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The Influence of Tellurium and Folic Acid Administration on Coping Behavioural Parameters in Maturing Rats: Transgenerational Effects

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Abstract

A previous study of our laboratory have shown that Tellurium (Te), a metalloid with low concentrations in soil and water in the earth, is able to modify important behavioural parameters related to cognitive functions when administered orally in maturing rats. Exposition of chronic non-toxic doses of Te affected spontaneous lateralized exploration, social interaction behaviour, and survival responses in the treated rats. Te effects were blocked by the simultaneous administration of folic acid, a well-known methyl group donor in the cell, suggesting an epigenetic mode of action of Te. Te behavioural effects on the second generation (F_1) still were found in the next third generation (F_2). In order to evaluate if these transgenerational behavioural alterations in F_2 were depending on DNA methylating mechanisms, as observed in the F_1 generation, F_1 rats were mated at 90 days of age. Two groups of animals in the F_2 offspring were formed; one treated with and the other not treated with folic acid. Results showed that the untreated folic acid F_2 maturing rats, conserved the same pattern of behavioural alterations than its parents (F_1), in spite that they were not exposed to Te. Those F_2 animals treated with folic acid, instead recovered the normal behavioural responses in the three tests performed to evaluate coping behaviour. Results suggest that the molecular mechanism of Te is dependent on DNA methylating reactions, which is one of the molecular processes of epigenetic modulation in mammals.

Keywords: Tellurium; Lateralized behaviours; Epigenetic changes; Folic acid; Transgenerational effects

Introduction

Tellurium (Te) is an inorganic trace element occupying position 16 in the periodic table of elements and is one representative of a group of inorganic chemicals classified as metalloid [1]. The most abundant chemical form in nature is the oxyanion $(TeO_3)^{2-}$, which reacts with many other elements, being relatively stable. Perhaps the most notorious application of Te in the early medicine of 1900 was its recognized toxicity to microbial and other microorganism agents leading to its applications in human beings for treating bacterial infections before antibiotics appeared in the health history of microbial control [2,3]. Unfortunately, the common side effect of an intense garlic odor in breath and urine of patients was an important handicap in those early medicinal treatments [4]. Although the first impression about Te in the scientific community was centered on its toxic effects, some isolated descriptions after exposition to compounds containing the metalloid put the first notion that Te in biological systems could have additional biological actions other than the obvious antiseptic properties. The most early notorious description about additional biologic effects of Te was a report about a chemist synthesizing batches of TeO_2, who by unadvertised inhalation of dust in the preparation, suffered later of depression with sustained periods of sleeping in addition to garlic breath odor [5], suggesting that the nervous system showed some selective sensitivity to the metalloid in the body. Several decades later, it was found that Te inhibits the enzyme squalene epoxidase resulting in blockade of cholesterol synthesis in peripheral nerves [6,7]. Demyelination, as the Te consequent effect of cholesterol decrease, leaded to repression of the expression of mRNA for myelin specific proteins [8,9].

Biological effects of Te are not selectively restricted to peripheral nerves in the nervous system. *In vitro* cultures of astrocytes isolated from rat hippocampal structure, the incubation with tellurium tetrachloride and diphenyl ditelluride caused marked cytotoxicity [10]. It is reasonable to think that the adverse effect of Te in animals was related to the exposition dose. At lower doses, other biologic effects were apparent connected to brain functions. Thus, contrary to what it was expected in rats exposed to Te several behavioural parameters related to exploration and motivation, important responses for proper adaptation of animals to environmental changes (coping behaviour), were not affected in treated rats. Even in some tests, behavioural responses were positively increased, such as the number of entries and permanency in the fear-inducing arm of the elevated plus-maze, suggesting a decrease in emotionality and an increase in motivation [11]. In some other studies, beneficial non-toxic actions of Te in animals have been reported using ammonium trichloro(dioxoethylene-O,O') tellurate (AS101) which was able to induce hair growth in nude mice and also in teenagers with alopecia [12]. In addition, this same molecular complex gives protection and restoration of dopaminergic neurotransmission of neurons in a model

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of Parkinson's disease [13], suggesting that the metalloid is acting on important biochemical pathways regulating cell natural homeostasis.

