General Toxicology

Toxic Effects of Metals

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Mustansiriyah University/College of Pharmacy
Department of Pharmacology & Toxicology
Lecturer Noor Haidar Albayati

What Is a Metal?

- A characteristic of metals of toxicological importance is that they **exhibit variable oxidation states** and may react **in biological systems by losing one or more electrons to form cations**.

- Various names are applied to subsets of metallic elements including **alkali metals** (e.g., lithium and sodium), the **alkaline earth metals** (e.g., beryllium and magnesium), the **transition** (or “heavy”) metals (e.g., chromium and nickel), and the **metalloids** (e.g., arsenic and antimony), the latter of **which show characteristics of metals and nonmetals**.

Metals as Toxicants

- They are all naturally occurring and, in many cases, are ubiquitous to some level within the human environment.

- Thus, regardless of how safely metals are used in industrial processes.

Routes of Exposure and Absorption of Metals

- The main routes of human exposure to metals include **oral ingestion, inhalation, dermal contact, and rarely through parenteral routes**.

- Oral ingestion of naturally occurring metals comes primarily from **drinking water** drawn from contaminated groundwater sources (e.g., arsenic, fluoride, manganese, and iron) and **food**.

- Metals accumulate in various foods, especially those grown on lands or soils naturally containing or anthropogenically contaminated with metals.

- For example, leafy vegetables such as spinach or tobacco accumulate large amounts of cadmium from the soil in which they are grown. Rice and some other grains concentrate hazardous levels of arsenic, cadmium, and copper.

- Mercury bioamplification through the aquatic food chain and ingestion of fish is the major route of human exposure.

- Inhalation of metal-containing fumes generated by welding and related processes may result in the “metal fume fever” that presents with nonspecific complaints including influenza-like symptoms. This usually resolves and is benign.

- Many elemental metals such as chromium, copper, iron, cadmium, aluminum, arsenic, and beryllium exert the respective health effects after inhalation and absorption in the respiratory tract.

- Dermal exposures are usually limited due to poor uptake of the small, charged metal ions across the impervious and lipophilic epidermis.

- However, corrosive forms of metals such as strong acids (e.g., chromic acid) or bases (e.g., metal hydroxides) cause dermal and mucus membrane corrosion and chemical burns.

- Exogenous factors that increase dermal exposure include dose, vehicle, molecular volume, counter ion, valence, protein reactivity and tissue deposition, solubility, and pH.

Distribution of Metals in the Body

- The distribution of metals to various tissues or organs **depends on** the rate of **blood flow to the organs** and **organ-specific properties for accumulation** of metals.

- Metals disrupt metabolic functions by accumulating in organs or by displacing vital nutrients or metals.
- The majority of lead (94%) accumulates in the bone and teeth, while 99% of blood lead is associated with red blood cell.
- In contrast, after 2 to 4 weeks of exposure, arsenic accumulates in keratin-rich tissues such as hair, nails, and skin.

Metal Transporters and Metal-Binding Proteins

- Ionic metals do not cross lipid membranes. Thus, they must be absorbed into the body and in cells by transport through selective and relatively nonselective ion channels.

- All cells possess mechanisms for metal ion homeostasis that involve a balance between uptake and efflux systems.

- Wilson diseases, which are caused by genetic mutations in copper-transport protein.

- The 30 different transporters and channels for zinc regulate metal ion concentrations in the circulation, in cells, and within cellular compartments.

- Magnesium has seven transporters and channels that are distributed differentially throughout the body.

- Toxicity occurs when toxic metals or high concentrations of essential metals outcompetes an essential metal for transport and action.

- Metal ions are rarely free during distribution and transport, because free metal is reactive.

- Transferrin is a glycoprotein that binds most of the ferric iron in plasma and helps transport iron across cell membranes where it is delivered to ferritin, the primary cellular iron storage protein.

- Transferrin also transports aluminum and manganese and may serve as a general metal **detoxicant protein**, because it binds many toxic metals including cadmium, zinc, beryllium, and aluminum.

