fective in preventing experimental lipoidosis but also capable of optimizing hydro- and hemodynamic parameters in animals with established lipoidosis, a feature which opens up prospects for therapeutic application of such biopolymers.

REFERENCES

1. G. G. Avtandilov, *Medical Morphometry* [in Russian], Moscow (1990).
2. V. I. Burakovskii, S. S. Grigoryan, M. V. Kameneva, *et al., Dokl. Akad. Nauk SSSR*, **263**, № 2, 310 (1982).
3. I. V. Gannushkina, A. L. Antelava, and M. V. Baranchikova, *Byull. Eksp. Biol. Med.*, **116**, № 10, 367-370 (1993).
4. S. S. Grigoryan, M. V. Kameneva, and A. A. Shakhnazarov, *Dokl. Akad. Nauk SSSR*, **231**, № 5, 1070-1073 (1976).
5. R. F. A. Altman, *Experientia*, **29**, 256 (1973).
6. J. Davignon, *Arch. Surg.*, **113**, 28-34 (1978).
7. B. Folkow, M. Hallback, J. Lundgren, *et al., Acta Physiol. Scand.*, **80**, 93-106 (1970).
8. H. L. Greene, R. A. Mostardi, and R. F. Nokes, *Polym. Eng. Sci.*, **20**, № 7, 499-504 (1980).
9. K. J. Hutchison, J. D. Campbell, and E. Karpinski, *Microvasc. Res.*, **38**, № 1, 102-109 (1989).
10. R. A. Mostardi, L. S. Thomas, H. L. Greene, *et al., Biorheology*, **15**, 1-14 (1978).

Adaptation to Altitude Hypoxia Limits Lipid Peroxidation during Inflammation and Stress

V. V. Malyshev, L. S. Vasil'eva, S. B. Belogorov, and T. V. Nefedova

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 119, № 6, pp. 590-593, June, 1995
Original article submitted June 10, 1994

Preadaptation of rats to altitude hypoxia results in reduced activation of lipid peroxidation during subsequent stress, inflammation, or both, as compared to hypoxia-unadapted animals, with the result that secondary changes in organs and tissues of adapted rats are much less pronounced and conditions are created for alleviating the acute inflammation and the stress reaction.

Key Words: *adaptation to hypoxia; lipid peroxidation; inflammation; stress*

Activation of lipid peroxidation (LPO) is now known to be one of the main injurious factors in stress and may determine the development of secondary changes in organs and tissues [2,8]. It should be noted that the deleterious effects from LPO activation in inflammatory diseases are intensified by leukocyte-generated free oxygen radicals released into the inflammatory focus [13-15]. This is an important point, since the inflammatory process is usually accompanied by a marked stress reaction [5]. Recent research has shown that stress-associated damage can be significantly reduced by suppressing LPO through adaptation of the organism to hypoxia [8,9].

Accordingly, we assumed that enhancing the antioxidative potential of animals by adapting them to hypoxia should mitigate the secondary changes arising in their tissues during stress, inflammation, or both.

MATERIALS AND METHODS

Male white rats weighing 160-180 g were used; 40 of them served as controls and 80 were adapted to altitude hypoxia in a pressure chamber by exposing them to an "altitude" of 5500 m for 6 h per

Central Research Laboratory, Medical Institute, Irkutsk. (Presented by E. D. Gol'dberg, Member of the Russian Academy of Medical Sciences)

0007-4888/95/0006-0567$12.50

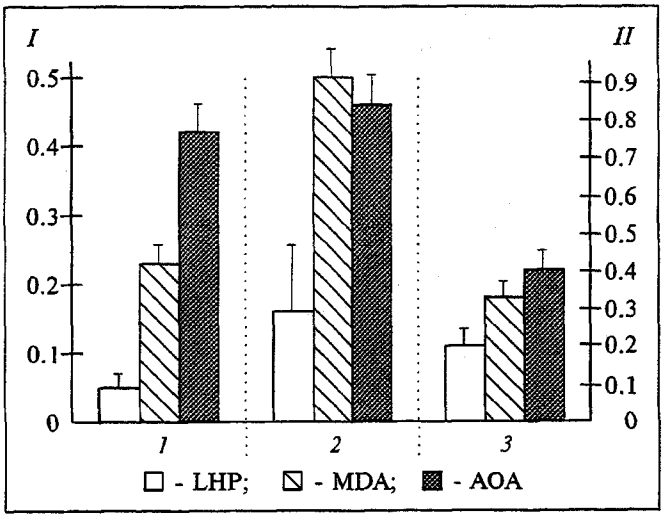

Fig. 1. Serum levels of LPO products and antioxidant activity (AOA) in intact controls (*1*), unadapted stressed rats (*2*), and hypoxia-adapted stressed rats (*3*). Ordinate: *I*) LHP and MDA in rel. units; *II*) AOA in arb. units.

