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RESEARCH ARTICLE

Lateralized spontaneous exploratory behavior in maturing rats induced by new geometrically differentiated environments after administration with trace elements

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ABSTRACT

Functional laterality is known as an intrinsic property of the brain. Since several studies have shown the presence of laterality in many species other than humans, it has been suggested that this is an adaptive mechanism to aid survival. Previous studies have shown that lateralized behavior observed during exposure to different environmental stimuli is not constant in normal animals, depending on the geometrical form of the exploratory field. In these exploratory fields, animals showed right- or left-biased exploratory behavior, according to the nature of the geometrical properties of the environment. Previously, it was found that tellurium (Te) was able to block spontaneous left-biased exploration in one defined geometrical environment. In the present work, the influence of Te and selenium (Se) in animals exposed to novel geometrically different environments were studied. Three geometrically different testing fields (square, rectangle, and T-shaped) were presented to Se- and Te-treated groups of rats. The results show that in the square field, only the Se treatment was able to block spontaneous right-biased exploratory responses; in the rectangular field, both Se and Te treatments blocked right-biased exploratory responses, and in the T-shaped field, only Te was able to block spontaneous left-biased exploratory responses. Data suggest that trace elements modify lateralized behavioral responses independently of the form of the novel exploratory field, suggesting the presence of a specific action in the brain.

1 Introduction

Following the discovery of the lateralization of language functions in the brain by the French neurologist Marc Dax in the nineteenth century [1], many researchers have investigated the specialization of neural circuits in the hemispheres of the brain for modulating and controlling

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physiological processes [2]. The differential control of behavioral functions by left and right brain structures is a neural property present in many animal species apart from human beings [3–9], suggesting that this is a functional mechanism that has evolved to enable animals to cope efficiently with environmental changes [3, 10, 11]. Some researchers have postulated that in addition to local adaptations in the neuronal circuits of the left and right hemispheres, biochemical changes to increase the conduction speed through the transverse fibers connecting the hemispheres have also taken place, permitting the simultaneous delivery of input signals to both hemispheres [3, 11]. Regarding laterality, it is known that specific neural circuits in the brain are involved [4, 12, 13], and it has been assumed that lateralized behaviors in subjects should remain constant in different environmental conditions. This behavioral characteristic is known as the "consistency" of a lateralized response, and can be compared to the spontaneous reflex. However, when tests have been performed in laboratory conditions, some unexpected results have been obtained that apparently contradict this assumption, suggesting that neuronal circuits controlling the differential responses are more sophisticated than formerly thought [14–16].

Previous evidence from our laboratory, working with intact rats, showed that lateralized responses depended on the geometrical characteristics of a new environment, i.e., the behavioral response was "non-consistent" [17]. Cubic and cubic rectangular environments elicited the same lateralized response (right-biased exploration of walls), while T-shaped cubic rectangular environments elicited reverse-biased exploration (left-biased exploration) [4, 17, 18]. These results suggest that the rat brain is able to discriminate between environments with different shapes and geometrical layouts, and this ability relies on the differential activation of neuronal groups in the hemispheres of the brain.

Regarding the identification of the neuronal circuits involved, some evidence points to the involvement of the hippocampus and the basolateral amygdala [4, 18]. Both these structures of the limbic system are plastic neuronal regions, where the processing of external stimuli depends on environmental changes [4, 18]. It would not be surprising to find that these brain structures interact dynamically with changes in the environment, triggering appropriate responses.

The meaning of "the environment" is broad in biology. However, if an individual animal is the point of reference, then everything that surrounds it can be identified as "the environment". Until recently, little attention was paid by the scientific community to the most conspicuous and omnipresent environmental factors affecting living organisms: the inorganic chemical elements present in the soil, water, and plants. Interest was only shown when these chemicals reached very high, and potentially toxic, concentrations in soil. However, the idea has slowly gained purchase that these simple inorganic elements are not necessarily inert, but on the contrary, they are able to produce biological effects in organisms [19].

