HEME SYNTHESIS FROM GLYCINE AND SUCCINYL COA

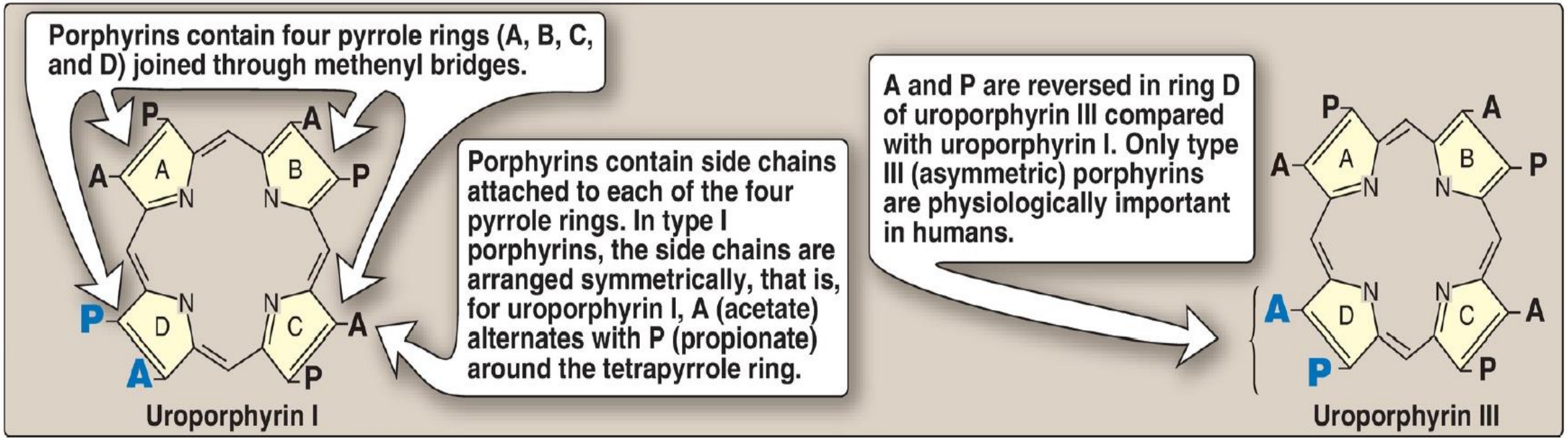
Ahmed Salem, MD, MSc, PhD, FRCR

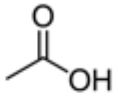
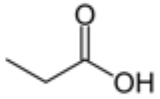
Heme & Heme function

- **Heme** is produced by the combination of iron with a porphyrin ring
  - Chlorophyll, the photosynthetic green pigment in plants is **magnesium-porphyrin** complex

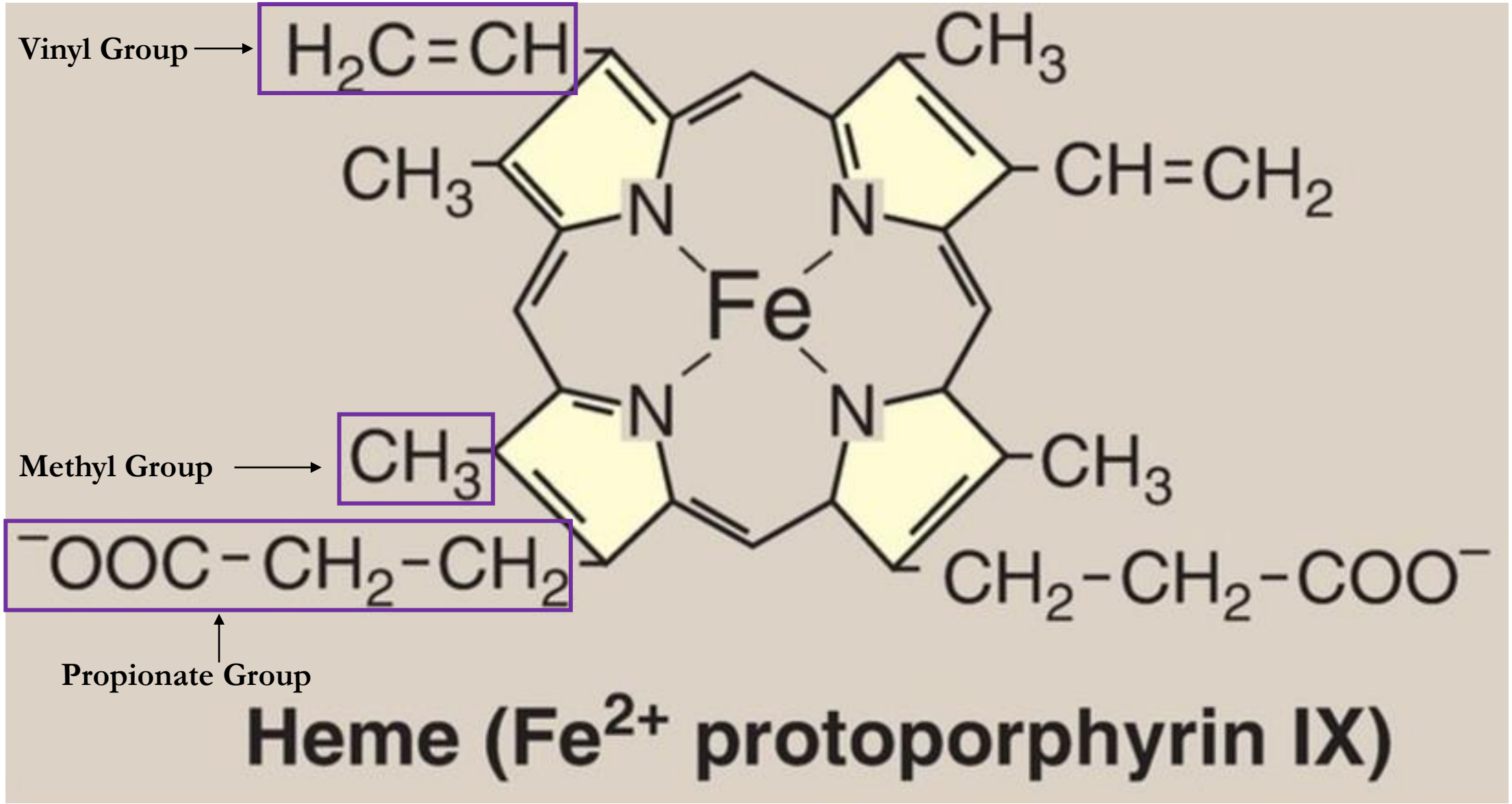
- Heme is present in:
  - Hemoglobin
  - Myoglobin
  - Cytochromes in ETC
  - Peroxidase
  - Catalase
  - Nitric oxide synthase

