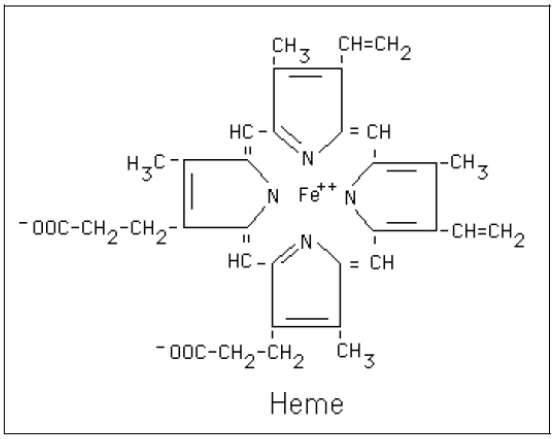
METABOLISM OF PORPHYRINE AND PORPHINURIAS, FORMATION OF BILE PIGMENTS AND JAUNDICE.

Porphyrins are cyclic compounds composed of four pyrole rings linked through methyne bridges i.e. (-HC=). Heme is a member of the family of porphyrins. The parent porphyrin is porphine, and substituted porphines are called porphyrins. Many important proteins contain heme as a prosthetic group for example Hemoglobin (oxygen transport), Myoglobin (oxygen transport), Cytochromes (electron transport) and Catalase (H_2O_2 utilization).

Porphyrins are generally known to form complexes with metal ions such as iron, magnesium, copper etc at the nitrogen atom. When an iron complex is formed the resulting compound is Heme, while chlorophyll is formed with a magnesium porphyrin complex. In nature the hydrogen atoms of the pyrole rings are substituted by chemical groups or substituents such as A = acetic acid (-CH2COOH), P = propionic acid (-CH2CH2COOH), M = methyl (-CH3), V = vinyl (-CH=CH2) groups and depending on which substituent groups are attached the porphyrins are named differently for example Coproporphyrin contains M and P only, protoporphyrin contains M and P and V, uroporphyrin contains A and P only etc.
Asymmetrically arranged chemical groups in a porphine (another name for porphyrin) are termed type III porphins while those which are symmetrical in arrangement of substituents are called type I. Types II and IV do not occur in natural systems. Heme is an example of type III porphine.
General properties of porphins

1. Solubility depends on number of carboxylate groups, -COO- e.g. uroporphyrins, 8 carboxylates (more soluble) and protoporphyrins, 2 carboxylates (less soluble).
2. Color: dark red/purple
3. Fluorescent
4. Chelate metal ions.

