

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

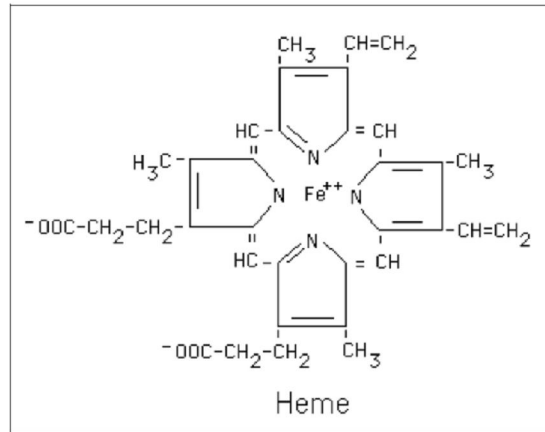
Porphyrins are cyclic compounds composed of four pyrrole rings linked through methyne bridges i.e. (-HC=). Heme is a member of the family of porphyrins. The parent porphyrin is porphine, and substituted porphines are called porphyrins. Many important proteins contain heme as a prosthetic group for example Hemoglobin (oxygen transport), Myoglobin (oxygen transport), Cytochromes (electron transport) and Catalase (H₂O₂ 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 pyrrole 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 a type of type III porphine.

General properties of porphins

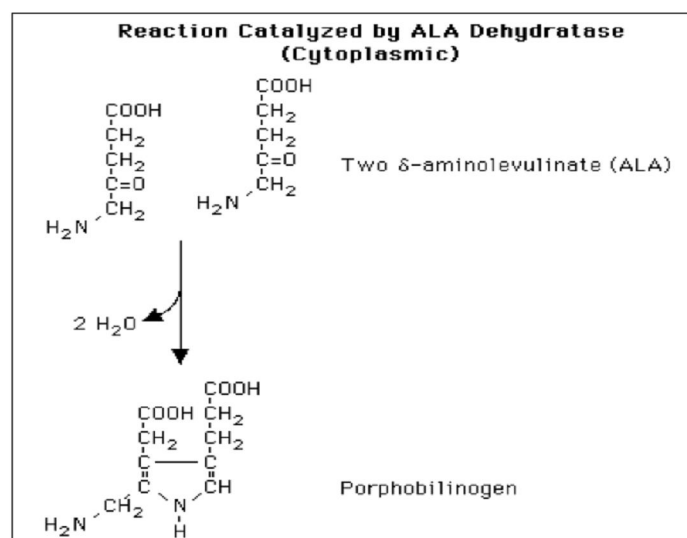
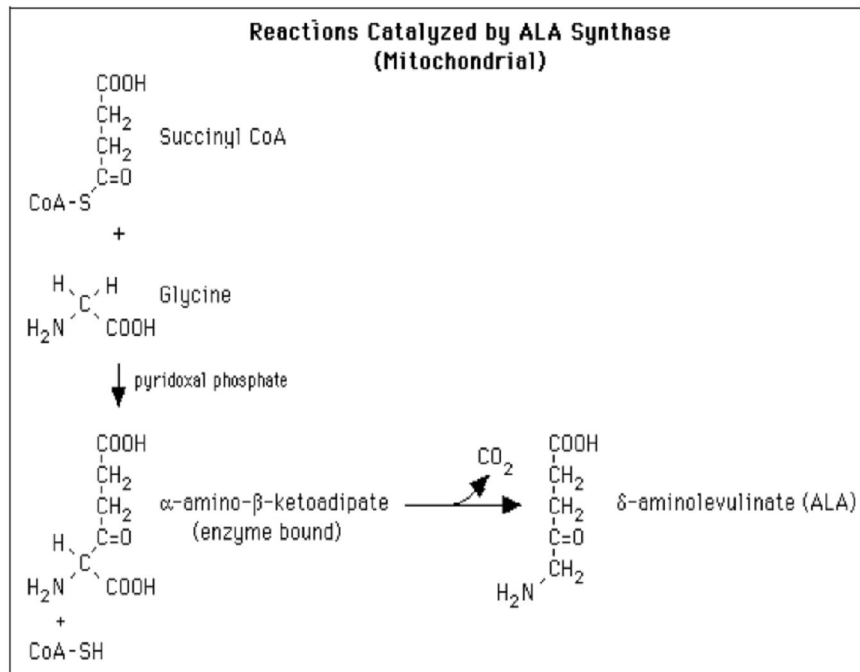
1. Solubility depends on number of carboxylate groups, -COO- e.g. uroporphyrins, 8 carboxylates (more soluble) and protoporphyrins, 2 carboxylates (less soluble).
2. Color: dark red/purple
3. Fluorescent
4. Chelate metal ions.