- Hemoglobin is a **conjugated protein** having heme as the prosthetic group and the protein, the **globin**



- Acetate groups 
- Propionate groups 

methine bridges =CH−


Vinyl Group
H2C=CH
CH3
CH3
CH=CH2
N
N
Fe
N
N
Methyl Group
CH3
CH3
−OOC−CH2−CH2
CH2−CH2−COO−
Propionate Group
Heme (Fe2+ protoporphyrin IX)

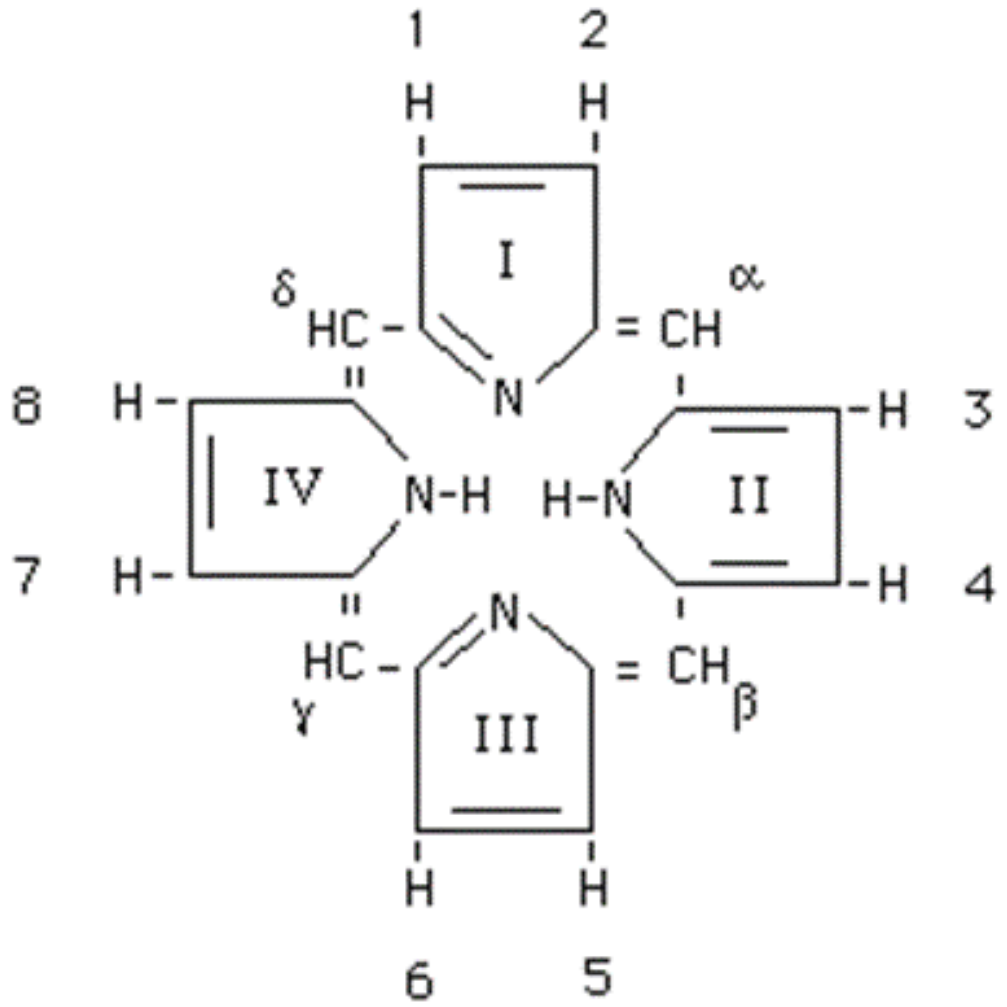
Structure

- **Side chains**: Different porphyrins vary in the nature of the side chains attached to each of the four pyrrole rings.

1. **Uroporphyrin** contains acetate (−CH2–COO–) and propionate (−CH2–CH2–COO–) side chains.

2. **Coproporphyrin** contains methyl (−CH3) and propionate groups.

3. **Protoporphyrin IX** (and heme b, the most common heme) contains vinyl (−CH=CH2), methyl, and propionate groups.


