Heme Biotransformation

How is the complex molecule heme degraded to yield bilirubin and carbon monoxide? In the body, the majority of heme molecules (80%) occur in red blood cells as oxygen-binding prosthetic groups in hemoglobin. Senescent red blood cells (life span 120 days) are removed from the bloodstream by reticuloendothelial cells, the phagocytic cells in liver, spleen, bone marrow, lung, and lymph nodes that ingest worn-out or abnormal body cells. Heme is released from hemoglobin, and globin is converted to amino acids. Heme is then rapidly degraded because of its cytotoxic properties (due to ROS generation). As described previously (p. 538), heme is oxidized by heme oxygenase (HO), an ER enzyme. HO is a component of an electron transport system similar to that of cytochrome P_{450}. The products of this reaction are the dark blue-green pigment biliverdin, iron, and carbon monoxide (CO).

The reaction (Figure 15A) begins with the O_2 and NADPH-dependent hydroxylation of the α-methene carbon. The subsequent reaction of the intermediate, α-hydroxyhemin, with O_2 (probably a nonenzymatic step) yields biliverdin, CO (the α-methene carbon), and a ferric iron ion. CO diffuses out of the cell, and is transported in the blood to the lungs; it leaves the body on exhalation. NADPH converts Fe^{3+} to Fe^{2+} before its release. Biliverdin is subsequently converted into bilirubin in a reaction catalyzed by the cytoplasmic enzyme biliverdin reductase.

Bilirubin is a very toxic molecule. It is known to inhibit RNA and protein synthesis and carbohydrate metabolism in the brain. Mitochondria appear to be especially sensitive to its effects. Bilirubin is also a metabolically expensive molecule to produce. For example, bilirubin is virtually insoluble in water, because of intramolecular hydrogen bonding. Therefore, sophisticated

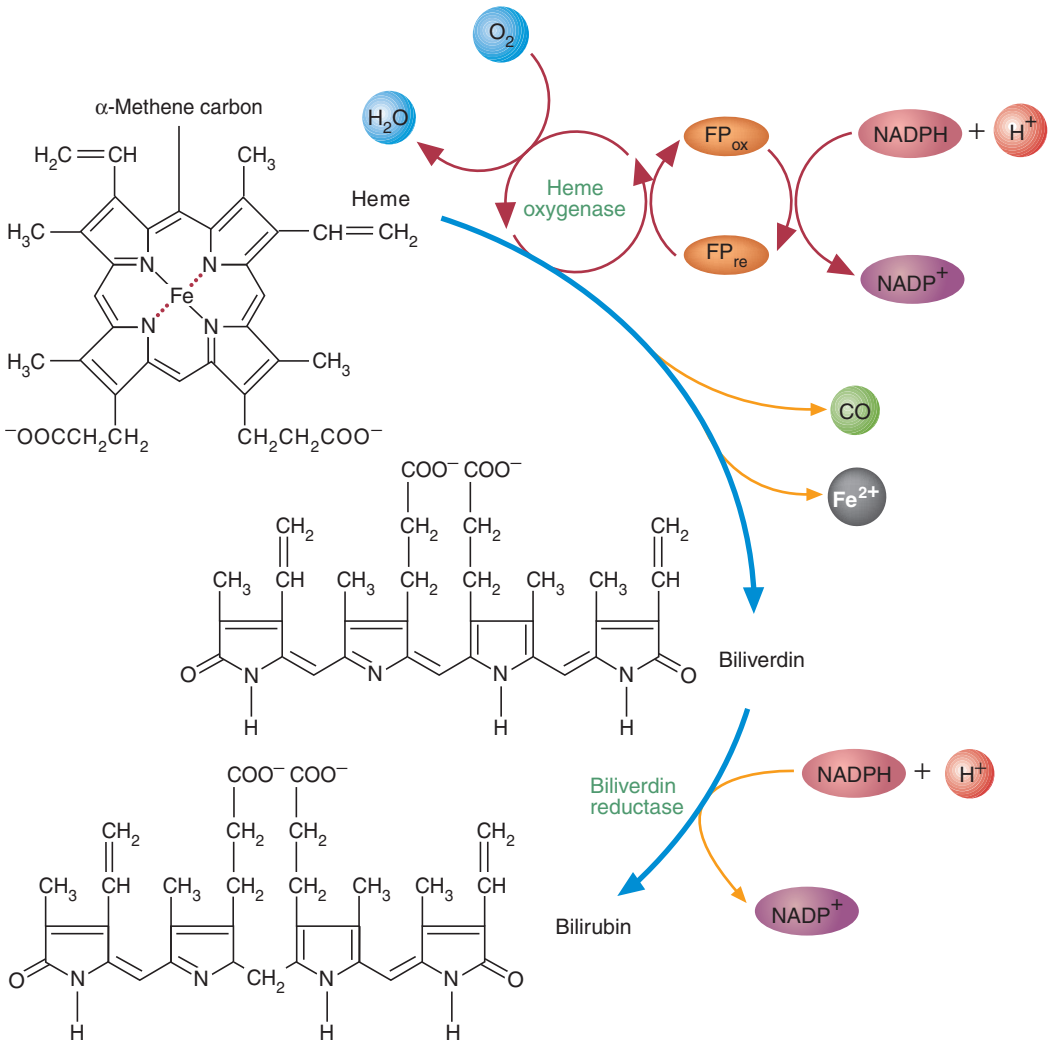

FIGURE 15A

Bilirubin Synthesis

Heme oxygenase, which catalyzes the conversion of free heme groups to biliverdin and CO, functions as part of a microsomal electron transport system similar to that of cytochrome P_{450} (FP = NADPH-cytochrome P_{450} reductase). Heme oxygenase requires three molecules of O_2 and five of NADPH. Biliverdin reductase can use NADPH or NADH as a reductant.

