

The role of metal ions in biological oxidation – the past and the present

M. Kleczkowski^{1,2}, M. Garncarz¹

¹ Department of Pathology and Veterinary Diagnostics, Faculty of Veterinary Medicine, Warsaw University of Life Sciences, Nowoursynowska 159C, 02-787 Warsaw, Poland

² Veterinary Hygiene Laboratory, Nowogrodzka 160, 18-402 Lomza, Poland

Abstract

Two theories, one based on the metabolism of inorganic substances, the other on metabolism of organic substances, have played an important role in the explanation of the origin of life. They demonstrate that the original environment of life on Earth was seawater containing micronutrients with structural, metabolic and catalytic activity. It is assumed that the first primitive organisms lived around 3.8 billion years ago and it was also then that the first catalytic reaction involving metal ions occurred. Biological oxidation leading to oxidative stress and cell damage in animals represents one of these types of reactions which are responsible for many animal diseases. The role of prooxidative and antioxidative actions of transition metal ions as well as their neuropathological consequences have therefore been the topic for many research projects. There is hope that metal chelates and antioxidants might prove to be a modern mode of therapy for i.e. neurodegenerative diseases. The aim of this review is to show the evolution of scientific knowledge on metal ions, their biological oxidation, and an overview of their role in physiology and in pathological processes.

Key words: metal ions, oxidative stress, prooxidants, antioxidants

Introduction

The historical account of the role of bioelements in the evolutionary process of life on Earth goes back to ancient times. Geochemistry deals with movement and distribution of trace elements in nature taking into account their movement within space, time and different systems and so it is a science that continues to provide important information to the understanding of the phenomena which have occurred in the past and continue to occur presently. The development of life in our ecosystem is based on an intricate relationship between the soil, which provides basic and essential minerals,

and air, water and solar energy. There are presently two separate general theories that try to explain the origin of life: the inorganic theory and the organic theory. Cairns introduced the theory of inorganic origin (Meyer 1996), that states that life originated from basic forms of minerals found in clay and that the capability to self-replicate and evolve is important in this developmental process. The second theory describing an organic origin was presented by Haldane and Oparin (Pennazio 2009, Tirard 2010). Their belief was that biorganic compounds such as amino acids, amongst others, could be found within simple mixtures of conglomerates like H₂, H₂O, CH₄ and NH₃ (Ferry et al.

2006). Chemical reactions could have then led to the formation of polypeptides and other compounds. However, such chemical reactions have not been soundly documented. It is believed that these processes were catalyzed by minerals such as and especially transition metal ions. Two types of organisms, autotrophic and heterotrophic, have been proposed based on the two above mentioned metabolic processes (Pennington and Ellis 1993). Inorganic compounds like water, metallic ions, and sulfur and oxygen metallic compounds are found in the environment and play crucial roles in the development of life (Meyer 1996). This quandary has however been largely ignored in most studies with the exception of the idea of clay surface adsorption of organic compounds, which has to the contrary received some attention. Also the concentration of minerals in tissues and body fluids of animals and in the environment, correlate with the influence of the inorganic environmental factors (i.e. water, soil, plants, food, fodder) (Cairns 1982). Importantly, the elements mentioned above were created as a result of a series of interactions leading to the development of metabolic processes of animal organisms.

The influence of earthly metallic elements on living organisms can be divided into three categories: structural, metabolic and catalytic (Olf et al. 2009). This influence can be seen through studies of the trophic chain. Of the more important structural elements, Ca, Si, Cu and Fe can be found in biomolecules, bones and cell membranes. The main metabolic elements include Mg, Ca, Fe and Mn. Catalytic elements including Cu, Fe, Zn, Mo, Mn, Mg, Ca, Ni and Co are needed for proper function of many enzymes and the metabolism in animal organisms. The formation of ions and neutral molecule complexes with various ligands is characteristic for transition metals. By contrast, complex compounds play an enormous role in the natural environment. Some examples include vitamin B₁₂ (a cobalt complex), hemoglobin (a complex of iron (II)), chlorophyll (a magnesium complex). Because copper and iron are amongst transition metal ions with unpaired electrons, they usually participate in free radical reactions and serve as substrates for the formation of highly reactive hydroxyl radicals. Their number in the body is limited, but each released metal ion should be bound to a protein in a non-reactive form. The so-called preventive antioxidants in animals serve precisely this purpose. They include ceruloplasmin, which binds copper, transferrin, which is a major iron-transporting protein in the body and lactoferrin, an iron binding protein (Takayama and Takezawa 2006). These minerals are also involved in the formation of antioxidant systems responsible for counteracting damage to subcellular structures.

The key mechanisms listed below play an import-

ant protective role against radicals. One of these mechanisms is based on suppressive reactions of excited molecules by compounds such as carotenes and vitamin E. Non-enzymatic mechanisms involve such substances as metallothionein, sequestered metals, transition metal ions, ceruloplasmin, transferrin, and polyamides. Enzymatic mechanisms involve superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, glutathione S-transferase and a group of secretory phospholipases as well as mechanisms involving heat shock proteins (Woźniak and Czyż 2008). A prooxidative-antioxidative balance necessary for good health and high production state of animals is maintained particularly thanks to metal-dependent antioxidants. This review presents the evolution of knowledge on metal ions in the organic world with an emphasis on their role in oxidative stress, prooxidative and antioxidative activity and their neuropathological effects.