At even lower doses of Te exposition (less than 0.5μg/L) surprising well defined behavioural effects related to cognition have been found in maturing rats [14-17] putting in perspective that the biological effects of the trace element strongly depend on the amount of exposition to animals.

Contrary to the idea that Te is a foreign external inorganic element and as such it should not normally be present in living beings, there is evidence supporting the opposing concept. Te has been found in appreciable amounts in bone tissue in humans [18]. Its presence also has been detected in blood and urine [19,20]. In addition, Te was found to form structural part of some amino-acids, such as tellurocysteine and telluromethionine in some bacterial proteins [21,22], yeast and fungi [23,24], suggesting some possible biological role for the metalloid.

Previous work in our laboratory have shown that Te administered in a chronic regimen at the non-toxic dose of 0.3μg/L in drinking water to maturing rats, inhibited the natural lateralized exploration in a novel environment; the social interaction response in an intruder/resident conflict, and the survival response in a forced swimming test [14,15,25]. Although it is not completely clear the intrinsic molecular mechanism by which Te is affecting these behavioural responses, considering that Te is transported in the red blood cells [26], it can cross the brain barrier easily and it can reach in theory many neuronal regions. It was not surprising to find in the hippocampal structure of rats treated with this trace element, a decrease of the cytosine methylation pattern of DNA, clearly suggesting an epigenetic modulation of behavioural responses of animals [15]. Epigenetic processes have been recognized to participate in several biologic functions of organisms, but particularly remarking is that they preferentially affect brain processes in mammals [27-29]. Additional support to the participation of Te in the transgenerational decrease of methylated cytosine of hippocampal DNA was the observation that a complete blocking of the trace element inhibitory effects on behaviours was found in Te treated animals with folic acid, a well-known methylating agent [30].

Epigenetic mechanisms have the property that after the primary inducing environmental stimulus, changes are inheritable persisting to the next generations [31,32]. Female rats treated with Te in the F_1 generation, allowed to mature without any treatment until they reach 90 days old, and mated with normal males, the next generation (F_2) still presented the modified behaviours previously observed in their parents, e.g. the Te biological changes persisted across generations, just as it would be expected to an epigenetic effect for this trace element [25]. This evidence suggests that permanency of the blocked behavioural responses in the F_2 offspring might be due to hypomethylation state of hippocampal DNA. However, the possibility that folic acid administered in the F_2 rat generation might provoke reversion of the Te biological effects is an aspect not been investigated so far. Thus, the objective of this work was to evaluate if treatment with folic acid in the third generation of animals, whose parents have been exposed to Te, the modified behavioural responses can return to normality.

Materials and Methods

Animals

Rats of a Holzman-derived colony, weighing 250-300 g, 90 days old and maintained in thermoregulated (22-24ºC) 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. For experimental rats, K_2TeO_3 (0.39μg/L), or folic acid (0.16gr/L), were given in the drinking water.

Drugs

Potassium Tellurite (K_2TeO_3, Tetrahedron Reactivos Analíticos, Argentina) and folic acid (Parafarm, Droguería Saporiti S.A.C.I.F.I.A., Argentina) were used.

Experimental design

The general experimental protocol used in the present work was described previously [25]. Briefly, chronic exposition to Te, beginning from fertilization of the mother rat up to prepuberal maturation stages of litter rats was applied. From 35 day-old up to 90 day-old, the trace element treated animals (F_1) remained at rest without any further treatment (Figure 1). At 90 days of age, female F_1 generation rats were mated with normal male animals giving the next F_2 generation.

There were 4 experimental groups:

(1) Control animals (no trace element treatment, water only, n=9)

(2) F_1 animals (with Te treatment, n=10)

(3) F_2 animals (no folic acid treatment in the second generation, n=19)

(4) F_2 + folic acid animals (with folic acid treatment in the second generation, n=12).

