بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Metabolism | Final 23

Conversion of A.A. to Specialized Products

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Conversion of A.A to Specialized Products 

Color code

- Slides
- Doctor
- Additional info
- Important

Part I:
Neurotransmitters 

- In this part, the doctor focuses on the **enzymes**, so be aware of **each reaction step**—not necessarily the enzyme names, but the **type of reaction** involved (such as **hydroxylation** or **carboxylation**, etc.).
- Also know the **Co-enzymes** that are involved in each reaction.
- Always check the **reaction pictures** while reading anything, doctor **mentioned all of them**.

Study this lecture well; it is a piece of cake 

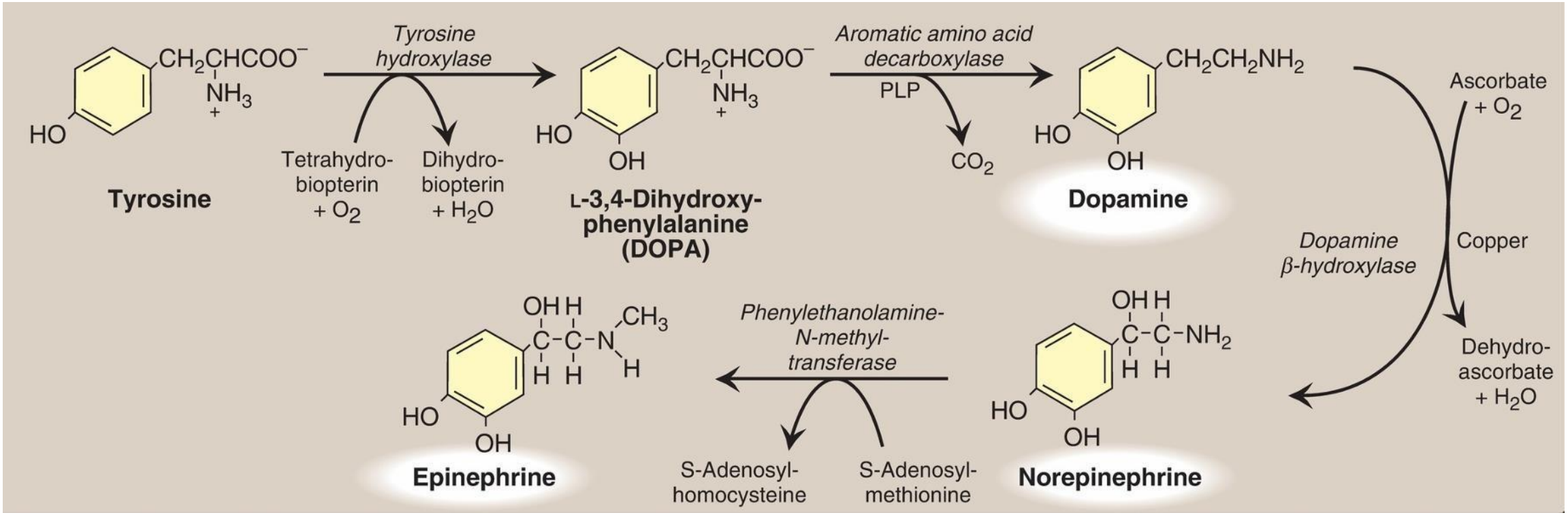
Part I:
Neurotransmitters from Amino Acids: Overview

- Catecholamines (tyrosine)
- Thyroid hormones (tyrosine)
- Serotonin (tryptophan)
- Histamine (histidine)
- GABA (glutamate)
- Glutathione
- Creatine

- These pathways are critical in the brain, periphery, and are targets for many pharmacological agents

Catecholamine Synthesis

- Synthesis/Clinical Correlation:
- Steps and Coenzymes!
- Parkinson disease: neurodegenerative, idiopathic loss of dopamine-producing cells in the brain, L-DOPA



- There is always a **decarboxylation step** in neurotransmitter synthesis.
- Decarboxylation occurs to remove the acidic group. Since the precursor is an amino acid, when decarboxylation occurs, it becomes an amine rather than an amino acid, and this is how it becomes biologically active.
- **PLP** acts as a co-enzyme, which is a **vitamin B6 derivative**.
- All **catecholamines** are derivatives of **tyrosine**, which itself is derived from **phenylalanine**.

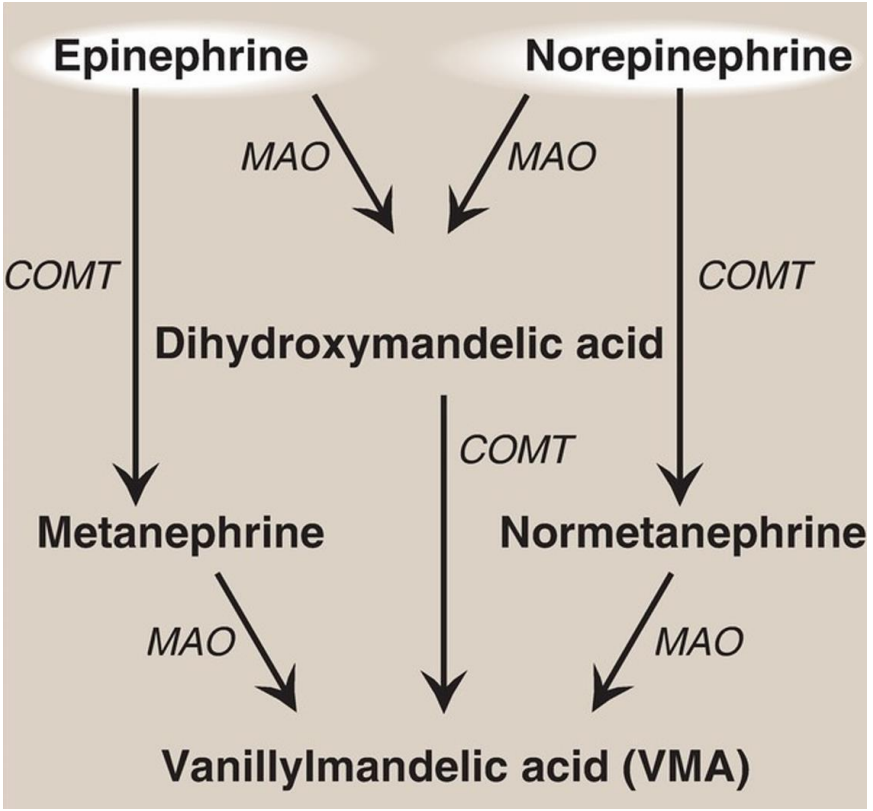
As we said last week, phenylalanine is converted to tyrosine by the enzyme **phenylalanine hydroxylase**. This hydroxylation reaction requires the co-enzyme **tetrahydrobiopterin (BH_4)**. During the reaction, BH_4 donates two electrons and becomes **dihydropterin**, which is then converted back to **tetrahydrobiopterin** by the enzyme **dihydropteridine reductase**.

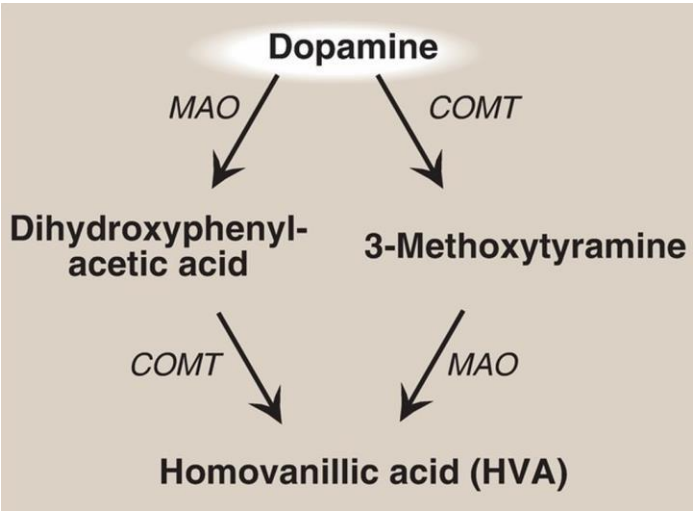
Now, let's get into the reactions🔥

- Tyrosine is converted to **DOPA** (a benzene ring with two hydroxyl groups) by the enzyme **tyrosine hydroxylase**.
- A benzene ring with two hydroxyl groups is called a **catechol ring**, so this is the first catecholamine produced, which is **DOPA**.
- As mentioned, to form a neurotransmitter, **decarboxylation must occur**. The important point to know is that the enzyme involved is **decarboxylase**, and this reaction step is **PLP-dependent**.
- The first neurotransmitter produced is **dopamine**.
- Dopamine is then hydroxylated to **norepinephrine**. We have already explained the difference between **norepinephrine and epinephrine**. In this reaction, it is important to know the **enzyme involved and the methyl donor**, which is **SAM (S-adenosylmethionine)**.
- **Check the previous picture when reading this to make it clear for u ‼️‼️‼️**

Catecholamine Degradation

- Degradation/Clinical Correlation:
  - MAO and COMT to VMA
  - Pheochromocytoma (adrenal medulla, excess catecholamines, episodic hypertension)
  - Diagnosis: urinary VMA or plasma metanephrines





Clinical Correlation: Parkinson's Disease 🧠

- In patients with Parkinson's disease, there is a **loss of dopamine**. The cells that release dopamine undergo destruction for **idiopathic reasons**, which leads to a **decrease in dopamine levels**.

