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REVIEW ARTICLE

The inorganic chemicals that surround us: role of tellurium, selenium and zinc on behavioural functions in mammals

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ABSTRACT

Living organisms live in continuous interaction with its environment. During this process changes in one can induce adaptive responses on the other. Many factors in the environment have been studied with the notorious distinction of been rare or to be of high intensity strength in its interaction with living organisms. However, little attention has been put on some factors that have constant interaction with organisms but usually have low intensity strength, such as the case of the inorganic chemical environment that surrounds us. In this review, the interaction between the chemical element and living organisms is discussed under a theoretical model of interaction between compartments, giving attention to tellurium (Te), zinc (Zn) and selenium (Se) on some cognitive functions in human and animals. After studies in our laboratory of the phenotypic expression of the *HSR* (Hand Skill Relative) gene in school children community living in geographic zone rich in minerals and mines of La Rioja province, Argentine, where Te was found to be in higher non-toxic concentrations, a translational experimental model to maturing rats exposed to this trace element was made. Te was found to increase some parameters related to locomotion in an open field induced by novelty and exploratory motivation. At the same time, inhibition of lateralized responses, survival responses and social activity was also observed. Some of these changes, particularly those related to lateralization had similarity with that found previously in children of La Rioja province. Discussion of similarities and discrepancies of biologic effects between animals and humans, about the possible meaning of Te and its interaction with Zn and Se with relevance to humans was analyzed.

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1 Introduction

During the evolution of living systems, a "successful" organism is that one which is able to persist during successive generations, leading to a constant lineage of its kind. To reach this goal, at least two gross factors must be present; on one side an efficient mechanism of reproduction of the organism, and on the other, an environment permitting the necessary external stability so reproduction may be successful. It can be said that there are two interacting processes into play, one external to the organism and the other internal. The dynamic interplay between these two processes can be described conveniently by referring to as interaction of two compartments, i.e., "system" and "environment" [1, 2] in a similar way as traditionally it has been considered in classical thermodynamics [3, 4].

The concept of "environment" has progressed in the history of knowledge, from a space referred mainly to the external medium surrounding the organism, to any relative space surrounding a particular system of interest. Thus, applying this point of view, during the evolution of living systems, when the primordial cell evolved the cytoplasmic membrane separating it from the outer space, providing an internal medium for cell organoids, the cytoplasm was the "environment" and the cell organoids the "system", generating a new dynamic process between these two compartments. The convenient plasticity and general application of the term has converted it in a very useful concept in biological sciences. For this reason, "environment" actually, is a relative term and it is necessary to specify to what system is referring to.

In spite that this approach may seems superficial and vague, it has the advantage to simplify the dynamic of the intrinsic mechanisms involved in the complex physical-chemistry of the interchange and its physiological consequences [2]. When an interaction exists between two compartments, several possibilities of changes may appear. Some modification in basal conditions of one of them may act as an "inducer", and after this, a corresponding change in the other is a "responder" [1, 5]. This dynamic process can be represented as a chemical equation such as $E \rightarrow S^*$. Where E is the environment and S^* represents the response of the system to the challenging change produced in E. For instance, constructing a fabric near a forest which in full functioning, the disposal dark smoke deposits on the cortex of nearby trees. Butterflies living in the forest with pale and bright colors on its wings can be easily seen by predators. In time, butterflies can dark the color of the wings and these members of the colony can escape from the predators.

The reductionism expression $E \rightarrow S^*$ can also occur in the reverse direction ($E \leftarrow S^*$). For instance, a mutation in the DNA of one microorganism could alter some metabolic enzyme producing as final product an excess of acid, and the released acids change the pH of the environment transforming it into a noxious medium to other microorganisms. On this line of reasoning a more realistic expression could be $E \circledcirc S^*$ as a more general approach to the dynamic relationship between environment and system.

