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Development of Superresistance to Hypoxic Hypoxia under the Effect of Adaptation to Short-Term Stress Exposure

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Key Words: *hypoxic hypoxia; adaptation; short-term stress*

It is known that adaptation to repeated short-term stress exposure produces wide cross-protective effects. It protects from cold [4], from chemical injury to the gastric mucosa [11], and, as has been recently found, from ischemic and reperfusion damage [7]; it also reduces disturbances in myocardial energy metabolism and contractile function during severe hypoxic hypoxia [2]. However, the influence of adaptation to stress on the respiratory and circulatory functions, oxygen uptake, acidosis severity, activation of lipid peroxidation, and phospholipolysis under conditions of severe hypoxia is still unknown. The investigation described below was aimed at solving these questions and at studying the effect of adaptation to repeated nondamaging immobilization stress on the resistance of animals to severe hypoxic hypoxia.

MATERIALS AND METHODS

The investigations were carried out on two groups of male Wistar rats (150-220 g) The experimental and control animals (20 rats per group) were kept under laboratory conditions for 24 days. The experimental rats were adapted to stress exposure during 24 days by fixing them in the supine position by 4 limbs for 15 min on the first day and for 30 min every other day for the rest of the experiment. The control and adapted animals were exposed to severe acute hypoxic hypoxia. This was produced by 120 min inhalation of a gas mixture with 6% oxygen. The animals were anesthetized with an intraperitoneal injection of chloralose (50 mg/kg) and urethane (50 mg/kg). After cannulation of the right common carotid artery and venae cavae, the trachea was incised and a tracheal tube inserted.

In the course of the experiment we estimated the effect of adaptation on the main factors which determine mortality during acute severe hypoxia. Previous studies performed in our laboratory have revealed that these factors include disturbances of external respiration and pulmonary gas exchange, a disparity between oxygen tissue supply and requirement, lactate acidosis, activation of lipid peroxidation and lipolysis, and reduced oxygen diffusion across biological barriers. Al these parameters were estimated by methods previously described [3,8-10].

Statistical significance was estimated by Student's *t*-test.

RESULTS

The data obtained provide evidence that adaptation to repeated stress exposure sharply raises the resistance

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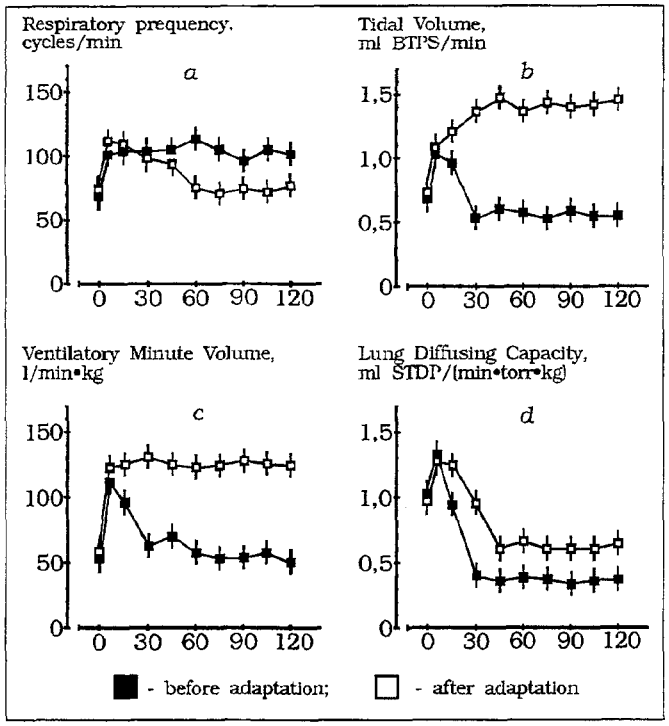

Fig. 1. Influence of adaptation on respiration and oxygen diffusion across biological barriers under severe acute hypoxic hypoxia (6% oxygen). Means±SEM are given. Abscissa: time (min).

of animals to acute severe hypoxia. About 65% of the nonadapted animals died within 120 min of inhalation of a gas mixture containing 6% oxygen, whereas after adaptation to stress the mortality during a comparable period of hypoxia was only 10%, i.e., it decreased 6.5 times. This finding is especially important, since it indicates that in the process of adaptation to stress the efficiency of the mechanisms responsible for adaptation to hypoxia, increased. Thus, subsequent efforts aimed at elucidating the reasons for such a dramatic drop in mortality.

