ENDOCRINE SYSTEM

Pharmacology

Lec. Enter no.3

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ما ينطق به الدكتور من شرح سيكون باللون الاحمر
وما يكون مهم في شرح الدكتور يكون باللون البنفسجي
ما يكون مهم في السلايدات يكون بخطين أو بخط

Adrenal Steroids
Mineralocorticoids & Glucocorticoids

Adrenal Gland

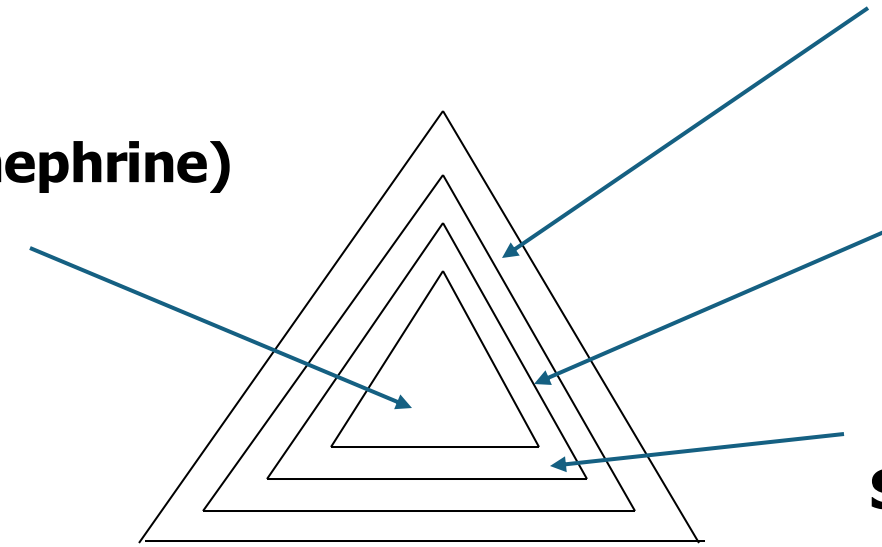
Outer Cortex

Consists of 3 zones :

The outer zone synthesize :

Mineralocorticoids (Aldosterone)

Inner Medulla
(Epinephrin , Norepinephrine)



The middle zone synthesize :

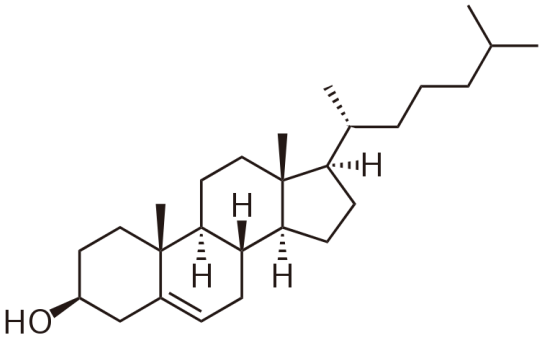
Glucocorticoids (Cortisol)

The inner zone synthesize :

Sex hormones (Testosterone, E2, P)

The problem of the inner zone especially affected by Adenoma tumor (most of tumor affecting endocrine cell are adenomas)

