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Bioinorganic Chemistry of Trace Elements: Possible Role in the Epigenetic Modulation of Homoeostatic Processes in Complex Organisms

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Trace elements are well known in the geochemistry disciplines. However, its relationship to the biological and medical sciences is very recent. In spite that knowledge about the influence of environment in living processes is a traditional concept, until about the middle part of the 20 century, the possible influence on physiological functions of chemical elements present in waters and soil surrounding man habitat was not particularly investigated. Principal concern was concentrated to evaluate toxic actions of chemical elements on living systems. However, evidence showing that chemical elements are able to interact with enzymes, transcription factors and DNA in several living systems, put the inorganic elements into a new perspective. Higher concentrations of inorganic elements in the environment do not necessarily must be the only requirement for biological interactions in living systems. In the present paper historical aspects, some chemical properties of trace elements, an emphasized discussion about selenium and tellurium on functional processes in living systems are reviewed. In addition, hypothesis about the role of trace elements on epigenetic changes in the expression of gene action is also discussed.

Keywords: Trace Elements, Se, Te, Bioinorganic Chemistry, Behavioural Effects, Epigenetic Modulation.

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1. INTRODUCTION

When a living organism in its surroundings is exposed to a new chemical element, it is possible that this element might be rejected or neutralized. However, if the element persists in the environment during long time, a new adaptive response might be evolved such as a signal carrier, that later it could transform to a messenger, and finally to a new essential chemical element during evolution.[51]

Historically, a separation between organic chemistry, biochemistry and the inorganic chemistry was established, because specialists considered that there were clear limits in extension and interest in all these disciplines. At that time overlapping and interaction of chemical compounds were not considered relevant. However, a few decades ago the role of metals, traditionally a subject of inorganic chemistry, was found to be important in many biological processes. Technological advances with the rising of new apparatus and techniques with a greater resolution and sensitivity permitted to identify the presence of chemical elements in complex functional processes in living systems, giving a renewed interest to study these chemical interactions and generating a new discipline known as the bioinorganic chemistry.[40, 45]

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Biological systems basically inhabit in an inorganic environment. It is not difficult to think that during the evolution, the necessity to adapt to these environments caused in primordial organisms sophisticated and selective mechanisms to deal with these chemical elements, and using them to its own benefit.[51] In some cases, up to the extent that some of these elements become essential to its metabolic processes.

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2. ESSENTIALITY OF ELEMENTS AND SOME CHEMICAL PROPERTIES RELEVANT TO LIVING SYSTEMS

In living beings an element is to be considered "essential" when somehow its presence in the organism is critical to life. Four conditions must be fulfilled:

(a) an inadequate ingestion induces functional deficiencies that are reversible if the element is again available to the organism;

(b) lack of the element stops growth and completion of the vital cycle;

(c) the element influences directly the organism and it is involved in its metabolic processes, and

(d) the biological effect of the element cannot be replaced by any other element.[17] About 25 elements of natural occurrence are considered essentials.

Mostly of these are light atoms, usually metals or metalloids.[45] According to its relative abundance, they are classified as macroelements, trace elements and ultra trace elements.[17] Frequently, trace and ultra trace elements also are known as oligoelements. Thus, chemical elements in human beings ordered by its relative abundance are oxygen, carbon, hydrogen, nitrogen, calcium, phosphor, sulfur, sodium, chloride, iron and magnesium (macroelements); fluorine, zinc, copper, silicon, vanadium, tin, selenium, manganese, iodine, nickel, molybdenum, chromium, and cobalt (trace elements). Regarding the ultra trace elements, these elements are required in a dose less than 1 μg per day. Nevertheless, its essentiality is not proved, except for iodine and molybdenum. In spite that one of the requirements to consider an element to be essential is that it cannot be replaced by other one, recent reports have shown that certain bacteria can substitute one essential element for another.[53] In addition, substitution of zinc for cadmium in diatoms has been observed in some metal enzymes *in vitro* and *in vivo*.[35] When ocean waters have zinc depletion or very low concentrations of this metal, cadmium is able to stimulate growth of the diatom *Thalassiosira weissflogii* by substituting zinc present in some macromolecules. Cobalt also can replace zinc, although with less efficiency than cadmium and possibly by other molecular mechanisms.[35]