History of the origin of metal ions in the organic world

At the time the earth was formed, about 4.7 billion years ago, it was made up solely of inorganic compounds. There was probably no oxygen in the early atmosphere and it was therefore a reducing rather than oxidizing environment when compared to the present time. At that time the environment mainly consisted of compounds such as nitrogen, methane, carbon dioxide, carbon monoxide and water vapor. Only about 2.4 one billion years ago, as a result of the great oxidation event, more oxygen was found in the environment. However, the general lack of oxygen contributed to the fact that many of the metals historically occurring earlier were found in the non-oxygenated form. Molecules vital for life were synthesized during this period of chemical evolution, starting with inorganic and small organic molecules via a series of reactions that led to the formation of nucleic acids and protein elements. Polyphosphates were one of the molecules synthesized during the extraordinary evolution of inorganic and organic molecules. Free energy was needed for the next step of evolution and with radiation from the sun the next steps occurred – polymerization and organization of molecules. It is possible that what followed were photoreactions and heterotrophic photoassimilation reactions. A fascinating question is when did first cells evolve? It is assumed that the first cells evolved about 3.8 billion years ago, the time when the first catalytic reactions with participation of metal ions probably took place. It is also believed that the first primitive organisms lived from 3.6 to 3.8 billion years ago. Finally, catalytic actions of metal ions and complex reactions

Table 1. Mineral concentrations in sea water and extra – and intracellular body fluids of mammals (Österberg 1995, Kabata-Pendias and Pendias 1999).

Mineral	Sea water (A)	Extracellular body fluids (serum) (B)	Intracellular body fluids (C)	Ratio (A:B)	Ratio (A:C)
Selected macronutrients					
Ca (mmol/dm ³)	10.0	3.0	0.01	3.33	1000.0
Mg (mmol/dm ³)	54.0	1.0	20.0	54.0	2.7
P (mmol/dm ³)	0.001	1.0	100.0	0.001	0.00001
Na (mmol/dm ³)	470.0	138.0	10.0	3.41	47.0
K (mmol/dm ³)	10.0	4.0	110.0	2.50	0.091
S (mmol/dm ³)	28.0	1.0	5.0	28.0	5.6
Selected micronutrients					
Cu (µmol/dm ³)	1.0	10.0	100.0	0.1	0.01
Zn (µmol/dm ³)	0.1	18.0	1000.0	0.006	0.0001
Co (µmol/dm ³)	0.0006	2.0	100.0	0.0003	0.000006
Fe (µmol/dm ³)	10.0	20.0	10 000.0	0.5	0.001

Table 2. Concentration of Mg, Ca, and P in the serum of cows (mmol/dm³) (Rutkowiak 1987, Underwood and Suttle 1999, Barszcz et al. 2009, Sobiech et al. 2010).

No	Indices	Mineral levels before and after the transition period	Physiological hypocalcemia after delivery	Cows with paresis puerperalis
1	Mg	0.74-1.23	0.62-1.23	0.41-1.85
2	Ca	2.12-2.99	1.75-2.12	0.62-1.75
3	P	1.61-2.26	0.97-1.61	0.32-1.45

with protein molecules came to play a role in the evolutionary process (Österberg 1995, Ingber 2000).

Archanobacteria were the first single celled organisms living in a hot environment (120°C). During the early period of evolution the temperature of sea water was also very high. We can tell that sea water was involved in early life processes when comparing concentrations of selected metal ions between sea water and extra- and intracellular body fluids (Table 1).

Table 1 shows that the ratio of macronutrient concentrations (except P) in sea water compared to extracellular body fluid was much higher than the micronutrients. However, the ratio of the majority of both macro – and micronutrient concentrations in sea water and intracellular body fluid, with the exception of Ca and Na, were significantly lower. This clearly demonstrates that the mineral concentration in sea water had a significant effect on the formation of metabolic processes in the organic world. Moreover, metal ions play an important role in many life processes yet knowledge of their position in biological systems has to date not been completely elucidated. Additionally, the role of

some metal ions are almost completely unclear (Kabata-Pendias and Pendias 1999). These include Al, Ba, Bi, Ge, Li, Pb, Rb and Ti, all ions that are present in living organisms because they can be obtained through physical or chemical processes upon contact with the environment.

The important role in early life processes of magnesium can be confirmed by its very high concentrations (54 mmol/dm³) in ocean water, being higher than any other metal ion with the exception of sodium. There are similar concentrations of magnesium and other macroelements in the serum of cattle and in the environment (Table 2).

