BIOCHEMISTRY ASSIGNMENT

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TOPIC: XENOBIOTICS

QUESTION

Discuss in detail the factors affecting drug metabolism.

Drug metabolism is the term used to describe the biotransformation of pharmaceutical substances in the body so that they can be eliminated more easily. It is the chemical alteration of a **drug** by the body. The majority of metabolic processes that involve drugs occur in the liver, as the enzymes that facilitate the reactions are concentrated there.

Many factors affect the rate and pathway of metabolism of drugs, some of which includes:

1. **Internal factors**:

a. **Enzyme Induction**: is an increase in the drug metabolizing ability of an enzyme. The agents responsible for such effect are called **drug inducers.**

It refers to an increase in the rate of hepatic metabolism, mediated by increased transcription of mRNA encoding the genes for drug-metabolizing enzymes. This leads to a decrease in the concentrations of drugs metabolized by the same enzyme.

When enzyme induction occurs, the ability of the enzymes of the liver to convert drugs to metabolites increases, generally speaking because of an increase in the availability of the enzymes.

With constant dosage, parent drug concentrations fall, and metabolite concentrations rise, so that metabolite to parent drug concentration ratios increase.

In some cases the drug itself may alter its own metabolic rate by induction or inhibition. ***Many drugs are capable of inducing enzyme activity, thereby increasing the rate of metabolism and hepatic***

clearance of concurrently administered drugs, typically resulting in a decreased pharmacologic effect.

b. **Enzyme Inhibition:** It is a decrease in the drug metabolizing ability of an enzyme. The direct consequence of **enzyme inhibition** is the delay in the biotransformation of certain **drugs**, resulting thus in increased plasma concentrations and potentiation or prolongation of their pharmacological action.

Drug-induced enzyme inhibition also occurs and typically results in prolonged clearance of a concurrently administered drug. The potential for toxicity or for an exaggerated pharmacologic response increases.

Enzyme inhibition can cause many adverse drug interactions that tend to happen more rapidly (within a couple of days) than those seen with enzyme induction, as they occur once the concentration of the inhibiting drug becomes high enough to compete with the affected drug.

c. **Age:** age-related changes in drug metabolism should be considered a typical phenotypic characteristic of the aging process.

- During development children go through periods of growth with extreme rates of metabolism.
- Generally, older age is associated with increased blood concentrations of drugs and altered metabolism, reduced effectiveness, and increased risk of adverse reactions for many medications.

In the elderly,

- the activity of drug metabolism enzyme in the liver is decreased so that the half-life of the drug is prolonged.
- Also, the age associated reduction of parenchymal cells in the liver and a reduction of liver blood flow affects the ability of the liver to metabolise drugs.

These factors further compound the drug scavenging capacity of the elderly, causing drug effect enhancement and more adverse reactions.

d. **Gender:** Sex differences in metabolism (phase I and II) are believed to be the major cause of differential pharmacokinetics between men and women. The majority of studies show that apparent cytochrome P450 (CYP) 3A4 activity is higher in women than in men, whereas the activity of many other systems involved in drug metabolism may be higher in men than in womenMany CYP450 enzymes (phase I metabolism) show a sex-dependent difference in activity.
    - Most of the phase II enzymes have a higher activity in men than in women.
    - Activities of these enzymes can also change during pregnancy and with the use of oral contraceptives.

Female-specific issues such as pregnancy, menopause, oral contraceptive use and menstruation may also have profound effects on drug metabolism. These effects can often be clinically important.

- Pregnancy may increase the elimination of antiepileptic agents, reducing their efficacy.
- Oral contraceptive use can interfere with the metabolism of many drugs and, conversely, certain drugs can impair contraceptive efficacy.

e. **Specie difference:**

Different species have their respective mode and rate of metabolizing particular drugs, which is peculiar to them.

Qualitative differences among species in phase I reactions generally result from the presence or absence of specific enzymes in those species.

Qualitative differences however, results from the variation in the amount and localization of enzymes, the amount of natural inhibitors and the competition of enzymes for specific substrates.

Specie difference in drug metabolism can be seen in the metabolism of hexobarbitone by both man and rat.

In rat, the half life of hexobarbitone is 19 +/- 7 and sleeping time is 12+/-8, indicating the rate of metabolism of hexobarbitone is high.

In man, the half life of hexobarbitone is greater than 360, thus prolonged effect of the drug is observed and the individual keeps sleeping as the rate of metabolism is low.

f. **Genetics:** influences on **drug metabolism** interact with other factors, such as: age, gender, race/ethnicity, disease states, concomitant medicines and social factors, determining the outcome from treatment with any pharmacological agent.

Polymorphisms may **influence** a **drug's** action by changing its pharmacokinetics or its pharmacodynamics.

Because of their **genetic** makeup, some people process (metabolize) **drugs** slowly and some others metabolize drugs rapidly.

g. **Hormones:**

Higher level of one hormone may inhibit the activity of a few enzymes while inducing that of others.

h. **Diseases:**

There are many disease states that affect the metabolism of drugs. Some of them are cirrhosis of liver, alcohol 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 diseases affecting the liver as liver is quantitatively the major site for metabolism. The possible cause in the effect of metabolism due to the diseases may be:

- Decreased enzyme activity in the liver.
- Altered hepatic blood flow.

Decrease enzyme activity in liver can cause the metabolism of drugs to be slow, thereby prolonging the effects of the drug in the system of the individual.

2. <u>External factors:</u>

a. Environmental factor: Besides genetic factors, environmental factors may play a significant role in explaining the variation observed in the rates of drug metabolism between different individuals. Intentional or unintentional exposure to environmental chemicals could enhance or inhibit

the activity of hepatic mixed function oxidases that metabolise drugs and other foreign chemicals, as well as endogenous substrates such as steroid hormones.

A major source of such exposure may be occupational.

- Exposure to the heavy metal, lead, has been shown to inhibit drug metabolism; whereas
- Intensive exposure to chlorinated insecticides, and other halogenated hydrocarbons such as poly chlorinated biphenyls, has been shown to enhance the metabolism of test drugs such as antipyrine and phenylbutazone.
- Cigarette smoking decreases the bioavailability of some drugs and increases their dosage requirements by enhancing their rate of metabolism.
- Heavy marijuana use may have an inhibitory effect on metabolism of some drugs and an inducing effect on others such as theophylline.

b. Diet: Foods can enhance, delay, or decrease drug absorption.Foods impair absorption of many antibiotics. They can alter metabolism of drugs;

- High-protein diets can accelerate metabolism of certain drugs by stimulating cytochrome P-450.
- Eating grapefruit can inhibit cytochrome P-450 34A, slowing metabolism of some drugs (eg, amiodarone, carbamazepine, cyclosporine, certain Ca channel blockers).
- Diets that alter the bacterial flora may markedly affect the overall metabolism of certain drugs.
- Some foods affect the body's response to drugs. For example, tyramine, a component of cheese and a potent vasoconstrictor, can cause hypertensive crisis in some patients who take monoamine oxidase inhibitors and eat cheese.

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