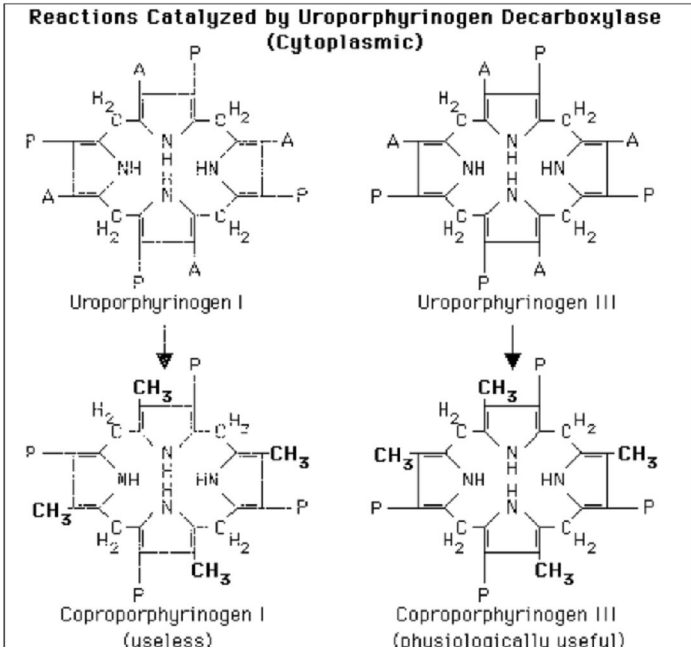
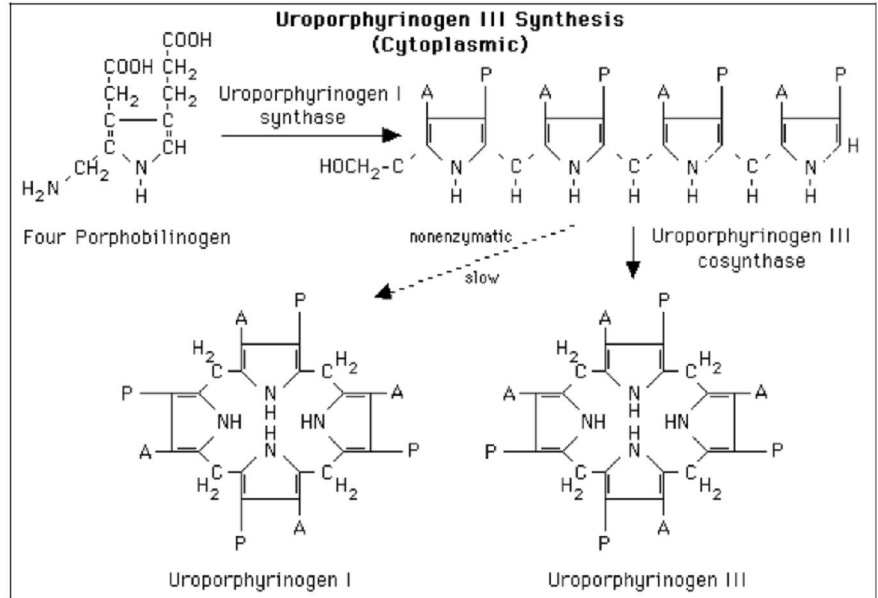


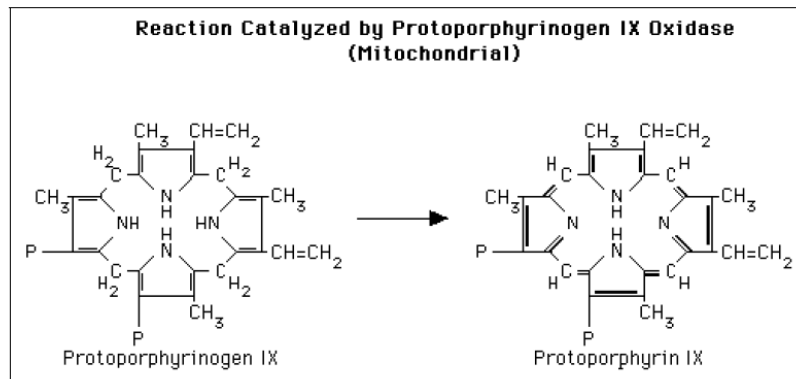
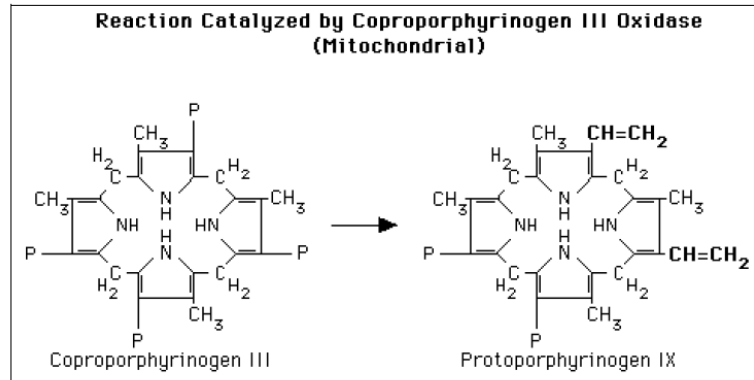
Porphyrinogens are a closely related compounds that have extra hydrogen atoms and also differ in pattern of double bonds available, hence are linked by methenyl bridges. They are colorless, do not fluoresce and are easily auto oxidized to porphyrins e.g. urobilinogen.

