بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Endocrine Biochemistry | Final 3

# Synthesis & Degradation of Hormones


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# Synthesis and Degradation of hormones

# Chemistry of Hormones

- Hormones that bind to intracellular receptors are lipophilic and are synthesized from cholesterol or some **amino acids (Thyroid hormone synthesised from tyrosine)**, and are generally not stored in **large quantities**; rather, their synthesis is **regulated by the level of enzyme expression**.

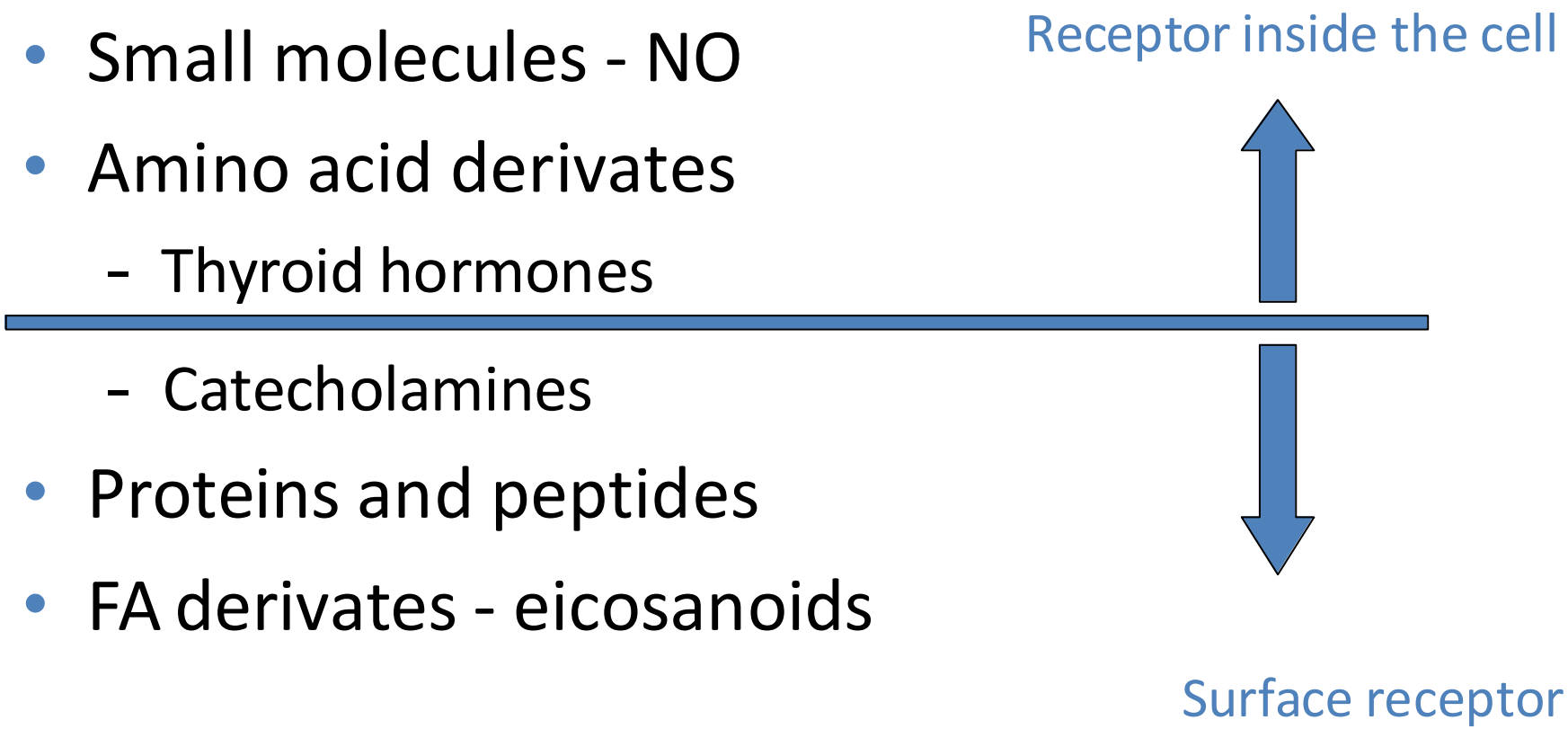
- Whereas hormones that bind to **cell-surface receptors are hydrophilic**, and synthesized as **larger precursors** and are released **rapidly in response to stimuli (They are either proteins, polypeptides, or some amino acid derivatives, like caticolamines).**

- This classification is important and has direct implications in pharmacology to determine route of administration and frequency.

- **Ex:** Peptide hormones **are injected** and act through **second messenger** pathways, while steroid hormones **are given orally and act in a slow manner (changing the rate of Gene expression).**

# Chemistry of Hormones

- **Steroids**
- Small molecules - NO
- Amino acid derivates
  - Thyroid hormones
  - Catecholamines
- Proteins and peptides
- FA derivates - eicosanoids

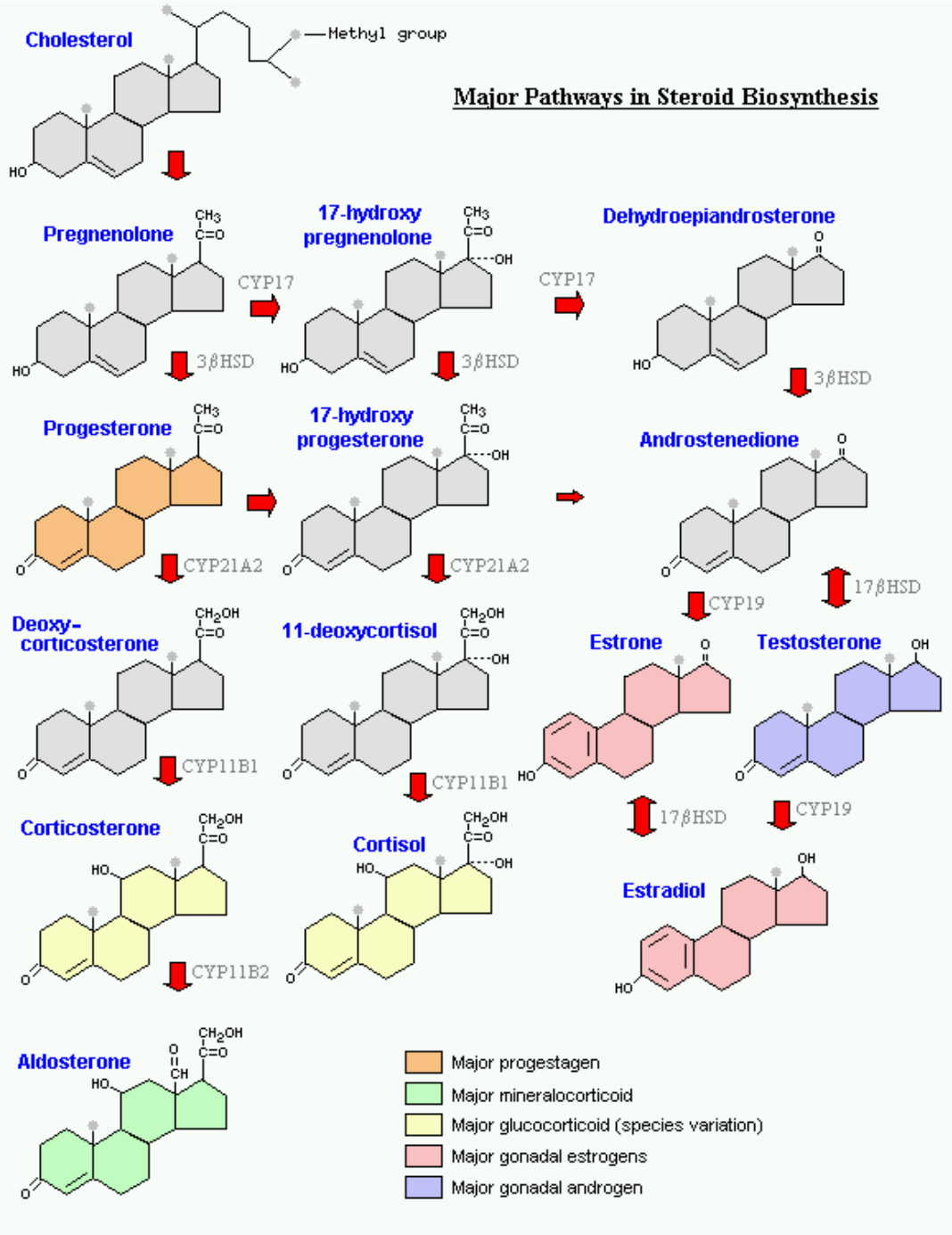


# Chemistry of Hormones

- Receptor location **determines the singling mechanism.**
- **Intracellular** receptors act as **transcription factors and directly bind to DNA to regulate gene expression.**
- **Cell-surface receptors** trigger **second messengers** through signaling pathways.
- **Lipophilic hormones** can cross the **plasma membrane**.
- **Hydrophilic hormones** bind to **cell-surface receptors** and activate **cell-signaling pathways.**
- **Eicosanoids** are **lipophilic** but act through **cell-surface receptors**.
- **Thyroid** hormones are **amino acids derivatives (usually hydrophilic)**, but they are **lipophilic and act on intracellular receptor**.

# Steroid hormone synthesis

- C21:
  - Progesterone: directly from pregnenolone
  - Cortisol & Aldosterone: from progesterone

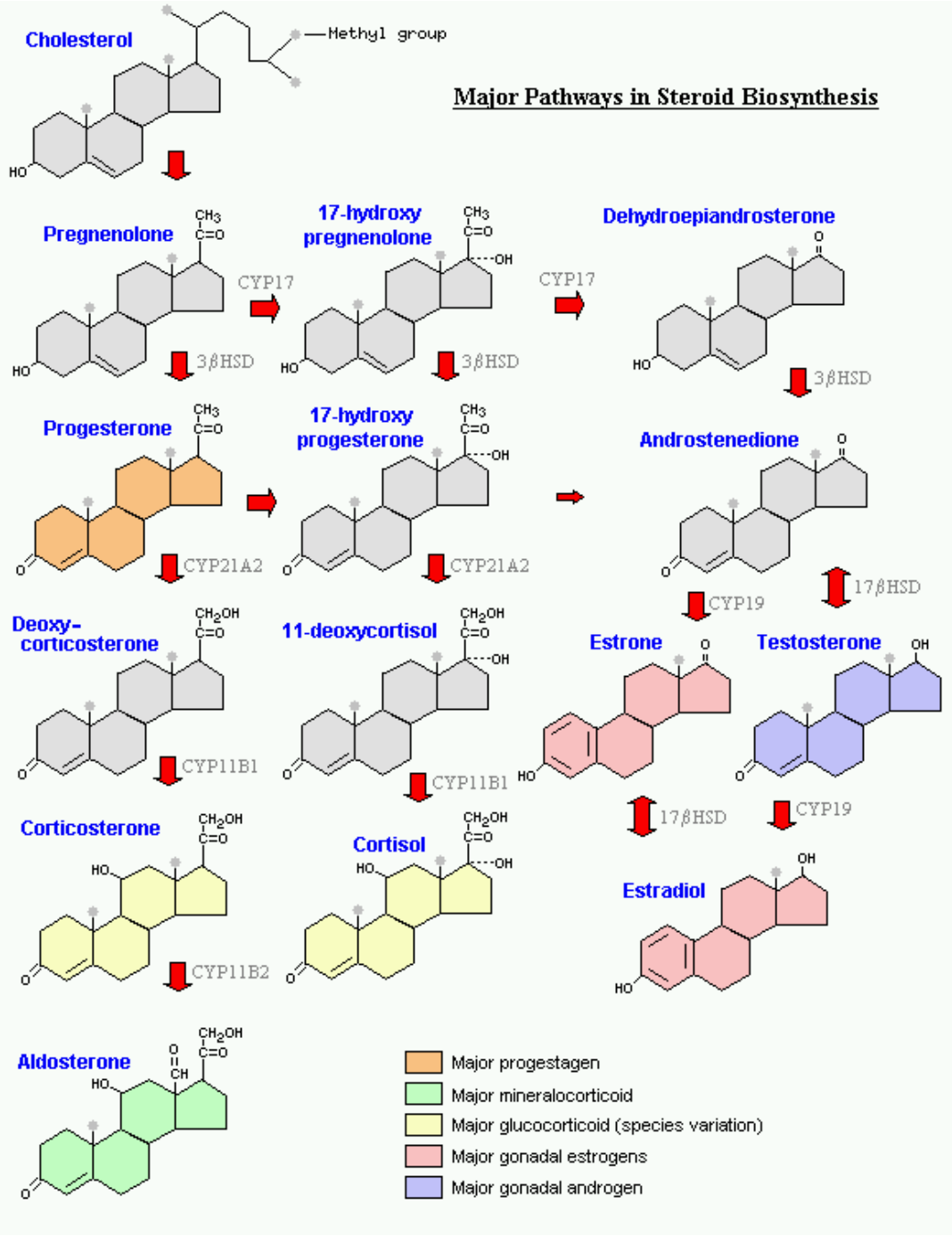


# Steroid hormone synthesis (C21 Steroids)

- **All steroid hormones are derived from cholesterol,** which is mostly derived from the plasma, but a small portion is synthesized in situ.
- This cholesterol is transported to the ***mitochondria*** of **steroidogenic cells** by **Steroidogenic Acute Regulatory Protein (StAR protein).**
- Inside the mitochondria, **cytochrome P450 side-chain cleavage enzyme (CYP11A1)**, also known as **Desmolase**, cleaves the **6 Carbon side chain** by **cleaving the bond between C20 and C22**, and **pregnenolone** is produced.
- This step is the **rate-limiting** step.
- The **first committed intermediate/committed** step of the pathway.
- ***This is shared in all steroidogenesis.***
- **Pregnenolone** is **transported to the SER**, where **3-β-hydroxysteroid dehydrogenase (3-β-HSD)** converts it to **progesterone**, which is the **precursor for both cortisol and aldosterone.**
- Where **cortisol requires 17-hydroxylation (CYP17A1), then 21-hydroxylation (CYP21A2)**, and **11-β-hydroxylation (CYP11B1)**, while **aldosterone synthesis** involves **21-hydroxylation (CYP21A2)**, and **11-β-hydroxylation (CYP11B2).**
- **Deletion** in these enzymes **causes congenital adrenal hyperplasia (CAH), with 21-hydroxylase** being **the most common**, leading to **decreased cortisol and aldosterone, and increased androgens.**

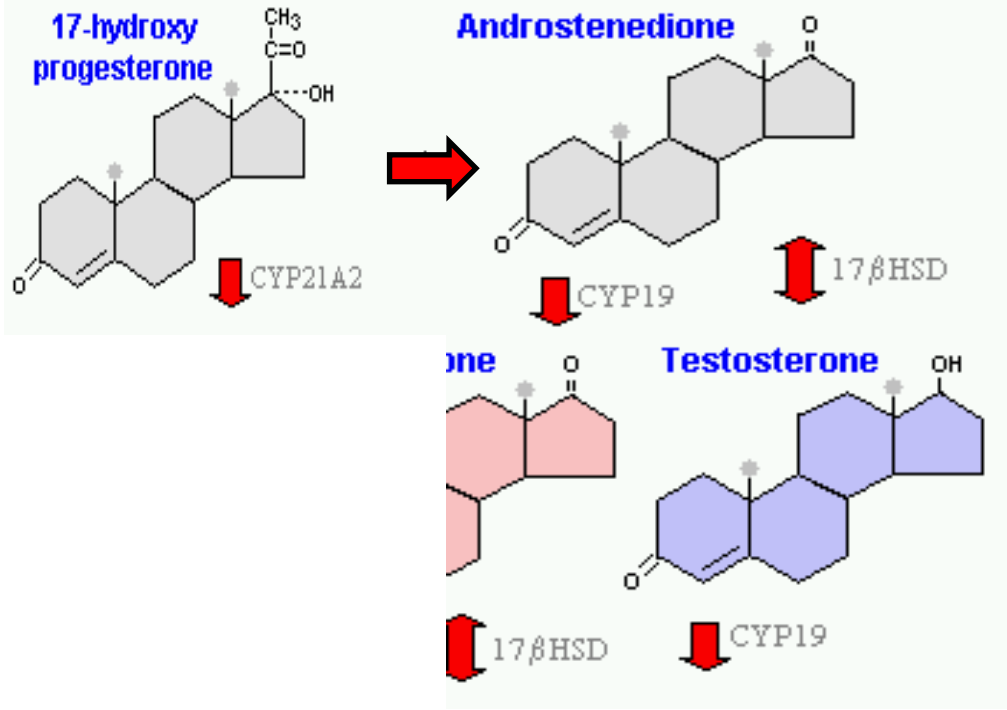
# Steroid hormone synthesis

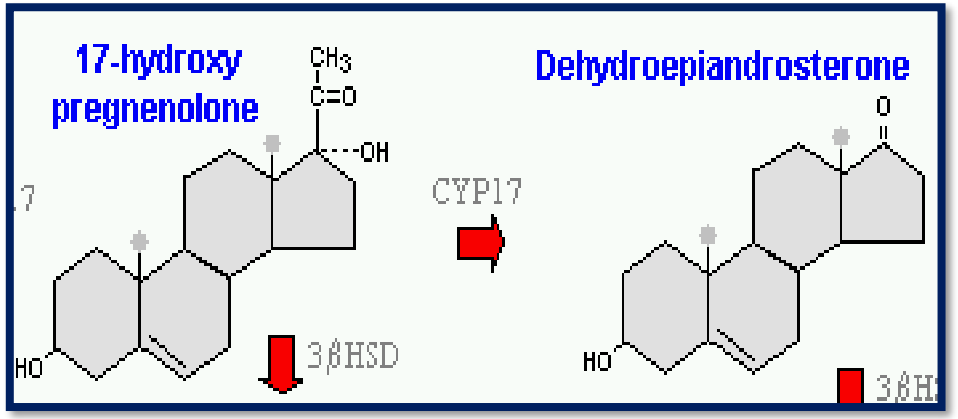
- C19
  - Testosterone
  - from progesterone or pregnenolone
  - 2c shortage
- C18 (estrogen):
  - Aromatase
  - Cleaves C18
  - Reduction



