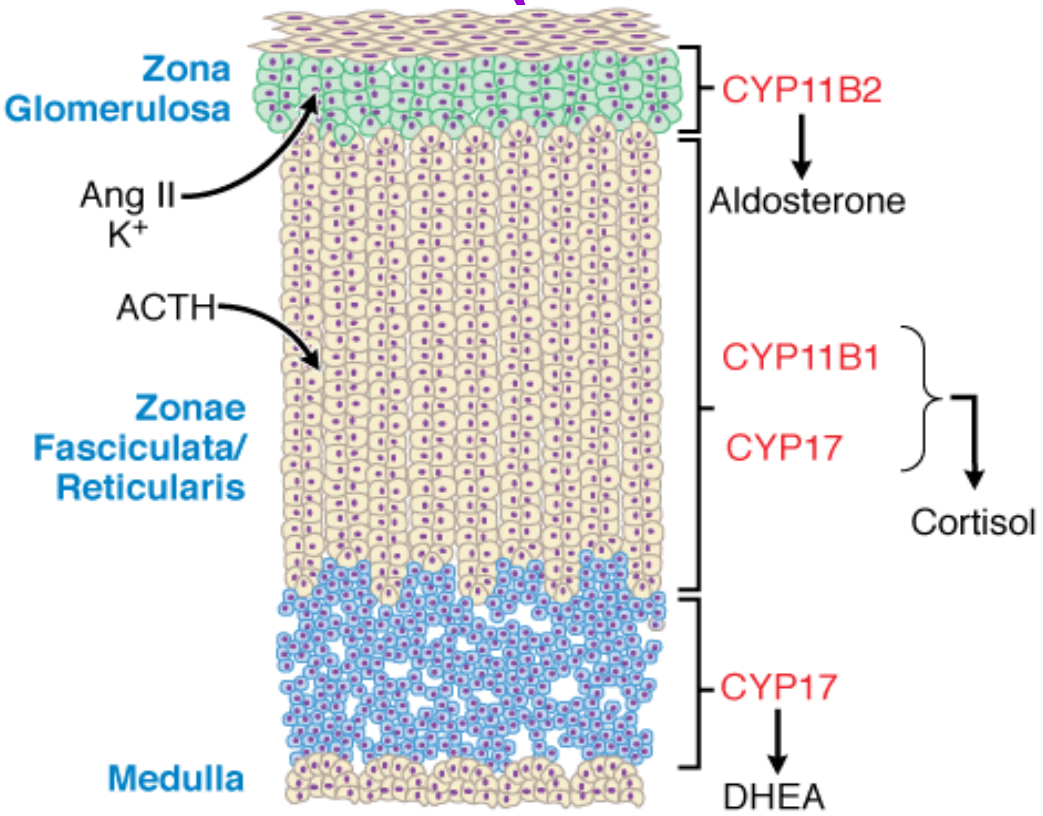
วัตถุประสงค์

เมื่อสิ้นสุดการเรียนการสอน นักศึกษาสามารถ

- อธิบายกลไกการออกฤทธิ์ ฤทธิ์ทางเภสัชวิทยา และผลข้างเคียงที่สำคัญของ **corticosteroids** ได้
- บอกหลักการเบื้องต้นในการนำ **corticosteroids** ไปใช้ทางคลินิกได้

