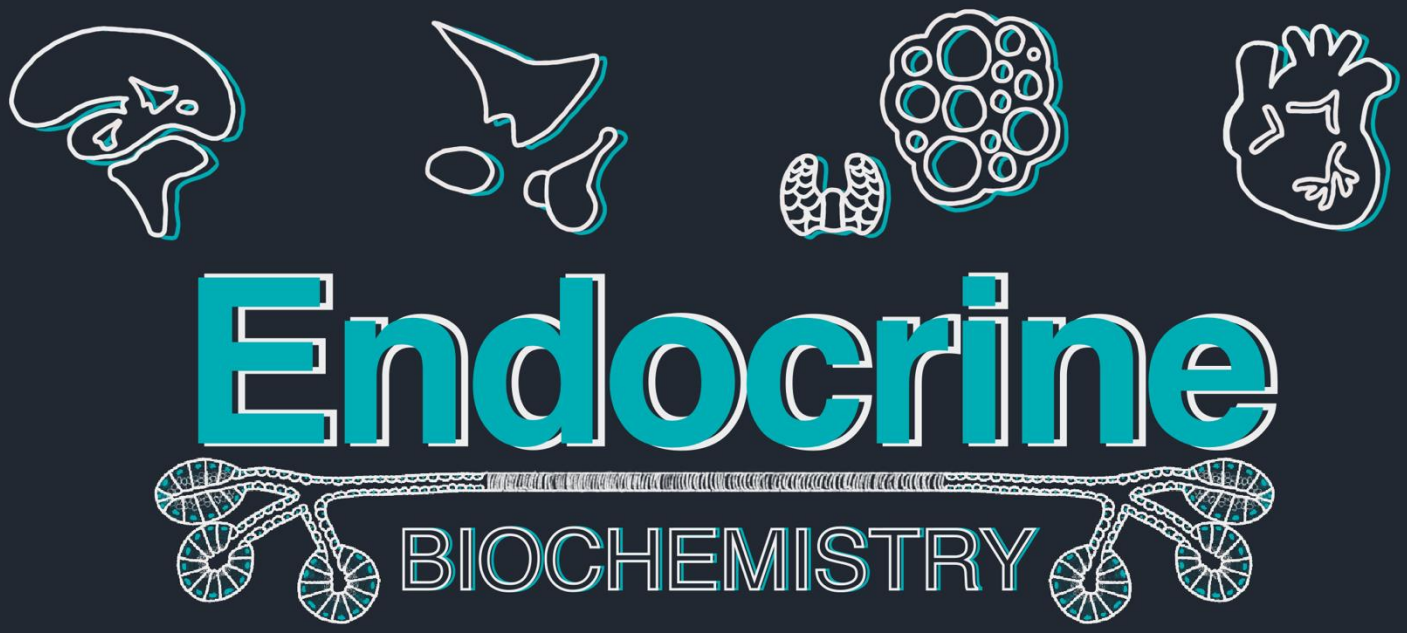

Endocrine

BIOCHEMISTRY

Title: Sheet 2 – Intracellular Receptors

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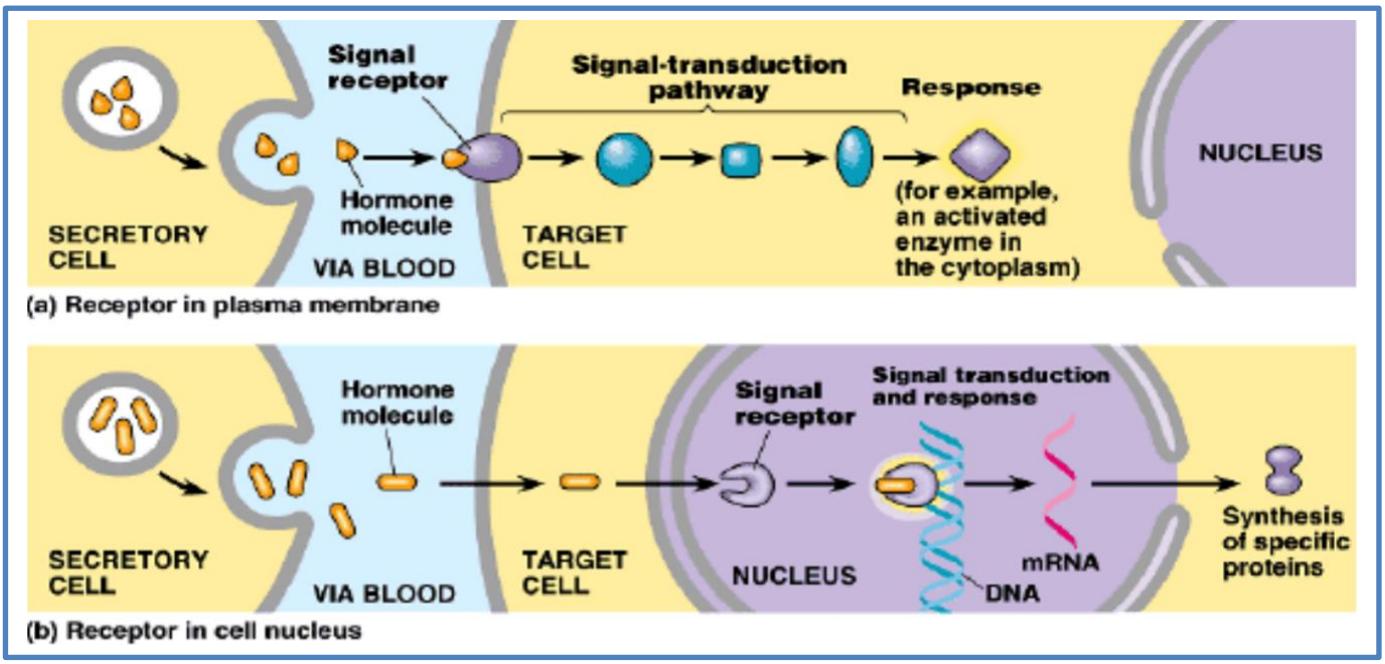
Mechanism of hormone actions I: Intracellular (nuclear) Receptors

