HELLENIC REPUBLIC
National and Kapodistrian University of Athens
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Steroid Hormones

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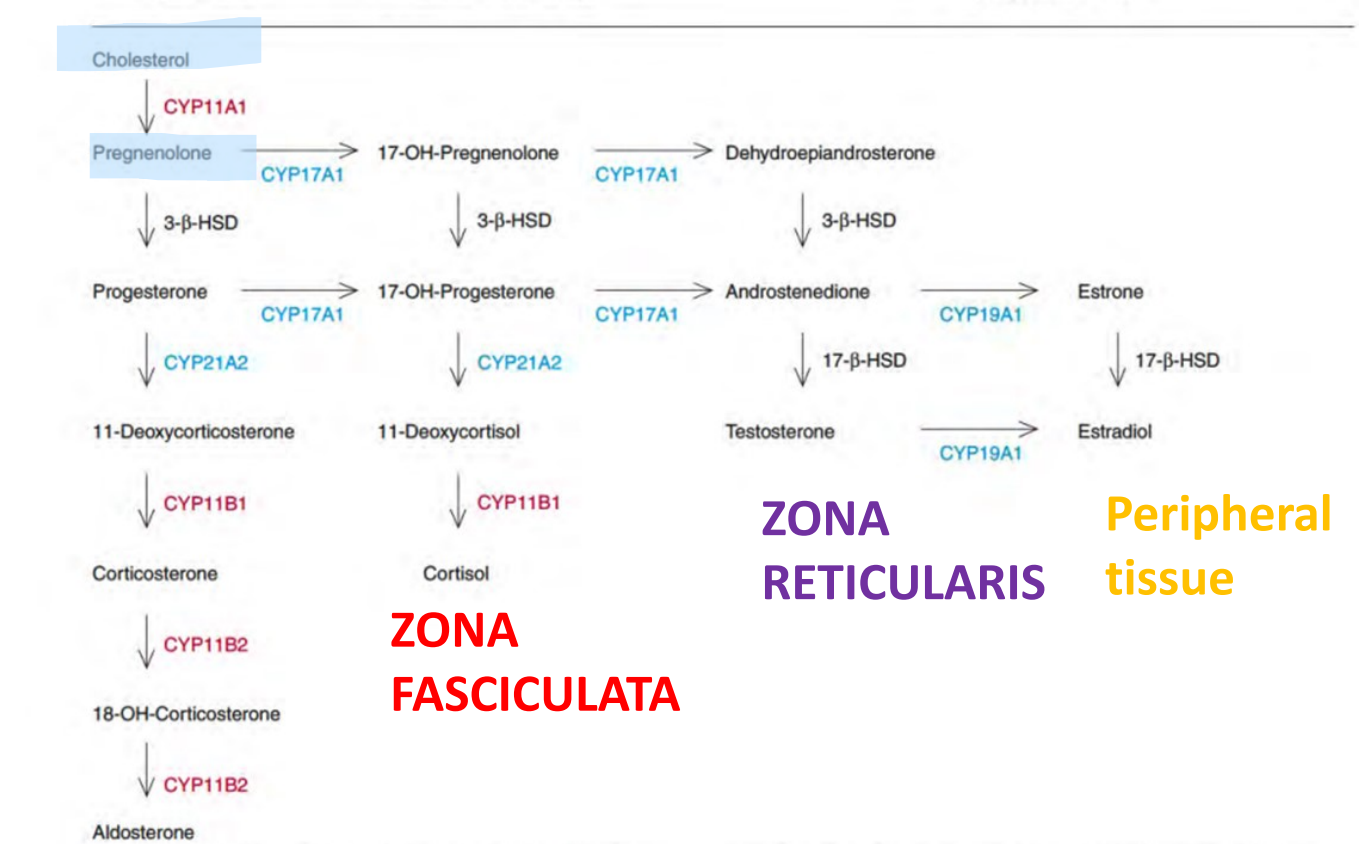
General Educational Goals: Students should be able to

- Understand the structure and biosynthesis of steroid hormones.
- Understand the molecular mechanism of action of steroid hormones in cells.
- Understand and identify receptors for steroid hormones.
- Understand their function through clinical examples.

Structures and Functions of Steroid Hormones

- Steroid hormones are divided into the **sex and progestational hormones , and the adrenocortical hormones.**
- They are **synthesized in the gonads (ovaries and testes) and adrenal cortex** from **cholesterol through Δ^5-pregnenolone as an intermediate.**

The precursor is cholesterol, which is modified by various **hydroxylations, methylations, and demethylations to form glucocorticoids, androgens, estrogens, and their biologically active derivatives**



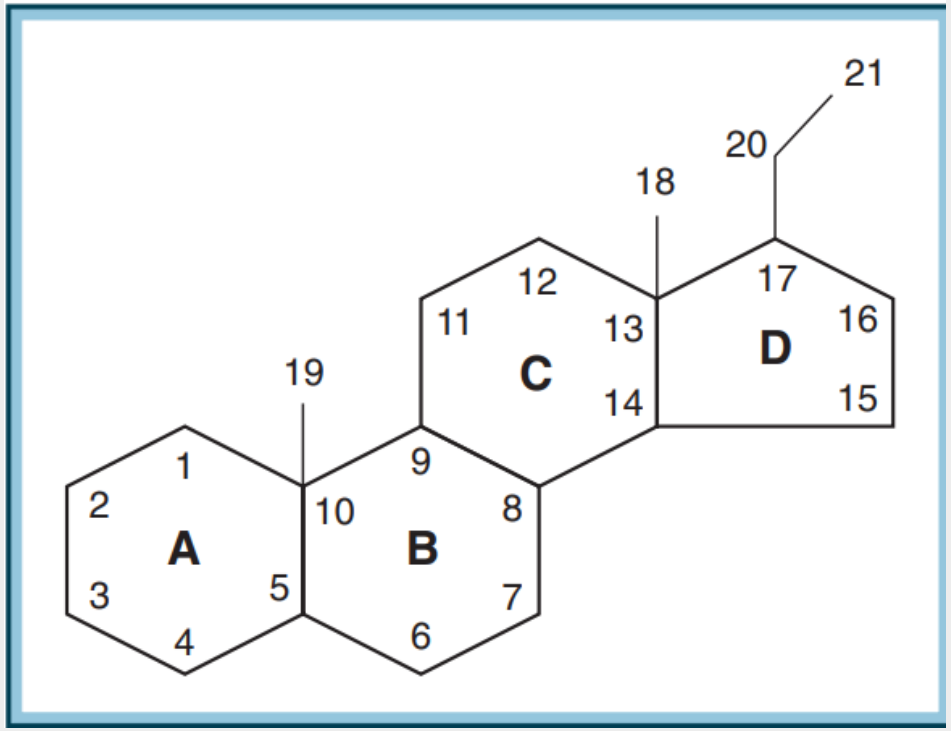
ZONA GLUMERILOSA

ZONA FASCICULATA

ZONA RETICULARIS

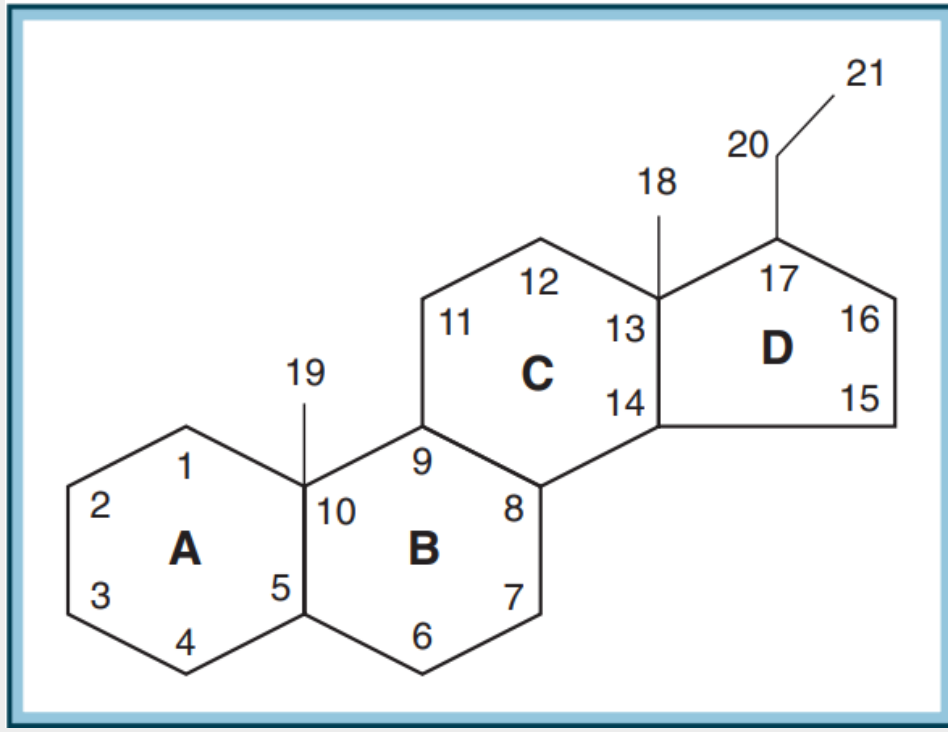
Peripheral tissue

- Their structure is based on **the cyclopentanoperhydrophenanthrene nucleus**; the numbering of this ring system and the lettering of the rings: **three cyclohexane rings and a single cyclopentane ring**
- Conversion of steroid hormones to **less active or inactive forms involves alteration of ring substituents** rather than the ring structure itself.
- Many steroid hormones are similar in overall structure, although **their receptors can be highly specific.**



Steroid Hormone Classification

- Steroid hormones are classified **on the basis of the number of carbons they contain**.
- **Progesterone, cortisol, and aldosterone are C_{21} steroids;**
- **Testosterone and dehydroepiandrosterone are C_{19} steroids**
- **17/β-estradiol is a C_{18} steroid.**
- Sex hormones can be distinguished easily as being androgens (C_{19}), estrogens (C_{18}), or progestational or adrenal steroids (C_{21}).
- Certain substituents in the **ring system are characteristic**.



Major Steroid Hormones of Humans

HORMONE: SECRETION FROM: SECRETION SIGNAL

- **Progesterone:** corpus luteum, LH
- **17/β-Estradiol:** ovarian follicle; corpus luteum; Sertoli cell, FSH
- **Testosterone:** Leydig cells of testis adrenal gland; ovary, LH
- **Dehydroepiandrosterone:** reticularis cells of adrenal cortex, ACTH
- **Cortisol:** fasisculata cells of adrenal cortex, ACTH
- **Aldosterone:** glomerulosa cells of adrenal cortex, Angiotensin II/III
- **1,25-Dihydroxyvitamin D_3:** arises in skin cells after exposure to UV light; successive hydroxylations in liver and kindney yield active form of hormone, PTH

Cholesterol: the precursor

Cholesterol is the precursor for adrenal steroidogenesis.

From circulation: low-density lipoprotein (LDL)

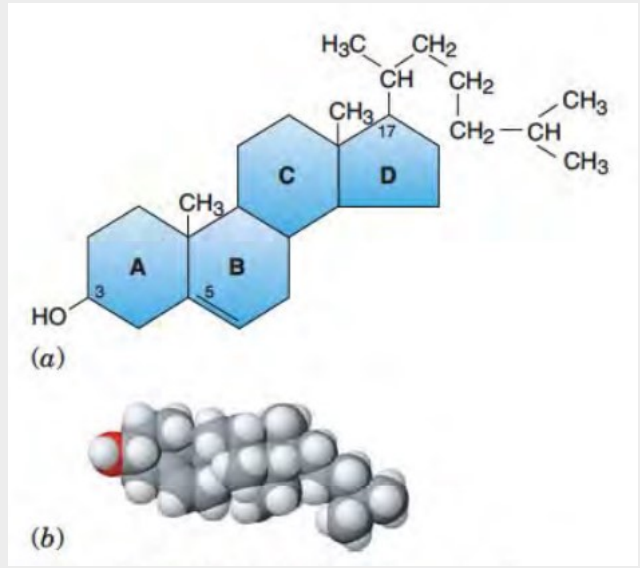
Uptake is by specific cell-surface LDL receptors present on adrenal tissue

LDL is then internalized via receptor-mediated endocytosis, the resulting **vesicles fuse with lysozymes, and free cholesterol is produced after hydrolysis.**

BUT NOT the sole source of adrenal cholesterol:

Cholesterol can be generated de novo within the adrenal cortex from acetyl coenzyme A (CoA).

The adrenal can also utilize high-density lipoprotein (HDL) cholesterol after uptake through the putative HDL receptor, SR-B1.



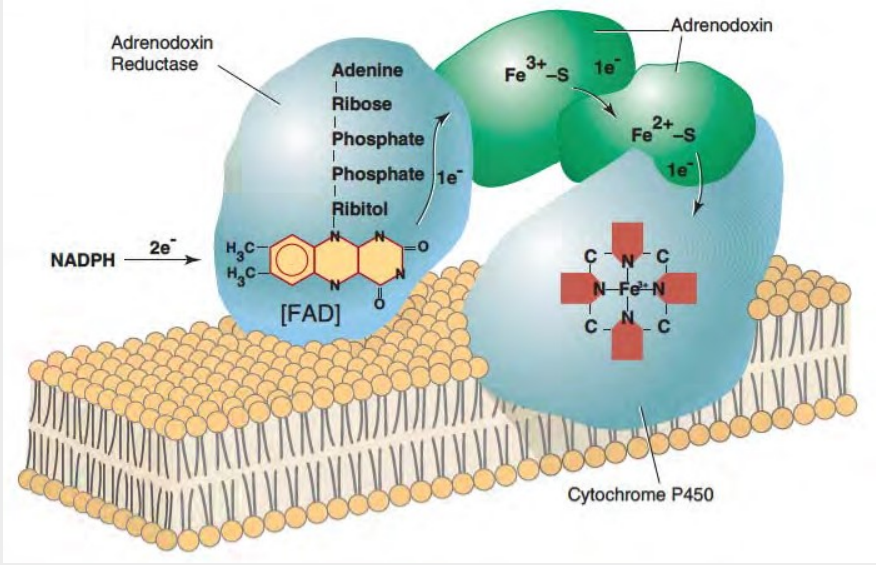
A compact, rigid, hydrophobic molecule with four fused rings and a C8-branched hydrocarbon chain attached to the D ring at position 17.

It has a polar hydroxyl group at C3. The **presence of cholesterol in membranes** alters the fluidity and **reduces permeability.**

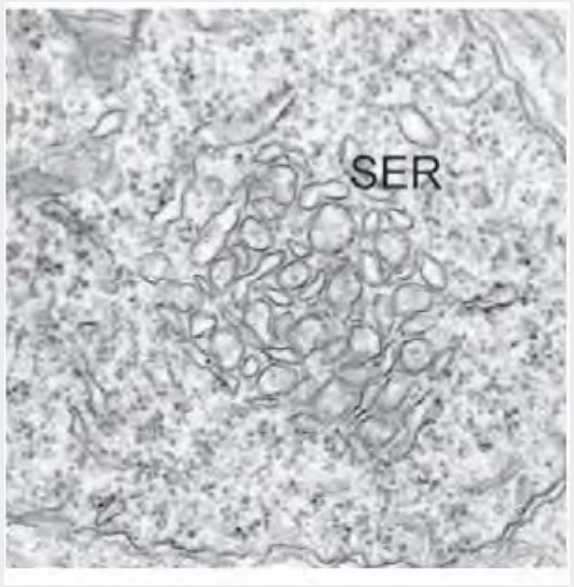
Steroidogenesis involves the concerted action of several enzymes, including a series of cytochrome P450 enzymes

- Cytochrome P450 enzymes are classified into two types according to their **subcellular localization and their specific electron shuttle system. Mitochondrial (type I)** rely on electron transfer facilitated by **adrenodoxin and adrenodoxin reductase.**

- **Micrososomal (type II) cytochrome P450 enzymes localized to the endoplasmic reticulum** include the steroidogenic enzymes 17α-hydroxylase (CYP17A1, or P450c17), 21-hydroxylase (CYP21A2, or P450c21), and P450 aromatase (CYP19A1, or P450aro).



Cytochromes P450 are so called because of the unique absorbance spectrum that is produced when CO is bound to the reduced, ferrous form of the heme. The spectrum exhibits a peak at approximately 450 nm.



Smooth endoplasmic reticulum of a mammalian cell

Both mitochondrial and microsomal (endoplasmic reticulum) cytochrome P450 systems are required to convert cholesterol to aldosterone and cortisol in adrenal cortex, testosterone in testes, and estradiol in ovaries.

Cytochromes P450 are integral membrane proteins containing a single iron protoporphyrin IX (heme) prosthetic group

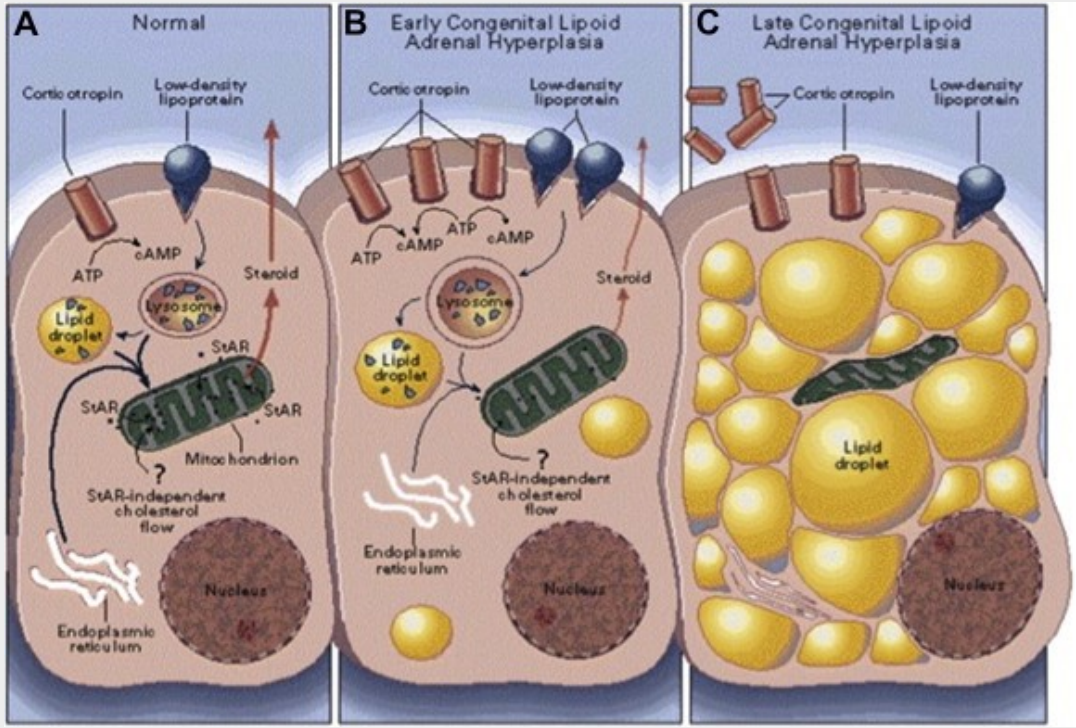
The general reaction catalyzed by a cytochrome P450 is:

$NADPH + H^+ + O_2 + SH \rightarrow NADP + + H_20 + SOH$

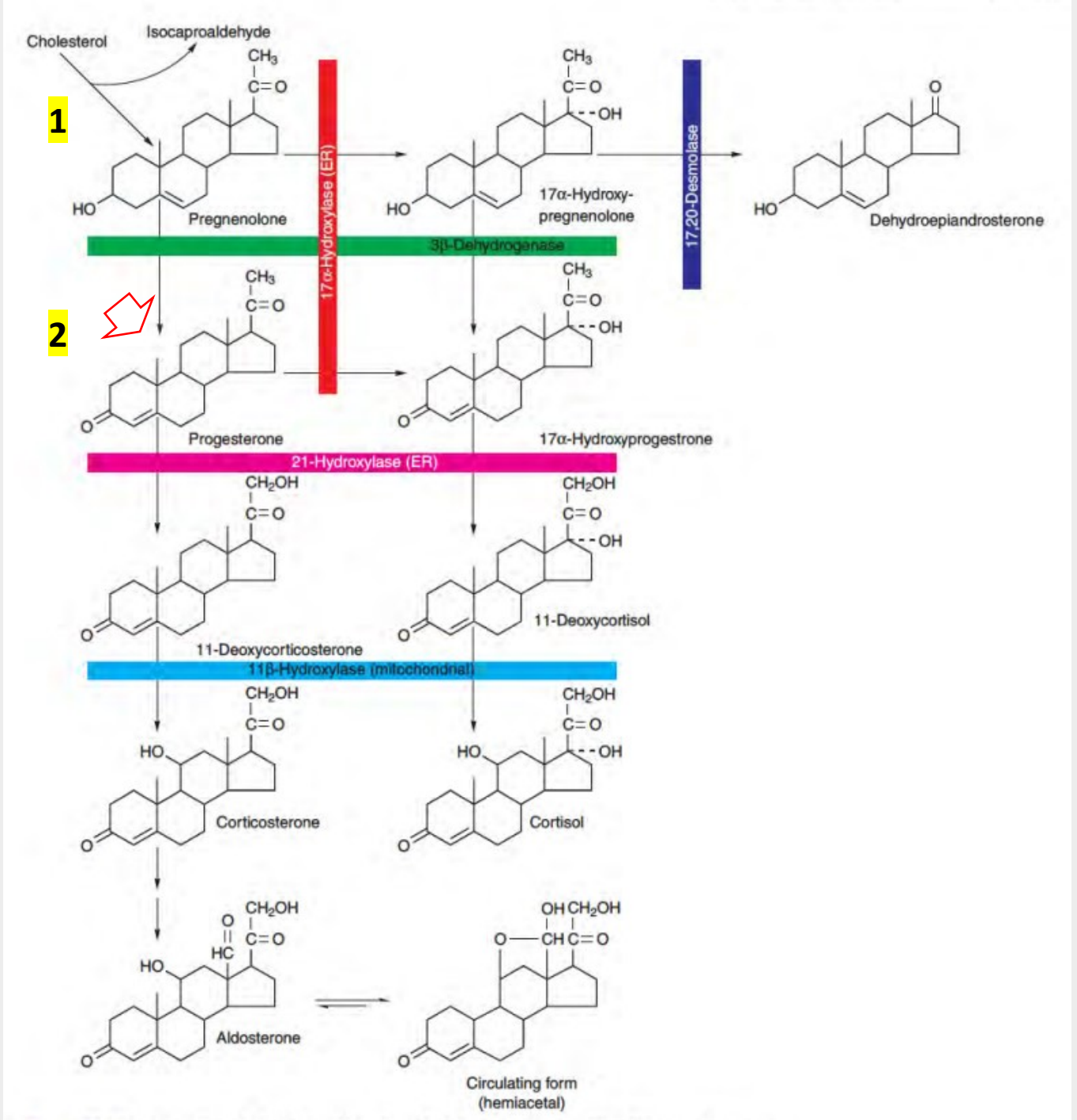
NADPH is a two-electron donor and **the substrate (S) may be a steroid, fatty acid, drug, or other chemical that has an alkane, alkene, aromatic ring, or heterocyclic ring substituent that can serve as a site for oxygenation.**

The reaction is a **monooxygenation**, and the enzyme is a **monooxygenase** as it incorporates only one of the two oxygen atoms into the substrate

- The **endoplasmic reticulum hydroxylases** involved in steroid hormone synthesis use **molecular oxygen (O_2) to introduce one oxygen atom into the steroidal substrate (as an OH), while the second atom is reduced to water.**
- Electrons generated from NADH or NADPH through a flavoprotein are transferred to ferredoxin or a similar nonheme protein.
- **There is movement of intermediates in and out of the mitochondrial compartment during biosynthesis of steroids.**
- Once the specific steroids are synthesized, they **diffuse through the plasma membrane and enter the general circulation , where they often bind to transport proteins.**
- **Unlike peptide hormones, steroids are not stored in secretory vesicles.**

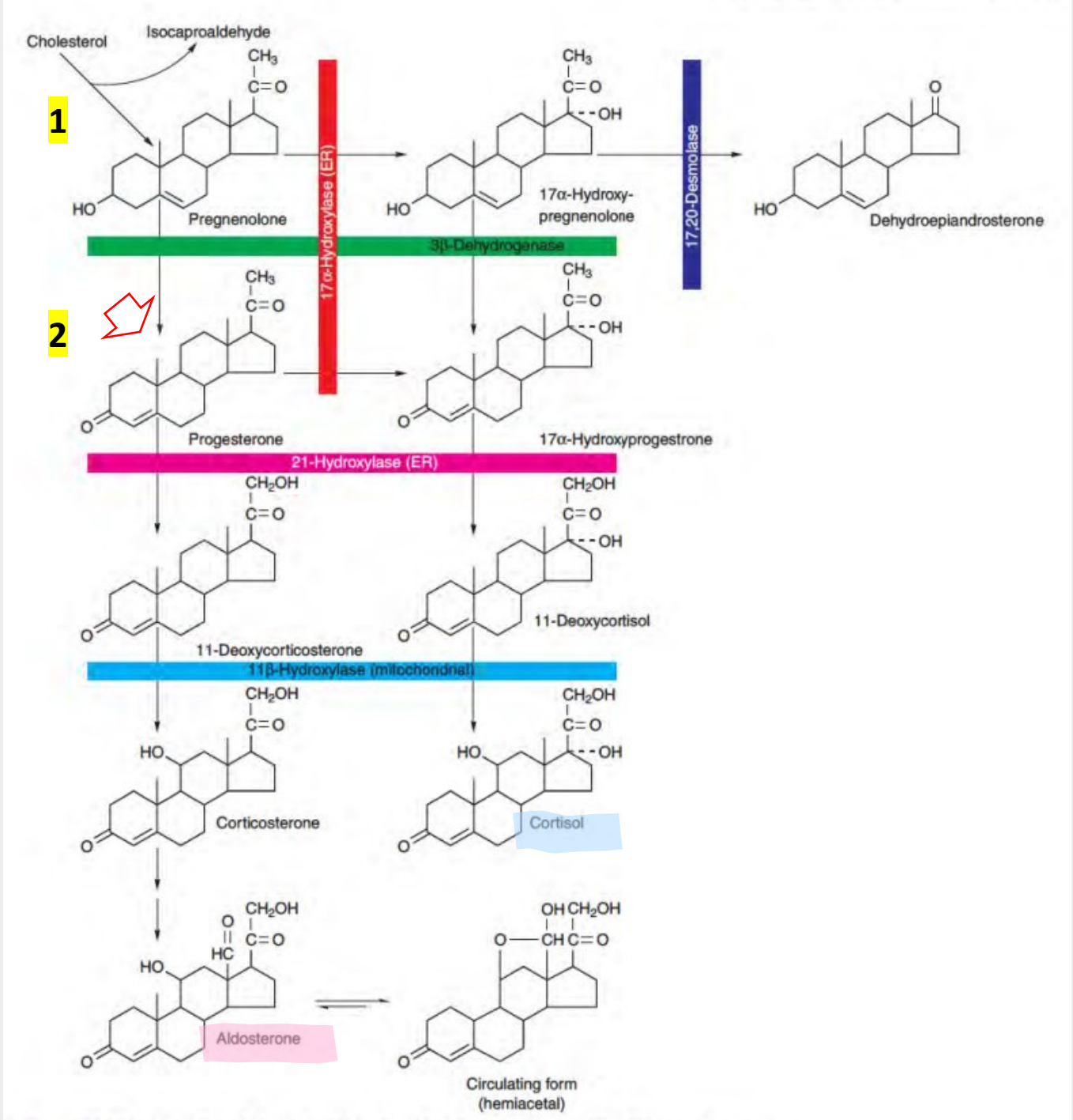


Papadopoulos V, Miller WL. Role of mitochondria in steroidogenesis. Best Pract Res Clin Endocrinol Metab. 2012 Dec;26(6):771-90. doi: 10.1016/j.beem.2012.05.002. Epub 2012 Jun 16. PMID: 23168279.



Conversion of cholesterol to adrenal cortical hormones

1. Cholesterol undergoes side chain cleavage to form Δ^5-pregnenolone and isocaproaldehyde.
2. **Δ^5-pregnenolone is a required precursor in the synthesis of all steroid hormones.**
3. Pregnenolone is converted directly to progesterone by 3β-Dehydrogenase and $\Delta^{4,5}$-isomerase.
4. **The dehydrogenase converts the 3-0H group of pregnenolone to a 3-keto group and the isomerase moves the double bond from the B ring to the A ring to produce progesterone.**
5. **In the ovarian corpus luteum** the bulk of **steroid synthesis stops at this point.**

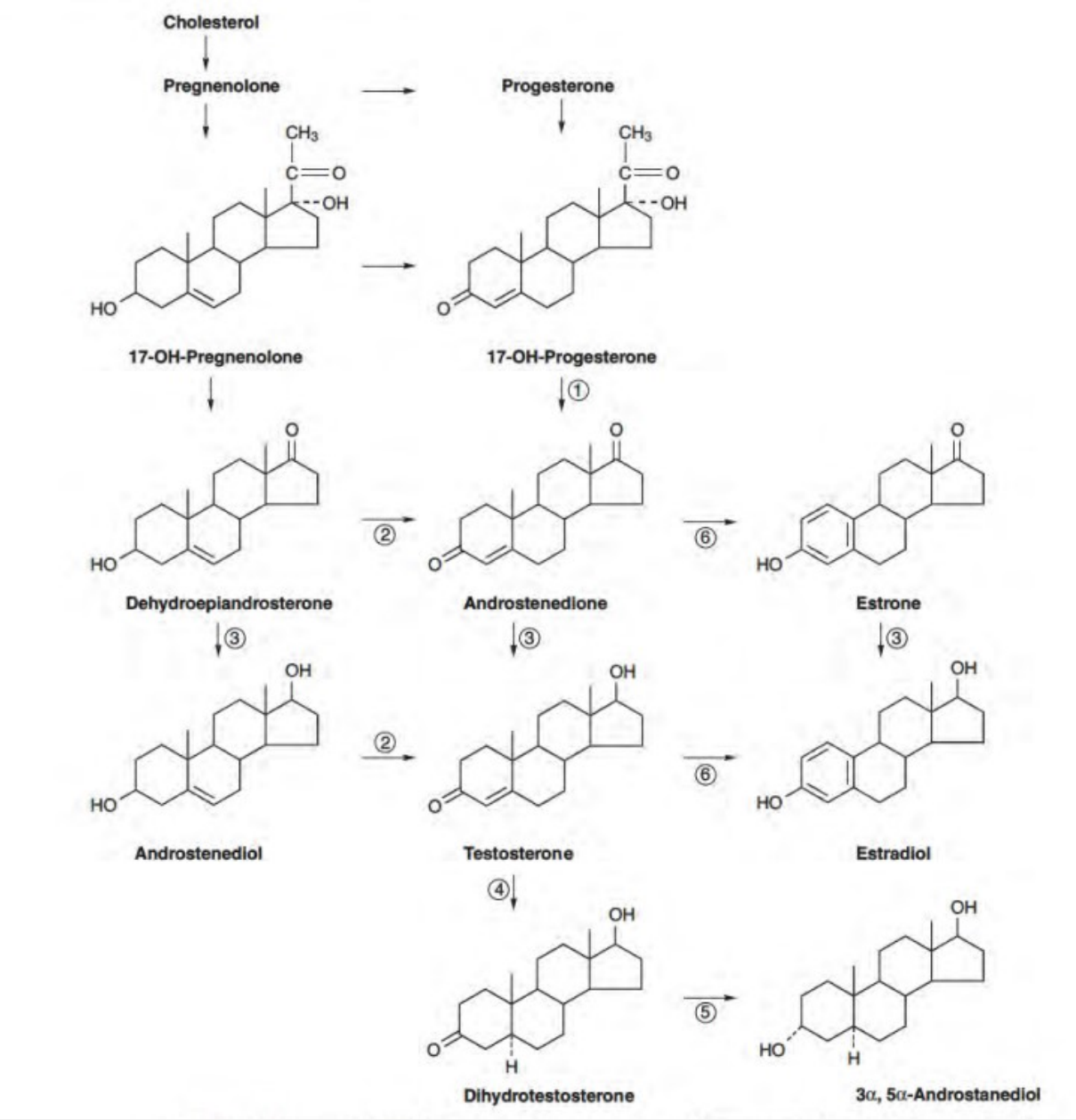


Conversion of cholesterol to adrenal cortical hormones

6. Conversion of pregnenolone to aldosterone in the adrenal zona glomerulosa cells **requires the endoplasmic reticulum 21-hydroxylase, and 11 β-hydroxylase and 18-hydroxylase located in mitochondria.**

To form cortisol, primarily in adrenal zona fasciculata cells, 17-hydroxylase and 21-hydroxylase in the endoplasmic reticulum are required along with mitochondrial 11β-hydroxylase.

