BIOCHEMISTRY

VEIN BATCH

Lecture : 17

Done by : Mohammad Alomari

Amino acid metabolism lecture 3 of 3

Heme synthesis from glycine and succinyl coA

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تفريغ : محمد العمري

Amino acids metabolism	1.Synthesis of non-essential amino acids 2.Catabolism of amino acids 3. Nitrogen metabolism and urea cycle 4. Heme synthesis from glycine and succinyl-CoA

What is heme, function of heme

أو بشكل أدق, هو عبارة عن ferrous protoporphyrin IX (IX = 9)

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

الheme بكون موجود in conjugation مع protein, زي الhemoglobin
مثلا اللي هو عبارة عن heme + globin, حيث الglobin هو protein

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

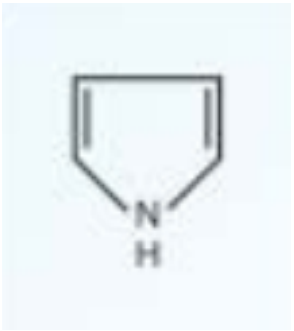
موجود بالenzymes اللي الهم علاقة بالdegradation of hydrogen peroxide,
زي الperoxidase والcatalase

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

اللهم افتح لنا أبواب حكمتك، وانشر علينا رحمتك، وامنن علينا بالحفظ والفهم

Structure of Heme

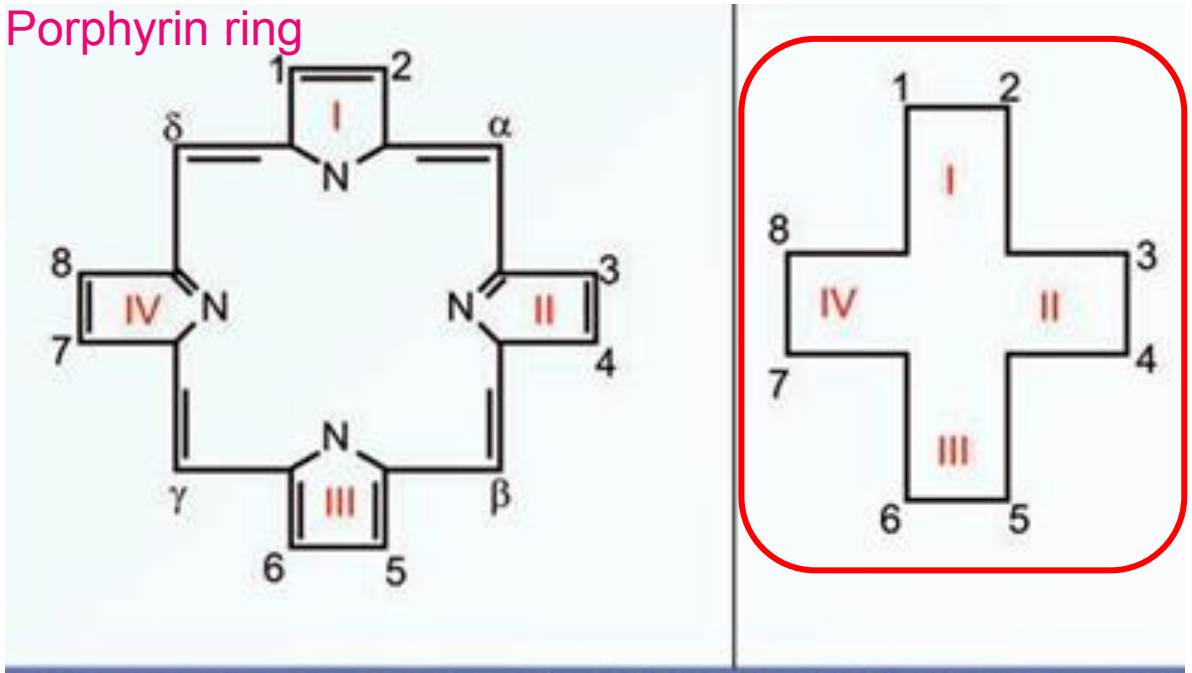
porphyrinال همه cyclic compounds مكونين من four pyrrole rings, متصلين عن طريق methenyl bridges (اللي هو =CH–), بالصورة هون بنشوف ال4 pyrrole rings بالترقيم اليوناني (I/ II/ III/ IV), وبنشوف الmethenyl bridges مرقمة من alpha إلى delta (الترقيم مع عقارب الساعة (clockwise)), ثم بنشوف ترقيم من 1 ل8, بمثل الsites الممكنة للsubstitutions, وبالصورة اللي تحت يمين معطيك مثال عال الsubstitutions. وبالporphyrins في system of conjugated double bonds (alternation بين الsingle والdouble), وهاض بعطيني خاصية ال absorption of light في فرق بين الporphyrins والporphyrinogens, حيث الporphyrinogens همه reduced form of porphyrins, فبدل ما يكون فيهم methenyl bridge رح يكون فيهم methyl bridge (-CH2-), ف صفّى ما فيهم double bonds, عشان هيك بكونوا colorless