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

Hormone Receptors:

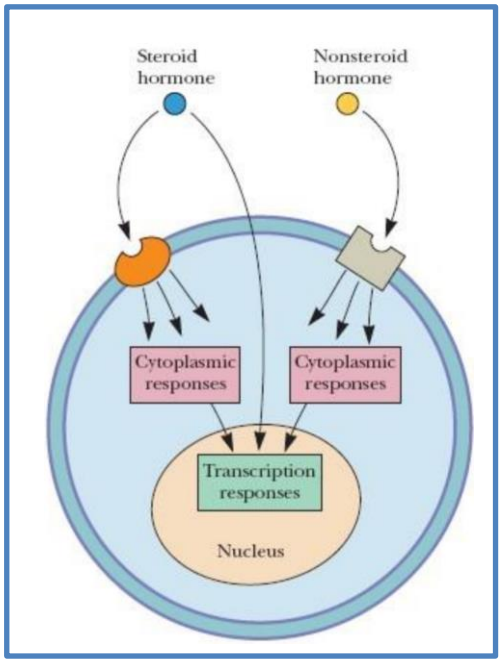
- Hormones cause cellular alterations via receptors.
- The cellular localization of hormonal receptors depends on the type of hormones.
- We can classify hormones according to their solubility: (refer to the pic below)
    1. **Lipid-soluble: intracellular:** Once lipid soluble hormones are released 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.
    2. **Water-soluble: extracellular:** hormones bind to a receptor that exists on the **cell surface** → Transduction of the signal occurs inside the cell→ An effect takes place.



General classification of hormones:

	Group 1	Group 2
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, Ca2+, kinase cascades, metabolites of phosphoinositols

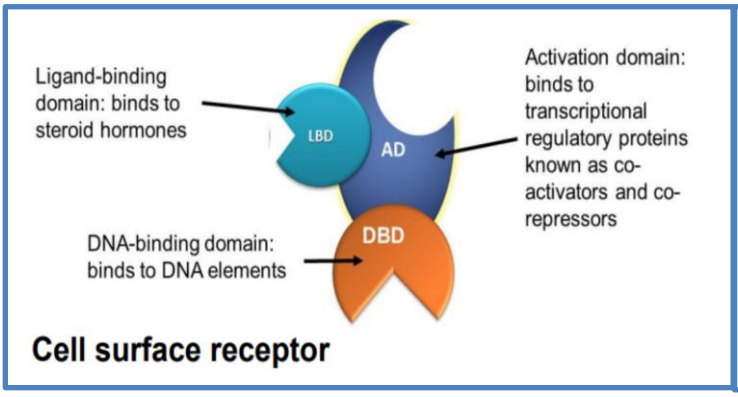
This table shows differences between these types of hormones. For instance:

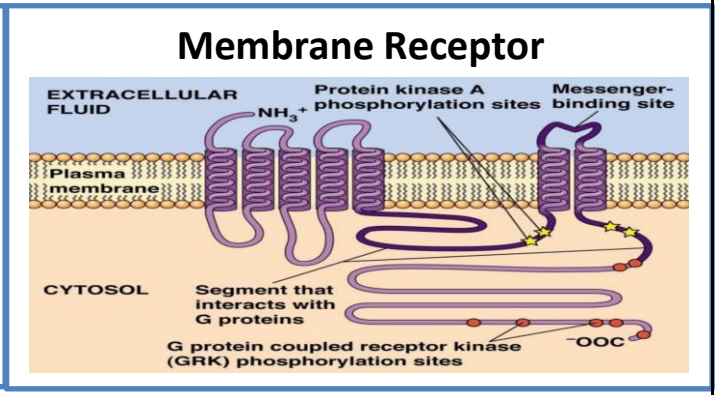


1) In terms of their action: The action of lipophilic hormones (group 1) is **slow** compared to the hydrophilic hormones (group 2). This is because group 1's action is actually **genomic: that is, they influence gene expression**. So, it takes time to synthesize mRNA and the protein, then modify the protein and eventually release it. Thus, it takes hours for this action to take place, and sometimes, even days, due to a reason mentioned on page 6. On the other hand, the hydrophilic (water-soluble) hormones (like protein and peptide hormones such as insulin) bind to a receptor, and then the signal is transmitted quickly into the cell.
2) In terms of their solubility and the requirement of transport proteins: Since group 1 hormones are lipophilic (lipid soluble), they need transport proteins. On the other hand, group 2 do NOT since they are hydrophilic, thus, they can mix with blood.
3) 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 a relatively short plasma half-life.