Conversion of cholesterol to adrenal cortical hormones

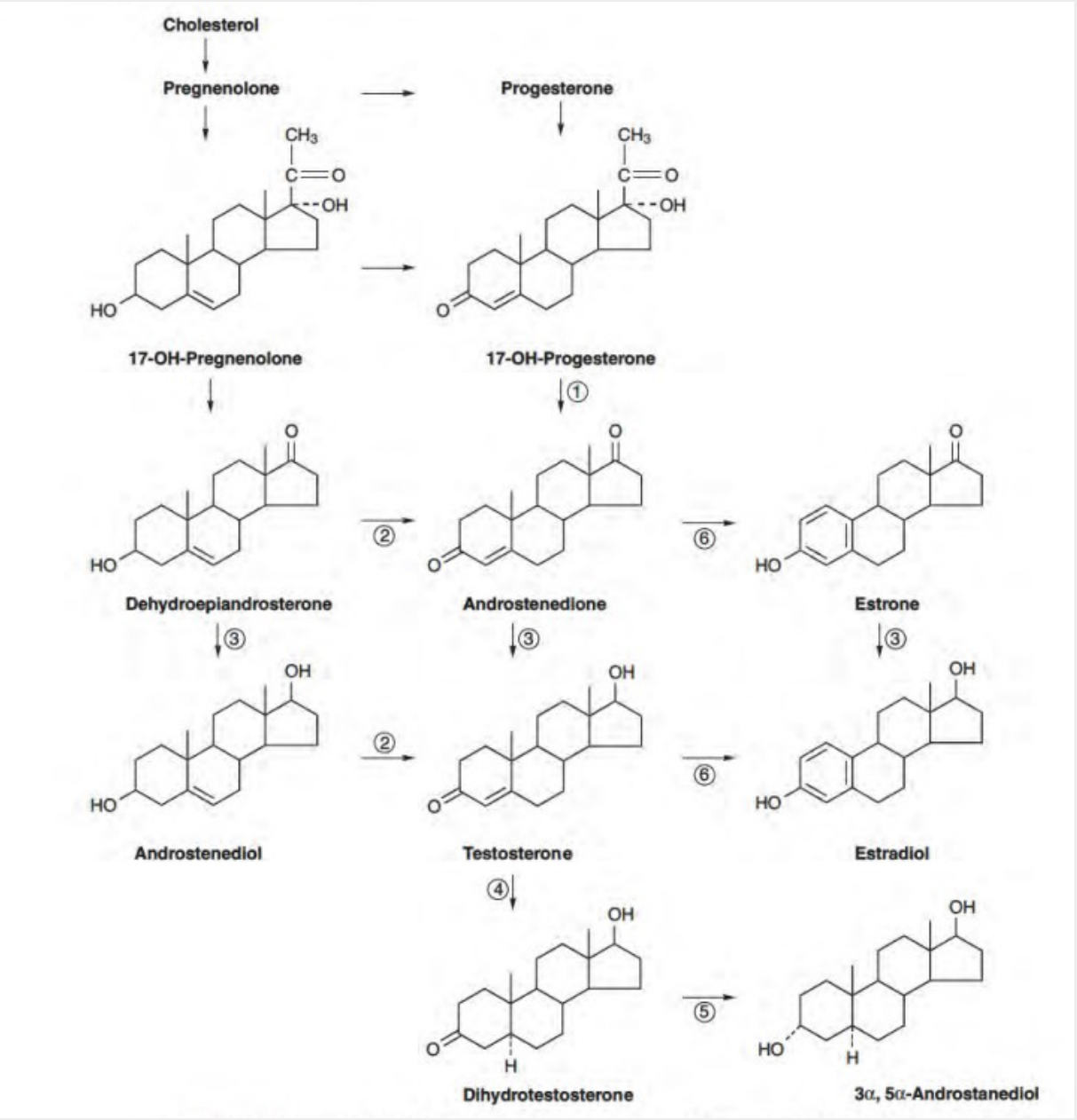


7. The endoplasmic reticulum hydroxylases are cytochrome P450 (CYP) enzymes

8. Δ^5-Pregnenolone is converted to dehydroepiandrosterone in the adrenal zona reticularis cells by 17 a-hydroxylase localized in the endoplasmic reticulum to form 17 a-hydroxypregnenolone and then by a side chain cleavage system to form dehydroepiandrosterone

Cholesterol is converted to the sex steroids by way of Δ^5-Pregnenolone and progesterone

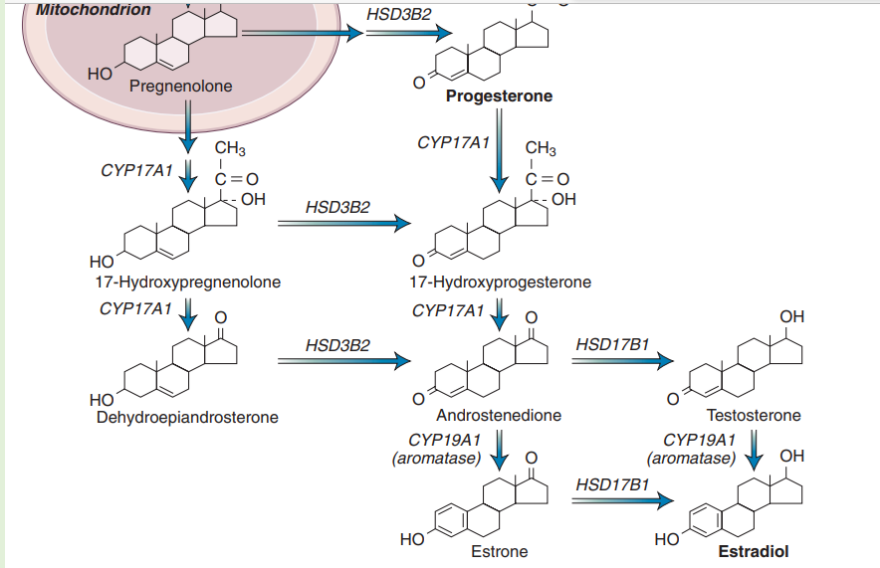
Progesterone is converted to testosterone by the action of cytoplasmic enzymes and 17-dehydrogenase



- **Testosterone is a major secretory product in the Leydig cells of the testis and is converted to dihydrotestosterone in some, but not all**, androgen target cells before binding with high affinity to the intracellular androgen receptor.
- **This reduction requires the activity of 5a-reductase located in the endoplasmic reticulum and nucleus.**
- **Pregnenolone** can enter an alternative pathway to form dehydroepiandrosterone - This **weak androgen** can then be converted to **androstenedione and then to testosterone.**
- **Estradiol is formed from testosterone by the action of the aromatase system**

The naturally occurring estrogens are C18 steroids characterized by the presence of an aromatic A ring, a phenolic hydroxyl group at C3, and a hydroxyl group (estradiol) or a ketone group (estrone) at C17

- **Aromatase is the key enzyme for estrogen production in the ovary**
- **The principal and most potent estrogen secreted by the ovary is estradiol.**
- Estrone is also secreted by the ovary or extraglandular conversion of androstenedione in peripheral tissues.
- Estriol (16-hydroxyestradiol) is the most abundant estrogen in urine and is produced by metabolism of estrone and estradiol in extraovarian tissues.
- **All C18 steroids, including estrone, estradiol, and estriol, are commonly referred to as estrogens BUT estrone and estriol are only weakly estrogenic and must be converted to estradiol to show full estrogenic action.**



Metabolism of steroid hormones

- **Slow metabolism:** bound to plasma proteins, which protects them from degradation .
- Examples: cortisol binds extensively to serum transcortin and has a plasma half-life of about 60-70 min. In contrast, aldosterone , which is not extensively bound to plasma proteins, has a half-life of only about 20 min.
- **The liver:** principal site for steroid metabolism/ number of metabolites are produced
- **Enzymatic reactions** involved: decrease biological activity and increase solubility in water, **thus facilitating their excretion in urine.**
- **Conjugation also increases the water solubility of steroid metabolites;** glucuronides and sulfates are the most common conjugates.
- **Estimates of steroid hormone secretion are often based on urinary metabolite levels.**
- **Age influences hepatic steroid metabolism** and the **clearance of some steroids is slower (lower metabolic clearance rate) in infants and the elderly.**
- The rates of steroid metabolism are also **increased in patients with hyperthyroidism and decreased in patients with hypothyroidism and in different types of liver disease**

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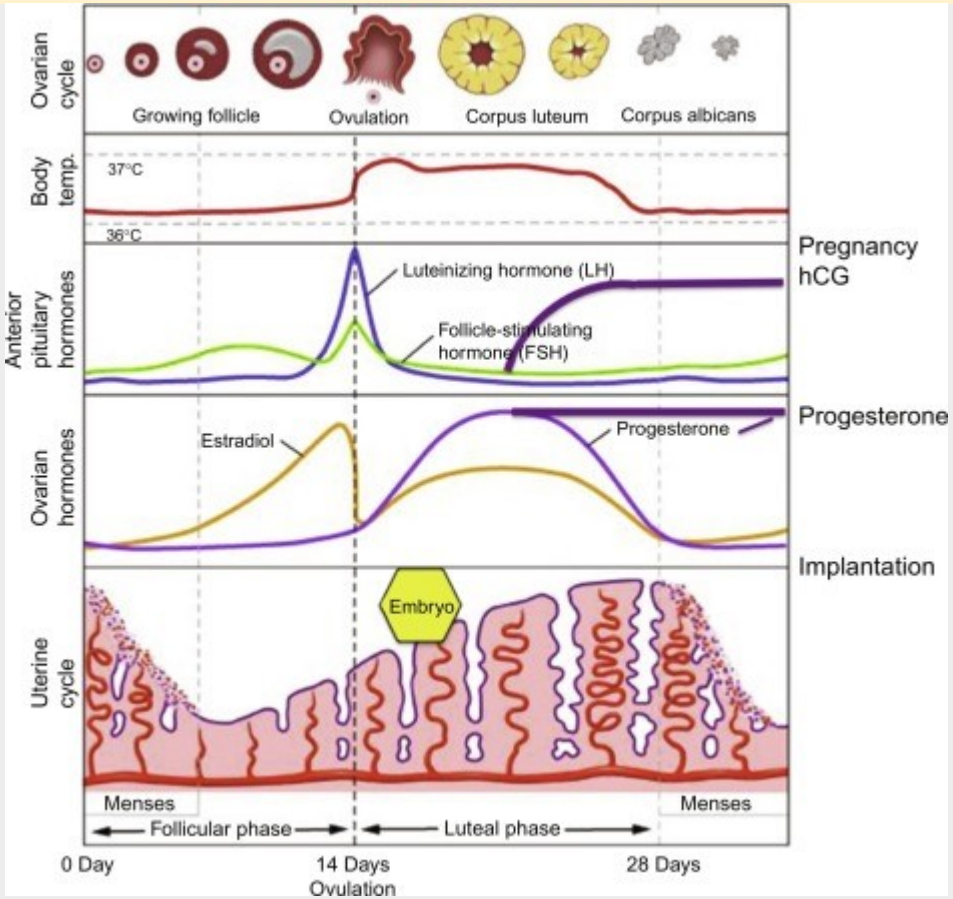
Progesterone

- An intermediate of testosterone, estrogen, cortisol, and aldosterone synthesis. **As a hormone it is indispensable for ovulation, nidation of the fertilized egg, and for the maintenance of pregnancy**
- **Increased concentrations of progesterone which are made in the corpus luteum block LH formation.**
- **Progesterone (PRG) inhibits the secretion of GnRH**.
- Maintenance of corpus luteum function. **Preparation of the endometrium for the reception, implantation, and development of the fertilized ovum**

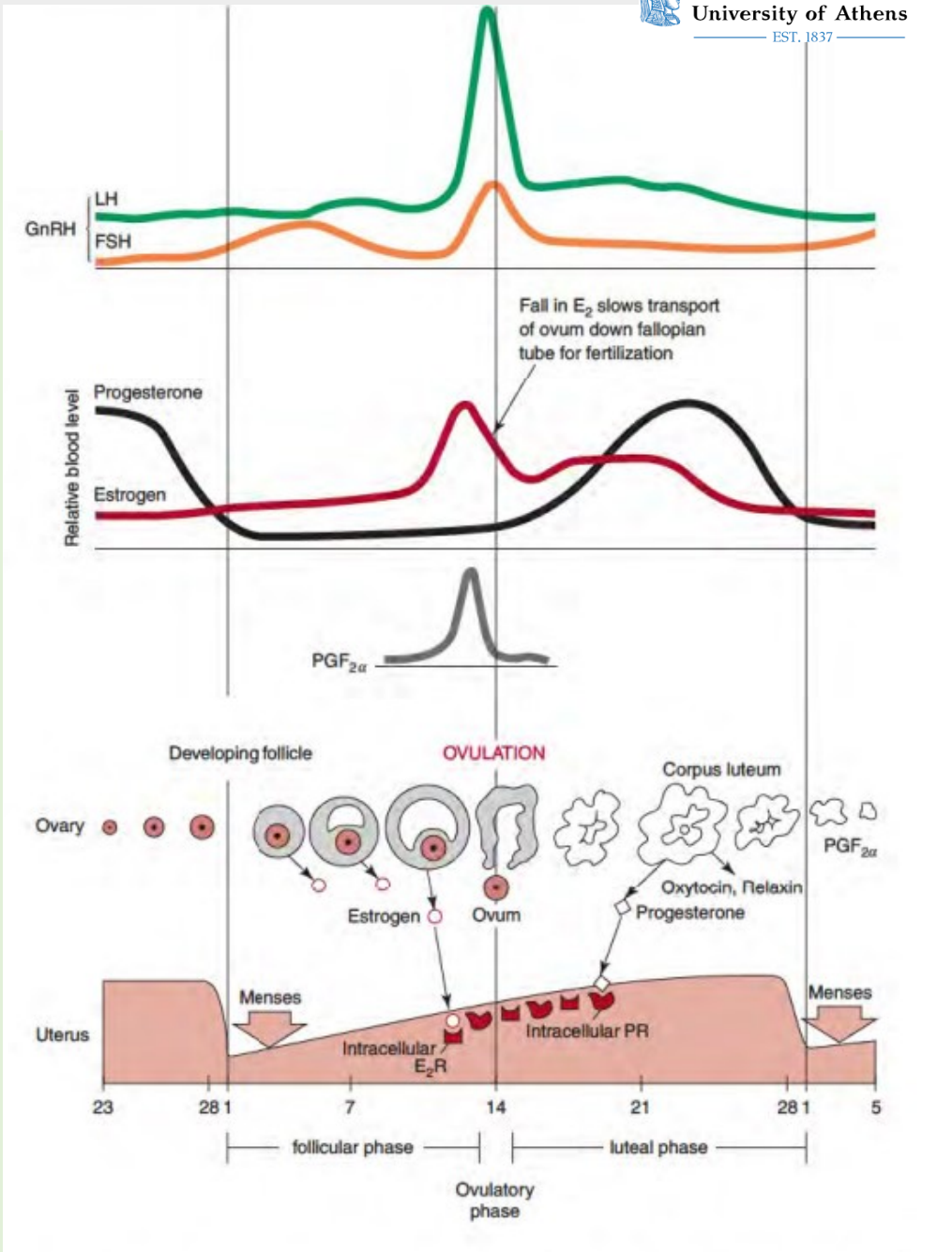
- **Higher levels of PRG are found between the 19th and 23rd day, with a peak on the 21st day.**
- **The corpus luteum, without LH, regresses, and PRG decreases, resulting in the shedding of the endometrium and the onset of bleeding.**
- **Estrogen levels decrease, and FSH levels begin to rise, initiating a new cycle.**



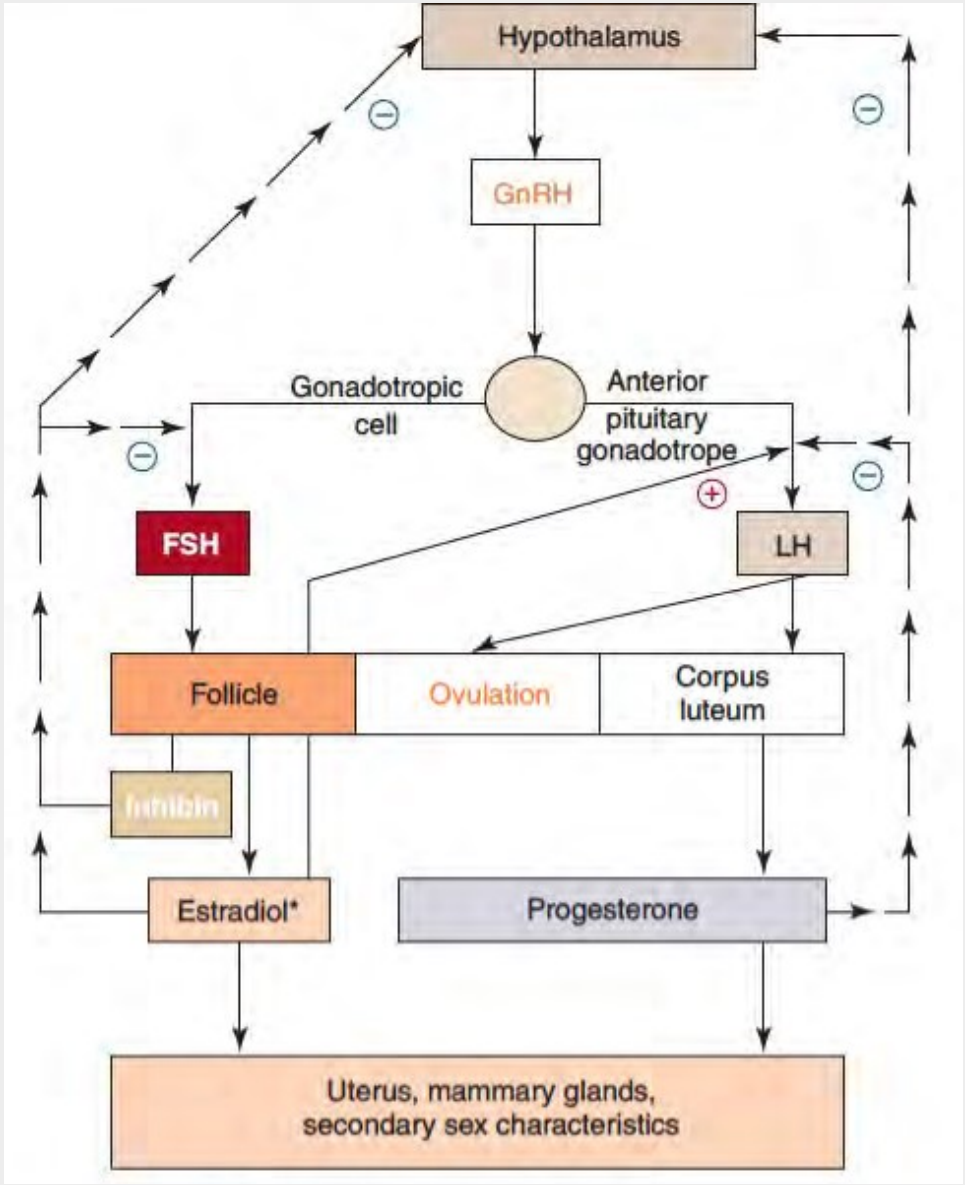
Richards JS. The Ovarian Cycle. Vitam Horm. 2018;107:1-25. doi: 10.1016/bs.vh.2018.01.009. Epub 2018 Feb 23. PMID: 29544627.

ESTRADIOL

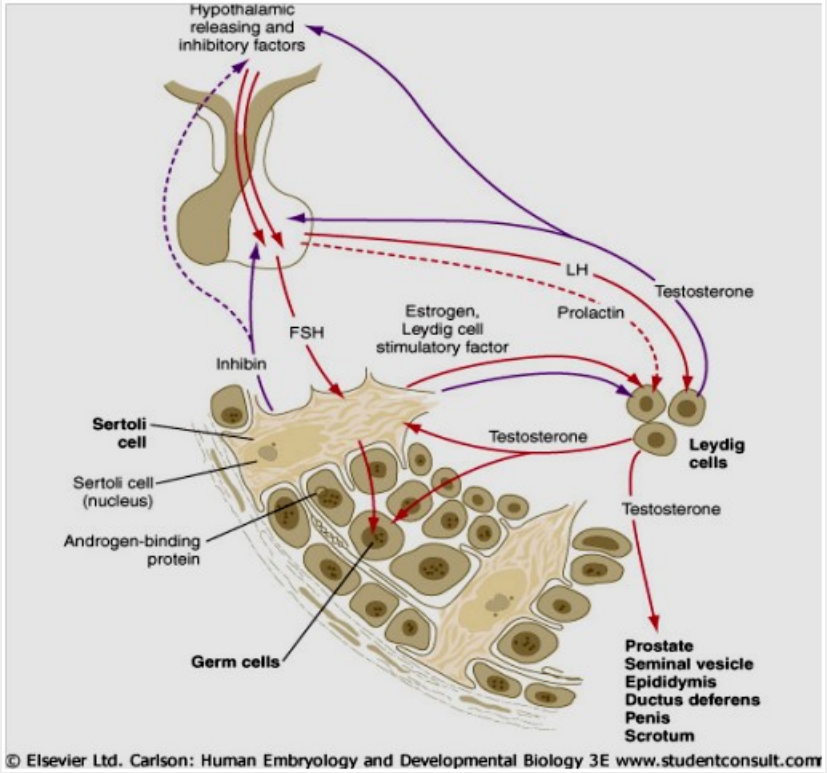
- **At puberty in females the secretion of GnRH**, which is under control from higher brain centers, **increases significantly.**
- During **adult life** this hypothalamic-releasing hormone **stimulates the release of FSH and LH from the anterior pituitary gonadotropes**
- **The FSH stimulates synthesis and secretion of 17β-estradiol in the ovary. This steroid exerts negative feedback on the pituitary gonadotropes, to suppress further secretion of FSH, and on the hypothalamic cells that secrete GnRH**
- Near **ovarian midcycle**, however, **17β-estradiol exerts a positive effect on the gonadotropes** which causes very **high levels of LH to be released (LH spike), as well as increased secretion of FSH**
- This **LH spike:** essential for **ovulation** to occur



- After ovulation has occurred, **a functional corpus luteum (CL)** forms from the ruptured follicle and **synthesizes progesterone and some estradiol.**
- **Progesterone inhibits continued LH synthesis and release.**
- **Eventually the corpus luteum dies (involutes), owing to a fall in the plasma LH level.**
- **The blood levels of progesterone and estradiol fall significantly, resulting in menstruation**
- Once the negative feedback exerted by estradiol and progesterone has been eliminated , **a new menstrual cycle is initiated.**

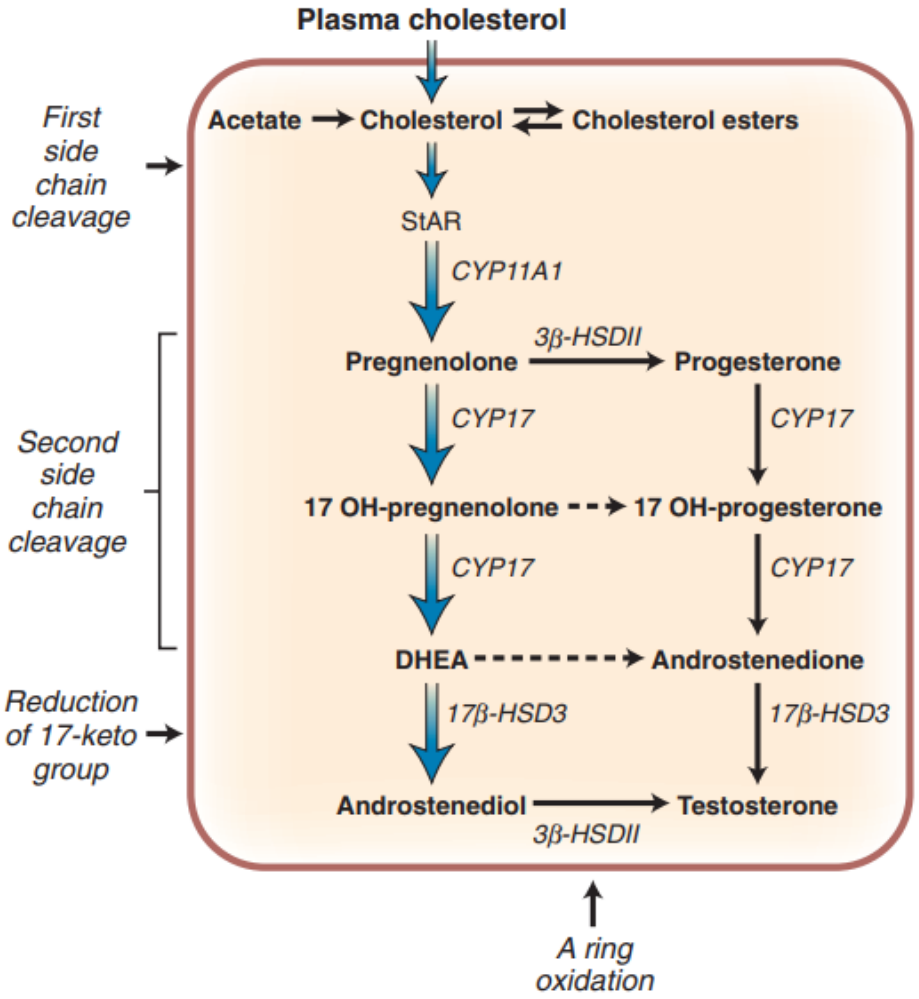


- **In males LH acts principally on Leydig cells to stimulate synthesis of testosterone.**
- **FSH acts on Sertoli cells to stimulate the conversion of testosterone secreted by the Leydig cells, into 17β-estradiol, which is required for spermatogenesis.**
- FSH also stimulates Sertoli cells to secrete an androgen-binding protein that binds testosterone and estradiol and carries them into the lumen of the seminiferous tubules, where they are required by the maturing sperm.
- **Testosterone itself exerts negative feedback that decreases secretion of GnRH.**
- Sertoli cells also secrete the glycoprotein hormone inhibin B, the same hormone secreted by ovarian granulosa cells, which selectively inhibits FSH secretion. These hormonal negative feedback loops reduce testosterone and estradiol secretion and inhibit the process of spermatogenesis.

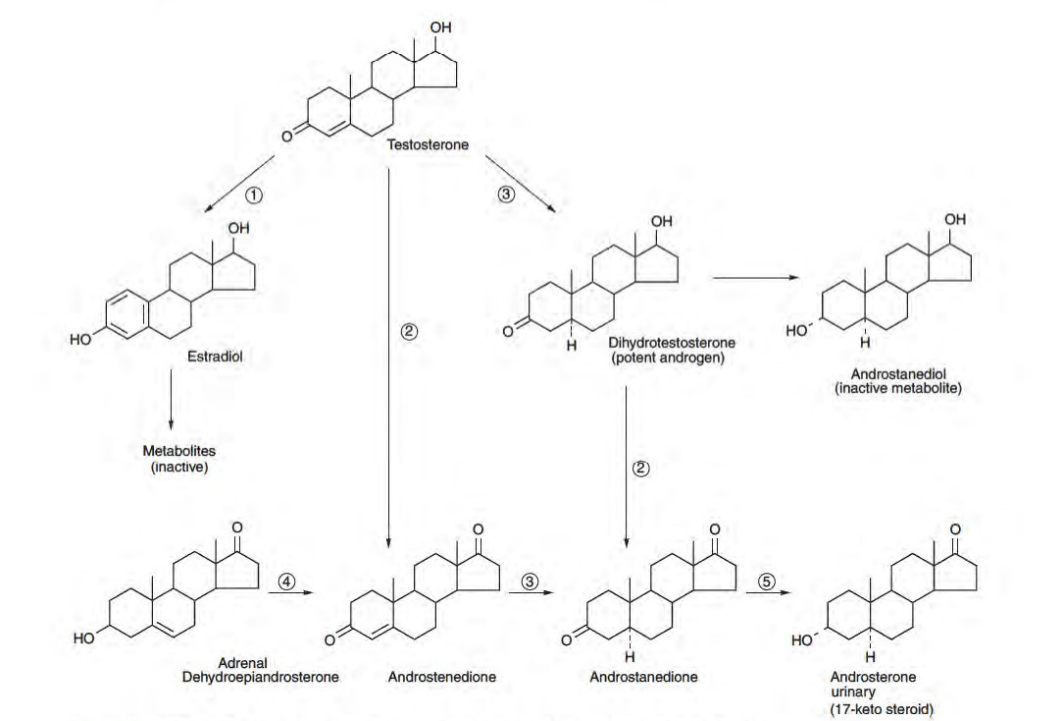


Testosterone biosynthetic pathways

- Biosynthesis of testosterone in the human testis proceeds predominantly through the Δ5 pathway: **pregnenolone is converted to 17-hydroxypregnenolone and then to dehydroepiandrosterone (DHEA), both by 17α-hydroxylase/17,20 lyase (CYP17),**
- Converted to androstenediol by 17β-hydroxysteroid dehydrogenase type 3 (17β-HSD3 or HSD17B3)
- To testosterone by 3β-hydroxysteroid dehydrogenase type II (3β-HSDII or HSD3B2).
- In the Δ4 pathway, pregnenolone is converted successively to 17-hydroxyprogesterone, androstenedione, and testosterone.



