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Effects of Selenium and Tellurium on the Activity of Selenoenzymes Glutathione Peroxidase and Type I Iodothyronine Deiodinase, Trace Elements Thyroid Level, and Thyroid Hormone Status in Rats

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ABSTRACT

Tellurium (Te) and selenium (Se) belong chemically to the VIa group of elements. Se represents an essential element closely related to thyroid function. Te has growing application in industrial processes. Little is known about the Te biological activity, particularly with respect to potential chemical interactions with Se-containing components in the organism. In this study, female Wistar rats (body weight: 115–120 g) received sodium selenite pentahydrate (10 mg/L) or sodium tellurite (9.4 mg/L) in drinking water for 6 wk. Additional groups of rats received their combination with zinc sulfate heptahydrate (515 mg/L). The stimulation of 5′-DI-I

AU: Pls spell out DI-I

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activity due to selenite (to 158%, $p<0.01$) or tellurite treatment (to 197%, $p<0.01$) was seen; however, no effect on glutathione peroxidase was demonstrated in this experiment. An elevation of T4, T3, and rT3 serum levels was measured in the Se+Te-treated group; T4 and rT3 levels were elevated in the Te+Zn-treated group. Te accumulates in the thyroid gland and influences the zinc thyroid level. Te treatment alone and in combination with Se or Zn decreased the iodine thyroid concentration to 65–70% of the control value. Further studies are needed to clarify the nature and effects of these events.

Index Entries: Selenium; tellurium; glutathione peroxidase; iodothyronine 5′deiodinase; thyroid hormones; zinc; iodine; thyroid gland; rats.

INTRODUCTION

Selenium (Se) and tellurium (Te) belong chemically to the VIa group of elements and possess remarkably similar chemical properties. Se represents an essential element of fundamental importance to human health. It has important health effects related to immune response and cancer prevention. These protective effects of Se are linked to its presence in selenoenzymes such as glutathione peroxidases and thioredoxin reductases, known to play a role in carcinogen metabolism, the control of cell division, apoptosis induction, detoxification processes, and immune system functioning *(1–4)*. Together with iodine, Se is closely associated with thyroid function *(5–7)*. Selenoenzyme iodothyronin-5′-deiodinase (5′DI) controls the transformation of thyroxine (T_4) into the biologically active thyroid hormone triiodothyronine (T_3) *(8,9)*. Selenoenzyme glutathione peroxidase (GPx) protects cellular components from damage by oxygen radicals produced by the synthesis of thyroid hormones.

Tellurium compounds have growing application in industrial processes, especially in the manufacturing of semiconductors and other electronic components and thus represent a potential danger to human health *(10,11)*. Unlike Se, Te is not an essential micronutrient and demonstrates properties similar to those elements known to be toxic to humans *(12,13)*. On the other hand, some organotelluric compounds are studied regarding possible antioxidative and anticancer effects *(14–18)*.

Whereas the aspects relevant to Se involvement in thyroid function are well documented, no data have been available concerning the possible influence of Te relating to the thyroid. Nothing is also known about the interaction of Te with its neighboring element in the periodic table—iodine. Therefore, we have decided to investigate interaction of inorganic tellurite with hepatic selenoenzyme activities, Se and iodine thyroid content, and thyroid hormone status in experiments in rats. Because zinc (Zn) and Se are linked in defense against reactive oxygen species and support of immune response of the organism *(19,20)*, the effects of combined Te and Se administration with Zn has been be evaluated as well.

MATERIALS AND METHODS

Chemicals

All chemicals, unless indicated otherwise, were supplied by Sigma, (St. Louis, MO, USA) and were of analytical-grade purity.

Animals

Female Wistar rats (Charles River, Germany; body weight; 115–125 g) were housed in a temperature- and humidity-controlled room with a 12-h light/dark cycle and with free access to the standard diet (Altromin C1000G). After an adaptation period of 6 d, 50 animals were randomly assigned to 6 experimental groups of 7 animals each and a control group of 8 animals treated as follows:

I. Control: drinking water
II. Se: 10 mg $Na_2SeO_3 \cdot 5H_2O$/L drinking H_2O
III. Te: 9.4 mg Na_2TeO_3/L drinking H_2O
IV. Se + Te: 10 mg $Na_2SeO_3 \cdot 5H_2O$ and 9.4 mg Na_2TeO_3/L drinking H_2O
V. Zn: 515 mg $ZnSO_4 \cdot 7\ H_2O$/L drinking H_2O
VI. Se + Zn: 10 mg $Na_2SeO_3 \cdot 5H_2O$ and 515 mg $ZnSO_4 \cdot 7\ H_2O$/L drinking H_2O
VII. Te + Zn: 9.4 mg Na_2TeO_3 and 515 mg $ZnSO_4 \cdot 7\ H_2O$/L drinking H_2O

