NAME: AKANIRO EBUBECHUKWU DEBORAH
MATRIC NO.: 18/MHS01/378
COURSE: BIOCHEMISTRY (BCH 313)
DEPARTMENT: MEDICINE AND SURGERY
LECTURER: MRS OWOLABI

QUESTION

Discuss in details the factors affecting drug metabolism

ANSWER

A variety of factors may affect the activities of the enzymes involved in metabolizing xenobiotics or drug metabolism and this in turn will affect the rate of drug metabolism. These factors are divided into two groups which are the internal and external factors and we will be discussing each of the factors under these two groups.

INTERNAL FACTORS

- Species
- Age
- Genetics
- Sex/Gender
- Hormones
- Diseases

SPECIES

It is well known that various species react differently to the same drug, drugs inactive in animals may be effective in man. Mice in general metabolize drugs more rapidly than do other animals. This probably explains the relatively low toxicity of many drugs in this species. In man the converse is usually true, though there are a number of exceptions. There has been a specie difference observed in both phases of drug metabolism. In Phase 1 reactions, both qualitative and quantitative variations in the enzyme and their activities have been observed. Qualitative differences/variations among species as a result of the absence or presence of specific enzymes in those species while Quantitative differences/variations result from variations in the localization of enzymes, amount of natural inhibitors and competition of enzymes for specific substrates. For instance:

- In humans, the liver contains less cytochrome P450 per gram tissue than in the liver of other species. The human liver contains about 10-20nmol/g of cytochrome P450 while a rat's liver contains 30-50nmol/g of cytochrome P450.
- In men amphetamine and ephedrine are metabolized by oxidative deamination where as in rats aromatic oxidation is the major route in Phase 2 reactions.
- In pigs, the phenol is excreted mainly as glucouronide whereas its sulphate conjugates that dominates in cats.
- Morphine depresses man, dogs and rats, but stimulates cats, horses and goats.

However, most species differences are in duration of drug action, due to variations in rate of drug inactivation or in sensitivity of the "receptor site".

AGE

The drug metabolic rate in different age groups is mainly due to variations in the enzyme content, enzyme activity and haemodynamic. In neonates and infants, the microsomal enzyme system is not fully metabolized so many drugs are metabolized slowly. For example, caffeine has a half-life of 4 days in neonates while in adults it is 4 hours. In children (1 – 12years), drug metabolism is more rapid than adults because the rate of metabolism of drug reaches a maximum at the age of 6months – 12 years. As a result they require large doses in comparison to adults. In elderly persons, the liver size is reduced and the microsomal enzyme activity is decreased an hepatic flow declines as a result of reduced cardiac output, all of which contributes to decreased metabolism of drugs.

GENETICS

Genetic influence on drug metabolism interacts with other factors such as age, race, gender and disease states. Many drugs are metabolized by cytochrome P450 and this enzyme and others responsible for drug metabolism are affected by genetic differences (polymorphism). The effect of genetic differences on catalytic activity is most prominent for three isoforms CYP2C9, CYP2C19 & CYP2D6 which collectively accounts for 40% of drug metabolism mediated by cytochrome P450. This gives rise to distinct population phenotypes of persons who have metabolism ranging from extremely poor to extremely fast. When a drug is in active form, it must be metabolized to form inactive metabolites so that they can be eliminated in the kidney. Poor metabolisers will only convert small amounts of the parent compound to inactive metabolites hence leading to possible drug toxicity while Ultra rapid metabolisers may convert larger amount of the parent compound leading to poor efficacy.

In the case of codeine however, it must be converted to its active form in the body which is morphine (about 10%). Poor to intermediate metabolisers will convert only small amounts of codeine to morphine which will cause pain relief while Ultra rapid metabolisers will convert a large amount to morphine leading to morphine toxicity. The example above is a case where an inactive drug must be converted to active metabolites so it can do its work.

SEX

Variations are observed following puberty in males and females. Sex related differences in the rate of metabolism of drugs may be due to sex hormones. Such differences are widely studied in rats where male rats have greater drug metabolizing capacity, *Holck et al*, reported that female rats anesthetized with certain oxy-barbiturates sleep considerably longer than males, but other species of animals do not show this sex difference. In humans, women metabolize benzodiazepines slowly than men. Several studies have shown that women on contraceptive pills metabolize a number of days at a slower rate..

HORMONES

Endocrine or Inflammatory conditions resulting in over secretion or under secretion of a hormone could have a potent effect on drug metabolism. This has been attributed to hormonal effects influencing:

- Drug binding protein system
- GIT drug absorption rates
- Drug distributing volume
- Renal/Hepatic drug excretion system
- Drug effector systems

Adrenolectomy, thyroidectomy and alloxan-induced diabetes in animals showed impairment in the enzyme activity with subsequent fall in rate of metabolism.

DISEASE STATES

Many disease states affect the metabolism of drugs. Some of them are cirrhosis of the liver, alcoholic liver disease, cholestatic jaundice, diabetes mellitus, acromegaly, malaria and various bacterial and viral infections. The major effects can be seen in diseases affecting the liver as the liver is the important site for metabolism. The effects seen may be seen as a result of:

- Decreased enzyme activity in the liver
- Altered hepatic blood flow
- Hypoalbuminaemia (leading to lower plasma binding of drugs)

An instance is in the case of glycine conjugation of salicylates, oxidation of vitamin D and hydrolysis of procaine which is impaired in kidney disease.

EXTERNAL FACTORS

- Diet
- Environment

DIET

The enzyme content and activity required for drug metabolism is altered by a number of dietary components. Generally:

- Low a protein diet decreases drug metabolizing ability and high protein diet increases the drug metabolizing ability. This is because enzyme synthesis is promoted by protein diet and it also raises the level of amino acids for conjugation with drugs.
- Fat free diet depresses cytochrome P450 levels because phospholipids which are important components of microsomes become deficient.
- Grape fruit inhibits metabolism of many drugs and improve their oral bioavailability.
- Dietary deficiency of vitamins like vitamin A, B2, B3, C & E and minerals such as Fe, Mg & Zn retard the metabolic activity of enzyme.
- Starvation results in decreased amount of glucouronides formed than under normal conditions.

ENVIRONMENT

Several environmental agents influence the drug metabolizing ability of enzymes. For instance:

- Halogenated pesticides such as DDT and polycyclic aromatic hydrocarbons contained in cigarette smoke have enzyme induction effects.
- 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, altitudes, pressure and atmosphere.