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ASSIGNMENT

Discuss in details the factors affecting drug metabolism.

The factors affecting drug metabolism is divided into two categories:

1. Internal factors: species, genetic variation, age, sex, hormones, disease.
2. External factors: diet, environment.

INTERNAL FACTORS INCLUDE:

AGE: The drug metabolic rate in individuals differs mainly due to variations in the enzyme content, enzyme activity and hemodynamic. In neonates(up to 2 months) and in infants (2months to 1 year), the microsomal enzyme system is not fully developed and so, many drugs are metabolized slowly, e.g. caffeine has a half life of 4 days in neonates while the adults takes about 4 hours to metabolize it. Children (between 1 year and above) metabolize several drugs much more rapidly than adults as the rate of metabolism reaches its maximum. 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 and all these contribute to decreased metabolism of drugs.

SEX DIFFERENCE: Since variations between and female are observed following puberty, 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 effect than women. Several studies show that on contraceptive pills metabolizes a number a number of drugs at slow rate.

SPECIES DIFFERENCE: Species differences have been observed both in phase I and II reactions. In phase I reaction, both qualitative and quantitative variations in the enzyme and their activity have 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 P450 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 human liver contains 10 to 20 nmol/g. Furthermore, human liver is 2 percent of the total body weight, whereas rat liver is approximately 4 percent. Also, in men, amphetamine and ephedrine are predominantly metabolized by oxidative deamination, whereas in rats aromatic oxidation is the major route in phase-II reactions.

DISEASES: 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 seen 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 may be:

Decreased enzyme activity in liver.

Altered hepatic blood flow.

Hypoalbuminaemia (leading to lower plasma binding of drugs).

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 on the pituitary growth hormone and stress related changes in ACTH levels.

EXTERNAL FACTORS INCLUDE:

DIET: The metabolism of drug is altered by a number of dietary components. Generally, low protein diet decreases and high protein increase 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. 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. Also starvation results in decreased amount of glucuronides formed than under normal conditions.

ENVIRONMENTAL FACTORS: Several environmental agents influence the drug metabolizing ability of enzymes. For example:

Halogenated pesticides like DDT and polycyclic aromatic hydrocarbons contained in cigarette smoke have enzyme induced 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.