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Discuss in details the factor affecting drug metabolism

ANS: Metabolism is a bio transformation or chemical alteration of a drug to other molecular species usually called the metabolites.

***FACTORS AFFECTING METABOLISM***

 A number of factors may influence the metabolic rate of drug. Some of them are:
1. CHEMICAL FACTOR

1. Enzyme induction-the phenomenom of increased drug metabolizing ability of enzyme by several drugs and chemicals is called as enzyme induction and the agents which brings about such an effect are called enzyme inducers.

Mechanisim of enzyme induction:

* Increase in both liver size and liver blood flow
* Increase in both total and microsomal protein content
* Increased stability of enzyme
* Decreased degradation of cytochrome p-450
* Proliferation of smooth endoplasmic reticulum

The consequences 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 hormones

Some examples of drug induction are:

ORAL STEROIDS CYP3A4 INACTIVE, EXCRETED

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1. Enzyme inhibition-A decrease in the drug metabolizing ability of an enzyme is called as enzyme inhibiton.The process of inhibition may be direct or indirect.
2. Direct Inhibition: It may result from interaction at the enzymatic site. The net outcome being a change in enzyme activity.
3. Indirect Inhibition: its caused by one of the following mechanism
4. Repression
5. Altered physiology

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

1. Enviromental chemicals-several environmental agents influence the drug metabolizing ability of enzyme. For example:
2. halogenated pesticides such as DDT and polycyclic aromatic hydrocarbons containednin cigarette smoke have enzyme induction effect.
3. Organophosphate insecticides and heavy metals such as mercury, nickel, cobalt and arsenic inhibit drug metabolizing ability enzyme.
4. Other environmental factors that may influence drug metabolism are temperature, altitude, pressure, atmosphere e.t.c

2. BIOLOGICAL FACTORS

a. age: the drug metabolic rate in the different age group differs mainly due to vr=ariation in the enzyme content, enzyme activity and hamodynamics.

> in neonates (up to 2 months) and infants (2 months to 1 year), the microsomal enzyme system is not fully developed .so many drugs are metabolized slowly.

 > children (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 the 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 dcreased metabolism of drugs.

b. diet: The enzyme content and activity is altered by a number of dietary components. Generally

> low protein diet decrease and high protein diet increase 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 microsome become deficient.

> grape fruit 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.

> starvation results in decreased amount of glucuronides formed than under normal condition

c. sex difference: Since variation 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. Several studies have shown that women on contraceptives pills metabolize a number 0f drugs at a slow rate.

d. species difference: species difference have been observed in both phase I and phase II reaction, both qualitative and quantitative variations in the enzyme and their activity have been observed. Qualitative differences among species generally result from the presense or absence of specific enzyme in those species. Quantitative differences result from variation in the amount of localization of enzymes, the amount of natural inhibitors and the competition of enzymes for specific substrate

e. strain difference: strain differences is under two headings which are the following:
I. PHARMACOGENETICS: A study of inter-subject variability in drug response is called pharmacogenetics. The inter-subject variations in metabolism may either be monogentically or polygenetically controlled. A polygenetic control is observed in twins.

II. ETHNIC VARIATION: Differences observed in the metabolism of drug among different races are called ethnic variations, such variations may be monophobic or polyphobic. Example approximately equal percent of slow and rapid acetylators are found among whites and blacks whereas the slow acetylators dominate Japanese and Eskimo populations

f. altered physiological factors:

1. PREGNANCY: Pregnancy is known to affect heptic drug metabolis. Physiological changes during pregnancy are probably rresponsible for the reported alteration in drug metabolism. These include elevated concentrations of various hormones such as estrogen, progesterones, placental growth hormones and prolactin. For example: in women, metabolism of promazine and pathidine in reduced during pregnancy.
2. DISEASES STATES: There are many diseases states that affect the metabolism of drugs. Some of them are cirrhosis of liver, alcoholic liver diseases, cholestatic jaundice, diabetes mellitus, acromegaly, malaria, various bacteria and viral infection infection, e.t.c. it can be seen that major effects are seen in the diseases 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).
1. HORMONAL IMBALANCE: higher level one hormone may inhibits the activity of few enzymes while inducing that of others. Adrenolectomy, thyroidectomy and aloxan-induced diabetes in animals showed impairment in the enzyme activity with subsequent fall in the rate of metabolism. A similar effect was also observed in the pituitary growth hormone and stress related changes in ACTH levels.

3.PHYSIOCHEMICAL PROPERTIES OF THE DRUG

Molecular size and shape pKa, acidity/basicity, lipophilicity and steric and electronic characteristics of a drug influence in interaction with the active size of enzyme and the metabolism to which it is subjected. However such as interrelationship is not clearly understood