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17/MHS01/266

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BIOCHEMISTRY ASSIGNMENT

Discuss in details the factors affecting Drug metabolism

Factors Affecting Drug Metabolism

Drug metabolism is the breakdown of drugs by living organism usually through specialized enzymatic systems. There are many factors that affect drug metabolism; some factors increase the rate of metabolism thereby decreasing the duration and intensity of the drug action while some do the opposite.

Factors of metabolism of drugs is divided into two; Internal Factors and External Factors. Internal factors consists of the physiological and pathological factors. Example of the Internal factors include;

I Age: Drug metabolic rate in the different age groups differ mainly due to variations in the enzyme content, enzyme activity and haemodynamics. Microsomal enzyme Cytochrome P450 is not fully developed in neonates and infants and so drugs are metabolized slowly. In Children, rate of metabolism is very rapid as rate of metabolism reaches maximum between 6 months and 12 years of age. The rate of metabolism in children is faster than that in adults. While in Elderly persons, due to reduced liver size, Cytochrom P450 activity is decreased as well as hepatic blood flow (due to reduced cardiac output) leading to decreased metabolism of drugs.

II Sex: Sex also plays a role in affecting drug metabolism. Since variations between male and female manifest during puberty, sex related differences in rate of drug metabolism may be due to sex hormones, In human, women metabolize benzodiazepines slowly than men. Also women on contraceptive pills metabolize several drugs at a slower rate than men.

III Species: Difference in species affects the rate of drug metabolism This species difference is observed in both Phase I and phase II

reactions. The differences or variations in Phase I reactions when considering species are divided into qualitative and quantitative differences. Qualitative differences result due to presence or absence of specific enzymes in the species while the quantitative differences result from variations in the amount and localization of enzymes, amount of natural inhibitors and the competition of enzymes for specific substances. An example of this is that in humans Cytochrome P450 is about 20 to 20 nmol/g in the liver which is less than other species like rats which have 30 to 50 nmol/g of Cytochrome P450 in their liver. Also while amphetamine and ephedrine are metabolized by oxidative deamination in humans, in rats it is metabolized by aromatic oxidation in Phase II reactions.

IV Disease: There are many diseases state that affect the metabolism of drugs. Examples of such diseases are Cirrhosis of liver, alcoholic liver disease, Cholestatic jaundice, diabetes mellitus, acromegaly, malaria etc. These diseases affect the liver and therefore affect rate of metabolism as liver is the most important site of drug metabolism. This diseases decrease enzyme activity in the liver, alter hepatic blood flow and cause hypoalbuminaemia (leads to lower plasma binding of drugs). Kidney diseases causes impairment in processes such as glycine conjugation of salicylates, oxidation of Vitamin D and hydrolysis of procaine

V Hormones: Hormonal imbalance causes an effect on metabolism of drugs. Higher level of one hormone may inhibit the activity of few enzymes while inducing the activity of others. Pituitary growth hormone and other related changes in Adrenocorticotropic Hormone decrease the rate of drug metabolism. Also the metabolism of promethazine and pethidine is reduced in women during pregnancy due to elevated levels of hormones like estrogen, progesterone, placental growth hormones and prolactin.

VI Genetics : Genetic factors accounts for 20 to 95 % of patient variability in drug metabolism. Genetic polymorphisms for many drug-metabolizing enzymes and drug targets have been discovered. Some of these genetic polymorphisms increase rate of drug metabolism while some do the opposite. Genetic factors account for the absorption distribution, metabolism, excretion, body weight, height rate, receptor sensitivity and sex variations in drug metabolism. This gives rise to distinct population phenotypes of persons who have metabolism ranging from extremely poor to extremely fast

External Factors of drug metabolism are the outside influences that affect the rate and process of drug metabolism. These external factors are:

I Diet : Enzyme content and activity is altered by a number of dietary components. Such dietary components are

a Protein : low protein diet decreases drug metabolism activity while high protein diet increases it as enzyme synthesis is promoted by protein diet

b Fats : Fat free diet depresses Cytochrome P-450 levels since phospholipids (important components of microsomes) becomes deficient.

c Vitamins : Deficiency of Vitamin A, B_2, B_3, C and E retard metabolic activity of enzyme

d Minerals : minerals deficiency of Fe (iron), Calcium, Magnesium, Zinc reduce metabolic activity of enzymes

e Grapefruit inhibits metabolism of many drugs and improve their oral bioavailability

f Starvation results in decrease in metabolism of drugs due to decreased amount of glucuronides formed.

II Environment : Several environmental agents influence drug metabolizing ability of enzymes. Examples are :

a Cigarette smoke (contains ~~halogenated pesticides such as Di~~ Poly aromatic hydrocarbons) have enzyme induction effect.

b Halogenated pesticides such as Dichloro-diphenyl-trichloroethane DDT have enzyme induction effect

c Organosulphate insecticides inhibit drugs metabolism

d Heavy metals like mercury, Nickel, Cobalt and arsenic inhibit drug metabolism

e Temperature, Altitude, Pressure and Atmosphere also influence drug metabolism.