

# Potassium iodide changes the levels of thyroid hormones in goitrogenic rats on selenium deficient diet

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## Abstract

**OBJECTIVE:** A possible link was proposed between selenium [Se(-)], iodine deficiency and thyroid pathology. The aim of the study was to examine changes in FT<sub>3</sub> and FT<sub>4</sub> concentrations, weights of the thyroid glands and ioduria after potassium iodide (KI) in normal and goitrogenic rats on Se(-) diet.

**METHODS:** Wistar rats in Group 1 received the standard diet. Other animals remained (3 months) either on a Se(-) diet alone [Groups 2–5] or supplemented with selenium [Se(+)] (Group 6–8). After 9 weeks, Groups 3, 4, 6, 7 received sodium perchlorate [I(-); 1 month]. KI (1 mg/rat) was injected in Groups 4, 5, 7, 8. The animals were decapitated 3 days after the injections.

**RESULTS:** FT<sub>4</sub> was higher in serum of Se(-) rats than in that of Se(+). The differences of FT<sub>3</sub> were not statistically significant. In I(-) Groups, the levels of FT<sub>3</sub> and FT<sub>4</sub> were very low. KI increased both thyroid hormones in I(-) rats but the effect was especially pronounced for FT<sub>3</sub>. KI decreased the weights of the glands, enlarged in the I(-) animals, both on Se(-) and Se(+) diet. Urine iodide concentrations were lower in Se(-) animals; KI increased ioduria.

**CONCLUSIONS:** These data demonstrate that selenium and iodine deficiencies may play an essential role in thyroid hormone metabolism.

## Introduction

It has been shown that adequate amounts of both iodine and selenium are required for the optimal metabolism of thyroid hormones [29]. Thyroxine (T<sub>4</sub>) is produced by the thyroid but has a limited biological activity. Triiodothyronine (T<sub>3</sub>), an active hormone, is produced by deiodination of T<sub>4</sub> in

peripheral tissues. A low iodide excess to the thyroid gland dramatically decreases the production of thyroid hormones [8]. Selenium is an integral component of the family of glutathione peroxidase enzymes (GSH-Px) and of the three types of iodothyronine deiodinases [1,3,7,12,19,20]. The

deiodinating enzyme, which produces most of the circulating  $T_3$ , type I deiodinase (5'D-I), is a selenoenzyme, especially active in the liver, the kidney and the thyroid. A possible link between selenium deficiency and thyroid pathology was proposed [13,28,32,48].

It has been suggested that selenium deficiency [Se(-)] could additionally influence the pathophysiology of endemic myxoedematous cretinism in patients, inhabiting iodine deficient [I(-)] areas [16]. Selenium deficiency decreases GSH-Px activity, which detoxifies hydrogen peroxide ( $H_2O_2$ ), and also catalyses lipid peroxidation reduction. It has been proposed that an excess of  $H_2O_2$  in a stimulated gland and a lack of  $H_2O_2$ -detoxifying enzyme could contribute to an involution of the gland, as observed during first years of this disease [27]. Additionally, it has been shown in animal experiments that Se(-) enhances protein iodination in the thyroid gland and inhibits 5'D-I, resulting, in both cases, in increased circulating serum  $T_4$  concentrations [9,10,34].

The effect of combined Se(-) and I(-) has been examined in different fluids and tissues, such, e.g., plasma [6,26,38,], liver [36,42], central nervous system [5,8,35], brown adipose tissue [35] and the thyroid gland [5,28,36]. It has been reported that combined Se(-) and I(-) significantly decreased thyroidal  $T_3$  and thyroidal and plasma  $T_4$  but increased plasma TSH concentrations and thyroid weight, when compared to respective values in the rats with only I(-) [6].

The aim of the study was to examine changes in concentrations of thyroid hormones ( $FT_3$  and  $FT_4$ ), ioduria and weights of the thyroid gland after potassium iodide (KI) in normal and goitrogenic rats on Se(-) diet.

## Materials and Methods

The experiment was performed in conformity with methods of the Local Bioethical Commission for Experiments on Animals in Lodz (LB99/2002).

