Adrenal Steroids
Mineralocorticoids & Glucocorticoids

Adrenal Gland

Cortex

Mineralocorticoids

(Aldosterone)

Glucocorticoids

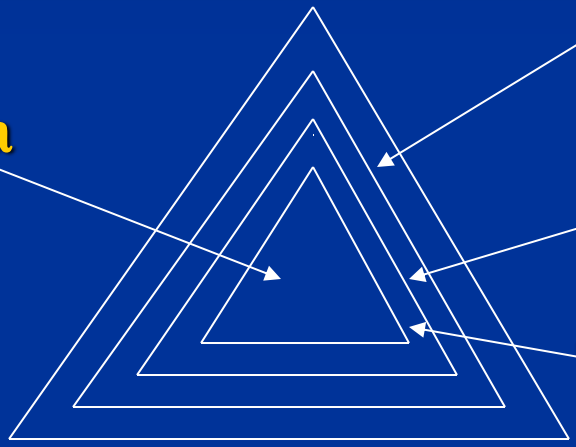
(Cortisol)

Sex hormones

(Testosterone, E2, P)

Medulla

(E, NE)

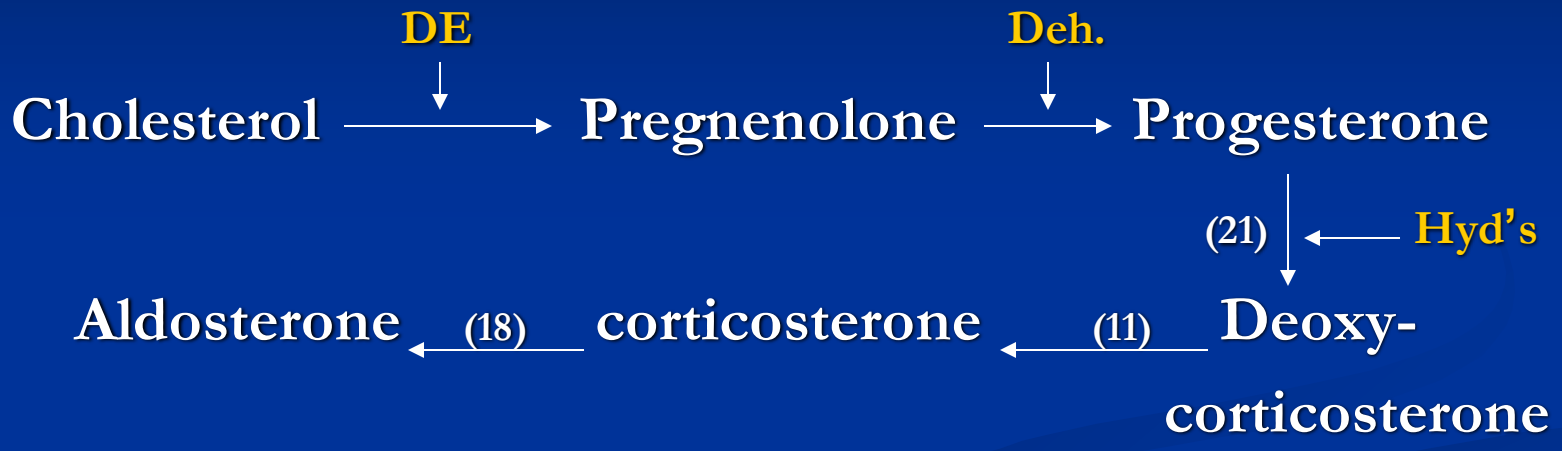


Mineralocorticoids (Aldosterone)