It has been claimed that there are also other cases where iron is replaced by copper. It is well known that among the many functions described for iron, the most studied is that of being constituent of globin molecules forming hemoglobin. In crustaceous, mollusks, and arthropods species iron is substituted for copper forming hemocyanine in the oxygen transporting function.[12] However, it appears not to be a case of "simple" substitution but rather to be a functional alternative for oxygen transporting metalloproteins. Nevertheless, there are the molybdopterins, enzymes of the oxidoreductase family that some bacteria use to reduce carboxylic acids to aldehydes, where in some occasions molybdenum is replaced by tungsten.[29] Recently, it has been described that phosphorus is substituted for arsenic in biomolecules of *Halomonadaceae bacteria* species, identified as GFAJ-1. This bacterium has been isolated from the Mono Lake, where its waters are alkaline and hypersaline.[53] In this report, authors confirmed the incorporation of arsenic into the molecule of DNA and also in a macro element. In all these cases, substitution has been of natural occurrence. Regarding the relative position in the periodic table of elements, replacement in general is made by an element in the same group (same column) and positioned immediately below of the substituted element. The question if these chemical substitution in the same group can be considered an opportunistic event affecting only lower scale species, or it is a more general mechanisms affecting other higher evolutioned organisms is still an unanswered subject. If these substitutions are produced by inherent chemical properties of certain elements, it should be expected that during evolution this chemical mechanism should affect also complex organisms. Nevertheless, up to now it has not been reported similar replacements of inorganic elements in biochemical functions in complex animals.

3. THE CASE OF SELENIUM IN LIVING ORGANISMS

The history of selenium is particularly interesting because the first known effects attributed to this element in humans and animals were physiological dysfunctions due to its toxicity.[9, 45] At the beginning of the 20th century, U.S. stockmen and farmers in certain regions of the western Great Plains had severe problems with cattle. In tests with laboratory animals feed samples were found to be poisonous and the agent was identified as selenium.[9] Selenosis was also observed in humans when ingestion was 900 μg/day or more producing a toxic syndrome of dermatitis, loose hair, diseased nails and peripheral neuropathy.[5]

In nature this element can be found as selenate (Se^{+6}), selenite (Se^{+4}), elemental selenium (Se^{0}), and selenide (Se^{-2}). The mean crustal concentration of selenium is 83 μg/Kg. However, its global concentration varies widely (5 μg/Kg to $8 \cdot 10^{6}$ μg/Kg). Because of this significant variation in natural concentrations it was possible to be aware of the biological role that this trace element has. In those regions of the world where selenium concentration was very low, such as certain parts of China, atrophy and degeneration of cartilage giving short stature in native people was observed.[9] Also, other pathologies related to endemic cardiomyopathy have been described in these low concentration selenium regions.[30] In addition, myxoedematous endemic cretinism has been found to be prevalent in those goiter-endemic countries where low selenium and glutathione peroxidase concentrations in serum were found.[24] It has been described also that these low levels in trace element has been associated

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to increased risk of cancer, cardiovascular and autoimmune diseases.[39] In addition, it has long been known that the thyroid is one of organs that posses the highest content in selenium in humans. Selenium is incorporated into several enzymes that are important in maintaining thyroid hormone metabolism such as deiodinases and cytosolic and plasma glutathione peroxidases.[27, 41] All this evidence supported the concept that selenium is indeed fulfilling a biological role in metabolic processes. Selenium in environmental and also microbial samples is found frequently as dimethylselenide, dimethylselenilsulfide and dimethyldiselenide.[14] Man incorporates selenium as selenomethionine and selenocysteine. The latter is the way how selenium constitutes part of selenoproteins and also represents the principal bioavailability to organism.[9] Natural sources of selenomethionines come from animal and plants, but selenocysteine come from animals only. The inorganic forms, selenates and selenites are minor contributors, but are quite relevant as diet supplements in chronic feedings or experimental diets.[31] Selenomethionine cannot be biosynthesized in the organism, and it is thought that might be a temporal reservoir for conditions where selenium deficits are produced. It has a good absorption and its incorporation follows the same mechanisms than methionine.