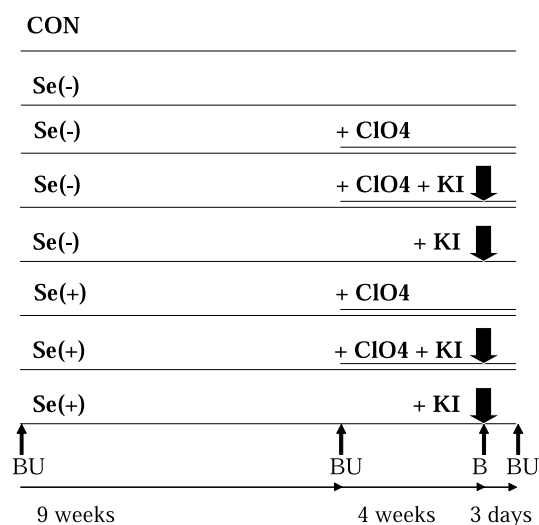
Male Wistar rats were used in the study, weighing approximately 180 g each at the onset of the study. The number of animals per cage was 8. They were housed in a light-controlled (light was turned on at 6.0 a.m. and turned off at 6.0 p.m.) and temperature-controlled room and, having a free access to food and water.

The control group of rats was on the standard diet with normal concentrations of iodine and selenium (Group 1; Motycz, Poland – 3.56  $\mu\text{g}$  Se/day/rat; 2  $\mu\text{g}$  I/day/rat). The animals were provided with either selenium deficient [Se(-)] diet for 13 weeks (Groups 2–5) or with Se(-) diet, supplemented with selenium [Groups 6–8; Se(+)]. Se(-) diet consists of natural, fresh low-selenium products (milk products, cereals, vegetables, corn oil) and selenium intake was 1.026  $\mu\text{g}$  Se/day/per rat. In the groups on Se(+), the animals received 2  $\mu\text{g}$  Se/day in drinking water + 1.026  $\mu\text{g}$  in Se(-) diet (an average 3.026  $\mu\text{g}$  Se/day/per rat).

After 9 weeks, goiters were induced by giving 1% sodium perchlorate ( $\text{NaClO}_4$ ) in drinking water for 4

weeks (Group 3, 4, 6, 7; I(-) – goitrogenic rats). Potassium iodide (KI) was i.p. injected in a single dose of 1 mg/ml/rat in the following groups: Groups 4, 5, 7 and 8. The animals were decapitated 3 days after the injections under aether anesthesia. The lobes of the thyroid glands were removed and weighed.

Blood samples for thyroid hormones measurements were collected at the beginning of the study, after 9 weeks (at time point 1 – TP1), before KI injection (at time point 2 – TP2) and at the end of the experiment (time point 3 – TP3). At the same time points, the animals were weighed and urine was collected to measure the loss of iodide (Scheme of experiment, below).



Blood samples were collected into heparinised microtubes, free of trace elements. After centrifugation, plasma was collected and red blood cells (RBC) were washed in 0.9% NaCl and centrifuged three times. Plasma and RBC samples were stored at  $-80^\circ\text{C}$  for 2 weeks maximum until biochemical analysis. The GSH-Px activities of RBC lysates and plasma were assayed by the coupled method of Paglia nad Valentine [37] with t-butyl hydroperoxide as substrate. Enzymatic activities were expressed as units (U) per gram of hemoglobin or units per ml of plasma. One unit of enzyme was defined as 1  $\mu\text{mol}$  NADPH oxidized per minute per gram of Hb (U/g Hb) or per ml of plasma (U/ml). The intra-assay coefficient of variation for both materials (six to eight analysis) was below 3%.

Iodide determination was performed at the Department of Thyroidology, Medical University in Lodz, by a modified catalytic method, based on Sandell and Kolthoff's original design [39].

For the electrochemiluminescence immunoassay of  $FT_3$  and  $FT_4$  concentrations kits from Roche Elecsys 1010/2010 were used.

A one-way analysis of variance (ANOVA) and the Newman-Keuls' test were applied to evaluate statistical significance. All the calculations were performed with the use of the Statistica'99 computer software.

## Results

At the beginning of the experiment, no differences were observed between particular groups, regarding the concentrations of thyroid hormones, GSH-Px activity, iodine loss in urine and body weight of animals (data not shown).

