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MBBS 300LVL

BIOCHEMISTRY ASSIGNMENT

QUESTION: Discuss in details the factors affecting drug metabolism

ANSWER

Drugs, as well as other xenobiotics are metabolised via various pathways, including phase I and phase II reactions, which involve participation of numerous enzyme systems. Therefore, it is reasonable to assume that there are many factors that can determine or influence along which pathway a particular drug will undergo biotransformation and the extent to which this will proceed. These factors are usually arbitrarily divided into internal and external Factors, with nevertheless considerable interaction between them.

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:

1. Internal: species and strain differences, hereditary or genetic factors, sex, age, hormones, disease (pathological conditions), pregnancy.
2. External: diet, environment.

INTERNAL FACTORS

SPECIES AND STRAIN DIFFERENCES

The metabolism of many drugs and foreign compounds is often species dependent. Different animal species may bio transform a particular xenobiotic by similar or markedly different metabolic pathways. Even within the same species, individual variations (strain differences) may result in significant differences in a specific metabolic pathway.

SPECIES: Species variation has been observed in many oxidative biotransformation reactions. Examples of species differences in drug biotransformation are numerous, continuously investigated, and encountered in both phases of biotransformation. An interesting observation is that they may involve the same route, but differ in the rate along that particular pathway (i.e. quantitatively different) or they may adopt different pathways (i.e. differing qualitatively)

Examples

A well-known quantitative example is that of species variation in Hexobarbitone metabolism, affecting half-life and sleeping time. Investigations have been made on man, dog, mice and the rat. The longest half-time was registered for man (~360 min). The sleeping time Increased in the following order: mice, rats, dogs and man. The main conclusion of the experiment, apart from

demonstrating that the oxidative metabolism of hexobarbitone is markedly influenced by species, was that the biotransformation is inversely related to the half-time and duration of action of the investigated drug, the highest metabolism being registered for mice and decreasing in the opposite order as for the sleeping time for example.

Another example is the metabolism of amphetamine which occurs by two main pathways, oxidative deamination or aromatic hydroxylation. In human, rabbit, and guinea pig, oxidative deamination appears to be the predominant pathway while in the rat, aromatic hydroxylation appears to be the more important route.

Phenytoin is another drug that shows marked species differences in metabolism. In the human, phenytoin undergoes aromatic oxidation to yield primarily GS) (-)-p-hydroxyphenytoin; in the dog, oxidation occurs to give mainly (R) (+)-m-hydroxyphenytoin. There is a dramatic difference not only in the position (i.e., Meta or para) of aromatic hydroxylation but also in which of the two phenyl rings (at C-5 of phenytoin) undergoes aromatic oxidation.

Species differences in many conjugation reactions also have been observed. Often, these differences are caused by the presence or absence of transferase enzymes involved in the conjugative process. For example, cats lack glucuronyltransferase enzymes and, therefore, tend to conjugate phenolic xenobiotics by sulfation instead. In pigs, the situation is reversed: pigs are not able to conjugate phenols with sulfate (because of lack of sulfotransferase enzymes) but appear to have good glucuronidation capability.

STRAIN DIFFERENCES: Strain differences in drug metabolism exist, particularly in inbred mice and rabbits. These differences apparently are caused by genetic variations in the amount of metabolizing enzyme present among the different strains. For example, in vitro studies indicate that cottontail rabbit liver microsomes metabolize hexobarbital about 10 times faster than New Zealand rabbit liver microsomes.

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 nortriptylline. 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 analogues. It now is realized that their CYP2D6 isozyme does not readily O-demethylate codeine to form morphine.

This genetic polymorphism is seen in about 8% of Caucasians, 4% of African Americans, and less than 1% of Asians.

SEX

The rate of metabolism of xenobiotics also varies according to gender in some animal species. A marked difference is observed between female and male rats. Adult male rats metabolize several foreign compounds at a much faster rate than female rats (e.g., N-demethylation of aminopyrine, hexobarbital oxidation, glucuronidation of o-aminophenol). Apparently, this sex difference also depends on the substrate, because some xenobiotics are metabolized at the same rate in both female and male rats. Differences in microsomal oxidation are under the control of sex hormones, particularly androgen, the anabolic action of androgens seems to increase metabolism.

