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Differential effects of zinc and tellurium on epigenetic changes of coping behaviour in maturing rats

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ABSTRACT

Trace element and its probable role in biological systems have attracted the attention of many researchers in recent years. Previous work has shown that ZnTe administered in drinking water to pregnant rats during pregnancy, delivery, lactation and offspring maturation up to prepuberal stage is able to modify several parameters of spontaneous behaviours related to cognition in offspring rats. Since Zn and Te have many biological properties, it's not possible to conclude if behavioural changes are due to Zn, Te or both trace elements activity. In the present work, K2TeO3 and ZnCl2 were used alone in order to evaluate single actions of trace elements. Four experimental groups were formed: Control (water), Zn-treated group, Te-treated groups, and Zn+Te group. At the end of the experiments at 30 days of age offspring of each group were tested individually in a Double-Hole Board Labyrinth to evaluate lateralized exploration. Open field enriched with a rack and hole-board to evaluate motivated exploration; single cage in an intruder-host test to evaluate social interaction, and forced swimming cylinder to evaluate the survival responses. Results showed selective changes in rearing for Te (first Test); blocking of the natural left-biased exploration (second Test) increased time to confront the intruder with decreased time to interact with the intruder (third Test), and decreased time to active swimming (fourth Test).

With the exception of duration of the social interaction, Zn has no effect. Results suggest that most of the behavioural changes found with ZnTe in previous studies are due to Te.

1 Introduction

Trace elements have a peculiar history in the biological and geochemical sciences. These inorganic elements presented in very low concentrations in soil and water in the earth, were early considered relevant to health only if their amounts were very high or low [1, 2], since the prevalent concept at that time was toxicity by accumulation of the suspected element in the organism. Zinc and iodine, both clear representatives of trace elements, were found later to be component of metalloenzymes, hormones and some metalloproteins participating in various metabolic activities in the cell [3], and this knowledge changed the irremissibly preconceived assumption about toxicity of trace elements in living systems. Zinc, for instance, has been found to be essential for several enzymatic activities, DNA replication, and consequently transcription and protein synthesis [4]. Its highest concentration in the hippocampus, part of the limbic system, and brain cortex suggests that this trace element is participating in many brain functions linked to cognitive
processes [5, 6].

On the other hand, tellurium (Te), another trace element that attracted the attention of many workers had the historical notorious application of being used for treating bacterial infections before antibiotics appeared in the health history of microbial control [7, 8]. Nevertheless, Te did not follow the path previously claimed for Zn or selenium (Se) to be an essential component in the biology of the cell [9]. This trace element is not considered yet as having a primordial role in biological systems. Nevertheless, peculiar characteristics regarding Te are worthwhile to mention. Te is not a foreign rare element in living systems, since it has been found in appreciable amounts in bone tissue in humans [10]. Its presence also has been detected in blood and urine [11, 12]. As it was established previously with Se, Te was found to form structural part of some amino-acids, such as telluro-cysteine and telluromethionine in some bacterial proteins [13, 14], yeast and fungi [15, 16], suggesting a biological role for the trace element in living systems not foreseen yet. The possible importance of Te is reinforced with some studies using ammonium trichloro(dioxoethylene–O, O') tellurate (AS101), which is able to induce hair growth in nude mice and also in teenagers with alopecia [17]. In addition, this same molecular complex gives protection and restoration of dopaminergic neurotransmission of neurons in a model of Parkinson’s disease [18].

Although several efforts have been made regarding the molecular mechanism whereby trace elements might be acting, still its intrinsic mechanism is not clear. Relevant data indicates that some elements appear to participate in complex interaction with DNA, inducing molecular conformation changes, or modulating methylation reactions inducing alterations in gene expression [19, 20–22]. Chemical reactions such as those mentioned can modify natural histone interactions, or methylation dynamic of cytosine in DNA which are two well established mechanisms of epigenesis [21–25]. Epigenetic processes represent plastic molecular mechanism of living beings where heritable changes in gene expression occur without alterations in the genetic code [21].