As expected, Se(-) diet decreased, by more than 50%, the activity of GSH-Px compared to the normal range, both, in erythrocytes and in plasma. Se supplementation increased the activity of GSH-Px, both in erythrocytes and in plasma (Fig. 1).

At time point 1, the difference in thyroid hormone concentration was not statistically significant between the control group and this on Se(-) diet but there was a tendency to increase the concentration of T<sub>4</sub> in Se(-), compared to respective values in the Se(+) (Fig. 2)

Serum concentrations of FT<sub>4</sub> were, at TP 2 and TP3 lower in the Se(-) animals than those in the animals on the standard diet but higher than those in the Se(+) animals. The differences of FT<sub>3</sub> were not statistically significant. (Figs. 3, 4).

Perchlorate is an antithyroidal agent, inhibiting iodide trapping in the thyroid gland. After its administration in

drinking water, the levels of FT<sub>3</sub> and FT<sub>4</sub> were very low, both in the animals on Se(-) diet and on Se(+) diet (Fig. 3). Potassium iodide increased both thyroid hormones but the effect was especially pronounced for FT<sub>3</sub> (Fig. 4).

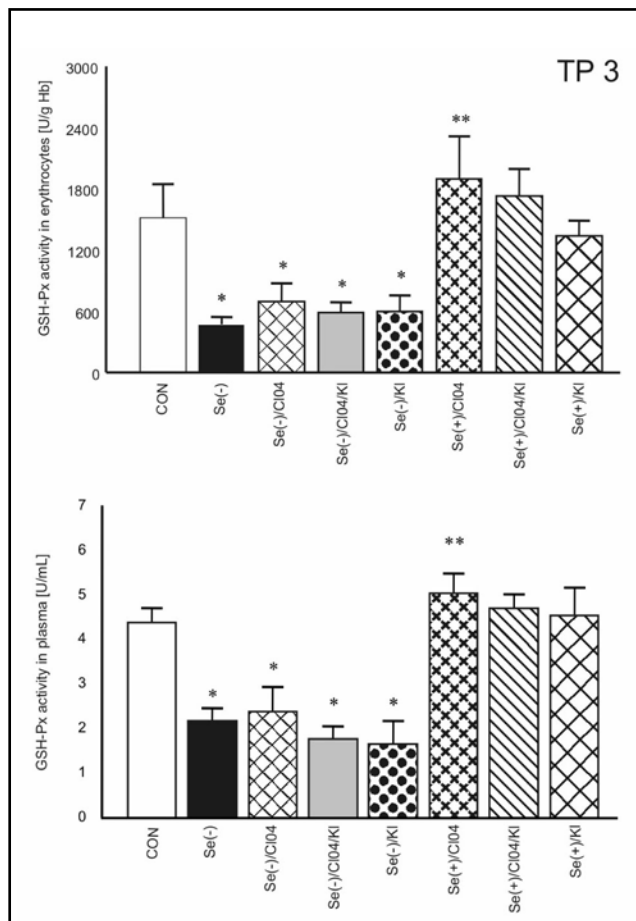
Urine iodide concentrations were lower both in Se(-) and Se(+) animals and, as expected, KI, given in drinking water, increased ioduria (Fig. 5).

The weights of the thyroid lobes were significantly higher ( $p < 0.05$ ) in the goitrogenic rats [I(-)] and tended to be higher in those on Se(-) diet. Potassium iodide decreased the weights of the glands in the I(-) animals on both Se(-) and Se(+) diet (Fig. 6)