Two types of metal ions are recognized. The first is found in metalloproteins – metal ions are integral elements of protein molecules. The second is a group of labile metal ions found as protein complexes. These metal ions have led us to believe in the existence of a redox potential, which is a biological system that evolved as a result of random mutations. Selected mutations might have caused the formation of metal ion binding sites. Of these, the Cu (II) binding site allows

for the most stable binding with amino acids. Zn(II) and many other metal ions can also have binding sites on specific proteins. Sodium and potassium ions play very important roles firstly in maintaining membrane potentials, as well as maintaining electric neutrality around macromolecules, proper ionic strength and osmotic pressure. In more advanced life forms calcium ions take part in early regulation of CO₂ in the environment and, in intracellular functions, in bone formation and nerve transmission, as well as hormonal signaling, blood coagulation, and muscle contraction. There is a different distribution of metal ions in tissues and body fluids of living organism, with Ca(II) dominating in the extracellular fluids (i.e. serum) and Mg(II) found mostly in intracellular fluids. This difference can provide a gradient between Ca(II) concentrations across cell membranes, which (gradient) in turn can change during early life periods in an environment of high CO₂ pressure and intensive biomineralization period.

The most important trace-elements in early redox reactions include iron and manganese. Iron is one of the most abundant elements found on Earth. Many of the first metalloproteins consisted of iron-sulphur complexes formed during photosynthesis that acted as a strong reducing factors (ferredoxin). There are two known structural properties of the old iron-sulphur proteins, the first is an inorganic part of the protein and the second is an amino acid composition.

Trace elements compete with each other for a relevant place within biological systems. Their movement across cell membranes, especially into and out of water, will be dependent on the rate of water exiting the environment in which they are found. Inherent metal properties responsible for the biological effects of ions comprise an area of great interest called metal speciation. Combined techniques of speciation analysis are continually developing, allowing for direct determination of speciation forms. Usually, there are two or more independent techniques used as a part of a system analysis and most often these include selective separation and determination. One system, for example, is based on the separation of marked forms via gas chromatography or high performance liquid chromatography, or with capillary electrophoresis. These and other methods are commonly used to determine the total content of elements; other methods include the technique of spectrometry, atomic absorption spectrophotometry or emission spectrometry, atomic fluorescence, plasma excitation via induction or microwave as well as plasma emission detection or mass spectrometry (Niedzielski 2005, Szpunar 2005, Taraska et al. 2009, Valachová and Šoltés 2010). In recent years a newly and intensively developing science has emerged – metalloproteomics and meta-

logica. It is the newest area of bioinorganic chemistry (metalloomics) that includes a widespread analysis of the chemical forms of a particular metal or metalloid in a cell or tissue. Metalloproteomics is the study of protein ligands and the use of hetero-elements found in proteins or introduced by the process of derivatization for the purpose of detecting and determining of certain proteins (*heteroatom-tagged proteomics*). Most recent studies also include methods that look into metalloprotein expression and their changes over time and biological space. Experimental methods include the genomics, which provides insight into the structure of metal binding sites in metalloproteins, and allows for the determination of ligand names as well as any disruptions in the area of metal ligation within the protein sequence. This information is then used to form signatures that can be used as templates for searches in a sequence homology database (Szpunar 2005).

Oxidative stress

Technological advances can be seen in research on biological oxidation processes in the last part of the XXth century. Oxidative stress, a result of biological oxidation, causes cell damage and leads to many pathological processes. This, in turn, can cause a decreased profitability in farm animals and discourages the practice of animal husbandry (Fig. 1). Pathological conditions in animals can lead to free radical processes (Kankofer 2002, Szpringer and Lutnicki 2003, Lutnicki et al. 2006, Kankofer and Albera 2007). Metal ions are often responsible for the damage and protection of biological systems (Dovinová et al. 1999). Fenton and the Fenton-like reactions can play a central role the oxidative stress and can be catalyzed by transition metal ions and their complexes (Naora et al. 1987, Kleczkowski et al. 2002, Ayensu and Tchounwou 2006, Hud 2008, Mounicou et al. 2009, Müller 2010).

Every third protein is believed to require a metal cofactor, usually a transition metal ion such as copper, iron, zinc or molybdenum. These proteins include metallothioneins, crucial in maintaining the body's equilibrium and detoxification processes. They directly protect metal ions within the cell, as well as the extracellular proteins, albumin and transferrin, which are essential for metal transport in blood. Metal ions are also responsible for controlling the expression of these proteins in cells (Naora et al. 1987, Ayensu and Tchounwou 2006, Mounicou et al. 2009, Müller 2010).

When considering the role of metal ions with respect to the prooxidative-antioxidative reactions, the character and oxidative stress must be considered. We

