

Bilirubin and Biliverdin Reductase

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Bilirubin is a yellow compound that is the product of the catabolism of aging heme. It can be used to determine abnormality in liver functions as characterized by the yellowing of the skin and mucous membranes such as sclera of the eyes and dorsum of the tongue. In this article, we will discuss the biochemistry of bilirubin; specifically, the synthesis of the compound and the important enzymes used in the synthesis of this biomolecule.



Bilirubin

Bilirubin is a yellowish compound that is produced in the catabolic pathway of the breakdown of heme in vertebrates. **Catabolism of heme is needed to clear the body of the waste products** due to the death of aging red blood cells. The structure of bilirubin consists of an open-chain of four pyrrole-like rings.

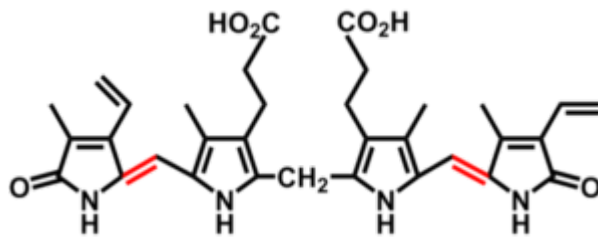


Image: "Chemical Formula of Bilirubin." by Stefcho2 - Own Work.
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Bilirubin is produced by the breakdown of the red blood cells in the body. It travels to the **liver** and is secreted to the **bile duct**. It is eliminated eventually from the body in the stool. A typical red blood cell has a lifespan of about 120 days. The hemoglobin present in the RBCs gets broken down into bilirubin and other substances.

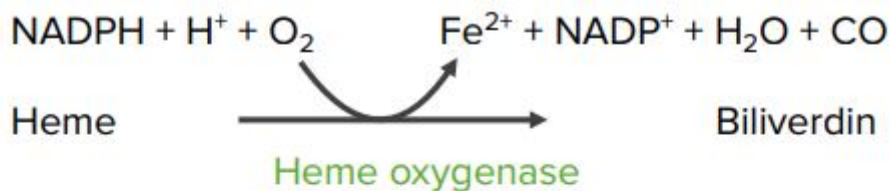
The immediate product of biliverdin reductase is unconjugated bilirubin that is accumulated in circulation. Due to its ability to cross the blood-brain barrier, it leads to **conditions that can impair normal brain functioning**. The conditions can be **fatal** if left untreated. Excessive levels of unconjugated bilirubin in the bloodstream can cause a condition called **kernicterus**.

Accumulation of this substance in circulation gives a yellow discoloration of mucous membranes and skin which is known as jaundice. This condition is a common symptom of liver disease.

Due to the toxicity of unconjugated bilirubin, the body must convert it to a less toxic conjugated bilirubin, a process that takes place in the liver.

Cellular Heme Metabolism and Bilirubin Production

Bilirubin is produced by a two-stage reaction that occurs in the **reticuloendothelial system** of cells. These cells include phagocytes, Kupffer cells of the liver, and cells in the bone marrow and spleen. The catabolism of heme proteins occurs in the microsomal fraction of the cell by **heme oxygenase**. The action of this enzyme is **substrate-inducible**, which means the heme serves both as the substrate and the cofactor for the reaction.



“Heme-oxygenase” Image created by Lecturio

The process begins with the breakdown of red blood cells that contain heme pigment, globin chains in association with iron pigments. After remaining in circulation for approximately 120 days, each of the individual components are broken down to various products.

The **amino acids** from the protein component of hemoglobin are released from the structure and are catabolized or re-used for protein synthesis. The heme portion, on the other hand, undergoes degradation starting with a **mixed-function oxidase reaction** that causes an opening of the ring and the conversion of one of the **methane bridge carbons** to **carbon monoxide**.

The next step in the process is the **release of the iron** from the resulting linear tetrapyrrole. The iron is then transported to storage pools in the bone marrow to be reused in erythrocyte production. This iron atom that reaches the heme oxygenase is usually oxidized to its **hemin or ferric form**.

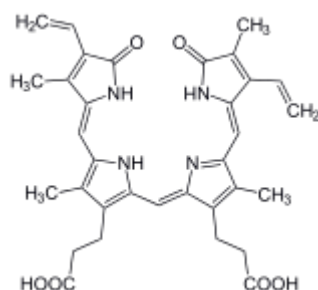


Image: “Structural Formula of Biliverdin.” by NEUROtiker - Own Work. License: [Public Domain](#)

After the release of the iron atom and the ring-opening of the heme group, **Biliverdin** is produced. Biliverdin is a green tetrapyrrolic bile pigment that is responsible for a greenish color during bruises.