1
2
H
H
I
δ
HC -
= CH
α
N
8
H -
H -
3
IV
N-H
H-N
II
7
H -
-H
4
N
HC -
= CH
γ
β
III
H
H
6
5

Structure

- **Side chain distribution**: The side chains of porphyrins can be ordered around the tetrapyrrole nucleus in four different ways, designated by Roman numerals I to IV.

- Only type III porphyrins, which contain an asymmetric substitution on ring D, are physiologically important in humans.

- **Porphyrinogens**: These porphyrin precursors (for example, uroporphyrinogen) exist in a chemically reduced, colorless form and serve as intermediates between porphobilinogen (PBG) and the oxidized, colored protoporphyrins in heme biosynthesis.

BIOSYNTHESIS OF HEME

- Heme can be synthesized by almost all the tissues in the body
  - Most active in bone marrow (85%) and liver.
- Heme is not synthesized in the matured erythrocytes.
- The pathway is partly cytoplasmic and partly mitochondrial.

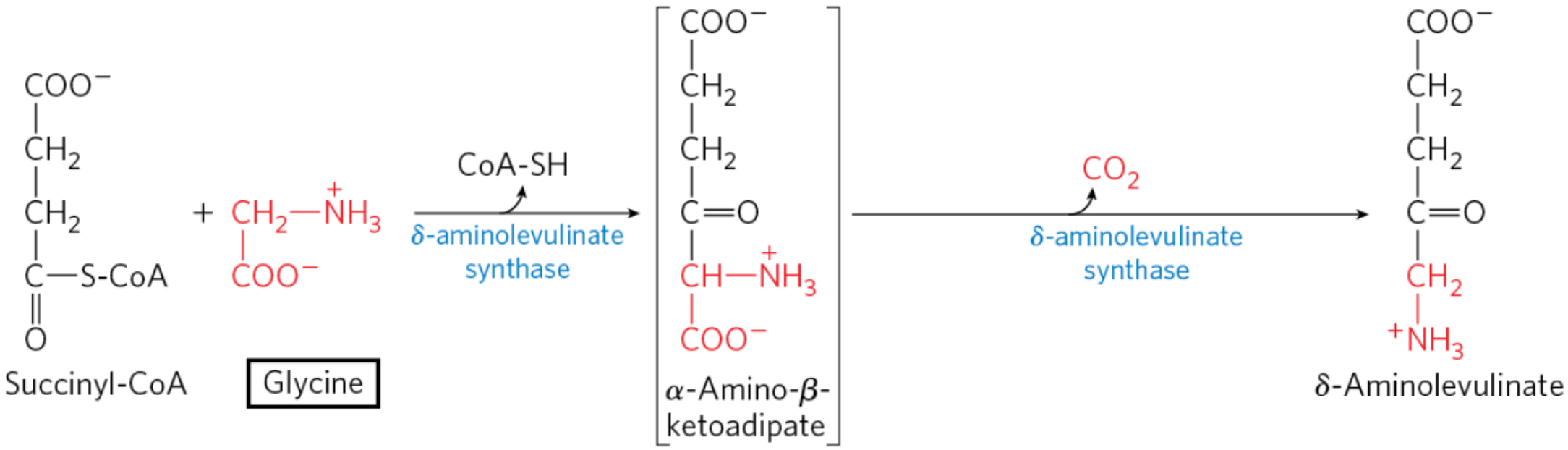
Step 1: ALA synthesis

- The synthesis starts with the condensation of succinyl CoA and glycine in the presence of **pyridoxal phosphate** to form **delta amino levulinic acid (ALA)**.

- Hence anemia may be manifested in pyridoxal deficiency.

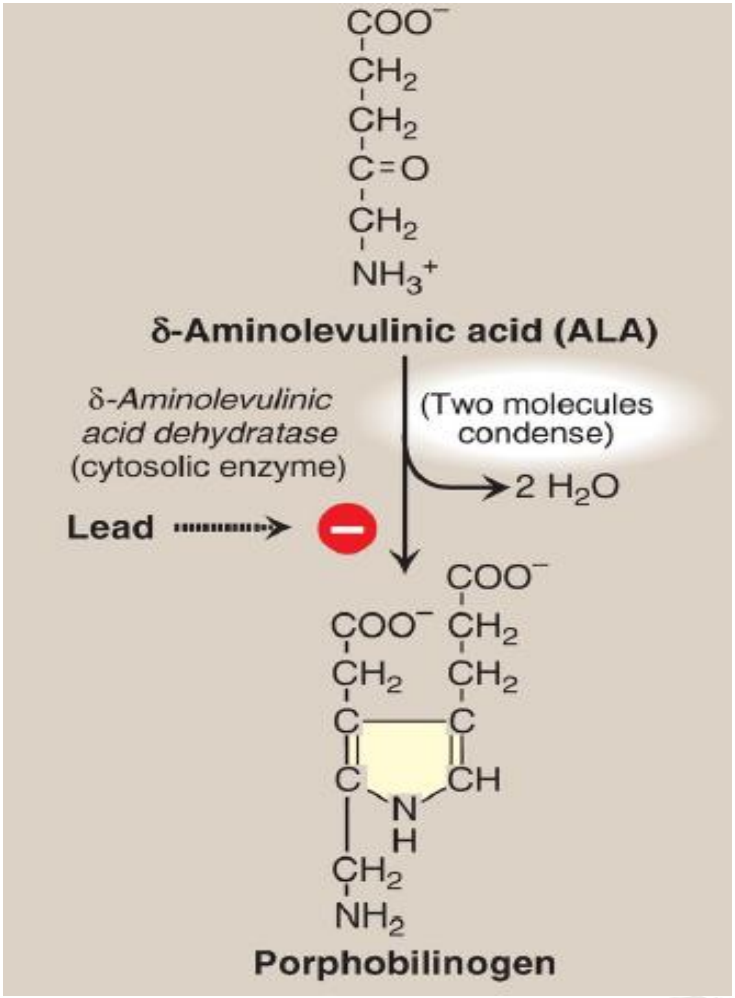
- The enzyme **ALA synthase** is located in the **mitochondria** and is the **rate-limiting** enzyme of the pathway.