In a previous study of our laboratory, school children living in two different geographical regions, where the most distinctive aspect of the regions was absence or presence of mineral mines with concentration of some trace elements in surface water, river sediments and vegetation slightly above the reference world ground levels [26], the phenotypic display of the HSR (Hand Skill Relative) gene was modified in those children coming from the metal mine zone [27]. This gene was shown to be imprinted and susceptible to be influenced by environmental factors [28, 29]. In addition, molecular analysis of methylation DNA patterns in blood samples from children of the two regions, only those coming from the mineral zone showed altered methylated pattern, suggesting that an epigenetic effect was present [29]. In experimental models in rats, cognitive parameters were altered in animals treated chronically with non-toxic low doses of ZnTe [22]. Analysis of the DNA methylating pattern from the hippocampal structure of these rats showed about the same demethylating cytosine DNA pattern previously found in humans [22]. One problem in these experiments is that Zn and Te are present simultaneously in the treated rats, making the possibility to distinguish each effect of these two bioactive elements difficult. Supporting evidence that the modified behavioural parameters were linked to Te instead of Zn was obtained from studies using ZnCl₂ and ZnTe [30]. Unfortunately, a possible synergism between the activity of Zn and Te on the behavioural responses in these rats could not be examined; and a hypothetical differential behavioural effect due to the interaction between Zn and Te was not discarded. Thus, the objective of the present investigation was to examine separate effects of both trace elements in maturing rats, using the same experimental scheme, in order to discriminate the behavioural influence of each trace elements and its molecular interaction.

2 Materials and methods

2.1 Animals

Rats of a Holzman-derived colony, weighing 250–300 g, 90 days old and maintained in thermoregulated (22–24 °C) and controlled light conditions (06.00 on–20.00 h off) were used. Standard rat chow and water were available ad libitum for control animals. Experimental rats received ZnCl₂, K₂TeO₃ or ZnTe at a concentration of 1.55 nM in the drinking water.
2.2 Experimental design

The general experimental protocol used in the present work was described previously [22]. Briefly, chronic exposition to trace elements, beginning from fertilization of the mother rat up to prepuberal maturation stages of litter rats was applied. Potassium tellurite (K₂TeO₃, Tetrahedron Reactivos Analíticos, Argentina) and ZnCl₂ (Dalton Argentina) was used as Te and Zn trace elements (Fig. 1).

There were 4 experimental groups:
1) Water (Control; n = 9)
2) ZnCl₂ (Zn; n = 10)
3) K₂TeO₃ (Te; n = 10)
4) ZnTe (Zn+Te; n = 10)

As formerly specified, at birth for all groups, pups were standardized to 10 animals per litter trying to maintain whenever possible the relationship of 1:1 of male to female rats. Thus, there were initially 10 animals for each group in the behavioural tests. When maturing rats were 21 day-old (Day 42 of treatment), young rats were weaned and separated from their mothers. At 30 day-old (Day 51 of treatment) young rats of both sexes were subjected to a battery of behavioural tests in order to evaluate general motor activity; motivated exploration; lateralization; social and defensive behaviour in the same way as previously described [22]. After ending the behavioural tests, all animals were sacrificed by lethal i.p. injections of Sodium Pentobarbital (40 g/100), and Sodium Diphenylhydantoin (5 g/100, Euthanyle, Brouwer Inc., Argentina).

2.3 Behavioural tests

The following behavioural tests were used to evaluate exploration of novel environments, lateralization, preferential decisions, and defensive behaviour.

2.3.1 General activity and exploratory behaviour detector (OVM)

It consists of rectangular open-field with acrylic walls, equipped with infra-red detectors and digital counting devices for measuring animal activity (Optovarimex instruments, U.S.A), as described in detail previously [22].

Three variables were measured in order to evaluate exploration motivated by novelty. Variables were:
1) Head dipping, number of times the animal dips its head up to the level of its ears into any of the holes in the floor of the OVM.
2) Rearing, number of times the animal rears on any lateral wall of the OVM with its anterior arms, or lifting its head up, leaning on its rear legs on the floor.
3) Focalized exploration, duration of the exploratory behaviour dedicated to a novel object located in the center of the OVM, measured by a digital counter at a rate of 2 counts per second.

Test was applied to single animal and had a total duration of 5 min.

2.3.2 Double Lateral Hole-board Labyrinth (DHBL)

This labyrinth evaluates motivated exploration that can be expressed in lateralized form, as described previously [31, 22].