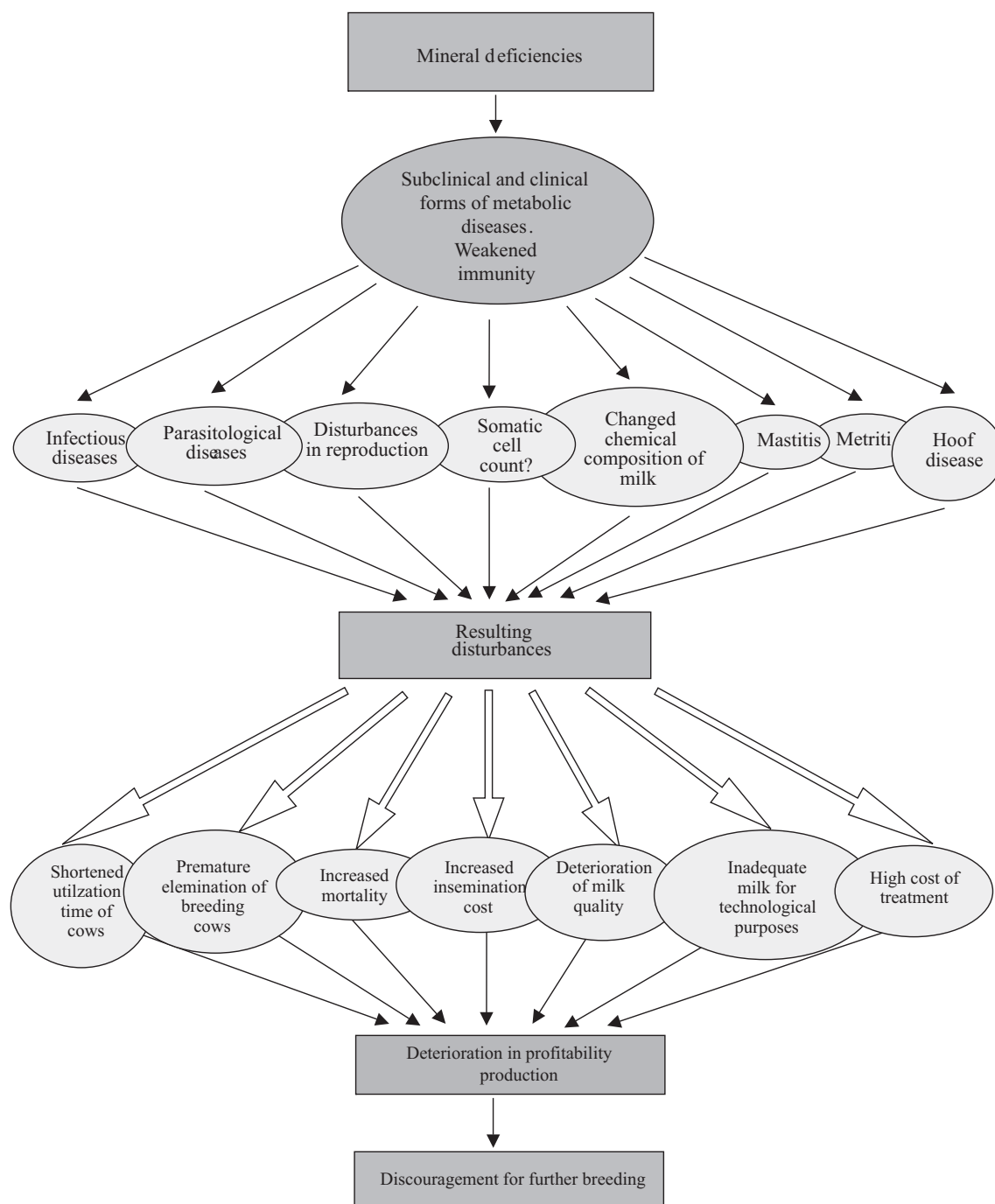


Fig. 1. The influence of mineral deficient feeding of cows on the motivation for further breeding (Kleczkowski and Klucinski 2011).

understand oxidative stress to be the state of imbalance between reactive oxygen and the biological ability for fast neutralization of reactive intermediates or the capability to repair damage to subcellular structures (Jedlinska-Krakowska 2006). Enzymes having reducing properties as well as a constant supply of energy maintain a reductive environment in cells, and any disturbances in the proper reduction potential can lead to surplus of free radicals causing damage to

many cell components, especially lipids, proteins and DNA (Darley-Usmar 1996, Brown et al. 2008).

From a chemical perspective, oxidative stress is characterised by a large increase in cellular reduction potential (reduction potential becomes less negative) as does a large decrease in the ability of reducing the redox cell links, such as occurs with glutathione. The effects of oxidative stress depend on the relative strength of the stress. On the one hand larger cells can

cope with local small perturbations and regain their original state, on the other, greater oxidative stress can cause cell death. Apoptosis can be triggered by even moderate oxidation, while necrosis can be a result of a stronger stress. Reactive oxygen species, including free radicals and peroxides, are especially destructive products of oxidative stress. Transition metals, or other regulators, can reduce some of these reactive oxygen species to a more reactive radical that can cause extensive cell damage (Zweier and Villamena 2003). Most of these oxygen species are produced in small amounts during normal aerobic metabolism, and the damage they cause are continually repaired. However, in a high oxidative stress cells are prevented from entering a controlled apoptotic path, causing instead cell necrosis (Fujii et al. 2003). Oxidative stress in cattle plays an important role in diseases such as ketosis, fatty liver syndrome, paresis puerperalis, mastitis, and reproduction disorders (Barszcz et al. 2009).

The role of metal ions in physiology and pathology

The role of metal ions in the peroxidation of cell membranes and their prooxidative role as well as the accumulation of BA4 amyloid in neurons, neural plexus and synaptic plates is particularly interesting. For example, deficiency of dietary copper was noted in the course of several of depressive disorders. Later research revealed that copper is essential for the activation of dopamine beta-hydroxylase and that copper deficiency leads to changes in the fetal brain as well as reduced activity of norepinephrine, dopamine beta-monooxidase, cytochrome C oxidase and peptidylglycine alpha-amide monooxidase (Zambrzycka et al. 2003).