Step 1: ALA synthesis



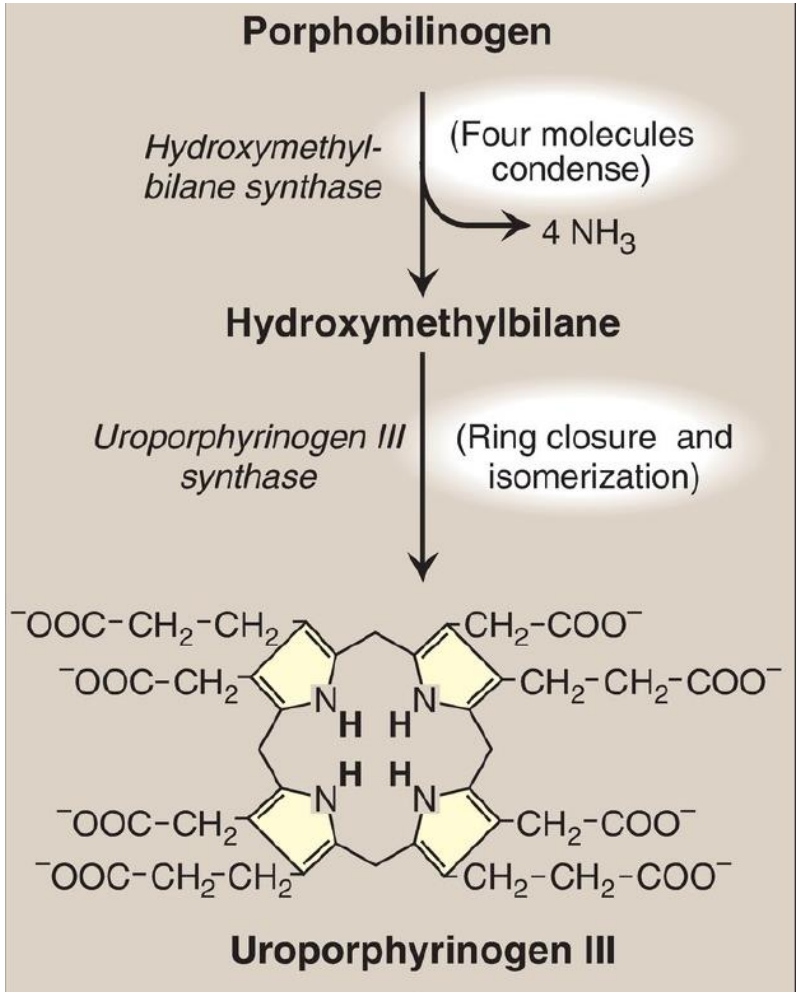
Step 2: Formation of PBG

- Next few reactions **occur in the cytoplasm**.
- Two molecules of ALA are condensed to form **porphobilinogen (PBG).**
- The condensation involves removal of 2 molecules of water and the enzyme is **ALA dehydratase.**
- Porphobilinogen is a monopyrrole.
- The enzyme contains zinc and is **inhibited by lead.**



