METABOLISM OF DRUGS

Metabolism involves the enzymatic conversion of therapeutically important chemical species to a new molecule inside the human body. The process may result in pharmacologically active, inactive, or toxic metabolite. Drug metabolic process involves two phases, the occurrence of which may vary from compound to compound.

DEFINITION

Drug metabolism may be defined as the biochemical modificatiion of one chemical form to another, occurring usually through specialised enzymatic systems.

The primary site of drug metabolism is the smooth endoplasmic reticulum of the liver cell. This is because of the presence of large amounts of many varieties of enzymes. The drug metabolism happening in the liver is termed as hepatic metabolism. In addition to the liver, everybiological tissue of the body has the ability to metabolize drugs.

The drug metabolism process occurring in organs other than the liver is called extrahepatic metabolism. The other sites include lungs, kidney, placenta, epithelial cells of gastrointestinal tract, adrenals and skin. However, these sites are involved to a limited extent in this process. Most drugs (around 70%) undergo metabolism, which is catalyzed by enzymes present in the above-mentioned sites.

Detoxification Reactions: Phase I Reactions: These reac.tions are termed as the nonsynthetic reactions, and include oxidation, reduction, hydrolysis, cyclization and decyclization reactions. These reactions are carried out mostly by mixed functionoxidases, usually involving CYP450 and occur in the liver.

In these reactions, a polar group is either introduced or unmasked if already present. These reactions are succeeded by Phase II reactions. Most of the Phase I products are not eliminated directly;

instead they undergo Phase II reactions. Various Phase I reactions are as follows, with several examples:

(i) Oxidation: This is the most commonly occurring reaction, by virtue of which hydrophilicty of the substrates is increased via the introduction of a polar functional group such as –OH.

(ii) Reduction: The reduction reactions result in the generation of polar functional groups such as amino and hydroxyl, which may undergo further metabolic reactions. These reactions may occur on several functional groups such as carbonyl, hydroxyl, etc.,

(iii) Hydrolysis: These reactions generally involve a large chemical change in the substrate. The hydrolysis reactions can occur in the following functional groups.Upon hydrolysis, esters lead to the formation of carboxylic acids and

alcohols. Mostly, esters are administered as prodrugs, which on hydrolysis are converted to active forms, e.g., aspirin (analgesic, antipyretic).

Detoxification Reactions: Phase II Reactions:

The PhaseII reactions follow Phase I reactions, and occur mostly in the products derived from Phase I reactions. In these reactions, a suitable moiety such as glucuronic acid, glutathione, sulphate, glycine, etc., get conjugated to the metabolites of Phase I reaction. The Phase II reactions are the real drug detoxification pathways. These are also termed as conjugation reactions, because the metabolites are conjugated with the above-mentioned moieties which are large in size and strongly polar in nature.

These reactions are catalyzed by a variety of transferase enzymes, such as uridine diphosphate (UDP)-glucoronsyltransferases, sulfotransferases, glutathione transferases.