Functional Domains: (3:25)

- The 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.
  - Important: they fold **independently** of the rest of the protein. So, if we separate this domain from the rest of the domains, it can still function.
- **All** receptors have at least 2 functional domains:
  1) **Recognition domain** where the hormone (ligand) binds to (hormone-binding domain):
     - For cell surface receptors: The ligand-binding domain is exposed to the **outside** of the cell.
     - 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):
     - It's the domain that transmits the signal or does the work.
     - For the cell surface receptors: It's **intracellular** so it can interact with regulatory proteins that can then transmit the signal.
     - For the intracellular receptors: It's 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 to hormones, but do not generate a signal.





Regulation of Receptors: (5:27)

1. **Down-regulation:** Receptor-mediated endocytosis:
   - Via receptor-mediated **endocytosis**, the hormone binds to the receptor, and the receptor is then internalized. Once internalized, it gets degraded, thus reducing the number of receptors present on the cell surface.
   - Examples: Insulin, glucagon, TRH, growth hormone, LH, FSH, and catecholamines all down-regulate their receptors.

2. **Covalent modification of the receptor:**
    - Both intracellular and surface receptors can be covalently modified.
    - Example: Phosphorylation without a change in receptor number.
3. **Upregulation:**
    - Upregulation is where a hormone binds to a receptor, which increases the number of receptors on the cell surface.
    - Example: Angiotensin II and prolactin increase their receptor number as the cell-surface receptors become more occupied.
4. **Interaction with modulators:** Intracellular receptors can bind to other protein **co-repressors or co-activators** modulating receptor function.
    - Once the receptor is hormone-bound, it can bind to other factors called coregulators. These can be co-repressors or co-activators.
    - Example: Steroid receptors.
5. **Modulation of an intermediary signaling molecule:**
    - Or once the receptor is hormone-bound, signaling takes place, affecting another enzyme, or modifying the DNA.

Spare Receptors: (6:52)

- Receptors do NOT get saturated. There are free receptors 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.
- Most maximal biological responses are achieved when only a small percentage of receptors is occupied. The remaining free receptors (which are found on the side just in case) are known as spare receptors.
- When do we need them? These fully functional spare receptors would compensate in two situations:
    - A **low affinity** binding of the hormone to the receptor →So, the interaction is not really that strong.
    - A **low level** of hormone concentration in the system →So, the cell needs to sensitize itself to the hormone.
    - In both situations, spare receptors increase the sensitivity of target cells to the hormone.
- The greater the proportion/number of spare receptors:
    - The more sensitive the target cell is to the hormone → the more sensitive the signal is
    - the lower the concentration of hormone required to transmit the signal, and achieve half-maximal response.
      (Why half-maximal? Recall: Km is a measure of affinity, which indicates the substrate's concentration at which V0 is half-maximal (Vmax)).
- Examples:

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

2) The requirement of 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 receptors.

Types of receptors: (8:52)

- There are three different types of receptors:
  1) Intracellular (nuclear) receptors
  2) G protein-coupled receptors
  3) Receptor tyrosine kinases

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

- These are the hormones that bind to intracellular receptors:

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)

- These are the hormones that bind to cell surface receptors:
  - As you can see, they can be further categorized 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. We will focus on the ones we need to know later.

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)

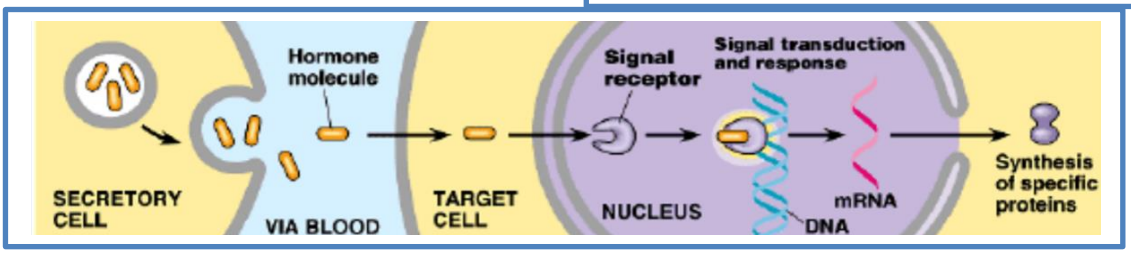
Nuclear receptors: (10:15)

- 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 binds to specific DNA promoter/enhancer sequences.

