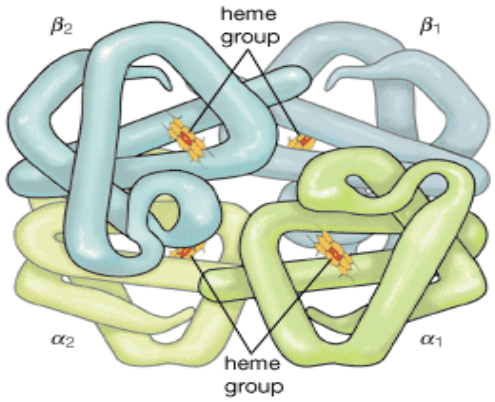
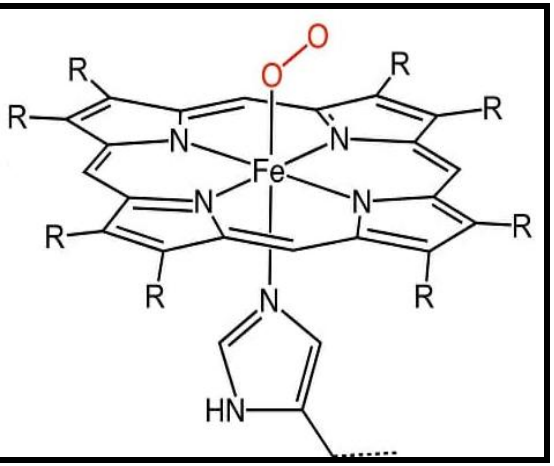
Mansoura National University
Faculty of Medicine

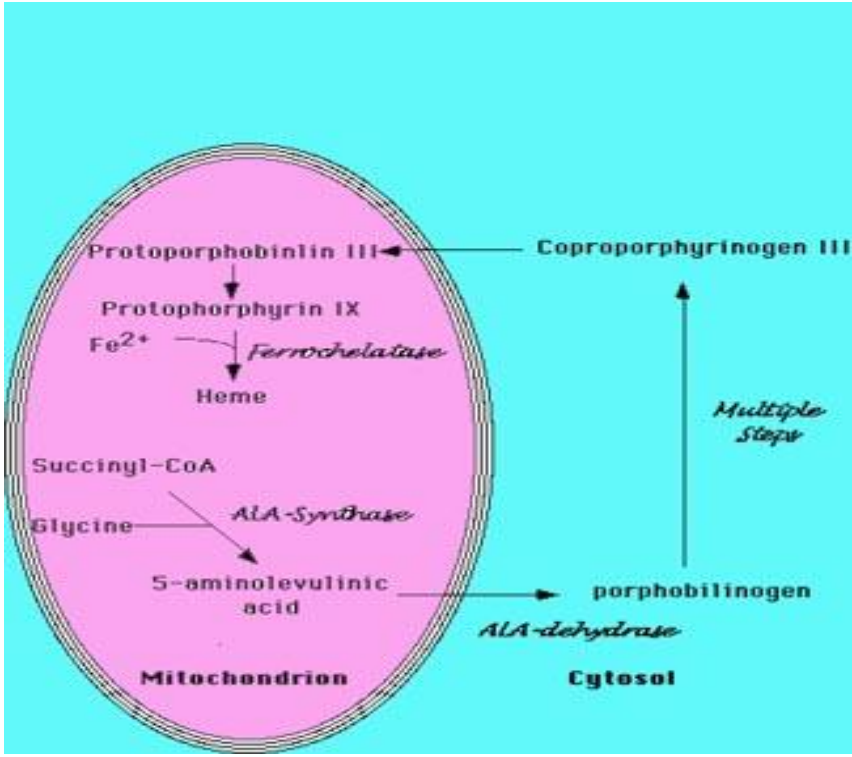
Level: 1

Semester: 2

Heme synthesis







By

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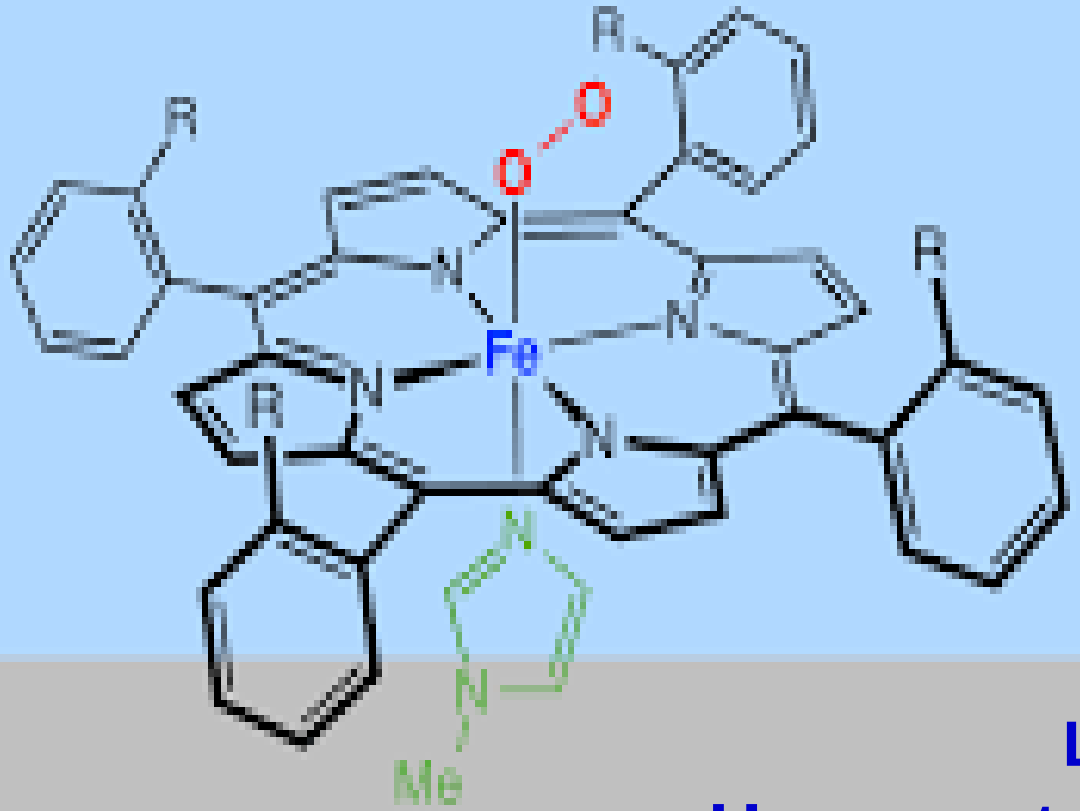
Agenda

- Heme and hemoproteins.
- Porphyrins structure.
- Biosynthesis of heme.
- Regulation of heme biosynthesis.
- Disorders of heme biosynthesis (Porphyrias).

Learning Outcomes (LOs)

At the end of this session, the students should be able to:

- Identify hemoproteins and their functions.
- Understand the structure of porphyrins.
- Identify the steps of heme biosynthesis.
- Understand the regulation of heme biosynthesis.
- Discuss metabolic disorders of heme biosynthesis (Porphyrias).
- Correlate their knowledge to a clinical situation.

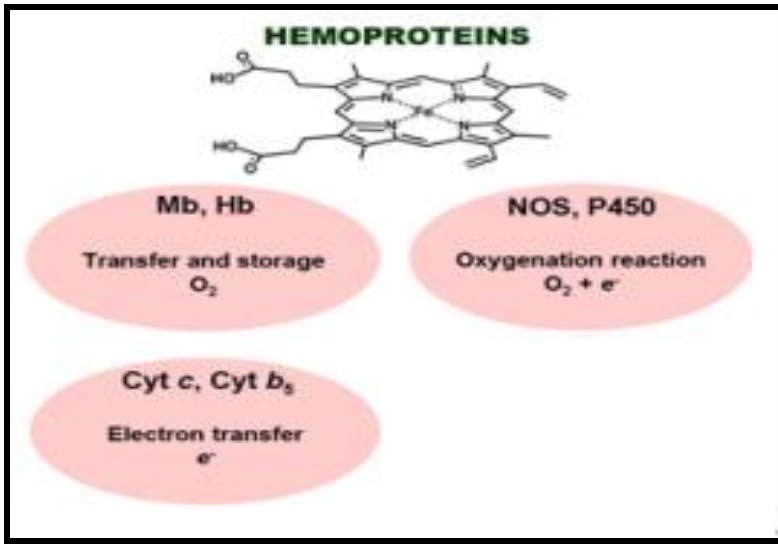


LO 1
Hemoproteins and their functions

Heme

❖ **Heme** is an **essential prosthetic group** in proteins, known as **hemoproteins**, such as **hemoglobin**, **myoglobin**, **cytochromes**, **catalases** and **heme peroxidase**.