Traditionally it has been assumed that living organisms are in dynamic steady state with its environment ($E \circledcirc S^*$). Appropriate responses are given by the system to standard changes in the environment, and under this condition, both one and the other are "stable" in time. However, assume that due to human intrusion or ecologic

and natural events, some new and unknown change is produced in the environment. Responses to this different interacting signal may give a diverse response from the system, leading to a new unusual dynamic state. A theoretical example to this reasoning might be a genetically manipulation by man on some food seed originating a new breed more resistant to plagues. The normal consumption of the new breed could produce in some people intestinal dysfunction, increasing the prevalence of this alteration in the population. Consequences of this unfortunate unexpected result are easily to see.

Several factors in the environment can influence and change the conditions where an organism lives, and undoubtedly have received dedicated attention in some other studies [2, 6–9]. However, it is interesting to note that inorganic elements that surround us in every type of environment, only called the attention of the scientific community regarding their toxicology aspect, usually related to its abnormal concentrations [10, 11]. A surprising variety of inorganic chemicals exist in all media of human communities offering great possibilities to be "inducers", but very little studies have examined their possible biologic meaning.

In the present review, special interest is dedicated to some trace elements which in recent years have been found surprisingly linked to physiological functions in the organism, and particular emphasis is given to tellurium (Te), with a moderate comment to zinc (Zn) and selenium (Se).

2 Trace elements as environmental inducer agents

Two conditions that components in the environment should have in order to act as "inducer" is its constant presence in contact to the system, and its ability to interact biologically with some cell function. It would be useless to a particular compound to be in great concentrations and being completely inert to the biology of the system. No interaction should be generated and no changes it should be expected. Regarding this point, trace elements fulfill these requirements since are component of rocks, soil and waters and all of them always in some way or another interact with the living organism [12–14]. Other condition for the inducing agent is its chemical nature that can facilitate the interaction with molecules or structures in the responder system. Since trace elements in the organism are electrically charged, its chemical reactivity to anions or cations in the cell is favored. Thus, it is completely reasonable to assume that these inorganic elements inside the cell have a great chance to affect selected cell components and produce some physiological changes leading finally to discrete phenotypic expressions.

Regarding this issue, the cell contains many compounds with ionic charges at the normal cytoplasmic pH, but perhaps the most relevant charged molecule in the cell is DNA. There is evidence that the positively charged ions of trace elements interact directly with molecular regions of high density charged micro environment residues, particularly with phosphate bonds in the DNA strands [15]. This interaction can change the three dimensional conformation of DNA which is the basic molecular requirement to modulate epigenetically the activity of gene regions to express determined translation products [16–19]. Thus, trace elements in theory have the physical chemical requirements to act as inducers, fulfilling a biological interaction in the cell metabolism.

3 The role of tellurium (Te).

Te in chemical terms is a metalloid with intermediate properties of metals and non-metals of the table of periodical elements. In a certain way, its atomic characteristic gives Te a special facility to interact with many other chemical groups having strong or intermediate electronegativity. Te was discovered near the end of the 18th century by Müller [11], and owns its name to *tellus* meaning earth. However, Te importance as a new element came several years after the discovery by Müller, which at that time (1782) he named the element as *metallum problematicum* [20].

The most abundant and natural chemical form of Te in nature is as TeO_3^{2-} which as early in the 20th century was discovered to be toxic to several microorganisms, supporting its use as a primitive antibiotic in human health [21, 22]. During a long time, Te was not considered to play some important role in living systems. However, with this trace element some particularities have been found regarding its interaction with organisms that call the attention, giving the concept of its inactivity in biological actions, a second thought. The first notorious fact about Te is that it is present in considerable amounts in bone tissue of the human body [23]. Thus, it is not surprising that the trace element also has been found in blood and urine [24, 25]. The second important fact is that in some bacterial proteins, Te has been found to be part of the molecular constitution of the amino acids tellurocysteine and telluromethionine [26, 27] suggesting that the metalloid could be exerting some physiological function. A third finding is the biological actions that some Te complexes (AS101, trichoro[dioxoethylene-O-O']tellurate) induce hair growth in some experimental models, such as nude mice, and also in human teenagers with alopecia [28]. In addition, this organotellurium complex has shown some additional properties regarding immunological responses such as inhibition of the production of inflammatory cytokines, and ameliorating the pathogenic reactions of the experimental autoimmune encephalomyelitis [29]. Furthermore, AS101 restores and protects the dopaminergic neuronal activity in an animal model of Parkinson's disease [30], and reverse the deleterious effects of type 1 diabetes in NOD/ShiLt female mice [31], suggesting that Te could be participating in some key physiological processes in the organism.

