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**1. 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. These factors range from the species of organism studied to the environment in which that organism lives. The factors affecting drug metabolism are splited into internal (physiological and pathological) factors and external factors diet and environment.

Internal

• Species

• Genetic (strain)

• Age

• Sex

• Hormones

• Disease

External

• Diet

• Environment

**Internal**

**Age Differences**

Age-related differences in drug metabolism are generally quite apparent in the newborn.487,488 In most fetal and newborn animals, undeveloped or deficient oxidative and conjugative enzymes are chiefly responsible for the reduced metabolic capability seen. In general, the ability to carry out metabolic reactions increases rapidly after birth and approaches adult levels in about 1 to 2 months. An illustration of the influence of age on drug metabolism is seen in the duration of action (sleep time) of hexobarbital in newborn and adult mice.489 When given a dose of 10 mg/kg of body weight, the newborn mouse sleeps more than 6 hours. In contrast, the adult mouse sleeps for fewer than 5 minutes when given the same dose.

The effect of old age on drug metabolism has not been as well studied. There is some evidence in animals and humans that drug metabolism diminishes with old age.491,492 Much of the evidence, however, is based on prolonged plasma half-lives of drugs that are metabolized totally or mainly by hepatic microsomal enzymes (e.g., antipyrine, phenobarbital, acetaminophen). In evaluating the effect of age on drug metabolism, one must differentiate between "normal" loss of enzymatic activity with aging and the effect of a diseased liver from hepatitis, cirrhosis, etc., plus decreased renal function, because much of the water-soluble conjugation products are excreted in the liver.

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. This are a problem when a new drug is under development. A new drug application requires the developer to account for the product as it moves from the site of administration to final elimination from the body. It is difficult enough to find appropriate animal models for a disease. It is even harder to find animal models that mimic human drug metabolism. Species variation has been observed in many oxidative biotransformation reactions. For example, metabolism of amphetamine occurs by two main pathways: oxidative deamination or aromatic hydroxylation. In human, rabbit, and guinea pig, oxidative deamination appears to be the predominant pathway; in the rat, aromatic hydroxylation appears to be the more important route. 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 heredi tary factors are responsible for the large differences seen in the rate of metabolism of these drugs. The frequently cited example of the biotransformation of the antituberculosis agent isoniazid is discussed previously under acylation. 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

**Sex differences**

Sex differences in drug metabolism 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. For women, the focus is on drugs used for contraception.the antibiotic rifampin, a CYP3A4 inducer, can shorten the half-life of oral contraceptives

**Hormonal imbalance:**

Higher level of one hormone may inhibits the activity of few enzymes while inducing that of others

**Disease state**

Enhanced half-life of almost all drugs

**External.**

**Enviromental**

* Halongnated pesticides and polycyclic aromatic hydrocarbon
* Organphosphate insecticide and heavy metals
* Temperature pressure atmosphere etc

**Diet**

* The enzyme content and activity is altered by a number of sdietary components:
* Low protein diet and high protein
* Protein-carbohydarte ratio
* Fat free diet
* Dietary deficiency of vitmines and minerals
* Grapefruit
* Starvation
* Malnutrition in women
* Alcohol ingestion