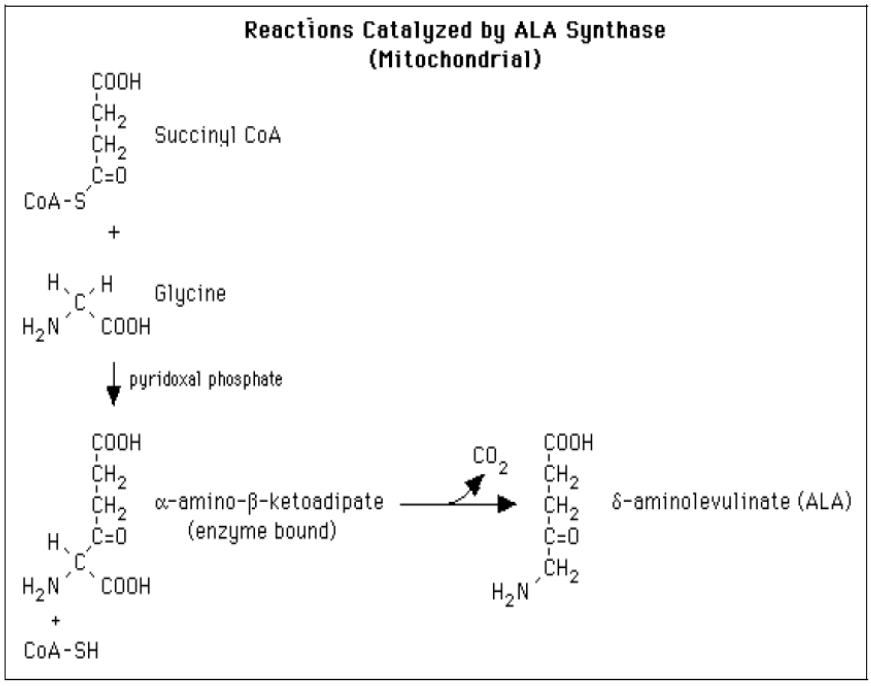


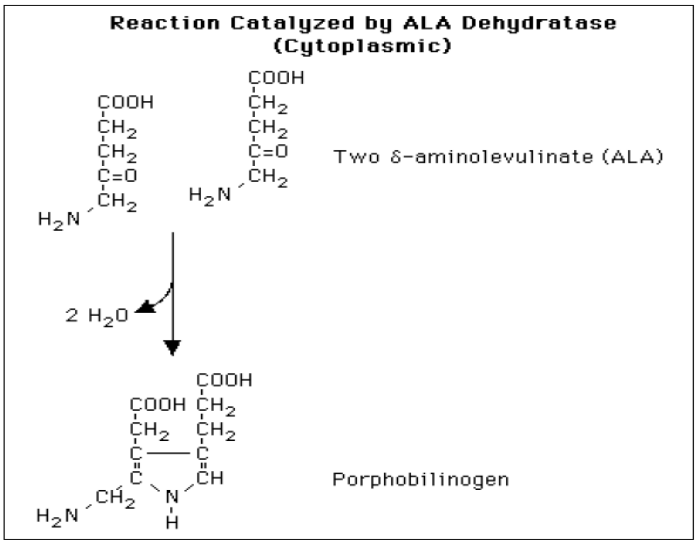
Heme

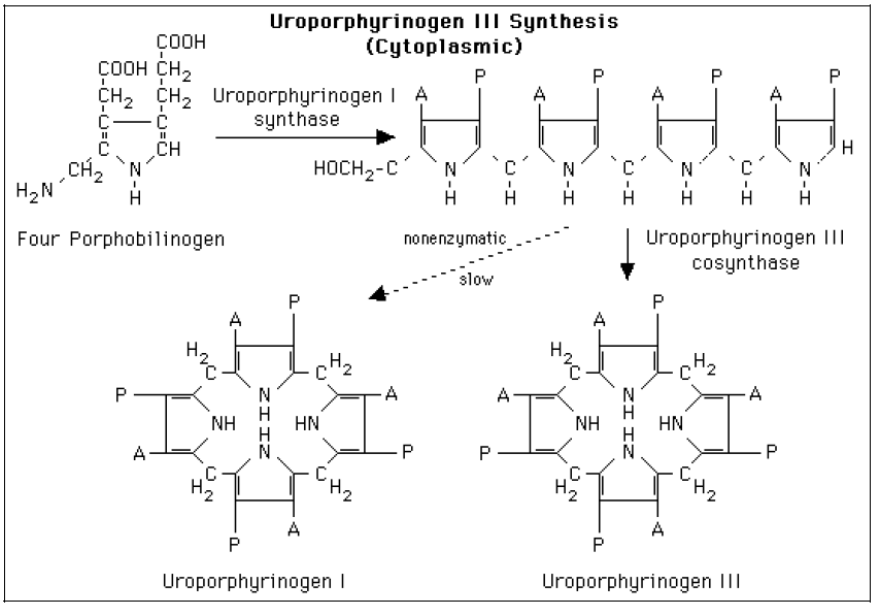
Porphyrinogens are a closely related compounds that have extra hydrogen atoms and also differ in pattern of double bonds available, hence are linked by methenyl bridges. They are colorless, do not fluoresce and are easily auto oxidized to porphyrins e.g. urobilinogen.