Concentration of trace elements in biological fluids is a critical determinant to affect the normal dynamic homeostasis. Te is present in natural bedrock underground waters in very low concentrations about 0.005 μg/L [14]. However, in other places of the world, such as the mountain regions, rich in mineral mines, as La Rioja province, Argentina, Te in river waters can reach a median of 0.313 μg/L [32]. Nevertheless, even at first sight this amount appears to be a very high concentration, still it is far away from that reported to be toxic to animals and man [33, 34]. Thus, Te in La Rioja waters is not a health problem to the population. Interestingly, in this same geographical region of La Rioja province, a study of the phenotypical expression of gene *HSR* (Hand Skill Relative) that is related to right handedness, cognitive abilities and reading-writing capacity, school children showed altered phenotypic expression attributed to this gene. In blood samples of these children, demethylation of cytosine in DNA was found, suggesting that the alterations found were by epigenetic mechanisms [35, 36].

Suspicion that Te, which in this geographical region has a higher concentration than in other parts of the world, could be acting as an inducer, is supported by studies in animal models using the same concentrations of Te. Animals showed

altered responses to several lateralized behaviours related to cognition [37–40]. Perhaps, the most relevant finding in these parallel studies, suggesting that Te might be involved in the phenotypic changes was that rats treated with Te, in addition to the altered phenotypic expressions, the same demethylation patterns of DNA found in humans were observed in the rat hippocampal tissue [37]. Demethylation of DNA in the hippocampus was specific because no changes in methylation patterns were found in the prefrontal cortex of the same animals [37]. No dose response curve was observed at increasing exposition amounts of Te to the animals, where a low dose of 0.03 μg/L was enough to affect the lateralizing exploratory behaviour [37], suggesting that the biological effect of the metalloid showed an "on-off" response.

4 Toward a possible molecular mechanism of Te

The exact molecular mechanism of the biological actions of Te still is not known. However, several facts about its action in the organism permit to speculate possible biochemical pathways. For instance, it is known that Te modifies the methylation patterns of DNA in selected brain structures [37]. This clearly suggests that the metalloid is able to induce the phenotypic changes by at least, interaction with DNA. Up to this point, we can examine all the evidence supporting the hypothesis of an epigenetic mechanism for Te on the behavioural responses linked to cognition.

1) If demethylation of cytosine nucleotides seems to be a part of the mechanism of Te, it is possible to speculate that the reverse process of demethylation, the Te-dependent biological effects should be reversed. Folic acid (a water soluble vitamin, B9) is a complex molecule that is well known by its chemical properties to regulate essential development, regeneration and function of the nervous system, and particularly is involved as a methyl donor to methylation regulation of DNA [41–45]. Using the same experimental design of the chronic administration of Te in the studies of cognition [37], the administration of Te and folate reversed the inhibitory effects of Te found previously, supporting the concept that the metalloid is acting at the methylation-demethylation processes in the cell [46].

2) A second point to be discussed is related to knowledge that epigenetic processes are stable through generations. If Te is inducer acting partly by an epigenetic mechanism, it is possible to think that once the metalloid interacts with the organism, a chained process is evolved leading to the establishment of the biological effects affecting cognition, extending to the next generations. This assumption was tested applying the standard chronic administration of Te only to the parent (F_0) and first generation animals (F_1), letting the F_1 offspring to grow up without any treatment up to 90 day-old. Then, F_1 female rats were mated with normal males and F_2 offspring at 30 days were tested for their behavioural responses (Fig. 1) [47]. The F_2 animals showed the same inhibitory behavioural responses in motivated exploration in moderate conflictive environments; complete abolishment of the natural left-biased exploration in lateralized environments; decreasing social activity in intruder-resident tests, and decreased survival responses, as previously observed in their F_1-parent rats [47]. These results support the assumption that the mechanism of Te on cognitive behavioural parameters is through an epigenetic change, satisfying the second point of the analysis of Te mechanism of action.