# Steroid hormone synthesis (C19 Steroids)

- **C19 steroids (androgens)** are synthesized from **21C precursors** (but only one) by **removal of the 2C side chain (C20 and C21)** through the **17,20-lyase activity of the CYP17A1 enzyme**.
- This converts **17-hydroxyprogesterone** to **androstenedione**, which is **converted to testosterone by 17-β-hydroxysteroid dehydrogenase** in the gonads.
- However, the main androgen in the adrenal cortex is **dehydroepiandrosterone (DHEA)**, which is produced from **17-hydroxypregnenolone** and the **consequent 17,20-lyase**.
- This can be converted to **androstenedione or testosterone in the peripheral tissue**.
- ***Summary***:
  - **17-hydroxyprogesterone → Androstenedione → Testosterone**
  - **OR**
  - **17-hydroxypregnenolone → DHEA → Testosterone**



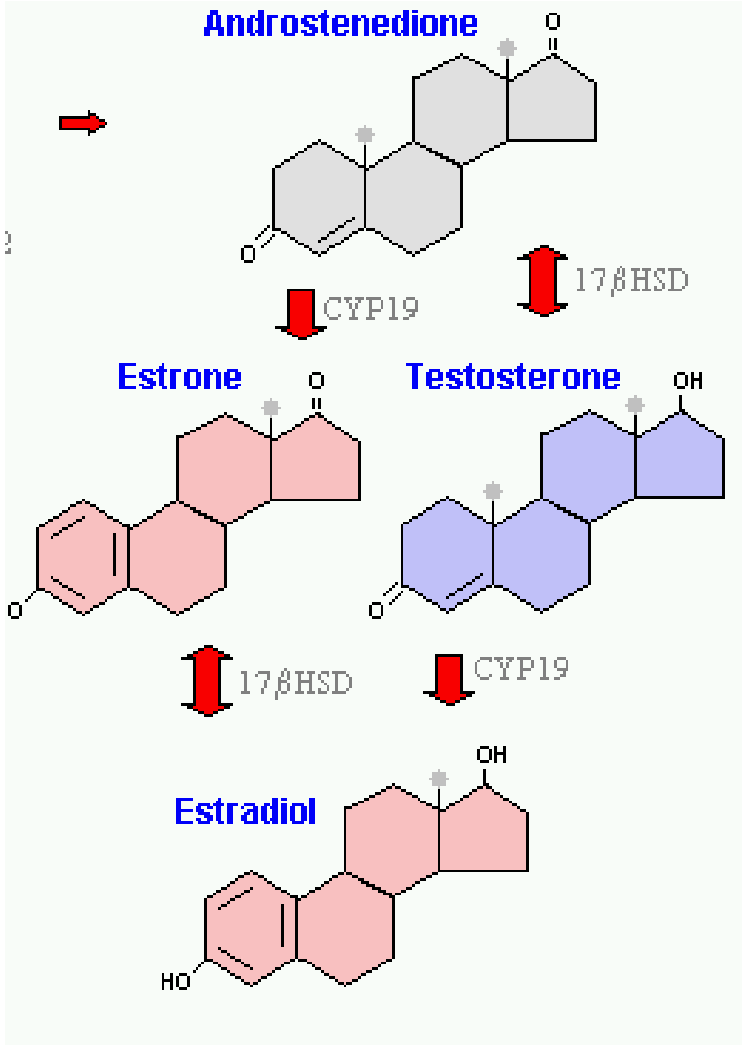



# Steroid hormone synthesis (C18 Steroids)

- **C18 steroids (estrogens)** are synthesized from the **aromatization of C19 androgens** by **aromatase enzyme (CYP19A1)**, which **removes the C19 methyl group** and **aromatizes the A-ring (multifunctional enzyme)**, converting **androstenedione to estrone**, which is **converted to estradiol, or testosterone to estradiol directly.**

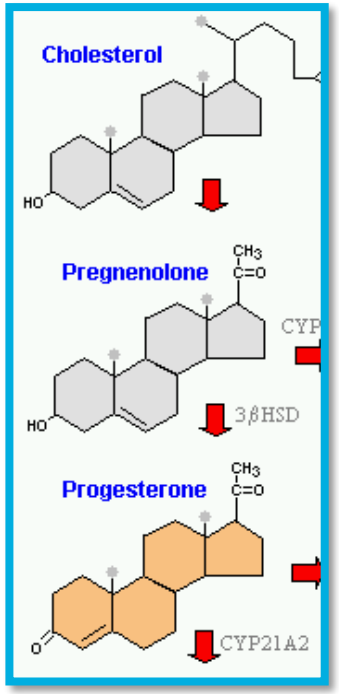
- Aromatase is expressed in the ovaries, adipose tissue, brain, and placenta.

- Clinical:
- Aromatase inhibitors (Anastrozole, Letrozole) are used to treat estrogen receptor-positive breast cancer.
- 5-α-reductase inhibitors (Finasteride) inhibit the conversion of testosterone to dihydrotestosterone, used for BPH and male pattern baldness.



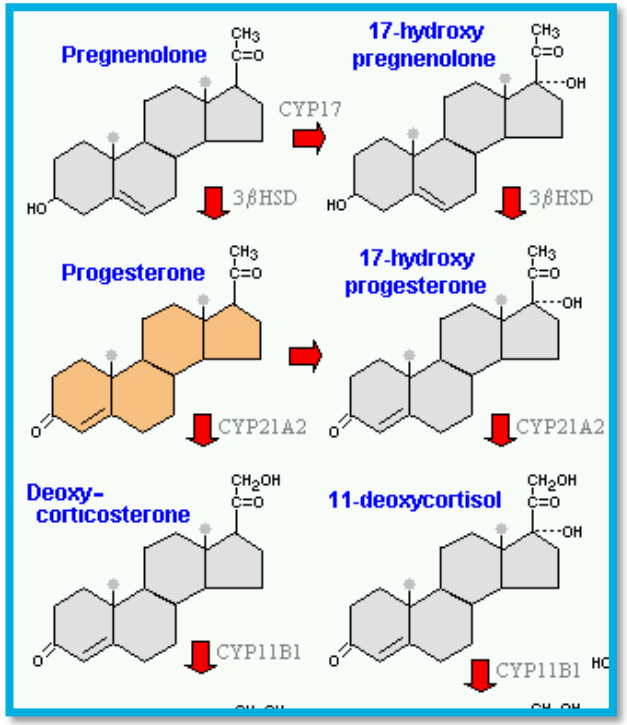
# Cortisol Synthesises

The whole process starts with the removal of 6C from the side chain, by cleaving the bond between carbon-20 and carbon-22, by desmolase (**CYP11A1** → refers to the gene name), the 6C are removed as isocaproic aldehyde, converting cholesterol into pregnenolone (a ketone).




**Cortisol synthesis:**

1. **Pregnenolone** can be **hydroxylated at carbon-17 by CYP17A1 or 17-α-hydroxylase, yielding 17-hydroxypregnenolone**, or it can be oxidized at carbon-3 by **3β-HSD**, and it also catalyzes the isomerization of the double bond between carbons Δ5,6 to Δ4,5.




This converts pregnenolone to progesterone to 17-hydroxyprogestrone, or to 17-hydroxypregnenolone then to to 17-hydroxyprogesterone.

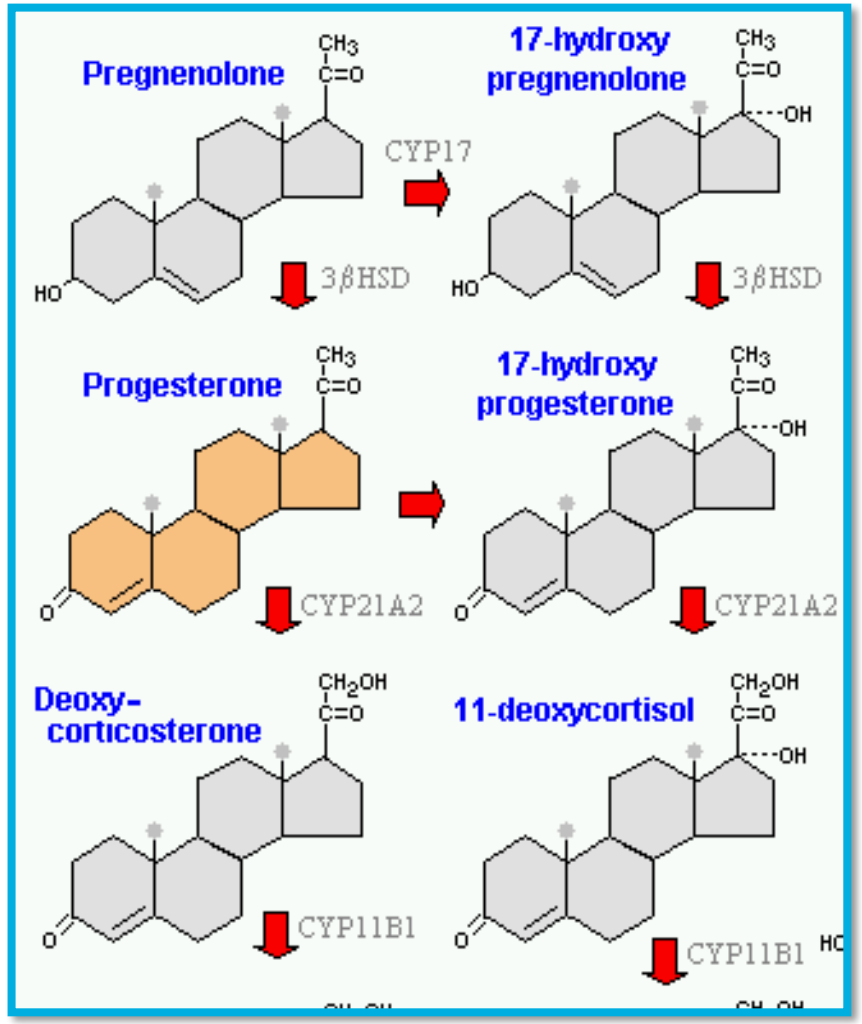
**Pregnenolone** → 17-hydroxypregnenolone → 17-hydroxyprogesterone.
OR :
**Pregnenolone** → Progesterone → 17-hydroxyprogesterone.

# Cortisol Synthesises con.

2. The 17-hydroxyprogesterone is hydroxylated by **21-hydroxylase (CYP21A2)** to produce **11-deoxycortisol**.

3. The 11-deoxycortisol is hydroxylated at carbon 11 by a mitochondrial enzyme called: **11-β-hydroxylase (CYP11B1)**, which converts it to cortisol.

So 11-deoxycortisol must move to the mitochondria, usually by simple diffusion.



# Aldosterone Synthesis

**Aldosterone synthesis:**

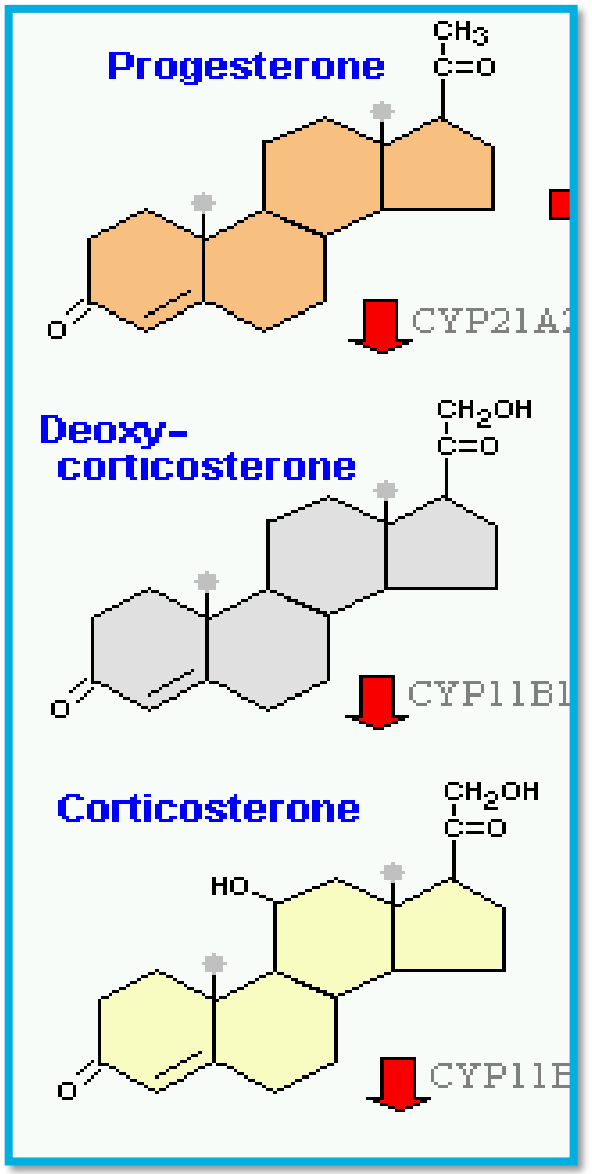
1. The same steps reach progesterone.

2. Progesterone is **hydroxylated at carbon 21 by 21-hydroxylase** to get **11-deoxycorticosterone (11-DOC).**

3. **11-DOC moves to the mitochondria**, and it is **hydroxylated by 11β-hydroxylase** to get **corticosterone.**

- **Corticosterone** possesses a glucocorticoid activity, but **it is not of significance in humans**, but some organisms such as mice and rats have corticosterone as the main glucocorticoid, but it is a glucocorticoid with a weak mineralocorticoid activity.

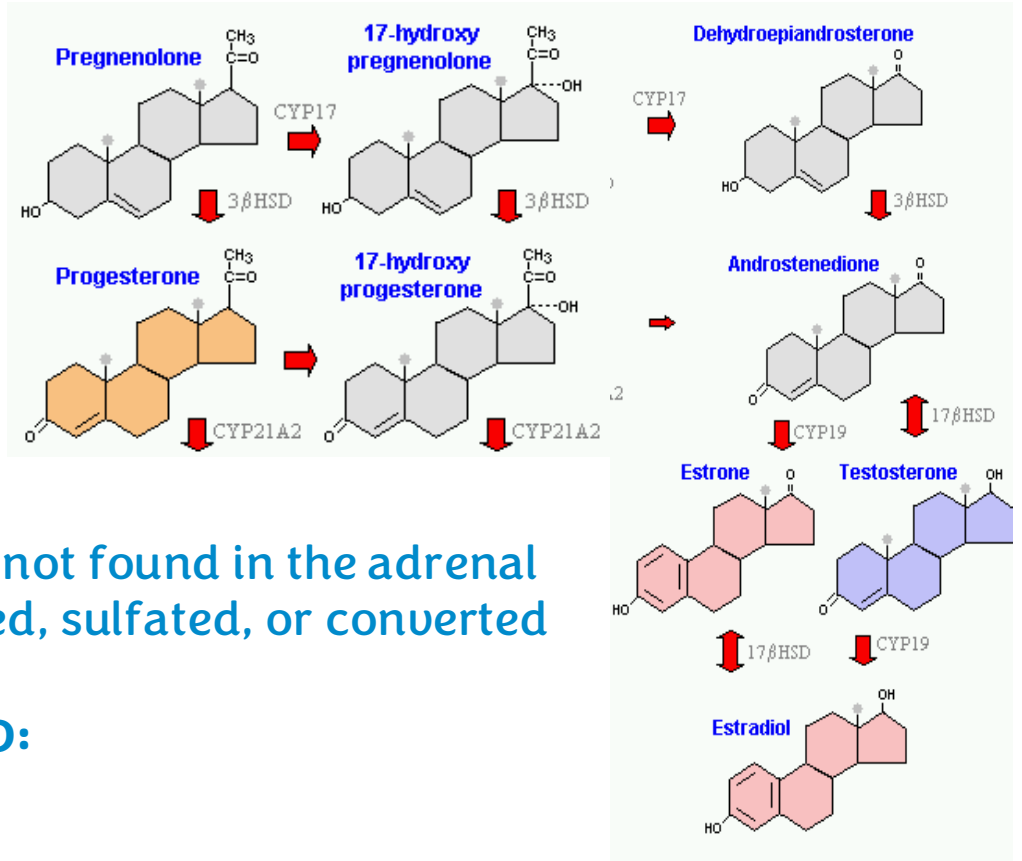
4. **In the mitochondria**, the enzyme **18-hydroxylase (Aldosterone synthase – CYP11B2)** has **multiple functions. At first it hydroxylases carbon 18, and this will also be oxidized to an aldehyde (dual-function) – which produces aldosterone.**



# Androgens Synthesis

1. In order to make **androgens**, **progestogens are needed**, either **17-hydroxyprogesterone or 17-hydroxypregnenolone**.