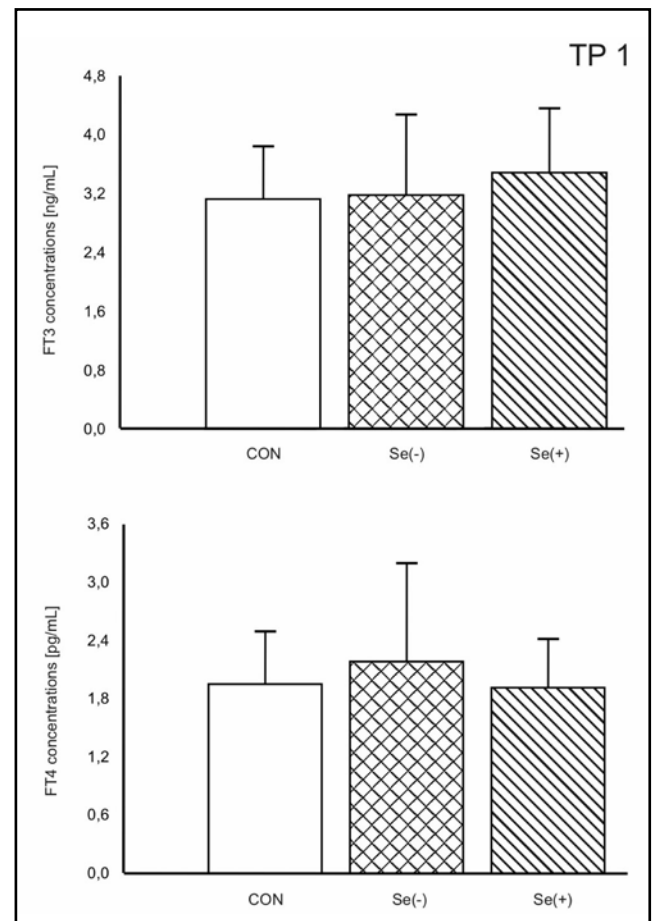
Body weights of the animals tended to be lower in the animals on Se(-), when compared to those in the Se(+) diet animals (Fig. 7).

## Discussion

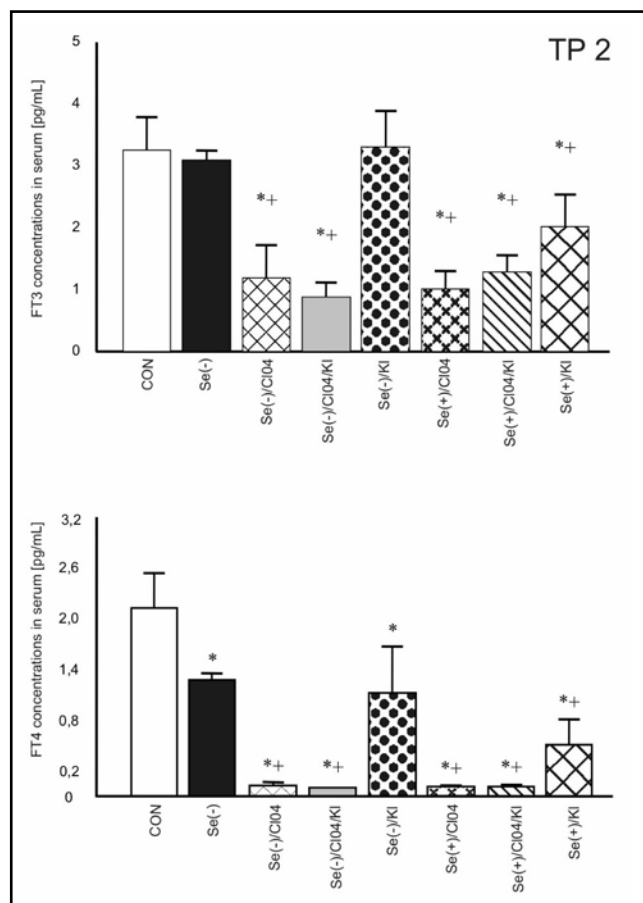
In the presented experiment, the rats were provided with Se(-) diet, containing 0.0128 mg Se/kg for 13 weeks. As expected, Se(-) diet decreased the activity of GSH-Px, both in plasma and in erythrocytes more than by 50%. Se supplementation normalized the activity of GSH-Px,