Introduction

- **Corticosteroids (Adrenocortical steroids)**

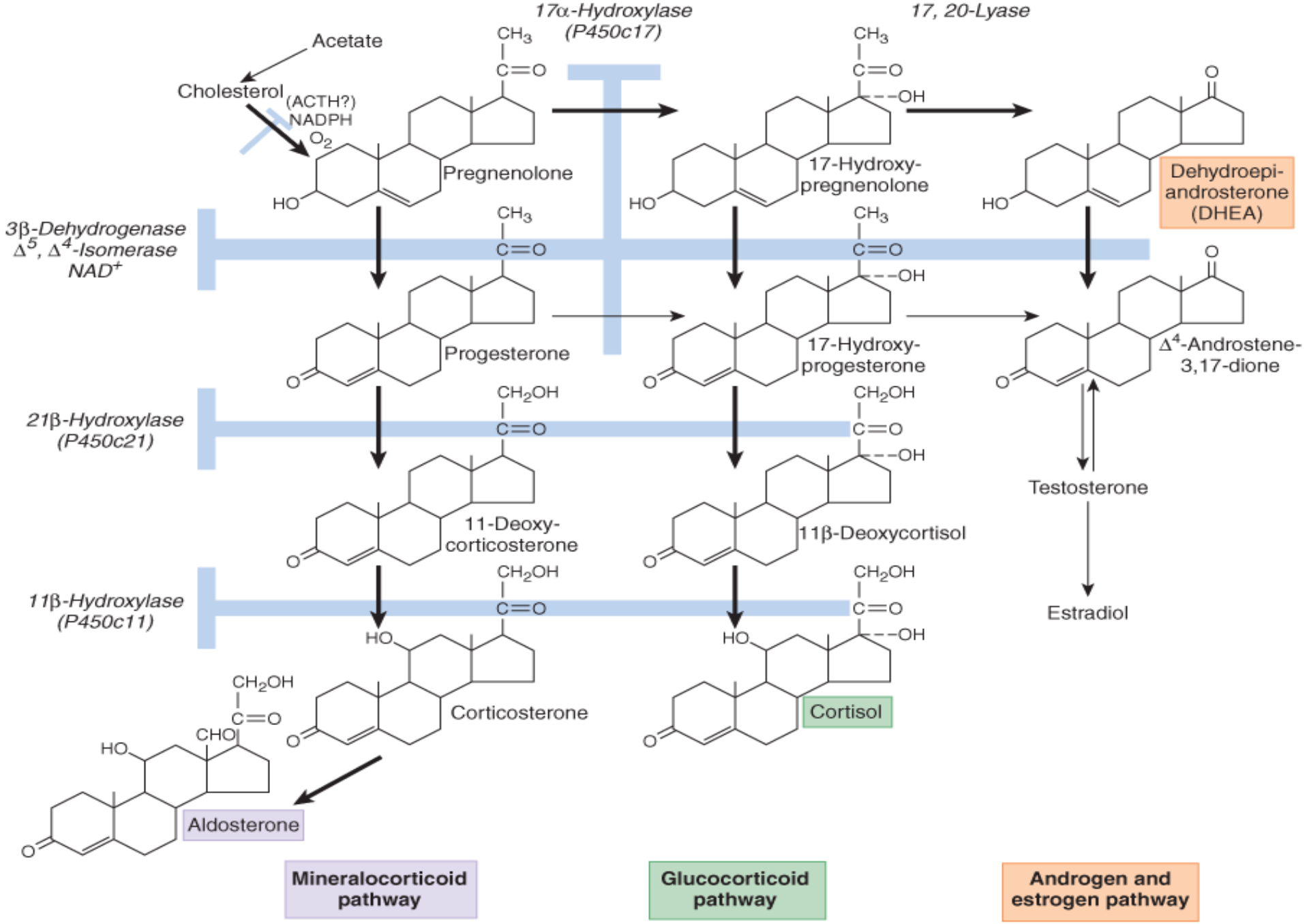


Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

Mineralocorticoids

Glucocorticoids

Sex steroids



Introduction

- **Corticosteroids (Adrenocortical steroids)**

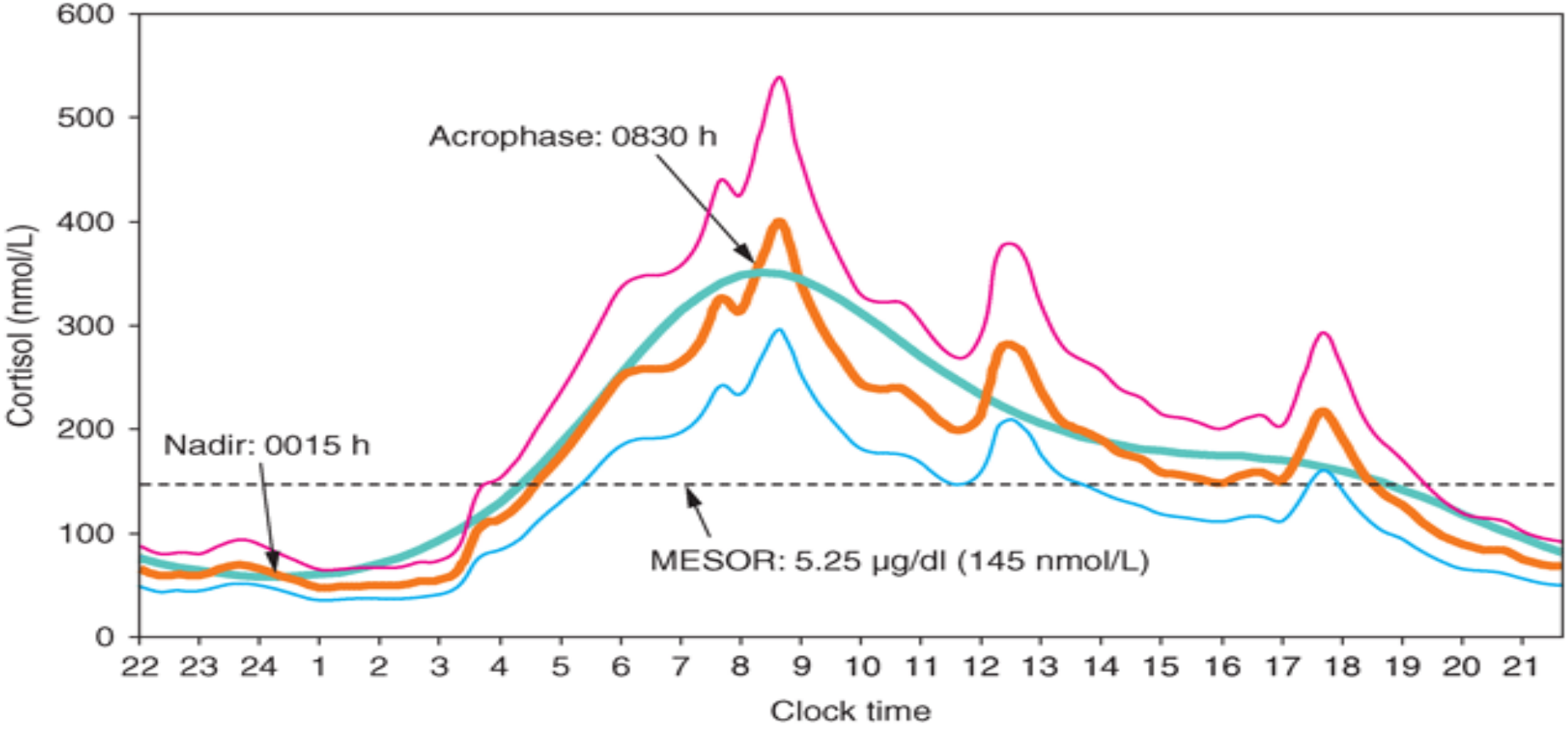
Normal Daily Production Rates and Circulating Levels of the Predominant Corticosteroids