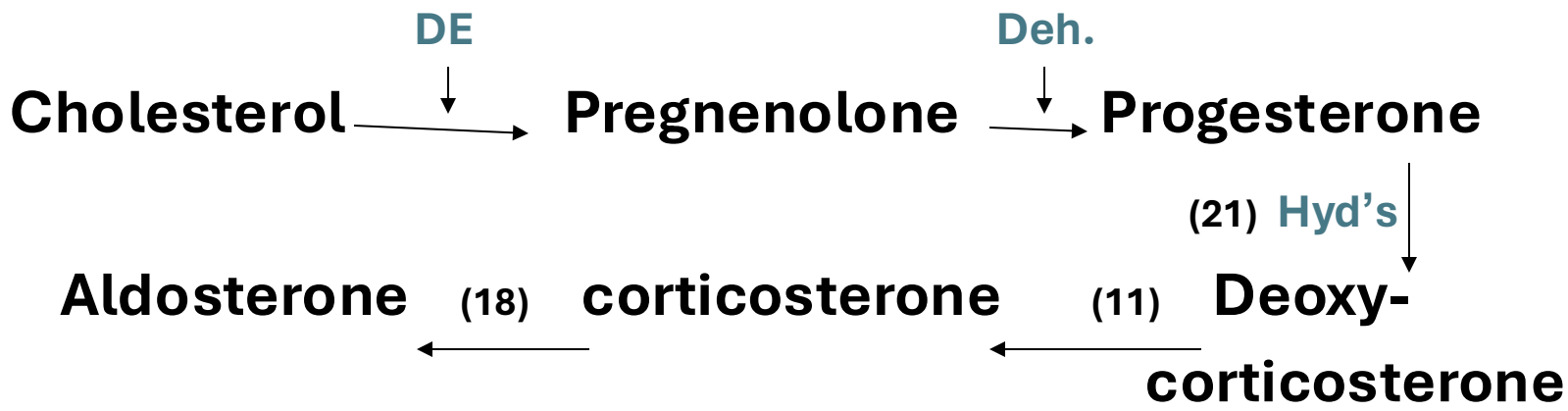
Mineralocorticoids (Aldosterone)



Synthesis: From cholesterol (with its famous 4 ring structure, called steroid nucleus)

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 (has a little effect)**
- **↓ ECF or blood volume; metabolic acidosis**



In addition to adrenal cortex , progesterone also synthesized in ovaries and placenta , despite the places are different but the steps are the same in all sites

DE= debranching enzyme; side chain cleavage enzyme; desmolase

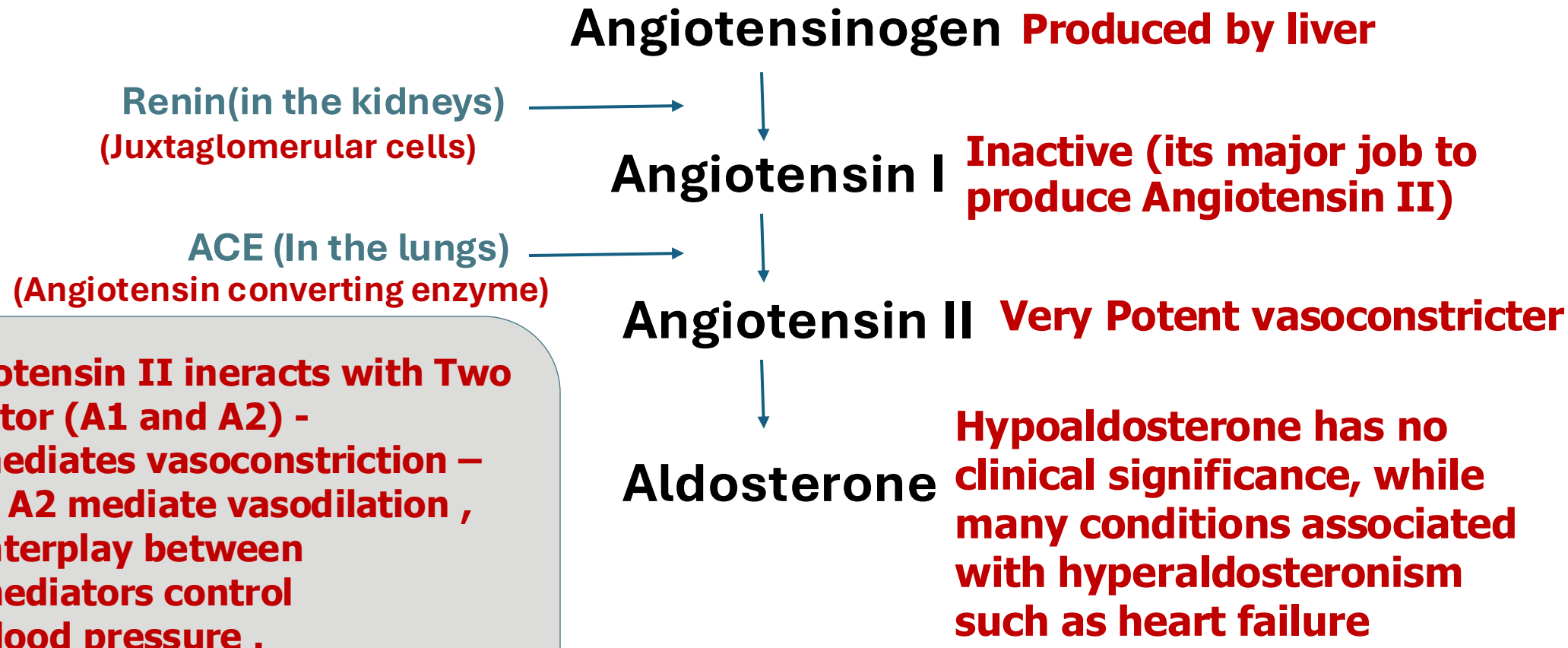
Deh.= 3β-hydroxysteroid dehydrogenase enzyme

