12.4: Modifiers of Biotransformation

Modifiers of Biotransformation

The relative effectiveness of biotransformation depends on several factors that can inhibit or induce enzymes and dose levels. Factors include:

- Species
- Age
- Gender
- Genetic variability
- Nutrition
- Disease
- Exposure to other chemicals

Species

It is well known that the capability to biotransform specific chemicals varies by **species**. These differences are termed selective toxicity, which refers to differences in toxicity between species similarly exposed. Research uses what is known about selective toxicity to develop chemicals that are effective but relatively safe in humans.

- For example, the pesticide malathion in mammals is biotransformed by hydrolysis to relatively safe metabolites, but in insects, it is oxidized to malaoxon, which is lethal to insects.

Age and Gender

Age may affect the efficiency of biotransformation. In general, human fetuses and newborns have limited abilities to carry out xenobiotic biotransformations. This limitation is due to inherent deficiencies in many of the enzymes responsible for catalyzing Phase I and Phase II biotransformations. While the capacity for biotransformation fluctuates with age in adolescents, by early adulthood the enzyme activities have essentially stabilized. The aged also have decreased biotransformation capability.
Gender may influence the efficiency of biotransformation for specific xenobiotics. This is usually limited to hormone-related differences in the oxidizing cytochrome P-450 enzymes.

Genetic Variability

Genetic variability in biotransforming capability accounts for most of the large variation among humans. In particular, human genetic differences influence the Phase II acetylation reaction. Some persons have rapid acetylation ("rapid acetylator") while others have a slow ability to carry out this reaction ("slow acetylator"). The most serious drug-related toxicity occurs in those who have slow acetylators, often referred to as "slow metabolizers." With slow acetylators, acetylation is so slow that blood or tissue levels of certain drugs (or Phase I metabolites) exceed their toxic threshold.

Table 12.4.1 includes examples of drugs that build up to toxic levels in slow metabolizers who have specific genetic-related defects in biotransforming enzymes.

Drug	Drug Category	Metabolic Defect	Toxic Effect
Isoniazid	antituberculosis drug	slow acetylation	nerve and liver damage
Hydralazine	antihypertensive drug	defect in mono-oxygenase enzyme	excessive fall in blood pressure
Dapsone	antibacterial agent	slow acetylation	systemic lupus erythematosus
Primaquine	antimalarial agent	defective G6PD	acute hemolytic anemia

Table 1. Examples of drugs that build to toxic levels in slow metabolizers with specific genetic-related defacts in biotransforming enzymes

Nutrition

Poor **nutrition** can have a detrimental effect on biotransforming ability. Poor nutrition relates to inadequate levels of protein, vitamins, and essential minerals. These deficiencies can decrease a person's ability to synthesize biotransforming enzymes. Many diseases can impair an individual's capacity to biotransform xenobiotics.
For example, hepatitis (a liver disease) is well known to reduce hepatic biotransformation to less than half of its normal capacity.
Prior or Simultaneous ExposurePrior or simultaneous exposure to xenobiotics can cause enzyme inhibition and enzyme induction. In some situations, exposure to a substance will inhibit the biotransformation capacity for another chemical due to **inhibition of specific enzymes**. A major mechanism for the inhibition is competition between the two substances for the available oxidizing or conjugating enzymes. The presence of one substance uses up the enzyme needed to metabolize the second substance.
Exposure to Other Environmental Chemicals and DrugsEnzyme induction is a situation where prior exposure to certain environmental chemicals and drugs results in an enhanced capability for biotransforming a xenobiotic. The prior exposures stimulate the body to increase the production of some enzymes. This increased level of enzyme activity results in increased biotransformation of a chemical subsequently absorbed.
Examples of enzyme inducers include:

- Alcohol
- Isoniazid
- Polycyclic halogenated aromatic hydrocarbons (for example, dioxin)
- Phenobarbital
- Cigarette smoke

The most commonly induced enzyme reactions involve the cytochrome P450 enzymes.
Dose level can affect the nature of the biotransformation. In certain situations, the biotransformation may be quite different at high doses compared to low dose levels. This difference in biotransformation contributes to a dose threshold for toxicity. The existence of different biotransformation pathways can usually explain what causes this dose-related difference in biotransformation. At low doses, a xenobiotic may follow a biotransformation pathway that detoxifies the substance. However, if the amount of xenobiotic exceeds the specific enzyme capacity, the biotransformation pathway is saturated. In that case, it is possible that the level of parent toxin builds up. In other cases, the xenobiotic may enter a different biotransformation pathway that may end up producing a toxic metabolite.
An example of a dose-related difference in biotransformation occurs with acetaminophen (Tylenol®):

- At normal doses:
  - About 96% of acetaminophen is biotransformed to non-toxic metabolites by sulfate and glucuronide conjugation.
  - About 4% of the acetaminophen oxidizes to a toxic metabolite.
  - That toxic metabolite is conjugated with glutathione and excreted.
- At 7-10 times the recommended therapeutic level:
  - The sulfate and glucuronide conjugation pathways become saturated and more of the toxic metabolite is formed.
  - The glutathione in the liver may also be depleted so that the toxic metabolite is not detoxified and eliminated.
  - It can react with liver proteins and cause fatal liver damage.

Knowledge Check

1) Selective toxicity refers to a difference in the toxicity of a xenobiotic to different species. This selective toxicity can usually be attributed to differences in:

a) The ability to absorb the xenobiotic
b) Organ systems between species
c) Capability to biotransform the xenobiotic

Answer

Capability to biotransform the xenobiotic - **This is the correct answer.**
A difference between species in their capability to biotransform a specific chemical is normally the basis for a chemical's selective toxicity.