Sex differences in drug metabolism also appear to be species dependent. Rabbits and mice, for example, do not show a significant sex difference in drug metabolism. In humans, there have been a few reports of sex differences in metabolism. For instance, nicotine and aspirin seem to be metabolized differently in women and men. On the other hand, gender differences can become significant in terms of drug-drug interactions based on the drug's metabolism.

AGE

It has long been recognized that the new-born, young and elderly display marked differences in drug biotransformation and are more susceptible to drug action. These differences are chiefly due to the enzymatic systems Involved in drug biotransformation and the development of their metabolising capacity. Thus, the increased sensitivity of neonates may be related to their very low, undeveloped metabolising capacity, until adult levels of enzyme activity are achieved. On the other hand, in the elderly, the decrease in drug-metabolising capacity also appears to be dependent on these factors, important changes in the overall metabolism occurring with ageing.

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

- In neonates (up to 2 months) and in infants (2 months to 1 year), the microsomal enzyme system is not fully developed. So many drugs are metabolized slowly. For example, caffeine has a half-life of 4 days in neonates in comparison to 4 hours in adults.
- Children (between 1 year and 12 years) metabolize several drugs much more rapidly than adults as the rate of metabolism teaches a maximum somewhere between 6 months and 12 years. As a result they require a 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 bioavailabillty within the elderly, therefore they require a lower dose.

Typically, drug metabolism is significantly reduced in the neonatal period because of lack of enzymatic activity. A recent investigation reviewed the effect of age on the biotransformation of four drugs. The subjects were infants and children, and the tested drugs included caffeine, Midazolam, morphine and paracetamol. The first observation was that in the neonatal period, for all four tested drugs, clearance was markedly reduced. Further observations confirmed that (with the exception of paracetamol) this reduced clearance is maintained in infants and children under the age of two years, and that there is considerable inter-individual variation in clearance values for all ages and for all tested drugs, appearing to be the greatest for Midazolam. The third important observation suggests that for children older than two years, the mean plasma clearance values for all four drugs are more or less similar to those in adolescents and even adults.

Important changes in drug metabolism also occur with ageing. For example, the significant reduction in liver volume accompanying ageing will be reflected in a reduction in the total amount of cytochrome P450 produced, and this could be associated with reduced ability of these enzymes to function. Two other important aspects of age-related changes are sensitivity to environmental factors and nutritional effects on hepatic drug metabolism in the elderly.

HORMONES

Hormones, known to play a major role in the general metabolism, have similarly been proven to control the biotransformation of drugs, in direct connection with other factors such as age, sex, or in particular physiological states, such as pregnancy. An example is the apparent connection between certain sex-specific drug- and steroid-metabolising enzyme activities in rats and the sex dependent expression of those specific enzymes, under gonadal steroid and growth hormone control.

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 also observed in the pituitary growth hormone and stress related changes in ACTH level.

DISEASE (PATHOLOGICAL CONDITIONS)

There are many disease states that affect the metabolism of drugs. Some of them are cirrhosis of the liver, alcoholic liver disease, diabetes mellitus, acromegaly, and malaria, various bacterial and viral infections. Etc. It can be seen that major effects are seen in the disease affecting liver as the liver is quantitatively the important site for metabolism. The possible cause in the effect of metabolism due to diseases may be:

1. Decreased enzyme activity in liver
2. Altered hepatic blood flow
3. Hypoalbuminemia (leading to lower plasma binding of drugs).

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 oestrogen, 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.

EXTERNAL FACTORS

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 levels 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.

ENVIROMENT

These are usually considered to be those influences in our surroundings that can affect (sometimes markedly) drug metabolism. Of course, there are a large number of environmental chemicals that potentially could affect drug biotransformations, usually grouped into heavy metals, industrial pollutants and pesticides. The most important industrial pollutants are typically aromatic or aromatic polycyclic compounds and polychlorinated biphenyls. Pesticides are also of various types (insecticides, herbicides), and are considered environmental contaminants in air, soil, water and food.

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

- Halogenated pesticides such as DDT and polycyclic aromatic hydrocarbom 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.

REFERENCES

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