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EFFECTS OF COMBINED HYPOTHYROIDISM AND SELENIUM DEFICIENCY ON SELENOENZYME GLUTATHIONE PEROXIDASE ACTIVITY IN RATS

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The effects of propylthiouracil (PTU) treatment and selenium-deficient diet on selenium and thyroid status of Wistar male rats were examined in this study. Wistar male rats (n =128) were divided into four groups: (1) control group – selenium-adequate rats fed a diet supplemented with 0.334 mg Na selenite/kg feed and received regular drinking water (Se+PTU-); (2) selenium adequate rats fed a diet supplemented with 0.334 mg Na selenite/kg feed and received a dose of 150 mg/L of PTU in drinking water, (Se+PTU+); (3) selenium-deficient rats fed a diet containing 0.031 mg Na selenite/kg and received regular drinking water (Se-PTU-); (4) selenium deficient rats fed a diet containing 0.031 mg Na selenite/kg and received 150 mg/L of PTU in drinking water (Se-PTU+). After three and seven weeks of treatment, all Se – animals had significantly lower whole blood Se concentrations and GPx1 and GPx3 activities. PTU induced a significant decrease in T4 and T3 plasma concentrations after three weeks of treatment in both PTU+ groups. Furthermore, after seven weeks, the T3 level was close to its detection limit in Se – animals. A negative correlation was spotted between GPx activity and concentration of T3 after three and seven weeks. It could indicate an inhibitory influence of thyroid hormones on the expression and/or activities of GPx enzymes related to the available Se in conditions of systemic decrease of T4 concentration. This effect was particularly pronounced in Se – animals.

Keywords: glutathione peroxidase, propylthiouracil, rats, selenium, thyroid hormones.

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INTRODUCTION

Selenium (Se) is a micronutrient essential for several important metabolic pathways, including antioxidant defense, thyroid hormone activation, and deactivation. The physiological roles of Se are carried out through selenoproteins and selenoenzymes. All selenoenzymes contain Se as selenocysteine at their active sites [1]. Metabolism of selenium and thyroid hormones are connected in several ways. Selenium is a member of the group of antioxidant selenoenzymes, glutathione peroxidases (GPx), which have a crucial role in the antioxidative protection [2-4] of thyrocytes during thyroid hormone synthesis, considering the large production of hydrogen peroxide in this process [5]. In addition, selenium, in the form of selenocysteine, is part of the catalytic site of iodothyronine deiodinases (ID). Activities of all three types of iodothyronine deiodinases determine the blood and intracellular levels of thyroid hormones [6,7]. Type 1 deiodinase (ID1) in peripheral tissues, and type 2 deiodinase (ID2), mainly in the brain, convert T4 to T3. Type 3 deiodinase (ID3) is the selenoenzyme that inactivates T3 and T4 [8]. Therefore, selenium incorporated in ID should be important in regulating T4/T3 levels at the plasma and cellular level [9].

The activities of cellular GPx1 and GPx3 plasma are highly correlated with the selenium status in the body [10-12]. Activities of these enzymes significantly decrease in selenium deficiency. However, some other selenoproteins, like ID1 [13] in the thyroid and GPx4, are protected during selenium deficiency, and the mechanisms responsible for achieving this hierarchy have not yet been elucidated.

Considering that regulatory mechanisms of synthesis, activation, and inactivation of thyroid hormones are complex and not yet wholly understood during selenium deficiency, this experiment was designed to determine the short and long-term combined hypothyroidism and selenium deficiency on T3, T4, and TSH levels and selenoenzyme glutathione peroxidase activity in rats. In this study hypothyroidism in juvenile rats was induced by treatment with propylthiouracil (PTU) via drinking water.

