Drug metabolism

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The terms “xenobiotic metabolism” and “xenobiotic-metabolizing enzyme” will be used in preference to drug metabolism” and drug-metabolizing enzyme because most of the enzymes involved recognize various substrates including drugs, industrial chemicals and environmental contaminants), which is central to bioavailability, drug clearance, and first-pass effects. It comprises Phases 0 (entry into cells), I (introduction of a reactive group), II (conjugation with polar moieties), and III (export). Xenobiotic-metabolizing enzymes usually mediate detoxification but can form reactive intermediates causing toxicity. Cytochrome P450s (CYPs) dominate Phase I. In particular, the CYP1, CYP2, CYP3, and CYP4 families (induced by polycyclic aromatic hydrocarbons, barbiturates, glucocorticoids, and peroxisome proliferators, respectively) are central to xenobiotic metabolism. Phase II metabolism by glutathione S-transferases, Uridine 5′-diphospho(UDP)-glucuronosyltransferases, sulfotransferases, N-acetyltransferases, and epoxide hydrolases typically generates excretable hydrophilic metabolites. Finally, Phase III xenobiotic transporters in the liver and intestine remove xenobiotics and metabolites from cells. These processes are key to the disposition and excretion of lipophilic compounds. Medicines are required for humans to cure diseases but at the same time, they are foreign objects to the body. Hence, the human body tries to excrete the mat the earliest. It is highly desirable that the medicines get eliminated from the human body immediately after showing their drug action. The longer time the drug spends in the body, the greater are its side effects. The human body has a natural mechanism to eliminate these foreign objects (medicines). This is mainly facilitated by the process known as drug metabolism. Drug metabolism also known as xenobiotic metabolism is the biochemical modification of pharmaceutical substances or xenobiotics respectively by living organisms, usually through specialized enzymatic systems. Drug metabolism often converts lipophilic chemical compounds into more readily excreted hydrophilic products.it takes place mostly in liver,and other sites in the body like Intestinal mucosa, kidney, lungs, skin and adrenals. An inactive or weakly active substance that has an active metabolite is called a prodrug, especially if designed to deliver the active moiety more effectively.There are three phases of metabolism: Phase I (functionalization): Non polar drugs are either inactivated; or activated in some cases, by metabolic introduction of polar functional groups like carboxyl (-COOH), hydroxyl (-OH), amino (NH_2), and sulfhydryl (-SH) into the substrate molecule through: (A) Oxidation: hydroxylation, oxide formation, alcohol oxidation, aldehyde oxidation, deamination, dealkylation, desulfuration and dehalogenation. (B)Reduction: azo reduction, nitro reduction and aldehyde or ketone reduction. (C) Hydrolysis of amides and esters. (d) Removal of non-polar alkyl group to expose potential polar group. Phase II (conjugation and enzymatic synthesis): In this phase an existing functional group (already presents in the drug molecule or created by phase I metabolism) such as alcohol, phenol, amine is masked or inactivated by a process of: Synthesis, such as methylation, acylation, thiocyanate formation and mercaptouric acid formation,sulfation. (B) Conjugation with glucuronic acid, amino acids or sulfate which further increase the polarity of the drugs or (xenobiotics). Thus the administered drug can be excreted in one foreign ingested chemical of the following forms: 1- Unaltered. 2- Oxidized, reduced or hydrolyzed. 3- Conjugated. Examples of some intrinsically active drugs that converted to active metabolites: The oxidation of phenylbutazone to oxyphenbutazone. The demethylation of imipramine to desimpramine. The cleavage of the ethyl ether group of phenacetin to acetaminophen. Hepatic microsomal enzymes (oxidation, conjugation) Extrahepatic microsomal enzymes (oxidation, conjugation) Hepatic non-microsomal enzymes (acetylation, sulfation, GSH, alcohol/aldehyde dehydrogenase, hydrolysis, ox/red) Phase III, the conjugated xenobiotics may be further processed, before being recognised by efflux transporters and pumped out of cells. Drug metabolism often converts lipophilic compounds into hydrophilic products that are more readily excreted. Reversal of order of the phases**:** Not all drugs undergo Phase I and II reactions in that order. For example, isoniazid is first acetylated (a Phase II reaction) and then hydrolyzed to isonicotinic acid (a Phase I reaction).Enzymes involved in xenobiotics metabolismPhase 1 oxygenases: Cytochrome P450s (P450 or CYP) C and O oxidation, dealkylation, others Flavin-containing monooxygenases (FMO) N,S,and P oxidation Epoxide hydrolases (mEH, sEH) Hydrolysis of epoxides Phase 2 transferases: Sulfotransferases (SULT) Addition of sulfate, UDP-glucuronosyltransferases (UGT) Addition of glucuronic acid Glutathione-S-transferases (GST) Addition of glutathione N-acetyltransferases (NAT) Addition of acetyl group Methyltransferases (MT) Addition of methyl group.Example of drug metabolism:Acetaminophen metabolism**:** At therapeutic doses, 90% of APAP is metabolized in the liver to sulfate and glucuronide conjugates that are then excreted in the urine. The remaining 10% is metabolized via the cytochrome CYP2E1 (P450 2E1) to a toxic, reactive, N-acetyl –P-Benzoquinone (NAPQI). NAPQI binds covalently with hepatocyte macromolecules, producing hepatic cell lysis with normal doses, NAPQI is rapidly conjugated with hepatic glutathione, forming a nontoxic compound which is excreted in the urine. With toxic doses, however, the sulfate and glucuronide pathways become saturated, resulting in an increased fraction of acetaminophen being metabolized by CYP2E1. NAPQI begins to accumulate once glutathione stores are depleted by about 70%. Chronic alcoholics are at increased risk of developing severe hepatic disease even at therapeutic doses.In contrast, acute alcohol ingestion is not a risk factor for hepatotoxicity and may even be protective by competing for CYP2E1.Alcohol acts at least in part by induction of CYP2E1, which results in enhanced generation of NAPQI.

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