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Does *Withania somnifera* mitigate the structural alterations of the rat brain associated with propylthiouracil?

L.I. Al-Allaf[1] and O.M. Al-Iraqi[2]

[1]Department of Anatomy, College of Medicine, [2]Department of Internal and Preventive Medicine, College of Veterinary Medicine, University of Mosul, Mosul, Iraq

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Correspondence:
L.I. Al-Allaf
lik@uomosul.edu.iq

Abstract

The repercussion of propylthiouracil (PTU) use postnatally on brain histology have not yet been intensely scrutinized. To examine whether *Withania somnifera* mitigate the structural effects of propylthiouracil on rat brain, rats were distributed into group A enrolled ten pups that were received -orally- distilled water (D.W) daily from postnatal day (PND) 3 to PND 43. Group B: enrolled pups (n=8) subjected to oral doses of PTU (1 mg/kg/day) from PND 3 to PND 25. Then they were gavaged with D.W till PND 43. Group C: included pups (n=8) that were subjected orally to PTU (1mg/kg/day) PND 3 to PND 25 with receiving levothyroxine (four microgram /100g/day) from PND 25 to PND 43. Group D included pups (n=8) that were treated with oral PTU 1 mg/kg/day PND 3 to PND 25 with receiving *Withania somnifera* extract (200 mg/kg/day) from PND 25 to PND 43. Cerebellar sections of rats of group B exhibited disorganization of the cerebellar cortex with a falling off in the Purkinje cells' count and the appearance of degenerated cells. Hippocampal sections (of rats of group B) proclaimed a falling off in the breadth of the pyramidal zone of cornu Amonis. Sections of the cerebral cortex of rats in group B exhibited the presence of large degenerated neurons. Sections of rats' brains belonging to groups C and D showed improved cerebellar and cerebral cortex segments and hippocampal and cerebral cortical segments. Levothyroxine and *Withania somnifera* mitigates the structural changes in the peripubertal rat brain induced by postnatal PTU administration.

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Introduction

Among the traditional Indian medical herb is *Withania somnifera* (L.) (1). It is rich in saponins, steroidal lactones, flavonoids, and alkaloids (2). This herb is regarded as one of the main tonics among geriatric in India beside its narcotic, stimulant, diuretic, and antifatigue effect. Concerning the nervous system, *Withania somnifera* has regenerative characters as it used to treat memory-associated conditions, nervous exhaustion, learning problems and insomnia (3). According to many reports, *Withania somnifera* has multifaceted pharmacological actions including anti-convulsive, antiaging, sedative anti-inflammatory, anticancer, antioxidant, and aphrodisiac functions (4-6). Experimental studies suggested the role of *Withania somnifera* in improving the cognition and memory (7,8) beside its protection against neurodegeneration and impaired cognition after neuro-inflammations via NF-κB modulation and signaling tracks of mitogen-activated protein kinase signaling (9). Mood disturbances and cognitive impairment have consistent accompanying with hypothyroidism, indicating that thyroid hormones are condemnatory for normal brain employment especially those concerned with cognitive and memory (10,11) as these hormones including T3 (triiodothyronine), T4 (thyroxine) contributes essentially in the central nervous system development and functional

preservation. These hormones, during developmental periods, manage the brain growth and maturation of neuronal cellular elements. Purkinje cells in the cerebellar cortex need thyroid hormones for their dendritic growth besides the role of these hormones in granule cells' proliferation and migration and cerebellar neurons' synaptogenesis (12). The shortage of the thyroid hormones throughout maturation causes disruption of adult motor integration (13). Further, dysfunction of thyroid gland may cause disarrayment of hippocampal granule cells' migration occurs beside the disruption of dendritic growth (of hippocampal pyramidal cells). Synapse functions and learning suffered from abnormalities by this gland dysfunction (14). Behavioral reports were found in rodents including elevated of anxiety with hypothyroidism, and often cases of depression were seen (15).