It was found that the usual response to a decrease in oxygen concentration, an increase in the minute volume of respiration, was observed only during the first few minutes of hypoxia. This index then dropped to its initial value. At the same time, the animals adapted to stress maintained a 2.5 times higher ventilation volume throughout the period of hypoxic exposure (Fig. 1). Besides total ventilation, the groups of animals showed significant differences in the breathing pattern. Thus, in the nonadapted animals under hypoxia lung ventilation was realized due to energy-wasting tachypnea. Their respiration volume (tidal volume) increased only during the first 15 min of hypoxic inhalation and thereafter it abruptly dropped and was only 75% of the value characteristic of normoxia. The adapted animals, by contrast, demonstrated a progressive increase in the depth and a progressive decrease in the frequency of respiration with prolongation of hypoxic exposure. As a result, starting from the 60th min of hypoxia their tidal volume appeared to be almost twice as high as in the controls, while tachypnea was absent. This led to an enhancement of alveolar ventilation. In fact, calculations showed that such an important indicator of external respiration efficiency as the ratio of alveolar ventilation to tidal volume in nonadapted animals under hypoxia was 60-70%, whereas after adaptation it increased to 80-95%. The increase of alveolar ventilation in turn produced a sharp rise in the level of oxygen transport to gas-exchange surface of the lungs (from 2-3 to 6-7 ml per 100 g·min, i.e., two-threefold). Hence, preliminary adaptation to moderate stress exposure enhanced the efficiency of and reduced the energy required for external respiration, thus allowing for improved pulmonary gas exchange. In the stress-adapted animals, besides an increased alveolar oxygen supply, an increase in the velocity of oxygen uptake from the air to the blood was also observed. Thus, whereas prior to hypoxia in both groups of animals the difference between the alveolar air and mixed venous oxygen partial pressures was about 60 mm Hg and the alveolar arterial difference was about 15 mm Hg, under hypoxia these values dropped to 15-20 and 1-5 mm Hg, respectively. In the other words, the gradient forcing oxygen diffusion from

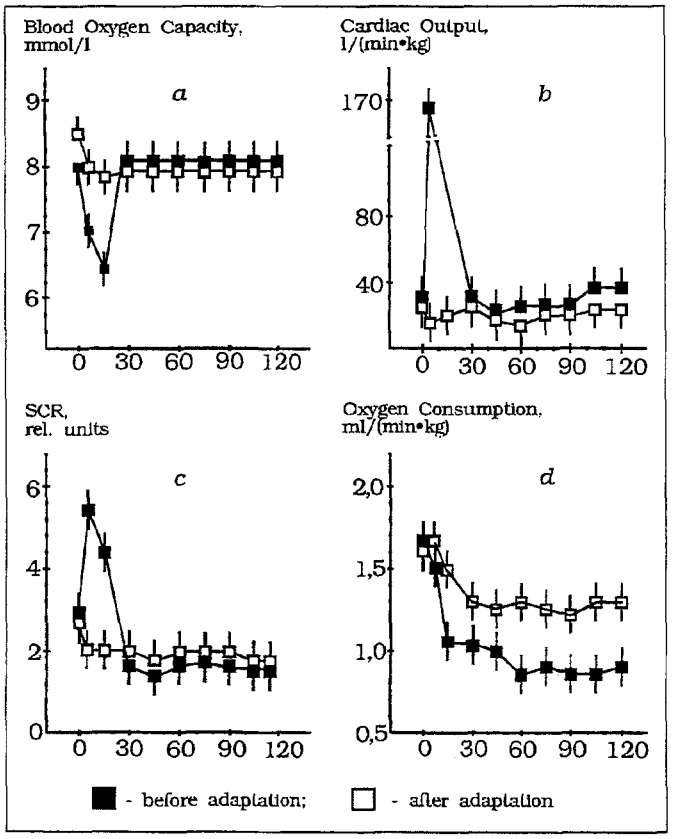

Fig. 2. Influence of adaptation on oxygen supply and consumption under severe acute hypoxic hypoxia (6% oxygen). Means±SEM are given. Abscissa: time (min).

