

Diphenyl Ditelluride Induces Neurotoxicity and Impairment of Developmental Behavioral in Rat Pups

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O objetivo deste estudo foi investigar se a exposição aguda ao ditelureto de difenila [(PhTe)₂] causaria prejuízo no desenvolvimento comportamental de filhotes de ratos. Os filhotes receberam uma injeção subcutânea de (PhTe)₂ (0,1 mg kg⁻¹, 3 mL kg⁻¹) ou veículo (3 mL kg⁻¹) no 14º dia após o nascimento (DPN). Do 15º ao 21º DPN, foram realizados testes comportamentais nos filhotes e, imediatamente após estes testes, os filhotes foram submetidos à eutanásia. As análises histológicas, a determinação do conteúdo de mielina e a atividade da acetilcolinesterase (AChE) foram realizadas. O período crítico de intoxicação ocorreu no 4º e 5º dias após a injeção de (PhTe)₂, quando os sinais de toxicidade foram mais evidentes, caracterizados pelo aparecimento de sinais sistêmicos de toxicidade, disfunções comportamentais, neurotoxicidade e uma alteração no sistema colinérgico. Desta forma, conclui-se que o (PhTe)₂ induziu neurotoxicidade e prejuízos no desenvolvimento comportamental de filhotes de ratos.

The purpose of the present study was to investigate if acute exposure to diphenyl ditelluride (PhTe)₂ causes impairment of developmental behavioral performance in rat pups. Rat pups received a single subcutaneous injection of (PhTe)₂ (0.1 mg kg⁻¹, 3 mL kg⁻¹) or vehicle (3 mL kg⁻¹) at 14th postnatal day. After exposure to (PhTe)₂, the general parameters of neurotoxicity, behavioral tasks, cerebral myelin content, histological analysis and acetilcholinesterase (AChE) activity were performed during seven days. The appearance of classic signs of toxicity, behavioral alterations and the reduction in myelin content were dependent on the time after (PhTe)₂ exposure to pups. Neuronal damage, reduction of myelin content, and the increase in AChE activity occurred mainly at 4th and 5th day after (PhTe)₂ exposure, indicating that the critical period of neurotoxicity is coincident with the major behavioral alterations. In conclusion, exposure to (PhTe)₂ induced neurotoxicity and impairment of developmental behavioral in rat pups.

Keywords: tellurium, neurotoxicity, developmental behavioral, myelin, acetylcholinesterase

Introduction

Tellurium (Te) is a metalloid with increasing utilization in rubber, metallurgic and electronics industry because of its unique chemical and physical properties. Similarly, the use of organic Te compounds will increase due to its importance in organic synthesis.^{1,2} Thus, the incidence of occupational exposure to Te either in elemental, organic or inorganic form has growing rapidly, but the biochemistry and clinical significance of such exposure are poorly understood.

Diphenyl ditelluride (PhTe)₂ is an organotellurium compound widely used as intermediate in organic synthesis.² Besides its use as an organic reactant, (PhTe)₂ has been reported as a neurotoxic compound in adult rodents.³⁻⁵ (PhTe)₂, administered to dams, is teratogenic to rat fetuses, changes behavioral parameters related to neural function and causes oxidative stress in cerebral areas in young rats.⁶⁻⁸ Moretto and co-workers⁹ demonstrated that (PhTe)₂ impaired function of calcium channels in the brain, a fact that helps to explain its neurotoxic effects. Although the specific molecular targets that mediate organochalcogen toxicity are not known, these compounds

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can interact directly with low molecular thiols, oxidizing them to disulfides.¹⁰

Additionally, there has been reported that rats exposed to tellurium develop a demyelination process following a remyelination process.^{11,12} The effects of tellurium intoxication on the nervous system have been established as suggestive of peripheral neuropathy during a period of active myelinogenesis affecting transcription of the myelin proteins at the gene level and inhibiting the cholesterol synthesis.¹³⁻¹⁶

Acetylcholinesterase (AChE) is one of the most efficient biological catalysts known and plays a key role in cholinergic neurotransmission by hydrolyzing the transmitter acetylcholine (ACh), thus terminating its action.^{17,18} However, the biological role of AChE is not limited to cholinergic transmission. AChE has been implicated in several non-cholinergic actions including cell proliferation, neurite outgrowth and other responses to various insults including stress and amyloid formation.¹⁹⁻²¹ Although, the neurotoxic effect of (PhTe)₂ has been reported, the interaction of this organotellurium compound with cholinergic system has not been documented.