	CORTISOL	ALDOSTERONE
Rate of secretion under optimal conditions	10 mg/day	0.125 mg/day
Concentration in peripheral plasma:		
8 A.M.	16 µg/100 mL	0.01 µg/100 mL
4 A.M.	4 µg/100 mL	0.01 µg/100 mL

Normal cortisol production rate in children: 10-13 mg/m^2 per day

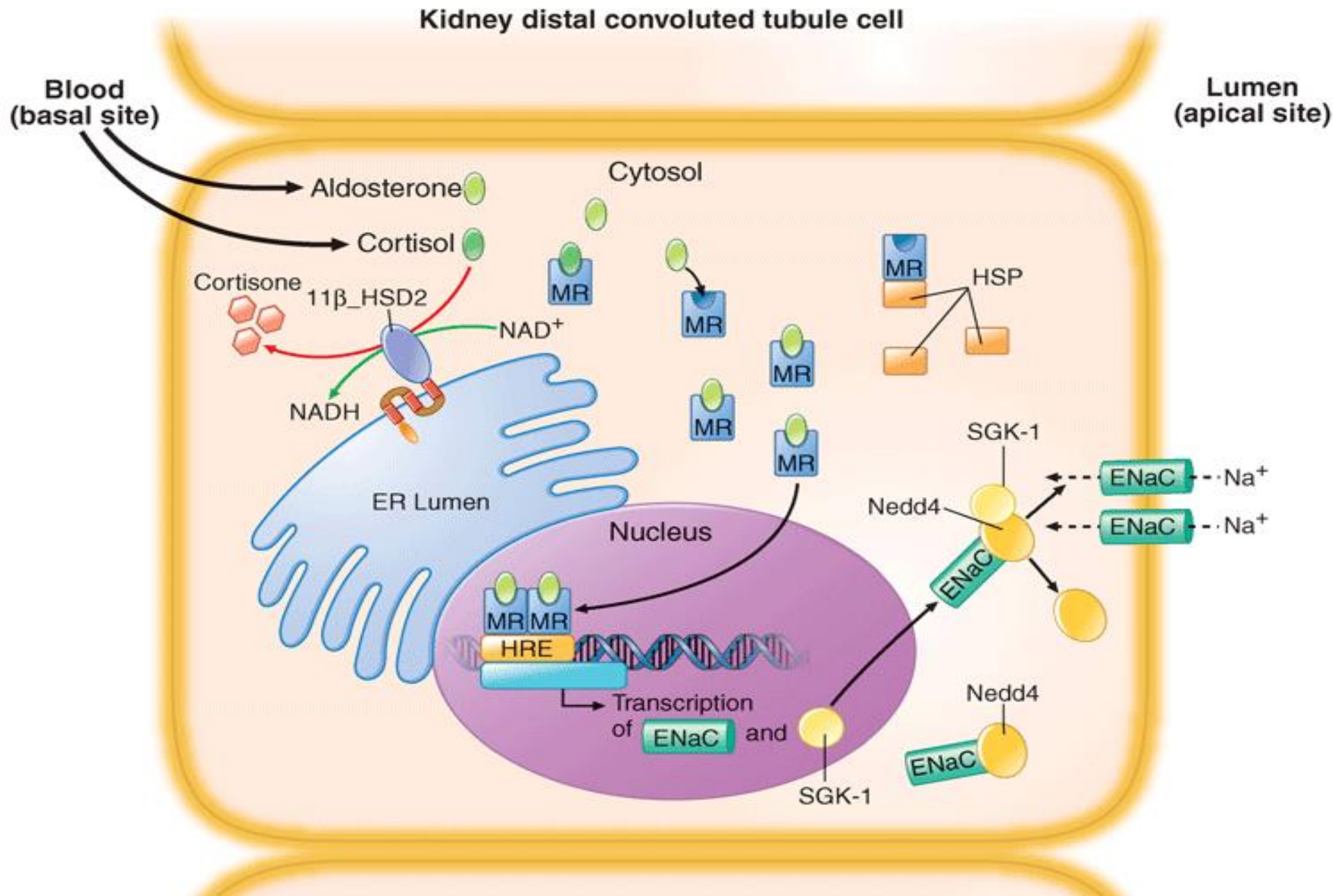
Introduction

- **Corticosteroids (Adrenocortical steroids)**



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

Mineralocorticoids


Kidney distal convoluted tubule cell
Blood
(basal site)
Lumen
(apical site)
Aldosterone
Cortisol
Cortisone
11β_HSD2
NAD+
NADH
Cytosol
MR
HSP
ER Lumen
Nucleus
HRE
Transcription
of
ENaC
and
SGK-1
Nedd4
ENaC
Na+