- Giving dopamine directly to these patients will not improve their condition because dopamine **cannot cross the blood–brain barrier (BBB)**. Therefore, we give **L-DOPA**, which **can cross the BBB**, and once inside the brain, it is **decarboxylated to dopamine**.

Degradation of Catecholamines

- Catecholamines contain **one amine group** and a **catechol ring**, so degradation can occur at **both sites**.

- There are enzymes that act on the **amine group**, and others that act on the **catechol ring**.

The enzyme that acts on the amine group is an oxidase called **monoamine oxidase (MAO)**. MAO removes the amine group, rendering the molecule **inactive**.

On the other hand, there is an enzyme called **catechol-O-methyltransferase (COMT)**, which adds a **methyl group** to the catechol ring at the oxygen atom, also inactivating the molecule.

Degradation can start with either enzyme:

- If **COMT** acts first, it is followed by **MAO.**
- If **MAO** acts first, it is followed by **COMT.**

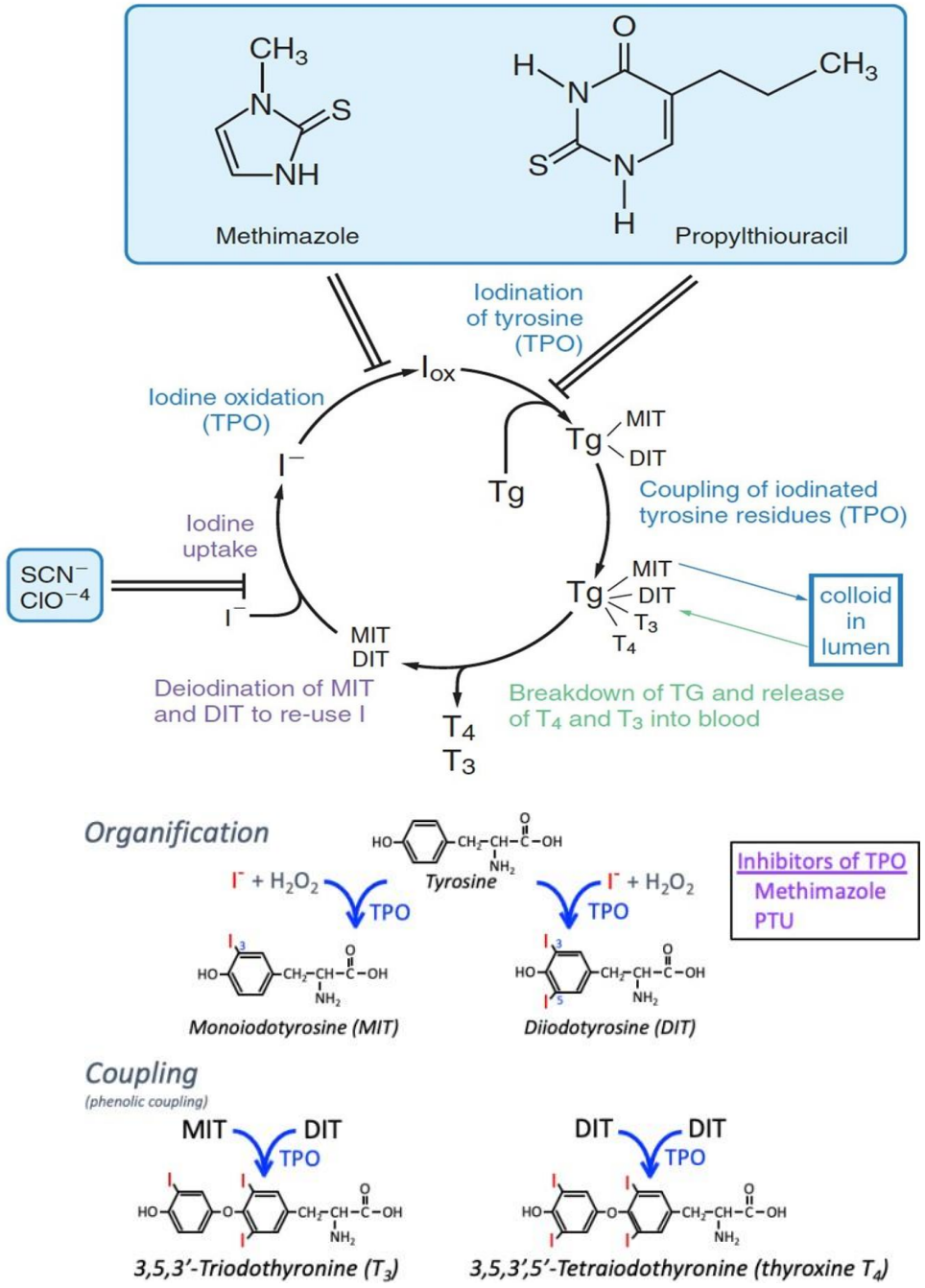
The final product of catecholamine metabolism is vanillylmandelic acid (VMA).

- VMA is a commonly measured molecule in **urine tests**. If its level is elevated, this indicates **increased catecholamine levels** in the body.

Thyroid Hormones: Synthesis from Tyrosine

- Thyroid Peroxidase catalyzes:
  - 1) Iodine oxidation
  - 2) Iodination of tyrosine to form MIT/DIT
  - 3) Coupling of MIT/DIT to form T3 and T4

- TSH is the major stimulator
- Synthesis requires iodine



Thyroid Hormone Synthesis

- Thyroid hormones are synthesized in the **thyroid gland** on a protein called **thyroglobulin**, which serves as the **scaffold (matrix)** for hormone synthesis.

- There is an enzyme acting on tyrosine residues within thyroglobulin called **thyroid peroxidase (TPO)**. This enzyme is responsible for **multiple actions**.

- Iodine, which is negatively charged in the form of **iodide (I^-)**, must first be **oxidized** by thyroid peroxidase. The enzyme also facilitates the **binding of iodine to tyrosine** residues. Depending on the number of iodine atoms added, tyrosine becomes either:

  - **Monoiodotyrosine (MIT)** when one iodine is added.
  - **Diiodotyrosine (DIT)** when two iodine atoms are added.

- Thyroid peroxidase then facilitates the **coupling reactions** between these iodinated tyrosines:

  - Coupling of **MIT with DIT** produces **triiodothyronine (T_3).**
  - Coupling of **DIT with DIT** produces **tetraiodothyronine (T_4)**, also known as **thyroxine.**

Inhibitors of Thyroid Hormone Synthesis

- There are inhibitors that can act at **multiple steps** of this synthesis pathway. These inhibitors may be:
    - **Pharmacological** agents.
    - **Toxic substances**, such as **cyanide**, which inhibits the **uptake of iodine** by the thyroid gland.

