ENDOCRINE
PHARMACOLOGY

#07

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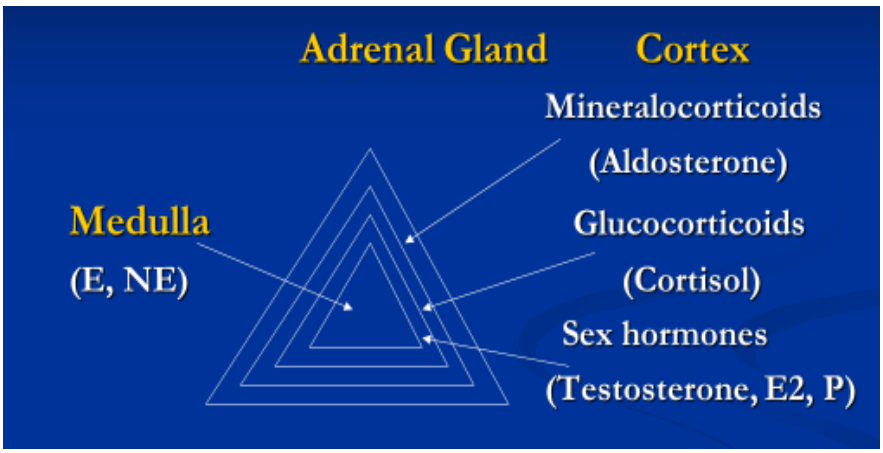
Adrenal Steroids
Mineralocorticoids & Glucocorticoids

Adrenal Gland consists of ;- <u>Medulla</u> & <u>Cortex</u>.

- **Medulla (Epinephrine and Norepinephrine)**
- **The adrenal cortex is divided into three concentric zones: the zona glomerulosa, zona fasciculata, and zona reticularis. Each of these zones secrete different set of hormones as seen in this picture.**

I. **Mineralocorticoids (Aldosterone) – outer zone.**
II. **Glucocorticoids (Cortisol) - middle zone .**
III. **Sex hormones (Testosterone, Estradiol (E2), Progesterone) - inner zone .**



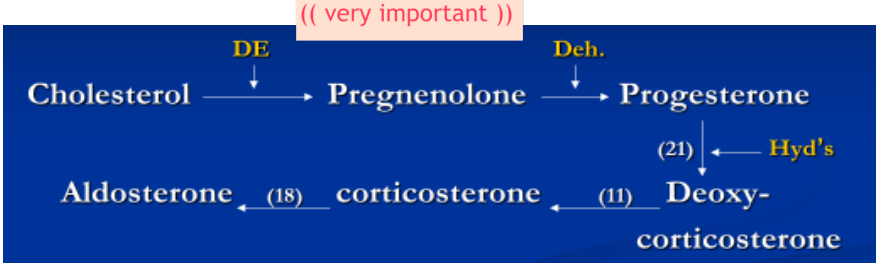
Mineralocorticoids (Aldosterone)

- **Synthesis: From cholesterol (highly lipid soluble).**
- **Control of synthesis and release ;-**
  - **↑ in the plasma concentration of Angiotensin III, a metabolite of angiotensin II .**
  - **↑ plasma angiotensin II (enhances or increases synthesis and release of aldosteron) .**
  - **↑ K^+ blood levels (potassium levels are the most sensitive stimulator of aldosterone) .**
  - **ACTH .**
  - **↓ ECF or blood volume; metabolic acidosis .**