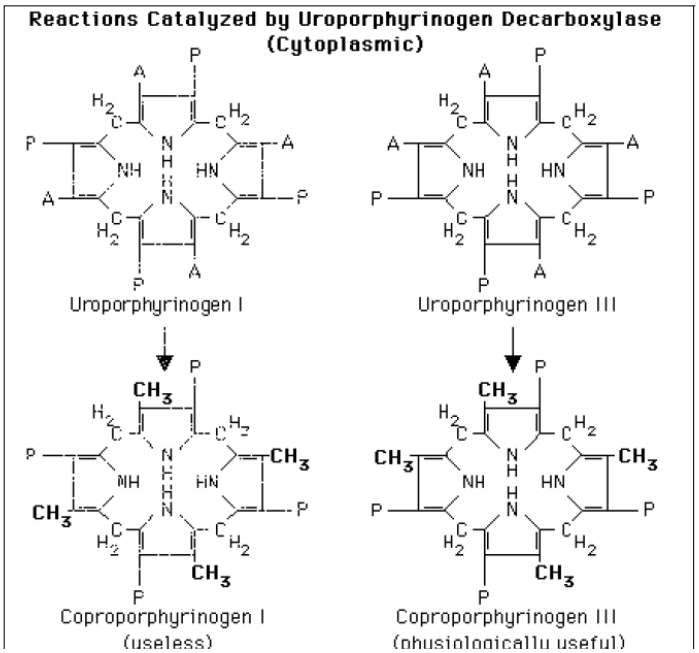
BIOSYNTHESIS OF HEME

The synthesis of porphyrins is an essential pathway to the synthesis of heme for hemoglobin in the RBC. Site of reaction is partly in the mitochondria and partly in the cytoplasm. Heme is synthesized mainly in the erythropoietic and liver cells.

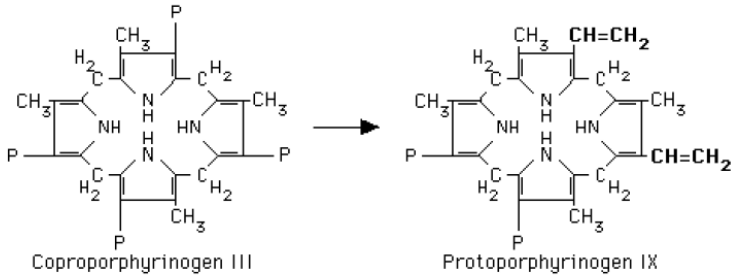

Reactions Catalyzed by ALA Synthase
(Mitochondrial)
Succinyl CoA
Glycine
pyridoxal phosphate
α-amino-β-ketoadipate
(enzyme bound)
δ-aminolevulinate (ALA)
CO2
CoA-SH


Reaction Catalyzed by ALA Dehydratase
(Cytoplasmic)
Two δ-aminolevulinate (ALA)
2 H2O
Porphobilinogen

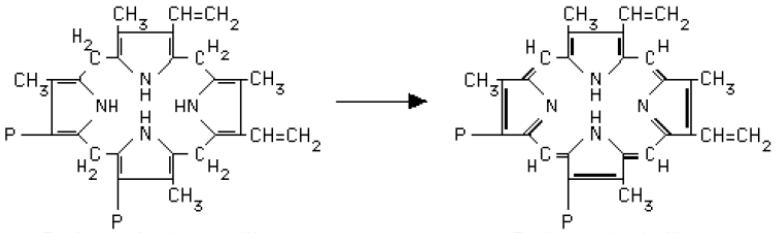

Uroporphyrinogen III Synthesis
(Cytoplasmic)
Uroporphyrinogen I synthase
Four Porphobilinogen
nonenzymatic
slow
Uroporphyrinogen III cosynthase
Uroporphyrinogen I
Uroporphyrinogen III


Reactions Catalyzed by Uroporphyrinogen Decarboxylase
(Cytoplasmic)
Uroporphyrinogen I
Uroporphyrinogen III
Coproporphyrinogen I
(useless)
Coproporphyrinogen III
(physiologically useful)

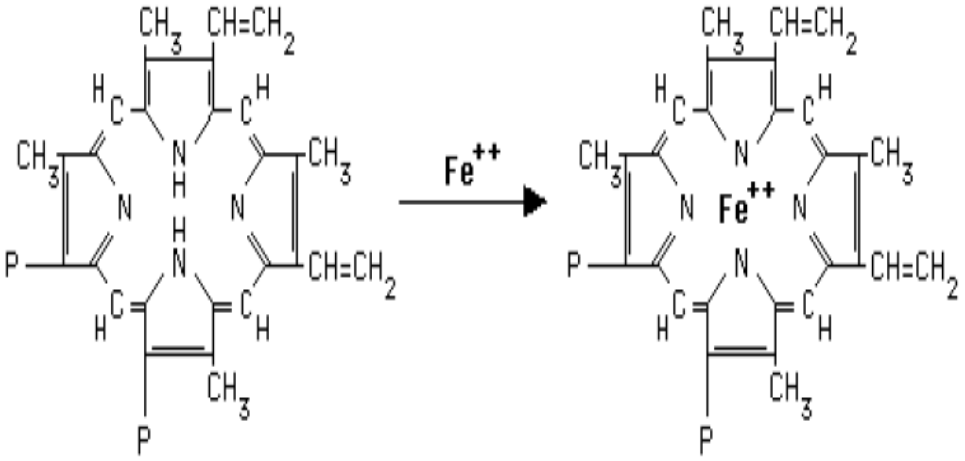
Reaction Catalyzed by Coproporphyrinogen III Oxidase (Mitochondrial)