2. The same enzyme catalyzes the hydrolysis of the bond between carbon 17 and carbon 20, that is the **17,20-lyase** enzyme, which is **the same enzyme as 17α-hydroxylase (CYP17A1)** – multifunctional enzyme. This converts the **17-hydroxypregnenolone** to **DHEA**, and the **17-hydroxyprogesterone** to **androstenedione**.




The latter is done by **17β-hydroxysteroid dehydrogenase**, which is not found in the adrenal cortex, so the only fate in the cortex for DHEA is either to be secreted, sulfated, or converted to androstenedione.

3. **In peripheral tissue, such as the testes, by the action of 17β-HSD:**

1. **DHEA → Androstenedione (3β-HSD) → Testosterone**
2. **Androstenedione → Testosterone**
3. **DHEA → Androstenediol (17β-HSD) → Testosterone (3β-HSD)**

The goal is to get to **testosterone**, which is **the strongest of the above 3,** but The **most potent androgen is dihydrotestosterone**, which is the **product of the enzyme 5-α-reductase** (uses NADPH to reduce testosterone at the 4,5 double bond), and this increases the potency by 20–100 times.

# Androgens Synthesis

**In females:**

- To synthesize **estrogens**, **androstenedione and testosterone are needed**, which means that **to synthesize estrogens, androgens are needed.**

1. The first step is catalyzed by **aromatase (CYP19A1)**, which **aromatizes the A-ring into an aromatic ring, with reduction of the ketone group at carbon 3:**

- **Testosterone → Estradiol → [aromatic ring / alcohol group].**

- **Androstenedione → Estrone → [less active].**

**The aromatic A-ring is a characteristic of estrogens.**

2. Both of these estrogens can be metabolized in the liver and placenta to **estriol**.

Estrone requires 2 steps, while estradiol requires 1 step.

**First step:** reduction at carbon 17 (17β-HSD).
**Second step:** hydroxylation of the D-ring by 16-hydroxylase (because it happens at carbon number 16).
**The second step is common between the 2.**
While cholesterol is the parent steroid, but progestogens could also be considered parent.

# Steroid hormone breakdown

- Steran core cannot be cleaved
- In the liver: hydroxylation and conjugation with glucuronides or sulphates
- Urinary excretion:
  - ✓ Of metabolites
  - ✓ Of unchanged hormones

# Steroid hormone breakdown Notes

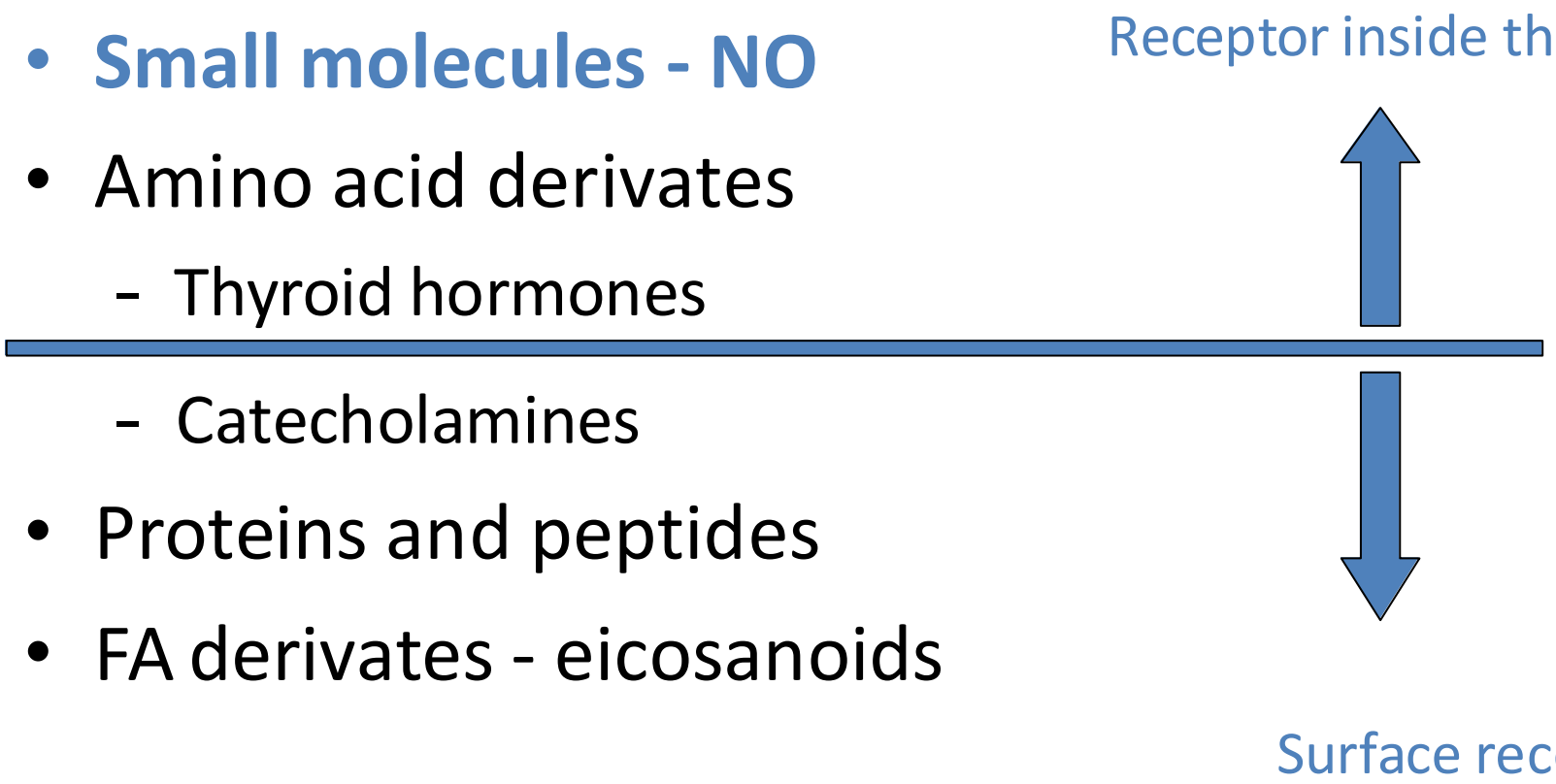
Steroid hormones undergo **biotransformation in the liver**, because the **steroid nucleus** (sterane, composed of the 17C arranged in the 4 fused rings) **can't be completely degraded into $CO_2$ and water**. This happens **in the classical 2 phases**:

1. **Phase I** involves **hydroxylation** by **CYP450 enzymes** to **increase solubility**.

2. **Phase II** involves **conjugation** with **glucuronic acid or sulfate, producing even more soluble metabolites** that are **excreted either in urine or bile**. The latter is important for the **enterohepatic circulation** of steroids, where conjugates can be removed by intestinal bacteria and the steroids are reabsorbed.

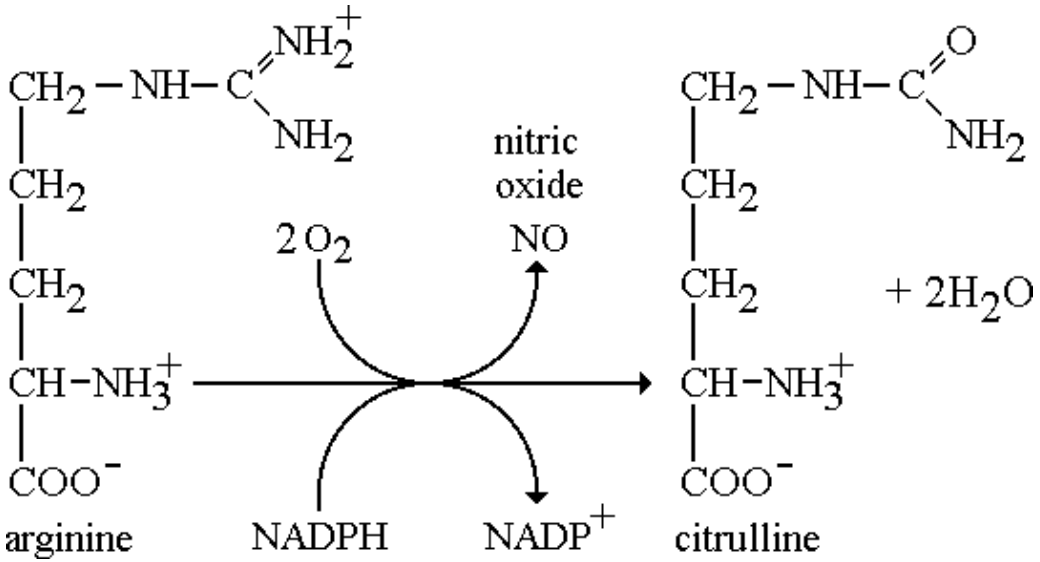
# Chemistry of Hormones

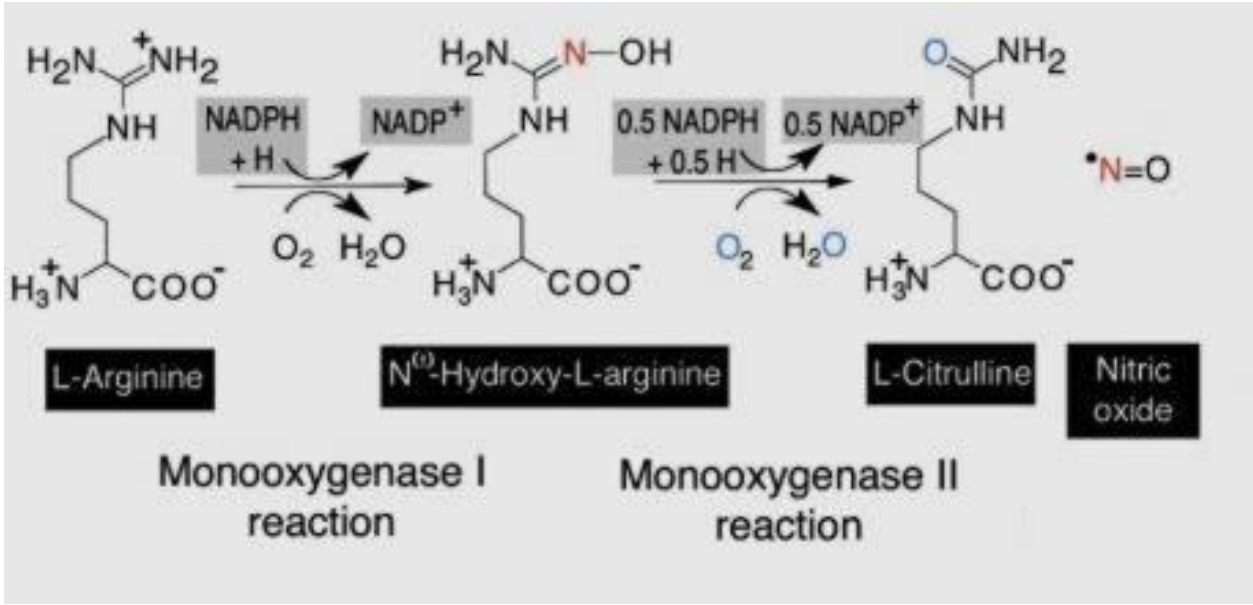
- Steroids
- **Small molecules - NO**
- Amino acid derivates
  - Thyroid hormones
  - Catecholamines
- Proteins and peptides
- FA derivates - eicosanoids

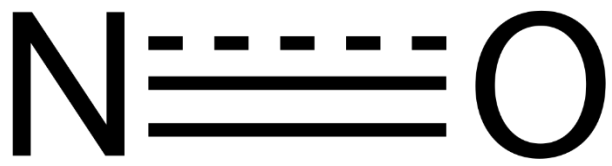


# Nitric oxide (NO)

- NO: synthetized by NO-synthase



# Nitric oxide (NO)

- NO is a gas molecule with a very short **T½ (seconds)**.

- It is synthesized by **NO synthase (NOS)**, which catalyzes the oxidation of L-arginine to L-citrulline using NADPH as a cofactor.

- There are **3 NOS isoforms:**

1) The constitutive forms, which are **neuronal NOS (nNOS)**
2) **The endothelial NOS (eNOS)**,
3) The inducible NOS (**iNOS**).

- NO doesn't bind to a classical receptor; rather, it diffuses across the plasma membrane and activates **guanylyl cyclase** by binding to its heme group, and increases cGMP production.

- Its primary effects are:
- **Vasodilation** (by vascular smooth muscle relaxation, because cGMP lowers intracellular $Ca^{2+}$ levels).
  **Neurotransmission** (nNOS).
- **Immune defense** (iNOS).
- **Synaptic plasticity** through a process called **Long-Term Potentiation**, which is the persistent strengthening of synapses by increasing the connection between them. It is also involved in GIT motility and penile erection.

# Nitric oxide synthase isozymes

- NO-synthase (NOS)
  - ✓ In neurons (NOS-I): neurotransmission
  - ✓ In macrophages (NOS-II): kills bacteria
  - ✓ Endothelial (NOS-III): smooth muscle → **cGMP** → vasodilation

- Clinical correlation:
  - ✓ Nitrates in the treatment of angina
  - ✓ Refractory hypotension during septic shock

# Nitric oxide synthase isozymes

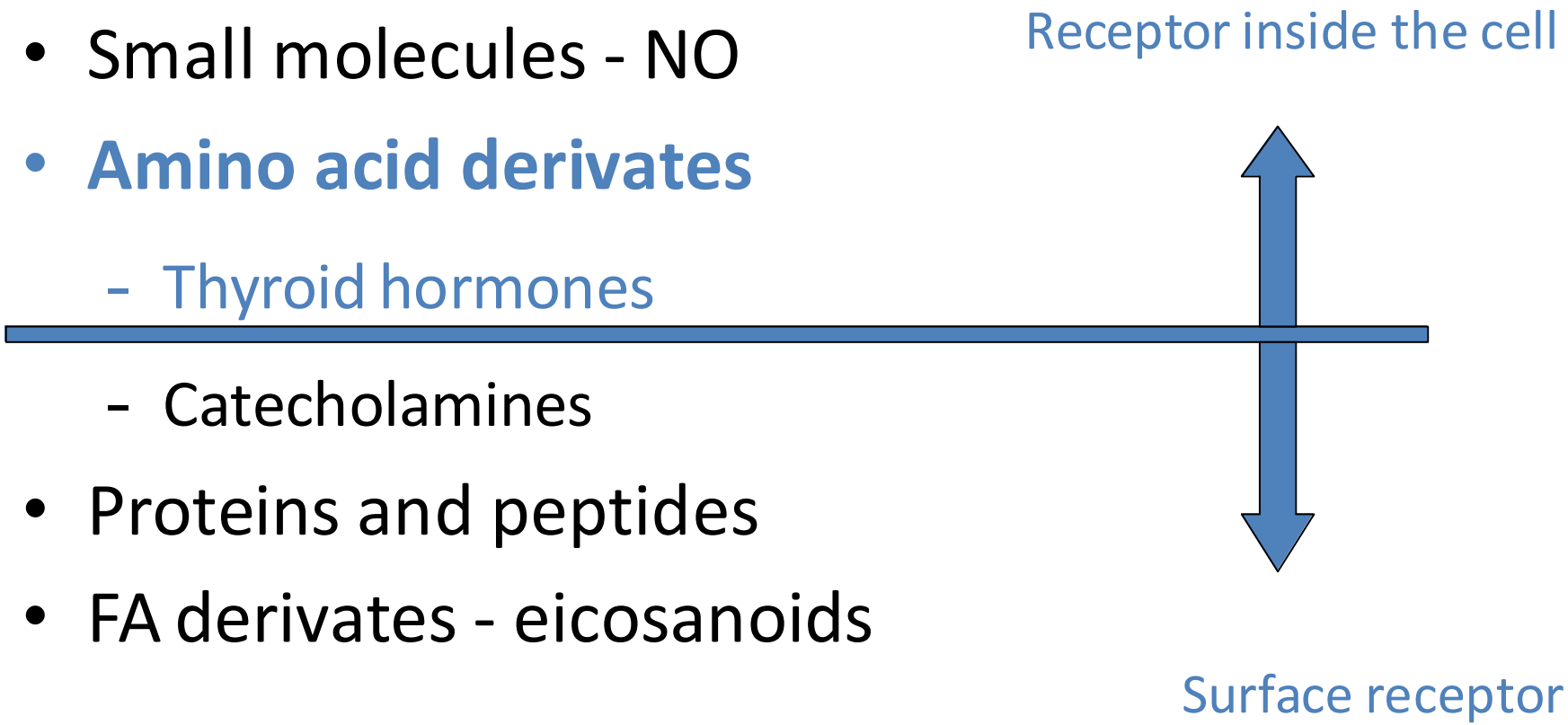
- **NO Synthases Types:**
  - **nNOS**: NOS in **neurons**, it is **calcium-dependent and constitutive.**
  - **eNOS**: NOS in **endothelium**, it is **calcium-dependent and constitutive.**
  - **iNOS**: NOS in **Macrophages,** it is **calcium-independent and induced by inflammatory cytokines (IFN-γ).**

