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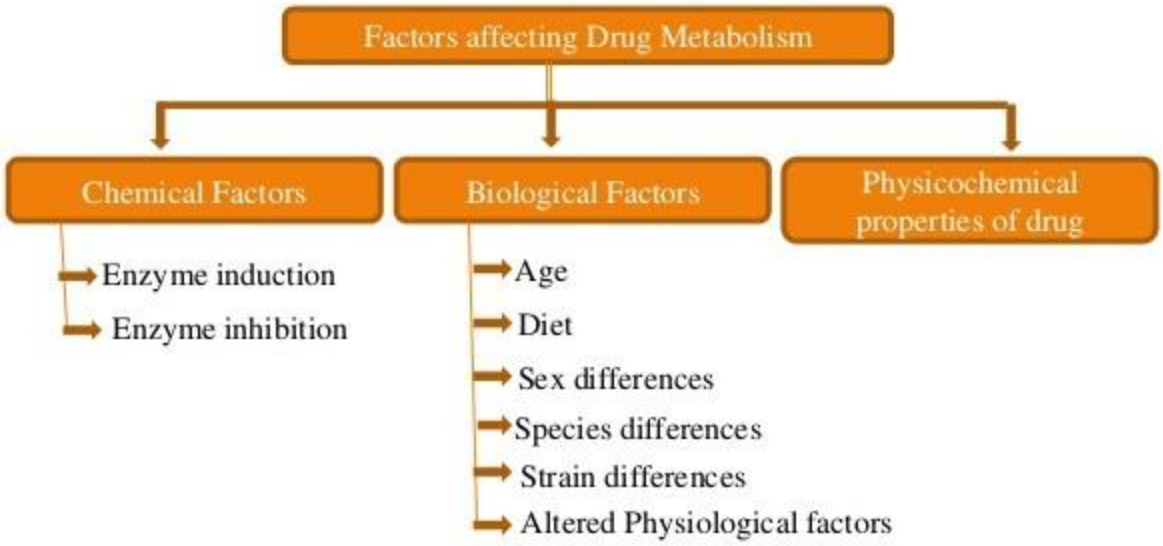
Factors Affecting Drug Metabolism

Drug metabolism is the metabolic breakdown of drugs by living organisms, usually through specialized enzymatic systems. These pathways are a form of biotransformation. The duration and intensity of pharmacological action of most drugs are determined by the rate they are metabolized to inactive products. A variety of factors may affect the activities of the enzymes involved in metabolizing drugs. They are grouped into;

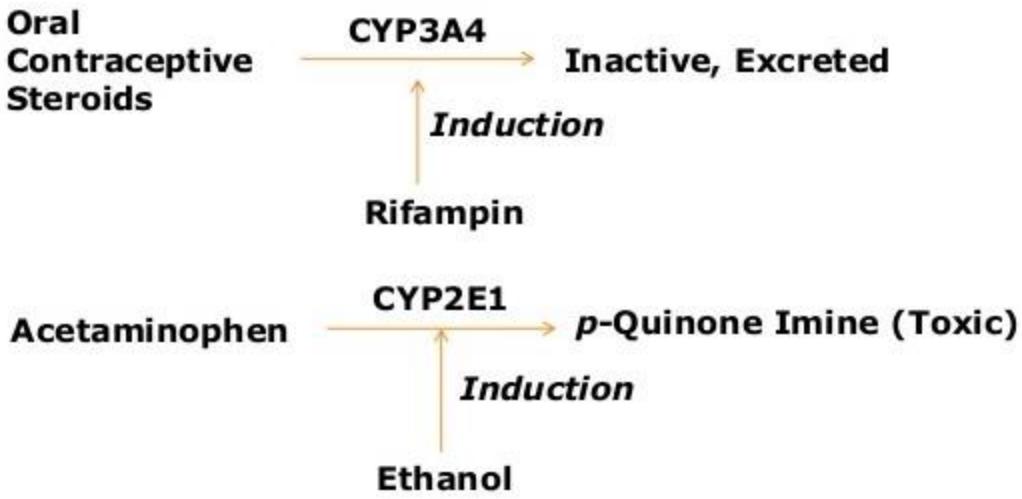
1. Chemical factors
    - Enzyme induction
    - Enzyme inhibition
    - Environmental chemicals
2. Biological factors
    - Age
    - Diet
    - Sex differences
    - Species differences
    - Strain differences
    - Altered physiological factors
3. Physiochemical properties of the drug



