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Correction of Regulatory and Microcirculatory System Disturbances in the Early Stages of Experimental Atherosclerosis by Synthetic Antioxidants

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It is well established that the expression of pathological alterations in the major arteries and in the microcirculatory bed (MCB) in experimental dyslipoproteinemia (DLP) correlates with the functional state of the hypothalamic-hypophyseal neurosecretory (HHNS) and sympathico-adrenal systems [7,12]. Recently, attention has been focused on the MCB state in such complications of atherosclerosis as coronary heart disease, chronic coronary heart disease, acute myocardial infarction, and intravascular blood coagulation [1,4,5,10,13]. Microcirculatory disturbances and chronic ischemia arising on tissue and cellular levels in DLP are shown to underlie chronic noncommunicable pathology in different organs [6,7, 12]. An activation of lipid peroxidation (LPO) is considered to be a key event in hypoxic, ischemic, and reperfusion injuries [2,3,11]. From this point of view it is important to study the role of LPO in regulatory and microcirculatory disturbances in DLP and the possibility of correcting these disturbances by antioxidants. This is also interesting in the light of the "oxidative modifications" hypothesis of atherogenesis [14].

The aim of the present work was to study the antiatherogenic effect of the synthetic antioxidants mexidol and fenbutol (probucol) on lipid metabolism and on structural changes in the central and autonomic nervous systems and in different parts of the circulatory system in experimental DLP.

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MATERIALS AND METHODS

The experiments were carried out on 32 male chinchilla rabbits weighing 2.0-2.5 kg. The first group of animals received an atherogenic diet (ATD) containing 0.3 g cholesterol /kg body weight with vegetables during 2 months. Animals of the 2nd and 3rd groups were treated with either mexidol (30 mg/kg) or fenbutol (25 mg/kg) starting from the second month of the experiment. The 4th group of animals (control) were maintained on standard chow. Morphohistochemical study of the neurohypophysis and the supraoptic nucleus (SO) of the hypothalamus as well as the adrenergic innervation of the MCB was carried out according to Falk and Owmen. The intensity of specific fluorescence of catecholamines was estimated photometrically with a Lyumam I-3 microscope, the MCB was studied using total mesentery membrane preparations (according to V.V.Kupriyanov), morphometry of the cells and microvessels was performed with a "Leitz ASM" semiautomatic system for structural analysis (Germany), and erythro-

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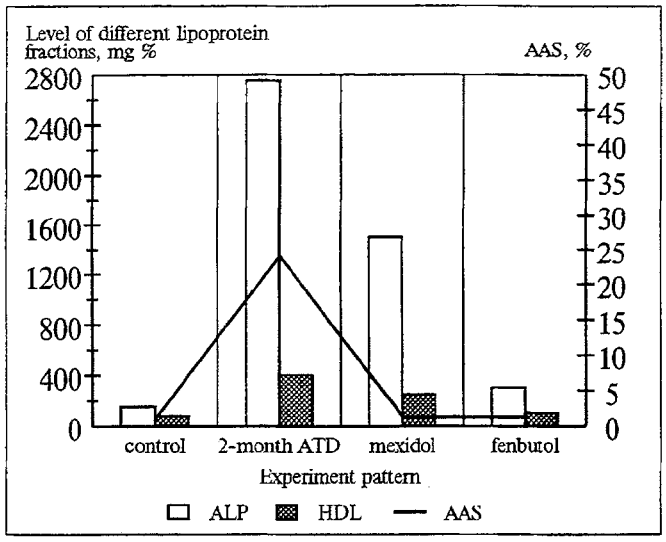

Fig. 1. Changes in lipoprotein level and AAS in DLP and in antioxidant treatment.

cyte transformation was studied with a "Hitachi" scanning electron microscope (Japan). The degree of expression of the atherosclerotic process was estimated as an aorta atherosclerotic score (AAS) (after G. G. Avtandilov). Different lipoprotein (LP) fractions and malonic dialdehyde (MDA) levels were assayed in the blood serum.