Iron is yet another mineral that has an influence on the development of the nervous system, as its deficiency in children under 2 years results in inadequate psychomotoric development, delayed speech and poor abstract thinking ability in later life. Moreover, there is a decrease in the amplitude of all sleep waves in the electroencephalogram (EEG) in humans with iron deficiency, which may be related to serotonin reduction in the brain (Brigham and Beard 1996, Unger et al. 2008). In addition, dietary iron deficiency can lead to a decline of serotonin levels in brain tissue and an increase of noradrenaline concentration in blood, urine and other tissues, as well as an increase of blood dopamine levels with a coexisting decrease in TRH and TSH levels. A delay of vagus nerve myelinisation and reduced number of D2 receptors causing further neurological disorders can also be seen in the iron deficiency. A higher stimulatory effect of Fe^{2+} and

Fe^{3+} on the peroxidation of linoleic acid was noted when compared to other prooxidants. An excess of ascorbic acid can reduce Fe^{3+} to Fe^{2+} , causing more severe peroxidation. This is evident when looking at peroxidation of linoleic acid induced by the Fenton reaction, as this is a weaker reaction than that induced by iron ions, which is further increased by the addition of ascorbic acid to the system to maintain the regeneration of Fe^{2+} and the production of hydroxyl radicals (Gow-Chin et al. 1999, Yedjou et al. 2008).

Zinc deficiency can also lead to depression as it is an essential modulating factor of NMDA (N-methyl-D-aspartate) glutaminianergic receptor activity. Its deficiency impairs the function of the gamma-amino butyric acid (GABA) neural pathway. Zinc is an important modulator in the central nervous system of mammals. In the central nervous system (CNS), the largest concentrations of Zn was found in presynaptic boutons of the hippocampal neuron and cortex and its main function is related to opiate receptors (Johnson 2000). In vitro addition of zinc accelerated neurite outgrowth from the hippocampus. Stress causes a reduction in serum Zn concentrations, which may lead to a decrease of this trace element in the structures of the brain. Dietary supplementation of Zn in adults improves association and psychomotor skills as well as the function of taste (Erikson et al. 1997, Nelson et al. 1997, Yedjou et al. 2008, Patlolla et al. 2009). Also an experimentally induced deficiency of zinc in animals causes reduced of brain size, underdevelopment of the cerebral cortex and slowed growth of dendrites. An increased binding of heavy metals by metallothioneins within the brain, especially cadmium and lead, is seen in Zn deficiency. The impact of excessive binding of these metals in the central nervous system with respect to an increase in aggressive behavior has become the topic of a great many research projects throughout the world.

Studies have also been performed on the antioxidative and prooxidative potential of other trace metal ions, including aluminum (Al), manganese (Mn), and selenium (Se) (Markiewicz et al. 2007). It was shown that the effect of Al and Mn was anion independent and that the prooxidative potential of Al was stronger than its antioxidative potential, which may be a result of its inert redox nature (Koivula and Eeva 2010). Another finding was related to the etiology of aluminum toxicity, which may result in part from an increase in lipid peroxidation rates in placental syncytiotrophoblast membranes. Yet another finding was the antioxidative potential of selenium only in whole-cell homogenates, which appears to be mediated by glutathione peroxidase (Se is a cofactor of glutathione peroxidase). Another trace element of importance is manganese, which decreases production

Table 3. Mineral requirements in microorganisms and ruminants (ppm) (Grys 1988, Underwood and Suttle 1999).

Minerals	Microorganisms	Ruminants
Iron*	2.0-5.0	35.0
Copper*	0.1	5.0-10.0
Nickel*	0.1	1.0
Zinc*	3.0-10.0	25.0-40.0
Cobalt ¹	1.0-3.0	0.05-1.0
Jodum ¹	20.0	0.2
Manganese ²	5.0-30.0	20.0
Selenium ²	0.1	0.08-0.15

* Mineral requirements lower in microorganisms are than in ruminants.

¹ Mineral requirements higher in microorganisms than in ruminants.

² Mineral requirements equal in microorganisms and in ruminants.

of thiobarbituric acid- reactive substances. This is most likely a result of manganese's ability to reduce superoxide anion and hydroxyl radicals as well as its chain-breaking capacity (Ravinderjit and Kanwar 2001). Possible explanations for these differences between Mg^{2+} and other metal ions, such as cobalt (Co^{2+}) and nickel (Ni^{2+}), in the activation of calcineurin are also discussed (Martin et al. 2000).

There are possible benefits from reactive oxygen species. The immune system can take advantage of their presence to attack and kill pathogens during respiratory bursts. Redox signaling, a type of cell signaling, also takes advantage of reactive oxygen species. Fundamental beneficial processes of reactive oxygen species include signaling, gene expression, and catalysis.