MATERIAL AND METHODS

The study involved one hundred twenty-eight male Wistar rats, Charles-River origin (Hungary), 21 days old and weighing 48.6±7.8 g. Four experimental groups, each consisting of 32 individual animals, were formed as follows: 1) Control group – rats fed with a diet supplemented with 0.334 mg Na selenite/kg feed (C-1000, Altromin, Germany) and received regular drinking water (Se+PTU-); (2) selenium adequate rats fed a diet supplemented with 0.334 mg Na selenite/kg feed and received a dose of 150mg/L of PTU (Sigma) in drinking water (Se+PTU+); (3) selenium-deficient rats fed a diet containing 0.031 mg Na selenite/kg and received regular drinking water (Se-PTU-); (4) selenium-deficient rats fed a diet containing 0.031 mg Na selenite/kg and received 150 mg/L of PTU in drinking water (Se-PTU+). After three weeks of the experimental period, half of the animals from each group were anesthetized with

ether, and approximately 5 mL of blood was sampled by cardiac puncture into glass tubes containing heparin (15 IU/mL). Animals were euthanized by the prolonged effect of ether. GPx1 activity and Se concentration were determined immediately in whole blood samples. GPx3 activity and concentrations of triiodothyronine (T3), thyroxin (T4), and thyroid-stimulating hormone (TSH) were determined in blood plasma samples. The activity of GPx3 was determined immediately after obtaining blood plasma samples by centrifugation for 20 min at 1000 × g. The remaining blood plasma was stored at – 20°C until analyeses.

After seven weeks of the experimental period, the remaining individuals from each group were subjected to the same procedure.

The Ethical Committee of the Faculty of Veterinary Medicine, University of Belgrade, approved animal use following the National Regulation on Animal Welfare.

The selenium status of the experimental animals has been estimated using the following parameters: blood selenium concentration, GPx1 and GPx3 activities in whole blood and blood plasma, respectively.

Blood selenium concentration was measured using the hydride technique on an atomic absorption spectrophotometer (Thermo electron Solar AA, Series 4) with a hydride module and electrical heating of quartz cuvettes in an EC 90 furnace. Quality control was performed using the referent material BCR 185 (IRMM, Belgium). The obtained values in the replicate were within the range of the certified values.

Glutathione peroxidase activity was measured in whole blood (GPx1) and blood plasma samples (GPx3) using a coupled test as described by Günzler et al. and modified by Sankari [14,15]. All chemicals were obtained from Sigma Aldrich. Blood samples were hemolysed using Drabkin's reagent (1.6 mM KCN, 1.2 mM $K_2Fe(CN)_6$ and 0.023 M $NaHCO_3$). The final concentrations of the reagents used were 100 mM phosphate buffer (pH 7.4), 4 mM EDTA, 6 mM GSH, 0.375 IU/mL GR, 0.3 mM NADPH, and 1.575 mM TBH. The decrease in NADPH concentration was measured for 3 min at 366 nm using a Cecil Ce2021 spectrophotometer with a Peltier thermostat unit. The activity of GPx1 and GPx3 were expressed in microkatals per liter (μkat/L).

Concentrations of T3 and T4 were measured using commercial RIA kits (INEP, Zemun, Serbia). The concentration of TSH was measured using RIA kits (MP Biomedicals, Belgium). The radioactivity of the sediment was measured with a gamma scintillation counter (CompuGamma LKB, Belgium).

Statistical analyses were conducted using MS Excel 2007 and Graph Pad Prism 5 statistical software packages. To evaluate the individual or combined effect of selenium and propylthiouracil on the parameters, we used Excel two-way ANOVA. All results were expressed as mean ± SD for homogeneous data sets or medians for heterogeneous data. The significance of the differences between average values was evaluated using one-way ANOVA Tukey's test or Kruskal – Wallis test depending

on data homogeneity. Results were deemed as statistically significant for $p<0.05$. Correlations between selected parameters were tested by linear regression analysis.

The values of some parameters were not taken for statistical processing because they were inadequate (e.g. GPx 3 could not be determined from hemolyzed samples). Some of the analyzes could not be performed due to an insufficient amount of sample, thus the number of animals included in the experiment and the number of analyzed samples differ.

RESULTS

After three weeks of treatment, the activity of GPx1 and GPx3 was affected by selenium, and a joint effect of selenium and PTU was also determined. PTU administration did not affect the blood selenium concentration in selenium-deficient and adequate individuals during that time (Table 1.).

