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Biochemistry Assignment

**Factors affecting drug metabolism are:**

**1) Species(strain):** in phase I reaction, 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 difference result from variation in the amount and localization of enzymes, the amount of natural inhibitors and the competition of specific substrate.

Human liver contains less cytochrome P450-Based per gram of tissue than the liver of other species.

For example, ray liver contains approximately 30 to 50 nmol/g whereas human liver contains 10 to 20 nmol/g. Furthermore, human liver is 2% of body weight whereas rat is 4%.

Similarly in men, amphetamine and ephedrine predominantly metabolized by oxidative deamination whereas in rats, aromatic oxidation is the major route in phase II reaction.

Similarly in pigs, the phenol is excreted mainly as glucuronide whereas its sulphate conjugate dominates in cats.

2)**Genetics:** just as the difference in drug metabolising ability between different species is attributed to genetics, it may be studied under the following;

• **pharmacogenetics**: a study of inter-subject variability is called pharmacogenetics. The inter-subject variations in metabolism may either be mono genetically or polygenetically controlled. A polygenetic control is observed in twins.

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

• **Ethnic Variations:** differences observed in the metabolism of drug among races are called Ethnic variations. Such variations may be monomorphic or polymorphic.

Ex: Approx. equal percent of slow and rapid acetylators are found among whites and blacks whereas the slow acetylators dominate Japanese and Eskimo population.

**3) Age:** the drug metabolism 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-1year), the microsomal enzyme system is not fully developed so, many drugs are metabolized slowly. For Ex: caffeine has a half-life of 4 days in neonates in comparison to 4hrs in adults.

• Children ( between 1 year to 12years) metabolize drugs more rapidly than adults as the rate of metabolism reaches a maximum somewhere between 6months and 12yrs. As a result, they require large mg/kg dose compared to adults.

• In elderly persons, the liver size is reduced, the microsomal enzyme activity is decreased and the hepatic blood flow also declines as a result of reduced cardiac output, all of which contributes to decreases metabolism of drugs. For example, chlomethiazole shows a high bioavailability within elderly, therefore they require a lower dose.

**4) Sex differences:** since variations between male and females are observed following puberty. So, sex related 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.

**5) Diseases:** There are many diseases that 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 diseases affecting liver as 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 ( leading to lower plasma binding of drugs).

**6) Hormonal imbalance:** Higher levels 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 is also observed in the pituitary growth hormone and stress related changes in ACTH levels.

**External factors that affect drug metabolism are;**

**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 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 P450 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 and Zn retard the metabolic activity of enzymes

• Starvation results in decreases amount of glucuronides formed under normal conditions

**2) Environment:** several environmental agents influence the drug metabolizing ability of enzymes. For example;

• Halogenated pesticides such as DDT and polycystic 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, atmosphere etc.