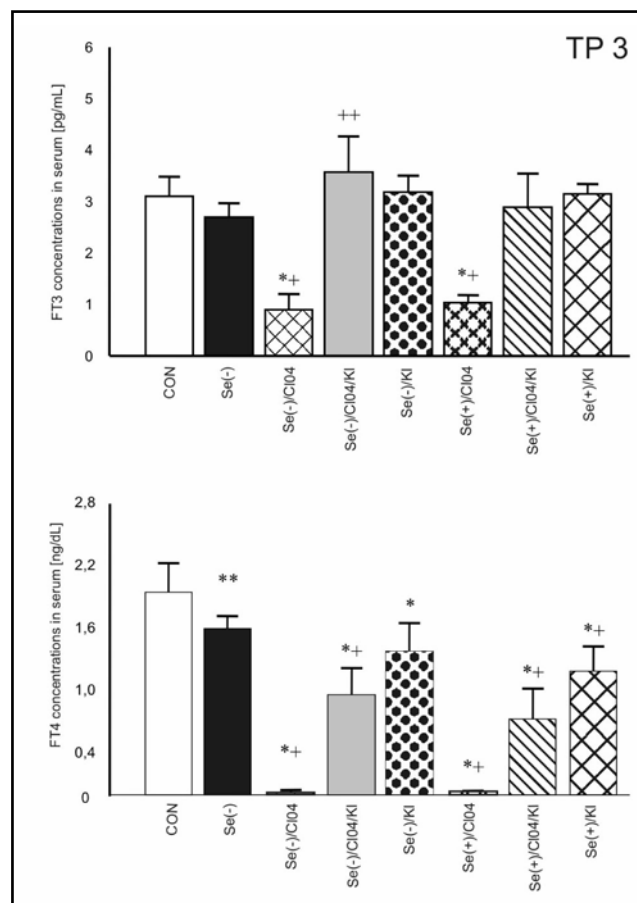
**Fig. 1.** The activity of glutathione peroxidase (GSH-Px) in erythrocytes and in plasma at time point 3 (TP3). Mean values  $\pm$  SEM. Statistical significance: \*\*  $p < 0.05$ ; \*  $p < 0.005$  vs. Controls.



**Fig. 2.** Concentrations of free thyroid hormones (FT3 and FT4) in serum at time point 1 (TP1). Mean values  $\pm$  SEM.



**Fig. 3.** Concentrations of free thyroid hormones (FT3 and FT4) in serum at time point 2 (TP2). Mean values  $\pm$  SEM. Statistical significance: \*  $p < 0.005$  vs. Controls; +  $p < 0.005$  vs. Se(-).



**Fig. 4.** Concentrations of free thyroid hormones (FT3 and FT4) in serum at time point 3 (TP3). Mean values  $\pm$  SEM. Statistical significance: \*  $p < 0.005$ ; \*\*  $p < 0.05$  vs. Controls; +  $p < 0.005$ ; ++  $p < 0.05$  vs. Se(-).

both in erythrocytes and in plasma. Those results support the findings obtained in previous studies. Ruz et al. [38] observed that plasma and erythrocyte GSH-Px activities were dramatically reduced in groups of rats on low selenium diet (selenium content lower than 0.05 mg/kg diet). Holz et al. [28] have shown that with low Se intake (0.05 mg/kg diet), liver, kidney and erythrocytes activity of GSH-Px was about 50% of that in the controls, whereas in the groups on high Se diet, the activity was greater than that in the kidneys and erythrocytes of the controls.

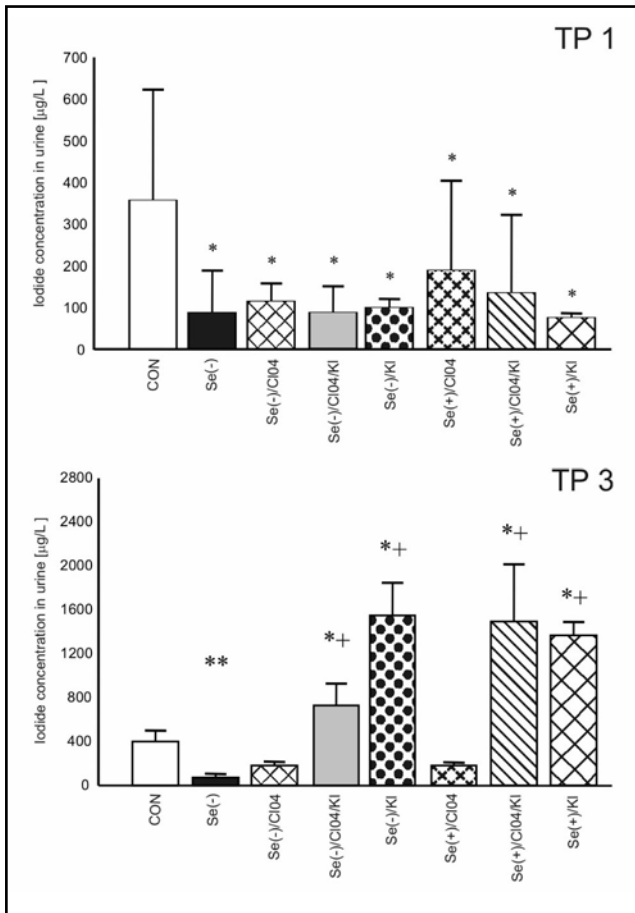
It was shown that 5'D-I in the liver and in the kidney was almost completely lost in Se(-), resulting in decreased T<sub>4</sub> deiodination and increased circulating T<sub>4</sub> levels. T<sub>3</sub> levels were only marginally decreased [6]. On the other hand, I(-) dramatically diminished serum T<sub>4</sub> and T<sub>3</sub> concentrations [8].

