



# Biochemistry

**Title =** Heme synthesis

**Lec no =** 8

**Done By =** Baraa Safi

وَقُلْ رَبِّ زِدْنِي عِلْمًا

✳ بنقدّر تصنيع الـ (Heme) منـ (Glycine) أبطـ (AA) و (succinyl CoA)

✳ وظيفة الـ (Heme) ؟ بيحصل الـ (oxygen)

# HEME SYNTHESIS FROM GLYCINE AND SUCCINYL COA

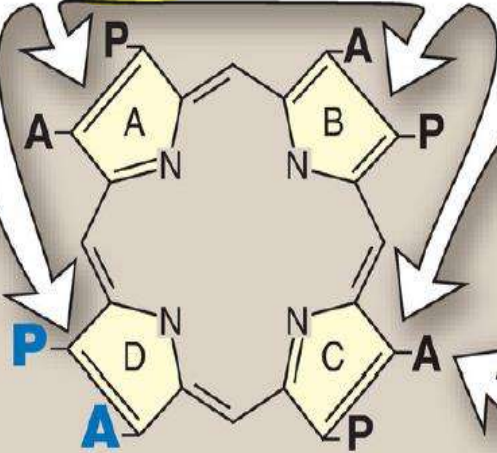
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Ahmed Salem, MD, MSc, PhD, FRCR

# 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
- Handwritten notes:*
- Drings (pointing to porphyrin ring)
  - هو الذي يعطي ال (Heme) اللون الأحمر (Heme gives the red color)
  - it has the ability to reflect the colour
  - هو اليه كثير (It has many)
  - وهو فيه كثير (structures) (It has many structures)
  - بميزها بلا (side chain) (It has side chains)
- NO**

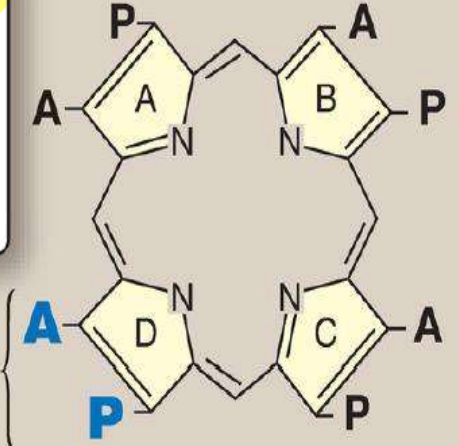
Porphyrins contain four pyrrole rings (A, B, C, and D) joined through methenyl bridges.



Uroporphyrin I

Porphyrins contain side chains attached to each of the four pyrrole rings. In type I porphyrins, the side chains are arranged symmetrically, that is, for uroporphyrin I, A (acetate) alternates with P (propionate) around the tetrapyrrole ring.

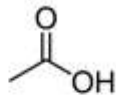
A and P are reversed in ring D of uroporphyrin III compared with uroporphyrin I. Only type III (asymmetric) porphyrins are physiologically important in humans.



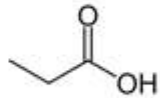
Uroporphyrin III

*structure: هفزا*

- Acetate groups

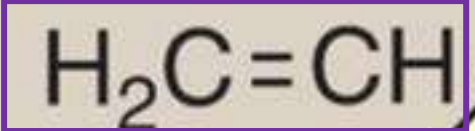


- Propionate groups



methine bridges =CH-

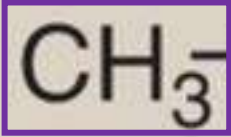
Vinyl Group →



الفرقة عنه (uroporphyrin III) هو أنه بدل acetate و propionate  
هو أنه في (vinyl, methyl, propionate)  
بس ما في (acetate)

