CHAPTER THREE
METAL POISONING

Outline

- Objectives
- Lead
- Mercury
- Arsenic
- Cadmium
- Chromium
- Nickel

Objectives

At the end of this chapter students will be able to discuss the toxicity of:

- Lead
- Mercury
- Arsenic
- Cadmium
- Chromium
- Nickel

Metal Toxicity

- Most metals are trace elements required for a normal functioning of the body, being involved in over 200 essential metabolic pathways.

- Another common feature is that metals can be toxic by inhibiting enzymatic pathways, in lysosomes or mitochondria.

- Interestingly, varied chemical entities of the same metal may exert widely different toxic effects

- The mechanism of action may be:
  - By producing for the toxicities of most of their compounds
  - by forming very toxic ions
  - By being very toxic in their elemental forms

Metal Toxicity

- Inorganic forms of most metals tend to be strongly bound by protein and other biologic tissue
  - Such binding increases **bioaccumulation** and inhibits **excretion**
- There is a significant amount of tissue selectivity in the binding of metals, For example, toxic lead and radioactive radium are accumulated in osseous (**bone**) tissue, whereas the **kidneys** accumulate **cadmium and mercury**
- Metal ions most commonly bond with amino acids, which may be contained in proteins (including enzymes) or polypeptides
- The electron-donor groups most available for binding to metal ions are amino and carboxyl groups

Metal Toxicity cont'd

- Metals tend to accumulate in target organs, and a toxic response is observed when the level of the metal in the organ reaches or exceeds a **threshold** level
- **Often the organs most affected are those involved with detoxication or elimination of the metal**
  - Therefore, the liver and kidneys are often affected by metal poisoning
- The form of the metal can determine which organ is adversely affected, for example, lipid-soluble elemental or organometallic mercury damages the brain and nervous system, whereas Hg^{2+} ion may attack the kidneys

1. Lead

- Lead is a naturally occurring bluish-gray metal found in the earth's crust
- Lead can combine with other chemicals to form what are known as lead salts
  - These compounds are water soluble, while elemental lead is not
- Lead is used in the production of batteries, ammunition, metal products, as well as scientific and medical equipment
- Most of the lead mobilized in the environment is the result of human activities

Lead cont'd

- Exposure to inorganic and inorganic lead compounds can occur in environmental or occupational circumstances
- Inorganic lead exposure is most applicable to general and occupational exposure
- Human body burdens of lead result from inhalation and oral exposure to inorganic lead
- In humans, oral absorption of ingested lead occurs primarily in the gastrointestinal tract
- 50 percent of the oral dose is absorbed by children and 15 percent is absorbed by adults

Lead cont'd

- Typically, the lead body burden of an average adult human has been reported to range between 100 and 300 mg
- **Inhalation** contributes a greater proportion of the dose for occupationally exposed groups
- The **oral route** contributes a greater proportion of the dose for the general population
- The effects of lead are the same regardless of the route of entry into the body and are well correlated with blood lead level
- **Lead in soil and dust are important sources of exposure in children**

Lead cont'd

- Death from lead poisoning occurred in children with blood lead levels >125 μg/dL
- Several deaths in children exhibited severe encephalopathy
- Lead affects on the hematopoietic system is by altering the activity of enzymes involved in **heme biosynthesis**
- The impairment of heme synthesis has a number of subsequent effects, including decreased hemoglobin levels and anemia
- These effects have been observed in lead workers and in children with prolonged lead exposure

Lead cont'd

- Lead may cause kidney damage as a result of acute or chronic exposure
- Reversible proximal tubular damage can result from **acute lead exposure**
- **Chronic exposure** can result in nephritis, interstitial fibrosis, and tubular atrophy
- Symptom of lead poisoning in occupationally exposed cases and in children:
  - Colic—characterized by abdominal pain, constipation, cramps, nausea, vomiting, anorexia, and weight loss

