INHIBITION OF DEVELOPMENT OF ADJUVANT ARTHRITIS IN RATS BY VITAMIN E

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Besides its specific coenzyme functions [11], vitamin E also has a number of properties by virtue of which it can be used as a pharmacological agent in various physiological and pathological processes. Vitamin E is a powerful antioxidant [11], a stabilizer of subcellular and cellular membranes [13], an antitumor [15] and anti-inflammatory [16] agent, and also in immunomodulator [5, 10].

In the present investigation the effects of vitamin E on the development and generalization of adjuvant arthritis (AA) was studied, for in the modern view AA is an adequate experimental model of human rheumatoid arthritis. Previously the writers studied the effect of lipid-soluble vitamins A and D on the course of AA in rats [6, 7]. The basis for the present investigation was data showing intensification of lipid peroxidation (LPO) in patients with rheumatoid arthritis [17], on inhibition by vitamin E of the development of experimental encephalomyelitis, another autoimmune disease [2, 9], and also information that vitamin E possesses anti-inflammatory [16] and membrane-stabilizing properties [13], encouraging the hope that it could be used with success for the prevention and treatment of AA.

EXPERIMENTAL METHOD

Experiments were carried out on 100 noninbred male rats weighing 200-250 g, for it was shown previously [7] that noninbred rats develop AA more rapidly than inbred animals and the disease follows a more severe course. In the experiments of series I the animals were given an oily solution of D,L-α-tocopheryl acetate (TPA) orally once a day for 3 days in a daily dose of 100 IU per animal. Rats of the control group received the oil used as the solvent for vitamin E in accordance with the same scheme. AA was produced in the animals 24 h after the final dose of the vitamin or oil, by injection of Freund's complete adjuvant (FCA), containing 2 mg of BCG vaccine in 1 ml, into the footpads of both hind limbs. During the experiment the time course of body weight, changes in the neighborhood of the ankle joints, and the character of generalization of the pathological process were determined in the animals. In series II the therapeutic properties of vitamin E, rather than its prophylactic properties, were investigated; for this purpose administration of TPA to the animals began 24 h after FCA, and continued for 6 days. In special experiments to discover the possible mechanisms of the effect of vitamin E on the development and generalization of AA, the pathological process was induced in the animals and vitamin E administration began 24 h later, and continued for 6

TABLE 1. Effect of Vitamin E on Activity of Lysosomal Enzymes in Blood Plasma of Rats with AA (M ± m)

Group of animals, experimental conditions	Lysozyme activity, conventional units	Increase in lysozyme activity, % of control	Activity of aryl sulfatases A and B, μmoles/100 ml/min	Increase in activity of aryl sulfatases A and B, % of control
Intact control	16,9±1,3	100	0,0665±0,034	100
AA + vitamin E	29,5±1,1*	174,6	1,094±0,058*	164,5
Vitamin E	17,7±1,7	104,7	0,681±0,05	102,4
AA	29,6±0,8*	175,1	1,145±0,034*	172,2

Legend. Asterisk indicates statistically significant differences between parameters (comparison of results of experimental groups with intact control).

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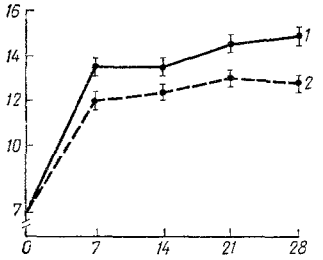

Fig. 1

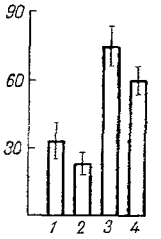

Fig. 2

Fig. 1. Effect of vitamin E on local manifestation of AA in rats. Abscissa, time after injection of FCA (in days); ordinate, diameter of cross-section of angle joints (in mm). 1) AA; 2) AA + vitamin E.

Fig. 2. Effect of vitamin E on concentration of LPO products in plasma of normal rats and rats with AA. Ordinate, level of Schiff bases (in conventional units). 1) Rats with AA receiving vitamin E; 2) intact rats receiving vitamin E; 3) rats with AA not receiving vitamin E; 4) intact control.

days, after which the rats were decapitated and activity of the lysosomal enzymes — lysozyme [1] and aryl sulfatases A and B [8] — was determined in the blood plasma. Activity of LPO in the rats was deduced from the level of LPO products (Schiff bases) in the plasma lipids. Lipids were extracted from the plasma by the method in [12] and the level of Schiff bases in the extract was determined [14]. The concentration of Schiff bases in the plasma was expressed as a percengage of the standard, reduced to the level of total lipids (per milligram). A solution of quinine sulfate (1 mg of the substance in 1 ml of 0.1 N H_2SO_4) was used as the standard, the intensity of which was taken as 100%. The concentration of total lipids in the blood plasma was determined by using a set of standard reagents (from Lachema, Czechoslovakia), based on the reaction of the lipid hydrolyzate with phosphovanillin reagent. The numerical results were subjected to statistlcal analysis by nonparametric methods and by Student's t and the chi-square tests.