Fludrocortisone

- Synthetic mineralocorticoid with glucocorticoid activity
- Oral form
- Long duration of action
- Replacement R_x in mineralocorticoid deficiency (Addison's disease, moderate to severe CAH)

Mineralocorticoid antagonists

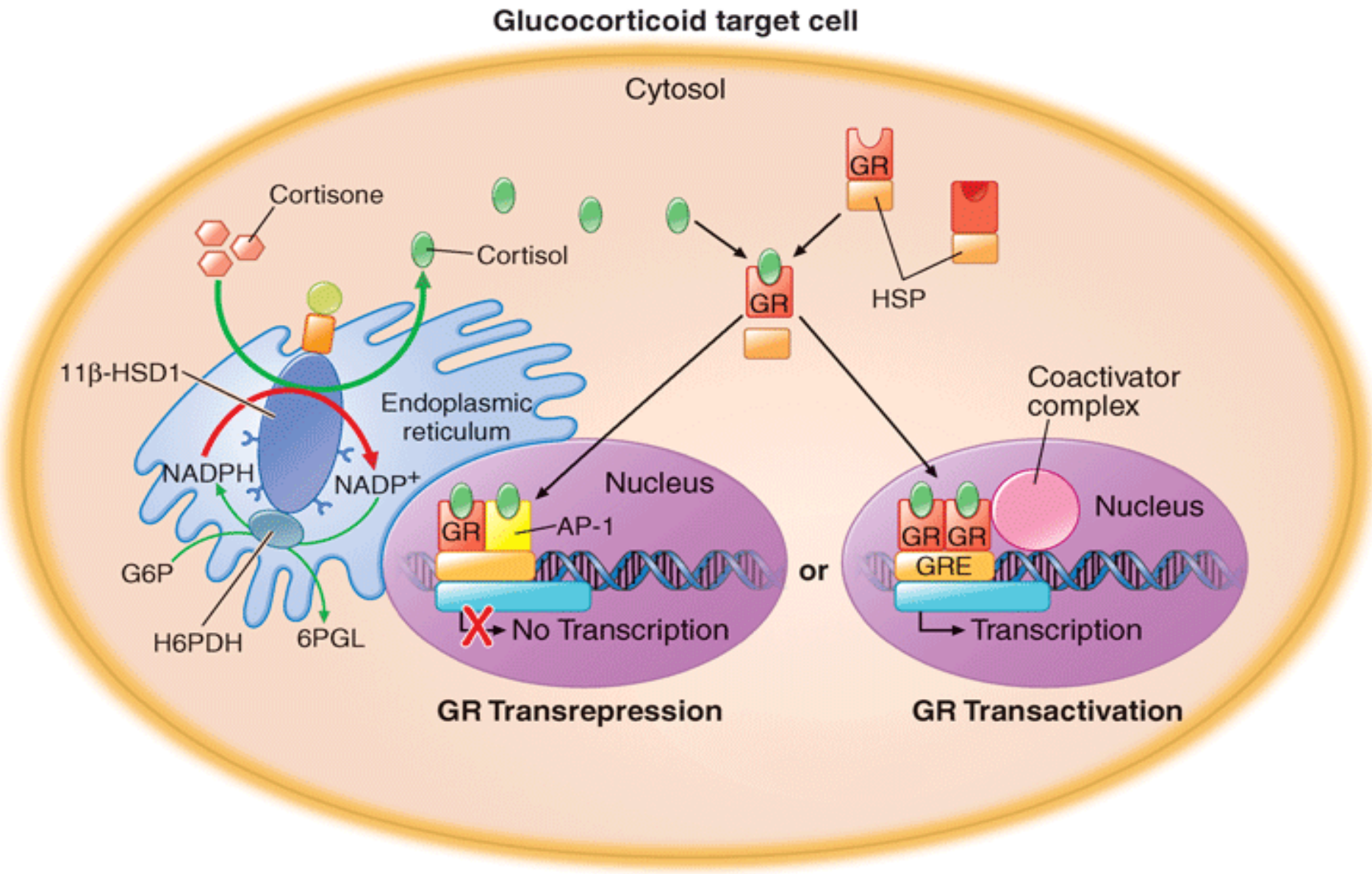
Spironolactone & Eplerenone

- Mineralocorticoid (aldosterone) receptor antagonists
- Use in 1° & 2° hyperaldosteronism, chronic HF
- ADRs ---> based on selectivity to receptor