Water consumption was monitored daily and body weights were determined weekly. The concentrations of compounds used in this experiment were previously proven not to influence hepatic lipid peroxidation and glutathione level (data not shown). The concentrations of Te and Se are equimolar. The calculated dose of tellurite oral intake is 0.4 mg/kg body weight and represents the 1/50 LD_{50} dose of sodium tellurite *(21)*.

After a 6-wk of experimental period, the animals were sacrificed under ether anesthesia and blood, liver, and thyroid gland were collected for analyses. The experimental treatment protocol was approved by the local Animal Care and Use Committee. The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the US National Institute of Health.

Sample Preparation and Analytical Procedures

Glutathione Peroxidase and Iodothyronine-5′-deiodinase Assay

Glutathione peroxidase (GPx) activity was assayed in liver homogenates by a coupled test system *(22)*, in which glutathione reductase is employed for regeneration of GSH and butylhydroperoxide used as the acceptor substrate.

The decrease in NADPH concentration was registered photometrically at 340 nm. The GPx activity was expressed in micromoles of $NADP^+$ per minute per gram of tissue.

The activity of type I iodothyronine-5′-deiodinase (5′-DI-I) was quantified by the release of ^{125}I from ^{125}I-rT_3 in the liver microsomal fraction according to Leonard and Rosenberg *(23)*. The 5′-DI-I activity was expressed in picmoles per milligram per minute.

Thyroid Hormone Assay

Serum thyroxine (T_4) and serum triiodothyronine (T_3) concentration were determined by radioimmunoassay (Immunotech, Czech Republic). Serum reverse triiodothyronine (rT_3) concentration was measured using the radioimmunoassay kit provided by BIOCODE (Belgium).

Thyroid Selenium, Tellurium, Zinc, and Iodine Estimation

Digestion of thyroid glands was carried out in 30-mL Teflon vials (Savillex) using 2 mL of concentrated nitric acid (purris p.a.; Fluka Chemie, Switzerland), capped, and left overnight on a heating desk at 150°C. The content in the vials was almost evaporated and then diluted with 2% HNO_3. As an internal standard, 10 ppb of In (Astasol, Analytica Ltd., Czech Republic) was added. Iodine, Te, and Zn concentration in the thyroid were determined using inductively coupled plasma–mass spectrometry (PQ3, fy VG Elemental). The Se concentration was estimated by electrothermal atomic absorption spectrometry (SpectrAA FS 220; Varian Australia Ltd.). Digestion and analysis accuracy was checked by the measurement of the reference material (8414 Bovine Muscle Powder; NIST, Washington DC). The element contents are expressed in micrograms of the element measured per gram of wet tissue weight (μg/g wt w).

Statistical Analysis

The data in the tables and figures are presented as means ± SD values. The statistical significance of differences between experimental groups was determined by unpaired Student's *t*-test for each parameter separately after ascertaining the homogeneity of variances between treatment groups. The significance was set at $p<0.05$.

RESULTS

Body and Thyroid Weight

The growth curves were similar in all groups of animals supplemented with respective compounds in drinking water. At the end of the 6-wk experimental period, the weight of rats and the weight of the thyroid gland were lower in the Se, Te, Se+Te, and Te+Zn group in comparison

Table 1
Effect of Se, Te, and Zn Treatment on the Body and Thyroid Weight

Group	Body weight [g]	thyroid weight [mg]	Body /thyroid weight [%.10^3]
Control	255 ± 25	16.7 ± 3.8	6.6 ± 1.4
Se	215 ± 18 **	13.0 ± 2.2 *	6.1 ± 1.1
Te	209 ± 9 **	10.7 ± 1.3 **	5.3 ± 0.4
Se+Te	185 ± 13 **	10.6 ± 2.1 **	5.7 ± 1.0
Zn	246 ± 13	12.3 ± 4.2	5.5 ± 1.0
Se+Zn	229 ± 26	13.7 ± 2.2	6.0 ± 1.1
Te+Zn	210 ± 10 **	12.2 ± 1.5 *	5.8 ± 0.8

Note: Results are given as mean ± SD.
* $p<0.05$ versus control group.
** $p<0.01$ versus control group.