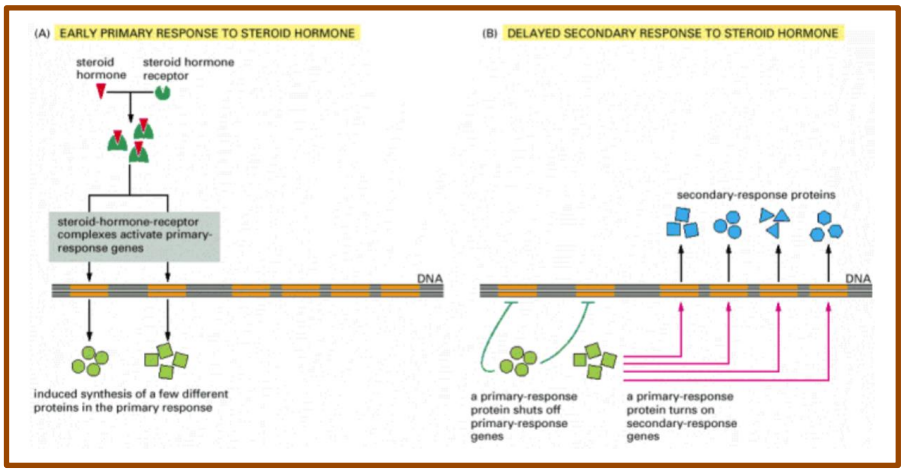
- The basic mechanism of these hormones and how they function:

The lipophilic hormone would diffuse through the plasma membrane into the cell.

Then binds to its receptor. This hormone receptor complex binds to DNA, thus, regulating gene expression.



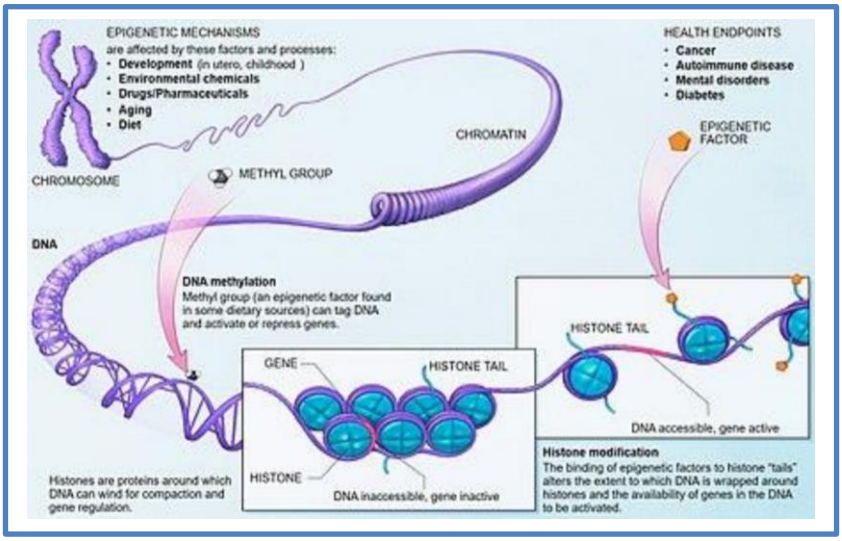
Types of response: (10:33)



1) **Primary response:**
   - Direct activation of a small number of specific genes. So, the receptor hormone complex binds to DNA, inducing gene expression (usually takes 30 minutes).
   - The activated molecules themselves are the ones that do the work.
2) **Secondary response:** the protein products of active genes in the primary response in turn activate other genes.
   - The response can be relatively immediate or delayed when it comes to gene expression.
   - These genes themselves can express transcriptional factors that, in turn, activate other genes to produce a delayed, secondary response; and so on.
     - Explanation: Sometimes, the activated molecules can be transcription factors themselves. 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 sites can also express transcription factors, inducing a tertiary response. So, sometimes it really takes, not only a few hours, but maybe a few days for the action to take place.

Cell-specific response: (11:37)

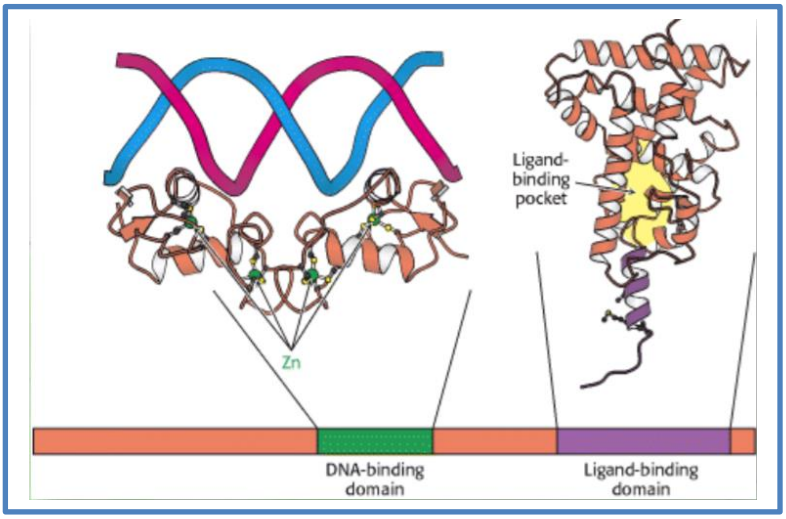
- The response or the control of gene expression is **cell specific (cell dependent).** The reason is that there is involvement of other co-regulatory molecules. When we have hormone-receptor complex bound to DNA, other proteins are recruited and thus they can change gene expression by modifying the structure of DNA.



