ings it is important that, along with the vessel growth during adaptation to hypoxia, a reduction of their muscle tone is observed [4, 8], as well as a reduction of the response of the resistive vessels to vasoconstrictors and an enhancement of the response to vasodilators [4]. This may limit the rise of pressure in the brain vessels and decrease the likelyhood of rupture of the venous walls, damage to which plays a decisive role in the development of subdural hemorrhage for audiogenic epilepsy in KM rats [1,10]. This factor, as well as the possible growth of the venous bed and structural changes in the vein walls, appear to determine the adaptive protection of the brain against subdural hemorrhage during the development of audiogenic epilepsy.

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Animal Resistance to Sublethal Hypoxia May Be Raised More by Adaptation to Stress than by Adaptation to Hypoxia

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Adaptation to moderate hypoxia is thought to raise human and animal resistance to sublethal hypoxia [5], and this has been used in the training of mountain climbers and pilots [2]. In addition to this direct protective effect of adaptation, there is a possibility of increasing resistance to hypoxia due to cross-protective effects of adaptation to other factors. For instance, adaptation of animals to repeated stress lowers 6.5-fold the mortality for the

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TABLE 1. Effect of Adaptation to Periodic Hypoxia and Adaptation to Stress on the Respiration Indexes during Sublethal Hypoxia (Breathing a Mixture with 6% O_2)

Index	Breathing atmospheric air (control I)	Sublethal hypoxia		
		control (II)	adaptation to hypoxia	adaptation to stress
	1	2	3	4
Mortality	–	65%	29%	10%
Respiration rate, cycles/min	74.10±1.60	104.0±1.0*	59.35±7.40+	65.60±1.61*,+
Respiration volume, ml BTPS/100 g	0.71±0.03	0.53±0.07*	1.36±0.24*,+	1.39±0.24*,+
Minute respiratory volume, ml BTPS/100 g×min	52.60±2.2	55.60±6.9	82.71±22.29	91.20±8.85*,+
Maximal rate of inspiration flow, ml/sec	7.88±0.38	7.94±0.24	8.33±1.77	13.79±0.55*,+,○
Mean rate of inspiration flow, ml/sec	4.92±0.53	4.96±0.21	6.33±0.99	8.62±0.78*,+
Mean rate of expiration flow, ml/sec	4.92±0.21	4.96±0.45	5.097±0.48*,+	8.62±0.02*,+,○
Oxygen content in arterial blood, ml/100 ml	17.89±0.09	6.91±0.45	7.52±2.07*	9.19±0.43*,+

Note. Here and in Tables 2 and 3: an asterisk, a plus sign, and a circle indicate $p<0.05$ as compared to 1, 2, and 3, respectively.

standard severe hypoxia caused by inhalation of a mixture containing 6% oxygen [5]. A quantitative comparison of the protective-antihypoxic effect of adaptation to hypoxia and stress has not yet been carried out.

The aim of the present study was to compare the effect of adaptation to periodic hypoxia in a pressure chamber and that of adaptation to immobilization stress on animals' resistance to severe hypoxic hypoxia.

MATERIALS AND METHODS

The experiments were carried out on male Wistar rats weighing 150-220 g. Adaptation to hypoxia was performed by daily "elevations" of the animals in a pressure chamber, increasing the "altitude" from 1000 m to 4000 m. Adaptation to immobilization stress was performed by fixing the rats in the supine position for 1 h every other day (in all, 8 sessions). Acute hypoxic hypoxia was induced by making the animals inhale a gas mixture containing 6% oxygen for 120 min. Eighty animals adapted to stress or to hypoxia and the same number of controls were involved in the experiments. During the experiments with inhalation of the gas mixture, tracheotomy and catheterization of the common carotid artery and of the vena cava openings was performed on urethane-narcotized (50 mg/kg, i.p.) animals. The indexes of external respiration and pulmonary gas exchange were measured in the animals of all series with the aid of an automated device which we had developed for these purposes [6]. The blood gases and acid-base equilibrium were analyzed using Radiometer microelectrodes (Denmark). The correlation between the blood transport of oxygen and its demand was assessed as the supply/uptake ratio calculated by dividing the rate of arterial blood transport of oxygen by the tissue uptake of oxygen. The degree of tissue hypoxia was judged by the blood and tissue accumulation of lactic acid, its concentration being enzymatically assayed with the aid of Boehringer standard kits (Germany). The processes of lipid peroxidation were evaluated by measuring the blood and tissue concentration of thiobarbituric acid-reactive substances on an F-4000 Hitachi spectrophotometer (Japan), using tetramethoxypropane (Sigma, USA) as the reference.

