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MATRIC NUMBER: 17/MHS01/303

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BIOCHEMISTRY ASSIGNMENT

Question

Discuss in details the factors affecting drug metabolism.

ANSWERS

METABOLISM

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

The following are the factors affecting metabolism;

* Chemical factors- enzyme induction, enzyme inhibition, environmental chemicals.
* Biological factors- age, diet, sex difference, specie difference, strain difference, altered physiological factors
* Physicochemical properties of the drug.

**Biological factors**

a)DIET; Enzyme content and activity is altered by a number of dietary components. Low protein diet decreases and high protein diet increases the drug metabolizing ability of enzymes 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-450levels 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.

b)AGE:- Drug metabolic rate in the different age groups differs mainly due to variations in the enzyme content, enzyme activity, and hemodynamics. In neonates and in infants, 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 ages 1-12) metabolize several drugs much more rapidly than adults as the rate of metabolism 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 people, the liver size is reduced, the microsomal 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

c)SEX DIFFERENCE- sex related differences in the rate of metabolism may be due to sex hormones. Women for instance, metabolize benzodiazipinesslowler than men. Studies have also shown that women on contraceptive pills metabolize a number of drugs at a slow rate.

d)STRAIN DIFFERENCE- it can be studied in two ways

-Pharmacogenetics- this is a study of inter-subject variability in drug response. the inter-subject variations in metabolism may either be monogenetically or polygenetically controlled. A polygenetic control is observed in twins. In identical twins, very little or no difference in metabolism of halothane, phenylbutazone, dicoumaral and antipyrine was detected but large variations were observed in fraternal twins.

-Ethnic variations- these are the differences observed in the metabolism of drugs among different races. The variations may be monomorphic or polymorphic. For example, approximately equal percent of slow and rapid acetylators are found among whites and blacks whereas, the slow acetylators dominate Japanese and Eskimo population.

*e)ALTERED PHYSIOLOGICAL FACTORS:*

* 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 hormone and prolactin. For example, in women, the metabolism of promazine and pethidine is reduced during pregnancy.
* Disease state- there are many diseases that affect drug metabolism, some of them are; liver cirrhosis, alcoholic liver disease, cholestatic jaundice, diabetes mellitus, acromegaly, malaria, various bacterial and viral infections etc. The possible cause of the effect in metabolism due to diseases may be; decreased enzyme activity in liver, altered hepatic blood flow, hypoalbulminaemia (leading to lower plasma binding of drugs).
* 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.

**CHEMICAL FACTORS**

a)ENZYME INDUCTION:- This is the increased drug metabolizing ability of enzymes by several drugs and chemicals. The agents that bring about such effectare called enzyme inhibitors. The mechanism of enzyme induction is:

* 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 this enzyme induction are:

* Decreased 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.

b)ENZYME INHIBITION: This is a decrease in the drug metabolizing ability of an enzyme. The inhibition may be direct or indirect.

-Direct inhibition may result from interaction at the enzymic site, the net outcome being a change in enzyme activity. It can occur by any of these mechanisms

-Competitive inhibition- occurs when structurally similar compounds compete for the same site as an enzyme

-Non-competitive inhibition- occurs when a structurally unrelated agent interacts with the enzyme and prevents the metabolism of drugs

-Product inhibition- occurs when the metabolic product competes with the substrate for the same enzyme.

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

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

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

c)ENVIRONMENTAL CHEMISTRY- several environment influence metabolizing abilities of enzymes.

* 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.

**Physicochemical properties of the drug**

Molecular size, shape, pKa, acidity/basicity, lipophilicity, and steric and electronic characteristics of a drug influence in interaction with the active site of enzymes and metabolism to which it was subjected.