As formerly specified, at birth for all groups, pups were standardized to 10-12 animals per litter trying to maintain whenever possible the relationship of 1:1 of male to female rats. Thus, there were initially about 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 motivated lateralized exploration; social, and defensive behaviour in the same way as previously described [15]. After ending the behavioural tests, all animals were sacrificed by lethal i.p. injections of Sodium Pentobarbital (40g/100), and Sodium Diphenylhydantoin (5g/100, Euthanyle, BrouwerInc, Argentina).

Behavioural tests

The following behavioural tests were used to evaluate lateralized exploration of novel environments, social interaction, and defensive behaviour:

The Double Lateral Hole-board Labyrinth (DHBL): This labyrinth evaluates motivated exploration that can be expressed in lateralized form, as described previously [33,15].

DHBL is made of wood and is composed by a rectangular cage 39cm wide, 70cm length and 15cm height. Inside there are

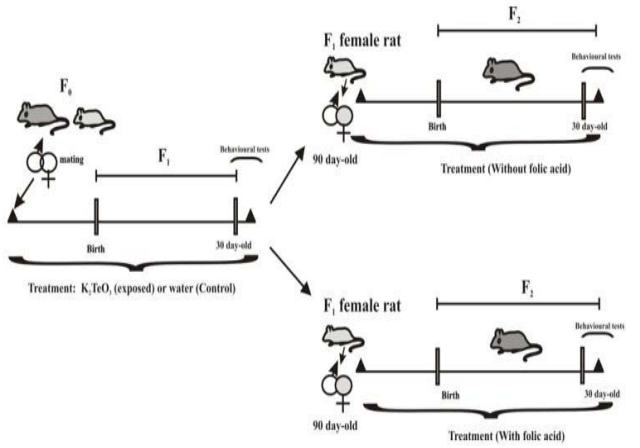

Figure 1: Experimental design used to evaluate the transgenerational effect of Te and folic acid in maturating rats.
F_0 = First generation (parent rats); F_1 = second generation (offspring); F_2 = third generation.

two compartments disposed in 90º each. The first compartment (Initial) has 39cm length and 15cm wide with a central entrance to the second compartment (Corridor). Corridor has 55cm of length, 17cm wide, and on its side walls there are 4 lateral holes, each 3cm 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 are 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/sec) 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 nearby 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 than 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 animals and had a total duration of 3 min.

The 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. Test was performed in a rectangular steel cage (26cm width, 42cm long and 20cm height) with wood shavings in the floor. Total duration of testing was 5 min. In the two initial min the testing animal (host rat) was put alone in the arena in order to familiarize with the cage. At the beginning of min 3, a different and new rat 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 of the duration of α social interaction displayed by the host animal in the test.

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 [15]. Device consists of a transparent acrylic tube measuring 50cm height by 12cm 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/sec 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.

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

Results of the behavioural measures are expressed as Counts/3 min (C/3 min).

Experiments

The following experiments were performed:

Effects of Te administration in F_1 generation, with or without folic acid treatment to F_2 generation on lateralized exploratory behaviour.

Behavioural parameters related to lateralized exploratory activity were measured in F_1 and F_2 generation animals, after exposition to Te in F_1, and no other treatment in F_2.

Effects of Te administration in F_1 generation, with or without folic acid treatment to F_2 generation on social interaction behaviour.

Behavioural parameters related to social interaction activity in an intruder/resident test were measured in F_1 and F_2 generation animals, after exposition to Te in F_1, and no other treatment in F_2.