RESULTS

The 2-month atherogenic diet during s produced a more than 20-fold rise of the level of atherogenic lipoproteins (ALP) (Fig. 1) and a 3-fold rise of the MDA level (36 nmol/ml vs. 12 nmol/ml in the control). The AAS was 22%.

In the analysis of the morphofunctional state of the HHNS, the sizes of the neurosecretory neurons and their nucleus, the structural features, the amount of pycnomorphic cells, and the proportion between "light" synthetically active neurons and "dark" nonactive ones were studied. Morphometry of "light" and "dark" neurons revealed some decrease of their functional activity. In the neurohypophysis an accumulation of neurosecretory substance was observed. On the whole, the functional activity of the HHNS was depressed (Fig. 2). All elements of the MCB had marked vascular, intra-, and extravascular alterations such as arteriole constriction, venule tortuosity, and extensive intravascular aggregates. The intensity of catecholamine fluorescense in the adrenergic component of the microvessel innervation was increased (Fig. 3). Among the venous blood erythrocytes the number of echinocytes was elevated with a simultaneous decrease in normocytes (Fig. 4), suggesting the impairment of blood oxygen transport.

When antioxidants were added to the ATD, the ALP blood level in the 2nd and 3rd group was considerably lower as compared to the control (Fig. 1). In the SO nucleus of the hypothalamus the number of pycnomorphic cells was reduced; the shape of the neurons, their nuclei, and of other intracellular structures was similar to that in intact animals. Taken together with the near-control proportion between "light"and "dark" cells (Fig. 2), this indicates the restoration of the morphofunctional state of the

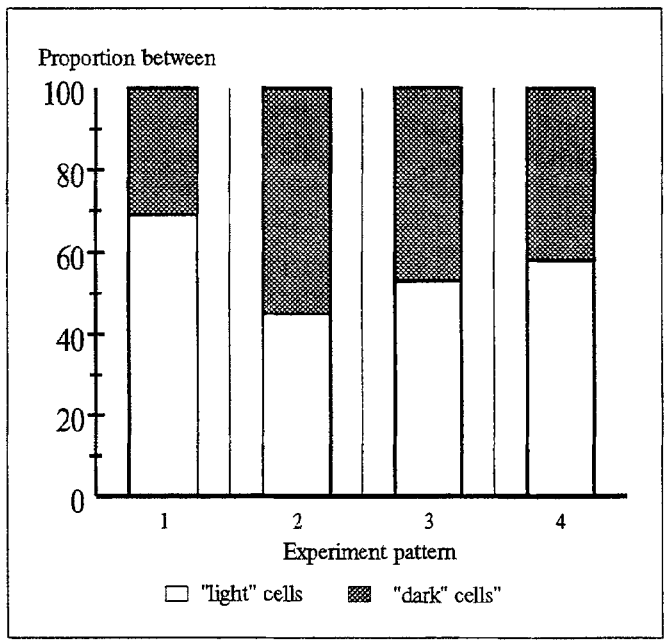

Fig. 2. Changes in proportion between "light" and "dark" cells in SO nucleus of the hypothalamus in DLP and in antioxidant treatment.

