EFFECT OF ADAPTATION TO HIGH ALTITUDE HYPOXIA ON NONSPECIFIC RESISTANCE, HEMAGGLUTININ PRODUCTION, AND THE DEVELOPMENT OF ADJUVANT ARTHRITIS IN RATS

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Experiments on rats showed that adaptation to periodic high-altitude hypoxia enhances the immune response to sheep's red blood cells, increases the serum lysozyme activity, weakens the manifestation of adjuvant arthritis, and prevents the inhibition of antibody formation induced thereby.

KEY WORDS: hypoxia; immune response; antibodies; adjuvant disease.

In persons residing permanently in the mountains and in animals adapted to the periodic action of moderate hypoxia the immune response to bacterial antigens is enhanced and the serum immunoglobulin level is raised [4, 5]. It has also been shown that acute hypoxia induces a decrease in resistance to respiratory infections and depression of alveolar macrophage function in animals not adapted to it [3]. The effect of adaptation to periodic hypoxia on immunogenesis and its disturbances in adjuvant arthritis have not hitherto been studied. The aim of the present investigation was to assess the effect of adaptation to periodic hypoxia on certain indices of nonspecific resistance and the immune response in healthy animals and in animals with adjuvant polyarthritis.

EXPERIMENTAL METHOD

Noninbred male rats weighing 250-300 g, divided into four groups, were used. In the animals of groups 1 (nine rats) and 2 (seven rats) a state of adaptation to high-altitude hypoxia was induced by keeping the animals for 6 h daily in a pressure chamber at an "altitude" of 5000 m for 1.5 months. The animals of groups 3 (seven rats) and 4 (nine rats) were kept under ordinary conditions and served as controls for the first two groups.

On the 31st day after the beginning of adaptation to hypoxia adjuvant arthritis was produced in the rats of groups 2 and 3. Freund's complete adjuvant was injected in a dose of 0.2 ml into the hind footpads of the animals. On the 52nd day after the beginning of adaptation the animals of all groups were immunized by a single intraperitoneal injection of a 10% suspension of sheep's red blood cells (SRBC) in a dose of 2.5 ml. Hemagglutinin production was tested on the 7th, 14th, and 21st days after immunization by the usual method and the dynamics of nonspecific resistance (lysozyme, complement) was studied on the 30th, 38th, 45th, and 52nd days after the beginning of adaptation. The serum lysozyme concentration was determined by a nephelometric method using Micrococcus lysodeikticus [2]. The serum complement titer was determined for 50% hemolysis photometrically and expressed in conventional units. The intensity of manifestation of arthritis was assessed by the edema index [6], reflecting the increase in volume of the affected joints in per cent. The dynamics of spread of the inflammatory changes in the animals also was recorded.

The results were subjected to statistical analysis by Student's t-test.

EXPERIMENTAL RESULTS

In rats adapted to high altitude hypoxia the immune response to SRBC was intensified. The hemagglutinin titers in the adapted animals were significantly higher than in the control rats at all times of observation after

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TABLE 1. Effect of Adaptation to High Altitude Hypoxia on Development of Adjuvant Disease in Rats (M ± m)

Group of animals	Number of animals	Edema index			Lysozyme				Complement			
		time after beginning of experiment, days										
		38	45	52	30	38	45	52	30	38	45	52
Control	9	—	—	—	31,4±1,0	30,1±0,53	30,6±0,7	31,2±1,3	121,6±6,8	110,0±2,8	120,0±6,2	114,0±2,8
Adjuvant *arthritis*	7	136,1±14,7	147,1±20,0	162,0±22,0*	28,8±1,0	38,1±0,5*	38,3±0,5*	39,6±1,05*	121,6±6,8	186,6±6,8*	179,0±14,5*	204,6±5,9*
Adaptation to high altitude hypoxia	9	—	—	—	30,5±1,0	33,7±0,15*	39,8±0,6*	39,2±0,45*	138,2±8,9	125,3±6,9	130,7±2,8	124,5±9,9
Adaptation to high altitude hypoxia + adjuvant arthritis	7	101,3±8,2	110,8±13,6	103,5±8,1	31,2±1,0	38,5±0,3*	38,7±0,3*	37,4±1,05*	118,1±5,6	139,0±2,6*	134,6±6,9*	159,2±8,5*

*Differences significant compared with control.