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

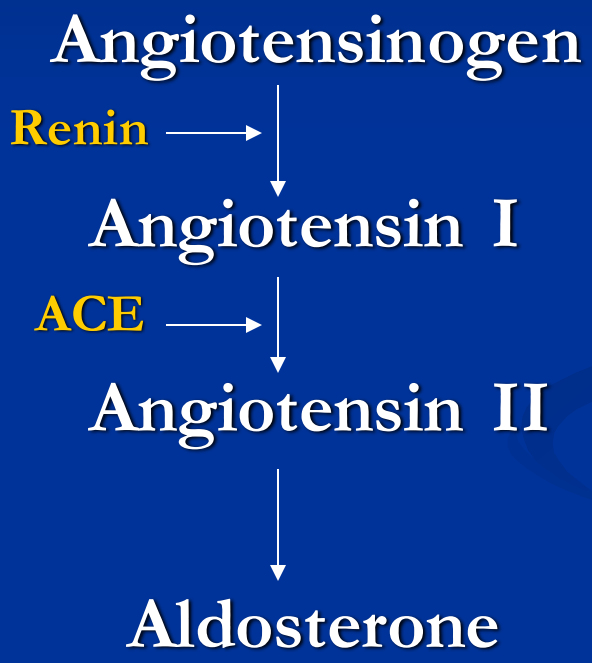


DE= debranching enzyme; side chain cleavage enzyme; desmolase

Deh.= 3β-hydroxysteroid dehydrogenase enzyme

Hyd's= Hydroxylases

Renin-angiotensin-aldosterone axis



- **Factors/drugs ↑ renin-angiotesin-aldosterone:**

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

- **Factors/drugs ↓ renin-angiotesin-aldosterone:**

- Blood volume expansion

- Renin release inhibitors (also known as renin antagonists)

Aliskiren, Remikerin, 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

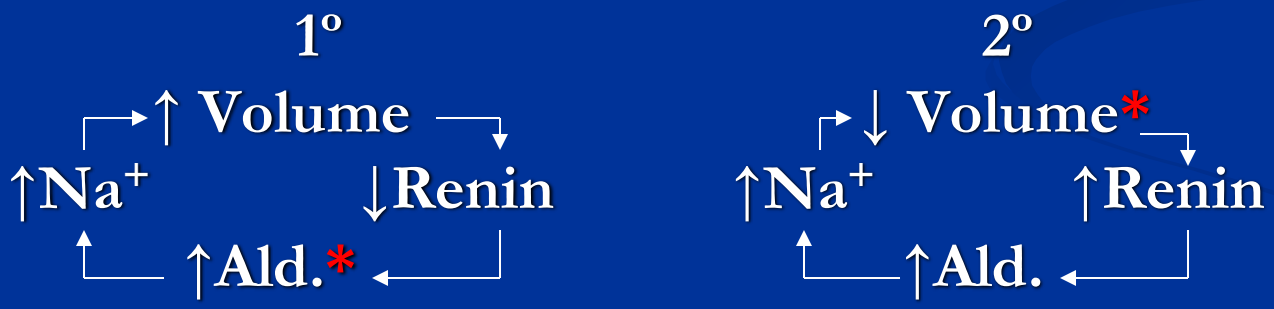
- ↑ reabsorption of Na^+ → hypertension
- ↑ excretion of K^+ & H^+ → hypokalemia & metabolic alkalosis
- ↑ EC volume
- ↑ BP

- **Disorders affecting aldosterone release:**

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

Rx: Fludrocortisone

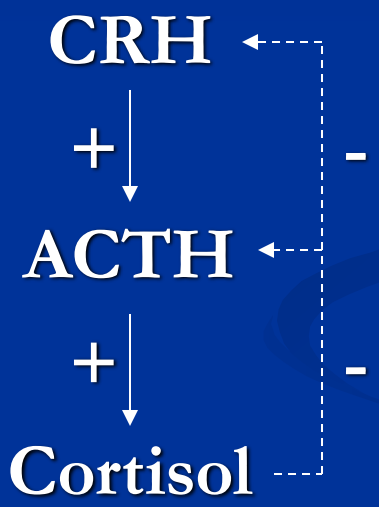
- Hyperaldosteronism



* Initial defect

Glucocorticoids (Cortisol)

