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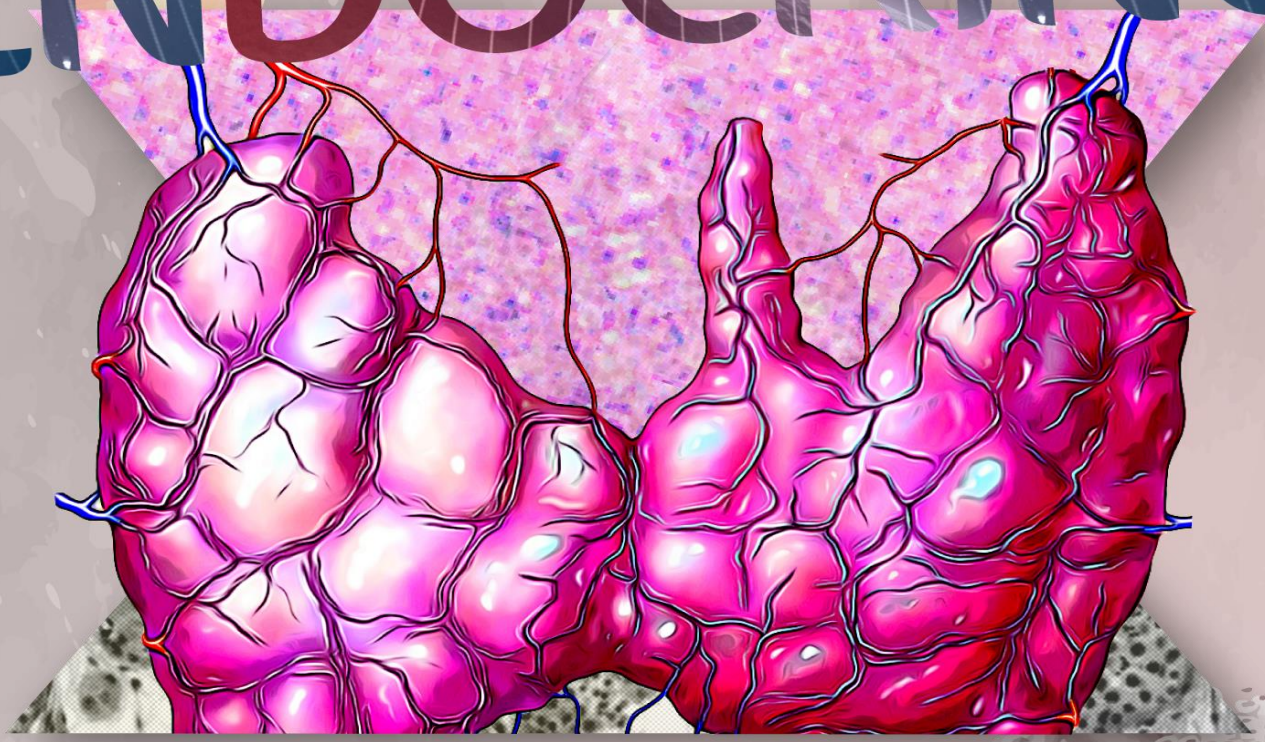
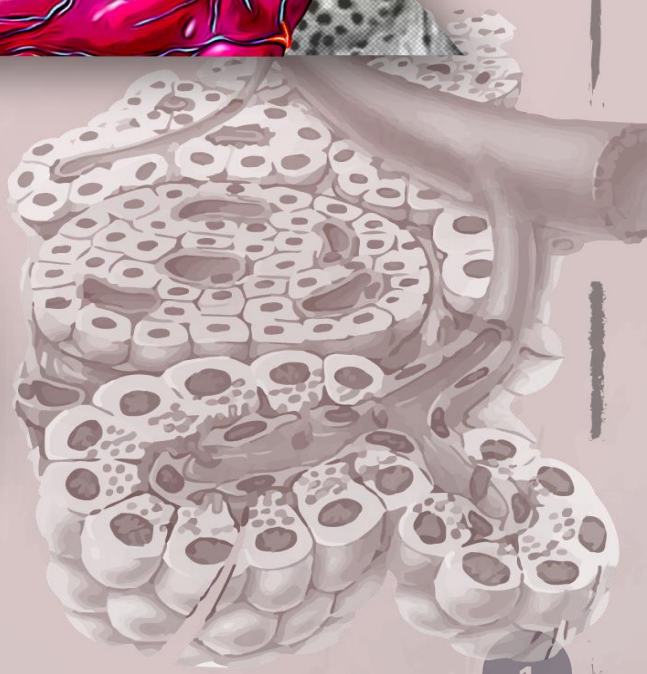




SUBJECT: Biochemistry

DONE BY: Hashem Al-Dujaily

CORRECTED BY: Farah Albustanji

DOCTOR: Ma'moun Ahram

Mechanism of hormone actions (1) Intracellular (nuclear) Receptors

We have two lectures regarding mechanisms of hormone actions. This lecture will cover intracellular or nuclear receptors and in next lecture we will talk about cell surface receptors and hormones that function via cell surface receptors.

Hormone Receptors

- **Hormones cause cellular alterations via receptors.**
- **The cellular localization of hormonal receptors depends on the type of hormones.**

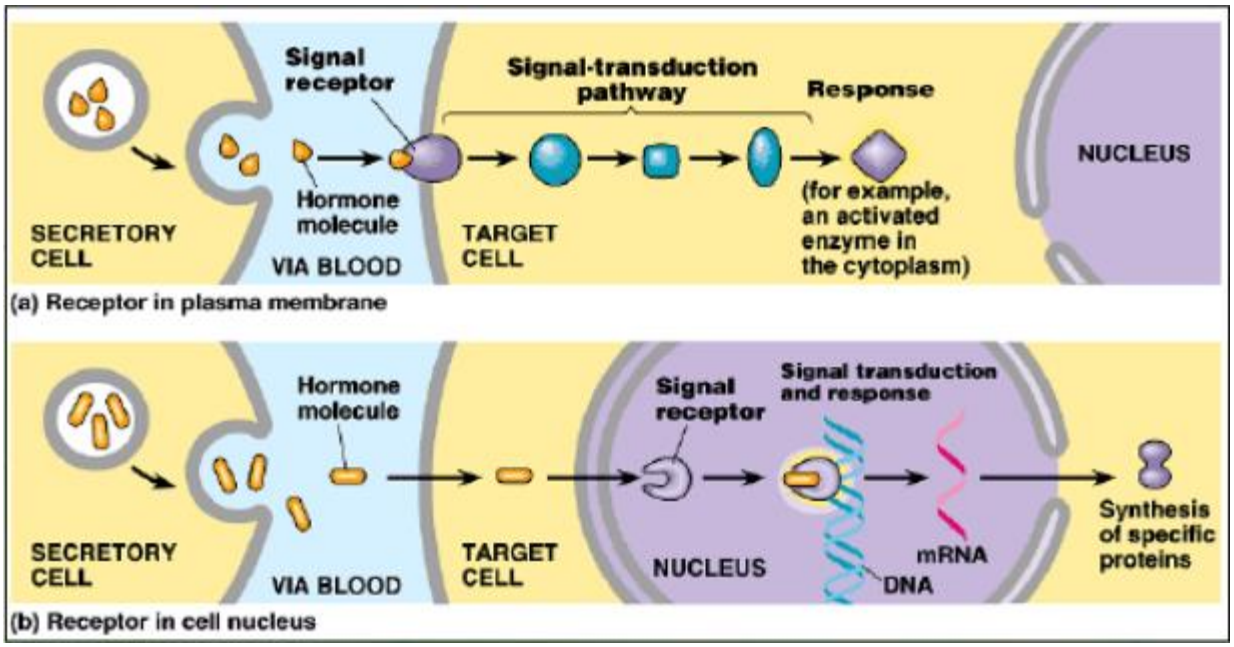
➢ We can classify hormones according to their solubility into:

1) Lipid-soluble hormones: which are intracellular.

2) Water-soluble hormones: which are extracellular.

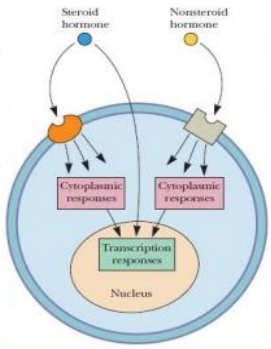
Once lipid soluble hormones are released into the blood stream, they diffuse through the plasma membrane (because they are small and lipophilic), then they bind to intracellular receptors to finally bind to DNA, regulating gene expression.

On the other hand, Water soluble hormones bind into a receptor that exists on the cell surface then transduction of signal occurs inside the cell and therefore, an effect that takes place.



General classification of hormones

	Group I	Group II
Types	Steroids, iodothyronines, calcitriol, retinoids	Polypeptides, proteins, glycoproteins, catecholamines
Action	Slow	Fast
Solubility	Lipophilic	Hydrophilic
Transport proteins	Yes	No
Plasma $t_{1/2}$	Long (hrs - days)	Short (minutes)
Receptor	Intracellular	Plasma membrane
Mediator	Receptor-hormone complex	cAMP, cGMP, Ca^{2+}, kinase cascades, metabolites of phosphoinositols



There are differences among these different types of hormones. For instance:

- **in terms of their action:**

The action of the lipophilic hormones is slow compared to the second group; the hydrophilic hormones. The reason why action of steroid hormones of group 1 is slow is due to the fact that their action is actually **genomic: they influence gene expression**. So, it takes time to synthesize mRNA then the protein, modify the protein then release it. **Conclusion:** it takes hours for this action to take place and sometimes it may take days due to a reason we will mention in page 8.

On the other hand, the hydrophilic hormones or water-soluble hormones like protein and peptide hormones like insulin for example they bind into a receptor and the signal is transmitted quickly into the cell.

- **In terms of their solubility and the requirement of transport proteins:**

Since group 1 hormones are lipophilic (lipid soluble), they need transport proteins, while the other group do not since they are hydrophilic, thus, they can mix with blood.

- **In terms of their Plasma half-life:** for lipophilic hormones, plasma half-life is long since they are bound to transport proteins, so they are protected. On the other hand, hydrophilic hormones have short plasma half-life relatively.

Functional Domains

- **A Domain:** is a 3-dimensional secondary structure of a protein. It is composed of multiple secondary structures such as alpha helices, beta strands, loops, turns and so on.
  - These multiple secondary structures fold independently of the rest of the protein. So, if we take this domain separated from the rest of the domains, it can still function.

Now if we talk about hormones, whether they are cell surface hormone receptors or intracellular receptors, **all receptors have at least 2 functional domains:**

1) Recognition domain where the hormone binds to. (hormone-binding domain)

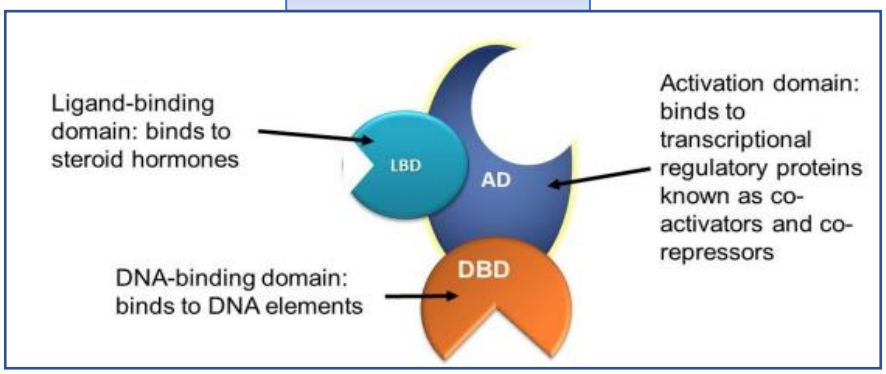
- **For cell surface receptors:** ligand binding domain is exposed to outside of the cell, the hormones bind to recognition or ligand binding domain.
- **For the intracellular receptors:** it's a domain that is independent of all other domains.

2) Coupling domain generates a signal that couples hormone recognition to some intracellular function (activation domain or functional domain).

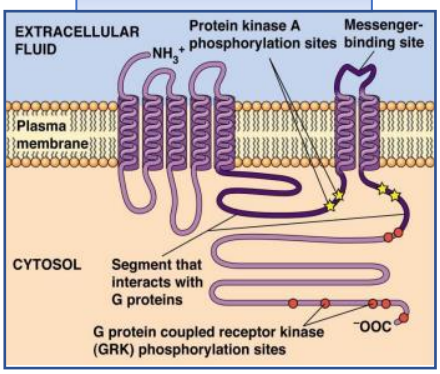
- the domain that transmits the signal or does the work.
- **For the cell surface receptors:** it is intracellular so it can interact with regulatory proteins that can then transmit the signal.
- **For the intracellular receptors:** the activation or coupling domain is the domain that interacts with other molecules once the receptor is activated and bound to the hormone.