Testosterone Metabolism: Example



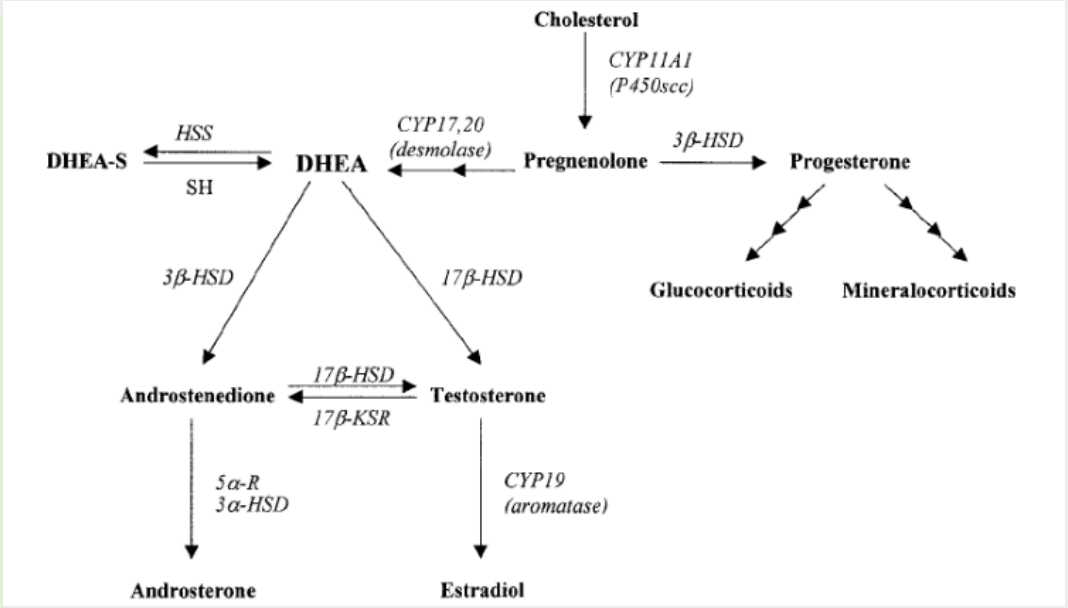
Testosterone by aromatase active steroid, **estradiol**
Reduction of testosterone by 5a –reductase: dihydrotestosterone a more potent androgen.
Androsterone, the major inactive metabolic end product produced in this pathway, is conjugated and **excreted in the urine.**
The major adrenal androgen, dehydroepiandrosterone (DHEA), source of urinary 17-ketosteroids.
Two other testosterone metabolites appear in urine in relatively small amounts: **androstanediol,** which is formed by reduction of the 3-keto group of dihydrotestosterone, and **estrogen metabolites**, which are formed **once testosterone has been converted into estradiol**

Adrenal Androgens-DHEA-DHEA-S

MEN

- DHEA, DHEA sulfate, and androstenedione, have minimal intrinsic androgenic activity, and they contribute to androgenicity by their **peripheral conversion to the more potent androgens testosterone and dihydrotestosterone.**
- DHEA and DHEA sulfate are secreted in greater quantities

BUT **Androstenedione is qualitatively more important, because it is more readily converted peripherally to testosterone**



Biologic Activity: Function primarily as **precursors for peripheral conversion to the active androgenic hormones, testosterone and dihydrotestosterone.**

Adrenal Androgens-DHEA-DHEA-S

FEMALES

- Total androgen production by the peripheral conversion of **androstenedione to testosterone.**
- In the follicular phase of the menstrual cycle, **adrenal precursors account for two-thirds of testosterone production and one-half of dihydrotestosterone production.**
- **During midcycle**, the ovarian contribution increases, and the adrenal precursors account for only 40% of testosterone production.
- Abnormal adrenal function as seen in Cushing syndrome, adrenal carcinoma, and congenital adrenal hyperplasia results **in excessive secretion of adrenal androgens, and their peripheral conversion to testosterone results in androgen excess, manifested by acne, hirsutism, and virilization**

Produced as free hormone (DHEA) and as a compound with sulfate radical (DHEA-S).

In pregnancy, DHEA-S is the precursor, where the adrenal glands of the fetus and placenta produce huge quantities of estrogens

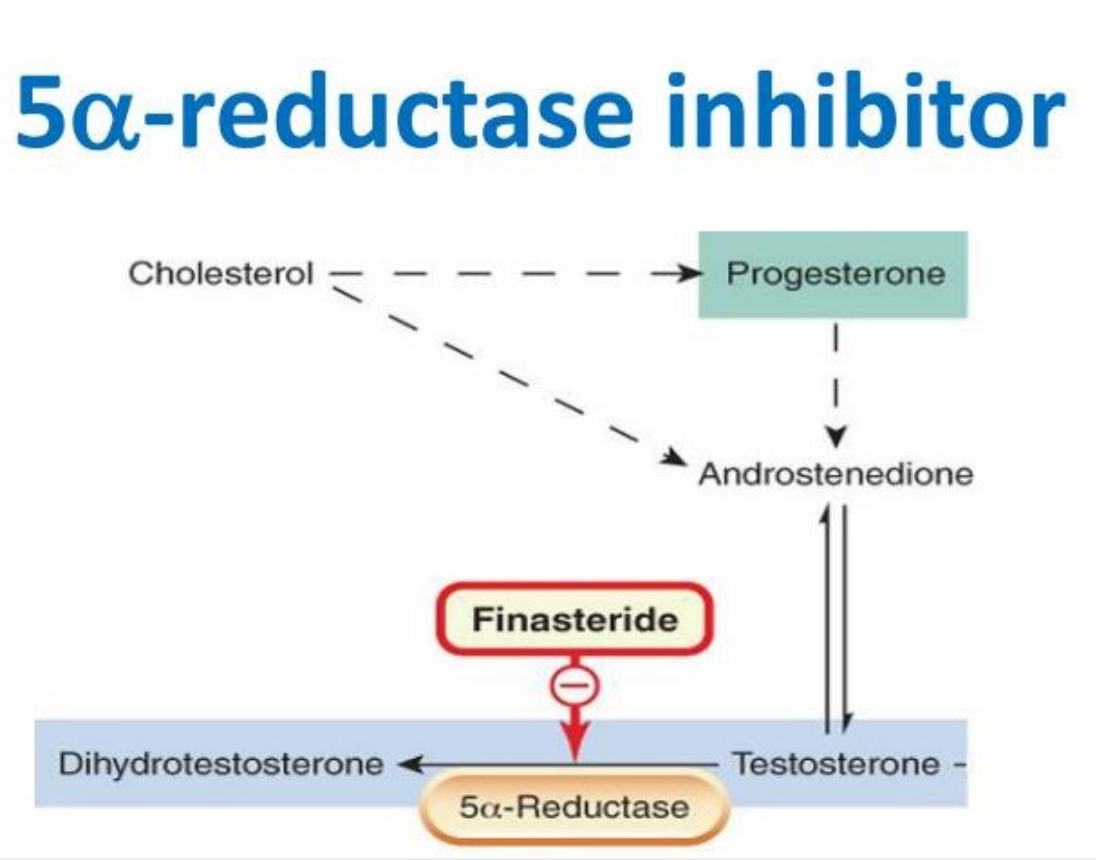
DHEA-S → DHEA → Δ4-androstenedione → testosterone

CLINICAL CORRELATION : 5-Alpha-Reductase Inhibitors

The 5-alpha-reductase inhibitors (finasteride and dutasteride) are a class of medication used in the **management and treatment of benign prostatic hyperplasia (BPH) and androgenic alopecia (male pattern hair loss).**

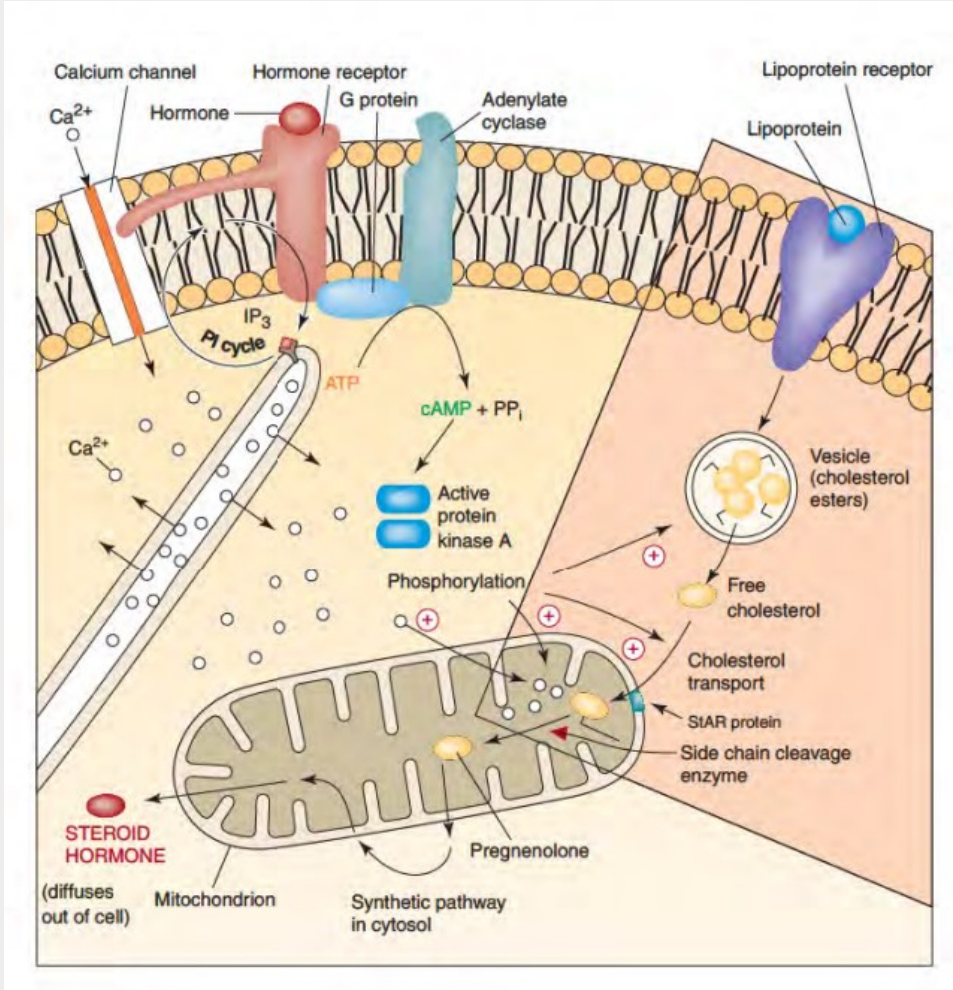
Dihydrotestosterone (DHT), binds intracellular androgen receptors in the prostate leading to an increase in transcription of proteins that are responsible for increased cellular proliferation.

Finasteride, as well as dutasteride, have both been shown to be efficacious in the treatment of BPH. Researchers have found that finasteride has reduced prostatic DHT by up to 90% and serum DHT by up to 70%. It is worth noting that these reductions in DHT were independent of dosage.



Regulation of Steroid Hormone Synthesis

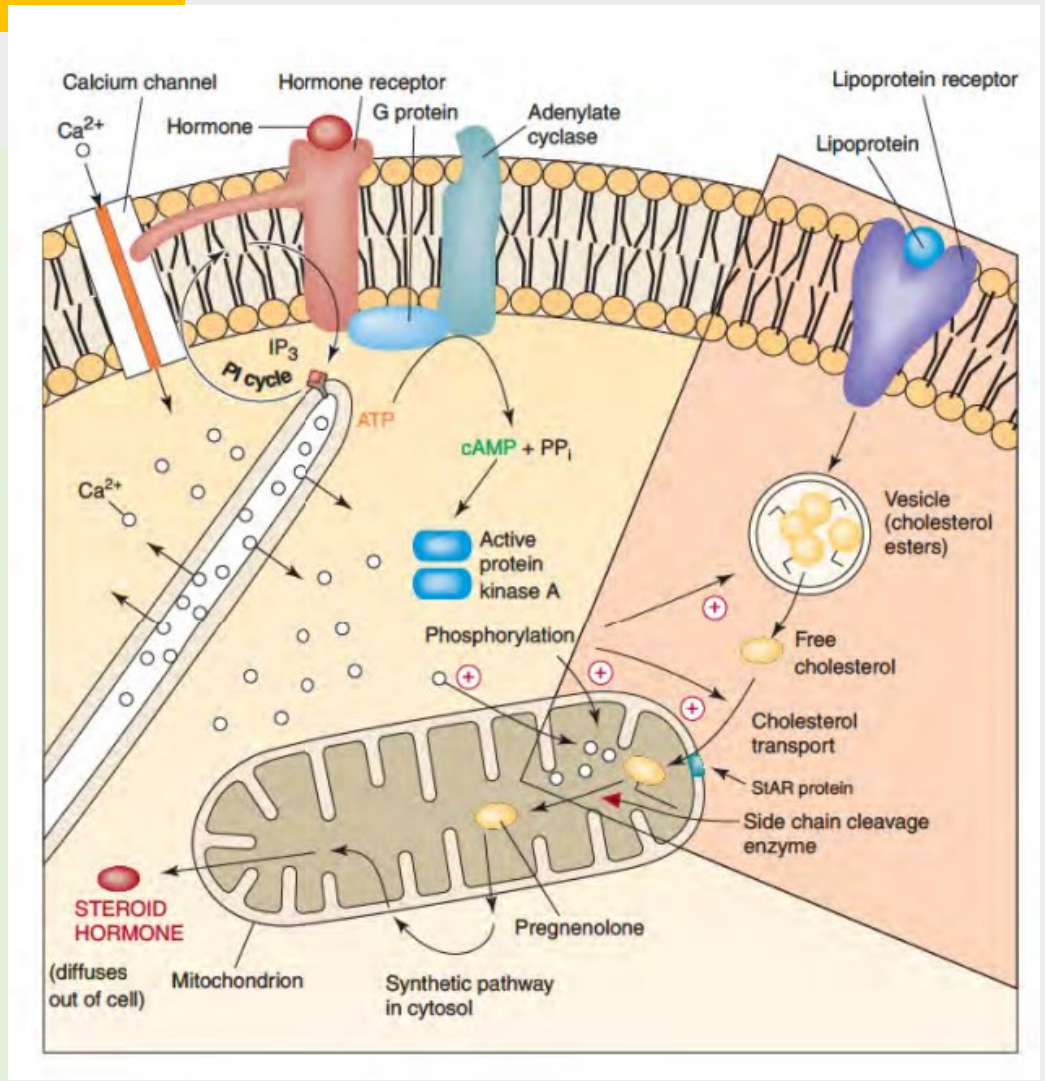
- **Regulation of steroid hormone biosynthesis is mediated by increased intracellular concentrations of cAMP and Ca^{2+}, although generation of IP3 may also be involved**
- **cAMP exerts rapid (seconds to minutes) and slow (hours) effects on steroid synthesis.**
- **The rapid effect is the mobilization and delivery of cholesterol to the inner membrane of mitochondria**, where it is metabolized to pregnenolone by the cholesterol side chain cleavage enzyme.
- **The slower effects involve increased transcription of genes for steroidogenic enzymes that are responsible for maintaining optimal long-term steroid production.**



Overview of hormonal stimulation of steroid hormone biosynthesis.

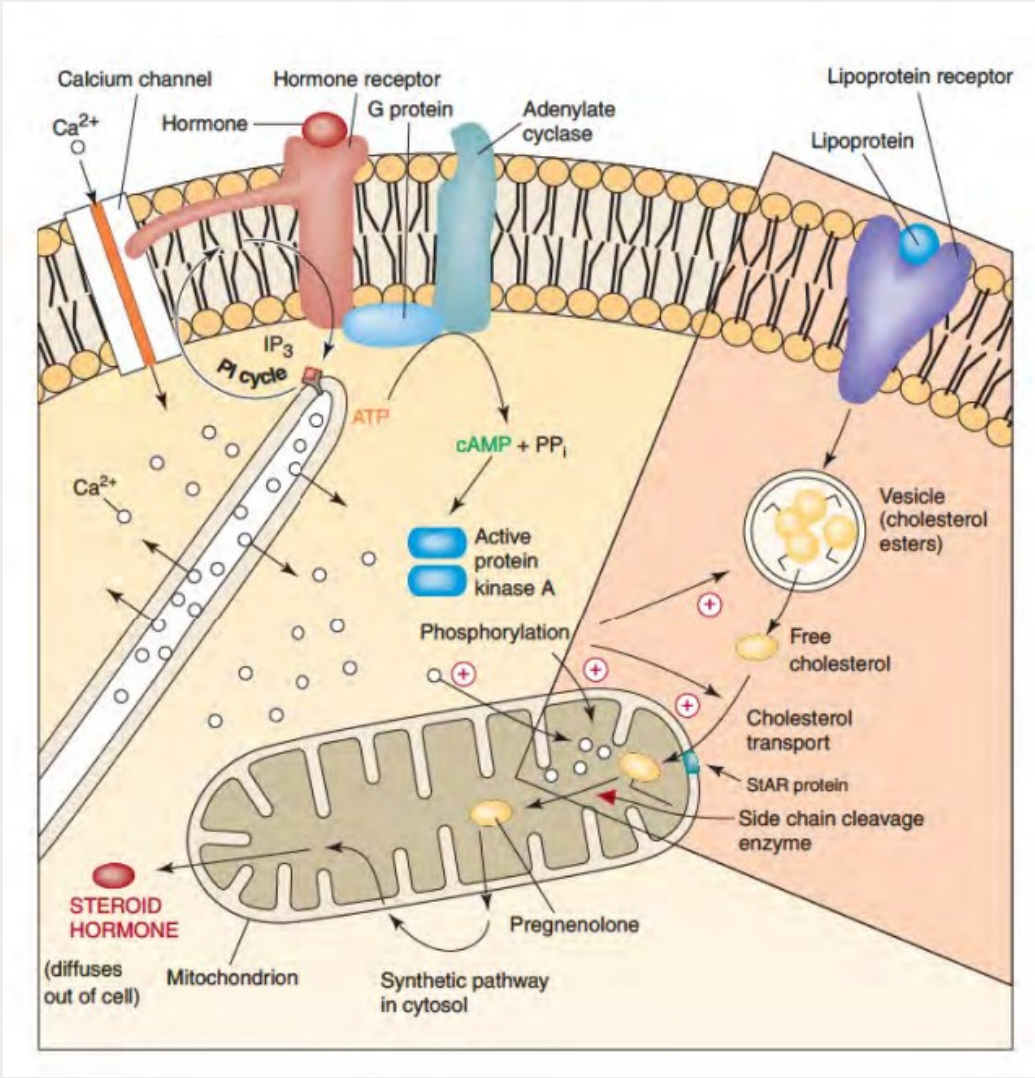
1. **Nature of the hormone: cell type and receptor** (ACTH for cortisol synthesis, FSH for estradiol synthesis, LH for testosterone synthesis etc.)

2. **This activates adenylate cyclase via a stimulatory G protein or may stimulate a calcium channel directly or indirectly by activating the phosphatidylinositol cycle (PI cycle).** If the PI cycle is stimulated, IP3 augments cytosol Ca^{2+} levels from the ER store.



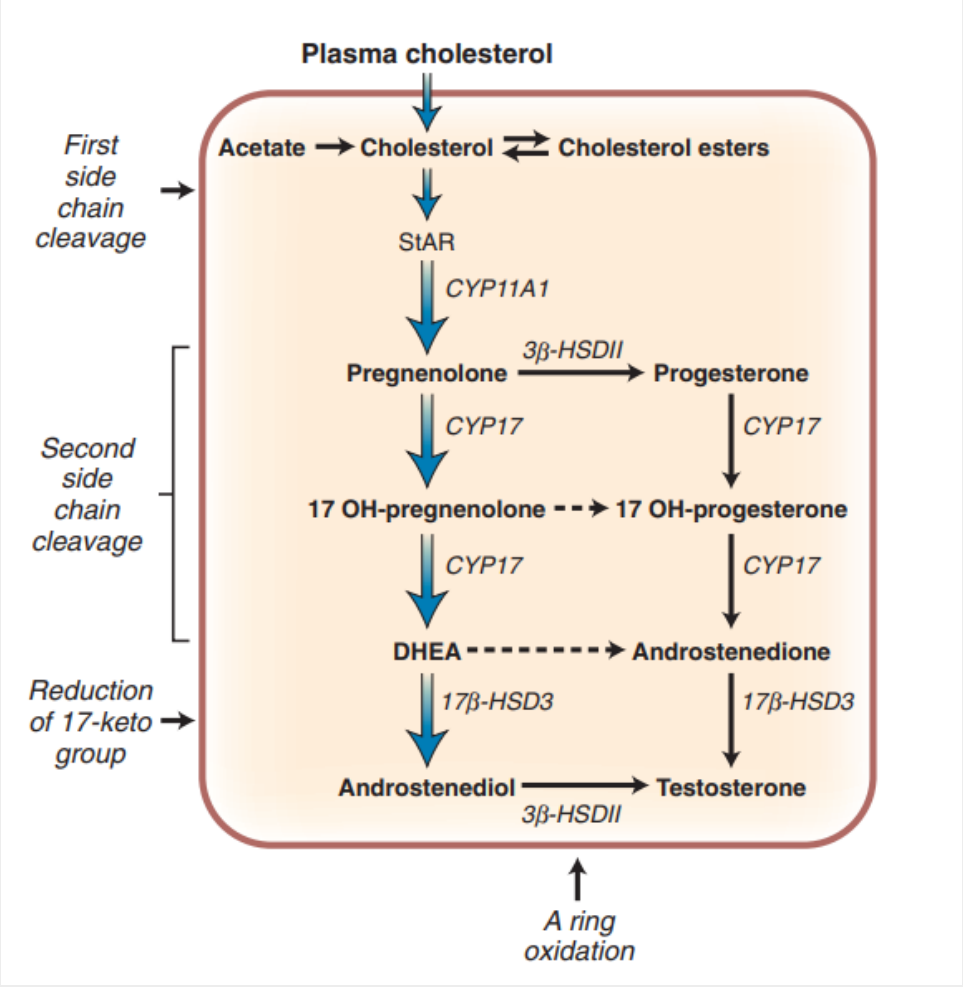
3. **cAMP activates protein kinase A: via phosphorylation, increases hydrolysis of cholesteryl esters from the vesicles to free cholesterol and increase cholesterol transport into the mitochondrion.** The elevated Ca^{2+} levels and protein phosphorylation and induction of the StAR protein, result in **increased side chain cleavage and steroid biosynthesis.**

- These reactions **overcome the rate-limiting steps (availability of cholesterol from cholesterol esters stored in vesicles, transport of cholesterol to inner mitochondrial membrane, and side chain cleavage reaction)** in steroid biosynthesis, and **more steroid is synthesized and secreted.**

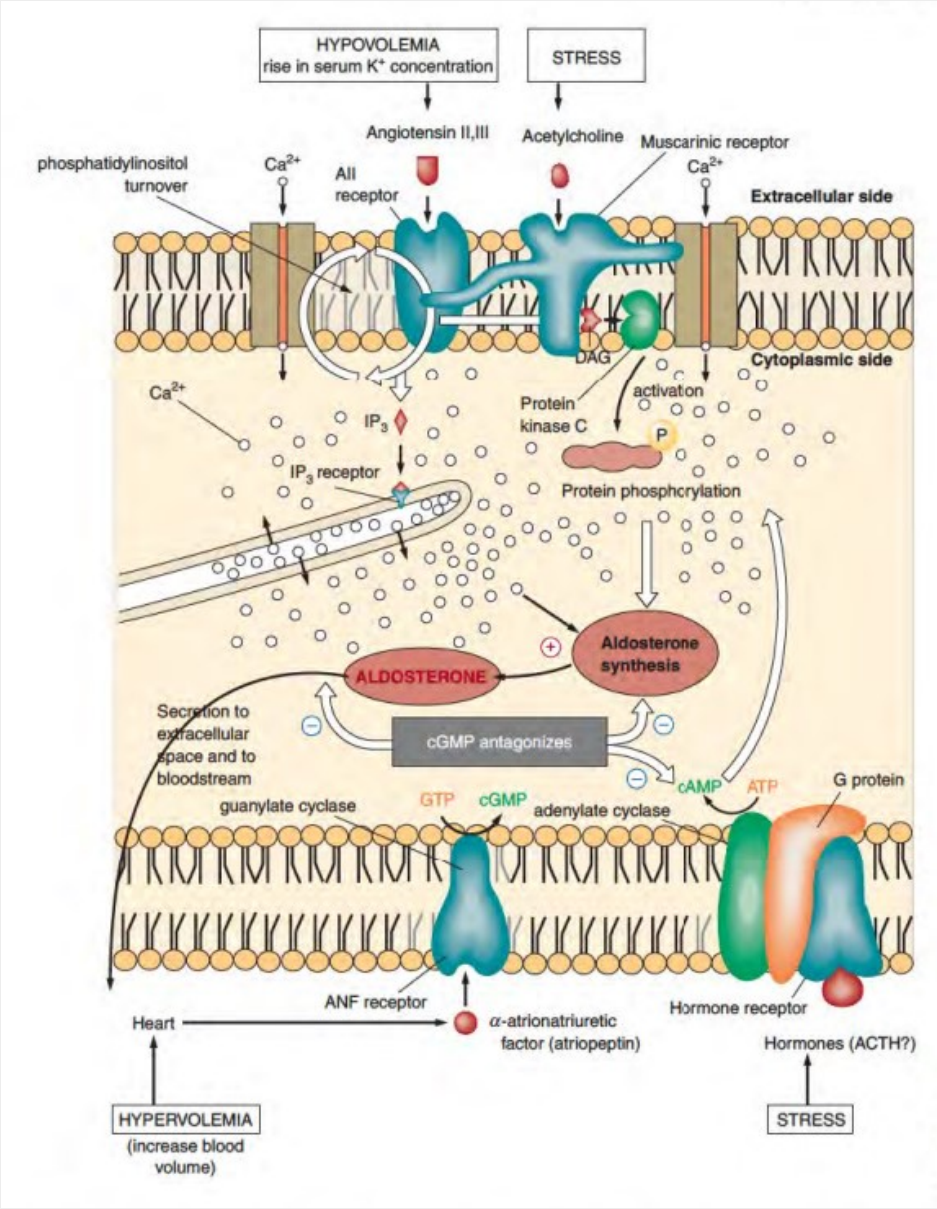


STEROIDOGENIC ACUTE REGULATORY (StAR) PROTEIN

- The 30-kDa phosphoprotein, steroidogenic acute regulatory (StAR) protein, **facilitates translocation of cholesterol from the outer to the inner mitochondrial membranes.**
- In humans, StAR mRNA is specifically **expressed in testes, ovaries, and adrenals, which are known sites of steroidogenesis.**
- **Patients with lipoid congenital adrenal hyperplasia (LCAH), an inherited disease in which adrenal and gonadal steroidogenesis is significantly impaired and lipoidal deposits occur, express truncated and nonfunctional StAR proteins.**
- This suggests that the **StAR protein is the hormone-induced protein that mediates acute regulation of steroid hormone biosynthesis.**

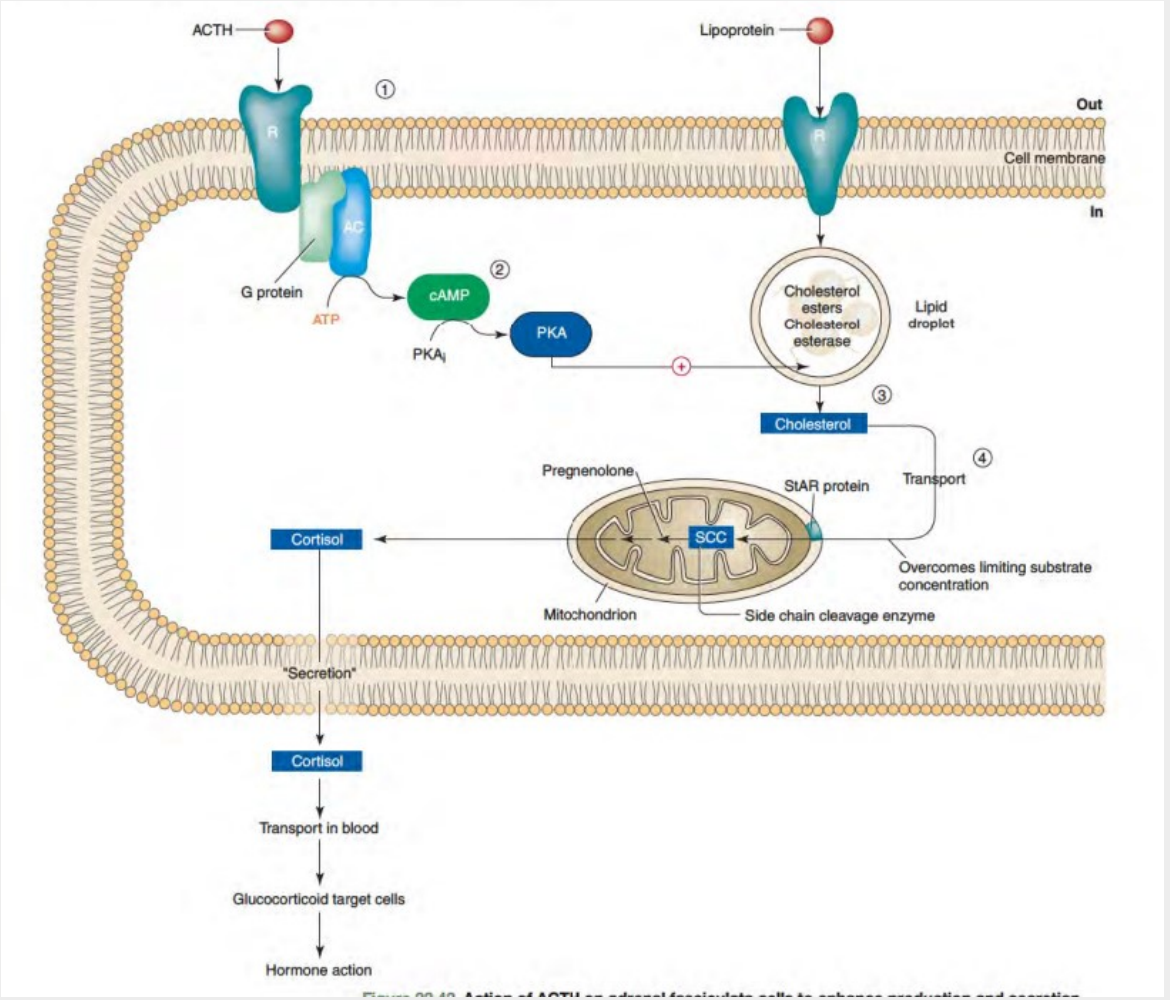


SECRETION OF ALDOSTERONE IN A CELL LOCATED IN THE ADRENAL ZONA GLOMERULOSA

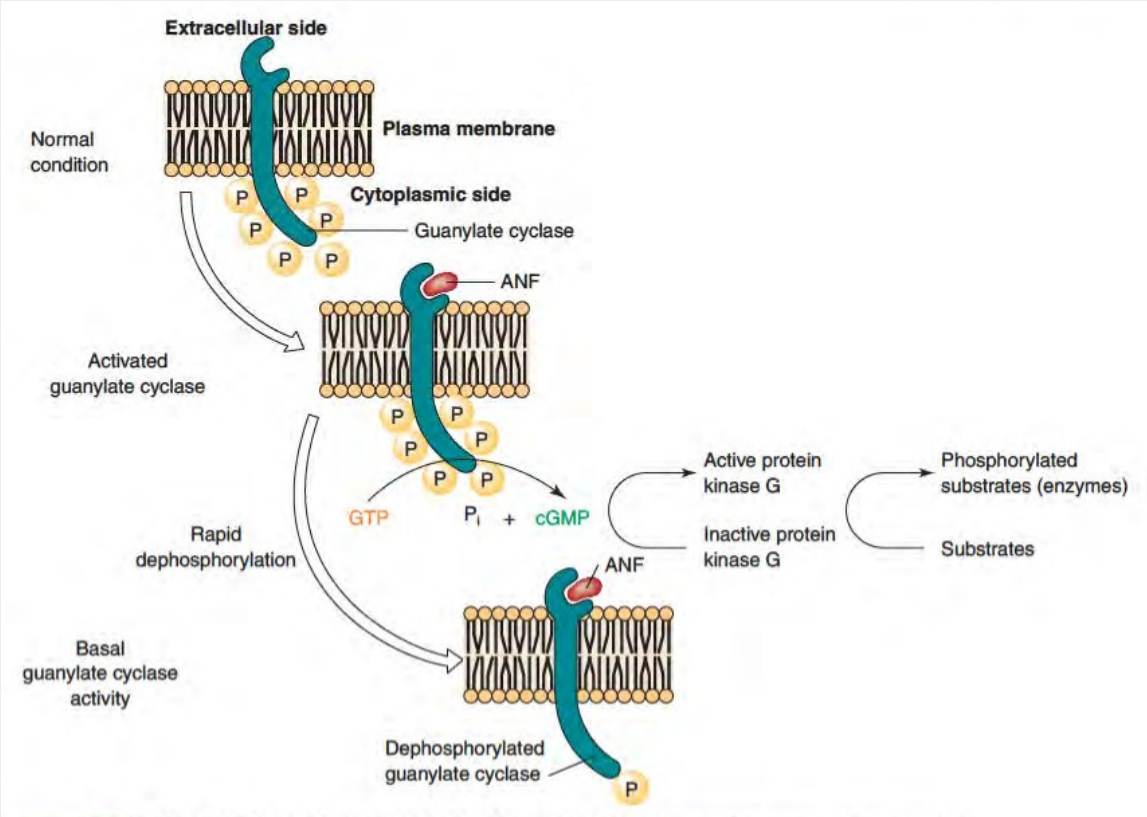


1. A major driving force for aldosterone biosynthesis is **angiotensin II, which is generated by the renin-angiotensin system.**
2. The signal for aldosterone secretion is generated under conditions when **blood Na^+ concentration and blood pressure (blood volume) need to be increased.**
3. The N-terminal decapeptide of a plasma a_2 -globulin **(angiotensinogen) is cleaved by the proteolytic enzyme renin**.
4. Decapeptide: inactive angiotensin I- converted to the active octapeptide, angiotensin II, by angiotensin -converting **enzyme (ACE), which is found on the surface of pulmonary and renal endothelial cells.**
5. **Angiotensin II is then converted to the heptapeptide, angiotensin III, by an aminopeptidase.**
6. **Both angiotensins II and III bind to the angiotensin receptor which activates phospholipase C to generate IP3 and DAG.**

