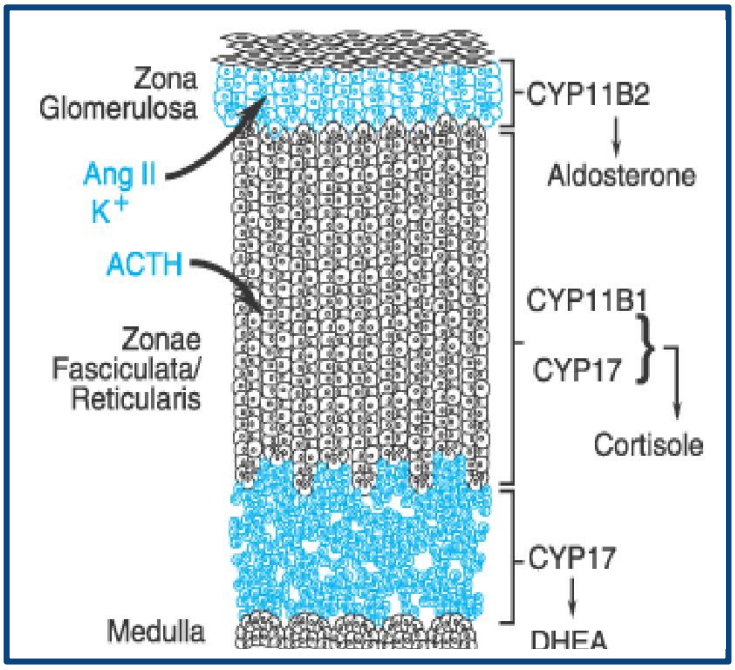
Endocrine System
Biochemistry-Lec(5)

✍Brief Intro:

•Grossly,if you make a c/s of the adrenal gland you'll finds two parts ⏩ The yellowish cortex (90%) and the brownish ,red-mahogany medulla (10%).
•The cortex secretes ⏩ Steroids which are all made from cholesterol whereas the medulla secretes catecholamines (Epi,Nepi) which are classified as aa-derived (Tyrosine).
•Histologically , the cortex can be divided into three areas each of them has a different cellular morphology & secretion :

Zone	*1°ry Reg by*	*Hormone Class*	*1° Hormone Produced*
Zona Glomerulosa (G)	Angiotensin II	Mineralocorticoids	Aldosterone
Zona Fasciculata (F)	ACTH	Glucocorticoids	Cortisol
Zona Reticularis (R)	ACTH	Androgens	DHEA



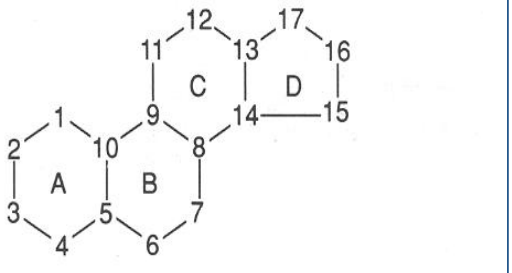
⋆ Steroid hormones play important roles in:
(1) Carbohydrate metabolism regulation ⏩ glucocorticoids.
(2)Mineral balance ⏩ Mineralocorticoids.
(3)Reproductive functions ⏩ Gonadal steroids

⋆ Steroids also play roles in ➡ inflammatory responses, stress responses, bone metabolism, cardiovascular fitness, behavior, cognition, and mood.

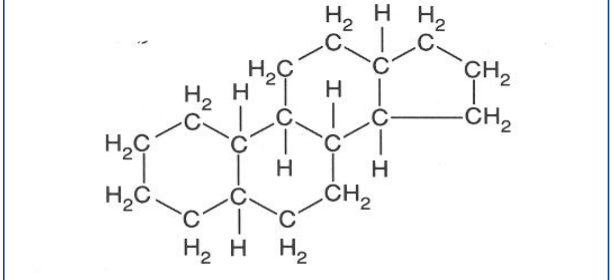
Now the lec;

Steroid Hormones

•Structure :
-Steroids are **lipophilic** molecules.
-All steroids, except calcitriol, have **cyclopentanoperhydrophenanthrene** structure (sterane).
-The parental precursor of steroids is cholesterol.
-Steroid Hormone Classes :Progestins ,Glucocorticoids,Mineralocorticoids ,Androgens,Estrogens Vit D.



Numbering system of carbons


Cyclopentanoperhydrophenanthrene nucleus

Signaling pathways of steroid hormones :

• Steroid hormone receptors are found in the nucleus, cytosol, and also on the plasma membrane of target cells. They are generally intracellular receptors (typically cytoplasmic or nuclear) and initiate signal transduction for steroid hormones which lead to changes in gene expression over a time period of hours to days.

• In addition to nuclear receptors, several GPCRs and ion channels act as cell surface receptors for certain steroid hormones.