Based on these considerations, the purpose of the present study was to investigate if acute exposure to (PhTe)₂ causes impairment of developmental behavioral performance in rat pups. To better understand the effect of (PhTe)₂ in the developmental period of life (14 to 21 days), parameters of neurotoxicity, such as histology, myelin content and activity of AChE, were studied in brain of rat pups.

Experimental

(PhTe)₂ was synthesized in our laboratory according to the method described in the literature by Petragrani.²² Analysis of the ¹H NMR and ¹³C NMR spectrum showed that (PhTe)₂ obtained presented analytical and spectroscopic data in full agreement with its assigned structure. The chemical purity of compound (99.9%) was determined by GC or HPLC. This drug was dissolved in canola oil, which was obtained from a standard commercial supplier. All other chemicals were of analytical grade and obtained from standard commercial suppliers.

Animals

Virgin female Wistar rats (180-240 g) from our own breeding colony were used. The animals were kept on a 12 h light/dark cycle, at a room temperature of 22 ± 2 °C, with free access to food and water. The animals were used according to the guidelines of the Committee on Care and Use of Experimental Animal Resources, the Federal University of Santa Maria, Brazil. Sexually virgin female rats were mated

with male (three females and one male in each cage). The onset of pregnancy was confirmed by the presence of sperm in vaginal smears (day 0 of pregnancy) and pregnant dams were immediately housed in individual cages.

The day of delivery was counted as postnatal day (PND) 0. At birth, all litters were culled to eight pups (four males and four females if possible) to ensure good nutrition. The rat pups were kept with their mothers during the period of the experiment.

Procedure

Previously, a toxicological pilot study with (PhTe)₂ was performed in rat pups. In this pilot study, three different doses of compound were used to determine the dose that is not lethal but causes signs of toxicity in rat pups. Based on this pilot study, the dose of 0.1 mg kg⁻¹ of (PhTe)₂ was chosen.

Thirty-two litters were used in this study, as shown in Figure 1, each litter was divided into two groups: control (canola oil, 3 mL kg⁻¹) and tellurium groups (0.1 mg kg⁻¹ (PhTe)₂, 3 mL kg⁻¹). The rat pups received a single subcutaneous injection of (PhTe)₂ or vehicle (canola oil) at 14th PND. In the following days, from day 1 to 7 (Figure 1, PND 15 to 21) after exposure, behavioral tests were performed in rat pups. Rat pups were euthanized daily (from day 1 to 7) immediately after the behavioral tests. Brains were quickly removed for enzymatic assay and myelin isolation. The brain and cerebellum were used to histological analysis.

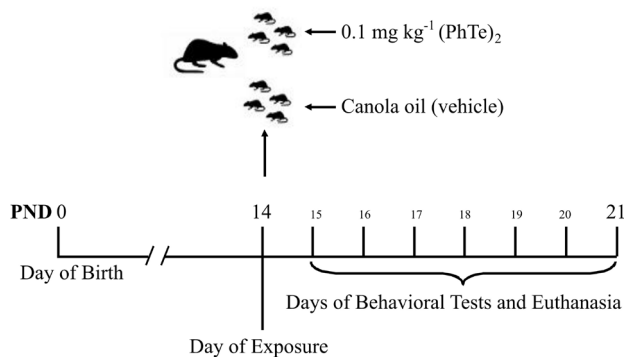


Figure 1. Experimental protocol.

Signs of tellurium toxicity

Signs of tellurium toxicity were observed in rat pups from the 1st day (PND 15) after exposure to 0.1 mg kg⁻¹ (PhTe)₂ to the end of the experimental period. The signs of toxicity, such as garlic-like odor, partial or complete paralysis of hind legs, diarrhea, tremors, body hair loss and reduction of the body weight were recorded.

Behavioral tests

Negative geotaxis

Rat pups were placed in the middle of sandpaper covered 30° inclined surface plane, in a head down position and the latency to turn 180° to a head-up position was recorded. Negative geotaxis reflects vestibular function, motor development and activity.²³

Forelimb support

Rat pup forepaws were placed on a horizontally suspended wire (1 mm in diameter), 47 cm above a soft foam rubber landing area. Each pup was timed from the moment it was placed on the wire until it was unable to remain on the wire.²⁴ This test reflects muscular strength in neonate rats.