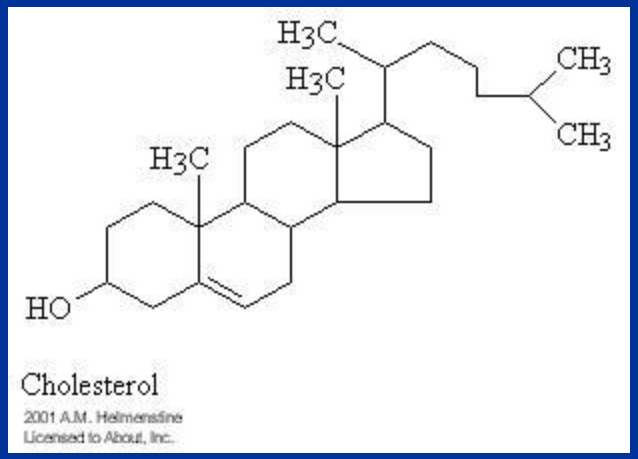
- Feedback control

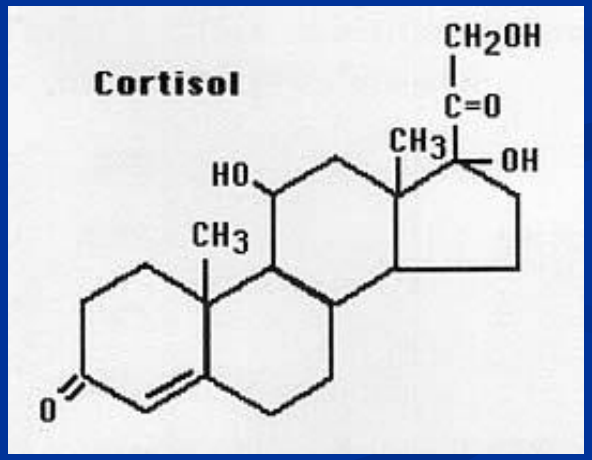


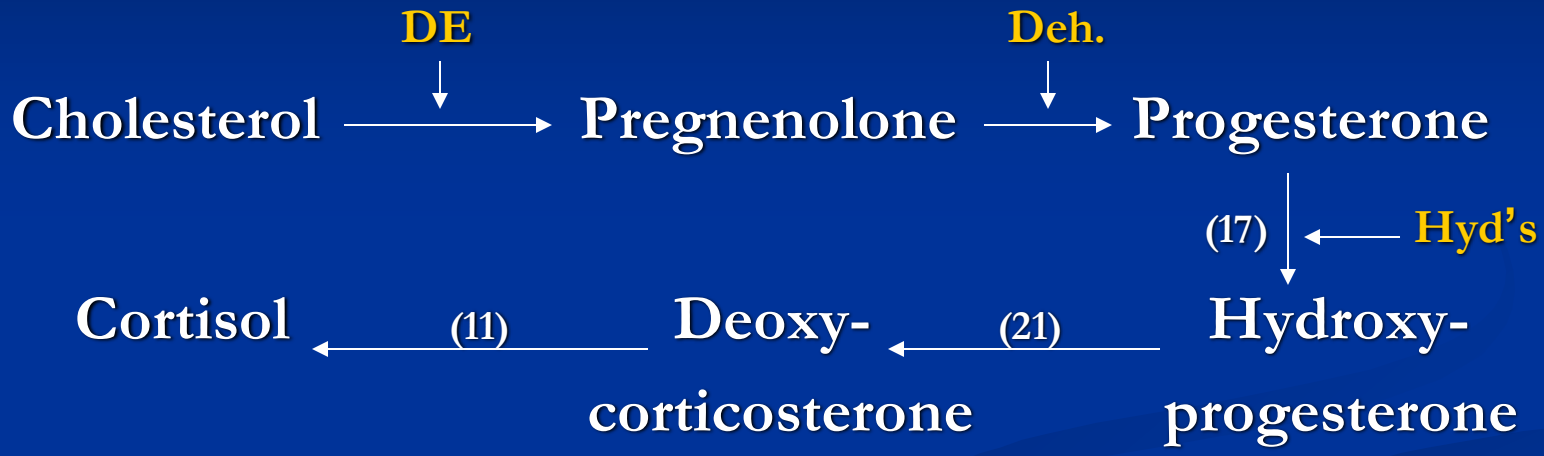
Circadian rhythm

Pt's on cortisol therapy…

Cortisol synthesis (from cholesterol)







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- **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

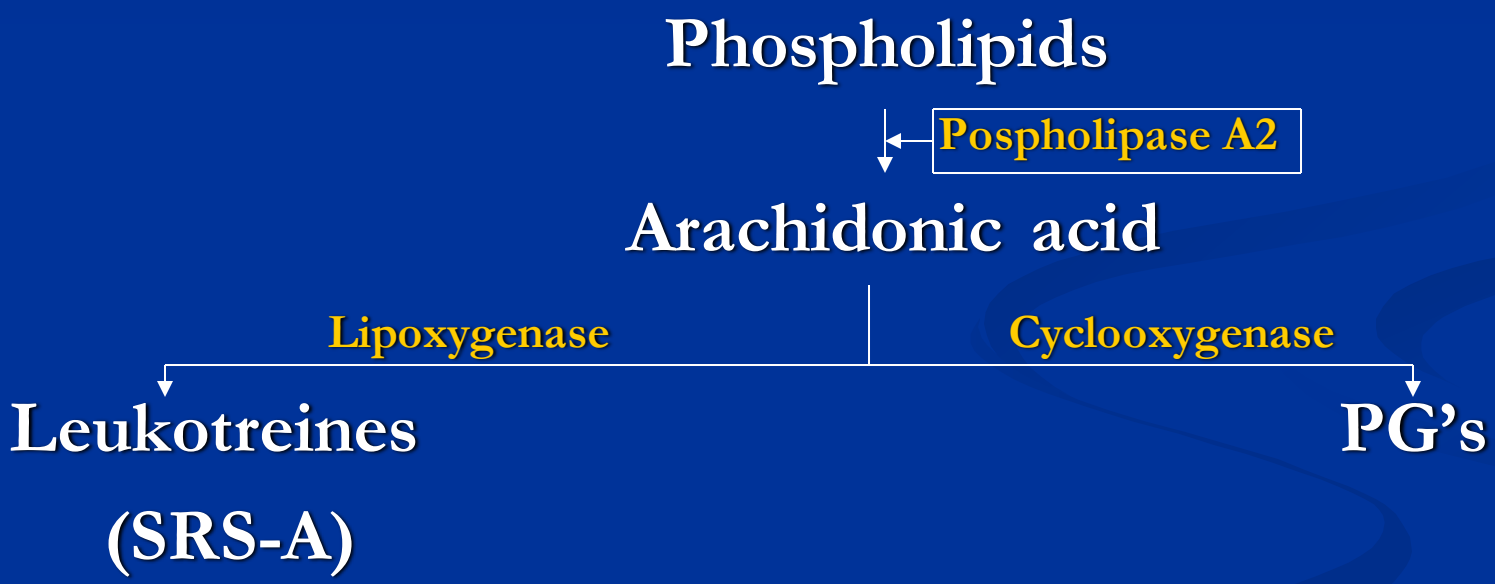
↓ Ca^{++} absorption from intestine

↑ 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**

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

	Half-life	AIA	Ald.-like
Methylprednisolone	20	6	-
Triamcinolone	20	6	-
Beclomethasone	20	6	-
Long-acting:			
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 lee suppression to growth of children and to the hypothalamic-pituitary-adrenal axis and fewer side effects

- Don't stop glucocorticoid therapy abruptly