- **eNOS** is regulated by **shear stress**, **hormones (estrogens and insulin)**, and **pharmacological agents.** This explains the vascular damage seen in DM. Also, explains the **spider angiomas seen in males with hyperestrogenism.**

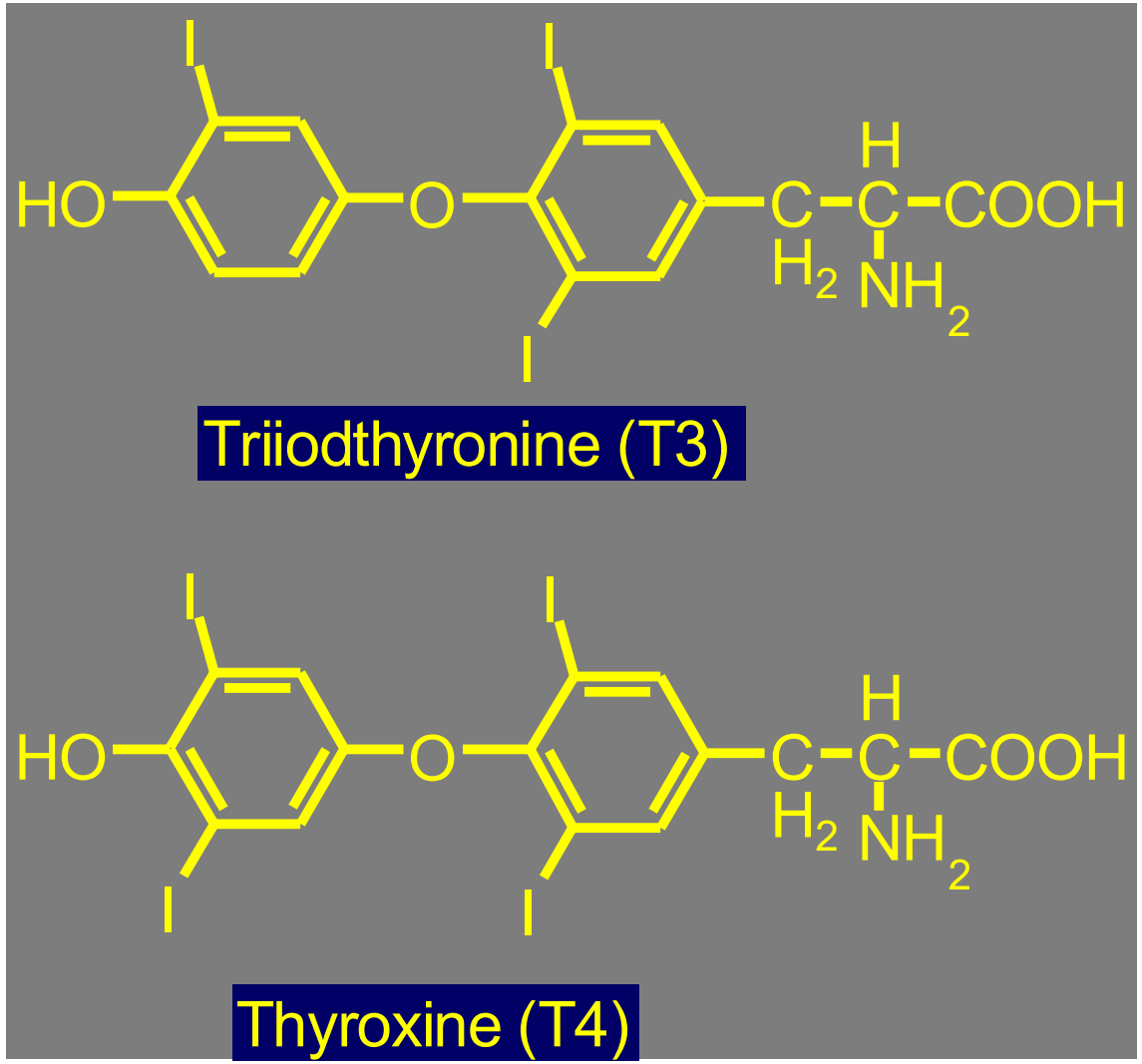
- Large amounts of NO from iNOS contribute to tissue damage and profound vasodilation.

# Chemistry of Hormones

- Steroids
- Small molecules - NO
- **Amino acid derivates**
  - Thyroid hormones
  - Catecholamines
- Proteins and peptides
- FA derivates - eicosanoids



# Thyroid hormones



# Thyroid hormones

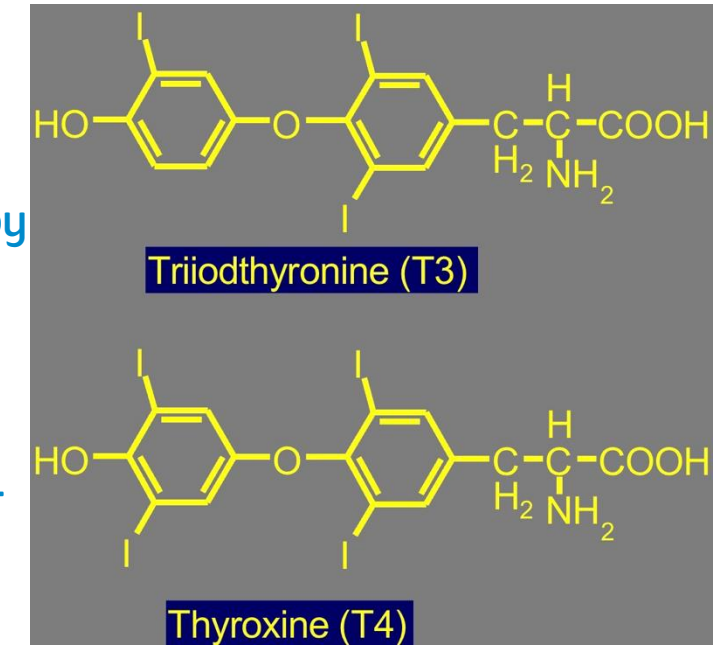
- Thyroid hormones are unique as the only biologically active molecules that contain iodine.

**Their synthesis:**

1. Active transport of iodide ($I^-$) into thyroid follicular cells by **Sodium-Iodide Symporter (NIS)** located at the basolateral membrane, and then into the colloid by iodide-chloride antiporter.

2. Iodide is oxidized to iodine by **Thyroid Peroxidase (TPO)**.

3. Iodine is attached to tyrosine residues on **thyroglobulin** (precursor of $T_3$ and $T_4$ – a glycoprotein), also catalyzed by TPO in a process called **iodination/organification**.

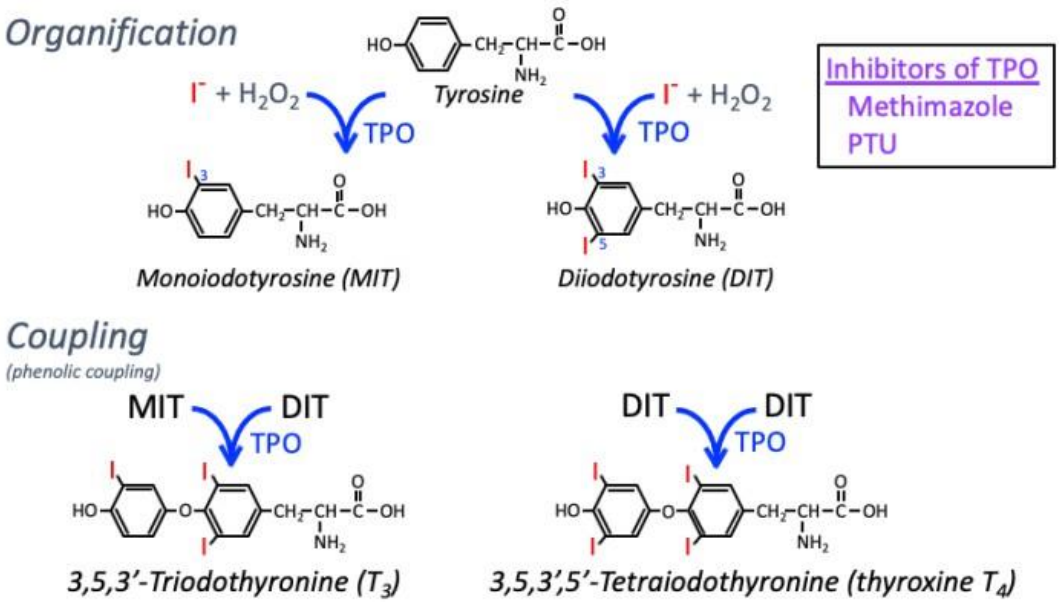



4. TPO catalyzes coupling of MIT with DIT ($T_3$) or DIT with DIT ($T_4$) and they are stored in the follicular colloid.

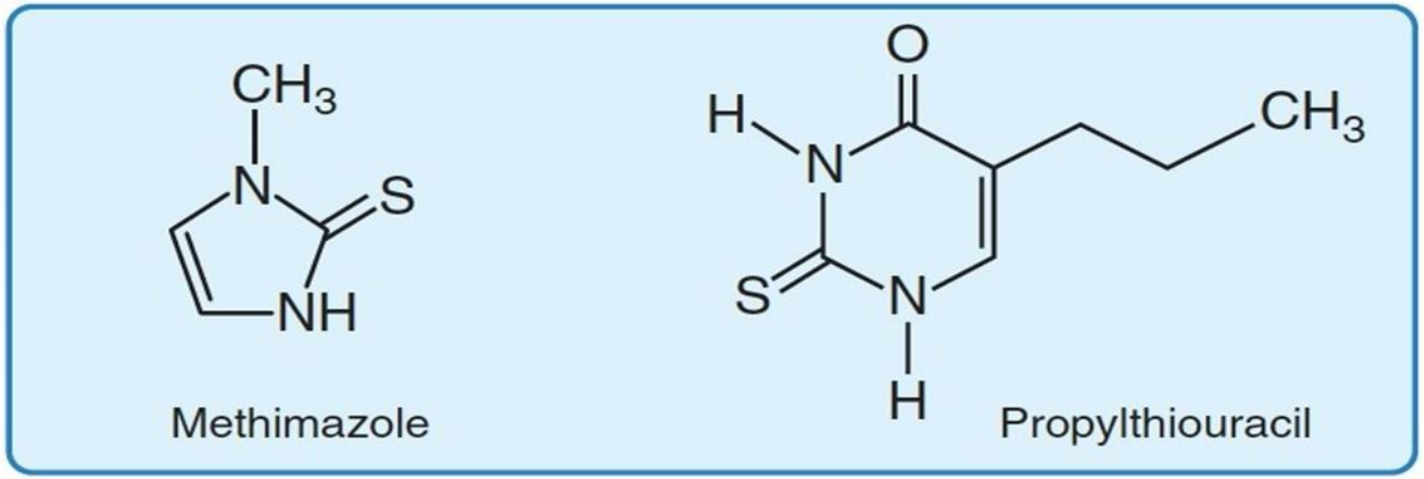
5. When TSH binds to the TSH receptor, it stimulates all processes, including the endocytosis of thyroglobulin to be ingested by lysosomal enzymes to release **$T_3$ (10%) and $T_4$ (90%)**, which diffuse across the membrane to the blood.

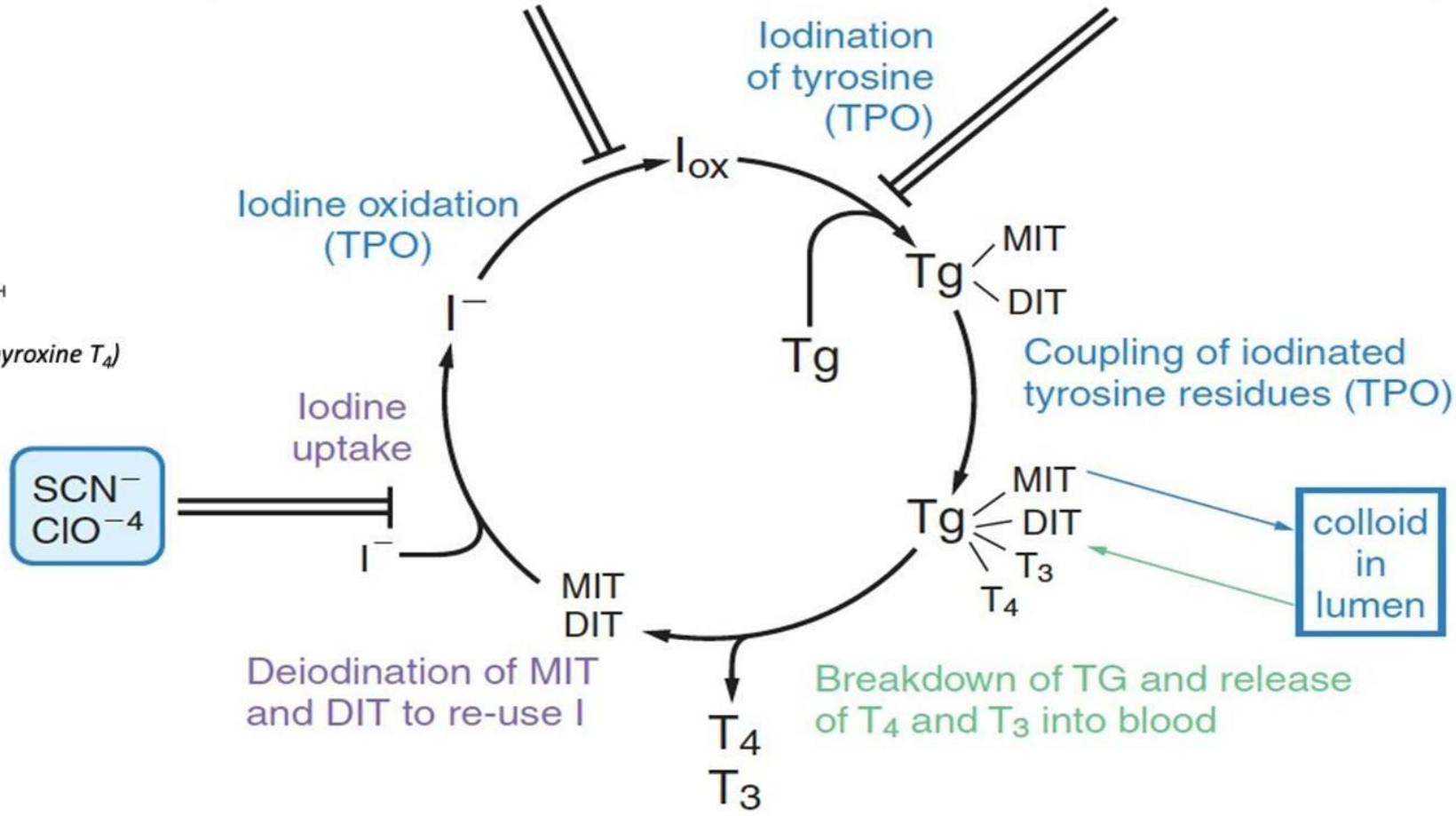
- Iodine deficiency leads to decrease in thyroid hormone synthesis and a compensatory increase in TSH, leading to **goiter → iodization of salt** solves this problem.
- Thyroid hormones are essential for normal CNS development, in utero and infancy. Therefore, maternal hypothyroidism caused by iodine deficiency can lead to **cretinism**, characterized by severe mental and growth retardation.

# Thyroid hormones




Inhibitors of TPO
Methimazole
PTU




- ✓ TPO, thyroid peroxidase;
- ✓ Tg, thyroglobulin;
- ✓ MIT, monoiodotyrosine;
- ✓ DIT, diiodotyrosine;
- ✓ $SCN^-$, thiocyanate;
- ✓ $ClO^{-4}$, perchlorate.

