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XENOBIOTICS

**Question**

Discuss in details the factors affecting drug metabolism.

**Answers**

Drug metabolism is the metabolic breakdown of drugs by living organisms, usually through specialized enzymatic systems. The metabolism of pharmaceutical drugs is an important aspect of pharmacology and medicine. The biological fate of a drug depends on host of factors, including those which determine its volume of distribution, its excretion into air, bile, and urine, and its metabolism by various enzyme systems in the body.

The duration and intensity of pharmacological action of most lipophilic drugs are determined by the rate they are metabolized into inactive products. These factors range from the species of organism studied to the environment in which that organism lives. The Cytochrome P450 monooxygenase system is the most important pathway in this regard. Anything that increases the rate of metabolism (e.g. enzyme induction) of a pharmacologically active metabolite will decrease the duration and intensity of the drug action and the opposite is also true. In cases where an enzyme is responsible for metabolizing a pro-drug into a drug, enzyme induction can speed up this conversion and increase drug levels, potentially causing toxicity.

Factors affecting drug metabolism are divided into:

1. **Internal factors**

* Physiological
* Pathological

1. **External factors**

* Diet
* Environment

1. **Internal factors:**

Physiological factors that can influence drug metabolism include age, individual variation (e.g. pharmacogenetics), enterohepatic circulation, nutrition, intestinal flora, or sex differences. Drugs are slowly metabolized in fetal, neonatal and elderly humans and animals than in adults. In neonates (up to 2 months) and infants (2 months to a year), the microsomal enzyme system is not fully developed. 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 declines, all of which contributes to decreased metabolism of drugs.

Polymorphism (genetic variation) accounts for some of the variability in the effect of drugs. With N-acetyltransferase, individual variation creates a group of people who acetylate slowly ( dominated by Japanese and Eskimo population), and those who acetylate quickly. Slow acetylators are prone to dose-dependent toxicity.

Cytochrome P450 monooxygenase system enzymes can also vary across individuals, with deficiencies occurring in 1-30% of people, depending on their ethnic background. Dose, frequency, route of administration, tissue distribution and protein binding of the drug affect its metabolism.

Sex related differences in the rate of metabolism may be due to sex hormones. Women metabolize benzodiazepines slowly than men.

Human liver contains les 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.

Pathological factors can also influence drug metabolism, including liver, kidney, or heart diseases. It can be seen that the major effect are seen in diseases affecting the liver a sliver is quantitatively the important site for metabolism. The probable cause in the effect of metabolism due to diseases may be

* Decreased enzyme activity in the liver
* Altered hepatic blood flow
* Hypoalbuminaemia (leading to lower plasma binding of drugs)

1. **External factors**

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 deficiencies of vitamins like Vitamin A, B2, B3, C and E and minerals such as Fe, Ca, Mg, and Zn retard the metabolic activity of enzymes. Starvation results in decreased amount of glucuronides formed than under normal conditions.

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

* Halogenated pesticides such as DDT and polycyclic aromatic hydrocarbon 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.