

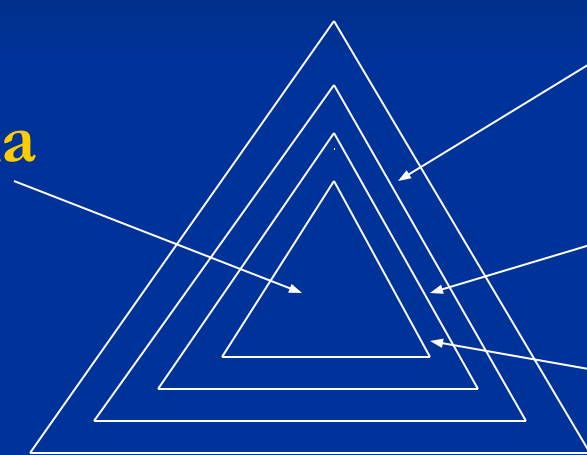
Adrenal Steroids

Mineralocorticoids & Glucocorticoids

Adrenal Gland

Cortex

Medulla
(E, NE)



Mineralocorticoids

(Aldosterone)

Glucocorticoids

(Cortisol)

Sex hormones

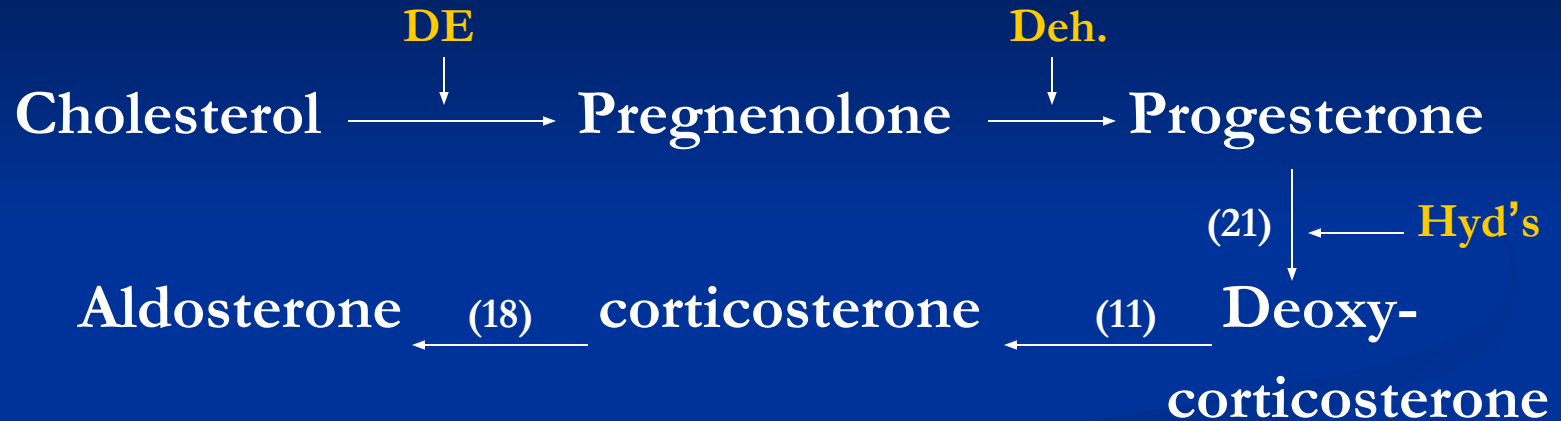
(Testosterone, E2, P)

Mineralocorticoids (Aldosterone)

Synthesis: From cholesterol

Control of synthesis and release

- ↑ in the plasma concentration of Angiotensin III, a metabolite of angiotensin II
- ↑ plasma angiotensin II
- ↑ K^+ blood levels (potassium levels are the most sensitive stimulator of aldosterone)
- ACTH
- ↓ ECF or blood volume; metabolic acidosis



DE = debranching enzyme; side chain cleavage enzyme; desmolase

Deh. = 3β -hydroxysteroid dehydrogenase enzyme

Hyd's = Hydroxylases

Renin-angiotensin-aldosterone axis



■ **Factors/drugs ↑ renin-angiotensin-aldosterone:**

- Volume depletion (hemorrhage, low Na^+ intake, dehydration, overuse of diuretics...)
- Upright posture
- K^+
- ACTH
- Vasodilators
- Adrenoreceptor antagonists

■ **Factors/drugs ↓ renin-angiotensin-aldosterone:**

- Blood volume expansion

- Renin release inhibitors (also known as renin antagonists)

Aliskiren, Remikiren, Enalkiren, β_1 -blockers

- ACE inhibitors

Captopril, Enalapril, Benzopril, fosinopril, Lisinopril,
Ramipril ...