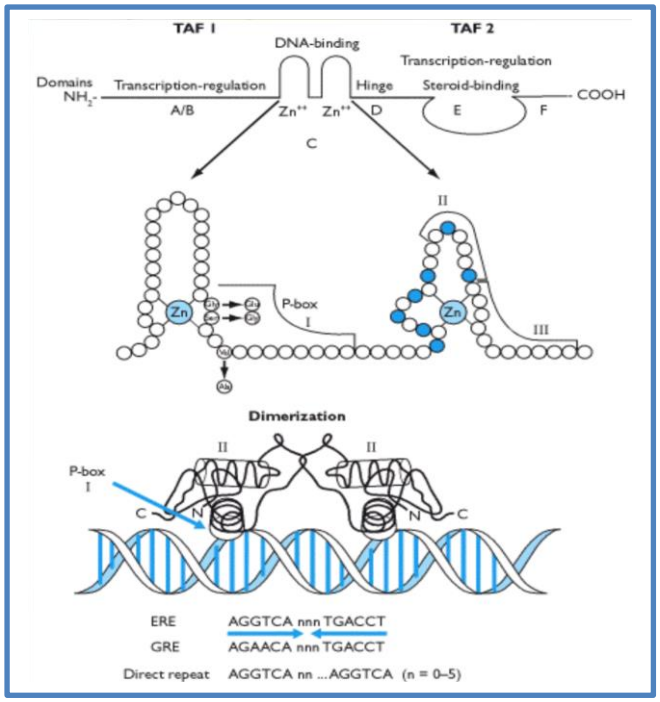
- Only certain types of cells have receptors for the hormones.
- Even if cells have identical intracellular receptors, each cell type contains a different combination of other cell-type-specific gene regulatory proteins that influence the gene transcription.
- Epigenetic regulation (DNA packaging and 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. This allows regulatory molecules to bind to DNA or prevent them from binding to DNA. So, that's how these receptors function.

Structure of receptors: (12:55)

- All intracellular hormone receptors have at least two domains:
  1) **Hormone-binding domain:** The domain that interacts with the hormone. Also called Ligand-binding domain.
  2) **DNA-binding domain:** Is the domain that interacts with certain sequences of DNA.



Zinc finger Domain: (13:22)



- A special DNA-binding domain is known as zinc finger.
- **DNA binding domain** belongs to a family of domains known as the **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 to inverted repeats or to certain sequences of DNA, and usually these sequences are defined by the amino acids on the zinc finger domain.
- 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. Thus, it also determines the specificity of the transcriptional activity of the receptor.
- So, the hormone receptor complex binds to certain regions of DNA depending on the amino acid composition on zinc finger domain. For example, the estrogen response element is specific for the estrogen hormone receptor complex.

Mechanisms of control of gene expression: (14:20)

- 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.
- There are two ways by which steroid hormones can alter gene expression:
  1) **Mechanism 1:** Direct binding to DNA sequences, known as **hormone response elements,** and these elements have specific sequences.
     Examples:
     -glucocorticoid response element (GRE)
     -estrogen response element (ERE) specific for estrogen hormone receptor
     -Androgen receptor element, specific for androgens and so on.
  2) **Mechanism 2:** Binding to and activating/repressing other transcription factors that recognize a particular site on DNA.

Non-genomic cellular effects: (14:44)

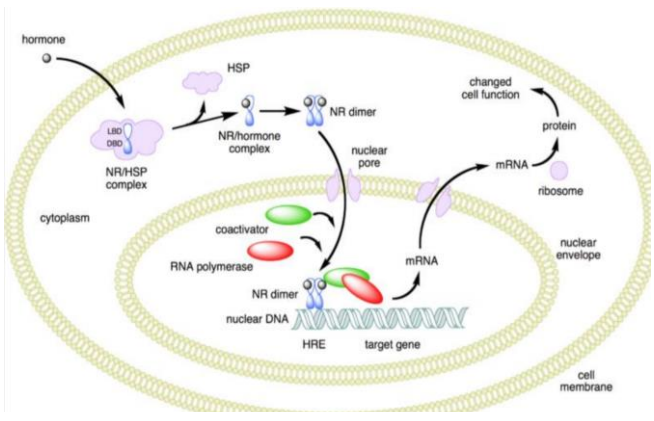
- It is an effect **independent** of regulating gene expression.

- 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, can bind to G proteins, G protein coupled receptors, and can bind and affect tyrosine kinase receptors.
- This is a new area in research that seems to be important in regulating the physiology of our body.