The works on the potential role of *Withania somnifera* in mitigation of the effect of propylthiouracil on rat brain are constrained. Précising the structural alteration in the peripubertal rat brain after exposure to propylthiouracil (PTU) in early postnatal period with examining whether *Withania somnifera* has an ameliorating role on these alterations (if present) using sonographic and microscopic assessments is the study plan.

Materials and methods

Ethical permission

Under well optimized laboratory environments for animals, this experimental study was accomplished at postgraduate studies' laboratory of Anatomy Department, Medicine College, Mosul's University, Northern Iraq conducting on thirty-four male Albino rats with permission from the Medical Research ethical Committee, Medicine College, Mosul's University, code UOM/COM/MREC/21-22-68.

Animals grouping

After purchasing of rats from Veterinary College (Animal House), Mosul's University, their –randomly distribution-to the four groups was consummated as the following. The first group (Group A) enrolled ten pups that were received -orally -distilled water (D.W) daily beginning with postnatal day 3 to postnatal day 43 (for regarding as control group) (Figure 1). The second group (Group B) enrolled another age matched pups (n=8) that were treated with propylthiouracil PTU (1 mg/Kg/day/orally) that bought from private pharmacy for 23 days (16) from postnatal day 3 to postnatal day 25. Then administration with D.W till post-natal day 43 was done. The third group (Group C) included another age matched pups (n=8) that were treated with propylthiouracil -PTU (1 mg/Kg/day) from postnatal day 3 to postnatal day 25 with receiving oral levothyroxine (four microgram /100 g/day) from day post-natal day 25 to 43th -postnatally (16). The fourth group (Group D) included another age matched pups (n=8) that were treated with propylthiouracil -PTU (1 mg/Kg/day) from postnatal day 3 to postnatal day 25, with receiving an extract of herb-*Withania somnifera* - as 200 mg/kg/day from 25 (post-natal day) to 43th postnatally (17).

Study's termination

After euthanization of each rat by ether (18) at PND 45, the brain was harvested from each rat to be examined by an ultrasound transducer (19) via water bath (D.W inside sterilized container) using portable ultrasound machine (Kx5100vet, KeeboMed, United states of America) with 5 Mega Hertz -MHz micro convex transducer. Then the specimens (brain) were embedded in paraffin and stained with hematoxylin-eosin (H&E) (20). In blinded fashion to treatment and any data, the examination was done.

Statistical analysis

From IBM- New York, Packaging of the Social Sciences' statistics is used to analyze the data with $P<0.05$ is regarded as decisive.

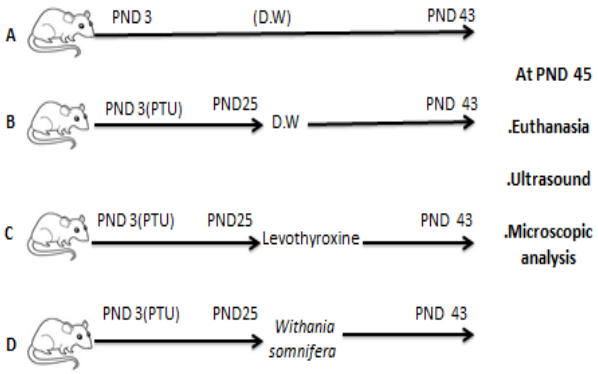

Figure 1: A study design's scheme.

Results

The current work analyzes the impact of *Withania somnifera* on the morphology of the peripubertal rat brain after postnatal exposure to PTU. No case of mortality was found during the study. The differences in the weight of animals of all groups, at postnatal day 3 and at postnatal day 45, are shown in table 1.

Assessment of brain ultrasonography

Using ultrasound, the current work recognized a diminishing in the diameter of the brain in rats of group B. On the other hand, the early treatment with either levothyroxine or *Withania somnifera* leads to an alleviation of the effect of PTU as the diameter returned to seminormal in rats of group C and D (Figure 1 and Table 2).