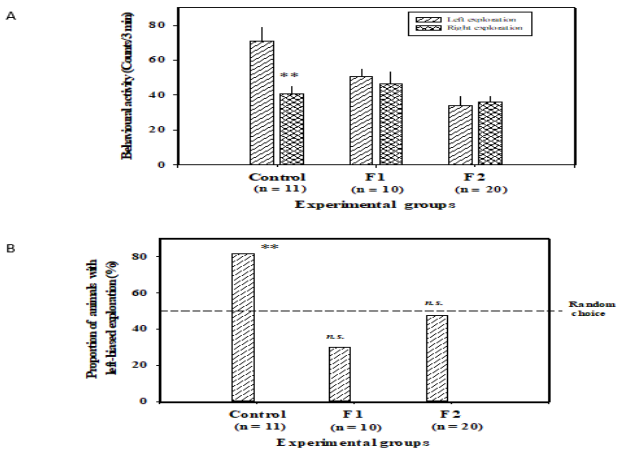

Figure 2: A) Behavioural scores as measured in the DHBL of lateralized exploration induced by novelty in several generations of rats.
Control animals received water as unique treatment. F_1 animals were exposed to K_2TeO_3 (1.55nM) in the drinking water up to 30 days of age. From there on, no further chemical treatment was applied. F_2 was the third generation without any treatment. (F_2+Fol Ac) was the third generation treated with folic acid.
***p*<0.01 *Vs*. left exploration.
B) Population estimates of the proportion of left-biased exploration animals in the different groups of rats.
***p*<0.01 *Vs*. 50% which indicates random choices between left and right exploration of the corridor in the DHBL.

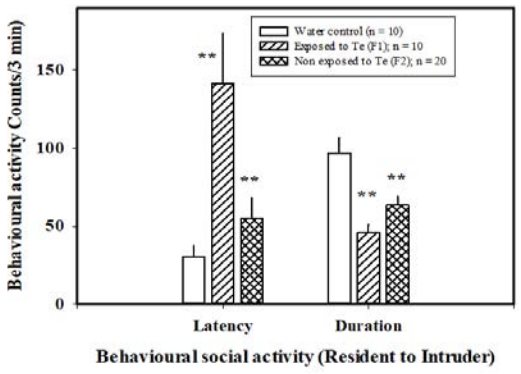

Figure 3: Behavioural scores of social activity displayed by several generations of rats.
***p*<0.01 *Vs*. Control rats.

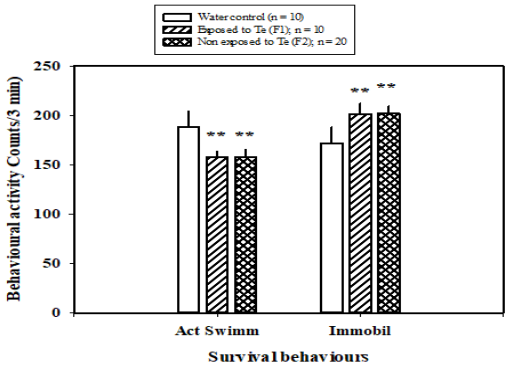

Figure 4: Behavioural scores of defensive behaviour in several generations of rats.
Act Swimm = active swimming activity displayed by rats during the 3 min duration of the test; Immob = period where animals showed no activity or the minimum to stay floating in the water.
***p*<0.01 *Vs*. Control.

Effects of Te administration in F_1 generation, with or without folic acid treatment to F_2 generation on survival behaviour.

Behavioural parameters related defensive behaviour in a forced swimming test were measured in F_1 and F_2 generation animals, after exposition to Te in F_1, and no other treatment in F_2.

Statistical analysis

Multiple comparisons for behaviours between experimental groups, was made by the Non-Parametric Test of Dunn [34,35]. 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 the median.

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 [36], and guidelines of animals care of CJ Foltz [37]. Whenever it was possible, number of animals was reduced to the minimum acceptable allowing statistical discrimination.

Results

Experiment 1

Lateralized exploration parameters in the LDHB of maturing rats treated with K_2TeO_3 or water in F_1; and with or without folic acid in F_2 generation animals are shown in Figure 2.

Control animals showed a statistically higher left exploration of walls of the labyrinth, as is shown in (Figure 1.A). Exposition of rats to Te treatment (F_1) the left-biased response was not present. After F_1 female rats were mated with normal untreated rats, the next progeny (F_2) not treated with folic acid, still displayed the absence of the lateralized response (Figure 2.A). However, F_2 offspring receiving the folic acid treatment, the lateralized response was present again.

