of the potentiated baseline synthesis of NO) to the NO released under the influence of acetylcholine.

Thus, stress stimulates the baseline synthesis of NO by coronary endothelium. This probably causes a decrease in coronary tone and lowers sensitivity to sodium nitroprusside, and it is also accompanied by a reduction of stimulated endothelium-dependent coronary dilatation.

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Dynamics of Aseptic Inflammation against the Background of α-Tocopherol

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Administration of α-tocopherol before the induction of inflammation reduces the vascular response and inhibits the leukocyte phase, which limits the development of secondary alterations in tissues. During the reparative period fibroblast proliferation is suppressed and differentiation is accelerated, whereas the synthetic activity is lowered. As a result, the formation of the fibroblast capsule is slowed down.

Key Words: *inflammation; α-tocopherol acetate*

Activation of free-radical oxidation (FRO) is an integral component of any inflammatory process [8,9]. On the one hand, the products of lipid peroxidation play an important role in membrane renewal and in the regulation of cell functions [3], while on the other hand, excessive accumulation of FRO products is an important pathogenic link in the development of inflammation: it increases vascular permeability, aggravates DNA and plasma membrane damage, and affects the metabolism [2], i.e., it potentiates secondary alterations. Consequently, elucidation of the regularities and mechanisms governing inflammation under conditions where the organism's antioxidant potential is high would be conducive toward optimizing the inflammatory process. The objective of this study was therefore to investigate cell and vascular reactions in inflammation initiated against the background of the naturally occurring antioxidant α-tocopherol (α-TPH).

MATERIALS AND METHODS

Experiments were performed on 90 male rats. Inflammation was induced by subcutaneous insertion of a 1×5 mm celloidin plate in the shank area. The animals were assigned to two groups: α-TPH was injected once to group 1 (100 mg/kg intraperitoneally) one day before the induction of in-

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flammation. This dose of α-TPH is known to generate the most potent antioxidant and stress-limiting effects [7]. The concentration of a-TPH in the liver increases 5-fold and the native antioxidant content increases 20-fold [11]. Group 2 animals served as the control. Cell reactions in the inflammatory focus were assessed using morphometric methods.

RESULTS

Administration of α-TPH markedly changed the response of the microcirculatory bed in the inflammatory focus (Fig. 1). Twelve hours after insertion of the celloidin plate, i.e., during the leukocyte phase, the inflammatory focus of experimental animals contained 6.6-fold fewer plethoric capillaries ($p<0.01$), which indicates a markedly suppressed vascular reaction. There were no appreciable differences in the functional activity of mast cells in either group (these cells play an important role in the microcirculatory response); the density of the leukocyte infiltrate was similar in both groups. However, in group 1 animals the peripheral areas of the inflammatory focus contained twice as many neutrophils ($p<0.05$), and the thickness of the leukocyte rampart and the maximum neutrophil density were 1.5- and 1.9-fold lower ($p<0.05$), respectively, than in the control group (Fig. 2). Moreover, by the end of the 1st day of inflammation the thickness of the leukocyte rampart increased due to migration of neutrophils, being 2.4-fold thicker than in group 1 animals ($p<0.05$, Fig. 2). These observations indicate that administration of α-TPH lowers the rate of neutrophil migration from the periphery of the inflammatory focus toward the foreign body. Proceeding from the known fact that the lateral mobility of lipids and membrane fluidity are increased upon activation of FRO [4], it is logical to assume that α-TPH diminishes this effect by limiting the accumulation of free radicals in the tissues, thus increasing plasma membrane rigidity, and this in turn alters cell adhesive, migration, phagocytizing, and proliferative activities, hormonal sensitivity, etc. [3], probably including the ability of neutrophils to form a solid leukocyte rampart. The lack of chemoattractants may be another reason for the suppressed migration of neutrophils from the periphery toward the foreign body, since α-TPH binds reactive oxygen species that form active chemotactic factors while interacting with albumin-lipid complexes in the plasma; these factors facilitate the infiltration of the inflammatory focus with neutrophils [2]. Therefore, the leukocyte rampart formed in the focus in experimental animals differs from that formed in control animals not only in thickness but also in cell composition. It can be seen from Fig. 2 that the neutrophil:macrophage ratio in group 1 animals is 1:1, whereas in controls it is 2:1.

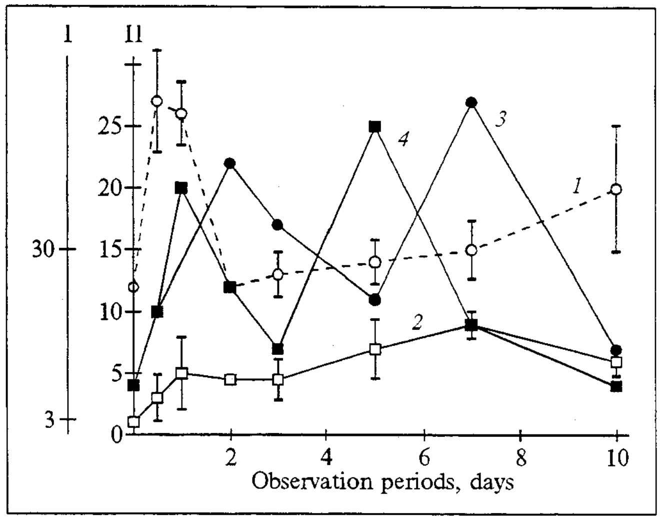

Fig. 1. Dynamics of the density of blood vessels and mast cells at the periphery of the inflammatory focus in control and α-TPH-treated animals. Ordinate: number of vessels (per 5000 μ²) (*I*) and mast cells (per mm²) (*II*). Vessel density in control (*1*) and experimental (*2*) animals; mast cell density in control (*3*) and experimental (*4*) animals.