DHBL is made of wood and is composed by a rectangular cage 39 cm width, 70 cm length and 15 cm height. Inside there are two compartments disposed in 90° each. The first compartment (initial) has 39 cm length and 15 cm width with a central entrance to the second compartment (corridor). Corridor has 55 cm of length, 17 cm width, and on its side walls there are 4 lateral holes, each 3 cm in diameter. In this test, behavioural activity of animals was driven only by exploratory motivation induced by novel environments.

The following variables were measured:
1) Corridor behavioural activity. All behaviours displayed by rats while they were in the corridor of the labyrinth, such as walking, rearing, head-dipping, and sniffing on the left or right-side walls, including non-exploratory behaviours such as grooming and immobilization was measured by a digital automatic counter (counting rate 2 counts/s) monitored by an
observer unaware of treatments.

2) Lateralized exploration. It is included in this variable all behaviours related to exploration displayed when the animal chooses one side of the corridor during exploration. Behaviours included: (i) Walking near the left or right wall of the corridor, at constant speed, with vibrissae touching the wall. (ii) Lateral head-dipping. (iii) Rearing against the left or right walls of the corridor. This score was measured in the same way as Corridor Behavioural Activity.

3) Non-exploratory activity, such as immobilization at any site of the corridor, walking at the center and not approaching to any side wall, or grooming were not measured.

In this test, behavioural laterality was considered to be present when the median of lateralized exploration on one side of the walls statistically outnumbers the opposite exploration.

Test was applied to single animal and had a total duration of 3 min.

2.3.3 Forced swimming test

This test measures the defensive behavioural response of animals subjected to a stressful situation represented by active swimming in a closed environment having no escape [22]. Device consists of a transparent acrylic tube measuring 50 cm height by 12 cm diameter (internal diameter), filled with water at room temperature up to half of the cylinder height. Two variables were measured:

1) Active swimming activity, all the vigorous swimming movements displayed by animals involving all four extremities at approximately constant rate, and motor activity showed during immersion looking for an escape. Activity was measured by digital automatic counting at a rate of 2 counts/s monitored by an expert observer unaware of treatments.

2) Immobilization, the time lapse where animals do not swim, floating without movements or displaying slow motion of its extremities enough to avoid sinking into the water. Since test had a total duration of 3 min (360 counts), this behavioural activity was obtained by subtracting the active swimming activity from total counting.

2.3.4 Social interaction test

This test (intruder-host territorial test) measures the social display of two interacting rats in a determined territory challenge by an intruder [30]. Test was performed in a rectangular steel cage (26 cm width, 42 cm length and 20 cm height) with wood shavings in the floor. Total duration of testing was 5 min. In the initial 2 min, the testing animal (host rat) was put alone in the arena in order to familiarize with the cage. At the beginning of 3rd minute, a different and new rat of the same size and sex (intruder rat) was put in one corner of the cage. Behavioural display was recorded until testing period was finished. The following variables were measured:

1) Latency to interact, time measured by digital counting that the host animal takes to face the intruder (α behaviour). Sniffing, touching, gentle biting, and dragging the intruder were recorded as social behavioural display.

2) Duration of α contact, time measured by digital counting the duration of α social interaction displayed by the host animal in the test.

All behavioural tests were filmed by a digital video camera, and recorded in a DVD player/recorder Phillips, model DVDR3455H.

2.4 Experiments

The following experiments were performed.

2.4.1 Differential effects of Te and Zn and its combination, on exploration behaviour induced by novelty

In this experiment the influence of Te, Zn and its combination on general motor and motivated behaviour induced by novelty was evaluated. Measuring of the behavioural activity was performed using the OVM device as described above.

2.4.2 Effect of chronic administration of Te, Zn and its combination on lateralized and motivated behaviour.

In this experiment, the influence of Te, Zn and its combination on lateralized and motivated behaviour induced by novelty was evaluated. Measuring of the behavioural activity was performed using the DHBL.

2.4.3 Effect of chronic administration of Te, Zn and its combination on social behaviour

In this experiment, the influence of Te, Zn and its combination on social behaviour was evaluated. This
behavioural activity was measured in the intruder-host territorial test.

2.4.4 Effect of chronic administration of Te, Zn and its combination on defensive behaviour

In this experiment, the influence of Te, Zn and its combination on defensive behaviour was evaluated. Measuring of the behavioural activity was performed in the forced swimming test.

