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ROLE OF LIPID PEROXIDATION IN REGRESSION OF THE HYPERTROPHIED HEART

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KEY WORDS: hypertrophy of the heart; lipid peroxidation

During adaptation to periodic hypoxia under pressure chamber conditions, nucleic acid and protein synthesis is activated, with the result that hypertrophy of the right ventricle (due to pulmonary hypertension) and, to a lesser degree, hypertrophy of the left ventricle (due to an increase in cardiac output) develops [5]. After the end of exposure to hypoxia, regression of the hypertrophied heart quickly takes place [4]. However, the concrete molecular mechanisms of disassembly of the myocardial structures have not been studied. In our view, one factor which may play a role in this process is lipid peroxidation (LPO), which is involved in destruction and disassembly of biological membranes [1, 2].

It was accordingly decided to compare the dynamics of regression of the hypertrophied heart with activity of LPO, estimated as concentrations of diene conjugates.

EXPERIMENTAL METHOD

Male Wistar rats weighing initially 185 ± 6 g were used. The rats were adapted to periodic high-altitude hypoxia by "raising" them to an altitude, increasing by 1000 m daily up to a peak value of 7000 m, in a hypobaric pressure chamber. The animals were kept at this "altitude" for 18 days (6 days a week) for 6 h daily. At the end of the period of adaptation the rats weighed 232 ± 9 g, whereas animals kept under standard animal house conditions (control) weighed 281 ± 8 g. Altogether five groups of rats were studied: control (without adaptation), 1, 3, and 7 days after the last session of hypoxia, and 7 days after hypoxia, during which period the rats were given ionol by intraperitoneal injection in a dose of 50 mg/kg on the 1st, 3rd, and 5th days.

TABLE 1. Weight of Heart and Its Divisions and Content of Hemoproteins in Them after Adaptation and during Regression (M ± m)

Parameter	Control (without adaptation)	Adaptation	Regression		
			3 days	7 days	7 days + ionol
Relative weight of heart, g/kg body weight	2,62±0,04	3,77±0,17***	3,23±0,08***	2,75±0,06	3,28±0,14**
Relative weight, g/kg body weight					
of right ventricle	0,74±0,02	1,46±0,08***	1,06±0,03***	0,77±0,06	1,00±0,05***
of left ventricle	1,88±0,02	2,31±0,11**	2,17±0,08*	1,98±0,04*	2,27±0,11***
Myoglobin concentration, mg/g					
in right ventricle	0,27±0,02	0,35±0,05*	0,32±0,06	0,30±0,06	0,33±0,33*
in left ventricle	0,38±0,05	0,46±0,06	0,42±0,04	0,37±0,05	0,39±0,05
Hemoglobin concentration, mg/g					
in right ventricle	0,16±0,02	0,29±0,05**	0,20±0,04	0,18±0,05	0,25±0,04*
in left ventricle	0,18±0,02	0,30±0,05*	0,22±0,05	0,21±0,03	0,29±0,05*

Legend. ***p < 0.01, **p < 0.02, *p < 0.05.

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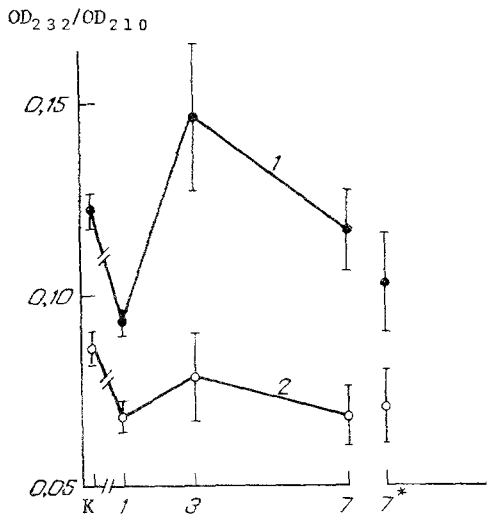

Fig. 1. Concentration of LPO products (diene conjugates) in phospholipids of right (1) and left (2) ventricles. Abscissa: C) control (without adaptation); 1) first days after end of adaptation (maximum of hypertrophy); 3, 7) 3 and 7 days, respectively after end of adaptation (regression); 7') 7 days after adaptation during which the antioxidant ionol was injected; ordinate, ratio of optical densities of lipid solution at 232 and 210 nm, proportional to concentration of diene conjugate.