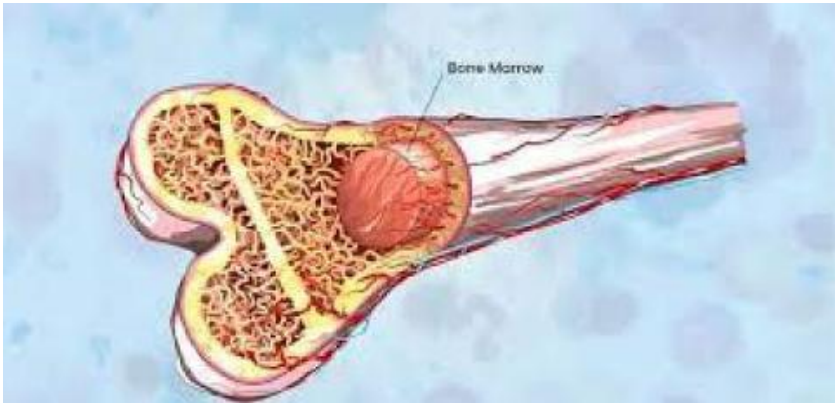
❖ These proteins are necessary to perform diverse biological functions as **oxygen transport and storage** (hemoglobin and myoglobin), **electron transport** (cytochrome c), **degradation of H2O2** (catalase) and other chemical **catalysis**.

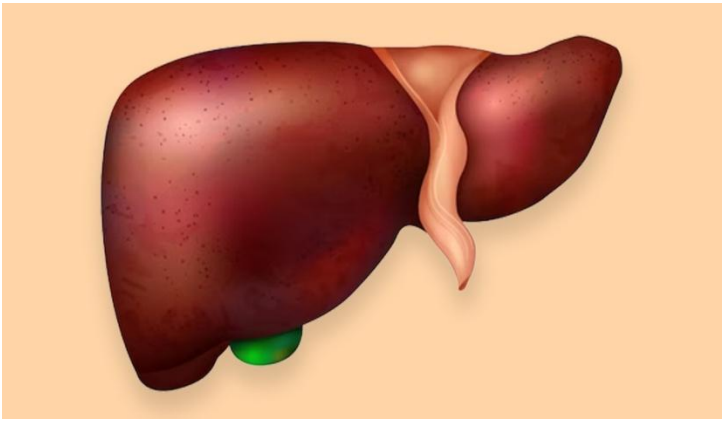


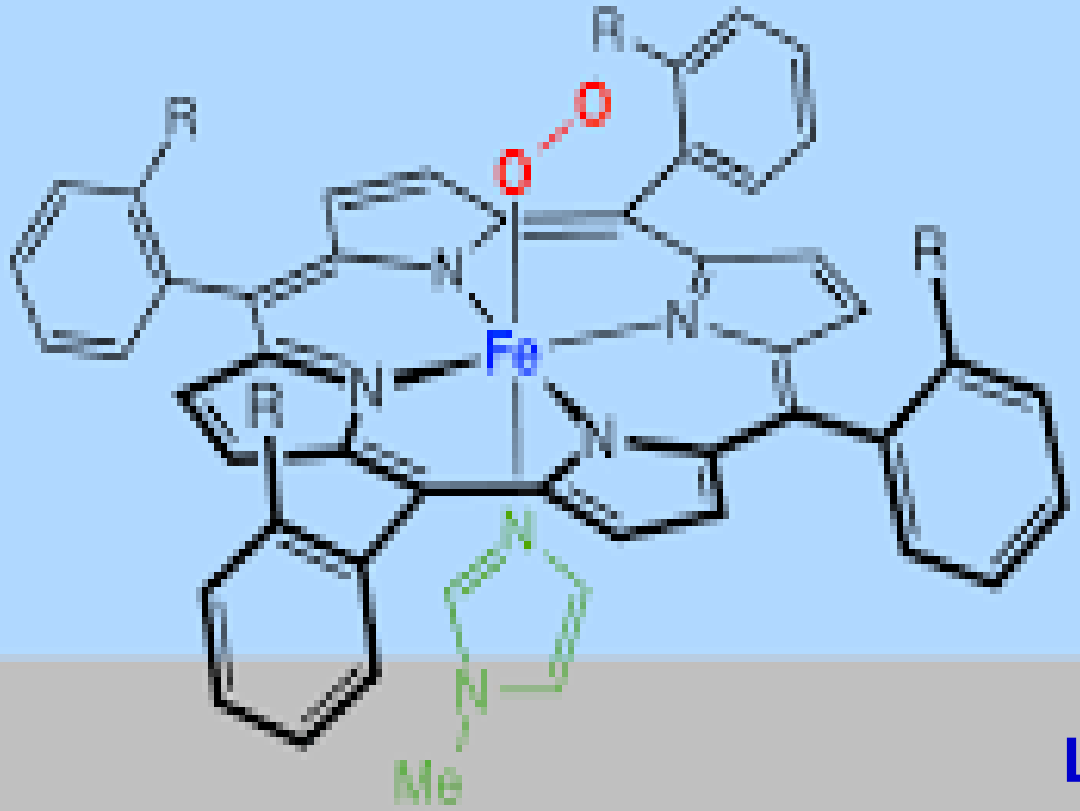
Heme

❖ **Heme is the most important porphyrin containing compound, synthesized from porphyrins and iron.**

❖ **The major tissues for heme synthesis are bone marrow by developing erythrocytes (not mature erythrocytes) and the liver by hepatocytes.**



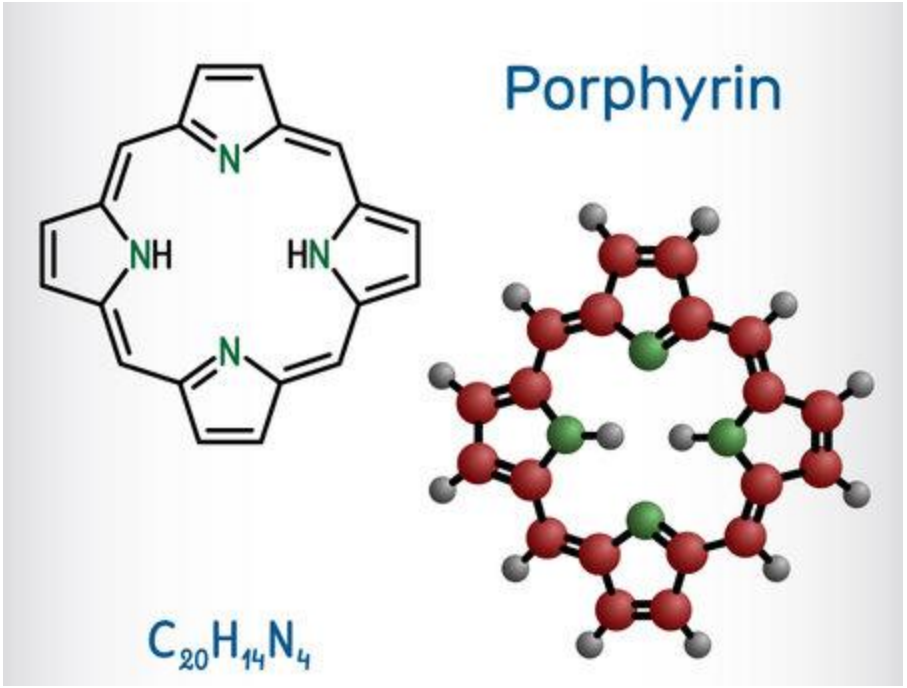


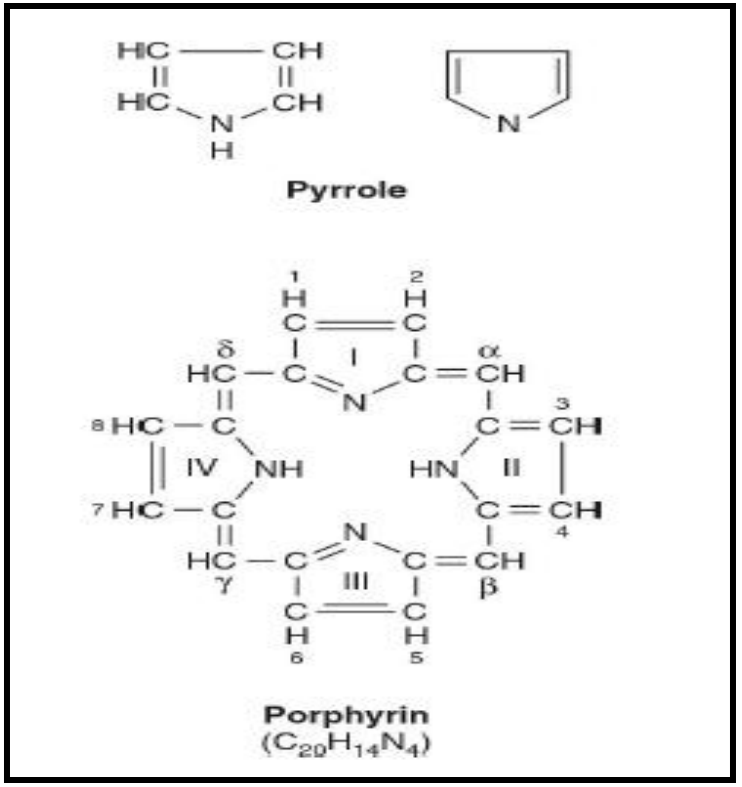


LO 2
Structure of porphyrins

Porphyrins

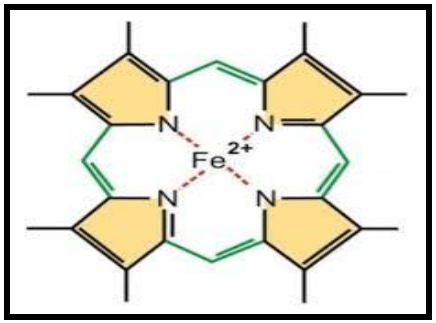
❖ **Porphyrins** are cyclic compounds formed by the linkage of four pyrrole rings (tetrapyrroles) through methyne (——HC—) bridges.