2.5 Statistical analysis

Multiple comparisons for behaviours between experimental groups, were made by the Non-Parametric Test of Dunn [32, 33]. When comparisons involved paired groups, the Mann-Whitney Test was used. The significance of single percentage differences was analyzed by the Binomial Distribution (the Sign Test). A p value of less than 0.05 was considered as statistical significant. Results are presented as the median ± standard error.

2.6 Ethical care of animals.

The present experimental protocol followed the recommendations of the Guide for the Care and Use of Laboratory Animals (8th edition, NIH) [34], and guidelines of animals care of Foltz [35]. Whenever it was possible, number of animals was reduced to the minimum acceptable allowing statistical discrimination.

3 Results

Experiment 1

The motivated exploration parameters displayed by rats in the OVM, exposed to Te, Zn, or ZnTe are shown in Fig. 2.

No significant changes in head-dipping were observed in those animals treated with Te or Zn. However, those animals receiving ZnTe showed an increased frequency of head-dipping that was statistically significant compared to control (Panel A). On the other hand, rearing behaviour was increased significantly in those animals receiving Te and Zn+Te; meanwhile, Zn had no effect (Panel A). Focalized exploration instead, was not affected by treatments (Panel B).

Experiment 2

Lateralized exploration score in the DHBL for animals exposed to Te, Zn or Zn+Te is shown in Fig. 3.

Fig. 2 Motivated exploration scores of animals treated chronically with Zn, Te or Zn+Te. Foc Expl = Focalized exploration. * p < 0.05 versus Control; ** p < 0.01 versus Control.

Fig. 3 (A) Lateralized exploration in animals treated chronically with Zn, Te or Zn+Te measured in the DHBL. (B) Percentage of animals with left-biased exploration in the DHBL, treated with chronic doses of Zn, Te or Zn+Te. n.s. = Non significant from Random level.
Control animals showed significant left-biased exploration, while rats exposed to Te or to the combination of Zn and Te showed no preference for left or right side exploration (Fig. 3(A)). Rats exposed to Zn however conserved the left-biased exploration (Fig. 3(A)).

When percentage of rats with biased exploration was calculated, significant deviation for random choice was found for control rats, and Zn-treated rats, while percentages not different from random choice were found for Te and Zn + Te groups (Fig. 3(B)).

Experiment 3
Social behavioural activity in rats exposed to Te, Zn or ZnTe is shown in Fig. 4.
Animals exposed to Te or to the combination of Zn and Te showed a significant increase in latency to confront the intruder animal compared to control in the resident-intruder test (Fig. 4(A)). Meanwhile animals exposed to Zn, did not differed from control rats. Duration of the $\alpha$-activity was significantly decreased in the three groups (Zn, Te, and Zn+Te), compared to control, where the most pronounced effect was observed in the Zn+Te group (Fig. 4(B)).

Experiment 4
Survival behaviours in the forced swimming test of animals exposed to Te, Zn or Zn+Te are shown in Fig. 5.
Only those rats exposed to Te and the combination of Zn+Te showed a decrease in the score of active swimming when compared with control rats.

4 Discussion
The main problem related to evaluation of the possible effects of Te on cognitive functions in animals is to discriminate Te effects from Zn effects when both elements are present as Zn+Te, since Zn and Te have been shown to be bioactive. An additional issue is the possibility of some synergistic or inhibitory activity when both elements are present in living system. In the experimental design used in this work, administration of K$_2$TeO$_3$ and ZnCl$_2$ for specific stimulation of Te and Zn was well thought-out to discriminate the effects of trace elements. Since the main biological effects of Zn+Te were found on selective motivated exploratory responses, lateralized exploration, defensive and social behaviours; all components of a spectrum known as coping behaviour [22],
discrimination of Zn or Te activity influence was important to discern, considering the well-known actions that Zn had on the central nervous system [36–38].