Glucocorticoids

Cortisol

- ACTH ---> regulate secretion
- 95% of cortisol in plasma bound to CBG
- Mechanism of action: enter cell and bind to cytosolic receptor that transport steroid into nucleus ---> steroid-receptor complex bind to glucocorticoid-responsive element ---> alter gene expression



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Cortisol

- **Effects**

  * **Metabolic effects**

    - **stimulate gluconeogenesis ---> insulin resistance, DM**
    - **stimulate lipolysis and lipogenesis ---> net increase of fat deposition in certain areas (face, shoulders, back)**

Buffalo hump (dorsocervical fat pad)

Cortisol

- **Effects**

  * **Catabolic effects**

    - **muscle protein catabolism (proteolysis)**

      ---> proximal muscle weakness

    - **wasting of skin & CNT ---> telangiectasia**

    - **inhibit bone growth in children**

    - **osteoporosis**

Cortisol

- **Effects**

  * **Immunosuppressive effects**

    - **inhibit lymphocyte function & CMI**
    - **actively lymphotoxic (apoptosis)**
    - **use in R_x of autoimmune diseases & some hematologic malignancies, prevention of organ transplant rejection**

Cortisol

- **Effects**

  * **Anti-inflammatory effects**

    - **increase neutrophil and decrease lymphocyte, eosinophil, basophil, and monocyte**
    - **interfere chemotaxis**

Cortisol

- **Effects**

  * **Anti-inflammatory effects**

    - **induce synthesis of lipocortin ---> inhibit phospholipase A_2**
    - **decrease mRNA for COX-2**
    - **decrease proinflammatory cytokines**

Cortisol

- **Effects**

  * **Other effects**

    - **weak mineralocorticoid activity ---> required for normal renal excretion (hypercortisolism ---> HT)**
    - **inhibit PGs ---> peptic ulcer**
    - **CNS effect ---> behavioral change**

Synthetic glucocorticoids

- Effects ---> same as cortisol
- Oral form ---> well absorbed from GI tract & cleared by liver
- Topical form ---> diffuses poorly across normal skin, but readily absorbed across inflamed skin and mucous membranes

Synthetic glucocorticoids

- **Oral** prednisolone, dexamethasone, hydrocortisone, triamcinolone
- **I.V.** dexamethasone, hydrocortisone, methylprednisolone
- **Topical (skin)** betamethasone, clobetasol, triamcinolone acetonide, prednisolone, hydrocortisone, mometasone

Synthetic glucocorticoids

- **Inhaled** budesonide, beclomethasone, fluticasone
- **Intranasal** triamcinolone acetonide, budesonide, beclomethasone, fluticasone, mometasone
- **Injection (intra-articular, intralesional)** triamcinolone acetonide

TABLE 182-1 GLUCOCORTICOID PREPARATIONS

Generic Name	Relative Potency		Dose Equivalent
	Glucocorticoid	Mineralocorticoid	
Short-acting			physiologic doses
Hydrocortisone	1.0	1.0	20.0
Cortisone	0.8	0.8	25.0
Intermediate-acting			
Prednisolone	4.0	0.25	5.0-7.5
Methylprednisolone	5.0	0	4.0
Triamcinolone	5.0	0	4.0
Long-acting			
Dexamethasone	30.0	0	0.75
Betamethasone	25.0	0	0.8

Synthetic glucocorticoids

- **Clinical uses**

  * **Adrenocortical disorders**

    - **1° / 2° acute & chronic adrenocortical insufficiency ---> replacement R_x**
    - **congenital adrenal hyperplasia**
    - **dexamethasone suppression test (DD_x cause of hypercortisolism)**

Synthetic glucocorticoids

- **Clinical uses**

  * **Non-adrenocortical disorders**

    - **rheumatic diseases (SLE, vasculitis, RA)**
    - **renal diseases (NS, membranous nephropathy, lupus nephritis)**
    - **allergic diseases (asthma, AR)**

Synthetic glucocorticoids

- **Clinical uses**

  * **Non-adrenocortical disorders**

    - **pulmonary diseases (prevention of RDS in preterm infant, COPD)**
    - **infectious diseases (PCP, Hib meningitis)**

Synthetic glucocorticoids

- **Clinical uses**

  * **Non-adrenocortical disorders**

    - **skin diseases (eczema, psoriasis, pemphigus vulgaris)**
    - **GI diseases (IBD)**
    - **malignancies (ALL, lymphoma)**
    - **hematologic diseases (AIHA, ITP)**

Synthetic glucocorticoids

- **Clinical uses**

  * **Non-adrenocortical disorders**

    - **organ transplantation**

    - **CNS conditions (cerebral edema, spinal cord injury)**

Synthetic glucocorticoids

- **Clinical uses** — supraphysiologic doses

TABLE 182-2 A CHECKLIST FOR USE PRIOR TO THE ADMINISTRATION OF GLUCOCORTICOIDS IN PHARMACOLOGIC DOSES

Presence of tuberculosis or other chronic infection (chest x-ray, tuberculin test)
Evidence of glucose intolerance, history of gestational diabetes mellitus, or high risk for type 2 diabetes mellitus
Evidence of preexisting osteoporosis (bone density assessment in organ transplant recipients or postmenopausal pts)
History of peptic ulcer, gastritis, or esophagitis (stool guaiac test)
Evidence of hypertension, cardiovascular disease, or hypertriglyceridemia
History of psychological disorders — Stool exam for parasites