Open field

Open-field was made of plywood and surrounded by walls 30 cm in height. The floor of the open-field, 45 cm in length and 45 cm in width, was divided by masking tape markers into 9 squares (3 rows of 3). Each animal was placed individually at the centre of the apparatus and observed for 4 min to record the locomotor (number of segments crossed with the four paws) and exploratory activities (expressed by the number of time rearing on the hind limbs).²⁵ The open field test was only carried out in rat pups belonging to the 7th day after exposure to (PhTe)₂ group.

Ex vivo assay

Acetylcholinesterase (AChE) activity

For AChE activity assay, samples of cerebral cortex were homogenized in 0.25 mol L⁻¹ sucrose buffer (1:10, m/v) and centrifuged at 2,400 × g at 4 °C for 15 min. Activity of AChE was carried out according to the method of Ellman and co-workers,²⁶ using acetylthiocholine as substrate. The activity of AChE was spectrophotometrically measured at 412 nm. The activity of AChE was expressed as nmol h⁻¹ mg protein⁻¹.

Protein determination

Protein concentration was measured according to the method of Lowry *et al.*²⁷

Myelin content

The myelin isolation was conducted using the method of Norton and Poduslo.²⁸ Brains were homogenized in approximately 20 vol. (m/v) of 0.32 mol L⁻¹ sucrose. The myelin was isolated using discontinuous sucrose gradient of 0.32 to 0.85 mol L⁻¹. After isolation, myelin was dry until

the weight of the sample was stabilized. Myelin density was expressed as mg myelin/g brain.

Histological analysis

Samples of brain and cerebellum of each group from four different litters were randomly selected for histological study. The brain, cerebellum and spinal cords were placed in a fixative solution of 10% buffered formalin, processed by routine histological techniques, and embedded in paraffin. The histological evaluation was made on 4 μm tissue sections of brain and cerebellum. The tissue sections were stained by haematoxylin-eosin (HE) to further analysis in a light microscope. The analyzed areas of the cerebellum were nigra and white matter.

Statistical analysis

The results are presented as means ± S.E.M. Comparisons between experimental and control groups were performed by one-way analysis of variance (ANOVA) followed by the Duncan's test when appropriate. *P* values less than 0.05 (*P* < 0.05) were considered as indicative of significance.

Results

Signs of tellurium toxicity

After exposure to (PhTe)₂ rat pups presented the following signs of toxicity: garlic-like odor and diarrhea (started at 1st day and persistent through the end of the experiment), partial or complete paralysis of hind legs and tremors (started at 3rd day and persistent through 5th day), body hair loss (5th day) and gradual recovery of paralysis (6th and 7th day). The animals exposed to (PhTe)₂ demonstrated a significant reduction in the body weight gain from 3rd day to the end of the experiment (Figure 2).

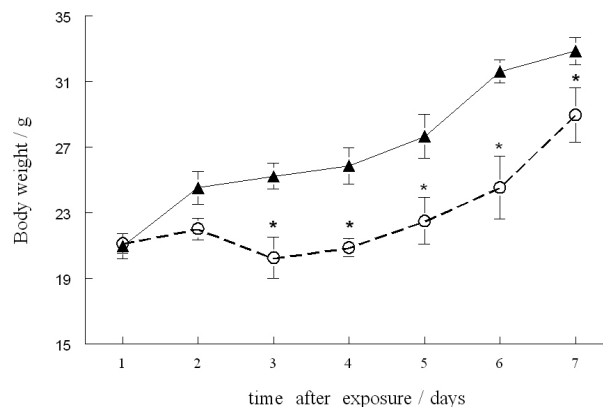


Figure 2. Effect of (PhTe)₂ on the body weight of rat pups. Data are reported as means ± S.E.M. of 5 litters *per* group. (*) Denotes *p* < 0.05 as compared to the respective control groups (one-way ANOVA/Duncan); (▲) control and (○) (PhTe)₂ groups.

Behavioral tests

Negative geotaxis

At 3rd and 4th day after exposure to (PhTe)₂, rat pups presented a significant increase in the latency to correct body position when compared to the respective control groups. From 5th day to the end of the experiment, the latency for animals to correct body position returned to control levels. Negative geotaxis was not altered in rat pups from all other time points (Figure 3).

