

# Metal Biology: Aspects of Beneficial Effects

## METAL BIOLOGY

The biology of metals is not a new concept. It may be expressed as trace element biology, which in a sense is a broader concept. Nevertheless, in this presentation we also include nonmetals in metal biology. Trace elements are often described as minerals—from a fundamental point a misconception. Depending on the platform from which trace elements are defined we find different approaches. An analytical chemist would probably define them as elements appearing in concentrations below 100 mg kg<sup>-1</sup>. If a biologist is asked, you would most certainly be presented with an exclusion definition.

We start with excluding the major elements of life: hydrogen, carbon, nitrogen, and oxygen. In the next phase the minor elements sodium, magnesium, potassium, and calcium as well as phosphorus, sulfur, and chlorine are excluded. In addition, the noble gases helium, neon, argon, krypton, xenon, and radon are excluded for obvious reasons. At the end of this process, we have excluded 17 of the elements. The number of naturally occurring elements is disputed but here we will assume that they are 90. Seventy-three of these elements are defined as trace elements.

The fascinating aspect of these two different approaches in defining trace element is that both sides arrive at about the same elements, at least with occurrence in living systems as a basis. There are further distinctions among trace elements that have to be accounted for. Not all 73 elements are essential for life. Significant unanimity is reached for 14 or 15 elements.

## ESSENTIALITY AND DOSE RESPONSE

What is essential for life is not easy to express. During the last decades various definitions have emerged, some very strict and others primarily pragmatic. The current definition of essentiality is that an element is considered essential to an organism when reduction of its exposure below certain limit results consistently in a reduction in a physiologically important function, or when an element is an integral part of an organic structure performing a vital function in the organism.

What is said above has the implication that the dose response of nonessential elements goes from normal function to malfunction and eventually to death. For essential elements the dose response shows a different behavior. At low doses, deficiency occurs and with increasing doses we approach an interval of safe and adequate intake (dose). With even higher doses, toxicity appears, and death may result. As Paracelsus claimed, toxicity is only a matter of dose. Even essential trace elements in excessive amounts can cause toxicity (Fig. 1).

## IRON: SAVIOR AND THREAT

If it is meaningful to classify essential trace elements, we would probably put iron among the most important ones. Most people know that iron is necessary for the transport of oxygen by hemoglobin in the red cells. However, this is only one of the important tasks performed by iron in interaction with certain biomolecules. Iron functions are of two major classes. Either it performs the function as an ion, most often in conjunction with sulfur in iron-sulfur proteins as well as in some iron proteins using simple N/O coordinating ligand, or as an integral part of the heme group. The biosynthesis of heme takes place in mitochondria (Box 1). It is synthesized through insertion of iron into protoporphyrin by ferrochelatase.

The start of the synthesis is different in eukaryotes and prokaryotes (Box 1) as compared with plants. Glycine and succinyl-CoA is combined with  $\delta$ -aminolevulinic acid in eukaryotes and prokaryotes by the enzyme  $\delta$ -aminolevulinic synthetase. In plants glutamate is linked to a specific tRNA and successively acted upon by ligase producing glutamyl-tRNA. This compound is transferred to glutamate 1 semialdehyde by a reductase (1). Then an amino transferase catalyzes the formation of  $\delta$ -aminolevulinic acid. The enzymatically driven sequence is thereafter identical for plants and animals until the production of protoporphyrin IX. In prokaryotes and eukaryotes, as well as in plants, iron is incorporated through the catalysis by ferrochelatase to form heme. Plants possess the alternative pathway of incorporating magnesium catalyzed by magnesium chelatase and the end product is chlorophyll (2).

Heme proteins are very important in biology. It is definitely not only hemoglobin and myoglobin, the two oxygen-transporting proteins in animals, that are of vital interest. Myoglobin is a smaller molecule relative to hemoglobin and is the principal oxygen storage protein. An interesting property of hemoglobin, in addition to its oxygen-binding ability, is its enzymatic activity. It has been thought that the oxygen carrier function was so specialized that globins were not recruited to new tasks; however, it has recently been found that the globin of some marine worms (*Amphitrite ornata*) has evolved into a powerful peroxidase, more precisely dehaloperoxidase. This enzyme catalyzes the oxidative dehalogenation of polyhalogenated phenols in the presence of hydrogen peroxide at a rate at least ten times faster than all known halohydrolyses of bacterial origin (3). Catalase is an enzyme that can transfer hydrogen peroxide into water, a process of utmost importance in the metabolism of molecular oxygen to water in the mitochondria.

Cytochromes constitute a group of heme proteins with distinctive visible-light spectra that function as electron carriers from biological fuels to oxygen. Thus they are vital members of the mitochondrial electron-transfer chain. In addition, the cytochromes are also essential components in plant chloroplast for photosynthesis. It is the ability of the iron center to undergo reversible Fe(III)  $\leftrightarrow$  Fe(II) changes to allow them to act as electron-transfer centers.

Cytochrome P-450 enzymes are heme proteins that function as monooxygenases to catalyze the insertion of oxygen into a C–H bond of an aromatic or aliphatic hydrocarbon (Box 1). Examples of the biological functions of cytochrome P-450 are drug metabolism and steroid synthesis (Box 1). One of the many interesting aspects of cytochrome P-450 is that some are inducible, which means that following exposure of the cell to an inducing chemical enzyme activity increases, in some cases several orders of magnitude (4).

There are also iron-activated enzymes. The most prominent example of this class of enzymes is heme oxygenase, which has evolved to carry out oxidative cleavage of heme, a reaction essential in several physiological processes as diverse as iron reuse and cellular signaling in mammals and synthesis of essential light-harvesting pigments in cyanobacteria (Box 1) and higher plants, as well as the acquisition of iron by bacterial pathogens (5).

The porphyrin ligand environment of iron that occurs in hemoglobin and myoglobin is also important in redox enzymes (Box 1). Iron-sulfur clusters were not familiar to inorganic