- ARB's (Angiotensin II receptor blockers)

Candesartan, Losartan, Irbesartan, telmesartan...

- Aldosterone antagonists

Spironolactone, Eplerenone

■ Aldosterone effects:

Receptor-mediated

Acts on distal convoluted tubules in the kidney

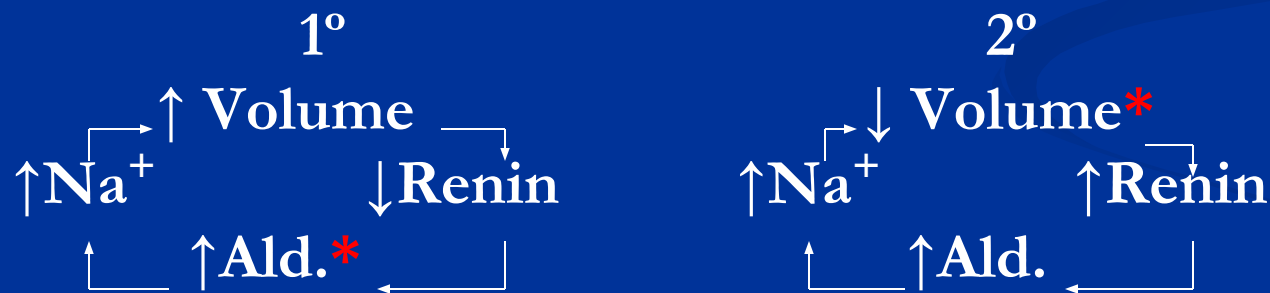
- ↑ reabsorption of Na^+ → hypertension
- ↑ excretion of K^+ & H^+ → hypokalemia & metabolic alkalosis
- ↑ EC volume
- ↑ BP

■ Disorders affecting aldosterone release:

- Hypoaldosteronism manifested by hypotension, hyponatremia, hypovolemia, hyperkalemia, and metabolic acidosis

Rx: Fludrocortisone

- Hyperaldosteronism



* Initial defect

Glucocorticoids (Cortisol)

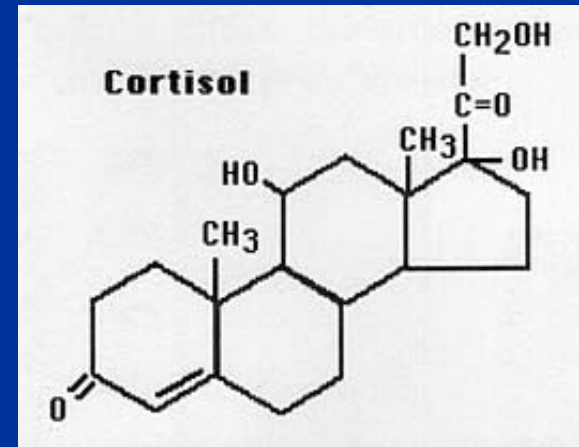
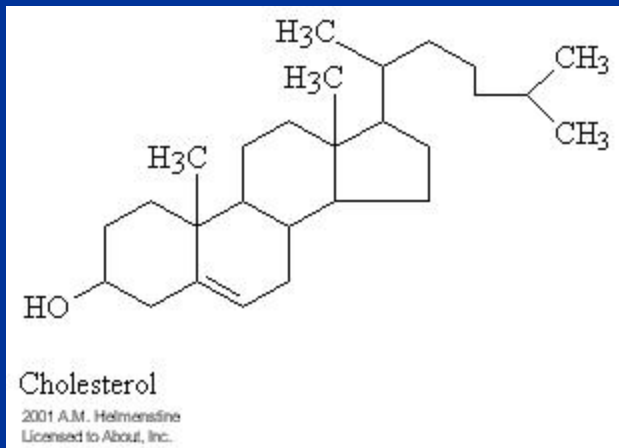
- Feedback control