- 5-HT (5-Hydroxytryptamine)

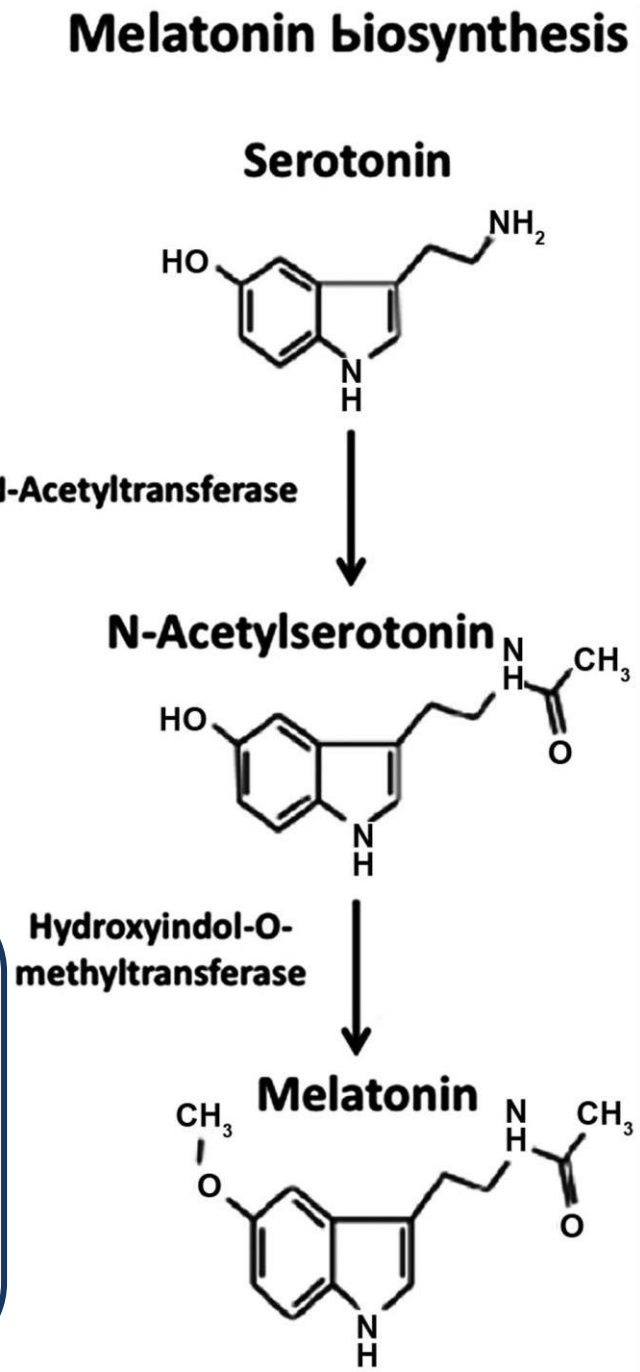
هرمون السعادة 😊

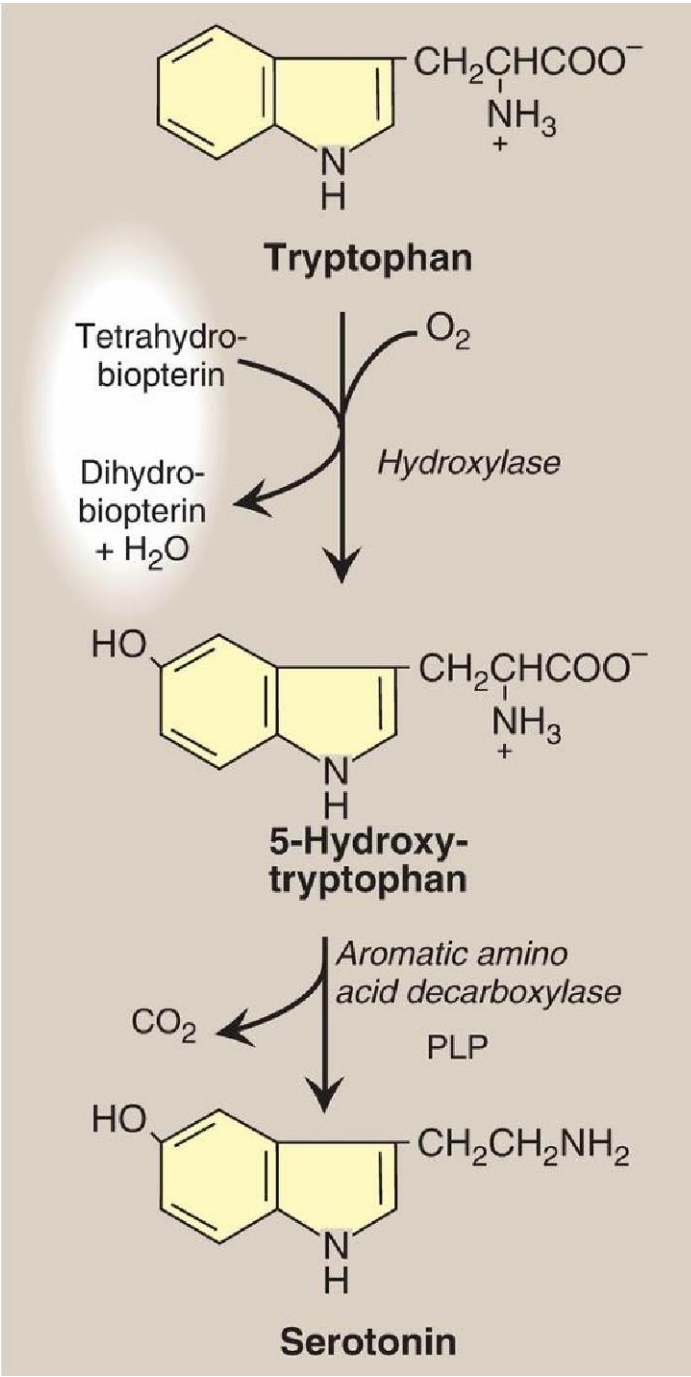
Serotonin

- Serotonin (5-HT): Regulates mood, sleep, appetite
- Precursor to melatonin in the pineal gland

Melatonin Formation

- Serotonin can be **acetylated** and then **methylated** to form **melatonin**.
- Melatonin is produced by the **pineal gland**, which is located near the **third ventricle**, and it is responsible for regulating the **sleep–wake cycle (circadian rhythm)**.





Tips from the doctor for exam questions 😳

The doctor said he may ask a question such as:
"In serotonin synthesis, what is the problem in this step?"

To answer this type of question, you must think about:

- The **enzyme**
- The **co-enzyme**
- The **enzyme that regenerates or converts the co-enzyme**

You can identify the exact problem by looking at **other related reactions**.
For example:

- If **phenylalanine, tyrosine, and tryptophan levels are all high**, this suggests that the problem is either:
  - A defect in the **enzyme that regenerates the co-enzyme**, or
  - A **co-enzyme deficiency**
  - In this pathway, the important co-enzyme is **tetrahydrobiopterin (BH_4)**, which is regenerated from **GTP.**

However:

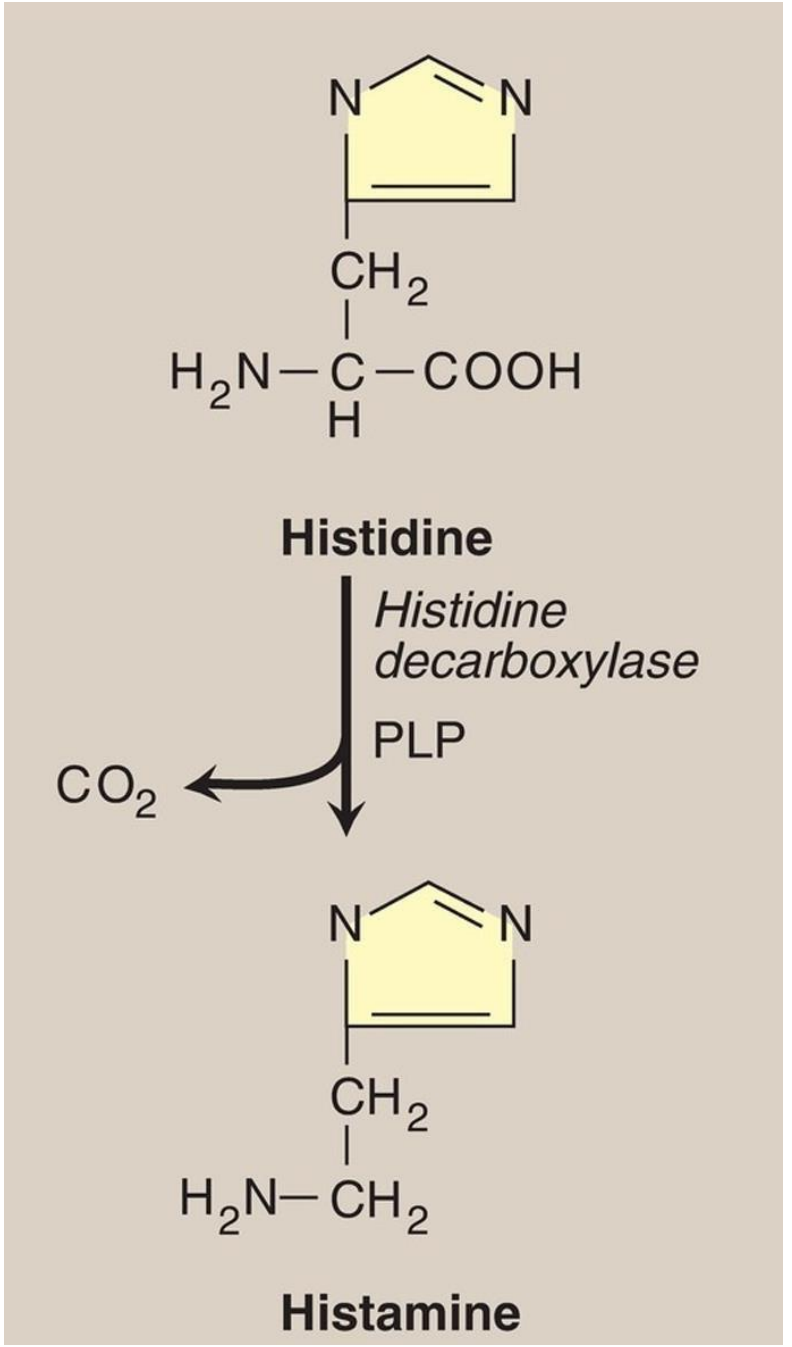
- If **only serotonin is low**, while **tryptophan is high** and **phenylalanine and tyrosine levels are normal**, this indicates that the problem is **specific to the serotonin synthesis step itself**.