day 5 days per week for a total of 6 weeks [9]. Stress was induced by immobilizing the animals on the back for 6 h. Aseptic inflammation was produced by implanting a sterile 1×5 mm celloidin plate under the skin. Morphological changes in the inflammatory focus were evaluated morphometrically on histological preparations [1,7]. The activity of LPO and antioxidant systems was estimated by measuring serum levels of the LPO products lipid hydroperoxides (LHP) [3] and malonic dialdehyde (MDA) [11], antioxidative activity (AOA) of the serum [4], and the content of reduced glutathione in the brain, heart, kidneys, and liver [12].

In the first experimental series we measured LPO products in the serum and reduced glutathione in the vital organs of unadapted and hypoxia-adapted stressed rats. The LPO products were measured when secondary changes in the tissues were at their maximum, i.e., 39 h after the 6-h immobilization, which corresponds to the time when the anxiety stage of the stress reaction is succeeded by a stage of resistance [6].

In the second series, the time course of LPO activity was followed during the acute period of inflammation development (the first 3 days) in rats with altered bodily resistance. There were three groups in this series. Group 1 had not been subjected to any treatment before inflammation was induced. Group 2 comprised rats adapted to hypoxia before inflammation induction, while group 3 animals were first adapted to hypoxia, then immobilized for 6 h, and finally implanted with a celloidin plate to produce inflammation.

RESULTS

The hypoxia-unadapted stressed rats had significantly higher serum levels of the LPO products than the intact controls or the rats adapted to hypoxia before being stressed ($p<0.01$, Fig. 1); the latter rats contained MDA at levels even lower than did the intact controls. The preliminary adaptation to hypoxia was therefore effective in preventing LPO activation during stress, apparently by making the antioxidant systems more capable of countering the activation process. This hypothesis is supported by the elevated concentrations of reduced glutathione (which is necessary for effective functioning of antioxidant systems [2]) in the organs of hypoxia-adapted rats (Table 1).

The results of the second experimental series are summarized in Figs. 2 and 3. Figure 2 shows

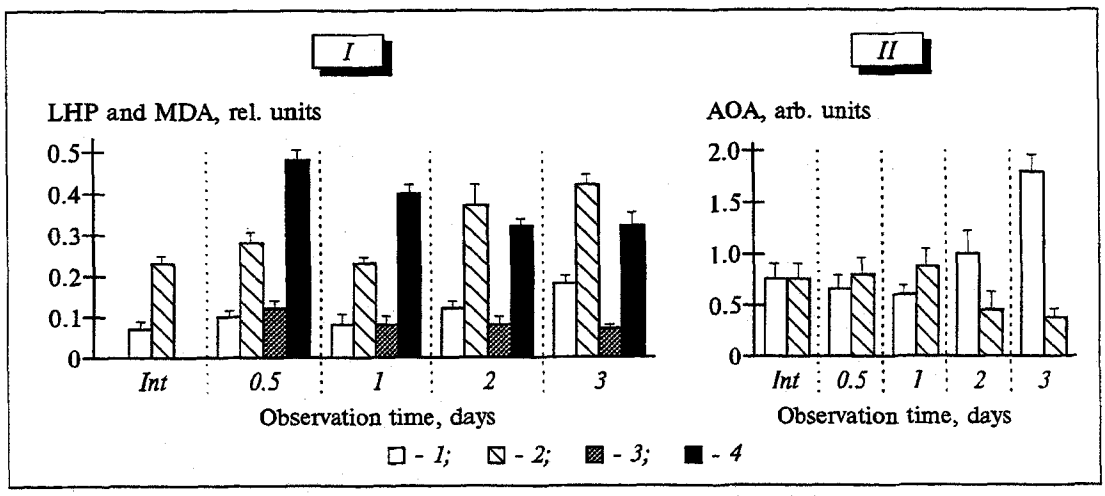

Fig. 2. Serum levels of LPO products (*I*) and antioxidant activity (AOA) (*II*) in the course of inflammation in unadapted and hypoxia-adapted rats. *Int*: intact rats. *I*: *1* and *2*) LHP and MDA in intact and unadapted rats during the acute period of inflammation; *3* and *4*) LHP and MDA in hypoxia-adapted rats during that period. *II*: *1*) AOA in intact and unadapted rats; *2*) AOA in hypoxia-adapted rats.