ACTH is the major stimulator of the synthesis and secretion of cortisol by cells in the zona fasciculata



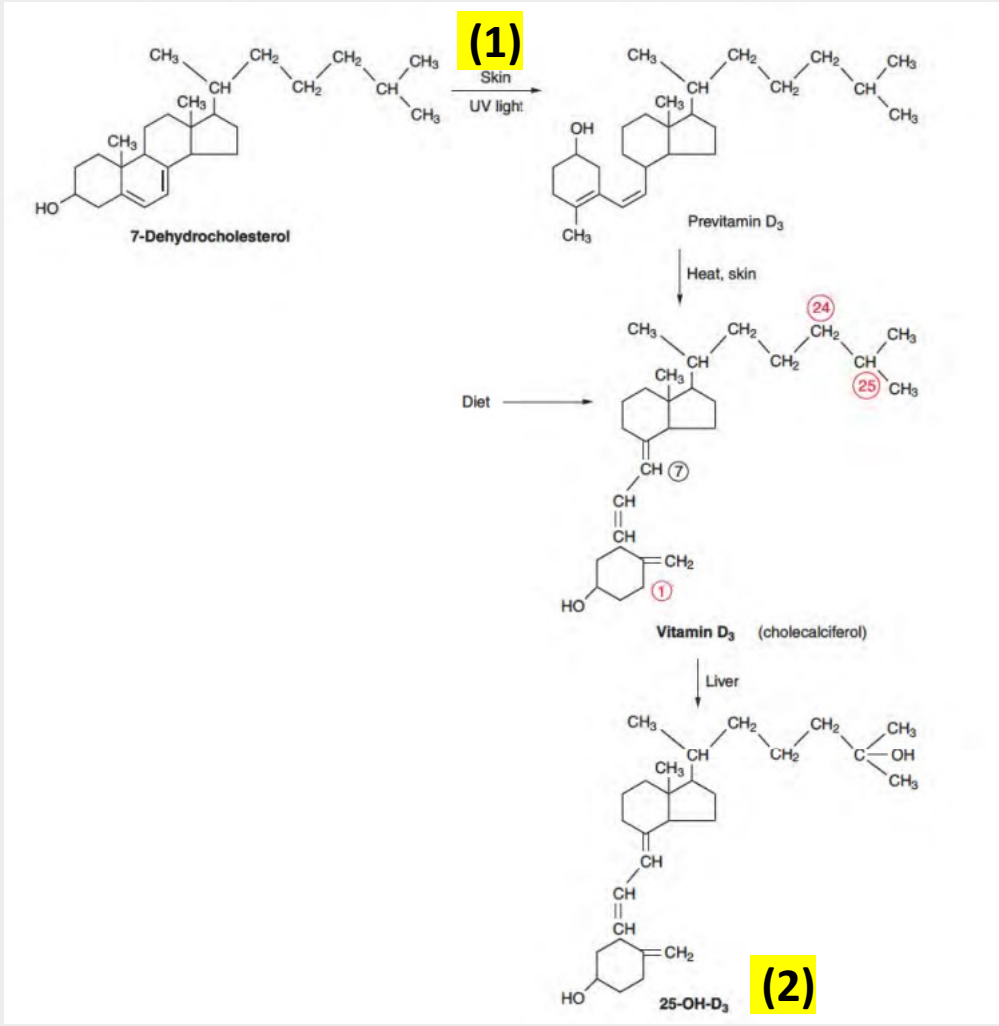
- Physiological conditions opposite to those that activate the formation of angiotensin I and II **generate atrial natriuretic factor (ANF), or atriopeptin, from the heart atria**
- **An increase in blood volume results in increased stretching of the atria and increased synthesis and secretion of ANF.**
- **In the zona glomerulosa cell, ANF activates its receptor guanylate cyclase activity to increase cGMP levels and inhibit synthesis and secretion of aldosterone and formation of cAMP by adenylate cyclase**



The guanylate cyclase domain is in a highly phosphorylated state under normal conditions.
Binding of hormone markedly enhances enzyme activity and dephosphorylation of the guanylate cyclase domain

VITAMIN D_3

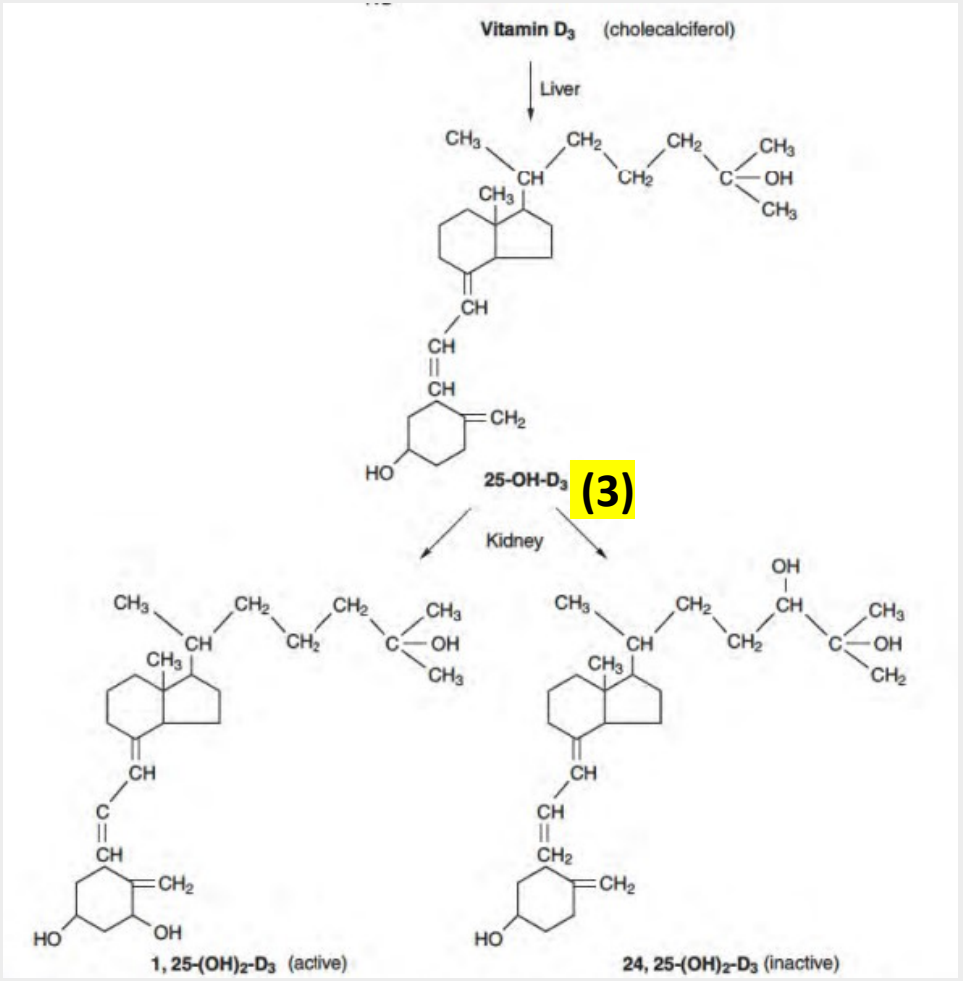
- **The active form of vitamin D, called calcitriol**, is referred to as a **secosteroid,** which is **a steroid in which one of the rings has been opened.**
- **7-dehydrocholesterol is activated in the skin by sunlight to generate vitamin D_3 (cholecalciferol). (1)**
- Then, **hydroxylated in the liver to generate 25-hydroxy vitamin D_3** (25-hydroxycholecalciferol). **(2)**
- **In the kidney this is further hydroxylated to either 1a,25-vitamin D3** (1 ,25(0H)$_2$D$_3$) **(1a, 25-dihydroxychol-ecalciferol), which is the active form of the hormone,** or **24,25-vitamin D_3** (24, 25 (OH-D$_3$) (24,25 -dihydroxycholecaliciferol), which is **an inactive metabolite of the hormone (3)**



- **Nuclear $1,25(OH)_2D_3$ receptors are expressed in target cells including intestinal epithelial cells, bone cells, and cells of kidney tubules.**

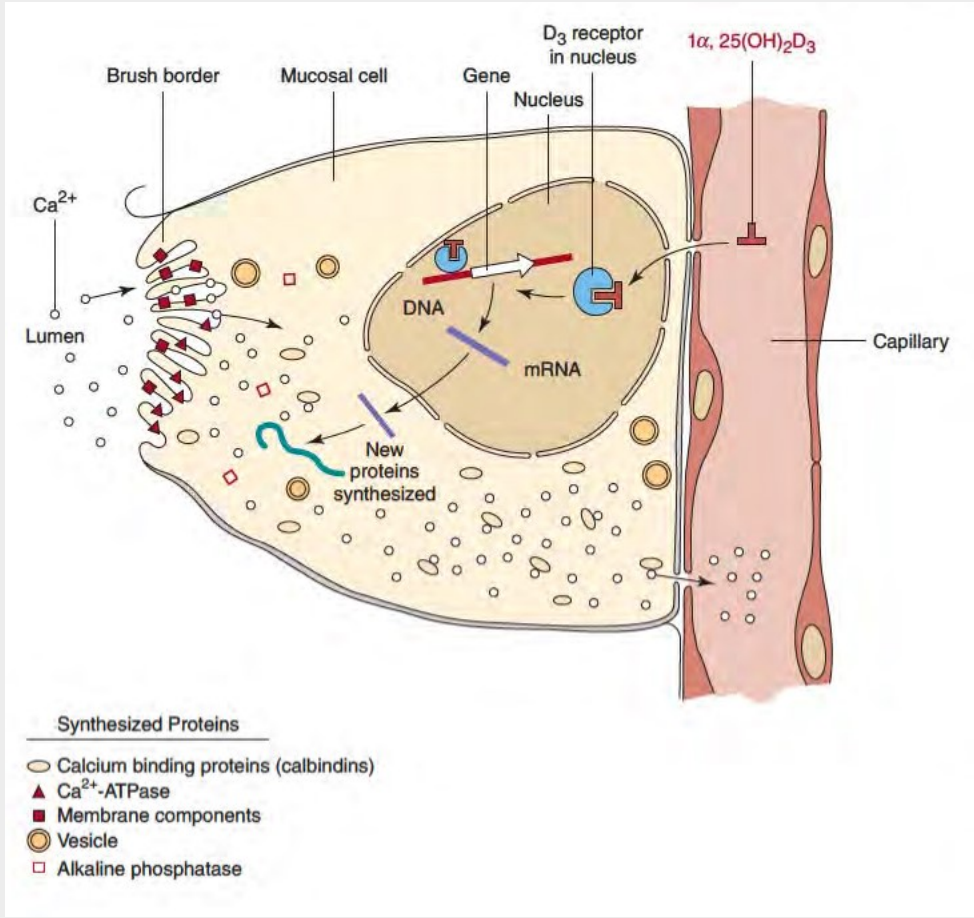
Elevated **$(1,25(0H)_2D_3$** levels can stimulate bone resorption by osteoclasts

The **major effect of $(1,25(0H)_2D_3)$** is to **stimulate the transcellular (across intestinal epithelial cells) absorption of Ca^{2+} and phosphate from the intestinal lumen against a concentration gradient,** and thus it **plays an important role in bone mineralization.**



Vitamin D may also be responsible for autocrine and paracrine effects that are important in the regulation of **immune responses**. In the kidney **$1,25(OH)_2D_3$** weakly stimulates Ca^{2+} reabsorption by increasing the number of Ca^{2+} pumps.

- Binding of **(1,25(0H)$_2$D$_3$)** induces receptor phosphorylation, and binding of the hormone-receptor complex to vitamin D_3 -response elements in the DNA.
- This **binding results in an increased rate of transcription of vitamin D_3 -responsive genes that encode a number of Ca^{2+}-binding proteins called calbindins**, Ca^{2+}- ATPase and other ATPases, and membrane components and facilitators of vesicle formation.
- **Calbindins may ferry Ca^{2+}- across the intestinal cell, or may simply buffer the cytoplasm against high Ca^{2+}- levels.**



Transport of Steroid Hormones: Plasma-Binding Proteins

Four major plasma proteins bind the steroid hormones in blood:

corticosteroid-binding globulin

sex-hormone-binding globulin

androgen-binding protein

albumin

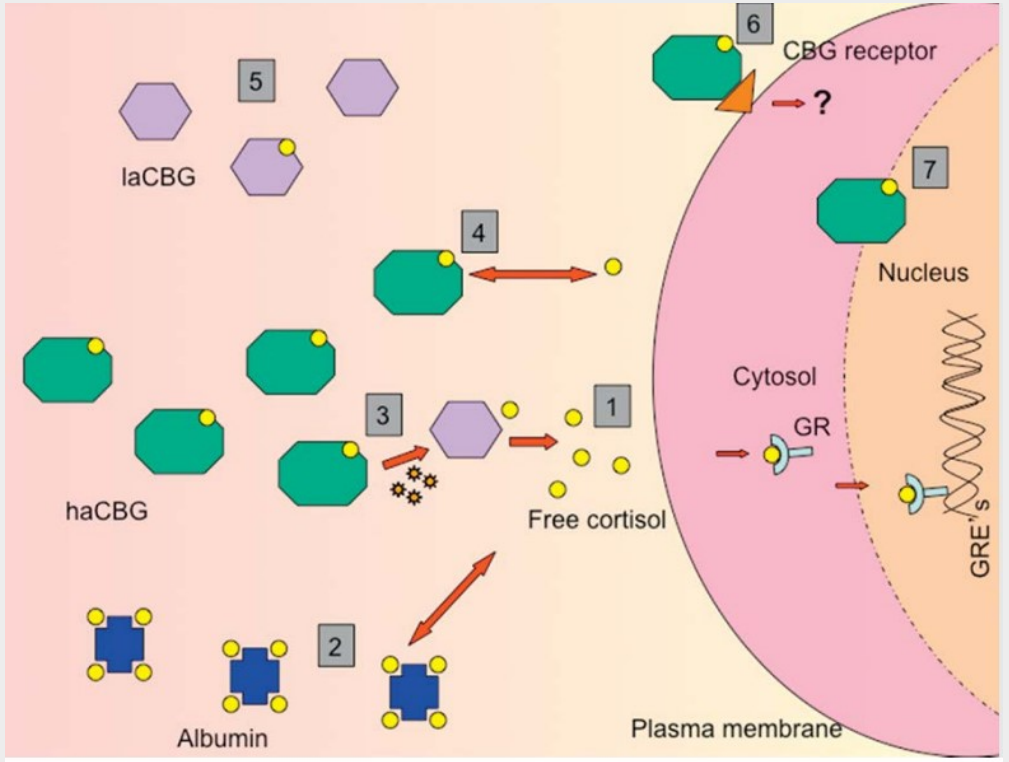
ALBUMIN

Regulate the non-protein-bound or ‘free’ fractions of circulating steroid hormones that are considered to be biologically active

REGULATION OF CORTISOL BIOAVAILABILITY

- Most of the **circulating cortisol (75%-80%)** binds to a **specific corticosteroid binding a2-globulin (CBG)** known as **transcortin.**
- About **15% of plasma cortisol is bound to albumin with a much lower affinity.**
- **The concentration of transcortin increases during pregnancy and after estrogen administration.**

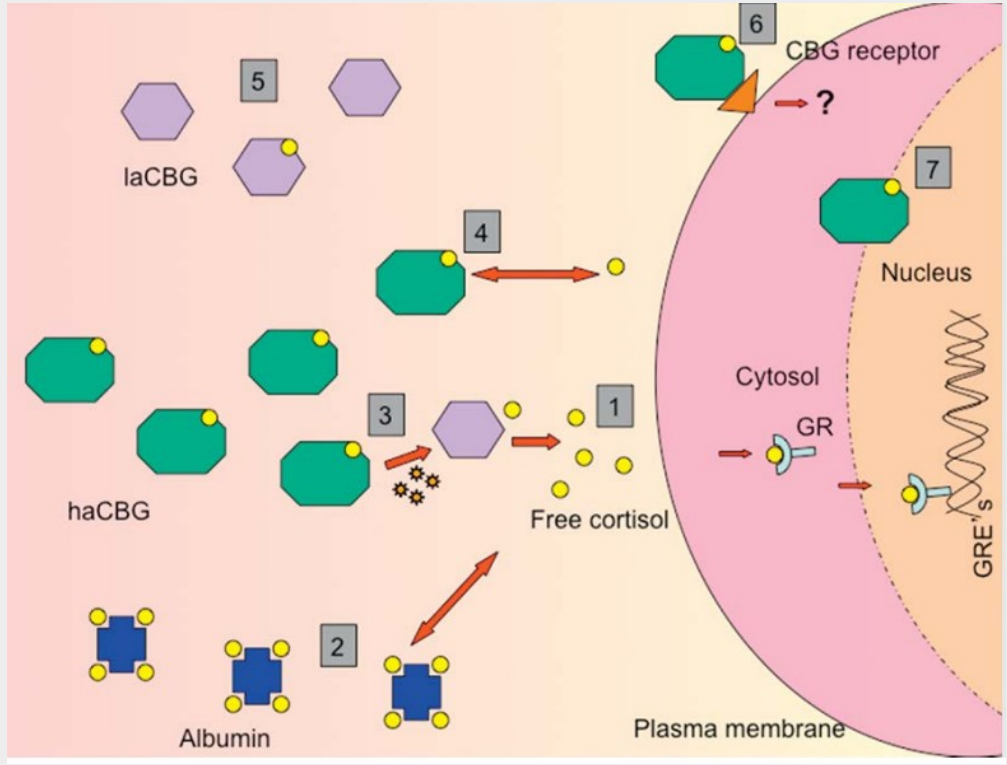
1) Free cortisol (yellow circle): diffuses into cells and modulates intracellular processes.
2) 15% of circulating cortisol is bound with high capacity but low affinity to albumin.
3) The haCBG: cortisol pool allows targeted delivery cortisol to inflamed sites.



Meyer EJ, Nenke MA, Rankin W, Lewis JG, Torpy DJ. Corticosteroid-Binding Globulin: A Review of Basic and Clinical Advances. Horm Metab Res. 2016 Jun;48(6):359-71. doi: 10.1055/s-0042-108071. Epub 2016 May 23. PMID: 27214312.

REGULATION OF CORTISOL BIOAVAILABILITY

- **STRESS:** cortisol levels are high, **the CBG binding sites become saturated first and the excess cortisol binds to albumin.**
- Only **5%- 10% of plasma cortisol is normally free (unbound).**
- It is this **free cortisol that diffuses across the plasma membrane, binds to glucocorticoid receptors, and mediates a biological response.**
- About **50%- 70% of the circulating aldosterone binds with low affinity** to albumin and transcortin, and the remainder is unbound.
- **Aldosterone has a lower plasma half-life (20 min) as compared to cortisol (70 min).**



Meyer EJ, Nenke MA, Rankin W, Lewis JG, Torpy DJ. Corticosteroid-Binding Globulin: A Review of Basic and Clinical Advances. Horm Metab Res. 2016 Jun;48(6):359-71. doi: 10.1055/s-0042-108071. Epub 2016 May 23. PMID: 27214312.

Transport of Steroid Hormones: Plasma-Binding Proteins

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androgen-binding protein

albumin

65% of circulating testosterone is bound to a liver-derived glycoprotein called sex hormone-binding globulin (SHBG).

1 %- 2% is in the free form and **the rest is bound to albumin and other proteins.**

Approximately 60% of estrogens are transported bound to SHBG, 20% are bound to albumin, and 20% are in the free form.
However, estradiol binds to SHBG with a much lower affinity than testosterone.

Estradiol bound to SHBG dissociates very rapidly, and it is taken up by target tissues.

- ✓ **Free testosterone is about 20 times greater in males than in females.**
- ✓ The total (bound plus unbound) **concentration of testosterone is about 40 times greater in males.**
- ✓ **Testosterone itself lowers SHBG levels and increases the amount of free testosterone in blood**, whereas **17β-estradiol and thyroid hormone raise SHBG levels in blood.**

SHBG and CBG play much more dynamic roles in **controlling steroid access to target tissues and cells.** They **bind steroids with high affinity and specificity**, with SHBG binding androgens and estrogens and CBG binding glucocorticoids and progesterone.

Transport of Steroid Hormones: Plasma-Binding Proteins

Four major plasma proteins bind the steroid hormones in blood:

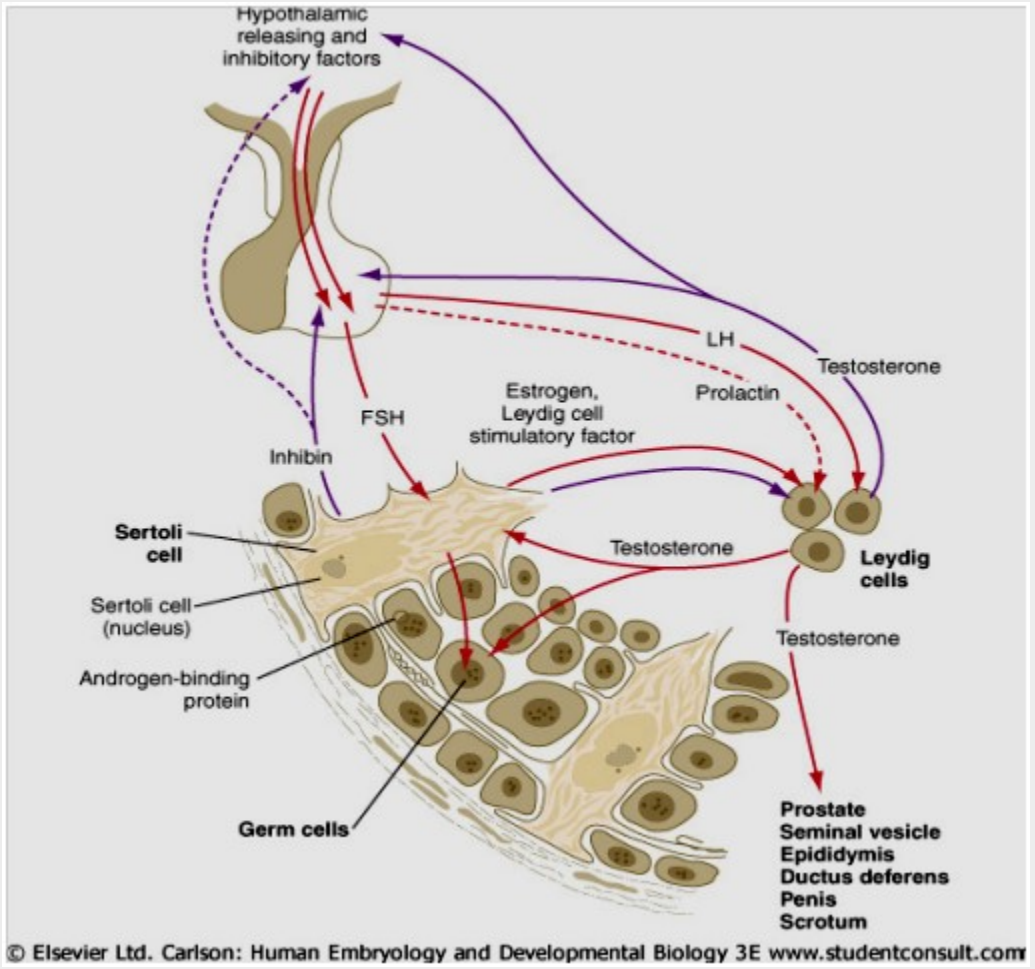
corticosteroid-binding globulin

sex-hormone-binding globulin

androgen-binding protein

albumin

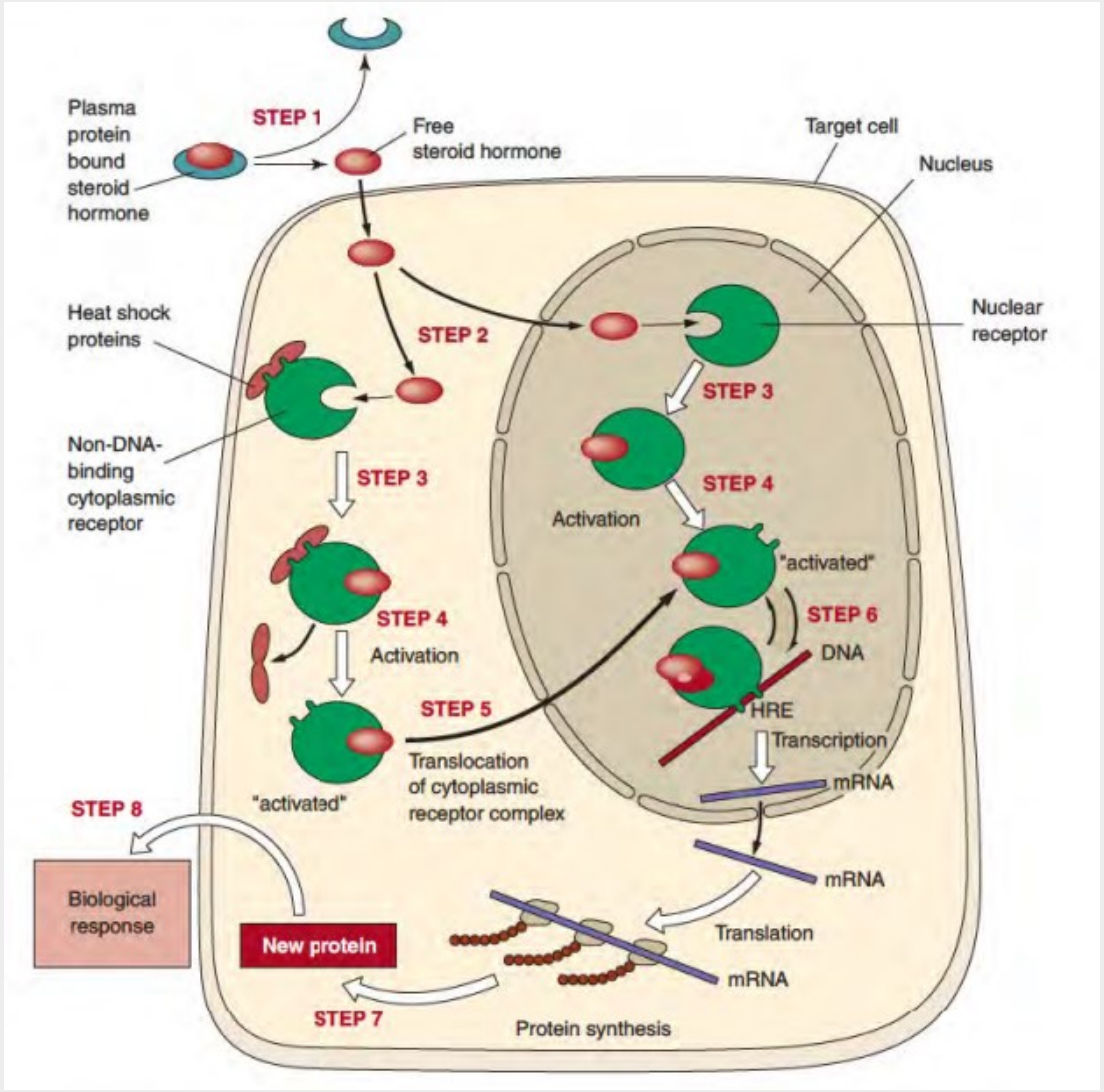
- **Androgen-binding protein (ABP) is produced by the Sertoli cells in response to testosterone and FSH.**
- ABP is also called testosterone-estrogen-binding globulin (TeBG): **maintains high androgen levels within the testis and seminal fluids. High local androgen levels:** <u>important for the development and maturation of sperm.</u>
- **Progesterone binds primarily to transcortin and albumin.** Because this steroid has a relatively **<u>low affinity for these plasma proteins</u>, its circulating half-life is only about 5 min.**



