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**COLLEGE OF MEDICINE AND HEALTH SCIENCES**

**MEDICINE AND SURGERY**

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**BIOCHEMISTRY ASSIGNMENT**

Discuss in details the factors affecting drug metabolism.

Drugs can be metabolised by many different pathways and many factors can determine which pathway is used by which drug and to what extent a particular drug is biotransformed by a particular pathway. The relative amount of any particular metabolite is determined by the concentration and activity of the enzyme(s) responsible for the biotransformation as well as dose, frequency, route of administration, tissue distribution and protein binding of the drug. The rate of metabolism of a drug is particularly important for its pharmacological action as well as its toxicity. Decreased metabolic elimination may lead to accumulation of toxic levels of the drug. Conversely, an increased rate of metabolism decreases the intensity and duration of action as well as the drug's efficacy. These factors range from the species of organism studied to the environment in which that organism lives. Factors affecting drug metabolism can be split into the internal which are physiological and pathological factors and the external factors.

The following are the internal factors;

* genetic
* Enzyme induction and enzyme inhibition.
* sex
* age
* disease
* hormones
* species

The following are the external factors;

* diet
* environment

**SOME INTERNAL FACTORS**

**Hereditary or Genetic Factors:** Marked individual differences in the metabolism of several drugs exist in humans. Many of these genetic or hereditary factors are responsible for the large differences seen in the rate of metabolism of these drugs. Genetic factors also appear to influence the rate of oxidation of drugs such as phenytoin, phenylbutazone, dicumarol, and nortriptyline. The rate of oxidation of these drugs varies widely among different individuals; however, these differences do not appear to be distributed bimodally, as in acetylation. In general, individuals who tend to oxidize one drug rapidly are also likely to oxidize other drugs rapidly. Numerous studies in twins (identical and fraternal) and in families indicate that oxidation of these drugs is under genetic control.

Many patients state that they do not respond to codeine and codeine analogs. It now is realized that their CYP2D6 isozyme does not readily O-demethylate codeine to form morphine.

**Enzyme Induction:** The activity of hepatic microsomal enzymes, such as the CYP mixed-function oxidase system, can be increased markedly by exposure to diverse drugs, pesticides, polycyclic aromatic hydrocarbons, and environmental xenobiotics. The process by which the activity of these drug-metabolizing enzymes is increased is termed enzyme induction. The increased activity is apparently caused by an increased amount of newly synthesized enzyme. Enzyme induction often increases the rate of drug metabolism and decreases the duration of drug action.

Inducing agents may increase the rate of their own metabolism as well as those of other unrelated drugs or foreign compounds. Concomitant administration of two or more drugs often may lead to serious drug interactions as a result of enzyme induction. For instance, a clinically critical drug interaction occurs with phenobarbital and warfarin. Induction of microsomal enzymes by phenobarbital increases the metabolism of warfarin and, consequently, markedly decreases the anticoagulant effect. Therefore, if a patient is receiving warfarin anticoagulant therapy and begins taking phenobarbital, careful attention must be paid to readjustment of the warfarin dose. Dosage readjustment is also needed if a patient receiving both warfarin and phenobarbital therapy suddenly stops taking the barbiturate. The ineffectiveness of oral contraceptives in women on concurrent phenobarbital or rifampin therapy has been attributed to the enhanced metabolism of estrogens (e.g., 17a-ethinylestradiol) caused by phenobarbital513 and rifampin514 induction.

Mechanisms 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 P-450
* Decreased degradation of cytochrome P-450
* 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. Some examples of drug induction are: Oral Contraceptive Steroids CYP3A4 Inactive, Excreted Induction 3 Rifampin

**Diseases**:While drug metabolism can occur in other organs, the primary site of drug metabolism is the liver, as the enzymes that facilitate the reactions are concentrated there. Cytochrome P450 refers to a family of liver enzymes that play an important role in drug metabolism. The activity of these enzymes varies depending on people’s age and genetic predisposition. Also, a number of cytochrome P450 mutations have been observed which can affect the rate of drug metabolism and thus affect the patient's response to treatment. Once the drug has been converted to an inactive substance through metabolism, the body must excrete it. The kidneys are the main organs of the body’s excretory system. However, small amounts of the drug can also be excreted in the bile and through minor excretion routes, such as sweat, saliva, exhalation, etc.

This implies that any damage to these organs will affect its function. Inability of the liver to metabolize drugs due to diseases such as cirrhosis or hepatitis and inability of the kidney(Nephritis) and other parts of the body to excrete said drugs following (or in the absence of) metabolism, leads to accumulation of the drug and its metabolites in the body which will have adverse effects on the body. Failure to metabolize a drug will lead to increase in the duration and intensity of drug action.

**EXTERNAL FACTORS**

**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 as enzyme synthesis is promoted by protein diet and also raiss 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.

**Environmental chemicals:** Several environmental agents influence the drug metabolizing ability of enzymes through induction. 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 metabolizing ability of enzymes.

**Pregnancy: (altered physiological factor):** 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. It was also confirmed by the study in animals. In pregnant Sprague-Dawley rats, hexobarbital biotransformation indicated unchanged or slightly elevated microsomal enzyme activity compared to normal rats.