Synthetic glucocorticoids

- **Clinical uses**

  * Short-term use, normally administered in 2-3 doses each day (initial dose equivalent to 5-60 mg of prednisolone/day)

  * Response will be seen within 10-14 days

Synthetic glucocorticoids

- **Clinical uses**

  * Once a response has been observed, the dose should be carefully reduced to the lowest dose that will provide adequate control

Synthetic glucocorticoids

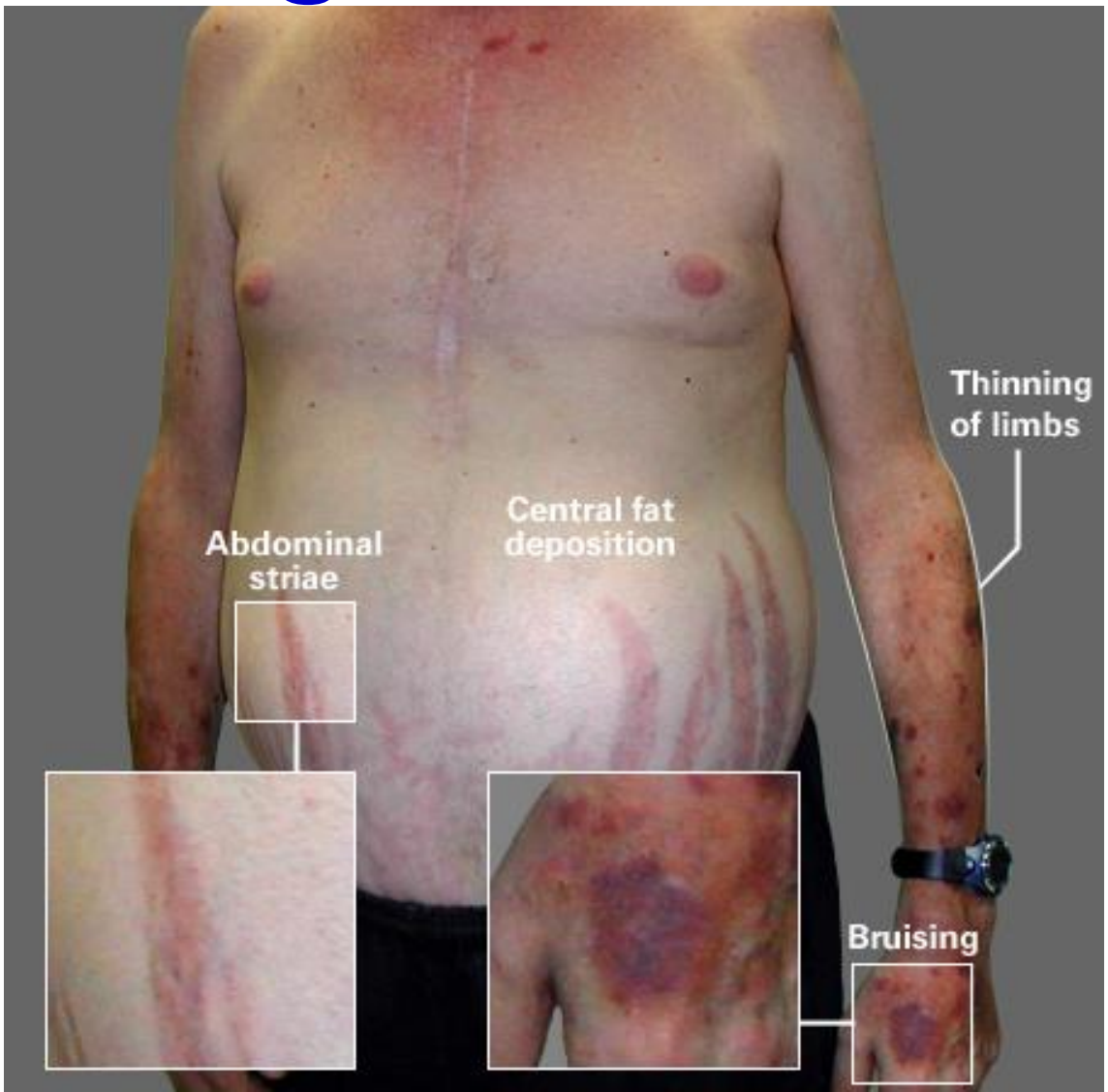
- ADRs

  * Continued use of supraphysiologic doses

    - cushingoid appearance (Cushing's syndrome)
    - fat redistribution ---> truncal obesity, dorsocervical fat pads
    - striae, ecchymoses, facial plethora

Synthetic glucocorticoids

- ADRs



Synthetic glucocorticoids

- ADRs

  * Continued use of supraphysiologic doses

    - suppression of HPA axis

    - growth arrest (in children)

