NUTRITION AND DIET RESEARCH PROGRESS

THE ROLE OF ESSENTIAL METALS IN HUMAN NUTRITION

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Contents

Description

Minerals, like the essential metals of the human body, are crucial for human health. Although sometimes occurring in only minuscule amounts, their presence or absence can have major consequences for our cells and tissues. However, the function and interaction of metals with proteins and other metabolites in our body are not well investigated. Therefore, this book gives an introduction to metal biology and does so in a unique manner. It is based on research conducted at the University of Limerick, Ireland. It is written with students in Food and Health Sciences interested in metals and a delicious dinner. To describe the biological cycle of metals, the book starts with unique recipes developed by the students, cooked with selected ingredients based on the content of a specific metal, thereby creating a dish with maximum metal content. We then follow each metal through the gastrointestinal system, explore its distribution in the body, and describe its major functions until it is finally excreted, and the reader is hungry for the next metal and meal.

This book is written for students in Life Sciences, especially Physiology, Food and Health Sciences, Nutritional Sciences, Biosciences, related fields, researchers, teachers, and the interested public. Every day, we make choices about what we eat. So why not think about which metal we may like most today and cook a meal that reminds us again of the role of this metal in the human body? Reading this book will hopefully fill the stomachs as much as the readers' brains. Bon appetite.

Preface

Our body's physiology depends on the functional interplay of organ systems. These organ systems comprise organs formed by one or multiple tissues (muscle tissue, nervous tissue, connective tissue, and epithelial tissue). The tissues are created by various cell types organized to form a functional biological structure. Thus, the cell is recognized as the smallest functional unit, and, in turn, the physiology of our body is dependent on the correct function of cells.

Cells harbor subcellular compartments vital to their physiology, such as the cell membrane, the nucleus, and the cytoplasm. The latter contains the cytosol (fluid part) and a variety of organelles. These components are built by various molecules classified as proteins, RNA, DNA, phospholipids and other lipids, polysaccharides, inorganic ions (e.g., metals), and other smaller metabolites in an aqueous solution.

Much emphasis today is put on the functional role of proteins made from instructions encoded in the DNA. The proteins are created from different amino acids and generated through the transcription of genes found in the DNA. In transcription, the DNA sequence of a gene is used to form a copy resulting in an mRNA. In translation, the mRNA sequence is decoded to specify the protein's amino acid sequence. Errors in the DNA sequence, such as missing sequence information, shuffled sequences, or inverted sequences, known as mutations, have been linked to the dysregulation of cellular functions that may cause diseases.

Identifying mutations linked to specific disorders has contributed enormously to our understanding of the role of proteins in cells, the physiology of cells, and, ultimately, our body. In fact, the function of most proteins in our body is at least partially known. However, this focus on genes and their encoded proteins as key determinants of cellular and bodily functions has led to a neglect in recognizing the contribution of other components present in cells, such as lipids or trace metals.

Inorganic ions (e.g., metals) work hand in hand with proteins as they bind to, activate, or de-active them, thus having structural and regulatory roles. In addition, free metal ions have an important signaling function within and between cells. Nevertheless, our knowledge about the physiology of metals is still very limited.

A major difference between studying the gene expression of a cell, for example, using transcriptomics (evaluating the complete set of RNA transcripts that are produced by the genome) and studying the presence of metals (metallomics, studying the distribution and quantity of metal ions in a defined space) is that we are born with a specific genome. Today, we are still very limited in our ability to actively change the DNA code inside the nucleus of our cells. In contrast, the presence of metals is very variable. Our bodies do not produce metal ions. Cells cannot synthesize them like proteins made of single amino acids or other metabolites our cells create. Instead, metal ions must be taken up and supplied to cells; many factors influence their amount and presence. Likely the most crucial factor is nutrition. Our diet is the major and sole source of metals for most. However, other factors, such as environmental pollution with non-essential metals, may impact the presence and quantity of essential metal ions in our bodies.

Given that the metallome (the distribution of metal ions in a compartment) is dependent on our actions and is more and more known to influence the function of cells, and thereby our whole body's physiology, for example, through crosstalk with genes and proteins, it is time to increase awareness and knowledge around the function of these metals. Therefore, this textbook is dedicated to the role of essential metals (that we mostly get through nutritional choices). It will discuss the function of proteins and other cellular components. However, only insofar they are linked to the physiological role of metals. Thus, the reader must remember basic knowledge of cell biology that covers non-metal-related processes.

The fact that most metals that currently reside in your body have entered it through your diet means that we need to consider not only the role of metals in our body but also whether it is likely that the metals are present and in sufficient quantity. Undoubtedly, our diet has significantly changed over time and has done so much quicker than any adaptions that could be made on a genetic level that would allow us to compensate for any significant shift in metal availability through new dietary patterns.