• Steroid receptors of the nuclear receptor family are all transcription factors. Depending upon the type of receptor, they are either (1)located in the cytosol and move to the cell nucleus upon activation, or (2)remain in the nucleus waiting for the steroid hormone to enter and activate them. This uptake into the nucleus is facilitated by ➡ NLS found in the hinge region of the receptor which is covered up by HSPs remain bound to the receptor until the hormone is present ➡Upon binding by the hormone the receptor undergoes a conformational change ➡releasing the HSP, and the receptor together w/ the bound hormone enter the nucleus to act upon transcription.

The pathway :

Steroid hormones are soluble in the plasma membrane and readily enter the cytosol.

⏬

Steroids bind to intracellular receptor either in the cytosol or in the nucleus.

⏬

The hormone-receptor complex acts as a transcription factor which turns on / turns off the genes.

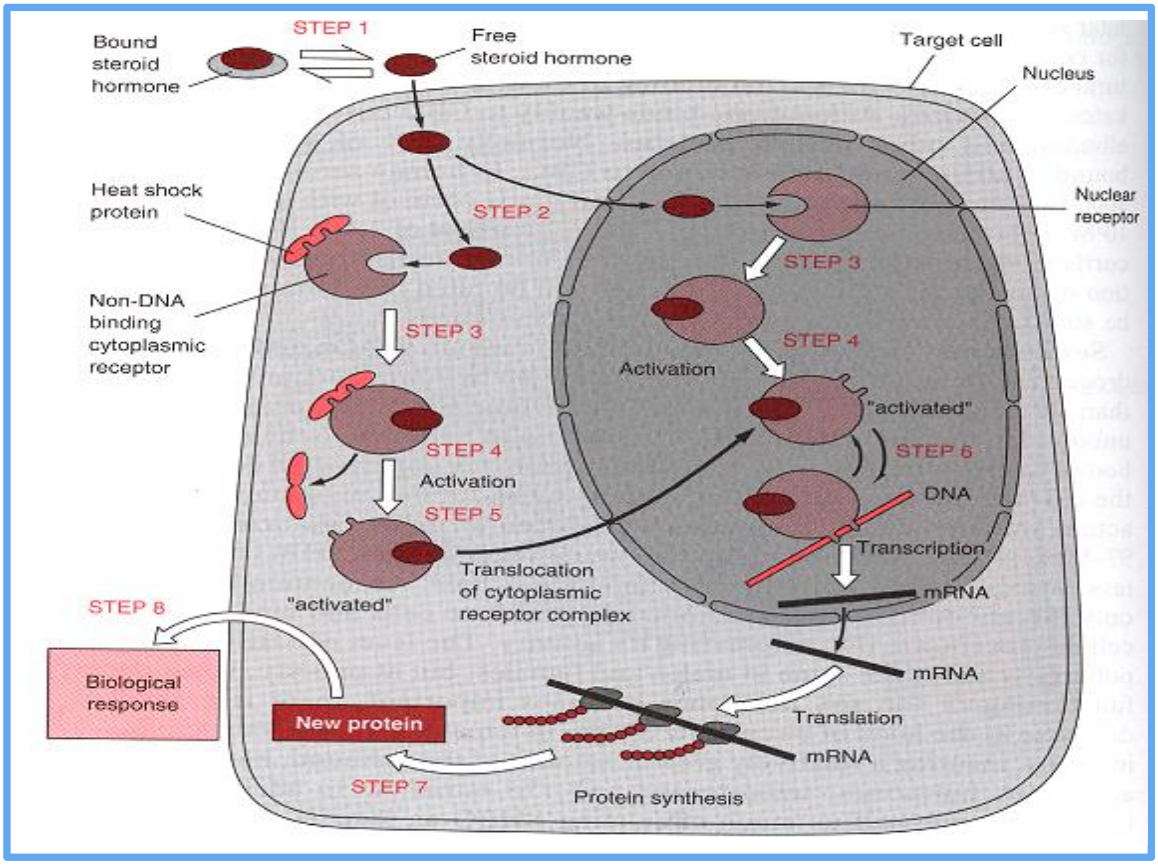
⏬

Messenger RNA is transcribed, leaves the nucleus, and is translated into a specific protein by ribosome.

⏬

The specific proteins then carry out function in the target cell.

⭑ Because steroid hormones initiate protein synthesis *their effects are produced more slowly, but are more long-lasting* than those produced by other hormones.