EXPERIMENTAL RESULTS

Preliminary administration of vitamin E to rats for 3 days, followed by reproduction of AA, did not affect changes arising in joints of those limbs into which FCA was injected, and (compared with the control) it did not act on the time course of body weight, changes in which are one of the most characteristic indices of the severity of AA. Meanwhile prophylactic administration of vitamin E significantly inhibited the generalization of AA. For instance, in the control group spread of the pathological process to the forelimbs and tail was observed in 46.6% of cases, but in animals receiving TPA secondary arthritis developed in only 20% of cases ($P < 0.01$). Data on the therapeutic action of vitamin E in AA are given in Fig. 1 (administration of the vitamin began 24 h after injection of FCA). At all times of observation local changes in animals receiving TPA were significantly weaker than in the control. Vitamin E also inhibited generalization of the pathological process: secondary arthritis developed in 20% of cases in the experimental group but in 42.8% in the control ($P < 0.01$).

To discover the mechanisms of the protective action of vitamin E in AA, the level of LPO products was studied in intact animals and also in rats with AA. It will be clear from Fig. 2 that administration of vitamin E caused a marked decrease in LPO activity in the rats with AA. Administration of vitamin E to intact rats also reduced the intensity of LPO in these animals.

Data given in Table 1 on the effect of vitamin E on activity of the mediators of inflammation (lysosomal enzymes) in the plasma in AA are evidence of a considerable increase in this parameter, accompanying the development of AA, and characteristic of a well-marked inflammatory process. Meanwhile, no effect of vitamin E on enzyme activity was observed either under

normal conditions or in AA. This state of affairs raises doubts about the data given by some investigators on the membrane-stabilizing properties of vitamin E [13]. Meanwhile these results, which demonstrate that vitamin E has the properties of a true antiarthritic agent (capable of inhibiting generalization of the pathologic process), can with full justification be linked with the antioxidant properties of TPA. It will be evident that LPO processes play a far more important role in the pathogenesis of rheumatoid arthritis and its experimental model (AA) than has hitherto been considered. Considering the abundant data in the literature on the role of LPO in other forms of pathological processes [3, 4], it can be tentatively suggested that the intensification of LPO, leading to injury to cell membrane structures, is an initial factor in the development of various pathological forms.

LITERATURE CITED

1. V. G. Dorofeichuk, Lab. Delo, No. 1, 28 (1968).
2. G. N. Kryzhanovskii, G. A. Vilkov, and E. M. Stepanenko, Byull. Éksp. Biol. Med., No. 9, 336 (1984).
3. G. N. Kryzhanovskii, E. V. Nikushkin, V. A. Voronko, et al., Zh. Nevropatol. Psikhiat., No. 6, 806 (1984).
4. E. V. Nikushkin, V. E. Braslavskii, and G. N. Kryzhanovskii, Zh. Nevropatol. Psikhiat., No. 6, 810 (1981).
5. K. D. Pletsityi, Ter. Arkh., No. 2, 131 (1980).
6. K. D. Pletsityi, Immunologiya, No. 1, 62 (1981).
7. K. D. Pletsityi and I. N. Shaternikova, Patol. Fiziol., No. 4, 40 (1984).
8. A. A. Pokrovskii and V. A. Tutel'yan, Lysosomes [in Russian], Moscow (1976).
9. E. M. Stepanenko, G. A. Vilkov, and G. N. Kryzhanovskii, Byull. Éksp. Biol. Med., No. 9, 336 (1984).
10. W. R. Beisel, Am. J. Clin. Nutr., 35, Suppl. 1, 417 (1982).
11. J. G. Bieri, Vitam. Horm., 34, 31 (1976).
12. E. G. Bligh and W. J. Dyer, Can. J. Biochem., 37, 911 (1959).
13. J. H. Brown and S. H. Pollock, M. Nutr., 102, 1413 (1972).
14. A. S. Csallany and K. L. Ayaz, Lipids, 11, 412 (1976).
15. P. M. Horvath and C. Ip, Cancer Res., 43, 5335 (1983).
16. M. Kamimura, J. Vitaminol., 18, 204 (1972).
17. D. Rowley, J. M. C. Gutteridge, D. Blake, et al., Clin. Sci., 66, 691 (1984).

EFFECT OF ACTH ON RATE OF ^{32}P-ORTHOPHOSPHATE UPTAKE INTO SYNAPTOSOMAL PHOSPHOINOSITIDES OF THE ISCHEMIC RAT BRAIN

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The close attention paid by many investigators to phosphoinositides (PI) is due both to the high metabolic activity of these phospholipids and their sensitivity to changes in the functional state of the body [2], and also to the important role which they play in synaptic transmission [5, 10]. There is much evidence of the action of certain neuromodulators and hormones in PI metabolism in nerve tissue, and also on the possible regulatory role of these phospholipids in phosphoprotein phosphorylation under the influence of ACTH [7, 8]. PI metabolism in nerve tissue in pathology has been studied mainly at the tissue level. It has been shown, for example, that cerebral ischemia in rats caused marked changes in metabolism of

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