❖ **So, Receptors are different from plasma carrier proteins that bind hormone, <u>but do not generate a signal.</u>**

Cell Surface Receptor



Membrane Receptor



Regulation of Receptors

These receptors can be regulated by:

1. **Down-regulation: Receptor-mediated endocytosis:**
   - Via receptor mediated endocytosis; the hormone binds to the receptor and the receptor is internalized. Once internalized, it gets degraded, and therefore reducing number of receptors present on cell surface.
   - **Examples:** Insulin, glucagon, TRH, growth hormone, LH, FSH, and catecholamines down regulate their receptors.
2. **Covalent modification of the receptor:**
   - **Example:** Phosphorylation without a change in receptor number; will be discussed in the next lecture.
3. **Upregulation:**
   - Upregulation is where a hormone binds to a receptor and that increases number of receptors on cell surface.
   - **Examples:** Angiotensin II and prolactin increase their receptor number as receptors on the cell surface become occupied.

❖ Receptors can be upregulated, down-regulated or covalently modified whether they are intracellular or cell surface receptors.

4. **Interaction with modulators: intracellular receptors can bind to other protein corepressors or coactivators modulating receptor function.**
   - Once the receptor is hormone bound or ligand bound, it can bind to other factors, coregulators. These can be co-repressors or co-activators.
   - **Example:** Steroid receptors.
5. **Modulation of an intermediary signaling molecule.**
   - Or once this interaction happens, signaling takes place affecting another enzyme for example or modifying the DNA.

Spare Receptors

- **Most maximal biological responses are achieved when only a small percentage of receptors is occupied. The remaining free receptors (put on the side just in case) are known as Spare receptors.**
  - Receptors do not get saturated. There are free receptors whether they are present on the cell surface or inside the cell. So, not all receptors are occupied by hormones. These free receptors are known as **Spare receptors.**
- **These fully functional spare receptors would compensate in two situations:**

1) a low affinity binding of the hormone to the receptor.

2) a low level of hormone concentration in the system.

- **In both situations, spare receptors increase the sensitivity of target cells to the hormone.**

Clarification: The reason behind cells having spare receptors is when there is low affinity between the hormone and the receptor; which means that the interaction is not really that strong. Or, when the level of the hormone is very low, and the cell needs to sensitize itself to the hormone**. To do that**, they increase the number of the receptors to increase the possibility of having the hormone binding to the receptor.

- **The greater the proportion of spare receptors on the cell surface:**
- the more sensitive the signal is (sensitivity of target cell to the hormone).
- the lower the concentration of hormone required to transmit the signal and achieve half-maximal response.

Why half-maximal? Recall from summer semester: Km is a measure of affinity, which indicates the substrates concentration at which V0 is half-maximal (Vmax)

Examples

1) A maximal stimulation of steroidogenesis by Leydig cells is achieved when only 1% of LH (Luteinizing hormone) receptors are occupied.

2) The requirement of only 10% occupancy of steroid hormone receptors at a certain time in normal conditions for a full steroid-induced transcriptional response.

3) A maximum glucose oxidation in adipocytes is induced by having insulin bound to only 2-3% of insulin receptors.

Type of Receptors

There are three different types of receptors:

1) Intracellular (nuclear) receptors.

2) G protein-coupled receptors

3) Receptor tyrosine kinases

These two types fall under the category of cell surface receptors, which will be discussed in next lecture.

Group I. HORMONES THAT BIND TO INTRACELLULAR RECEPTORS

Estrogens	Calcitriol (1,25 $[OH]_2$-D_3)
Glucocorticoids	Androgens
Mineralocorticoids	Thyroid hormones (T_3 and T_4)
Progestins	Retinoids (Vit A)

Group II. HORMONES THAT BIND TO CELL SURFACE RECEPTORS

A. The second messenger is cAMP	
Adrenocortropic hormone (ACTH)	Parathyroid hormone (PTH)
Angiotensin II	Opioids
Antidiuretic hormone (ADH)	Acetylcholine
Follicle-stimulating hormone (FSH)	Glucagon
Human chorionic gonadotropin (hCG)	α_2-Adrenegic catecholamines
Lipotropin (LPH)	Corticotropin-releasing hormone (CRH)
Luteinizing hormone (LH)	Calcitonin
Melanocyte-stimulating hormone (MSH)	Somatostatin
Thyroid-stimulating hormone (TSH)	β-Adrenergic catecholamines
B. The second messenger is calcuim or phosphatidylinositides (or both)	
α_1-Adrenergic catecholamines	Acetylcholine (muscarinic)
Cholecystokinin	Substance P
Gastrin	Angiotensin II
Thyrotropin-releasing hormone (TRH)	Gonadotropin-releasing hormone(GnRH)
Vasopressin	
C. The intracell messenger is a protein kinase cascade (started by tyr phosphorylation)	
Growth hormone (GH)	Oxytocin
Insulin	Nerve growth factor (NGF)
Insulin-like growth factors (IGF-1, IGF-II)	Epidermal growth factor(EGF)
Prolactin (PRL)	Platelet-derived growth factor
	Fibroblast growth factor (FGF)

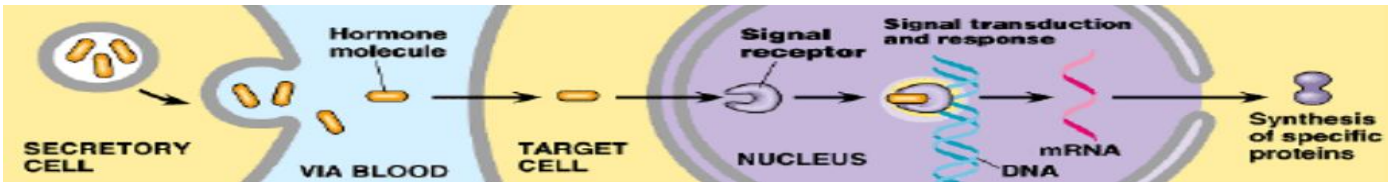
- And these are the hormones that bind to cell surface receptors this is a long list and maybe they can be categorized further into the secondary messengers that they use, whether they are cAMP, cGMP, calcium, phosphatidylinositol or other mechanisms.
- ❖ We do not have to memorize this list; this is just for you to read and we will focus on the ones we need to know.