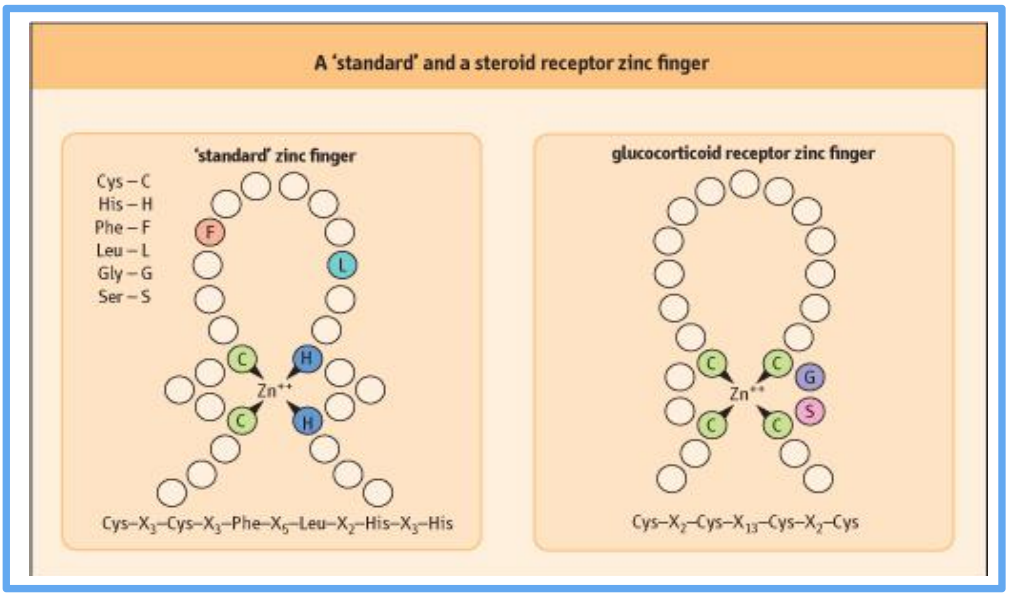


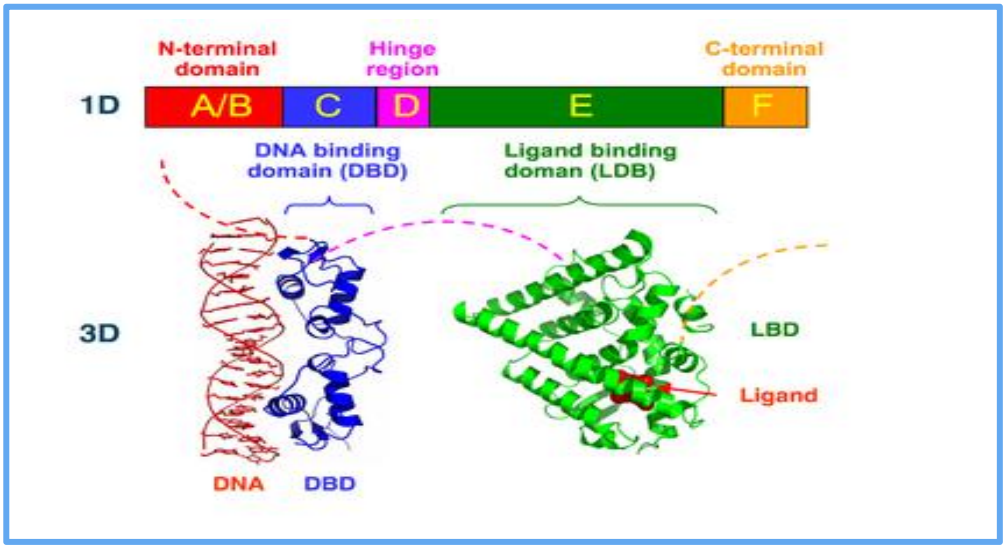
Model of typical steroid hormone receptor:

• Intracellular steroid hormone receptors share a common structure of four units that are functionally homologous :

- ✓ Variable domain ➡interacts w/ other transcription factors
- ✓ DNA binding domain ➡highly conserved, consists of two zinc fingers(where zinc is coordinated w/ four cysteine and no histidine residues.)Their 2ry and 3ry structure is distinct from that of classic zinc fingers.This region controls which gene will be activated. On DNA it interacts w/ the HRE.
- ✓ Hinge region ➡controls the movement of the receptor to the nucleus.
- ✓ Ligand binding domain ➡Induces a conformational change in the receptor which results in dissociation from the HSP complex and translocation to the nucleus where target genes are activated or repressed w/ corresponding changes in specific mRNAs and hence the encoded proteins which mediate the physiological resp.

Note :Nuclear receptors that bind steroid hormones typically form homodimers,dimer formation is facilitated mainly through interactions b/w the LBDs of both receptors, and is essential for their function, as mutations in the dimerization domain typically render the receptor inactive.





(1)Steroid hormones are not packaged, but synthesized and immediately released.
(2)Enzymes which produce steroid hormones from cholesterol are *located in mitochondria and smooth ER*.
(3)In some cases a steroid is secreted by one cell and is converted to the active steroid by the target cell ex ➡ androgen is secreted by the gonad and converted into estrogen in the brain.
✍Note : FSH stimulates ovarian production of estrogens by granulosa cells of the ovarian follicles and corpus luteum.In addition, some estrogens are also produced in smaller amounts by other tissues such as ➡*liver,pancreas,bone,adrenals,skin,brain,adipose tissue and the breasts*.
(4) Progesterone & Estradiol mainly produced by ➡Corpus luteum & Ovary .
(5) Testosterone & Dihydrotesosterone produced by ➡Testes .

