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**DEPT: MEDICINE AND SURGERY**

**COURSE: MEDICAL BIOCHEMISTRY IV**

ASSIGNMENT

1) Discuss in details the factors affecting drug metabolism

Drug metabolism is the metabolic breakdown of drugs by living organisms, usually through specialized enzymatic systems. More generally, xenobiotic metabolism (from the Greek xenos "stranger" and biotic "related to living beings") is the set of metabolic pathways that modify the chemical structure of xenobiotics, which are compounds foreign to an organism's normal biochemistry, such as any drug or poison. These pathways are a form of biotransformation present in all major groups of organisms, and are considered to be of ancient origin. These reactions often act to detoxify poisonous compounds (although in some cases the intermediates in xenobiotic metabolism can themselves cause toxic effects). The study of drug metabolism is called pharmacokinetics.

The metabolism of pharmaceutical drugs is an important aspect of pharmacology and medicine. For example, the rate of metabolism determines the duration and intensity of a drug's pharmacologic action. Drug metabolism also affects multidrug resistance in infectious diseases and in chemotherapy for cancer, and the actions of some drugs as substrates or inhibitors of enzymes involved in xenobiotic metabolism are a common reason for hazardous drug interactions. These pathways are also important in environmental science, with the xenobiotic metabolism of micro organisms determining whether a pollutant will be broken down during bioremediation, or persist in the environment. The enzymes of xenobiotic metabolism, particularly the glutathione S-transferases are also important in agriculture, since they may produce resistance to pesticides and herbicides.

Drug metabolism is divided into three phases. In phase I, enzymes such as cytochrome P450 oxidases introduce reactive or polar groups into xenobiotics. These modified compounds are then conjugated to polar compounds in phase II reactions. These reactions are catalysed by transferase enzymes such as glutathione S-transferases. Finally, in 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.

**FACTORS AFFECTING DRUG METABOLISM**

A number of factors may influence the metabolic rate of a drug. Some of the are:

1) Chemical factors:they include

a) Enzyme induction

b) Enzyme inhibition

c) Environment chemicals

2) Biological factors : they include

a)Age

b) Diet

c) Sex difference

d) Species difference

e) Strain difference

f) Altered physiological factors

3) Physicochemical properties of the drug

1) **CHEMICAL FACTORS:**

A) Enzyme induction: The phenomen of increased drug metabolizing ability of enzymes by several drugs and chemicals. The agents which bring about such an effect is called enzyme inducers.

Mechanism of enzyme induction:

1. Increase in both liver size and liver blood flow
2. Increase in both total and microsomal protein content
3. Increased stability of enzymes
4. Increased stability of cytochrome P-450
5. Decrease degradation of cytochrome P-450
6. Proliferation of smooth endoplasmic reticulum

Consequences of enzyme induction include

1. Decrease in pharmacological activity of drugs
2. Increased activity where the metabolites are active
3. Altered psychological status due to enhanced metabolism of endogenous compounds such as sex hormones.

B) Enzyme inhibition: A decrease in the drug metabolizing activity of an enzyme. The process of inhibition may be direct or indirect.

1. Direct inhibition: It may result from interaction at the enzymic site, the next outcome being a change in the enzyme activity. Direct enzyme inhibition can occur by one of the following mechanisms:
2. Competitive inhibition: Occurs when structurally similar enzymes compete for the same site on an enzyme.
3. Non-Competitive inhibition: Occurs when a structurally unrelated agent interacts with the enzyme and prevents the metabolism of drugs.
4. Product inhibition: Occurs when the metabolic product competes with the substrate for the same enzyme
5. Indirect inhibition: It is caused by the following mechanisms:
6. Repression: It may be due to a fall in the rate of enzyme synthesis or rise in the rate of enzyme degradation.
7. Altered physiology: It may be due to a nutritional deficiency or hormonal imbalance.

NOTE: Enzyme inhibition is more important clinically than Enzyme induction especially for drugs with narrow therapeutic index. Eg anticoagulants, anti epileptics, hypoglycemias etc

C) Environmental Chemicals: Several environmental agents influence the drug metabolizing ability of enzymes. For example:

* Halogenated pesticides such as DDT and polycyclic aromatic hydrocarbons contained in cigarette smoke have enzyme induction effect.
* Organophosphate insecticides and heavy metals such as mercury, nickel, cobalt and arsenic inhibit drug metabolizing ability of enzymes.
* Other environmental factors that may influence drug metabolism are temperature, altitude, pressure and atmosphere.
1. ) **BIOLOGICAL FACTORS**
2. Age: The drug metabolic rate in the different age groups differs mainly due to variations in the enzyme content, enzyme activity and haemodynamics.
* In neonates( up to 2 months) and in infants ( 2 months to 1 year), the microsomal enzyme system is not fully developed. So many drugs are metabolized slowly. For example caffeine has a half life of 4 days in neonates and in comparison to 4 hours in adults.
* Children( between 1 year and 12 years) metabolize several drugs much more rapidly between than adults as the rate of metabolism reaches a maximum somewhere between 6 months and 12 years. As a result they require large mg/kg dose in comparison to adults.
* In elderly persons, the liver size is reduced, the microsomal enzyme activity is decreased and hepatic blood flow also declines a s a result of reduced cardiac output, all of which contributes to decreased metabolism of drugs. For example, chlomethaziole shows a higher bioavailability within the elderly, therefore they require a lower dose.
1. Diet: The enzyme content and activity is altered by a number of dietary components. Generally
* Low protein diet decreases and high protein diet increases the drug metabolizing ability and enzyme synthesis is promoted by protein diet and also raise the level of amino acids.
* Free fat diet depresses cytochrome P-450 levels since phospholipids which are important components of microsomes become deficient.
* Dietary deficiency of vitamins like vitamin A, B2, B3, C and E and minerals such as Fe, calcium, magnesium and zinc retard the metabolic activity of enzymes
* Grapefruit inhibit metabolism of many drugs and improve their oral bioavailability
* Starvation results in decreased amounts of glucorosides formed than under normal conditions