- Ceruloplasmin is a ferroxidase enzyme that is the major copper- carrying protein in blood and helps convert ferrous iron to ferric iron, which then binds to transferrin.

- Its importance is demonstrated by genetic reduction in expression causing Wilson's disease, a copper storage disease with iron overload.

- Metallothioneins are an important class of **metal chaperones** whose expression is induced by metal exposure and that play an important role in essential metal homeostasis and metal detoxification.

Excretion of Metals

- Metals are excreted through fecal, biliary, and urinary elimination, as well as through sweat and storage in hair and nails.

- Several metals including lead, cadmium, arsenic, inorganic mercury, organic mercury, iron, manganese, magnesium, chromium, zinc, copper, nickel, cobalt, tin, and aluminum are **excreted through bile and urine**.

- factors that affect excretion of metals include induction of chaperone proteins.

- Essential calcium is decrease bone deposition of lead and increases its excretion and deposition to other target organs.

- In contrast, **highly soluble metals that have low protein affinity**, such as inorganic arsenic, urinary excretion is the main route of **bulk excretion**.

- Arsenic is metabolized to monomethylated and dimethylated **metabolites** that are **excreted** in the urine **more** readily **than** the **parent compound**.

- Metals, such as cadmium, lead, and mercury, are known to be **excreted through the skin** where the excretion rate might be higher than urinary excretion.

- Hair and nails **sequester metals in keratin matrices** to reduce toxicity, and this provides important media for monitoring long-term exposure to metals.

Biomarkers of Metal Exposure

- Exposure biomarkers, such as concentrations in **blood urine, nails, and hair**, have long been used for metals.

- Thus, in the case of chromium, **DNA–protein complexes** may serve as a biomarker of both exposure and carcinogenic potential.

- The biological half-life varies according to the metal as well as the organ or tissue.

- The blood, urine, hair, and nails are the most accessible tissues for **quantifying metal exposure.**

- **Blood and urine** concentrations usually, but not always, **reflect recent exposures** and correlate with **acute adverse effects**.

- An exception is urinary cadmium, which may reflect kidney damage related to renal cadmium accumulation over several decades.

- The **hair** can be useful in assessing variations in exposure to metals **over the period** of its growth.

Chemical Mechanisms of Metal Toxicology

- Enzyme Inhibition

- Metals bind to important functional groups in enzymes, especially –SH (sulfhydryl groups)

- This blocks enzyme activity and disrupts normal metabolism.

- For example, lead inhibits enzymes in heme synthesis causes anemia

- Oxidative Stress

- Some metals (Fe, Cu, Cd) produce Reactive Oxygen Species (ROS)

- ROS cause lipid damage (cell membrane), DNA damage, protein damage.

- For example Iron by Fenton reaction result in free radicals

- Metal Mimicry

- Toxic metals imitate essential metals and replace them.

- For examples lead replaces calcium that affects brain & bones.

- Cadmium replaces zinc cause enzyme dysfunction.

- Arsenic mimics phosphate lead to disrupts ATP production.

Molecular Responses to Metal Exposure

- Exposure to essential metals produces homeostatic signaling for normal tissue maintenance and regeneration

- while nonessential metals signal for homeostatic disruption or directly damage macromolecules and tissues.

- The results include inappropriate activation of growth or metabolic signaling, loss of essential enzymatic activity, direct structural damage, and if severe, cellular apoptosis and/or necrosis.

Major Toxic Metals

Arsenic

- Arsenic (As) is a toxic and carcinogenic metalloid. today are very effective against acute promyelocytic leukemia.

- Occupational exposure to arsenic occurs in the manufacture of pesticides, herbicides, and other agricultural products.

- Exposure to arsenic fumes and dusts occurs in smelting industries, especially copper smelting.

- Environmental arsenic exposure mainly occurs from arsenic **contaminated drinking water.**

- **Food**, especially seafood and rice, may contribute significantly to daily arsenic intake.

- Arsenic in **seafood** is largely in an **organic form called arsenobetaine** that is much **less toxic** than **the inorganic forms**.