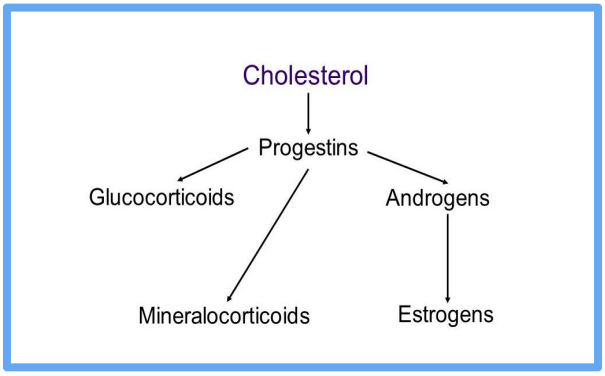
(6)Steroids are lipid soluble and thus have to be carried in the blood complexed to specific binding globulins :

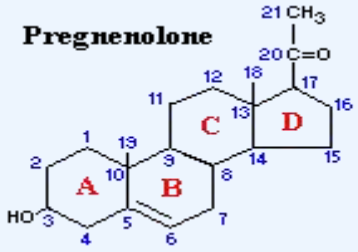
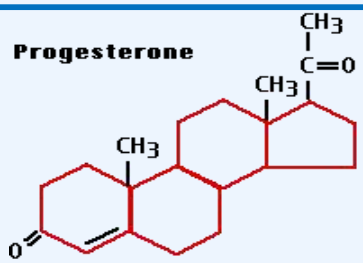
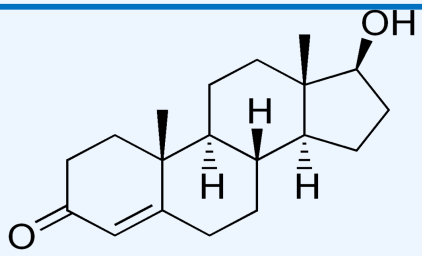
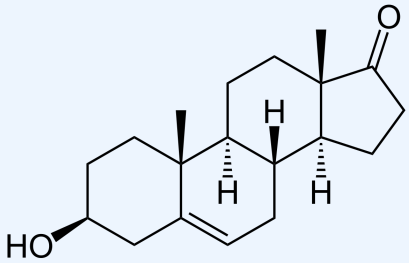
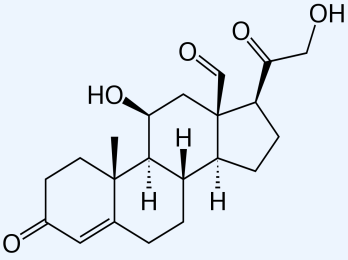
Binding protein	Hormone(s)
SHBG(=TEBG)	Testosterone Estradiol
CBG(=Transcortin)	Progesterone Cortisol
Gc-Globulin	Vit D and its derivatives
Albumin	

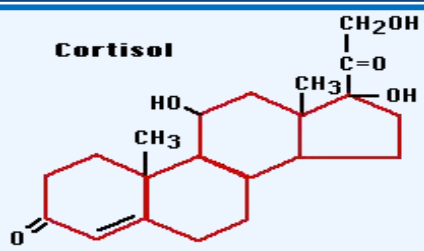
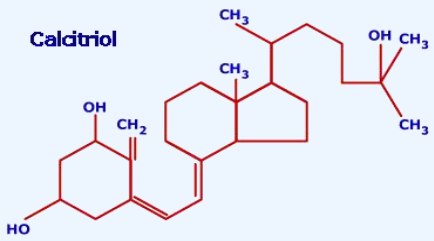
• Only the free fraction is biologically active usually less than 10%.
⭐ Notes r/t SHBG :
• Affinity of SHBG for testosterone is higher than its affinity for estradiol.
• Before puberty - the level of SHBG is about the same in males and females .
• At the puberty - there is a small decrease in the level of circulating SHBG in females and larger decrease in males ⏩ In adults, males have half of the amount of SHBG than females ⏩ insuring relatively greater amount of the unbound, biologically active sex hormones.
• In men, ⬆ SHBG ➡ ⬇ free testosterone➡Gynecomastia.
• In women, ⬇ SHBG➡⬆ free tesosterone➡Hirsutism.
• OCPs &Pregnancy ➡⬆ SHBG.
(7)Transcortin is produced in the liver and its synthesis is increased by estrogens.
(8)Hormone bound to transport proteins are protect from metabolism and inactivation.
(9)Transport proteins assist in maintaining a level of hormones in circulation.