Our laboratory has studied the possible role of selected inorganic elements, especially trace elements, as natural environmental factors that can influence biological functions in animals [20]. Previous evidence has shown that tellurium (Te), administered chronically to maturing rats in very low and nontoxic concentrations, appears to act as an epigenetic modulator, changing the methylation of cytosine in the DNA of the rat hippocampus, and altering the normal left-biased exploratory behavior in a T-maze [20]. On the other hand, selenium (Se), another trace element chronically administered in the same equivalent concentration as Te, did not affect lateralized

exploratory behavior in the T-maze but blocked the inhibitory effect of Te when both trace elements were administered together [21]. Contrary to what is known about Te, Se is an essential inorganic element for living organisms, and the interaction with Te found in the experiments described above introduced new thinking about the interaction between Te and Se and their biological effect on living organisms [21].

Given that lateralized exploratory responses in rats depend on the geometrical aspects of the environment [17], and Te affects this response in cubic T-shaped mazes [4, 17, 21], the question was raised whether this element could also modify lateralized responses in other differently shaped geometrical environments. If this were the case, the trace element could have a common neural mechanism. Despite the primordial nature of thisquestion, ithas not been studied yet. In addition, the biological actions of trace elements are associated with some other complications. There is evidence that Se can interact with Te, modifying the final behavioral response when animals explore a cubic T-shaped maze [21]. The possibility that Te can modify lateralized responses in different geometrical environments and that these effects be altered at the same time by Se has also not been analyzed. Thus, the objective of the present work, continuing our previous research, was to examine if Te can affect lateralized responses in different types of environments and if Se interacts with Te in these experimental conditions.

2 Materials and methods

2.1 Animals

Rats of a Holzman-derived colony, 30 days old with no distinction of sex, maintained in thermoregulated (22–24°C) and controlled light conditions (06:00–20:00) were used. Standard rat chow and water were available ad libitum for the control group. In the experimental groups, the rats had access to solutions containing the trace elements with no restrictions.

2.2 Experimental design

Three different geometrical environments were used in order to measure the "consistency" of biased behavioral responses, as described elsewhere [17]. As shown previously, rats were able to differentiate between the different geometrical forms of the testing environments [17]. A total of 47 rats were used for the tests. Animals in each experimental groupwere passed individually and in sequence through the three different environments on different testing days. The duration of the tests was 3 min. For the purpose of description, each type of environment wasidentified by its two-dimensional form (square, rectangle, and T-rectangle) instead of the actualthree-dimensional volume.

Experimental groups were:

1) Control rats (no treatment, tap water, $n = 14$)

2) Se group ($n = 10$, animals treated with Na_2SeO_3, 1.55 nM)

3) Te group ($n = 10$, animals treated with K_2TeO_3, 1.55 nM)

4) Se + Te group ($n = 13$, animals treated with the combination of Na_2SeO_3 + K_2TeO_3, 1.55 nM, respectively)

Treatments were applied during all pregnancy, delivery, lactation, weaning and prepuberal periods of maturing rats. At birth, the number of pups was set up to 12 (both sexes) per each experimental group. Whenever possible, a 1:1 relationship between male and female rats was maintained. When maturing rats were 21 days old, young rats were weaned and separated from their mothers. Mothers were discarded and only their pups were used in the experiment. At 30 days old, all rats were subjected to the behavioral tests individually, as described previously [17].

2.3 Chemicals

The following chemicals were used:

1) K_2TeO_3 (Tetrahedron, Laboratorio Andes, Industria Argentina)

2) Na_2SeO_3 (Biopack, Industria Argentina)

2.4 Testing fields

2.4.1 Geometrical form 1: square

This environment was an open field cubic box with acrylic walls and a black plastic floor, measuring 43 cm × 43 cm and 24 cm in height. This environment was designated as a "square". At the beginning of the test, the animals were placed singly in one corner of the square.

2.4.2 Geometrical form 2: rectangle

This environment was a solid rectangular box made of steel, measuring 40 cm long, 26.5 cm wide, and 30 cm high. The floor was covered with wood shavings. This environment was designated as a "rectangle". At the beginning of the test, animals were put singly in one corner of the rectangle.

