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**MATRIC. NO: 17/MHS01/191**

**DEPARTMENT: MEDICINE AND SURGERY**

**LEVEL: 300L**

**ASSIGNMENT TITLE: XENOBIOTICS**

**COURSE TITLE: MEDICAL BIOCHEMISTRY**

**COURSE CODE: BCH 313**

**Question: Discuss in details the factors affecting drug metabolism**

Drug metabolism is the metabolic breakdown of drugs by living organisms, usually through specialized enzymatic systems. The study of drug metabolism is called **pharmacokinetics.**

The metabolism of pharmaceutical drugs is an important aspect of pharmacology and medicine.The smooth endoplasmic reticulum of the liver cell is the principal organ of drug metabolism, although every biological tissue has some ability to metabolize drugs. Other sites of drug metabolism include epithelial cells of the gastrointestinal tract, lungs, kidneys, and the skin. These sites are usually responsible for localized toxicity reactions.

**FACTORS THAT AFFECT DRUG METABOLISM**

1. **Species and specimens**: The metabolism of many drugs and foreign compounds is often species dependent. Different animal species may bio-transform a particular xenobiotic by similar or markedly different metabolic pathways. Even within the same species, individual variations (strain differences) may result in significant differences in a specific metabolic pathway. This is a problem when a new drug is under development. A new drug application requires the developer to account for the product as it moves from the site of administration to final elimination from the body. It is difficult enough to find appropriate animal models for a disease. It is even harder to find animal models that mimic human drug metabolism. Strain differences in drug metabolism exist, particularly in inbred mice and rabbits. These differences apparently are caused by genetic variations in the amount of metabolizing enzyme present among the different strains. For example, in vitro studies indicate that cottontail rabbit liver microsomes metabolize hexobarbital about 10 times faster than New Zealand rabbit liver microsomes.
2. **Nutrition**: Malnutrition may also affect drug metabolism. Depletion of amino acids and glycine may affect drug metabolizing capacity, especially during the phase II, which depends on the food stores. Synthesis of microsomal enzymes depend on nutritional status.
3. **Exposure to pollutants from environment or industry**: Cigarette smokers might act as enzyme inducers. Chronic alcoholism might lead to enzyme induction as well. Similarly, pesticides or insecticides may act as enzyme inducers. In hot and humid climate drug metabolism is decreased and vice versa. At high altitude, decreased drug metabolism occurs due to decreased oxygen leading to decreased oxidation of drugs.
4. **Pathological conditions**: Most of the drugs are metabolized in the liver, any disease of which (cirrhosis, viral hepatitis, drugs induced hepatitis, hepatocarcinoma) may affect and slow down the metabolizing capacity. Jaundice depresses glucuronic acid conjugation and oxidative function of liver microsomes.
5. **Sex differences**: The rate of metabolism of xenobiotics also varies according to gender in some animal species. A marked difference is observed between female and male rats. Adult male rats metabolize several foreign compounds at a much faster rate than female rats. Apparently, this sex difference also depends on the substrate, because some xenobiotics are metabolized at the same rate in both female and male rats. Differences in microsomal oxidation are under the control of sex hormones, particularly androgens; the anabolic action of androgens seems to increase metabolism. Females, during pregnancy, have an increased rate of metabolism. Thus, the drug dose has to be increased. After the pregnancy is over, the dosage is decreased back to normal levels
6. **Enzyme induction**: The activity of hepatic microsomal enzymes, such as the CYP mixed-function oxidase system, can be increased markedly by exposure to diverse drugs, pesticides, polycyclic aromatic hydrocarbons, and environmental xenobiotics. The process by which the activity of these drug-metabolizing enzymes is increased is termed enzyme induction. The increased activity is apparently caused by an increased amount of newly synthesized enzyme. Enzyme induction often increases the rate of drug metabolism and decreases the duration of drug action. Inducing agents may increase the rate of their own metabolism as well as those of other unrelated drugs or foreign compounds. Concomitant administration of two or more drugs often may lead to serious drug interactions as a result of enzyme induction.
7. **Enzyme inhibition**: The process in which drug metabolizing capacity of cytochrome is decreased is known as enzyme inhibition. The rate of metabolism is decreased. Drugs bringing about these changes are known as enzyme inhibitors. Examples include ketoconazole- antifungal drug, cimetidine and verapamil- calcium channel blocker.
8. **Age differences**: Age-related differences in drug metabolism are generally seen in the newborn. In most fetal and newborn animals, undeveloped or deficient oxidative and conjugative enzymes are chiefly responsible for the reduced metabolic capability seen. In general, the ability to carry out metabolic reactions increases rapidly after birth and approaches adult levels as the child develops. In humans, oxidative and conjugative (e.g., glucuronida-tion) capabilities of newborns are also low compared with those of adults. Drug metabolism also diminishes with old age.
9. **Hereditary or genetic factors**: Marked individual differences in the metabolism of several drugs exist in humans. Many of these genetic or hereditary factors are responsible for the large differences seen in the rate of metabolism of these drugs. Inter-individual variations might occur, as drugs behave differently in different individuals due to genetic variations resulting from absent or malformed enzymes. Mostly non microsomal enzyme show genetic variations. Genetic factors also appear to influence the rate of oxidation of drugs such as phenytoin, phenylbutazone, dicumarol, and nortriptyline. Numerous studies in twins (identical and fraternal) and in families indicate that oxidation of these drugs is under genetic control.