Steroid Hormones Bind Intracellular Receptor Proteins

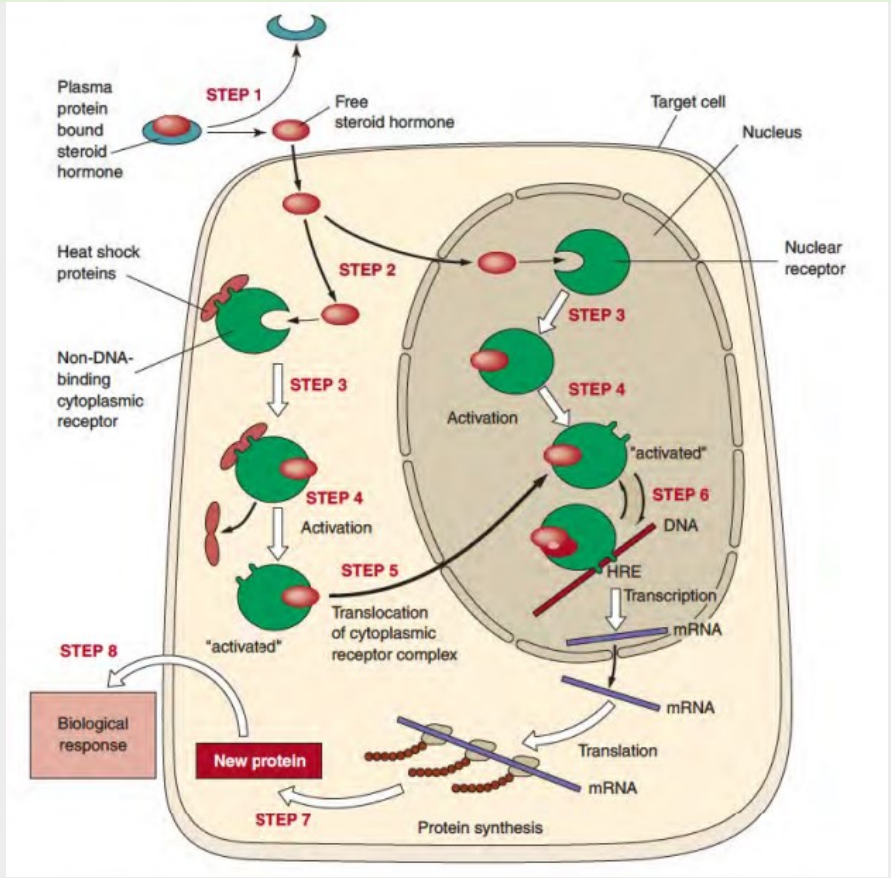
- **Receptors for steroid hormones are located intracellularly.**
- **The unbound glucocorticoid receptor and possibly the aldosterone receptor appear to reside in the cytoplasm**
- **The rest are located within the nucleus, presumably in association with chromatin.**

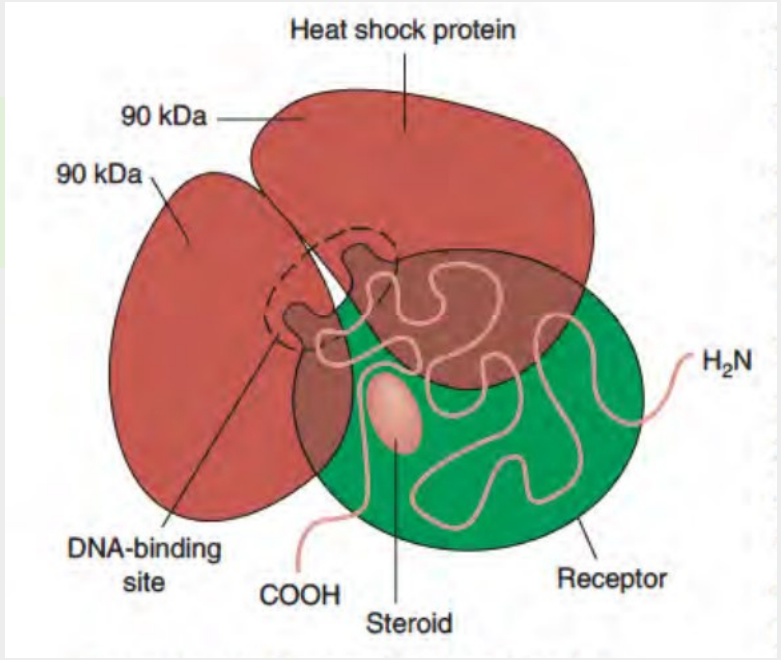
1: A steroid hormone dissociating from a plasma transport protein

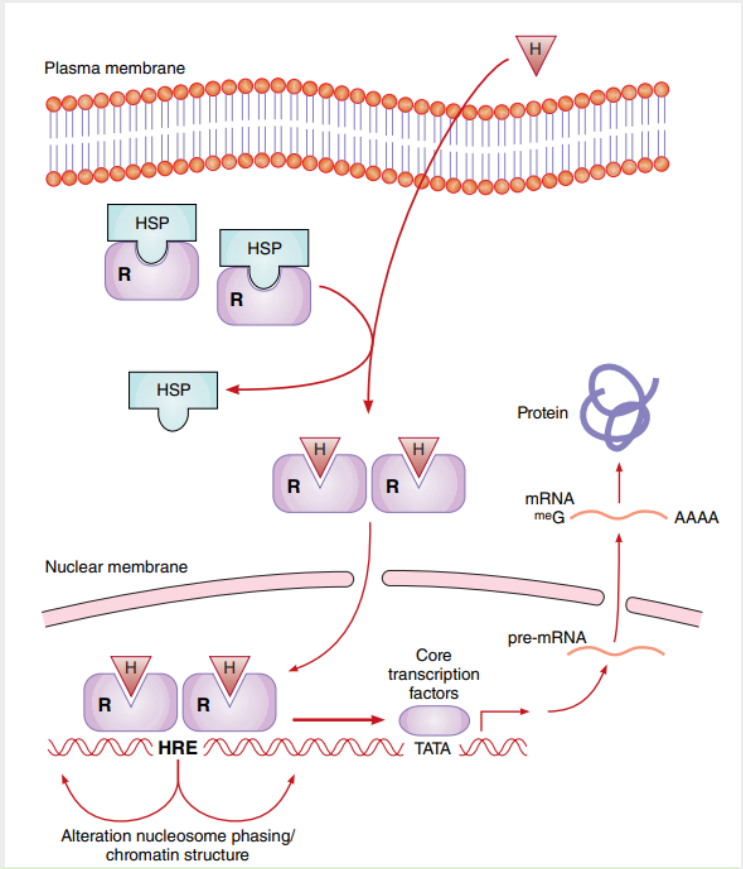


Steroid Hormones Bind Intracellular Receptor Proteins

2: The free steroid diffuses into the cell through the lipid bilayer







(3). Steroid receptors under basal conditions, exist as cytoplasmic, multimeric complexes that include the heat shock proteins (HSPs) and immunophilins of the FK506 family .

Association of the steroid ligand with the receptor results in dissociation of the HSP.

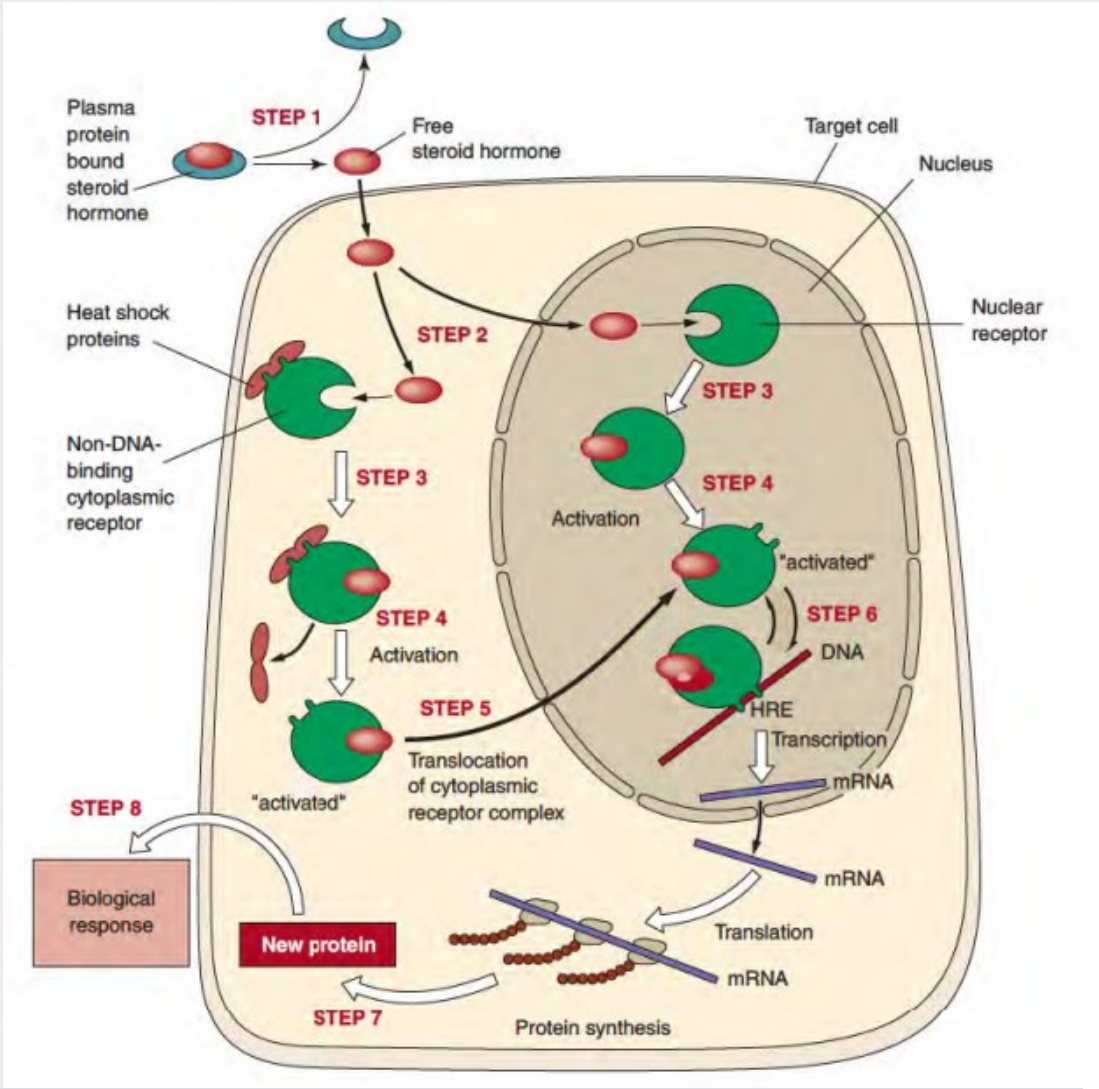
3. Binding of the steroidal ligand (step 3) causes a conformational change (activation) in the receptor protein causing release of the associated proteins, including the dimer of Hsp 90

4. Exposure of positively charged amino acid residues located within the DNA-binding domain

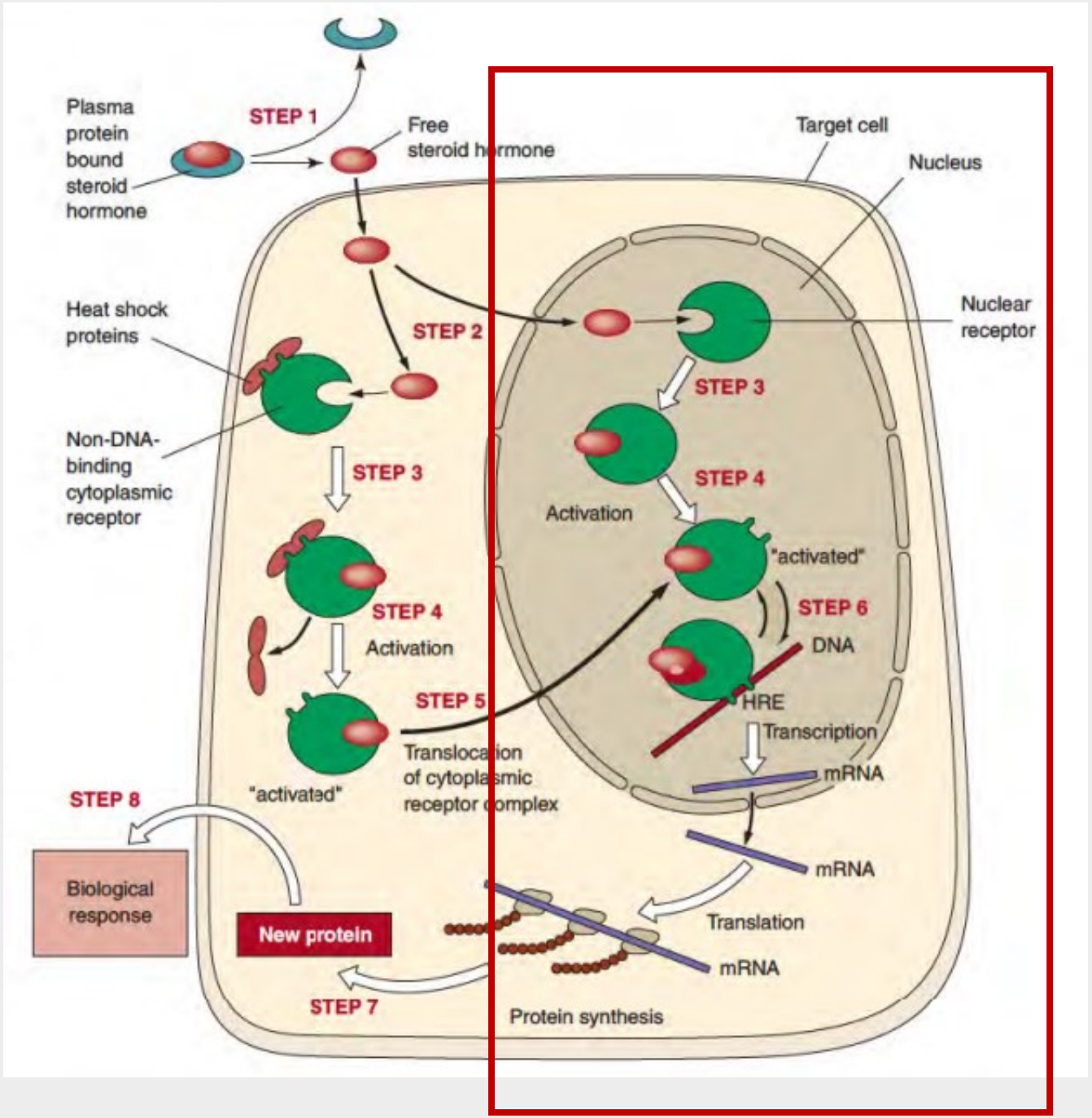
5.The ligand-receptor complex translocates to the nucleus, binds to DNA, searches the DNA for specific, high-affinity acceptor sites.

6. Once the ligand-receptor complex has bound to specific hormone response elements (HRE) in the DNA, it regulates gene transcription and frequently enhances gene transcription.

7 +8. New mRNAs are translocated to the cytoplasm and direct the synthesis of proteins that alter the metabolism and functioning of the target cell



Steroid- receptor complexes can either repress or induce, specific gene transcription.



The unbound steroid hormone receptors for estradiol, progesterone , androgens, and the secosteroid vitamin D3 are located in the nucleus.

Once inside the nucleus the hormone

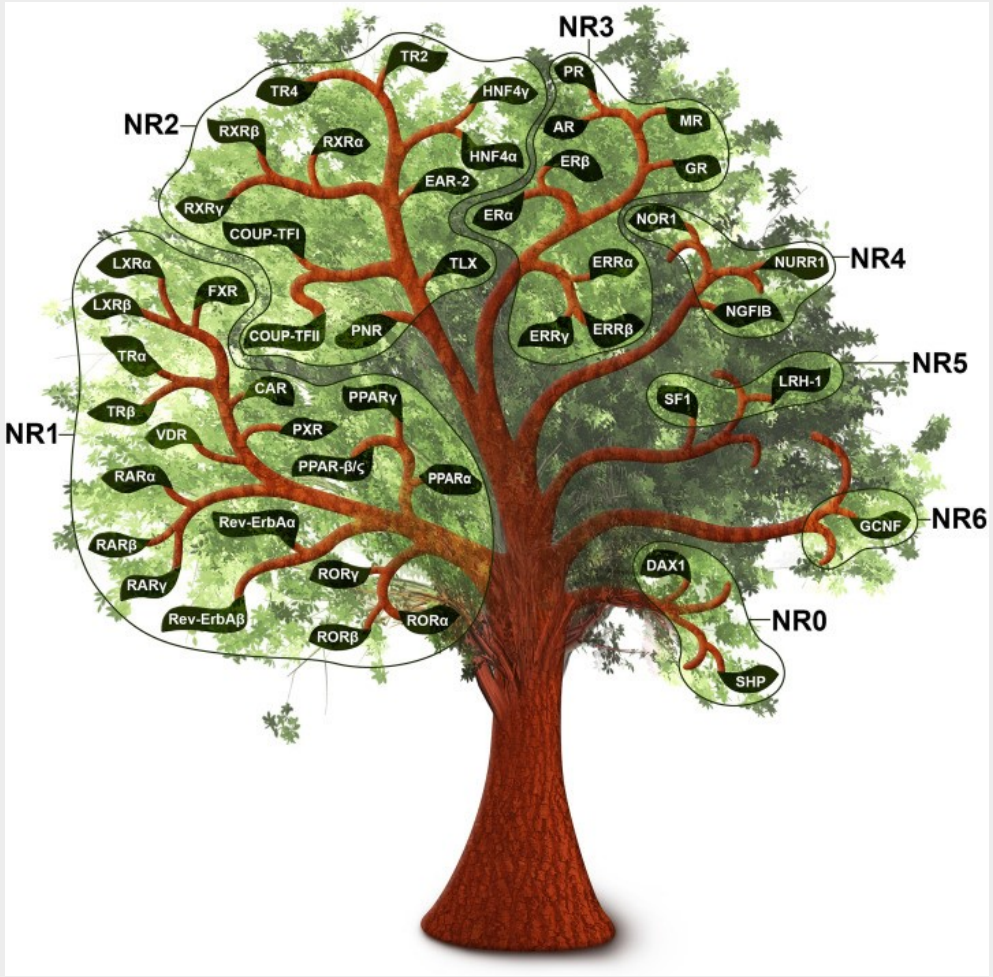
1. binds to its specific receptor,
2. induces the dissociation of receptor associated proteins, and
3. regulates gene transcription.

STEROID- RECEPTOR COMPLEXES FUNCTION AS POSITIVE OR NEGATIVE REGULATORS OF GENE TRANSCRIPTION.

- Binding of a **steroid receptor homodimer to a hormone response element (HRE) may allow it to interact synergistically with a positive transcription factor and hence induce gene transcription**
- Alternatively, **binding of the homodimer to a HRE may sterically block the binding of a positive transcription factor, thus causing repression of gene transcription**

Complex physiological responses to steroid hormones may involve induction or inhibition of gene transcription.

NUCLEAR RECEPTORS



Frigo DE, Bondesson M, Williams C. Nuclear receptors: from molecular mechanisms to therapeutics. Essays Biochem. 2021 Dec 17;65(6):847-856. doi: 10.1042/EBC20210020. PMID: 34825698; PMCID: PMC8628184.

TYPE I NUCLEAR RECEPTORS

In the absence of ligand, the receptors are held in the cytoplasm in an inactive state by heat shock proteins.

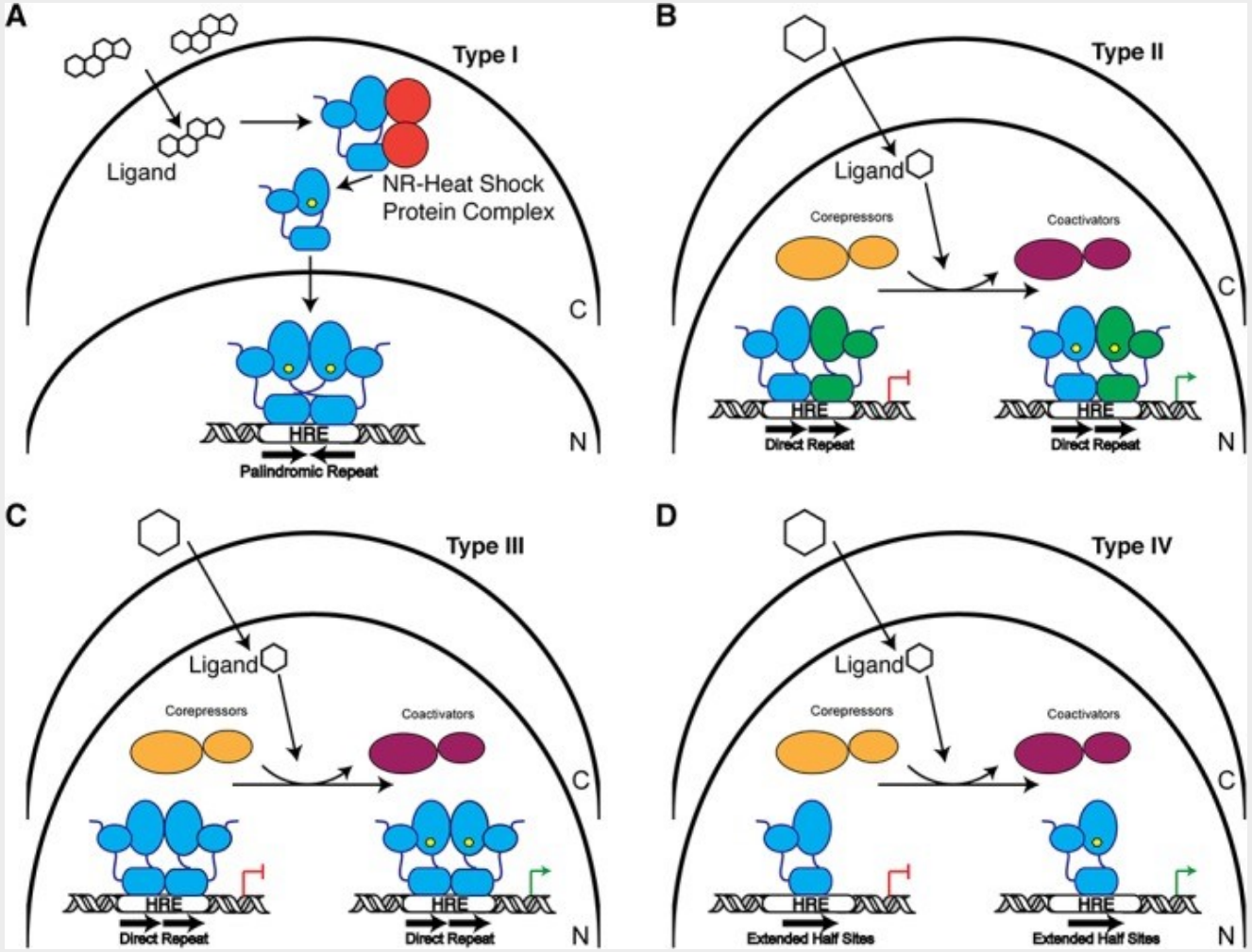
Ligand-binding induces a conformational change that causes the release of the heat shock proteins, nuclear translocation, and dimerization and association with chromatin at specific sequences of DNA termed hormone response elements (HREs).

Activated by cholesterol-derived steroidal hormones such as estrogens, androgens, progestagens, and corticoids. In the nucleus, SRs generally bind as homodimers to DNA REs that consist of two inverted repeats

NUCLEAR RECEPTORS

Type II Nuclear Receptors*:* Receptors of this type, such as RAR and LXR, are often retained in the nucleus, regardless of the presence of activating ligand.

Upon ligand binding, the receptor is released from a co-repressor complex and swapped for co-activators and the transcriptional machinery. **These receptors commonly form heterodimers with RXR on direct repeat DNA REs**

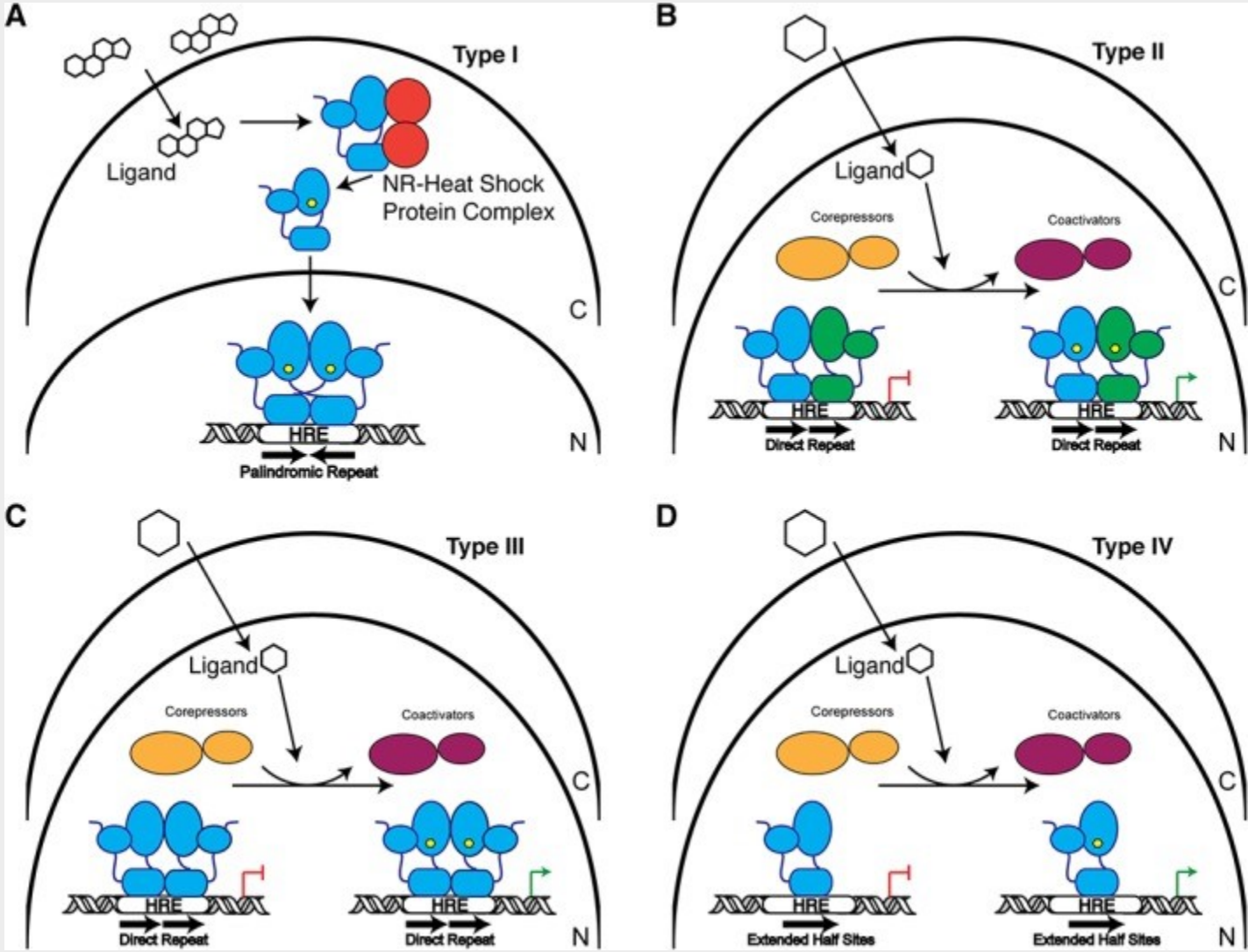


Weikum ER, Liu X, Ortlund EA. The nuclear receptor superfamily: A structural perspective. Protein Sci. 2018 Nov;27(11):1876-1892. doi: 10.1002/pro.3496. PMID: 30109749; PMCID: PMC6201731.

NUCLEAR RECEPTORS

Type III Nuclear Receptors: This type of NR has a similar mechanism of action to Type II NRs but instead **form homodimers on their REs, which are direct repeat sequences**

Type IV Nuclear Receptors: This type of NR has a similar mechanism of action to Type II NRs but **instead bind to DNA as a monomer and recognize extended half-sites within REs**

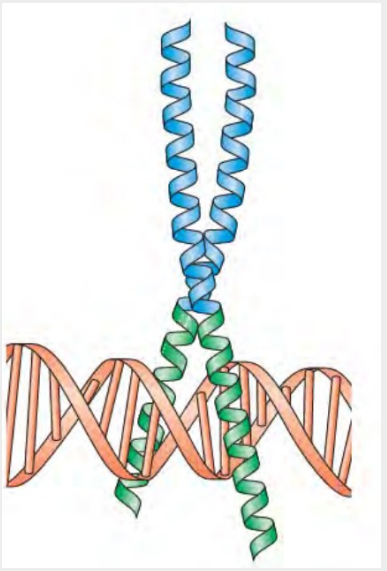


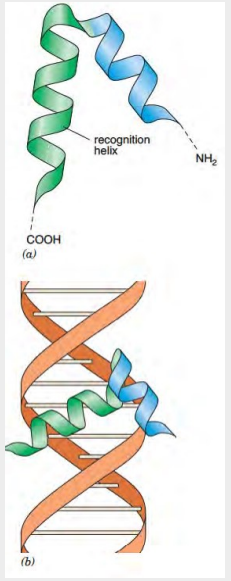
Weikum ER, Liu X, Ortlund EA. The nuclear receptor superfamily: A structural perspective. Protein Sci. 2018 Nov;27(11):1876-1892. doi: 10.1002/pro.3496. PMID: 30109749; PMCID: PMC6201731.

- **Dimerization is a prerequisite for efficient DNA binding and transcriptional activation by most steroid receptors, and is mediated by their ligand-binding domains.**

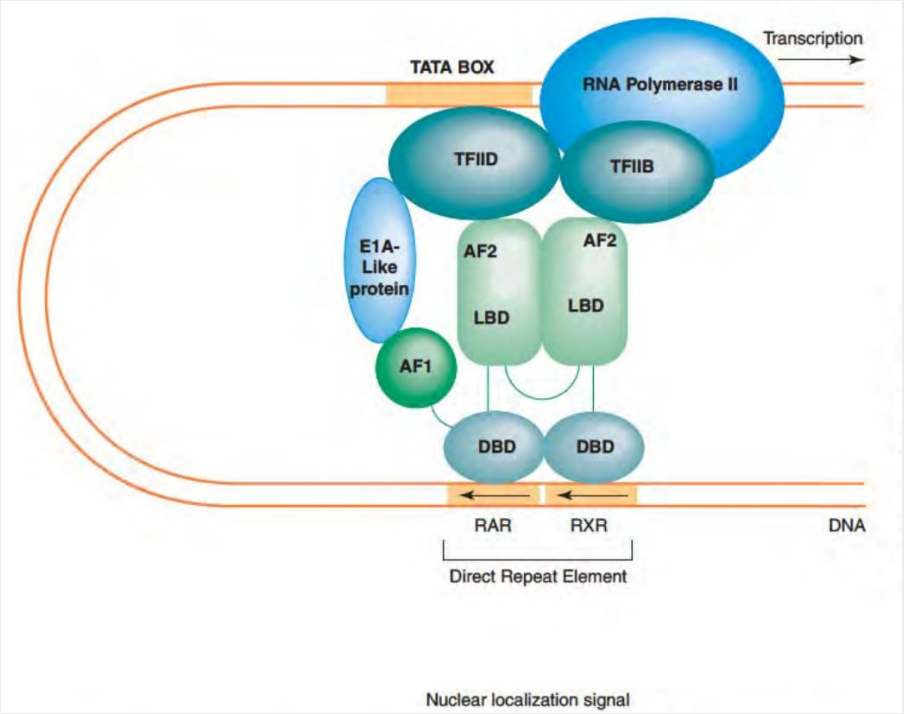
The dimerization region of this domain may form a leucine zipper-like structure or a helix-turn-helix motif which is necessary for dimerization in other transcription factors.