2.4.3 Geometrical form 3: T-shaped solid rectangle form

The double hole-board labyrinth (DHBL) was made of wood and was composed of a rectangular cage 39 cm wide, 70 cm long, and 15 cm high. Inside, there were two compartments at a 90° angle to each other. The first compartment (initial) was 39 cm long and 15 cm wide with a central entrance to the second compartment (corridor). The corridor was 55 cm long, 17 cm wide, and on its side walls, there were four lateral holes, each 3 cm in diameter.This environment was designated as a "T-rectangle". At the beginning of the test, the animals were put singly in the initial compartment (the rectangular box at 90° to the corridor). A detailed description of the testing environment was given previously [17].

2.5 Measures of lateralized behavior

The following behaviors were considered to represent motivated exploratory behavior in each of the environments:

1) Walking along the walls at a distance not farther away than 0.5 cm, sniffing and with whiskers touching the walls.

2) Not walking on one side of the walls, but actively sniffing at one point, at the base or the body of the wall.

3) Not walking but rearing up on the walls.

4) Not walking but performing head-dipping on the lateral walls of the T-maze.

Other behaviors, such as walking to the center of the environment, rearing far away from the walls, or grooming were not considered to be exploratory behaviors and were not measured.

Since lateralized behavior implies an axis of symmetry for distinguishing between right- or left-hemisphere controlledactivity, the rostral-caudal axis of the animal in the direction of advance was taken as the reference line. Thus, it was possible to unequivocally define right- and left-based behavioral activity. In rectangular environments, the biased exploratory activity of rats starts in a clockwise direction (left exploration) or a counterclockwise direction (right exploration).

All behavioral tests were filmed with a digital video camera and recorded using a DVD player/recorder (Phillips, model DVDR3455H), at an artificial illumination of about 180–206 lux.

In the case of the T-rectangle environment (DHBL), rats could explore the right side of the wall (right exploration) or the left side of the wall (left exploration) from the entrance to the end of the corridor. When the animals returned to the entrance, the reverse was true for the left and right exploration. The behavioral activity was measured with a digital electronic counter at a rate of two counts per sec, and the recordings were monitored by an observer unaware of the

treatments. When exploratory activity on one side was significantly greater than on the other side, an instance of exploratory biaswas recorded.

2.6 Statistical analysis

Multiple comparisons of behaviors between experimental situations were made using Dunn's non-parametric test [22]. 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 statistically significant. Results are presented as the median ± standard error, with the exception of the percentage of animals shown in Figs. 1–3B.

2.7 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 [23], and the guidelines of C. J. Foltz [24].

Whenever possible, the number of animals used was reduced to the minimum acceptable. Statistical discrimination was employed to reduce the number of rats used in the experiments.

3 Results

The lateralized exploratory activity (A) and the population exploratory preference distribution (B) in control and trace element-treated rats exposed to the square environment are shown in Fig. 1.

In this environment, control animals displayed significantly higher exploratory activity in a counterclockwise direction ($p < 0.001$, right versus left exploration, Fig. 1A). In those animals treated with Te (Te group), the same pattern of right-biased exploratory behavior also was observed (Fig. 1A). Meanwhile, for those animals treated with Se or a combination of Se + Te, the biased pattern of exploratory behavior was lost (Fig. 1A). When the population distribution of the left-biased exploratory behavior of the control- and trace element-treated animals was analyzed, significant right-biased exploratory behavior was found in the control and Te-treated animals

