Metal Deficiency and Diseases

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Abstract

Metals can be both friend and foe to human health. Metal ions are required for many critical functions in humans. Well known examples include pernicious anemia resulting from iron deficiency, growth retardation arising from insufficiency in dietary zinc and heart disease in infants owing to copper deficiency. An overdose of other metals also can be bad news. People with a genetic disorder called Wilson's disease must take drugs to remove toxic levels of copper from their tissues. Iron overload, whether from a genetic disease or from taking too many iron supplements, is also relatively common and sometimes fatal.

At least 24 elements are currently thought to be essential for human beings. H, C, O, P, S, V, K, I, Na, Mg, Si, Cl, Ca, Mn, Co, Ni, Cu, Zn, Se, Mo and Sn. The mammalian biochemistry of several essential elements is poorly understood (e.g. V, Ni and Sn). For Co, only one specific compound, the coenzyme vitamin B_{12}, appears to be essential. Selenium is an essential element yet some of its

compounds are highly toxic. It is important to ask which parts of the compounds are essential for activity: the metal itself, the ligands or the entire complex of metal plus at least some Of The Ligands.

Anemia & Iron

Anemia results from insufficient oxygen supply, often because of a decrease in hemoglobin (Hb) blood levels. Approximately 65 to 70% of total body iron resided in Hb. In the US, many foods, especially those derived from flour, are enriched in iron. In third world countries, however, scarcity of dietary iron is a major contributor to anemia. This information illustrates one important fact about disease that results from metal deficiency, namely, the need for an adequate supply of essential metals in food.

Causes And Consequences Of Zinc Deficiency

The average adult contains ~2 gram of zinc and requires a daily intake of 15 to 20 mg, only half of which is absorbed, to maintain this level. Although food in many technological advanced societies contains sufficient zinc to afford this balance, zinc deficiencies occur in certain populations where there is either an unbalanced diet of food that inhibits zinc absorption. Zinc deficiency produces growth retardation, testicular atrophy, skin lesions, poor appetite and loss of body hair. Sickle - back disease may be due to zinc deficiency.

Copper Deficiency

Copper is found in the brain and heart, but the liver is rich in copper, where it is stored as copper thionine and

released as ceruloplasmin or in the form of a complex with serum albumin. Oysters contain 137 ppm and black pepper contains 53 ppm copper. Excess of copper in humans is toxic and causes hypertension, sporadic fever and even death. It also produces pathological fever in the brain. Wilson's disease results from a genetically inherited metabolic defect in which copper can no longer be tolerated at normal levels.

Calcium Deficiency

It is an essential macro element which performs functions in bone structure, muscle contraction, blood clotting etc. The main cause of arthritis is calcium deficiency. The functioning of muscles is affected by calcium deficiency.

Chromium Deficiency

A human body contains 6 mg chromium. It accumulates in lungs with age. Deficiency of chromium reduces glucose tolerance factor which is connected to diabetes.

Fluorine Deficiency

Deficiency of fluorine contributes to poor dental health and to a lesser extent in copper and chromium also occur.

Selenium Deficiency

Deficiency of selenium, associated with cardiomyopathy, muscular dystrophy, leukocyte inefficiency, liver necrosis and with higher incidence of some cancers.

Iodine Deficiency

Iodine deficiency leads to goitre.The biological consequences of metal deficiency are seen to result from a

breakdown in one or more of the following steps Adequate supply in ingestible form in foodstuffs, absorption and circulation in the body, uptake into cells, insertion into clinical proteins and enzymes requiring the element, adequate storage to supply needed metal in case of stress and an appropriate mechanism to trigger release of the needed element under such circumstances.

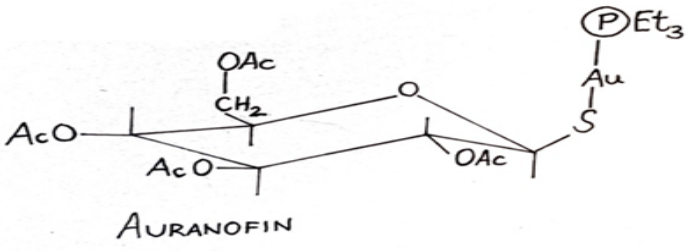
Metals In Medicine

Metals in medicine is the study of the design and mechanism of action of metal containing pharmaceuticals and compounds that interact with endogenous metal ions in enzyme active sites. This diverse field includes the platinum and ruthenium, gold drug chaperons and gadolinium contrast agents. The ability to recognise, to understand at molecular level and to treat diseases caused by inadequate metal ion function constitutes an important aspect of medicinal bioinorganic chemistry. Medicinal inorganic chemistry is a multi-disciplinary field combining elements of chemistry (synthesis,reactivity),pharmacology,biochemistry and medicinal Chemistry.

Some important metals used as medicine are as follows:

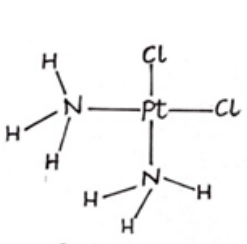
1. **Gold** Au (1) compounds are currently the only class of pharmaceuticals known to halt the progression of rheumatoid arthritis. Gold compounds were painfully administered as intramuscular injections. Colloidal gold sulfides (Sanocrysin), gold thiomalate and its sodium and calcium salts (Myochrisin) and polymeric gold thio glucose (Solganol) are generally included. Auranofin is equally

effective against rheumatoid arthritis and could be orally administered.



AURANOFIN

2. **Calcium** Chelation therapy, using K_2Ca (EDTA), the Ca ion being added to replenish body calcium stores depleted by EDTA coordination, d-penicillamine to remove excess copper causes the symptoms of Wilson's disease.
3. **Platinum** The Pt(II) complex, Cisplatin is one of the most widely used anticancer drugs. Other anticancer drug, platinum complexes are carboplatin and nedaplatin.