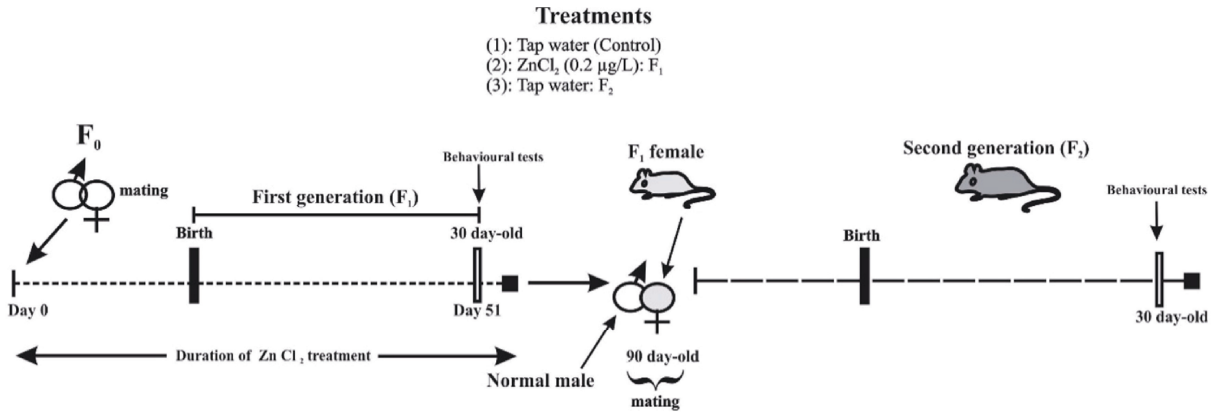

Fig. 1 Experimental design of the intergenerational effect of Te in maturing rats. Experiment was performed in two parts. In the first one, Te was administered to the mother rat (F_0) during pregnancy, delivery and lactation periods. At 21 days, maturing rats were weaned and separated from its mother, but treatment of Te continued up to 30 day-old (left side of the panel), where animals were tested for behavioural responses. F_1 animals received no further treatment and remained at rest for 60 days. In the second part, male rats were discarded and F_1 female rats were mated with a normal male rat (right side of the panel). At 30 days the F_2 rats were subjected to the behavioural tests. Abbreviations: F_0 = parental generation; F_1 = first generation; F_2 = second generation. Reproduced from Ref. [48], ©The authors.

3) A third point to be considered is to evaluate if the persistence of the deleterious behavioural effects observed in F_2 animals by Te treatment in F_1 rats [47] can be reversed by the administration of folate in the F_2 rats. Recent experiments performed in our laboratory following the experimental design shown in Fig. 2, showed complete reversion of the lateralized exploratory behaviour (Fig. 3), social interaction behaviour (Fig. 4), and defensive behaviour (Fig. 5) in full concordance with the expected epigenetic mechanism described before. What this evidence reveals is that the methylation-demethylation dynamic of cytosine residues in DNA seems to be an important step in the molecular action of Te, showing reversibility that also is other characteristic of epigenetic processes [46].

