RESPONSE OF RATS TO HYPERBARIC OXYGEN AFTER PRELIMINARY ADAPTATION TO HYPOXIA

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Preliminary adaptation of rats to hypoxia under conditions increasing resistance to many stress-producing agents not only had no protective effect against exposure to hyperbaric oxygen at pressures up to 6 kgf/cm^2 but, conversely, lowered the resistance of the animals. The latent period of onset of seizures in the adapted rats was shortened especially if exposure to hyperbaric oxygen began 1 or 2 days after the end of adaptation to hypoxia, and was a little shorter in the experiments carried out after 3-4 days. The responses returned completely to normal 1 month after the end of adaptation to hypoxia. The possible causes of development of the phenomena are discussed.

KEY WORDS: adaptation to hypoxia; hyperbaric oxygen; resistance.

Previous investigations [1, 2] have shown that adaptation of rats to hypoxia increases their resistance to many harmful agents. Similar results have been described [3] for mice and guinea pigs, adapted to hypoxia, with respect to subsequent exposure to hyperbaric oxygen (HO). However, in experiments on rats [5], on the other hand, the earlier onset of seizures has been found under the influence of HO, despite preliminary adaptation of the animals to hypoxia. This paper describes the study of the effect of HO on rats adapted to hypoxia under conditions which, in previous experiments, increased the general resistance of the animals.

EXPERIMENTAL METHOD

Sexually mature male rats weighing 150-200 g were used. Every day except Sundays the animals were kept for 5 h in a pressure chamber at an altitude initially of 2500 m, increasing thereafter by 500 m daily to 7500 m for a period of 6 weeks. The rats were then placed in pairs (experimental and control) in a hyperbaric oxygen chamber. After 10-15 min, to become accustomed to the new situation, the chambers were ventilated with pure oxygen for 4 min. This was followed by compression with pure oxygen to 6 kgf/cm^2 for 3 min. Three series of experiments were carried out: in series I the adapted rats were exposed to HO 1-2 days, in series II 3-4 days, and in series III 30 days after the last day of adaptation to hypoxia.

EXPERIMENTAL RESULTS AND DISCUSSION

The results are given in Table 1 and Fig. 1. Table 1 shows that adaptation to hypoxia not only did not improve resistance to HO but, on the contrary, reduced the resistance of the animals to this extremal factor, as shown by the shortening of the time of onset of seizures (TOS). This effect was particularly marked in the experiments of series I. Whereas TOS in the control animals varied from 21 to 74 min (Fig. 1), in the rats adapted to hypoxia (AH rats) the pathological symptoms began much earlier: TOS varied from 11 to 42 min. The differences between the mean values of the latent period are significant (Table 1).

The AH rats likewise showed no advantage in the experiments of series II. Although their TOS varied between 9 and 67 min, which was close to the control (12 and 66.5 min), this simply indicated an increase in the scatter of the values in the AH rats, as shown by the coefficient of variation (C_V), which was almost doubled. As regards the mean value of TOS, in this series of experiments it was significantly shorter than in the control (25.7 and 41.0 min respectively). Not until 30 days after the end of adaptation to hypoxia was the response of the experimental and control rats to HO the same (experiments of series III).

These results agree with those obtained by Brauer et al. [5], who described the earlier onset of seizures in rats during exposure to HO at 7 kgf/cm^2 if preceded by adaptation to an altitude of 5300 m for 24 h daily for

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TABLE 1. Latent Period of Seizures (in min) in Intact Rats (control) and Rats Adapted to Hypoxia (experimental) during Exposure to Hyperbaric Oxygen at 6 kgf/cm^2

Series of experiments	Group of animals	n	$M \pm m$	$\pm mt$ at $P<0,05$	C_v
I	Experimental	8	21,2±3,3	7,8	44,0
	Control	10	42,2±4,9	11,3	36,9
	P		<0,01		
II	Experimental	12	25,7±5,28	11,6	70,9
	Control	10	41,0±5,23	12,1	40,4
	P		<0,05		
III	Experimental	7	47,7±7,1	17,1	38,7
	Control	7	47,7±6,4	15,3	34,8

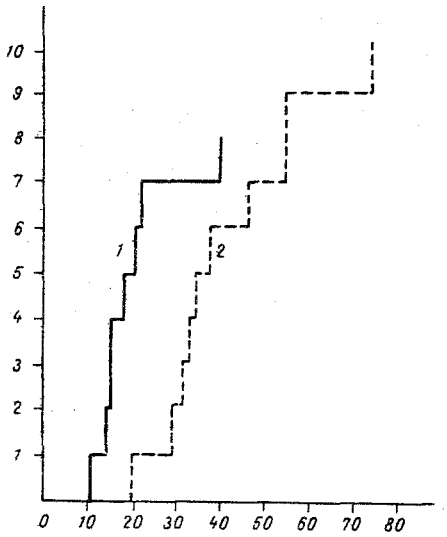

Fig. 1. Latent period of seizures in rats adapted to hypoxia (1) and control rats (2) during exposure to hyperbaric oxygen. Abscissa, time of onset of seizures (in min); ordinate, number of rats.