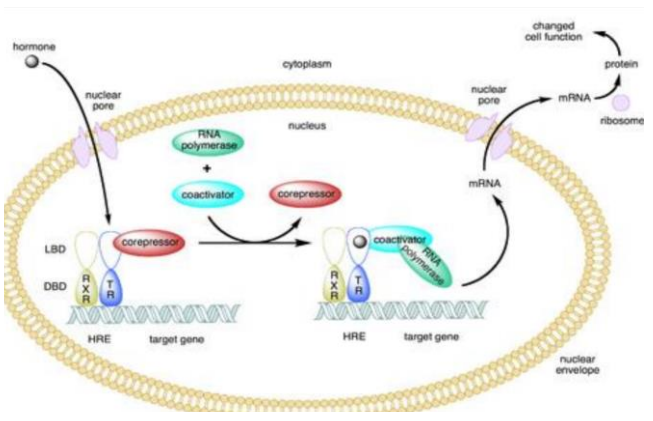
Hormone classification (location of intracellular receptors): (15:26)

- 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 the 2 classes:
- **Type 1 receptors:**
  - Predominantly cytoplasmic.
  - They are bound to **heat shock proteins (HSP).** However, once the steroid hormone goes into the cell and binds to this receptor →HSP is released→ The receptor dimerizes with another receptor, usually of the same type→ The dimer is then translocated into the nucleus, binding to the DNA.
  - Examples: the glucocorticoid, mineralocorticoid, estrogen, androgen and progesterone receptors.
- **Type 2 receptors:**
  - They are nuclear (NOT cytoplasmic), and some are bound to DNA (not bound alone, but in association with 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 with coactivators and thus we will have induction of gene expression.
  - They characteristically form heterodimers. Example: The thyroid hormone receptor can bind with retinoid X receptor, thus binding in a heterodimer fashion. However, they can also form homodimers.

Type I receptors



Type II receptors



Glucocorticoid receptors: (18:10)

- Mineralocorticoids and glucocorticoids.
  - The physiological **mineralocorticoid** is **aldosterone**.
  - The physiological **glucocorticoid** is **cortisol**.
- They are synthesized in the adrenal cortex of mammals.
- 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 (e.g. pro-opiomelanocortin gene).
- Example: The activation that results in the expression of certain genes 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. So, 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 serum protein that transports cortisol: **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 this results in the activation of adenylate cyclase.

Types of estrogen receptors: (19:36)

- 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, while others can only produce beta. However, some cells can produce both of them, and in these cells, 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 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 (Breast cancer, for example). However, what if ERβ were to have an inhibitory effect on breast cancer? So, this area of study is still under research and could lead to great findings.

Progesterone receptor: (21:35)

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

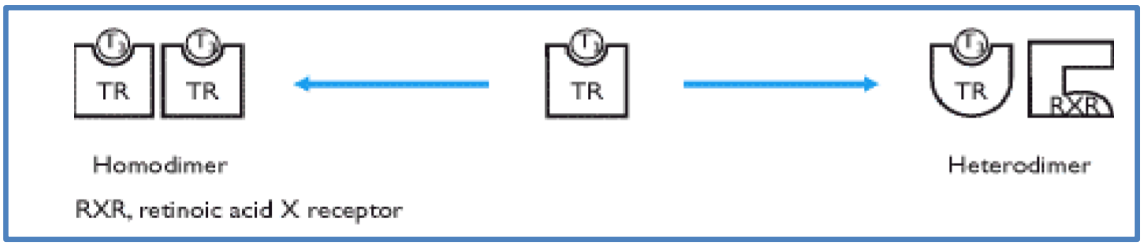
Androgen Receptor: (22:09)

- The 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**. DHT is a 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. Or maybe, the intracellular receptor itself can regulate adenylate cyclase indirectly.

Thyroid hormone receptors: (23:08)

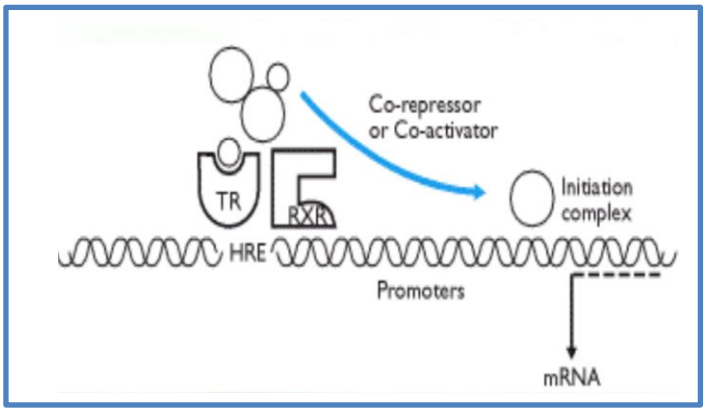
- Unlike some steroid receptors, thyroid hormone receptors belong to **type 2** receptors and thus exist in the nucleus and are free of heat shock proteins (HSP).
- The receptors may remain bound to DNA in the absence of hormone binding. However, they are associated with co repressors. When the hormone 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.