BIOSYNTHESIS OF HEME

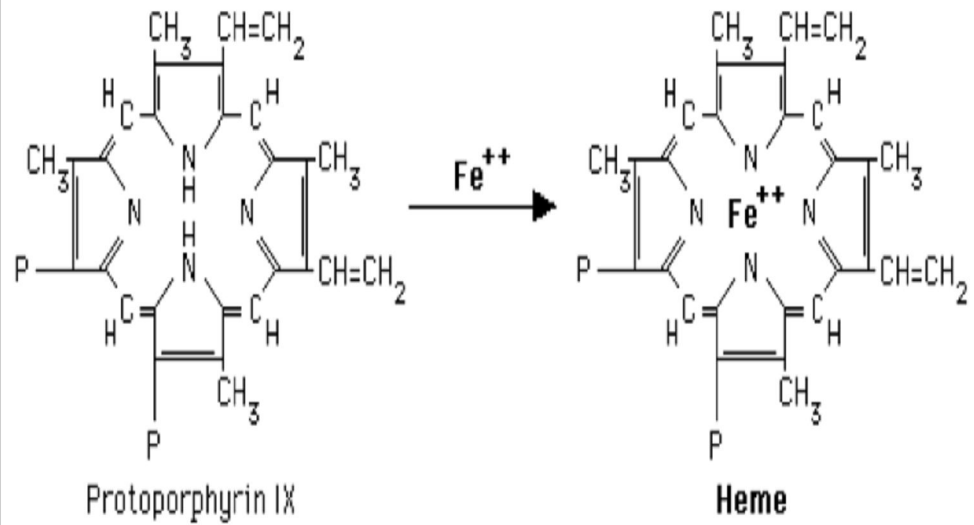
The synthesis of porphyrins is an essential pathway to the synthesis of heme for hemoglobin in the RBC. Site of reaction is partly in the mitochondria and partly in the cytoplasm. Heme is synthesized mainly in the erythropoietic and liver cells.