The biliverdin is reduced by **biliverdin reductase**. Biliverdin reductase is an enzyme found in all tissues, especially in **reticulo-macrophages of the liver and spleen**. This enzyme is responsible for converting the biliverdin to bilirubin by reducing the double

bond between the second and third pyrrole ring to form a single bond. The reduction process of biliverdin requires **NADH** or **NADPH** as a cofactor.

The biliverdin reductase catalyzes the reaction through an overlap in the binding sites of the Lys¹⁸, Lys²², Lys¹⁷⁹, Arg¹⁸³, and Arg¹⁸⁵ as key residues. These binding sites attach to the biliverdin molecule causing the dissociation of the biliverdin from the heme oxygenase, eventually leading to a reduction of the green biliverdin to the yellow bilirubin.

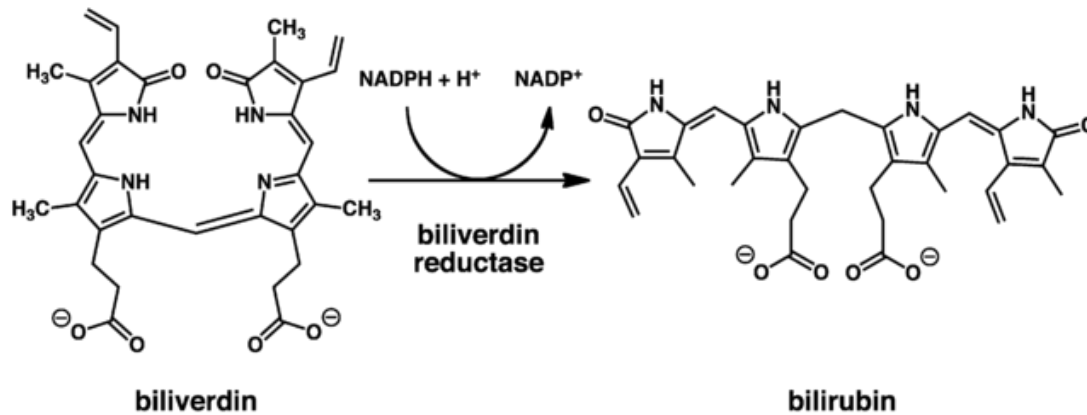


Image: "Reduction of biliverdin to bilirubin catalyzed by biliverdin reductase." by Boghog2 - Own Work. License: [Public Domain](#)

In the uptake to the liver, bilirubin is taken up at the **sinusoidal surface** of liver cells by a facilitated transport system. Once the bilirubin molecule enters the cell, it is bound to the cytosolic proteins like **glutathione S-transferase**, also called ligandin, to prevent its re-entry to the bloodstream.

In the liver, reacting it with two glucuronic acid molecules solubilizes bilirubin. This is then as for bilirubin not to persist in cells because of its highly non-polar nature. The **conjugation with glucuronic acids** converts bilirubin into a more polar molecule.

The enzyme **UDP-glucosyltransferase**, a bilirubin-specific enzyme in the endoplasmic reticulum, catalyzes the step-wise transfer of two glucosyl moieties from a UDP-glucuronate to the bilirubin molecule. The solubilized bilirubin, **bilirubin diglucuronide** is then secreted to the bile and finally excreted via the intestine.

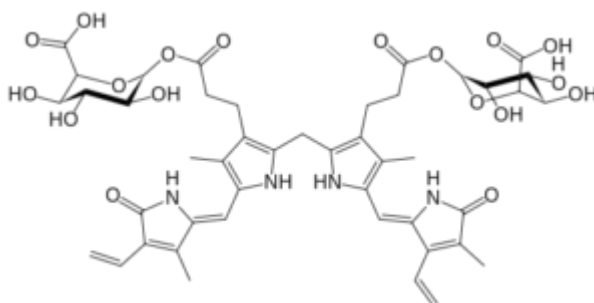


Image: "Skeletal formula of bilirubin diglucuronide." by Fvasconcellos. License: [Public Domain](#)

Enterohepatic Circulation and Health

Enterohepatic circulation

Most of the soluble bilirubin (conjugated) is excreted via the bile into the intestines. Most of the bile acids are reabsorbed into circulation at the terminal ileum, whereas the conjugated bilirubin passes into the large intestines where colonic bacteria deconjugates it into urobilinogen. The product is later oxidized into stercobilin that gives feces its characteristic color and urobilinogen in urine. A trace of urobilinogen is reabsorbed to enter the hepatic circulation into the liver where it is excreted again via the intestines forming the enterohepatic circulation

Health

- Jaundice arises from excess bilirubin in the body (hyperbilirubinemia)
- Yellowish skin, sclera of eye
- Bilirubin degraded by light

Many possible jaundice causes:

- Deficient glucuronyltransferase enzyme — Gilbert's Syndrome
- Liver disease/damage
- [Pancreas cancer](#)
- [Sickle cell crisis](#)
- Obstruction of the biliary tract
- Newborn physiology — usually minor
- Excess hemolysis of blood cells

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