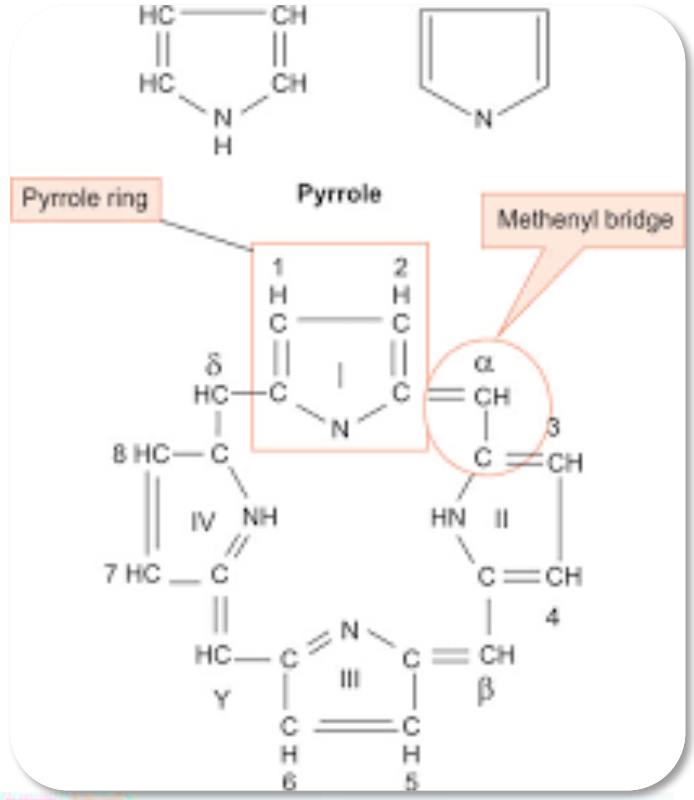
Pyrrole ring

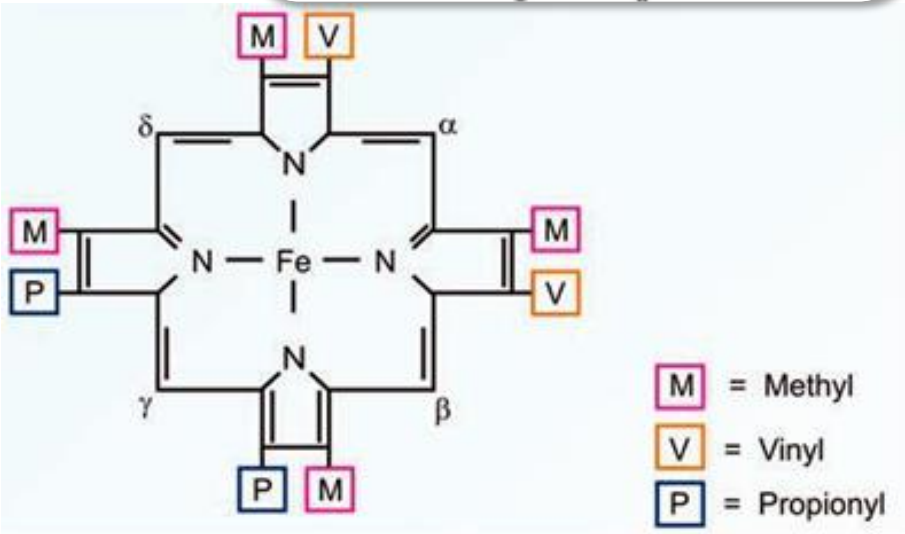
وللاختصار, احيانا يتم رسم الring بدون الdouble bonds والbridges (زي الشكل اللي عليه مربع أحمر بالوسط)

Porphyrin ring



The pyrrole rings are numbered I to IV; the bridges named as alpha to delta and the possible sites of substitutions are denoted from 1 to 8. (For brevity, the bridges and double bonds are sometimes omitted, as shown on the right).





Structure of heme

Structure of Heme

- Heme is a derivative of the porphyrin. **Porphyrins** are cyclic compounds formed by fusion of **4 pyrrole rings** linked by methenyl (=CH–) bridges
- Since an atom of iron is present, heme is a **ferroprotoporphyrin**
- The pyrrole rings are named as I, II, III, IV and the bridges as alpha, beta, gamma and delta. The possible areas of substitution are denoted as 1 to 8
- When the substituent groups have a symmetrical arrangement (1,3,5,7 and 2,4,6,8) they are called the I series
- The III series have an asymmetrical distribution of substituent groups (1,3,5,8 and 2,4,6,7)
- The usual substitutions are:
  - propionyl ($–CH_2–CH_2–COOH$) group
  - acetyl ($–CH_2–COOH$) group
  - methyl ($–CH_3$) group
  - vinyl ($–CH=CH_2$) group

BIOSYNTHESIS OF HEME

- Heme can be synthesized by almost all the tissues in the body
  - Most active in bone marrow (85%) and liver