Most steroid receptors form homodimers.



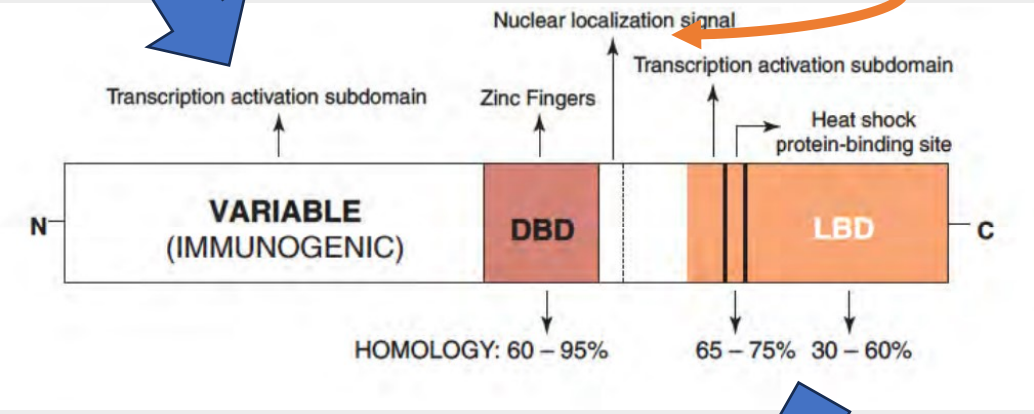


Retinoid X receptors (RXRs) form heterodimers with the retinoic acid receptor, the thyroid hormone receptor, or other members of this receptor superfamily



Steroid Receptor Domains

Transcription activation region and a nuclear localization signal, : provide recognition for the nuclear pore.



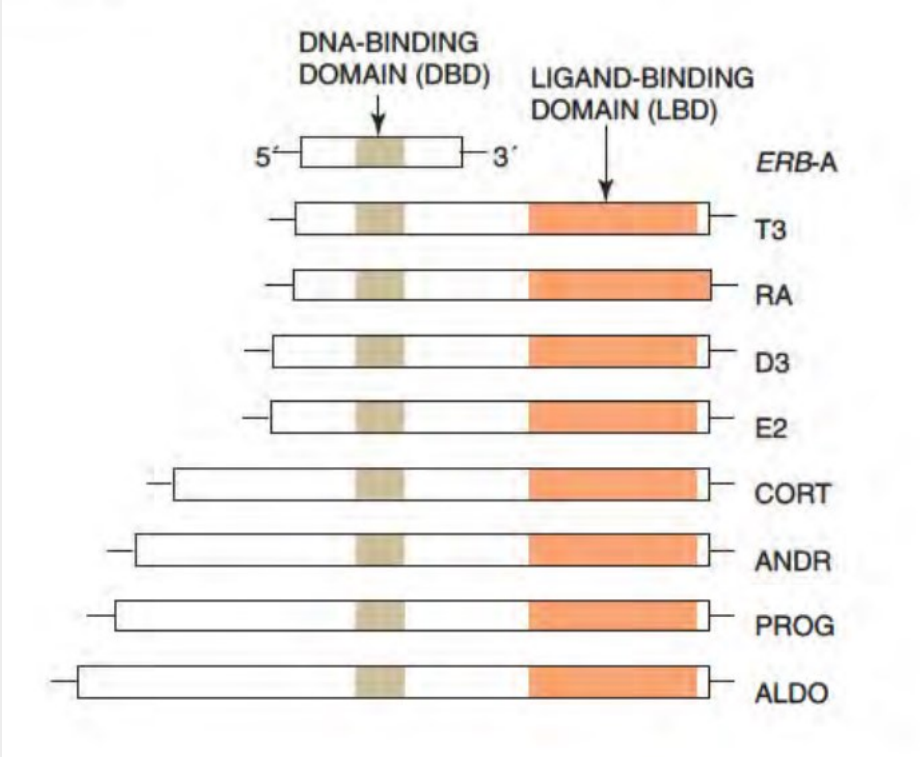
DNA-binding domain: 60%- 95% homology among steroid receptors, contains two zinc fingers that recognize specific HREs and stabilize binding to these DNA sequences.

Located at the C-terminus, the steroid-binding domain has 30-60% homology with the ligand-binding domains of other steroid receptors
Involved in the binding of a dimer of the 90-kDa heat shock protein,

(1) maintains this domain in optimal conformation for steroid binding
(2) prevents unliganded receptor from binding to DNA

The N-terminal domain is highly variable and contains the principal antigenic region and a region that modulates transcriptional activation. These features are common to all members of the steroid receptor superfamily

Steroid receptor gene superfamily



Orphan receptors, as no physiological ligands or activators were known for them/ found in almost all animal species.

Examples of orphan receptors for which the ligand has now been identified include BXR (benzoate X receptor), RXR (retinoid X receptor), PPAR (peroxisome-proliferator-activated receptor), CARJ3 (constitutive androstane receptor), PXR (pregnane X receptor); SXR (steroid and xenobiotic receptor), and FXR (farnesoid X receptor).

Down-regulation of Steroid Receptor by Ligand

Many hormone receptors are down-regulated when the cell has been exposed to a certain concentration of the cognate hormone.

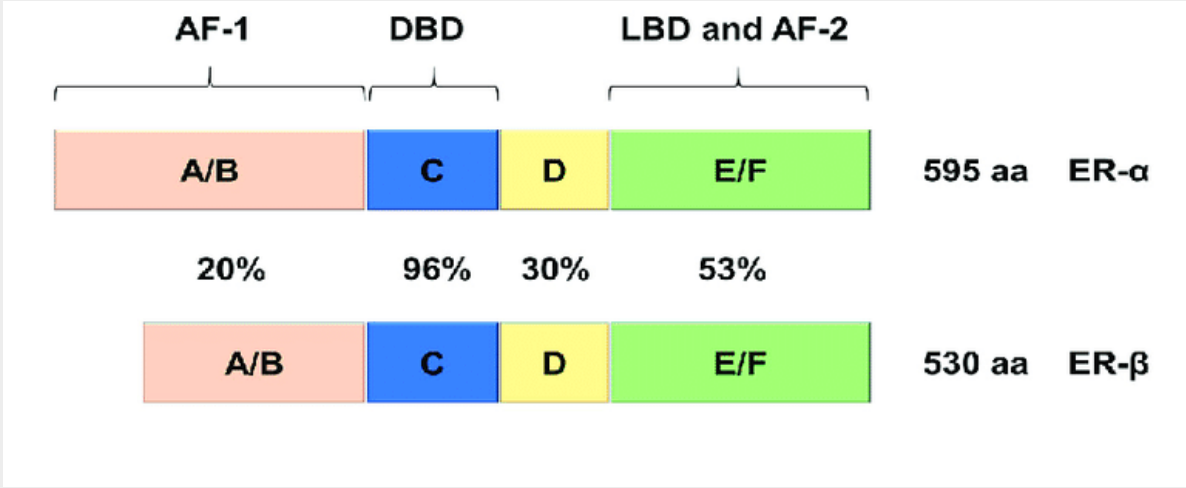
- In the case of **intracellular hormone receptors**, down-regulation generally means a ligand-induced decrease in the half-life of the receptor protein and a decreased receptor gene expression with a decrease in the concentration of receptor molecules.
- **Down-regulation of receptors by their own ligands plays an important physiological role, because it desensitizes the target cell and therefore prevents overstimulation when circulating hormone levels are elevated: form of autoregulation- NOT IN ALL TARGET CELLS**
- Glucocorticoid-mediated up-regulation of its own receptor levels has been reported in a number of responsive cells: could increase hormonal responsiveness.

The ability of the estrogen receptor to increase the concentration of progesterone receptors in key target tissues is an example of heterologous up-regulation

ESTROGEN RECEPTOR

- The estrogen receptor (ER), whose ligand is estradiol, plays a key role in female reproduction. There are two isoforms of the ER known as ERα and ERβ, which are structurally distinct and perform different functions.
- ERβ plays an essential role in the proliferation of prostatic epithelial cells, which is a feature of prostate cancer progression.
- Subset of patients with high-grade tumors had a loss of the ERβ gene locus

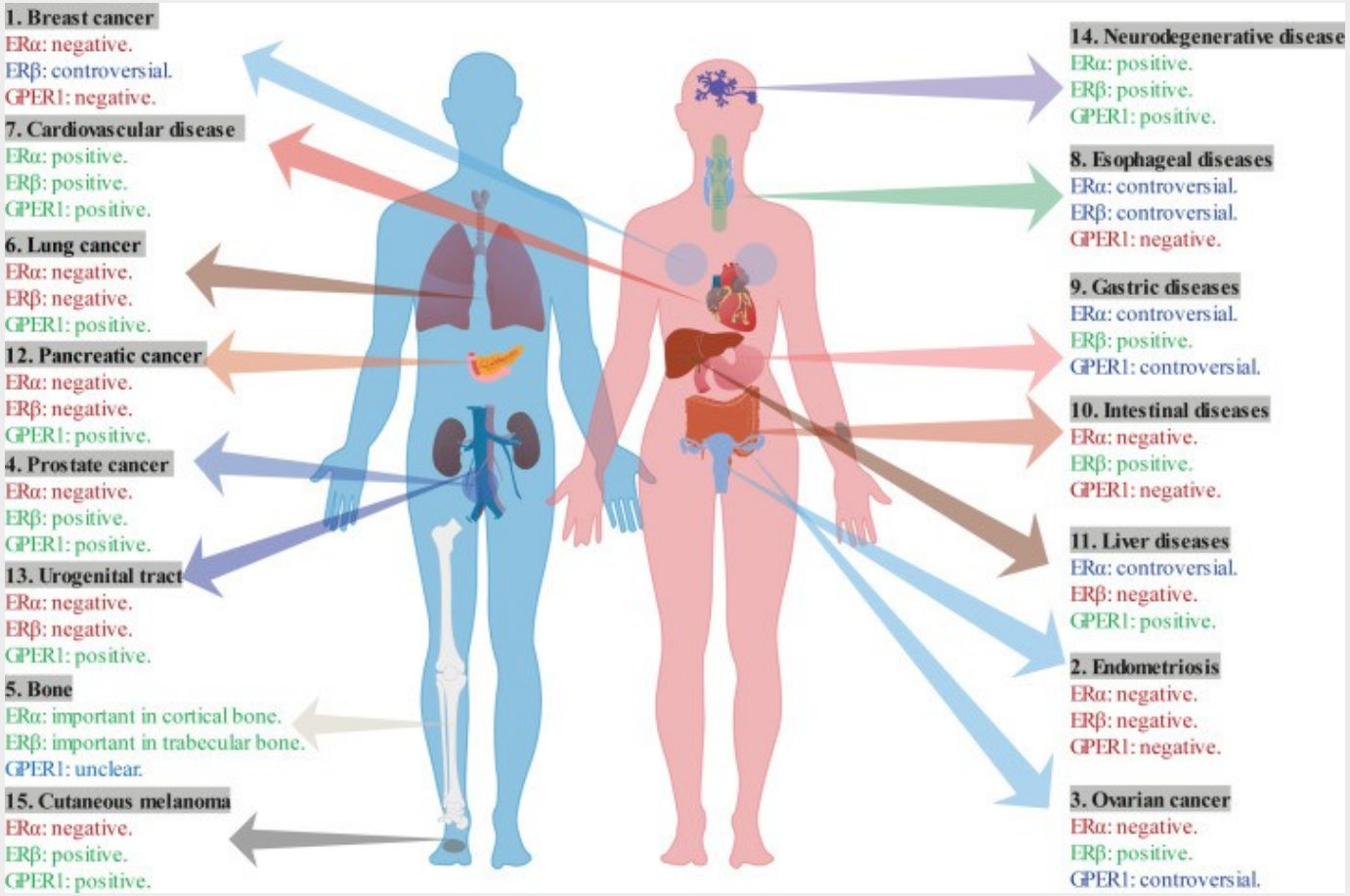
ER has a pivotal role in the female reproductive system and secondary sexual characteristic development and function. ER has been well characterized as a key player in breast cancer development.



Rong, Chao & Meinert, Étienne & Hess, Jochen. (2018). Estrogen Receptor Signaling in Radiotherapy: From Molecular Mechanisms to Clinical Studies. International Journal of Molecular Sciences. 19. 713. 10.3390/ijms19030713.

ESTROGEN RECEPTOR

- Breast cancer is subdivided into distinct biologic groups based on receptor expression: Estrogen Receptor (ER+), Progesterone Receptor (PR+), those that express the epidermal growth factor receptor 2 (HER2+), and those that do not express either are classified as triple negative BC .



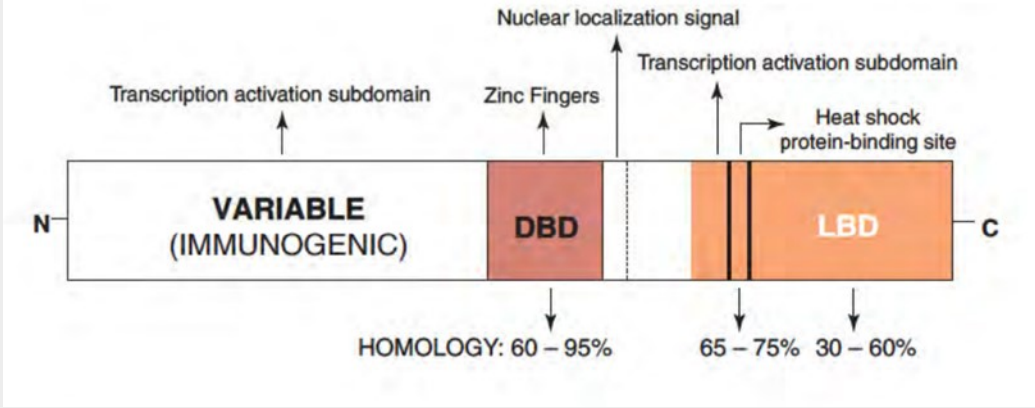
Chen P, Li B, Ou-Yang L. Role of estrogen receptors in health and disease. Front Endocrinol (Lausanne). 2022 Aug 18;13:839005. doi: 10.3389/fendo.2022.839005. PMID: 36060947; PMCID: PMC9433670.

Nuclear Hormone Receptors, Coactivators, and Corepressors

- **Co-activators and co-repressors are co-factors that increase or decrease the transcriptional functions of most nuclear steroid-receptor complexes.**
- **Co-activators,** such as the p160 family of coactivators: **increase the amount of induced gene product with a saturating concentration of a steroid hormone.**
- **Co-repressors** such as nuclear receptor co-repressor (NcoR) and the silencing mediator of retinoid and thyroid hormone receptor (SMRT) **decrease the amount of gene product.**

Binding of the cognate ligand to one of these receptors acts like a "molecular switch", causing dissociation of co-repressors from the receptor and association of co-activators.

The sites of interaction in steroid and nuclear receptors for both co-activators and co-repressors have been shown to be present in the ligand-binding domain , and these two binding sites may overlap.



Receptor binds its ligand specifically, once activated they bind to the same hormone response element

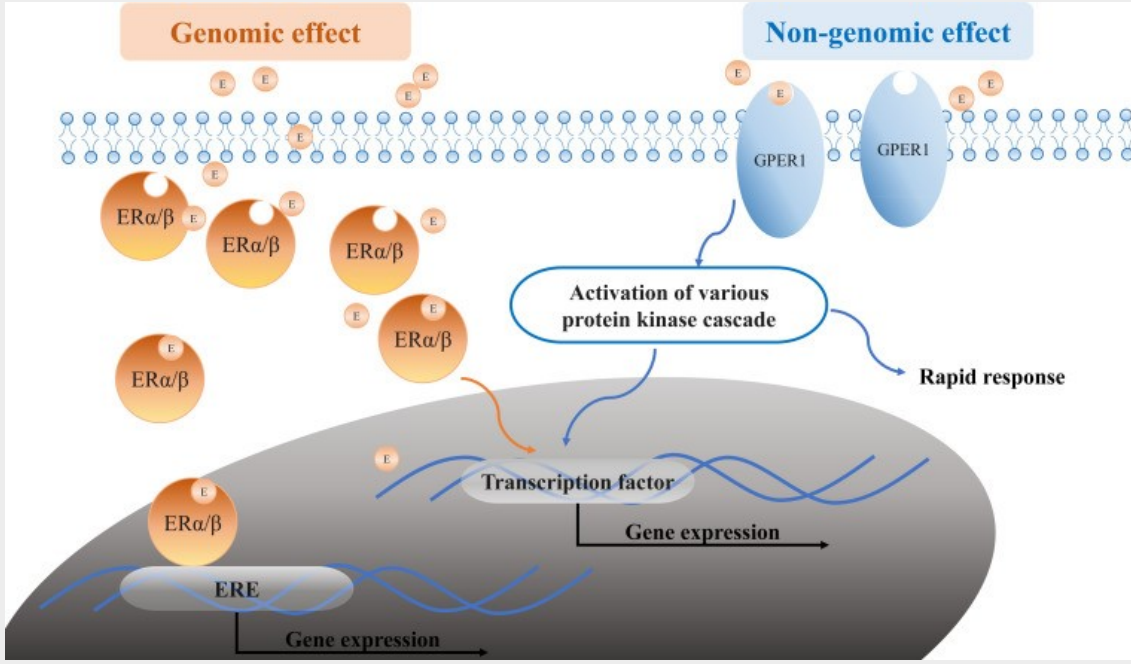
TABLE 22.10 • Steroid Hormone Receptor Responsive DNA Elements: Consensus Acceptor Sites

Element	*DNA Sequence*[a]
POSITIVE	
Glucocorticoid response element (GRE)	5′-GGTACAnnnTGTTCT-3′
Mineralocorticoid response element (MRE)	
Progesterone response element (PRE)	
Androgen response element (ARE)	
Estrogen response element (ERE)	5′-AGGTCAnnnTCACT-3′
NEGATIVE	
Glucocorticoid response element	5′-ATYACNnnnTGATCW-3′

Interactions between cell-specific co-repressors and DNA-bound receptors can restore some of the specificity that appears to be lost on binding to a common HRE.

Nongenomic Steroid Effects

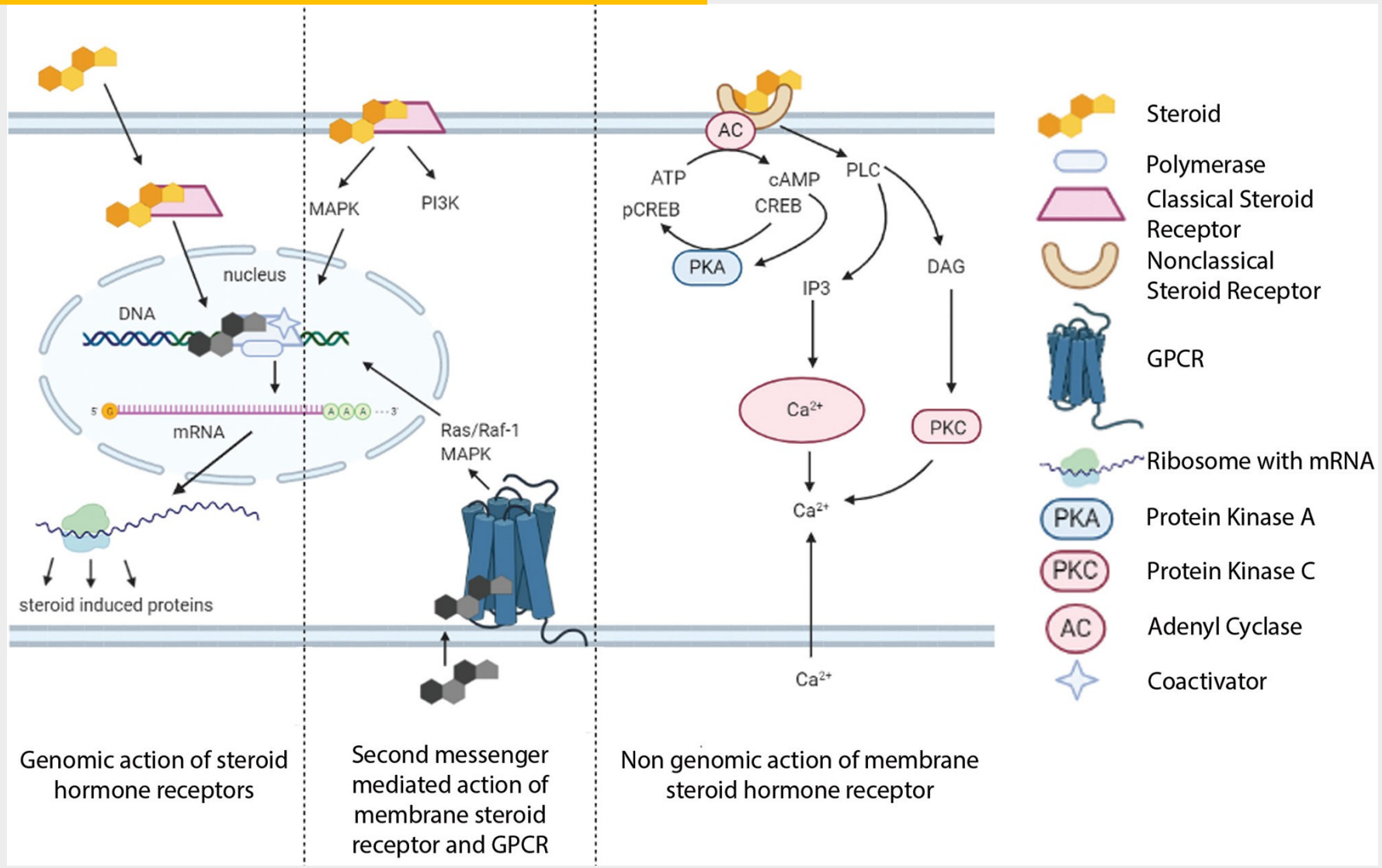
- **Not all effects of steroid hormones are mediated at the level of gene transcription.**
- Many steroid hormones, including **aldosterone, 17β-estradiol, progesterone, glucocorticoids, and androgens,** exert rapid (within minutes) **stimulatory effects on the activities of a wide variety of signal transduction molecules** (protein kinase C, diacylglycerol, and IP3) and pathways.
- These **non-genomic effects appear to be initiated at the plasma membrane rather than in the nucleus of a target cell.**
- **Mediated: either by a sub-population of conventional nuclear receptors localized in the cell membrane** or **by distinct membrane receptors that are unrelated to classical intracellular steroid receptors.**



Chen P, Li B, Ou-Yang L. Role of estrogen receptors in health and disease. Front Endocrinol (Lausanne). 2022 Aug 18;13:839005. doi: 10.3389/fendo.2022.839005. PMID: 36060947; PMCID: PMC9433670.

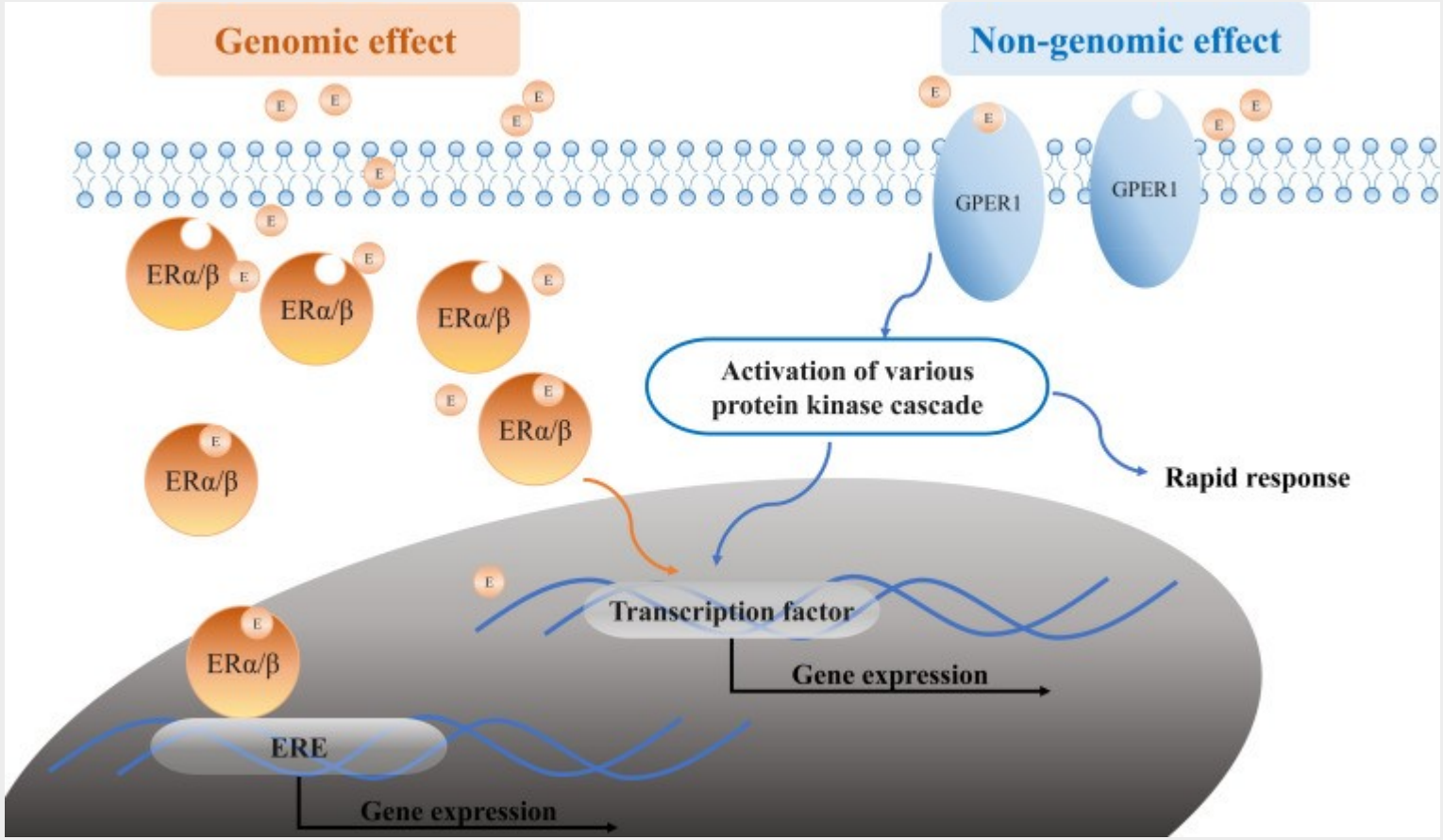
Convergence of genomic and nongenomic mechanisms of steroid hormone receptor action

Drugs that specifically affect non-genomic steroid action may find applications in various clinical areas including **cardiovascular and central nervous system disorders, electrolyte homeostasis, and infertility.**



Saha S, Dey S, Nath S. Steroid Hormone Receptors: Links With Cell Cycle Machinery and Breast Cancer Progression. Front Oncol. 2021 Mar 12;11:620214. doi: 10.3389/fonc.2021.620214. PMID: 33777765; PMCID: PMC7994514.

Convergence of genomic and nongenomic mechanisms of steroid hormone receptor action-example: ESTROGEN SIGNALING PATHWAYS



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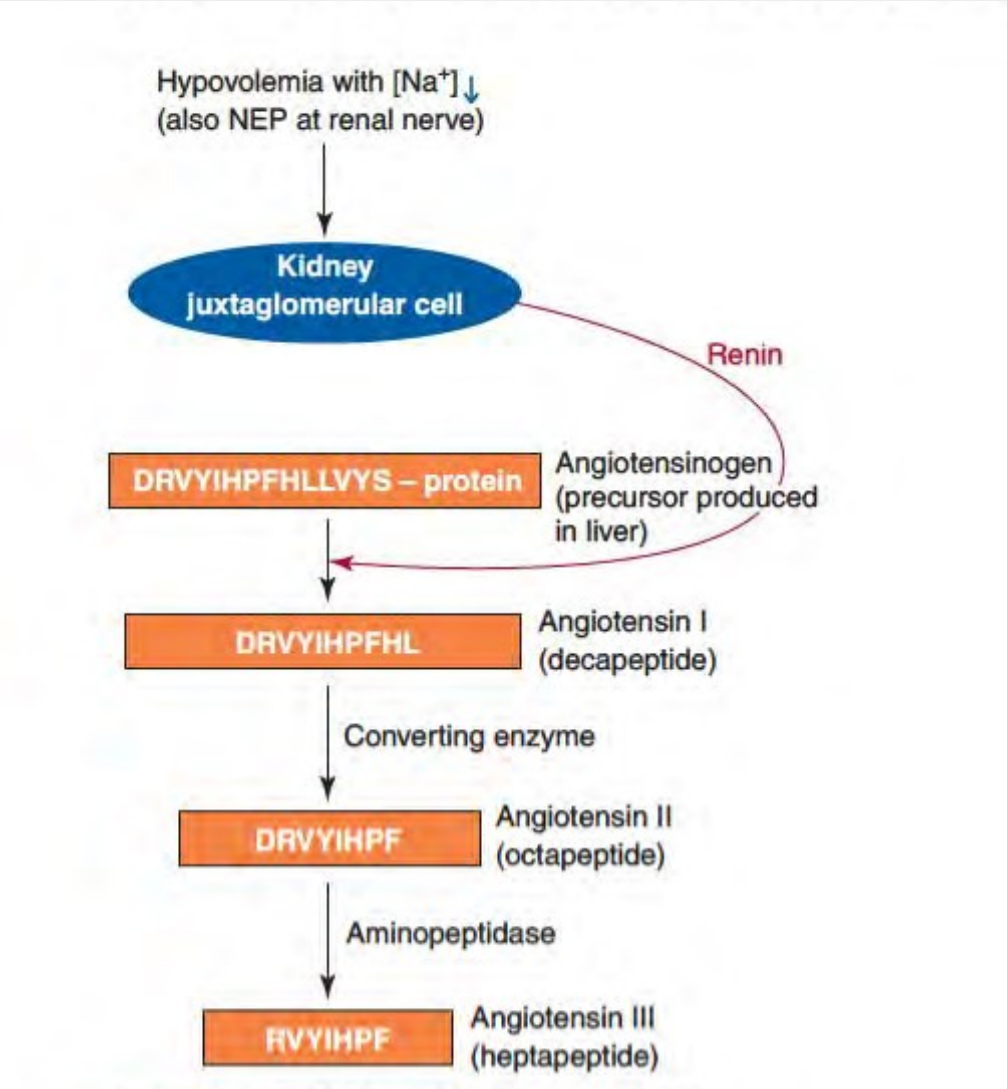
Mineralocorticoids

A major driving force for aldosterone biosynthesis is angiotensin II, which is generated by the renin-angiotensin system

The **signal** for **aldosterone secretion** is generated under conditions when blood Na^+ concentration and blood pressure (blood volume) need to be increased.