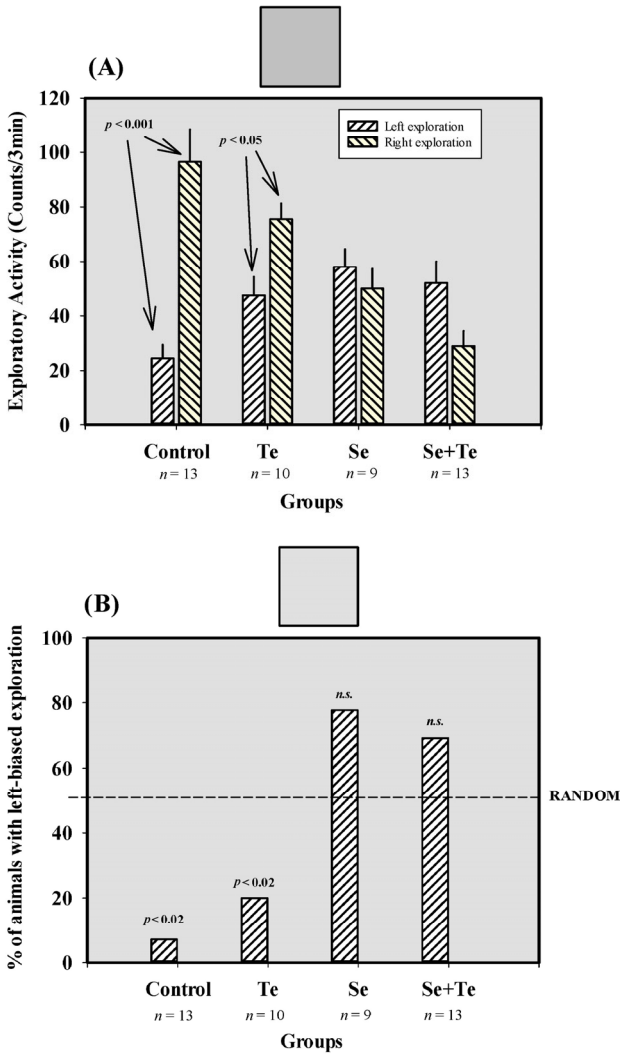

Fig. 1 Lateralized exploratory behavior of maturing rats exposed to Te or Se in the square (cubic) environment. (A) Lateralized exploratory activity. Te group: animals treated with K_2TeO_3 (1.55 nM); Se group: animals treated with Na_2SeO_3 (1.55 nM); Se + Te group: animals treated with K_2TeO_3 (1.55 nM) and Na_2SeO_3 (1.55 nM). Data are shown as the median ± standard error. (B) Estimated population distribution of left-biased exploratory behavior of maturing rats exposed to Te or Se. All statistical comparisons were made to random exploratory behavior, considered as exploratory activity without any side preference ($p = 0.5$).

(Fig. 1B). Those groups treated with Se or a combination of Se + Te showed random exploratory behavior with no left or right preferences (Fig. 1B).

The lateralized exploratory activity and the population exploratory preference distribution of control and trace element-treated rats exposed to the rectangular environment are shown in Fig. 2.