Reaction Catalyzed by Protoporphyrinogen IX Oxidase (Mitochondrial)

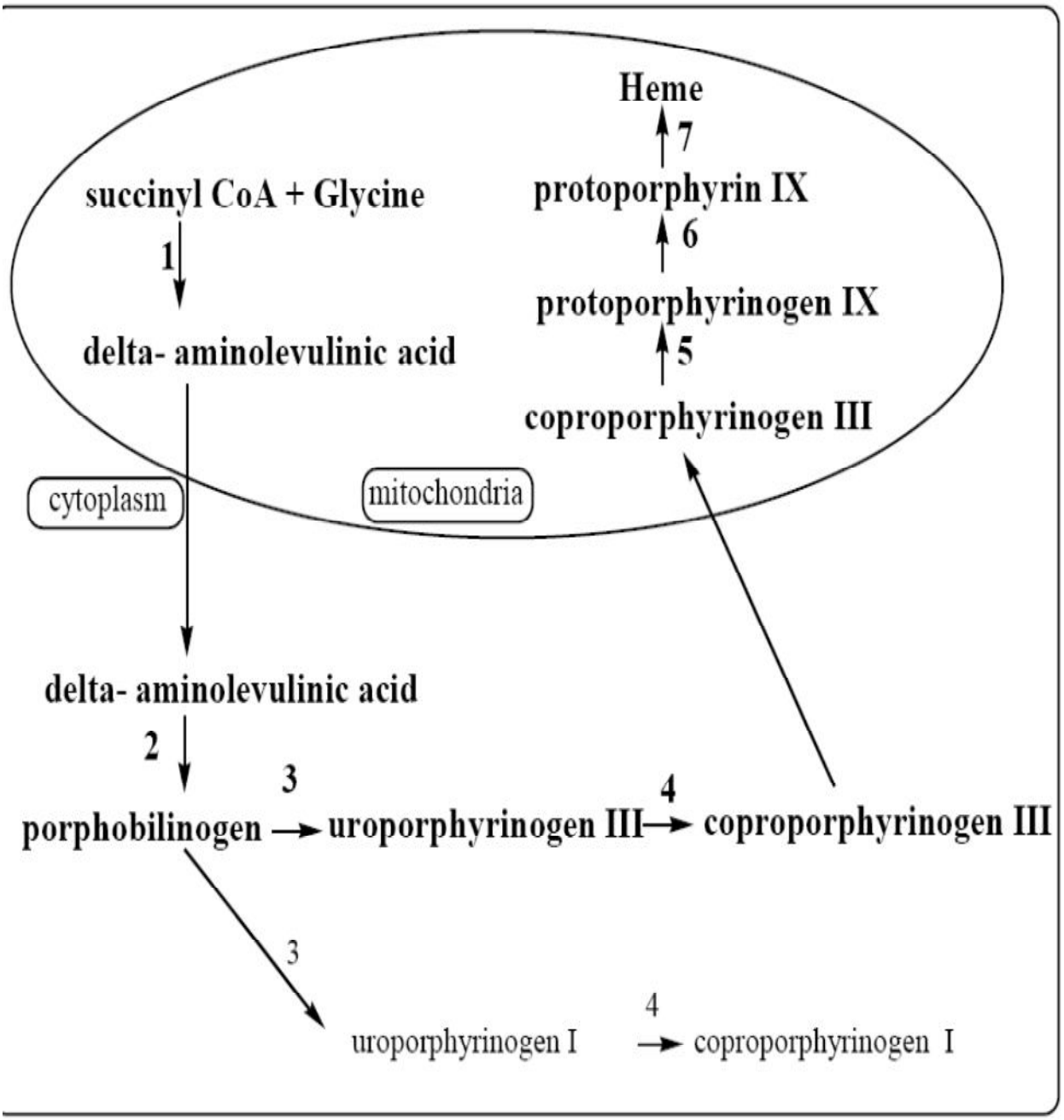


Reaction Catalyzed by Ferrochelatase
(Mitochondrial)