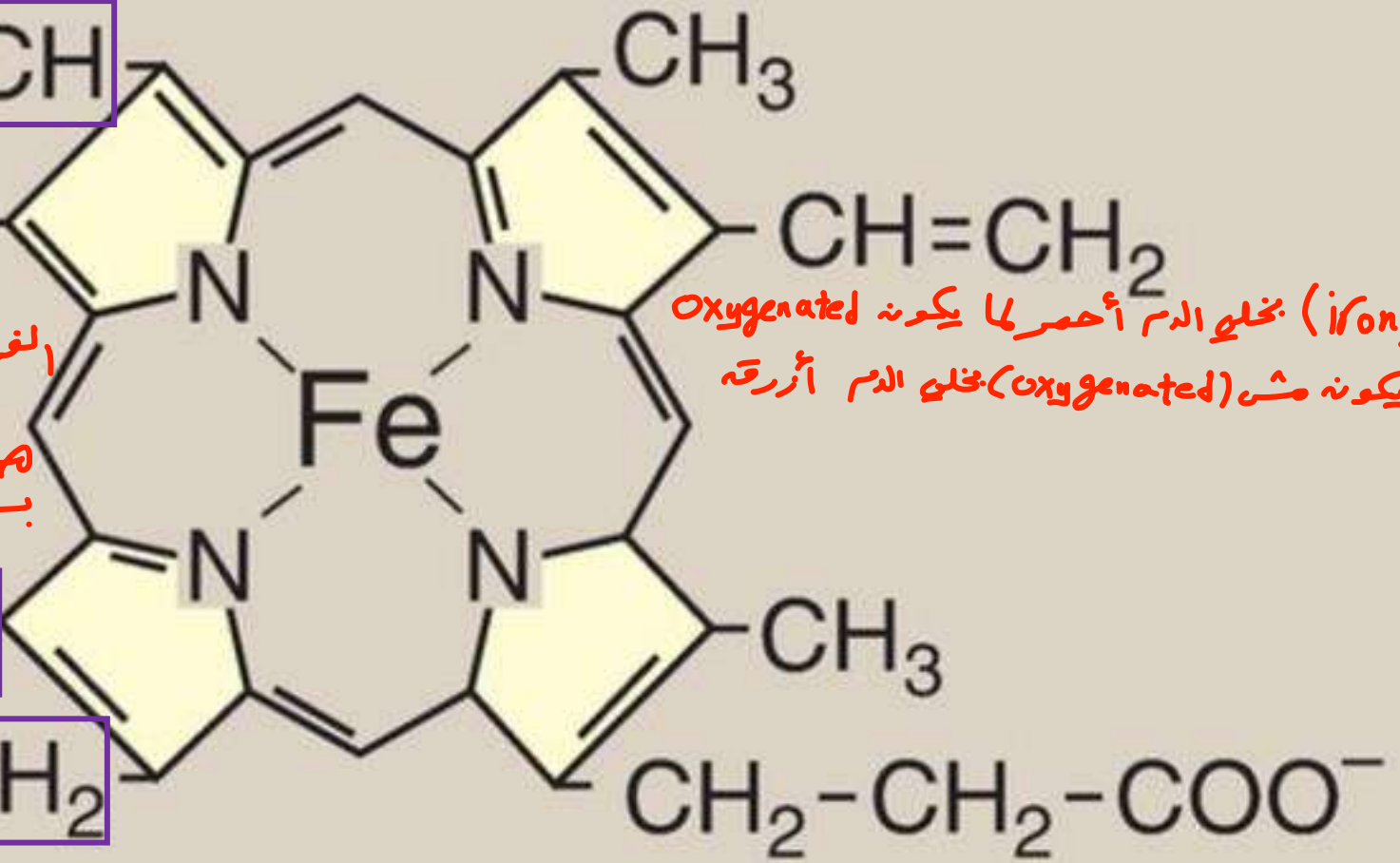
ال (iron) بخلي الدم أحمر لما يكونه oxygenated  
ولما يكونه مش (oxygenated) خلي الدم أزرقه

Methyl Group →



Propionate Group

# Heme ( $Fe^{2+}$ protoporphyrin IX)



# Structure

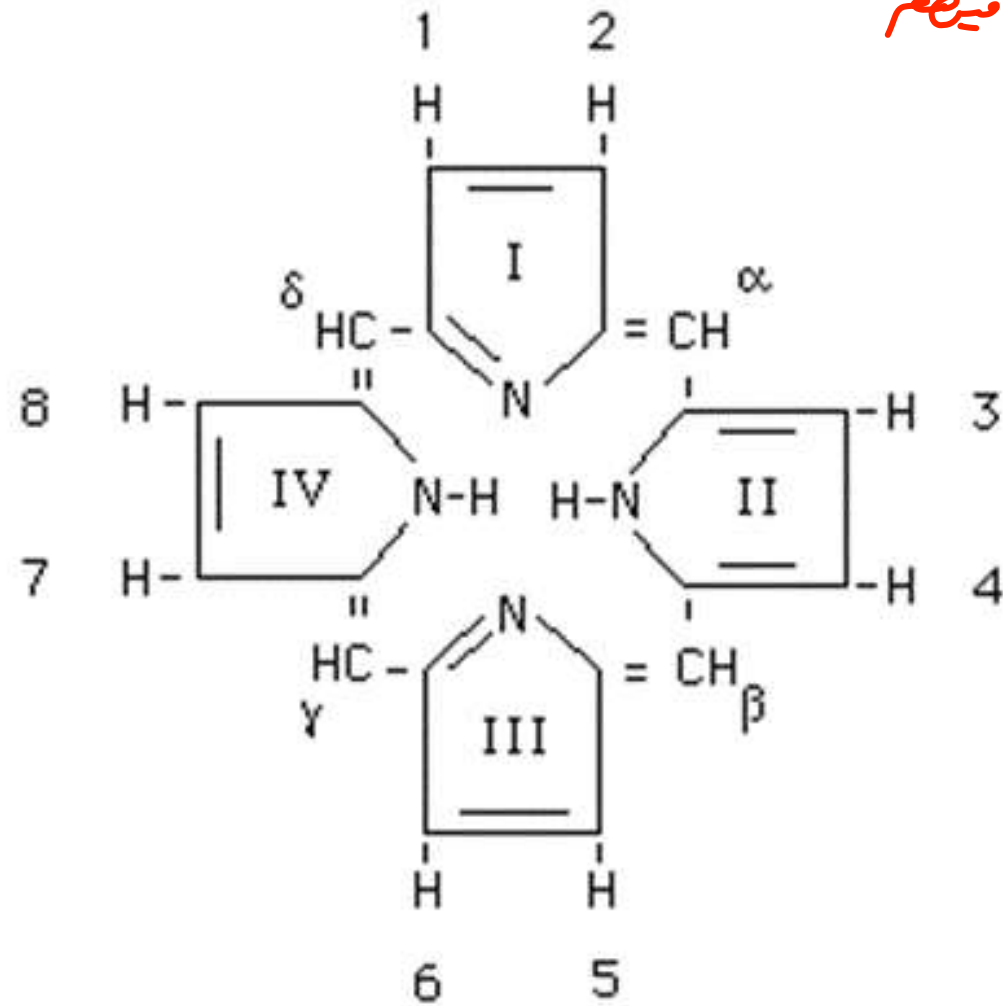
- **Side chains:** Different porphyrins vary in the nature of the side chains attached to each of the four pyrrole rings.
  1. **Uroporphyrin** contains **acetate** ( $-\text{CH}_2-\text{COO}-$ ) and **propionate** ( $-\text{CH}_2-\text{CH}_2-\text{COO}-$ ) side chains.
  2. **Coproporphyrin** contains **methyl** ( $-\text{CH}_3$ ) and **propionate** groups.
  3. **Protoporphyrin IX** (and heme b, the most common heme) contains **vinyl** ( $-\text{CH}=\text{CH}_2$ ), **methyl**, and **propionate** groups.