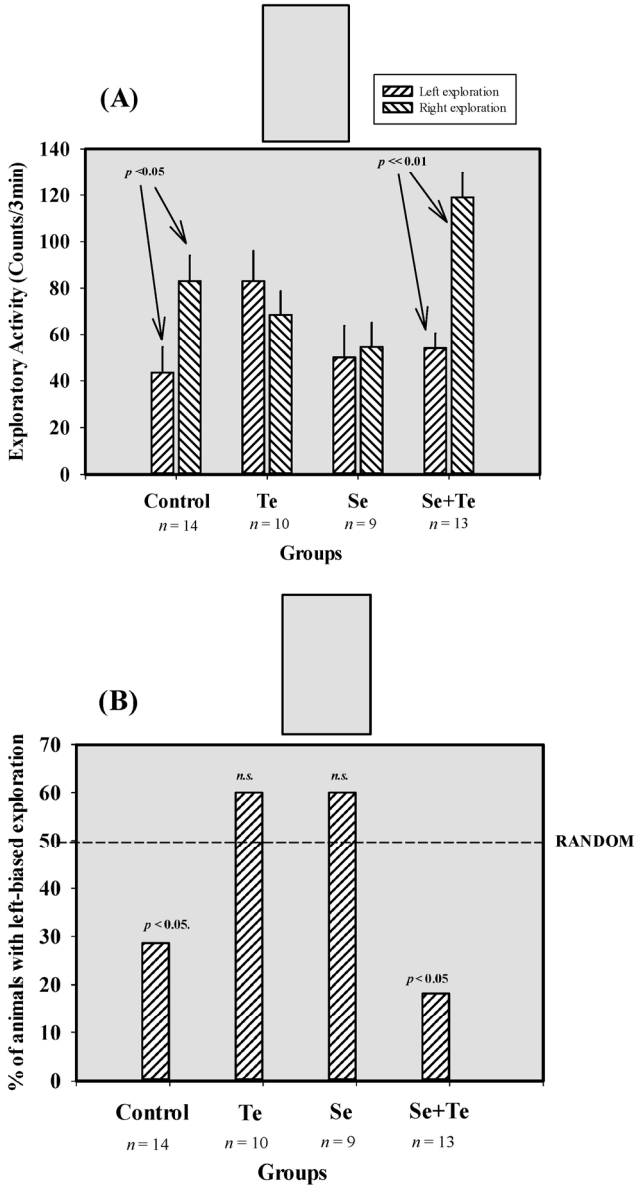

Fig. 2 Lateralized exploratory behavior of maturing rats exposed to Te or Se in the rectangular environment. (A) Lateralized exploratory activity. (B) Estimated population distribution of left-biased exploratory behavior. For further details, see Fig. 1.

Control rats showed a significantly higher score for right-biased exploration in this environment, quite similar to that observed in the square environment (Fig. 2A). Animals receiving the Te or Se treatment showed no lateralized exploratory behavior, and right and left exploratory activity appeared to be random (Fig. 2A). However, those animals receiving the combination treatment displayed significantly right-biased exploratory behavior, similar to that observed in the control group (Fig. 2A).

When the population distribution of the left-biased exploratory behavior of the control and trace element-treated animals was analyzed in this rectangular environment, significantly right-biased exploratory behavior was found in the control group and animals treated with the combination (Fig. 1B). Animals receiving Te or Se, however, displayed a random exploratory preference (Fig. 2B).

The lateralized exploratory activity and the population exploratory preference distribution of the control and trace element-treated rats exposed to the T-rectangle environment are shown in Fig. 3.

In this environment, control rats showed significantly left-biased exploratory behavior (Fig. 3A), while rats receiving Te showed random exploratory behavior. Animals receiving Se or the combination (Se + Te) showed significantly left-biased exploratory behavior, similar to that found in control rats (Fig. 3A).

When the population distribution of left-biased exploratory behavior of control and trace element-treated animals was analyzed in this rectangular T environment, only Te-treated animals showed a random exploratory preference, meanwhile the control, Se and Te combination treatment groups showed a significantly left-biased exploratory preference (Fig. 3B).

