
V The Porphyrias

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Classification

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The porphyrias are a group of diseases characterized by the overproduction of porphyrin compounds and their precursors. In animals, porphyrin synthesis is required for the production of heme, which is a component of hemoglobin, cytochromes (including cytochrome P450), catalase, peroxidase, and other oxidative enzymes involved in drug metabolism. Just as the iron-containing porphyrin heme catalyzes oxidative phosphorylation in animals through the action of mitochondrial cytochromes, the magnesium-containing porphyrin chlorophyll catalyzes photosynthesis in plants, replenishing the atmosphere with oxygen. More poetically, as described by the Nobel prize winner Hans Fischer, porphyrins are the substances that make blood red and grass green. (ref 1)

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The porphyrias are best understood by the examination of the basic scheme of heme synthesis [see Figure 1]. The rate of synthesis is controlled by the initial enzyme, ë-aminolevulinic acid (ALA) synthetase, in the mitochondrion. Subsequently, in the cell fluid, the tetrapyrrole rings remain in their reduced state, but the number of carboxyl residues per ring progressively decreases from eight to two. The last three enzymatic reactions take place in the mitochondrion, resulting in heme, which exercises a repressive action on the production of ALA synthetase. The loss of carboxyl groups makes each successive compound less water soluble.

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The conversion of protoporphyrinogen to protoporphyrin by removal of six hydrogen atoms results in a molecule with a series of alternating double bonds. This configuration absorbs ultraviolet light with a wavelength of approximately 400 nm (the Soret band), which accounts for the fluorescence characteristic of all porphyrins. Porphyrinogen intermediates oxidize spontaneously, especially in the presence of light. The resulting porphyrins are lost to the heme synthetic pathway and are excreted in the urine, the stool, or both, depending on their relative water solubility.

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Each specific abnormality in the pattern of excretion of porphyrins and porphyrin precursors is caused by a reduction in the level of one of the enzymes of the heme synthetic pathway [see Table 1]. A deficiency in any of the enzymes from ALA dehydratase to ferrochelatase may occur. Because the major sites of heme production are the bone marrow