Hyd's= Hydroxylases

The importance of knowing the synthetic machinery of specific hormone is that we consider the enzyme as receptor of drugs , and we have certain drugs that can inhibit synthesize of whole steroids , especially if they inhibit the first step in their synthesize (by desmolaze enzyme inhibitor) and can be used in the excess production of whatever steroids .

Renin-angiotensin-aldosterone axis

Major system involved of aldesterone synthesize and release from adrenal gland



Angiotensin II ineracts with Two receptor (A1 and A2) -
A1 mediates vasoconstriction – while A2 mediate vasodilation , the interplay between the mediators control our blood pressure .
A1 and A2 work in balance to control blood pressure .

Angiotensin II is a potent vasoconstrictor that plays a significant role in regulating blood pressure and fluid balance. On the other hand, bradykinin is a strong vasodilator that helps lower blood pressure by relaxing blood vessels and increasing their diameter.

Additional note regarding A1 – A2 receptors:

These receptors play crucial roles in regulating vascular tone and blood pressure. Angiotensin II Type 1-receptors typically cause vasoconstriction, increasing blood pressure, while Angiotensin II Type 2- receptors can inhibit norepinephrine release, leading to vasodilation and a decrease in blood pressure. The balance between these receptors helps maintain proper blood pressure regulation.

- **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 … [PRIL]

- ARB's (Angiotensin II receptor blockers) Selective for A1 receptors (preventing vasoconstriction):

Candesartan, Losartan, Irbesartan, telmesartan… [SARTAN]

- Aldosterone antagonists

Spironolactone, Eplerenone

The ACE inhibitors inhibit converting enzyme , there is another enzyme called kininase which breaks down and metabolise bradykinin which is vasodilator and it is the similar to ACE inhibitors ,so when I prevent the enzyme of converting enzyme, I inhibit bradykininase also and make accumulation of bradykinin which is an advantage for hypertension.

The bradykinin has a very dangerous side effect in certain individuals (not at all), which is a dry cough, so it is contraindicated in conditions with dry cough.

It should be controlled well because severe hypotension causes death.

Important: the major side effect of ACE inhibitors is dry cough.

Advantages of using Angiotensin II Blockers (ARBs):

1.Prevention of Bradykinin Accumulation:

ARBs do not cause the accumulation of bradykinin, unlike ACE inhibitors, which can lead to dry cough. Therefore, ARBs are often referred to as "non-cough" ACE inhibitors.

2.Selective Receptor Blocking:

ARBs selectively block angiotensin II A1 receptors while not affecting angiotensin II A2 receptors, providing targeted action.

3.Comprehensive Inhibition of Angiotensin II Production:

Angiotensin II can be produced by various pathways, including mast cells, basophils in all tissues, and chymases. ARBs prevent the effects of angiotensin II produced through these alternative pathways, offering comprehensive inhibition.

These advantages make ARBs effective in managing conditions like hypertension without some of the side effects associated with ACE inhibitors.