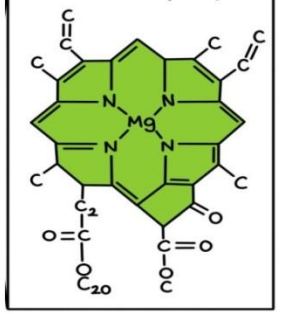


Porphyrins

❖ **Porphyrins** can form complexes with **metal ions** that form coordinate bonds to the **nitrogen atom of each pyrrole ring**.



Chlorophyll

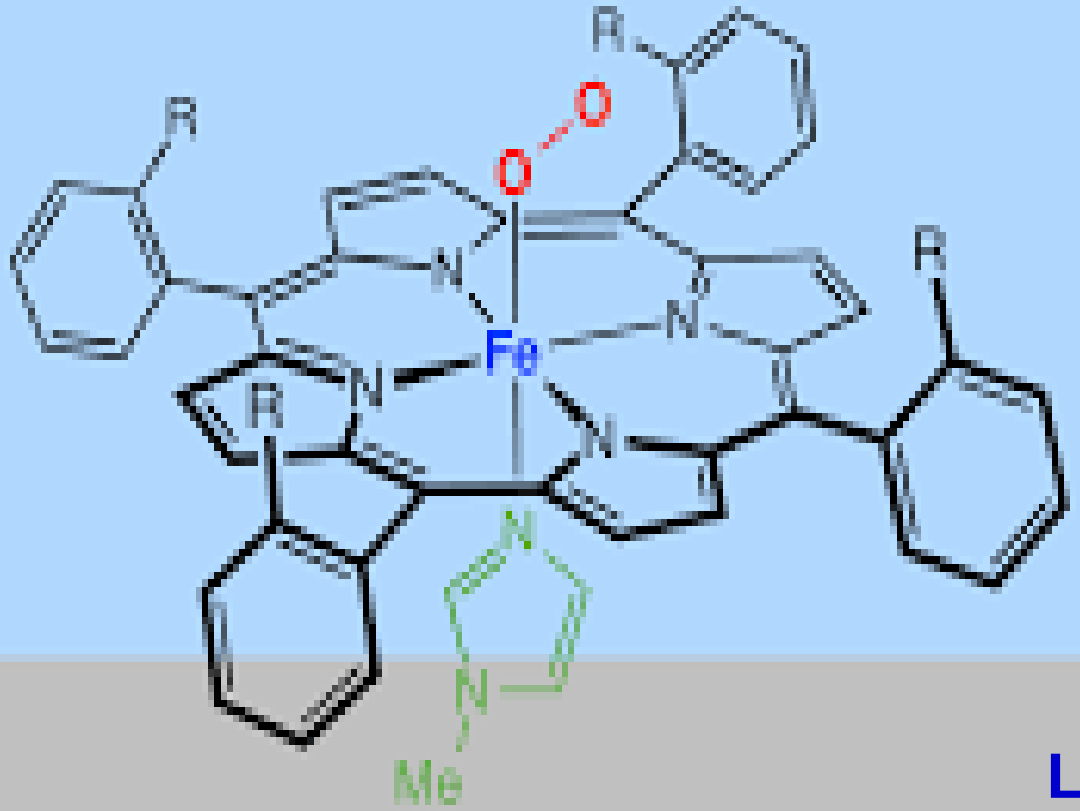


❖ ***Examples:***

✓**iron porphyrins** (heme of hemoglobin)

✓**magnesium-containing porphyrin chlorophyll** (photosynthetic pigment of plants)

→ **metalloproteins**



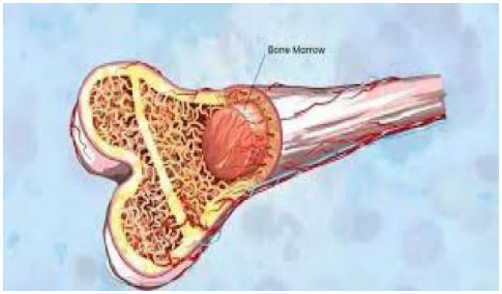
LO 3

Steps of heme biosynthesis

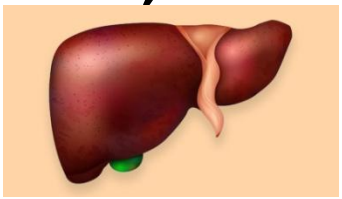
Biosynthesis of heme

❖ **Heme biosynthesis involves both cytosolic and mitochondrial reactions and intermediates.**

❖ **It occurs in most mammalian cells except mature erythrocytes, which lack mitochondria.**



❖ **Approximately 85% of heme synthesis occurs in erythroid precursor cells in the bone marrow, and the majority of the remainder in hepatocytes.**



Biosynthesis of heme

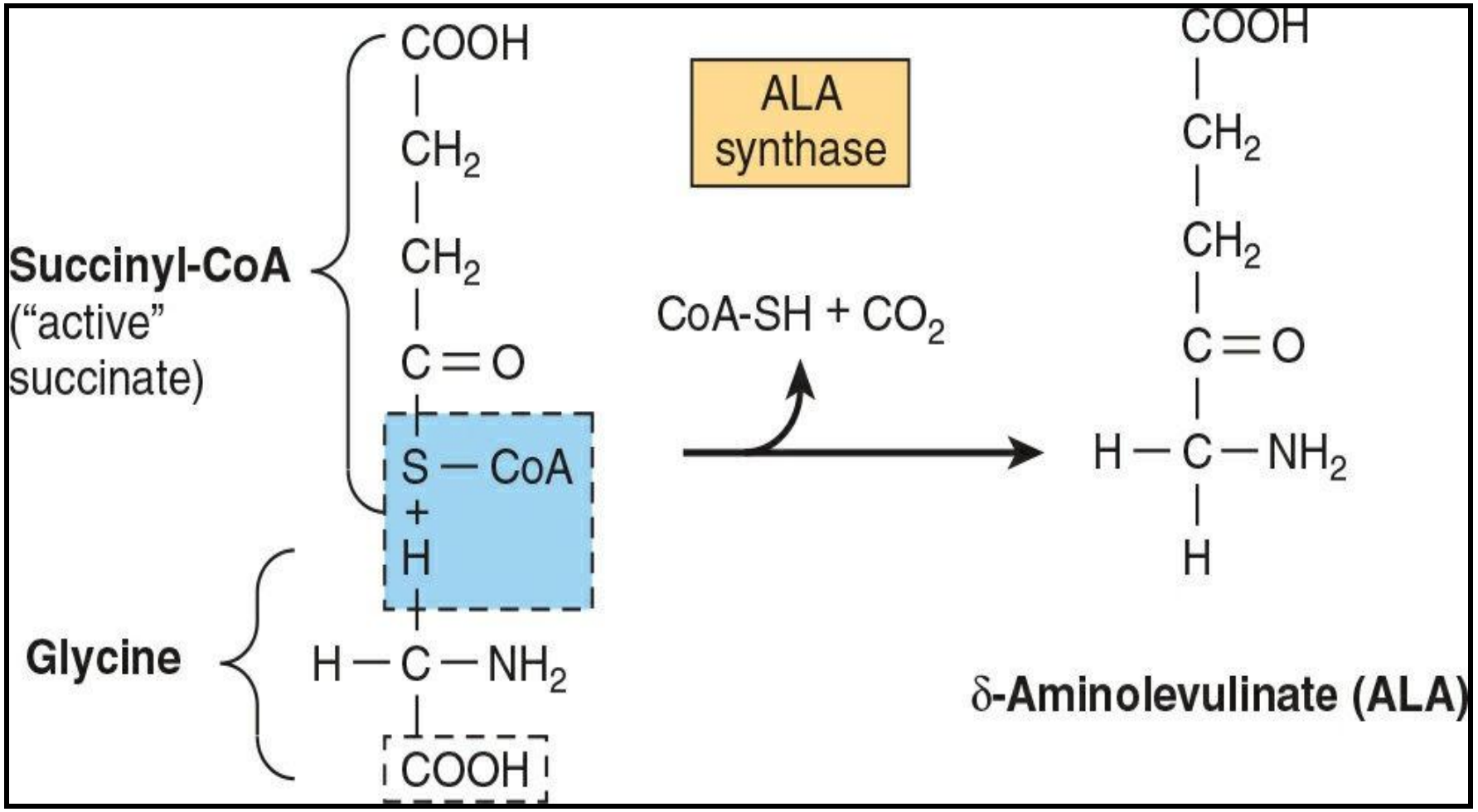
❖ ***Steps:***

1) **In mitochondria, condensation of succinyl-CoA and glycine, in a pyridoxal phosphate-dependent reaction (vitamin B6-dependent reaction), is catalyzed by mitochondrial δ-aminolevulinate synthase (ALA synthase) ⟶ *δ-aminolevulinate*.**