Toxicokinetics

- Inorganic arsenic is well absorbed (80% to 90%) from the gastrointestinal tract, distributed throughout the body, often metabolized by methylation, and then excreted primarily in urine.

- The whole-body biological half-life of ingested arsenic is about 10 hours, and 50% to 80% is excreted into the urine over 3 days.

- It also concentrates in forming fingernails and hair bound to keratins.

Toxicity

Acute Poisoning

- Ingestion of large doses (70 to 180 mg) of inorganic arsenic can be fatal.

- **Acute** arsenic ingestion can **damage mucous membranes of the gastrointestinal tract**, causing irritation and vesicle formation.

- **Sensory loss in the peripheral nervous system** is the most common **neurological effect**, appearing at 1 to 2 weeks after large doses and consisting of Wallerian degeneration of axons, a condition that is reversible if exposure is stopped.

- Approximately 30% of patients under going arsenic chemotherapy experience **life-threatening arrhythmias** caused by arsenic impairment of cardiac potassium channels.

Chronic Toxicity

- The **skin is a major target organ** in chronic inorganic arsenic exposure.

- In humans, chronic exposure to arsenic induces a **series of characteristic changes in skin epithelium**.

- Palmar-plantar **hyperkeratosis** usually follows the initial appearance of arsenic-induced pigmentation changes **within a period of years**.

- Chronic exposure to arsenic is associated with a range of **nonmalignant respiratory effects** including respiratory symptoms, chronic obstructive pulmonary disease (COPD), and respiratory disease mortality.

- In addition, arsenic exposure is associated with increased **respiratory tract infections** and chronic lung infections, **including pulmonary tuberculosis**.

Mechanisms of Toxicity

- The trivalent compounds of **arsenic are thiol-reactive**, and thereby activate or inhibit enzymes or alter protein structure by reacting with thiol groups.

- reaction with thiols in critical proteins produces **transcriptional and epigenetic changes** that promote **cancers and tumor growth**.

- Arsenic and its metabolites stimulate oxidant production through **activation of NADPH oxidases** and inference with mitochondrial respiration.

Treatment

- For acute arsenic poisoning, treatment is symptomatic, with particular attention to **fluid volume replacement and support of blood pressure.**

- The **oral chelator** penicillamine or succimer[DMSA]) is effective in removing arsenic from the body.

- The best current strategy for preventing chronic arsenic poisoning is **by reducing exposure**.

Cadmium

- Cadmium (Cd) is a toxic transition metal. Now it has become an important metal with many uses.

Exposure

- Cadmium exposure to the general population occurs mainly through **ingestion of plant-derived foods** and certain types of **seafood**, as well as inhalation of **tobacco smoke and industrial emissions**.

- **Shellfish** accumulate relatively **high levels of cadmium**, and animal liver and kidney can have levels.

- **Tobacco leaves** accumulate high levels of cadmium from the soil making cigarette smoking a major non occupational source of cadmium exposure.

Toxicokinetics

- The **half-life** of cadmium in humans is estimated to **be more than 26 years.**
- Cadmium is **stored in the liver** primarily as cadmium–MT.
- Cadmium–MT may be **released** from the liver and **transported via blood to the kidney**.
- Cadmium is **nephrotoxic**, and when renal pathology is present the **urinary excretion of cadmium is increased.**

Toxicity

- Acute, high-dose cadmium toxicity in humans is now a rare event.
- Cadmium **is toxic to tubular cells and glomeruli**, markedly impairing renal function.
- Cadmium-induced renal toxicity is reflected by **proteinuria as a result of renal tubular dysfunction**.
- **Urinary excretions of proteins and cadmium** have been used **as biomarkers** for cadmium exposure.

- The **long-term** consumption of cadmium contaminated rice caused **Itai-Itai disease**, characterized by **severe osteomalacia and osteoporosis**, resulting in **bone deformities** and concomitant **renal dysfunction.**

- **Vitamin D deficiency** and perhaps other **nutritional deficiencies** are thought to be **cofactors** in Itai-Itai disease.

Lead

- Lead's elemental symbol, Pb. Inorganic lead compounds are used as pigments in paints, dyes, and ceramic glazes.