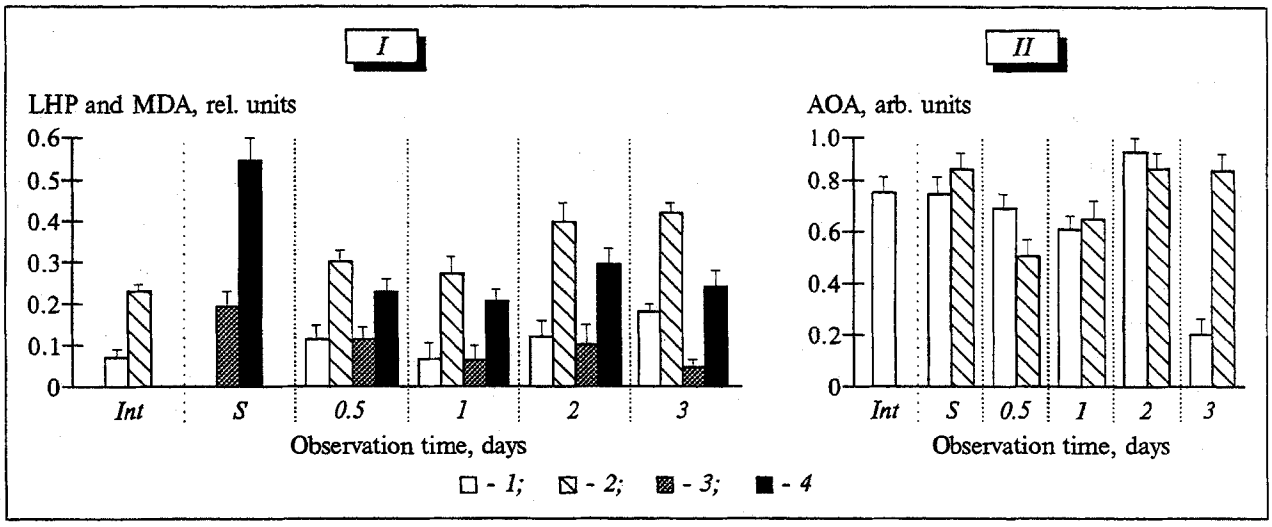

Fig. 3. Serum levels of LPO products and antioxidant activity (AOA) during the development of inflammation in unadapted stressed rats and in rats adapted to hypoxia before stressing. *Int*: intact rats; *S*: rats subjected to stress (39 h after 6-h immobilization). *I*: *1* and *2*) LHP and MDA in intact rats and in rats of the control group in the course of inflammation; *3* and *4*) LHP and MDA in unadapted and hypoxia-adapted stressed rats in the course of inflammation. *II*: *1*) AOA in intact rats and in rats of the control group in the course of inflammation; *2*) AOA in unadapted and hypoxia-adapted stressed rats in the course of inflammation.

serum levels of the LPO products on different days of the acute period of inflammation in unadapted and hypoxia-adapted rats. Their levels in the unadapted rats are seen to have reached their peak later (on day 3 of inflammation) than in the hypoxia-adapted animals, in which the levels of both LHP and MDA were highest as early as after 12 h of inflammation and then fell to approach on day 2 the values recorded for the intact controls. As shown in Fig. 2, the variations in serum AOA paralleled those in the LPO products.

Morphological examination of inflammation foci pointed to a more intensive, though transient, leukocyte reaction in the hypoxia-adapted rats in the acute period of inflammation, which can probably be associated with the early activation and rapid suppression of LPO. The adaptation to altitude hypoxia thus substantially shortened the period of LPO activation during inflammation, thereby limiting the degree of secondary changes in tissues of the inflammatory focus.

Serum levels of the LPO products in the course of inflammation in rats adapted to hypoxia and then subjected to 6-h immobilization are shown in Fig. 3. The hypoxia-adapted rats had much lower serum LHP and MDA concentrations during stress in the acute period of inflammation than did the unadapted or control animals, although by 48 h of inflammation the LPO products showed some rise, with a corresponding increase of serum AOA activity.

Morphological examination of the inflammatory foci from stressed rats showed that the acute period of inflammation was characterized by severe suppression of the leukocyte reaction and reduced phagocytic activity by macrophages. The preadaptation to hypoxia virtually normalized the course of acute inflammation, probably as a result of LPO suppression.

On the basis of the results of this study, we may speak of the following three interrelated beneficial effects to be expected from adaptation to altitude hypoxia:

1) substantially reduced LPO activation during stress;

2) increased lability of the systems activating and inhibiting LPO processes, which leads to an early onset of acute inflammation and its shortened duration and, hence, to much less pronounced secondary changes in the tissues concerned;

3) mitigation of the inflammatory process because of the adaptation-induced limitation of LPO activation.

