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Biochemistry(xenobiotics)

Drug 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. In this article, we discuss the basics of drug metabolism, the process, metabolizing organs and enzymes (especially CYP450) involved, chemistry behind metabolic reactions, importance, and consequences with several interesting and significant examples to epitomize the same. We also cover the factors influencing the process of drug metabolism, structure–toxicity relationship, enzyme induction and inhibition.

Drug metabolism may be defined as the biochemical modification of one chemical form to another, occurring usually through specialized enzymatic systems. It often involves the conversion of lipophilic chemical compounds (drugs) into highly polar derivatives that can be easily excreted from the body.

Drug metabolism is divided into three phases. In phase 1, enzymes such as cytochrome P450 oxidases introduces reactive or polar groups into xenobiotics. These modified are then conjugated to polar compound in phase II reactions. These reactions are catalyzed by transferase enzymes such as glucathione S-transferases. Finally, in phase III, the conjugated xenobiotics may be further processed before being recognized by efflux transporters and pumped out of cells. Drug metabolism often converts lipophilic compounds into hydrophilic products that are more readily excreted.

**Factors Influencing Drug Metabolism**

Factors like the physiochemical properties,Biochemical factors and Biological factors affect the metabolism of drugs in the body and it varies for different individuals

**1.Physicochemical Properties of the Drug**

These include the molecular size, shape, lipophilicity, acidity/basicity, electronic characteristics, pKa, etc. These propertiesinfluence the interaction of drug with the metabolizing enzymes and control the drug action.

**2 .Biochemical Factors**

**-Metabolic Enzyme Induction**: Any process that increases the rate of metabolism of a drug is termed as the metabolic enzyme induction, which results in a decrease in the duration and intensity of the drug action. Agents which carry out such effects are termed as enzyme inducers. This increase in drug metabolism arises usually due to the increased synthesis of enzyme protein.

For example: barbiturates (anxiolytics) are the inducers which enhance the metabolism of coumarins, phenytoin, cortisol, testosterone, etc., because of induction. Similarly, alcohol (CNS stimulant) increases the metabolism of pentobarbital, coumarins and phenytoin because of induction. Environmental chemicals such as pesticides (DDT), and polycyclic aromatic hydrocarbons present in cigarette smoke are well known to be enzyme inducers.

**-Metabolic Enzyme Inhibition**: Some chemical species block the catalytic site of cytochromes and decrease the catalytic conversion of drugs to metabolites. This process is known as enzyme inhibition, which results in an increase in duration of the drug in the body, thereby, leading to the accumulation of drug in the body and also an increase in toxicity. For example: metacholine (anti-asthmatic) inhibits the metabolism of acetyl choline by competing with it for cholinesterase. Similarly, isoniazid (antitubercular) inhibits the metabolism of phenytoin. Such influence of one drug on the metabolism of another drug leads to drug–drug interactions. Environmental chemicals such as heavy metals including nickel, mercury, arsenic are known to be potent enzyme inhibitors.

**3.Biological Factors**

The biological factors include species differences, strain differences, pharmacogenetics, ethnic variations, gender differences, age, etc. Other biological factors include diet, pregnancy, hormonal imbalance and presence of disease states in the individuals. For example, the activity of drug-metabolising enzymes decrease in people with cardiac failure. Similarly, hormonal factors during pregnancy affect the metabolic process, usually in third trimester, such as in case of anticonvulsant drugs carbamazepine and phenytoin. The circadian rhythm of an individual is also a major influencing factor on drug metabolism. Genetic polymorphism (two or more variants of an enzyme encoded by a single locus within the population) has appeared to be the common phenomenon, leading to variations in metabolic process in humans. This results in a higher or lower activity for one form of polymorphic enzyme as compared to the other form (enzyme isoforms specificity). The enzyme polymorphism is an inherited process, and thereby a major cause of inter-individual differences with respect to the rate of drug metabolism. The individuals are classified accordingly as poor metabolizers and extensive metabolizers. For example, Caucasians are poor metabolizers as compared to Asians and blacks for CYP2D6 (an

isoform of CYP450). All these factors have their varied influence on the rate of metabolic process, which has a critical influence on its outcome, which may vary from a therapeutic to toxic activity .