Assessment of brain histology

No gross brain lesions were identified in all rats at the macroscopic assessment. Concerning the microscopic evaluation, this study showed sections of the brains of rats in group A (control group) exhibited normal cerebellar cortex dwells of the triple layers (molecular, Purkinje, and granular) (Figure 2). On the other hand, hippocampal region of rats of group A showed normal architecture of three layers (molecular, pyramidal, and multiform) with modification in dentate gyrus (pyramidal layer is replaced by granular layer) (Figure 3). In addition, normal histologic organization as the cerebral cortex of rats of group A formed of the six layers (Figure 4). This study displayed those cerebellar sections of rats of group B (which were exposed to PTU) exhibited some structural alterations including disorganized cerebellar cortex with falling off in Purkinje cells' count plus appearance of degenerated cells. In addition, a minimizing in the breadth of granular cell segment with few cerebellar areas between them were recognized (Figure 2).

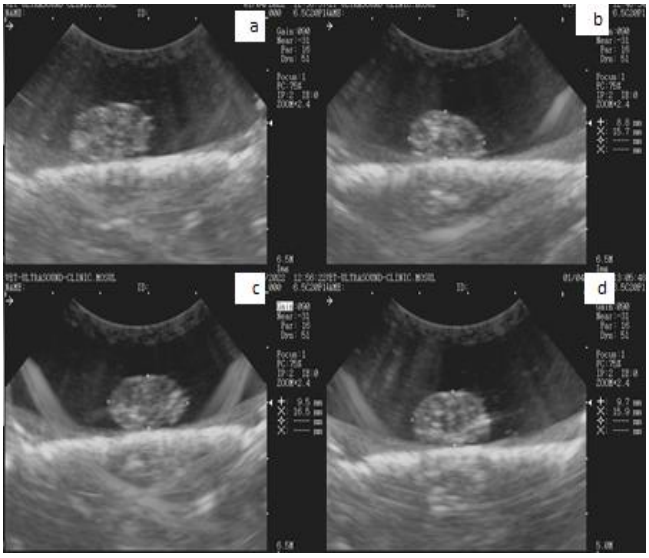

Figure 2: An ultrasound of brain of normal size and echo texture of a rat of control group (a), an ultrasound of brain of subnormal size and increase in echogenicity in the center of a PTU received group (b), an ultrasound of brain with an improvement in size and echogenicity a rat of PTU and then treated with Levothyroxine (c), an ultrasound of brain with regaining of size and normal echo texture), a rat of PTU and then treated with *Withania somnifera* (d).

Microscopic appraisal (judgment)of hippocampal segments of rats of group B showed a minimizing in the breadth of pyramidal segments of cornu Amonis with evidence of dense nuclei (Figure 3). Sections of cerebral cortex of rats in group B exhibited presence of large degenerated neurons with dark nucleus and abnormal arrangement of Nissl substances (Figure 4).

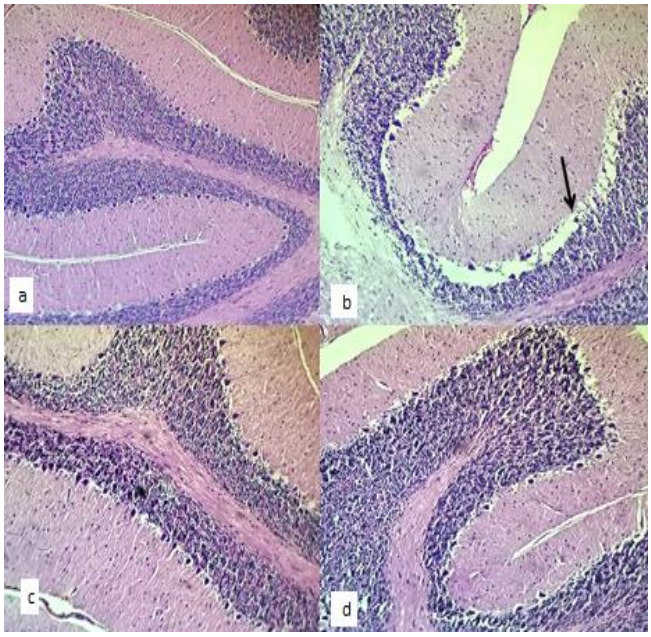

Figure 3: A microphotograph of a cerebellar section of a rat of control group (a), a rat of PTU received group (b) with degenerated Purkinje cells (arrow), a rat of PTU and then treated with Levothyroxine (c), a rat of PTU and then treated with *Withania somnifera* (d). (H&E×250).

