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LIMITATION OF STRESS-INDUCED ACTIVATION OF LIPID PEROXIDATION BY SMALL DOSES OF THYROID HORMONES

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KEY WORDS: stress; lipid peroxidation; thyroid hormones.

Near-physiological doses of thyroid hormones protect the heart against stress-induced damage to the sarcolemma and mitochondria of the cardiomyocytes and against a fall in the ratio of areas of the mitochondria and myofibrils to the level of the contractile function of the myocardium [1-3]. A leading mechanism of the disturbance of cardiomyocyte structure and function induced by stress is known to be activation of lipid peroxidation (LPO) [7].

Taking account of existing data on the effect of thyroid hormones on enzyme systems connected with the antioxidant system of the cells [8, 12], it can be postulated that one mechanism of the protective effect of thyroid hormones during stress is the limitation by them of LPO processes in the heart.

The aim of this investigation was to study the possibility of limiting stress-induced activation of LPO in the rat myocardium by small doses of thyroid hormones and to study the effect of these hormones on some components of the antioxidant systems of the cells.

EXPERIMENTAL METHOD

Experiments were carried out on 57 noninbred male albino rats weighing 180-220 g. The animals were divided into the following groups: 1st — control (n = 21), end — stress (n = 15), 3rd — thyroid hormone (n = 11), 4th — thyroid + stress (n = 10). Immobilization stress was created by fixing the animals in the supine position for 6 h. Blood samples (taken with a catheter introduced into the carotid artery) and pieces of myocardium were obtained 1 h after the end of immobilization under urethane anesthesia. Thyroid was given by the intragastric route in starch mucilage for 28 days in a daily dose of 1.5-3 mg/100 g, as in [1]. Control rats received starch mucilage only. Activation of LPO both in the myocardium and in the whole animal was judged by determining concentrations of initial and final LPO products respectively in myocardial homogenates (diene conjugates and mal-

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TABLE 1. Effect of Small Doses of Thyroid Hormones on Stress-Induced Changes in 11-HCS Concentration and Weight of Adrenals and Spleen ($M \pm m$)

Group of animals	11-HCS, μmoles/liter	Adrenals, mg/g body weight	Spleen, mg/g body weight
1	396,2±62,7	0,12±0,01	3,0±0,5
2	888,5±52,3*	0,18±0,09*	2,1±0,3*
3	377,3±39,8	0,13±0,09	6,8±0,4*
4	726±46***	0,15±0,01***	4,7±0,25***

Legend. Here and in Table 2: $*p < 0.01$ denotes significance compared with control, $**p < 0.01$ significance compared with stress.

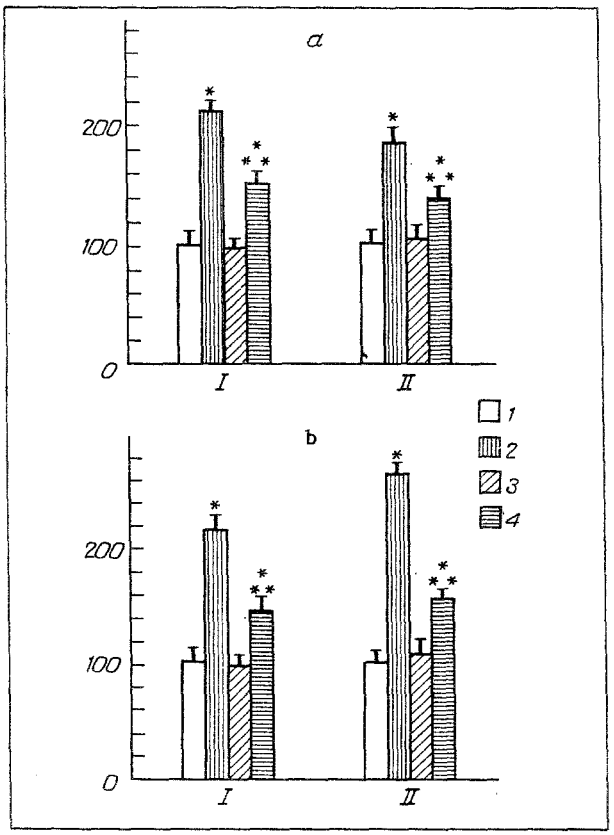

Fig. 1. Effect of small doses of thyroid on stress-induced changes in concentration of initial and end products of LPO in myocardium (a) and blood plasma (b). a: ordinate, concentration of diene conjugates (I) and MDA (II) (in %). 1-4) Groups 1-4 respectively, b: ordinate, concentration of lipid hydroperoxides (I) and MDA (II) (in %). Groups of animals as before. $*p < 0.05$ Indicates significance compared with control; $**p < 0.05$ denotes significance compared with stress.

onic dialdehyde — MDA) and in blood plasma (lipid hydroperoxides and MDA) by the usual methods [4, 9]. The power of the antioxidant systems was studied as superoxide dismutase (SOD) activity of the erythrocytes and as the degree of induction of LPO during incubation of myocardial homogenates with Fe^{2+}. SOD activity was determined by the method in [6]. The rate of LPO in myocardial homogenates was studied by measuring MDA formation during incubation for 60 min with the addition of $FeSO_4$ (10^{-5} M) as pro-oxidant to the incubation mixture [9].

