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**BIOCHEMISTRY ASSIGNMENT**

**ASSIGNMENT TITLE: XENOBIOTICS**

**COURSE CODE: BCH 313**

**QUESTION**

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

**INTRODUCTION**

Metabolism is a biotransformation or chemical alteration of a drug to other molecular species usually called metabolites, within 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.

Metabolism of a drug may lead to:

* Inactivation: most drugs get inactive due to metabolism, eg: Ibuprofine, paracetamol
* Active metabolite form an active drug: Eg: Codeine – morphine, pyrimidine - phenobarbitone
* Activation of an inactive drug: Eg: Levodopa-dopamine, prednisone-prednisolone

**Metabolic Enzymes:**

For a drug to be metabolized, it requires various enzymes which can be broadly divided into two categories:

1. Microsomal Enzymes: this enzyme is located on smooth endoplasmic reticulum in liver, kidney, lungs and intestinal mucosa eg: Cytochrome p450, monoxygenase, glucurunyl transferase, etc. This type of enzyme catalyse oxidative, reductive, hydrolytic and glucuronidation reactions.
2. Nonmicrosomal Enzymes: This enzyme is present in cytoplasm and mitochondria of hepatic cells and plasma eg: flavoprotein oxidase, esterase, amidase and conjugase. This enzymes catalyses all conjugations, many hydrolytic reactions and some oxidation and reduction reactions.

**Factors Affecting Metabolism**

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. **Chemical Factors**
14. **Enzyme induction:**

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

Mechanism of enzyme induction:

* Increase in both liver size and liver blood flow
* Increase in both total and microsomal protein content
* Increased stability of enzymes
* Increased stability of cytochrome p450
* Decreased degradation of cytochrome p450
* Proliferation of smooth endoplasmic reticulum

 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 enzyme inhibition. The process of inhibition may be direct or indirect.

1. Direct inhibition: it may result from interaction at the enzymatic site, the net outcome being a change in enzyme activity. Direct enzyme inhibition can occur by one of the following mechanisms:
2. Competitive inhibition: occurs when structurally similar compounds compete for the same site on an enzyme.
3. Non- competitive inhibition: occur when a structurally unrelated agent interacts with the enzyme and prevents the metabolism of drugs.
4. Product inhibition: occurs when the metabolic product competes with the substrate for the same enzyme
5. Indirect inhibition: it is caused by one of the following mechanism:
6. Repression: it may be due to fall in the rate of enzyme synthesis or rise in the rate of enzyme degradation.
7. Altered physiology: it may be due to nutritional deficiency or hormonal imbalance
8. **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 make enzyme induction effect.
* Organophosphate 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.

**2. Biological factors**

**a.) Age**

The drug metabolic rate in the different age groups differs mainly due to variations in the enzyme content, enzyme activity and haemodynamic.

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

**b.) Diet**

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

* Low protein diet decreases and high protein diet increases the drug metabolizing ability as enzyme synthesis is promoted by protein diet and also raise the level of amino acids for conjugation with drugs.
* Fat free diet depresses cytochrome p450 level 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 vitamin 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 glucuronides formed than under normal conditions.

**c. ) Sex difference**

Since variations 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 situated in rats where male rats have greater metabolizing capacity. In humans, women metabolize benzodiazepins slowly than men. Several studies have shown that women on contraceptive pills metabolize a number of drugs at a slow rate.

1. **Altered physiological factors**
2. **Pregnancy**

Pregnancy is known to affect hepatic drug metabolism. Physiological changes during pregnancy are probably responsible for the reported alteration in drug metabolism. These include elevated concentrations of various hormones such as estrogen, progesterone, placental growth hormones and prolactin. For example: in women, the metabolism of promazine and pethidine is reduced during pregnancy.

1. **Disease states**

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. It can be seen that major effects are seen in the disease affecting the liver is quantitatively the important site for metabolism. The possible cause in the effect of metabolism due to diseases may be:

* Decreased enzyme activity in liver
* Altered hepatic blood flow
* Hypoalbuminaemia (leading to lower plasma binding of drugs)
1. **Hormonal imbalance**

Higher level of one hormone may inhibit the activity of few enzymes while inducing that of others. Adrenolectomy, thyroidectomy and alloxan-induced diabetes in animals showed impairment in the enzyme activity with subsequent fall in the rate of metabolism. A similar effect was observed in the pituitary growth hormone and stress related changes in ACTH levels.

**3. Physiochemical properties of the drug**

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

**Conclusion**

The therapeutic efficacy, toxicity and biological half life of a drug greatly depends on the metabolism of the drug and a number of factors affect the metabolism of the drug. Hence various factors affecting drug metabolism must be considered during administration and also in proper dosing of any drug to the patients.