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**LEVEL :300LEVEL**

**BCH ASSIGNMENT**

**Discuss in details the factors affecting drug metabolism**

1. Drug metabolism is the metabolic breakdown of drugs by living organisms, usually through specialized enzymatic systems. More generally, xenobiotic metabolism (from the Greek xenos "stranger" and biotic "related to living beings") is the set of metabolic pathways that modify the chemical structure of xenobiotics, which are compounds foreign to an organism's normal biochemistry, such as any drug or poison. These pathways are a form of biotransformation present in all major groups of organisms, and are considered to be of ancient origin. These reactions often act to detoxify poisonous compounds (although in some cases the intermediates in xenobiotic metabolism can themselves cause toxic effects). The study of drug metabolism is called pharmacokinetics.

**FACTORS AFFECTING DRUG METABOLISM**

There are several factors which affects drug metabolism and they include

* **internal**
  + species
  + genetic (strain)
  + age
  + sex
  + hormones
  + disease
* **external**
  + diet
  + environment

**INTERNAL FACTORS**

**Age**

The drug metabolic rate in the different age group differs mainly due to variation in the enzyme content, enzyme activity and haemodynamics

* In neonates (up to 2 months) and in infants ( 2months to 1 year) , the microsomal enzyme system is not fully developed .So, many drugs are metabolized slowly .For eg : caffeine has a half life of 4 days in neonates in comparison to 4hrs in adults
* Children ( between 1 year and 12year) metabolize several drugs much more rapidly than adults as the rate of metabolism reaches a maximum somewhere between 6 months and 12years. As a result they require large mg/ kg dose in comparison to adults
* In elderly persons, the liver size is reduced the microsomal enzymes 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 chlomethiazole shows a high bioavailability within the elderly, therefore they require a lower dose

**SEX**

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 make rats have greater drug metabolizing capacity. In humans, women metabolize benzodiazepines slowly than men. Several studies have shown that women on contraceptive pills metabolize a number of drugs at a slow rate

**SPECIES**

Species difference have been observed in both phase 1 and phase 2 reactions.In Phase 1 reaction, both qualitative and quantitative variations in the enzyme and their activity have been observed. Qualitative difference among species generally result from the presence or absence of specific enzyme in those species. Qualitative difference results from variations in the amount of localization of enzymes, the amount of natural inhibitors, and the competition of enzymes for specific substrate.

Human liver contains less cytochrome P-450 per gram of tissue than do the livers of other species. for example, rat liver contains approximately 30-50nmol/g of cytochrome P-450, whereas human liver contains 10-20nmol/g. Furthermore, human liver is 2 percent of body weight, whereas rat liver is approximately 4 percent

Similarly, In men, amphetamine and ephredine are predominantly metabolized by oxidative deamination, whereas in rats aromatic oxidation is the major route is phase 2 reactions .

Similarly in pigs, the phenol is excreted mainly as glucoronides whereas its sulphate conjugate dominates in cats.

**STRAIN**

Just as the difference in drug metabolizing Ability between different species is attributed to genetics, the difference are observed between strains of same species also. It may be studied under two headings

* Pharmacogenetics: A study of inter- subject variability in drug response is called pharmacogenetics. The inter-subject variation in metabolism may either be monogenetucally or polygenetically controlled. A polygenetically control is observed in twins. In identical twins , very little or no halothane, phenylbutazone, dicouramaral and antipyrine was detected but large variations were observed in fraternal twins
* Ethnic variations: Difference observed in the metabolism of drugs among different races are called with ic variations . Such variations may be monomorphic or polymorphic .

**HORMONES:** Cytochrome P450 (CYP) is a group of enzymes that metabolize drugs to a more water-soluble form, rendering them available for renal excretion. The major site of CYP expression is the liver. Nearly 50% of all medications currently on the market are metabolized by the enzyme CYP3A4, while metabolism of another 35-40% occurs through enzymes CYP1A2, CYP2C19, CYP2D6, CYP3A5 CYP3A6, and CYP3A7. Here, we summarize the current knowledge of the effects of hormones on the CYP family.

The term "hormone" is used in its broad sense and includes products of the major endocrine glands (i.e., thyroid, adrenals, gonads, pancreas) and compounds that are not classically considered hormones, such as neurogenic amines, cytokines, interleukins, and eicosanoids. In addition, we comment on the effects on CYP expression of states associated with profound hormonal changes, such as pregnancy, malnutrition, obesity, diabetes mellitus, systemic inflammation, and conditions of altered extracellular fluid volume or osmolality. Available data are limited and are derived primarily from in vitro and animal studies. Moreover, the picture is obscured by conflicting results among studies and the complexity of the regulation of the expression and activity of elements of the CYP system. While the clinical significance of hormonal effects on the CYP system remains to be determined, we anticipate that such effects will be most pertinent to drugs with a narrow therapeutic range. Further research is needed to determine the scope and significance of these effects in view of rapid advances in the field of pharmacogenomics and the ever-increasing number of drugs available for therapeutic use.

**EXTERNAL FACTORS**

**DIET**

This enzymes content and activity is altered by a number of dietary components. generally

Low protein diet decrease and high protein diet increases the drug metabolizing ability as enzyme synthesis is promoted by protein diet and also raids the level of amino acids for conjugation with dugs

Fat free diet depresses cytochrome p-450 levels since phospholipids, which are important components of microsomes before deficient

Grapefruit inhibit 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 Fe, Ca, Mg, Zn retard the metabolic activity of enzymes

Starvation results in decreased amount of glucoronides formed than under normal conditions

**ENVIRONMENT**: Pesticides are major xenobiotic compounds and environmental pollutants, which are able to alter drug-metabolizing enzyme as well as pharmacokinetics of drugs. Subsequent to the release of the human genome project, genetic variations (polymorphism) become an integral part of drug development due to their influence on disease susceptibility/ progression of the disease and their impact on drug absorption, distribution, metabolism of active metabolites and finally excretion of the drug. Genetic polymorphisms crucially regulate pharmacokinetics and pharmacodynamics of drugs under the influence of physiological condition, lifestyle, as well as pathological conditions collectively.