↳ Type (9) of Protoporphyrin

↳ (الأقرب إلى الـ Heme)

اهدول المواقع التي ممكنه مختلفه فيهم

(side chain )



# 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**.

- (الأمثلة لها Precursors)*
- \* **• 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.
- (لهذا السبب هو colourless) → (بدل -C=O بصير -CH<sub>2</sub>-)*
- (H)*
- (H)*



# BIOSYNTHESIS OF HEME

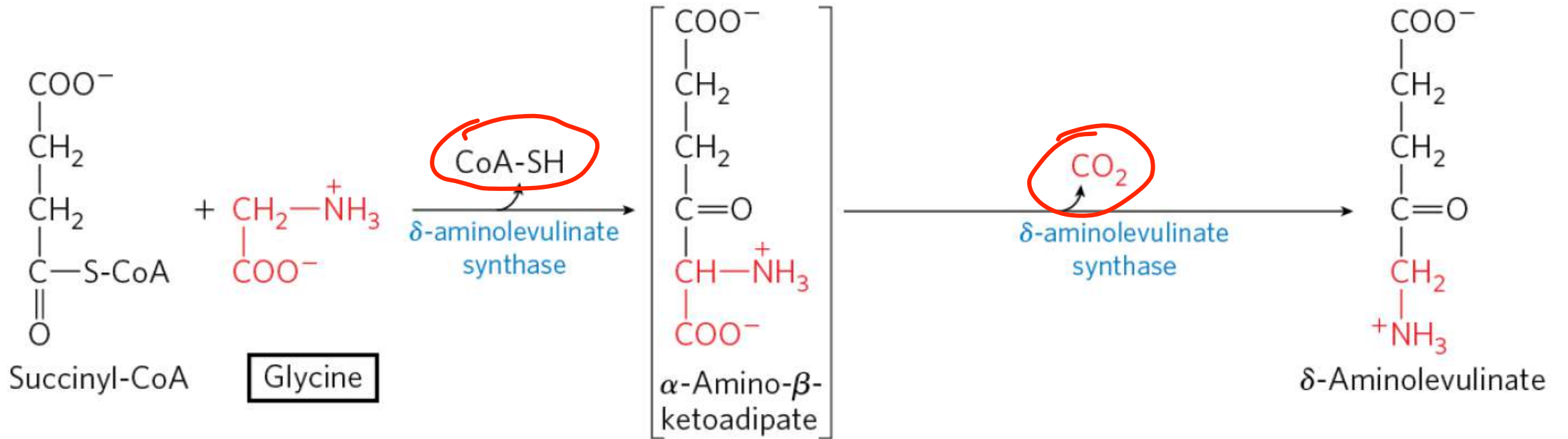
- Heme can be synthesized by almost all the tissues in the body
  - Most active in bone marrow (85%) and liver.
- Heme is not synthesized in the matured erythrocytes.  
*loss of nucleus and cellular organelles*
- The pathway is partly cytoplasmic and partly mitochondrial.

# 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).  
که سر بہتغلہ إذا فی PIP (cofactor) تتجلی
- 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

