increased utilization of O_2 from the blood, and this in turn led to exhaustion of the O_2 reserves and to a critical fall of pO_2 in the venous blood. This picture is evidence of a congestive type of circulation and the development of circulatory hypoxia.

LITERATURE CITED

1. A. I. Abesadze, R. I. Kravivili, R. G. Dgebuadze, et al., Probl. Gematol., No. 2, 37 (1974).
2. V. I. Burakovskii, V. A. Agranenko, and Ya. A. Rudaev, Khirurgiya, No. 5, 62 (1968).
3. B. V. Petrovskii, Khirurgiya, No. 8, 10 (1967).
4. B. V. Petrovskii, O. K. Gavrilov, and Ch. S. Guseinov, Probl. Gematol., No. 2, 3 (1974).
5. V. S. Yarochkin, V. B. Koziner, and N. A. Gorbunova, Patol. Fiziol., No. 1, 12 (1975).
6. V. S. Yarochkin and V. B. Koziner, Probl. Gematol., No. 3, 43 (1976).
7. J. W. Dow, J. F. Dickson, N. A. J. Hamer, et al., J. Thorac. Cardiovasc. Surg., 39, 449 (1960).
8. H. L. Gadboys, R. Slonim, R. S. Litwak, et al., Ann. Surg., 156, 739 (1962).

ACTION OF VARIOUS DOSES OF PHYTOMITOGENS ON BLOOD LYMPHOCYTE PROLIFERATION IN SCHIZOPHRENIA

A. I. Pivovarova and G. I. Kolyankina

UDC 615.273.3.015.4:[616.155.3:616.895.8

KEY WORDS: phytohemagglutinin; concanavalin A; proliferation of lymphocytes; schizophrenia.

It was shown previously [1-4] that lymphocytes in the blood of schizophrenic patients are less able to proliferate in response to stimulation by phytohemagglutinin (PHA) and concanavalin A (con A). This phenomenon may be based on a number of factors, including a shift of the optimal dose of stimulator in this disease into the region of lower or higher concentrations of mitogen, as is observed in ataxia-telangiectasia, Bruton's disease, and systemic lupus erythematosus [5-7].

The aim of the present investigation was to compare the proliferative activity of lymphocytes, stimulated by different doses of PHA and Con A, of healthy subjects and patients with schizophrenia.

EXPERIMENTAL METHOD

Lymphocytes from 24 healthy subjects aged from 18 to 49 years and from 19 patients with schizophrenia (10 with a continuous-progressive and 9 with an episodic-progressive type of course), aged from 18 to 59 years, were tested. Blood was taken from the patients and healthy subjects into test tubes with heparin (10 i.u./ml). After sedimentation of the erythrocytes the plasma was drawn up into a Pasteur pipet and $1 \cdot 10^6$ lymphocytes were cultured in 1 ml of medium containing 20% autologous serum and 80% Eagle's medium with glutamine, for 72 h at 37°C. To stimulate the lymphocytes the following concentrations of PHA and Con A were used: 5, 10, 25, 50, 100, and 200 μg/ml. Two hours before the end of culture 1 μCi thymidine-^{3}H (specific radioactivity 19.6 Ci/mmole) was added to each flask. The cells were transferred to membrane filters (Hawg, 0.45 μ) and treated successively with physiological saline, 5% TCA, and 96° alcohol. The radioactivity of the samples was measured on a Mark II liquid scintillation counter. Proliferative activity was calculated on the basis of radioactivity in three parallel cultures.

Laboratory of General Pathophysiology, Institute of Psychiatry, Academy of Medical Sciences of the USSR, Moscow.

(Presented by Academician of the Academy of Medical Sciences of the USSR A. M. Chernukh.) Translated from Byulleten' Eksperimental'noi Biologii i Meditsiny, Vol. 90, No. 11, pp. 552-554, November, 1980. Original article submitted January 16, 1980.

0007-4888/80/9011-1522$07.50

© 1981 Plenum Publishing Corporation

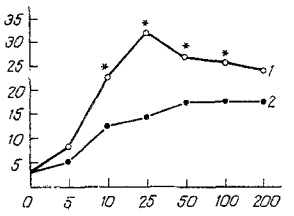

Fig. 1

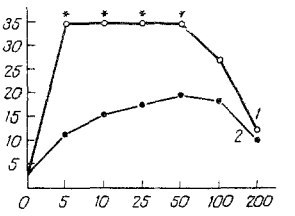

Fig. 2

Fig. 1. Proliferation of blood lymphocytes stimulated by different doses of PHA. Abscissa, dose of PHA (in μg/ml); ordinate, incorporation of thymidine-^{3}H (in cpm/10^3). 1) Healthy subjects; 2) Patients with shizophrenia. *P < 0.05.

Fig. 2. Proliferation of blood lymphocytes stimulated by various doses of Con A. Abscissa, dose of Con A (in μg/ml). Remainder of legend as to Fig. 1.

