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**Discuss in details the factors affecting drug metabolism.**

**DRUG METABOLISM**

**INTRODUCTION:**

Drug metabolism may be defined as the biochemical modification of one chemical form to another, occurring usually through specialised enzymatic systems. It often involves the conversion of lipophilic chemical compounds (drugs) into highly polar derivatives that can be easily excreted from the body.

Drugs, as well as other xenobiotics are metabolized via various pathways, including phase I and phase II reactions, which involve participation of numerous enzyme systems. Therefore, it is reasonable to assume that there are many factors that can determine or influence along which pathway a particular drug will undergo biotransformation and the extent to which this will proceed.

**FACTORS AFFECTING METABOLISM:**

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

1. Chemical factors
2. Enzyme induction
3. Enzyme inhibition
4. Environmental chemicals
5. Biological factors
6. Age
7. Diet
8. Sex difference
9. Species difference
10. Strain difference
11. Altered physiological factors
12. Physicochemical properties of the drug
13. **CHEMICAL FACTORS**
14. **Enzyme Induction:**

The phenomenon of increased drug metabolizing ability of enzymes by several drugs and chemicals is called as 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
* 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 hormone.

Some examples of drug induction are:

Oral CYP3A4

Contraceptive Inactive, Excreted

Steroids Induction

 Rifampin

1. **Enzyme Inhibition**

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

1. Direct Inhibition: It may result from interaction at the enzyme site, the net outcome being a change in enzyme activity. Direct enzyme inhibition can occur by one of the following mechanisms:
2. Competitive inhibition: occurs when structurally similar compounds compete for the same site on an enzyme.
3. Non-competitive inhibition: occur when a structurally unrelated agent interacts with the enzyme and prevents the metabolism of drugs.
4. Product inhibition: occurs when the metabolic product completes with the substrate for the same enzyme.
5. Indirect Inhibition: It is caused by one of the following mechanism:
6. Repression: it may be due to fall in the rate of enzyme synthesis or rise in the rate of enzyme degradation.
7. Altered physiology: it may be due to nutritional deficiency or hormonal imbalance.

Some examples of enzyme inhibition are:

 CYP3A4

Terfenadine Inactive, Excreted

 Inhibition

 Erythromyocin

 Ketoconazole

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

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 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.

2) **BIOLOGICAL FACTORS**

A) 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 (2 months to 1 year), the microsomal enzyme system is not fully developed. So, many drugs are metabolized slowly. For e.g: 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 contributes to decreased metabolism of drugs. For example, chlomethiazole shows a high bioavailability within the elderly, therefore they require a lower dose.

B) 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 bioavailabilty.
* 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 formed than under normal conditions.

C) **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.

D) **Species Difference**

Species difference have been observed in both phase-I and phase-II reactions.

E) **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 studies under **PHARMACOGENETICS** or **ETHNIC VARIATIONS.**

**F) Altered Physiological Factors**

i) 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 gr4owth hormone and prolactin.

ii) Disease state: There are many disease states that affect the metabolism of drugs. Some of them are acromegaly, malaria, various bacterial and viral infections, etc.

3) **PHYSIOCOCHEMICAL PROPERTIES OF THE DRUG**

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.

**CONCLUSION**

The therapeutic efficacy, toxicity and biological half-life of a drug greatly depends on the metabolism of the drug and a number of factors affect the metabolism of the drug. Hence these factors should be considered during administration and also in proper dosing of any drug to the patients.