↑ in mitochondria



The rate limiting step  
 first step  
 slowest step

لہجوقف ہایے ال (step)  
 وعا (step) ہتمیے

# Step 2: Formation of PBG

2/3/4  
in cytoplasm

له بديء أوصله لـ (ring) في الـ Heme

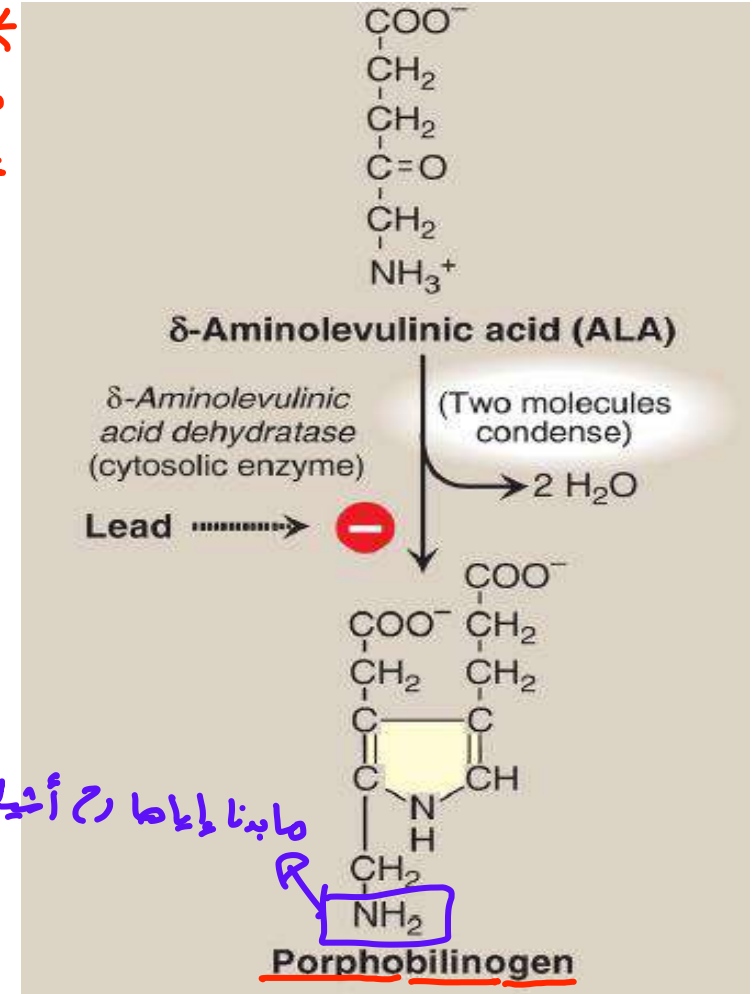
\* هو نه بقول يا (ALA)  
ما بتكفي لـ الحالك فبديء كمانه واحد  
عشانه يصير عندنا 2 وبتطلع (2H2O)

- 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**.

product

بدنا كمانه (4)

ما بدنا لـ ما رح أشيلها بالخطوة الجاي



\* الـ (structure) تابع ممتاز فيه (pyrrole ring) بديء منه 4 و (iron) عشانه أعمله (Heme)

# Step 3: Formation of UPG

- Condensation of 4 molecules of the **PBG** → formation of the **first porphyrin of the pathway**, namely uroporphyrinogen (UPG).

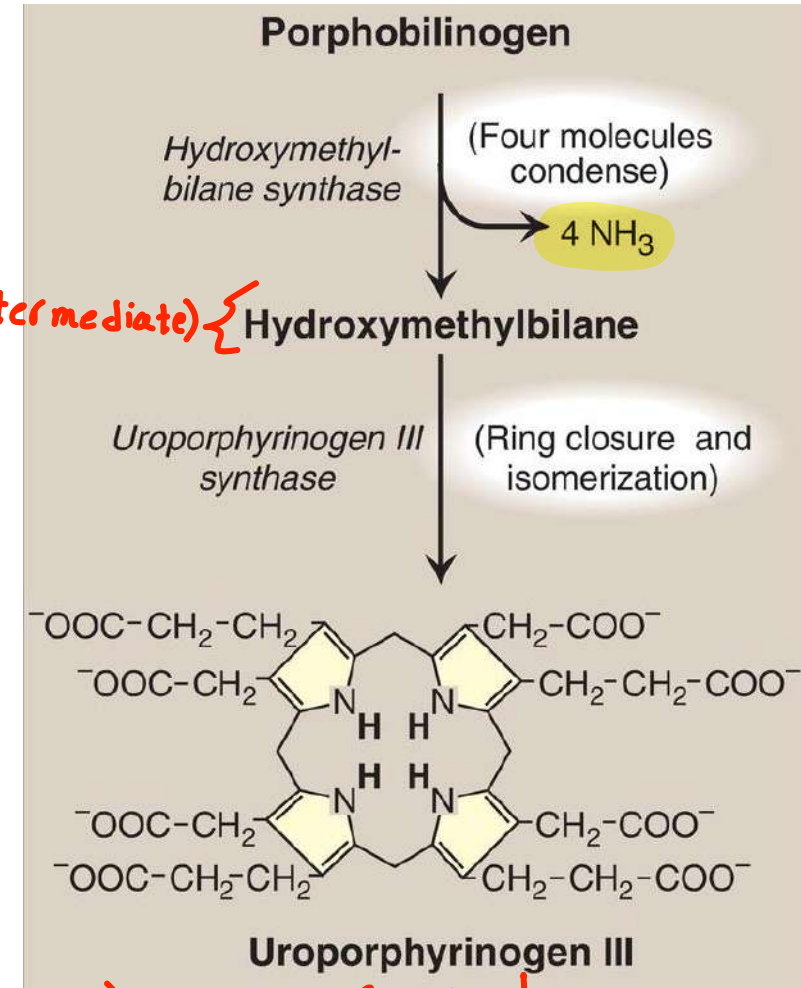
- Condensation of PBG produces a linear tetrapyrrole; **hydroxy methyl bilane** (HMB)

- 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.

