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Medicine and surgery

Biochemistry assignment

**QUESTION- discuss in details the factors affecting drug metabolism**

Metabolism is a biotransformation or chemical alteration of a drug to other molecular species usually called the metabolites, within the body via an enzymatic or non-enzymatic process.

For a drug to be metabolized. It requires various enzymes which can be broadly categorized into two categories:

1. Microsomal enzymes: this enzyme is located in the smooth endoplasmic reticulum in liver, kidney, lungs and intestinal mucosa e.g cytochrome p450, monooxygenase etc these type of enzymes catalyze oxidative, reductive, and hydrolytic and glucuronidation reactions.
2. Nonmicrosomal enzymes: this is present in the cytoplasm and mitochondria of hepatic cells and plasma e.g flavoprotein oxidase, esterase, amidase and conjugase.

Factors affecting drug metabolism

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

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

It has been long recognized that the newborn, young and elderly display marked differences in drug biotransformation and are more susceptible to drug action. These differences are chiefly due to the variations in enzyme content, enzyme activity and hemodynamics.

* 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 metabolizing slowly e.g **caffeine has a half-life of 14 days in neonates 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 persons, the liver size is reduced, the microsomal enzyme activity is decreased and hepatic blood blow 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.
1. **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 amino acid level for conjugation with drugs.
* Fat free diets depresses cytochrome p450 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 Vitamins A, B2, B3, C and E and minerals such as iron, calcium, magnesium etc retard the metabolic activity of enzymes.
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 in rats where male rats have greater metabolizing capacity. In humans, women metabolize benzodiazepines slowly than men.

1. **Species difference**

Species difference have been observed in phase-I and phase-II reactions, 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 of and localization of enzymes, the amount of natural inhibitors, and the competition of enzymes for specific substances.

Human liver contains less cytochrome p450 prt gram of tissue than do the liver of other species e.g

**Human liver contains 10 to 20 nmol/g of cytochrome p450**

**Rat liver contains approximately 30 to 50 nmol/g of cytochrome p450**

1. **Strain differences/genetic factors**

This can be viewed under two headings:

1. Pharmacogenetics: a study of inter-subject variability in drug response is called pharmacogenetics. In identical twins, very little or no difference in metabolism of halothane, phenylbutazone, dicoumaral and antipyrine but large variations were observed in fraternal twins.
2. Ethnic variations: differences observed in the metabolism of drug among races are called ethnic variations. Approximately equal percent of slow and rapid acetylators are found among whites and blacks whereas the slow acetylators dominate Japanese and Eskimo populations.
3. **Altered physiologic factors**
4. Pregnancy: pregnancy is known to affect hepatic drug metabolism. Physiological changes during pregnancy are probably responsible for the alteration in drug metabolism. These include elevated concentrations of various hormones such as estrogen, progesterone and prolactin.

**Example; in women, metabolism of promazine and pethidine is reduced during pregnancy.**

1. Disease states: there are many disease states that affect the metabolism of drugs.

**Examples include:**

**Cirrhosis of the liver, alcoholic liver disease, cholestatic jaundice, diabetes mellitus, acromegaly, malaria etc.**

The 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)

For example: glycine conjugation of salicylates, oxidation of vitamin D and hydrolysis of procaine are impaired in kidney diseases.

1. Hormonal imbalances: higher level of one hormone may inhibit the activity of few enzymes while inducing that of others. Adrenalectomy, thyroidectomy, and alloxan-induced diabetes in animals showed impairment in the enzyme activity with subsequent fall in the rate of metabolism.
2. **Chemical factors**
3. **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 include:

* Proliferation of smooth endoplasmic reticulum
* Decreased degradation of cytochrome p450
* Increased stability of cytochrome p450
* Increased stability of enzymes
* Increase in both total and microsomal protein content
* Increase in both liver size and liver blood flow

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 hormones.

**Examples of drug induction:**

**Inactive, excreted**

CYP3A4

**Oral contraceptive steroids**

*induction*

rifampin

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.

1. 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:
2. Competitive inhibition: occurs when structurally similar compounds compete for the same site on an enzyme.
3. Non-competitive inhibition: occurs when a structurally unrelated agent interacts with the enzyme and prevents the metabolism of drugs.
4. Product inhibition: occurs when the metabolic product competes with the substrate for the same enzyme.
5. Indirect inhibition: it is caused by one of the following mechanisms:
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.

**Examples of enzyme inhibition:**

CYP3A4

**Terfenadine**

**Active Antihistamine**

*Inhibition*

Erythromycin

Ketoconazole

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

1. **Environmental chemicals**

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

1. Halogenated pesticides such as Dichlorodiphenyltrichloroethane (DDT) and polycyclic aromatic hydrocarbons contained in cigarette smoke have enzymatic induction effect.
2. Organophosphate insecticides and heavy metals such as mercury, nickel, cobalt, and arsenic inhibit drug metabolizing ability of enzymes.
3. Others environmental factors include temperature, altitude, pressure etc
4. **Physiochemical properties of drugs**

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

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, various factors affecting drug metabolism must be considered during administration and also in proper dosing of any drug to the patients.