Nuclear Receptors

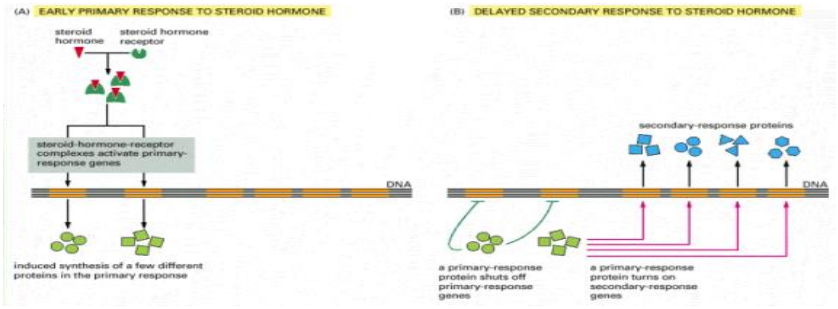
- **The receptors to which lipophilic steroid hormones bind are ligand-activated proteins that regulate transcription of selected genes.**
- **They are found in the cytosol and the nucleus.**
- **Upon hormonal binding, the hormone-receptor complex bind to specific DNA promoter/enhancer sequences.**

Basic mechanism Of these hormones and how they function.

the lipophilic hormone would diffuse through the plasma membrane into the cell. → **hormone receptor complex bind to DNA regulating gene expression.**



Types of Responses



1) Primary response: direct activation of a small number of specific genes, thus the receptor hormone complex binds to DNA inducing gene expression. **(primary response usually takes 30 minutes).**

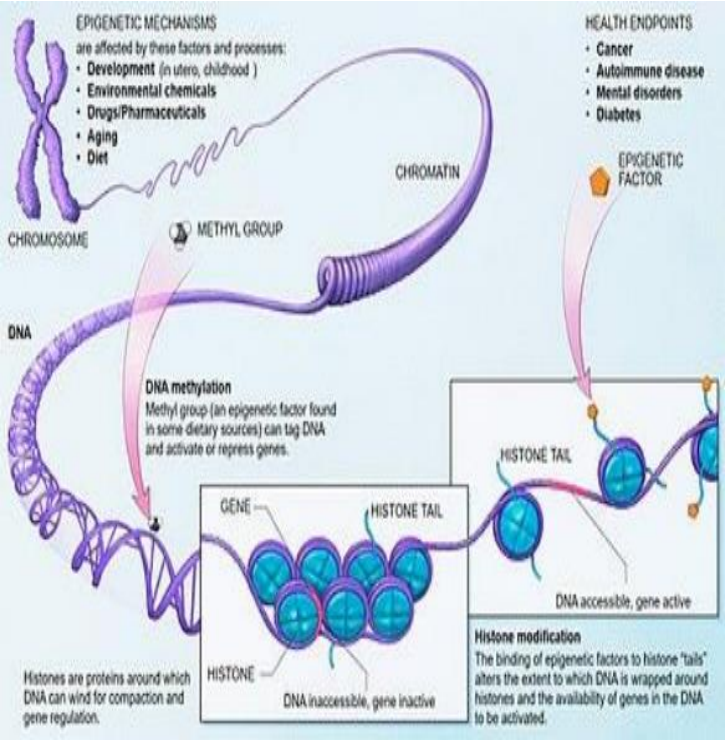
2) Secondary response: the protein products of active genes in the primary response in turn activate other genes.

These genes can themselves be transcriptional factors that, in turn, activate other genes to produce a delayed, secondary response; and so on.

- **Clarification:** The response can be relatively immediate or delayed when it comes to gene expression. We can have a primary response where the activated molecules themselves are the ones that do the work. **On the other hand,** sometimes the activated molecules can be transcription factors. So, what they do is that they induce a secondary effect whereby they can bind to promoter regions of other genes inducing gene expression of those genes. And these binding cells can also be transcription factors, inducing **a tertiary response**, so sometimes it really takes not few hours **but maybe a few days for the action to take place.**

Cell-specific response

- The response or the control of gene expression is cell specific or cell dependent.
  - ➢ **Only certain types of cells have receptors for the hormones.**
  - ➢ The reason is that we have involvement of other co-regulatory molecules. When we have hormone receptor complex bound to DNA, other proteins are recruited and thus they can change gene expression by modifying the structure of DNA.



- ❖ **Even if cells have identical intracellular receptor, each cell type contains a different combination of other cell-type-specific gene regulatory proteins that influence the gene transcription.**
- **Epigenetic regulation (DNA packaging and modification).**
  - ➢ **Recall the definition of epigenetics in molecular biology:** Modification or the packaging of DNA. So, you can have methylation of DNA itself (of cytosine AA), tight packaging of DNA or loosening of DNA, exposing the regulatory elements of DNA, thus allowing regulatory molecules to bind to DNA or preventing them from binding to DNA. So, that's how these receptors function.

Structure of Receptors

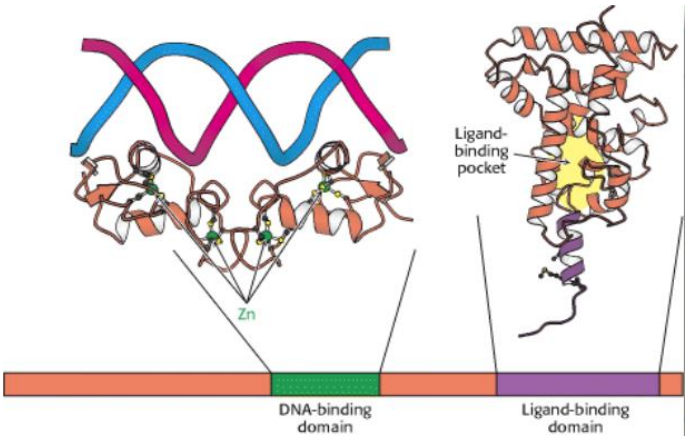
- **Intracellular hormone (Nuclear) receptors have at least two domains:**

1) A hormone-binding domain.

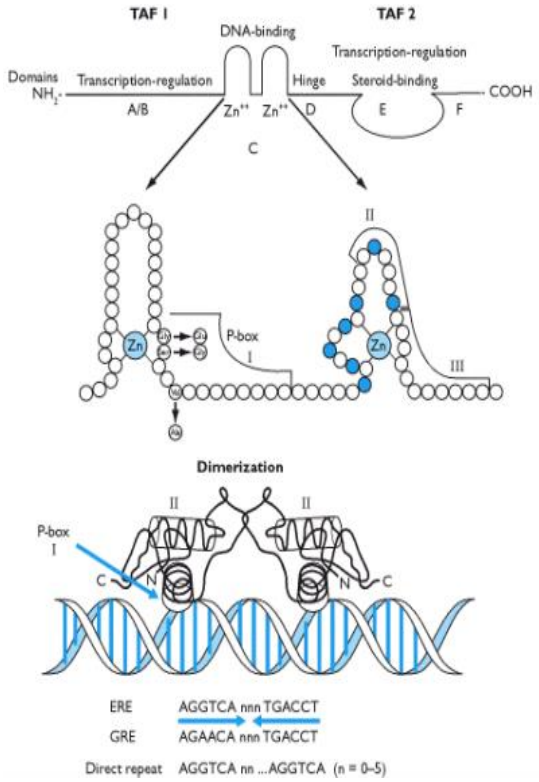
The domain that interacts with the hormone. Also called Ligand-binding domain.

