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**Course Title: Medical Biochemistry**

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**Assignment**

1. Discuss **i**n details the fact**o**rs affecting d**ru**g metabolism.

**Answer**

Fact**o**rs affecting d**ru**g metabolism are divided into two, namely;

**1). Internal Factors**

* + Species differences
  + Genetic (Strain) differences
  + Age
  + Sex differences
  + Hormones
  + Disease

**2).External Factors**

* + Diet
  + Environment

**1). Internal Factors**

**a). Species Differences**

The species difference can be observed in both the phase I and phase II metabolism and can be either quantitative (same metabolic route but differing rates) or qualitative (differing metabolic routes). Among species, the qualitative differences in result generally from the presence of absence of specific enzymes in those species. The quantitative differences result from the variations in the amount and localization of enzymes, the amount of natural inhibitors and the competition of enzymes for specific substrates. The human liver contains less cytochrome P-450 per gram of tissue than the livers of other species. For example, in humans, amphetamine and ephedrine are predominantly metabolized by oxidative deamination, whereas in rats aromatic oxidation is the major route in Phase-II reactions. Different species can differ in their routes of metabolism as well as in the rates at which the Metabolism occurs. In general, drug metabolism in non-mammalian species is lower than in mammals. Species differences in drug metabolism are important to industries involved in testing new chemicals, such as drugs, in order to achieve a suitable model of human toxicity. For such purposes an animal model is required that as nearly as possible mimics the metabolism of the compound seen in man.

**b). Genetic (strain/racial) differences**

Differences In d**ru**g metabolism, such differences exist within species. It is becoming apparent that most genetic differences in drug metabolism arise because of the presence of genes coding for different enzymes. A variation in drug metabolism may be either monogenetically or polygenetically controlled. A polygenetic control is observed in twins. In identical twins (monozygotic), there is little or no difference in metabolism of halothane, phenylbutazone, dicoumaral and antipyrine but large variations were observed in the fraternal twins (dizygotic). Racial differences can also bring about differences in drug metabolism, which can either 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.

**c). Age**

The rate of drug metabolism in the different age groups differs mainly due to variations in the enzyme content, enzyme activity and haemodynamics. The major site of drugs metabolism is the liver. In neonates and infants (2 months to 1 year), the microsomal enzyme system is not fully developed. Therefore, many drugs are metabolized slowly. For example: caffeine has a half-life of 4 days in neonates but 4 hours in adults. In elderly humans, the liver size is reduced, the microsomal enzyme activity is decreased and hepatic blood flow also declines as a result of reduced cardiac output and altered plasma binding of drugs, all of which contributes to decreased metabolism of drugs.

**d). Sex difference**

Variations in sex difference are observed following puberty. This is due to the sex hormones produced in the male and female. The male have greater drug metabolizing capacity than female. Androgens are the regulators of the sex differences. The male have more androgens than the female. The perinatal androgen 'imprints' a pattern of growth hormone secretion from the pituitary gland and it is this male or female pattern of growth hormone secretion that gives the sex differences in drug metabolism. With respect to cytochrome P450-dependent drug oxidation, the differing patterns of growth hormone (GH) are known to cause the induction or repression of particular isoenzymes of cytochrome P450. For instance the female pattern of growth hormone (GH) (a continuous low level of hormone) gives a reduction in cytochrome P4502Cll and an increase in 2Cl2 by altering the transcription of the particular gene. For example, in humans, women metabolize benzodiazepines slowly than men. Sex differences in drug metabolism are of great importance when dealing with rats, mice and some farm animal (e.g. goats) but seem to be of less importance in a clinical context.

**e). Hormones**

In humans, the thyroid gland has also been implicated in the control of drug metabolism. For the limited number of substrates used (antipyrine, paracetamol and aspirin), thyroidectomy always decreases their apparent metabolism. Phase II metabolism can also be affected by thyroidectomy. Sulfation and gamma-glutamyltranspeptidase activities are thyroid-dependent. The pancreas produces and secretes one hormone of particular relevance to the control of drug metabolism, i.e. insulin. Diabetes mellitus (a reduction in the amount or action of insulin caused by genetic abnormalitie or chemically induced by means of streptozotocin administration) causes marked changes in hepatic phase I and II metabolism.

**f). Disease**

The major effects are seen with diseases affecting the liver. This is hardly surprising as the liver is quantitatively the most important site of drug biotransformation. Other diseases, however, such as infections and endocrine disorders are also important when looking at drug metabolism. In cirrhosis, parts of the liver are replaced by fibrous tissue and the number of functional hepatocytes is reduced. Drug metabolism is impaired in this condition and, indeed,the oxidative metabolism of chlordiazepoxide to its primary metabolite, desmethylchlordiazepoxide is slower in cirrhotic patients. n Alcoholic liver disease, Chronic alcohol administration can lead to a condition similar to that of cirrhosis with large portions of the liver replaced by fibrous masses following the death of the parenchymal cells. Before this stage is reached, however, alcohol administration can markedly affect drug metabolism in different ways. Acute ethanol exposure in general decreases drug metabolism such that drugs metabolised primarily by phase I routes e.g. chlordiazepoxide, diazepam, aminopyrine, pentobarbitone and chlorpromazine or phase II routes e.g. lorazepam, p-nitrophenol, harmol and paracetamol exhibit longer half-lives if administered with ethanol.

**2).External Factors**

**a). Diet**

The enzyme content and activity is altered by a number of dietary components. Generally, low protein diet deceases and high protein diet increases the drug metabolising 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 vitamins (A, B2, B3, C and E) and minerals such ad Fe, Can, Mg, Zn retard the metabolic activity of enzymes. Starvation results in decreased amount of glucuronides formed than under normal conditions.

**b).Environment**

Environmental factors are those influences in our surroundings that can affect drug metabolism. 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 metabolising ability of enzymes. Other environmental factors that may influence drug metabolism are temperature, altitude, pressure, atmosphere, e.t.c.