The results of the present experiment have shown that serum FT<sub>4</sub> concentrations were lower in the Se(-) animals than those in the animals on the standard diet but higher than those in the Se(+) diet at TP 2 and at the TP3. At the same time points, the differences in FT<sub>3</sub> concentration were not statistically significant. FT<sub>4</sub> concentrations were higher – but not statistically significant – in the animals,

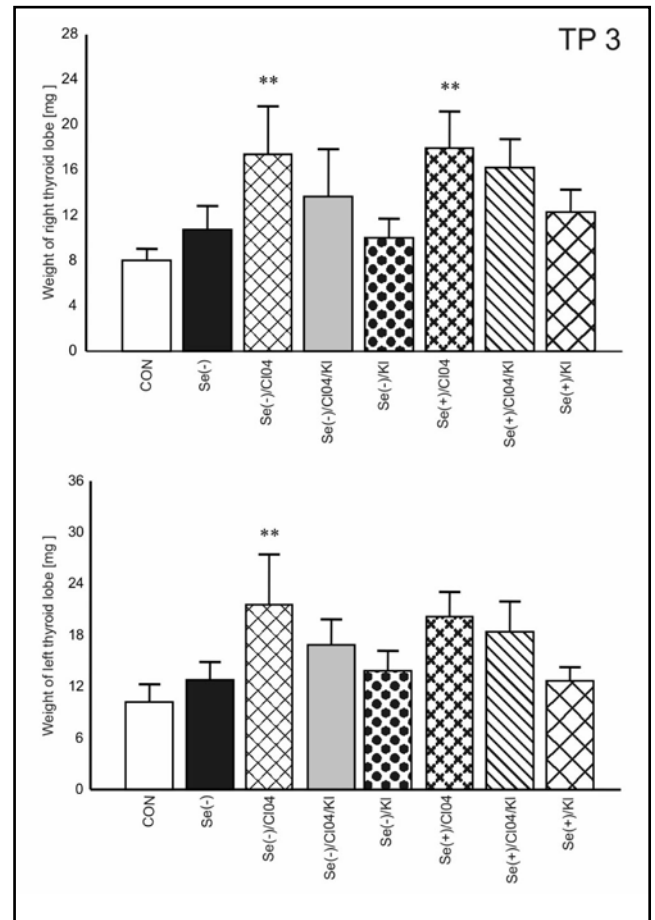
kept on Se(-) diet, compared to the values in the control and Se(+) rats at TP1.

The information, concerning the effects of Se(-) on thyroid hormone concentrations, are not consistent, e.g.; in plasma of kittens on low-Se diet, T<sub>4</sub> increased and T<sub>3</sub> decreased significantly [47]. In reports of other authors [22], Se levels in serum and in the liver, T<sub>3</sub> and T<sub>4</sub> in serum, GSH-Px levels in the liver, and 5'-DI activity in the liver, the aorta and the thyroid, were estimated after 1, 2, and 3 months of Se-deficient (0.02 ppm), Se-adequate (0.2 ppm), and Se-excessive (1 ppm) diet. All of those parameters, except 5'-DI, decreased significantly in Se(-) diet, as compared to the values in the groups with adequate concentrations of Se. Within the Se(-) group, as the Se deficiency progressed, all of the parameters decreased after 2 and 3 months, in comparison to month-1 data. A significant increase was observed in all the above parameters in the Se(+) group, when compared to the values in the group with adequate Se.

