**NAME: ABIWO, ENIAYO AYOWOLE.**

**DEPARTMEENT: MEDICINE AND SURGERY.**

**COURSE: MEDICAL BIOCHEMISTRY IV (BCH 313).**

**ASSIGNMENT TITLE: XENOBIOTICS.**

 **QUESTION.**

1. Discuss in details the factors affecting drug metabolism.

 **ANSWER.**

1. A number of factors can influence the metabolic rate of a drug. They are classified into two groups;
2. Internal factors.
3. External factors.

INTERNAL FACTORS.

These include; Age, Sex difference, Species difference, Strain difference, physicochemical properties of the drugs, Altered physiological factors.

- Age: The drug metabolic rate in different age groups differs mainly due to variations in the enzyme content, enzyme activity and hemodynamics.

i). In neonates and infants, the microsomal enzyme system is not fully developed. So, many drugs are metabolized slowly.

ii). Children metabolize several drugs much more rapidly than adults as the rate of metabolism reaches a maximum somewhere between 6 months and 12 years.

iii). In elderly persons, the liver size is reduced, the microsomal enzyme activity is decreased and hepatic blood flow also declines as a result of reduced cardiac output, all of which contributes to decreased metabolism of drugs.

- Sex difference: Since variations between male and female are observed following 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 benzodiazepines slowly than men. Several studies have shown that women on contraceptive pills metabolize a number of drugs at a slow rate.

- Species difference: Species difference have been observed both in Phase-I and Phase- II reactions. In Phase- I reactions, both qualitative and quantitative variations in the enzyme and their activity have been observed. Qualitative differences among species generally results from the presence or absence of specific enzymes in those species. Quantitative differences result from variations in the amount or localization of enzymes, the amount of natural inhibitors, and the competition of enzymes for specific substrates.

- Strain difference: Just as the difference in drug metabolizing ability between different species is attributed to genetics, the differences are observed between strains of the same species. Ii may be studied under two headings;

\* Pharmacogenetics: A study of inter subject variability in drug response is called Pharmacogenetics. The inter subject variation in metabolism may either be monogenetically or polygenetically controlled. A polygenetic control is observed in twins. In identical twins (monozygotic), very little or no difference in metabolism of halothane, phenylbutazone, dicicumaral and antipyrine was detected but large variations were observed in fraternal twins (dizygotic).

\* Ethnic variations: Differences observed in the metabolism of drug among different races are called ethnic variations. Some variations may be monomorphic or polymorphic. E.g. Approximately equal percent of slow and rapid acetylators are found among whites and blacks whereas the slow acetylators dominate Japanese and Eskimo population.

- Physicochemical properties of the drugs: 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 inter-relationship is not clearly understood.

- Altered physiological factors:

i) 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 concentration of various hormones. E.g. In women, the metabolism of promazine and pethidine is reduced during pregnancy.

ii) Diseases: There are many disease states that can affect the metabolism of drugs. Some of them are cirrhosis of liver, alcoholic liver disease, cholestatic jaundice, diabetes mellitus, acromegaly, malaria, various bacterial and viral infections etc. It can be seen that major effects are seen in the disease affecting the liver as the liver is quantitatively the important site for metabolism. The possible cause in the effect of metabolism due to diseases may be; Decreased enzyme activity in the liver, Altered hepatic blood flow, Hypoalbuminaemia etc.

iii) Hormonal imbalance: Higher level of one hormone may inhibit the activity of few enzymes while inducing that of others.

EXTERNAL FACTORS.

These include diet and environmental factors.

- 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 as enzyme synthesis is promoted by protein diet and also raises the level of amino acids for conjugation with drugs.

\* Fat free diet depresses cytochrome P-450 levels since phospholipids which are important components of microsomes become deficient.

\* Grapefruit inhibits metabolism of many drugs and improves their oral bioavailability.

\* Dietary deficiency of vitamins like Vitamin A, B2, B3, C and E and minerals such as Fe, Ca, Mg, Zn retard the metabolic activity of enzymes.

\* Starvation results in decreased amount of glucuronides formed under normal conditions.

- Environment: Several environmental agents influence the drug metabolizing ability of enzymes;

\* Halogenated pesticides such as DDT and polycyclic aromatic hydrocarbons contained in cigarette smoke have enzyme induction effects.

\* Organophosphate insecticides and heavy metals such as mercury, nickel, cobalt and arsenic inhibit drug metabolizing activity of enzymes.

\* Other environmental factors that may influence drug metabolism are temperature, altitude, pressure, atmosphere etc.