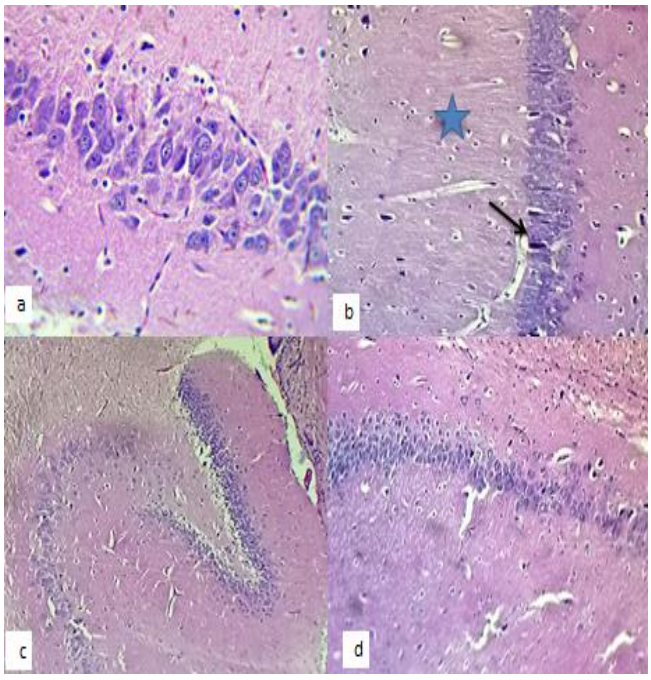

Figure 4: A microphotograph of a hippocampal segment of a control group rat (a), a rat of PTU received group (b) with degenerated cells (arrow), a rat of PTU and then treated with levothyroxine (c), a rat of PTU and then treated with *Withania somnifera* (d). (H&E×400).

Table 1: The effect on the value of mean body weight of rats at PND 3 and PND 45 in all groups

Days	Mean ± standard deviation			
	Group A	Group B	Group C	Group D
PND3	9.417±0.5 a	10.228±1.459 a	9.070±.176 a	10.271±1.460 a
PND45	118.2±2.087 a	86.1±1.763 b	122.1±0.420 a	123.3±2.360 a

The non-similar (different) letters mean presence of significant difference- at P<0.05.

The present work evaluated microscopically the role of levothyroxine and *Withania somnifera* in mitigating the structural changes in peripubertal rat brain induced by postnatal PTU administration and revealed that sections of brain of rats belonged to group C (after treatment with levothyroxine from postnatal day 25 to postnatal day 43) showed features of mild improvement in cerebellar cortex, hippocampus and cerebral cortex (Figures 2-4). In fact, sections of brain of rats belonged to group D (which were received *Withania somnifera* from postnatal day 25 to postnatal day 43) revealed structural mitigation in cerebellar cortex, hippocampus and cerebral cortex (Figures 2-5).

Table 2: The differences in the values among rats of all groups

	Longitudinal	Transverse
Group A	9.5750±0.8 ab	16.5750±1.2 a
Group B	8.7625±0.5 c	15.6875±0.9 b
Group C	9.5250±0.8 a	15.5500±0.9 c
Group D	9.6625±0.7 b	15.8250±1.3 d

The different letters mean presence of significant difference- at P<0.05(through analysis of variance-ANOVA).

Discussion

Thyroid hormones may have an impact on growing neurons in early postnatal animals since the majority of mammals produce their neurons during pregnancy and the early postnatal period (21). Particularly, it has been demonstrated that thyroid hormone excess or deficit affects cell differentiation, migration, and gene expression. Therefore, stunted thyroid hormone levels at full length of key stages of neurodevelopment can result in interminable cognitive and behavioral shortfalls (22).