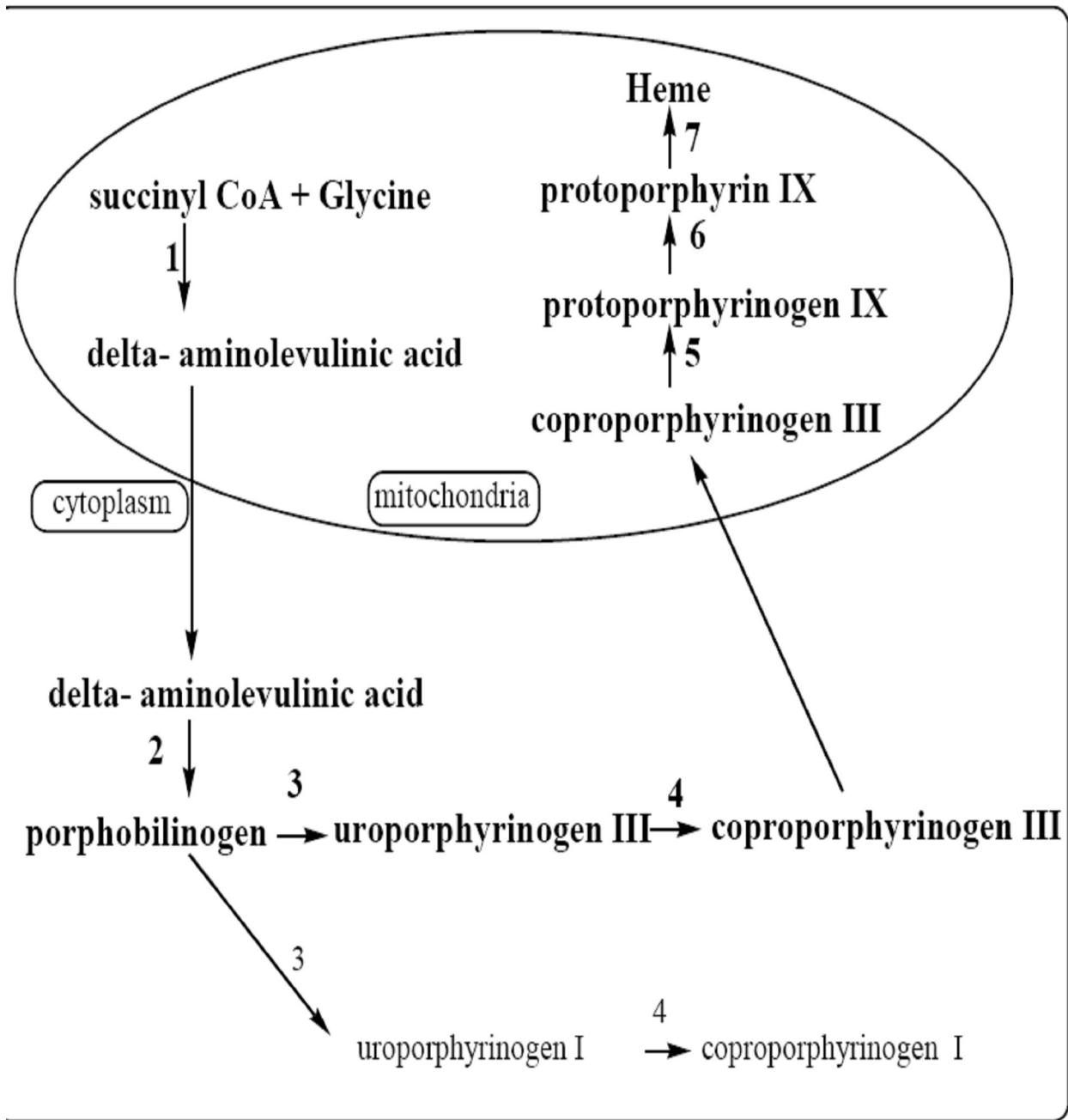






**Reaction Catalyzed by Ferrochelatase
(Mitochondrial)**





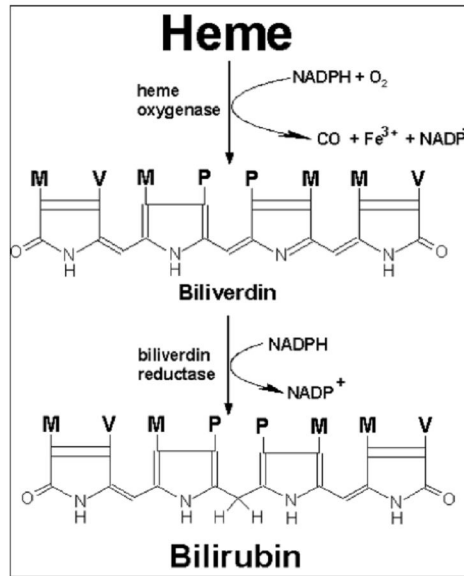
Site and reactions of heme synthesis

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.

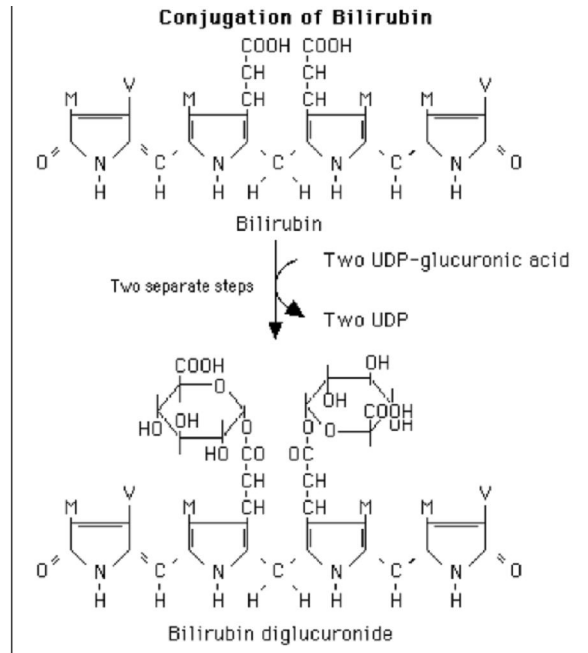
CATABOLISM OF HEME

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 tetrapyrrole 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).

