Heme Metabolism
Robert F. Diegelmann, Ph.D.

Objectives

1. Describe the interactions of heme, globins and oxygen.
2. Understand the biosynthesis of protoporphyrin, the porphyrin of hemoglobin & myoglobin.
3. Define how altered enzyme activity results in Porphyrias.
4. Outline the degradation of Heme to yield Bile Pigments.

Myoglobin (muscle) & Hemoglobin (Red Blood Cell) were the first proteins for which three-dimensional structures were determined. Therefore they are perhaps the most studied & best understood proteins. Below is the basic heme group structure. It consists of a complex organic ring structure named Protoporphyrin.

Recommended Reading

- Lehninger, Principles of Biochemistry, 5th edition, Chapter 5
- Mark’s Basic Medical Biochemistry, 3rd Edition, Chapter 44
- http://web.indstate.edu/thcme/mwking/hemoglobin-myoglobin.html#hemoglobin
Oxygen is not very soluble in aqueous solutions and therefore needs a special molecule to be carried to tissues and cells. The **Protoporphyrin** ring structure of Heme binds a single iron atom in its ferrous (Fe$^{2+}$). The iron atom has six coordination bonds, four are found bound to the nitrogens in the **Porphyrin ring** system and two additional sites perpendicular to the **Porphyrin**. The **Cytochromes (a, b & c)** are proteins that also contain porphyrin structures. **Cytochromes** are generally membrane-bound proteins that contain heme groups and carry out electron transport or catalyse reductive/oxidative reactions. They are found in the mitochondrial inner membrane and endoplasmic reticulum of eukaryotes.

**Protoporphyrin Ring**

Combines with the protein **Globin** to form **Hemoglobin**

**Bond Orientation**

This diagram shows the orientation of the bonds.
Biosynthesis of Protoporphyrin, the porphyrin of hemoglobin & myoglobin. Succinyl-CoA and Glycine form delta Aminolevulinate, then 2 molecules of delta Aminolevulinate form Porphobilinogen. Then four molecules of Porphobilinogen form 1 molecule of Protoporphyrin.

The most important enzyme is (1) delta-aminolevulinate (ALA) synthase because this enzyme regulates Heme production. Heme itself represses the synthesis of delta-ALA synthesis and thereby regulates the pathway (also see below).
Overview of the pathway for Heme Biosynthesis and steps where altered enzyme activity results in **Porphyrias**. This disorder consists of a group of pathologies resulting from deficiencies of enzymes in the Heme biosynthetic pathway. Intermediates in the pathway accumulate and may have toxic effects on the nervous system that cause **neuropsychiatric** symptoms. In addition, these intermediates can be converted by light to porphyrins, which can react with O\(_2\) to form **Reactive Oxygen Species (ROS)** and in turn cause severe skin damage.

**Acute Intermittent Porphyria:**

- Most Common genetic porphyria
- More common in females

**Clinical Features**

- **Neurological symptoms**
- **Nausea**
- Vomiting
- Abdominal pain
- Diarrhea
- Muscle hypotonia
- Sensory neuropathy
- Respiratory failure
- Seizures

Biochemical cause: Porphobilinogen deaminase is altered (see pathway above)

Degradation of Heme yields Bile Pigments. When Red Blood Cells die in the spleen, they release hemoglobin that is degraded to release free Fe$^{3+}$ and ultimately Bilirubin. The Bilirubin binds to serum albumin and is transported to the Liver where it is converted to the Bile Pigment Bilirubin Diglucuronide. This product is very water-soluble and is secreted into the bile and then into the small intestine. Therefore, under normal circumstances, the by-products of Heme go into the bile as Glucuronides. However, if liver function is impaired, then Bilirubin leaks into the blood and the skin and the white of the eye becomes yellow indicating the clinical condition known as Jaundice. Neonatal jaundice is shown in photo below:
Overview of Heme degradation:

Note: Iron is usually found bound to proteins because free Iron is very toxic. Iron sources and metabolism will be discussed in the Nutrition lectures.