ال synthesis بصير في معظم الخلايا, لكن أكثر اشي في ال bone marrow ثم ال liver

- Heme is not synthesized in the matured erythrocytes

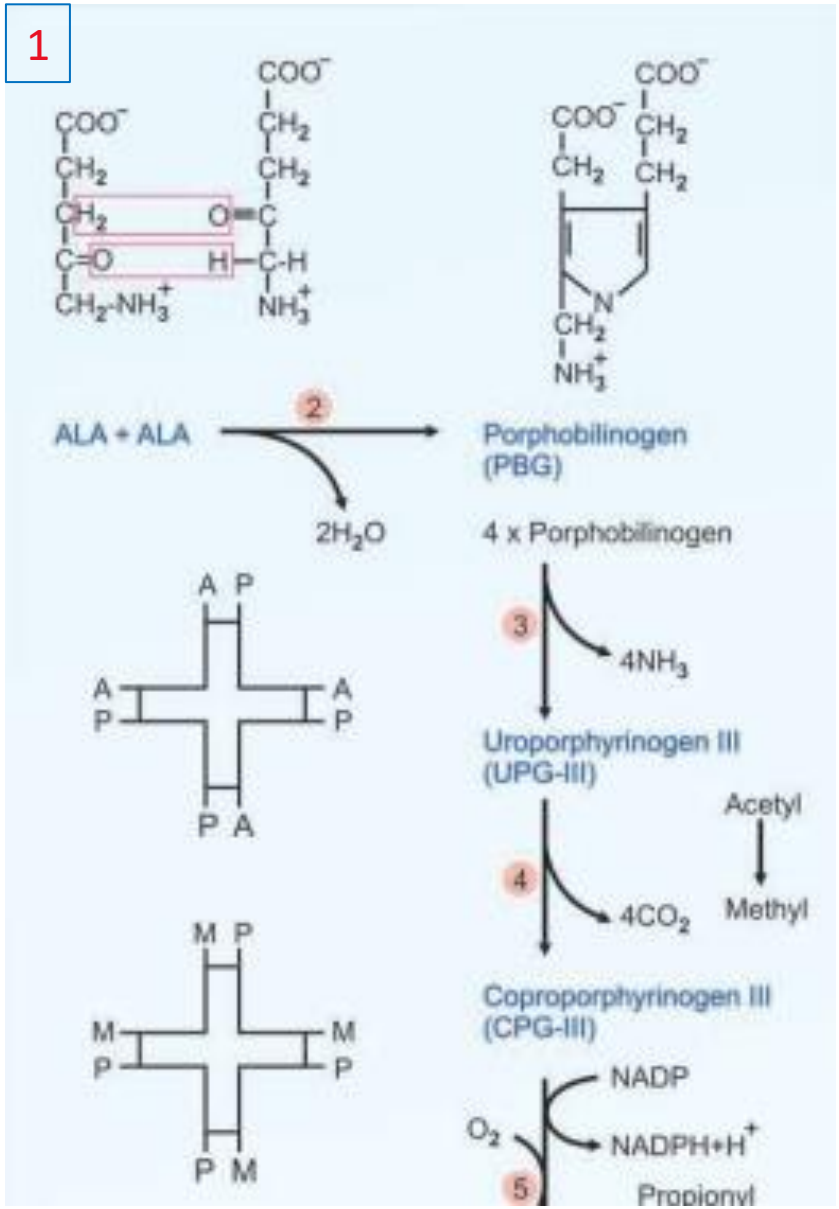
ال matured RBCs هي تقريبا ال exception الوحيد, حيث ما بصير فيها تصنيع لل heme

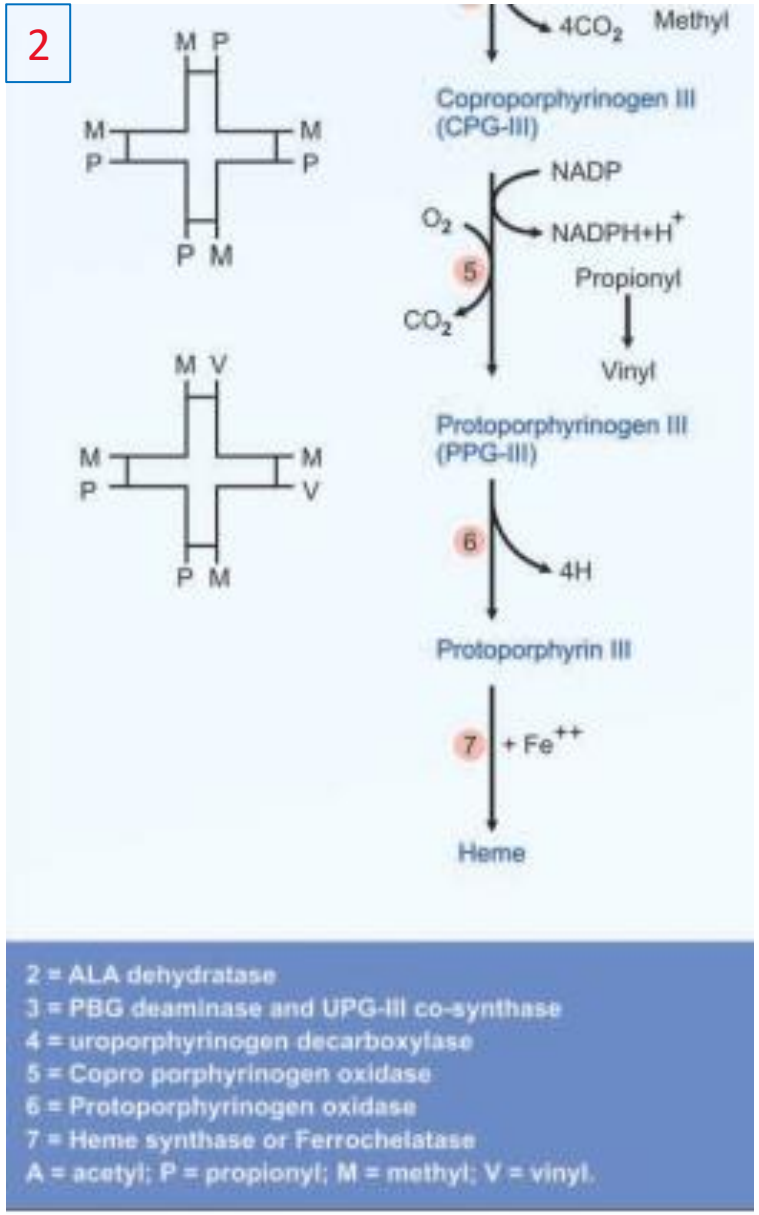
- The pathway is partly cytoplasmic and partly mitochondrial