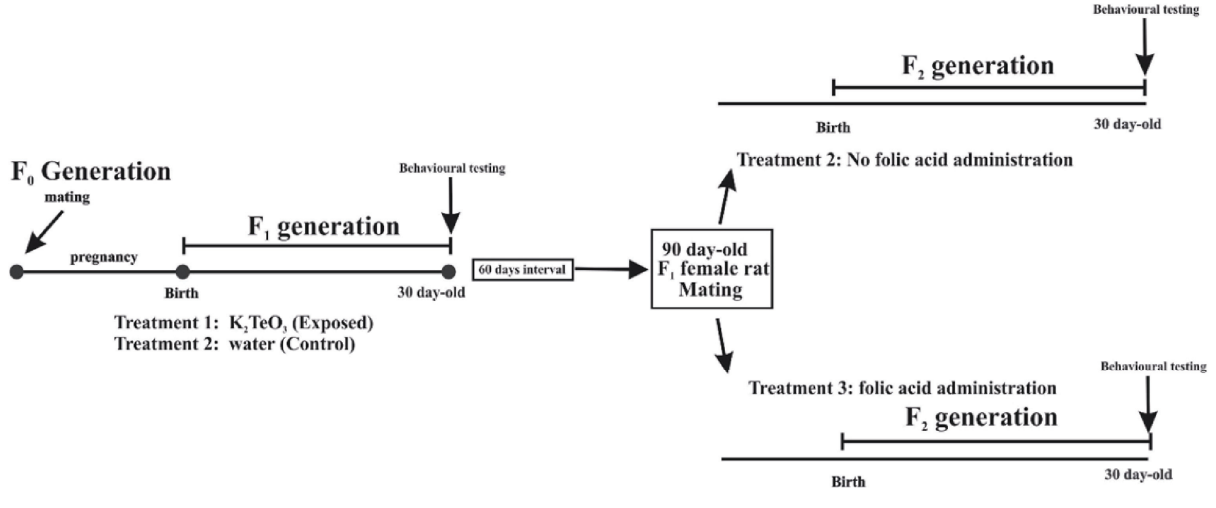

Fig. 2 Experimental design of the multigenerational effect of Te and folic acid in maturing rats. The first part of the experiment was the same that described in Part 1 of Fig. 1. After the behavioural measures at 30 days of the different groups, all groups remained at rest with no further Te treatment or water as control. At 90 day-old, F_1-female rats were mated with a normal male (right side of the panel). Two independent groups were set. One did not receive folic acid (upper side of the panel), and the other one received folic acid (lower side of the panel). At 30 day-old, both groups were subjected to the behavioural measures.

