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**Course:** Biochemistry

1. Discuss in details the factors affecting drug metabolism

There are different factors that can affect drug metabolism and they are:

a.)**Intrinsic factors:** These factors are ;

i.) **Age**:- It has been observed that the newborn, young and elderly display marked differences in drug biotransformation and are more susceptible to drug action. These differences are chiefly due to the enzymatic systems involved in drug biotransformation and the development of their metabolising capacity. Thus, the increased sensitivity of neonates may be related to their very low, undeveloped metabolising capacity, until adult levels of enzyme activity are achieved. On the other hand, in the elderly, the decrease in drug-metabolising capacity also appears to be dependent on these factors, important changes in the overall metabolism occurring with ageing. Age can affect drug metabolism. The enzymes involved in both phase 1 and phase 2 metabolism mature gradually following the first 2 to 4 weeks following postpartum. Full maturity appears in the second decade of life with a subsequent slow decline in function associated with aging. The overall decrease of metabolic clearance is around 1% per year. The Drugs that were investigated with respect to the role of drug metabolising enzymes and the effects of age included different alkylphenoxazone derivatives, benzodiazepines and neuroleptics, bisphosphonates (BPs) as therapeutic drugs for osteoporosis, anxiolytics and others

ii.) **Species**:- An example is the total metabolism of caffeine is highest in humans decreasing in the order- monkey, rat and rabbit. Another example is that of species variation in hexobarbitone metabolism affecting half-life and sleeping time. Investigations were carried out on man, dog, mice and rat, The longest half-time was registered for man (~360 min). The sleeping time increased in the order: mice, rats, dogs and man. The biotransformation of this drug is inversely related to the half-time and duration of action of the drug. Another example is a study was performed to investigate the maintenance of drug-metabolising capacities in collagen gel sandwich and immobilisation cultures of human and rat hepatocytes. L-proline was added to the medium to improve albumin secretion. As far as most important phase I enzyme systems are concerned, namely the cytochrome P450- dependent monooxygenase (CYP) and microsomal epoxide hydrase (mEH) systems, comparative measurements of enzyme activities in the absence and presence of L-proline, revealed that their biotransformation enzyme activities were not affected by the addition of L-proline. Instead, the activity of an important phase II enzyme, GST, was decreased in rat hepatocytes, whereas in humans it remained almost unchanged. As human hepatocytes showed a better maintenance of GST activities than the rats in the presence of L-proline, species differences were again demonstrated.

iii.) **Sex**:- This was initially observed when researchers noticed that female rats required only half the dose of a barbiturate compared to male rats to induce sleep. Later observations indicated that this was due to the reduced capacity of the female to metabolise the barbiturates. As an example, I am going to refer to such a combined study for the in vitro investigation of sex and species differences in the metabolism of BOF-4272, a drug intended for the treatment of hyperuricaemia. Rats, mice and monkeys of both sexes were used in the study. The results of the investigations made on various incubation mixtures revealed that both the pathways involved (i.e. types of metabolites resulting) as well as the rates of biotransformation of the tested drug were significantly influenced by both sex and species differences.

iv.) **Pathological factors(diseases):**- Disorders in the body affect drug metabolism, for example, In Cirrhosis, replacement of parts of the liver by fibrous tissue leads to a reduction in the number of functional hepatocytes. In this situation, it seems absolutely reasonable that drug metabolism should be impaired. Considering the liver as the main location for the most important enzymatic systems, it is expected on the other hand that in patients with liver diseases, drug metabolism should be impaired.

V.) **Hormonal control of drug metabolism**:- Hormones are known to play a major role in the general metabolism and have been proven to control the biotransformation of drugs in direct connection with other factors such as age, sex or in particular physiological states such as pregnancy. A sex and age connection with the control of the growth hormone (GH) was the focus of interesting cDNA cloning investigations [83,84]. The study examined especially cytochrome P450, it being established that GH is involved in the control of rat hepatic drug- and steroid-metabolism, particularly through the action of this enzymatic system. The results showed low levels of CYTP450 in neonates, and an increase after one month, both in male and female rats. At adult stage, important sex differences were recorded, in female rats the content being about three times higher than in male rats.

**b.) Environmental factors**:- These are the influences in our surroundings that can affect drug metabolism sometimes. There are a large number of environmental chemicals that potentially could affect drug biotransformations, usually grouped into heavy metals, industrial pollutants and pesticides. The most important industrial pollutants are typically aromatic or aromatic polycyclic compounds and polychlorinated biphenyls. Pesticides are also of various types (insecticides, herbicides), and are considered environmental contaminants in air, soil, water and food. Many of these have been already discussed under different circumstances (inductive enzyme effects, procarcinogenic effects).