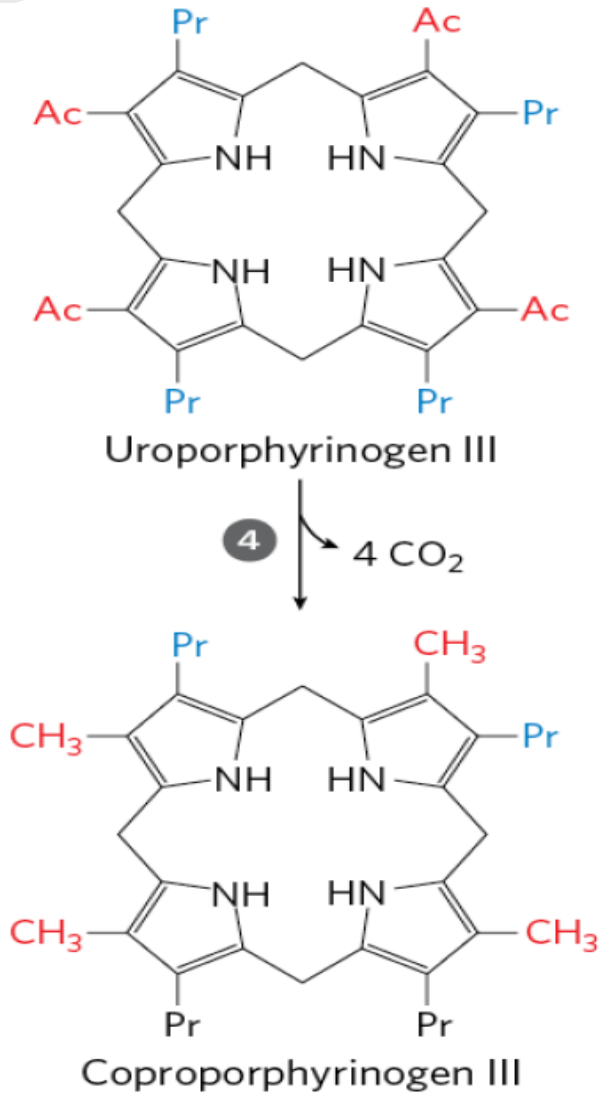
Step 3: Formation of UPG

- Condensation of **4 molecules of the PBG → formation of the first porphyrin of the pathway**, namely uroporphyrinogen (UPG).
- Condensation of PBG produces a linear tetrapyrrole; **hydroxy methyl bilane** (HMB)
  - The enzyme for this reaction is **hydroxymethyl-bilane synthase**
  - HMB molecule will cyclize and isomerize to form uroporphyrinogen III
- HMB is converted to **uroporphyrinogen III** by the enzyme, **uroporphyrinogen III synthase.**
- During this deamination reaction 4 molecules of ammonia are removed.



Step 4: Synthesis of CPG

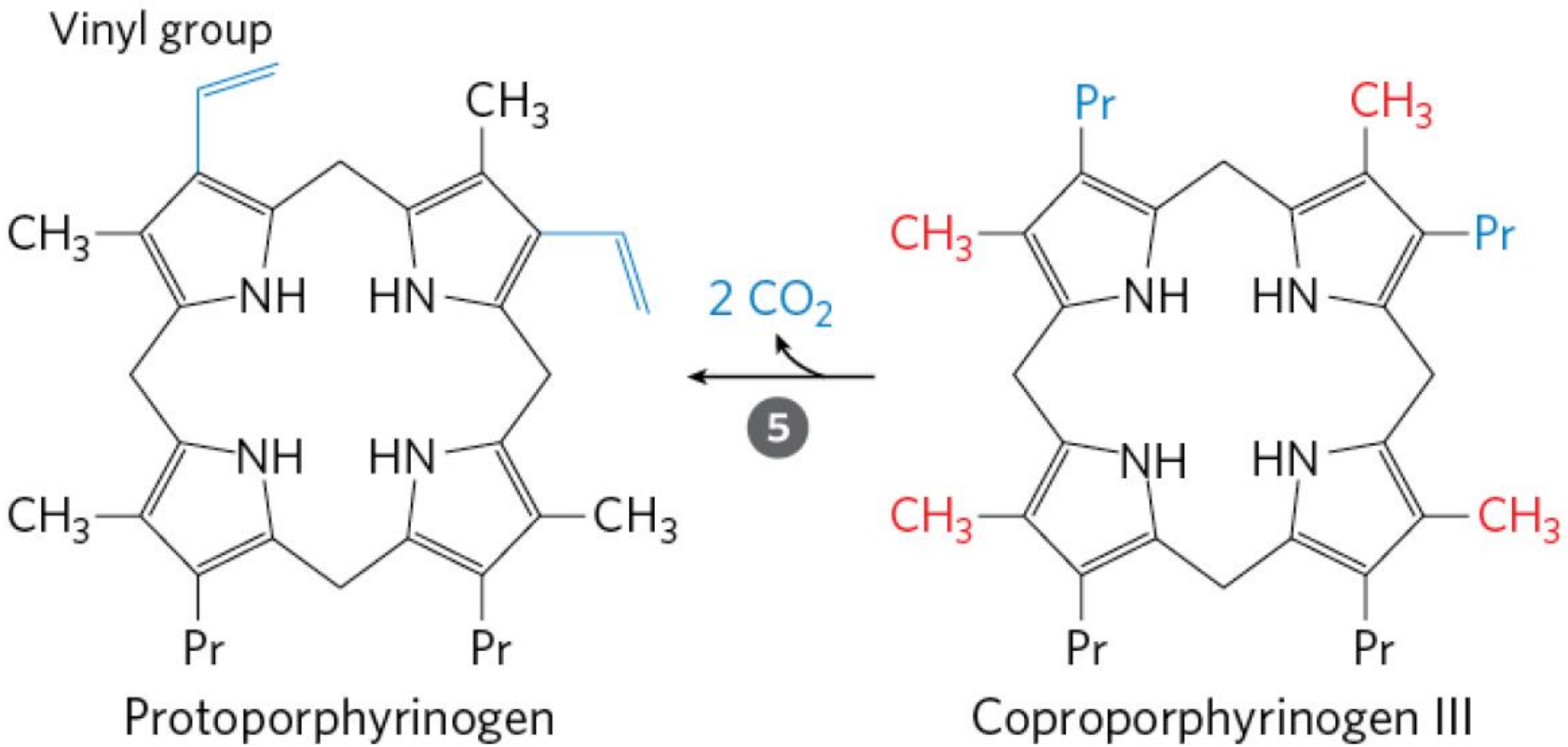
- The UPG-III is next converted to **coproporphyrinogen (CPG-III)** by decarboxylation.
- Four molecules of CO_2 are eliminated by **uroporphyrinogen III decarboxylase**.
- The **acetate** groups (CH_2–COOH) are decarboxylated to **methyl** (CH_3) groups.



Step 5: Synthesis of PPG

- Further metabolism takes place in the ***mitochondria.***
- CPG is oxidized to **protoporphyrinogen** (PPG-III) by **coproporphyrinogen oxidase.**
- This enzyme specifically acts only on type III series, and not on type I series.
- Two **propionic acid side chains** are oxidatively decarboxylated to **vinyl groups**.
- This reaction requires molecular oxygen.

