Biotransformation and Elimination of Toxicants

Food Toxicology

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Learning Objectives

- Explain the role of biotransformation in toxicokinetics.
- Describe how biotransformation facilitates elimination of toxicants.
- Distinguish between Phase I and Phase II reactions.
- Define bioactivation or toxication.

Learning Objectives, 2

- Identify tissues and factors involved in biotransformation.
- Summarize the role of elimination in toxicokinetics.
- Describe processes occurring in the kidney, liver and lung related to the elimination of toxicants.

Metabolism

- Sum of biochemical rxns occurring to a molecule within the body.
  - Anabolism - “build-up”
  - Catabolism - “break-down”
- Occurs in the cytoplasm or at specific organelles within the cell.
- Storage affects the body’s ability to biotransform and eliminate.
  - Bone, lipid.

Biotransformation

- Process that changes substances from hydrophobic to hydrophilic to aid in elimination (grease to salt).
  - Hydrophilic molecules are less able to cross cellular membranes, hence fluid filterable (kidneys).

  - Major elimination routes are feces (biliary) and urine.
  - Biological half-life, $T_{½}$ allows comparison of rates of removal.

Biotransformation Reactions

- Grouped as Phase I (functional group modification) and Phase II (conjugation).
- Goals
  - Produce water soluble metabolites.
  - Activate natural/endogenous compounds for normal function.
- Some compounds undergo bioactivation.
  - The biotransformed metabolite is more toxic than the original compound.

Results of Biotransformation

- Increase toxicity via a toxic metabolite.
- Decrease toxicity via metabolism of a toxic parent compound.
- No effect on toxicity.
- Present to metabolize endogenous compounds.

Major Categories/Reactions Enzymes of Biotransformation

- Oxidation (most important).
  - Add O, remove H, increase valence.
  - Cytochrome P-450, MFO, alcohol dehydrogenase, oxidases, others.
- Reduction (less important).
  - Remove O, add H, decrease valence.
  - Reductases.
- Hydrolysis.
  - Add water.
  - Esterases, phosphtases, others.

Phase I Reactions Enzymes of Biotransformation, 2

- Conjugation reactions.
- Enzymes (tranferases) + cofactor.
  - Enzyme catalyzes.
  - Cofactor donates group.

  - Glucuronic acid, glutathione, sulfate, acetyl group, methyl group.
  - Tends to increase molecular size and polarity for excretion.

PII Cofactors: GSH

PII Cofactors: Acetyl-CoA

PII Cofactors: PAPS

PII Cofactors: UDPGA

Benzene Metabolism

Aniline

De-Alkylation

Free Radical Generation

Case Study: Fluorocitrate and Kangaroos

- Fluorocitrate found in legume pasture plants of Western Australia.
  - *Gastrolobium* and *Oxylobium.*
- Highly lethal (TD 1 mg/1080 kg).
  - Leaf concentrations can be 2.6 g/kg.
- The rat and gray kangaroo of Western Australia have evolved resistance.
  - *In vivo* defluorination w/ glutathione.
  - Other kangaroos from areas w/o these plants are not tolerant.

Rodenticide: Fluoroacetic Acid

Fluorocitrate Metabolite

Krebs Cycle

Deoxynivalenol, Vomitoxin

Aflatoxin B_1

Benzo[a]pyrene

Heavy Metal Toxicity - Pb

- Absorbed via Ca channels as divalent ion.
- Capable of reacting with a variety of binding sites.
  - Protein precipitation.

- Specific toxic effect depends on rxns with ligands that are essential for the living system.
- Metal ligands are formed with sulfhydryl groups, as well as amino, phosphate, imidazole, and hydroxyl groups of enzymes and essential proteins.

Heavy Metal Toxicity - Pb, 2

- Sensitivity of a system and degree of interference determines clinical effects.
  - Digestion/respiration → absorption.
  - Liver → detoxication.
  - Kidney → excretion.
- Antidotes are competing ligands.

Heavy Metal Toxicity - Pb, 3

- Metallic lead absorbed most efficiently by the respiratory tract.
- 10% of ingested lead is absorbed.
  - Small intestine.
  - Lead salts are soluble in gastric juices; absorbed.
- Plasma to blood cells – erythrocytes.
- After oral ingestion:
  - 60% bone (also hair, teeth).
  - 25% liver (hepatocytes).
  - 4% kidney (renal tubules).
  - 3% intestinal wall.

Heavy Metal Toxicity - Pb, 4

- Some endpoints.
  - Sulfhydral enzyme inhibition.
  - K transport in RBC inhibited
    - Anemia.
  - Porphyrinuria.
- Excreted chiefly in feces and urine.
- Chelating agents:
  - Ca - EDTA.
  - Penicillamine.
  - Dimercaptrol (BAL).

Case Study: Elevated PbB Associated with Illicitly Distilled Alcohol, Alabama 1991

- The use of automobile radiators containing lead-soldered parts in the illicit distillation of alcohol (i.e., "moonshine") is an important source of lead poisoning among persons in some rural Alabama counties.
- In 1991, eight persons were diagnosed with elevated blood lead levels (BLLs) at a local hospital.
- 9 patients had been evaluated for alcohol-related medical conditions at the hospital. Manifestations included generalized tonic-clonic seizures (six), microcytic anemia (five) (hematocrit mean: 32.1%), encephalopathy (two), upper extremity weakness (one), and abdominal colic (one). BLLs ranged from 16 ug/dL to 259 ug/dL (median: 67 ug/dL).

Case Study: “Moonshine” Lead Toxicity

- Seven patients required hospitalization for 48 hours or longer (range: 2-18 days). Three of these received chelation therapy; initial BLLs were 67, 228, and 259 ug/dL. One patient, whose BLL was 67 ug/dL, died during hospitalization from alcohol-withdrawal syndrome complicated by aspiration pneumonia.
- Patients reported moonshine ingestion ranging from 0.2 L per day to 1.5 L per day.
- The lead contents of specimens of moonshine confiscated from two radiator-containing stills in the county in 1991 were 7400 ug/L and 9700 ug/L, compared with nondetectable amounts (less than 1.0 ug/L) in municipal water from the county.
- Consumption of 0.5 L per day of moonshine containing 9700 ug/L lead would result in a steady state BLL of approximately 190 ug/dL.

Elimination of Toxicants

- Urinary.
- Fecal.
- Respiratory.
- Other:
  - Saliva.
  - Sweat.
  - Milk (transfer to child).
  - Nails, Hair, Skin.
  - Cerebrospinal fluid.

Kidney
Renal Macrostructure
Renal Filtration Microstructure
Renal Histology
Urinary Excretion

- Glomerular filtration
- Tubular secretion
- Tubular reabsorption

Fecal Excretion

- Excretion in bile to intestine.
  - Active transport of toxicant parent and metabolites.
  - Highly soluble Phase II metabolites (large, ionized)
- Excretion into the lumen of the GI tract.
  - Direct diffusion from capillaries.

Exhaled Air

- Gas phase xenobiotics.
- Passive diffusion from blood to alveolus via concentration gradient.
  - The total alveolar epithelial surface area within an average adult human lung has been estimated to be as large as 100-140 m^2.