Estimation of the population proportion of left-biased exploration animals showed 77.8% in Control animals, 40% in F1 animals, 47.3% in F_2 folic acid non treated rats, and 83.3% in F_2 folic acid treated rats (Figure 2.B).

Experiment 2

Social interaction parameters in the Intruder/Resident test of maturing rats treated with K_2TeO_3 or water in F1; and with or without folic acid in F_2 generation animals are shown in Figure 3.

Control animals showed a latency score of about 30 C/3 min to confront the intruder rat and displayed duration of the social interaction activity of about 97 C/3 min. Animals treated with Te in F_1 showed a significant increase, and decrease in the behavioural score of latency and duration, respectively (Figure 3).

F_2 animals not treated with folic acid showed a behavioural pattern similar to its parents (F_1 generation) regarding latency and

duration of social activity, while F_2 animals treated with folic acid showed behavioural scores in latency and duration similar to control rats (Figure 3).

Experiment 3

Survival behaviour parameters in the Forced swimming test of maturing rats treated with K_2TeO_3 or water in F_1; and with or without folic acid in F_2 generation animals are shown in Figure 4.

As shown in the figure, Control animals displayed about the same behavioural activity score to active swimming and immobilization in the 3 min forced swimming test (188 ± 16 C/3min and 172 ± 16 C/3min, respectively). F1 animals treated with Te showed a significant decreased active swimming with an increased score of immobilization, compared to control rats (Figure 4). F_2 animals not treated with folic acid, showed similar behavioural parameters to that observed in its parent F_1 generation, meanwhile the F_2 rats treated with folic acid, active swimming and immobilization scores were similar to control rats (Figure 4). Particularly noticing was the observation that F_2 folic acid treated rats showed active swimming and immobilization scores statistically higher and lower respectively compared to control values (Figure 4).

Discussion

As shown in Figures 2-4, results show a clear transgenerational effect due to Te treatment in several behavioural responses in the maturing rat. Lateralized exploration induced by novelty (Figure 2), social interaction behaviour (Figure 3), and survival behaviour (Figure 4), three outstanding biologic adaptive responses of coping behaviour in the rat were clearly affected in F_2 generation. Previous studies have shown that the trace element administration following the same experimental schedule modified the hippocampal DNA methylated cytosine pattern in F_1 maturing rats [15], suggesting that Te might be acting through an epigenetic modulation of the behavioural responses. This hypothesis was supported by experiments where folic acid administration at the same time that Te to the F_1 prepuberal rats blocked the trace element biological effects previously observed [30].

Folic acid as folate is an important one carbon carrier in the cell and it has been recognized as a vital intermediate to epigenetic modulation by provision of the one carbon unit to S-adenosylmethionine formation [38,39]. As shown in Figures 2-4 in the present work, the administration of folic acid in F_2 generation blocked completely the transgenerational behavioural effect of Te, giving a further support to the idea that the trace element is acting through a methylation-dependent mechanism, and possibly by an epigenetic action.

The meaning of the present results is invariably linked to concepts of epigenesis. Epigenetic processes have attracted the attention of many workers in the past years, since they offer a more plausible mechanism to explain several cases in genetics that were not adequately justified by the traditional genetics [40-43,31]. Most researchers accept that a convenient definition of epigenesis is the appearance of a modified phenotypic expression that does not depend on alterations of the primary codons sequence in the DNA [41,44,45]. The principal mechanisms that have been found to be linked to this process are regulation of cytosine methylation of DNA, post-translation histone modification, participation of non-coding RNA, and chromatin structural remodeling [44]. All these molecular events lead to transmission of epigenetic coded information from one generation to the next one, e.g. molecular changes leading to a specific phenotype which are inheritable. Regarding to our own evidence, to assign a plausible explanation for Te effects through the mechanism of epigenesis has some problems. As shown in Figure 1, describing the experimental design used in this and previous work [30], the administration of Te can be viewed as an "environmental stimulus" affecting F_0 and F_1 at the same time. Thus, appearance of altered behavioural parameters in F_1 generation is not surprising, since prospective offspring in the mother rat uterus also were initially affected [41,44,40]. Under this point of view some authors see this situation as not properly "transgenerational" [44], and consequently an unexposed F_2 generation displaying the altered phenotype, such as it was observed in the present experimental design do not constitute a truly "epigenetic effect".