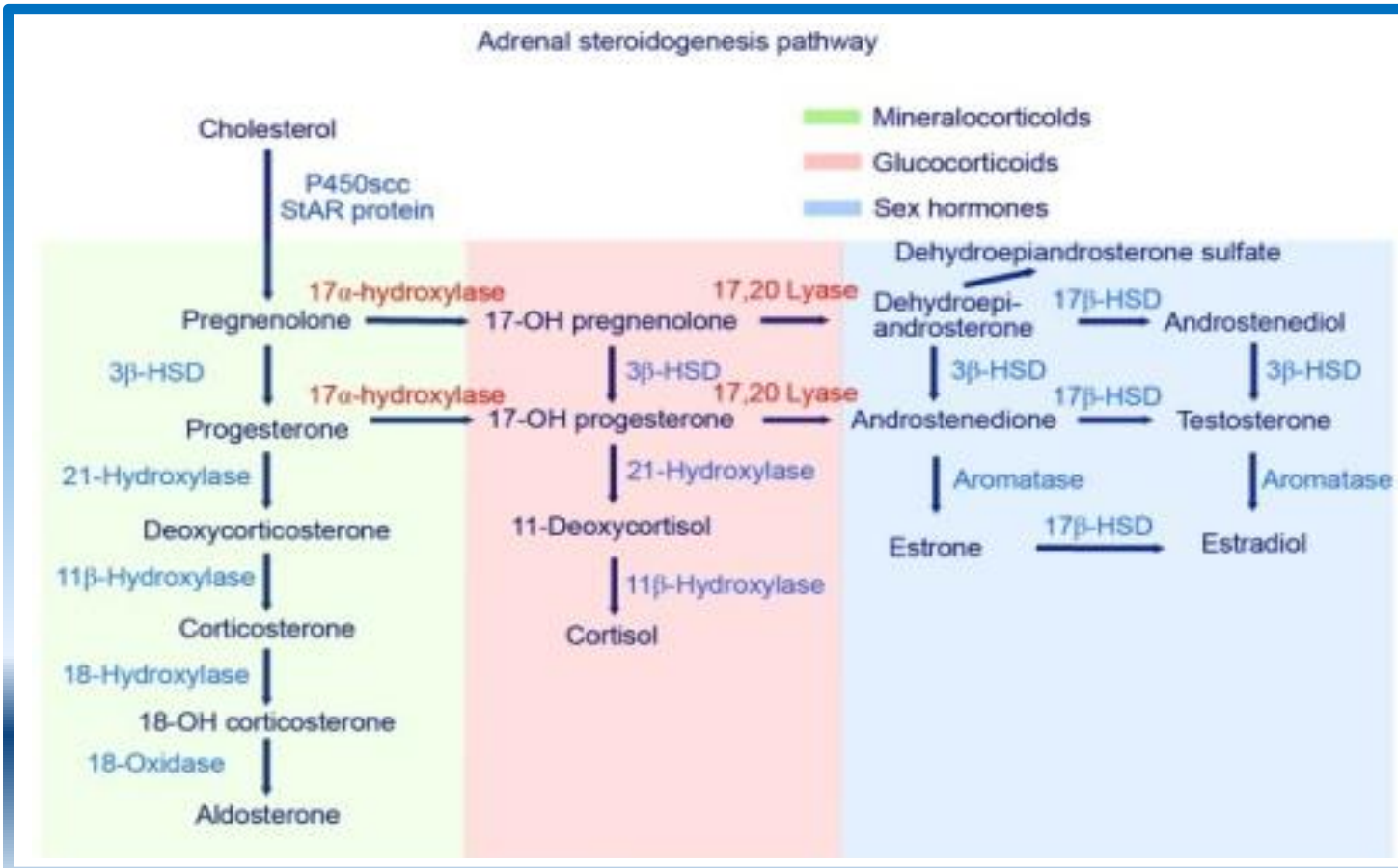
Cortisol	Aldosterone
70% is bound to transcortin.	10 % is bound to transcortin.
22% of cortisol is bound to albumin	60% of aldosterone is bound to albumin
8% free cortisol	A small amount of aldosterone is bound to other plasma proteins

(10)The biosynthetic precursors of the all Steroid Hormones ➡Progestins .



