Peculiarities of the Antioxidant Status of the Thyroid Gland

L. I. Nadolnik and O. I. Valentyukevich

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 144, No. 10, pp. 410-412, October, 2007
Original article submitted March 14, 2007

The intensity of lipid peroxidation and activity of the antioxidant system in the thyroid gland were compared with those in the liver, kidney, heart, and frontal lobes of the cerebral hemispheres in euthyroid male Wistar rats. The thyroid gland was characterized by low activity of first-line antioxidant enzymes superoxide dismutase and catalase, considerable concentration of reduced glutathione, and high activity of glutathione peroxidase and glutathione reductase. Our results suggest that the system of glutathione metabolism determines antioxidant status of the thyroid gland.

Key Words: *thyroid gland; antioxidant system; lipid peroxidation; rats*

The antioxidant system (AOS) plays a universal role in cell protection from increased concentrations of reactive oxygen species (ROS) and activation of lipid peroxidation (LPO). The main sources of endogenous ROS in cells are mitochondrial and microsomal oxidation and function of NADPH oxidases. Thyroid cells have specific features, since metabolism in thyrocytes is accompanied by the production of H_2O_2 in high concentrations. H_2O_2 is an essential compound for oxidation and organification of iodide. Moreover, iodide biosynthesis is a rate-limiting stage in thyroid hormone biosynthesis [6]. Hence, activity of AOS is critical for the function of thyrocytes. Functional activity of AOS was compared in various tissues, but only few investigations included the thyroid gland [3,14]. It was shown that thyroid tissue of euthyroid rats is characterized by the highest concentration of aldehyde products of LPO (compared to the liver, kidneys, and heart) and low activity of catalase [14].

Here we compared activity of AOS and intensity of LPO in the thyroid gland and other tissues of euthyroid rats.

Research-and-Production Center, Institute of Pharmacology and Biochemistry, Belarussian Academy of Sciences, Grodno. ***Address for correspondence:*** lnadolnik@tut.ty. L. I. Nadolnik

MATERIALS AND METHODS

Experiments were performed on male Wistar rats weighing 120-140 g and maintained in a vivarium under standard conditions. Samples of the thyroid gland, liver, heart, kidney, and frontal lobes of the cerebral hemispheres were taken from 10 intact animals. The concentration of stable aldehyde LPO products reacting with thiobarbituric acid (TBA) was measured in tissue homogenates under basal conditions and after spontaneous activation (incubation at 37°C for 1 h) [4]. Antioxidant enzyme activity in partially purified cytosol was estimated by the standard method. SOD activity was evaluated in the reaction of quercetin autooxidation. Catalase activity was determined in the reaction of residual H_2O_2 with ammonium molybdate. Glutathione reductase (GR) activity was estimated from NADH oxidation. Glutathione peroxidase (GPx) activity and reduced glutathione concentration were measured using Ellman's reagent.

The results were analyzed by Student's *t* test at a significance level of 5%.

RESULTS

The intensity of oxidative processes was high in the thyroid tissue. The concentration of TBA-reactive stable aldehyde LPO products in the thyroid tissue

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under physiological conditions is 61.78±9.23 μmol/g (Table 1), which exceeds that in the kidney (by 1.54 times), liver, and heart (more than by 2 times). The basal level of TBA-reactive products in the cerebral hemispheres was 2.12-fold higher than in the thyroid tissue. The main sources of free radicals in the thyroid gland are microsomal oxidation and reaction of iodide oxidation with thyroperoxidase on the apical membrane of thyrocytes. This process involves H_2O_2, which is formed in the NADPH-thyroperoxidase reaction, and superoxide anion [9]. The concentration of TBA-reactive products in all tissues increased during spontaneous activation of LPO. Accumulation of TBA-reactive products in the thyroid gland (103.6%) was less pronounced than in the liver (138.7%), kidney (207%), and cerebral hemispheres (150.1%). These data reflect high activity of AOS in the thyroid gland of euthyroid rats.

SOD activity in the thyroid gland (11.13±0.58 U/g) is lower than in the liver and kidney (by 2.64 and 2.13 times, respectively, Table 2). SOD activity in the thyroid gland did not differ from that in the heart, but was 5.79-fold higher than in the cerebral hemispheres. It should be emphasized that catalase activity in the thyroid gland was lower than in the liver and kidney (by 5.54 and 6.59 times, respectively). These findings are of considerable interest since thyrocytes constantly produce H_2O_2 in response to stimulation with thyrotropic hormone. H_2O_2 in low concentrations is inactivated with GP. However, inactivation of H_2O_2 in high concentrations involves thyrocyte catalase [10].