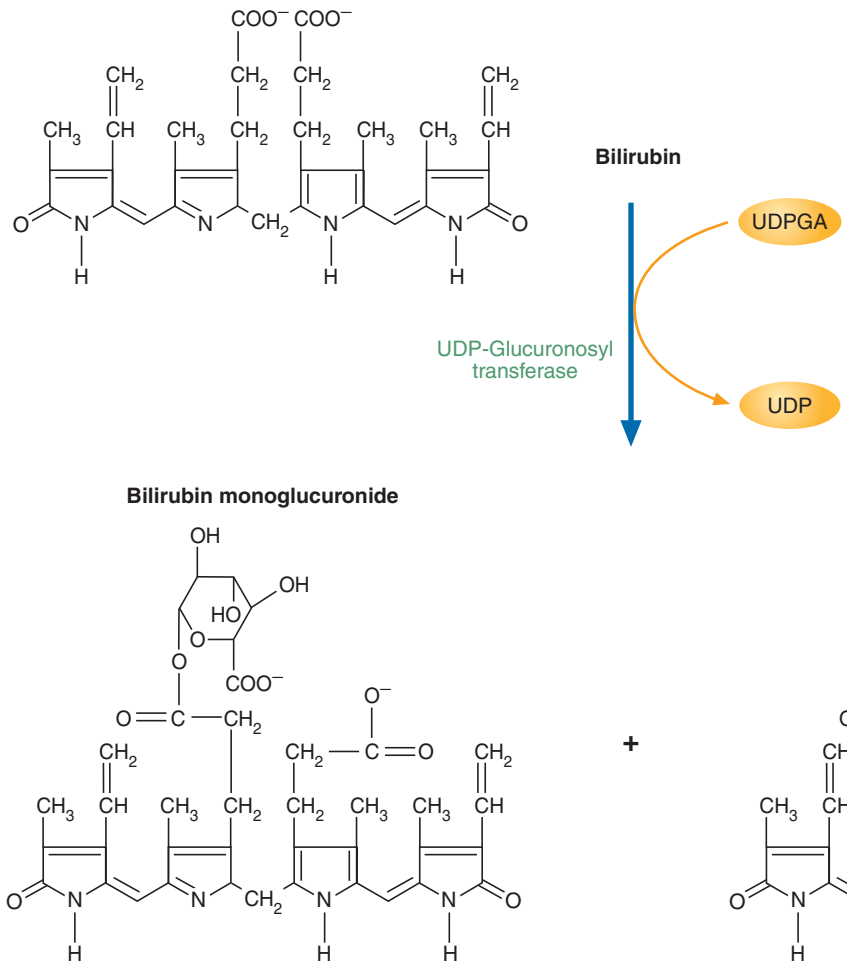

FIGURE 15B

Bilirubin Conjugation

Before bilirubin is excreted in bile, its propionyl carboxyl groups are esterified with glucuronic acid to form both monoglucuronides and diglucuronides. (UDPGA = UDP-glucuronic acid.) The diglucuronide is the major form produced in many animals. In a number of species, especially mammals, bilirubin conjugation is required for efficient secretion into bile.

transport mechanisms and conjugation reactions in the liver (Figure 15B) are required for excretion as components of bile in the gastrointestinal tract. Because bilirubin creates so many problems, considerable effort has been devoted to elucidating its purpose. (Amphibians, reptiles, and birds excrete the water-soluble precursor biliverdin.) Despite its toxic properties (at higher than normal levels) in humans, bilirubin is now recognized as a powerful antioxidant. During bilirubin transport in blood, the radical-scavenging pigment is distributed throughout the circulatory system. (The association of bilirubin with the plasma protein albumin protects cells from the molecule's toxic effects.) Plasma levels of bilirubin have been linked inversely to risk of atherosclerosis-related diseases. Free heme, oxidized LDL, and other risk factors for cardiovascular disease induce increased expression of HO1, one of two isozymes with heme oxygenase activity. The subsequent generation of CO, biliverdin, and bilirubin provides an adaptive response to injury associated with ROS generation. The antioxidant capacity of bilirubin, in particular, provides resistance to the maturation of atherosclerotic changes in the vasculature. It also inhibits the white blood cell adhesion processes associated with inflammation and plaque development. The CO product of HO1 action inhibits the production of a number of growth factors associated with smooth muscle proliferation, a key component of plaque development.

SUMMARY: Heme, a molecule that owing to its O_2-binding capacity forms ROS, is oxidized by heme oxygenase to yield biliverdin and CO. Biliverdin is subsequently converted to bilirubin.