- Lead **in blood** is primarily (about **99%**) in erythrocytes **bound to hemoglobin**.

- The fraction of lead **store in bone** and **increases with age** from 70% of body burden in childhood to as much as 95% in adulthood.

- Lead **released from bones** may contribute up to 50% of the lead in blood, and can be a significant **source of endogenous exposure.**

Toxicity

- Lead can induce a wide range of **adverse effects** in humans **depending on the dose** and **duration** of exposure.

- **Children** are most sensitive to **effects in the central nervous system**, while **in adults**, **peripheral neuropathy and hypertension** are concerns.

- Other target tissues include the **gastrointestinal, immune, skeletal, and reproductive systems**.

- Effects on heme biosynthesis provide a sensitive biochemical indicator even in the absence of other detectable effects.

- Clinically overt lead **encephalopathy may occur in children with high exposure to lead**, probably at blood lead level of 70 µg/dL or higher.

- **Symptoms** of lead encephalopathy begin with **lethargy, vomiting, irritability, loss of appetite, and dizziness**.

- The pathological findings at **autopsy** are **severe edema of the brain** due to extravasations of fluid from capillaries in the brain.

- The most **sensitive indicators** of adverse neurological outcomes are **psychomotor tests, and broad measures of IQ.**

- Adults with occupational exposure may demonstrate abnormalities in a number of measures in neurobehavior.

- However, **bone lead**, a more reliable marker of **chronic exposure**, is more consistently **associated with both hypertension and cardiovascular mortality**.

- Lead has **multiple hematologic effects**, ranging from increased urinary porphyrins, coproporphyrins, δ-aminolevulinic acid (ALA), and zinc protoporphyrin to anemia.

Treatment

- **Chelation therapy** is warranted in workmen with blood lead level BLL more than 60 µg/dL. For children, criteria have been established.

- The oral chelating agent **DMSA** (also called **succimer)** has advantages over **EDTA** in that it can be given orally and is effective in temporarily reducing BLL.

- However, DMSA neither improves long-term BLL in children nor reduces brain lead levels beyond the cessation of lead exposure alone.

Mercury

- mercury was used to make amalgams with other metals.

- **Mercury vapor** (Hg0) is much **more hazardous** than the liquid form.

- Mercury binds to other elements (such as chlorine, sulfur, or oxygen) to form **inorganic mercurous** (Hg1+) or **mercuric (Hg2+) salts**.

- This metal can form a number of stable **organometallic compounds** by **attaching to one or two carbon atoms.**

Exposure

Dietary Exposure

- Consumption of **fish** is the major route of exposure to methylmercury.

- Occupational exposure may also occur during **manufacture** of a variety of scientific instruments and electrical control devices, and in **dentistry** where **mercury amalgams** are used in tooth restoration.

Toxicity

Mercury Vapor

- Inhalation of mercury vapor at extremely high concentrations may produce an **acute**, corrosive **bronchitis** and interstitial **pneumonitis**

- With **chronic** exposure to mercury vapor, the **major effects are on the central nervous system.**

- The **tremors, gingivitis, and erethism (memory loss, increased excitability, insomnia, depression)** has been recognized as the **major manifestation** of mercury poisoning from inhalation of mercury vapor.

Inorganic Mercury

- **Kidney** is the major target organ for inorganic mercury.

Methylmercury

- The major human health effect from exposure to methylmercury is **neurotoxicity**.

Mechanism of Toxicity

- **High-affinity binding of divalent mercury to sulfhydryl groups of proteins** in the cells is an important mechanism for **producing nonspecific cell injury.**

- **oxidative stress plays a significant role in mercury toxicity.**

- **Reduced glutathione** concentrations and antioxidant enzymes have been reported in mice exposed to methylmercury.

Treatment

- Therapy for mercury poisoning should be directed toward **lowering the concentration** of mercury at the critical organ or site of injury.

- For the most severe cases, administration of **chelating agents** for mercury, such as **cysteine, EDTA, or penicillamine.**

- Chelation therapy is not very helpful for alkyl mercury exposure.

THANK YOU