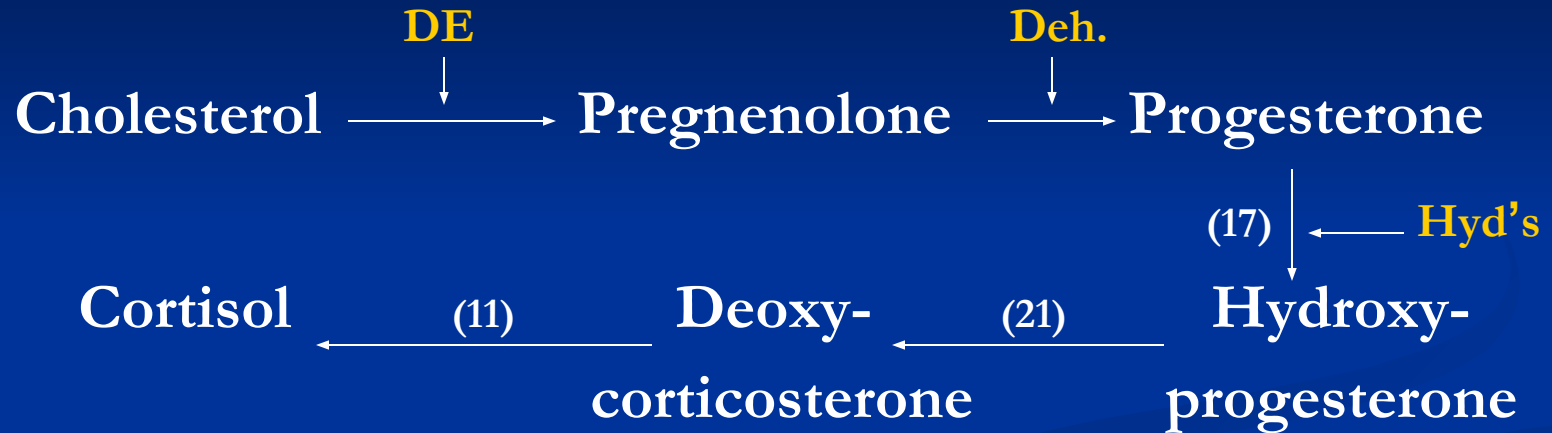


Circadian rhythm

Pt's on cortisol therapy...

Cortisol synthesis (from cholesterol)





DE= debranching enzyme; side chain cleavage enzyme; desmolase

Deh.= 3 β -hydroxysteroid dehydrogenase enzyme

Hyd's= Hydroxylases

■ **Steroid synthesis inhibitors:**

- **o,p'-DDD (Mitotane)**

Causes selective atrophy of Zona Fasciculata and Zona Reticularis

Useful in R_x of adrenal Ca when radiotherapy or surgery are not feasible and in certain cases of breast cancer

- **Aminoglutethimide**

Selective desmolase inhibitor and non selective aromatase inhibitor, same uses as mitotane and Cushing's syndrome

- Trilostane

Competitive inhibitor of 3β -hydroxysteroid dehydrogenase enzyme effective in Cushing's syndrome and breast cancer

- Ketokonazole

An antifungal agent

An inhibitor of different hydroxylases; inhibits steroidogenesis in adrenals and testes

Effective in Cushing's syndrome and Ca of prostate

- Etomidate

Etomidate is used for induction of general anesthesia and sedation. At subhypnotic doses it inhibits 11β -hydroxylase and it is a very effective drug in severe Cushing's syndrome that is refractory to ketoconazol. It is the only parenteral medication available in the treatment of severe Cushing's syndrome

- Metyrapone (Metopirone)

11β -hydroxylase inhibitor

Effective as a diagnostic tool (metyrapone test) and in the management of Cushing's syndrome

■ Release and transport of glucocorticoids

Glucocorticoids receptors

■ Pharmacological effects/side effects:

- On proteins

↑ Catabolism ↓ anabolism

→ Osteoporosis; steroid myopathy; delayed wound healing; delayed peptic ulcer healing...

- On CHO

↑ blood sugar level (↑ gluconeogenesis; ↓ peripheral utilization of glucose)