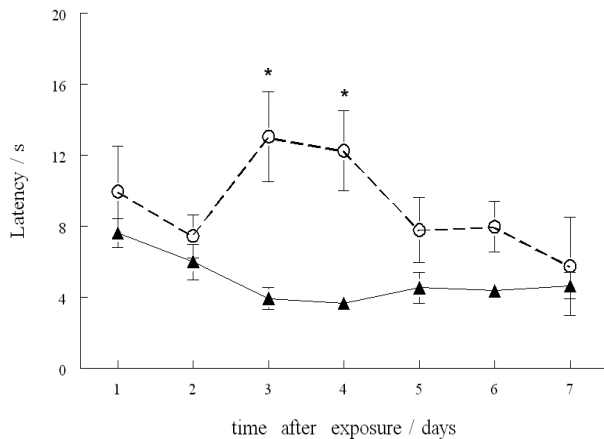


Figure 3. Effect of (PhTe)₂ on the negative geotaxis test. Data are reported as means \pm S.E.M. of 5 litters *per* group. (*) Denotes $p < 0.05$ as compared to the respective control groups (one-way ANOVA/Duncan); (▲) control and (○) (PhTe)₂ groups.

Forelimb support

Forelimb support latency of rat pups was similar in (PhTe)₂ and the respective control groups up to 5th day after exposure. From 6th day to the end of the experiment, the latency of forelimb support was higher in the respective control groups than in (PhTe)₂ groups (Figure 4).

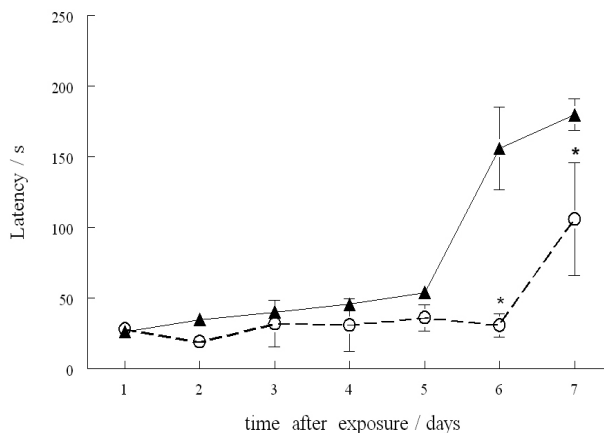


Figure 4. Effect of (PhTe)₂ on the forelimb support test. Data are reported as means \pm S.E.M. of 4 to 5 litters *per* group. (*) Denotes $p < 0.05$ as compared to the respective control groups (one-way ANOVA/Duncan); (▲) control and (○) (PhTe)₂ groups.

Open field

At 7th day after (PhTe)₂ exposure, rat pups presented a significant decrease in locomotor (crossing: control = 31.2 ± 4.1 and (PhTe)₂ = 15.1 ± 2.8) and exploratory (rearing: control = 17.9 ± 2.1 and (PhTe)₂ = 6.7 ± 3.1) activities when compared to the respective control groups.

Ex vivo assay

AChE activity

AChE activity was increased in cerebral cortex of rat pups at 4th and 5th day after exposure to (PhTe)₂ when compared to the respective control groups. There was no alteration in AChE activity in cerebral cortex of rat pups from all other groups (Figure 5).

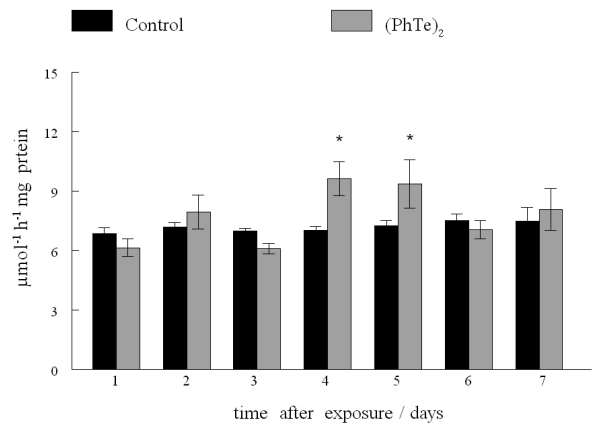


Figure 5. Effect of (PhTe)₂ on AChE activity in cerebral cortex of rat pups. Data are reported as means \pm S.D. of 5 litters *per* group. (*) Denotes $p < 0.05$ as compared to the respective control groups (one-way ANOVA/Duncan).