A working hypothesis regarding the antioxidative action of catechins stated that their role as such was mostly a result of free radical scavenging and not via metal chelation. If this were true, all catechins should have the same preventative efficiency against metal-induced lipid peroxidation regardless of the metal ion species. This is not the case though, as each catechin shows a different degree of efficiency in preventing lipid peroxidation depending on the type of metal ion (Sugihara et al. 2001).

It is generally believed that the use of antioxidants in the prevention of metal-dependent diseases is favorable, however this mode of therapy is sometimes quite controversial because the administration of high doses of copper, zinc and beta-carotene in animals in high-risk groups is not always successful. Treatment with Cu, Zn, Se and vitamin E appears to reduce the risk of degenerative diseases and mammary glands inflammation in lower-risk animals. There are mixed results on the beneficial use of vitamin E supplementation

in other diseases. It may be that this difference in the reaction to treatment is a result of a multi-step metabolism as well as indirect effects of the supplementation before a beneficial clinical effect is attained. For example the protozoal metabolism in ruminants is not insignificant and much differs from metabolism of macroorganism resulting in very different requirements for micronutrients (Table 3) (Murata 2005).

The information contained in Table 3 allows a better understanding of the clinical successes and failures during mineral supplementation of animals (Curis et al. 2009).

Neuropathological effects of metals

The specific neuropathological effects of metals have been intensely investigated by scientist from many fields of study in the late twentieth and early twenty-first century. The favorable impact of metal ions such as Cu, Mn, Pb, Hg, Sn, and others as well as their neurotoxic effects have been fairly well documented. Several neuropathological conditions in humans and animals, specifically neurodegenerative phenomena associated with abnormal homeostasis or abnormal accumulation of metal ions in the brain have been the subject of research. Several fields have received extensive attention including Parkinson's disease, Alzheimer's disease, Wilson's disease, bovine spongiform encephalopathy, and dialysis encephalopathy syndrome, as well as the aging process and the mitohormesis mechanism (Agarwal and Prabakaran 2005).

The neurodegenerative diseases described above were associated with an abnormal metal ion metabolism and oxidative stress, which were reportedly a result of abnormal metal ion interactions. This shows that homeostasis of metal ions in cells must be rigorously regulated by biomolecules, i.e. metallochaperones and metallothioneins. Copper chaperones are necessary to protect and guide copper ions and activate superoxide dismutase (SOD) via specific protein-protein interactions during which SOD is activated by incorporating a Cu^+ ion. Superoxide dismutase molecules are important antioxidants that contribute to a state of decreased oxidative stress within cells (Müller 2010). Moreover, copper is essential for dopamine beta-hydroxylase (DBH) activation and its deficiency has been noted in many depressive disorders. Changes in fetal rat brains can be caused by dietary copper deficiency in the mothers, including reduced levels of noradrenaline, SOD, DBM (dopamine beta monooxidase), CCO (chrome C oxidase), and PAM (peptidylglycine alpha-amidating monooxygenase), as well as a delayed reaction to auditory stimuli – changes at the locus coeruleus and

noradrenergic neurons. Research showed that after 4 months of proper nutrition cuproenzyme (SOD, DBM and PAM) activity returned to normal in these neonatal rats.

The role of metallothioneins in physiology is not fully understood. Metallothioneins are expressed in three isoforms: MT-I, MT-II and MT-III. The expression of the MT-III form seems to be restricted to neurons, especially neurons containing zinc (hippocampus). It is generally believed that metallothioneins play a role in copper and zinc homeostasis and in the protection against biophysical and chemical cytotoxicity that can be caused by metal ions, reactive oxygen species, mutagens and radiation (Rochet 2007).

Conclusions

Various studies on the origin of life have shown that a variety of important metal ions and oxygen played important roles in the evolutionary process. During the early life period there was an increase in transition metal ions in the ionic radius, which could have led to tremendous evolutionary changes in the biological systems. Trace elements continue to play an important biological role mainly in the form of enzymes responsible for redox processes. These enzymes take part in putting trace elements into the protein metabolism as well as the cellular transport processes. These processes, in turn, are regulated by genetic factors. Biominerals also play important roles in the regulation and modulation processes of metabolism. They act as potential nutraceuticals and functional factors, reducing the risk for disease in animals. Catalytic mineral antioxidants can be used as an aid in the treatment improving therapeutic efficiency and the use of metal chelation and antioxidants may potentially be used as a treatment method for neurodegenerative diseases. Novel therapeutic strategies for treatment of neurodegenerative disorders can be the subject of the next paper.

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References

Agarwal A, Prabakaran SA (2005) Mechanism, measurement, and prevention of oxidative stress in male reproductive physiology. *Indian J Exp Biol* 43: 963-974.