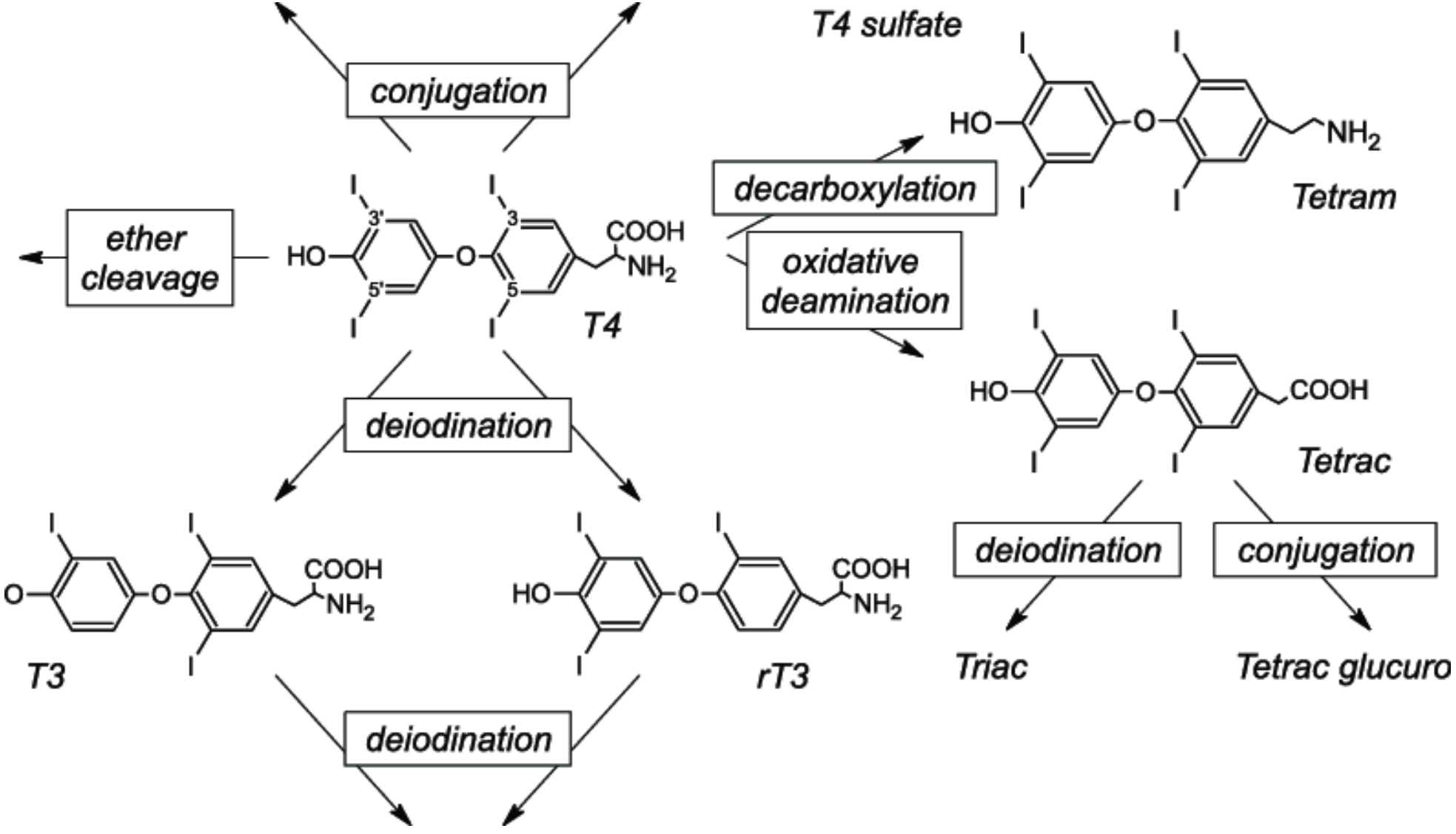
# Thyroid hormones

- As mentioned before, $T_3$ and $T_4$ are derived from tyrosine with iodination of the phenol ring in the side chain.
- $T_4$ has 4 iodine atoms, and it's the prohormone, and $T_3$ has 3 iodine atoms and is the biologically active form, because $T_3$ binds to the thyroid receptor with approximately 10 times higher affinity (lower kd than $T_4$).

- **Conversion of $T_4$ to $T_3$ is catalyzed by deiodinase enzymes:**
  - **D1** in the liver, kidney, and thyroid.
  - **D2** in brain, pituitary, and brown adipose tissue → activation ($T_4 \rightarrow T_3$).
  - **D3** in brain, placenta, and skin → inactivates thyroid hormones.
- ✓ $D_2$ is particularly important for providing local $T_3$ in the brain and pituitary, which allows for regulation of the Hypothalamus pituitary thyroidal axis (HPT axis) via negative feedback.

- $D_3$ protects the fetus from excessive maternal thyroid hormone.
- The $T_{1/2}$ for $T_4$ is 7 days, while for $T_3$ it's 1 day. This makes $T_4$ the preferred formulation for thyroid hormone replacement therapy.
- The primary route of thyroid metabolism is deiodination of the thyronine ring, for degradation or activation.
- In illness, sepsis, MI, starvation → $D_1$ and $D_2$ activity is reduced, while $D_3$ activity is increased, which is a protective mechanism used by the body to conserve energy and suppress metabolism, leading to **Euthyroid Sick Syndrome**, with a lab pattern of: **↓$T_3$, ↓$T_4$ and ↑rT3.**

# Thyroid hormones degradation



# Thyroid hormones degradation

- As was mentioned before, **the main route of metabolism is deiodination**, but thyroid hormones can be oxidatively deaminated, decarboxylation, and conjugation with glucuronic acid or sulfate in the liver, with metabolites also secreted in urine or bile.

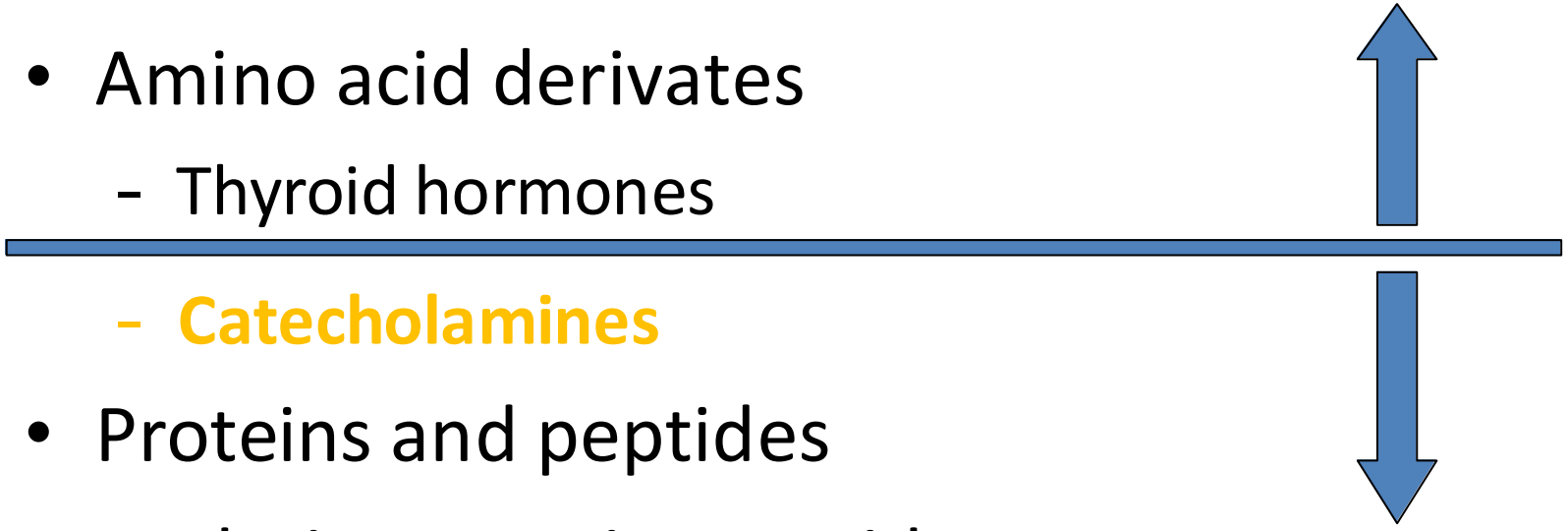
- **Propylthiouracil inhibits $D_1$ and TPO**, while **Methimazole** only inhibits TPO.

- Glucocorticoids and β-blockers inhibit $D_1$, reducing $T_4 \rightarrow T_3$ conversion, and are used as additional therapy in hyperthyroidism.

# Chemistry of Hormones

- Steroids
- Small molecules - NO
- Amino acid derivates
  - Thyroid hormones

Receptor inside the cell



  - **Catecholamines**
- Proteins and peptides
- FA derivates - eicosanoids

Surface receptor

# Catecholamine synthesis

Catecholamines are derived from tyrosine, which is obtained from diet, or hydroxylation of phenylalanine by **phenylalanine hydroxylase**.
Synthesis of these hormones happens in the adrenal medulla (Epi, NE), and sympathetic nerve terminals (NE).

The first step of synthesis is the **rate-limiting step**, and it is the conversion of **tyrosine to dihydroxyphenylalanine (DOPA)** by **tyrosine hydroxylase**, which requires **$O_2$**, **iron**, and **tetrahydrobiopterin ($BH_4$)** as **cofactors**.

It is highly regulated as it catalyzes the **rate-limiting step**, and one of the ways is **through negative feedback through its end-products (NE, Epi).**

L-DOPA is then decarboxylated by **DOPA decarboxylase** to form dopamine.

The dopamine is transported into **secretory vesicles**, where **dopamine β-hydroxylase** converts it to NE.
In the adrenal medulla, NE is converted to epinephrine by **phenylethanolamine-N-methyltransferase (PNMT)**, which requires cortisol as an inducer.

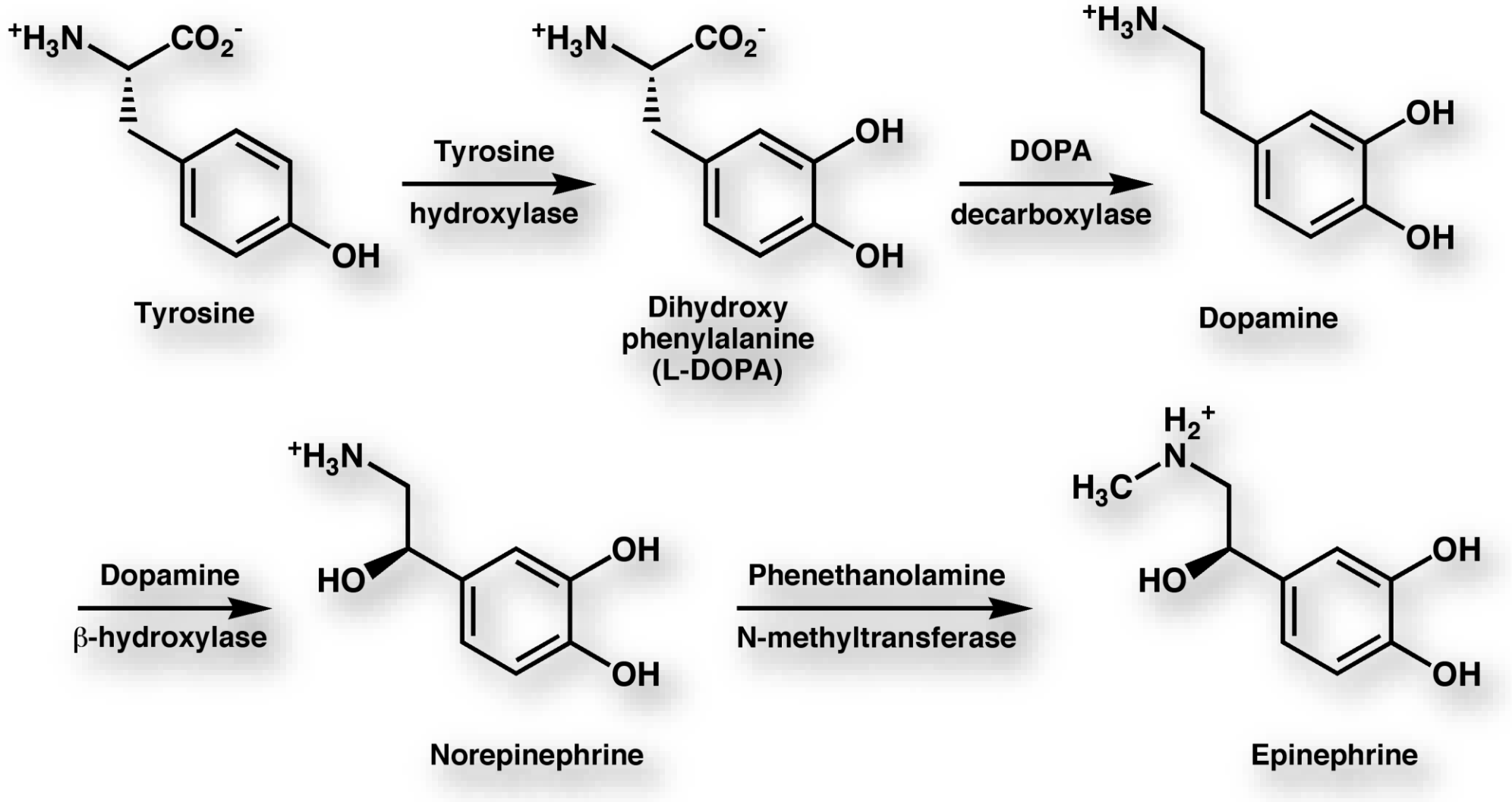
**Important: Tyrosine hydroxylase, DOPA decarboxylase, and NE to Epi all happen in the cytoplasm**. However, **dopamine β-hydroxylase is located inside the secretory vesicle.**
The adrenal medulla is the primary site for **Epi synthesis**, while **NE is mainly synthesized by nerve terminals.**

