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MBBS

1. Discuss the factors that affect drug metabolism

 Factors affecting drug metabolism are discussed under internal and external factors

  **INTERNAL FACTORS**

1. **Species differences** - this difference has been observed in both qualitative and quantitative variations in enzyme and their activity have been observed. Qualitative differences among species generally results from presence or absence of specific enzymes of those species while quantitative differences results from variation in the amount and localization of enzymes, the amount of natural inhibitors and the competition of enzymes for specific substrates. Examples of some differences in certain species are;

- human liver contains less cytochrome P 450 per gram of tissue then do the livers of other species

- In pigs, phenol is excreted mainly as glucuronide whereas it’s sulphate conjugate is dominate in cats

2. **Strain difference** - just as drug metabolism varies in species as a result of genetics, differences are also observed between strains of the same species too . It may be studied under 2 headings;

\* Pharmacogenetics - the inter subject variations in metabolism may either be monogenetically or polygenetically controlled. A poly genetic control is observed in twins, in identical twins very little or no difference in metabolism of halothane, antipyrine was detected but large variations were detected in fraternal twins

\* Ethnic variations - these differences are observed among race and if may be polymorphic or monomorphic e.g fast acetylators are found among whites and blacks while slow acetylators dominate Japanese and Eskimo population

3. **Age** - drug metabolic rate in different age groups is mainly due to variations in enzyme content, enzyme activity and haemodynamics

- in neonates ( up to 2 months) and infants ( 2 months to 1 year) drug metabolism is slow due to partially developed microsomal enzyme system

- Children between 1 - 12 years have the most rapid rate of drug metabolism than adults

- In elderly persons drug metabolism is reduced due to reduced size of liver, reduced hepatic blood flow and reduced microsomal activity

4. **Sex difference** - sex related differences in metabolism rate may be due to sex hormones , In rats the male sex have greater drug metabolizing capacity. In humans, women metabolize benzodiazepine slowly than men

5. **Altered physiological factors**:

- pregnancy : physiological changes during pregnancy are probably responsible for the altered rate of drug metabolism , they include elevated hormones such as estrogen, progesterone, prolactin, placental growth hormone this reduces metabolism of some drugs like promazine and pethidine

- Disease state : some diseases like cirrhosis of liver, cholestatic jaundice, diabetes mellitus, acromegaly, malaria, etc. The possible cause in the effect of metabolism due to disease may be

\* decreased enzyme activity in liver

\* Altered hepatic blood flow

\* Hypoalbuminaemia

Some reactions are also impaired in kidney diseases

- hormonal Imbalance : higher level of one hormone may inhibit activity of few enzymes while inducing that of others. Adrenolectomy & thyroidectomy in animals showed impairment in enzyme activity with fall in metabolism rate also similar effect was observed in pituitary growth hormone and stress related changes in Adrenocorticotropic hormone levels

6. **Physochemical properties of the drug** : molecular size and shape, pKa, acidity/basicity, lipophilicity, steric And electronic characteristics of a drug influence its interaction with active site of enzymes

**EXTERNAL FACTORS**

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

- low protein decreases drug metabolizing ability as it is needed for enzyme synthesis and for conjugation of drugs while the opposite happens in the case of high protein levels

- Fat free diet depresses cytochrome p450 levels since phospholipids which are important components of microsomes become deficient

- Grapefruit inhibits inhibits metabolism of many drugs and improve their oral bioavailability

- Dietary deficiency of enzymes like vitamin A, B2, B3, C and E with minerals such as Fe, Ca, Mg, Zn retard the metabolic activity of enzymes

- Starvation results in low level of glucuronides

2. **Environment** : factors such as tobacco, alcohol, smoke, pollutants, food contaminants for example;

- Halogenated pesticide such as DDT and polycyclic aromatic carbon found in cigarette smoke have enzyme inhibition effects

- Organophosphate insecticide and heavy metal inhibit drug metabolizing ability of enzymes

- Other factors like temperature, pressure, altitude, atmosphere etc also affect drug metabolism