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DEPARTMENT: **MEDICINE AND SURGERY**

LEVEL: **300L**

COURSE: **MEDICAL BIOCHEMISTRY IV**

Discuss in details the factors affecting drug metabolism.

A number of factors may influence the metabolic rate of a drug. They include:

1. **Chemical factors**
    - Enzyme induction
    - Enzyme inhibition
    - Environmental chemicals

2. **Biological factors**
    - Age
    - Diet
    - Sex difference
    - Species difference
    - Strain difference
    - Altered physiological factors

3. **Physicochemical properties of the drug**

Chemical Factors

1. **Enzyme induction:**

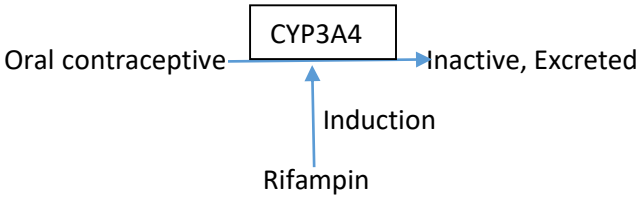
The phenomenon of increased drug metabolizing activity of enzymes on several drugs and chemicals is known as enzyme induction and the agents which bring about such an effect are called enzyme inducers. Mechanisms of enzyme induction are:

- Increase in both liver size and liver blood flow
- Increase in both total and microsomal protein content
- Increased stability of enzymes
- Increased stability of cytochrome P-450
- Decreased degradation of cytochrome P-450
- Proliferation of smooth endoplasmic reticulum

Consequences of enzyme induction include:

- Decrease in pharmacological activity of drugs
- Increased activity where the metabolites are active
- Altered physiological status due to enhanced metabolism of endogenous compounds such as sex hormones

Example of drug induction:



2. <u>Enzyme Inhibition:</u>

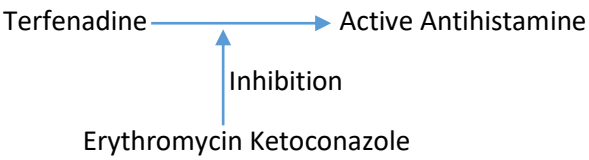
A decrease in the drug metabolizing activity of an enzyme is known as enzyme inhibition. The process of inhibition may be direct or indirect.

I. **Direct inhibition:** It may result from interaction at the enzymic site, the net outcome being a change in enzyme activity. Direct enzyme inhibition can occur by one of the following mechanisms:
   - **Competitive inhibition** which occurs when structurally similar compounds compete for the same site on an enzyme.
   - **Non-competitive inhibition** which occurs when a structurally unrelated agent interacts with the enzyme and prevents the metabolism of drugs.
   - **Product inhibition** which occurs when the metabolic product competes with the substrate for the same enzyme.

II. **Indirect inhibition:** It is caused by one of the following mechanisms:
   - **Repression** which may be due to fall in the rate of enzyme synthesis or rise in the rate of enzyme degradation.
   - **Altered physiology** which may be due to nutritional deficiency or hormonal imbalance.

Enzyme inhibition is more important clinically than enzyme induction especially for drugs with narrow therapeutic index e.g anticoagulants, hypoglycaemics, antiepileptics.

Example of enzyme inhibition is:



3. <u>Environmental chemicals:</u>

Some environmental agents influence the drug metabolizing ability of enzymes;

- 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 activity of enzymes.
- Other environmental factors that may influence drug metabolism are temperature, altitude, pressure and atmosphere.

Biological Factors

1. Age:

The drug metabolic rate in the different age groups differs mainly due to variations in the enzyme content, enzyme activity and hemodynamics.

- In neonates and in infants, the microsomal enzyme system is not fully developed. Therefore, many drugs are metabolized slowly. For example, caffeine has a half-life of 4 days in neonates in comparison to 4hrs 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 6 months 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 microsomal enzyme activity is decreased and hepatic blood flow also declines as a result of reduced cardiac output, all of which contribute to decreased metabolism of drugs. For example, chlomethiazole shows a high bioavailability within the elderly, therefore they require a lower dose.

2. 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 activity 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.
- Starvation results in decreased amount of glucuronides formed under normal conditions.

3. Sex difference:

Since variations between males and females are observed during puberty, sex related differenced in the rate of drug metabolism may be due to sex hormones. Such sex differences are widely studied in rats where male rats have greater drug metabolizing activity. In humans, women metabolize benzodiazepines slower than men. Several studies have shown that women on contraceptive pills metabolize a number of drugs at slower rates.

4. **Species difference:**

Species difference have been observed in both phase I and phase II reactions. In phase I reactions, both quantitative and qualitative variations in the enzymes and their activities 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 localisation 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 livers of other species. For example, rat liver contains approximately 30 to 50 mmol/g of cytochrome P-450 whereas human liver contains 10 to 29 mmol/g. Furthermore, human liver constitutes 2% of body weight while rat liver is about 4%.

Similarly, in men, amphetamine and ephedrine are predominantly metabolized by oxidative deamination, whereas in rats, aromatic oxidation is the major route in phase II reactions. Also, in pigs, the phenol is excreted mainly as glucuronide whereas its sulphate conjugate dominates in cats.

5. **Strain difference:**

This may be studied under 2 headings:

- **Pharmacogenetics:** This is a study of inter-subject variability in drug response. The inter-subject variations in metabolism may either be monogenetically or polygenetically controlled. A polygenetic control is observed in twins. In identical twins, very little or no difference in metabolism of halothane, phenylbutazone, dicoumaral and antipyrine was detected but large variations were observed in fraternal twins.

- **Ethnic variations:** Differences observed in the metabolism of drugs among different races are called ethnic variations. Such variations may be monomorphic or polymorphic. For example, approximately equal percent of slow and rapid acetylators are found among whites and blacks whereas the slow acetylators dominate Japanese and Eskimo population.

6. **Altered physiological factors:**

- **Pregnancy:** 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 estrogen, progesterone, placental growth hormones and prolactin. For example, in women, the metabolism of promazine and pethidine is reduced during pregnancy.

- **Disease states:** There are many diseases that affect the metabolism of drugs. Some of them are cirrhosis of liver, alcoholic liver disease, cholestatic jaundice, diabetes mellitus, malaria, acromegaly and various viral and bacterial infections. It can be seen that major effects are seen in the diseases affecting liver as liver is quantitatively the important site for metabolism. However, glycine conjugation of salicylates, oxidation of vitamin D and hydrolysis of procaine are impaired in kidney diseases. The possible cause in the effect on metabolism due to diseases may be:

i. Decreased enzyme activity in liver
ii. Altered hepatic blood flow
iii. Hypoalbuminaemia

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

Physicochemical properties of the drug

Molecular size and shape, pKa, acidity/basicity, lipophilicity and steric and electronic characteristics of a drug influence its interaction with the active sites of enzymes and the metabolism to which it is subjected. However, such an interrelationship is not clearly understood.