8 weeks. However, in Zhironkin's experiments [3], conducted on mice and guinea pigs, adaptation to hypoxia in a pressure chamber at an altitude of 6000 m for 25-30 days gave the opposite results. TOS in these animals exposed to HO was longer than in the control. The possible cause of these differences was the specificity of the responses in animals of different species.

It will be recalled that the conditions of adaptation to hypoxia were chosen so that the rats had increased resistance to the action of ionizing radiation, acceleration, changes in gravitational loads, injection of foreign protein, cyanide poisoning, infection with Mycobacterium tuberculosis [1], and to the action of hypokinesia [2]. However, no increase in resistance to the action of HO (10 kgf/cm^2) could be detected. The resistance of the AH rats, measured as the cerebral blood volume, pulse rate, character of respiration during exposure, and death of the animals during decompression, in most cases corresponded to that in the control and was increased only in individual experiments.

At this stage it is worth recalling the description of the second part of the experiments by Brauer et al. [5], in which AH rats were exposed not to HO, but to hyperoxia at normal barometric pressure (an atmosphere of 53% O_2 and 47% N_2). In these experiments preliminary AH, judging from the milder lung pathology and lower mortality among the rats, gave a distinct prophylactic effect.

With these facts in mind, it can tentatively be suggested that the increase in the sensitivity of the AH rats to HO seizures was due to depression of defensive-adaptive reactions developing at the level of the cerebral circulation in response to an increase in the blood PO_2 [6]. The protective role of these reactions – an increase in the resistance of the cerebral vessels and a decrease in the cerebral blood flow – consists of the prevention of an excessive supply of oxygen to the brain tissue during inhalation of HO [4]. The weakening of the adaptive

reactions of the animals at the level of the cerebral circulation is probably attributable to the fact that during adaptation to hypoxia the capilarization of the tissues (especially in the brain) increases, as also does the permeability of the vessel walls. All these effects inevitably lead to an increase in the oxygen supply to the nerve cells, both on account of the increased volume of the blood flow and as a result of increased diffusion of oxygen from the blood into the tissue. Conditions favoring the earlier onset of seizures are thereby created. Consequently, despite the increased resistance of the animals to various extremal factors after adaptation to hypoxia, in the case of exposure to HO the negative effect of inadequacy of the protective reactions at the level of the cerebral circulation predominates.

From the practical point of view it is important to emphasize the need to allow for the negative effect of preliminary adaptation to hypoxia when individual sensitivity to the paroxysmal action of HO is assessed. In clinical practice, during the treatment of persons exposed for long periods to hypoxia, milder conditions of hyperbaric oxygenation should probably be recommended.

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EFFECT OF CHOLERAGEN ON STRUCTURE AND OXIDATIVE PHOSPHORYLATION OF ISOLATED MITOCHONDRIA IN EPITHELIUM OF RABBIT SMALL INTESTINE

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The mitochondrial fraction was isolated from the epithelium of the rabbit small intestine by differential centrifugation in isotonic sucrose. When a malate-glutamate mixture was used as the substrate the respiratory quotient of these mitochondria was 3-5. Changes in the functional state of the mitochondria were accompanied by stereotyped structural changes of configuration of the "orthodox–condensed" type. Addition of unpurified choleragen to the incubation medium of the mitochondria caused no change in the rate of oxygen utilization in Chance's third or fourth state.

KEY WORDS: mitochondria; structure; oxidative phosphorylation; intestine; choleragen.

The mitochondria are among the most vulnerable organelles of the cell and they undergo functional and structural changes in a variety of pathological processes, including in cholera intoxication, for under these circumstances active ion transport, for which these organelles supply energy, is significantly disturbed [5, 14]. Involvement of the mitochondria in the pathological process could be the result either of direct interaction between the penetrating subunit of choleragen [7] or of activation of nucleotide-cyclase systems [4, 12, 13]. The available data on the direct action of choleragen on isolated mitochondria in vitro are contradictory. Mitochondria isolated from the epithelium of the alimentary tract are rarely used as a test object, for hydrolases and mucus, which could injure or contaminate the mitochondrial fraction, are present in the initial homogenate.

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