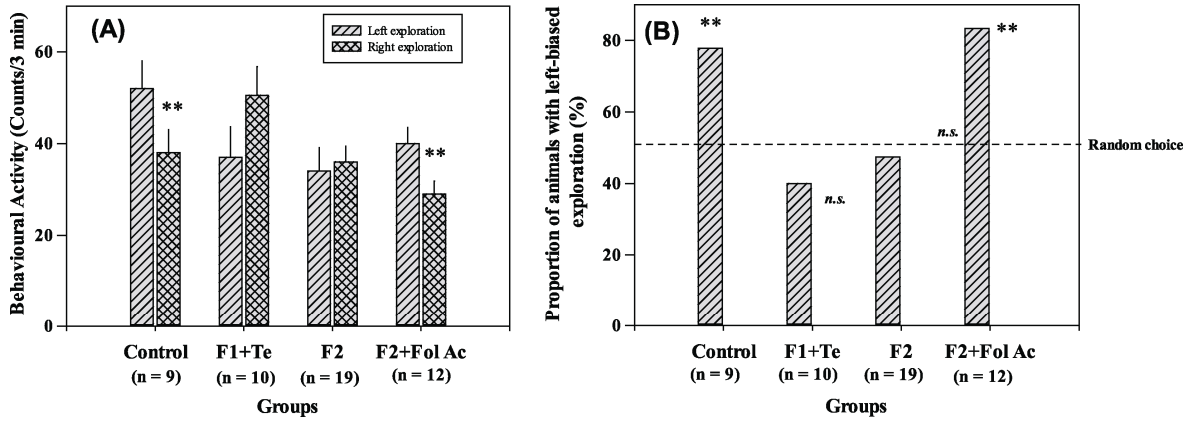

Fig. 3 Lateralized behaviour in the Double-Vertical Hole Board Labyrinth (DHBL; [40]) of maturing rats in the second generation, after exposure to Te in F_1 generation. The DHBL is a labyrinth composed of one cubic compartment (Initial) disposed in 90° with a cubic rectangular compartment with walls on either side with lateral holes (Corridor). An open door communicates both compartments. Animals are put in the initial compartment and exploration of the corridor is displayed by the animal motivated by novelty. Exploration of one side of the wall is considered lateralized if the score significantly exceeds the exploration score of the other side. Exploration by the center of the corridor is considered without decision (non-lateralized). (A) Behavioural activity during the exploration of both walls of the corridor. Abbreviations: F_1 + Te = group that received Te in the F_1 generation; F_2 = group from F_1 parental rat receiving no treatment; F_2 + Fol Ac = group from F_1 parental rat receiving Folic acid. ** $p < 0.01$ compared with left-biased exploration. (B) Proportion of animals with left-biased exploration in rats exposed to Te in F_1, and F_2 generations were treated or not treated with Folic acid. Abbreviations: Control = animals with no Te treatment; F_1 + Te = animals exposed to Te in the first generation; F_2 = animals without folic acid treatment; F_2 + Fol Ac = animals with folic acid treatment. Line of 50% = proportion of animals with no lateralized exploration (random decision). ** $p < 0.01$ compared with 50%; n.s. = non statistically different

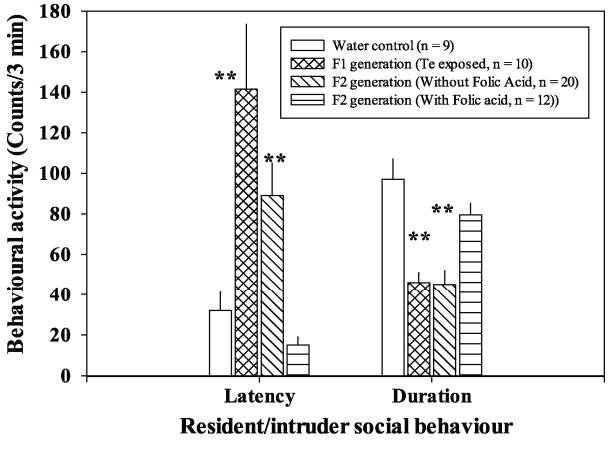

Fig. 4 Social interaction activity of maturing rats in the second generation (F_2), after Te exposure of its parents in the first generation in the Resident/Intruder Test. Target animal is put in a larger steel cage with wood shavings alone during 2 min. At min 3, a new intruder rat about the same size and sex is put into the cage for social interaction during an additional 3 min period. All behaviours of interaction are measured. The total duration of the test was 5 min. ** $p < 0.01$ compared to control group.

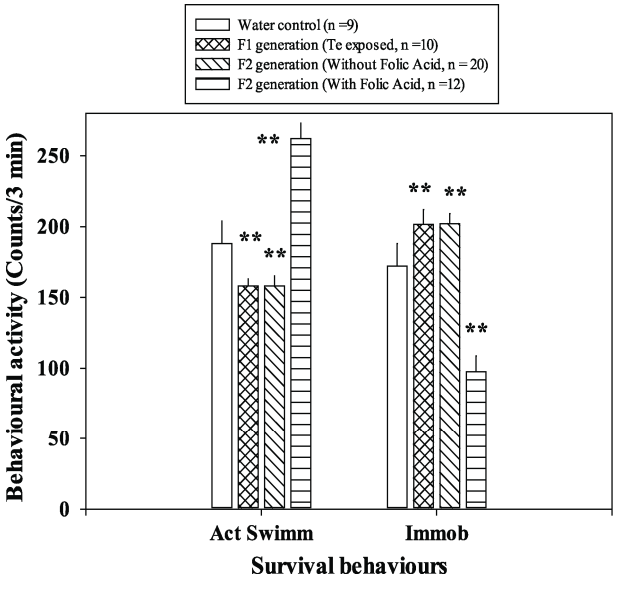

Fig. 5 Surviving responses in the forced swimming test of maturing rats in the second generation (F_2), after Te exposure of its parents in the first generation. Animals were put in a plastic cylinder with water at room temperature and the active swimming activity, and its periods of immobilization are measured in a 3 min duration test. ** $p < 0.01$ compared to control animals. Immobilization behaviour and the active swimming activity represent the total behavioural activity showed by each animal.