In plasma one third of total selenium is bound to selenoprotein *P*, one sixth to selenoprotein *W*, and the rest is bound to albumin in an unspecific manner.[2] Target organs are kidneys, liver, pancreas and muscles. Selenium can be transferred to fetus through the placenta and after delivery also to the mother's milk at a proportional rate according to the diet bioavailability. Selenomethionine can be bound randomly to proteins, displacing methionine and its catabolism will release selenium in selenide form.[26] Inorganic forms of selenium (selenate and selenite) are stored in the organism as selenide that later can be transformed to selenophosphate, a precursor to selenocysteine.[26] Some authors think that releasing selenium from stored forms as selenocysteine is essentially linked to the methionine metabolism and not to a compensatory chemical response of "reserve stores" when a decrease in selenium concentration in the organism occurs.[26] Elimination of selenium from the organism mainly occurs in the kidney but in some animals the liver also participates through biliary secretions. Experiments in rats have shown that biliary elimination of selenium increase if animals are exposed simultaneously to metalloids of group 15 of the periodic table. Selenite content in bile secretion was increased when at the same time rats were injected with arsenite. This response did not occur when arsenite was replaced with bismuth or antimony.[10]

4. THE CASE OF TELLURIUM IN BIOLOGICAL SYSTEMS

Tellurium, one of the Group 16 chalcogens[16] follows a similar history than selenium, where the main biological effects found are related to its toxic actions.[8] Its soluble oxyanions tellurite (TeO_3^{2-}) and tellurate (TeO_4^{2-}) are toxic to a great variety of life forms in spite that its concentration might be very low.[8, 46] Nevertheless, some microorganisms have developed internal mechanisms resisting the actions of tellurium.[8] Tellurium median concentration in bedrock groundwaters is 0.005 μg/L,[21] thus this metalloid is not distinguished by its abundance on earth. Nevertheless, in some regions of the world, for instance the mountainous regions of the semiarid endorheic area of Famatina, located in the province of La Rioja, Argentina, tellurium can reach a mean of 0.313 μg/L in surface waters.[15] Since these concentrations are below the toxic limits described for this trace element no deleterious effects have been found for people and animals exposed to tellurium in these Argentinean regions. Tellurium frequently is found associated with copper and sulfur-bearing ores,[33] but also is present in some gold ores such as calaverite ($AuTe_2$) and sylvanite ($AgAuTe_4$).[7] Tellurium is considered teratogenic. Evaporation at 20 °C is insignificant, but when the fine dust is dispersed it may reach particle concentration in the air that can be dangerous. Effects by inhalation are somnolence, dry mouth, metallic taste, cephalea, body and breath garlic smelling, and sometimes nausea.[8, 9, 52] Toxic effects of tellurium were early described affecting pregnancy in rats where nonobstructive hydrocephalus was present in newborn rats after mothers were fed with 500–3500 μg/L of the trace element in the diet.[13] On the other hand, maturing rats fed with a diet of 1.1% tellurium was sufficient to produce primary demyelination of peripheral nerves.[9] Interestingly, this alteration lasted about a week and remyelination process began even in presence of tellurium in the diet.[9] Tellurium effects on demyelination appear not to be a simple unspecific action of a metalloid toxic element on nerve cells, but the trace element affects cholesterol synthesis by inhibiting squalene metabolism, reducing at about 50% the squalene epoxidase activity.[49, 50] In another detailed study regarding the effects of tellurium on pregnancy in rats, the single maternal injection of 0.12 mg/Kg of diphenyl ditelluride at day 10 of gestation provoked the appearance of a series of alterations such as, malformation in fore- and hind limbs, absent or short tail, exophthalmia, subcutaneous blood clots, hydrocephalus and absence of cranial bone and cutaneous tissues in fetuses at day 20.[43] If the tellurium compound were administered later in gestation (day 17), severe malformations were produced with a 73% of fetal mortality.[43] In adult rats, 0.1–0.4 mg/Kg sodium tellurite subcutaneous administration caused a significant impairment in the acquisition of a spatial learning task but retaining normal locomotor responses.[52] In these animals, morphological alterations were observed in the medial prefrontal