Table 1. Levels of Reduced Glutathione in Control Rats and Rats Adapted to Altitude Hypoxia (nmol/g Tissue; $M \pm m$)

Group	Brain	Heart	Kidneys	Liver
Control rats ($n=10$)	1.62±0.04	1.33±0.09	2.52±0.09	3.86±0.2
Test rats ($n=10$)	1.89±0.08*	1.56±0.04*	3.15±0.12*	3.8±0.3

Note. *$p<0.05$ in comparison with the control group.

REFERENCES

1. G. G. Avtandilov, *Medical Morphometry* [in Russian], Moscow (1970).
2. V. A. Baraboi, I. I. Brekhman, *et al., Lipid Peroxidation and Stress* [in Russian], St. Petersburg (1992).
3. V. B. Gavrilov and M. I. Mishkorudnaya, *Lab. Delo*, № 3, 33-35 (1983).
4. G. I. Klebanov, I. V. Babenkova, *et al., Lab. Delo*, № 5, 59-62 (1988).
5. V. V. Malyshev, L. S. Vasil'eva, and V. V. Kuz'menko, *Byull. Eksp. Biol. Med.*, **116**, № 10, 348-349 (1993).
6. V. V. Malyshev, V. A. Petrova, and B. N. Manukhin, *Byull. Eksp. Biol. Med.*, **99**, № 3, 267-269 (1985).
7. A. A. Maiboroda, *Rationalization: A Collection of Articles* [in Russian], № 6, Irkutsk (1974), p. 90.
8. F. Z. Meerson and M. G. Pshennikova, *Adaptation to Stressful Situations and to Physical Exercise* [in Russian], Moscow (1988).
9. F. Z. Meerson, *The Physiology of Adaptive Processes (A Handbook)* [in Russian], Moscow (1986).
10. F. Z. Meerson, Yu. V. Arkhipenko, I. I. Rozhitskaya, *et al., Byull. Eksp. Biol. Med.*, **114**, № 7, 14-15 (1992).
11. V. N. Orekhovich, *Modern Methods in Biochemistry* [in Russian], Moscow (1977).
12. M. E. Anderson, *Glutathione: Chemical, Biochemical, and Medical Aspects*, Part A, New York (1989), pp. 333-405.
13. S. Jenkinson, R. Lawrence, and W. Tucker, *Amer. Rev. Respir. Dis.*, **130**, № 2, 302 (1984).
14. T. Slater, *Biochemistry*, **222**, № 1, 1 (1984).
15. Y. Keisari, *Cell. Immunol.*, **67**, № 1, 60 (1982).

Response to Airway Phagocytes to Lung Damage Before and After Strenuous Physical Exercise

O. P. Makarova, A. A. Zubakhin, and D. N. Mayanskii

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 119, № 6, pp. 593-596, June, 1995
Original article submitted May 17, 1994

Quantitative ratios between alveolar polymorphonuclear leukocytes (PML) and macrophages and the ingesting and reducing potentials of these phagocytic cells were studied after lung damage in unstressed mice and mice that had just been stressed by strenuous physical exercise (swimming for 60 min). Three days after the lung damage induced in unstressed mice by $AgNO_3$ (0.1 ml instilled intratracheally), PML numbers in the airway lumens were significantly increased, while the bronchoalveolar lavage fluid samples taken on day 14 after lung damage indicated intensified macrophage activity. In the mice instilled with $AgNO_3$ immediately after being stressed, the recruitment of PML and macrophages to the lungs was markedly decreased, although the percentage of macrophages reducing nitro blue tetrazolium had significantly increased. That the lungs of stressed mice sustained less injury than those of unstressed animals was indicated by the finding that lactate dehydrogenase activity in the cell-free fraction of bronchoalveolar lavage fluid was less damaged in response to intratracheal instillation of the destructive agent.

Key Words: *bronchoalveolar lavage fluid; macrophages; polymorphonuclear leukocytes; strenuous physical exercise; lung damage*

We showed earlier that different classes of macrophages react to strenuous physical exercise in different or opposite ways [1]. For example, the function of Kupffer cells is inhibited, whereas both fixed and free pulmonary macrophages exhibit heightened phagocytic activity, accompanied by enhanced migration of polymorphonuclear leukocytes (PML) to the airways. Since the resistance of the lungs to damage is largely dependent upon pulmonary phagocytes [2], alterations in the reactivity of respiratory tract ph-

Laboratory of Pathophysiology, Institute of General Pathology and Human Ecology, Siberian Division of the Russian Academy of Medical Sciences, Novosibirsk. (Presented by V. P. Kaznacheev, Member of the Russian Academy of Medical Sciences)

0007-4888/95/0006-0570$12.50