Table 1. Results (p value) of two-way ANOVA – influence of selenium or/and PTU on Se blood level, GPx1 and GPx3 activity and T4, T3 and TSH level after three weeks of treatment

	Se	GPx1	GPx3	T4	T3	TSH
Selenium	<0.001	<0.001	<0.001	>0.05	>0.05	>0.05
PTU	>0.05	>0.05	<0.05	<0.001	<0.001	<0.001
Interaction (Se x PTU)	>0.05	<0.01	<0.05	>0.05	>0.05	>0.05

Selenium-deficient animals (Se-) manifested significantly lower levels of blood selenium concentration ($p<0.001$), GPx1 ($p<0.001$ in PTU untreated rats; $p<0.01$ in PTU treated rats), and GPx3activities ($p<0.01$ in PTU untreated rats; $p<0.001$ in PTU treated rats) compared to control (Table 2.). In the selenium-deficient group treated with PTU (Se – PTU+), GPx1 activity was twice as high as the selenium-deficient group not treated with PTU (Se – PTU-) and it was statistical significant ($p<0.05$).

As expected, three weeks of treatment with PTU caused significantly lower levels of T4 and T3 compared to control. Low thyroid hormone concentrations were accompanied by high plasma TSH levels in PTU+ individuals (Table 2.).

After seven weeks of treatment, the activity of GPx1 and GPx3 was affected by selenium, and the level of thyroid hormones was affected by the PTU administration. The joint effect of selenium and PTU on blood selenium level, GPx3 activity, and thyroid hormones level was also determined (Table 3).

Table 2. Selenium and thyroid hormones status of rats after three weeks of treatment.

	Selenium adequate (Se+)		**Selenium deficient (Se-)**	
	Control (PTU$^-$)	**PTU $^+$**	**PTU $^-$**	**PTU $^+$**
Se (µg/L)	435±116 (n=12)	*352 (271-483)* (n=12)	61.20±11.70 ^{c} (n=14)	66.90±12.10 ^{c} (n=9)
GPx1(µkat/L)	166±43 (n=12)	145±41 (n=12)	*58.40 ^{c} (44.70-66.50)* (n=14)	*91.00 $^{b\,a}$ (69.20-137.20)* (n=12)
GPx3 (µkat/L)	60.50±15.20 (n=14)	80.00±22.00 ^{a} (n=15)	*30.70 ^{b} (24.60-47.10)* (n=15)	*37.00 ^{c} (25.10-46.10)* (n=13)
	Selenium adequate (Se+)		**Selenium deficient (Se-)**	
	Control (PTU$^-$)	**PTU $^+$**	**PTU $^-$**	**PTU $^+$**
T4 (nmol/L)	89.60±18.60 (n=14)	30.20±7.00 ^{c} (n=14)	90.40±14.10 (n=15)	*18.60 $^{c\,\#}$ (11.70-28.10)* (n=15)
T3 (nmol/L)	2.27±0.26 (n=14)	*1.16 ^{c} (0.62-1.58)* (n=15)	2.05±0.30 (n=13)	*1.49 ^{c} (0.79-1.77)* (n=15)
TSH (ng/L)	*4.17 (2.84-8.76)* (n=11)	80.30±12.80 ^{c} (n=11)	*5.11 (2.72-8.52)* (n=12)	84.20±13.60 $^{c\,\#}$ (n=12)

mean ± SD and *medians (1. and 3. quartile)*
(^{a})-p<0.05, (^{b})-p<0.01, (^{c})-p<0.001 (compare to control selenium adequate group);
($^\#$)-p<0.01 between Se – groups
($^\alpha$) – p<0.05 between Se – groups

Table 3. Results (p value) of two-way ANOVA – influence of selenium or/and PTU on Se blood level, GPx1 and GPx3 activity and T4, T3 and TSH level after *seven weeks of treatment*

`	**Se**	**GPx1**	**GPx3**	**T4**	**T3**	**TSH**
Selenium	<0.001	<0.001	<0.001	>0.05	>0.05	<0.001
PTU	<0.05	>0.05	<0.05	<0.001	<0.001	<0.001
Interaction (Se x PTU)	<0.05	>0.05	<0.01	<0.001	<0.001	<0.001

Blood selenium concentration of the Se+PTU+ group was significantly lower ($p<0.05$) compared to the control group and in selenium deficient individuals ($p<0.001$) (Table 4). GPx1 and GPx3 activities in selenium deficient rats were significantly lower compared to control group ($p<0.001$). Selenium-deficient rats treated with PTU had significantly lower T4 levels compared to the control group and the group of selenium-adequate PTU-treated rats ($p<0.001$).

