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**COLLEGE: MEDICINE AND HEALTH SCIENCES**

**DEPARTMENT: MEDICINE AND SURGERY**

**COURSE: MEDICAL BIOCHEMISTRY**

**ASSIGNMENT: DISCUSS IN DETAILS THE FACTORS AFFECTING DRUG METABOLISM**

Metabolism is a biotransformation or chemical alteration of a drug to other molecular species usually called metabolites, within the body via an enzymatic or non-enzymatic process. The primary site for drug metabolism in liver and other sites are kidney, intestine, lungs and plasma. Metabolism of a drug may lead to:

* Inactivation: Most drugs get inactive due to metabolism e.g. ibuprofen, paracetamol
* Active metabolite from an active drug e.g. codeine – morphine
* Activation of inactive drug e.g. levedopa- dopamine

A number of factors may influence the metabolic rate of a drug. Some of them are:

1. Chemical factors
* Enzyme induction :The phenomenon of increased drug metabolizing ability enzymes by several drugs and chemicals is called an 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 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
* Enzyme inhibition

A decrease in the drug metabolizing ability of an enzyme is called an enzyme inhibition. The process of inhibition may be direct or indirect.

1. Direct inhibition: It may result from interaction at the enzymic site, the net outcome being a change in enzyme activity. Direct inhibition can occur by one of the following mechanisms: competitive inhibition, non-competitive inhibition, and product inhibition.
2. Indirect inhibition: It is caused by one of the following mechanism:
3. Repression: it may be due to fall in the rate of the enzyme synthesis or rise in the rate of enzyme degradation.
4. Altered physiology: it may be due to nutritional deficiency or hormonal imbalance.
* Environmental chemicals

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

* Halogenated pesticides such as DDT have enzyme induction effect
* 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, altitude, pressure, atmosphere e.t.c .
1. Biological factors
* Age

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

* In nonates (up to 2 months) and in infants (2months to 1 year), the microsomal enzyme system is not fully developed. So, many drugs are metabolized slowly. For eg. Caffeine has a half life of 4 days in nonates in comparison to 4 hours 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 person, 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 deceased metabolism of drugs.
* 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 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 bio viability.
* Dietary deficiency of vitamins (like A, B2, B3. C) retard the metabolic activity of enzymes.

* 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 rats have greater drug metabolizing capacity. In human, women metabolize benzodiazephines slowly than men. Several studies have shown that women on contraceptive pills metabolize a number of drugs at a slow rate.

* Species difference

Species difference have been observed in both phase I and phase II reaction. In phase I reactions, both qualitative and quantitative variations in the enzyme and their activity 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 localization of enzymes, the amount of natural inhibitors and the competition of enzymes for specific substrates.

* Strain difference

Just as the difference in drug metabolizing ability between different species is attributed to genetics, the differences are observed between strains of same species also. It may be studied under: pharmacogenetics and ethnic variations.

* 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 concentration of various hormones such as estrogen, progesterone, placental growth hormones and prolactin.

* Diseased states:

There are many disease states that affect the metabolism of drugs. Some of them are cirrhosis of liver, alcoholic liver disease, cholestatic jaundice, diabetes mellitus, acromegaly, malaria, various bacterial and viral infections.

* Hormonal imbalance:

Higher level of one hormone may inhibit the activity of few enzymes while inducing that of others.

1. Physiochemical properties of the drug

Molecular size and shape, pKa, acidity/basicity and electronic characteristics of a drug influence in interaction with the active sites of enzyme and the metabolism to which it is subjected.