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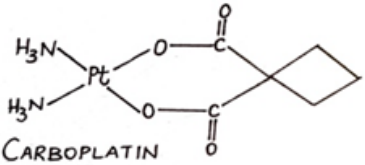
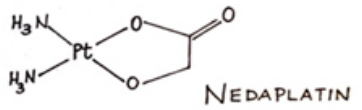


CARBOPLATIN



NEDAPLATIN

4. **Gadolinium -** The gadolinium complex [Gd (DTPA) (H_2O)], an agent currently used in the clinic has been successfully employed to image brain tumors.
5. **Iron -** An iron compound of ferric chloride can be used in MRI. It improves gastro-intestinal images in humans.
6. **Gallium -** Gallium (I) nitrate is active against human

lymphomas but with dose limiting side effects on the kidneys and gastrointestinal tract.

7. **Germanium -** Organic germanium compound, spirogermanium is effective against cancer and can be used as an anticancer agent.

SPIROGERMANIUM

8. **Copper -** The copper containing compounds, Cupralene (sodium-3-allyl cuprothiouredo)-1-benzoate and Dicuprene [bis [8-hydroxyquinoline bis (diethyl ammonium sulfonate)] Cu (II)] can be employed as anti-arthritis drug. Bovine copper - zinc superoxide dismutase has been developed as a drug for treatment of rheumatoid and osteoarthritis.
9. **Ruthenium -** Ruthenium complexes $[RuCl_2 (DMSO_4)]$,$[Ru(NH_3)_4(Asc)]$ (CF_3SO_3), where Asc is ascorbate dianion are believed to bind to DNA, hence used as an anticancer drug.

Metals Used for Diagnosis and Chemotherapy

1. **Radiodiagnostic Agents** Metal complexes having radioactive nuclei find many applications in medicine, such as, in tumor organ and tissue imaging. Early detection of cancer, for example, by selective update and imaging of the tumor using a radioactive metal compound, can facilitate surgical removal or chemotherapeutic treatment

before the disease reaches an advanced stage. Ideally, radioisotopes used for diagnostic purposes should be short-lived, emit low-energy photons and emit no or particles. ^{99m}Tc is perhaps the most desirable, for it gives off 140 keV ray that is readily detected by scintillation cameras and produces clear images. An alternative approach to radionuclide based tumor – imaging agents for diagnosis of disease is to modify, with metal chelating agents, antibodies raised against a biological substance, such as tumor – cell antigen, hormone or other target. Antibodies are proteins that are synthesized by specialized cells of the immune system in response to an external stimulant or antigen. The high specificity and affinity of antibodies for the antigen can be used to target the antibody to a particular biological site, such as a site on the membrane of a particular cell type. Chelating agents are now routinely attached to antibodies and used to find radioactive metal ions. Radionuclide most commonly employed in diagnostic nuclear medicine:

Radionuclide	Half life	Energy (keV)
^{77}Co	271 days	836
^{67}Ga	78 hours	1,001
^{99m}Tc	6 hours	140
^{123}I	13 hours	1,230
^{197}Hg	64 hours	159

2. **Magnetic Resonance Imaging (MRI)** Nuclear Magnetic Resonance (NMR) spectroscopy can be used to image

specific tissues of biological specimens because of differences in the relaxation times of waterproof resonances, usually brought about by paramagnetic metal ions. An early example was the demonstration that manganese salts localize in normal heart muscle tissue in dogs rather than in regions affected by blocked coronary arteries. Since the paramagnetism of the d^5 Mn (II) ion alters the relaxation rate of nearby water protons, the normal and diseased tissue can be distinguished. Of the various metal ions surveyed in attempts to provide clinically useful NMR images in humans, Gd (III), Fe (III) and Mn(II) were found to give best proton relaxation enhancements. The gadolinium complexes [Gd (DTPA) $(H_2O)]^{2-}$, an agent currently used in the clinic, has been successfully employed to image brain tumors. Ferric Chloride improves gastrointestinal images in humans, and manganese salts can be used for heart imaging. An advantage of paramagnetic NMR over radio isotopic imaging agents is that there is no possibility of radiation damage; on the other hand the need for 10-100 mM concentrations at the sight of imaging is a distinct drawback.

3. **Lithium and Mental Health –** One in every thousand people in the United States currently receives lithium, as lithium carbonate, treatment and prophylaxis of manic depressive behavior. Doses of 250 mg to 2g per day are administered in order to maintain a 0.05 to 2.0 mM concentration window, outside of which the drug is either

toxic or ineffective. Use of lithium NMR spectroscopy to study lithium transport in human erythrocytes suggests that it might be possible to apply this method to unravel details of the bioinorganic chemistry of lithium associated with the management of manic depression.

4. **Gold and Rheumatoid Arthritis** Gold compounds have been used in medicine for centuries, an application known as chrysotherapy. Au (I) compounds are currently the only class of pharmaceutical known to halt the progression of rheumatoid arthritis. Until recently, gold compounds needed to treat arthritis were painfully administered as intramuscular injections. Included were colloidal gold metal, colloidal gold sulfides, $Na_3[Au(S_2O_3)_2]$ (Sanocrysin), gold Thiomalate and its sodium and calcium salts (Myochrisin), and polymeric gold thioglucose (Solganol, approved by the FDA). The triethyl phosphine gold (I) tetra-o-acetyl thioglucose (Auranofin) was equally effective against rheumatoid arthritis and could be orally administered.
5. **Anticancer Therapeutic Agents –** Cancer is one of the top killers of the world - wide and is a difficult disease to treat. It is hard to find drugs that are both effective and have low toxicity to the human body as a whole.