This is the **logical approach** you should use when answering such questions. (Logic not habid ya shabab😉)

Histamine

- Histamine:
- Histidine Decarboxylase (PLP-dependent)
- Mediates
  - allergic responses
  - gastric acid secretion (via H2 receptors)
  - wakefulness

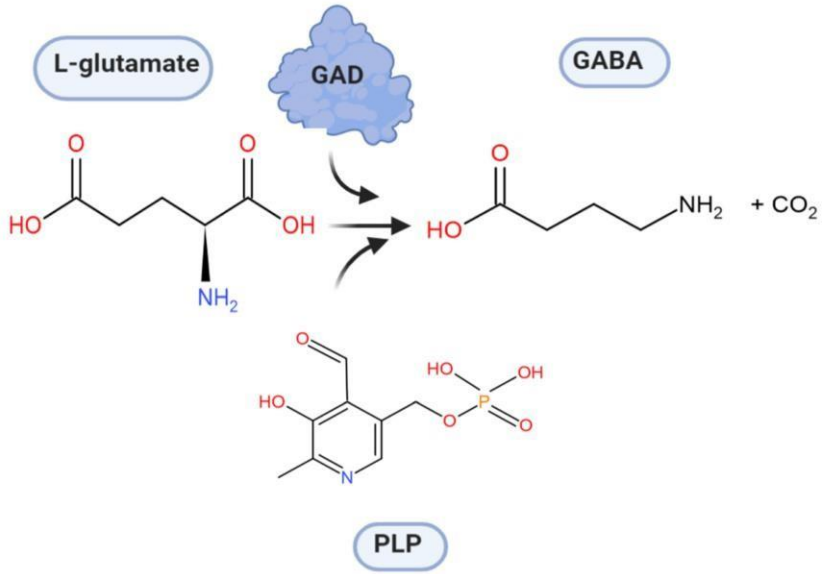
- Giving an **antihistamine** will **decrease body secretions**, such as **gastric secretions, sweating, and urine output**.
- At the same time, it can **induce sleep** and **reduce allergic symptoms**.



GABA

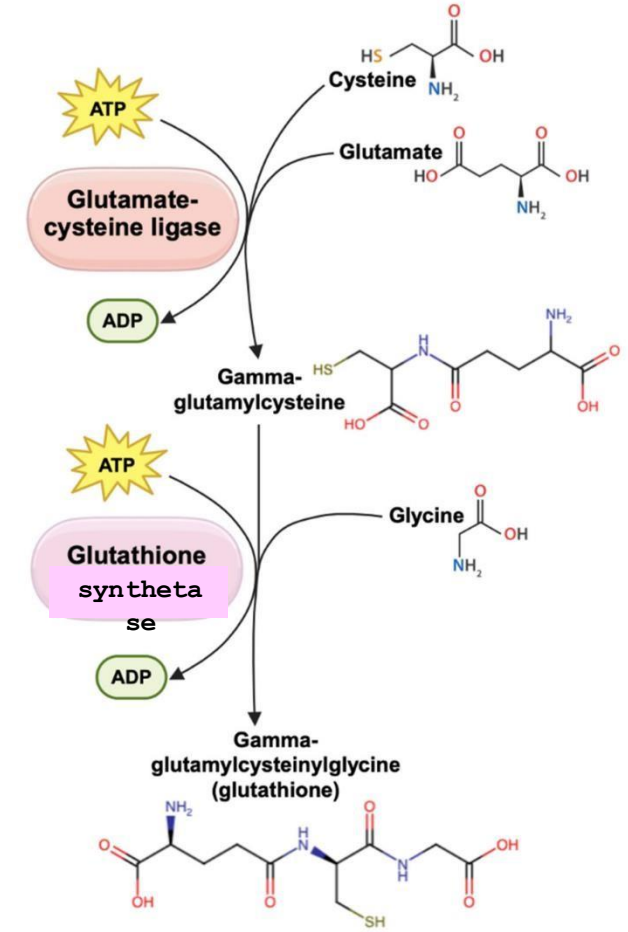
- GABA: The major inhibitory neurotransmitter
- **Produced by** Glutamate Decarboxylase (requires PLP)
- Autoantibodies against this enzyme are seen in Stiff-person syndrome and type 1 diabetes

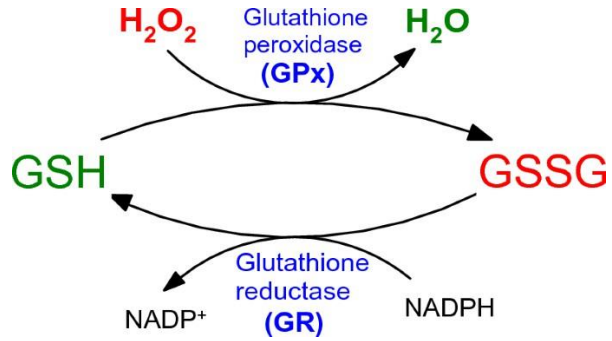
- It is released in the **central nervous system (CNS)** and in the **β-cells of the pancreas**.
- Since it is an **inhibitory neurotransmitter**, a **deficiency** of it—such as that caused by **autoantibodies against the enzyme responsible for its synthesis**—leads to an **increase in excitatory activity**. This results in **stiff-person syndrome** and can also cause **type 1 diabetes**, since it is released in pancreatic **β-cells**.



Glutathione: Synthesis and Functions

- γ-glutamylcysteinylglycine
- Major intracellular antioxidant
- Synthesis:
  - Glu + Cys (by γ-glutamylcysteine synthetase, rate-limited by cysteine) → + Gly (by glutathione synthetase).
- Glutathione Peroxidase (requires Selenium)
- Regenerated by Glutathione Reductase (requires NADPH)





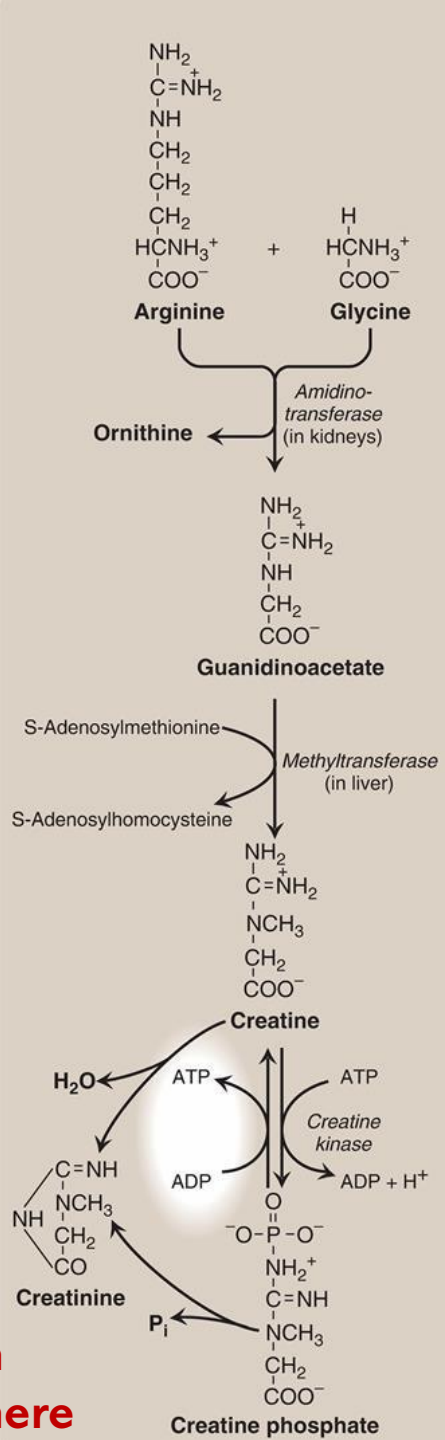
- It is the **major intracellular antioxidant** in the body, protecting against **free radicals** through the hydrogen present in its **thiol (–SH) group**. During this process, **two glutathione molecules** are oxidized and become linked by a **disulfide bond**, a reaction catalyzed by **glutathione peroxidase**, which is a **selenium-dependent enzyme**.