اللهم إني أسالك التوفيق والنجاح, في الدنيا والآخرة

Steps of heme synthesis

قصّيت الصورة لنصين عشان أقدر أوضّحها, بس بشكل عام الخطوات كلها موضحة لقدام ما في داعي تضيعوا وقت كثير عالسلايد





BIOSYNTHESIS OF HEME
Step 1: ALA synthesis

بصير condensation للـsuccinyl CoA والـglycine, بوجود الـ pyridoxal phosphate ك Co-factor عشان يعطينا delta amino levulinic acid

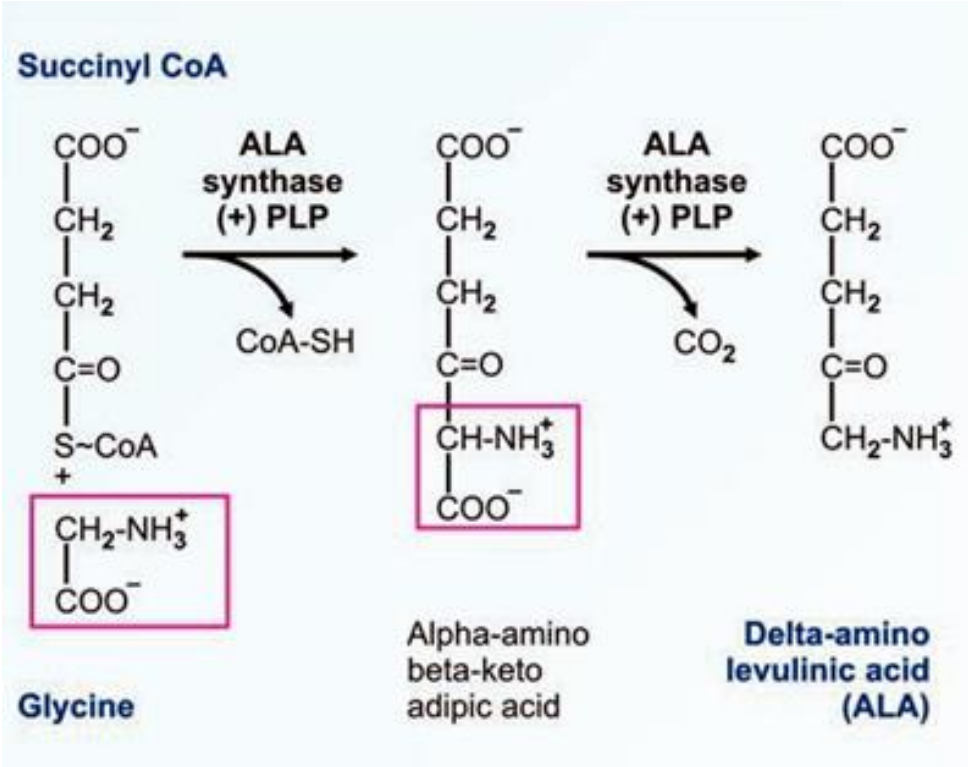
التفاعل بصير على خطوتين, # الأولى الـcondensation فيها رح يعطينا alpha-amino beta-keto adipic acid (بخروج CoA-SH). # الثانية بنتج عنها الـALA بخروج الـCO2, والخطوتين بصيروا عن طريق نفس الـenzyme اللي هو الـALA synthase (اللي ما بتسهلك ATP)

- 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

  و لإنه الـpyridoxal phosphate هو Co-factor مهم هون, فالـanemia هي وحدة من الـmanifestations (مظاهر/ أعراض) للـpyridoxal deficiency

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



Step 1 in heme synthesis

BIOSYNTHESIS OF HEME
Step 2: Formation of PBG

هون بصير condensation لـ2 molecules of ALA,
وبنتج عنهم porphobilinogen (PBG), وبخرج منهم
2 H2O, والتفاعل عن طريق الALA dehydratase