2) A DNA-binding domain.

DNA binding domain is the domain that interacts with certain sequences of DNA.



Zinc finger Domain



- **A special DNA-binding domain is known as zinc finger.**
- **The specific amino acid sequence of the zinc fingers in the DNA binding domain is important for determining the bases in the DNA helix to which the receptor binds and, thus, the specificity of the transcriptional activity of the receptor.**

Clarification: This domain, DNA binding domain, belongs to a family of domains known as zinc finger domain which is composed of two fingers with the involvement, association or stabilization of this domain by two zinc atoms. Then, they can bind in inverted repeats or to certain sequences on DNA, and usually these sequences are defined by the amino acids on the zinc finger domain.

❖ **So, hormone receptor complex bind on certain regions of DNA depending on the amino acid composition on zinc finger domain.**

Mechanisms of control of gene expression

- **There are two ways by which steroid hormones can alter gene expression:**

Mechanism 1: Direct binding to DNA sequences known as hormone response elements and these elements have specific sequences. **Examples:**

- **a glucocorticoid response element (GRE)**
- **estrogen response element (ERE),** specific for estrogen hormone, receptor.
- **Androgen receptor element**, specific for androgens and so on.

Mechanism 2: Binding to and activating/repressing other transcription factors that recognize a particular site on DNA.

Summary: Receptors bind to DNA at certain elements (certain DNA sequences) and they can regulate gene expression directly or they can bind to other transcription factors regulating gene expression.

Non-genomic cellular effects

Non-genomic cellular effect: an effect independent of gene expression.

Many steroids and thyroid hormones (lipophilic hormones) can stimulate rapid responses by interaction with cell surface receptors.

Such receptors may initiate the opening of ion channels or activate classical second messenger systems.

They induce signaling; they can bind to G proteins, G protein coupled receptors, and can bind and affect tyrosine kinase receptors. This is sort of like a new area in research that seems to be important in regulating the physiology of our body.

Hormone classification (location of intracellular receptors)

Intracellular receptors can be classified into type 1 or type 2 receptors. They can both bind to DNA at the end, **but** there are differences between those 2 classes:

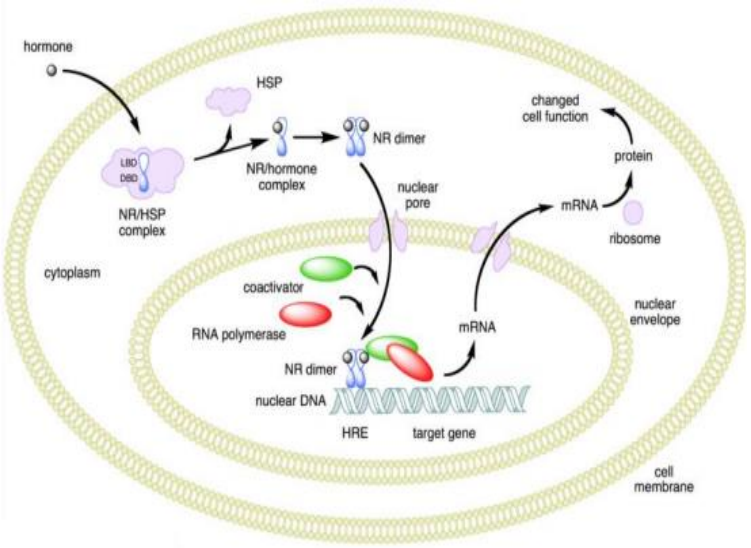
Type 1 receptors

- **Predominantly cytoplasmic.**
- **They are bound to heat shock proteins. However, once the steroid hormone goes into the cell and binds to this receptor, HSP is released and the receptor dimerizes with another receptor, usually of the same type, and then the dimer is translocated into the nucleus, and binds to DNA.**
  - **Examples: the glucocorticoid, mineralocorticoid, estrogen, androgen and progesterone receptors.**

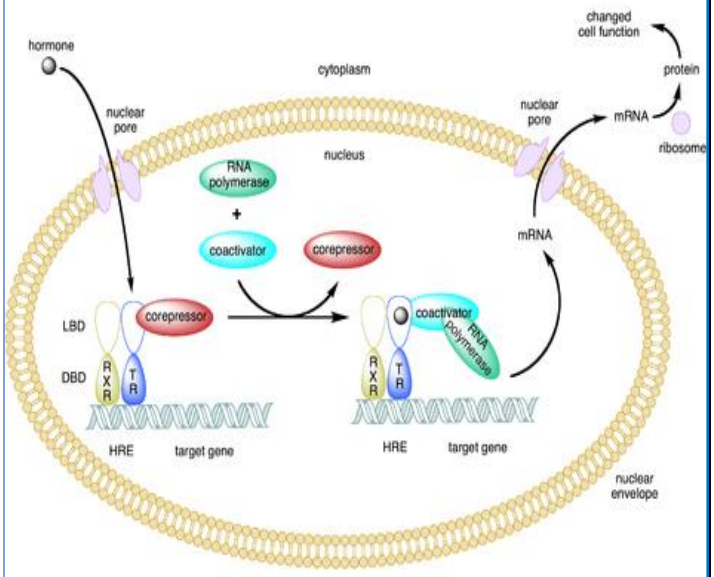
Type 2 receptors

- **They are nuclear and some are bound to DNA, not alone but with association of corepressors which prevent and block gene expression. However, when the hormone goes into the cell and into the nucleus, and binds to the DNA bound receptor, they replace corepressors by coactivators and thus we will have induction of gene expression.**
- **They characteristically form heterodimers.**
  - **Example: thyroid hormone receptor can bind with retinoid X receptor, thus binding into heterodimer fashion. However, they can also form homodimers as well.**

Type I Receptors



Type II Receptors



Examples of these receptors:

Glucocorticoid receptors

- **Mineralocorticoids and glucocorticoids.**
  - **The physiological mineralocorticoid is aldosterone.**
  - **The physiological glucocorticoid is cortisol.**
- **They are synthesized in the adrenal cortex of mammals.**
- **The idea here is that the Ligand-bound corticosteroid receptors form complexes with other transcription factors, such as the Jun protein, a famous and well-studied transcription factor. Such interactions are responsible for the activation of certain elements on DNA known as AP-1 sites and for the glucocorticoid mediated suppression of transcription.**
- **Example: The activation that results in the expression of certain genes (e.g. proopiomelanocortin gene) and that eventually induce the enkephalins and endorphins (the analgesics). And this is why cortisol is good for minimizing pain and reducing inflammation.**

Non-genomic effects

- These hormones can have non genomic effects; they can bind to receptors **other than** nuclear receptors and these receptors that they bind to are on the cell surface.