- **Formation of δ-aminolevulinate is rate-limiting for porphyrin biosynthesis in mammalian liver.**

Biosynthesis of heme

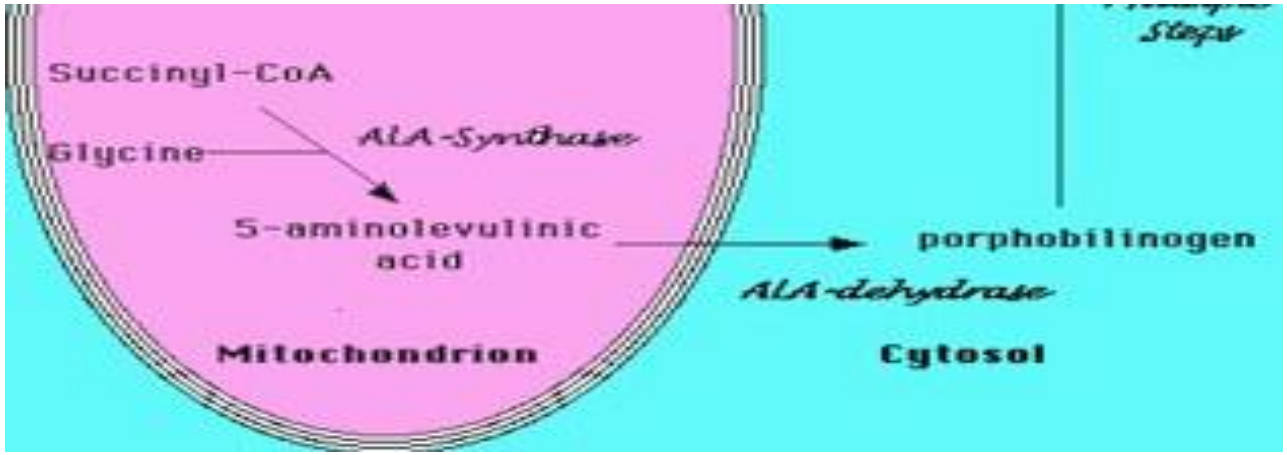
❖ ***Steps:***



Biosynthesis of heme

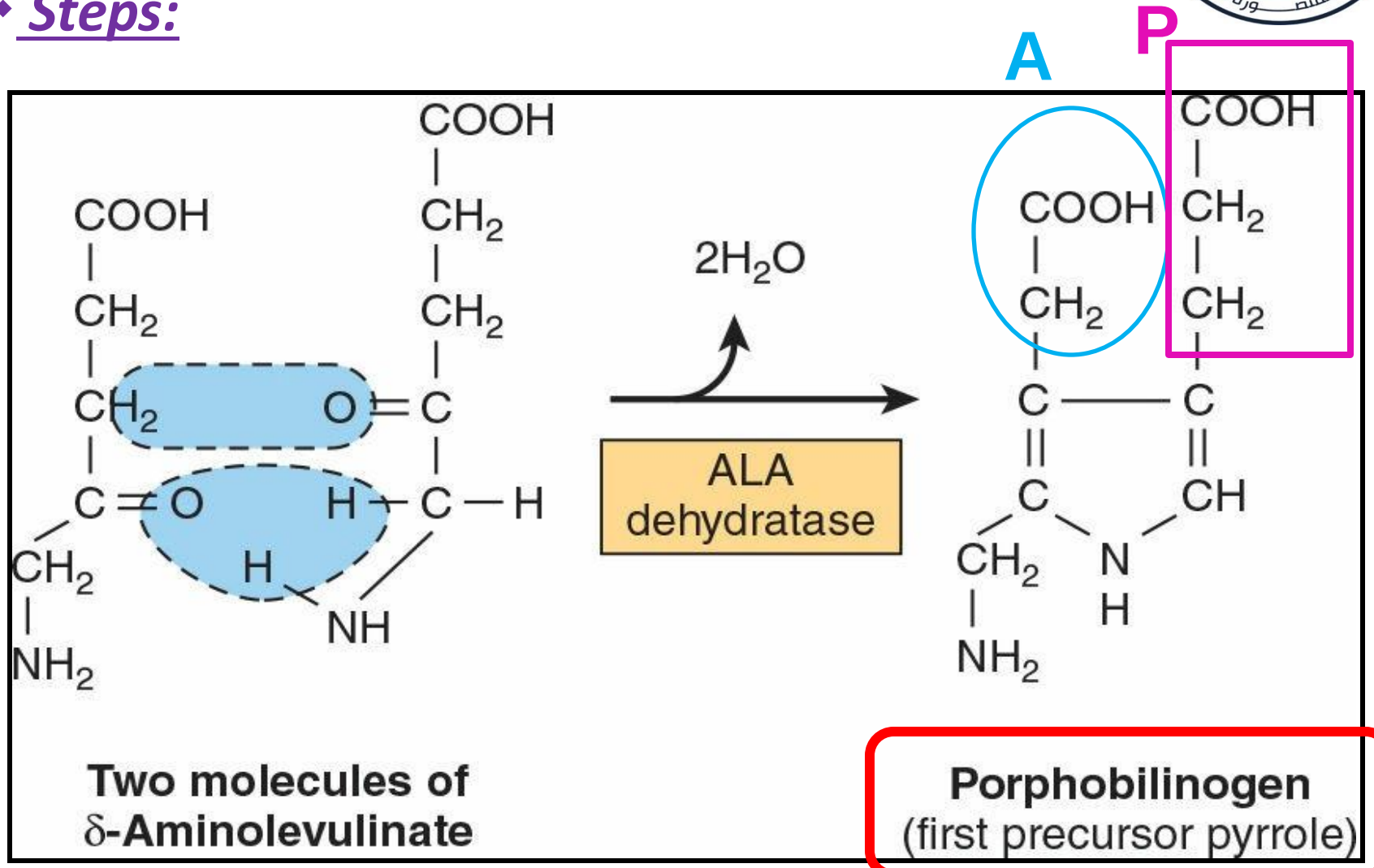
❖ ***Steps:***

2) Following the exit of δ-aminolevulinate into the cytosol, the reaction catalyzed by cytosolic ALA dehydratase (porphobilinogen synthase) condenses two molecules of ALA ⟶ *porphobilinogen*.



Biosynthesis of heme

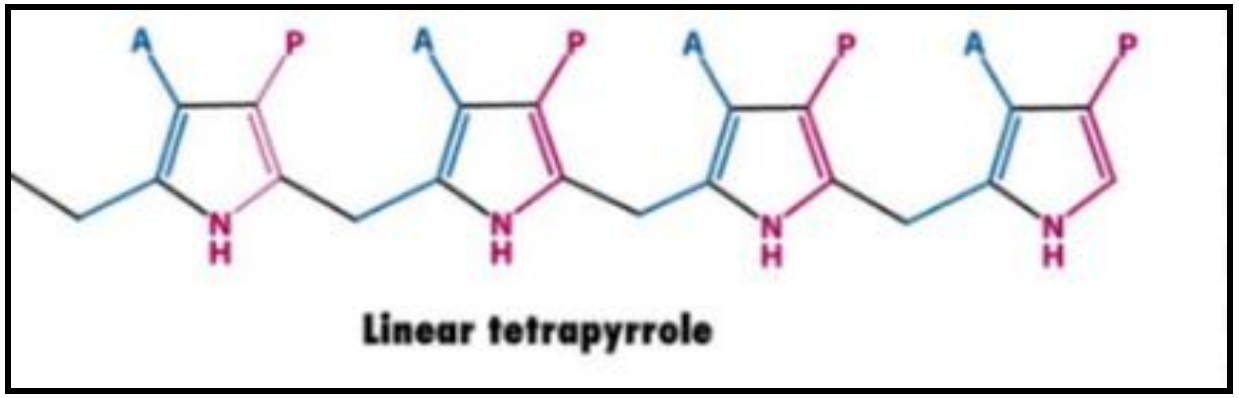
❖ ***Steps:***



Biosynthesis of heme

❖ ***Steps:***

3) Head-to-tail condensation of four molecules of porphobilinogen is catalyzed by cytosolic hydroxymethylbilane synthase (uroporphyrinogen I synthase) ⟹ linear tetrapyrrole hydroxymethylbilane.