Step 5: Synthesis of PPG



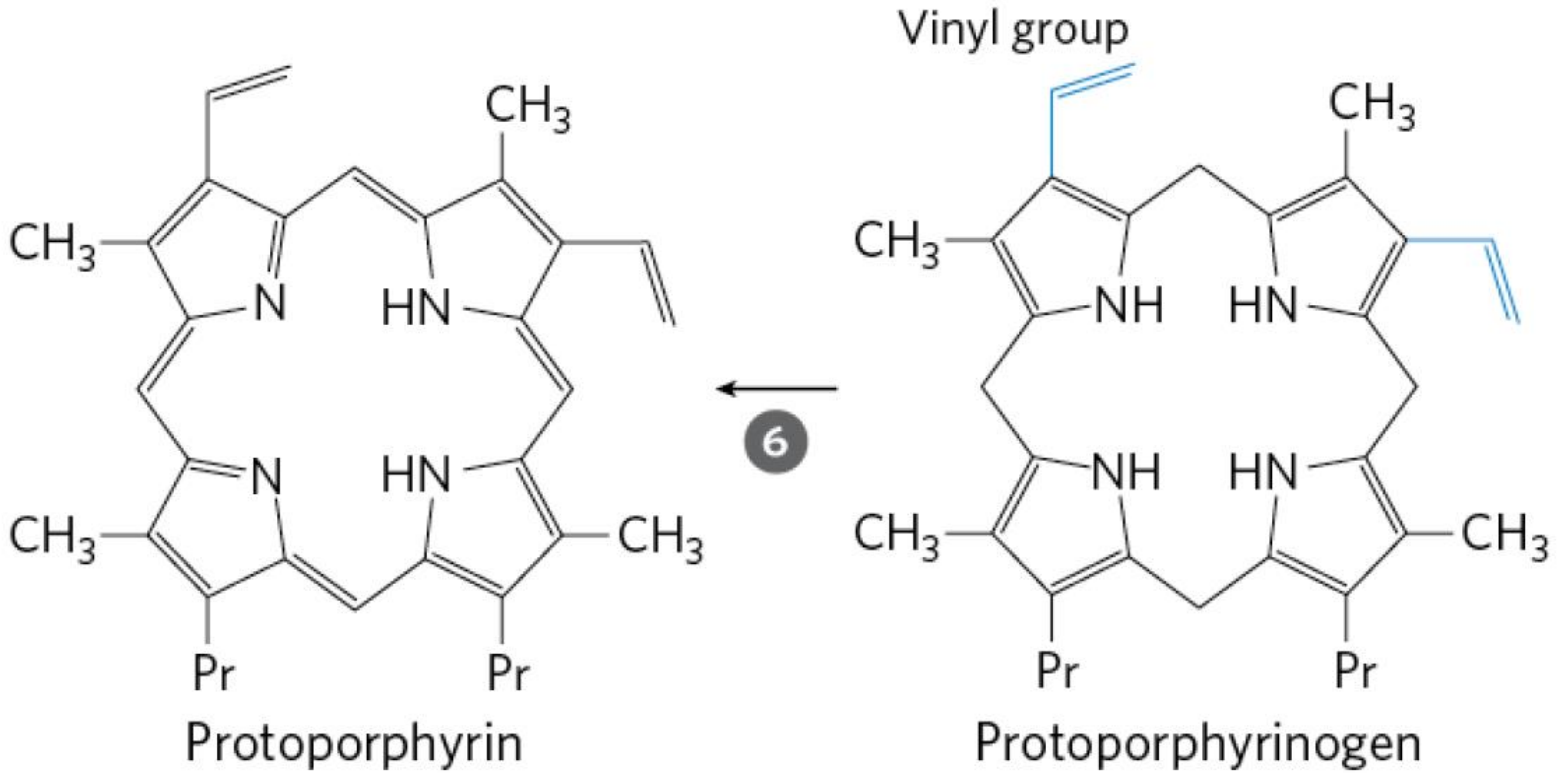
Step 6: Generation of PP

- The Protoporphyrinogen-III is oxidized by the enzyme **protoporphyrinogen oxidase** to **proto-porphyrin-III** (PP-III) in the **mitochondria**.

- The oxidation requires molecular oxygen.

- The methylene bridges ($–CH_2$) are oxidized to **methine bridges** ($–CH=$) and **colored porphyrins are formed**.

