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**MATRIC NUMBER: 17/MHS01/190**

**DEPARTEMENT: MEDICINE AND SURGERY**

**COURSE: BIOCHEMISTRY**

**COURSE CODE: BCH 313**

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

**Answer:**

A number of factors may influence the metabolic rate of a drug. We have Internal and External factors.

**INTERNAL FACTORS*:*** includes species difference, age, sex, strain difference and physiological factors (hormones, diseases and pregnancy).

***1) Species difference:*** species difference 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 have been observed. Qualitative differences among species generally results from the presence or absence of specific enzymes in those species. Quantitative differences results from variations in the amount and localization of enzymes, the amount of natural inhibitors, and the competition of enzymes for specific substrates. Human liver contains less cytochrome P-450 per gram of tissue than do the liver of other species. For example, rat liver contains approximately 30 to 50 nmol/g of cytochrome P-450, whereas human liver contains 10 to 20nmol/g. Furthermore, human liver is 2 percent of body weight, whereas rat liver is approximately 4 percent. Similarly, in man, amphetamine and ephedrine are predominantly metabolized by oxidative deamination, whereas in rats aromatic oxidation is the major route in phase-II reactions. Similarly in pigs, the phenol is excreted mainly as glucuronide whereas its sulphate conjugate dominates in cats.

***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 mircosomal enzyme system is not fully developed. So, many drugs are metabolized slowly. For example; caffeine has a half-life of 4 days in neonates in comparison to 4 hrs in adults.
* Children (between 1 year and 12 years) metabolize several drugs much more rapidly than adults as the rate of metabolism reaches a maximum somewhere between 6months 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 mircosomal 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. For example, chlomethiazole shows a high bioavailability within the elderly, therefore they require a lower dose.

***3) Sex differences***: 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.

***4) Physiological factors:***

* 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 estrogens, 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 of animals. In pregnant Sprague- Dawley rats, hexobarbital biotransformation indicated unchanged or slightly elevated mircosomal enzyme activity compared to normal rats.
* Disease states: There are many disease states 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 noted that major effects are seen in the disease affecting liver as liver is quantitatively the important site for metabolism. The possible cause in the effect of metabolism due to disease may be: i) decreased enzyme activity in liver ii) altered hepatic blood flow iii) hypoalbuminaemia (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.
* Hormonal imbalances: 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 ACTH levels.

***5) Strain difference***: Just as the difference in drug metabolising ability between different species is attributed to genetics, the differences are observed between strains of same species also. It may be studied under two headings:

* Pharmacogenetics: A study of inter-subject variability in drug response is called pharmacogenetics. The inter-subject variations 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, dicoumaral 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. Such variations may be monomorphic or polymorphic. Example: Approximately equal percent of slow and rapid acetylators are found among whites and blacks whereas the slow acetylators dominate Japanese and Eskimo population.

**EXTERNAL FACTORS:** This includes diet and environmental chemicals.

***1) Diet:*** The enzyme content and activity is altered by a number of dietary components.

* 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 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 decreased amount of glucuronides formed than under normal conditions.

2) 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, atmosphere, etc.