The isolated hearts were washed in cold physiological saline, the walls of the left and right ventricles and septum were dissected, and each part was weighed. The weight of the left and right ventricular wall was homogenized in an "Ultra-Turrax" homogenizer, with the ratio of weight of tissue to volume of medium (50 mM Tris-HCl, 100 mM NaCl, pH 7.4) of 1:5. The concentration of myoglobin and hemoglobin in the homogenate was determined spectrophotometrically [8]. Lipids were extracted with a chloroform—methanol mixture by the method in [6]. The concentration of primary LPO products (diene conjugates) was determined as the ratio of optical densities of the lipid solution (0.1 mg/ml in a mixture of heptane—methanol = 1:5) at 232 and 210 nm.

EXPERIMENTAL RESULTS

Adaptation to periodic high-altitude hypoxia under the conditions specified above led to hypertrophy of the heart by 44%. As a result of hypoxia, hypertrophy mainly of the right ventricle developed, its weight being doubled, whereas the weight of the left ventricle was increased by only 24% (Table 1). The myoglobin content in the myocardium of the right and left ventricles increased by 30 and 21%, respectively, and this fact may play a role in the adaptive acceleration of oxygen transport to the myocardial mitochondria. Meanwhile the hemoglobin concentration almost doubled in the myocardium of both ventricles, a fact evidently linked with a selective increase in volume of the coronary vascular bed [7] and with in increase in the hematocrit index during adaptation.

It also follows from Table 1 that after the end of exposure to hypoxia comparatively rapid regression of all changes arising in the heart during adaptation was observed. After only 7 days the weight of the right and left ventricles and the concentrations of myoglobin and hemoglobin in them became the same as in unadapted animals. The antioxidant ionol, an LPO inhibitor, significantly retarded regression and, as a result, 7 days after the end of exposure to hypoxia the weight of the right ventricle remained increased by 35%, and that of the left ventricle by 21%. The hemoglobin concentration also remained 50% higher than in the control. This fact itself suggests that activation of LPO may play a role in regression of the structural changes arising in the heart during adaptation, and that suppression of LPO is a factor inhibiting this process.

The time course of the concentration of diene conjugates in the ventricles is shown in Fig. 1. In the adapted animals (1 day after the last session of hypoxia) myocardial hypertrophy was accompanied by a fall in the concentration of LPO products compared with the unadapted control. During regression of the hypertrophied heart (3 days) the level of diene conjugates rose sharply, and by the time of complete regression (7 days) it fell again.

When the results are discussed it will be clear that long-term adaptation to periodic hypoxia leads to a considerable increase in the intensity of function of the right ventricle especially, combined with a marked lowering of the level of LPO products in it compared with the left ventricle. These data are in agreement with the negative correlation demonstrated previously [3] between the degree of functional activity and the intensity of free-radical processes in different parts of the heart. Inhibition of LPO during adaptation of animals to hypoxia evidently reflects also a shift of equilibirum between biosynthesis and catabolism

in favor of the former, and as a result, a larger number of membrane structures, necessary for functioning of the tissue under conditions of increased loading, can be maintained in the cardiomyocytes. After removal of the inducing factor (in this case, periodic high-altitude hypoxia) the presence of an excessive number of structures becomes energetically disadvantageous for the cell, and they are eliminated through activation of various catabolic processes, of which LPO is one. In fact, on the 3rd day of regression of hypertrophy of the right ventricle, whose weight was doubled, an increase of 56% was observed in the concentration of diene conjugates compared with the hypertrophied heart. Hypertrophy of the left ventricle was slight and its regression was not accompanied by any significant increase in the concentration of LPO products.

The results agree on the whole with our ideas on the role of LPO in regression of hypertrophy of the heart and also, perhaps, of other changes arising during long-term adaptation, and they justify the view that the further study of this problem will be promising.

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CARDIOPROTECTIVE PROPERTIES OF 1,4-DIHYDROPYRIDINE DERIVATIVE GLUTAPYRON IN DEEP HYPOTHERMIA

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A general rule in animals of different species during the primary response to cold is an increase in activity of free-radical lipid peroxidation (LPO) in the myocardium, followed by a decrease in the activity of these processes as the temperature falls to the region of deep hypothermia, with reactivation during continued exposure to deep hypothermia (for 40 min or more) [6, 8]. Intensification of peroxidation during cooling and in deep hypothermia causes changes in the structure of the cell membranes and in 13-lipid interactions [5]. Changes in membrane structure improve access to substrates for pro-oxidants. LPO products found in membrane phospholipids increase permeability of membranes of the sarcoplasmic reticulum for Ca^{++} ions, which in turn induce activation of LPO. The LPO products thus formed inhibit Ca^{++}-ATPase in myocyte membranes [4]. The reaction chain described above ends with an increase in the outflow of Ca^{++} from the myocytes, with a resulting decrease in myocardial contractility [10]. When deep hypothermia is used in cardiac surgery these disturbances of

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