Myelin content

Exposure to (PhTe)₂ caused a significant reduction in cerebral myelin weight of rat pups from 4th day after exposure to the end of the experiment. At 5th day after exposure to (PhTe)₂, rat pups presented the lowest cerebral myelin content (Figure 6).

Histological analysis

In the cerebellar cortex of animals at 3th day after exposure to (PhTe)₂, the Purkinje cell monolayer, located between the molecular and granular layers, demonstrated moderated chromatolysis, a sign of histological alteration (compare Figures 7 A and B).

Cerebellar white matter in the animals exposed to (PhTe)₂ at 4th but mainly at 5th day after exposure presented the widened endoneural space between individual axons and inflammatory cells in some areas of parenchyma (compare Figures 8 C and D). In the brain areas, (PhTe)₂-exposed rat pups showed morphological changes

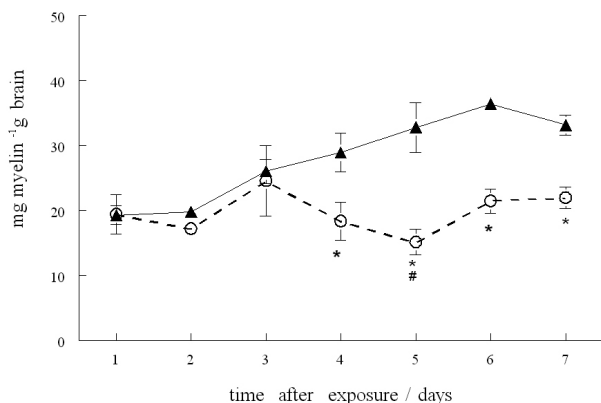


Figure 6. Effect of (PhTe)₂ on myelin content. Data are reported as means \pm S.E.M. of 4 litters *per* group. (*) Denotes $p < 0.05$ as compared to the respective control groups and (#) denotes $p < 0.05$ as compared to all other groups (one-way ANOVA/Duncan); (\blacktriangle) control and (O) (PhTe)₂ group.

of neurons, such as eosinophilic cells, chromatolysis, loss of multipolar appearance and Nissl substance migration towards the cell periphery (compare Figures 7 C and D). The neurons clearly showed nucleus and nucleoli with retraction, hyperchromasia and pycnosis. Some of these morphological changes, although with less intensity, were observed at 3rd day after exposure to (PhTe)₂.

At 6th and 7th day after exposure to (PhTe)₂, the disorder in the cerebellar white matter induced by this compound

was smaller than that of presented at 4th and 5th days, demonstrated by the appearance of filled spaces between axons, with linear axons of uniform thickness and cellular organization with a central nucleus (Figure 8).

Discussion

The present study showed that exposure to (PhTe)₂ caused systemic toxicity in rat pups, demonstrated by a garlic-like odor, the classic sign of tellurium intoxication in rats.²⁹ Hind leg paralysis, which could be related to neuronal damage, accompanied by behavioral alterations were also observed in rat pups exposed to (PhTe)₂.

The appearance of signs of toxicity, neurotoxicity and behavioral alterations were dependent on the time after (PhTe)₂ exposure to rat pups. The critical toxic period was at 4th and 5th day after (PhTe)₂ exposure, in which histological analysis revealed alterations in the morphology of cerebral and cerebellar tissues and a reduction in the myelin content. Besides, the increase in AChE activity also occurred at 4th and 5th day after (PhTe)₂ exposure, indicating that the critical period of neurotoxicity is related to the action of this compound in the cholinergic system.

Abnormal myelin deposition could potentially be the result of an insult to one or more of several different stages