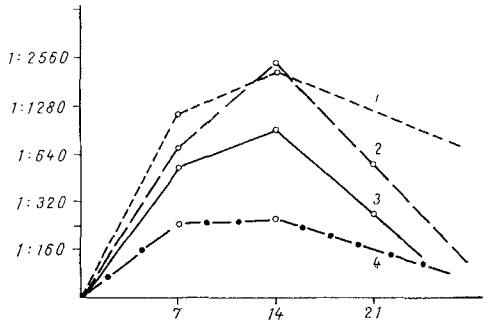

Fig. 1. Changes in hemagglutinin titer in rats during adaptation to high altitude hypoxia. Abscissa, days after immunization; ordinate, hemagglutinin titer. 1) Rats adapted to high altitude hypoxia; 2) rats with adjuvant disease adapted to high-altitude hypoxia; 3) rats of control group; 4) rats with adjuvant disease.

immunization (Fig. 1). The most marked difference between the experimental and control series was found on the 14th day after immunization, when the hemagglutinin level in the adapted rats was more than three times higher than in the intact animals.

During adaptation of the rats their serum lysozyme activity increased. For instance, in the control animals the lysozyme level was 30.1 ± 0.53 conventional units (c.u.), on the 30th day after the beginning of adaptation it was 30.5 ± 1.05 c.u., and on the 45th day 39.8 ± 0.6 c.u. ($P < 0.001$). As regards the serum complementary activity, no significant changes were found in rats adapted to high altitude hypoxia.

Adaptation to high altitude hypoxia led to a significant decrease in the severity of adjuvant polyarthritis measured by the edema index (Table 1) and the index of spread of inflammatory changes. For instance, the spread of inflammatory changes to joints of the four limbs and involvement of the tail was observed in only one of the seven experimental rats but in five of the seven control animals ($P < 0.001$). Meanwhile adaptation affected changes in nonspecific resistance and the immune response usually observed in adjuvant arthritis. It will be clear from Table 1 and Fig. 1 that the serum complement level in unadapted animals with adjuvant arthritis was increased by 50-80% and the lysozyme concentration by more than 25% compared with the control. On the other hand, the immune response in these animals was considerably weakened at all times after injection of the antigen. Adaptation reduced these deviations characteristic of adjuvant arthritis considerably: the complement level was 30% lower in the adapted animals during development of arthritis than in unadapted animals, whereas the immune response was close to that in the adapted animals without arthritis. Correspondingly, on the 14th day after immunization the hemagglutinin titer in animals with adjuvant disease and unadapted to hypoxia was only one-eighth as high as in rats with arthritis adapted to hypoxia (Fig. 1).

These experiments thus show that adaptation to high altitude hypoxia leads to an increase in the serum lysozyme activity, strengthens the immune response to SRBC, and prevents depression of the immune response characteristic of adjuvant arthritis, and reduces the inflammatory changes in the joints. The main result of this investigation is the establishment of the fact that adaptation to periodic hypoxia activates antibody production in normal animals and also prevents the depression of antibody production and the increase in complement titer observed in adjuvant arthritis. When attempts are made to explain this fact the well-known views that B lymphocytes play the decisive role in antibody production and that T lymphocytes are essential participants in allergic inflammation associated with adjuvant arthritis must be borne in mind. It can therefore be postulated that adaptation to periodic hypoxia, by increasing antibody formation by B cells, reduces activation of T lymphocytes.

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