

Factors influencing drug metabolism

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Introduction

- Drugs and xenobiotics often are metabolized by several different phase I and phase II pathways to give several metabolites.
- The relative amount of any particular metabolite is determined by the concentration and activity of the enzyme(s) responsible for the biotransformation.
- The rate of metabolism of a drug is particularly important for its pharmacological action as well as its toxicity.

- For example, if the rate of metabolism of a drug is decreased, this generally increases the intensity and duration of the drug action. In addition, decreased metabolic elimination may lead to accumulation of toxic levels of the drug.
- Conversely, an increased rate of metabolism decreases the intensity and duration of action as well as the drug's efficacy. Many factors may affect drug metabolism, and they are discussed in the following sections.
- These include age, species and strain, genetic or hereditary factors, sex, enzyme induction, and enzyme inhibition.

- **Age Differences**

- Age-related differences in drug metabolism are generally quite apparent in the newborn.
- 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.

- **Species and Strain Differences**
- The metabolism of many drugs and foreign compounds is often species dependent. Different animal species may biotransform 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.

- **Hereditary or Genetic Factors**
- Marked individual differences in the metabolism of several drugs exist in humans.⁴⁶³ Many of these genetic or hereditary 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.

- **Sex Differences**

- 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).

- **Enzyme Induction**

- The activity of hepatic microsomal enzymes, such as the CYP mixed-function oxidase system, can be increased markedly by exposure to diverse drugs, pesticides, polycyclic aromatic hydrocarbons, and environmental xenobiotics.
- The process by which the activity of these drug-metabolizing enzymes is increased is termed enzyme induction