- **Aldosterone effects:**

Receptor-mediated (nuclear receptor)

Acts on distal convoluted tubules in the kidney

- ↑ reabsorption of Na^+ → hypertension

- ↑ excretion of K^+ & H^+ → hypokalemia (the major problem) & metabolic alkalosis

- ↑ EC volume

- ↑ BP

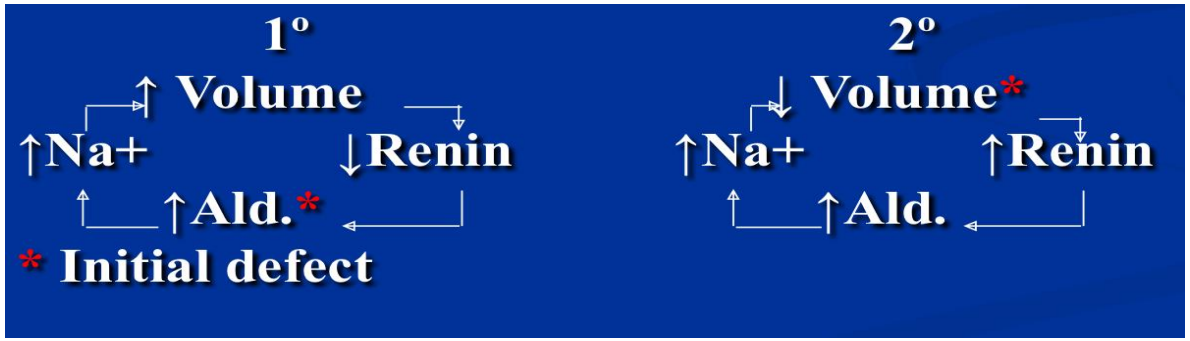
- **Disorders affecting aldosterone release:**

- **Hypoaldosteronism manifested by <u>hypotension,</u>**
- **<u>hyponatremia, hypovolemia, hyperkalemia, and metabolic acidosis</u>**

Rx:Actually we don't have synthetic analog for aldosterone, we have synthetic analog of cortisol with strong aldosterone like activity like Fludrocortisone

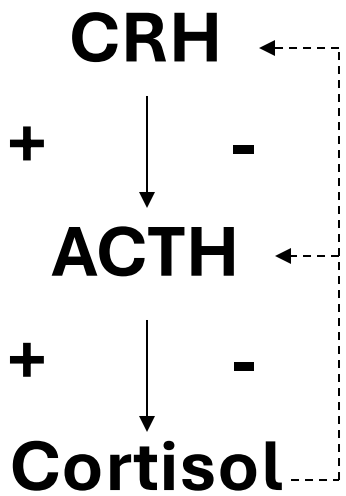
- **Hyperaldosteronism which could be primary(the problem is adrenal), an adenoma affecting aldosterone secreting cells leading to retention of Na+ and increase blood volume and we should make a control of secretion of aldosterone.**

The secondary is toward any thing with decreases blood volume leading to increase release of renin from the kidney and increase synthesis and release of aldosterone from adrenal gland.



Glucocorticoids (Cortisol)

- **Feedback control**



CRH:cortisol releasing hormone

ACTH:adrenocorticotropic hormone

Circadian rhythm are the physical, mental, and behavioral changes an organism experience over a 24-hour cycle. Light and dark have the biggest influence on circadian rhythms, but food intake, stress, physical activity, social environment, and temperature also affect them.

when ever we replace with cortisol in cases of adrenal insufficiency we try as much as to mimic physiology, two third of the dose if the patient works during the day and one third of the dose if he works evening because the most severe side effect of cortisol therapy from out side is suppression of the access.

Steroids aren't only used in case with deficiency states, they are used in many other clinical situations not related to endocrine system.

It is very important in strategy if using glucocorticoids as a therapy to try as much as possible to mimic physiology.