Step 6: Generation of PP



Step 7: Generation of Heme

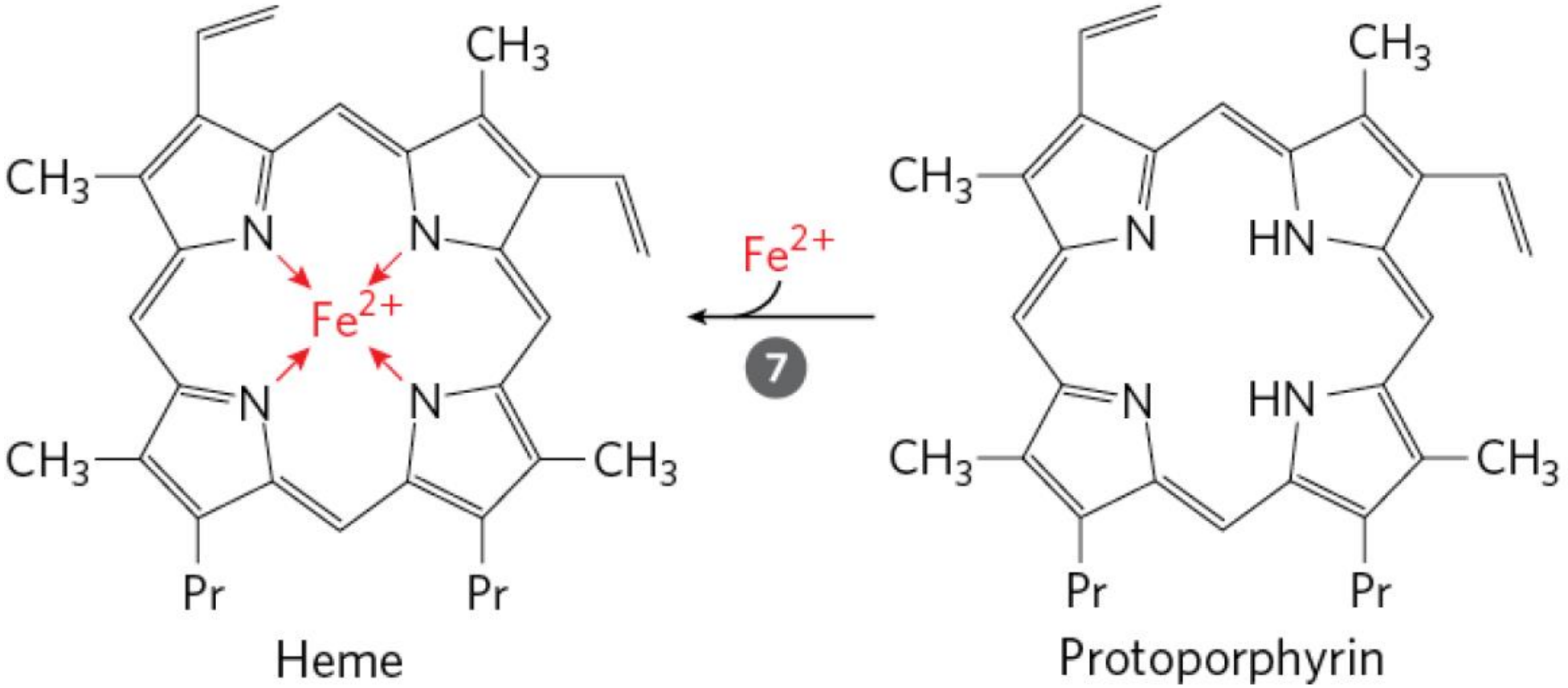
- The last step in the formation of heme is the attachment of **ferrous iron** to the protoporphyrin.
  - The enzyme is **ferrochelatase (heme synthase)** which is also located in **mitochondria.**

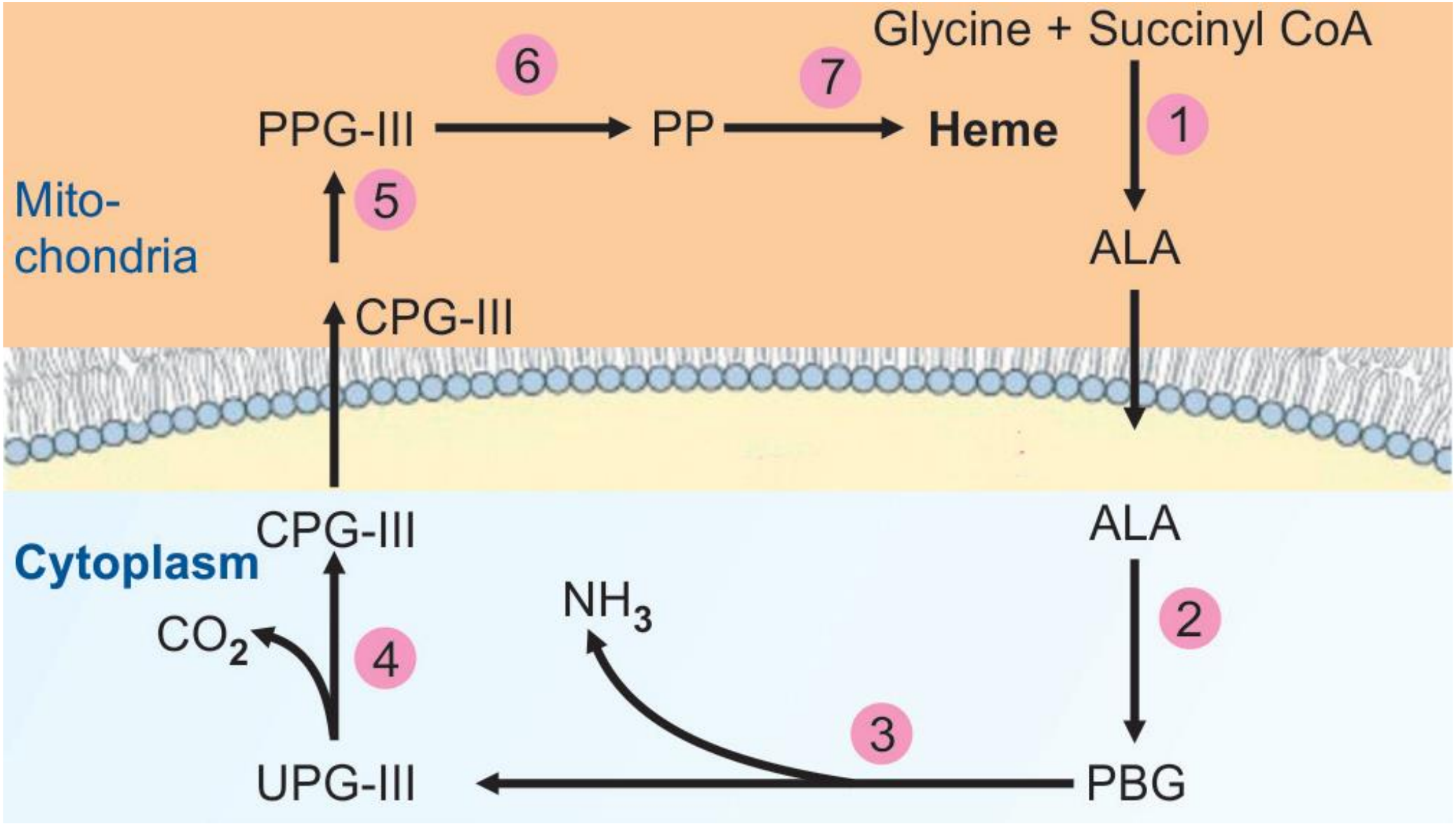
- Iron atom is coordinately linked with **5 nitrogen atoms** (4 nitrogen of pyrrole rings of proto-porphyrin and 1st nitrogen atom of a histidine residue of globin).