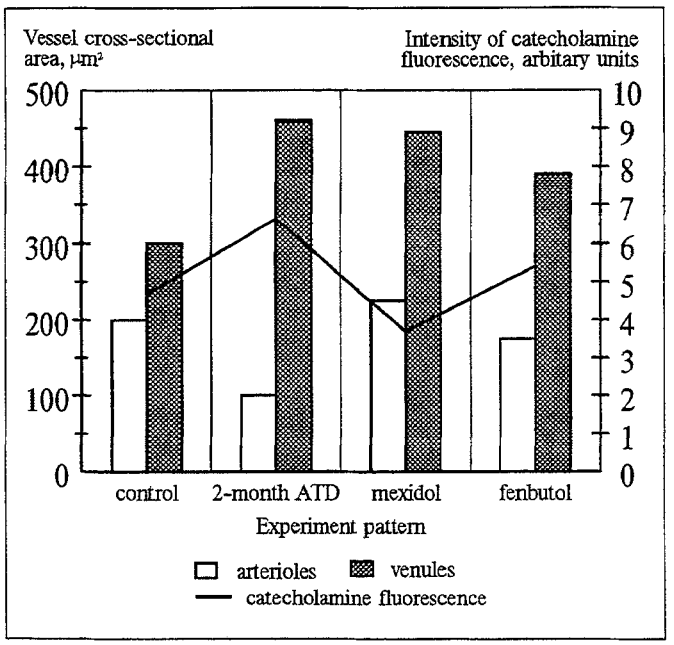

Fig. 3. Changes in cross-sectional area of arterioles and venules and intensity of catecholamine fluorescence in DLP and in antioxidant treatment.

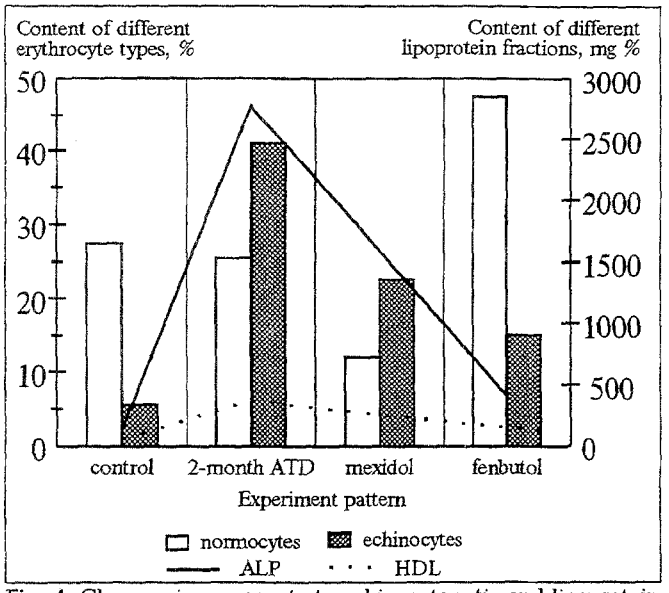

Fig. 4. Changes in normocyte to echinocyte ratio and lipoprotein fractions in rabbit blood in DLP and in antioxidant treatment.

hypothalamus. Apparently, both antioxidants (but especially fenbutol) possess a pronounced stabilizing effect on the neuron membrane structures.

The structure of the microvessel adrenergic axons was near normal and the intensity of catecholamine fluorescence in varicose vesicles was decreased; however, the effect of fenbutol on the adrenergic innervation of the microvessels was less pronounced. Simultaneously a regression of pathological alterations in the MCB was observed: there was no constriction of arterioles and precapillaries, and their diameter differed little from that in the control. Only local aggregates were found in venules. Mexidol completely abolished the spasm of afferent microvessels, while fenbutol affected mainly efferents (postcapillaries and venules) (Fig. 3). In the peripheral blood, the number of normocytes was significantly elevated with a simultaneous decline of pathological types of erythrocytes, which suggests the recovery of blood oxygen transport (Fig. 4).

The decline of the ALP fraction in the blood was accompanied not only by the normalization of MCB structure but also by a substantial decrease in AAS (1.5% and 1% in the 2nd and 3rd groups, respectively, versus 22% in the 1st group).

Thus, the antioxidants mexidol and fenbutol, when applied in the early stages of atherosclerosis development, prevent disturbances or lead to the restoration of lipid homeostasis, LPO inhibition, improvement in the microcirculatory and regulatory systems, and considerable regression of atherosclerotic lesions in the main arteries. It should be noted that the reaction to atherogenic DLP is a generalized one.

The fact that LPO inhibition and DLP correction prevented the onset and development of pathological alterations in the regulatory systems deserves special attention and is undoubtedly critical for the pathological process. The differences between the effect of mexidol and fenbutol indicate that the antioxidants, together with the prevention of oxidative modifications in ALP, affect other pathogenetic events as well.

Consequently, the regulatory and microcirculatory disturbances which appear in the early stages of atherogenesis are reversible, in particular through DLP correction by antioxidants.

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