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17/MHS01/013

MEDICINE AND SURGERY

300 LEVEL

BIOCHEMISTRY

Discuss in details the factors affecting drug metabolism.

ANSWER

Drug metabolism is the metabolic breakdown of drugs by living organisms, usually through specialized enzymatic systems. 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
2. Biological factors
 - Age
 - Diet
 - Sex
 - Species difference
 - Altered physiological factors

CHEMICAL FACTORS

- **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:
 - a. Increase in both liver size and liver blood flow
 - b. Increase in both total and microsomal protein content
 - c. Increased stability of enzymes
 - d. Increased stability of cytochrome P-450
 - e. Decreased degradation of cytochrome P-450
 - f. Proliferation of smooth endoplasmic reticulumConsequences of enzyme induction include:

- a. Decrease in pharmacological activity of drugs
 - b. Increased activity where the metabolites are active
 - c. Altered physiological status due to enhanced metabolism of endogenous compounds such as sex hormones.
- **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.
 - a. 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:
 - i. Competitive inhibition: Occurs when structurally similar compounds compete for the same site on an enzyme.
 - ii. Non-competitive inhibition: Occur when a structurally unrelated agent interacts with the enzyme and prevents the metabolism of drugs.
 - iii. Product inhibition: Occurs when the metabolic product competes with the substrate for the same enzyme.
 - b. 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. Some examples of enzyme inhibition are: CYP3A4 Active Antihistamine Terfenadine Inhibition Erythromycin Ketoconazole
- Enzyme inhibition is more important clinically than enzyme induction especially for drugs with narrow therapeutic index. Eg: anticoagulants, antiepileptics, hypoglycemias etc.**
- **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.

BIOLOGICAL FACTORS

- **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 example: caffeine has a half-life of 4 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 flow also declines as a result of reduced cardiac output, all of which contributes to decreased metabolism of drugs. For example, chlorthalidone shows a high bioavailability within the elderly, therefore they require a lower dose.

- **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 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 Iron (Fe), Calcium (Ca), Magnesium (Mg), Zinc (Zn) retard the metabolic activity of enzymes.

Starvation results in decreased amount of glucuronides formed than under normal conditions.

- **Sex:** 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.

- **Species difference:** Species difference have been observed in both 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 and localization of enzymes, the amount of natural inhibitors, and the competition of enzymes for specific substrates. Human liver contains less 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 P450, whereas human liver contains 10 to 20 nmol/g. Furthermore, human liver is 2 percent of body weight, whereas rat liver is approximately 4 percent. Similarly, in men, amphetamine and ephedrine are predominantly metabolized by oxidative deamination, whereas in rats aromatic oxidation is the major route in Phase-II reactions. Similarly in pigs, the phenol is excreted mainly as glucuronide whereas its sulphate conjugate dominates in cats.

- **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. For example: in women, the metabolism of promazine and pethidine is reduced during pregnancy. It was also confirmed by the study in animals. In pregnant Sprague-Dawley rats, hexobarbital biotransformation indicated unchanged or slightly elevated microsomal enzyme activity compared to normal rats.
- ii. **Disease states:** There are many disease states that affect the metabolism of drugs. Some of them are cirrhosis of liver, alcoholic liver disease, cholestatic jaundice, diabetes mellitus, acromegaly, malaria, various bacterial and viral infections, etc.
It can be seen that major effects are seen in the disease affecting liver as liver is quantitatively the important site for metabolism. The possible cause in the effect of metabolism due to diseases may be:
Decreased enzyme activity in 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.

- iii. Hormonal imbalance: 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.