In fact, PTU has been found to induce hypothyroid status successfully in rats (22,23). In the current work, there is a marked lessen in the mean body weight of rats which were received PTU compared with that of control group. This may be due to the defect in their metabolism or due to adrenal atrophic changes associated with PTU (23,24). On the other hand, improving of the weight was noticed among animals with levothyroxine and *Withania somnifera* administration. These findings are similar with those of Hwang *et al.* (24) and of Sultana *et al*. (25) which allocated that to the positive effect of *Withania somnifera* on the liver. There is report that this herb acts as an antioxidant, so improve the cells functions in general in hypothyroid cases (26,27). In fact, the administration of levothyroxine restores the thyroid function.

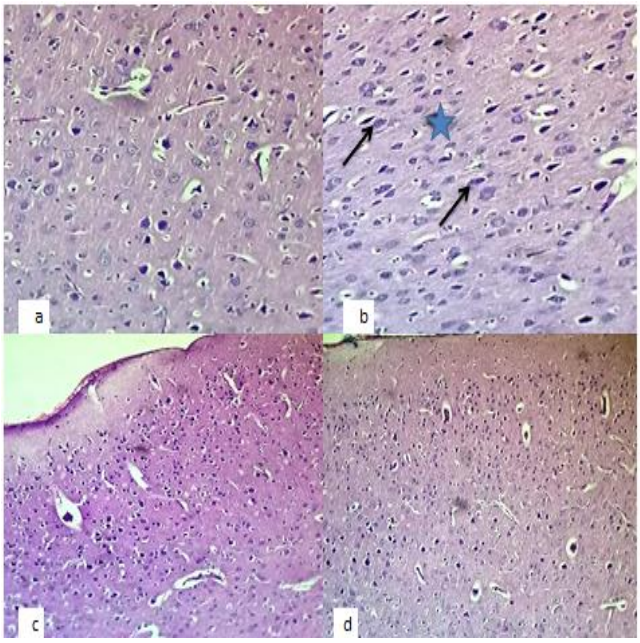

Figure 5: A microphotograph of a cerebral plate of a control group rat (a), a rat of PTU received group (b) with degenerated neuron (arrow), a rat of PTU and then treated with levothyroxine (c), a rat of PTU and then treated with *Withania somnifera*. (H&E× 400).

In this work, using of the ultrasound is to study the postnatal influence of PTU on the rat's brain with or without administration with levothyroxine (or *Withania somnifera*) within the periods of lactations (early and late) in a trial to mimicking the cases of congenital thyroid dysfunction and that related to a deficiency of Iodine. The findings of the current work are similar to those of Hasegawa *et al.* (28), of Tajima *et al.* (29), and of wheeler *et al.* (30). To the best of comprehension, the work that focused on the rat brain after early receiving of PTU on such different levels (songraphic and structural) are limited.

As Salas-Lucia *et al*. (31) reported regarding the changes in the size of the brain using ultrasound, the reduction of the brain's size may be due to the diminishing in the number of axons after exposure to PTU. These changes were reversible

as the replacement with Levothyroxine was at early time. They reported an irreversibility of these changes when there is a delay in treatment (31).

A review of Hernández *et al.* (32) reported contradictory opinions concerning the findings of imaging approaches in cases of thyroid dysfunction in both levels (human and experimental) and that due to the method used and the region examined. Regarding the microscopic evaluation, this work displayed that sections of rats which were submitted to PTU exhibited structural changes in cerebellar cortex indicating the adverse effect of this agent as it induces the thyroid dysfunction (33). In fact, in mammals including human, during the early period, the cerebellum suffers from several developmental processes including migration and differentiation (mainly the granular cells) which make this organ susceptible to injury (34,35). Hypothyroidism may cause long-term cognitive and behavioral shortfall especially during early stages of development including those related to motor function (36,37) and this may be via oxidative action on cerebellum (33). The majority of neurons of human brain is located in the cerebellum and mainly the granular cells (38,39). These cells proliferate during the postnatal period (40). RG *et al.* (26) and Deniz *et al.* (33) reported that there was an involvement of microscopic changes in cerebellar cortex in hypothyroid cases.