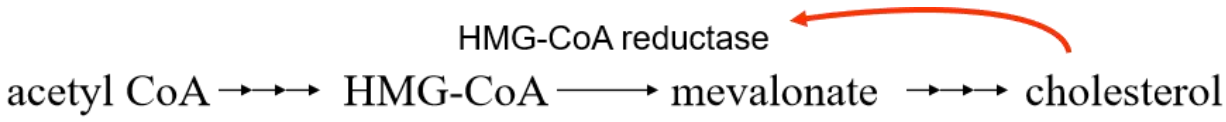
Hormone	Structure	Description
Pregnenolone		• Produced directly from cholesterol. • The precursor molecule for all C18, C19 and C21 steroids. • A double bond b/w (C5-C6). • =O at position 20.
Progesterone (C-21)		• produced directly from pregnenolone. • Secreted from the corpus luteum. • Maintains (w/ estradiol) the uterine endometrium for implantation. • Differentiation factor for mammalian glands. • Keto-group C3, Double bond(C4-C5) ,=O at positions (3) & (20).
Estradiol(C-18)		In females: • Regulates gonadotrope secretion in ovarian cycle. • Maintains (w/ progesterone) uterine endometrium. • Differentiation of mammalian gland. • Responsible for 2ry female sex characteristics. In males : -ve feedback inhibitor of Leydig cell synthesis of testosterone. • 2 OH's at (3) & (17) , 3 double bonds in the A ring .
Testosterone (C-19)		• Produced from progesterone. • After conversion to DHT,production of sperm proteins in Sertoli cells. • Responsible for secondary male sex characteristics. • Double bond(C4-C5),-OH at(17),Keto-gp at(3).
DHEA		• Week androgen, which can be converted to estrogen. • Various protective effects. It may play a role in the aging process. • Regulates NAD+ coenzymes. • -OH at (3) ,Keto-gp at (17),double bond (C5-C-6)
Aldosterone(C-21)		• The principal mineralocorticoid. • Produced from progesterone in the zona glomerulosa of adrenal cortex. • Causes sodium ion uptake via conductance channel. ✍Aldactone ⏩ aldosterone antagonist. • Occurs in high levels during stress. • Rises blood pressure and fluid volume. • Double bond(C4-C5),-OH at(11)& (21),keto group at (3) & (20),-CHO at(18).

Cortisol (C-21)		• Dominant glucocorticoid in humans, synthesized from progesterone in the zona fasciculata of the adrenal cortex. • Stress adaptation through various cellular phenotypic expression. • Slight elevation of liver glycogen. • Numerous effects on the immune system, killing effect on certain T cells in high doses. • Na+ uptake in epithelia lumen. • Double bond (C4-C5),Keto at(3) & (21),OH at (11) & (17).
Calcitriol(C-27)		• Causes synthesis of Ca2+ transport protein. • Regulates calcium and phosphorus homeostasis. • 3 OH's (1) (3) (25) ,CH3 (20) (18) 2(25).

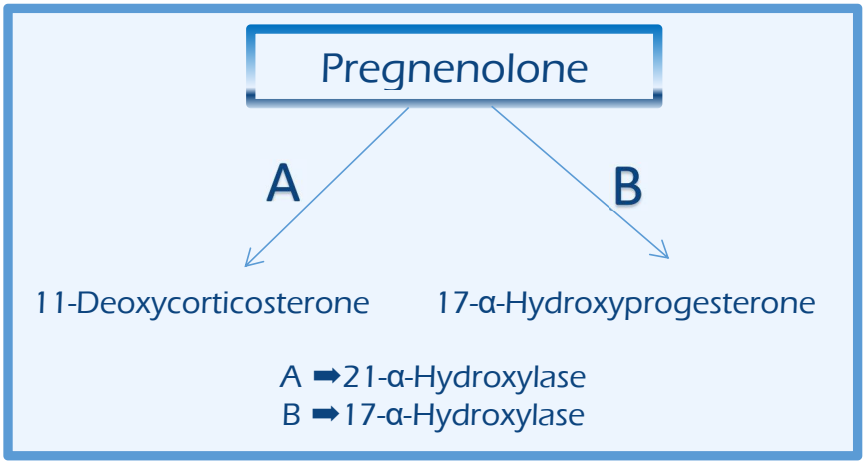


(1) Inactive metabolites of testosterone involve ➡ Androsterone & Eticholanolone.
(2) Testosterone is converted to DHT (active form) in peipheral tissues by the enzyme ➡ 5α-reductase.
(3) Testosterone can also be converted to Estadiol by the enzyme ➡ aromatase.
(4) Both DHT and Estradiol considered as active metabolites of testosterone .
(5) Peptide hormones are encoded by specific genes ,whereas steroid hormones are synthesized from the enzymaticaly modified cholesterol ⏩ there is no gene which encodes individual hormone.
(6) The regulation of steroidogenesis involves control of the enzymes which modify cholesterol into the steroid hormone of interest.
(7) Cholesterol can be made w/n the cell from acetyl CoA (de novo synthesis) ➡ a multistep process, involving many enzymatic reactions.
(8) A key rate-limiting enzyme is HMG-CoA reductase.

(9)There is -ve feedback regulation of HMG-CoA reductase activity by cholesterol, so that high intracellular cholesterol inhibits de novo synthesis.



(10)Cholesterol is converted to pregnenolone "synthetic precursor of C-18 ,C19,C21" by the enzyme ➡Desmolase.
(11)After pregnenolone being synthesized it has 2 pathways to undergo they are ➡Conversion to 11-Deoxycorticosterone or Conversion to 17-α-Hydroxyprogesterone.



(12)11-Deoxycorticosterone converted by 11-β-Hydroxylase to ➡Corticosterone which gives rise to aldosterone by the enzyeme aldosterone synthase.
(13)17-α-Hydroxyprogesterone is converted by 21-α-Hydroxylase to ➡11-Deoxycortisol which gives rise to cortisol.