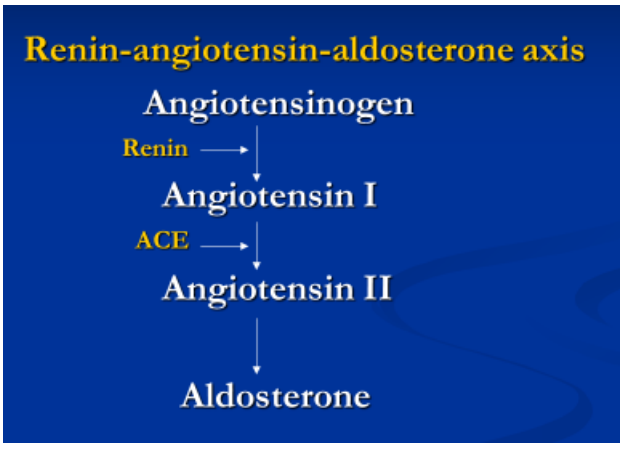
Synthesis pathway:

- **All steroids are originating from cholesterol.**
- **The importance of knowing the enzymes involved in the Steroidogenesis is to understand the mechanisms of drugs that manage the excess of any steroid in the body.**
- **Aldosterone is synthesized in the body from corticosterone, a steroid derived from cholesterol.**

((very important))



- **DE= debranching enzyme; side chain cleavage enzyme; desmolase.**
- **Deh.= 3β-hydroxysteroid dehydrogenase enzyme**.
- **Hyd's= Hydroxylases** .
- **We can target the enzymes in this pathway to manage the excess in hormones production** .
- **Production of aldosterone is regulated by the renin-angiotensin system.**
- The renin-angiotensin-aldosterone system (RAAS) involves several steps, including: When your blood pressure falls, your kidneys release the enzyme renin into your bloodstream. Renin splits angiotensinogen, a protein your liver makes and releases, into pieces. One piece is the hormone angiotensin I. Angiotensin I, which is inactive (doesn't cause any effects), flows through your bloodstream and is split into pieces by angiotensin-converting enzyme (ACE) in your lungs. One of those pieces is angiotensin II, an active hormone. Angiotensin II increases blood pressure. Angiotensin II also triggers your adrenal glands to release aldosterone .



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, β1-blockers .
- ACE inhibitors -- Captopril, Enalapril, Benzopril, fosinopril, Lisinopril, Ramipril … **(widely used in the management of hypertension).**
- ARB's (Angiotensin II receptor blockers) -- Candesartan, Losartan, Irbesartan, telmesartan… **(widely used in the management of hypertension and better than ACE inhibitors).**

Not Required

- Aldosterone antagonists -- Spironolactone, Eplerenone (Not Required) **(widely used in females in cases of acnes and hirsutism).**

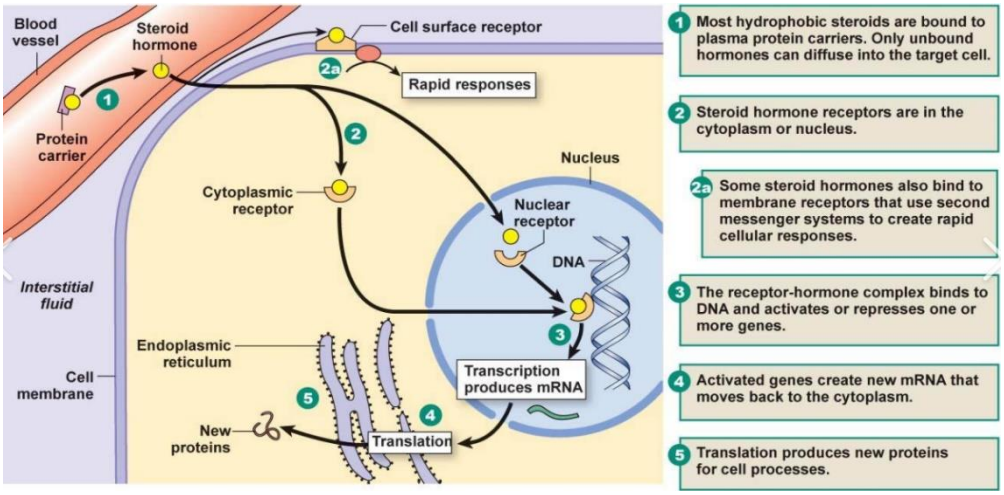
  - Hirsutism is a condition in women that results in excessive growth of dark or coarse hair in a male-like pattern -- face, chest and back.