RESULTS

Tables 1 and 2 characterize the effect of preadaptation to periodic hypoxia and of adaptation to a short-term immobilization stress on mortality, as well as on the circulation and respiratory function for acute sublethal hypoxia. What is most remarkable is that during the first 2 h, the mortality for acute severe hypoxia in the control (unadapted) animals was 65% (Table 1). Adaptation to hypoxia reduced this parameter to 29%, while adaptation to stress lowered it to 10%, that is, 6.5-fold. This powerful effect of adaptive protection is beyond all question, since the groups examined comprised from 80 to 82 animals. In accordance with the

above, all the data in the tables have to be assessed in such a way that the mechanism of the protective effect of adaptation to two diverse factors is elucidated. Table 1 shows that adaptation to stress sharply raised the resistance of external respiration to sublethal hypoxia. During hypoxia, all indexes of this function, from the minute volume of respiration (MVR) to the expiration and inspiration flow rates, characterizing the work of the respiratory center and respiratory muscles, were markedly higher than those in the control. They also proved to be higher in comparison with the same indexes in the animals adapted to periodic hypoxia. The overall index of external respiration was in full agreement with the above: the O_2 content in the arterial blood was reliably higher in the stress-adapted animals than in the nonadapted animals. Furthermore, as seen from Table 1, the O_2 content in the arterial blood under conditions of acute hypoxia was reliably unchanged as compared to the nonadapted controls. In other words, during a sublethal deficiency of oxygen, adaptation to stress provided for a more effective mobilization of external respiration and for the maintenance of a higher arterial O_2 than adaptation to periodic hypoxia. This advantage of adaptation to stress was reliable vs. adaptation to hypoxia, but comparatively small.

As seen from Table 2, adaptation to either factor markedly increased the O_2 transport to the tissues; however this enhancement of O_2 transport was more pronounced for adaptation to hypoxia than for adaptation to stress and was achieved by a 56% increase (vs. nonadapted controls) of the minute volume blood flow rate (MVFR). On the other hand, during adaptation to stress, the MVR is one-third reduced; nevertheless, as mentioned above, the O_2 supply to the tissues is 78% higher in this case than in the hypoxic controls. This was due to the above-mentioned shift (a higher O_2 content in the arterial blood), as well as to a 20%-increased arteriovenous difference. On the whole, the arterial transport of O_2 to the tissues is achieved more economically during adaptation to stress than during adaptation to hypoxia. Evidently, the overall result of adaptive mobilization of the circulatory and respiratory functions may be evaluated depending on to what extent such mobilization helps preserve the O_2 uptake by the organism's tissues during acute hypoxia.

As is seen from Table 2, both variants of adaptation are very effective in this regard. During acute hypoxia, the O_2 uptake in adapted animals was approximately 60-90% higher than that in nonadapted controls during hypoxia. At the same time, this increase constituted 90% for adaptation to hypoxia, and only 60% for adaptation to stress. Furthermore, of interest is the fact that the supply/uptake ratio is reliably higher for adaptation to hypoxia than for adaptation to stress, i.e., the conditions of oxygen uptake by the cells are definitely better in the former case.

Thus, despite a richer O_2 supply and its higher uptake by the tissues, adaptation to hypoxia lowers the mortality of animals from acute O_2 deficiency just 2.3-fold, while adaptation to stress lowers it 6.5-fold.

TABLE 2. Effect of Adaptation to Periodic Hypoxia and Adaptation to Stress on the Circulation Indexes during Sublethal Hypoxia

Index	Breathing atmospheric air (control I)	Sublethal hypoxia		
		control (II)	adaptation to hypoxia	adaptation to stress
	1	2	3	4
Oxygen content in arterial blood, ml/100 ml	17.88±0.090	6.910±0.450*	7.529±2.077*	9.190±0.431*
Oxygen uptake, ml/100 g×min	1.710±0.080	0.820±0.040*	1.556±0.23+	1.310±0.160*,+
Arterial transport of oxygen, ml/100 g×min	6.020±0.03	1.35±0.09*	3.79±0.68*,+	2.41±0.15*,+
Oxygen supply/uptake ratio, rel. units	3.52±0.02	2.04±0.17	2.42±0.40*	1.83±0.02*
Oxygen uptake/supply ratio, rel. units	0.284±0.008	0.607±0.001*	0.410±0.002*	0.543±0.001*,+
Carbon dioxide emission, ml/100 g×min	1.400±0.80	0.660±0.60*	1.279±0.155+	1.032±0.190
Respiration coefficient, rel. units	0.820±0.030	0.800±0.010	0.824±0.109	0.788±0.073
MVFR, ml/100 g×min	33.70±2.000	39.50±1.200*	61.12±19.76	26.20±2.900*,+
Arteriovenous difference, ml/100 ml	5.08±0.42	4.16±0.14	3.48±1.48	4.99±0.34+

TABLE 3. Effect of Adaptation to Periodic Hypoxia and Adaptation to Stress on the Blood Indexes of Acid–Base Equilibrium, Lipolysis, and LPO, and on the Concentration of Lactic Acid during Sublethal Hypoxia

