Transport of nonessential metals across mammalian cell membranes

Nazzareno Ballatori and Michael S. Madejczyk

Abstract

Nonessential metals are opportunistic. They compete with essential metals for binding to various cofactors, receptors, transcription factors, transporters, and other metalloproteins, and in doing so they gain access to various cellular and subcellular compartments, and interfere in the functions of the essential metals. Because of their high chemical reactivities, nonessential metals also interact nonspecifically with a multitude of other cellular ligands, and interfere with many other cellular processes. In general, nonessential metals cross biological membranes by three mechanisms. First, as indicated above, they often compete with endogenous metals for transport on the various metal ion transporters, pumps, and channels. Alternatively, they may form complexes that are then substrates for other ion and organic solute transporters and pumps. A third general mode of transport involves both signal-induced (e.g. receptor-mediated) and constitutive endocytosis of metals ions and metal complexes. In contrast with these mediated transport pathways, simple diffusion appears to play only a minor role in metal transport. Collectively, these permeation pathways allow toxic metals to reach diverse cellular and subcellular targets, but can also be exploited in the design of therapeutic strategies aimed at accelerating the removal of these toxic elements from the body.

1 Introduction

Metal ions are unusually reactive species: they can participate in reduction or oxidation reactions, acid-base chemistry, or ligand coordination reactions. These chemical properties allow the essential metals to catalyze a variety of biochemical reactions and physiological processes. However, both the essential and nonessential metals have comparable reactivities, and thus their concentrations must be maintained below a certain level to avoid nonspecific or toxic reactions. As described in other chapters in this series, many of the genes and gene products that regulate the concentrations and chemical activities of essential metals have now been identified and characterized, including metal-sensitive transcription factors, chaperones, cofactors, transport proteins, and enzymes. Genetic or acquired defects in many of these genes are associated with a variety of human diseases (Andrews 2002; Chung and Wessling-Resnick 2004; Cox and Moore 2002; Eide

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2004; Mackenzie and Hediger 2004; McKie and Barlow 2004; Miyajima 2002; Nittis and Gitlin 2002; Petris 2004; Pietrangelo 2004; Schaefer and Gitlin 1999; Vulpe et al. 1999).

In contrast with the essential metals, the nonessential metals generally lack these regulatory controls, and thus these elements are particularly hazardous to living organisms. The present report provides an overview over the general mechanisms by which nonessential metals permeate cellular and subcellular compartments. The elucidation of these pathways should help to define their mechanism of action and toxicity in living organisms; it should facilitate the discovery of novel biomarkers of exposure and dose, and may identify novel therapeutic strategies for metal intoxication.

2 Metal ion interactions with biological molecules

Transport of a given nonessential metal is dependent to a large extent on its chemical form in biological fluids. Because formation of metal complexes is highly favored thermodynamically, most heavy metals are present in biological tissues and fluids as complexes, rather than as the free cations. Although the thermodynamic stability of coordinate-covalent bonds is typically quite high, they are kinetically labile, so that a given metal may exchange rapidly from one ligand to another. This kinetic lability has proven to be the greatest stumbling block to the isolation and identification of metal complexes in biological fluids and tissues. For example, during tissue homogenization or chromatographic separation, additional binding sites may be exposed (or some eliminated), thus altering the distribution of the metal. Reactivity varies between metals, and is influenced by the nature of the ligand, whether mono- or multidentate, and the pH and ionic strength of the media. Copper, for example, forms relatively low affinity complexes with albumin or amino acids, but is tightly bound to ceruloplasmin. Similarly, mercury and cadmium form kinetically labile complexes with amino acids, glutathione, or albumin, but more stable complexes with metallothionein. Chelating agents normally display low specificity for metals, and bind a wide range of metals.

For the heavy metals, detoxification or protection from toxicity usually involves binding to specific proteins, including metallothioneins which form complexes with copper, zinc, cadmium, mercury, and other metals; ferritin, transferring, and hemosiderin, which are predominantly iron binding proteins, but also have some affinity for other metals; and ceruloplasmin, which chelates copper and possibly other metals. Similarly, the biological activity of the essential trace metals is due to their ability to attach to specific prosthetic groups on proteins. Manganese may be an exception to this generalization, since at least some of its biological functions are related to the free divalent metal.

Conversely, metal-induced toxicity is usually attributed to the reactivity of the "free" metal, and is most often observed in tissues involved in their transport, such as the intestine, liver, and kidney. Toxic metals, or an excess of essential metals