    - hypokalemic metabolic alkalosis

    - hypertension, hyperglycemia

    - increased susceptibility to infection

Synthetic glucocorticoids

- ADRs

  * Continued use of supraphysiologic doses

    - peptic ulcer

    - osteoporosis

    - osteonecrosis (avascular necrosis)

    - myopathy, proximal muscle weakness

Synthetic glucocorticoids

- ADRs

  * Continued use of supraphysiologic doses

    - behavioral disturbance (nervousness, mood disorders, psychosis)

    - cataracts, glaucoma

Synthetic glucocorticoids

- **Clinical uses**

  * **Discontinued use of glucocorticoids**

    - **reduce the dose gradually, over several days (tapering regimen)**
    - **reduced by the equivalent of 2.5-5 mg of prednisolone every 3-7 days until the physiologic dose is reached**

Synthetic glucocorticoids

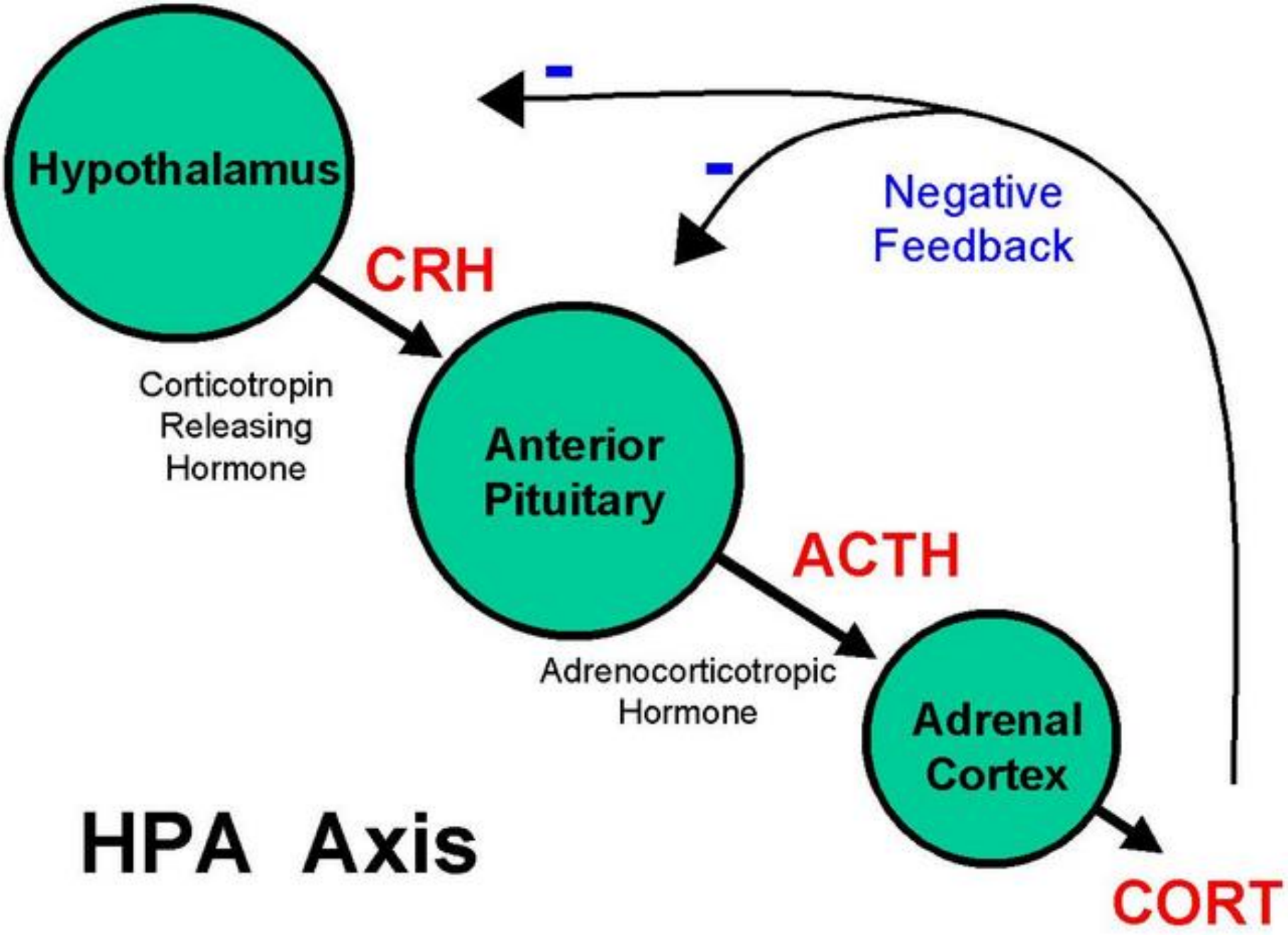
- Clinical uses

  * Withdrawal of therapy

    - flare-up of underlying disease

    - acute adrenocortical insufficiency

      ---> rapid withdrawal after prolonged use (2-4 weeks) with supraphysiologic (pharmacologic) doses