- Glutathione is then regenerated back to its reduced form by the enzyme **glutathione reductase**.

Creatine and Creatinine Metabolism

- Occurs in the liver
- Gly + Arg → → + SAM (methyl donor) → Creatine
- Transported to muscle/brain and phosphorylated to Phosphocreatine (high-energy reserve)
- Creatinine is the non-enzymatic, irreversible breakdown product of creatine/phosphocreatine
- Its constant production and exclusive renal filtration make serum creatinine a key marker for GFR

know here it is SAM dependunt pathway



cyclization happens here

- We talked in the summer (على أساس إنكم متذكّرين😄) about an enzyme called **creatine kinase (CK)**. It has **three isoforms**:
  - **CK-BB** in the **brain**
  - **CK-MM** in **skeletal muscle**
  - **CK-MB** in the **heart**, and it is a **marker of myocardial infarction (MI)**

Creatine Phosphate

How is **creatine phosphate** produced, and why do we produce it?

- Creatine phosphate is a **high-energy molecule** that acts as an **energy reservoir**. It is stored mainly in the **brain and skeletal muscles**.
- It is produced by the enzyme **creatine kinase (CK)** from **creatine and phosphate**.

Clinical Correlation

- If **serum creatinine levels** are high, this indicates that the **kidneys are not functioning properly**. Creatinine is therefore used as an important marker in **kidney and renal failure**.

- If **urinary creatinine levels** are high, this suggests that the **kidneys are functioning well**. However, it may also indicate that **creatine and creatine phosphate are being depleted from tissues**. In such cases, the problem may be in tissues with high energy demand, such as the **brain or skeletal muscles**.

PART II:
HEME SYNTHESIS 

Heme Synthesis: Overview & Location

- Heme is a porphyrin ring chelating an iron atom
- It is a prosthetic group for hemoglobin, myoglobin, cytochromes (P450), catalase, and peroxidase
- Erythroid cells **(Immature blood cells in bone marrow)** synthesize ~85% for hemoglobin; the liver synthesizes the rest for cytochromes

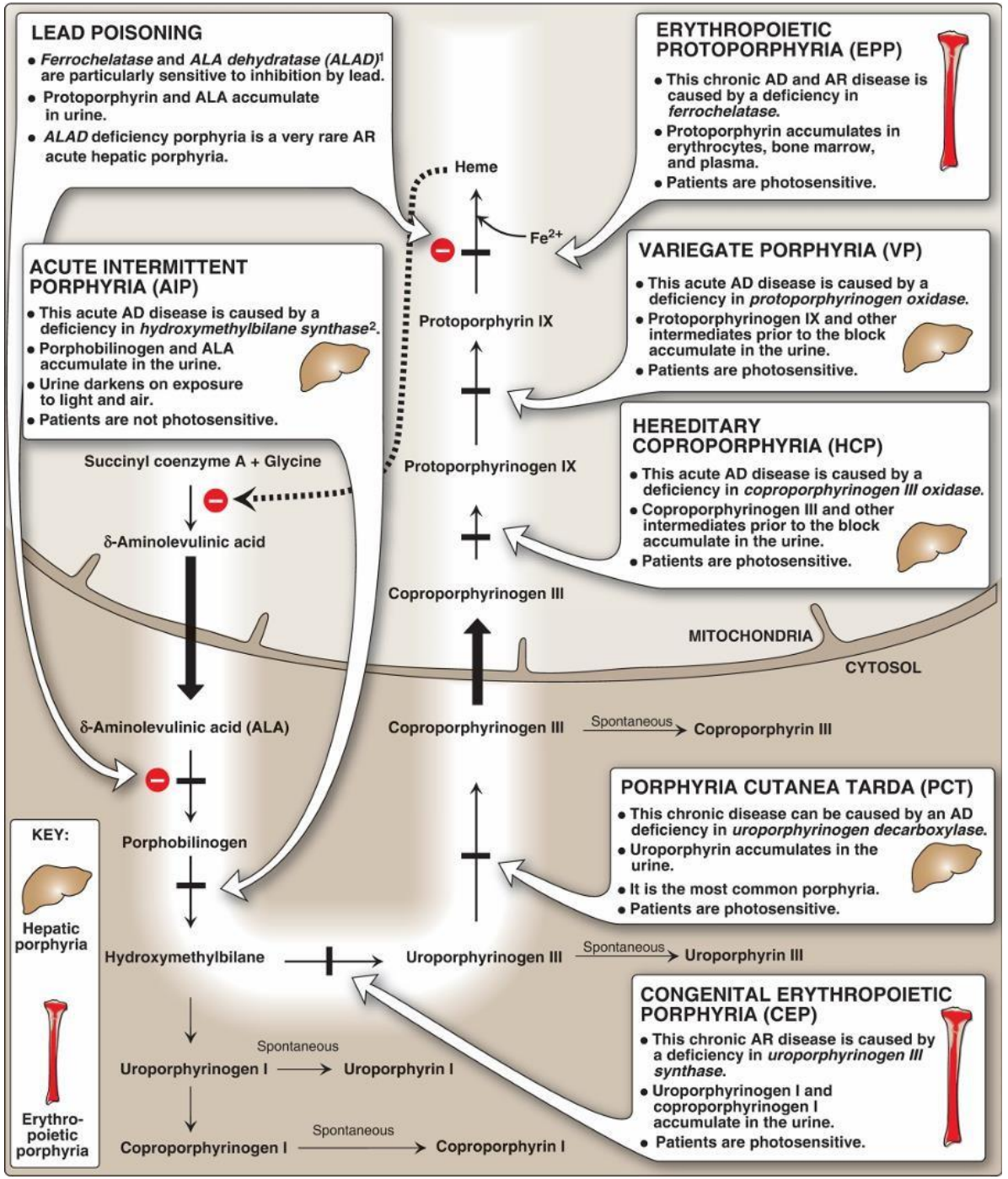
not synthesized in RBCs because there is no nucleus or mitochondria

- The pathway is partitioned between the mitochondrion and cytosol
- Precursors: Succinyl-CoA (TCA cycle) and Glycine

Heme Synthesis: Overview & Location

9 Step Mechanism

The **First step** and the **last 3 steps** occurs in **mitochondrion**, while the **intermediates** occurs inside the **cytosol.**