- Next few reactions occur in the cytoplasm

  الخطوات من 2 لـ4 بتحدث في الcytosol

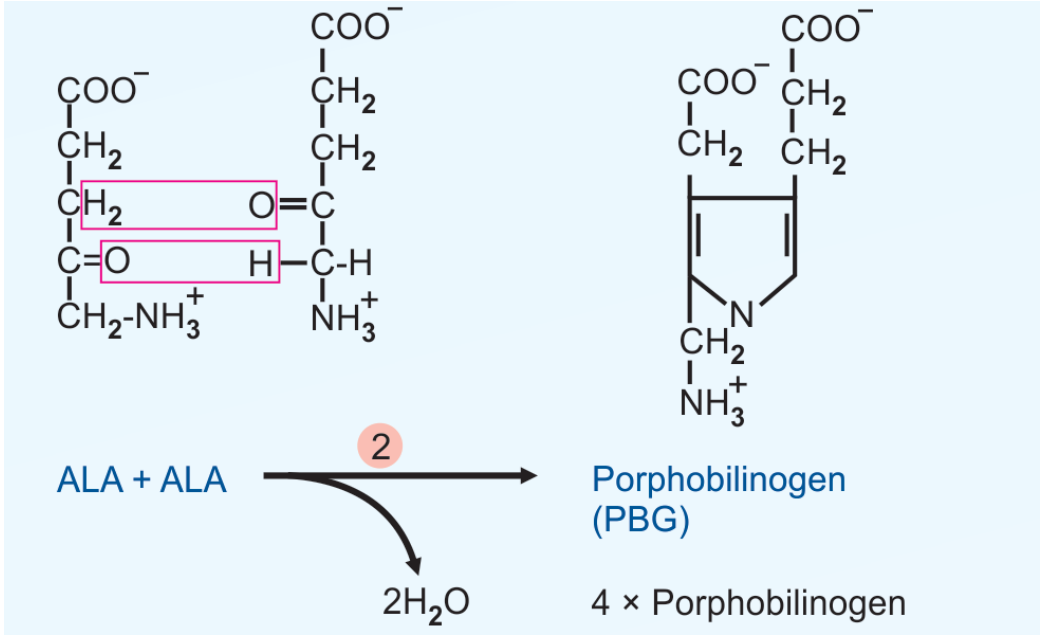
- Two molecules of ALA are condensed to form porphobilinogen (PBG)

- The condensation involves removal of 2 molecules of water and the enzyme is **ALA dehydratase**

- Porphobilinogen is a monopyrrole

  الPBG بحتوي على one pyrrole ring فقط
  (لكن احنا محتاجين 4)

- The enzyme contains zinc and is **inhibited by lead**



يا حيّ يا قيوم برحمتك أستغيث, أصلح لي شأني كله, ولا تَكِلْني إلى نفسي طرفة عين

BIOSYNTHESIS OF HEME
Step 3: Formation of UPG

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

  بما إنه الPBG بحتوي على one pyrrole ring, ف بنعمل condensation لـ4 منه عن طريق
  الPBG deaminase, وهيك بنحصل على أول porphyrin, اللي اسمه uroporphyrinogen

- Condensation occurs in a head-to-tail manner, so that a linear tetrapyrrole is produced; this is named as **hydroxy methyl bilane** (HMB)

- The enzyme for this reaction is PBG-deaminase

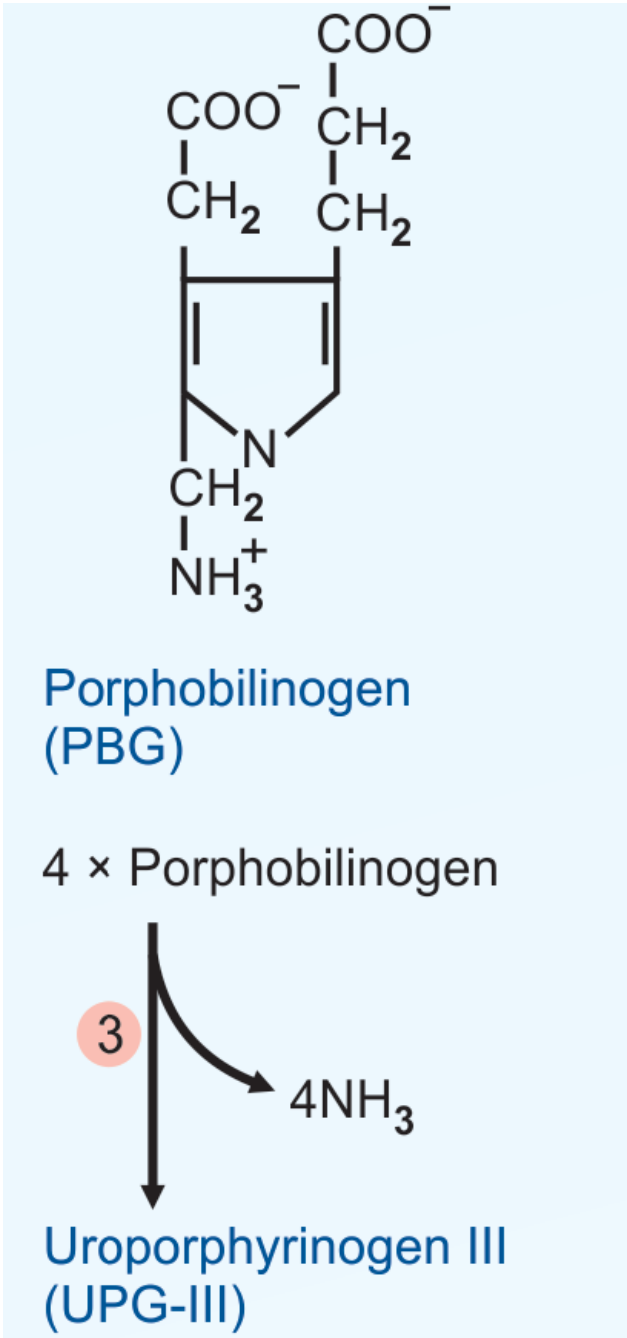
- HMB molecule will cyclise spontaneously to form uroporphyrinogen I

  الHMB بصير على شكل cycle بشكل تلقائي, وبعطينا uroporphyrinogen I

- It is converted to **uroporphyrinogen III** by the enzyme, uroporphyrinogen III synthase

- When the fusion occurs, the III series of isomers are predominantly formed; and only the **III series** are further utilized