**Cofactors for Enzymes:**
1. TH → $BH_4$
2. DBH → Vitamin C

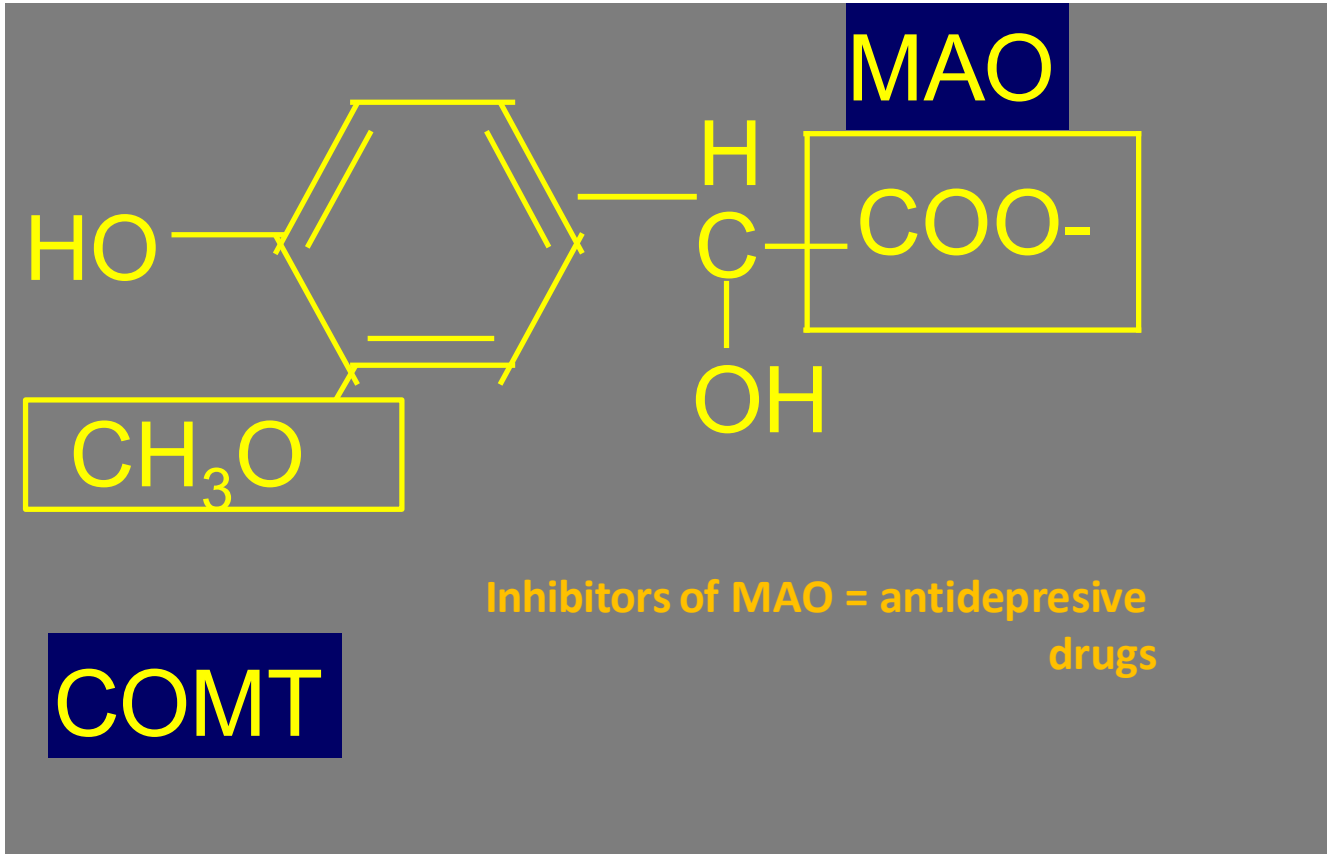
# Catecholamine synthesis

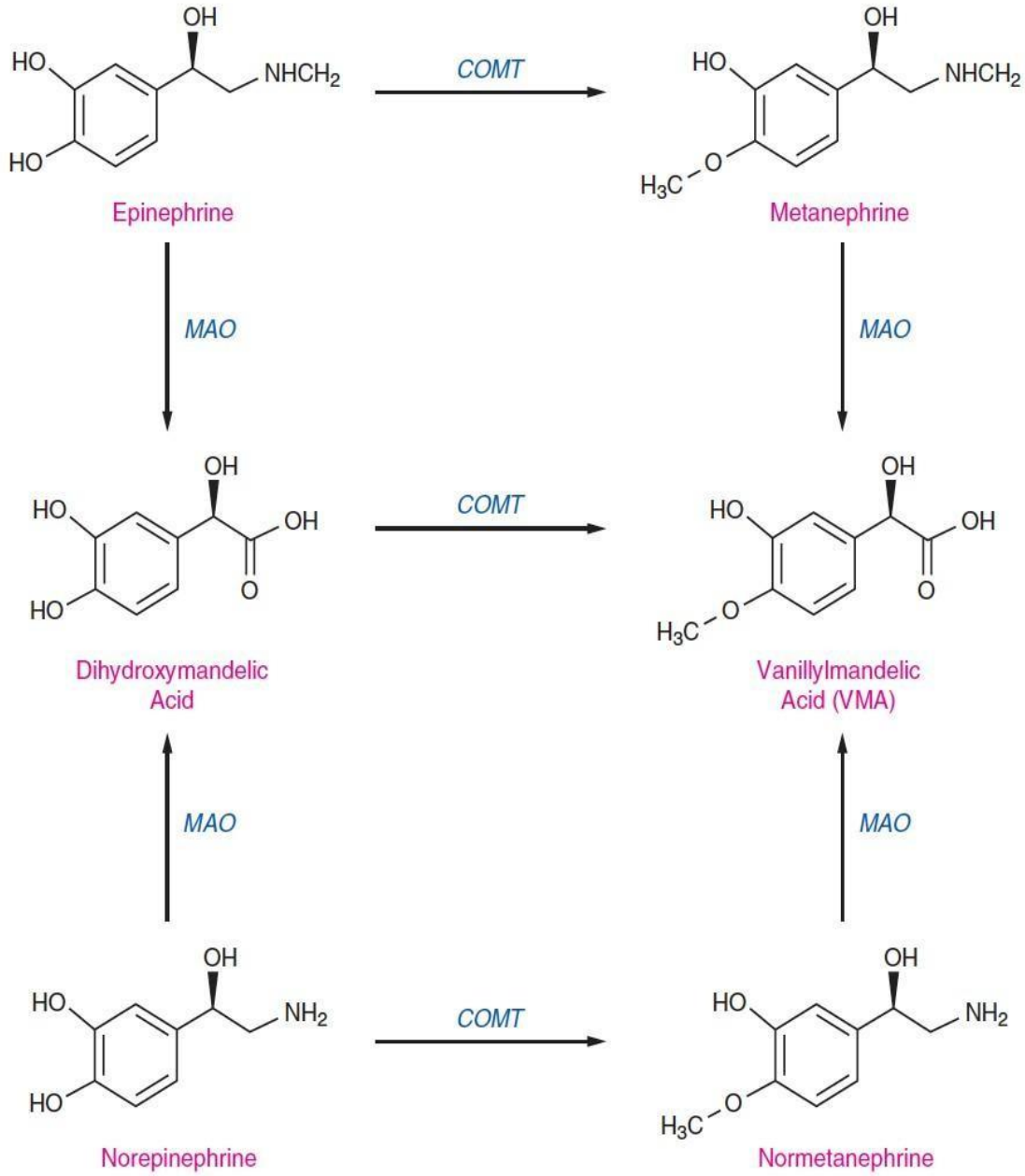
- Substrate = Phe or Tyr
- Synthesis located in: adrenal medulla, nerve tissue
- Products:
  - Dopamine, adrenaline (hormones)
  - Noradrenaline (neurotransmiter)

# Catecholamine synthesis



# Catecholamine breakdown



# Catecholamine synthesis

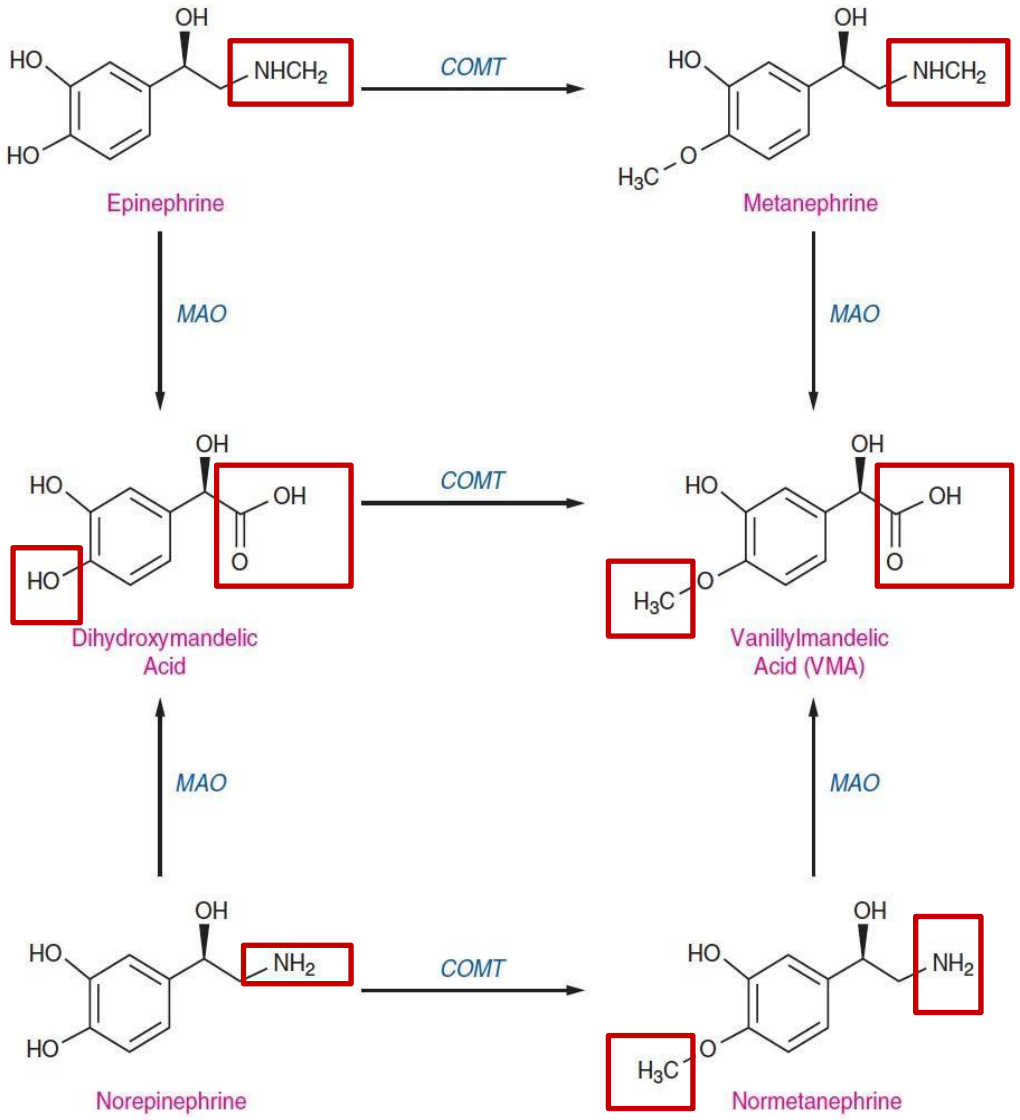
- **Catecholamines** have a **very short T½ (minutes)**, because they are **rapidly metabolized** by 2 main enzyme classes: **Monoamine oxidase (MAO)** and **Catechol-O-methyltransferase (COMT) ::**

1) **MAO** is a mitochondrial enzyme that **oxidatively deaminates catecholamines to aldehyde intermediates** that are rapidly **metabolized → oxidized to carboxylic acid, OR reduced to alcohol.**

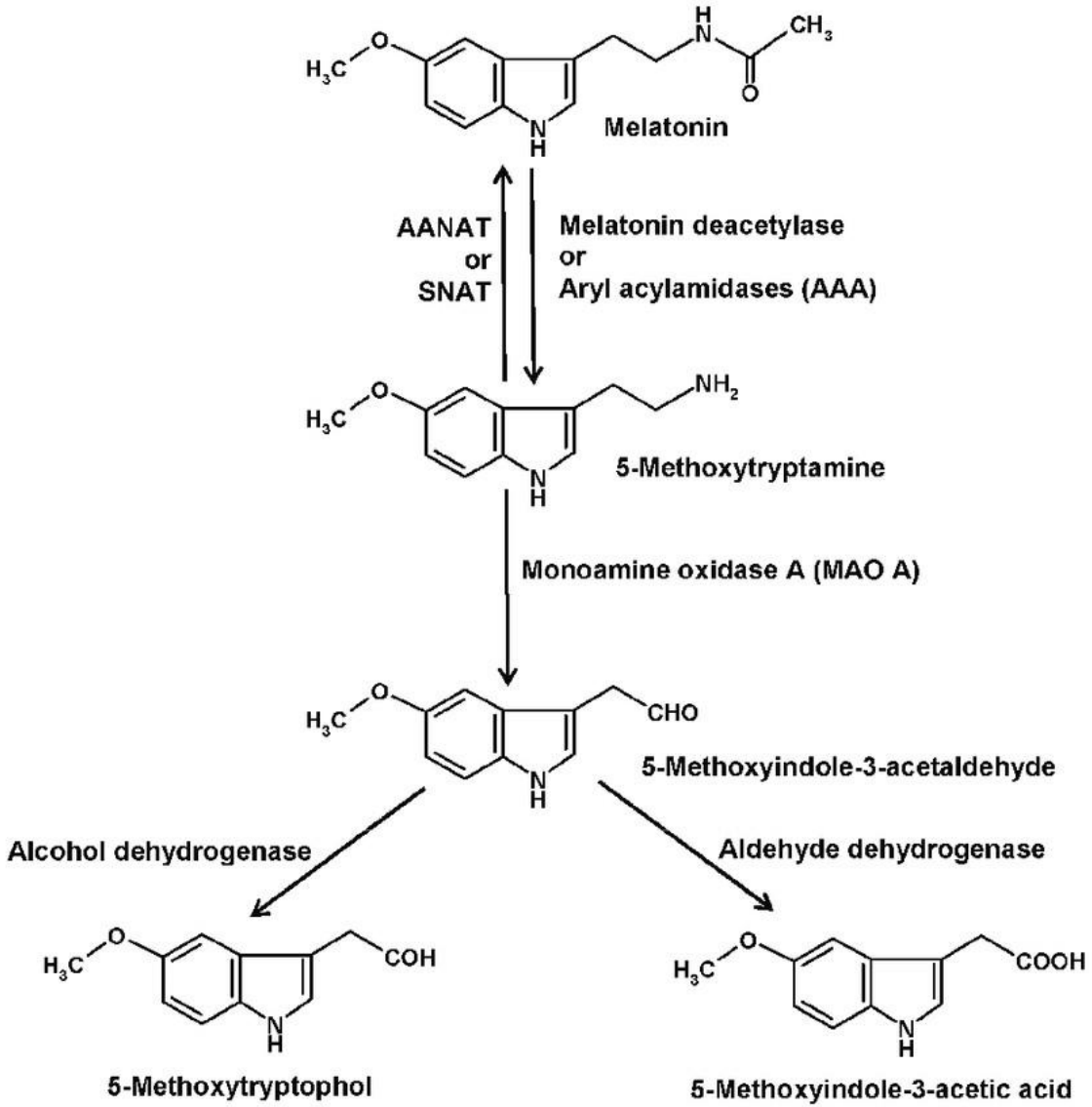
2) **COMT** is a cytoplasmic enzyme that **methylates the catechol ring.**

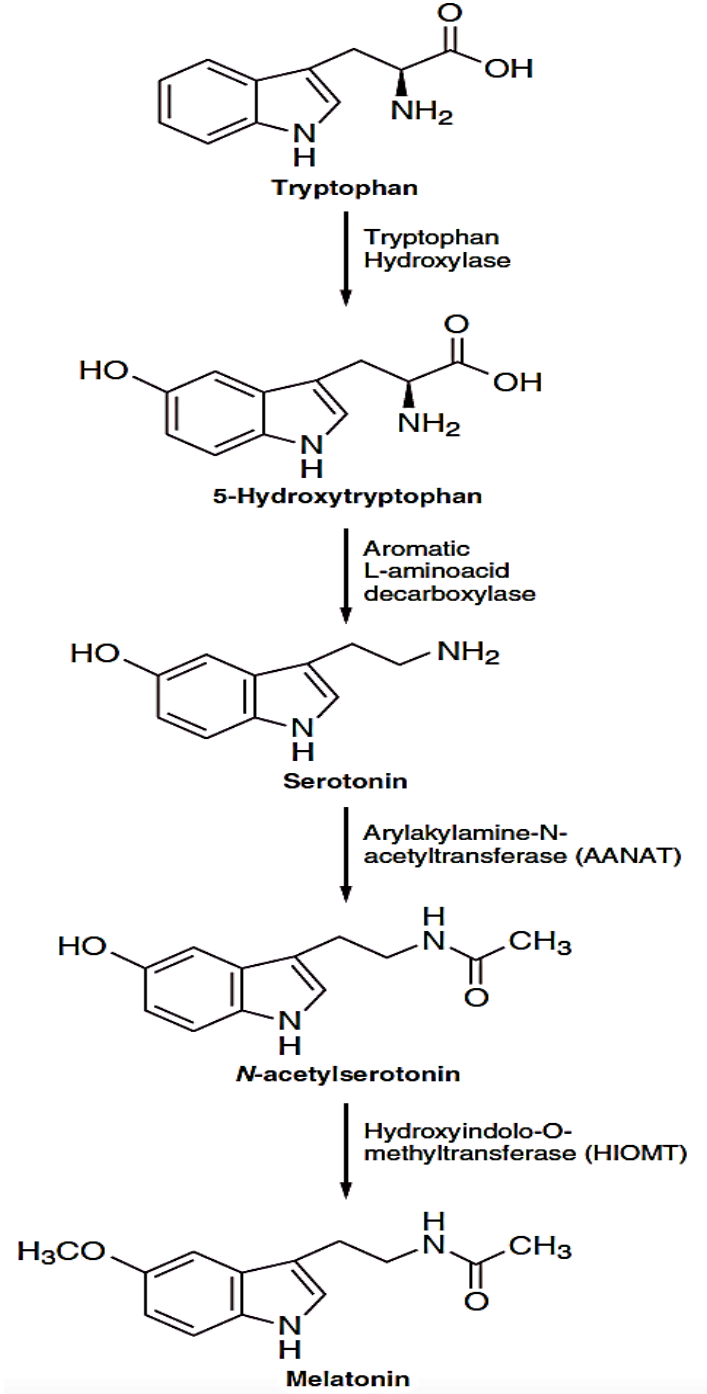
- Their combined action **produces the major urinary metabolites, vanillylmandelic acid (VMA)**, and **metanephrines (normetanephrine and metanephrine).**

- Preferred for pheochromocytoma because tumor cells have high levels of COMT.