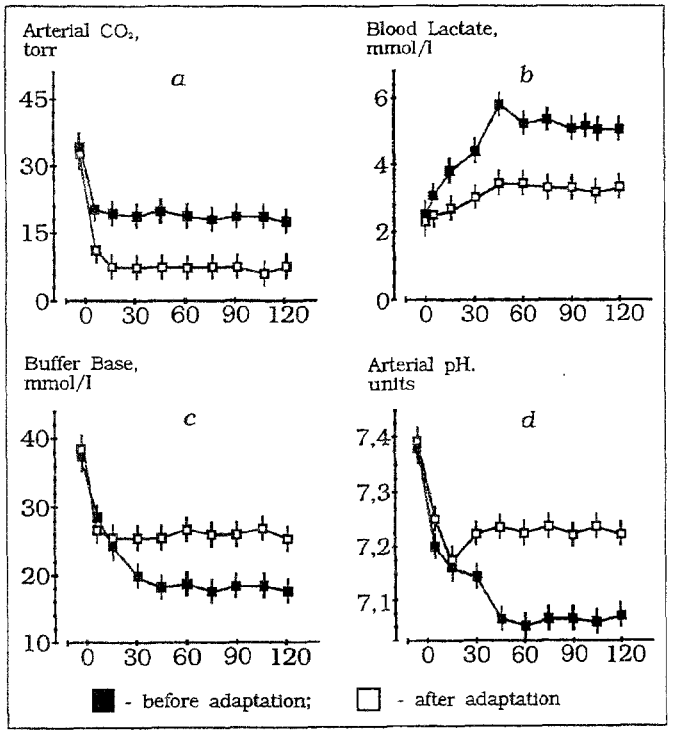

Fig. 3. Influence of adaptation on blood gases and acid–base status under severe acute hypoxic hypoxia (6% oxygen). Means±SEM are given. Abscissa: time (min).

the air to the blood under conditions of hypoxic hypoxia decreased 3-4 times. The only way to compensate for this extremely unfavorable phenomenon under hypoxia is to increase the diffusing capacity of the lungs. In the control animals an increase in diffusing capacity was observed only during the first few minutes of hypoxia, after which there was a 3-fold drop of that value (Fig. 1). In animals adapted to stress under severe hypoxia the diffusing capacity of the lungs was 1.5-2.5 times higher and oxygen uptake per cycle 1.3-2.0 times higher than the corresponding values in the control. This produced a 4-5 mm Hg increase in blood oxygen pressure or a 15-20% increase in oxygen concentration.

Thus, tissue oxygen supply was not significantly increased in the adapted animals, and therefore this factor did not play a crucial role in raising resistance to hypoxia. At the same time the data in Fig. 2 show that such an important index as tissue oxygen uptake appears to be 60% higher than that of the control animals.

It is further seen from Figs. 3 and 4 that this increment of tissue oxygen uptake limited the reduction of pyruvate to lactate, lowered lactate accumulation in the liver almost 2-fold, in the heart by 34%, in the lungs by 30%, and in the blood by 36%. This considerable restriction of lactic acids accumulation, together with the concurrent hyperventilation which contributed to CO_2 elimination from the organism, produced a drop in the hydrogen ion concentration, an increase in the bicarbonate concentration, and, finally, a reliable elevation of the blood pH (Fig. 3)

Further analysis of the data shows that severe acute hypoxia led to a more than 3.4-fold rise in the concentration of free fatty acids (FFA) in the blood as well as to the elevation of this index in all organs studied. The concurrent activation of lipid peroxidation (LPO) was observed. At the same time, adaptation to stress limited the hypoxic activation of lipolysis and LPO in all organs investigated (Fig. 4). In fact, the FFA concentration proved to be 1.7-2.3 times lower than in the control, while the accumulation of LPO initial products - conjugated dien - dropped 1.6 times in the brain and by 30-40% in the liver, heart, and lungs compared with the control. The concentration of LPO products reacting with thiobarbituric acid in the adapted animals was lower 1.3 times in the heart, 15% lower in the lungs, and 1.5 times lower in the tissues as compared with the nonadapted animals.

