Porphyris and bile pigments: metabolism and disorders
Porphyryns

• Porphyryns are cyclic compounds formed by the linkage of four pyrrole rings through methyne (\(\text{C}_2\)) bridges. In the naturally occurring porphyryns, various side chains replace the eight numbered hydrogen atoms of the pyrroles.

• Porphyryns have had different structures depend on side chains that are attached to each of the four pyrrole rings. For example; Uroporphyrin, coporrophyrin and protoporphyrin IX (heme).

• The most prevalent metalloporphyryn in humans is heme, which consists of one ferrous (Fe2+) iron ion coordinated at the center of the tetrapyrrole ring of protoporphyrin IX.
What is bilirubin?

- Bilirubin is a yellowish pigment found in bile, a fluid made by the liver.
- The breakdown product of Hgb from injured RBCs and other heme containing proteins.
- Produced by reticuloendothelial system
- Released to plasma bound to albumin
- Hepatocytes conjugate it and excrete through bile channels into small intestine.
Bilirubin di-glucoronid
Structure of heme:

- **Heme structure:**
  - a porphyrin ring coordinated with an atom of iron
  - side chains: methyl, vinyl, propionyl
- **Heme is complexed with proteins to form:**
  - Hemoglobin, myoglobin and cytochromes
Pathway of Heme Biosynthesis. Heme biosynthesis begins in the mitochondria from glycine and succinyl-CoA, continues in the cytosol, and ultimately is completed within the mitochondria. The heme that it produced by this biosynthetic pathway is identified as heme b. PBG: porphobilinogen; ALA: δ-aminolevulinic acid.
Mitochondria

Succinyl CoA + glycine

\[ \delta - \text{Aminolevulinic acid synthase} \]

\[ \delta - \text{Aminolevulinic acid (}\delta - \text{ALA}) \]

Porphobilinogen

\[ \text{Porphobilinogen deaminase} \]

Hydroxymethylbilane

Uroporphyrinogen III cosynthase

Uroporphyrinogen III

\[ \text{Uroporphyrinogen decarboxylase} \]

Coproporphyrinogen III

\[ \text{Coproporphyrinogen oxidase} \]

Protoporphyrinogen IX

\[ \text{Protoporphyrinogen oxidase} \]

Protoporphyrin IX

\[ \text{Ferrochelatase} \]

Heme

Porphyrias

\[ \delta - \text{ALA dehydratase porphyria} \]

Acute intermittent porphyria

Congenital erythropoietic porphyria

Porphyria cutanea tarda

Hereditary coproporphyria

Variegate porphyria

Erythropoietic protoporphyria
Synthesis of δ-aminolevulinic acid:

Induced by: drugs (barbiturates), oral contraceptive pills

Pyridoxal phosphate (vit. B₆)
Formation of porphobilinogen:

**Diagram:**

- **2 δ-ALA**
- **δ-ALA dehydratase**
- **2H₂O**

*Inhibited by lead*
Iron metabolism:

Dietary iron

Many tissues
- Cytochromes
- Iron-enzymes
- Myoglobin

Bone
- Erythropoiesis

Blood loss
- Bleeding
- Menstruation

RBC
- Hemoglobin

Phagocytosis

RE cells
- Ferritin (Fe³⁺)

Liver
- Ferritin (Fe³⁺)
- Hemosiderin

Serum ferritin

Intestinal epithelial cell
- Fe²⁺

Feces

10–15% absorbed (by vitamin C)

Bile (Fe)

Fe²⁺

Ferrooxidase (ceruloplasmin)

Transferrin

Dietary iron

Feces

Urine

Sweat

Skin desquamation

Iron loss
Iron metabolism:

- Recommended dietary allowance 10-15 mg (only 10-15% is normally absorbed)

Iron distribution:

<table>
<thead>
<tr>
<th></th>
<th>g</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>2,5</td>
<td>68</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>0,15</td>
<td>4</td>
</tr>
<tr>
<td>Transferrin</td>
<td>0,003</td>
<td>0,1</td>
</tr>
<tr>
<td>Ferritin, tissue</td>
<td>1,0</td>
<td>27</td>
</tr>
<tr>
<td>Ferritin, serum</td>
<td>0,0001</td>
<td>0,004</td>
</tr>
<tr>
<td>Enzymes</td>
<td>0,02</td>
<td>0,6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3,7</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>
Intestinal absorption of iron:
- in the duodenum
- regulation (by the synthesis of apoferritin within mucosal cells)

1. The heme iron (unknown mechanism)
2. The nonheme iron
   • is not readily absorbed (chelates with oxalates, phytates, etc.)
   • vit. C increases the uptake
Iron transport:

- **Transferrin** $(\text{Fe}^{3+})$:
  - Transferrin + Fe$^{3+}$ + CO$_3^{2-}$ $\rightarrow$ Transferrin $\cdot$ 2(Fe$^{3+}$CO$_3^{2-}$)
  - only one third saturated with iron
  - unsaturated transferrin protects against infections (iron overload and infection)

- **Lactoferrin**
  - binds iron in milk
  - antimicrobial effect (protects newborns from gastrointestinal infections)

- **Haptoglobin**
  - binds hemoglobin in the plasma

Iron storage:

- **Ferritin** $(\text{Fe}^{3+})$
  - storage of iron (hepatocytes, RES, muscles)
  - in the blood $\rightarrow$ sensitive indicator of the amount of iron in the body

- **Hemosiderin**
  - when iron is in excess (amorphous iron deposition)
Iron-containing proteins:

1. Heme proteins
   - Hemoglobin
   - Myoglobin
   - Enzymes that contain heme as their prosthetic group (catalase, peroxidase, NO synthase)

2. Nonheme proteins
   - Transferrin
   - Ferritin
   - Enzymes that contain iron at the active site
   - Iron-sulphur proteins
Degradation of heme:
Conversion of heme to bilirubin:

ER enzyme system

Heme

$\text{O}_2$ → Heme oxygenase → CO, Fe$^{2+}$

Biliverdin IX$\alpha$

NADPH → Biliverdin reductase → NADP$^+$

Bilirubin IX$\alpha$

Cytoprotective role:

• CO
• biliverdin

the major source is Hg
Formation of bilirubin diglucuronide:

increase the water solubility of bilirubin
Hyperbilirubinemia

- Elevated bilirubin levels in the blood (>10 mg/l); bilirubin may diffuse into peripheral tissues, giving them a yellow color (jaundice)
- Cause:
  1. Pre-hepatic: excessive formation of bilirubin by increased degradation of erythrocytes (icterus neonatus, hemolytic anemia)
  2. Hepatic: insufficient processing of bilirubin as a result of liver defects (hepatitis, liver toxic damage, cirrhosis, hepatic failure)
  3. Post-hepatic: by impaired excretion of gall (obstructive jaundice due to gallstones, inflammation of biliary tract)

- Unconjugated bilirubin can cross the blood-brain barrier, leading to brain damage
- Jaundice in neonates (increased bilirubin degradation+immaturity of the conjugation enzymes): phototherapy – isomerization of bilirubin to more soluble pigments
<table>
<thead>
<tr>
<th>Type</th>
<th>Cause</th>
<th>Example</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prehepatic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemolysis</td>
<td>Autoimmune Haemoglobinopathy</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>According to the region</td>
</tr>
<tr>
<td><strong>Hepatic</strong></td>
<td>Infection</td>
<td>Hepatitis A,B,C</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Damage</td>
<td>Alcohol, drugs</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Genetics</td>
<td>Gilbert´s syndrome</td>
<td>1 in 20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wilson´s disease</td>
<td>1 in 200 000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α₁-Antitrypsin deficiency</td>
<td>1 in 1000</td>
</tr>
<tr>
<td></td>
<td>Autoimmune</td>
<td>Chronic hepatitis</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Newborn</td>
<td>Physiologic</td>
<td>Very common</td>
</tr>
<tr>
<td><strong>Posthepatic</strong></td>
<td>Intrahepatic</td>
<td>Drugs</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>bile ducts</td>
<td>Primary biliary cirrhosis</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cholangitis</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gallstones</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreatic cancer</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Extrahepatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>bile ducts</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilirubin</td>
<td>Urobilinogen</td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------------</td>
<td>-------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>blood</td>
<td>urine</td>
<td>deriv. in feces</td>
</tr>
<tr>
<td><strong>Prehepatic</strong></td>
<td>↑↑(UC)</td>
<td>N</td>
<td>↑</td>
</tr>
<tr>
<td><strong>Intrahepatic</strong></td>
<td>↑↑(both)</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td><strong>Posthepatic</strong></td>
<td>↑↑(C)</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

**Diagram:**
- Hemoglobin
- Globin
- Haem
- Iron
- Bilirubin
- Bilirubin-albumin (unconjugated)
- Albumin
- Liver
- Spleen; reticuloendothelial cells
- Bilirubin-glucuronide (conjugated)
- Hepatocyte
- Bile duct
- Small intestine
- Large intestine
- Urobilinogen
- Porto-vascular system