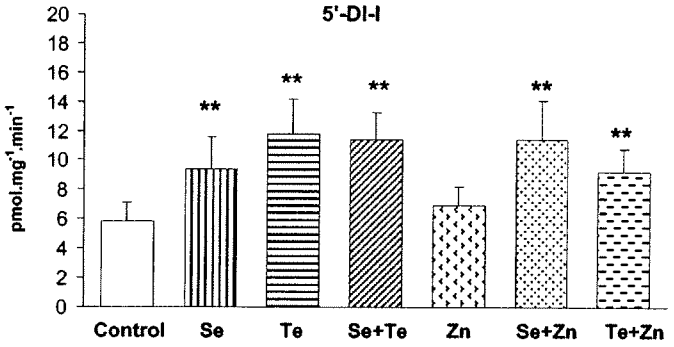

Fig. 1. The activity of type I 5′-DI-I in the liver microsomal fraction of rats after the treatment with sodium selenite, sodium telurite, or zinc sulfate for 6 wk. Results are given as mean ± SD. **$p<0.01$, significantly different from control group.

with the control group (Table 1). The ratio of thyroid gland to body weight of rats was not significantly different from the control value.

Activity of Selenoenzymes 5′-DI-I and GPx

A significant increase of 5′-deiodinase activity was estimated in all groups treated with sodium selenite, sodium tellurite, and their combination with zinc sulfate when compared to controls (Fig. 1). The 6-wk treatment with sodium selenite resulted in a 1.6-fold increase of type I 5′-deiodinase activity and the treatment with sodium tellurite resulted in a 2-fold increase of 5′-DI-I activity when compared to the control group. Similar effect was seen in all animals with combined treatment. Zn supplementation alone did not influence the 5′-DI activity.

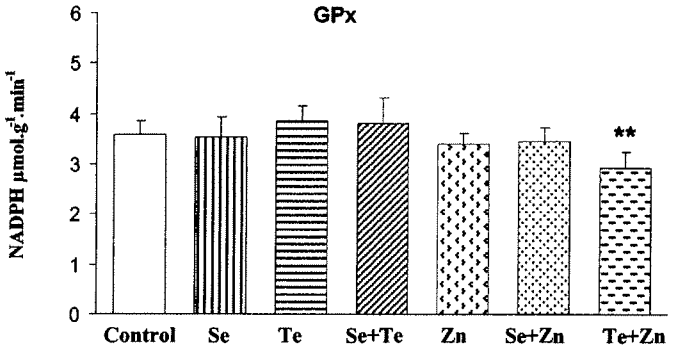

Fig. 2. Activity of GPx in the liver homogenate of rats after the treatment with sodium selenite, sodium telurite, or zinc sulfate for 6 wk. Results are given as mean ± SD. **$p<0.01$, significantly different from control group.

Table 2
Serum T_4, T_3 and rT_3 in Rats Treated with Sodium Selenite, Sodium Tellurite, or Zinc Sulfate

Group	T4 [nmol/l]	T3 [nmol/l]	rT3 [ng/dl]
Control	56.6 ± 8.0	0.75 ±0.15	176 ± 26
Se	56.8 ± 6.5	0.85 ±0.10	170 ± 21
Te	52.7 ± 7.5	0.98 ±0.30	161 ± 27
Se+Te	76.4 ±14.9 **	0.95 ±0.20 *	257 ± 49 **
Zn	63.6 ±12.3	0.76 ±0.14	205 ± 33
Se+Zn	71.0 ±12.7 *	0.89 ±0.23	232 ± 35 **
Te+Zn	65.0 ± 9.4	0.66 ±0.17	168 ± 13

Note: Results are given as mean ± SD.
* $p<0.05$ versus control group.
** $p<0.01$ versus control group.

The activity of GPx was not influenced with an exception of the Te+Zn group, in which a decrease in GPx activity was seen (Fig. 2).

Thyroid Hormones Level

The serum levels of T_4, T_3, and rT_3 were not influenced by the subchronic treatment with sodium selenite or sodium tellurite (Table 2). However, the combined treatment with sodium selenite and tellurite caused an elevation of T_4, T_3, and rT_3 and the combined treatment with sodium selenite and zinc sulfate resulted in an elevation of T_4 and rT_3 serum levels.

