9.1: Metal Deficiency and Disease

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.

Table 9.1 - Essential metals and medical consequences resulting from their deficiency.[a]

a) Data taken from E.-i. Ochiai, *Bioinorganic Chemistry*, Allyn & Bacon, 1977, p. 6

Metal	Abundance	Abundance	Diseases Resulting from Metal Deficiency
	Sea Water mg/1 (ppm)	Earth's Crust mg/1 (ppm)	
Na	1.05×10^{4}	2.83×10^{4}	
K	380	2.59×10^{4}	
M-	1.35×10^{4}	2.09×10^{4}	
Ca	400	3.63×10^{4}	bone deterioration
V	2×10^{-3}	135	
Cr	5×10^{-3}	100	glucose tolerance (?)
Mn	2×10^{-5}	950	
Fe	1×10^{-2}	5.00×10^{4}	anemia
Co	1×10^{-4}	25	anemia
Ni	2×10^{-4}	75	
Cu	3×10^{-3}	55	brain disease, anemia, heart disease
Zn	1×10^{-2}	70	growth retardation, skin changes
Mo	1×10^{-2}	1.5	
Cd	1.1×10^{-4}	0.2	

Anemia and Iron[2]

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 adequate supply of essential metals in food. A related aspect, one of greater interest for bioinorganic chemistry, is the requirement that metals be adequately absorbed by cells, appropriately stored, and ultimately inserted into the proper environment to carry out the requisite biological function. For iron, these tasks, among others, are performed by specific iron-chelating agents, the storage protein ferritin and the transport protein transferrin, the bioinorganic chemistry of which is extensively discussed in Chapter 1.

Another cause of anemia exists in individuals who have a mutant variety of hemoglobin, HbS, in which valine has been substituted for glutamic acid in the sixth position of the β subunits.[3] Interestingly, extensive studies have shown that this phenomenon, which leads to sickling of the red blood cells, does not result from failure of the protein to bind heme or from changes in the O_2 binding constant of the iron atom. Rather, deoxy HbS polymerizes into soluble, ordered fibrous structures that lower the ability of blood to

carry oxygen effectively to the tissues. These results illustrate the importance of structural features remote from the metal-binding domain in determining the functional characteristics of a metalloprotein.

Causes and Consequences of Zinc Deficiency[4-6]

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. An especially interesting example of the latter phenomenon is found in certain villages in the Middle East where phytates, organic phosphates present in unleavened bread, chelate zinc ion and render it inaccessible. Zinc deficiency produces growth retardation, testicular atrophy, skin lesions, poor appetite, and loss of body hair. Little is known about the biochemical events that give rise to these varied consequences, although the three most affected enzymes are alkaline phosphatase, carboxypeptidase, 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 $ZnSO_4$, but high doses (>200 mg) cannot be given without inducing secondary effects of copper, iron, and calcium deficiency.

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-β-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.

Summary

From the above anecdotal cases, for which similar examples may be found for the other metals in Table 9.1, 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 critical 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. Only for iron, and to a lesser extent copper and zinc, is there a reasonably satisfying picture of the molecular processes involved in this chain of events. The elucidation of the detailed mechanisms of these phenomena, for example, the insertion of iron into ferritin, remains an exciting challenge for the bioinorganic chemist (see Chapter 1).