- **For example: Cortisol may exert effects via membrane receptors.** This binding is mediated by a transport protein; **a serum protein that transports cortisol, which is called cortisol binding globulin (CBG). This transport protein can bind to cell surface receptors and then cortisol may then bind to the CBG-receptor complex and results in the activation of adenylate cyclase.**

Types of estrogen receptors

- **Two forms of the estrogen receptor have been identified: α and β**
- **These receptors can form different dimers: either a homodimer α/α or β/β, or a heterodimer α/β.**

➢ The expression is cell specific. Some cells can only produce alpha, others can only produce beta. However, some cells can produce both of them; where we have the formation of heterodimers occurs.

- **Both receptors bind estrogen with high affinity and bind to ERE (estrogen receptor element). They also share high degree of amino acid homology. However, ERα and ERβ have different effects.**

○ **Example:**
ERβ has an additional repressor domain that that is inhibitory to ERα transcriptional activity. So, this inhibition occurs when ERαβ heterodimer forms, inhibiting gene expression instead of activating it.

- **However, in some cases, they have different distributions in target tissues indicating they may have different biological effects.**

○ **For example: ERα induces the expression of progesterone receptor in glandular epithelia cells of uterine tissues. On the other hand, ERβ downregulates the expression of the same receptor in luminal epithelial cells**

❖ **The doctor stated that the** involvement of these receptors in cancer is very essential. The idea here is that **ERα** may be an inducer of cancer, for example breast cancer. **However, what if ERβ** has an inhibitory effect on breast cancer? So, this area of study is still under research and may lead to great findings.

Progesterone receptor

The progesterone receptor can form heterodimers and an important feature is that the progesterone-bound receptors can bind to GRE (glucocorticoid response element) on DNA similar to that of glucocorticoids.

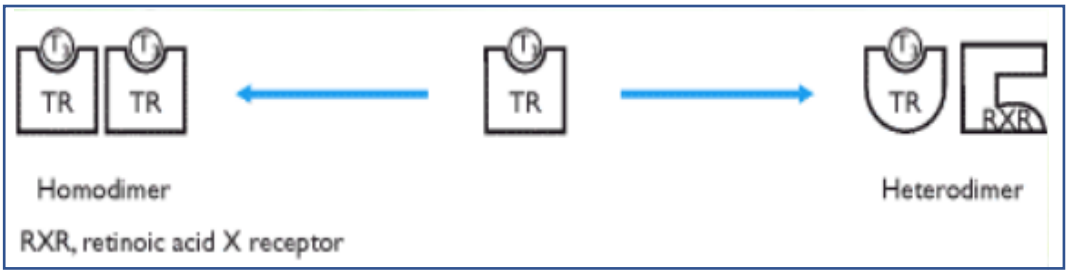
Androgen Receptor

- **Androgen receptor is regulated by androgen. Testosterone is an androgen. However, it's not the final active form of it. Thus, in many target tissues, before testosterone interacts with the androgen receptor, it is rapidly converted to dihydrotestosterone (DHT) by the 5α-reductase enzyme and this is the potent agonist.**
- ➢ **When activated, androgen receptor binds to androgen-response element.**

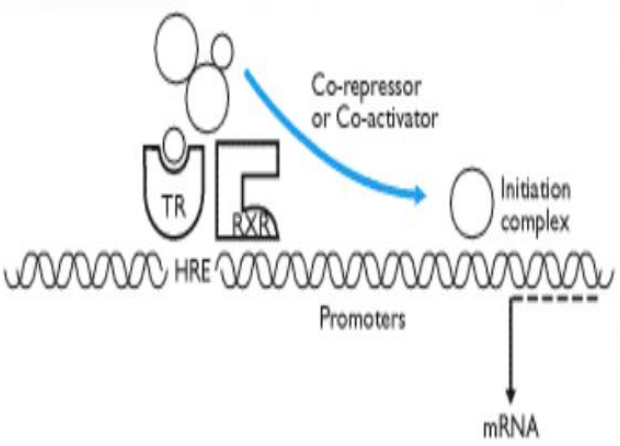
As with other steroid hormones there is evidence that androgens may exert non-genomic effects on certain cells via cell surface molecules, and thus regulate adenylate cyclase indirectly.

Thyroid hormone receptors

- **Unlike some steroid receptors, thyroid hormone receptors belong to type 2 receptors (nuclear receptors) and thus exist in the nucleus and are free of heat shock proteins (HSP).**
- **The receptors may remain bound to DNA in the absence of hormone binding. However, they are associated with co repressors.** When the hormone goes into cell and into nucleus then binds with the receptor, co-repressors are replaced with co-activators.
- A feature of thyroid hormone receptor is that it can either form a homodimer with the receptors of the same type or heterodimer with different receptors.
- **Clarification:**
  - ➢ **Many of the actions of thyroid hormones are mediated by binding to nuclear receptors that have a preferential affinity for triiodothyronine (T3).**
  - ➢ **Once inside the nucleus, T3 binds to its receptor.**
  - ➢ **This dimerizes with another T3 receptor (to form a homodimer) or with a different receptor, particularly the retinoic acid receptor, to form a heterodimer.**



DNA binding

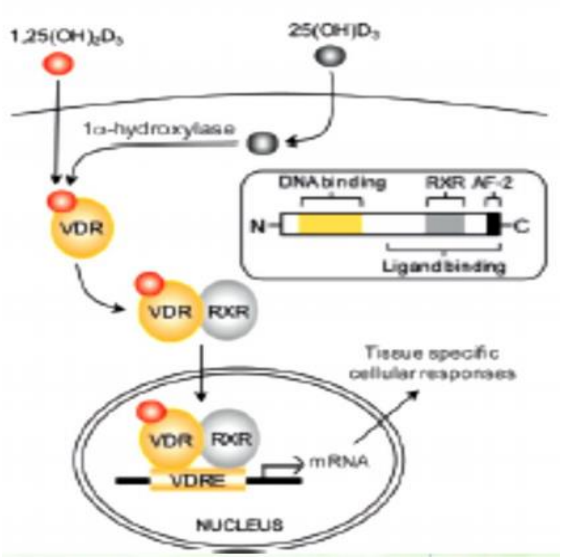


As dimers, the zinc fingers of the DNA binding domain bind into a hormone response elements (HRE) on the DNA helix.