صونه بكونه خطي (intermediate) } Hydroxymethylbilane



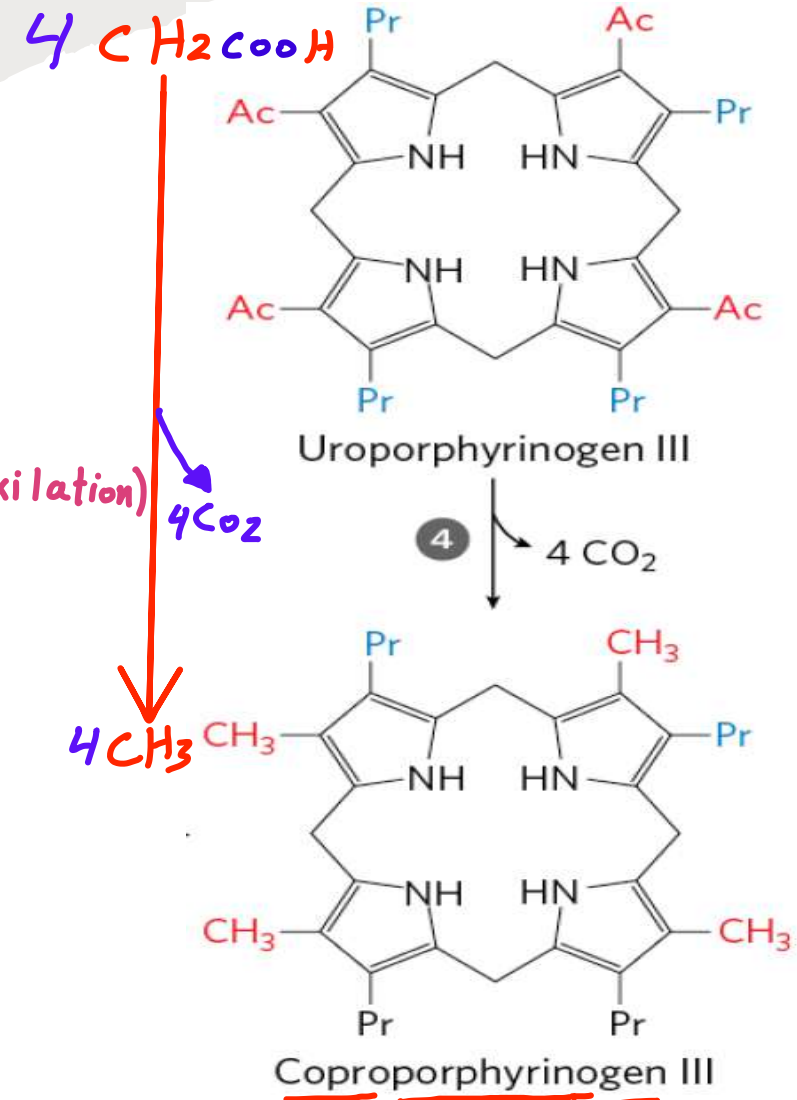
له تذكر انه بكونه من (acetate, propionate)

أنا وصلت لـ (uroporphyrinogen III) شو بتفرقه عنه الـ (Heme) ؟ بتفرقه بالـ ( side chain )

## Step 4: Synthesis of CPG

بدية أضيفين (methyl / vinyl) وأزيل (acetate) على خصوصيتين  
S4 | S5  
Cytoplasm | mitochondria

- The UPG-III is next converted to coproporphyrinogen (CPG-III) by decarboxylation.
- Four molecules of  $\text{CO}_2$  are eliminated by **uroporphyrinogen III decarboxylase**.
- The **acetate** groups ( $\text{CH}_2\text{-COOH}$ ) are decarboxylated to **methyl** ( $\text{CH}_3$ ) groups.



5 mitochondria

أضيق ال ( vinyl ) يرجع لـ ( mitochondria )