- On lipids

↑ lipolysis

Fat redistribution

- On electrolytes

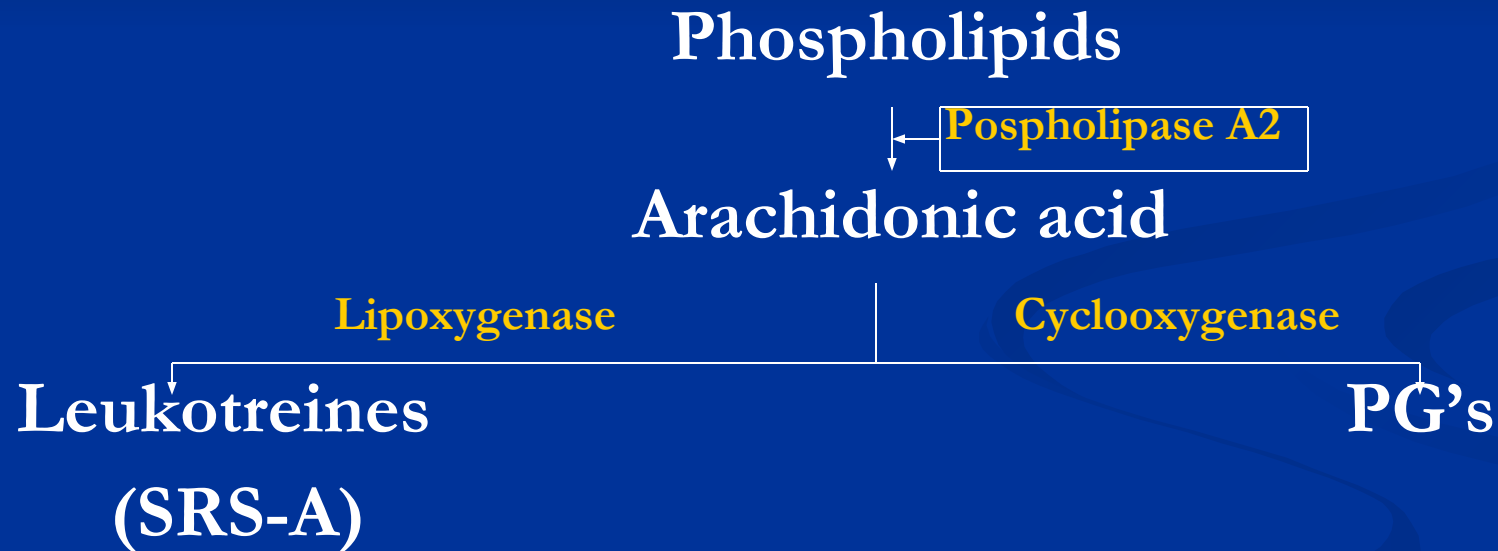
Aldosterone-like effect

↓ Ca^{++} absorption from intestine

↑ Ca^{++} excretion by kidney

↑ uric acid excretion

- Antiinflammatory effect
major mechanism:



Other possible mechanisms:

- Also inhibit neutrophil and macrophage function
- Inhibition of platelet activation factor (PAF)
- Inhibition of tumor necrosis factor or receptor (TNF; TNR)
- Inhibition of nitric oxide reductase...

- Immunosuppressant effect

Major mechanisms

↓ initial processing of Ag

Ab formation ↓

↓ effectiveness of T-lymphocytes

↓ lymphocyte induction & proliferation

↓ lymphoid tissue including leukemic lymphocytes
(antileukemic effect)

- **Antiallergic effect**

Suppress allergic response

↓ **histamine release**

↓ **eosinophils**

- **CNS manifestations**

Euphoria

Psychosis

- **Glucocorticoids dosage forms**

Available in all dosage forms

Available in many preparations

- **Structure activity relationship**

Major objective: Good antiinflammatory effect, less or no aldosterone-like activity

- **Metabolism:**

In the liver by reduction and conjugation (90-95%);
little hydroxylation reactions (5%)

■ Glucocorticoid preparations

<u>Short-acting</u>	<u>Half-life</u>	<u>AIA</u>	<u>Ald.-like</u>
Corisol	10	1	1
Cortisone	10	0.8	1
Corticosterone	10	0.3	30
Fludrocortisone	10	10	150
<u>Intermediate-acting:</u>			
Prednisone	20	4	0.8
Prednisolone	20	5	0.8

	<u>Half-life</u>	<u>AIA</u>	<u>Ald.-like</u>
Methylprednisolone	20	6	-
Triamcinolone	20	6	-
Beclomethasone	20	6	-
<u>Long-acting:</u>			
Betamethasone	50	25	-
Dexamethasone	50	30	-

**** Plasma half-life; Nuclear half-life**

■ Clinical uses to glucocorticoids:

- Adrenal insufficiency (acute; chronic, Addisonian crisis, Addison's disease...)
- Inflammatory conditions (rheumatoid arthritis, SLE, arteritis, dermatomycosis, cerebral edema, ulcerative colitis, rheumatic carditis, active chronic hepatitis, proctitis, acute gout...)
- Allergic reactions (hay fever, eczema, dermatitis), bronchial asthma, status asthmaticus

- Immunosuppressant effect (organ transplantation, hemolytic anemia, leukemias, many tumors...)
- Hypercalcemia associated with Vit. D intoxication or sarcoidosis or hyperparathyroidism or cancer...)
- Many eye, ear, and skin diseases (allergic or inflammatory)
- **Side effects to glucocorticoids:**
 - Suppression of hypothalamic-pituitary-adrenal axis (major and most dangerous side effect)

- Cushing's syndrome
- Salt & water retention, edema, ↑ BP, obesity
- Peptic ulcer disease and GIT ulcerations
- Osteoporosis
- Diabetes mellitus
- ↑ incidence of viral and fungal infections
- ↓ wound healing and skin atrophy and myopathy
- Suppression of growth of children
- Cataract...

■ Strategy in the use of glucocorticoids:

- Use a short-acting steroid
- Use a minimal possible dose
- Give 2/3 of the dose in morning and 1/3 in evening
- Use alternate day therapy which is associated with less suppression to growth of children and to the hypothalamic-pituitary-adrenal axis and fewer side effects