Hypovolemia (rise in serum K^+ concentration), stress, Hypervolemia (increase blood volume)



Mineralocorticoids

Promote sodium reabsorption in transporting epithelia of the kidneys, salivary glands, and large intestine.

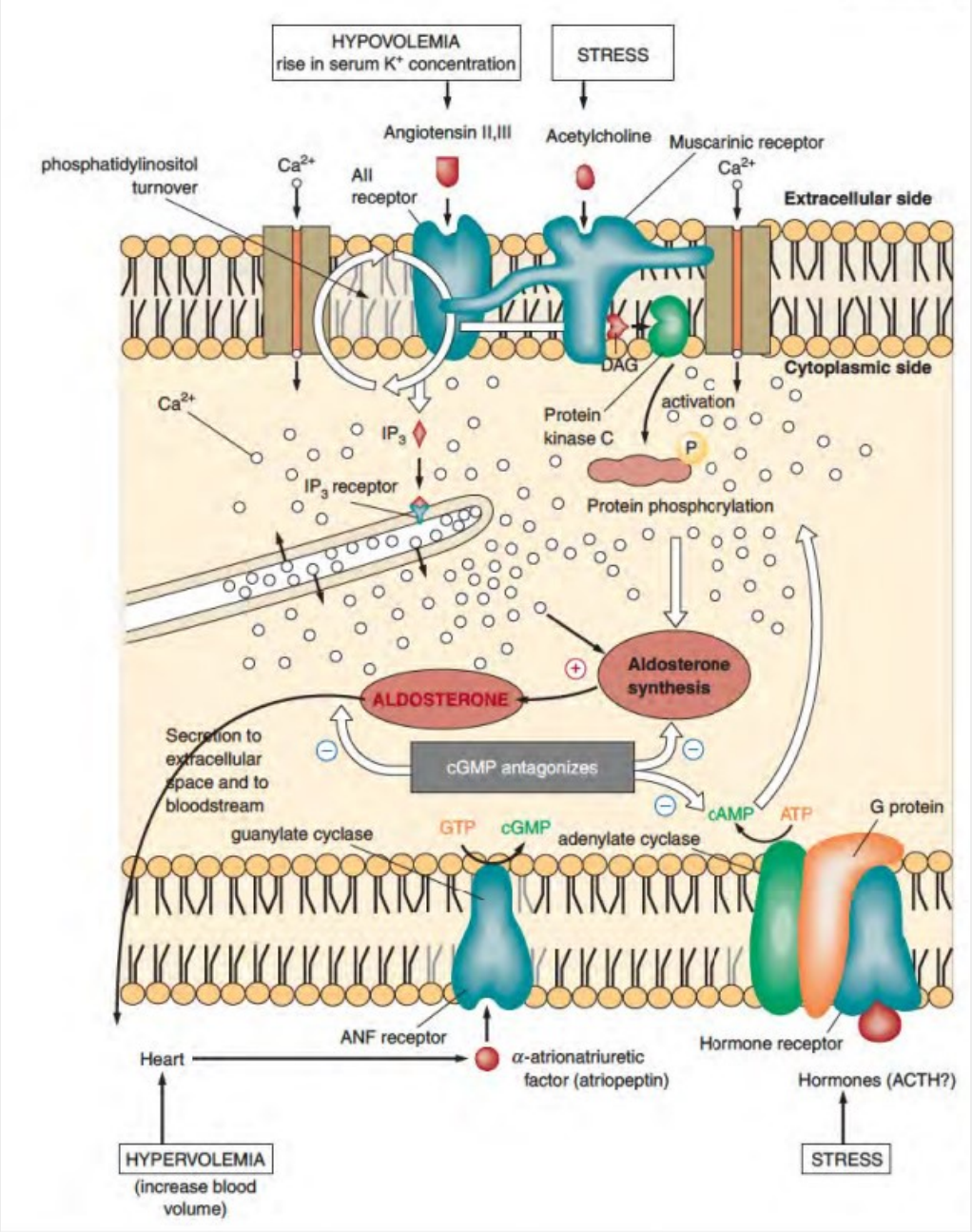
Sodium reabsorption is followed by passive reabsorption of water.

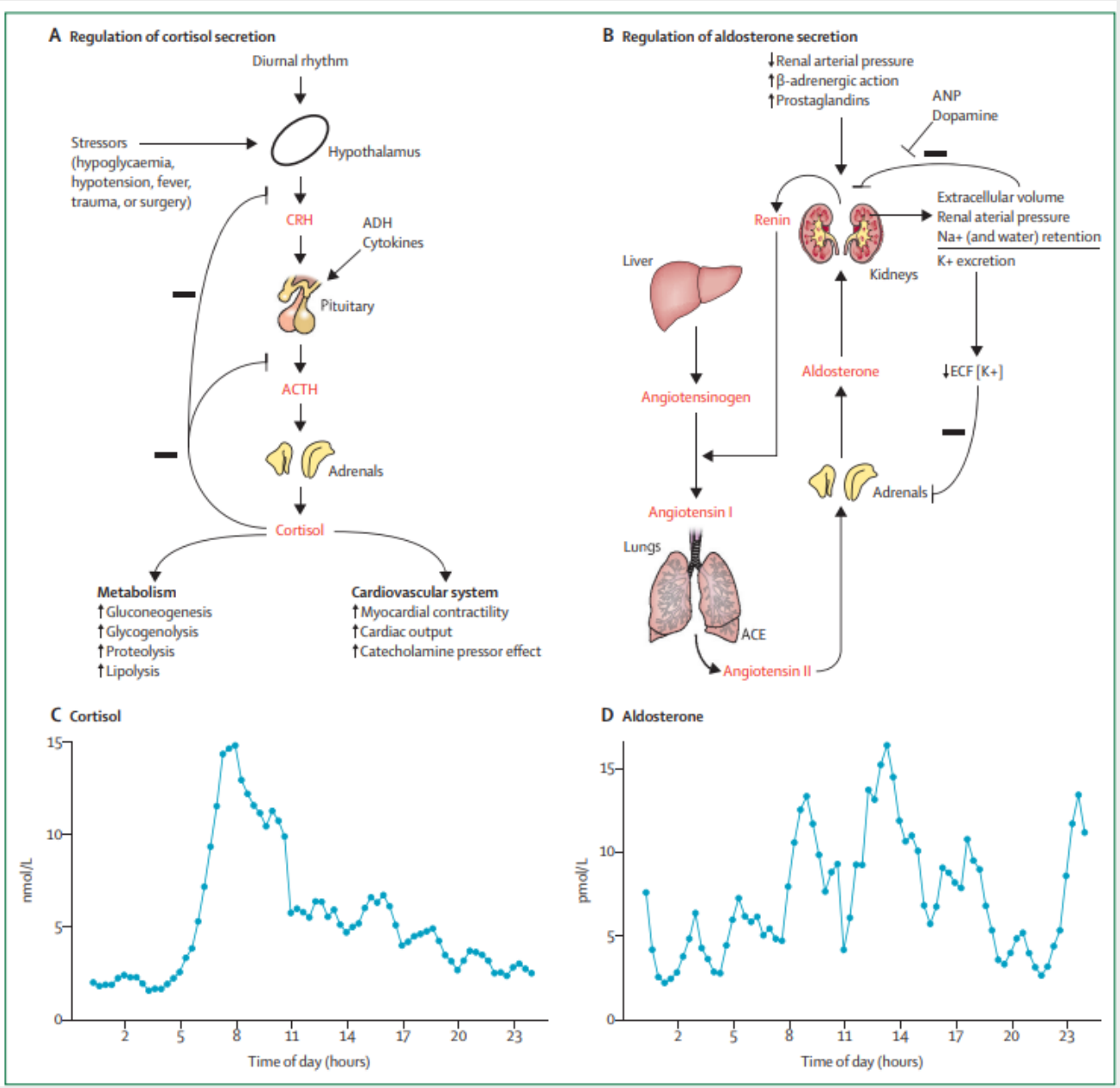
Circulating aldosterone concentrations rise in response to low blood volume or sodium depletion under control of the renin-angiotensin system (RAS).

The kidneys release renin, which converts angiotensinogen to angiotensin I.

Angiotensin I is then cleaved by angiotensin-converting enzyme (ACE) to active angiotensin II.

Angiotensin II stimulates mineralocorticoid production by the zona glomerulosa of the adrenals.





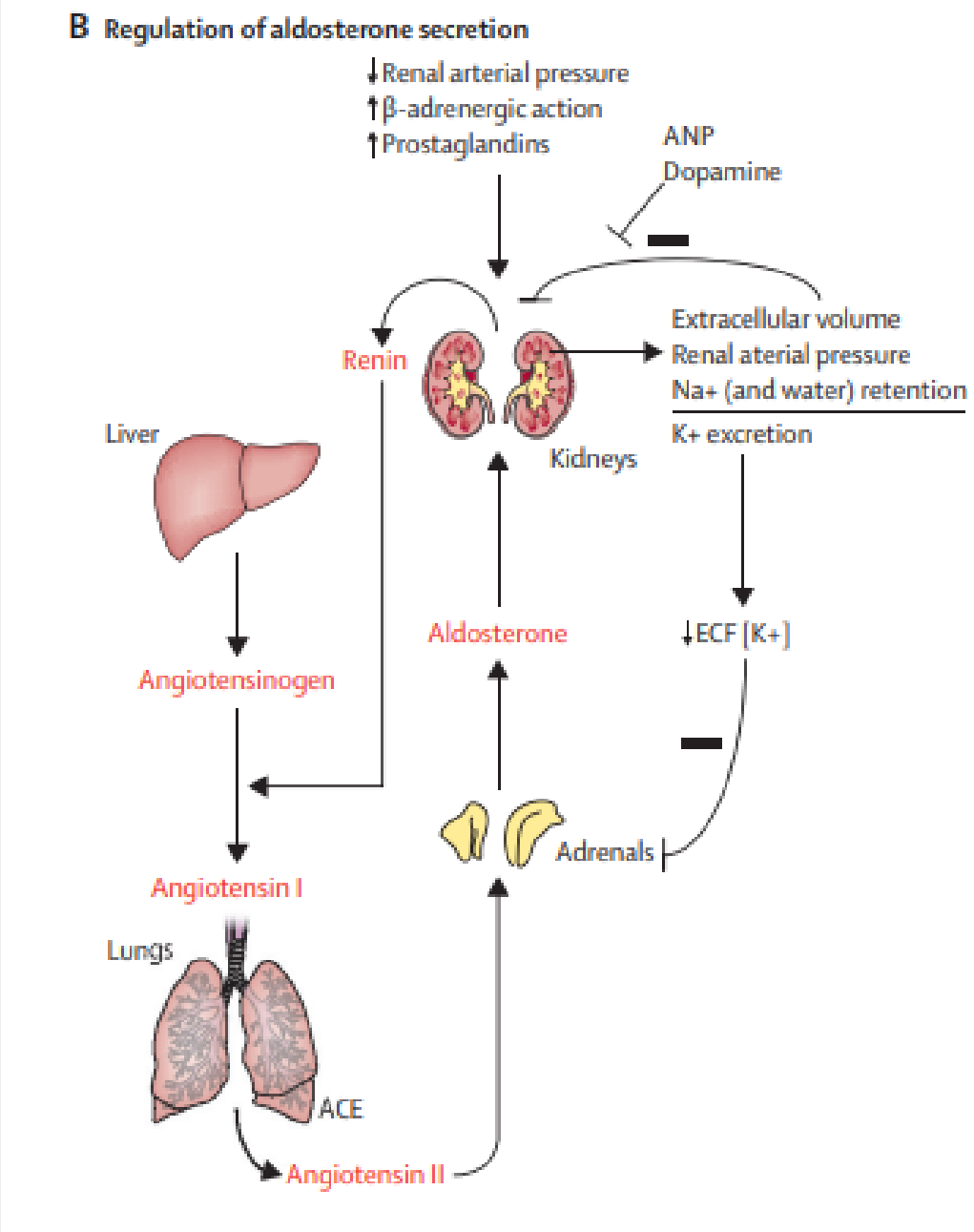
Adrenal steroid secretion is tightly regulated at multiple levels

The hypothalamic–pituitary–adrenal axis regulates cortisol production in response to light, stress,

A robust, but adaptable, circadian and ultradian cortisol rhythm, characterised by secretory bursts every 60–90 min

Aldosterone production is mainly regulated by the renin–angiotensin system, but the HPA axis also causes circadian variation of aldosterone

Husebye ES, Pearce SH, Krone NP, Kämpe O. Adrenal insufficiency. Lancet. 2021 Feb 13;397(10274):613-629. doi: 10.1016/S0140-6736(21)00136-7. Epub 2021 Jan 20. PMID: 33484633.



The renin-angiotensin-aldosterone pathway, also known as the renin-angiotensin system (RAS), is a complex physiological mechanism in the human body that **helps regulate blood pressure, fluid balance, and electrolyte homeostasis. It plays a crucial role in maintaining overall cardiovascular and renal health**

Dysregulation of this pathway can contribute to various medical conditions, including hypertension (high blood pressure), congestive heart failure, and kidney diseases

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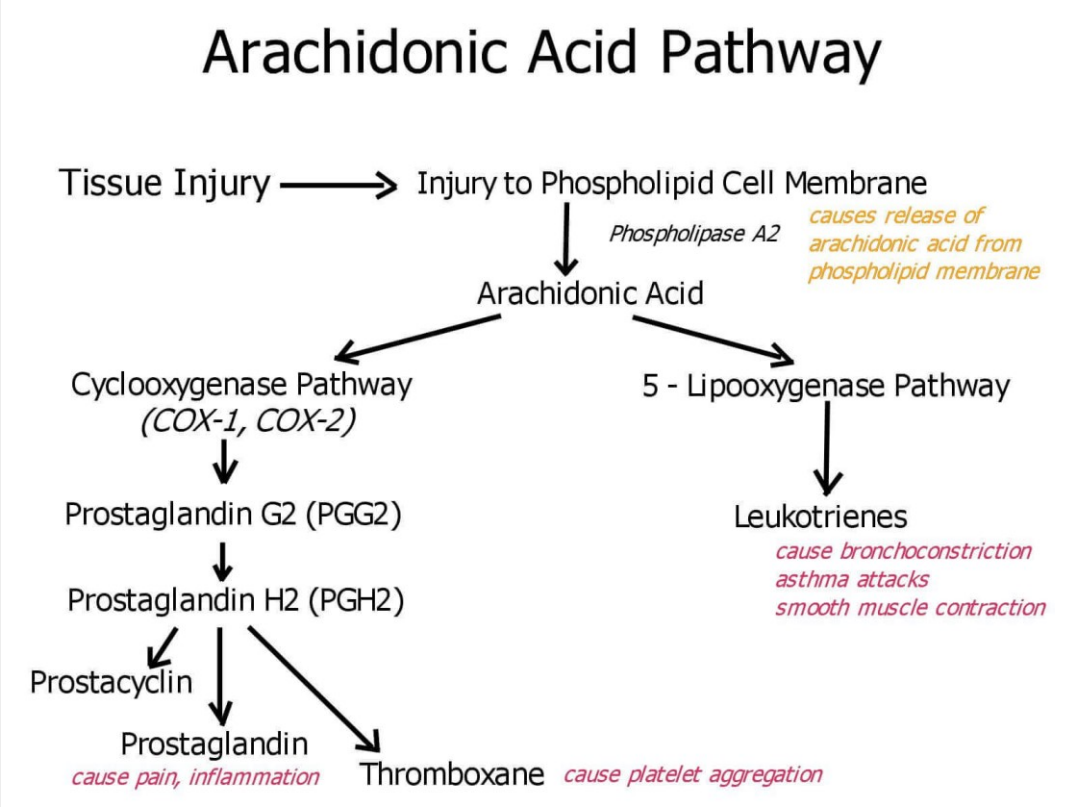


Glucocorticoids: anti-inflammatory- inhibit prostaglandin production.

1. Glucocorticoid- receptor complexes induce annexin-1 (or lipocortin), a 40-kD protein , which inhibits membrane phospholipase A2, and hence the release of arachidonic acid for prostaglandin synthesis.

2. Glucocorticoids also inhibit expression of cyclooxygenase (COX) that generates prostaglandins and related compounds.

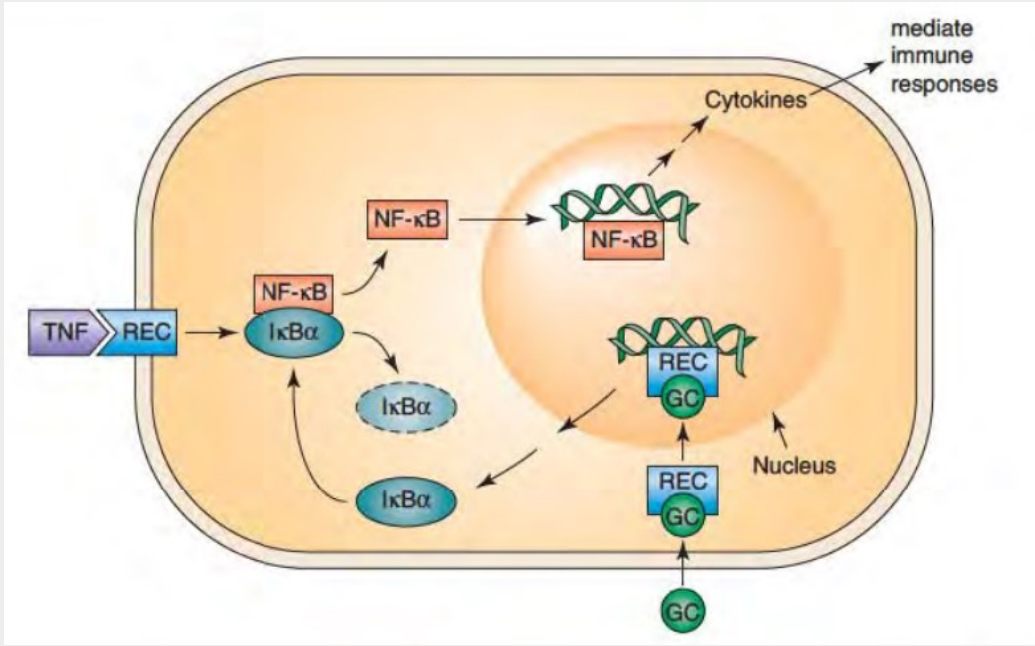
COX-1 is constitutively expressed and produces prostaglandins under noninflammatory conditions.

COX2 is induced in inflammatory cells and suppression of its synthesis by glucocorticoids accounts for a major part of their anti-inflammatory effects

Glucocorticoids interfere with the transcription factor nuclear factor kappa B (NF-KB).
Stimulation: causes **phosphorylation of IKBa which leads to ubiquitination and subsequent degradation via proteasomes.**

Degradation releases NF-KB, which has been trapped in the cytoplasm in an inactive form, from this complex and **it migrates into the nucleus.**

In the nucleus it induces genes for cytokines: activates immune cells, cell adhesion molecules that draw immune cells into inflammatory sites.



Glucocorticoids suppress this immune cell activation by inducing lKBa gene transcription and ensuring that NF-KB is retained in the cytoplasm in its inactive form under conditions where it should migrate into the nucleus and induce gene transcription .

Hyperaldosteronism

Excessive production of ALDOSTERONE ➡ **Balances potassium and sodium in the body**

- **Primary hyperaldosteronism:**

excess production: zona glomerulosa: presents as a primary tumor in the gland known as **Conn syndrome** or bilateral adrenal hyperplasia.

Primary hyperaldosteronism is an important and increasingly prevalent cause of hypertension that is characterized by UNREGULATED ALDOSTERONE EXCESS

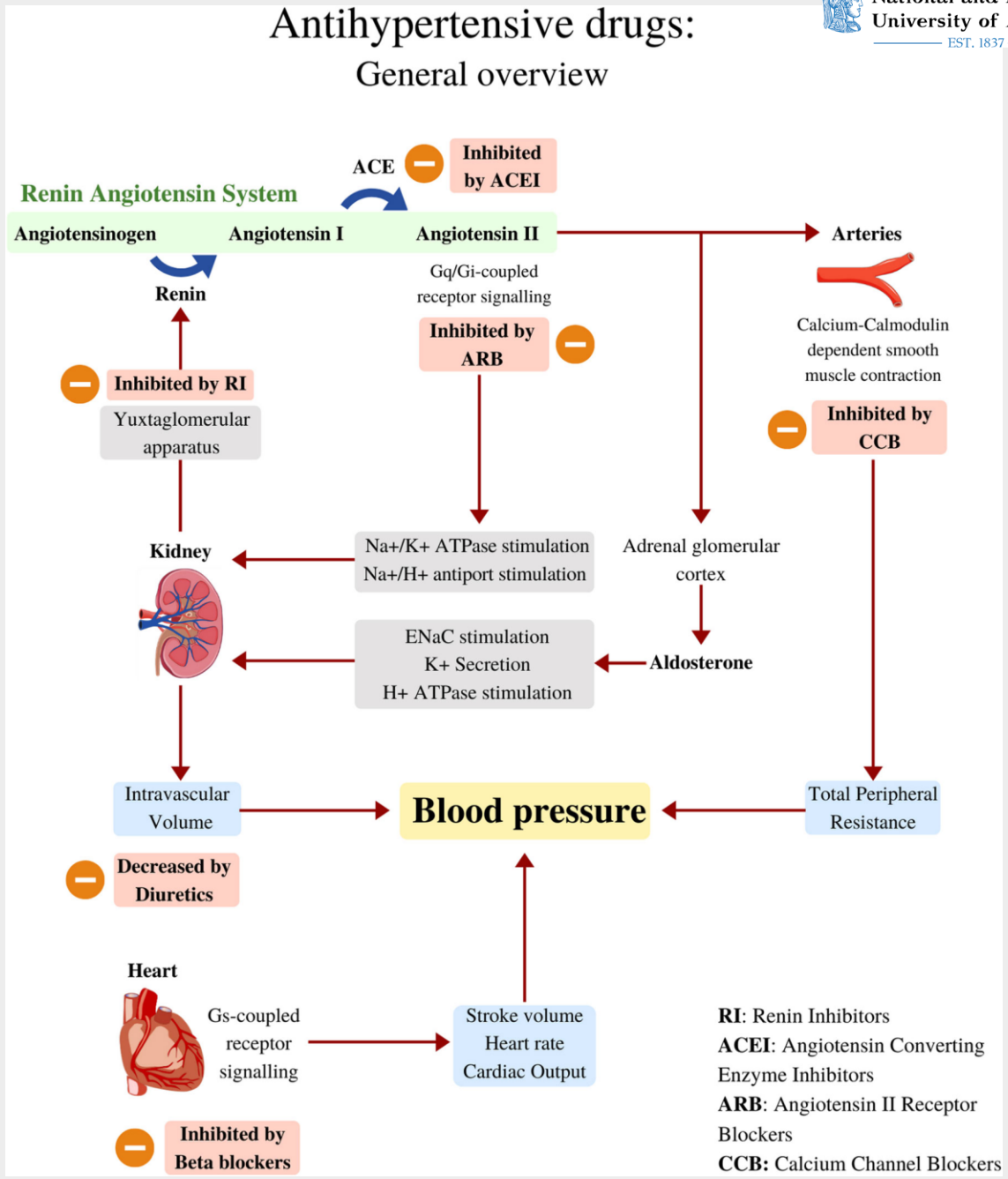
90% of primary hyperaldosteronism cases are attributable to either idiopathic adrenal hyperplasia or aldosterone-producing adenomas.

- **Secondary hyperaldosteronism**

occurs due to excessive activation of the renin-angiotensin-aldosterone system (RAAS). **This activation can be due to a renin-producing tumor, renal artery stenosis etc.**

This results in:
low renin levels
more sodium and less potassium
elevated blood pressure

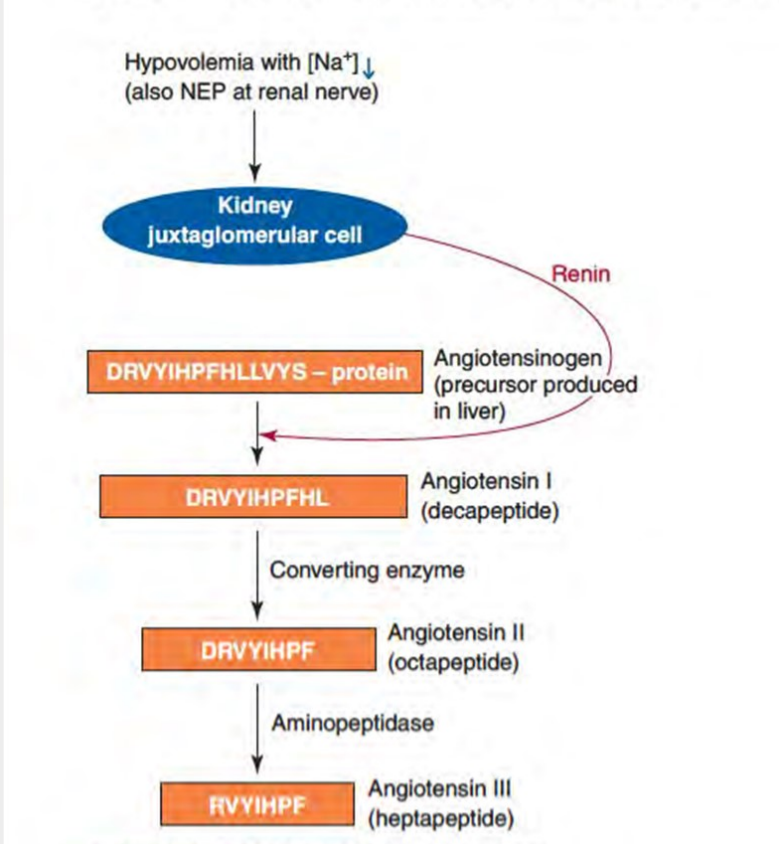
Antihypertensive drugs are medications designed to lower high blood pressure (hypertension).



Carlos-Escalante JA, de Jesús-Sánchez M, Rivas-Castro A, Pichardo-Rojas PS, Arce C, Wegman-Ostrosky T. The Use of Antihypertensive Drugs as Coadjuvant Therapy in Cancer. Front Oncol. 2021 May 20;11:660943. doi: 10.3389/fonc.2021.660943. PMID: 34094953; PMCID: PMC8173186.

Apparent Mineralocorticoid Excess Syndrome

- Some patients (usually children) exhibit the **hypertension, hypokalemia, and suppression of the renin-angiotensin-aldosterone system**
- **It is caused by defects in the HSD11B2 gene, encoding the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which is primarily involved in the peripheral conversion of cortisol to cortisone.**
- **Assays of plasma and urine may fail to identify excess mineralocorticoids, these patients are said to have the apparent mineralocorticoid excess (AME) syndrome.**
- **Since the plasma levels of cortisol are about I00-times higher than the plasma levels for aldosterone, cortisol saturates the renal mineralocorticoid receptor, causing sodium retention and suppression of the renin-angiotensin aldosterone axis.**

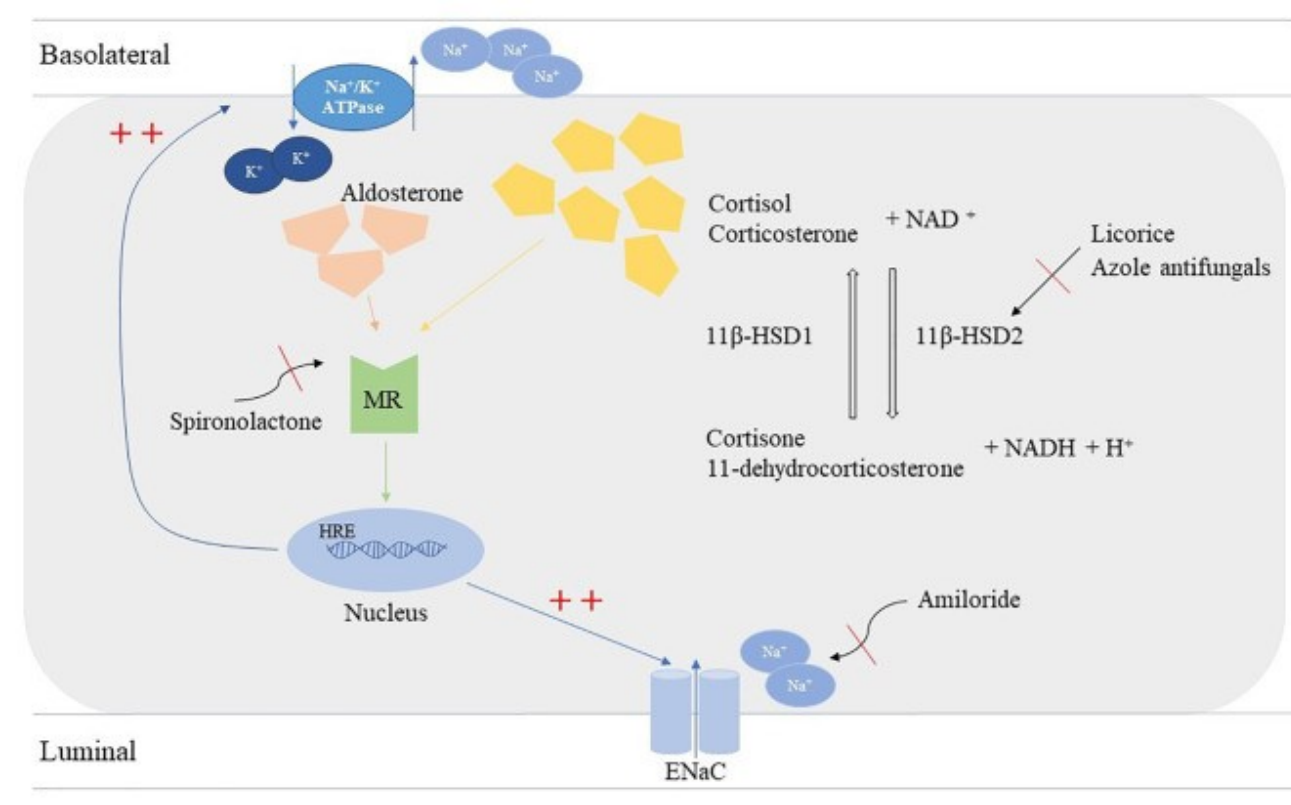


Apparent Mineralocorticoid Excess Syndrome

11β-HSD2 enzyme facilitates the conversion from active cortisol to inactive metabolite form, cortisone;

ALDOSTERONE AND CORTISOL ARE BOTH LIGANDS OF MINERALOCORTICOID RECEPTORS

The deficiency of 11β-HSD2 fails in the metabolism of cortisol and results in excessive mineralocorticoid, so as the over-ingestion of licorice and azole antifungals causes the same effects.



