EFFECT OF HYPOXIA ON FUNCTION AND METABOLISM OF THE ALVEOLAR MACROPHAGES

G. N. Durnova, A. S. Kaplanskii, and V. V. Portugalov*

UDC 616.24-008.853-008.13-02:616-008.922.1.04

Cytophysiological and cytophotometric investigations showed that hypoxic hypoxia equivalent to an altitude of 5000 m effective for 9-11 days inhibits the phagocytic activity of the alveolar macrophages in rabbits. Meanwhile the activity of lactate and glucose-6-phosphate dehydrogenases in the macrophages is increased but the activity of malate dehydrogenase falls; this is indirect evidence of stimulation of glucose metabolism in the pentose shunt and of glycolysis and also of inhibition of metabolism in the Embden–Meyerhof–Krebs cycle. On the basis of experiments in vitro showing that respiration is the main source of energy supplying the phagocytic function of the pulmonary macrophages it is concluded that inhibition of respiration of the macrophages in hypoxia is the cause of the depression of their phagocytic activity.

Key words: alveolar macrophages; hypoxia; phagocytic activity.

Keeping animals in an atmosphere with a reduced oxygen concentration lowers their resistance to the agents of respiratory infections [2, 5]. Since the alveolar macrophages play the leading role in the removal of pathogenic microorganisms from the lungs [7, 9, 15, 17, 20] it is natural to suppose that the phagocytic activity of precisely these cells is disturbed in hypoxia. The macrophages have a predominantly oxidative type of metabolism [1, 4, 10, 11, 16], and there is therefore reason to suppose that keeping animals under hypoxic conditions will disturb the metabolism of the alveolar macrophages and so disturb their function.

The object of this investigation was to study the effect of hypoxic hypoxia on the phagocytic function and some aspects of the metabolism of the alveolar macrophages.

EXPERIMENTAL METHOD

Experiments were carried out on ten rabbits weighing about 2.5 kg. The rabbits (5) of the experimental group were kept for 9-11 days in a ventilated pressure chamber under a pressure of 405 mm Hg (temperature 22°C, relative humidity 70%, CO_2 concentration 0.03-0.06%). Every day the animals were taken from the chamber for 30 min to be given food and water and to allow the cages to be cleaned. The animals (5 rabbits) of the control group were kept throughout the experiments in an atmosphere with a normal oxygen concentration. After the end of 9-11 days the rabbits were killed by air embolism. A suspension of alveolar macrophages obtained by the method of Myrvik et al. [13] was used to determine the phagocytic activity of the macrophages and for cytochemical investigations. The technique of determining the phagocytic activity of the macrophages was described previously [1]. Activity of lactate, malate, glucose-6-phosphate, and NAD·H_2 dehydrogenases in the pulmonary macrophages was determined by a quantitative cytochemical method, using the MUF-5 microspectrophotometer. The mean activity of the dehydrogenases in the macrophages of each rabbit was calculated from the activity of the enzyme determined in 50 macrophages.

*Corresponding Member, Academy of Medical Sciences of the USSR.

Institute of Medicobiological Problems, Ministry of Health of the USSR, Moscow. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 79, No. 3, pp. 113-115, March, 1975. Original article submitted April 18, 1974.

In addition, in experiments in vitro with alveolar macrophages of guinea pigs the effect of inhibitors of respiration (sodium cyanide, 2×10^{-3} M), glycolysis (sodium fluoride, 2×10^{-2} M), and the pentose shunt (phenylbutazone, 10^{-3} M) [12, 19] on the phagocytic activity of the pulmonary macrophages was studied.