# Melatonin


Melatonin
AANAT
or
SNAT
Melatonin deacetylase
or
Aryl acylamidases (AAA)
5-Methoxytryptamine
Monoamine oxidase A (MAO A)
5-Methoxyindole-3-acetaldehyde
Alcohol dehydrogenase
Aldehyde dehydrogenase
5-Methoxytryptophol
5-Methoxyindole-3-acetic acid


Tryptophan
Tryptophan Hydroxylase
5-Hydroxytryptophan
Aromatic L-aminoacid decarboxylase
Serotonin
Arylakylamine-N-acetyltransferase (AANAT)
N-acetylserotonin
Hydroxyindolo-O-methyltransferase (HIOMT)
Melatonin

# Melatonin

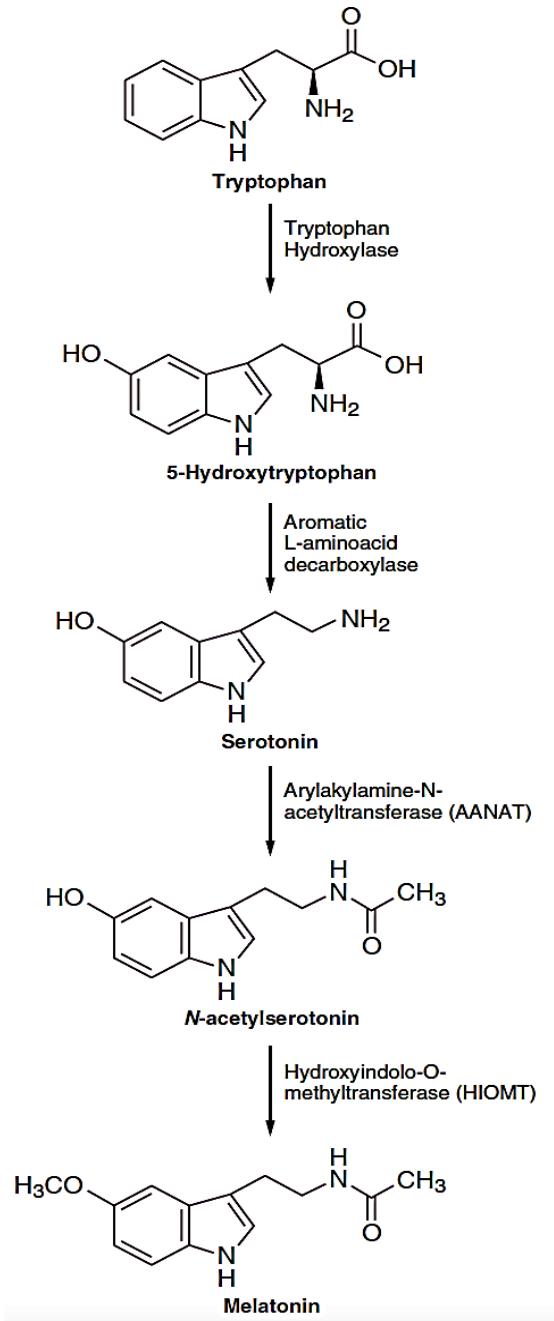
Melatonin is synthesized from tryptophan:

1. **Tryptophan** is converted to **5-hydroxytryptophan** by tryptophan hydroxylase.
2. **5-HTP** is converted to **serotonin** by **aromatic L-amino acid decarboxylase.**
3. **Serotonin** is converted to **N-acetyl serotonin** by **serotonin N-acetyltransferase (NAT)**, which is the **rate-limiting step**, and it's activated by NE from sympathetic neurons that binds to β1 receptors on pineocytes.

Synthesis is regulated by **circadian clock**, where **light exposure inhibits synthesis by reducing the SCN signal to the gland**, and at **night the SCN signals the gland to produce melatonin.**

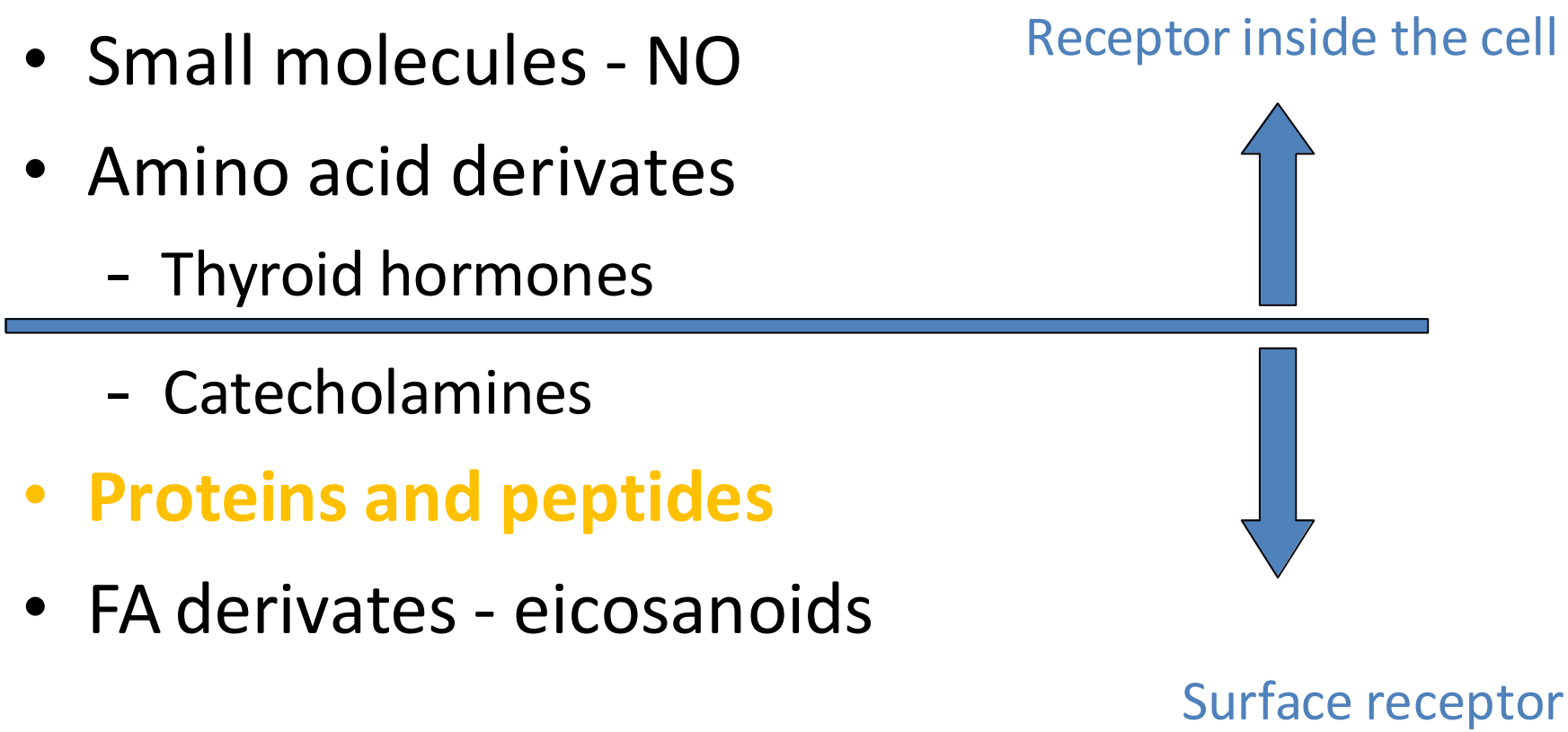
Melatonin acts on **MT1 and MT2 receptors** to regulate circadian rhythm, sleep, and seasonal reproduction.

4. N-acetyl serotonin is converted into melatonin by **hydroxyindole O-methyltransferase.**



# Chemistry of Hormones

- Steroids
- Small molecules - NO
- Amino acid derivates
  - Thyroid hormones
  - Catecholamines
- **Proteins and peptides**
- FA derivates - eicosanoids



# Protein and peptide hormones

**Protein and peptide hormones** constitute the largest and most diverse class.

- CNS mediators: neuropeptides, opioids
- Hypothalamic releasing hormones and pituitary peptides
- Insulin and glucagone
- Growth factors: IGF, CSF, EPO

…and many others

# Protein and peptide hormones

Incretins are also important, and the major 2 are:

1. **Glucagon Like peptide 1 (GLP-1)**, secreted by **L-cells** and is made of 30-31 amino acids, and it works by increasing glucose-dependent insulin secretion, decreasing glucagon, delaying gastric emptying and inducing satiety.

- It acts through **GLP-1 receptor**, increasing cAMP levels.

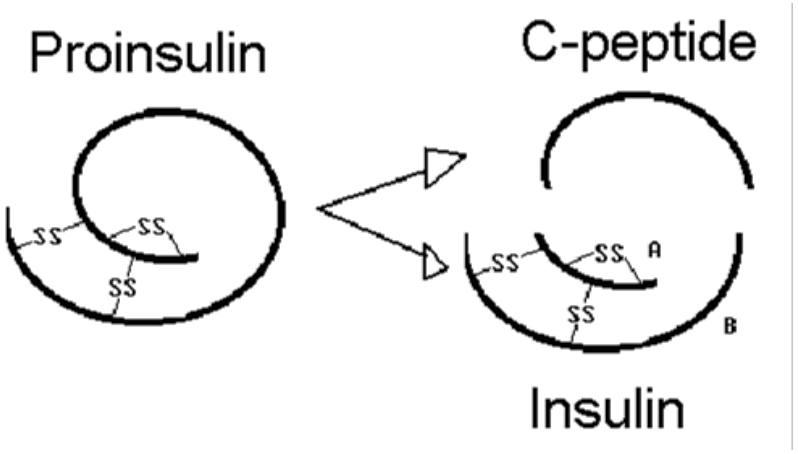
2. **Glucose dependent insulinotropic polypeptide (GIP),** secreted by **K-cells**

Synthetic agonists (**Ozempic**) are used for treatment of Type 2 DM, with substantial effect on the heart, kidneys and weight.

# General steps of peptide synthesis

## "Precursor Polypeptides"

- Generally peptide hormones are being synthesised as a larger precursor.
- Expression of "pre-pro" protein
- Transport to ER
- Splitting the signaling sequence




- Cleavage to definite peptide(s) and final modification in Golgi
  - Proinsulin to insulin
  - Proopiomelanocortine (POMC) to MSH and ACTH

# General steps of peptide synthesis

## "Precursor Polypeptides"

Many peptide hormones are used as drugs, including insulin, gonadotropins, FSH, and GLP-1 agonists, and because they're soluble and can be hydrolyzed by proteases in the GIT, they're usually given as an injection.

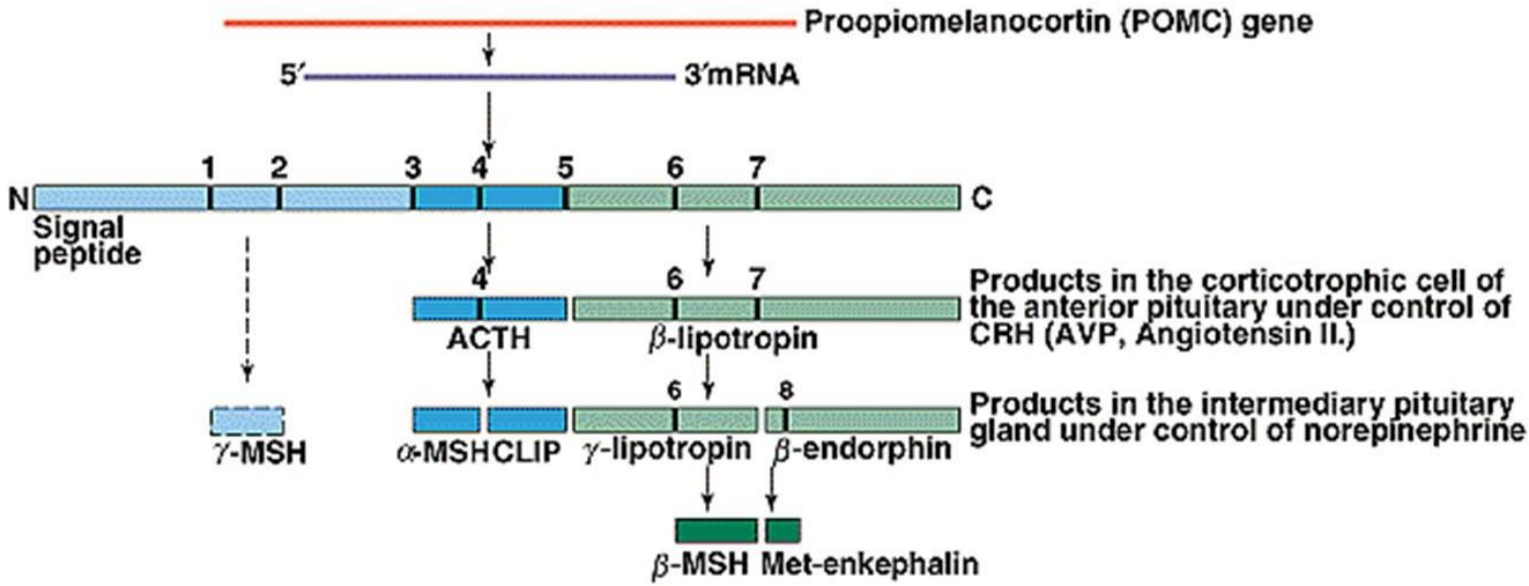
However, oral semaglutide (**Rybelsus**) is an oral GLP-1 agonist.
Peptide hormones are synthesized as larger precursors (**preprohormones**) and undergo post-translational processing.

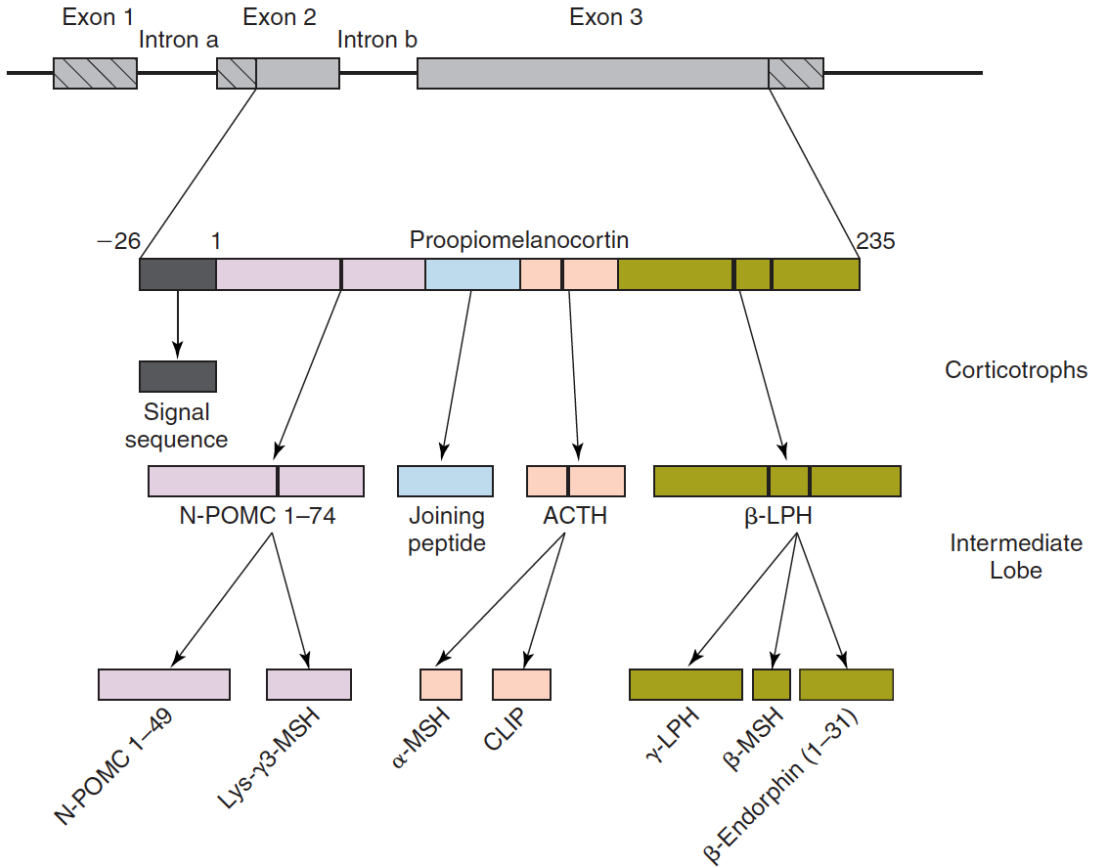
The process starts **with transcription of the gene and production of the preprohormone**; the pre portion is a signal peptide at the N-terminus that directs the protein from the cytoplasm to the RER, recognized by the **signal recognition particle (SRP)**; once it's translocated to the ER, the **signal sequence** is cleaved by **signal peptidase, producing the prohormone.**

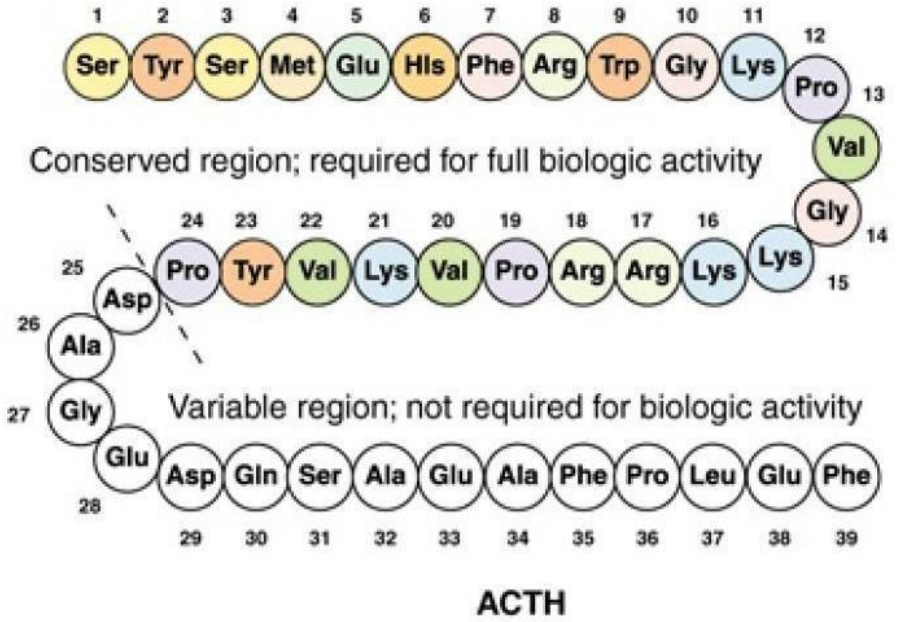
The prohormone is then transported to **Golgi**, where it undergoes **proteolytic cleavage** by **prohormone convertases (PCs)** to remove the **propeptide and modify the hormone to get the final mature hormone.**
This mature hormone is **stored in vesicles** and released by **exocytosis upon binding of a stimulus**.

