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QUESTION: DISCUSS IN DETAILS THE FACTORS AFFECTING DRUG METABOLISM

ANSWER: Drug metabolism refers to the metabolic breakdown or biotransformation of drugs via enzymatic systems into metabolites. The primary site for this process is the liver bit it can also take place in the kidney, intestines, lungs and plasma. There are various factors that determined the rate of drug metabolism which include:

**Enzyme Induction:** this is a situation where the drug induces or increases the expression of an enzyme. The rate of metabolism increases here but the duration and intensity of the drug will be reduced. The mechanism of enzyme induction includes:

1. Increase in size of liver
2. Increasing stability of enzymes
3. Increase in stability of cytochrome-P450
4. Decrease in degradation of cytochrome-P450
5. Proliferation of smooth endoplasmic reticulum

Enzyme induction causes increased activity where the metabolites are active, decreases the pharmacological activity of the drug and alters the physiological status due to enhanced metabolism of endogenous compounds such as sex hormones

**Enzyme Inhibition**: this refers to the decrease in the drug metabolizing ability of an enzyme. The rate of metabolism is reduced but the intensity and donation of the drug is increased. It can be direct or indirect. Direct enzyme inhibition occurs as a result of interaction with the enzymatic site causing a change in enzymatic activity. Indirect enzyme inhibition can be due to reduced enzyme level or due to nutritional deficiency and hormonal imbalance.

**Environmental Chemicals**: these refer to chemical agents like pesticides, insecticides, etc. Halogenated pesticides like polycyclic aromatic hydrocarbons have enzyme induction effect, organophosphate insecure have enzymes induction effect. Other environmental factors that may affect drug metabolism include temperature, pressure, etc.

**Age**: Generally, drugs are metabolized more slowly in fetal, neonatal and elderly humans that in adults. This is mainly due to enzymes content, enzyme activity and hemodynamics. The neonates don’t have their microsomal system fill developed thereby reducing drug metabolism rate. The elderly have reduced liver size meaning the microsomal enzymes are reduced and so is drug metabolism.

**Diet**: a low protein diet decreases drug metabolism rate while a high protein diet increases it since more among acids will be available for conjugation. A fat free diet reduces cytochrome P-450 levels due to reduced available phospholipids. Lack od vitamins and minerals reduce the metabolic activity of enzymes.

**Sex Differences**: this may be due to sex hormones. Studies have shown that women on contraceptive metabolize a lot slower than men. Women generally metabolize benzodiapones slower than men.

**Strain/Genetic Variation:** this can be divided into pharmacogenetics and ethnic variations. Pharmacogenetics deals with inter-subject variations in metabolism which can be controlled monogenetically or polygenetically. Ethnic variations deals with differences in metabolism among different races. It can be polymorphic or monomorphic. Example, with N-acetyltransferases (involved in phase II reactions), individual variation creates a group of people who acetylate slowly (slow acetylators) and those who acetylate quickly. This variation may have dramatic consequences, as the slow acetylators are more prone to dose-dependent toxicity. Approximately equal percent of slow and rapid acetylators are found in blacks and whites while the slow acetylators are dominated by the Japanese and Eskimo population.

**Species Variation**: it can either be classified under qualitative or quantitative variations of the enzyme. Qualitative variation has to do with the presence or absence of specific enzymes in a particular specie. Quantitative variation has to do with the number present or localization of the enzymes needed. An example is how humans contain lower level of cytochrome P-450 per gram if tissue than liver of other species.

**Physiochemical Properties of the Drug**: during interaction with active sites of the enzyme and metabolism, features such as molecular size biological half-life, pKa, acidity/basicity, lipophilicity, etc. are taken into consideration.

**Pathophysiology**: there are many diseases that affect drug metabolism most of which are liver related. They include liver cirrhosis, alcoholic liver disease, jaundice, diabetes mellitus, malaria, acromegaly. They may cause decreased enzymatic activity, alter hepatic blood flow and cause hypoalbuminaemia which reduces plasma binding of drugs.