- During this deamination reaction 4 molecules of ammonia are removed



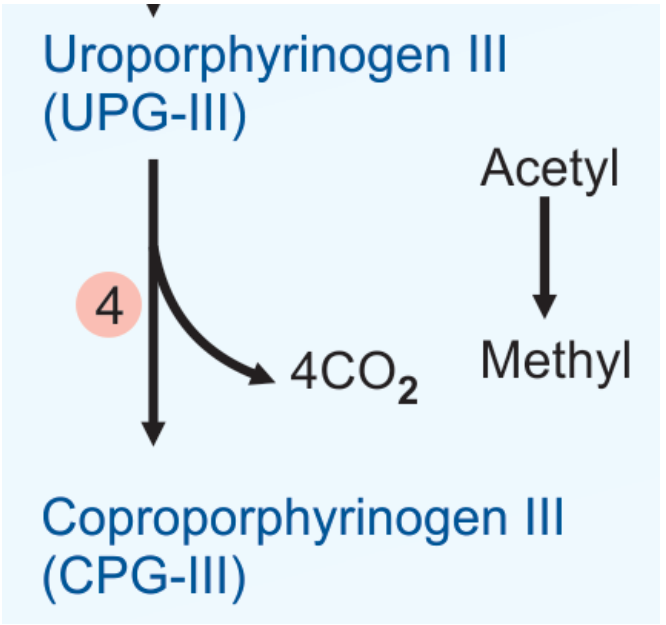
BIOSYNTHESIS OF HEME
Step 4: Synthesis of CPG

- The UPG-III is next converted to coproporphyrinogen (CPG-III) by decarboxylation

  التفاعل بصير عن طريق uroporphyrinogen decarboxylase

- Four molecules of CO_2 are eliminated by uroporphyrinogen **decarboxylase**

- The acetate groups (CH_2–COOH) are decarboxylated to methyl (CH_3) groups



BIOSYNTHESIS OF HEME
Step 5: Synthesis of PPG

- Further metabolism takes place in the ***mitochondria***

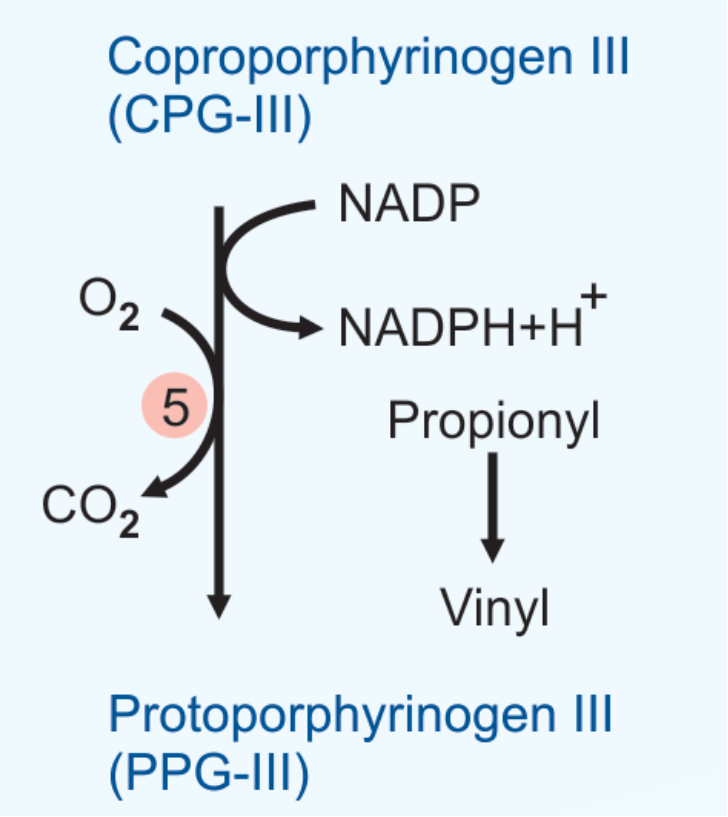
  من هاي الstep لنهاية الreaction بتصير بالmitochondria

- 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



اللهم إنك عفوّ تحب العفو فاعفُ عنا

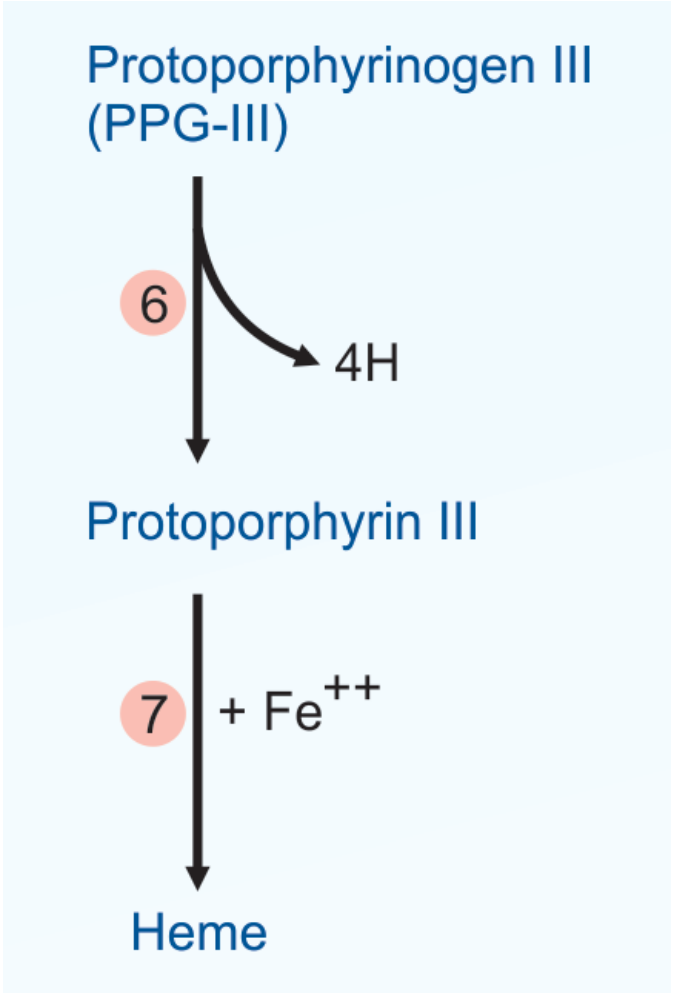
BIOSYNTHESIS OF HEME
Step 6: Generation of PP