Aldosterone effects:

✓ **Receptor-mediated.**

- Steroid Hormones and their Receptors:
  - Synthesized by glands and then secreted to travel throughout the blood in the bound form (bound to carrier proteins), only the unbound hormones can then affect their target cells via 3 routes:
    i. Pass through the membrane to bind cytoplasmic receptors forming complexes that then go towards to nucleus to regulate DNA-expression.
    ii. Pass through the membrane to immediately bind nuclear receptors
    iii. Some of these hormones bind cell surface receptors to elicit a rapid cellular response.

➢ Route 1,2 usually require time because the process of protein synthesis while Route 3 elicits a faster response.



Again, Aldosterone Effects ;-

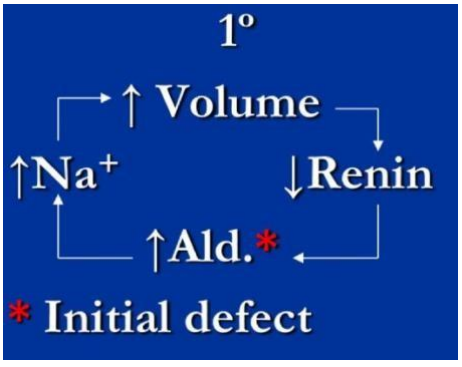
- ✓ **Acts on distal convoluted tubules in the kidney .**
- ✓ **↑ reabsorption of Na+ → hypertension.**
- ✓ **↑ excretion of K+ & H+ → hypokalemia & metabolic alkalosis.**
- ✓ **↑ EC volume .**
- ✓ **↑ BP .**

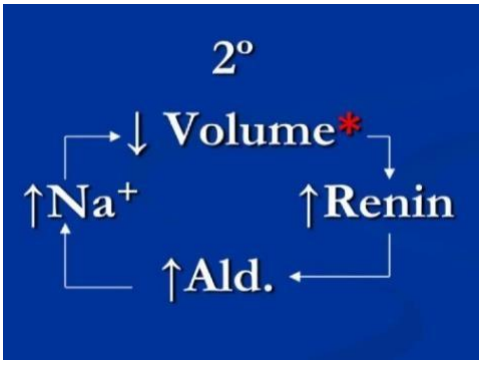
Disorders affecting aldosterone release : -

- ❖ **Hypoaldosteronism manifested by hypotension, hyponatremia , hypovolemia, hyperkalemia, and metabolic acidosis**
- ✓ **Rx (Treatment) : Fludrocortisone** ((very important))

- Hyperaldosteronism

- ❖ **Primary: the problem is in the adrenal Excess production of aldosterone, eventually leads to increase reabsorption of Na+ , resulting in expansion of volume & inhibition of renin.**
- ❖ **Secondary : depletion in blood volume , which in turns stimulates the renin-angiotensin pathway leading to excess production of aldosterone, eventually leads to increase reabsorption of Na+.**

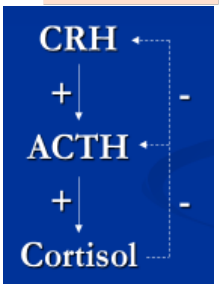




Glucocorticoids (Cortisol)

❖ Feedback control

((very important))



- ✓ CRH stimulates ACTH acts on adrenal gland to form Cortisol.
- ✓ This figure represents the Hypothalamic-pituitary-adrenal axis which is controlled by negative feedback mechanisms, Cortisol back feeding into ant-pituitary or the hypothalamus inhibiting ACTH, CRH release.
- ✓ When cortisol level is high, it inhibits the ACTH & CRH.
- ✓ When ACTH level is high, it inhibits the CRH.
- ✓ Understanding the basis of negative feedback helps put the strategy in the management of such diseases.