The concentration of reduced glutathione in the thyroid gland was 47.49±1.10 μmol/g, *i.e.* surpassed that in the heart, liver, and cerebral hemispheres (by 1.41, 1.61, and 1.34 times, respectively). GPx activity in the thyroid gland was 3.75-fold higher than in the cerebral hemispheres, but did not differ from that in tissues of the liver and heart. However, GP activity in the thyroid gland was lower than in the kidney by 1.44 times. It should be emphasized that GR activity was high in the thyroid land (8.34±0.41 mmol/g/min) and exceeded that in other tissues by 1.58-3.00 times. The only exception was renal tissue, where GR activity 2.49-fold surpassed that in the thyroid gland. High concentration of reduced glutathione and high activity of GP and GR in the thyroid gland suggest that the system of glutathione metabolism determines antioxidant status of the thyroid gland. However, the thyroid gland was characterized by low activity of first-line antioxidant enzymes SOD and catalase. Glutathione plays an important role in the thyroid gland. This conclusion is derived from the data that inhibition of glutathione synthesis in cultured FRTL-5 thyrocytes results in a decrease in activity of two thyroid-specific promoters of thyroglobulin and thyroperoxidase [12]. Moreover, activation of oxidative stress under these conditions is followed by the induction of apoptosis and necrosis in thymocytes [8]. Taking into account the fact that GPx is a selenium-dependent enzyme, our results explain the importance of selenium supply for normal function of thyrocytes. Activity of AOS in cells of the thyroid gland significantly decreases during selenium deficiency. This conclusion is supported by the data on a protective effect of the antioxidant selenium-containing complex during therapy of patients with Graves' disease [11].

TABLE 1. Concentration of TBA-Reactive Products of LPO in Rat Tissues under Basal Conditions and after Spontaneous Activation (*M*±*m*)

Tissue	Concentration of TBA-reactive products, μmol/g	
	basal level	spontaneous activation
Liver	24.96±4.20***	59.57±12.42*
Kidney	40.00±2.03*	122.81±10.85
Heart	21.06±2.34***	36.21±4.32**
Cerebral hemispheres	131.02±6.98***	327.71±9.79***
Thyroid gland	61.78±9.23	125.83±29.31

Note. Here and in Table 2: *$p<0.05$, **$p<0.01$, and ***$p<0.001$ compared to thyroid tissue.

TABLE 2. Activity of AOS in Rat Tissues (*M*±*m*)

Tissue	SOD, U/g	Catalase, mmol/g/min	Reduced glutathione, μmol/g	GP, μmol/g/min	GR, mol/g/min
Liver	29.42±2.91***	27.09±2.51***	29.4±1.62***	139.54±21.13	5.28±0.21***
Kidney	23.75±2.70***	32.21±3.12***	59.91±9.26	170.18±25.62	20.75±1.20***
Heart	13.05±1.30	2.87±0.25***	33.67±4.68*	100.36±29.66	2.78±0.18***
Cerebral hemispheres	1.92±0.19***	0.416±0.010***	35.45±1.19***	31.54±8.83**	2.83±0.19***
Thyroid gland	11.13±0.58	4.89±0.54	47.49±1.10	118.27±20.50	8.34±0.41

Taking into account the specific features of thyrocyte metabolism, it should be emphasized that biosynthesis of thyroid hormones occurs in the follicular lumen (not in thyrocytes). This is the site of H_2O_2 production, iodide oxidation, and thyroglobulin iodation and accumulation. There are no data on the localization of antioxidant enzymes or low-molecular-weight antioxidants in the follicular space. The amount of low-molecular-weight scavengers of free radicals probably plays an important role in thyrocyte protection from oxidative damage. Hypofunction of the thyroid gland can result from the deficiency of vitamins A [5] and E [15]. Hypertrophy of the thyroid gland in rats was less pronounced after administration of mercazolyl in combination with antioxidants (vitamins C and E) [7].

Previous observations revealed activation of oxidative stress in the thyroid gland of patients with euthyroid nodular goiter [2], increased consumption of iodine [1], and nodular goiter and diffuse toxic goiter [13]. Antioxidants hold much promise for the correction of oxidative damage to thyroid cells in patients with these disorders. However, this problem requires further investigations.

Our results indicate that the intensity of LPO is high in thyroid cells. The concentration of TBA-reactive aldehyde products in thyroid tissue is higher than in the liver, kidney, and heart. These differences are associated with specific features of thyrocyte metabolism. Activity of SOD and catalase that play a key role in detoxification of ROS is low in the thyroid gland. However, activity of the system for glutathione metabolism (concentration of reduced glutathione and activity of GP and GR) is high in the thyroid gland. These data suggest that the system of glutathione metabolism determines antioxidant status of the thyroid gland.

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