EXPERIMENTAL RESULTS

The results of determination of the phagocytic activity of the pulmonary macrophages of the rabbit show that in hypoxic hypoxia the ingestive power of the alveolar macrophages was reduced on the average by 53%. Keeping the rabbits in an atmosphere with a low pO_2 led to an increase in the activity of lactate and glucose-6-phosphate dehydrogenases (by 53 and 50% respectively) and a decrease of 39% in the malate dehydrogenase activity in the alveolar macrophages. A significant decrease in the activity of $NAD\cdot H_2$ dehydrogenase, however, occurred in only one of the five experimental rabbits. Investigation of the effect of the metabolic inhibitors on the phagocytic activity of the pulmonary macrophages of guinea pigs showed that ability of the macrophages to carry out phagocytosis of foreign material was most seriously disturbed after blocking of respiration (the phagocytic activity of the macrophages was reduced by 74%), whereas inhibitors of glycolysis and of the pentose shunt produced a less marked and approximately equal inhibition of the phagocytic activity of the pulmonary macrophages (the phagocytic activity of the pulmonary macrophages was reduced by 59 and 56% respectively). These results correlate well with those obtained in vitro by other workers [3, 10, 11, 15, 16], who found that blocking respiration and glycolysis disturbs the ingestive power of the alveolar macrophages. At the same time an important role of glucose metabolism in the pentose shunt for the phagocytic function of the macrophages was demonstrated, in agreement with the views of those workers [6, 8, 14] who have observed the stimulation of direct glucose oxidation during phagocytosis.

In the light of the data indicating the leading role of respiraton in the supply of energy for the phagocytic function of the pulmonary macrophages, the inhibition of the ingestive power of these cells in hypoxia will be understood. The decrease in the amount of energy formed as a result of inhibition of oxidative processes in the Embden–Meyerhof–Krebs cycle, as shown indirectly by the decrease in malate dehydrogenase activity, was evidently not compensated by activation of glycolysis and of metabolism in the pentose shunt, indicating an increase in the activity of lactate and glucose-6-phosphate dehydrogenases and leading to a disturbance of the phagocytic activity of the pulmonary macrophages. The results of determination of the phagocytic activity of the pulmonary macrophages of rabbits kept in an atmosphere with a low pO_2 are in agreement with observations made in vitro [3, 15, 18] that suggest a decrease in the phagocytic activity of the pulmonary macrophages under anaerobic conditions.

Comparison of the results of these experiments with those obtained previously [1] suggests that the phagocytic function of the pulmonary macrophages, with their characteristic oxidative type of metabolism, is disturbed much more by hypoxia than the analogous function of the peritoneal macrophages, which have a predominantly glycolytic type of metabolism.

LITERATURE CITED

1. A. S. Kaplanskii and G. N. Durnova, Tsitologiya, 15, 462 (1973).
2. N. N. Sirotinin, Vrach. Delo, No. 12, 1107 (1951).
3. A. B. Cohen and M. Y. Cline, J. Clin. Invest., 50, 1390 (1971).
4. A. M. Dannenberg et al., J. Cell Biol., 17, 465 (1963).
5. R. Ehrlich and B. J. Mieszkuc, J. Infect. Dis., 110, 278 (1962).
6. D. G. Evans and Q. N. Myrvik, J. Reticuloend. Soc., 3, 380 (1966).
7. J. B. L. Gee, Am. J. Med. Sci., 260, 195 (1970).
8. J. B. L. Gee et al., Arch. Intern. Med., 127, 1046 (1971).
9. G. M. Green and E. H. Kass, J. Exp. Med., 119, 167 (1964).
10. M. L. Karnovsky, Physiol. Rev., 42, 143 (1962).
11. M. L. Karnovsky et al., in: Mononuclear Phagocytes (Conference), Philadelphia (1970), p. 103.
12. J. E. Miller, Infect. Immun., 3, 390 (1971).
13. Q. N. Myrvik, E. S. Leake, and B. Farris, J. Immunol., 86, 128 (1961).
14. Q. N. Myrvik, J. Reticuloend. Soc., 11, 459 (1972).
15. D. S. Nelson, Macrophages and Immunity, Amsterdam (1969).
16. R. Oren et al., J. Cell Biol., 17, 487 (1963).
17. N. N. Pearsall and R. S. Weiser, The Macrophage, Philadelphia (1970).

18. A. J. Sbarra et al., J. Reticuloend. Soc., 12, 109 (1972).
19. R. R. Strauss, B. B. Paul, and A. J. Sbarra, J. Bact., 96, 1982 (1968).
20. C. Voisin et al., Bull. Physio-Path. Resp., 7, 775 (1971).