Very likely, humans have always been omnivorous. Nevertheless, humans may have mainly been carnivorous for millions of years in early human evolution. Only about 10,000 years ago, men became increasingly sedentary, and the development of agriculture led to a shift toward a much more plant-based diet. As described in the first chapter, the bioavailability of some metals in meat versus a plant-based diet is dramatically different. Furthermore, our dietary habits are still in flow. The industrial revolution in the 19th century led to urbanization and international trade, making it possible to consume "exotic" products. Food industrialization is an enormous business today, and the fast food phenomenon appeared only during the last 50 years. With its suspected impact on our physiology (health), leading to widespread obesity, diabetes, and cardiovascular diseases, it reminds us that changes in dietary patterns can have significant consequences for our body's physiology. The presence and availability of metals may have a vital role in this, as it is shifted dramatically from early carnivorous to fast food lifestyle, with our body still adapted to a diet we no longer consume.

Today it is evident that minerals, like the essential trace metals of the human body, are crucial for human health. Although sometimes occurring in only minuscule amounts, their presence or absence can have major consequences for our cells and tissues. This book uniquely introduces metal biology to combine the nutritional aspect with trace metal physiology in our body. It is based on research conducted at the University of Limerick and elsewhere. It is written with students in Food and Health Sciences of the University of Limerick interested in metals and a delicious dinner.

To describe the whole biological cycle of metals, the book starts with unique recipes developed by the students, cooked with selected ingredients that are chosen based on the content of a specific metal, thereby creating a dish with maximum metal content. We will then follow each metal through the gastrointestinal system, explore its distribution in the body, and describe its major functions until it is finally excreted and the reader is hungry for the next metal and meal. Reading this book will hopefully fill the stomachs as much as the readers' brains.

Bon appetite.

Andreas M. Grabrucker
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I would be unable to get my work done without the continual support of my colleagues at the Bernal Institute of the University of Limerick, the Department of Biological Sciences, and my research team. Because of their outstanding efforts, I find time to work on book projects like this.

Most of all, many thanks to everyone who continuously listens to my stories about biometals. Thanks for your patience.

Chapter 1

Introduction

The physiology of the human body is complex and sometimes difficult to understand. Luckily, in recent years, biological research benefitted incredibly from the ability to sequence whole genomes at an ever-increasing pace and decreasing costs, leading to the identification of many genes and their proteins that mediate key physiological processes. However, these proteins are in a complex environment where they interact with countless metabolites and, importantly, metal ions. Unfortunately, the role of metals is still much less understood, but getting more and more into the focus of research as metals and metal-protein interactions seem critical for many processes, and their dysregulation may even lead to diseases.

However, studying metals in the human body faces a significant problem. We still do not know exactly which metals should be there and which ones not. Similar to our DNA, which harbors sequences from viral DNA that are there, but without obvious function, an artifact from our past struggles with viruses integrating their genome into ours, we can measure today the presence of metals in minuscule quantities. However, we are unsure whether some metals we detect have a biological function.

Generally, in the periodic table, elements are classified as non-metals, metalloids, and metals (Figure 1.1). Surprisingly, the majority of the elements are metals. Metals can be grouped further as alkali, alkaline earth metals, transition metals, post-transition metals, and lanthanides and actinides.

Some metals are toxic to our bodies if their levels surpass a certain threshold. These will be discussed shortly in Chapter 15. In contrast, it is also clear that there are metals that we need in sufficient quantities to ensure health and well-being and even to stay alive. These are "essential metals" and will be summarized in the next chapter and each in more detail in the following chapters that are arranged according to the abundance of the metal in the average human body, starting with the highest concentration.

Detecting metals, especially trace metals and ultra-trace metals, is technically challenging. Only recently has it been possible to detect the extremely low amounts of some metals in the human body. Like most organisms on earth, our body contains only a fraction of all metals found in this universe. To 99.98%, our bodies are made of oxygen (O), carbon (C), hydrogen (H), nitrogen (N), phosphorus (P), sulfur (S), chlorine (Cl), and the four metals calcium (Ca), potassium (K), sodium (Na), and magnesium (Mg) (Emsley, 1998). Therefore, Ca, K, Na, and Mg are termed common elements or common metals (Table 1.1). The remaining metals are significantly less abundant and are therefore referred to as trace and ultra-trace metals. However, the boundaries are blurred, especially with technological advances that allow the detection of even lower concentrated metals. Often, iron (Fe), zinc (Zn), copper (Cu), manganese (Mn), molybdenum (Mo), and cobalt (Co) are classified as trace metals as they are found, on average, at concentrations of 4.2 g (Fe), 2.3 g (Zn), 0.072 g (Cu), 0.012 g (Mn), 0.005 g (Mo), and 0.003 g (Co) in a human body of 70 kg body weight (Table 1.1). However, Mn, Mo, and Co may be closer to the ultra-trace element concentration range (Table 1.1).