Linear tetrapyrrole

Biosynthesis of heme

❖ ***Steps:***

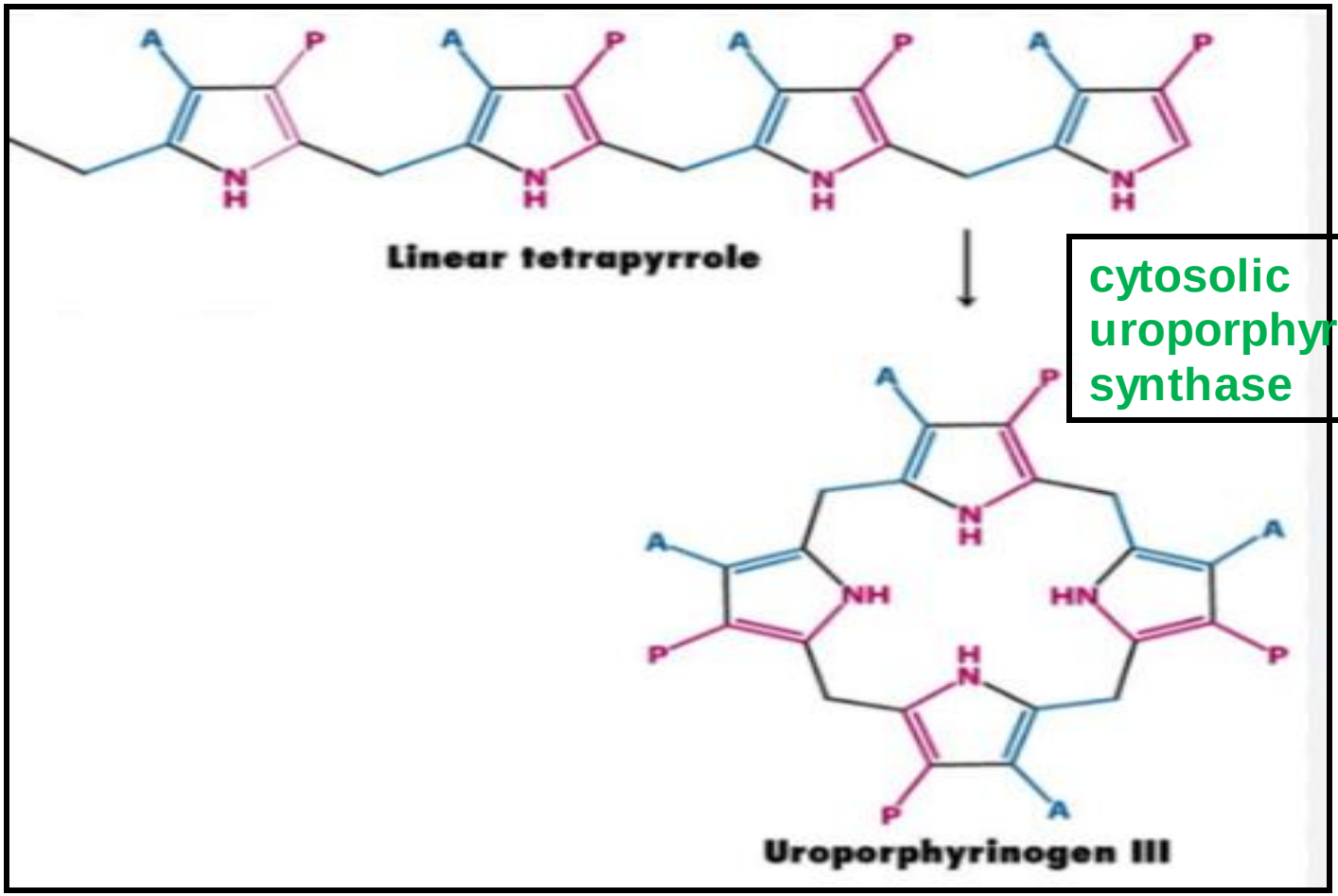
4) Subsequent **cyclization of hydroxymethylbilane** is catalyzed by **cytosolic uroporphyrinogen III synthase**,

➡ **uroporphyrinogen III.**

- **Hydroxymethylbilane can undergo spontaneous cyclization forming uroporphyrinogen I, but under normal conditions, the uroporphyrinogen formed is almost exclusively the type III isomer.**