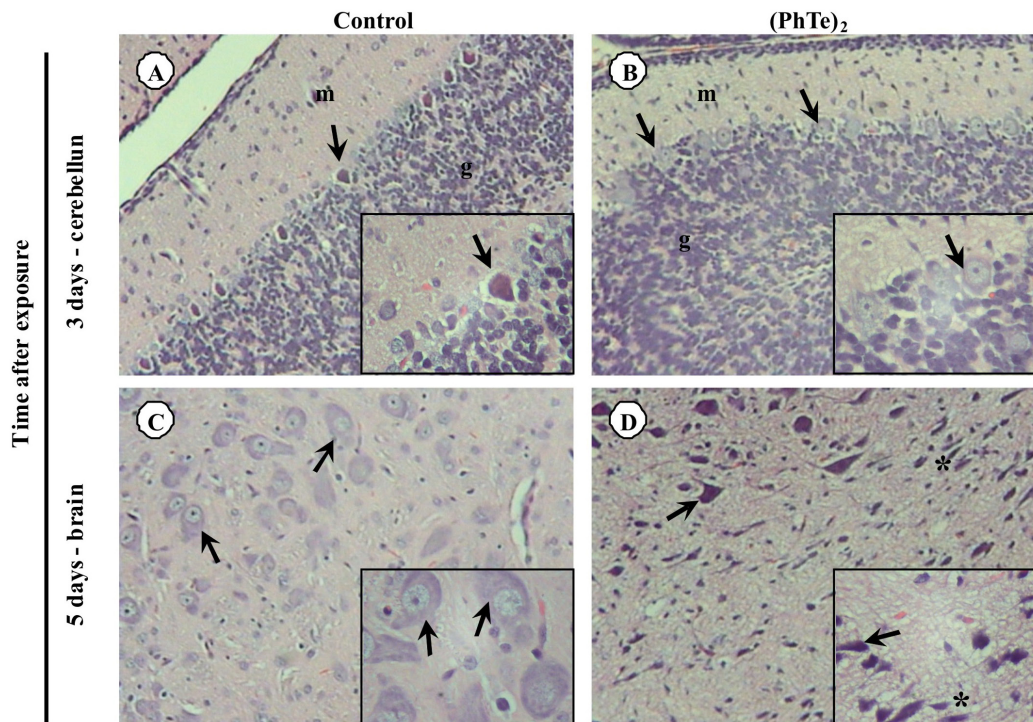


Figure 7. Photomicrography of brain and cerebellum showed different degrees of injury with detail on the right. A) Cerebellar cortex of control pups shows normal Purkinje cells (arrow) as a monolayer between the molecular (m) and granular layer (g). B) Observe the cerebellum of (PhTe)₂-exposed pups with chromatolysis signs in the Purkinje cells (arrow) localized between the molecular (m) and granular layer (g). C) Brain of control pups with multipolar neurons (arrow) presented Nissl substance and nucleus and nucleoli of normal appearance. D) (PhTe)₂-exposed pups presented neurons with retraction (arrow), hyperchromasia and pycnotic nucleus (*). H&E. 400 \times . See online version for colors.

