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**LEVEL: 300L**

**FACTORS AFFECTING DRUG METABOLISM**

A number of factors may affect drug metabolism, they include;

1. Chemical factors
2. Enzyme induction: the phenomenon of the increased drug metabolizing ability of enzymes by several drugs and chemicals is called enzyme induction and the agents which bring about such an effect are called enzyme inducers.

Mechanism of enzyme induction:

* Increase in both liver size and liver blood flow
* Increase in both 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 status due to the enhanced metabolism of endogenous compounds such as sex hormone.

1. Enzyme inhibition: a decrease in drug metabolizing ability of an enzyme is called enzyme inhibition. The process of inhibition maybe direct or indirect.

* 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: occurs when structurally similar compounds compete for the same site on an enzyme.
* Non-competitive inhibition: occurs when a structurally unrelated agent interacts with the enzyme and prevents the metabolism of drugs
* Product inhibition: occurs when the metabolic product competes with the substrate for the same enzyme.
* Indirect inhibition: it is caused by one of the following mechanisms:
* Repression: it may be due to fall in the rate of enzyme synthesis or the rise in the rate of enzyme degradation.
* Altered physiology: it may be due to nutritional deficiency or hormonal imbalance.

1. Environmental chemicals: several environmental agents influence the drug metabolizing ability of enzymes. For example

* Halogenated pesticides such as DDT and polycyclic aromatic hydrocarbons contained in cigarette smoke have enzyme induction effect
* Organophosphate in 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.

1. Biological factors:
2. Age: the drug metabolic rate in different age groups differs mainly due to variations in the enzyme content, enzyme activity and hemodynamics.

* In neonates (up to 2 months) and infants (2 months to 1 year), the microsomal enzyme system is not fully developed. So, many drugs are metabolized slowly. For example, caffeine has a half-life of 4 days in neonates in comparison to 4 hours in adults.
* Children (between 1 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, 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 contributes to decreased metabolism of drugs. For example, clomethiazole shows a high bioavailability within the elderly, therefore they require a lower dose.

1. 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 ability as enzyme synthesis is promoted by protein diet and also raise 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.
* Dietary deficiency of vitamins like vitamin A, B2, B3, C and E, and minerals such as Fe, Mg, Ca, Zn retard the metabolic activity of enzymes.
* Starvation results in decreased amount of glucouronides formed than under normal conditions.

1. Sex difference: since variations between male and female are observed following puberty. So, 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 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 slow rate.
2. Species difference: species difference have been observed in both phase 1 and phase 2 reactions. In phase 1 reactions, both qualitative and quantitative variations in enzyme and their activity has 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 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 nmol/g of cytochrome P-450, whereas human liver contains 10 to 20 nmol/g. furthermore, human liver is 2% of body weight, whereas rat liver is approximately 4%.

Similarly, in men, amphetamine and ephedrine are predominantly metabolized by oxidative deamination, whereas in rats aromatic oxidation is the major route in phase 2 reactions.

1. Strain difference: just as the difference in drug metabolizing ability between different specie is attributed to genetics, the differences are observed between strains of the same species also. It maybe studied under two headings;

Pharmacogenetics: a study of inter-subject variability in drug response is called pharmacogenetics. The inter-subject variations in metabolism may either be monogenetically or polygenetically controlled. A polygenic control is observed in twins.

In identical twins (monozygotic), very little or no difference in metabolism of halothane, phenylbutazone, dicoumaral and antipyine was detected but large variations were observed in fraternal twins.

Ethnic variations: differences observed in metabolism of drug among different races are called ethnic variations. Such variations may be monomorphic or polymorphic.

1. Physicochemical properties of the drugs: molecular size and shape, pka, acidity/basicity, lipophilicity and steric and electronic characteristics of a drug influence in interaction with the active sites of enzyme and the metabolism to which it is subjected. However such an interrelationship is not clearly understood.