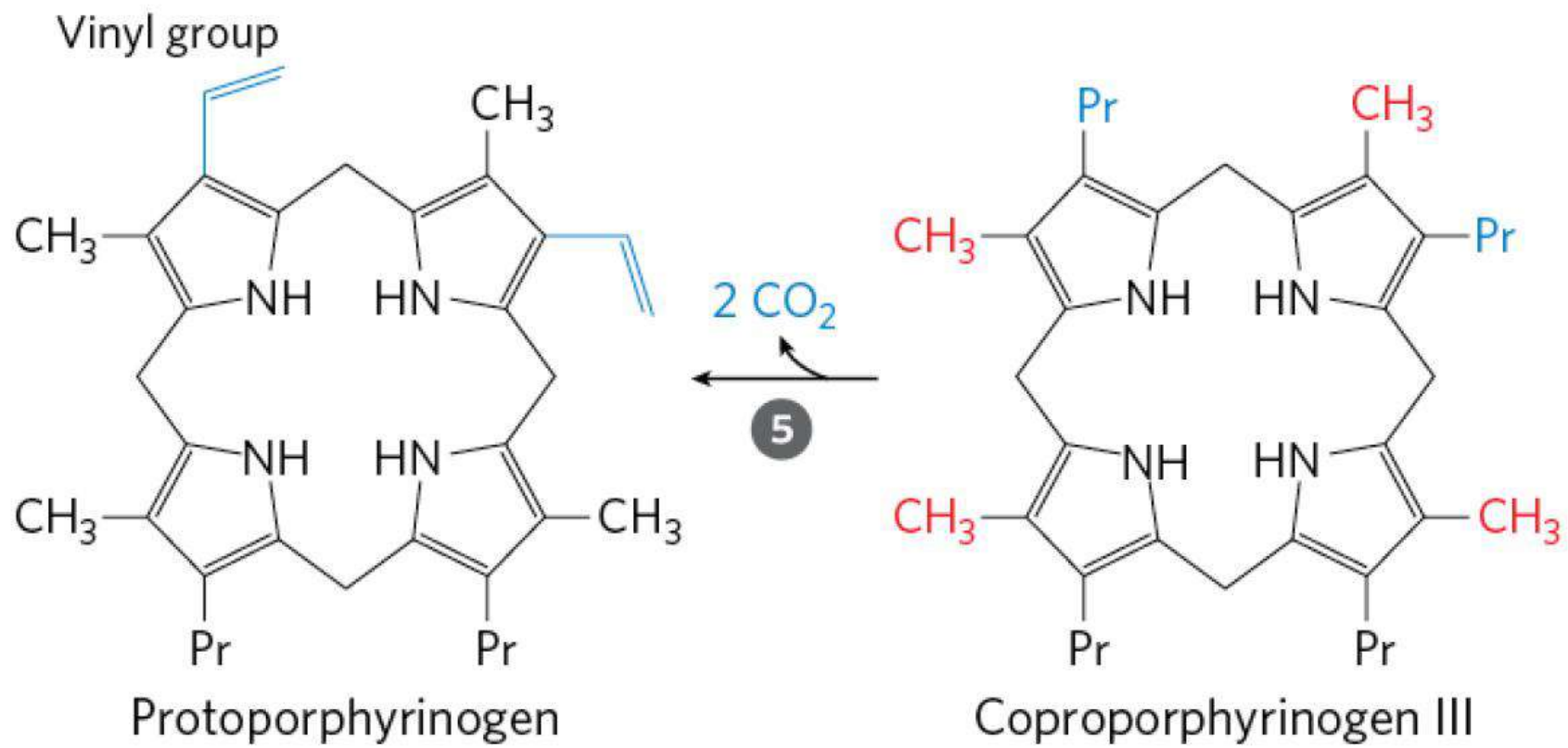
## Step 5: Synthesis of PPG

بدنا تحول ( CPG ) إلى ( PPG ) علنا نه بتحتوي ( vinyl )

←  
Copro porphyrinogen Oxidase  
molecular oxygen موجود

- 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

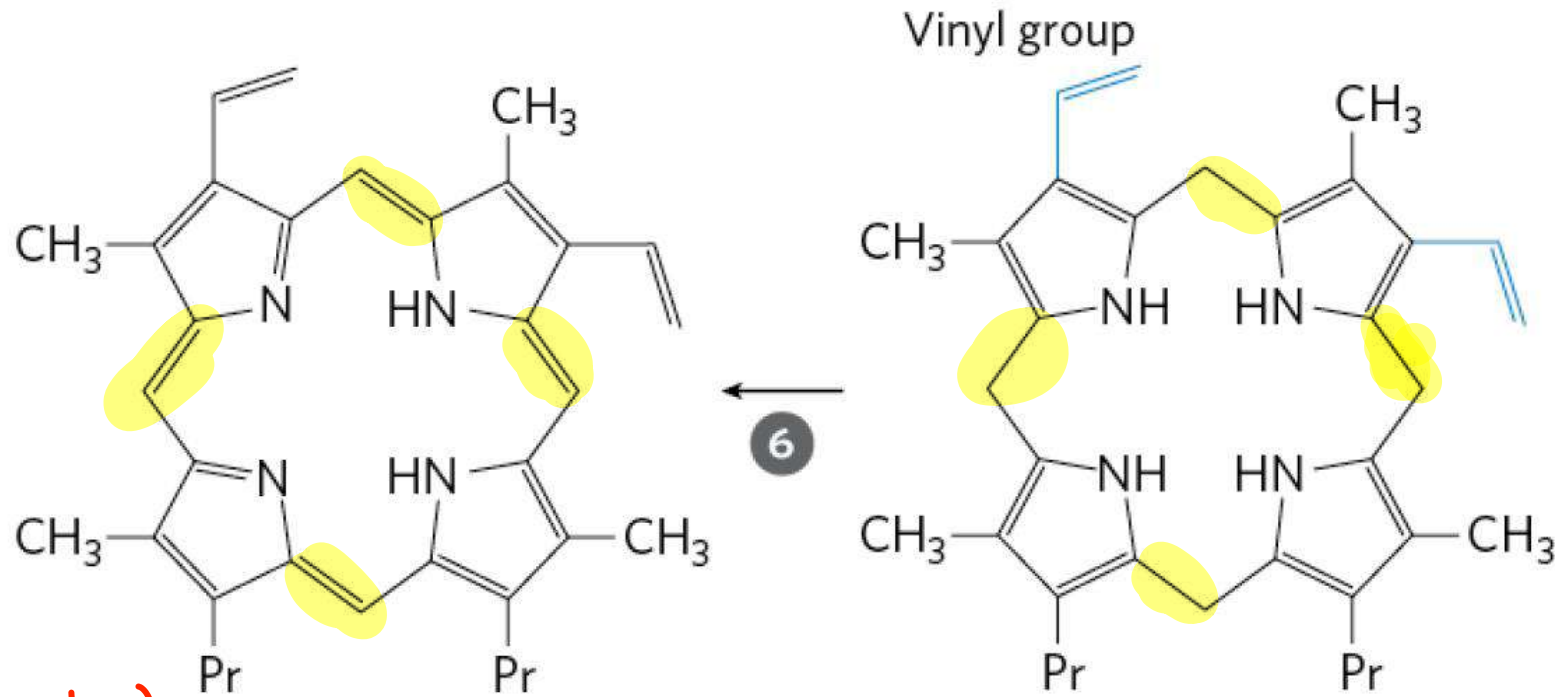




## Step 6: Generation of PP

- 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 ( $-\text{CH}_2$ ) are oxidized to methine bridges ( $-\text{CH}=\text{}$ ) and **colored porphyrins** are formed.