Table 4. Selenium and thyroid hormones status of rats after seven weeks of treatment.

	Selenium adequate		**Selenium deficient**	
	Control (PTU$^-$)	**PTU $^+$**	**PTU $^-$**	**PTU $^+$**
Se (µg/L)	504±142 (n=13)	*355* [a] *(209-453)* (n=10)	*72.00* [c] *(57.50-74.70)* (n=12)	*89.00* [c] *(56.00-107.00)* (n=11)
GPx1(µkat/L)	*303 (230-389)* (n=12)	380±109 (n=9)	83.10±19.10 [c] (n=13)	*89.30* [c] *(63.80-115.50)* (n=9)
GPx3 (µkat/L)	106±32 (n=15)	102±24 (n=16)	25.30±4.20 [c] (n=16)	49.20±7.20 [c #] (n=15)
	Selenium adequate		**Selenium deficient**	
	Control (PTU$^-$)	**PTU $^+$**	**PTU $^-$**	**PTU $^+$**
T4 (nmol/L)	73.90±18.60 (n=15)	*23.70* [c] *(14.90-30.90)* (n=16)	89.70±16.60 [a] (n=16)	*2.96* [c] *(2.05-5.70)* (n=15)
T3 (nmol/L)	1.74±0.18 (n=15)	1.92±0.16[b] (n=16)	2.12±0.26[c] (n=16)	*1.43* [a] *(1.05-1.67)* (n=15)
TSH (ng/L)	8.64 (3.98-9.35) (n=11)	73.90±20.28 [c] (n=11)	8.32±1.60 (n=9)	95.66±10.43 [c] (n=10)

mean ± SD and *medians*
([a])-$p<0.05$, ([b])-$p<0.01$, ([c])-$p<0.001$ (compared to control selenium adequate group);
([#])-$p<0.01$ between Se – groups

Apart from the expected correlation found between the blood Se concentration and GPx1 ($y=0.5416x+66.554$, $R^2=0.6259$, $p<0.01$) and GPx3 ($y=0.1437x+31.458$, $R^2=0.6034$, $p<0.01$), it is interesting to point out that there were significant negative correlations in selenium deficient animals, between T3 concentration and GPx1 activity after three weeks and between T3 concentration and GPx3 activity after seven weeks in the experiment (Figure 1a and 1b).

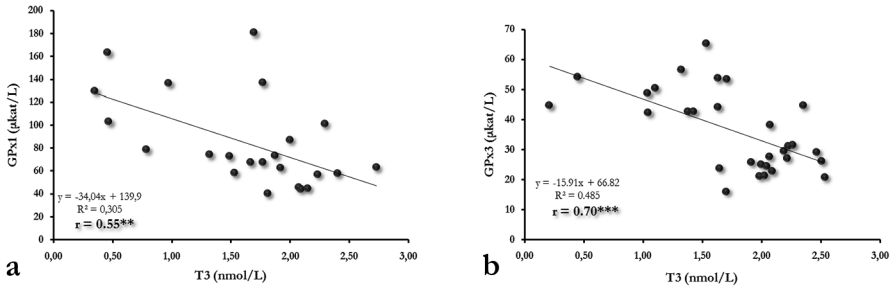


Figure 1. a) Negative correlation between T3 concentration and GPx1 activity of selenium deficient rats after three weeks of treatment. **b)** Negative correlation between T3 concentration and GPx3 activity of selenium deficient rats after seven weeks of treatment.