Protoporphyrin IX

Heme



Site and reactions of heme synthesis

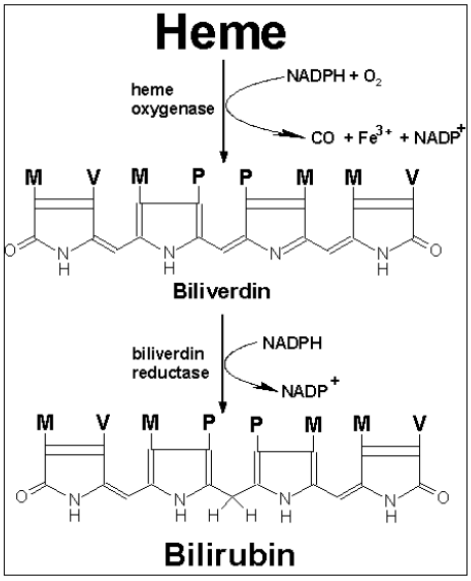
REGULATION OF HEME SYNTHESIS

1. Substrate availability: Fe++ must be available for ferrochelatase.
2. Feedback regulation: heme is a feedback inhibitor of ALA synthase. The Fe^{3+} oxidation product of heme is termed hemin. Hemin acts as a feed-back inhibitor on ALA synthase. Hemin also inhibits transport of ALA synthase from the cytosol (its' site of synthesis) into the mitochondria (its' site of action) as well as represses synthesis of the enzyme.
3. Effects of drugs and steroids: Certain drugs and steroids can increase heme synthesis via increased production of the rate limiting enzyme, ALA synthase.

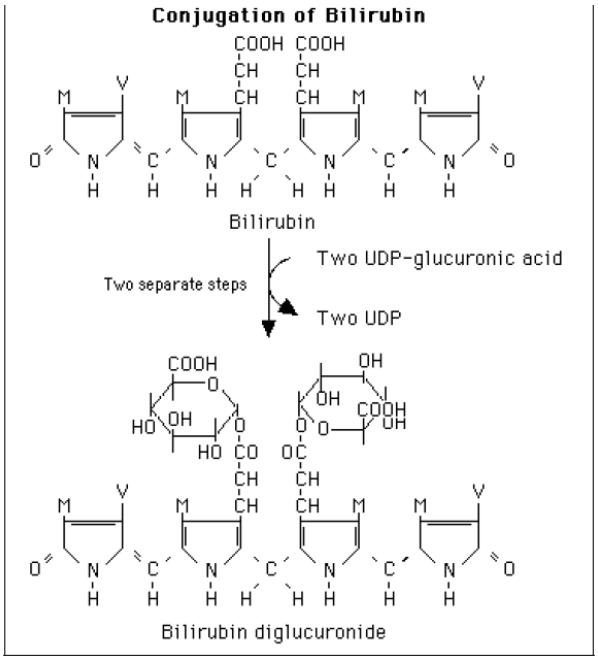
CATABOLISM OF HEME

Cells of the reticuloendothelial system in spleen, liver and bone marrow engulf aged RBCs to remove them from circulation releasing its contents of hemoglobin. The porphin portion of heme is degraded after the globin fragment is degraded to constituent amino acids and iron is recycled for use.

The catabolism of heme starts with its oxidation. The heme ring is opened by heme oxygenase (found in the endoplasmic reticulum); this oxidation produces a linear tetrapyrole called biliverdin, ferric iron and carbon monoxide. Subsequent reduction of biliverdin produces bilirubin.



Bilirubin is highly non-polar (lipid soluble) hence is not easily excreted from the body and has to be converted to a more polar –water soluble compound. Within the blood bilirubin is transported by a carrier the physiological carrier is serum albumin. Conjugation of bilirubin with glucuronic acid in the liver by hepatocytes increases its water solubility and eases its excretion. Conjugation is accomplished by attaching two molecules of glucuronic acid to it in a two step process by UDP glucuronyl transferase. The reaction is a transfer of two glucuronic acid groups sequentially to the propionic acid groups of the bilirubin. The major product is bilirubin diglucuronide which is excreted in the bile. It is subject to subsequent transformations to other species by the intestinal bacteria.



BILE PIGMENTS

These consist of bilirubin and its catabolic products they range from yellow red to orange yellow in color and give feces its characteristic brownish color. In the intestine (after conjugation of bilirubin by the hepatocytes) bacteria act on the compound to produce the final porphyrin products, urobilinogens and urobilins, that are found in the feces. A small fraction of urobilinogen is reabsorbed into the blood, extracted by the kidney, and excreted in the urine. Another portion of the reabsorbed urobilinogens are taken up by the liver and further reexcreted in bile what is known as undergoing enterohepatic circulation. In the distal portion of the GIT urobilinogens are oxidized to produce stercobilin, mesobilin and urobilin (the major pigments in feces).