❖ Pt's on cortisol therapy ...

- When a patient takes exogenous cortisol chronically (for a long time) CRH,ACTH and cortisol producing cells Atrophy ((exogenous cortisol supplementation suppress CRH, ACTH, endogenous Cortisol))
- the main problem here is to when to stop the exogenous cortisol therapy !! So, when the patient decide to stop the therapy, he should Stop the therapy gradually and not suddenly or it may lead to sudden death.
- the patient should make a <u>Metyrapone Stimulation Test</u>

✓ Explanation ;

✓ Function of metyrapone: inhibits the conversion of 11-deoxycortisol to cortisol by blocking 11 beta-hydroxylase

✓ Indication of the test: Diagnosing patients with adrenal insufficiency

✓ Results in healthy patient:

- High ACTH - High 11-deoxyCortisol - Low Cortisol

✓ Results in patient with adrenal insufficiency:

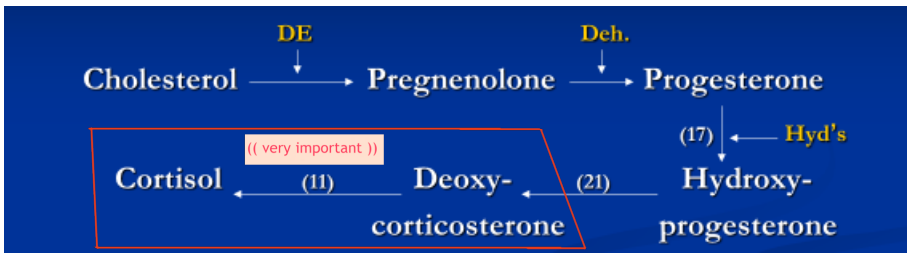
- High ACTH - Low 11-deoxyCortisol - Low Cortisol

❖ Circadian rhythm ;

- Diurnal pattern of secreting Cortisol
  - highest immediately before waking up in morning
  - lowest in midnight

Synthesis pathway:

- Cortisol synthesis (from cholesterol).
- Again, All steroids are originating from cholesterol.



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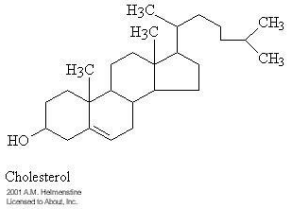

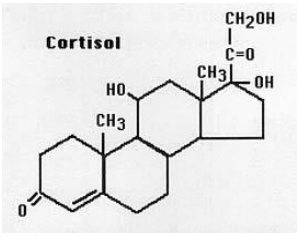

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Steroid synthesis inhibitors

1. o,p'-DDD (Mitotane) ((Not Required))
   - ✓ 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.

2. Aminoglutethimide ((Not Required))
   - ✓ Selective desmolase inhibitor and non selective aromatase inhibitor, same uses as mitotane and Cushing's syndrome.

3. Trilostane ((Not Required))
   - ✓ Competitive inhibitor of 3β-hydroxysteroid dehydrogenase enzyme effective in Cushing's syndrome and breast cancer.

4. Ketokonazole ((Not Required))
   - ✓ An antifungal agent
   - ✓ An inhibitor of different hydroxylases; inhibits steroidogenesis in adrenals and testes
   - ✓ Effective in Cushing's syndrome and Ca of prostate.

5. Etomidate ((Not Required))

- ✓ **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.**

6. Metyrapone (Metopirone) ((very important))

- ✓ **11β-hydroxylase inhibitor**
- ✓ **Effective as a diagnostic tool (metyrapone test) and in the management of Cushing's syndrome.**

THE END

V3

-- توضيح بعض النقاط المهمة جداً ((Very important))
وبعض النقاط الغير مطلوبة بالمحاضرة ((Not Required))
... تمّ اضافة معلومة صفحة ٧

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