DISCUSSION

Propylthiouracil (PTU) was used to elicit the inhibitory effect on the thyroid status of selenium-deficient and selenium-adequate juvenile rats. PTU is a thioamide compound that exhibits its effect in two ways: a) it inhibits thyroid peroxidase which oxidizes I^{-1} to I^{0} thus assisting its addition to tyrosine residues of thyroglobuline; b) it inhibits the activity of iodothyronine deiodinase 1 (ID1), the enzyme that converts T4 to T3, but also inactivates T4 converting it to rT3 and T2 [16,17]. Veronikis et al. [18] stated that inhibitory PTU doses range from 0.01-0.10% in drinking water. Therefore, we deemed the dose of 0.015% was sufficient to produce hypothyreosis. After three weeks of treatment, a significantly lower concentration of T4 has been recorded in rats treated with PTU. After seven weeks, the decrease in T4 concentration was even more pronounced, especially in the selenium-deficient group treated with PTU. Lower T4 values and selenium-deficient individuals treated with PTU were also recorded by other authors [19,20]. Beckett et al. [21] consider that the reduction of the amount of iodine in the thyroid and a lower T4 concentration during selenium deficiency is a form of defense mechanism. Namely, if thyroid hormone production was maintained, the consequent output of peroxides could overrun the protective capacity of selenium-dependent glutathione peroxidase (GPx), leading to local tissue damage. However, it is unknown in which way selenium deficiency could lead to a decrease of iodine in the thyroid tissue since no selenoenzyme is known to participate in iodine transport and thyroxine synthesis [4]. On the other hand, selenium deficiency alone caused the increase of blood T4 after seven weeks, probably due to diminished extra thyroid conversion of T4 and T3 due to a decrease in ID1 activity [22].

After three weeks, the T3 level in all PTU-treated rats was statistically lower than the control probably because of ID1 inhibition and reduced T4 to T3 conversion [7,8]. After seven weeks, T3 concentration in the selenium-adequate group treated with PTU has recovered to physiological limits. Similar results were recorded by Hood et al. [23] and Li Sui and Gilbert [24] and it could be the consequence of compensatory mechanisms, one of them being a manifold increase in ID2 activity [25]. In selenium-

deficient rats treated with PTU in which we recorded extremely low T4 concentrations, T3 level did not recover. The reason for this is that in hypothyroid rats, ID1 activity can be reduced up to 50%, which is additionally augmented by selenium deficiency. Even though ID2 activity increases in hypothyroidism, this is insufficient to compensate for the T3 production in selenium-deficient animals.

As expected, the TSH level in PTU-treated rats steadily increased above physiological limits after three and seven weeks. Selenium status didn't have any apparent effect on plasma TSH concentrations.

The selenium status of juvenile rats was assessed by measuring blood selenium concentration and activities of enzymes glutathione peroxidases 1 and 3 (GPx1 and GPx3). GPx are considered excellent biomarkers of selenium status since there is a high correlation between their activities and selenium availability in the diet [26]. Minimum food selenium concentration has been established using these biomarkers at 0.08 mg/kg. Therefore, the concentration of 0.30 mg/kg in our experiment provided the full activity of selenoenzymes in selenium-adequate rats (control group). Selenium deficient groups (0.03 mg Se/kg feed) expressed low blood selenium concentration and low GPx1 and GPx2 activities, as expected.

Blood selenium concentration in PTU-treated selenium-adequate animals was significantly lower after seven weeks. There is no explanation in the available literature on how PTU could affect selenium levels. We speculate that through thyroid hormones, PTU could indirectly affect selenium metabolism (resorption, incorporation into proteins or excretion). In hyperthyroid patients, Özdem et al. [27] recorded higher blood selenium concentrations and GPx activity, explaining the effect due to the increased oxidative stress in hyperthyroid individuals. In hypothyroidism caused by PTU, less intensive oxidative stress could have a *de facto* opposite effect.

Glutathione peroxidase 1 has a unique way in which its expression is regulated. The activity of this selenoenzyme is very highly dependent on the available selenium. In selenium-deficient animals, mRNA content and GPx1 activity decrease by over 90% [28,29]. Weiss and Sunde [30] discovered that selenium influences the stability of GPx1, mRNA, and in case of its deficiency, mRNA is degraded. Two authors propose the existence of a selenium-dependent "switch" that causes mRNA decay via a specific STOP codon (nonsense-mediated decay). This situation does not occur with GPx4 mRNA. Observing the efficiency of selenium incorporation into the selenoprotein, they revealed that it increases 17 – to 24-fold in selenium-adequate individuals, accounting for significantly higher GPx1 activity than selenium-deficient animals.

The increase of food selenium content above 0.1 mg/kg ceases to affect mRNA synthesis and GPx1 activity, it can be assumed that in our experiment, the dose of 0.30 mg/kg provided for the entire activity of GPx1 activity in the blood of juvenile rats [31].