Lead cont'd

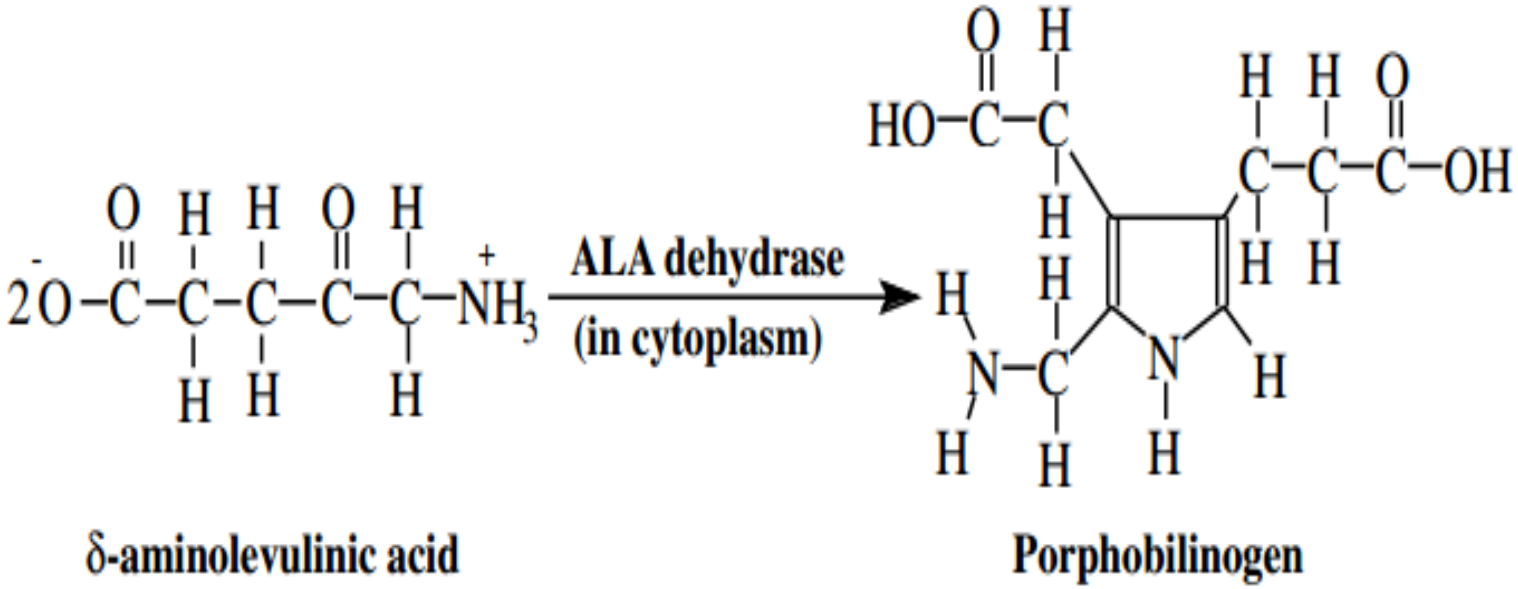

Figure. Synthesis of porphobilinogen from delta-aminolevulinic acid, a major step in the overall scheme of heme synthesis that is inhibited by lead in the body

2. Mercury

- Mercury is found in the environment in a metallic, as an inorganic compound, or as organic mercury compounds
- Mercury metal is the liquid used in thermometers and some electrical switches
- Metallic mercury will evaporate to some extent at room temperature to form mercury vapor
- Vaporization increases with higher temperatures

Mercury cont'd

- Some inorganic mercury compounds are used as fungicides, antiseptics, and preservatives
- Methyl mercury is produced primarily by microorganisms in the environment
- The toxicity of mercury depends on the specific compound in question
- Alkyl mercury compounds (e.g., methyl mercury) are extremely toxic in comparison to the inorganic mercury compounds

Mercury cont'd

- Inorganic mercury tends to localize in the kidneys as a result of filtration and reabsorption
  - While organic mercury exhibits a preference for the brain and, to a lesser extent, the kidneys
- Excretion may be in both urine (minor) and feces (major), depending on:
  - The form of mercury,
  - The magnitude of the dosage, and
  - The time post-exposure