Thus, the cross-protective effect of adaptation to stress considerably decreases the mortality and raises the resistance of animals to severe hypoxia. This occurs due to more efficient mobilization of respiration and circulation function, a significant increment in tissue capacity for taking up oxygen from the blood, and restriction of acidosis and the processes liable to damage cell membranes, namely lipolysis and lipid peroxidation.

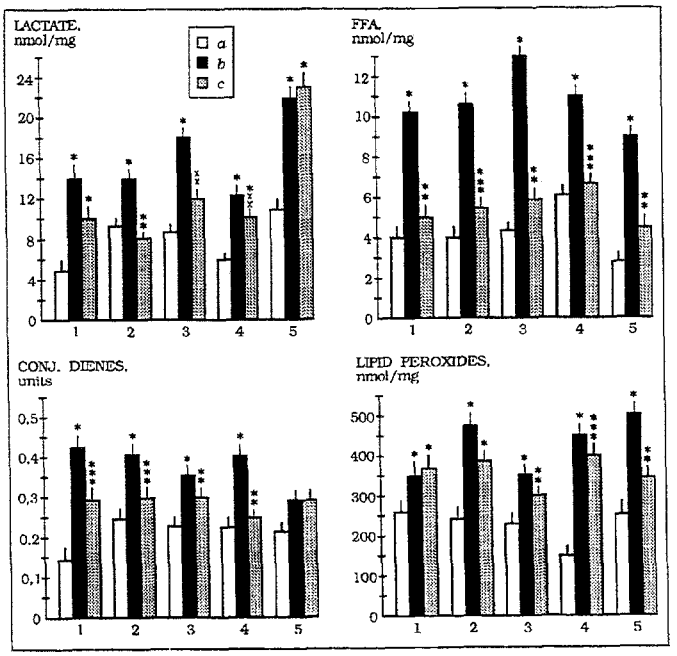

Fig. 4. Influence of adaptation on accumulation of lactate, free fatty acids (FFA), lipid peroxides and diene conjugation absorption in the brain (1), liver (2), heart (3), lungs (4), and muscles (5) under severe acute hypoxic hypoxia (6% oxygen). Means±SEM are given. *a*) control; *b*) before adaptation; *c*) after adaptation.

It is significant that the main mechanism of the cross-protective effect of adaptation revealed by us is an increased tissue capacity for utilizing the oxygen supplied by the blood. This important shift may be determined by at least two factors: 1) better preservation of the capillary-cell membrane barrier in adapted animals and, accordingly, accelerated oxygen diffusion across them; 2) more intense oxygen consumption in adapted animals, possibly due to better oxygen utilization and oxidative phosphorylation in the mitochondria. Of course, these conclusions should be experimentally verified. However, it has been recently revealed that adaptation to repeated restrained stress results in the development of the phenomenon of adaptive stabilization of structures (PASS). PASS manifests itself in an increased stability of the cytoplasmic membrane and sarcoplasmic reticulum structures of the mitochondria [5] and cell nuclei [6] to autolysis and lipid peroxidation. It may be asserted that under the conditions of our investigation PASS development played a certain role in the preservation of cellular structures under severe hypoxia and thereby in the maintenance of a high rate of oxygen diffusion and consumption in the cells.

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Na^+ and K^+ Permeability of Erythrocyte Membranes and their Phospholipid Composition in Patients with Essential Hypertension

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Recent investigations have provided substantial evidence for the existence of membrane cation transport disturbances in patients with essential hypertension (EH), either in electrically excitable or nonexcitable cell types [4-6]. These facts produce new insight into this pathology which allow us to consider EH as a peculiar kind of membrane pathology. Cell membrane permeability depends strictly on structure. The shape of erythrocytes is determined mainly by the membrane proteins as well as membrane lipid composition. The phospholipid composition of the erythrocyte membrane is of interest, since phospholipids (PL) are the main component

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