EXPERIMENTAL RESULTS

Data on the effect of different doses of PHA on DNA synthesis in lymphocyte cultures from schizophrenic patients and healthy subjects are shown in Fig. 1. Clearly, in the absence of stimulator the lymphocytes from patients and healthy subjects incorporated thymidine-^{3}H equally (2372 and 2354 cpm, respectively). After addition of PHA to the culture, cells both from patients and from healthy subjects respond by increased synthesis of DNA; the proliferative activity of the patients' lymphocytes, under these circumstances, was significantly depressed ($P < 0.05$), compared with that of the healthy subjects over the whole range of doses used, except 5 and 200 μg/ml. Maximal proliferative activity of blood lymphocytes from the healthy subjects was found after stimulation with a dose of 25 μg/ml, and a subsequent increase in the dose of mitogen led to a decrease in thymidine-^{3}H incorporation into DNA of the cells in culture. Consequently, the optimal stimulating dose of PHA for healthy blood lymphocytes was 25 μg/ml.

In schizophrenia the proliferative activity of the blood lymphocytes, stimulated by PHA, increased gradually with an increase in concentrations of the mitogen, to reach a maximum when 50 μg/ml PHA was used, and it was unchanged with a further increase in the dose of the stimulator. In schizophrenia the optimal dose of PHA for stimulation of blood lymphocytes was thus shifted toward higher values. The same conclusion could be drawn from subsequent analysis of individual dose-dependent curves, which showed that in schizophrenia the optimal dose for stimulation of lymphocytes in 58% of cases was 100-200 μg/ml. In healthy subjects the maximal proliferative response was recorded in 25% of cases. The relations were correspondingly reversed when the maximal stimulating effect of small doses (from 5 to 50 μg/ml) was analyzed: in the group of healthy subjects a maximal response to small doses was recorded in 75% of cases, compared with 48% in schizophrenia. The distribution of low and high optimal doses in the groups of patients and healthy subjects differed statistically significantly ($P < 0.01$).

The results of a study of the action of different doses of Con A on lymphocyte proliferation under normal conditions and in schizophrenia are shown in Fig. 2. It will be noted that stimulation with 5 μg/ml Con A led to a sharp increase in proliferative activity of the lymphocytes from healthy subjects. A further increase in the dose of Con A up to 50 μg/ml did not affect the level of proliferation of the cells in culture. However, the addition of 100 μg/ml or, to an even greater degree, 200 μg/ml of the mitogen to the lymphocyte culture inhibited incorporation of thymidine-^{3}H into DNA by the cells in culture.

In schizophrenia stimulation of lymphocytes with increasing concentration of Con A (from 5 to 50 μg/ml), just as in the case with PHA, led to a gradual increase in DNA-synthesizing activity of the cells. The proliferative response reached a maximum in this case when a dose of 50 μg/ml was used. Within the dose range of the stimulator from 50 to 100 μg/ml the level of lymphocyte proliferation was virtually unchanged, and only an increase in the dose to 200 μg/ml Con A led to inhibition of the proliferative response. It will be

clear from Fig. 2 that blood lymphocytes from the patients, just as when stimulated by PHA, incorporated thymidine-^{3}H much less intensively within the whole range of doses of Con A used than lymphocytes from healthy subjects. Significant differences between the dose-dependent curves of the two groups of subjects were observed when small doses of mitogen (from 5 to 50 μg/ml) were used; when larger doses of mitogen (from 100 to 200 μg/ml) were added, the differences were substantially less and were not significant.

The experiments thus showed that in schizophrenia the maximal response of the lymphocyte to both PHA and con A is shifted into the region of higher doses. Nevertheless, the response of lymphocytes to optimal doses of phytomitogens was much lower in schizophrenia than in normal subjects. It must be emphasized that the greatest difference between the two groups of subjects studied was obtained by the use of small doses of the mitogens.

The mechanism of the differences observed between the responses of patients' lymphocytes to stimulation by different doses of mitogens is not yet clear. It may perhaps be the result of the action of an inhibiting factor in the patient's blood serum [4]. Considering data showing that Tγ-subpopulations respond to small doses of mitogen, and the Tμ-subpopulation of lymphocytes respond to large doses [8], the results of the present investigation can be regarded as evidence of disturbance of the balance between suppressor cells in the body, and in turn, this could lead to changes in immunologic homeostasis. In this connection, identification of the above-mentioned lymphocyte subpopulations would help to solve the problem of the mechanism of origin of immunologic disturbances in schizophrenia.

LITERATURE CITED

1. G. I. Kolyaskina, Zh. Nevropatol. Psikhiatr., No. 7, 1017 (1970).
2. A. I. Pivovarova, Zh. Nevropatol. Psikhiatr., No. 8, 1191 (1974).
3. A. I. Pivovarova and T. P. Maznina, Zh. Nevropatol. Psikhiatr., No. 9, 1357 (1977).
4. T. K. Fetisova, in: Scientific and Practical Problems in Psychiatry in Research by Junior Specialists of the RSFSR [in Russian], Moscow (1975), p. 92.
5. C. S. Hosking, M. Fitzgerald, and M. I. Simmone, Clin. Exp. Immunol., 9, 467 (1971).
6. J. Malave, Z. Layrisse, and M. Layrisse, Cell. Immunol., 15, 231 (1975).
7. J. Malave and C. Cuadra, Int. Arch. Allergy, 55, 412 (1977).
8. L. Moretta, J. Immunol., 117, 2171 (1976).