**Tissue-specific processing**, as seen with POMC, **where different prohormone convertases (PCs) are expressed, leads to different hormone products.**
Mutations in PCs can cause endocrine disorders.

# Proopiomelanocortin (POMC)




ACTH

# Proopiomelanocortin (POMC)

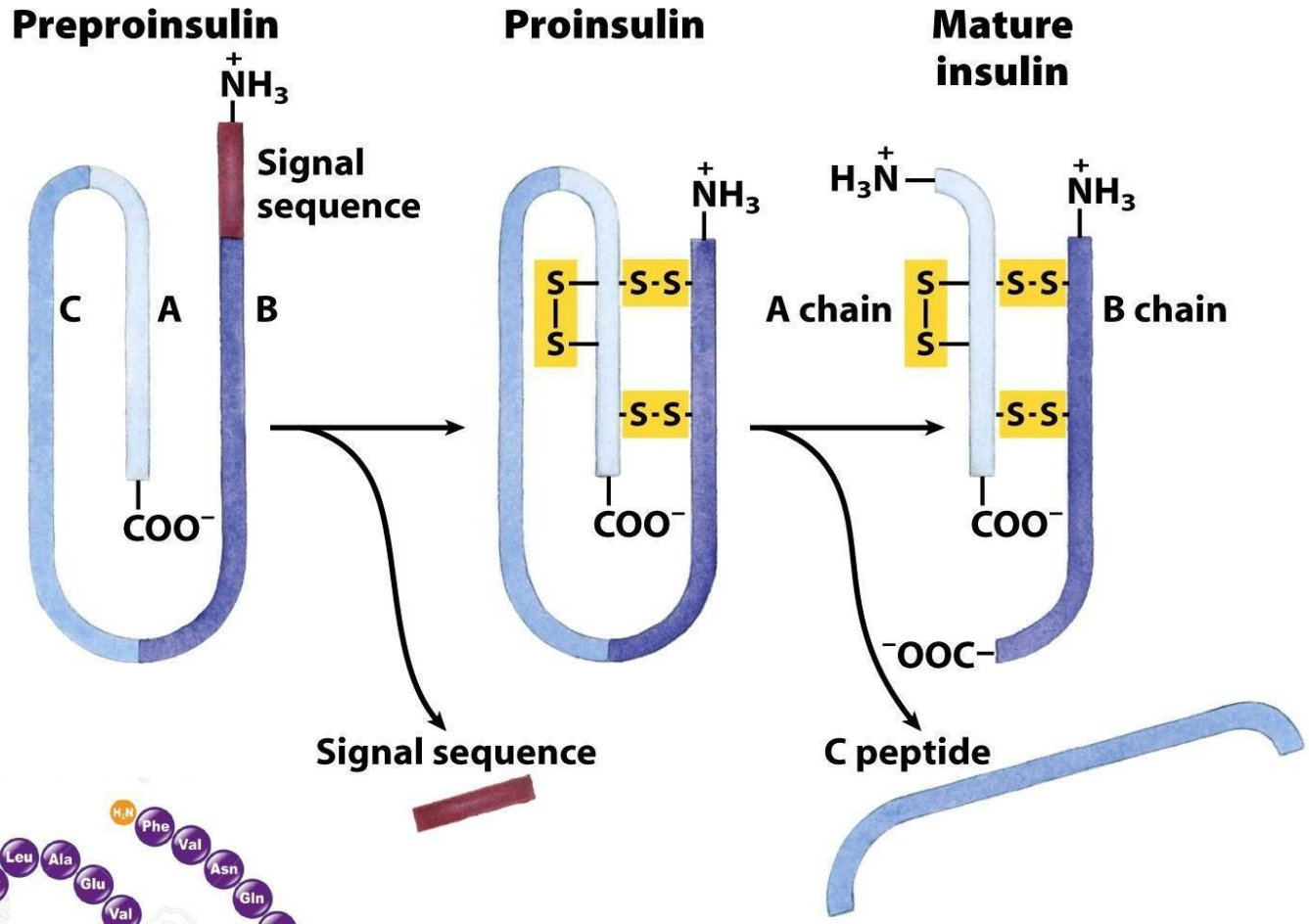
Mentioned before, but additional points include:

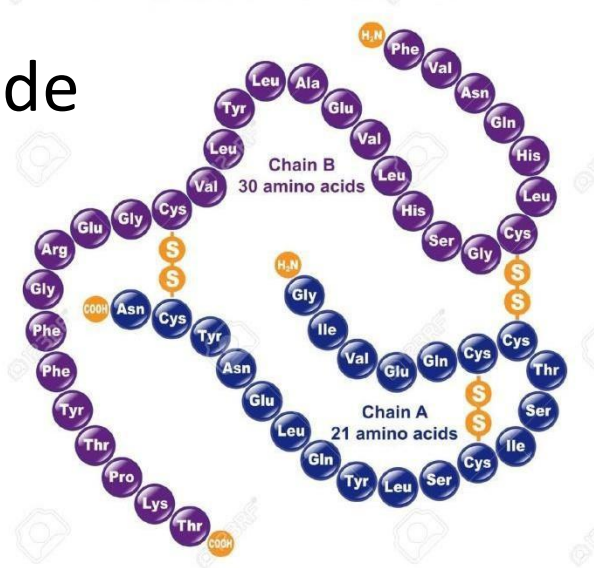
1. **POMC** is involved in the **stress response (ACTH production).**
2. **Pigmentation** through **MSH**.
3. **Appetite regulation** through the **α-MSH produced in the hypothalamus.**
4. **Pain modulation → β-endorphin**.

**POMC deficiency** leads to **adrenal insufficiency (hypocortisolism)**, **hypopigmentation**, and because the hypothalamus cleaves POMC into α-MSH, which has an anorexigenic effect in the hypothalamus, **loss of this effect leads to increased appetite which leads to obesity**.

# Insulin

- A larger precursor preproinsulin
  - ✓ 23 aa signal sequence
  - ✓ 3 disulfide bonds
- Proinsulin
  - ✓ Removal of the C peptide
- Mature insulin
  - ✓ A and B chains



# Insulin

The **signal sequence** directs it to the RER, where it is cleaved into **proinsulin (86 aa).**

**The 3 disulfide bonds include:**

- **1 intrachain (A chain)**
- **2 interchain (S-S between A and B) –** (A7-B7 and A20-B19).

In Golgi, **PC1/3 and PC2** remove the **C-peptide**, and **carboxypeptidase E** removes the **basic amino acids from the C-terminal**, yielding **mature insulin in the secretory vesicles.**

# Degradation of peptide hormones

- Lyzosomal after endocytosis of complex hormone-receptor
- Chemical modification (liver): rearrangement of S-S bridges, cleavage
- Renal excretion of small peptides

# Degradation of peptide hormones

- Peptide hormones have a **short T½** and are **degraded by 3 primary mechanisms:**

I. After it binds to its cell-surface receptor, **the hormone-receptor complex is endocytosed** and is **degraded** in the **lysosome**, allowing **either receptor recycling or degradation**.

II. **Chemical modification in the liver**, involving **proteolytic cleavage, disulfide bond rearrangement,** and **other modifications that inactivate the hormone. The liver is the primary site of degradation for most of the peptide hormones.**

III. **Renal excretion** is of particular significance **for small peptides that are filtered by the glomerulus and degraded in the proximal tubule.**

- In kidney disease, this filtration is impaired, leading to accumulation and prolonged effect.

# Target cell interactive effects

- **Permissive effects** – one hormone enhances the effect of a later hormone
  - ✓ **Estrogen up-regulates progesterone receptors** in uterus
  - ✓ **Thyroid hormone increases the effect of epinephrine** on breakdown of triglycerides in adipocytes

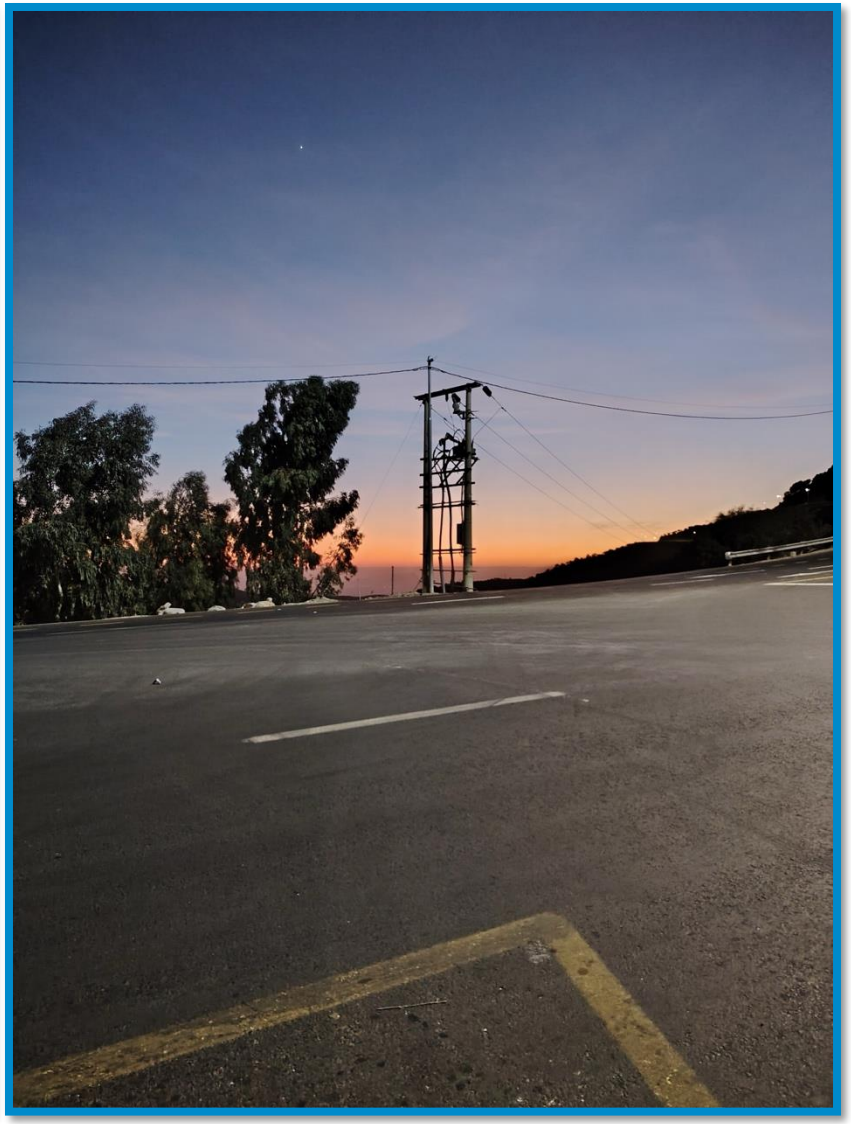
- **Integrative effects –** hormones produce complementary effects on different tissues
  - ✓ **PTH and calcitriol** increase ECF **calcium**

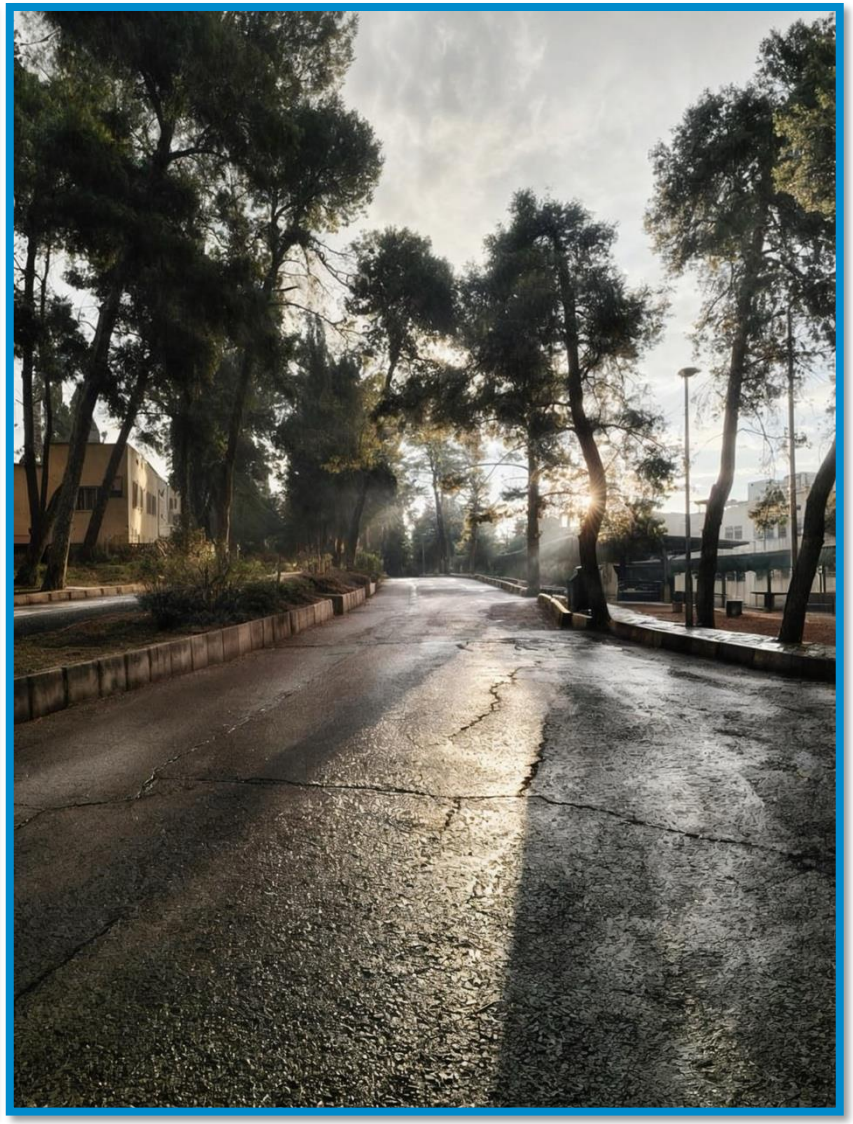
# Target cell interactive effects

- **Synergistic effects:**
  - ✓ Both **FSH and estrogen** necessary for **normal oocyte development.**
  - ✓ **FSH and testosterone** together increase **spermatogenesis.**

- **Antagonistic effects:**
  - ✓ **Insulin and glucagon.**
  - ✓ **PTH and Calcitonin.**
  - ✓ **Estrogen and Testosterone.**

# رسالة من الفريق العلمي:





# For any feedback, scan the code or click on it.

Corrections from previous versions:

| Versions | Slide # and Place of Error | Before Correction | After Correction |
|---|---|---|---|
| V0 → V1 | Slide 27 | $D_2$ is particularly important for providing local $T_3$ in the brain and pituitary, which allows for regulation of the Hypothalamus pituitary thyroidal axis (HPT axis) via negative feedback. | $D_2$ is particularly important for providing local $T_3$ in the brain and pituitary, which allows for regulation of the HPA axis via negative feedback. |
| | Slide 40 | Under the 2nd point<br>It acts through GLP-1 receptor, increasing cAMP levels. | Under the 1st point<br>It acts through GLP-1 receptor, increasing cAMP levels. |

# For any feedback, scan the code or click on it.

Corrections from previous versions:

| Versions | Slide # and Place of Error | Before Correction | After Correction |
|---|---|---|---|
| V1 → V2 | Slide 7 | This cholesterol is transported to the ***mitochondria*** of **steroidogenic cells** by **Steroidogenic Acute Regulatory Protein (StAR protein),** and this is the **rate-limiting** step regulated by tropic hormones such as ACTH (adrenal gland) or LH (gonads). | This cholesterol is transported to the ***mitochondria*** of **steroidogenic cells** by **Steroidogenic Acute Regulatory Protein (StAR protein).**<br><br>Inside the mitochondria, **cytochrome P450 side-chain cleavage enzyme (CYP11A1)**, also known as **Desmolase**, cleaves the **6 Carbon side chain** by **cleaving the bond between C20 and C22**, and **pregnenolone** is produced. This step is the **rate-limiting** step. |