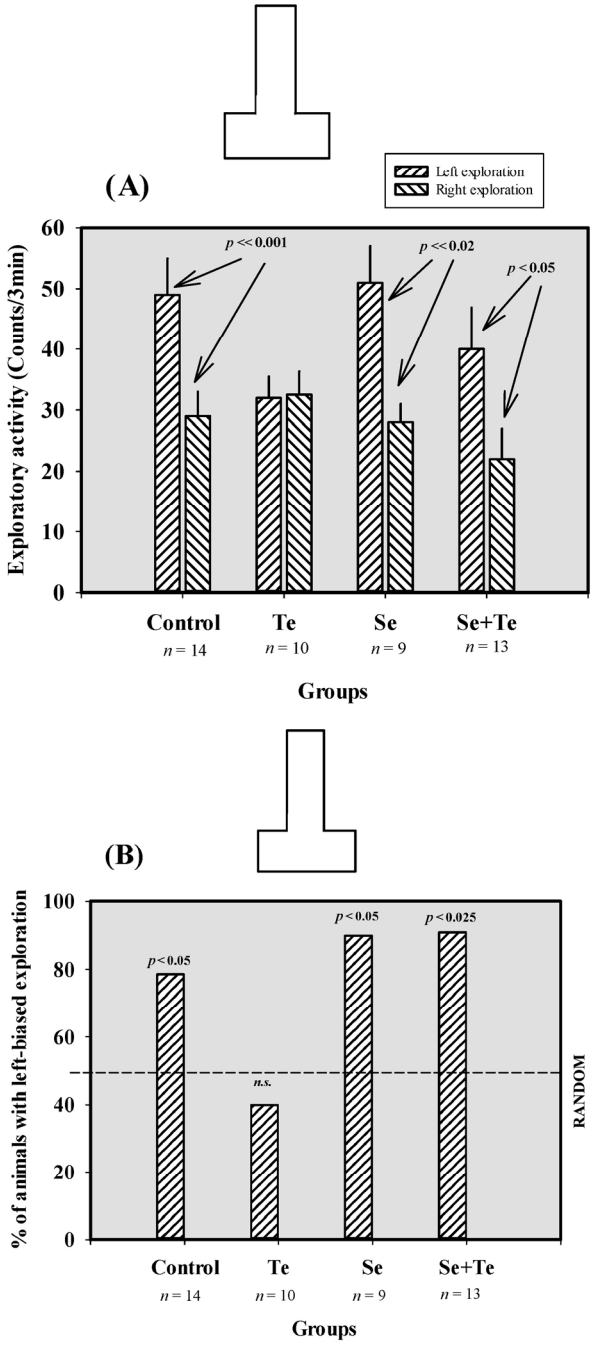

Fig. 3 Lateralized exploratory behavior of maturing rats exposed to Te or Se in the T-shaped environment. (A) Lateralized exploratory activity. (B) Estimated population distribution of left-biased exploratory behavior of maturing rats. For further details, see Figure 1.

4 Discussion

As previously described, intact normal animals showed clearly biased exploratory behavior in the different geometrical environments [17], and the results confirm the natural tendency to explore the right side of walls in a square (counterclockwise direction), and left side of walls in a T-maze, as already described previously elsewhere [17]. The non-consistent lateralized exploratory decision-making behavior that rats display in response to environmental modifications appears to be an evolutionary behavioral adaptation allowing animals to face environmental challenges. It is reasonable to assume that the neural structures of the brain involved in the generation of this behavior are established and relatively constant. Regarding the effect of Te in the T-shaped environment [20, 25], it is not surprising to find that this metalloid substance also can selectively affect behavior in other geometrically different environments, such as the rectangular field (Figs. 2A and 2B). This influence is independent of the direction taken (right side exploration in the rectangular field and left side exploratory behavior in the T-shaped environment, Figs. 2 and 3), suggesting a very specific and sophisticated inhibitory action on the neural pathways serving this behavioral expression. At the same time, it is worth noting that Te did not modify the spontaneous right-biased exploratory behavior of animals in the square field (Fig. 1), suggesting that this behavior appears to be insensitive to the metalloid or that Te is modifying some other brain response not measured. On the other hand, Se alone affected differentially the lateralized responses of animals, sometimes counteracting the Te effect (Fig. 2A, group Se versus group Se+Te) and in other occasions exerting the same inhibitory effect than Te (Fig. 3A, group Se versus group Se+Te). In the square and rectangular environments, Se had an inhibitory effect on the lateralized response, while it did not modify behavior in the T-shaped field. These results suggest that Se also has selective and differential actions on neuronal groups in the brain.

As previously found [21], the chemical interaction of Se and Te was evident in those animals receiving both trace elements since in the present work antagonistic behavioral effects were detected in the exploratory behavior induced by the rectangular environment (Fig. 2). In the T-shaped field, however, Se blocked the inhibitory effect of Te on the left-biased exploratory behavior displayed by animals in this environment (Fig. 3). This chemical interaction of Se and Te is not surprising in rats since it has been shown that Se also interacts with mercury and chromium in chickens in other experimental setups [26, 27]. Thus, the biology of Se and Te must be understood not only in terms of individual actions of the trace elements in the brain but also in terms of the interactional nature of metalloids in the physiological mechanisms of the brain.