Mercury cont'd

- Blood concentrations of mercury represent **recent** exposure to methyl mercury, while hair concentrations reflect average intake over a **long period**
- The mercury concentrations in successive segments of hair over the period of its formation can indicate the degree of **past** absorption of mercury compounds
- Metallic (elemental) mercury exposure may result from breathing mercury vapors released from dental fillings
- Spills of metallic mercury or release from electrical switches may result in exposure to metallic mercury and vapors released to indoor air

Mercury cont'd

- Exposure to metallic mercury may result from breathing contaminated air from various sources
- Exposure to mercury compounds can result from contaminated sources, as well as medicinal and household products
- Occupational exposure to mercury vapors may occur in various manufacturing and processing industries, as well as medical professions
- The toxicity of the inorganic salts of mercury is related to their comparative absorption rates
- Insoluble mercurous salts, such as calomel (Hg_2Cl_2; mercurous chloride), are relatively nontoxic in comparison to the mercuric salts

Mercury cont'd

- The immediate effects of acute poisoning with mercuric chloride ($HgCl_2$) are due to primary irritation and superficial corrosion of the exposed tissues
- Chronic oral effects for the mercuric salts include kidney damage, intestinal hemorrhage, and ulceration
- The principal problem of mercury toxicity is related to the ingestion of organic mercury compounds, which may accumulate in fish

Mercury cont'd

- Ingestion of meat from animals that have been fed grain treated with alkyl mercury compounds, or ingestion of the treated grain, may also result in toxic endpoints
- The most sensitive endpoint for oral exposure to alkyl mercury compounds is the development of nervous system effects
- Mercury may adversely affect a wide range of other organ systems after exposure to high levels
  - Includes: immune, respiratory, cardiovascular, gastrointestinal, hematologic, and reproductive systems

3. Arsenic

- Arsenic is a gray-colored metal found in the environment in both organic and inorganic compounds
- Inorganic arsenic occurs naturally in many kinds of rock
- Low levels of arsenic are present in soil, water, air and food
- Arsenic is used in a number of herbicides and insecticides
- The toxicity of arsenic compounds is extremely variable and depends on:
  - The animal species tested,
  - The form of arsenic (e.g., As^{3+} vs As^{5+}),
  - The route of exposure, as well as the rate and duration of exposure

Arsenic cont'd

- Human exposure may involve:
  - Inhalation of arsenic dusts
  - Ingestion of arsenic in water, food, or soil
  - Dermal contact with dust, soil or water
- Trivalent compounds of arsenic are the principal toxic forms
- Arsenic inhibits **succinic dehydrogenase** activity and uncouples oxidative phosphorylation

Arsenic cont'd

- This process results in the stimulation of mitochondrial ATPase activity.
- Arsenic inhibits the energy-linked functions of mitochondria
- Inhibition of mitochondrial respiration results in decreased cellular production of ATP and increased production of hydrogen peroxide

  - cause oxidative stress through the production of reactive oxygen species.

Arsenic cont'd

- Anemia and leukopenia are common effects of arsenic poisoning in humans following acute, intermediate, and chronic oral exposures
- The most common and characteristic effects of arsenic ingestion is skin changes that include:
  - Generalized hyperkeratosis and
  - Formation of hyperkeratotic warts or corns on the palms and soles,
  - Hyperpigmentation interspersed with small areas of hypopigmentation on the face, neck, and back

4. Cadmium

- Cadmium is usually not found in the environment as a pure metal
- It is usually found as a mineral, such as cadmium oxide, cadmium chloride, or cadmium sulfate, or in association with zinc
- These solids may dissolve in water and small particles of cadmium may be found in the air
- **Food** and **cigarette smoke** may be significant sources of cadmium exposure for the general public
- Inhalation exposure to high levels of cadmium oxide fumes or dust can cause severe irritation to respiratory tissue