Hypothalamus
-
-
Negative
Feedback
CRH
Corticotropin
Releasing
Hormone
Anterior
Pituitary
ACTH
Adrenocorticotropic
Hormone
Adrenal
Cortex
CORT
HPA Axis

Synthetic glucocorticoids

- **Drug-drug interactions**

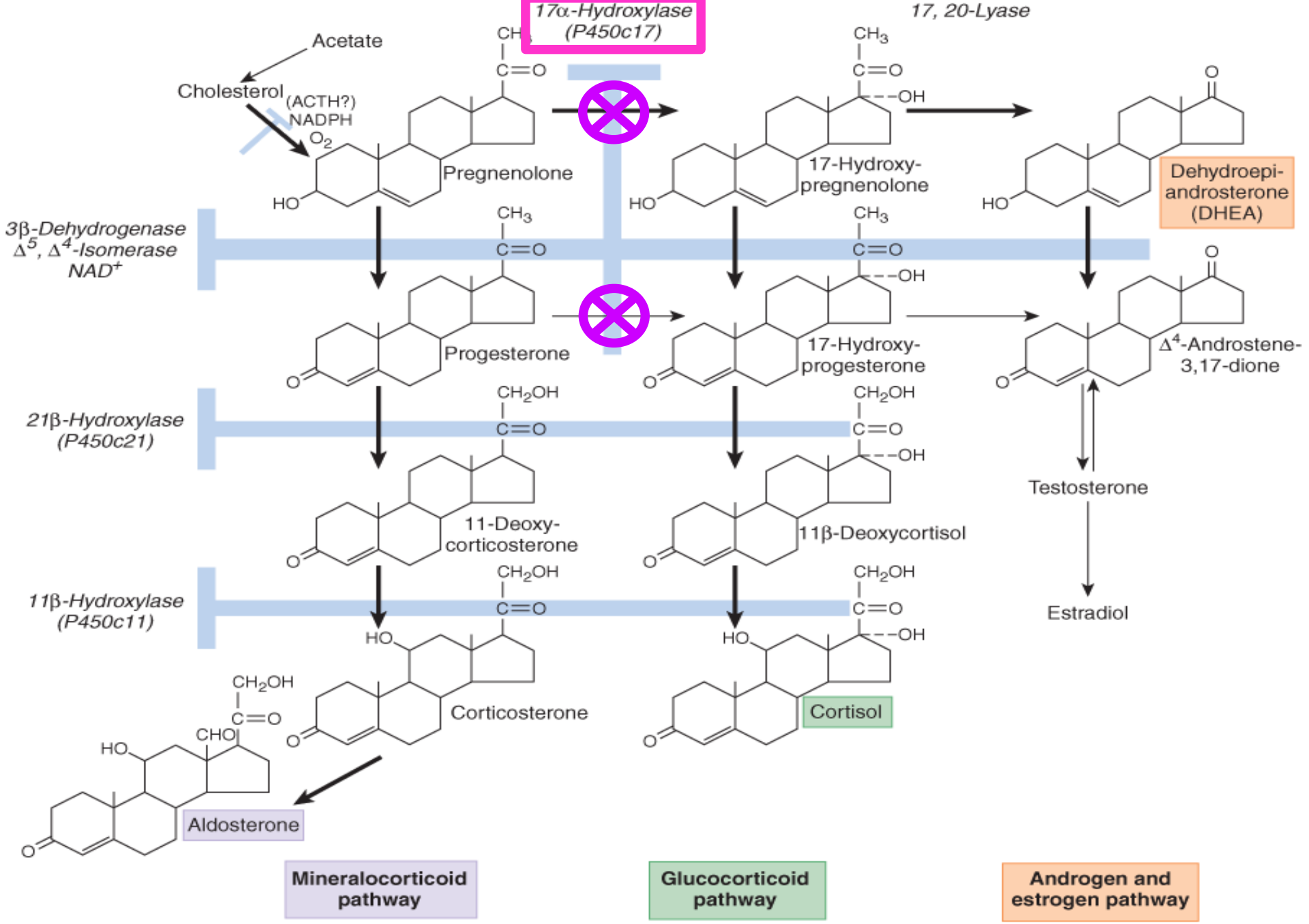
  * **Glucocorticoids ---> CYP450 substrate**

    - **CYP450 inducers (carbamazepine, phenytoin, rifampicin)**
    - **CYP450 inhibitors (macrolides, azole antifungals)**

Glucocorticoid synthesis inhibitors

Ketoconazole

- Usual dose ---> antifungal activity
- Higher dose ---> inhibit adrenal & gonadal steroidogenesis (esp. 17α-hydroxylase)
- R_x of hypercortisolism, adrenocortical carcinoma, hirsutism, prostate cancer
- Potent CYP450 inhibitor
- ADR: hepatotoxicity



Glucocorticoid antagonists

Mifepristone

- Usual dose ---> progesterone receptor antagonist
- Higher dose ---> inhibit glucocorticoid receptor
- Block feedback regulation of HPA axis
- R_x of hypercortisolism (inoperable causes)
- ADR: abortion

Additional reading