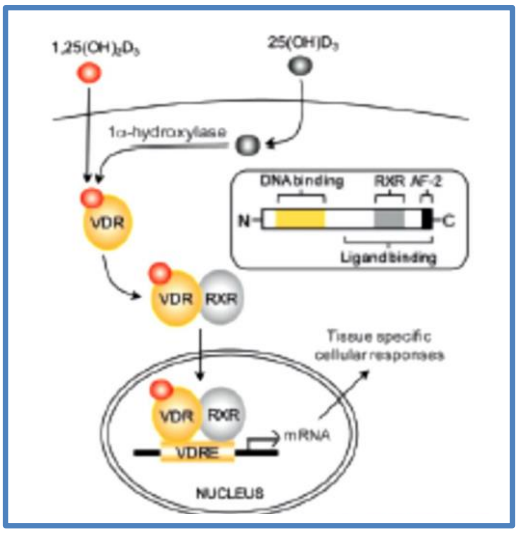
DNA binding: (23:53)

- As dimers, the zinc fingers of the DNA binding domain bind to a hormone response element (HRE) on the DNA helix.
- Along with other transcription factors (coactivators/repressors), they regulate gene expression.
- So, the idea here is the replacement of co-repressors by co-activators.



Vitamin D: (24:00)

- Vitamin D is a steroid hormone derived from cholesterol, and it has its own intracellular receptor.
- Binding of Vitamin D receptor (VDR) to its ligand, 1,25(OH)2D3, causes HSP 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 a responsive gene.
- Notice that the dimer formed is the vitamin D receptor with the 'Retinoid X Receptor' (heterodimer).



Other nuclear receptors: (24:38)

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).

NOTE: We will only focus on the first two receptors in details

1) Retinoid X receptors (RXRs): (24:58)

- RXR forms a heterodimer with other receptors, and you need to know what these receptors are: all-trans retinoic acid receptor (RAR), vitamin D3 receptor (VDR), thyroid hormone receptor (TR), the peroxisome proliferator-activated receptor (PPAR) and the nerve growth factor induced–B (NGFI–B) receptor.
  - Once we have the formation of the heterodimer, it can bind to the hormone response element. After that, the co-repressors are replaced with the coactivators.
- 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 corepressor proteins including a histone deacetylase (HDAC).
  - 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.

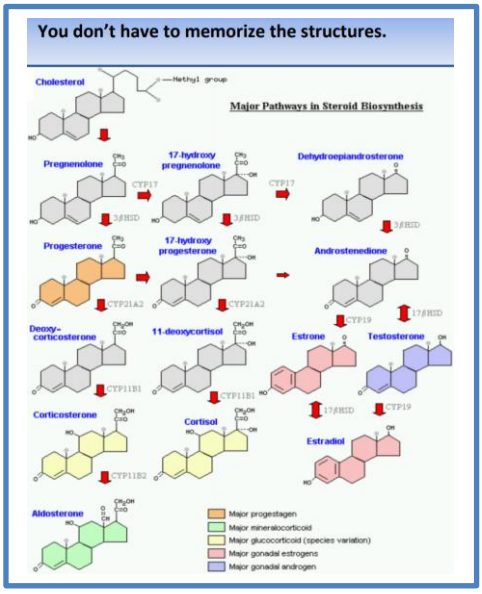
2) The peroxisome proliferator-activated receptors (PPARs): (25:40)

- These receptors are important because they are targets of many drugs whether in cancer or metabolic syndromes. Some are experimental, but some are currently used in-clinic.
- Three family members: **PPARα, PPARβ/δ, and PPARγ**.
- Each of these receptors forms a heterodimer with the RXRs.
- Notice that they are important in regulating 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**.

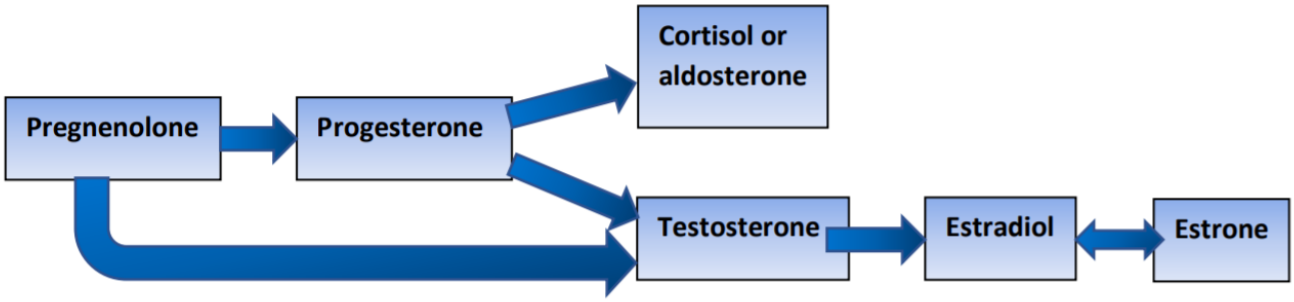
Steroid hormone Synthesis: (26:58)

- Steroid hormones are derived from cholesterol, which is converted to pregnenolone. 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 <u>independently</u> from progesterone as well, and you can have pregnenolone converted into testosterone.
- Moreover, formation of estrogen (estradiol) occurs by the reduction of testosterone. Estrogen can also be formed from 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: (28:32)

- The testis secretes over 95% of the circulating testosterone.
  - Most of it is secreted by the testes, but the 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 conversion into DHT.
- Only about 2% of circulating testosterone is in the free form (active form), while 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: (29:13)

- Estradiol is the most important steroid and is mainly secreted by the ovaries.
- It 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.