C ) Sex Difference: Since variations between male and female are observed during puberty. So, sex related differences in the rate of metabolism may be due to sex hormones. Such sex differences are widely studied in rats where male rats have greater drug metabolizing capacity. In humans, women metabolize benzodiazepine slowly than men. Several studies have also shown that women on contraceptive pills metabolize a number of drugs at a slow rate.

D ) Species Difference: This has been observed in both phase I and phase II reactions. In phase I reactions, both qualitative and quantitative variations in the enzyme and their activity has been observed. Qualitative differences among species generally result from the presence or absence of specific enzymes in those species. Quantitative differences result from variations in the amount and localization of enzymes, the amount of natural inhibitors and the competition of enzymes for specific substrate.

 Human liver contains less cytochrome P-450 per gram of tissue than do the livers of other species. For example, rat liver contains approximately 30 to 50 nmol/g of cytochrome P-450 whereas the human liver contains 10 to 20 nmol/g. Further more, human liver is 2 percent of body weight, whereas rat liver is approximately 4 percent.

Similarly in men, amphetamine and ephedrine are predominately metabolized by oxidation deamination, whereas in rats, aromatic oxidation is the major route in phase II reactions.

Similarly in pigs, the phenol is excreted mainly as glucoronide whereas it’s sulphate conjugate dominates in cats.

E) Strain Difference: Just as the difference in the drug metabolizing ability between the difference species is attributed to genetics, the differences are observed between strains of the same species. Also, it may be studied under two headings:

* Pharmacogenetics: A study of inter-subject variability in drug response. The inter-subject variations in metabolism maybe mono-genetically or poly-genetically controlled. A polygenetic control is observed in twins.

In identical twins(monozygotic), very little or no difference in metabolism of halothane, phenylbutazone,dicoumaral and antipyrine was detected but large variations were observed in fraternal twins.

* Ethnic Variations: Is the difference observed in the metabolism of drugs among different races. Such observations may be monomorphic or polymorphic. Example: Approximately equal percent of slow and rapid acetylators, the rapid acetylators are found among whites and blacks whereas the slow acetylators dominate Japanese and Eskimo population.

F) Altered Physiological Factors:

1. Pregnancy: Pregnancy is known to affect hepatic drug metabolism. Physiological changes during pregnancy are probably responsible for the reported alteration in drug metabolism. These include elevated concentrations of various hormones such as estrogen, progesterone, placental growth hormone and prolactin. For example, in women the metabolism of promazine and pethidine is reduced during pregnancy. It was also confirmed by the study in animals. In pregnant Sprague-Dawley rats, hexobarbital bio transformation indicated unchanged or slightly elevated microsomal enzyme activity compared to normal rats.

II) Disease states: There are many disease states that affect metabolism of drugs. Some of them are cirrhosis of liver, alcoholic liver disease, cholestatic jaundice, diabetics mellitus, acromegaly, malaria, various bacterial and viral infections etc. It can be seen that major effects are seen in the disease affecting liver is quantitatively the important site for metabolism. The possible cause in the effect of metabolism due to the diseases may be:

* Decreased enzyme activity in the liver
* Altered hepatic blood flow
* Hypoalbuminanemia ( leading to lower plasma binding of drugs).

For example: glycine conjugation of salicylates, oxidation of vitamin D and hydrolysis of procaine are impaired in kidney diseases.

iii) Hormonal Imbalance: Higher level of one hormone may inhibit the activity of few enzymes while inducing that of others. Adrenolectomy, thyroidectomy, and alloxan-induced diabetes in animals showed impairment in the enzyme activity with subsequent fall in the rate of metabolism. A similar effect was also observed in the pituitary growth hormone and stress related changes in the ACTH levels.

1. **PHYSICOCHEMICAL PROPERTIES OF THE DRUG:** Molecular size and shape, pKa, acidity/ basicity, lipophilicity and steric and electronic characteristics of a drug influence in interaction with the active sites of the enzyme and the metabolism to which it is subjected. However such an interrelationship is not clearly understood.

**CONCLUSION**

The therapeutic efficacy, toxicity and biological half life of a drug greatly depends on the metabolism of the drug and a number of factors affecting the metabolism of the drug. Hence various factors affecting drug metabolism must be considered during drug administration and also on proper dosing of any drugs to the patients.