At present, it is difficult to assign a particular intrinsic molecular and cellular mechanism by which Te or Se is influencing lateralized behavioral responses. On one hand, Te appears to modify the methylation pattern of cytosine bases in the DNA of hippocampal neurons [20], and this mechanism is characteristic of the epigenetic regulation of biological responses in living systems. This evidence suggests that the metalloid follows a biochemical path perhaps bound to the regulation of DNA methylating enzymes, or DNA itself. It is not surprising that Te might participate at this molecular level since it was found *in vitro* that other trace elements reacted with the N_7 atom of purine and the N_3 atom of pyrimidine in the DNA helix, molecular regions important for producing conformation changes in the DNA helix [28]. In addition, nickel and copper were able to interact with a metal-binding sequence of histone H_4 (AKRHRK) used as a model for the natural H_4-histone tail, suggesting that trace elements have the potential to chemically interact with DNA complex molecules [29].The biological effects of Te in living organisms can also be the result of some other interacting mechanism in the cell that does not necessarily fall within the spectrum of DNA interactions. The trace element specifically affects squalene epoxidase, a metabolic enzyme important in cholesterol synthesis [30, 31]. In addition, other behavioral functions apparently not related to lateralized exploratory behavior in rats can also be affected by Te treatment. Changes in behavior in offspring after exposure of mothers to Te derivate compounds [32], and significant improvements in the motor function of rats treated with 6-OH-dopamine in the substantia nigra by ammonium trichloro (dioxoethylene-O, O'-) tellurate have been described previously [33]. This evidence suggests that Te is a very biologically reactive element, which can potentially interact at many levels of the homeostatic regulationof the organism.

On the other hand, contrary to what is known about Te, Se has been recognized for many years as an essential element in living systems [34, 35]. The essential nature of this trace element for biochemical reactions in living cells can be easily understood when considering that Se constitutes part of the amino acids selenocysteine (Sec) and selenomethionine (SeMet) [35–37]. Sec is present in three major enzyme families (glutathione peroxidases, thioredoxine reductases, and iodothyronine deiodinases) and also in several selenoproteins [38]. Most of these enzyme sec-proteins are involved in cell oxide-reduction reactions, organism reproduction, thyroid gland/hormone metabolism, and immune reaction responses [35]. Such a wide spectrum of actions suggests that selenoproteins have an important role in the peripheral systems of organisms. Indeed, it has been found that the eight types of glutathione peroxidases identified so far are enzymes that have an intracellular localization

[39]. It could be inferred that those tissues where selenoproteins have a key function should present with a greater uptake and concentration of Se. However, the brain compartment, where Se has an important role in the maintenance of brain function, is not a site in the organism that accumulates higher amounts of Se [40]. A selective mechanism appears to operate in the rat brain since in conditions of low availability for Se, the trace levels in this compartment are conserved; even plasma Se concentrations are very low [41, 42]. Of the many neural regionsin the brain, the cortex and hippocampus are the sites where expression is significant [43], suggesting that these neural structures are the main targets for the biological effects of Se. Another point to be considered is the report that in chickens fed with a low diet of Se, a decrease in the global DNA methylation in several tissues, including the brain, was observed [44].

Considering all this evidence, some convergent effects of Te and Se appear to be evident. Both metalloids are able to interact at the brain level; both trace elements can interact with each other, and both trace elements appear to affect the methylation status of DNA. Although the results in this work do not clearly identify which of the many possible molecular pathways is operating to control the lateralized exploratory behavior observed, future research will uncover and determine which mechanism of the trace elements is participatinginthe complex brain laterality processes by which Te and Se, as environmental determinants of adaptation, intercede in living systems.

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Conflict of interests

The authors declare no conflict of interests for this paper.

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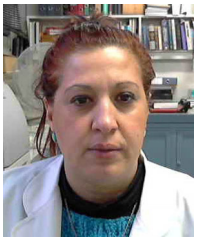

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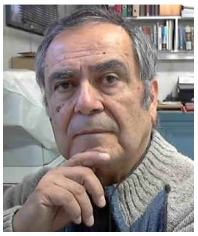

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