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QUESTION

Discuss in details the factors affecting drug metabolism.

FACTORS AFFECTING DRUG 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. Physicochemical properties of a drug.

CHEMICAL FACTORS

1. Enzyme induction- this is the increased drug metabolizing ability of enzymes of several drugs and chemicals and this is brought about by agents called enzyme inducers. Mechanisms of enzyme induction are:
2. Increase in both liver size and liver blood flow
3. Increased stability of enzymes
4. Increased stability of cytochrome P-450
5. Decreased degradation of cytochrome P-450
6. Proliferation of the smooth endoplasmic reticulum

Consequences of enzyme induction include:

1. Increased activity where the metabolites are active
2. Decrease in pharmacological activity of drugs
3. Enzyme Inhibition- this is the opposite of enzyme induction. It is the decrease in the drug metabolizing ability of enzymes. The inhibition could be direct or indirect.

**Direct Inhibition**- this may result from interaction at the enzymatic site and the net outcome being a change in enzyme activity. Direct inhibition can occur by one of the following mechanisms:

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

**Indirect Inhibition**- it can be caused by:

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

NOTE: Enzyme inhibition is more clinically important than enzyme induction especially for drugs with narrow therapeutic index.

1. Environmental chemicals-
2. Halogenated chemicals such as polycyclic aromatic hydrocarbons contained in cigarette smoke have enzyme induction effect.
3. Organophosphate insecticides and heavy metals like mercury, nickel, cobalt and arsenic inhibit drug metabolizing ability of enzymes.
4. Temperature, altitude, pressure relative to a drug to be metabolized also influence drug metabolism.

BIOLOGICAL FACTORS

1. Age- drug metabolism rate is different in different age groups mainly due to variations in enzyme content, activity and thermodynamics.

* In neonates (2 months) to infants (1 year), the microsomal enzyme system is not fully developed so many drugs are metabolized slowly e.g. caffeine has a half-life of 4 days in neonates but 4 hrs in adults.
* Children (1-12 years) metabolize some drugs rapidly than adults as the rate of metabolism reaches a maximum somewhere between 6 months and 12 years resulting in taking higher doses in comparison to adults.
* In elderly persons, the liver size is reduced hence, microsomal activity is decreased and hepatic blood flow as well as a result of decreased cardiac output, all of which contributes to decreased drug metabolism.

1. Diet- Generally,
2. Low protein diet decreases the drug metabolizing ability and high protein diet does the reverse as enzyme synthesis is promoted by protein diet and also raises the level of amino acid for conjugation with drugs.
3. Fat free diet depresses cytochrome P-450 levels since phospholipids which are important components of microsomes become deficient.
4. Dietary deficiency of vitamins such as Vitamin A, B2, B3, C and E and minerals such as Fe, Ca, Mg, Zn retard the metabolic activity of enzymes.
5. Sex Difference- Sex related differences n the rate of metabolism may be due to sex hormones. In humans, women metabolize benzodiazepines slowly than men. In rats, the males have higher metabolizing rate than the female.
6. Species difference- Qualitative differences among species generally from the presence or absence of specific enzymes in those species. Quantitative differences result from variation in amount and localization of enzymes, the number of natural inhibitors and the competition of enzymes for different substrates. For example, the human liver contains less cytochrome P-450 per gram of tissue than the livers of other species.
7. Strain difference- this can be explained under two headings:
8. Pharmacogenetics- this is the study of inter-subject variations in drug metabolism. The inter-subject variations may either be monogenetically or polygenetically controlled. For example, monozygotic twins have little or no difference in metabolism of halothane, antipyrine, dicoumaral but dizygotic twins have very large differences in the metabolism of the above.
9. Ethnic Variations- these are variations in drug metabolism in different races. For example, approximately equal percent of fast and slow acetylators are found among the blacks and whites whereas slow acetylators dominate the Japanese and Eskimo population.
10. Altered physiological factors
11. Pregnancy- it is known to affect hepatic drug metabolism. Physiological changes during pregnancy such as elevated concentration of various hormones such as estrogen, progesterone, placenta growth hormones and prolactin are probably responsible for the altered metabolism of drugs. For example, metabolism of promaxine and pethidine is reduced in women during pregnancy.
12. Diseased State- diseases affecting the liver, are the diseases which majorly affect the rate of drug metabolism e,g. liver cirrhosis, alcoholic liver disease and others like jaundice, acromegaly, diabetes mellitus and various viral and bacterial infections. The possible cause of the effect of diseases in metabolism are:
13. Decreased enzyme activity in the liver
14. Altered hepatic blood flow
15. Hypoalbuminaemia leading to lower binding plasma of drugs.
16. Hormonal Imbalance- Higher level of one hormone may inhibit the activity of few enzymes while inducing others. For example, adrenalectomy, thyroidectomy and alloxan-inuced diabetes in animals showed impairment in enzyme activity with subsequent fall in rate of metabolism.

PHYSICOCHEMICAL PROPERTIES OF DRUGS

Molecular size and shape, pH, steric and electronic characteristics of a drug influence its interaction with the active sites of the enzyme and the metabolism to which it is subjected. However, the relationship is not clearly understood.