# Step 6: Generation of PP



(coloured)

Protoporphyrin

Protoporphyrinogen (colourless)

بس بفرقه ال (Bridges)

(7) in mitochondria

## 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 protoporphyrin and 1st nitrogen atom of a histidine residue of globin).

سؤال بالإنجليزية: أنه من وين يتصيب (N5) وكيف

- 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.

↳ Heme with ferric

لو يكونه أوكسجين (oxygenated)

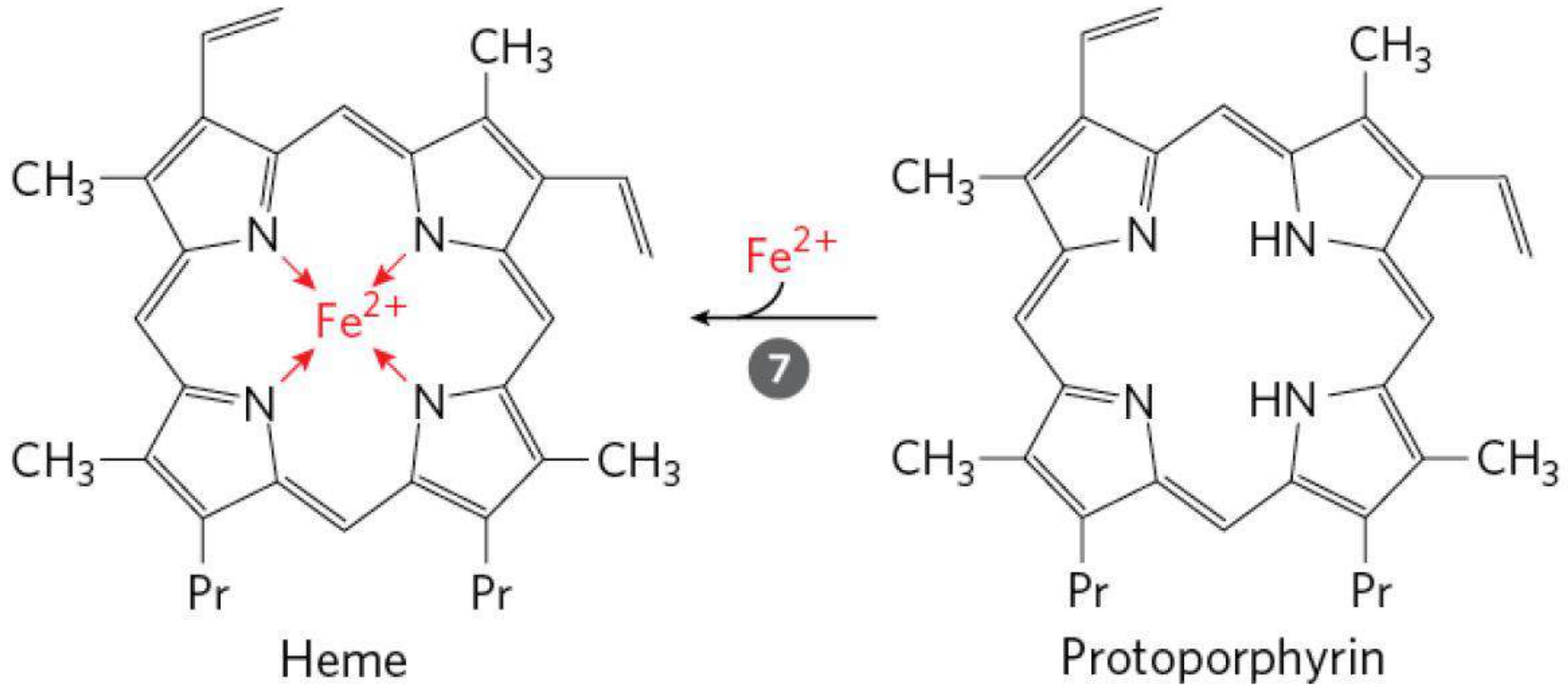
فبكونه لونه أغمق (بنى)