Along with other transcription factors (co-activators/repressors), they regulate gene expression.

So, the idea here is the replacement of co-repressors by co-activators.

Vitamin D



- **Vitamin D** is a hormone as well, a steroid hormone derived from cholesterol and has its own intracellular receptor.
- **Binding of Vitamin D receptor (VDR) to its ligand, 1,25(OH)2D3 causes** heat shock protein to be released and thus **enables dimerization of VDR and RXR, allowing nuclear translocation and binding of the VDR-RXR complex to VDREs in the promoter region of responsive gene.**
- Notice that the Dimer formed is the vitamin D receptor with Retinoid X Receptor (heterodimer).

Other nuclear receptors

1) Retinoid X receptors (RXRs).

2) The peroxisome proliferator-activated receptors (PPARs).

3) The liver X receptors (LXRs).

4) The farnesoid X receptors (FXRs).

5) The pregnane X receptor (PXR).

We will only focus on the first two receptors in details.

1) Retinoid X receptors (RXRs)

- **Three isotypes: RXRα, RXRβ, and RXRγ. (alpha, beta and gamma)**
  - Each isotype is composed of several isoforms.
- **The RXRs serve as obligatory heterodimeric partners for numerous members of the nuclear receptor family.**
  - **In the absence of a heterodimeric binding partner,** the RXRs are **bound** to hormone response elements (HREs) in DNA and are complexed with co-repressor proteins including **a histone deacetylase (HDAC).**
  - **However,** once we have the formation of heterodimer, it can bind to hormone response element then replacement of co-repressors with co-activators occurs.

❖ **Recall that HDAC removes acetyl group from histones, exposing the positive charge, which makes the interaction between histones and DNA strong, therefore packaging DNA tightly and repressing gene expression.**

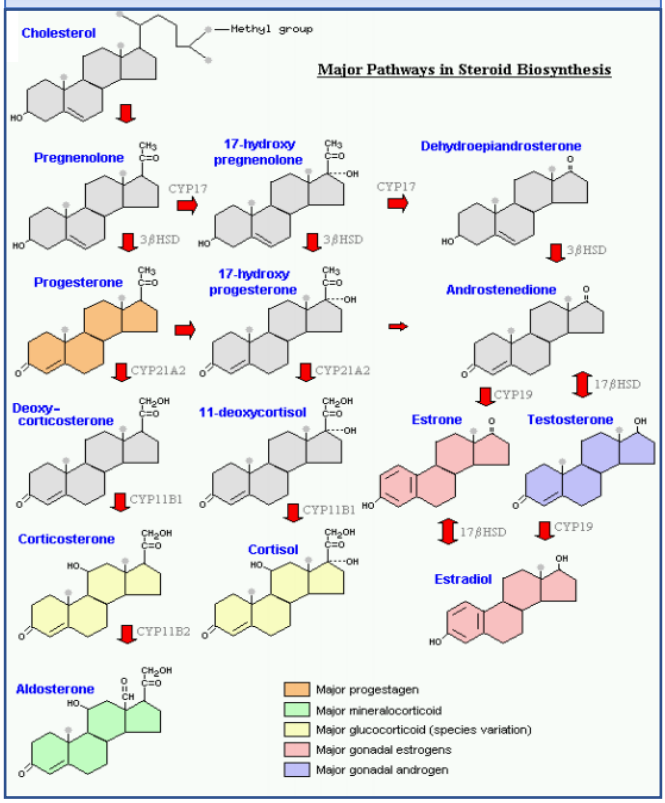
❖ The doctor said RXR forms a heterodimer with other receptors and **you need to know what these receptors** are; all-*trans* retinoic acid receptor **(RAR)**, vitamin D_3 receptor **(VDR)**, thyroid hormone receptor **(TR)**, the peroxisome proliferator-activated receptor **(PPAR)** and the nerve growth factor induced–B **(NGFI–B) receptor**, **(which wasn't mentioned in the slides).**

2) The peroxisome proliferator-activated receptors (PPARs)

- These receptors are important because they are actually targets of many drugs whether in cancer or metabolic syndromes. Some are experimental but some are actually used currently in the clinic.
- **Three family members: PPARα, PPARβ/δ, and PPARγ.**
- **Each of these receptors forms a heterodimer with the RXRs.**
- **Now notice that they are important in regulating/controlling lipogenesis or lipid metabolism:**
  - **PPARα (Alpha receptor)** is the receptor for polyunsaturated fatty acids. It induces hepatic peroxisomal fatty acid oxidation during periods of fasting.
  - **PPARγ (Gamma receptor)** is a master regulator of adipogenesis and is most abundantly expressed in adipose tissue.
  - **PPARδ (Delta receptor)** is expressed in most tissues and is involved in the promotion of mitochondrial fatty acid oxidation, energy consumption, and thermogenesis.

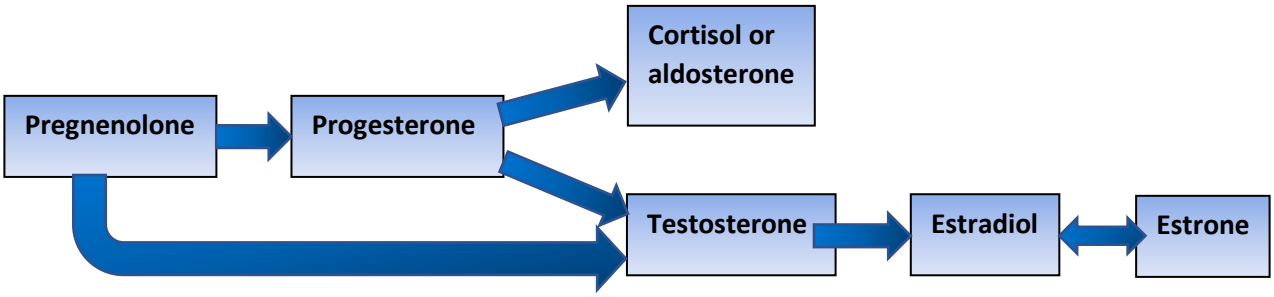
Steroid hormone Synthesis

You don't have to memorize the structures.



- Steroid hormones are derived from cholesterol which is converted to **pregnenolone** and this **pregnenolone** can then be used to synthesize all of the other steroid hormones, including progesterone.
- From progesterone, you can have the formation of aldosterone or the formation of cortisol.
- Progesterone itself is used to form testosterone and testosterone is converted to estradiol.
- Formation of testosterone can also be mediated independently from progesterone as well, you can have pregnenolone going into testosterone or progesterone going into testosterone.
- Moreover, formation of estrogen (estradiol) occurs from reduction of testosterone as well as estrone.