In addition, the precise mechanisms embracing the learning, memory, and cognition disablement induced by thyroid dysfunctions are hidden till now. It appears in certain zones of brain; thyroid dysfunction alters the oxidative stressing triggering subsequent processes. This affecting – biochemically-some actions as sodium ions Na^+/Potassium ions K^+ Adenosine triphosphatase (ATPase) task, polyunsaturated fatty acid, Neuronal nitric oxide synthase (nNOS), up taking of the neurotransmitter glutamate, acetylcholinesterase's activity, and intracellular Calcium ions (Ca^{2+}) concentration which constructs a multi-component condition with the aftermath of brain's tissues oxidative damaging (22). It is, also, trusted that, in hypothyroidism, a shortfall of the antioxidant's system has a task in the guiding of signaling track affixed to cellular elaboration and cellular demise. Variation in active oxygen metabolic justification has been proclaimed to straightly synchronize transcription and translation, which -in turn - guide the thyroid hormones (16,41). This work revealed a microscopic alteration in cerebral cortex in rats after PTU exposure as this agent has been proclaimed to attack the newborn's neuroendocrine system by free radicals' manufacturing, which might persuade strike neurological deterioration in the cerebral cortex (42). Via its disarrayment act on endocrine functional responsibility, there is a prevention of conversion of T4 to T3, that thyroid hormones have a burden on the brain development. Levothyroxine, as a replacement protocol is again and again effectual in keeping away the developmental abnormalities. As well, at the moment of preliminary discernment and therapy has been launched to refine masses of these dearth. There is proof that neurocognitive shortfall might keep up (43).

This work showed the structural alteration in the hippocampal region in animals which were received PTU. In fact, a study of Inal *et al.* (44) suggested a presence of receptors to triiodothyronine in hippocampal region and make this region vulnerable to thyroid dysfunction as it is one of the areas of continuous neurogenesis. As shown in the current study, previous data of (28), the impact of hypothyroidism was on both cerebellum and hippocampus. In fact, the impact of impaired thyroid function during early life (as in case of exposure to PTU) is critically and obviously shown more than that of older times as there was a defect in the synthesis of microtubules of neurons beside the involvement of neurotrophies (45).

A study of Uchida *et al.* investigated the functional contribution of thyroid hormones on the cerebral and hippocampal tissue in mice throughout the period of neurological development. There was a diminish in parvalbumin expression (and even thyroid hormones) in these areas by anti-thyroid drug (46,47), and as shown in this work, the effect of thyroid dysfunction is rescued by thyroxin. Lipid peroxidation of the cellular membrane in tissues is promoted by reactive oxygen species (42) and this may explain why the administration of rats with *Withania somnifera* mitigates the cellular damage that was occurred after PTU exposure (48) as this herb leads to expansion of both axons and dendrites (43).

In fact, early treatment with Levothyroxine (49) or even with *Withania somnifera* may help to form new neurons which are able to share in neuronal actions (50) and that indicated the mitigating effect of these agents to restore the adverse effect of thyroid dysfunction by PTU.

Depending on the data of previous work (51), *Withania somnifera* has a neuro -reconstructive action beside the rescue of glial cells by up regulating of plasticity markers including glial fibrillary acidic protein-GFAP, and neural cellular adhesion particles. In addition, the antioxidant effect of *Withania somnifera* is important as the brain contains lipid in high amount, so it has a raised aerobic metabolism and this indicating its ability to oxidative stress (51-53). Further, it may adjust the synthesis of glutathione, and microtubule-associated proteins (MAP2) as *Withania somnifera* can cross the blood brain barrier (54). These makes this herb useful to treat the complication of nervous tissues including those related with Covid-19 (55) and brain cancer (56). The strength of this study is to confirm the clinical and structural data found on the impact of thyroid dysfunction (due to any cause) by imaging and microscopic techniques which can provide a pathophysiological clarification of such condition.