cortex, and hippocampal CA_1, CA_4 and dentate gyrus neuronal layers.[52] In addition, inorganic tellurite is able to interact with some hepatocytes selenoproteins isolated from rat liver, such as the selenium-dependent glutathione peroxidase altering its enzymatic activity suggesting the possibility that tellurium actions might be mediated by modifying the activity of selenoproteins in the cell.[23] In spite that mostly of research of tellurium has been focused on its toxic effects, and large concentrations of this trace element have been used, very low levels of the trace element does not mean necessarily absence of any biological effects. In our laboratory, doses as low as 0.03 μg/L of ZnTe in drinking water chronically administered to pregnant rats during all gestation, delivery and maturing rats, induced significant behavioural changes in social, defense and lateralized exploration strategies at 30 day-old in the prepuberal rats.[36] Nevertheless, no physiological actions have been recognized yet for this trace element.

5. ELEMENTS REPLACEMENT IN A SINGLE GROUP OF THE PERIODIC TABLE AS POSSIBLE MECHANISM TO INFLUENCE LIVING SYSTEMS EVOLUTION

Previously it has been mentioned that chemical substitution of elements in the same group of the periodic table sometimes spontaneously occurs in living systems. Such is the case of molybdenum replaced by wolfram,[29] and phosphorus substituted for arsenic in biomolecules of *Halomonadaceae bacteria* species.[53] This process is completely natural, depending only on the physicochemical properties of chemical elements. Thus, it is possible to speculate that this element translocation might be one of the many "chemical striving forces" imposed on the ecosystem evolution of living systems.[51] A closer inspection to this elements interchange put into evidence some common features. For instance, in the well known cases described for molybdenum and wolfram;[29] phosphorus and arsenic;[53] the crystal structure, the atomic radius, the atomic volume and the electronegativity of the switching pairs are very similar. Although the intrinsic atomic mechanism for this interchange is not understood, it appears that these atomic properties in elements in the same group should predict possible chemical interchanges. It is interesting to note that selenium and tellurium fulfill these requirements also. The electronegativity index (2.4 Pauling's for Se, and 2.1 for Te); the hexagonal crystal structure; the covalent radius (1.16 A° for Se, and 1.35 A° for Te); the atomic radius (1.40 A° for Se, and 1.60 A° for Te), and first ionization energy (225 kCal/g mole for Se, and 208 kCal/g mole for Te) are similar,[6] suggesting the likelihood for a natural interchange.

Nevertheless, no direct evidence for these trace elements has been provided so far of such chemical replacements in complex living systems. However, some indirect findings with selenoproteins suggest that this mechanism might be in action in the cell.[29] Recently, an immunomodulating and anti-cancer properties for some tellurium containing compounds have been described.[42]