Progesterone	Cortisol & Aldosterone	Testosterone	Estrogen
C21	C21	C19 (2C Shortage)	C18
Directly from Pregnenolone	From Progesterone	From Progesterone or Pregnenolone	From reduction of testosterone as well as estrone. Aromatase cleaves C18.



Synthesis, metabolism and transport of testosterone

Testicular Hormones

We will discuss a little more details about synthesis of testosterone:

- **The testis secretes over 95% of the circulating testosterone.**
  - So, most of it is secreted by the testes, but adrenal gland also secretes it.
- **Most of the potent androgen, dihydrotestosterone (DHT) and estradiol circulating in men is derived from peripheral conversion of testosterone.**
  - **Recall that 5α-reductase is the enzyme responsible for that conversion.**
- **Only about 2% of circulating testosterone is in the free form (active form) and the rest is either bound to albumin (approximately 40%) or, mostly, to sex-hormone-binding globulin (SHBG) and is in equilibrium with the free form.**
- **Most circulating testosterone is metabolized in the liver, and thus converted to metabolites after conjugation with glucuronide or sulfate to facilitate excretion.**

Synthesis, metabolism and transport of estrogen and progesterone

Estradiol

- **Estradiol, the most important steroid secreted by the ovary, is transported bound to albumin (approximately 60%) and about 30% to SHBG (sex hormone binding globulin).**
- **It is also converted to metabolites which are conjugated with sulfate or glucuronide before excretion by the kidney.**

Note: Estradiol is mainly secreted by the ovary.

Progesterone

- **Progesterone is mainly bound to albumin in the circulation and, to a lesser extent, cortisol-binding globulin.**
- **It is rapidly cleared from the circulation and is also conjugated with glucuronic acid in the liver in which form it can be excreted.**

Critical Enzymes

Finally, we will mention critical enzymes that are important clinically.

1) 3β-hydroxysteroid dehydrogenase

This is the enzyme that converts pregnenolone into progesterone.

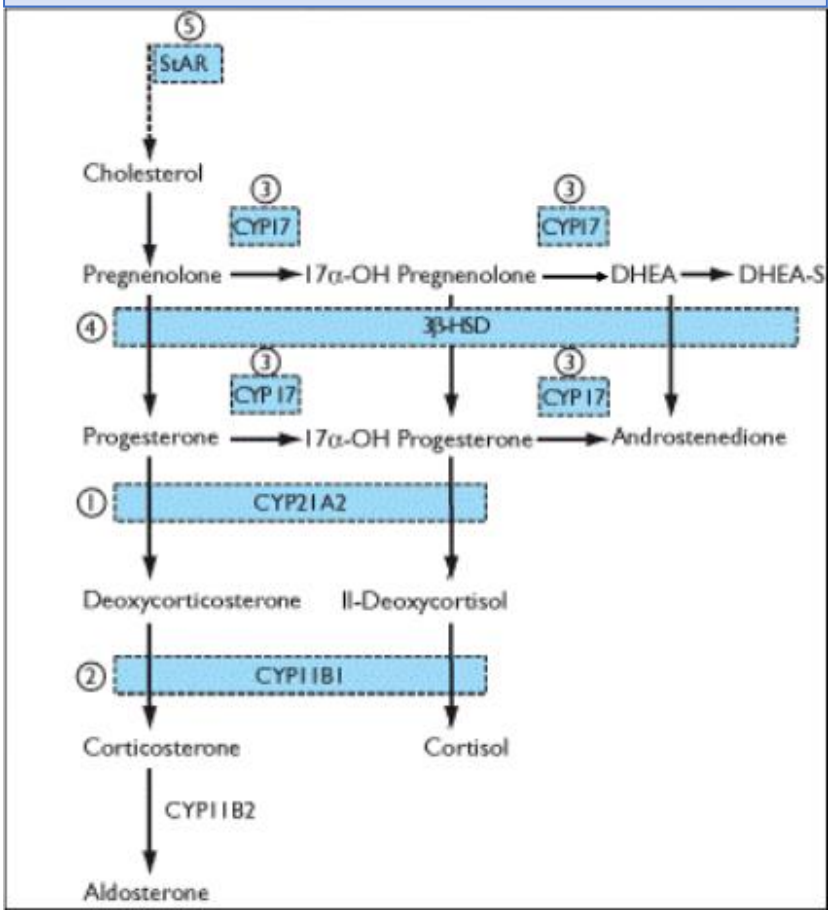
It is a very important enzyme because it produces all the other steroid hormones; cortisol, aldosterone, testosterone, estrogen and so on.

Deficiency in this enzyme would result in the formation of female genitalia in all patients, in addition to no production of glucocorticoids and mineralocorticoids.

2) 17α-hydroxylase (CYP17)

- This enzyme leads to the **formation of 17α-hydroxypregnenlone** and **17α-hydroxyprogesterone.**
- **Both of these can be used to make androstenedione, an androgen which is a precursor of testosterone and estrogens.**
- If this enzyme is defective, there would be no production of the androgen, testosterones, estrogens and cortisol as well. **However,** production of aldosterone would still occur.

Focus only on the ones we took in this photo.



Deficiency of 17α-hydroxylase:

- **Deficiency in this enzyme leads to the formation of female genitalia in all patients. In addition, no cortisol or sex steroid would be produced.**
- **On the other hand, mineralocorticoids will be overproduced, resulting in higher retention of Na+ and, consequently, leading to hypertension.**

3) 17β-hydroxysteroid dehydrogenase

- **Testes and ovaries contain the enzyme, 17β- hydroxysteroid dehydrogenase, which enables androgens to be converted to testosterone.**

➢ This is an **important** enzyme because it converts progesterone into testosterone.

4) 5α-reductase

In Sertoli cells and other target cells, testosterone is rapidly converted to DHT by the 5α-reductase enzyme before it interacts with the androgen receptor.

➢ An important enzyme for potent androgen.

5) Aromatase

And finally, the aromatase that converts androgen into estradiol.

➢ **Aromatase converts androstenedione and testosterone into the estrogens.**

- This enzyme is the target for breast cancer therapy mainly in postmenopausal women. Most of estrogen is secreted from the adrenal gland not from ovaries.

➢ So, to limit production level of estrogen in these ladies, they are given **aromatase inhibitors**, and this affects the tumor size or progression of tumor in these women.