Chemical Factors

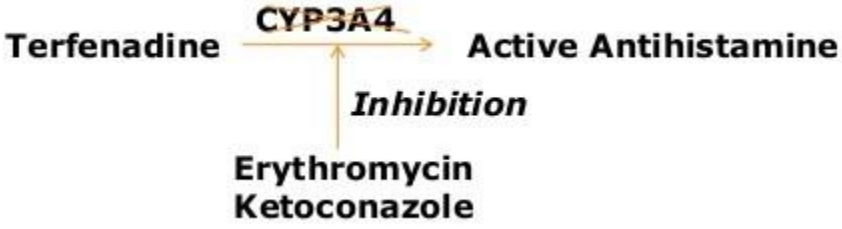
1. Enzyme Induction

Enzyme induction can be defined as the increased synthesis (higher amount) or decreased degradation (increased activity) of enzymes that occurs as a result of the presence of an exogenous substance (in this case, a drug). This mainly occurs by inducing transcription of cytochrome 450 mRNA which will lead to the overproduction of these enzymes in the liver and extra hepatic tissues. This leads to a decrease in the concentrations of drugs metabolized by the enzyme. As a result of drug induction, the drug may be metabolized to a less active metabolize which will lead to decreased activity or to a more toxic metabolite which will lead to increased activity. The agents that bring such an effect are called enzyme inducers. They include; aminoglutethimide, barbiturates, carbamazepine, glutethimide, griseofulvin, phenytoin, primidone, rifabutin, rifampin, and troglitazone.



2. Enzyme Inhibition

Enzyme inhibition is a decrease in the metabolizing ability of an enzyme. is a molecule that binds to an enzyme and decreases its activity. Substances that decrease the metabolizing ability of an enzyme are called enzyme inhibitors. By binding to enzymes' active sites, inhibitors reduce the compatibility of substrate and enzyme and this leads to the inhibition of Enzyme-Substrate complexes' formation, preventing the catalyzation of reactions and decreasing the amount of product produced by a reaction. Enzyme inhibition is more important clinically than enzyme induction especially for drugs with narrow therapeutic index (ratio of the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes toxicity). Some examples of enzyme inhibitors are; allopurinol, aspirin, erythromycin ketoconazole, methotrexate.



3. Environmental chemicals

Several environmental agents influence drug metabolizing ability of enzymes. For example, halogenated pesticides, cigarette smoke, insecticides, heavy metals and so on.

Biological factors

1. Age

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

- In neonates (up to two months) and in infants (2 months to one year), the microsomal enzyme system is not fully developed. So, many drugs are metabolized slowly. For examples caffeine has a half-life of four days in neonates in comparison to four hours in adults (neonates with difficult breathing are given caffeine to regulate their breathing by stimulating the parts of the brain that signal the lungs to inflate).
- Children (between 1-12 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 doses in comparison to adults
- In elderly people, 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. Therefore, they require lower doses.

2. Diet

The enzyme content and activity are altered by a number of dietary components. Generally;

- 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 acid for conjugation with the 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, Zn) without the metabolic activity of enzymes.
- Starvation resolves in decreased amount of glucuronides formed than under normal condition.

3. Sex Difference

variation between male and female are observed following puberty. Hence, sex related differences in the rate of metabolism maybe due to sex hormones. Such sex differences are widely studied in rat 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 slower rate.

4. Species Difference

Species difference affects the rate of drug metabolism due to the qualitative and quantitative variations in the enzyme and their activity in the species. Qualitative differences among species generally result from the presence or absence of specific enzymes in those species. Quantitative difference result from variation 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 the livers of other species. For example, rat liver contains approximately 30-50 nmol/g of cytochrome P-450, where as human liver contain 10-20 nmol/g. furthermore human liver is 2percent of body weight, whereas rat liver is 4percent of body weight. Similarly, in human amphetamine is predominantly metabolized oxidative deamination, where as in rat aromatic oxidation is the major route in phrase II reaction.

5. Strain differences

Differences in the drug metabolizing activity are also observed between strains of the same species. This can be studied under two headings.

- Pharmacogenetics: pharmacogenetic is the study of inter-subject variability in drug response. For example, in monozygotic twins, very little or no difference in metabolism phenylbutazone was detected but large variation where observed in dizygotic twins.
- Ethnic variation: differences observed in the metabolism of a drug among different races are called ethnic variation. For example, approximately equal percent of slow and rapid acetylators are found among whites and blacks where as 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. This include elevated concentrations of various hormones such as estrogen, progesterone, prolactin and so on. For example, in women the metabolism of promazine is reduced during pregnancy.

- Disease states

There are many disease states that affect metabolism of drugs some of them are cirrhosis of the liver, alcoholic liver disease, diabetes mellitus, malaria, various bacterial and viral infections and so on. The possible cause in the effect of metabolism due to diseases maybe;

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

Physiochemical properties of the Drug

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