**NAME: SALIHU UMAR GONTO**

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**FACTORS AFFECTING DRUG METABOLISM**

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

1. Chemical factors

* Enzyme induction
* Enzyme inhibition
* Environmental chemicals

1. Biological factors

* Age
* Sex
* Diet
* Sex difference
* Strain difference
* Altered physiological factors

1. Physiochemical properties
2. Chemical Factors
3. **Enzyme induction**: the phenomenon of 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.

Mechanisms 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

Consequences of enzyme induction include:

* Decrease 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.

1. **Enzyme inhibition:** a decrease in the drug metabolizing ability of an enzyme is called enzyme inhibition. The process of inhibition may be direct or indirect.
2. 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:
3. Competitive inhibition: occurs when structurally similar compounds compete for the same site on an enzyme.
4. Non-competitive inhibition: occur when a structurally unrelated agent interacts with the enzyme and prevents the metabolism of drugs.
5. Product inhibition: occurs when the metabolic product competes with the substrate for the enzyme.
6. Indirect inhibition: it is caused by one of the following mechanism:
7. Repression: it may be due to fall in the rate of enzyme synthesis or rise in the rate of enzyme degradation.
8. Altered physiology: it 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, antiepileptic, hypoglycemias etc.

1. **Environmental chemicals:** special environmental agents influence the drug metabolizing ability of enzymes. Example:

* Halogen pesticides such as DDT (dichloro-diphenyl-trichloroethane) and polycyclic aromatic hydrocarbons contained in cigarette smoke have enzyme induction effect.
* Organophosphate insecticides and heavy metals such as mecury, 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 the different age groups differs mainly due to variations in the enzyme content, enzyme activity and haemodynamics.

* In neonates (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 4days in neonates in comparison to 4hrs 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 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 contributes to decreased metabolism of drugs.

1. **Diet:** the enzyme content and activity is altered by a number of dietary compounds. 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 acid for conjugation with drugs.
* Fat free diet depresses cytochrome P-450 levels since phospholipids, which are important components of microsomes become deficient.
* Dietary deficiency of vitamins like vitamin A, B2, B3, C and E) and minerals such as Fe, Ca, Mg, Zn retard the metabolic activity of enzymes.
* Starvation results in decreased amount of glucuronides 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. Eg: women metabolize benzodiazepines faster than men.
2. **Species difference:** species difference has been observed in both phase 1 and phase 2 reactions. In phase 1 reactions, both qualitative and quantitative variations in the enzyme and their activity have been observed. Qualitative differences among species normally result in 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 competition of enzymes for specific substrates.
3. **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 two headings:

1. **Altered physiological factors**
2. 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.

1. Hormonal imbalance

Higher level of one hormone may inhibit the activity of few enzymes while inducing that of others. Adrenoloctomy, 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 changed in ACTH levels.

1. Physiochemical properties of the drugs

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