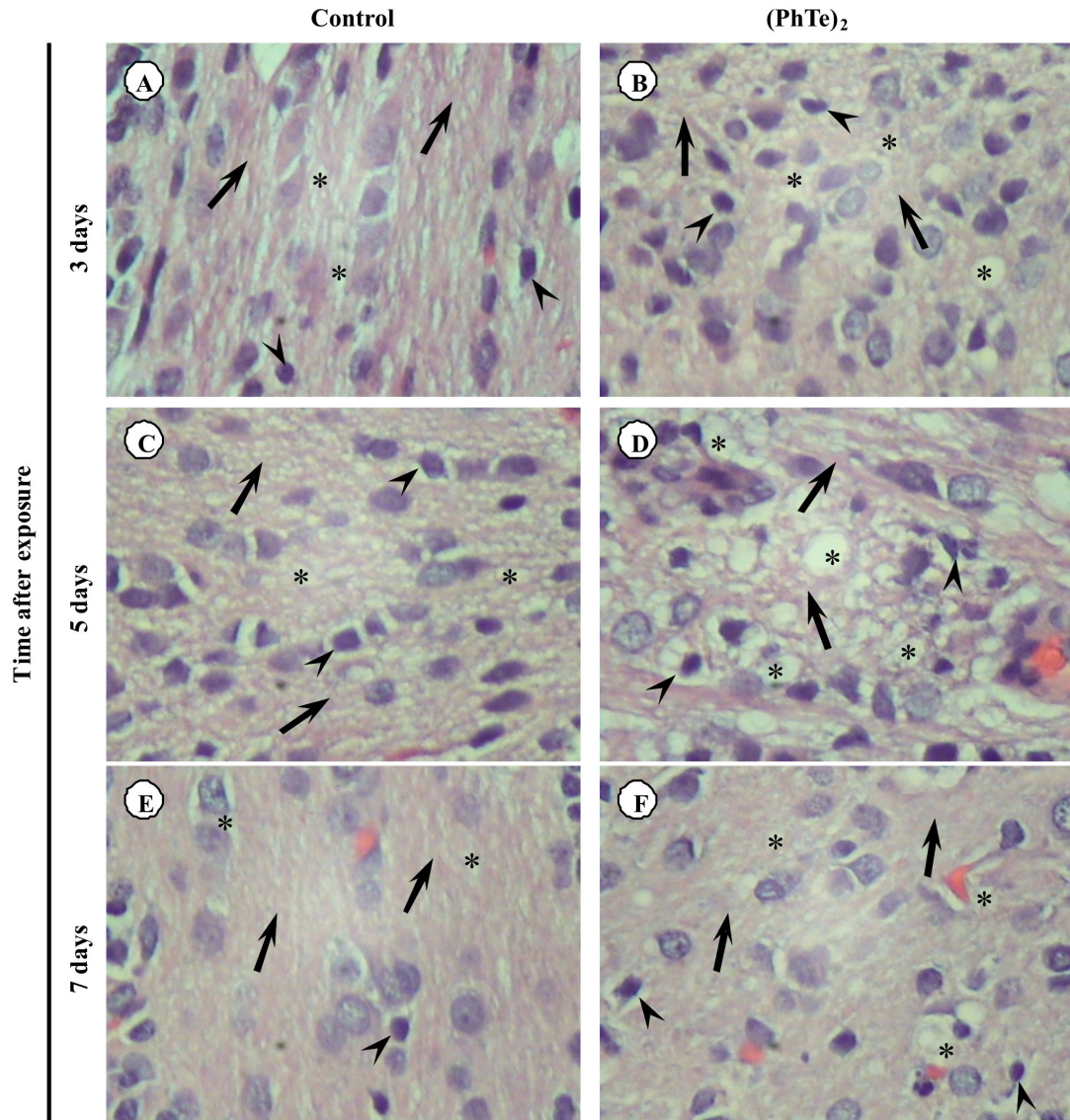


Figure 8. Photomicrography of the cerebellar white matter of: A,C,E) control group shows normal axons (arrow), myelin sheath (*) and oligodendrocytes (arrowhead). B) (PhTe)₂ exposed pups with slight spaces (*) between axons (arrow) and oligodendrocytes (arrowhead). D) Note the presence of widened spaces (*) between axons, endoneurial (arrow) and oligodendrocytes (arrowhead) in (PhTe)₂ rat pups. F) Observe diminution of axonal and endoneurial spaces (*). Note the filled spaces between axons (arrow) and oligodendrocytes (arrowhead). HE. 400x. See online version for colors.

of development. In the rat brain, most oligodendrocytes complete a proliferation phase between approximately 1-2 weeks after birth, which is followed by a period of a very rapid rate of myelination (16-30 days after birth). The rate of myelination increases to a maximum at about 20 days of age and then declines to a low level that appears to be maintained throughout the life of the rats. In the myelination period, in the developing rat model, the biochemical mechanism of hypomyelination features a specific reduction in myelin membrane synthesis rather than an increased turnover.³⁰

In this experimental protocol, (PhTe)₂ was given during physiological very rapid rate of myelination period when the CNS (central nervous system) is not yet myelinated in

the rat pups. Thus, one interpretation for the data found in this study is that (PhTe)₂ caused hypomyelination rather than demyelination. The data presented in Figure 6 provide further support for this idea. It is clearly demonstrated in Figure 6 that there is no major decrease in myelin content but rather stagnation with any new myelin being formed. The fact that tellurium blocks cholesterol synthesis and causes down-regulation of myelin gene expression³¹⁻³⁴ could help to explain the stagnation of myelin synthesis seen in rat pups exposed to (PhTe)₂. The unusual sensitivity of the enzyme to tellurium is due to reaction with sulfhydryls and the binding to the vicinal cysteines on squalene monooxygenase.³¹

In the current study, histological examination revealed neuronal damage in rat pups exposed to (PhTe)₂.

Neuronal damage was demonstrated by the appearance of chromatolysis; widened endoneural space between individual axons; inflammatory cells in some areas of parenchyma; eosinophilic cells; loss of multipolar appearance and Nissl substance migration towards the cell periphery; nucleus and nucleoli with retraction; hyperchromasia and pycnosis. Schwab and Bartholdi³⁵ have demonstrated morphological changes related to chromatolysis, a reaction to axon injury, present in most neurons of the pons nuclei. Several authors have reported that these changes are caused by the alteration of the cytoplasm and of the nuclear pH and to the presence of a metabolic stage.³⁶⁻³⁹ Moreover, the appearance of widened endoneural space between individual axons, demonstrated by histological examination of cerebellar white matter and brain, could be interpreted as a neural damage since edema could make this effect on tissue.