5 Biological interaction of zinc (Zn) and Te

Zn is a well-known trace element which has an

important role in biological systems [49, 50]. The most important action of Zn is the participation in the oxide-reduction reactions occurring in the cell [49–51], and it has been found that the trace element is a prosthetic group for several crucial enzymes in the normal metabolism [49, 52]. Perhaps, quite relevant to the epigenetically actions of Te, is the evidence that Zn participates in the formation of the Zn-finger proteins, a family of cell molecules that regulate the gene expression [51, 53]. In addition, biological actions of Zn are not strictly limited to those processes above mentioned. A variety of behavioural effects which include regulation of sleep, anxiety, depression, maintenance and regeneration of epithelial cells in the intestine have been also described [54–56]. The diverse physiological actions showed by Zn should be taken into consideration when the trace element is provided to a biological system.

When Te is administered in the chemical form of ZnTe, using the same experimental design previously discussed [37], and replaced with $ZnCl_2$, Zn showed a similar behavioural effect as Te in some selected behaviours in the open-field, but did no modify lateralized exploratory behaviour, nor defensive and social activity, which is inhibited by Te [38]. It is not clear the exact mechanism of Zn in these discrete behavioural responses found in the open-field experiments [38], since Zn appears sometimes to generate similar effects to Te, and in other occasions, influences selected behaviours not modified by Te [38]. What is clear from this evidence is that Te changes on behavioural responses seems to be specific, and the possible behavioural role of Zn, is presented as an avenue to further experiments.

6 Biologic interaction of selenium (Se) and Te

Se is other trace element which had a similar chemical history than Te in the sense that the first biological effect discovered was its toxic properties [57]. As previously discussed, a crucial point to understand the biological effects of a chemical element in animals is its concentration in the environment and in the organism. When Se concentrations in soil was very low, notorious pathological effects were found, such as congestive heart myopathy, showing that Se was an essential element in organism homeostasis [58], confirming early experiments on dietary hepatic necrosis in rats where it had been proposed the essentiality role of Se [59]. Se, shares the property, just likewise Te, to form amino acids. Thus, Se was found to be an important component of key enzymes as the amino acid selenocysteine, such as glutathione peroxidase [57], which actually is part of the family of seleno-proteins, an important group of enzymes present in peripheral glands and central nervous system [57, 60–62]. Since Se and Te are in the same group (column of the periodic chemical table) these trace elements share similar physicochemical properties, and in nature they show the interesting property of swapping or interchanging in molecular complexes [63]. This chemical interchanging is not a peculiar characteristic of Se and Te, but it is also found in selected bacteria and marine diatoms, with other chemical elements of the periodic chemical table [64–67]. Thus, a different perspective regarding the chemical interaction between trace elements for Te actions appears on consideration.

In the chronic administration experimental setup in rats, when Se is provided together with Te, Se was able to counteract the inhibitory actions of Te on lateralized exploratory behavioural responses, social behaviour activity, and survival-defense behaviour [68], suggesting that some Se chemical intermediary seems to be important in the molecular mechanism of the

brain behavioural responses affected by Te. It is not clear if these biological effects of Se are produced as a chemical element by itself, or because Se is forming part of bioactive molecules such as seleno-proteins of the cell. Undoubtedly, further investigation should be necessary to elucidate the intrinsic mechanism of Se during its interaction with Te.

7 Final considerations

It can be said that the chemical environment that surround us do not need to be in higher concentrations during the continuous interaction with living systems in order to provoke some biological effects. Trace and non-toxic concentrations can be sufficient to induce chemical and behavioural modifications in organisms, if the basic biological requirements of environmental continuous presence, and target organs for the trace element are met, as mentioned before.

Te has showed at very low doses surprising biological effects in organisms giving strength to the idea that the trace element might have some physiological actions not foreseen previously. In our laboratory, evidence has been found that Te might act by an epigenetic mechanism in the brain influencing cognitive processes that in humans affect the gene-environment interaction, and in animals their coping behaviour. It is considered that the experimental evidence so far encountered represent the beginning signs to a physiological role for Te in the cell metabolism.

Conflict of interests

The authors declare that they have no competing interests in this work.

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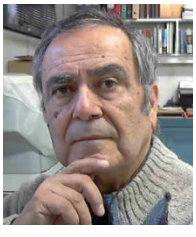

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