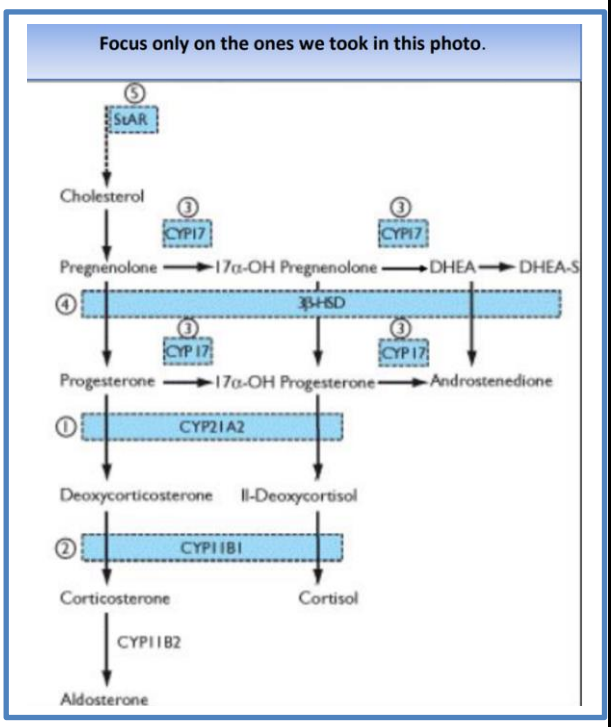
Progesterone: (29:37)

- 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 whichever form it can be excreted.

Critical enzymes: (29:54)

1) 3β-hydroxysteroid dehydrogenase:

- This is the enzyme that converts pregnenolone into progesterone.
- It is a very important enzyme because it leads to the production of all the other steroid hormones such as 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 which can be used to make **androstenedione**, an androgen that is a precursor of testosterone and estrogens.
- If this enzyme is defective, there would be no production of androgen, testosterones, estrogens and cortisol as well. However, production of aldosterone would still occur.

- 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:

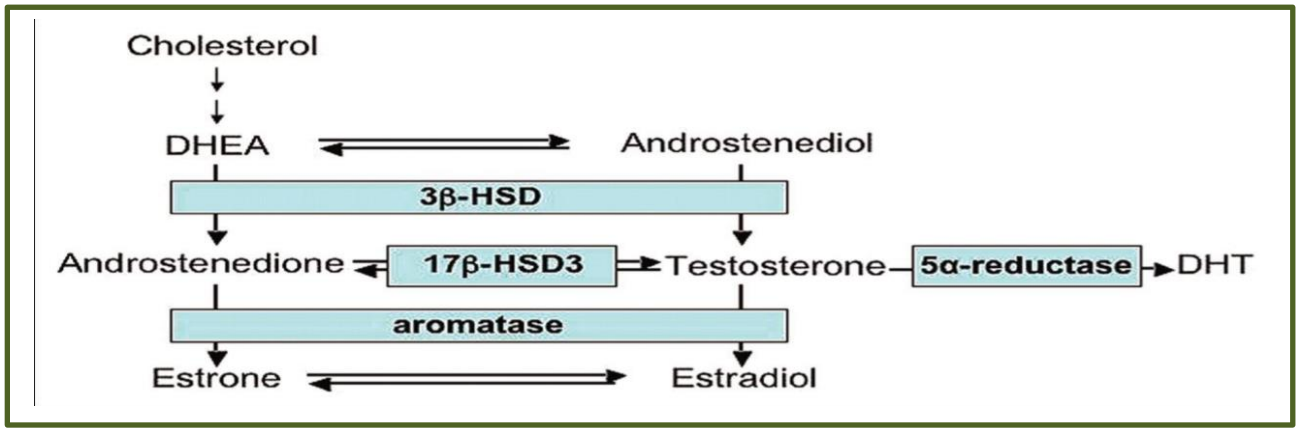
- Testes and ovaries contain this enzyme, which enables androgens to be converted to testosterone.
- This is an important enzyme because it converts progesterone into testosterone.

4) 5α-reductase:

- In Sertoli cells and other target cells, testosterone is rapidly converted to DHT (dihydrotestosterone) by the 5α-reductase enzyme before it interacts with the androgen receptor.
- An important enzyme for forming the **potent androgen (DHT)**.

5) Aromatase:

- This enzyme converts **androgen into estradiol**.
- Aromatase converts androstenedione and testosterone into estrogens.
- This enzyme is the target for breast cancer therapy mainly in postmenopausal women.
  - Most of the estrogen is secreted from the adrenal gland, not from ovaries.
  - So, to limit the production of estrogen in these women, they are given aromatase inhibitors. This affects the tumor size, or the progression of tumor.



Good Luck