

Lecture-13

Metabolism of Xenobiotics

Xenobiotics is a compound that is foreign to the body; is a chemical which is found in an organism but which is not normally produced or expected to be present in body. Endogenous: Pigments, hormones; nonendogenous: Such as drugs, food additives, pollutants, toxin, etc. Most of these compounds are subject to metabolism (biotransformation).

Definition of the biotransformation

Conversion of lipophilic xenobiotics to water-soluble chemicals by a process catalyzed by enzymes in the liver and other tissues. In most cases, biotransformation lessens the toxicity of xenobiotics, but many must undergo the process to exert their toxic effects.

Purpose of biotransformation

1. facilitates excretion: To Converts lipophilic to hydrophilic compounds.
2. Detoxification/inactivation: To converts chemicals to less toxic forms
3. Metabolic activation: To converts chemicals to more toxic active forms

General Metabolic Pathways:

Liver is the main site for biotransformation. Approximately 30 different enzymes catalyze reactions involved in xenobiotic metabolism; however, this note will only cover a selected group of them. It is convenient to consider the metabolism of xenobiotics in two phases. phase I and phase II.

Phase I: The reactions of Phase I are oxidation, reduction and hydrolysis.

Phase II: These are the conjugation reactions, involving compounds such as glucuronic acid, amino acids (glycine), glutathione, sulfate, acetate and methyl group.

Generally, detoxification of a compound involves phase I as well as phase II reactions. For instance, oxidation followed by conjugation is the most frequent process in the metabolism of xenobiotics.

Cytochrome p450 system

Cytochromes p450 (CYPs) are a superfamily of enzymes containing heme as a cofactor that function as monooxygenases. In mammals, these proteins oxidize steroids, fatty acids and xenobiotics and are important for the clearance of various compounds, as well as for hormone synthesis and breakdown. Cytochrome P450 enzymes are primarily found in liver cells but are also located in cells throughout the body. Within cells, cytochrome P450 enzymes are located in a structure involved in protein processing and transport (endoplasmic reticulum) and the energy-producing centers of cells (mitochondria).

cytochrome P450 enzyme system: A group of enzymes involved in drug metabolism and found in high levels in the liver. These enzymes change many drugs, including anticancer drugs, into less toxic forms that are easier for the body to excrete.

Salient features of cytochrome P450 :

- Multiple forms of cytochrome P450 are believed to exist, ranging from 20 to 200. At least 6 species have been isolated and worked in detail.
- They are all hemoproteins, containing heme as the prosthetic group.
- Cytochrome P 450 species are found in the highest concentration in the microsomes of liver. In the adrenal gland, they occur in mitochondria.
- The mechanism of action of Cytochrome p450 is complex and is dependent on NADPH.
- The Cytochrome p450 is an inducible enzyme.
- Molecular mass is about 55 kDa.
- Exhibit broad substrate specificity.
- Cause introduction of one atom of oxygen into the substrate and one into water.
- The hydroxylated products are more water soluble.