Conclusion

There are structural changes in rat brain after early postnatal exposure to PTU, however, these changes are

mitigated in some extent with replacement with Levothyroxine or even with administration of *Withania somnifera* indicating that this period is critically should be considered to prevent the adverse impact of thyroid dysfunction on the neuronal development as early as possible. These findings recommended the importance of early detection of thyroid dysfunction beside adjustment of the suitable dose of *Withania somnifera* in further studies to be use in the clinical application. In fact, further works are in demanded to explore the macroscopic alterations of the rat brain using radiographic tools as magnetic resonance imaging in cases of hypothyroidism.

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Conflicts of interests

None.

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هل تخفف الوثانيا سمنوفيرا التحويرات التركيبية لدماغ الجرذ المرتبطة بالبروبايل ثايوبوراسيل؟

لمى إبراهيم العلاف[1] و أسامة موفق العراقي[2]

[1]فرع التشريح، كلية الطب، [2]فرع الطب الباطني والوقائي البيطري، كلية الطب البيطري، جامعة الموصل، الموصل، العراق

الخلاصة

إن دراسة تأثير إعطاء البروبايل ثايوراسيل في فترة بعد الولادة على نسيجية الدماغ لم يدرس بشكل مكثف. تهدف الدراسة لفحص ما اذا تخفف الوثانيا سمنوفيرا التأثيرات التركيبية للبروبايل ثايوبوراسيل على دماغ الجرذ. تم توزيع الجرذان الى مجموعة أولى وتضم عشر جراء استلموا ماء مقطر بالفم من اليوم الثالث بعد الولادة الى اليوم الثالث والأربعين.

مجموعة ثانية شملت ثماني جراء تعرضوا الى جرع بالفم من البروبايل ثايوبوراسيل (١ مغم / كغم في اليوم) من اليوم الثالث بعد الولادة الى اليوم الخامس والعشرين ثم تم إعطاؤهم ماء مقطر بالفم الى اليوم الثالث والأربعين. مجموعة ثالثة تشمل جراء تم تعرضوا الى جرع بالفم من البروبايل ثايوبوراسيل (١ مغم لكل كغم في اليوم من اليوم الثالث بعد الولادة الى اليوم الخامس والعشرين ثم تم إعطاؤهم الليفوثايروكسين (٤ مايكروغرام لكل ١٠٠ غرام في اليوم) من اليوم الخامس والعشرين الى اليوم الثالث والأربعين. المجموعة الرابعة شملت جراء تم تعرضوا الى جرع بالفم من البروبايل ثايوبوراسيل (١ مغم لكل كغم في اليوم من اليوم الثالث بعد الولادة الى اليوم الخامس والعشرين ثم تم إعطاؤهم مستخلص الوثانيا سمنوفيرا (٢٠٠ مغم لكل كغم باليوم) من اليوم الخامس والعشرين الى اليوم الثالث والأربعين. إن شرائح المخيخ للجرذان للمجموعة الثانية قد شهدت عدم انتظام في قشرة المخيخ مع قلة بخلايا بيركنجي وظهور خلايا مضمحلة. وشرائح الجزء الحصين لتلك المجموعة كان فيها قلة في سمك الطبقة الهرمية (قرن أمون) وكانت شرائح قشرة المخ قد احتوت على وجود خلايا كبيرة مضمحلة. إن شرائح الدماغ التي تنتمي للمجموعة الثالثة والرابعة اتسمت بتحسن في قشرة المخيخ والجزء الحصين وقشرة المخ. تم استنتاج أن الليفوثايروكسين والوثانيا سمنوفيرا خففت التغيرات التركيبية في دماغ الجرذ في عمر حول البلوغ والتي نتجت من الروبايل ثايوبوراسيل.