(14)Collectively,the enzyme 21-α-Hydroxylase catalyzes the following :
- ✓ Conversion of pregnenolone to 11-Deoxycorticosterone .
- ✓ Conversion of 17-α-Hydroxyprogesterone to 11-Deoxycortisol

(15)Pregnenolone is converted to progesterone by the enzyme ➡ 3-β-Hydroxysteroid dehydrogenase.

Congenital Adrenal Hyperplasia

✔A familial disorder of adrenal steroid biosynthesis due to adrenal enzyme deficiency .
✔Inherited as autosomal recessive dz's resulting from mutations of genes for enzymes mediating the biochemical steps of production of mineralocorticoids , glucocorticoids or sex steroids from cholesterol by the adrenal glands.
✔3 major enzyme deficiencies are clinically important :

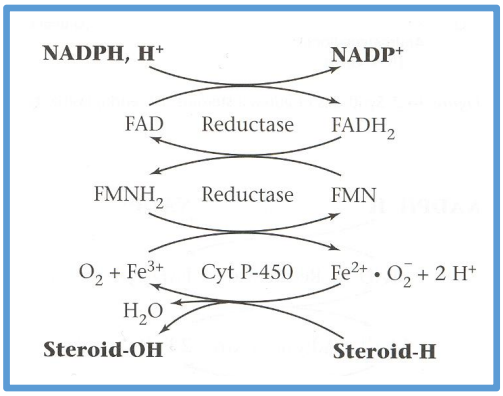
- ❖ 21-α-Hydroxylase deficiency ➡The most common type
  OVERALL effect ⏭ No cortisol , No aldosteron , Excess androgens
  ✔No cortisol effect:
  - ACTH secretions will be increased.
  - An increase in ACTH levels will in turn lead to adrenal hyperplasia.

  ✔No aldosterone effect:
  - No sodium reabsorption, which means that sodium will excreted through the kidneys, water will follow, and then we'll end up w/ decreased blood volume and decreased bloodpressure ➡- Hypotension. - Vomiting. - Low blood volume. - Dehydration.
  ➡Overall effect is salt wasting, which is an emergency and the patient could die w/n hours to days.
- ❖ 11-β-Hydroxylase deficiency ➡There will be an accumulation of 11-deoxycorticosterone and 11-deoxycortisol(as this enzyme is responsible for its conversion to cortisol), in addition to excess androgens.
  There will be no salt wasting ;Because the 11-deoxycorticosterone has a strong mineralocorticoid activity, enough to compensate for the loss of aldosterone.
  So no hypotension, on the contrary, affected pts will have hypertension, due to the accumulation of 11-deoxycorticosterone.
- ❖ 17-α-Hydroxylase deficiency➡No androgens (Male; could be born with ambiguous genitalia, in this case),No cortisol, excess aldosterone.

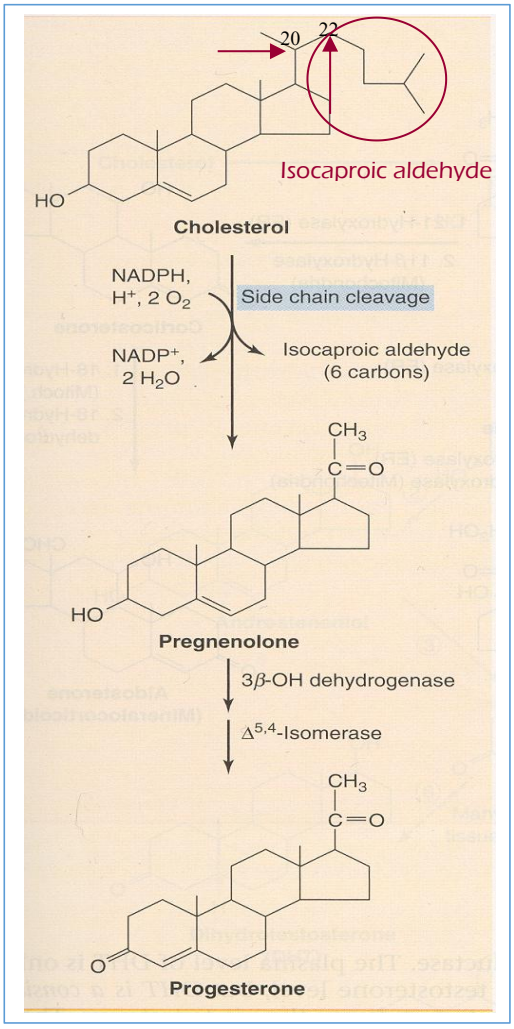
Synthesis of Progesterone

Mitochondrial side chain cleavage enzyme cholesteroldesmolase initiates the synthesis of the progestins ⏩ It hydroxylates C 20 and 22 and involves the cleavage of a 6-carbon group from cholesterol (isocaproic aldehyde) ⏩ pregnenolone .

- This reaction require cytochrom P- 450 as an intermediate electron carrier (integral part of the inner mitochondrial membrane, a flavoprotein containing both FAD and FMN). Electron pass from the reduced NADPH ➡ FAD ➡FMN ➡O2



- Pregnenolone will be converted to progesterone by the enzyme 3-β-Hydroxysteroid dehydrogenase.