TABLE 2. Effect of Thyroid on Stress-Induced Changes in Rate of LPO in Myocardial Homogenates and SOD Activity in Erythrocytes ($M \pm m$)

Group of animals	Increase in MDA during incubation of myoca	SOD activity of erythrocytes, conventional units/ml
1	34,8±1,27	85,6±0,68
2	82,6±2,20*	66,77±1,54*
3	28,8±1,61*	94,8±0,65*
4	47,2±1,73***	84,2±0,95**

The stress response of the animal was judged by the change in weight of the adrenals and spleen and the change in plasma 11-hydroxycorticosterone (11-HCS) concentration [10], and the degree of activity of thyroid on the heart rate determined from the ECG. The results were subjected to statistical analysis by the Wilcoxon–Mann–Whitney nonparametric test.

EXPERIMENTAL RESULTS

The doses of thyroid used were close to physiological, for they had no significant effect on heart rate or body weight and did not change the plasma thyroxine concentrations outside normal limits [1].

The results given in Table 1 show that immobilization stress caused an increase of 122% in the 11-HCS concentration, an increase of 50% in weight of the adrenals, and a decrease of 30% in the weight of the spleen. Administration of thyroid to intact animals had no significant effect on the 11-HCS concentration or the weight of the adrenals, but it led to an increase in the weight of the spleen by 126%. In rats receiving thyroid, stress was accompanied by elevation of the 11-HCS level by 92% and of the weight of the adrenals by 15% and by reduction of the weight of the spleen by 31%. Consequently, injection of the thyroid preparation restricted the stress-induced increase in the 11-HCS concentration by 30% and the increase in weight of the adrenals by 35%, but had no effect on the degree of stress-induced reduction in weight of the spleen, although it still exceeded the weight of the spleen in intact animals by 57%.

The data in Fig. 1 show that in intact animals stress was accompanied by a marked increase in concentrations of the initial and end products of LPO: of diene conjugates and MDA in the myocardium by 106 and 82% respectively, of lipid hydroperoxides and MDA in the blood plasma by 118 and 161% respectively.

Injection of thyroid extract into intact animals had no significant effect on these LPO products in the myocardium or blood plasma. Stress induced after injection of thyroid was accompanied by a less significant rise in the level of diene conjugates (by 51%) and of MDA (by 23%) in the myocardium and of lipid hydroperoxides (by 53%) and MDA (by 43%) in the blood plasma. Thus small doses of thyroid hormones significantly (by 55-118%) limited stress-induced activation of LPO.

Thyroid extract exerts its protective action by activating antioxidant systems. Immobilization was found to lead to an increase in the rate of Fe^{2+}-induced MDA formation in myocardial homogenates by 137% and to a decrease of 22% in SOD activity of the erythrocytes (Table 2). In animals receiving thyroid, stress induced an increase in MDI of only 64% in the case of induction by Fe^{2+}, and a decrease in SOD activity by only 12%. Consequently, the activating action of stress on induction of LPO in myocardial homogenates was significantly limited in animals receiving preliminary thyroid extract, evidently because of increased activity of antioxidant enzymes.

Thyroid hormones thus do not prevent the development of a stress reaction but limit stress-induced activation of LPO in the membranes, by strengthening the antioxidant systems both of the body as a whole and of the myocardial tissue.

The explanation of this fact may perhaps be that, first, thyroid hormones by interacting with DNA receptors [11] activate protein synthesis including, possibly, synthesis of antioxidant enzymes of the cell, and second, SH-containing proteins, whose concentration in the myocardium is increased by the action of thyroid hormones [5], may play the role of a "trap" for free radicals, and third, thyroid hormones are known to activate the pentose phosphate shunt [8], thereby replenishing the intracellular reserves of NADPH, which is essential for regeneration of glutathione peroxidase, an enzyme playing an important role in the antioxidant protection of cardiomyocytes [12].

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CHANGE IN ADRENAL FUNCTION IN DOGS WITH EXPERIMENTAL BRONCHOSPASM

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KEY WORDS: adrenal glands; dogs; bronchospasm; catecholamines; glucocorticoids

A tendency is observed nowadays for the prevalence of bronchial asthma (BA) to continue to rise, and it is reported to be 3.5% among children [7] and 3-8% among adults [6]. The role of glucocorticoids in the pathogenesis of BA has not been adequately studied.

The aim of this investigation was to study changes in blood levels of adrenocortical and adrenomedullary hormones during an attack of experimental bronchospasm in dogs.

EXPERIMENTAL METHOD

Experiments were carried out on 7 male mongrel dogs weighing 20-25 μg, sensitized with ovalbumin for 8 weeks in gradually increasing concentrations (50, 250, 500, and 1000 μg subcutaneously). As adjuvant, 30 mg of aluminum hydroxide was used [4]. For bronchial provocation, the dogs were anesthetized by intravenous injection of 1% thiopental sodium solution, incubated, and the endotracheal tube connection to an inhaler and pneumotachograph.

Physiological saline (5 ml) and the solution of ovalbumin (100, 500, and 1000 μg in 5 ml of physiological saline) were inhaled for 15 min (each solution). The depth of anesthesia was monitored by testing the corneal reflex and was maintained at a constant level by repeated injections of thiopental sodium after inhalation of ovalbumin. The parameters of ventilation were recorded on a "Godart" pneumotachograph and the volume velocity of expiration (V) calculated. The presence of bronchospasm was judged from a fall of 25% or more in the value of V during 1 sec compared with its value before inhalation of physiological saline. The measurements were made at the 15th minute of inhalation. Concentrations of 11-hydroxycorticosteroids (11-HCS), adrenalin, noradrenalin, dopamine, and histamine were determined by fluorometric methods in blood samples taken from a peripheral vein before inhalation, at the 15th minute of inhalation, and 2 h after its end [1, 2, 8].

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