JAUNDICE

Jaundice or hyperbilirubinemia also called icterus is the accumulation of bilirubin or bile pigments above normal levels in the plasma leading to the discoloration of skin, mucous membrane and tissues. Bilirubin has been shown to inhibit DNA synthesis, uncouple oxidative

phosphorylation, and inhibit ATPase activity in brain mitochondria. Bilirubin also inhibits a variety of different classes of enzymes including dehydrogenases, electron transport proteins, hydrolyases, and enzymes of RNA synthesis, protein synthesis and carbohydrate metabolism, hence very toxic in the system.

There are three major types of jaundice;

1. Prehepatic jaundice this occurs as a result of increased production of bilirubin as a result of more rapid breakdown of RBCs than normal more bilirubin is conjugated and excreted than normally, but the conjugation mechanism is overwhelmed, and an abnormally large amount of unconjugated bilirubin is found in the blood. This may occur as a consequence of a hemolytic disease causing massive destruction of RBCs.
2. Hepatic jaundice occurs because of an inability of the hepatocytes to adequately conjugate bilirubin either as a result of inability to take up bilirubin from the blood (As a result, unconjugated bilirubin accumulates), or an impairment of the conjugation pathway (also unconjugated bilirubin accumulates) or inability of the hepatocytes to secrete the already conjugated bilirubin after it is formed hence conjugated bilirubin returns to the blood.
3. Post hepatic jaundice is caused by an obstruction distal to the liver e.g. biliary obstruction like a calculi that interferes with secretion or passage of the conjugated bilirubin into the intestine hence there is reabsorption of conjugated bilirubin back into the system (a proportion normally exchanges back into the blood plasma but in health this is very small).

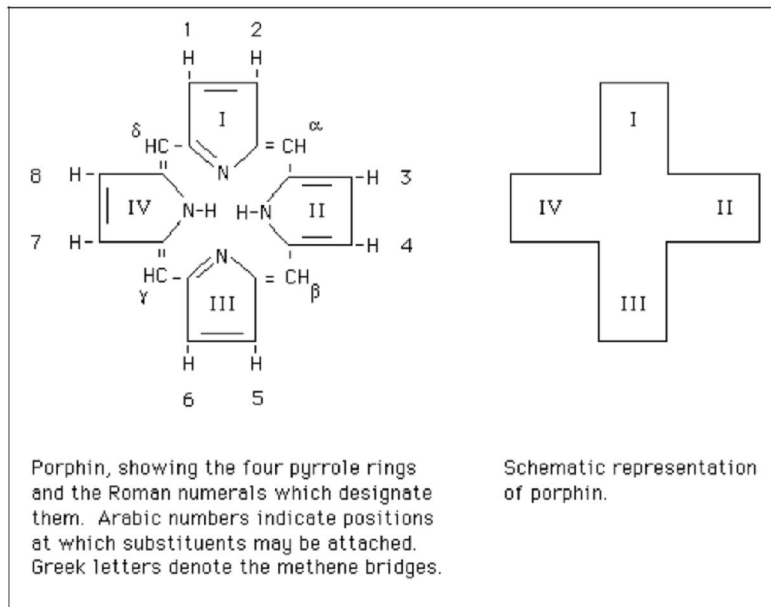
PORPHYRIAS

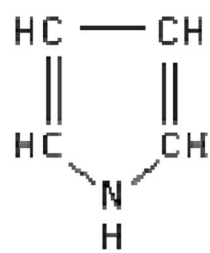
These are disorders that arise in heme biosynthesis as a result of defects in enzymes that catalyze the various reactions. Typically there is an increase in levels of intermediates of heme synthesis within the blood, urine and other body tissues and fluids and these can cause toxic effects.

Porphyrias may be either acquired (as a result of poisonous or drug effects on enzymes) or hereditary (caused by a gene defect). Porphyrias may also be classified as erythroid or hepatic depending on site of enzyme defect.

The most common porphyrias known is that caused by a defect in the enzyme porphobilinogen deaminase (PBG deaminase) called acute intermittent porphyrias.

Porphyrias generally lead to excretion of deposits in urine that color it red or reddish brown; they may also be deposited in teeth. Ulcerative and photosensitive systems on the skin may also results when the porphobilinogens are oxidized to porphins. There may also be neurological symptoms, which cannot be explained.





Pyrrole



Abbreviated version of pyrrole