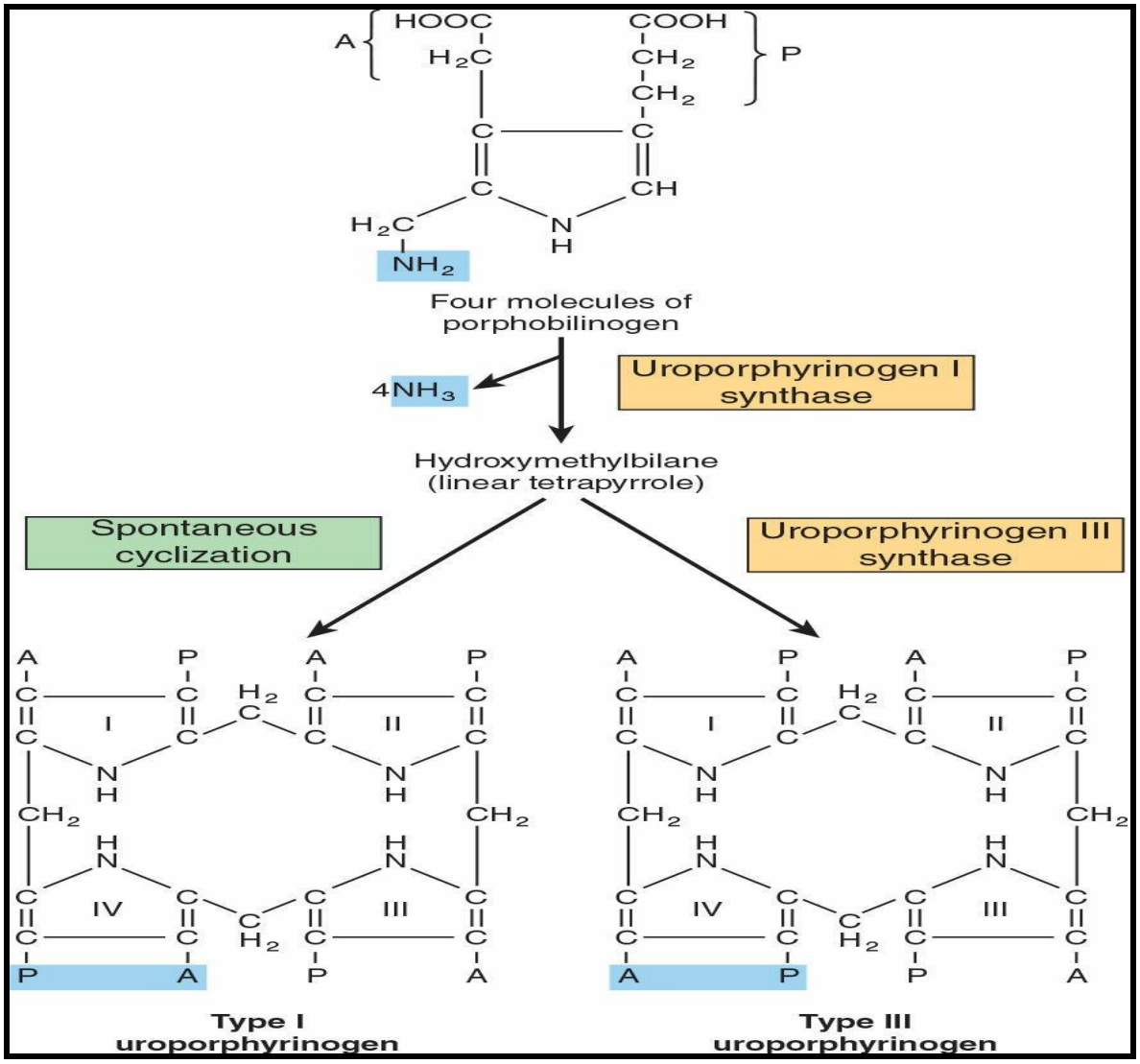
Biosynthesis of heme

❖ ***Steps:***



Biosynthesis of heme

❖ ***Steps:***

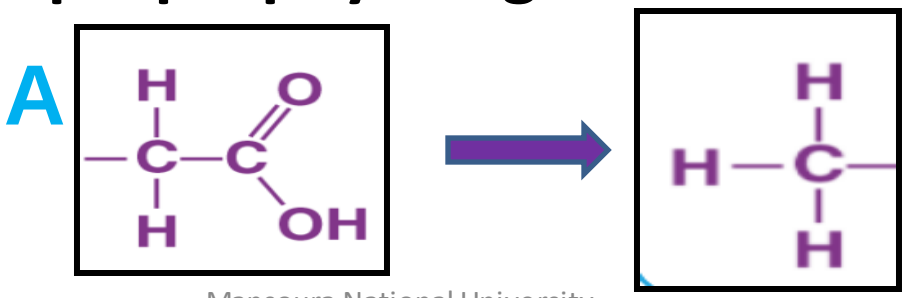


Biosynthesis of heme

❖ ***Steps:***

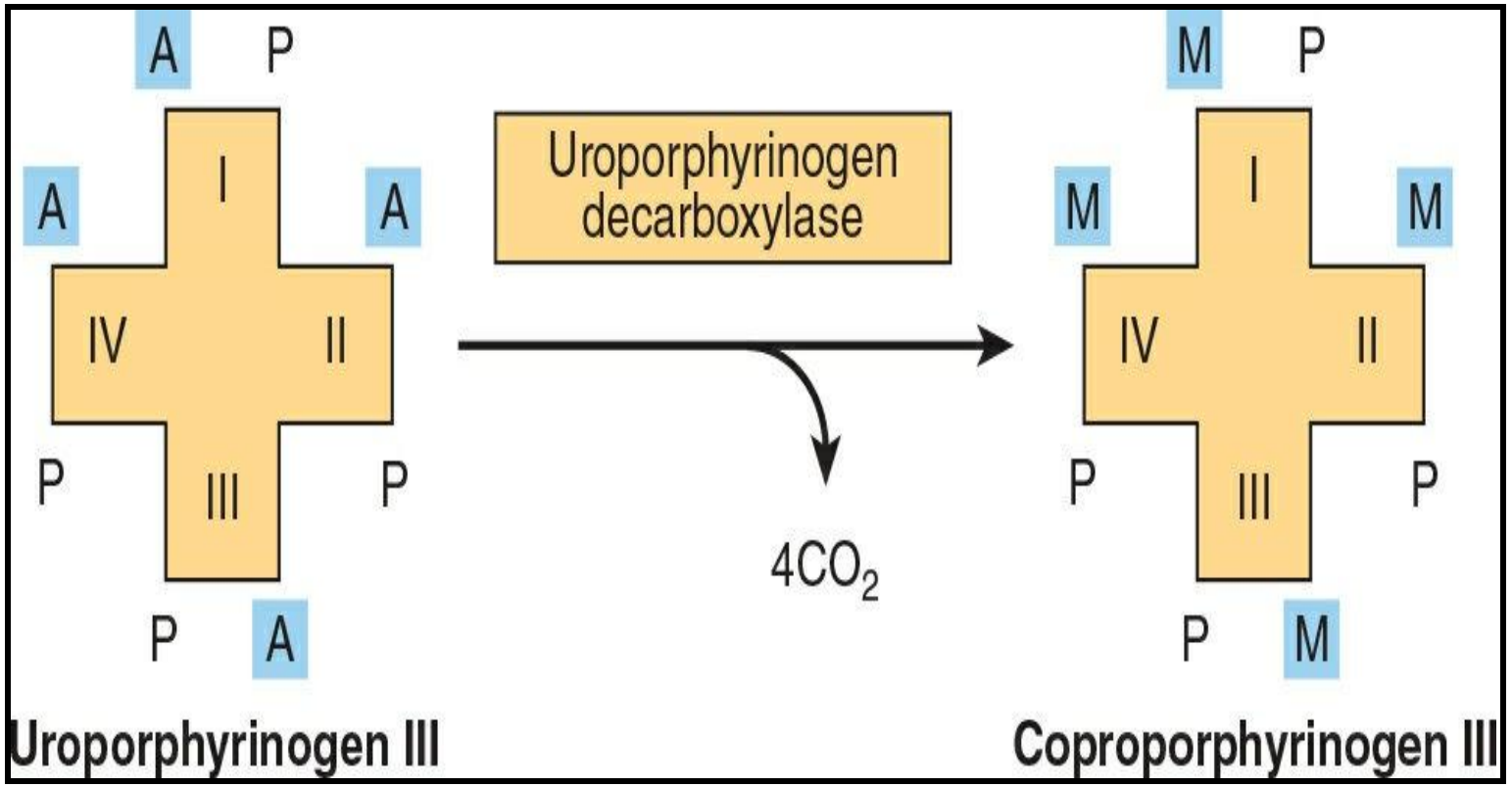
5) All four acetate moieties (A) of uroporphyrinogen III next undergo decarboxylation to methyl (M) substituents, ⟶ coproporphyrinogen III in a cytosolic reaction catalyzed by uroporphyrinogen decarboxylase.

- **This decarboxylase can also convert uroporphyrinogen I, if present, to coproporphyrinogen I.**



Biosynthesis of heme

❖ ***Steps:***



Biosynthesis of heme

❖ ***Steps:***

6) Coproporphyrinogen III enters the mitochondria and is converted to ⟶ protoporphyrinogen III by coproporphyrinogen oxidase (this oxidase is specific for type III coproporphyrinogen, so type I protoporphyrins generally do not occur in humans).

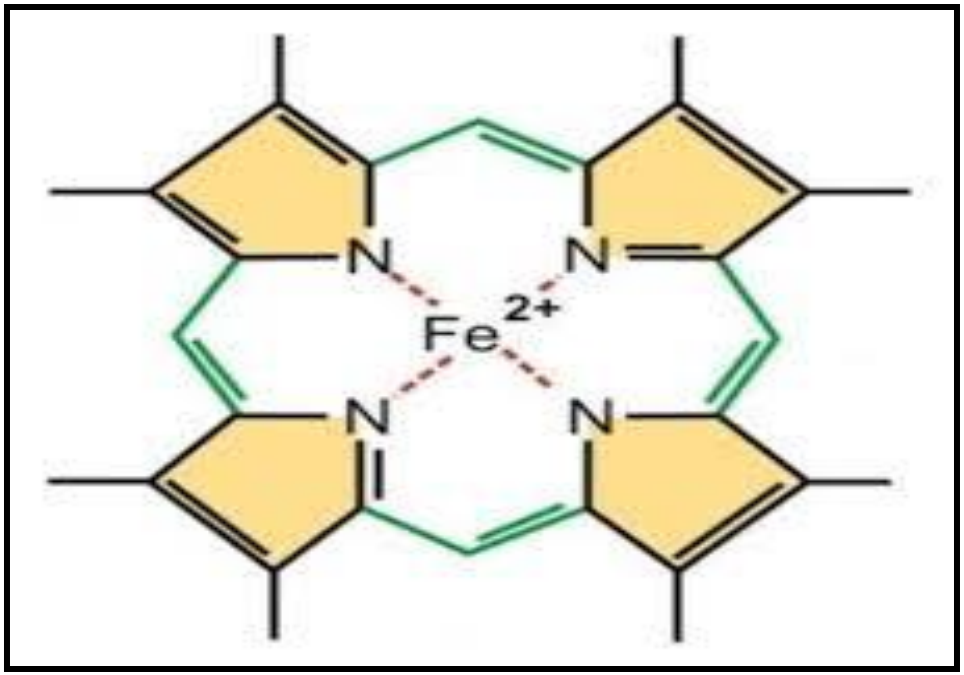
- **Protoporphyrinogen III is next oxidized to protoporphyrin III in a reaction catalyzed by protoporphyrinogen oxidase.**

Biosynthesis of heme

❖ ***Steps:***

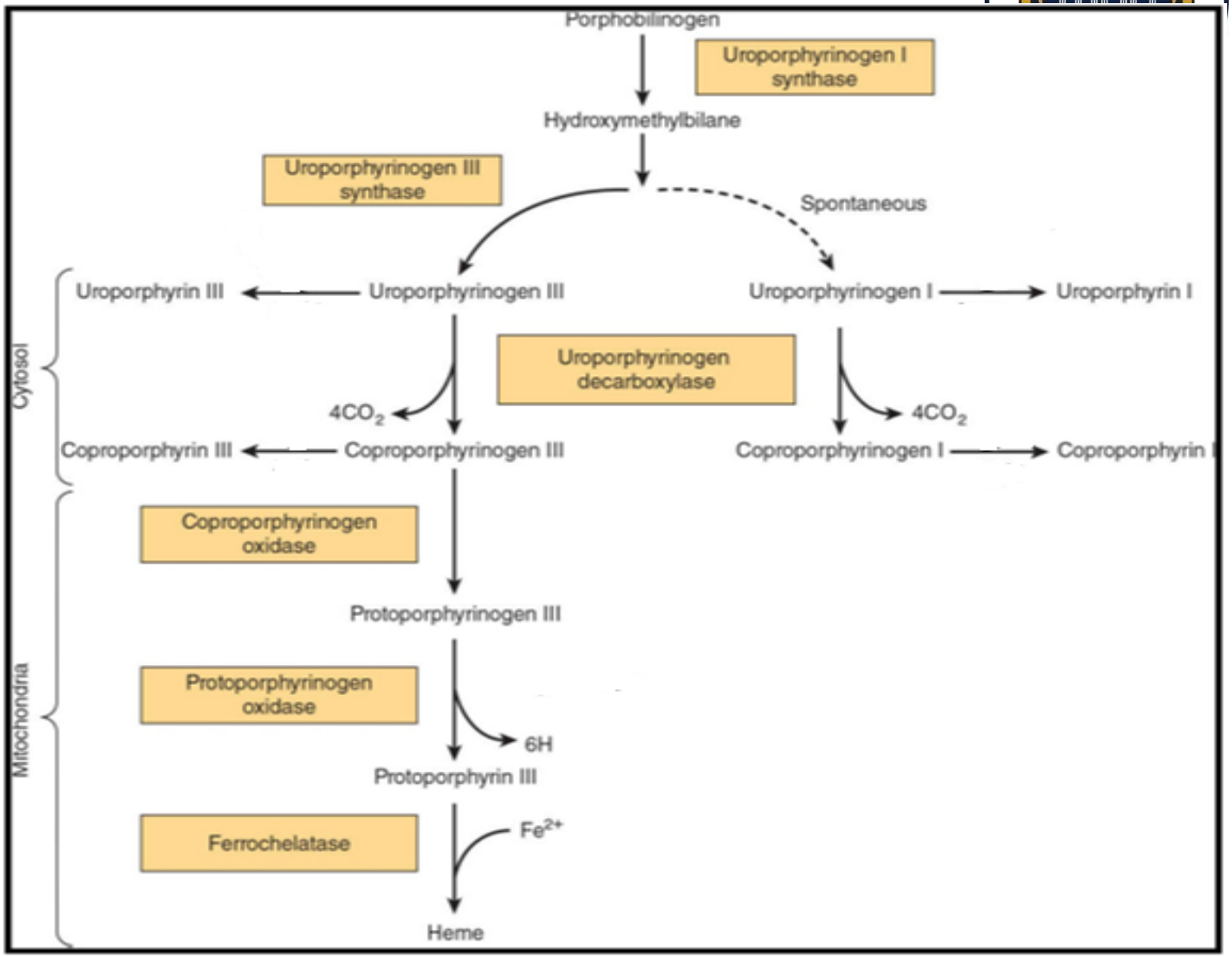
7) The ferrous iron is incorporated into protoporphyrin III by ferrochelatase enzyme (heme synthase),