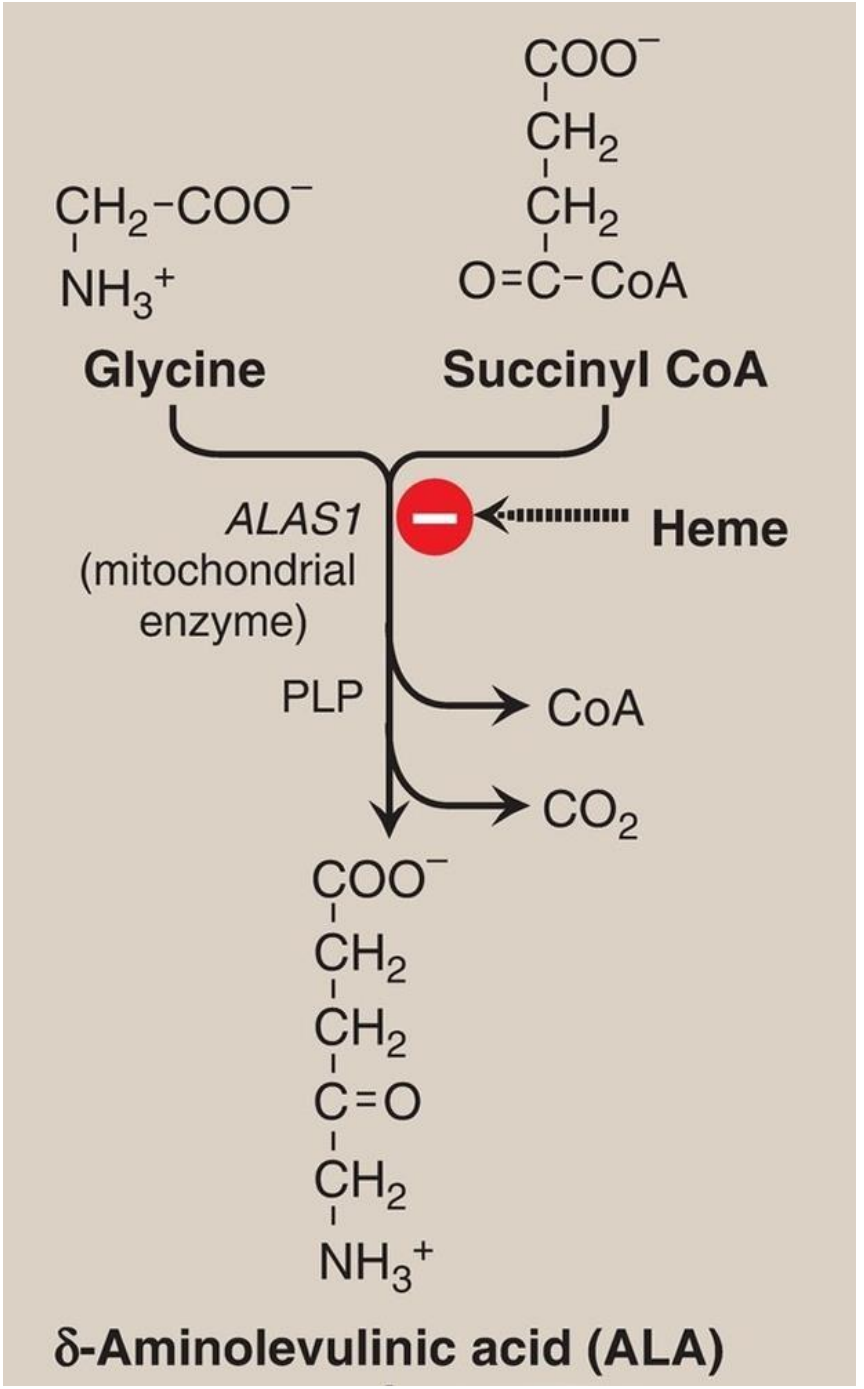


Heme Synthesis

You must be familiar with the product and the enzyme that catalyzes each step.
There is a summary in the last slides ☺

Step 1: Formation of δ-Aminolevulinic Acid (ALA)

- Mitochondrial
- ALA Synthase (ALAS) (PLP)
- The committed and rate-limiting step in heme synthesis
- There are two isozymes: ALAS1 (liver, regulated) and ALAS2 (erythroid, constitutive)
- Heme inhibits ALAS1



Step 1 (Rate-limiting step)

- Glycine combines with an energy component called **succinyl-CoA** through a **decarboxylation reaction** that is **PLP-dependent**, producing **δ-aminolevulinic acid (ALA)**.

- The enzyme that catalyzes this step is **ALA synthase**, which has **two isoforms**:
  - **ALAS2** in **erythroid cells**
  - **ALAS1** in the **liver**

Difference between them:

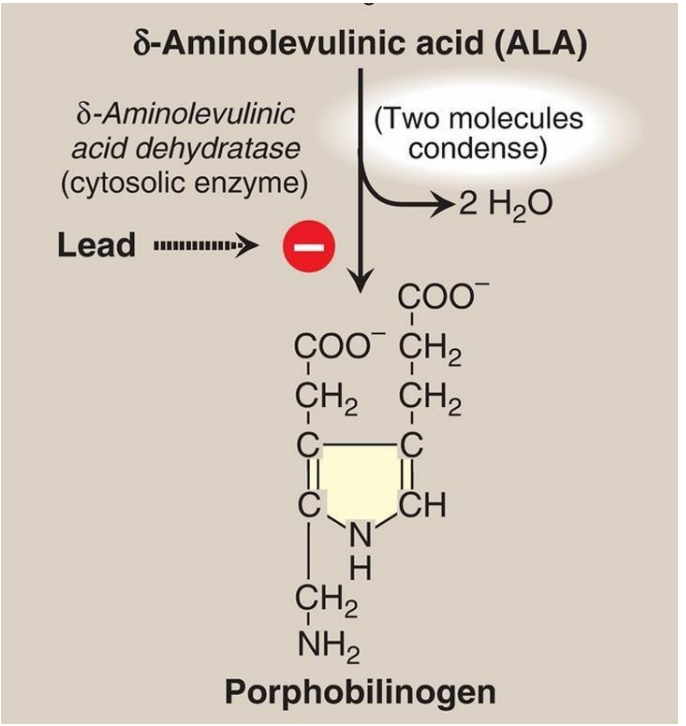
- In **erythroid cells**, heme must be produced continuously for hemoglobin synthesis. Therefore, ALAS2 is **constitutively expressed** and is not significantly affected by up- or down-regulation.
- In the **liver**, heme is used to synthesize **catalase, peroxidase, and cytochrome P450** enzymes. Its production depends on the patient's condition (drug intake, liver disease, illness, etc.), so ALAS1 is **regulated**.

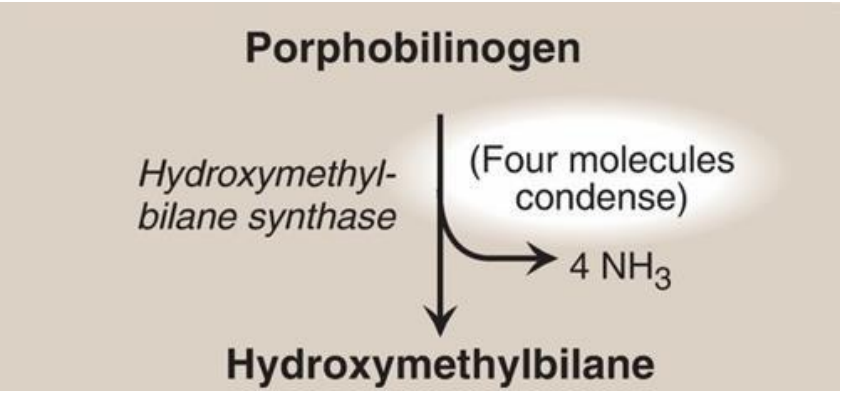
- High levels of **heme inhibit ALA synthase** (negative feedback).

- This step is the **rate-limiting**, **committed**, and **most important step** in heme biosynthesis.

Steps 2 & 3: From ALA to Porphobilinogen (PBG)

- Step 2 (Cytosol): Porphobilinogen (PBG)
  - ALA Dehydratase (Porphobilinogen Synthase)
  - Toxicity: highly sensitive to lead (↑ALA)
  - Major biochemical lesion in lead poisoning
- Step 3 (Cytosol): 4 PBG → Hydroxymethylbilane via PBG Deaminase (Hydroxymethylbilane synthase)





Step 2:

- Two ALA molecules combine to form the first nucleus of the **five-membered pyrrole ring**, producing **porphobilinogen**.

Enzyme: **Porphobilinogen synthase**
By-product: **H_2O**
This reaction is **inhibited by lead**

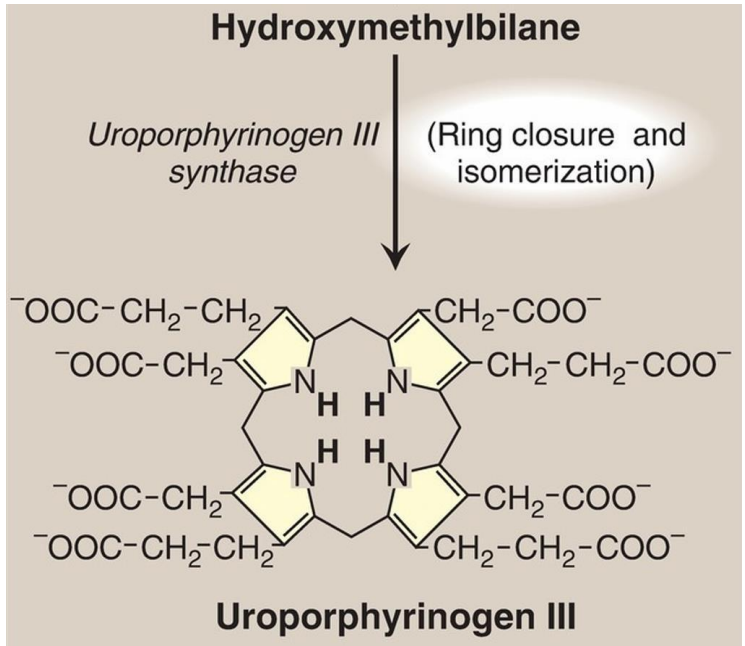
Step 3:

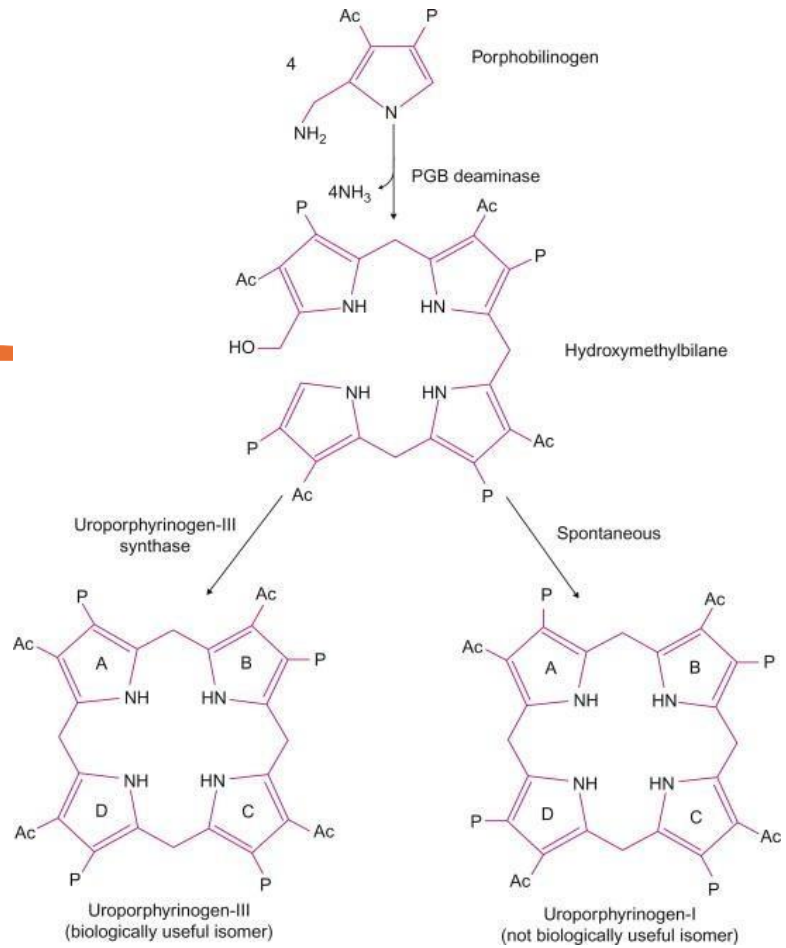
- Four porphobilinogen molecules combine to form **hydroxymethylbilane**, an **open-chain structure**.

Enzyme: **Hydroxymethylbilane synthase**
By-product: **4 NH_3**

Steps 4 & 5: Formation of Uroporphyrinogen III

- Step 4 (Cytosol): spontaneous cyclization to Uroporphyrinogen I
- Step 5 (Cytosol): Uroporphyrinogen III Synthase
- A deficiency causes Congenital Erythropoietic Porphyria





Steps 4 & 5: (Check the previous picture while reading this slide)

There are **two pathways**:

1- Spontaneous (non-enzymatic) pathway (Step 4)
Ring closure occurs spontaneously, producing an ordered isomer with alternating **propionyl (P)** and **acetyl (Ac)** groups.

This forms **uroporphyrinogen I**, which is an **inactive isomer**.

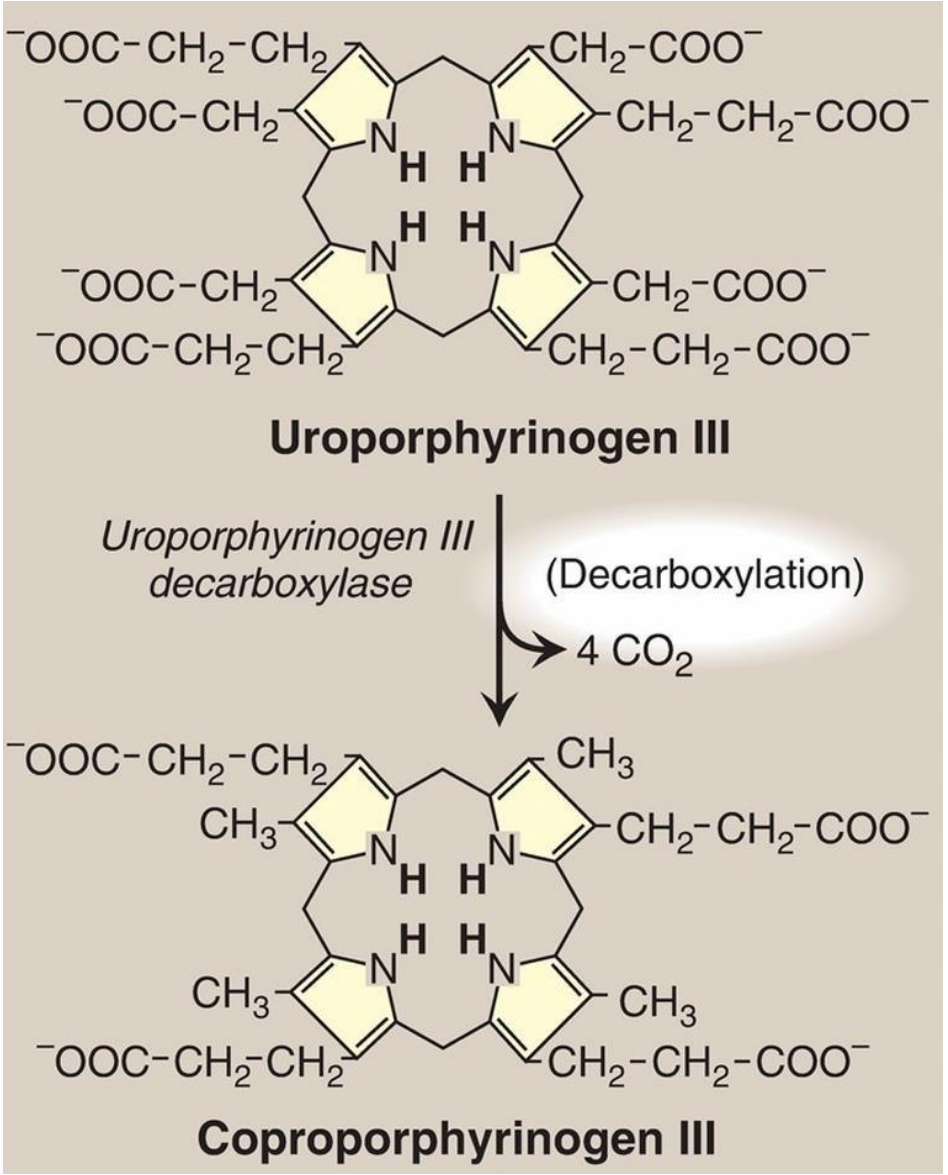
2- Enzymatic pathway (Step 5)
To produce a non-ordered structure, an enzyme is required. A switch occurs in **ring D** between acetyl and propionyl groups, allowing proper ring closure.

This produces **uroporphyrinogen III**, the **active isomer**.

Enzyme: **Uroporphyrinogen III synthase**
Deficiency of this enzyme causes a **type of porphyria**

Decarboxylation to Coproporphyrinogen III

- Step 6 (Cytosol): decarboxylation to methyl groups
- Uroporphyrinogen Decarboxylase
- Product: Coproporphyrinogen III
- Clinical Note: Deficiency causes Porphyria Cutanea Tarda, the most common porphyria, associated with photosensitivity and skin fragility