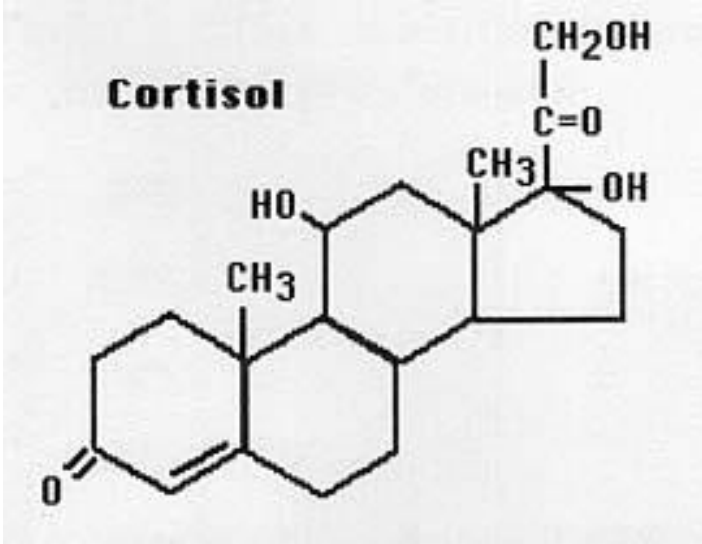
Pt's on cortisol therapy…they are compromised patients because another effect of cortisol is to suppress the immune system and suppress the access for this reason never ever stop it suddenly or rapidly especially in the management of hypertension. (Very strong and potent conditions).

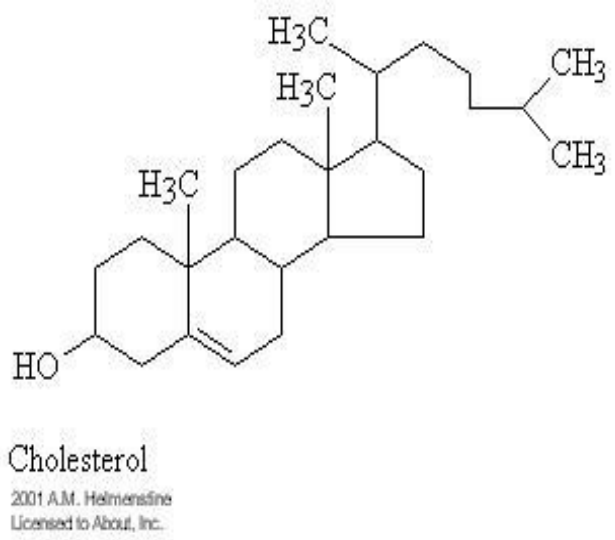
Cortisol synthesis (from cholesterol)(four rings nucleus with side chain).

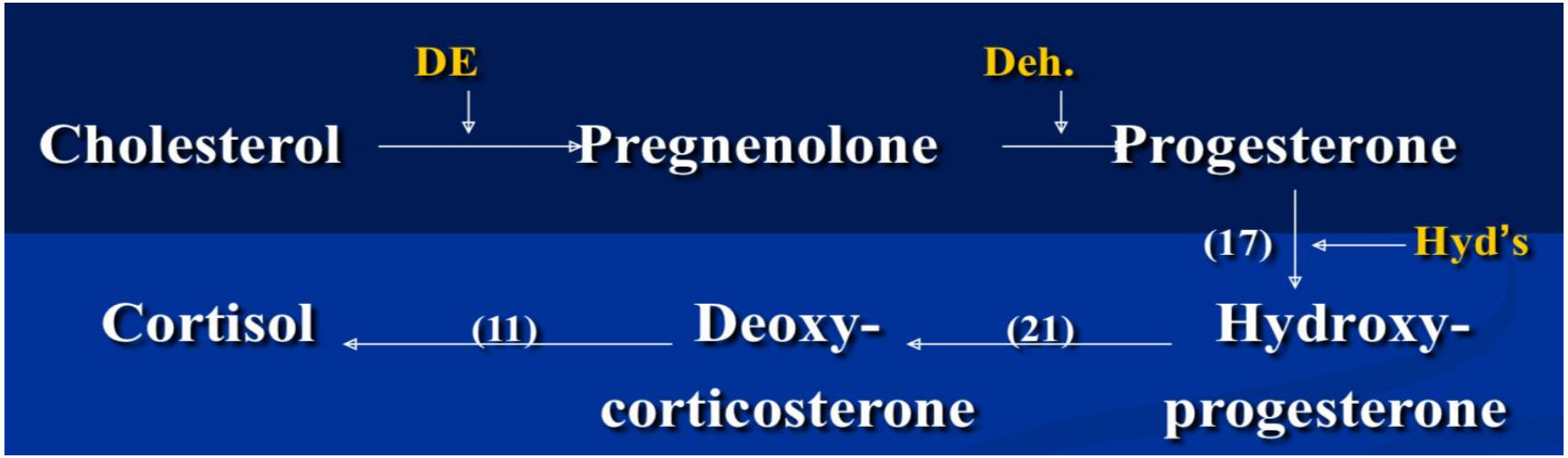
There is a similarity in structure with cortisol.