Trace Elements Thyroid Level

The 6-wk administration of sodium tellurite resulted in Te accumulation in the thyroid (Table 3). The thyroid tellurium concentration was higher

Table 3
Te, Se, Zn, and Iodine Concentration in the Thyroid Gland of Control and Treated Rats

Group	Te	Se	Zn	I
Control	<d.l.	0.21 ± 0.11	17.4 ± 2.8	446 ±108
Se	<d.l.	1.08 ± 0.40**	19.3 ± 1.5	455 ± 64
Te	0.78 ±0.08	0.34 ± 0.15	25.1 ± 6.2*	284 ± 51**
Se+Te	0.51 ±0.12#	1.31 ± 0.45**	22.1 ± 3.6*	318 ± 63*
Zn	<d.l.	n.a.	20.5 ± 2.5	380 ± 57
Se+Zn	<d.l.	1.44 ± 0.57**	20.6 ± 2.4*	313 ± 92*
Te+Zn	0.61 ±0.16#	n.a.	19.1 ± 1.5	287 ± 57**

Note: Results are given as mean ± SD; Concentrations are given in μg/g of wet tissue. n.a. = not analyzed; <d.l. = under detection limit.
* $p<0.05$ versus control group.
** $p<0.01$ versus control group.
# $p<0.05$ versus Te group.

in the Te group compared to the Te+Se or Te+Zn groups. A significant increase of thyroid Se level was estimated in all Se-administered groups. Enhanced Zn levels were found in the thyroid of the Te, Se+Te, and Se+Zn groups. A marked decrease of thyroid iodine level (to 65–70% of the control level) was estimated in all Te-administered groups and the Se+Zn group.

DISCUSSION

Selenium and Te possess similar chemical properties, among others manifested in vivo by interactions with mercury, cadmium, and Zn *(24–26)*. In experiments in mice, both Na-selenite and Na-tellurite were found to prolong the retention of mercury and cadmium in the organism and alter considerably their distribution in the organs. The effect of tellurite was weaker than that of selenite depending on the extent of their redoxpotentials. It is supposed that the products of selenite reduction and the equivalent Te react with the above-mentioned metals, forming compounds like sulfides, which are retained in the tissues.

Little is known about Te biological activity, particularly with respect to potential chemical interactions with Se-containing components in the organism. It has been suggested that Te might act as a metabolic antagonist of selenium *(27)*, but this has not been confirmed. No data have been available concerning the possible influence of Te relating to thyroid function.

The interaction of inorganic tellurite with hepatocellular selenoproteins, particularly with Se-dependent GPx was described in the study of Garberg et al. *(28)*. The accumulation of ^{121}Te into cultured primary hepatocytes was much more rapid than that of ^{75}Se. An incubation of peroxidase

with tellurite effectively inhibited its ability to catalyze GSH-dependent reduction of hydrogen peroxide. The authors suggest that inorganic tellurite delivers Te into the intracellular milieu in a form capable of binding to some intracellular selenoproteins, and in the case of GPx, it can cause inhibition of its catalytic activity.

In the present study in animals, the effects of subchronic treatment with inorganic tellurite and selenite and their combination with Zn on the activity of two selenoenzymes 5′-DI-I and GPx were compared. Selenite and tellurite exerted the same effect on both selenoenzymes; however, the activity of selenoenzymes were affected differently. Whereas both elements significantly induced 5′-DI-I activity, the activity of the antioxidant Se-containing enzyme GPx remained unaffected.

The thyroid hormone status was not altered after the 6-wk administration of selenite or tellurite alone. However, the combined selenite and tellurite treatment caused an elevation of T_4, T_3, and rT_3 serum concentrations and the combined selenite and zinc sulfate treatment caused an elevation of T_4 and rT_3 serum levels. We consider these findings of particular importance. No data are thus far available in the literature. To elucidate the mechanism of this effect, further studies are necessary (e.g., concerning the effect on the thyroid-stimulating hormone serum level).

The data from our experiment also demonstrate that Te accumulates easily in the thyroid. To date, nothing is known about the possible interaction of Te with its neighboring element in periodic table: iodine. Thus, the most important result in trace element thyroid status estimation is that tellurium administration decreased iodine concentration into the thyroid to 65–70% of the control level. The inhibition of iodine intake into the thyroid gland or displacement of iodine on a certain stage of its kinetics might be a possible mechanism of the action.

In conclusion, the results of the present study indicate that Te as well as Se, and especially their combinations, influence significantly the thyroid status. Further studies are needed to clarify the nature and effects of these events.

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