Cadmium cont'd

- The **kidney** is the main target organ of chronic cadmium exposure via inhalation
- The toxicity of cadmium to proximal renal tubular function is characterized by the presence of low- (but sometimes high- as well) molecular-weight proteins in the urine (proteinuria)
- Tubular dysfunction develops only after cadmium reaches a minimum threshold level in the renal cortex
- Negative effects on calcium metabolism may occur as a result secondary to kidney damage

Cadmium cont'd

- Cadmium may enter the blood to a limited extent by absorption from the stomach or intestine after ingestion in food or water
- The form of cadmium in food and water is generally the cadmium ion
- Once cadmium enters the body, it is strongly retained in a number of organs
- Oral exposure to high concentrations of cadmium causes severe irritation to the gastrointestinal epithelium, resulting in nausea, vomiting, abdominal pain, and diarrhea
- Painful bone disorders have been observed in some humans chronically exposed to cadmium in food

Cadmium cont'd

- Decreased calcium content of bone and increased urinary calcium excretion are common findings in rats and mice following oral exposure to cadmium
- Cadmium compounds have not been observed to cause significant health effects when exposure is by the dermal route

5. Chromium

- Chromium is a naturally occurring element, which is found in the environment in three major valence states:
    - Elemental chromium (0),
    - Trivalent chromium (+3), and
    - Hexavalent chromium (+6)
- Chromium (+3) occurs naturally in the environment,
- Chromium (+6) and chromium (0) typically are generated by industrial processes
- Natural geologic sources represent a component of chromium present in the environment

Chromium cont'd

- Chromium is released to the environment in much larger and more concentrated amounts as a result of human activities
- The most stable form of the chromium compounds is the trivalent state, the naturally occurring form
- The hexavalent form is uncommon in a natural setting and is easily reduced to the trivalent form by environmental processes
- The three major forms of chromium differ dramatically in their potential for causing effects on human health
- **Trivalent** chromium is an essential nutrient required for normal energy metabolism

Chromium cont'd

- **Hexavalent** chromium is irritating, and short-term high-level exposure can result in adverse effects at the site of contact such as :
  - Ulcers of the skin
  - Irritation of the nasal mucosa
  - Perforation of the nasal septum, and
  - Irritation of the gastrointestinal tract, as well as adverse effects in the kidney and liver
- The respiratory tract in humans is a major target of chromium inhalation exposure

6. Nickel

- Nickel is a hard, silver-white, malleable, ductile metallic element used extensively in alloys and for plating because of its oxidation resistance
- Nickel, combined with other elements, occurs naturally in the earth's crust
- Nickel released to the atmosphere typically exists in particulate form or adsorbed to particulate matter
- Primary removal mechanisms of atmospheric nickel include gravitational settling and precipitation
- Nickel released to soil may be adsorbed to soil surfaces depending on the soil conditions

Nickel cont'd

- Nickel released to aquatic systems generally exists in particulate forms that settle out in areas of active sedimentation
- However, nickel also may exist in soluble form under appropriate conditions
- Nickel salts exhibit significant solubility in water
- Nickel occurs naturally in drinking water at an average concentration of about 2 μg/L
- Adult daily intake of nickel from water is about 2 μg/day
- About 170 μg of nickel is consumed in food per day

Nickel cont'd

- Nickel does not pose a **toxicity** problem following ingestion because the absorption from food or water is low
- The most prevalent effect of nickel exposure is **nickel dermatitis** in nickel-sensitive individuals
- Nickel dermatitis typically exhibits two components:
  - Simple dermatitis localized in the contact area and
  - Chronic eczema or neurodermatitis without apparent connection to such contact
- Nickel sensitivity, once acquired, may be persistent

Nickel cont'd

- Toxicological information of concern to industrially exposed humans is primarily confined to two potential categories of effects:
  - Dermatoses, contact and atopic dermatitis, and allergic sensitization; and
  - Cancers of the lung and nasal sinuses

References and Suggested Reading

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