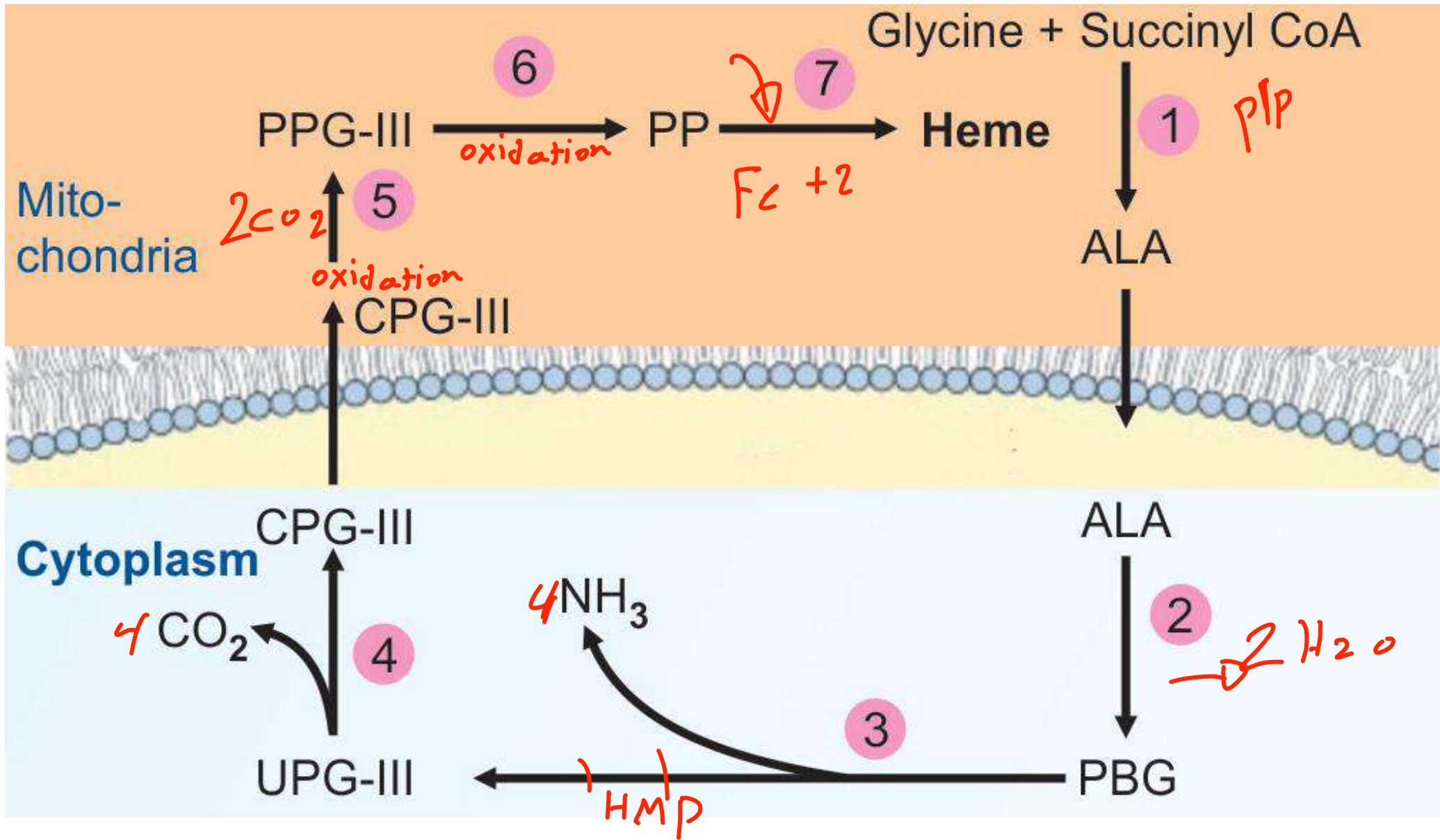
وبعير (Hematin)

بديل منه Heme

(hematin)

## Step 7: Generation of Heme





# Regulation of Heme Synthesis

- rate limiting step*      *لو زاد عندي (Heme) بقول ل (ALA) وقفني (negative feedback)*
- 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  $Fe^{2+}$  to  $Fe^{3+}$ . *→ وصوله زي كما انه يحكي ل (ALA) يحكي*
    - ALA synthase is also **allosterically** inhibited by hematin.
  - ALA synthase is **activated** by hypoxia due to increase in erythropoietin. *ازيد (RBC) فبصير في حاجة (Heme) اذ (ALA synthase) نقصه التردية امتحانه*
  - ALA synthase is also **activated** by availability of intracellular iron. *هرصونه*

# Regulation of Heme Synthesis

*antibiotic*

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

بجعله (inhibition) في الإنزيم اللي بعمله (Pyridoxal phosphate) فبصير قليل فنقل (ALA Synthase)

- 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

↳ disease

- 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.





(بس احفظوا منه الجدول)  
ارثاً شياء اللي محددة أو مكتوبة

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

porphyrin ring is coloured

TABLE 21.2: Features of important types of porphyrias

| Type  | Enzyme defect                                  | Inheritance         | Excretion in urine                                      | Other salient features   |
|---|--|---------------------|---|--|
| Acute intermittent porphyria (AIP)<br><i>the most common</i>        | 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 erythropoietic porphyria                                 | UPG-cosynthase (enzyme 3b)                     | Autosomal recessive | UP and CP; Portwine appearance                          | Marked photosensitivity. Erythrodontia. Incidence, rare  |
| Porphyria cutanea tarda<br><i>(skin) الـ the second most common</i> | UPG-decarboxylase (enz 4)                      | Autosomal dominant  | Uroporphyrins. Urine colored                            | Second most common; incidence 1 in 25,000. Photosensitivity (Fig. 21.9B)   |
| Hereditary coproporphyrin   | CPG-III-oxidase (enzyme 5)<br><i>بسبب نقصه</i> | Autosomal dominant  | UP and CP excreted in urine and feces. Colored urine    | Symptoms similar to AIP; but milder. Photosensitivity is also seen   |
| Hereditary protoporphyria   | 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)

\* يمكن أعالج ال (porphyrias) عند حرقه إعطاء (glucose) ، لأن ال (glucose) بقله منه عمل

(ALA synthase) لأن نه بس أعطى (carbohydrates) كثير (ح يصير عندى (crebs cycle)

→ I need to conserve succinal CoA from crebs cycle to Heme synthesase

فبالتالي ال (succinal CoA) اللي بروج على ال (Heme synthesase) يبطل يروح على (Heme synthesase)

ببطل يصير (induction of ALA synthase) فبضل عند ال (crebs cycle).