6. OTHER MOLECULAR MECHANISMS FOR TRACE ELEMENTS IN LIVING SYSTEMS

From the inorganic chemistry point of view, the most reasonable mechanism whereby a trace element can exert some type of influence on organic molecules present in complex organisms, resides in its capacity of displaying several redox potentials states. This chemical oxidizing-reducing property provides intermediate high reactive elements that can interact with biological charged molecules present in the cell. It is interesting to point out that key cell processes, related to defensive biological responses to environmental changes in cells appear to be affected by trace elements. For instance, NF-κB protein, a eucaryotic transcription factor existing in practically all type of cells,[28] evidence was found showing that Zn^{2+} is required to the formation of NF-κB-DNA complex, a necessary molecular intermediate to appropriate transcription of DNA.[47] On the other hand, a Zinc deficiency in the diet of adult male rats during 3 weeks produced a reduction of about 50% of stem cells in the subgranular and granular cell layers of the hippocampal dentate gyrus,[11] clearly suggesting that the trace element is important to some brain structures development. In addition, it has been described that the mouse MT-I gene involved in the transcription of metallothionein protein, active in detoxification and protection against reactive oxygen-species in the cell is regulated by zinc.[32] All this evidence supports a sophisticated and complex action for trace elements in the cell machinery related to cell homeostasis.

Selenium, forming part of the selenoproteins, particularly the thioredoxin reductase which regulates transcription factors and several cell receptors activity have been found to be inhibited with diaryl tellurium compounds.[34] In addition, Ni^{2+} and Cu^{2+} have been found *in vitro* to be bound to histidine residues in a synthetic peptide model for the *N*-terminal tail of histone H4, suggesting that a predictable participation between trace elements and chromatin proteins is possible.[48] Physicochemical studies amply support the concept that metals and metalloids are able to bind to specific sites in the nitrogen 7 of purine or nitrogen 3 of pyrimidine in the DNA.[3] Thus, chemical basis are available to understand conformational changes in the DNA molecules that might produce disruption or alterations in the transcription of information in the cell by direct or indirect mechanisms. A general and diagrammatic scheme of these mechanisms is shown in Figure 1.

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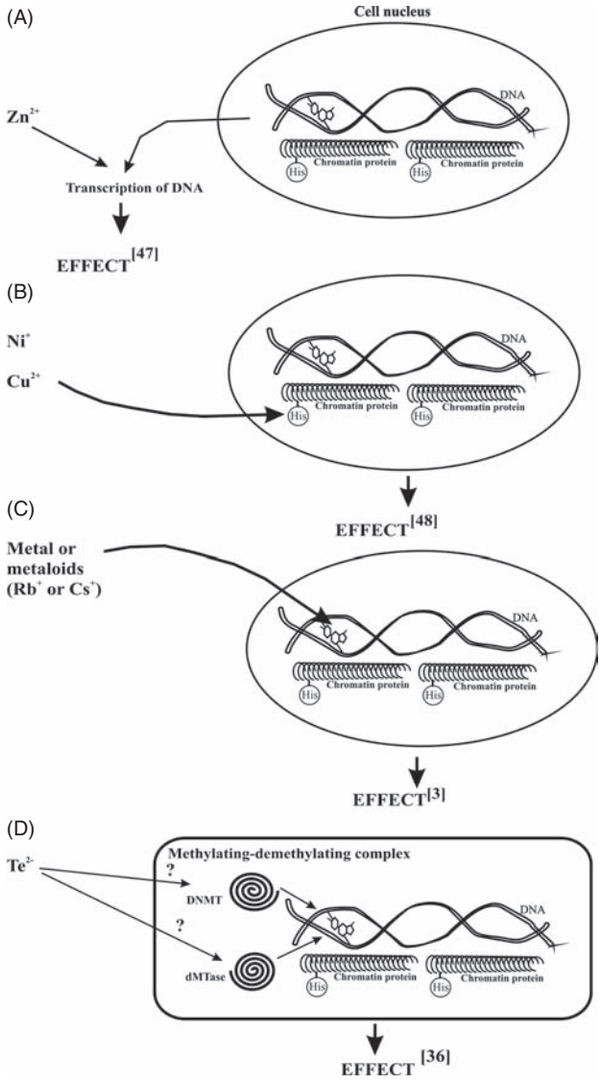

Fig. 1. Diagrammatic scheme of the main hypothetical molecular mechanisms proposed for the biological actions of trace elements. Number in the square brackets refers to the proper reference cited in the text. Trace elements can act by direct interaction with protein-DNA intermediate complexes in transcription of genes (A); by binding to histidine residues of histone H4 in the chromatin protein (B); by binding to purine nitrogen 7 or pyrimidine nitrogen 3 in the DNA (C), or by affecting the complex reactions involved in methylation processes of DNA (D). His = histidine residue; DNMT = DNA methyl transferases; dMTase = DNA demethylases.