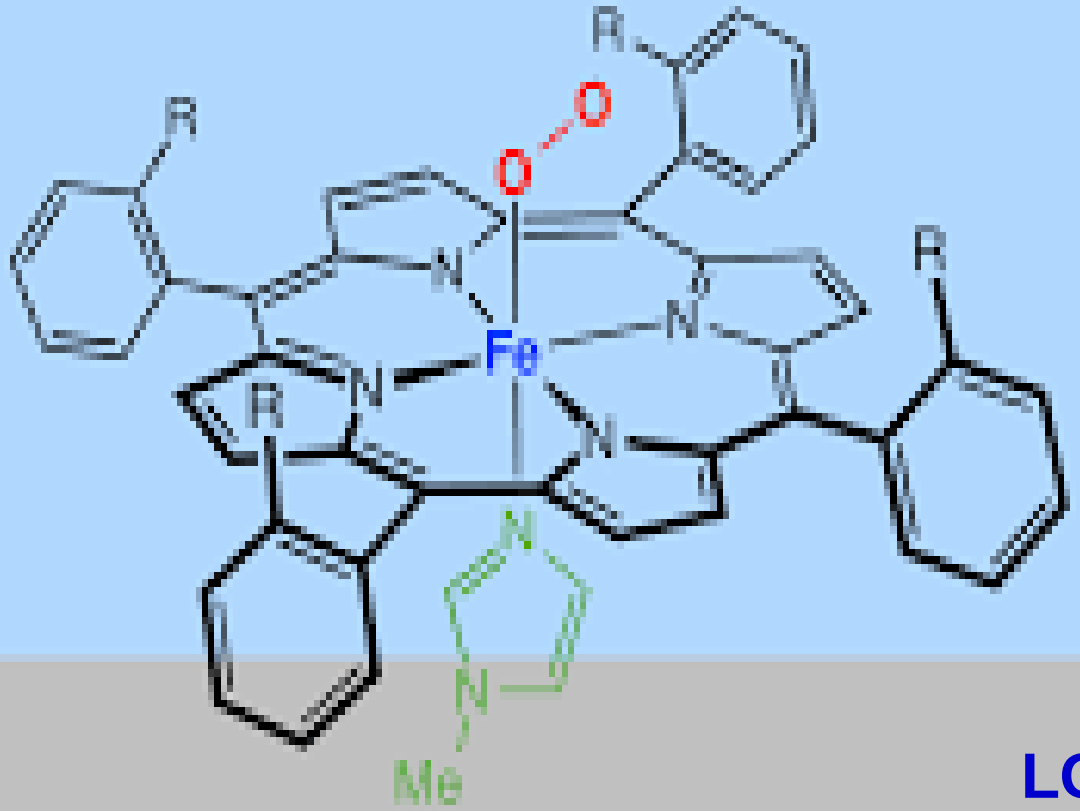
→ **heme.**



Biosynthesis of heme

❖ ***Steps:***





LO 4

Regulation of heme biosynthesis

Regulation of heme biosynthesis

❖ **The key regulatory enzyme is:**

***Mitochondrial δ-ALA synthase*.**

❑**It is inhibited by:**

✓**Excess heme formation: feedback mechanism.**

✓**Glucose.**

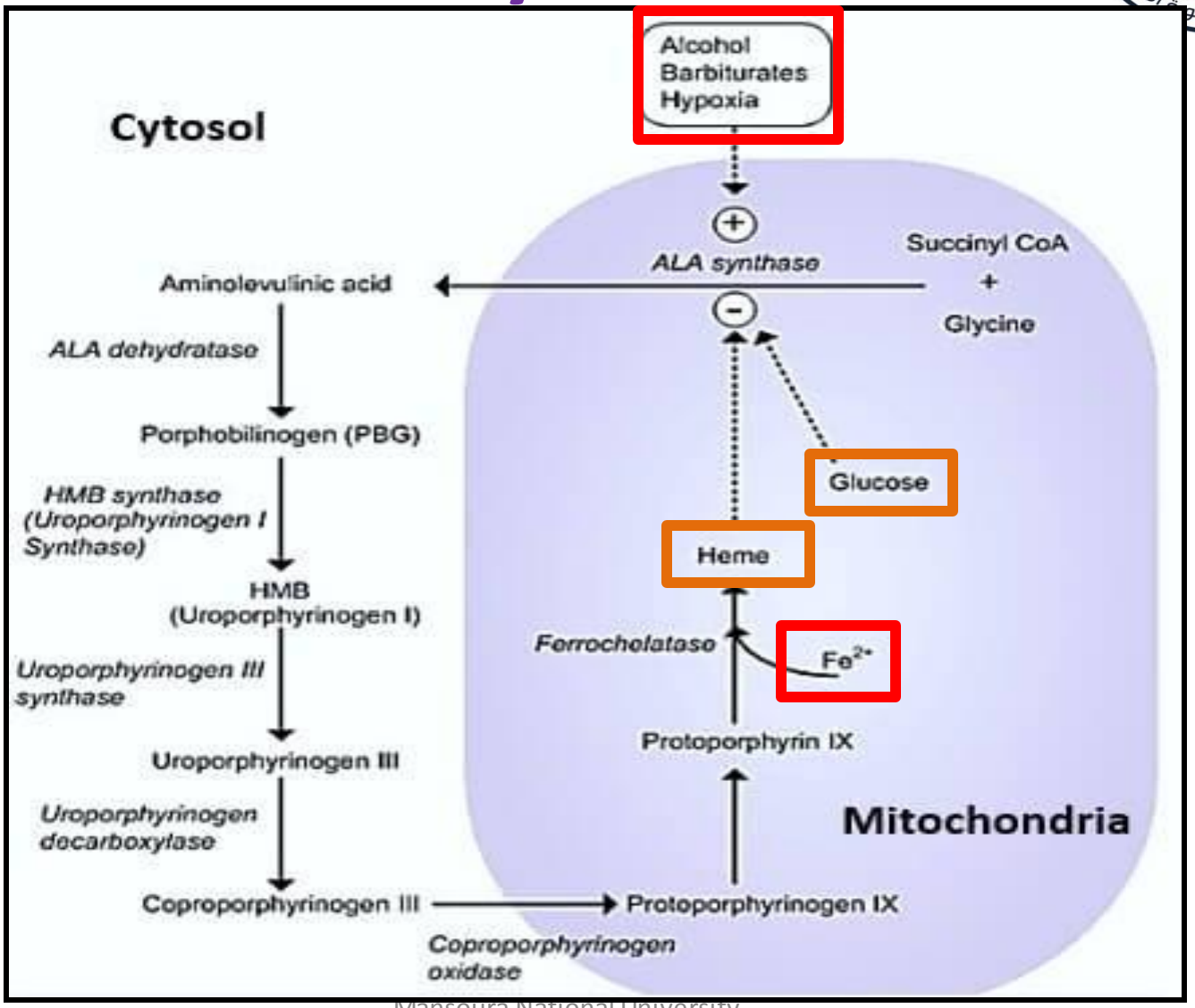
❑**It is stimulated by:**

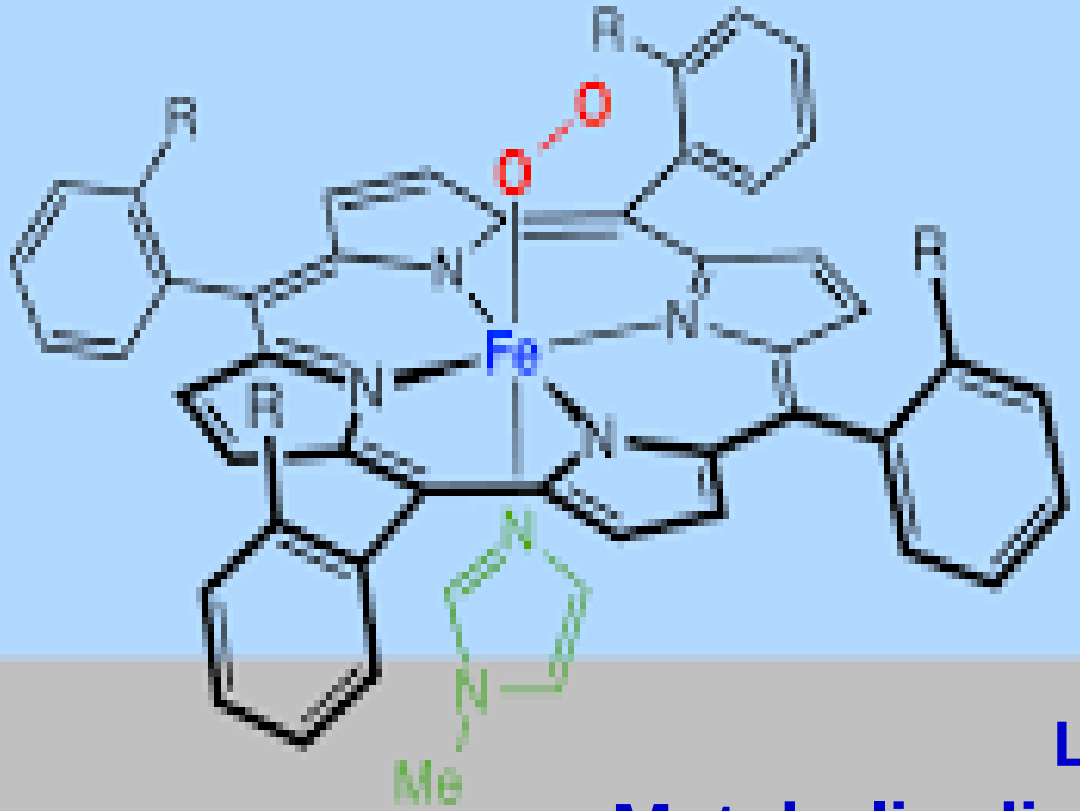
✓**Iron.**

✓**Phenobarbitol, rifampin and other drugs that induce production of cytochrome P450.**

❖ **ALA dehydratase and ferrochelatase enzymes are sensitive to inhibition by lead, as can occur in lead poisoning.**

Regulation of heme biosynthesis





LO 5

Metabolic disorders of heme biosynthesis (Porphyrias)

Disorders of heme biosynthesis *(Porphyrias)*

❖ ***Porphyrias*** **are rare metabolic disorders of heme biosynthesis, characterized by accumulation and increased excretion of porphyrins or their precursors.**

❖ ***Porphyrias*** **may be congenital or acquired.**

❖ ***Porphyrias*** **may be due to deficiency of one or more of heme biosynthesis enzymes → ↓ heme production → ↑ porphyrins.**

Disorders of heme biosynthesis *(Porphyrias)*

❖ The most *common acquired form* of porphyria is due to **lead poisoning**.

❖ *Drug-induced porphyria*:

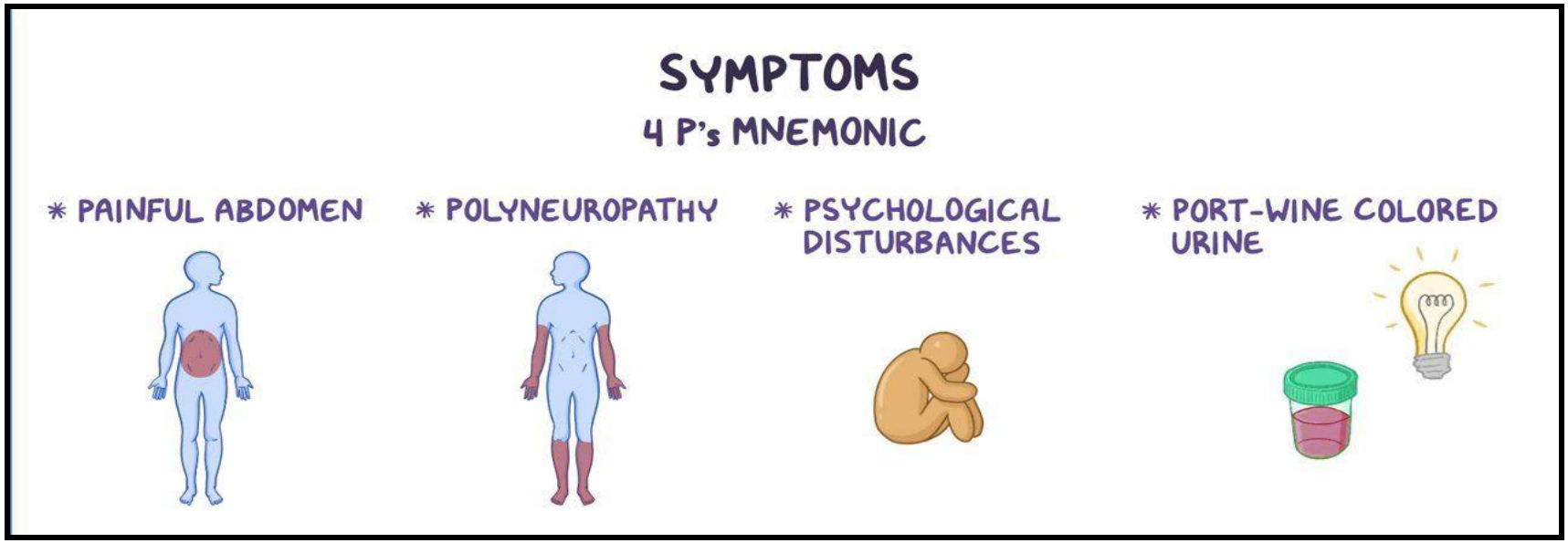
Certain drugs (eg, barbiturates and griseofulvin) induce the production of cytochrome P450. In patients with porphyria, these drugs can precipitate an attack of porphyria by depleting heme levels → decrease repression of δ-ALA synthase.