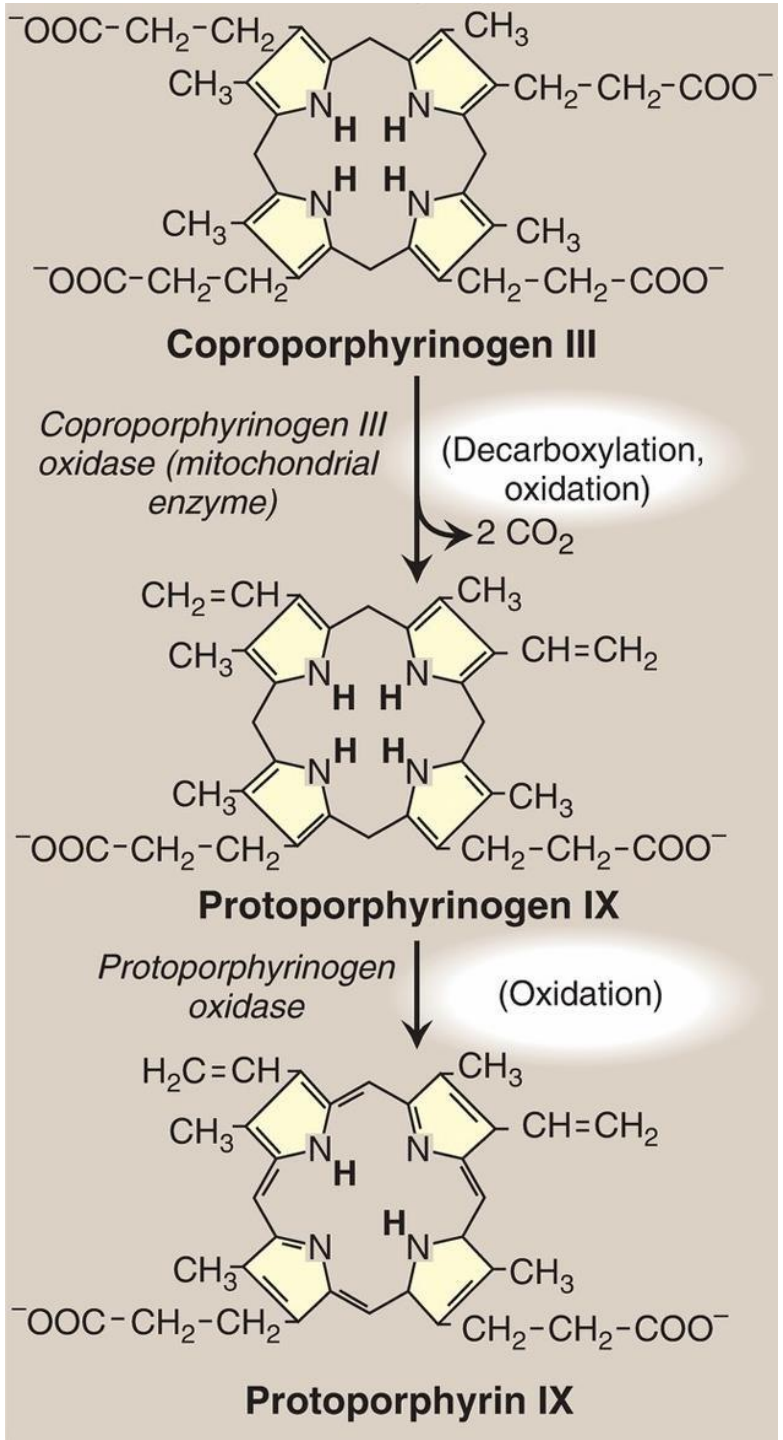
Step 6:

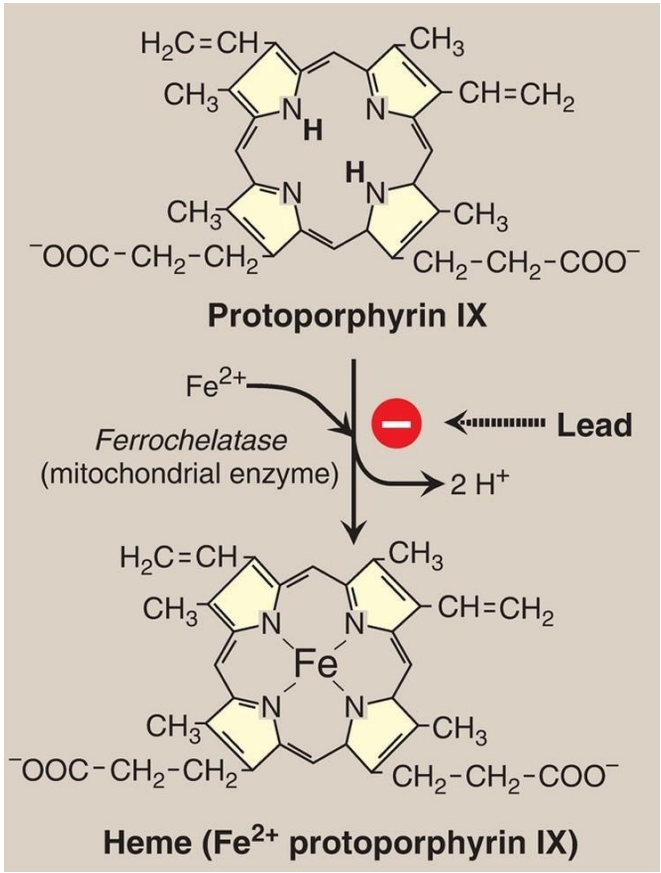
- A **decarboxylation reaction** occurs in which the **acetyl groups are converted to methyl groups**, releasing **4 CO_2 molecules**.

Product: **Coproporphyrinogen III**
Deficiency of this decarboxylase causes **another type of porphyria**, which is the **most common type.**

Steps 8 & 9: Mitochondrial Steps to Heme

- Coproporphyrinogen Oxidase & Protoporphyrinogen Oxidase (inhibited by lead)
- Final Step (Mitochondrion): (Ferrochelatase, lead)
- Iron deficiency results in Zinc being inserted instead, forming zinc protoporphyrin





Steps 7, 8, and 9:

Coproporphyrinogen III enters the **mitochondria**, where:

- Decarboxylation with oxidation occurs, producing **2 CO_2** and forming **2 vinyl groups** on the ring. **(Step 7)**
- Further oxidation creates **double bonds** in the ring via **protoporphyrinogen IX oxidase. (Step 8)**

This results in **protoporphyrin IX**, the final **porphyrin ring**.

The last step is the addition of **iron (Fe^{2+})**: **(Step 9)**

- Iron binding to an organic molecule is called **chelation.**

Enzyme: **Ferrochelatase.**
This enzyme is also **inhibited by Lead.**

👉 **Lead inhibits two steps**:
1- Formation of porphobilinogen (ALA → porphobilinogen)
2- Insertion of iron into protoporphyrin IX.

Iron Deficiency 

In **iron deficiency**, excess **zinc** may bind in place of iron, producing an ineffective molecule called **zinc protoporphyrin**, which cannot perform the normal functions of heme.

Summary

Step 1 (MOST IMPORTANT – Rate-limiting & Committed) 📍

- **Reaction:**
  Glycine + Succinyl-CoA → δ-Aminolevulinic acid (ALA)

Enzyme: ALA synthase

- **ALAS1** → Liver (regulated)
- **ALAS2** → Erythroid cells (constitutive)

Cofactor: PLP (Vitamin B6)

Key notes:

- Occurs in **mitochondria**
- **Inhibited by heme** (negative feedback)
- **Rate-limiting & committed step**

Step 2 ❓

Reaction:

2 ALA → Porphobilinogen

- **Enzyme: Porphobilinogen synthase**
- **By-product:** H_2O
- **Key notes:**
  - First **pyrrole ring** formation
  - **Inhibited by lead (Pb)**

Summary

Step 3
Reaction:
4 Porphobilinogen → Hydroxymethylbilane (open-chain)

- **Enzyme: Hydroxymethylbilane synthase**
- **By-product:** 4 NH_3
- **Key notes:**
  - Still an **open structure**
  - Precursor for ring closure

Steps 4 & 5 🔗
Reaction:
Hydroxymethylbilane → Uroporphyrinogen III

- **Enzyme: Uroporphyrinogen III synthase**
- **Key notes:**
  - **Uroporphyrinogen III = active isomer**
  - **Uroporphyrinogen I** (spontaneous pathway) = **inactive**
  - Deficiency → **Porphyria**

Summary

Step 6

Reaction:

Uroporphyrinogen III → Coproporphyrinogen III

- **Enzyme: Uroporphyrinogen decarboxylase**
- **By-product:** 4 CO_2
- **Key notes:**
  - Acetyl groups → **Methyl groups**
  - Deficiency → **Most common porphyria**

Steps 7 & 8

Reaction:

Coproporphyrinogen III → Protoporphyrin IX

- **Enzymes:**
  - Coproporphyrinogen oxidase
  - **Protoporphyrinogen IX oxidase**
- **Key notes:**
  - Occurs in **mitochondria**
  - Oxidation + double bond formation

Step 9 (Final Step)

Reaction:

Protoporphyrin IX + Fe^{2+} → Heme

- **Enzyme: Ferrochelatase**
- **Key notes:**
  - Iron insertion = **chelation**
  - **Inhibited by lead**
  - Lead inhibits **Step 2 & Step 9**

Additional Resources:

رسالة من الفريق العلمي:

نصيحة لِمن لا يُصلي الوتر!

حزنت ! كُسِرت ! الابواب مُغلقة بوجهك ! ليس لديك أحد تلجأ إليه ! ظُلِمت ! تراكمت الديون عليك ! خُذِلت ! تُرِكت وحيدًا ! علاجك بين يديك .. ركعة وتر وخشوع وشعور صادق ويقين بالإجابة وسجود طويل كل ما سبق كفيل بأن يُزيح همك ! عندما تعلم أن الله يسمعك لا تحتاج إلى عِباده الجأ إلى الله وسيبرد قلبك ويهدأ شعورك ويُنور وجهك ويُفتح لك باب الرحمن وتذهب وحدتك بقربك من ربك ويأخذ الله حقك مِن مَا أساء لك فقط سجود طويل فى جوف الليل .

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			
V1 → V2			