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, $T_{1/2}$ 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

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>oxidation</td>
<td>conjugation synthesis</td>
</tr>
<tr>
<td>reduction</td>
<td>synthesis</td>
</tr>
<tr>
<td>hydrolysis</td>
<td>very polar</td>
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</tbody>
</table>

Enzymes of Biotransformation

**Phase I Enzymes**
- 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, phosphatases, others.

Enzymes of Biotransformation, 2

**Phase II Enzymes**
- Conjugation reactions.
- Enzymes (transferases) + 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

Glutathione
PII Cofactors: Acetyl-CoA

Acetyl Coenzyme A

PII Cofactors: PAPS

3'-Phosphoadenosine 5'-phosphosulfate

PII Cofactors: UDPGA

Uridine-5'-diphosphoglucuronic acid

Benzene Metabolism

Glucuronide

Phenol

UDP-GT

Glutathione

Epoxidation

Two-phase system

Aniline

De-Alkylation

N-hydroxylation

Phase II

Dimethyl-propyl-amine

Methyl-propyl-amine

Acetaldehyde
**Free Radical Generation**

\[ \text{Tetrachloro-methane} \xrightarrow{\text{NADH, P450, Reductase}} \text{Toxic Free Radical} \]

**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**

- Fluoroacetate: Sodium Fluoroacetate
  - Compound 1080: rodenticide predator control

**Fluorocitrate Metabolite**

**Krebs Cycle**

**Deoxynivalenol, Vomitoxin**

- Fusarium trichothecene mycotoxin found on corn and barley
**Aflatoxin B₁**

Aspergillus mycotoxin found on corn, peanuts and cottonseed.

**Benzo[a]pyrene**

Polycyclic aromatic hydrocarbon.

Environmental carcinogen.

Cell cultures from rodents, fish and humans.

**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.
  - Sulfhydryl enzyme inhibition.
  - K transport in RBC inhibited
    - Anemia.
  - Porphyrinuria.
- Excreted chiefly in feces and urine.
- Chelating agents:
  - Ca - EDTA.
  - Penicillamine.
  - Dimercaprol (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.
Renal Histology
- Tubules
- Glomerulus

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 m².