- Ayensu WK, Tchounwou PB (2006) Microarray analysis of mercury-induced changes in gene expression in human liver carcinoma (HepG2) cells: importance in immune responses. *Int J Environ Public Health* 3: 141-173.
- Barszcz K, Badurek I, Kleczkowski M, Kluciński W, Gajewski Z, Jakubowski T (2009) Effect of copper and magnesium on prooxidative-antioxidative status in the blood of cows in the transition period from deficient regions. *Med Weter* 65: 857-861.
- Brigham D, Beard J L (1996) Iron and thermoregulation: a review. *Crit Rev Food Sci Nutr* 36: 747-763.
- Brown E, Yedjou CG, Tchounwou PB (2008) Cytotoxicity and oxidative stress in human liver carcinoma cells exposed to arsenic trioxide. *Met Ions Biol Med* 10: 583-587.
- Cairns Smith AG (1982) Genetic Takeover and the mineral origins of life. 1st ed., Cambridge University Press, Cambridge, pp 171-201.
- Curis E, Nicolis I, Bensaci J, Deschamps P, Bénazeth S (2009) Mathematical modeling in metal metabolism: Overview and perspectives. *Biochimie* 91: 1238-1254.
- Darley-Usmar VM (1996) Blood radicals: reactive nitrogen species, reactive oxygen species, transition metal ions, and the vascular system. *Pharm Res* 13: 649-662.
- Dovinová I, Vachálková A, Novotný L (1999) Potential carcinogenicity of some transition metal ions. *Biol Trace Elem Res* 67: 63-73.
- Erikson KM, Pinero JD, Connor JR, Beard JL (1997) Regional brain iron, ferritin and transferrin concentrations during iron deficiency and iron repletion in depletion in developing rats. *J Nutr* 127: 2030-2038.
- Ferry JG, House CH (2006) The stepwise evolution of early life driven by energy conservation. *Mol Biol Evol* 23: 1286-1292.
- Fujii J, Iuchi Y, Matsuki S, Ishii T (2003) Cooperative function of antioxidant and redox systems against oxidative stress in male reproductive tissues. *Asian J Androl* 5: 231-242.
- Gow-Chin Y, Hui-Yin Ch, Chi-En L (1999) Measurement of antioxidative activity in metal ion-induced lipid peroxidation systems. *J Sci Food Agric* 79: 1213-1217.
- Grys S (1988) Micronutrients as essential elements, toxic agents, and pharmacologically active substance. Materials of XV the National Research Conference of Biochemical Analysis. Divisions ZHW. PIWet, Lomza, Poland, pp 1-27.
- Inger DE (2000) The origin of cellular life. *Cell Mol Biol* 22: 1160-1170.
- Jedlińska-Krakowska M (2006) Effect of high doses of vitamin C and ozone on the course of oxidative stress in rats. *Med Weter* 62: 1183-1185.
- Johnson S (2000) The possible role of gradual accumulation of copper, cadmium, lead and iron and gradual depletion of zinc, magnesium, selenium, vitamins B2, B6, D, and E and essential fatty acids in multiple sclerosis. *Med Hypotheses* 55: 239-241.
- Kabata-Pendias A, Pendias H (1999) Biogeochemistry of trace elements. 1st ed., Scientific Publishers, Warsaw.
- Kankofer M (2002) Placental release/retention in cows and its relation to peroxidative damage of macromolecules. *Reprod Dom Anim* 37: 27-30.
- Kankofer M, Albera E (2007) The concentration of vitamin A and its provitamin-beta carotene in bovine retained and not retained placenta. *Acta Vet (Beograd)* 57: 181-179.