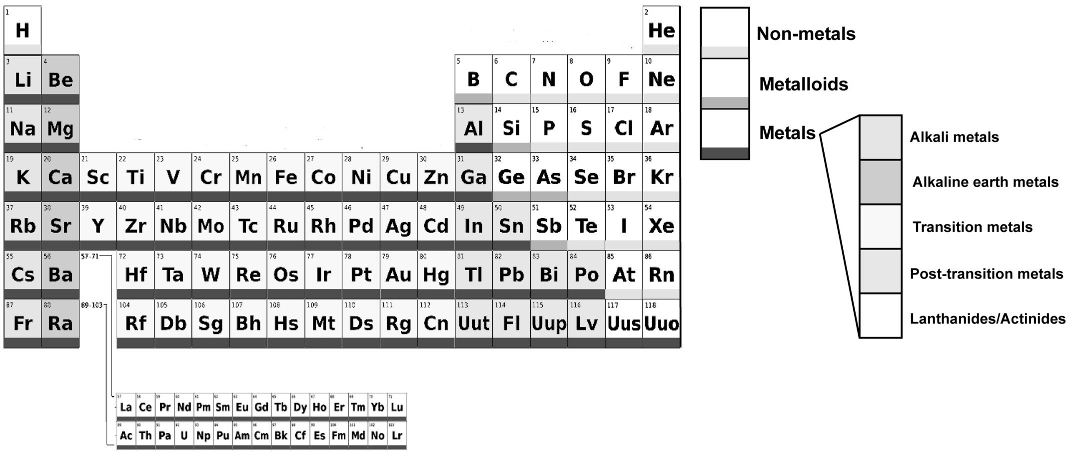

Figure 1.1 The periodic table of elements distinguishes between non-metals, metalloids, and metals.

All metals mentioned above are essential, meaning they have a biological function and are needed for survival. Whether chromium (Cr) joins this list is still under debate. Therefore, not surprisingly, they are among the highest concentrated metals detectable in human tissues. However, other metals can be measured. Most, but not all, are in the ultra-trace metal range, such as gallium (Ga), silver (Ag), niobium (Nb), zirconium (Zr), yttrium (Y), gold (Au), scandium (Sc), tantalum (Ta), vanadium (V), or tungsten (W) (Table 1.1). Exceptions are found, such as titanium (Ti), of which we can measure about 20 mg in the average human. While it is generally assumed that these metals are neutral to the human body and that their presence results from accidental uptake, this notion is not based on scientific data. Even ultra-trace metals may contribute to balancing metal profiles and thus indirectly play a physiological role. Unfortunately, for many metals, it is currently unknown how they affect the human body. In contrast, other metals that can be detected in the average human body, such as mercury (Hg) and lead (Pb), have been reported to be toxic even at a minimal concentration (Tchounwou et al., 2012).

However, like the transcriptome or proteome that differs between cell types, responds to external stimuli, and varies over time, the metallome is dynamic. In addition, metals may shift between their free ionic and protein-bound forms. To date, the physiological metallome is unknown for most organs, tissues, and in particular, cells or subcellular compartments, as it may vary significantly, and different stable metal profiles are possible. Thus, many organs, tissue, and cells will not follow the distribution shown in Table 1.1 and will selectively enrich specific metals. Nevertheless, we have a notion that some metal profiles may be characteristic of specific disorders. These may be potential biomarkers and consequence of altered physiology and metabolism due to pathologies or disorders (Pfaender and Grabrucker, 2014). Notably, an altered metal profile may also be causative for a pathology or specific disorder or act modulatory, influencing the clinical phenotype of patients.

Many factors lead to the establishment of a cell-, tissue-, or organ-specific metal profile. Apart from specific transport and storage proteins our body provides to regulate essential metals, which will be discussed for each metal in the corresponding chapter, general availability is key. However, availability, for example, the metal concentration in a food item, does not

Table 1.1 Average concentration of transition metals in the human body (based on Emsley, 1998)

Metal composition of the average human body			
Metal		g in 70 kg adult	essential
Ca	Calcium	1000	●
K	Potassium	140	●
Na	Sodium	100	●
Mg	Magnesium	19	●
Fe	Iron	4.2	●
Zn	Zinc	2.3	●
Rb	Rubidium	0.68	
Sr	Strontium	0.32	
Pb	Lead	0.12	
Cu	Copper	0.072	●
Al	Aluminum	0.06	
Ce	Cerium	0.04	
Ba	Barium	0.022	
Sn	Tin	0.02	
Ti	Titanium	0.02	
Ni	Nickel	0.015	
Cr	Chromium	0.014	?
Mn	Manganese	0.012	●
Li	Lithium	0.007	
Cs	Cesium	0.006	
Hg	Mercury	0.006	
Mo	Molybdenum	0.005	●
Co	Cobalt	0.003	●
Ag	Silver	0.002	
Nb	Niobium	0.0015	
Zr	Zirconium	0.001	
La	Lanthanum	0.0008	
Ga	Gallium	0.0007	
Y	Yttrium	0.0006	
Bi	Bismuth	0.0005	
Tl	Thallium	0.0005	
In	Indium	0.0004	
Au	Gold	0.0002	
Sc	Scandium	0.0002	
Ta	Tantalum	0.0002	
V	Vanadium	0.00011	
Th	Thorium	0.0001	
U	Uranium	0.0001	
Sm	Samarium	0.00005	
Be	Beryllium	0.000036	
W	Tungsten	0.00002	