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BIOCHEMISTRY ASIGNMENT

DISCUSS IN DETAILS FACTORS AFFECTING DRUG METABOLISM

ANSWER

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

Metabolism of a drug may lead to:

- Inactivation: Most drugs gets inactive due to metabolism
- Active metabolite from an active drug
- Activation of inactive drug

Factors Affceting Drug Metabolism

1. Chemical Factors
    a. Enzyme induction
    b. Enzyme inhibition
    c. Environmental chemicals
2. Biological Factors
    a. Age
    b. Diet
    c. Sex difference
    d. Species difference

e. Strain difference

f. Altered physiological factors

3. Physiochemical properties of the drug

1. Chemical Factors

a. **Enzyme induction**

The phenomenon of increased drug metabolizing ability of enzymes by several drugs and chemicals is known as enzyme induction and the agents which bring about such 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

Consequences of enzyme induction include

- Decrease in pharmacological activity of drugs
- Increased activity where the metabolites are active
- Altered physiological states due to enhanced metabolism of endogenous compounds such as sex hormones

b. Enzyme inhibition

A decrease in drug metabolizing activity of an enzyme is known as enzyme

inhibition. The process of inhibition may be direct or indirect.

- Direct inhibition: it may result from interaction at the enzyme site, the net outcomebeing a change in enzyme activity. Direct enzyme inhibition can occur by one of the following mechanisms:

i. Competitive inhibition: occurs when structurally similar compounds compete for the same site on an enzyme.

ii. Non-competitive inhibition: occurs when a structurally unrelated agent interacts with the enzyme and prevent metabolism of drugs.

iii. Product inhibition: when the metabolic product compete with the substrate for the same enzyme.

- Indirect inhibition: it is caused by one of the following mechanism

I. Repression: it may be due to fall in the rate of enzyme synthesis or rise in the rate of enzyme degradation.

II. Altered physiology: it may be due to nutritional deficiency or hormonal imbalance.

Note: Enzyme inhibition is more important clinically than enzyme induction especially for drugs with narrow therapeutic index. e.g anticoagulants, antiepileptics, hypoglycemias e.t.c

c. Environmental chemicals

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

- Halogenated pesticides such as DDT and polypeptide aromatic hydrocarbons contained in cigarette smoke have enzyme induction effect.
- Organophosphate insecticide 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 (upto 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 comparism 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 reduced, the microsomal enzyme activity is decreased and hepatic blood flow also declines as a result of reduced cardiac output, all which contributes to decreased metabolism of drugs. For example, chlomethiazoleshows 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

bioavailability

- 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.

c. Sex difference

Since variations between male and female are observed following puberty. So, sex related difference in the rate of metabolism may be due to sex hormones. Such sex diffrence are widely studied in where male rats have greater drug metabolizing capacity. In humans, 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. In phased 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 subtrates.

e.Strain difference

Just as the difference in drug metabolising 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:

- 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 polygenetic control is observed in twins.

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

- Ethnic variations: Differences observed in the metabolism of drug among different races are called etnic variations. Such variations may be monomorphic or polymorphic.

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 growth hormones and prolactin.

ii. Diseases states: There are many diseases states that affect the metabolism of drugs. Some of them are liver cirrhosis, alcoholic liver disease, chloestatic jaundice, diabetes mellitus acromegaly, malaria, various bacterial and viral infections e.t.c.the possible cause in the effect of metabolism due to diseases may be: decreased enzyme activity in the liver, altered hepatic flow, hypoalbuminaemia (leading to lower plasma binding of drugs.

iii. Hormonal imbalance: Higher level of one hormone may inhibit the activity of few enzymes while inducing that of others. Adrenolectomy, thyroidectomyand alloxin-induced diabetes in animals showed impairment in the enzyme activity with subsequent fall in the rate of metabolism.

3. <u>Physicochemical properties of the drug</u>

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