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

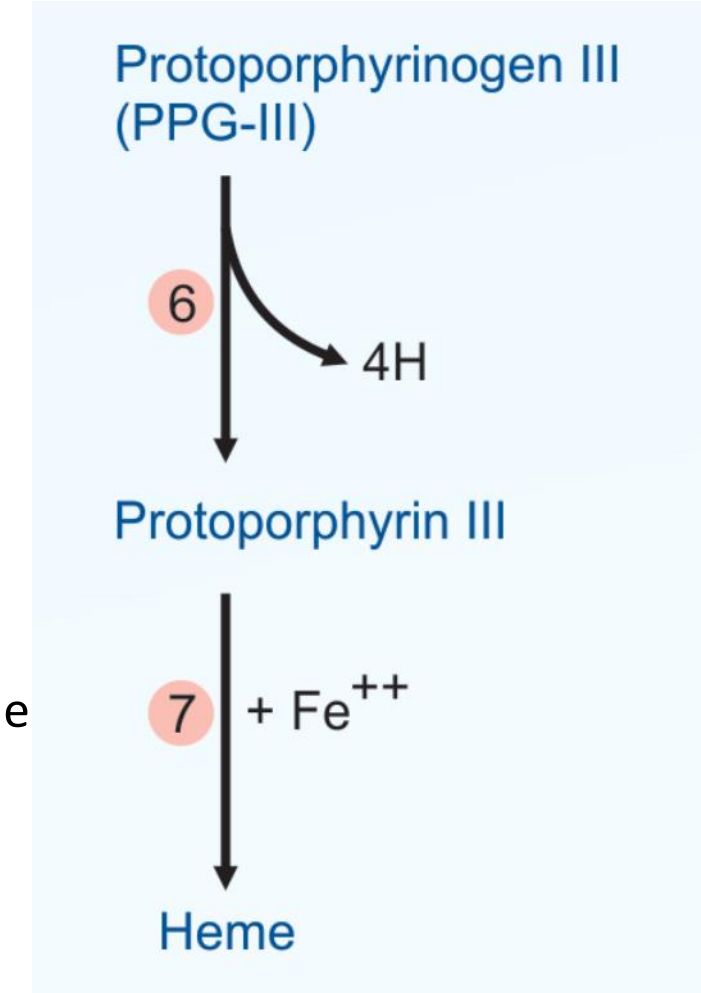
- The oxidation requires molecular oxygen

- The methylene bridges ($–CH_2$) are oxidised to methenyl bridges (–CH=) and colored porphyrins are formed

بهاض الreaction بتظهر الmethenyl bridges, وبسببهم
colored porphyrins are formedال