- Kleczkowski M, Kluciński W, Sikora J, Kasztelan R, Zdanowicz M (2002) Role of transition metals ion and reactive oxygen species in biological oxidation in cattle (part 1). *Pol J Vet Sci* 5: 263-268.
- Kleczkowski M, Klucinski W (2011) Parturient paresis-an important disease in transition cows. In: Klucinski W (ed) Diseases of cattle-monograph. *Magazyn weterynaryjny*, Warsaw, pp 1039-1048.
- Koivula MJ, Eeva T (2010) Metal-related oxidative stress in birds. *Environ Pollut* 158: 2359-2370.
- Lutnicki K, Szpringer E, Walczyna B, Marciniak A (2006) Damage of the protective system of gastric mucosa resulting from the aging process of rat's organism. *Bull Vet Pulawy* 50: 577-583.
- Markiewicz H, Gehrke M, Malinowski E (2007) Effect of vitamins C and E and selenium on the activity of leukocytes and blood antioxidant status of cows during the puerperium. *Med Weter* 63: 566-570.
- Martin BL, Li B, Liao C, Rhode DJ (2000) Differences between Mg(2+) and transition metal ions in the activation of calcineurin. *Arch Biochem Biophys* 380: 71-77.
- Meyer SC (1996) The origin of life and the death of materialism. *The Intercollegiate Review* 31: 1-11.
- Mounicou S, Szpunar J, Lobinski R (2009) Metallomics: the concept and methodology. *Chem Soc Rev* 38: 1119-1138.
- Müller J (2010) Functional metal ions in nucleic acids. *Metallics* 2: 318-327.
- Murata M (2005) Evaluation for safety of antioxidant chemopreventive agents. *Antioxid Redox Signal* 7: 1728-1739.
- Naora M, Miyahara K, Curnow R (1987) Origin of noncoding DNA sequences: molecular fossils of genome evolution. *Proc Natl Acad Sci USA* 84: 6195-6199.
- Nelson C, Erikson K, Pinero DJ, Beard JL (1997) In vivo dopamine metabolism is altered in iron-deficient anemic rats. *J Nutr* 127: 2282-2288.
- Niedzielski P (2005) The new concept of hyphenated analytical system: Simultaneous determination of inorganic arsenic(III), arsenic(V), selenium(IV) and selenium(VI) by high performance liquid chromatography-hydride generation-(fast sequential) atomic absorption spectrometry during single analysis. *Anal Chim Acta* 551: 199-206.
- Oloff H, Alonso D, Berg MP, Eriksson BK, Loreau M, Piersma T, Rooney N (2009) Parallel ecological networks in ecosystems. *Philos Trans R Soc* 364: 1755-1779.
- Österberg R (1995) The origins of metal ions occurring in living system In: Berthon G (ed) Handbook of metal-ligand interactions in biological fluids. Marcel Dekker Inc. New York, Vol 1, pp 10-28.
- Patlolla AK, Barnes C, Yedjou C, Velma VR, Tchounwou PB (2009) Oxidative stress, DNA damage and antioxidant enzyme activity induced by hexavalent chromium in Sprague – Dawley rats. *Environ Toxicol* 24: 66-73.
- Pennazio S (2009) Alexander Oparin and the origin of life on Earth. *Riv Biol* 102: 95-118.
- Pennington P I, Ellis R C (1993) Autotrophic and heterotrophic nitrification in acidic forest and native grassland soils. *Soil Biol Biochem* 25: 1399-1408.
- Ravinderjit KA, Kanwar U (2001) Role of some trace metal ions in placental membrane lipid peroxidation. *Biol Trace Elem Res* 82: 61-75.
- Rochet JC (2007) Novel therapeutic strategies for the treatment of protein-misfolding diseases. *Expert Rev Mol Med* 9: 1-34.
- Rutkowiak B (1987) Digestive and metabolic disorders in dairy herds. 1st ed., PWRiL, Warsaw, pp-72-128.
- Sobiech P, Rypuła K, Wojewoda-Kotwica B, Michalski S (2010) Usefulness of calcium-magnesium products in parturient paresis in HF cows. *J Elementol* 15: 693-704.
- Sugihara N, Ohnishi M, Imamura M, Furuno K (2001) Differences in antioxidative efficiency of catechins in various metal-induced lipid peroxidations in cultured hepatocytes. *J Health Sci* 47: 99-106.
- Szpringer E, Lutnicki K (2003) Current views on apoptosis in theory and medical practice. *Pol J Vet Sci* 6: 71-80.
- Szpunar J (2005) Metalomika – a new dimension to trace elements speciation analysis. Analysis Materials of XIV Seminar. "Modern Methods of Sample Preparation and Determination of Trace Elements", Poznan University of Technology, Poznan, pp 50-51.
- Takayama Y, Takezawa T (2006) Lactoferrin promotes collagen gel contractile activity of fibroblasts mediated by lipoprotein receptors. *Biochem Cell Biol* 84: 268-274.
- Taraska JW, Puljung MC, Olivier NB, Flynn GE, Zagotta WN (2009) Mapping the structure and conformational movements of proteins with transition metal ion FRET. *Nat Methods* 6: 532-537.
- Tirard S (2010) Origin of life and definition of life, from Buffon to Oparin. *Orig Life Evol Biosph* 40: 215-520.
- Underwood E J, Suttle N F (1999) The mineral nutrition of livestock. 3rd ed., CABI Publishing, Oxon.
- Unger EL, Wiesinger JA, Hao L, Beard JL (2008) Dopamine D₂ receptor expression is altered by changes in cellular iron levels in PC12 cells and rat brain tissue. *J Nutr* 138: 2487-2494.
- Woźniak M, Czyż M (2008) Superoxide dismutase mimetics: Possible clinical applications. *Postepy Hig Med Dosw* 62: 613-624.
- Valachová K, Šoltés L (2010) Effects of biogenic transition metal ions Zn(II) and Mn(II) on hyaluronan degradation by action of ascorbate plus Cu(II) ions. In: Zaikov GE (ed), *New Steps in Chemical and Biochemical Physics*. Pure and Applied Science Publishers, New York 2010, pp 219-298.
- Yedjou CG, Rogers C, Brown E, Tchounwou PB (2008) Differential effect of ascorbic acid and n-acetyl-cysteine on arsenic trioxide – mediated oxidative stress in human leukemia (HL-60) cells. *J Biochem Mol Toxicol* 22: 85-92.
- Yedjou CG, Haynes L, Dorsey W, McMurray R, Tchounwou PB (2008) Lead-induced cytotoxicity and oxidative stress in human leukemia (HL-60) cells. *Met Ions Biol Med* 10: 489-494.
- Zambrzycka A, Cakała M, Kaminska M (2003) Transition metal ions significantly decrease phospholipase C activity degrading phosphatidylinositol-4,5-isphosphate in the brain cortex. *Pol J Pharmacol* 55: 915-917.
- Zweier JL, Villamena, FA (2003) Chemistry of free radicals in biological systems. In: Kukin ML, Fuster V (eds) *Oxidative Stress and Cardiac Failure*. 5th ed., Futura Publishing Co, New York, pp 67-95.