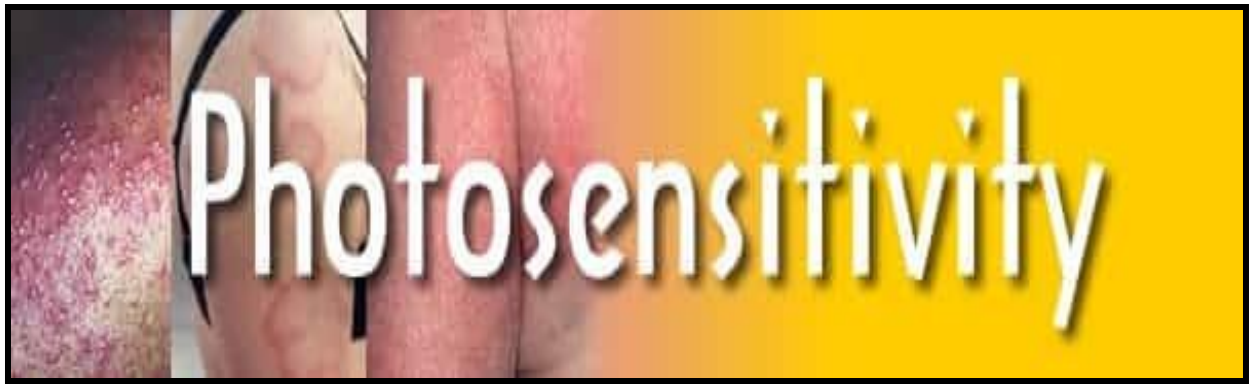
Disorders of heme Biosynthesis *(Porphyrias)*

❖ ***Porphyrias*** **can cause abdominal pain, neuropsychiatric symptoms, muscle weakness and photosensitivity.**

❖ **Porphyrinogens accumulation is responsible for photosensitivity as they can *absorb light and auto-oxidize to their corresponding porphyrin derivatives*. These porphyrins react with molecular oxygen to form oxygen radicals in the skin, that damage lysososmes which release degradative enzymes → variable degrees of skin damage, including scarring.**

Disorders of heme Biosynthesis *(Porphyrias)*





Disorders of heme Biosynthesis *(Porphyrias)*

❖ *Porphyrias* can be treated symptomatically by

→Avoiding drugs that induce production of cytochrome P450,

→Ingestion of large amounts of carbohydrate and administration of hematin.

❖ Patients exhibiting *photosensitivity* can benefit from sunscreens and possibly from administered β-carotenes, which appear to decrease production of free radicals, decreasing photosensitivity.

References

- Harper's Illustrated Biochemistry. 31e, Chapter 31, Rodwell & and Murray, eds.
- Chatterjea textbook of Medical Biochemistry, 8th edition, 2012.
- Manrique N, Aguilar F. Porfiria: reporte de un caso. Interciencia RCCI. 2017;7(1): 23-27.

Heme Synthesis Pathway - YouTube

Porphyria, Causes, Signs and Symptoms, Diagnosis and Treatment. - YouTube


Thank
You