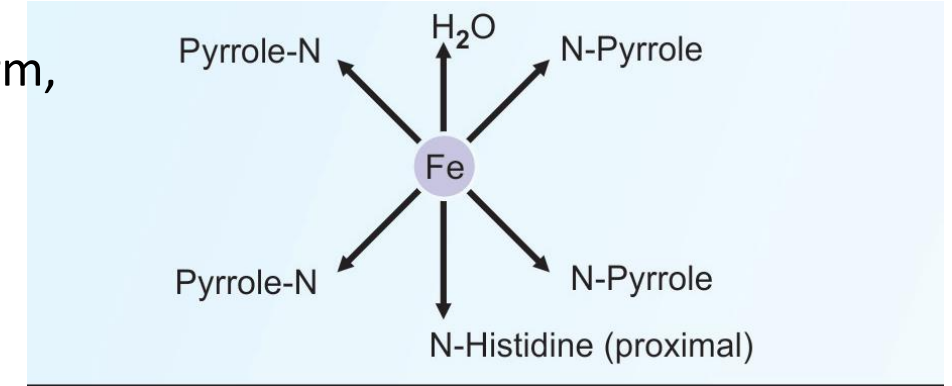


BIOSYNTHESIS OF HEME
Step 7: Generation of Heme

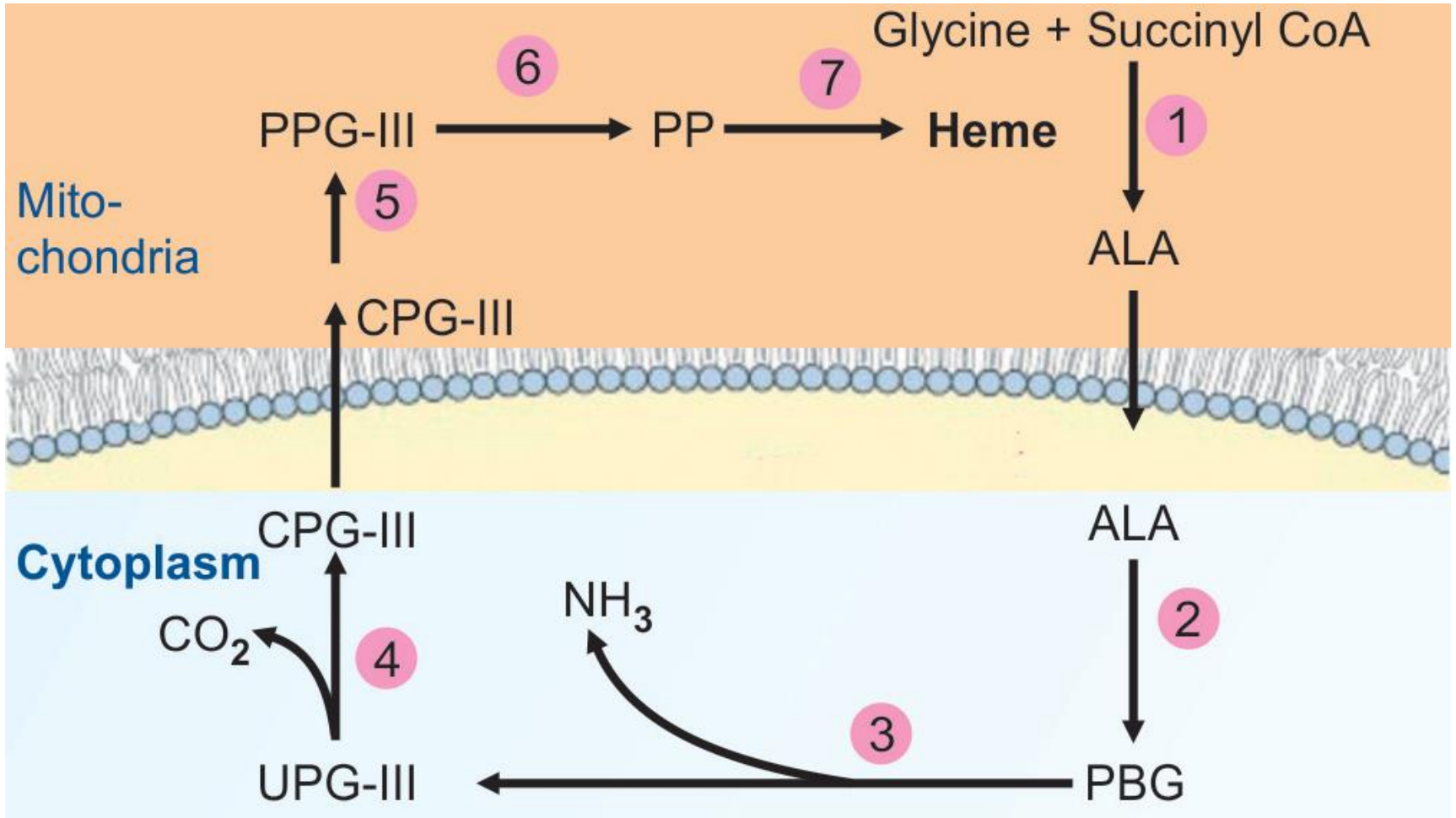


- The last step in the formation of heme is the attachment of ferrous iron to the protoporphyrin
- The enzyme is **heme synthase** or **ferrochelatase** which is also located in **mitochondria**
- Iron atom is coordinately linked with 5 nitrogen atoms (4 nitrogen of pyrrole rings of proto-porphyrin and 1st nitrogen atom of a histidine residue of globin)

  الiron atom بتكون متصلة بـ 4 N من الpyrrole rings, و 1 N من
  الhistidine (بمجموع 5), بالإضافة لـ 1 H2O
- 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



(هون بفرجيك مواقع الsteps)



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

*BM = bone marrow

لما يزيد الheme عن حدّه ببلش يتحول لhematin
والhematin بعمل inhibition للALA synthase

- **ALA synthase** is activated by hypoxia due to increase in erythropoietin
- **ALA synthase** is also activated by availability of intracellular iron
- 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

لما يصير ingestion (ابتلاع/ تناول) للdrugs اللي بتحتاجو cytochrome P450 هاض رح يعمل induction (تحفيز) للALA synthase enzyme

اللهم إني أعوذ بك من الهم والحزن, وأعوذ بك من العجز والكسل

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

الأمراض هاي نوعين, hereditary (وراثية) أو acquired (مكتسبة), والacquired ممكن تصير بسبب الlead poisoning,
والhereditary كلهم autosomal dominant باستثناء واحد فقط

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

معرفة الdefect enzyme مهمة, بالإضافة لأهمية معرفة الmode of inheritance, ونركز عالmost common types

Low levels of ALA synthase will lead to Anemia not porphyria

الacute attacks اسمها acute intermittent porphyria (AIP) والtreatment إلها empirical, وبتكون عن طريق high CHO diet أو glucose مرتفع بكون مفيد, لإنه بمنع الinduction للALA synthase , وهاض هو أساس الadministration للglucose خلال الattacks

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 Most commonepatic 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 Second most commonsitivity (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)

اللهم إني أستودعك ما درست وقرأت وحفظت وفهمت.. فرُدَّه لي عند حاجتي إليه