On the other hand, there are some data, showing that the concentrations of thyroid hormones depend on the rate of Se deficiency. Bates et al. [5] have shown that thyroid hormones economy and general health were successfully maintained over six generations of Se(-)



**Fig. 5.** Iodide concentrations in urine at time point 1 and 3 (TP1;TP3). Mean values  $\pm$  SEM. Statistical significance: \*  $p < 0.005$ ; \*\*  $p < 0.05$  vs. Controls; +  $p < 0.005$  vs. Se(-).



**Fig. 6.** The mass of right and left thyroid lobes. Mean values  $\pm$  SEM. Statistical significance: \*\*  $p < 0.05$  vs. Controls.

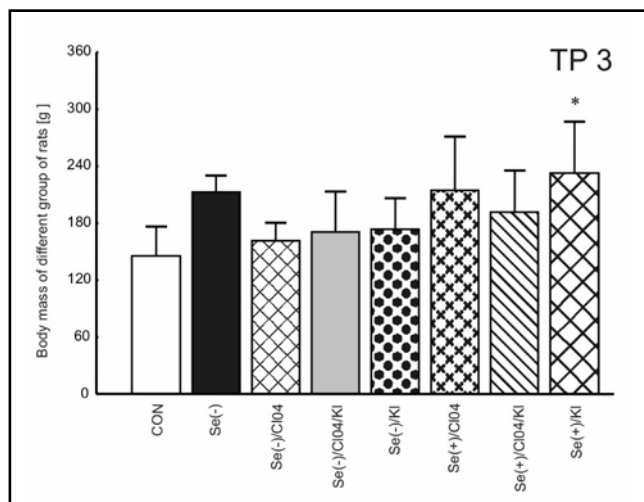
rats (0.005 mg Se/kg diet). In their report, the authors suggested, that only when Se levels were decreased by more than 80%, deiodinase activity decreased and those changes influenced thyroid hormone concentrations.

There are authors, who have presented data showing that Se(-) animals (0.038 mg Se/kg diet) had lower concentrations of total  $T_3$  and  $T_4$  than selenium-adequate Sprague-Dawley rats. But in that study, the concentration of FT $_4$  in serum was not affected by Se(-) [30]. The same research group has shown that serum  $T_3$  concentration and hepatic 5'D-I activity decreased in a group with Se(-), in contrast to animals fed with adequate selenium quantities (0.1, 0.3 mg/kg). There are same observations indicating that serum concentrations of  $T_4$  and FT $_4$  are not changed by various selenium intakes [24].

In the present study, in Se(-)+I(-) and Se(+)+I(-) groups, the concentrations of thyroid hormones were low. Those results support the ones of other authors, e.g.; it has been reported that combined Se(-) and I(-) significantly decreased thyroidal  $T_3$  and thyroidal and plasma  $T_4$  but increased plasma TSH concentrations and thyroid weights, compared to respective values in rats with I(-) only (6). In our experiment, KI increased the concentrations of FT $_3$  and FT $_4$ , both in Se(-) and

Se(+) rats but the effect was especially pronounced for FT $_3$ . Liu et al. [33] found that the levels of  $T_4$ , FT $_4$  and r $T_3$  increased also in an opposite condition i.e. in serum of I(-)-rats, supplemented with I or I + Se.

In the present study, sodium perchlorate was used for 1 month. Perchlorate is an antithyroidal agent, inhibiting iodide trapping, the synthesis of hormones in the thyroid gland and for that reason stimulating the goiter. Thyroid hormone concentrations significantly decreased in the animals on Se(-) and Se(+) diet, followed by perchloride induced I(-). Studies of other authors suggest that goitrogenic agents, like propylthiouracil (PTU) and Se(-) diet, have similar effects on  $T_3$  neogenesis [45]. It was observed that Se(-) diet and PTU treatment decrease hepatic 5'D-I activity, which is considered to be an important regulator of serum  $T_3$  levels derived from the peripheral  $T_4$  to  $T_3$  conversion ( $T_3$  neogenesis). The effects of PTU treatment or of Se(-) on  $T_4$  and  $T_3$  kinetics were compared in thyroid-ablated rats infused with stable  $T_4$  to determine whether PTU treatment was a more potent inhibitor of  $T_3$  neogenesis than Se(-) and to compare the degree of  $T_3$  production suppression with the degree of 5'D-I suppression [45]. This effect of PTU was used in our previous paper [43]. Both, PTU and Se(-) did reduce