- The remaining valency of iron atom is satisfied with water or oxygen atom.

- When the **ferrous iron (Fe^{++}) in heme gets oxidized to ferric (Fe^{+++}) form, hematin** is formed, which loses the property of carrying the oxygen.
  - Heme is red in color, but hematin is dark brown.

Step 7: Generation of Heme




Glycine + Succinyl CoA
6
7
PPG-III
PP
Heme
1
Mito-
chondria
5
ALA
CPG-III
CPG-III
ALA
Cytoplasm
NH_3
CO_2
4
2
3
UPG-III
PBG

Regulation of Heme Synthesis

- **ALA synthase** is key rate limiting enzyme.
  - Heme, lead poisoning and steroids **inhibit** its activity.
  - Excess heme in BM is converted to hematin by oxidation of Fe2+ to Fe3+.
    - ALA synthase is also **allosterically** inhibited by hematin.

- **ALA synthase** is **activated** by hypoxia due to increase in erythropoietin.

- **ALA synthase** is also **activated** by availability of intracellular iron.

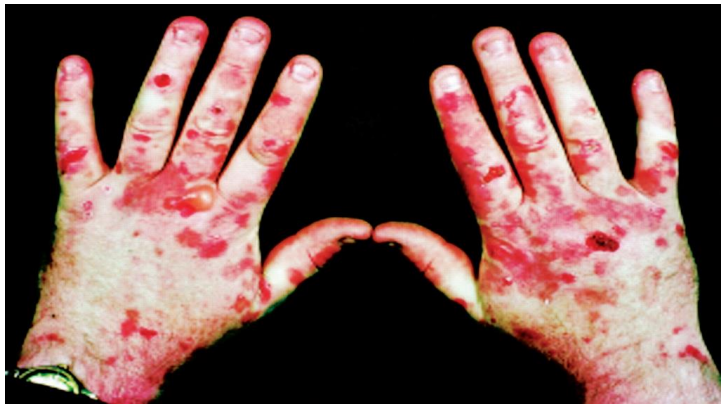
Regulation of Heme Synthesis

- **INH (Isonicotinic acid hydrazide)** that **decreases** the availability of pyridoxal phosphate may also affect heme synthesis.

- Drugs like barbiturates **induce heme synthesis**. Barbiturates require the heme containing cytochrome P450 for their metabolism.
  - Out of the total heme synthesized, two thirds are used for cytochrome P450 production.

Porphyrias

- Group of disease associated with abnormalities in the biosynthesis of heme.
- Characterized by accumulation and excretion of porphyrins or porphyrin precursors.
- Most inherited porphyrias are autosomal dominant except one.



High cellular concentration of glucose prevents induction of ALA synthase. This is the basis of administration of glucose to relieve the acute attack of porphyrias

TABLE 21.2: Features of important types of porphyrias

Type	*Enzyme defect*	*Inheritance*	*Excretion in urine*	*Other salient features*
Acute intermittent porphyria (AIP)	PBG-deaminase (UPG-1 synthase) (enzyme 3)	Autosomal dominant	Precursors, ALA and PBG. No color on voiding	Most common porphyria (1 in 10,000). Hepatic porphyria Abdominal and neurological manifestations. No photosensitivity
Congenital erythro-poietic porphyria	UPG-cosynthase (enzyme 3b)	Autosomal recessive	UP and CP; Portwine appearance	Marked photosensitivity. Erythrodontia Incidence, rare
Porphyria cutanea tarda	UPG-decarboxylase (enz 4)	Autosomal dominant	Uroporphyrins Urine colored	Second most common; incidence 1 in 25,000. Photosensitivity (Fig. 21.9B)
Hereditary copro-porphyria	CPG-III-oxidase (enzyme 5)	Autosomal dominant	UP and CP excreted in urine and feces Colored urine	Symptoms similar to AIP; but milder Photosensitivity is also seen
Hereditary proto-porphyria	Heme synthase or Ferrochelatase (enzyme 7)	Autosomal dominant	Neither porphyrins nor precursors are excreted in urine	Protoporphyrin increased in plasma, RBCs and feces. RBCs show fluorescence

PBG = Porphobilinogen; CP = Coproporphyrin; ALA = delta amino levulinic acid; UP = uroporphyrins. (Enzyme numbers are given as shown in Figure 21.9)

Thank you