Regarding these last arguments, perhaps it is appropriate to discuss three considerations:

1) The experimental design described in the present work, and also in the previous ones [15,30], was not specifically addressed to study epigenetic phenomena. Rather was an experimental model in animals fulfilling some genetic evidence with an imprinted gene, previously found in primary school children exposed to trace elements in La Rioja province of Argentina [46,47]. Exposition to trace element (mainly Te) affects mothers and children along their entire lives. Thus, the most nearly experimental model in rats covering this real situation was using the protocol shown in Figure 1. Criterion of an appropriate modeling of this design in exposed subjects was supported by finding the same alterations in DNA methylation pattern both in humans and rats, suggesting the same molecular mechanism [46,47,15].

2) Argument that an interfering stimulus affecting the pregnant mother (F_0) and at the same time, F_1, which in term affect the germ line of the next generation (F_2), assume as established fact a complete, direct and equal interaction of the disturbing stimulus with offspring in utero and the germ line of the future generation. This might be a misleading assumption and it reminds the model of the Russian doll, which contains inside another smaller doll, which contains in turn another smaller doll. A scratch in the first one does not necessarily mean that a similar damage has been produced in the others contained inside. In the present experimental model the stimulus (Te) has its only way into the organism through blood circulation. It is well known that for a substance traveling in blood, the presence of multiple and different compartments affect the chemical kinetics and its transport through to the ultimate compartment. In the case of a pregnant mother, fetus and the subsequent germ line in the incipient fetal gonad, the whole system contains many physical barriers to assume a freely and easy transport through all these cellular compartments. Even in this context it is highly speculative to know what functional fraction of the original signal will have the power to disrupt the DNA equilibrium in the last compartment. Thus, theoretically it is prudent to consider with some caution the extreme high probability assigned by some workers to the complete simultaneous exposition of an interfering stimulus (Te, in this case) to the (F_0-F_1-F_2) multi-compartment complex; taking for granted that it is an argument to discard an epigenetic effect because it can be attributed to a direct simple exposition of the disturbing agent to all generations at the same time.

3) A third point of interest lies in the same definition of epigenesis as physiological process. An epigenetic event occurs in a living system when an alteration in the gene expression appears in the life cycle of the cell, without any changes in the DNA sequence [48]. Accepting that Te can act as an environmental stimulus modifying one of the established molecular processes attributed to epigenesis (DNA methylation pattern); once this molecular event has occurred, the information will be established, independently if is detected or not by outside observers in the next generations. In other words, that a phenotype change may be detected in F1 after exposition to some factor in F_0, and later in the unexposed F_2 does not exclude absolutely that an epigenetic change has occurred anyway. This instance is applicable to Te effects on behavioural responses of adaptative behaviour found in this study. Nevertheless, experiments in our laboratory are under way extending observations up to F_3 animals.

Undoubtedly, present results do not strictly fulfill all the accepted requirements to consider that the Te influence on behaviour might be a truly epigenetic effect. Nevertheless, it is completely reasonable to think that data encourage the idea of an epigenetic action of the trace element on coping behaviour in the rat.

Final Remarks

In line with our previous findings, present results support the idea that Te is modifying the neuronal mechanisms controlling lateralized exploration; social behaviour and survival responses in the rat. After the initial stimulus in F_0 and F_1 generations, the unexposed next F_2 generation retains the affected behavioural responses observed in the precedent generation. The administration of folic acid, a methyl supplying agent in the cell in F_2 offspring blocked completely the effects due to Te. Evidence suggests that the probable mechanism for Te modifying effects on behaviour might be epigenetically mediated.

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