Regarding behavioral performance, rat pups exposed to (PhTe)₂ presented partial or complete paralysis of hind legs from 3rd to 5th day after exposure, a period coincident with the reduction in myelin content. The reduction of myelin content was accompanied by the most severe histological changes. Therefore, it is plausible to assume that paralysis of hind legs is associated with both events. Similarly, the results obtained on negative geotaxis, demonstrated a commitment of the motor and sensorial functions at 3rd and 4th day after exposure to (PhTe)₂. It is important to note that the group exposed to (PhTe)₂ presented similar results in negative geotaxis when compared to control animals, at latter stages after exposure (6th and 7th day), suggesting that (PhTe)₂-exposed pups reversed toxicity. These results are supported, at least in part, by those obtained by Lampert and co-workers.^{11,16} Lampert reported that weanling rats less than three weeks of age became paralyzed when fed with a diet containing elemental tellurium, rat pups showed paralysis resulted from segmental demyelination of sciatic nerves and spinal roots and remyelination took place despite continued ingestion of tellurium, suggesting that whatever induced the neuropathy is effective only during a very limited but critical age period, the period of most active myelinogenesis.

The neurobehavioral response depends on developmental stage of the offspring and their CNS. Besides, the muscular maturation is also very important. Accordingly, the absence of increasing in forelimb support latency in rat pups at 6th and 7th day after (PhTe)₂ exposure supports the idea that development of the pups muscular maturation was delayed when they were subjected to exposure to (PhTe)₂. It is important to point out that no difference was found in the latency in the forelimb support between control and exposed groups until 5th day after exposure to (PhTe)₂,

indicating that rat pups from PND 15 to 19 are still in developmental stage of muscular strength. At 7th day after exposure to (PhTe)₂, the content of myelin in brain of rat pups is still lower than that of control group at the same period, which would be consistent with the behavioral performance of rat pups in the open field test. In fact, rat pups at 7th day after exposure to (PhTe)₂ presented a significant decrease in locomotor and exploratory activities in the open field apparatus when compared to the respective control groups. The cholinergic neurotransmission is vital to normal behavior and muscular function.³⁹ In this way, AChE plays a major role in the regulation of several physiological events.⁴⁰ Alterations in the activity of AChE have been evidenced in several neurological disorders and intoxication with organophosphorus.⁴¹ However, this is the first study aiming to investigate the *in vivo* effect of an organotellurium, (PhTe)₂, on AChE activity. The results demonstrated an increase in AChE activity in cortex of rat pups at 4th and 5th day after (PhTe)₂ exposure, which suggest that some functions mediated by cholinergic system were affected by (PhTe)₂ exposure. In this context, we believe that the increase in AChE activity could be explained as: i) a direct effect of (PhTe)₂ on this enzyme or ii) a consequence of neuronal damage caused by (PhTe)₂.

From a mechanistic point of view, the increase in AChE activity leads to a reduction of cholinergic neurotransmission efficiency due to a decrease in acetylcholine levels in the synaptic cleft, thus contributing to neurological dysfunctions. It is well recognized that altered membrane functions in several tissues including brain occur due to an enhancement of free radical formation which promotes increased lipid peroxidation, having as major consequence oxidative deterioration of the cellular membranes.⁴² AChE is a significant biological component of the membrane that contributes to its integrity and changes in permeability during synaptic transmission and conduction.⁴² Because (PhTe)₂ causes oxidative stress in brain,⁸ alterations in the lipid membrane could lead to the increase in AChE activity. Thus, AChE activation in (PhTe)₂-exposed rat pups is probably precipitated by free radical generation and consequent oxidative stress in the brain.

Conclusions

In summary, rat pups exposed to (PhTe)₂ showed signs of tellurium toxicity and impairment of developmental behavioral performance. (PhTe)₂ caused neuronal damage in rat pups, which was revealed by histological examination and reduction of myelin content. Additionally, AChE activity was activated in rat pups exposed to (PhTe)₂.

Acknowledgments

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