Blood GPx1 activity in selenium-adequate rats after three weeks was 166±43 μkat/L, and after seven weeks, it almost doubled to 319±144 μkat/L. In selenium-deficient animals, GPx1 activity was 59.30±19.30 μkat/L, 64% lower compared to the control, and after seven weeks, it was 83.10±19.10 μkat/L, 74% lower than the control.

In PTU-treated rats, GPx1 activity was 145±41 μkat/L in the selenium-adequate group after three weeks and did not statistically differ from control (PTU-). On the other hand, in PTU-treated selenium-deficient rats, GPx1 activity was 105±43 μkat/L, significantly higher compared to the corresponding PTU – group (59.30±19.30 μkat/L). After seven weeks, this phenomenon couldn't be seen for GPx1, but it was recorded for GPx3. Again, the enzyme activity was almost double in the PTU-treated compared to the PTU – group.

We could not find a record of this phenomenon in the available literature. In the aforementioned experimental groups, there was severe hypothyreosis, combined with severe selenium deficiency, but also a significant negative correlation between both GPx1 and GPx3 activities and T3 concentrations after 3 and 7 weeks (Figure 1a and 1b). There are strong indications of an existing hierarchy in the synthesis of selenoenzymes/selenoproteins, although the underlying mechanisms are unclear [32]. Therefore, based on our results, we can hypothesize that thyroid hormones, namely T3, could have a particular suppressive effect on the synthesis of some selenoproteins. In severe PTU-induced hypothyreosis leading to a considerable decrease of T3 levels, this suppression could be relieved, and selenium can be directed to GPx production. Whether this effect can have a biological/medical significance should be the subject of further research.

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Author's contributions

MS wrote the manuscript, laboratory analyses, data analyses, VO laboratory analyses, draft sections of the manuscript, prepared manuscript for submission, corresponding author, KD laboratory analyses, blood sampling, data analysis, MD blood sampling and preparation, VĐS hormones laboratory analysis, GD statistical data analysis, JIB conceptualization, design of the study, project administration. All authors have read and approved the manuscript.

Competing interests

The authors declare that they have no competing interests.

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EFEKTI KOMBINOVANOG HIPOTIROIDIZMA I DEFICITA SELENA NA AKTIVNOST SELENOENZIMA GLUTATION PEROKSIDAZE KOD PACOVA

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U ovom radu prikazani su efekti davanja propiltiouracila (PTU) i ishrane deficitne selenom na status selena i štitne žlezde muških Wistar pacova. Pacovi (n =128) su podeljeni u četiri grupe: (1) kontrolna grupa – selen-adekvatni pacovi kojima je davana hrana sa dodatih 0,334 mg Na selenita/kg i obična voda za piće (Se+PTU-); (2) kojima je davana hrana sa dodatih 0,334 mg Na selenita/kg i voda za piće sa 150 mg/L propiltiouracila, (Se+PTU+); (3) pacovi kojima je davana selen-deficitna hrana koja sadrži 0,031 mg Na selenit/kg i obična voda za piće (Se-PTU-); (4) pacovi kojima je davana selen-deficitna hrana koja sadrži 0,031 mg Na selenit/kg i voda za piće sa 150 mg/L propiltiouracila (Se-PTU+). Posle tri i sedam nedelja tretmana, sve Se – životinje su imale značajno nižu koncentraciju Se i aktivnosti GPx1 i GPx3 u punoj krvi. PTU je izazvao značajno smanjenje koncentracije T4 i T3 u krvnoj plazmi nakon tronedeljnog tretmana u obe PTU+ grupe. Štaviše, posle sedam nedelja, nivo T3 je bio blizu donje granice detekcije kod Se – životinja. Nakon tri i sedam nedelja tretmana uočena je negativna korelacija između aktivnosti GPx i koncentracije T3. Ovo bi moglo da ukaže na postojanje inhibitornog uticaja hormona štitne žlezde na ekspresiju i/ili aktivnosti GPx enzima u odnosu na raspoloživi Se u uslovima koje je izazvalo sistemsko smanjenje koncentracije T4. Ovaj efekat je bio posebno izražen kod Se-deficitnih životinja.