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ISSN : 2348 - 5612 | Volume : 04 , Issue : 07 | October - December 2017

Review Of Metal Ions , Diseases due to Deficiency And Toxic Effects Of Metals

Amika, Guest Faculty as Assistant Professor,
Mahila Mahavidyalaya, Jhojhu Kalan, Charkhi Dadri

ISSN : 2348-5612 © URR
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Introduction : Metal ions are required for many critical functions in humans. Scarcity of some metal ions can lead to disease. Well-known examples include pernicious anemia resulting from iron deficiency, growth retardation arising from insufficient dietary zinc, and heart disease in infants owing to copper deficiency. The ability to recognize, to understand at the molecular level, and to treat diseases caused by inadequate metal-ion function constitutes an important aspect of medicinal bioinorganic chemistry.

Metal ions can also induce toxicity in humans, classic examples being heavy- metal poisons such as mercury and lead. Even essential metal ions can be toxic when present in excess; iron is a common household poison in the United States as a result of accidental ingestion, usually by children, of the dietary supplement ferrous sulfate. Understanding the biochemistry and molecular biology of natu- ral detoxification mechanisms, and designing and applying ion-specific chelating agents to treat metal overloads, are two components of a second major aspect of the new science that is evolving at the interface of bioinorganic chemistry and medicine.

Key Words : Anemia and lron, Zinc and Copper Deficiency Toxic Effects Of Metals

Metal deficiency and disease

A. Essential Metals : Four main group (Na, K, Mg, and Ca) and ten transition (V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Mo, and Cd) metals are currently known or thought to be required for normal biological functions in humans. Table 9.1 lists these elements, their

relative abundances, and the medical consequences of insufficient quantities where known. The nutritional requirements for selected members of the essential metals are discussed in the following sections.

B. Anemia and iron : Anemia results from insufficient oxygen supply, often because of a decrease in hemoglobin (Hb) blood levels. Approximately 65 to 70 percent of total body iron resides in Hb. In the U.S., 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 ade- quate supply of essential metals in food. A related aspect, one of greater interest for bioinorganic chemistry, is the requirement that metals be adequately ab- sorbed by cells, appropriately stored, and ultimately inserted into the proper environment to carry out the requisite biological function. For iron, these tasks,

C. Zinc Deficiency , Causes and Consequences

The average adult contains 2 g 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 technologically advanced societies contains sufficient zinc to afford this balance, zinc deficiencies occur in certain populations where there is either an unbalanced diet or food that inhibits zinc absorption. Zinc deficiency produces growth retardation, tes- ticular atrophy, skin lesions, poor appetite, and loss of body hair. Little is known about the biochemical events that give rise to these varied consequences, al- though the three most affected enzymes are alkaline phosphatase, carboxypep- tidase, and thymidine kinase. About 30 percent of zinc in adults occurs in skin and bones, which are also likely to be affected by an insufficient supply of the element. Zinc deficiency is readily reversed by dietary supplements such as ZnS04, but high doses (>200 mg) cannot be given without inducing secondary effects of copper, iron, and calcium deficiency.

D. Copper Deficiency 7

More copper is found in the brain and heart than in any other tissue except for liver, where it is stored as copper thionein and released as ceruloplasmin or in the form of a complex with serum albumin. The high metabolic rate of the heart and brain requires relatively large amounts of copper metalloenzymes including tyrosinase, cytochrome c oxidase, dopamine-{3-hydroxylase, pyridoxal-requiring monamine oxidases, and Cu-Zn superoxide dismutase. Copper deficiency, which can occur for reasons analogous to those discussed above for Fe and Zn, leads to brain disease in infants, anemia (since cytochrome oxidase is required for blood formation), and heart disease. Few details are known about the molecular basis for copper uptake from foods.

Toxic Effects Of Metals

The presence of excess quantities of an essential metal can be as deleterious as insufficient amounts. This situation can arise from accidental ingestion of the element or from metabolic disorders leading to the incapacitation of normal biochemical mechanisms that control uptake and distribution phenomena. These possibilities constitute one major class of metal toxicity. The other broad class results from entry of nonessential metals into the cell through food, skin absorption, or respiration. The toxicities associated with this latter class have received much recent attention because of the public health risks of chemical and radioisotopic environmental pollutants.

In this paper, we review examples of both categories, and discuss ways in which bioinorganic chemistry can contribute to the removal of toxic metals and restoration of normal function. One way involves chelation therapy, in which metal-specific chelating agents are administered as drugs to complex and facilitate excretion of the unwanted excess element. The use of desferrioxamine to treat iron poisoning is one example of this approach. A second role of bioinorganic chemistry is to identify fundamental biological mechanisms that regulate metal detoxification, and to apply the principles that emerge to help control the toxic effects of metal ions in the environment. Recent studies of mercury resistance and detoxification in bacteria provide an elegant example of the way in which biochemistry and molecular biology can be used to elucidate events at the molecular level.

B. Copper Overload and Wilson's Disease

Wilson's disease results from a genetically inherited metabolic defect in which copper can no longer be tolerated at normal levels. The clinical manifestations are liver disease, neurological damage, and brown or green (Kayser-Fleischer) rings in the cornea of the eyes. Patients suffering from Wilson's disease have low levels of the copper-storage protein ceruloplasmin; the gene and gene prod- ucts responsible for the altered metabolism have not yet been identified. Chela- tion therapy, using K2Ca(EDTA), the Ca 2 + ion being added to replenish body calcium stores depleted by EDTA coordination, 2,3-dimercaptopropan-1-ol (BAL, British Anti-Lewisite), or d-penicillamine to remove excess copper, causes the symptoms to disappear. The sulfhydryl groups of the latter two compounds presumably effect removal of copper as Cu(I) thiolate complexes. Wilson's dis- ease offers an excellent opportunity for modem methodologies to isolate and clone the gene responsible for this altered Cu metabolism, ultimately providing a rational basis for treatment.

C. Iron Toxicity 9

Chelation therapy is also used to treat iron overload. Acute iron poisoning, such as that resulting from accidental ingestion of FeS04 tablets, results in corrosion of the gastrointestinal tract. Chronic iron poisoning, or hemochromatosis, arises from digestion of excess iron usually supplied by vessels used for cooking. A classic case of the latter is siderosis induced in members of the Bantu tribe in South Africa, who consume large quantities of beer brewed in iron pots and who suffer from deposits of iron in liver, kidney, and heart, causing failure of these organs. The chelating agent of choice for iron toxicity is the siderophore desferrioxamine, a polypeptide having a very high affinity for Fe(III) but not for other metals. Ferrioxamine chelates occur naturally in bacteria as iron-transport agents.

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