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 BIOCHEMISTRY ASSIGNMENT

 FACTORS AFFECTING DRUG METABOLISM

1. Chemical factors

•Enzyme induction

•Enzyme inhibition

•Environmental chemical

1. Biological factors

• Age

• Sex difference

• Diet

• Species difference

• Strain difference

•Altered physiological factors

1. Physicochemical properties of the drug

Chemical factors

Enzyme induction; the phenomenon of increased drug metabolizing ability of enzymes by several drugs and chemicals. The agents which bring about such effects are called enzyme induces.

Mechanism of enzymes induction

▪ increase in both liver size and liver blood flow

▪ increase in both liver total and microsomal protein content

▪ increased stability of enzymes

▪increased stability of cytochrome p-450

▪Proliferation of smooth endoplasmic reticulum

Consequences of enzymes induction includes;

* 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:

 CYP3A4

$Type equation here.$Oral contraceptive steroids ------------------ inactive

 Induction Excreted

 Rifampin

Enzyme inhibition; a decrease in drug metabolizing ability of an enzyme. The process of inhibition might be direct or indirect.

Direct inhibition: it may result from an interaction at the endemic site, the net outcome being a change in enzyme activity. Direct enzyme inhibition can occur by one of the following mechanisms:

1. Competitive inhibition: occurs when structurally similar compounds compete for the same site on an enzyme
2. Non-competitive inhibition: occurs when a structurally unrelated agent interact with the enzyme and prevents the metabolism of drugs
3. Product inhibition: occurs when the metabolic products competes with the substrate for the same enzyme

Indirect inhibition: it is caused by one of the following mechanism

1. Repression: it may be due to the fall in the rate of enzyme synthesis or rise in the rate of enzyme degradation
2. Altered physiology: it may be due to nutritional deficiency or hormonal imbalance

Some examples of enzyme inhibition include:

Terfenadine ------------------ Active antihistamine

 Inhibition

 Erythromycin ketaconazole

Enzyme inhibition is more important clinically than enzyme induction especially for drugs with narrow therapeutic index. E.g. anticoagulant, antiepileptic, hypoglycemia, etc.

Environmental chemicals: several environmental agents influence the Drug metabolizing ability of enzyme. 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 .

☆. Other environmental factors that may influence drug metabolism are temperature, altitude, pressure, atmosphere, etc.

Biological factors

Age: the drug metabolic rate in 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 1 year), the microsomal enzyme system is not fully developed, so many drugs are metabolized slowly. For example caffeine hard half life of 4 days in neonates and 4 hours 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 result they require 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 contributes to decreased metabolism of drugs. For example, chlomethiazole shows a high bioavailability within the elderly, therefore they require a lower dose.

Diet: the enzyme content and activity is altered by a number of dietary components.

■. Low protein diet decreased and high protein diet increases the drug metabolizing ability as enzyme synthesis is promoted by protein diet and also raises the level of amino acids for conjugation with drugs.

■. Fat free diet depresses cytochrome p-450 levels since phospholipid, which are important components of microsomal become deficient.

■. Grape fruits inhibit 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.

Sex differences: it may be due to sex hormones. Several studies have shown that women on contraceptive pills metabolize a number of drugs at a slower rate. Women metabolize benzodiazepines slowly than men.

Species difference: qualitative differences among species generally result from the presence or absence 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. Human liver contains less cytochrome p-450 per gram of tissue than do the livers of other species. For example, rat liver contains approx. 30to 50 nmol/g of cytochrome p-450 whereas human liver contains 10 to 20 nmol/g. Furthermore, human liver is 2% of body weight whereas rat live sis approx. 4%. Similarly in pigs, the phenol is excreted mainly as glucuronides whereas its sulphate conjugate dominates in cats.

Strain difference: approximately equal percent of slow and rapid acetylators are found among white and black where as slow acetylators dominate the Japanese and Eskimo population.

Altered physiological factors:

Pregnancy is known to affect hepatic drug metabolism. The metabolism of promazine and pethidine is reduces during pregnancy. Disease states and hormonal imbalance also affect drug metabolism

 Physicochemical properties of the drug

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