NAME: ALFA UNEKWU-OJO MICHELLE

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ASSIGNMENT

**FACTORS AFFECTING DRUG METABOLISM**

Many factors affect the rate and pathway of metabolism of drugs, and the major influences can be sub-divided into internal (physiological and pathological) and external (exogenous) factors as indicated below:

Internal: species, genetic (strain), sex, age, hormones, pregnancy, disease.

 External: diet, environment.

Metabolism is a biotransformation or chemical alteration of a drug to other molecular species usually called the metabolites, ithin the body via an enzymatic or non-enzymatic process. The primary site for drug metabolism is liver, and other sites are kidney, intestine, lungs and plasma.

**Factors affecting metabolism**

A number of factors may influence the metabolic rate of a drug. Some of them are;

1. Chemical factors
2. Enzyme induction
3. Enzyme inhibition
4. Environmental chemicals
5. Biological factors
6. Age
7. Diet
8. Sex difference
9. Species difference
10. Strain difference
11. Altered physiological factors
12. Physiochemical properties of the drug
13. **Enzyme induction**

The phenomenon of increased drug metabolizing ability of enzymes by several drugs and chemicals is called as enzyme induction and the agents which bring about such an effect called enzyme inducers.

Consequences of enzyme induction 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 sex hormones
1. **Enzyme inhibition**

A decrease in the drug metabolizing ability of an enzyme is called as enzyme inhibition. It may result from interaction at the enzymic site, due to fall in the rate of enzyme synthesis or rise in the rate of enzyme degradation or nutritional deficiency or hormonal imbalance, the net outcome being a change in enzyme activity.

1. **Environmental chemicals**

Several environmental agents influence the drug metabolizing ability of enzymes. For example:

* Halogenated pesticides such as DDT and polycyclic aromatic hydrocarbons contained in cigarette smoke have enzyme induction effect
* Organophospate insecticides and heavy metals such as mercury, nickel, cobalt and arsenic inhibit drug metabolizing ability of enzymes
* Other environmental factors that may influence drug metabolism are temperature, altitude, pressure, atmosphere, etc.

 **Biological factors**

**a. Age**

The drug metabolism rate in the different age groups differs mainly due to variations in the enzyme content, enzyme activity and haemodynamics. In neonates and infants, the microsomal enzyme system is not fully developed. So, many drugs are metabolized slowly.

Children (between 1 to 12 years) metabolize several drugs much more rapidly than adults as the rate of metabolism reaches a maximum somewhere between 6 months to 12years.

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 decreased metabolism of drugs.

**b. Diet**

The enzyme content and activity is altered by a number of dietary components.

* Low protein diet decreases and high protein diet increases the drug metabolizing ability
* Fat free diet depresses cytochrome P450 levels since phospholipids which are important components of microsomes become deficient
* Grapefruit inhibits metabolism of many drugs and improve their oral bioavaliabilty
* Dietary deficiencies of vitamins like (vitamin A, B2, B3, C and E) and minerals (such as Fe, Ca, Mg, Zn) retard the metabolic activity of enzymes

**c. Sex difference**

Sex related differences in the rate of metabolism may be due to sex hormones. 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.

1. **Species difference**

Species difference have been observed in both phase I and phase II reactions. In phase I reactions, both qualitative and quantitative variations in the enzyme and their activity have been observed. Qualitative differences among species generally result from the absence or presence of specific enzymes in those species. Quantitative differences result from variations in the amount and localization of enzymes, the amount of natural inhibitors, and the competition of enzymes for specific substrates.

1. **Strain difference**

Just as the difference in drug metabolising ability between different species is attributed to genetics, the differences are observed between strains of same species also. There are differences observed among different races.

Example: approximately equal percent of slow and rapid acetylators are found among whites and blacks whereas the slow acetylators dominate Japanese and Eskimo population.

1. **Altered physiological factors**

Pregnancy is known to affect hepatic drug metabolism. There are many disease states that affect the metabolism of drugs. Some of them are cirrhosis of liver, alcoholic liver disease, cholestatic jaundice, diabetes mellitus, acromegaly, malaria, various bacterial and viral infections, etc.

Higher level of one hormone may inhibit the activity of few enzymes while inducing that of others.

**Physiochemical properties of the drug**

Molecular size and shape, pKa, acidity/basicity, lipophilicity, steric and electronic characteristics of a drug influence interaction with the active sites of enzyme and the metabolism to which it is subjected.