Index	Breathing atmospheric air (control I)	Sublethal hypoxia		
		control (II)	adaptation to hypoxia	adaptation to stress
	1	2	3	4
Normal buffer bases, mmol/liter	47.10±0.6	47.30±3.7	47.62±0.33	47.30±0.03
Buffer bases, mmol/liter	43.20±1.6	25.3±0.20*	35.80±1.57*	28.20±0.70*,+,○
Shift of buffer bases, mmol/liter	−3.9±0.3	−22.01±0.6*	−11.8±1.24*,+	−19.1±0.70*,+,○
Bicarbonate concentration, mmol/liter	20.50±0.9	5.07±0.95*	11.96±0.27*,+	4.57±0.26*,○
Tension of carbon dioxide, mm Hg	33.70±0.87	19.20±1.70*	25.64±3.33*	10.70±1.00*,+,○
pH of arterial blood	7.400±0.001	7.060±0.010*	7.297±0.053+	7.245±0.023*,+
pH of mixed venous blood	7.360±0.001	7.030±0.010*	7.275±0.55+	7.203±0.22*,+
Lactic acid concentration in blood, mmol/liter	2.449±0.127	5.24±0.17*	4.747±0.594*	3.850±0.270*,+
Concentration of LPO products in blood, μmol MDA/liter	1.141±0.057	2.650±0.130*	1.600±0.069*,+	2.130±0.237*
Nonesterified (free) fatty acids, μmol/liter	2.700±20.0	950.0±36.0*	193.9±4.7*,+	288.0±37.00+,○

Note. MDA: malonic dialdehyde.

We sought the causes of this paradox by analyzing the data concerning the effect of adaptation on the acid-base equilibrium, LPO activation, and lipolysis (Table 3). These data provide evidence that adaptation to either factor approximately equally restricted the drop of such a crucial index as the pH during acute hypoxia. The decrease of buffer bases content and bicarbonate concentration in the blood was more marked in stress-adapted animals than in the animals adapted to hypoxia. This can be explained by the more marked hyperventilation in the animals of this group (Table 1), but it is hardly a positive adaptive shift. On the other hand, the lactate concentration is somewhat lower in the stress-adapted animals than in the animals adapted to hypoxia, although this difference is hardly to be regarded as significant for equal pH values. Finally, the ability of adaptation to block LPO activation and lipolysis, manifesting itself as a multiple increase in the free fatty acid content in the blood, is approximately equally marked for both variants of adaptation.

On the whole, these data show that adaptation to hypoxia provides for a sufficient oxygen uptake by the tissues during its acute deficiency, mainly due to the increased O_2 supply resulting from a greater increase in the MVFR. Adaptation to stress solves this problem by developing a more effective external respiration, a higher O_2 tension in the blood, and an increased tissue capacity for O_2 uptake. However, under conditions of increased O_2 supply the overall O_2 uptake by the tissues proves to be higher for adaptation to hypoxia than for adaptation to stress. Thus, the data in the tables allow us to assert that, in contrast to adaptation to hypoxia, adaptation to stress results in a more economical response of the circulatory system and in an increased ability of cells to take up O_2 from the reduced volume of blood supplied. This, by itself, does not explain why the direct protective effect of adaptation to hypoxia is several times lower than the cross-protective effect of adaptation to stress. In discussing this problem, we must remember that, along with such an important factor as the adaptation regimes which were used in our experiments, the so-called phenomenon of adaptive stabilization of structures (PASS) may play an important role in the mechanism of the powerful antihypoxic cross-effect of adaptation to stress. PASS has been encountered during studies of diverse cross-effects of adaptation to stress, which protects not only against acute stress injuries [8], but also against chemical burns [16], ischemic necrosis [4], cardiac arrhythmias [3], radiation [1], and, as ascertained here, against sublethal hypoxia. This protection turns out to be afforded not only at the level of the whole organism, but also at the level of the isolated heart [11] and organelles isolated from it (elements of the sarcoplasmic reticulum, mitochondria, and nuclei), which acquire a high resistance to autolysis [9,10,13]. It is the complex of these shifts which was defined as PASS. Later, the induction of synthesis and accu-

mulation of several isoforms of proteins (hsp) with a molecular weight of 70 kD, which develop in cells under the influence of stress hormones, were found to play an important role in the mechanism of PASS. These proteins are known to exhibit the ability to disperse denaturation-destroyed proteins [14], to be bound to calmodulin receptors [15], as well as to suppress free-radical oxidation by activating antioxidation enzymes [7]. Due to these effects they stabilize the cell structures and contribute to PASS development during adaptation to repeated stress. With our use of adaptation to gradually exacerbated hypoxia, stress is reduced to the minimum, and hsp accumulation and PASS effects are little marked [12]. On the basis of this, we suggest that the cross antihypoxic effect of adaptation to stress is due to the development of PASS, i.e., to a direct increase of the resistance of cell structures to such factors as a high concentration of hydrogen ions, a reduced oxygen tension, deficiency of energy-rich phosphorus compounds, etc. During adaptation to hypoxia, PASS does not develop, and the protection is mainly associated with profound adaptive changes in the respiratory and circulatory function.

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Responsiveness of Mesenteric Arterioles to Epinephrine in Metabolic Coma

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One critical state of the human body is the metabolic coma resulting from disruption of metabolic processes [5]. Its prominent causes are insulin-induced hypoglycemia and ketoacidosis. These frequently aggravate diabetes mellitus and are important considerations in insulin shock therapy and in acetone poisoning, respectively [3].

It is generally recognized that the major role in the establishment and maintenance of metabolic homeostasis of tissues in health and disease is

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