**Fig. 7.** The body mass at time point 3 (TP3). Mean values  $\pm$  SEM. Statistical significance: \*\*  $p < 0.05$  vs. Controls.

serum  $T_3$  concentrations by 29% and 25%, respectively and increased serum  $T_4$  concentrations by 36% and 32%, respectively [45]. In our study, a statistically insignificant increase of  $T_4$  on Se(-) was observed, compared to concentrations in the animals on Se(+) diet.

A decreased iodide loss in urine was observed in the animals on both Se(-) and Se(+). It was in agreement with the results of other authors [17, 15]. It was noted that Se(-) inhibited  $5^3D$ -I activity, diminished iodide loss by the kidney, thus involving thyroid hormone and iodine economy which, together with the possibly increased hormone synthesis in the thyroid gland, could reduce the significance of the I(-). The authors suggest that such mechanisms compensate the consequences of double Se(-) and I(-), especially in pregnant women [17, 15].

In the present study, it was shown that Se(-) diet could increase the weight of thyroid lobes in rats. It is in agreement with the observations of others. In an experimental model, rats on a combined Se(-) and I(-) diet had significantly increased thyroid weights, comparing with the rats on I(-) diet [6]. There are also the same observation in human. The authors from Turkey observed significant goiter problems in school children, probably due to I(-) and Se(-) in the examined area [4]. The results of another study seem to support the view that the risk of goiter development may be increased in highly I(-) children with lower enzymatic antioxidant and Se status [25]. Derumeaux et al. [21] suggested that selenium could protect against goiter. They observed an inverse relation between selenium status and thyroid volumes in women.

The results of the present study demonstrate that selenium and iodine deficiencies may play an essential role in thyroid hormone metabolism. It is important to clarify the effects of both Se(-) and I(-) on thyroid hormone metabolism and to find the optimal balance between the two microelements in diet. It has been suggested that Se(-) could further enhance the adverse effects of I(-);

the increased TSH and thyroid weights, as observed with I(-), were further increased by concurrent Se(-) [6,2]. On the other hand, there are some data suggesting that Se(-) has a moderating effect on the serum variables associated with I(-), in which, decreased  $T_4$ ,  $T_3$  levels and increased thyroid weights, observed in hypothyroid rats, were reversed by Se(-) [27]. The other important aspect is connected with iodine and selenium supplementation on the area with deficiency of both minerals. A hypothesis has been suggested that supplementation of humans with Se, when both I(-) and Se(-) are present, may cause a rapid increase in thyroidal GSH-Px, neutralizing the production of  $H_2O_2$  and thus decreasing thyroid hormone production to dangerously low levels [18]. The restoration of DI-I activity after Se supplementation would increase the iodination of  $T_4$  to  $T_3$  and of  $T_3$  to  $T_2$ , and an increased catabolism of thyroid hormones could result in iodine loss from the system, thus exacerbating hypothyroidism in rats [27,11,23]. There are some suggestions that, in combined I(-) and Se(-), selenium supplementation is not indicated without prior iodine supplementation [17,44]. But it is necessary to know that high iodine doses, given to rats with I(-) and Se(-) may produce greater thyroid tissue damage than high iodine doses given to rats previously I(-) only [16,14]. High iodine intake to Se(-) rats may promote thyroid tissue damage in result of low thyroidal GSH-Px activity during thyroid stimulation. A moderately low selenium intake normalized circulating  $T_4$  concentrations in the presence of I(-) [28]. In our laboratory, stimulation of lipid peroxidation has been shown in peripheral tissues of rats, caused by different doses of iodide and protective effects of some antioxidants were observed [41,40].

In summary, the data of our experiment demonstrate that even mild selenium and iodine deficiency may play an essential role in thyroid hormones metabolism. This information is especially important because Poland, till the 90ties, had been iodine deficient [32] and still, it is a territory of very low selenium concentrations, both in humans and in the environment [46].

## Acknowledgements

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