Lu YT, Zhang D, Zhang QY, Zhou ZM, Yang KQ, Zhou XL, Peng F. Apparent mineralocorticoid excess: comprehensive overview of molecular genetics. J Transl Med. 2022 Nov 3;20(1):500. doi: 10.1186/s12967-022-03698-9. PMID: 36329487; PMCID: PMC9632093.

Apparent Mineralocorticoid Excess Syndrome

Classic AME usually starts in **infancy to juvenile** and typically manifests as **low birth weight, refractory hypertension, delayed growth, polyuria and polydipsia, failure to thrive**

Ingesting excessive amounts of licorice:
The major components of licorice are glycyrrhizic acid and its hydrolytic product, glycyrrhetinic acid (GE), which is a potent inhibitor of 11β-HSD2.

The New York Times

A Man Died After Eating a Bag of Black Licorice Every Day

Doctors at Massachusetts General Hospital said the unusual case highlighted the risk of consuming too much glycyrrhizic acid, which is found in black licorice.

Share full article

The black and chewy candy contains glycyrrhizic acid, a plant extract that can lead to high blood pressure if consumed in large doses. Anoek De Groot/Agence France-Presse —

Mineralocorticoid Receptor Mutation Results in Hypertension and Toxemia of Pregnancy

- **The underlying causes of hypertension, especially the hypertension associated with the toxemia of pregnancy, which is called eclampsia, include the renin-angiotensin system and the aldosterone receptor.**
- **Hypertension occurs in about 6% of pregnancies and in some cases is associated with a mutation in the mineralocorticoid receptor in which a serine residue at position 810 is replaced by a leucine residue (referred to as S810L mutation).**

Seizures
Severe distress or confusion
Losing consciousness

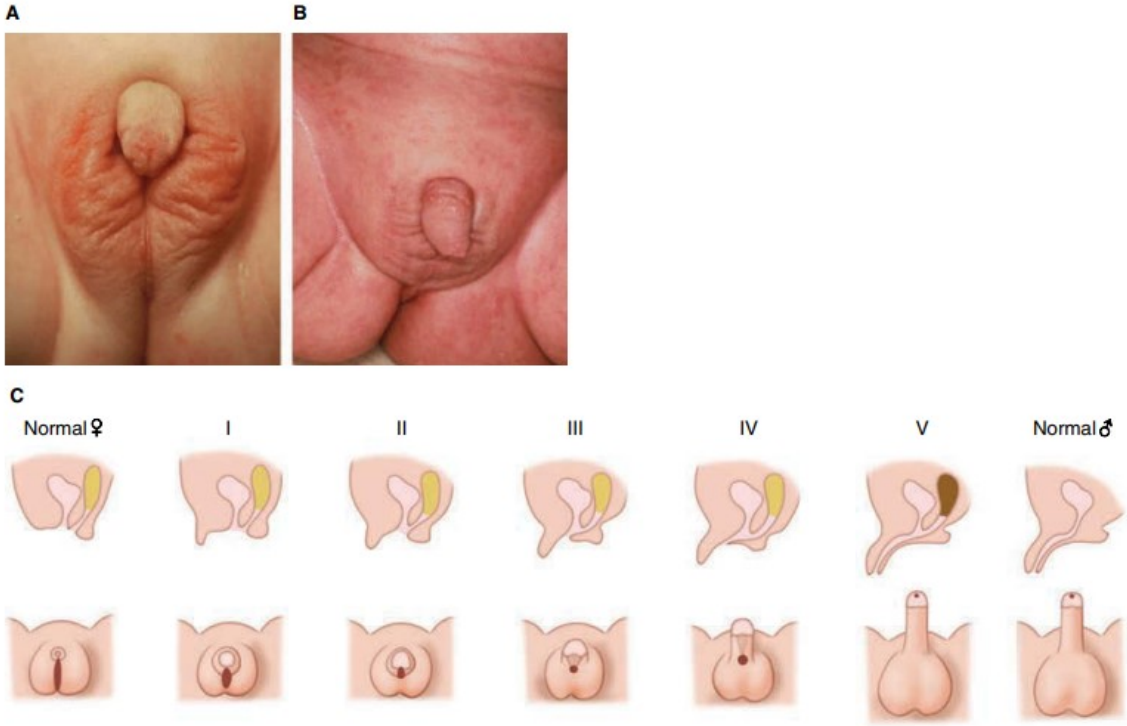
Blood tests: Red blood cell count or platelet count.
Urine tests: typically show large amounts of protein in urine.
Creatinine tests: Abnormally high levels of creatinine could be a sign of kidney failure.

Congenital Adrenal Hyperplasia

- **Autosomal recessive disorders that disrupt adrenal steroidogenesis/ insufficient cortisol production**
- The most common enzyme deficiency in CAH is in **CYP21A2, a 21-hydroxylase, resulting in the failure to metabolize 17 a-hydroxyprogesterone to 11-deoxycortisol**
- **NOT ENOUGH CORTISOL, SECRETION OF ACTH, the pituitary hormone that regulates production of cortisol, increases.**
- Prolonged periods of elevated ACTH levels cause **adrenal hyperplasia and an increased production of the androgenic hormones , dehydroepiandrosterone (DHEA) and androstenedione.**

FEMALES: excessive secretion of adrenal androgens, and their peripheral conversion to testosterone results in **androgen excess, manifested by acne, hirsutism, and virilization.**

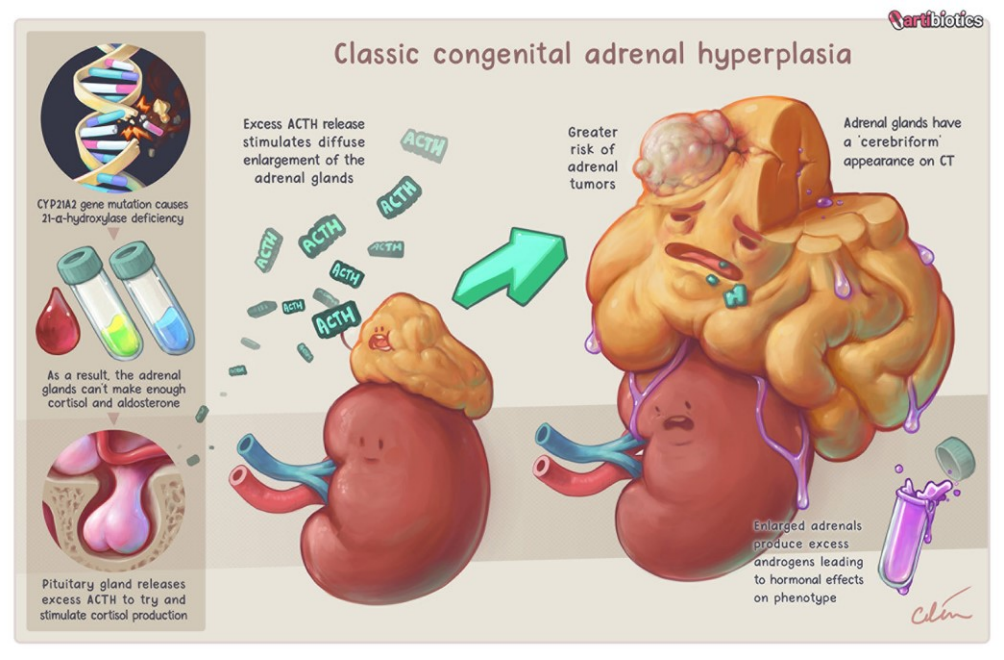
Congenital Adrenal Hyperplasia



Female infants with classic CAH might be born with an enlarged clitoris or external genitalia/ have the appearance of phenotypic males with micropenis and bilateral cryptorchidism.

In late onset CAH, clinical symptoms may vary considerably from early development of pubic hair, early fusion of epiphyseal growth plates causing premature cessation of growth, or male baldness patterns in females.

Congenital Adrenal Hyperplasia



The goal of CAH treatment is to reduce excessive androgens and replace deficient hormones.

- Corticosteroids (e.g., hydrocortisone, prednisone, dexamethasone) to replace deficient cortisol.
- Fludrocortisone to replace missing aldosterone and help the body retain salt and keep blood pressure normal.
- Salt supplements, which help increase intravascular volume (fluid in vessels) and blood pressure.
- Oral contraceptive pills for regulating menses.
- Anti-androgen drugs such as spironolactone to treat excess androgen levels.

Cushing Syndrome

Elevated cortisol levels- HYPERCORTISOLISM

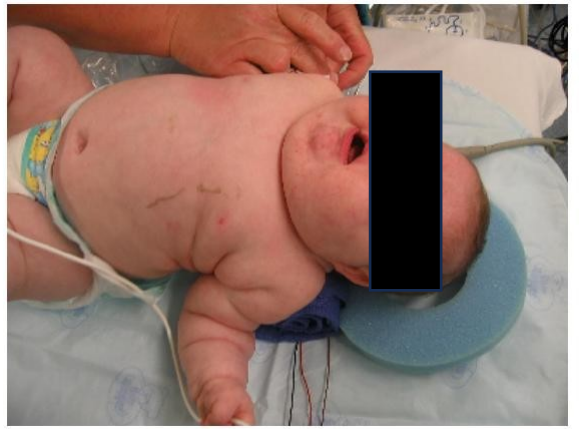
There are **two main etiologies** of Cushing syndrome:

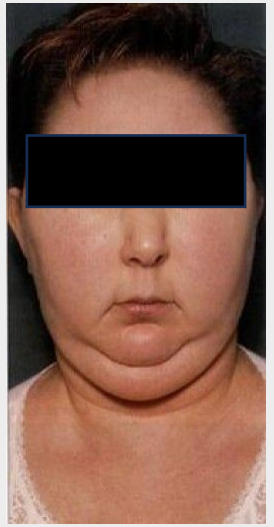
endogenous hypercortisolism:

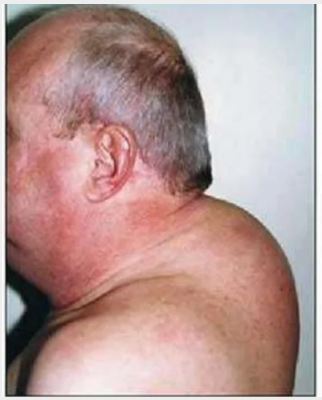
- increased ACTH release- ectopic ACTH release
- hyperplasia of CRH- or ACTH-secreting cells
- primary cortisol-releasing adrenal tumors- Adrenal hyperplasia, adenoma, and carcinoma

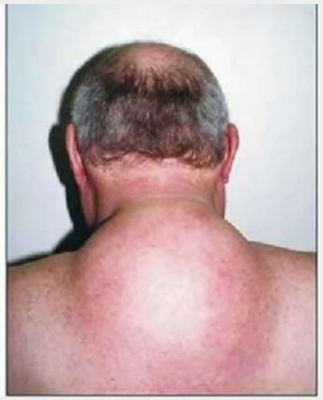
exogenous hypercortisolism (iatrogenic):

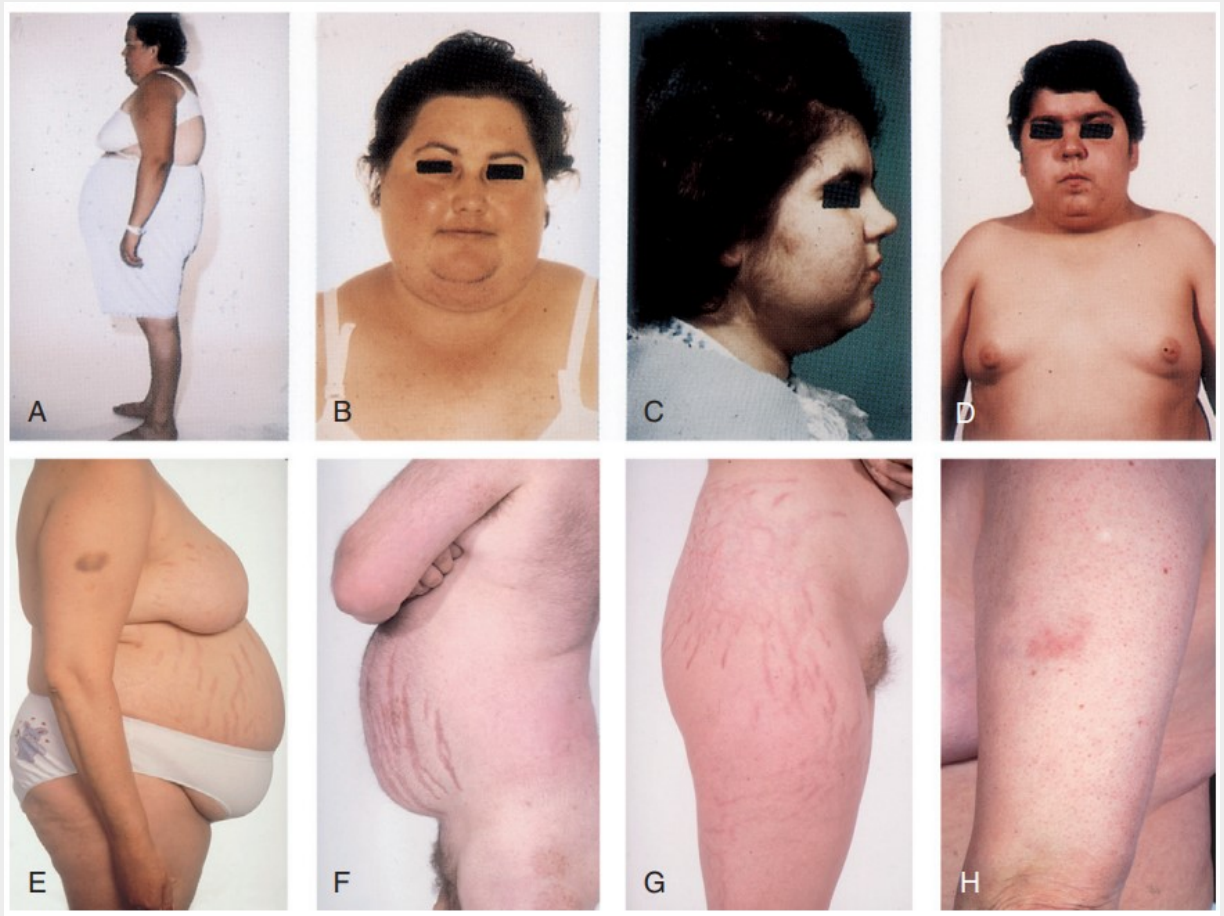
- prolonged use of glucocorticoids











The classic features of Cushing's syndrome: centripetal obesity, moon face, hirsutism, and plethora

Cushing Syndrome

Cushing syndrome is associated with:
hyperglycemia,
protein catabolism,
immunosuppression,
hypertension,
weight gain,
neurocognitive changes,
mood disorders

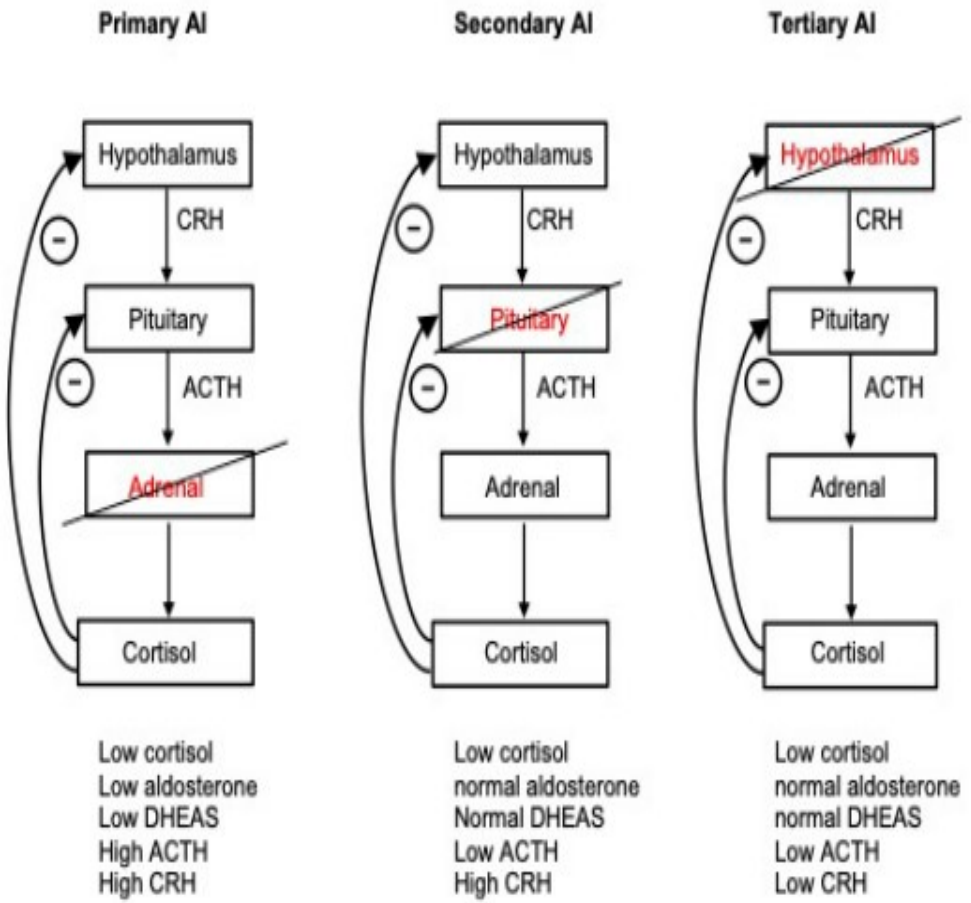
Savas M, Mehta S, Agrawal N, van Rossum EFC, Feelders RA. Approach to the Patient: Diagnosis of Cushing Syndrome. J Clin Endocrinol Metab. 2022 Nov 23;107(11):3162-3174. doi: 10.1210/clinem/dgac492. PMID: 36036941; PMCID: PMC9681610.

What causes adrenal insufficiency?

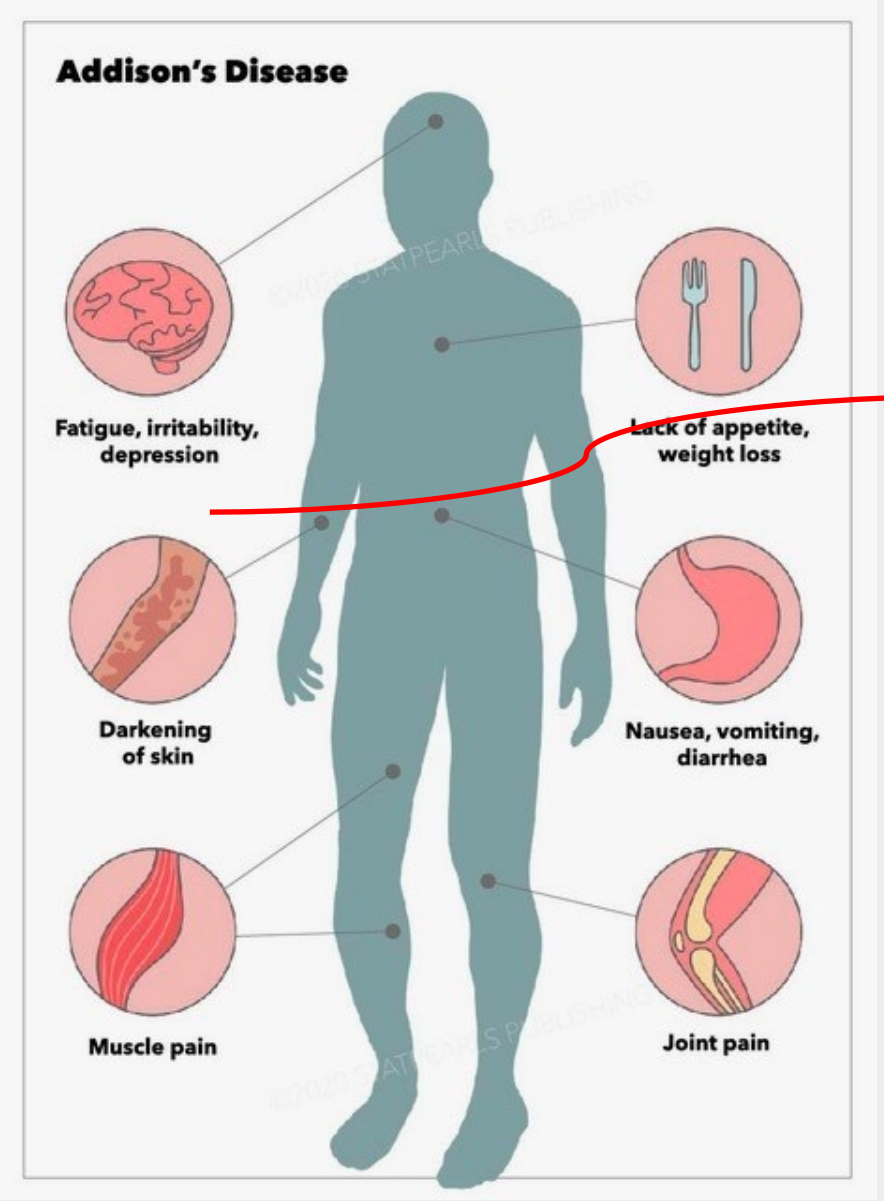
Primary adrenal insufficiency (PAI)- Addison's Disease
Adrenal glands are damaged.
Not enough cortisol/ aldosterone
Rare, at any age, women more frequently than men

Secondary adrenal insufficiency (SAI)
Pituitary gland: not enough ACTH
Not enough cortisol, normal aldosterone
More common, prevalence: 150–280 per million , more common in women than men.

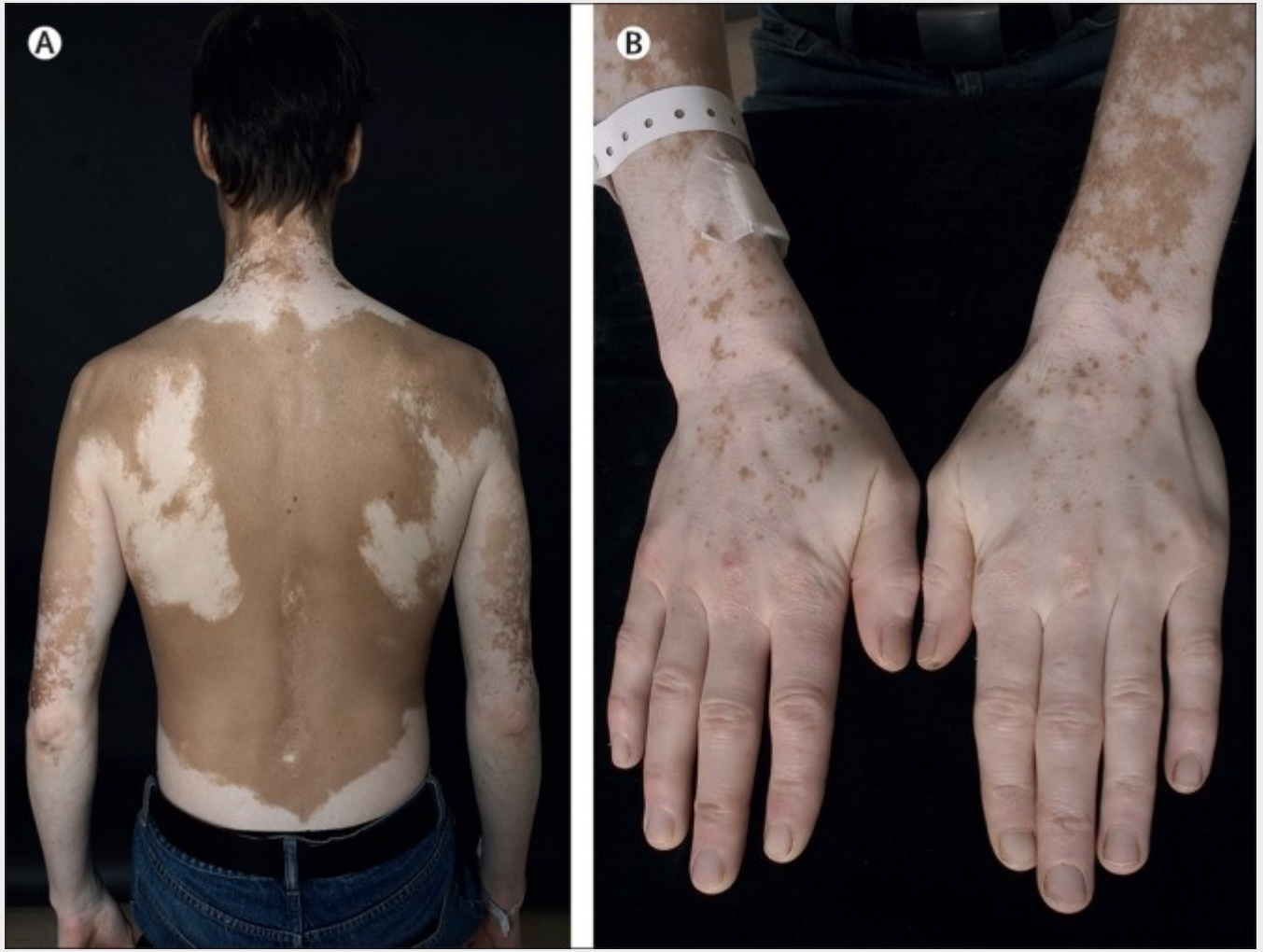
Tertiary adrenal insufficiency (TAI)
Defect at hypothalamic level, mostly caused by **exogenous steroid treatment.** Any disease involving the hypothalamus that interferes with **corticotropin-releasing hormone (CRH) secretion will result in TAI**



Kumar R, Wassif WS Adrenal insufficiency
Journal of Clinical Pathology 2022;**75:**435-442



Munir S, Quintanilla Rodriguez BS, Waseem M. Addison Disease. [Updated 2023 May 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441994/



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LEARNING OBJECTIVES

- What are steroid hormones? Describe their biosynthesis
- How are steroid hormones classified based on the number of their carbons?
- Explain cholesterol
- Describe the model of steroid hormone synthesis
- Explain the formation and secretion of 5α-reductase, aromatase and 18-aldosterone hydroxylase/synthase, 21-hydroxylase and 11-hydroxylase
- Describe testosterone biosynthesis pathway
- Explain StAR protein
- Describe estrogens, estradiol, Vitamin D_3
- Explain the transport of steroid hormones. How do steroid hormones circulate in the blood?
- Define the categories of nuclear receptors. Which receptors belong to the extended family of receptors of steroid hormones?
- Explain steroid receptor domains and activation/inactivation
- Explain the non-genomic effects of steroid hormones
- Explain the action of glucocorticoids in suppressing immune and inflammatory responses mediated by cytokines
- Explain Conn syndrome, Cushing syndrome
- Describe Congenital Adrenal Hyperplasia (CAH) and Apparent Mineralocorticoid Excess Syndrome

SAMPLE QUESTIONS

QUESTION 1

Steroid receptors under basal conditions

A. **exist as cytoplasmic, multimeric complexes that include hormone response elements**

B. **exist in the nucleus**

C. **exist as cytoplasmic, multimeric complexes that include the heat shock proteins (HSPs) and immunophilins of the FK506 family**

D. **None of the above**

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QUESTION 2

Type 1 nuclear receptors

A. In the absence of ligand, the receptors are held in the cytoplasm in an inactive state by heat shock proteins
B. Ligand-binding inhibits the conformational change that causes the release of the heat shock proteins, nuclear translocation, and dimerization and association with chromatin at specific sequences of DNA termed hormone response elements (HREs)
C. In the presence of ligand, the receptors are held in the cytoplasm in an inactive state by heat shock proteins
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QUESTION 3

Three siblings - two female and one male were presented with hypertension, hypokalemia, low renin, and low aldosterone levels. There is also the finding of abnormally high ratios of 24-h urine-free cortisol to cortisone in our three patients- what is our diagnosis?

A. pheochromocytoma

B. heart failure

C. Cushing syndrome

D. apparent mineralocorticoid excess syndrome

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QUESTION 4

Patient was diagnosed with ambiguous genitalia at birth but was subsequently lost to follow-up. Antenatal period was uneventful and she remained relatively well thereafter, having no reason to seek medical attention. In primary school, she was the tallest in class, but shortest when in secondary school. Academic performance was average. She is the 6th of 7 siblings from a consanguineous marriage and had a brother who died suddenly at 2 months of age. She exhibits external male body habitus and has a high pitched voice. Pubic hair was Tanner 4 with marked clitoromegaly measuring 3.5 cm, prominent labia majora and no palpable testes. She had never experienced vaginal bleeding. Blood investigations revealed FSH-8.2 IU/L (1.79-22.5), LH-6.4 IU/L (2.12-12.86), testosterone-7.6 nmol/L (0.3-2.1), progesterone-32.1 nmol/L (<5-60), estradiol-448 pmol/L (84-1068), TSH-1.82 mIU/ml (0.4-4.0) and cortisol-138.2 nmol/L (193-772). Serum 17-OH progesterone level was >60.6 nmol/L (0.9-7.58) and cytogenetic analysis showed 46,XX apparently normal female karyotype. **The diagnosis is**

A. Congenital Adrenal Hyperplasia

B. Cushing Syndrome

C. Hyperaldosteronism

D. None of the above

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B. Cushing Syndrome

C. Hyperaldosteronism

D. None of the above

QUESTION 5

A 20-year-old female patient was admitted in October with a 3-month history of persistent vomiting between 5 and 15 times a day and weight loss. She was dehydrated and unable to tolerate oral intake due to nausea and vomiting. Her bowel motions were normal; she had no problems with micturition or symptoms of infection, however had noticed significant weight loss in the preceding few months.

She had known hypothyroidism and had previously been referred directly to the gastroenterologists for persistent vomiting. She underwent an oesophagogastroduodenoscopy (OGD) which showed gastritis and therefore, she was started on proton pump inhibitor therapy. A blood test showed negative tissue transglutaminase antibodies, positive gastric parietal cell antibodies and she was scheduled for a CT enterograph.

The patient presented again 4 months later with persistent vomiting with some fresh blood at the end due to a Mallory-Weiss tear. She mentioned ongoing weight loss from 50 kg in August to 41 kg currently and ongoing lethargy. She described some right-sided abdominal pain and a pregnancy test was negative. She denied thyroxine abuse or forced vomiting. The patient was unsure about any relevant family history. She was a social smoker and denied any alcohol intake.

On examination she was very thin, hypotensive and tachycardic. She was clinically dehydrated and was noted to have some mild skin pigmentation. WHAT IS THE DIAGNOSIS?

QUESTION 5

A 20-year-old female patient was admitted in October with a 3-month history of persistent vomiting between 5 and 15 times a day and weight loss. She was dehydrated and unable to tolerate oral intake due to nausea and vomiting. Her bowel motions were normal; she had no problems with micturition or symptoms of infection, however had noticed significant weight loss in the preceding few months.

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On examination she was very thin, hypotensive and tachycardic. She was clinically dehydrated and was noted to have some mild skin pigmentation. WHAT IS THE DIAGNOSIS? ADDISON'S DISEASE

SUGGESTED BIBLIOGRAPHY

Williams "Textbook of Endocrinology"

Chapter 15

Devlin "Textbook of Biochemistry with clinical correlations"

Chapters 22.7-22.8

Greenspans "Basic and Clinical Endocrinology", Chapter 14

e-class slides

THANK YOU!