Hormonal Stimulation of Steroid Hormone Biosynthesis

Hormone stimulation depends on the cell type and receptor (ACTH for cortisol synthesis, FSH for estradiol synthesis, LH for testosterone synthesis etc.)

⏬

Hormone binds to cell membrane receptor and *activates adenylate cyclase mediated by a stimulatory G protein*.

⏬

Receptor, activated by hormone, may directly stimulate a calcium channel or indirectly stimulate it by activating the PI cycle.

⏬

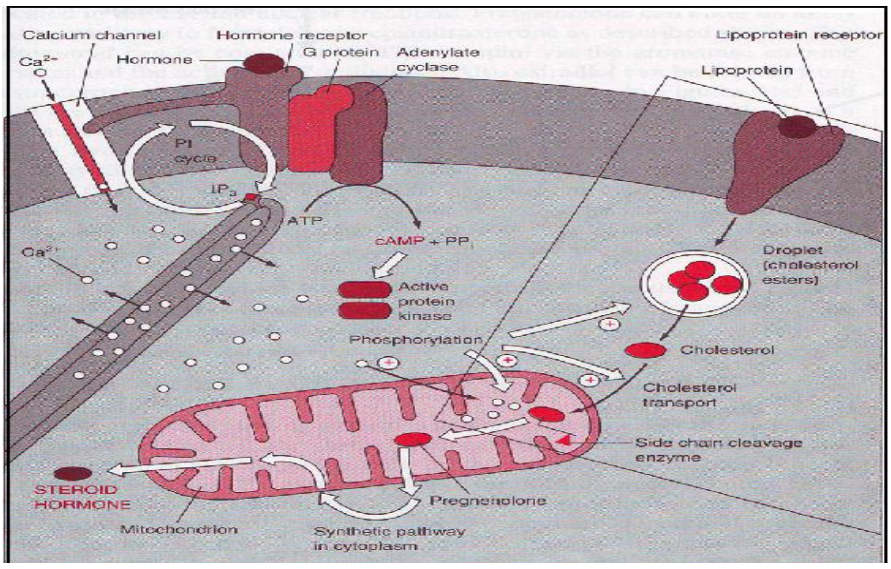
The increase in cAMP activates protein kinase whose phosphorylations cause increased hydrolysis of cholesteryl esters from droplet to free cholesterol and increase cholesterol transport into the mitochodrion.

⏬

Elevated Ca 2+ levels and protein phophorylation bring about induced levels of the side chain cleavage reaction.

⏬

Steroid is produced, secreted into the extracellular space and circulated to the target tissue in the blood stream

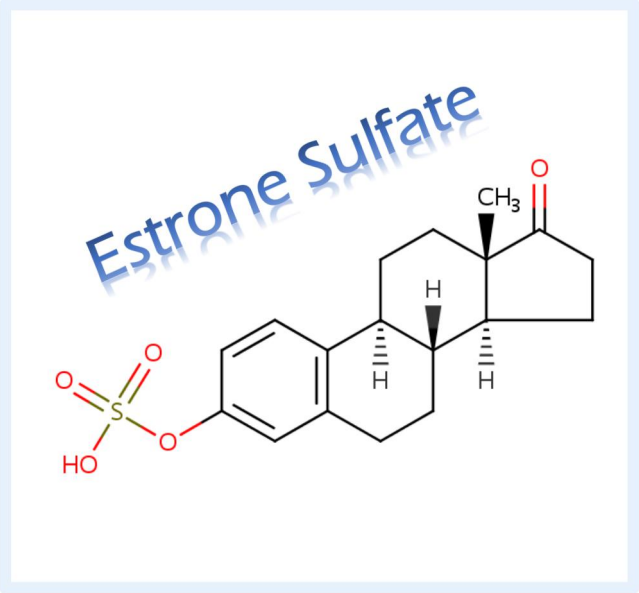


▪ Critical step in steroid hormones biosynthesis is the cell activity in mobilizing cholesterol stored in a droplets, transport of cholesterol to mitochondrion.

▪ The rate-limiting step is the *rate of cholesterol side chain cleavage in mitochondrion by the cytochrome P450 side chain cleavage enzyme complex*.

➡Hormone Catabolism and Excretion

✔Inactivation of steroids involves reductions and conjugation to glucuronides or sulfate to increase their water solubility.
✔Most are catabolized by ➡ *liver and kidneys.*
✔70% of the conjugated steroids are excreted in ➡ urine .
✔20 % of the conjugated steroids leave in ➡ feces and rest exit through the skin.



Adverse effects of Glucocorticosteroids :

- ✓ Cushing's syndrome
- ✓ Osteoporosis
- ✓ Tendency to hyperglycaemia
- ✓ Negative nitrogen balance
- ✓ Increased appetite
- ✓ Increased susceptibility
- ✓ to infections
- ✓ Obesity.