A simple change in the structure of cortisol could lead to tremendous changes in pharmacological uses.

The difference in structure between estrogen and testosterone is the first ring which is benzene ring in estrogen which is synthesized from androgen in ovaries (aromatization reaction by aromatase enzyme).







DE= debranching enzyme; side chain cleavage enzyme; desmolase

Deh.= 3β-hydroxysteroid dehydrogenase enzyme

Hyd's= Hydroxylases

All steroids exit from progesterone.

DE, Deh and cortisol (in the second zone of adrenal cortex) are important here

- **Steroid synthesis inhibitors:**

We have certain inhibitors that could be used in the management of production many steroids not only cortisol

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

Causes selective atrophy of Zona Fasciculata and Zona Reticularis(selective toxic effect which make damage effects on the inner two zones).

Useful in R_x of adrenal Ca when radiotherapy or surgery are not feasible and in certain cases of breast cancer(next year we will know that it could be managed by testosterone, antiandrogens, androgen, estrogen, antiestrogen, progesterone, antiprogesterone depend on type of cancer).

- Aminoglutethimide

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

Aromatase enzyme converts androgens to estrogens.

- Trilostane

Competitive inhibitor of 3β-hydroxysteroid dehydrogenase enzyme effective in Cushing's syndrome and breast cancer. (second step)

- Ketokonazole

An antifungal agent.

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

It is orally effective.

Effective in Cushing's syndrome and Cancer of prostate.(which is highly dependent on testosterone).

- 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

The doctor promise that the exam questions would be which of the following drugs are a ACE inhibitors, which of the following drugs inhibit…and so on 🙂

- Metyrapone (Metopirone)

11β-hydroxylase inhibitor

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

It inhibits the last step in the synthesis of cortisone.

We do metyrapone test to ensure that we can safely stop glucocorticoid therapy.

It affects endogenous glucocorticoids.

The metyrapone stimulation test is based upon the principle that it inhibits conversion of 11-deoxycortisol to cortisol. The resultant decrease in serum cortisol concentrations should be followed by an increase in corticotropin (ACTH) secretion and the immediate precursor of cortisol, 11-deoxycortisol.

Additional note regarding metyrapone test:

Normal Response:

- A significant decrease in cortisol levels.
- An increase in 11-deoxycortisol levels.
- An increase in ACTH levels.

Adrenal Insufficiency:

- Little to no increase in 11-deoxycortisol levels.
- ACTH levels may remain low or show insufficient increase.

Pituitary or Hypothalamic Dysfunction:

- Low ACTH levels.
- Correspondingly low 11-deoxycortisol levels despite metyrapone administration.

رب اشرح لي صدري، ويسر لي أمري، واحلل عقدة لساني، يفقهوا قولي، اللهم لا سهل إلا ما جعلته سهلاً، وأنت تجعل الصعب إن شئت سهلاً، يا أرحم الراحمين. اللهم افتح علي فتوح عبادك العارفين، اللهم انقلني من حولي وقوتي وحفظي إلى حولك وقوتك وحفظك، اللهم اجعل لي من لدنك سلطانًا نصيرا.

اللهم لا سهل إلا ماجعلته سهلا، وأنت تجعل الحزن سهلا إذا شئت.

V2: slide 11 important note is added
V3:slide 11 hypertebtion instead of hypotension
V4 : slide 8 **Angiotensin Receptors instead of alpha receptors**