7. EPIGENETIC MECHANISMS OF COGNITIVE AND LATERALIZATION PROCESSES IN HUMANS AND RATS PRESUMABLY LINKED TO TRACE ELEMENTS

Previous studies in our laboratory have shown that in primary school children of a certain geographical region of La Rioja province, Argentina, the phenotypic expression attributed to the *HSR* gene (*Hand Skill Relative*, OMIN 139900) was drastically changed compared to a nearby region, considered control.[38] Phenotypic expression attributed to this gene is linked to the preferential use of hand, generation of brain asymmetry, support to reading-writing ability and susceptibility of schizophrenia.[18, 19] In addition to the phenotypic changes observed in children in the problem region, analysis of the methylation patterns in blood samples showed that ratio of non methylated cytosine/methylated cytosine in DNA was about 9 times higher in those children from the problem region than in control region children.[37] Since the *HSR* chromosome locus has been described as imprinted,[20] this evidence suggests that this gene is under epigenetic control.[37] The only distinctive difference between the two geographical regions was the presence of mineral deposits and abundance of trace elements.[38] Many trace elements were found in higher concentrations in surface waters and soil in the problem region of La Rioja.[15] Considering the reactivity and molecular mechanisms that trace elements appear to have during interaction with living organisms as mentioned above, possibility that trace elements present in surface water and soil in this region of La Rioja might influence the expression of genes such as the *HSR* was proposed.[37] A direct evaluation of this hypothesis faces many practical and complicated problems, but an indirect and highly suggestive experimental approach involving animals, nevertheless deserves many promising results. Up to our knowledge, it has not been described a homologue of the *HSR* in animals. Some of the characteristics under control of this gene certainly do not exist, or at least there is not equivalence in lower living systems apart from humans. For instance, rats do not write, read, develop schizophrenia or possess asymmetrical brains. However, they have functional laterality in several neural circuits controlling complex behaviours such as exploration induced by novelty.[4, 22, 44] Since these phenotypic expressions remain constant from parents to offspring, alike genetic mechanism must exist resembling the functions of the *HSR* in humans. As expected, spontaneous lateralized behavioural responses have been found in the rat,[1] and this animal is not unique in these properties since lateralization appears to involve several species suggesting that this mechanism was a basic behavioural strategy in the evolution of species.[25] Using ZnTe as a trace element model and administered to pregnant mother rats in drinking water at 0.03–3 μg/L during all pregnancy, parturition, lactation and extending treatment to prepuberal period in the offspring, the behavioural testing at 30 day old in litter rats, show increased general motor activity and a complete blocking of the spontaneous left biased preference to explore in the animals.[36] Perhaps the most noticeable finding in the ZnTe-treated animals was that ratio of non-methylated cytosine / methylated cytosine in the DNA from the hippocampal tissue was about 2 times higher than in control animals. In contrast, in these same animals in prefrontal cortex, this molecular ratio was not affected by the trace element treatment.[36] This evidence

has a suggestive parallel with results found in humans, and certainly supports the concept that trace elements in low doses are exerting epigenetic biological effects in living systems (Fig. 1). Unfortunately, all these results cannot provide detailed information about the intrinsic molecular mechanism by which trace elements are able to change biological processes. Nevertheless, this recent evidence is opening a crucial role for the influence of environmental factors represented by inorganic elements that surround the habitat of man in the world.

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