**ABDULRAZZAQ HINDU MA’AJI**

**17/MHS01/004**

**MBBS 300LEVEL**

**BIOCHEMISTRY ASSIGNMENT (XENOBIOTICS)**

Question: discuss in details the factors affecting drug metabolism

Answer:

Biological factors

1. 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 and infants the microsomal enzyme system is not fully developed. Therefore, many drugs are metabolized slowly. In children, several drugs are metabolized much more rapidly than in adults as the rate of metabolism reaches a maximum somewhere between 6 months and 12 years. 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 contribute to decreased metabolism of drugs.
2. Diet: dietary components can also alter the enzyme content and activity. Generally 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 improve 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.
3. Sex difference: since variations between male and female are observed following puberty. Sex related differences in the rate of metabolism may be due to sex hormones. However, women metabolize benzodiazepines slowly than men. Several studies have shown that women on contraceptive pills metabolize a number of drugs at a slow rate.
4. Strain difference: just as the difference in drug metabolizing ability between different species is attributed genetics, the differences are observed between strains of same species also. It may be studied under pharmacogenetics which is the study of inter-subject variability in drug response. It may be monogenetically or polygenetically controlled. Polygenetic control is observed in twins. Identical twins (monozygotic) have very little or no difference in metabolism of halothane. Phenylbutazone, dicoumaral and antipyrine was detected but large variations were observed in fraternal twins (dizygotic). OR Ethnic variations which is differences in metabolism among different races. Such variation may be monomorphic or polymorphic
5. Pregnancy: pregnancy is known to affect hepatic drug metabolism. Physiological changes during pregnancy are probably responsible for the reported alteration in drug metabolism. These includes increase in concentration of various hormones such as estrogen, progesterone, placental growth hormone and prolactin. For example, metabolism of promazine and pethidine is reduced during pregnancy.
6. Disease states: there are many disease states that affect metabolism of drugs. They include cirrhosis of liver, alcoholic liver disease, cholestatic jaundice, diabetes mellitus, acromegaly and malaria, various bacterial and viral infections. The possible effect may be decreased enzyme activity in liver, altered hepatic blood flow, hypoalbuminaemia (leading to lower plasma binding of drugs). This is because the liver is quantitatively the important site for drug metabolism.
7. 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 of 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 ACTH levels.

Chemical factors

1. Enzyme induction: this is the phenomenon of increased drug metabolizing ability of enzymes by several drugs and chemicals whereas the agents which brings about such an effect are called enzyme inducers. Mecganisms of enzyme induction are decreased degradation of cytochrome P-450, increase in liver size and liver blood flow, increase in both microsomal protein content, proliferation of smooth endoplasmic reticulum, increased stability of enzymes. Consequences of enzyme induction include decrease in pharmacological activity of drugs and increased activity where the metabolites are active.
2. Environmental chemicals: several environmental agents influence the drug metabolizing ability of enzymes. It can be halogenated pesticides such as DDT and polycyclic aromatic hydrocarbons contained in cigarette smoke. Other environmental factors that may influence drug metabolism are temperature, altitude, pressure, atmosphere etc.
3. Enzyme inhibition: a decrease in the drug metabolizing ability of an enzyme is called enzyme inhibition. The process of inhibition may be direct or indirect. Direct inhibition may result from interaction at the enzymic site, the net outcome being a change in enzyme activity. It can occur by competitive inhibition, non-competitive inhibition and product inhibition. Indirect inhibition is caused by either repression or altered physiology. Repression may be due to fall in the rate of enzyme synthesis or rise in the rate of enzyme degradation. Altered physiology may be due nutritional deficiency or hormonal imbalance.

Physicochemical properties of the drug: molecular shape and size, pKa, acidity/basicity, lipophilicity and steric and electronic characteristics influence in interaction with the active sites of enzyme and the metabolism to which it is subjected.