Experiment 1 shows that only the combination of Zn and Te (Zn+Te) was able to increase the behavioural activity of head-dipping (Fig. 2, Panel A). Head-dipping is one of the motivated behavioural responses to novelty [39, 40]. This result suggests that an interactive effect of both trace elements is evident, since, Te or Zn alone has no effect on this behaviour (Fig. 2, Panel A). A completely different situation is observed with rearing (Fig. 2, Panel A), where the increase in the behavioural activity found in the Zn+Te treated animals, is due to Te. However, it cannot be discarded the possibility of a synergic effect due to Zn, since the rearing score is statistically higher than that found in the animals treated with Te alone (Fig. 2, Panel A). In the spontaneous exploration of the DHBL, results clearly suggest that the abolition of the left biased exploratory activity is induced only by the Te treatment (Experiment 2, Fig. 3(A)). The inhibition of the left-biased response of exploration in the combination (Zn+Te) treatment to rats can be explained by the presence of Te, since Zn has no effect on the lateralized response (Fig. 3(A)). It is not surprising then that the proportion of left-biased exploration animals was conserved in the Zn treated group, and completely abolished in the Te and Zn+Te treated animals (Fig. 3(B)). As shown in Fig. 4, social activity also is affected by the Te treatment to rats. This effect is specific for Te, since Zn did not increase the latency to confront the intruder rat (Fig. 4(A)). However, an interaction between both trace elements appears to be evident, as even if the score is significantly higher in the Zn+Te group compared to control, it was significantly lower than Te treatment alone (Fig. 4(A), Experiment 3). In the case of duration of social interaction (Fig. 4(B)), situation is different. Zn treatment was effective to decrease significantly the duration of active contacts. The administration of Te alone induced a more pronounced inhibition of the score. Some interaction like a synergistic effect was found with the combination of Zn and Te, which was effective to inhibit about 70% the response compared to control (Fig. 4(B)). Finally, in the forced swimming test that measures the motivated survival response (Fig. 5, Experiment 4), only Te was able to specifically inhibit the active swimming response. As it was aforementioned with the social intruder-resident test, some interaction appears to be with Zn and Te (swimming score of Zn+Te group was lower than control but higher than Te treated rats, Fig. 5), evidence giving additional support that both trace elements appear to act on the same brain structures [41, 30]. Results from the experiments shown in the present work; strongly suggest that the behavioural effects found in previous studies with Zn+Te [22, 30] are due to Te.

Te is a trace element that the scientific community has been reluctant to accept that it may have some biological role. Interest to study the nature of the interaction of Te and biological systems, has been focalized on the property of toxicity to living systems [42, 43, 7]. Te was used in 1926 as treatment for syphilis and leprosy [8]. Later it was found that Te affects specific sites in the peripheral nervous system blocking the cholesterol synthesis, by inhibiting the squalene epoxidase in the squalene metabolism of nervous cells [44–46]. Specifically, the trace element affects rat astrocytes of cerebral cortex and also of hippocampus, inducing cognitive deficits [47–49]. Although these data were found with different Te containing chemical compounds and at much higher doses than those used in the present study, there is a common denominator, Te is affecting neural circuits provoking behavioural changes, suggesting that the role of the metalloid in living systems might be more functional than ever before was thought [50, 51, 18, 22, 41]. This case is quite similar to previous studies with glutamic acid in the past century, where the initial impression was based on its specific toxicity to neuron cells, to change to its role as a neurotransmitter in the nervous system [39].

Mechanism by which Te could be acting on brain tissue still remains elusive. Some brain structures of the limbic system, such as the hippocampus, appear to be involved because Te administration in non-toxic doses was able to change the DNA methylation patterns in rats [22]. Although there are not specific molecular studies regarding Te and DNA interactions, it would be not surprising that the metalloid can intervene in a similar way as other trace elements with DNA [19]. On this line, Te can be regarded as an environmental factor inducing epigenetic changes in trace element
exposed living systems. That demethylation appears to be an important mechanism in the chain of molecular processes leading finally to a behavioural change, is supported by experiments where animals treated with Te in the same experimental schedule that used in the present work, administration of folic acid, a well-known methyl group donor [52, 53] reverted all behavioural Te changes [54]. Although at present there is not direct biochemical evidence, it is tempting to speculate that a DNA demethylase enzyme might be target of Te action.

In spite of these data, Te molecular mechanism is far from being simple. In previous experiments of our laboratory, the administration of selenium also was able to counteract the altered biological effects of Te in the same experimental design, putting the interaction between trace elements as a new factor to be investigated [55].

5 Final remarks

Evidence from the present study put into evidence that the major biological effects of Zn+Te are due to Te. In some cases, part of the behavioural effects of Te was modified by an internal interaction with Zn in a mode suggesting complex pharmacological synergy where the molecular mechanism still is not understood.

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Disclosure

The authors declare no conflict of interests for this paper.

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