During the macrophage phase (the 2nd-3rd day of inflammation) the vascular response was less pronounced in α-TPH-treated animals: the number of plethoric vessels and their diameters were 2.5-fold smaller ($p<0.05$), whereas in the control

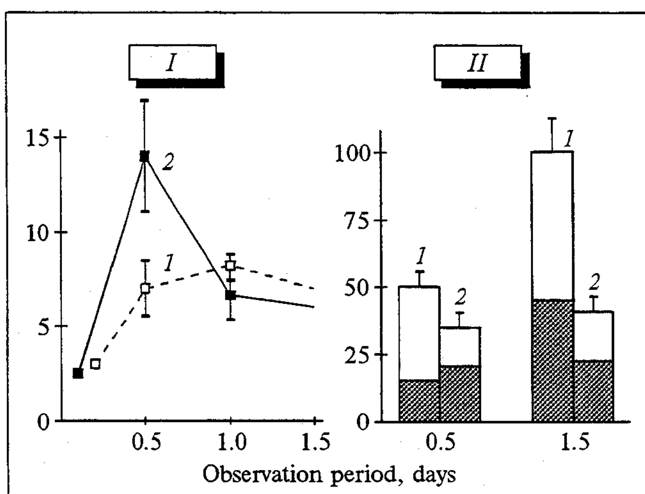

Fig. 2. Neutrophil density in leukocyte infiltrate at the periphery of the inflammatory focus, thickness of the leukocyte rampart, and the neutrophil:macrophage ratio in it in control (*1*) and α-TPH-treated (*2*) animals. Ordinate: *I*) number of cells in the peripheral zone (per 1000 μ²); *II*) thickness of leukocyte rampart, μ. Diagram: content of macrophages (black) and neutrophils (white) in the leukocyte rampart, %.

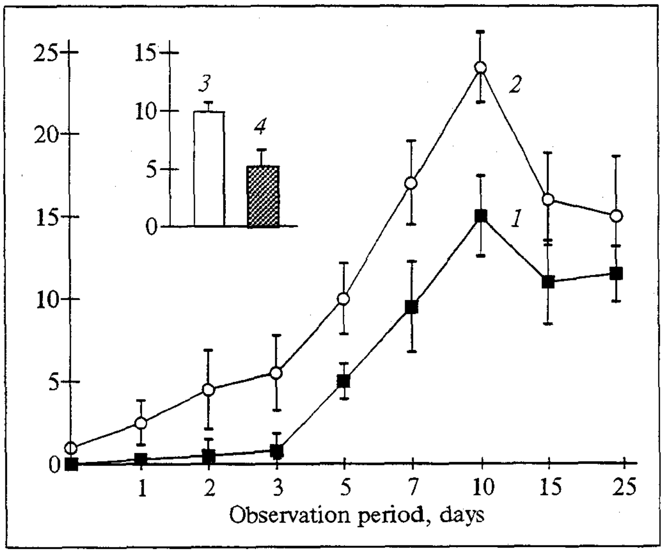

Fig. 3. Density of mature fibroblasts in the fibroblast capsule and maximum density of little-differentiated fibroblasts at the inflammatory focus periphery in control and α-TPH-treated animals. Ordinate: number of fibroblasts in the fibroblast capsule (per 1000 μ^2) and the peripheral zone (per 5000 μ^2). Density of mature fibroblasts in control (*1*) and experimental (*2*) animals; number of little-differentiated fibroblasts in control (*3*) and experimental (*4*) animals.

animals not only capillaries but also arterioles and venules were activated (Fig. 1). In both groups, the foreign body was surrounded by a cellular rampart consisting predominantly of macrophages.

Figure 3 shows that within this observation period many little-differentiated fibroblasts (11.0±0.7 cells per 5000 μ^2) appear in the control animals; in α-TPH-treated animals they are much less numerous (3.7±0.7, $p<0.01$), which indicates suppression of fibroblast proliferative activity. Considering the marked inhibition of the vascular reaction and functional activity of neutrophils after administration of α-TPH, one can assume that the concentration of plasma factors [10] and neutrophil-secreted transmitters [12] capable of stimulating proliferative processes in the inflammatory focus is decreased, which may account for the low proliferative activity of the fibroblasts.

At the same time, in the experimental animals more mature fibroblasts were present at the periphery of the inflammatory focus and around the remnants of the rampart (Fig. 3). These facts indicate that the rate of fibroblast differentiation is stepped up in α-TPH-treated animals. Moreover, in these animals the formation of collagen fibers starts earlier (day 3) than in the controls (day 5).

Despite the earlier and more active differentiation of fibroblasts, the rate of fibroblast capsule formation is lower in α-TPH-treated animals. On day 5 of inflammation the collagen content of the fibroblast capsule in control animals is 51.7±3.2%, while in experimental animals it is 32±2.9% ($p<0.05$). The decrease in the synthetic function of fibroblasts in experimental rats may be attributed to a higher activity of mast cells: their number increases dramatically by the 5th day of inflammation (Fig. 1), and they are concentrated near the fibroblast capsule. In control animals, the number of mast cells increases by the 7th day of inflammation, and the cells were concentrated predominantly at the periphery of the inflammatory focus. Since histamine in mast cells can inhibit collagenogenesis [6], the redistribution of these cells can cause a decrease in the rate of collagen synthesis by fibroblasts. It should be noted that the degree of vascularization of the inflammatory focus in α-TPH-treated animals is much lower. As a result, the fibroblast capsule formed after 25 days of observation in these animals is 1.6-fold thinner than in the control animals (18.6±1.3 *vs.* 31.2±22.7 μ, $p<0.05$), and it contains 1.2-fold more fibroblasts ($p<0.05$) and 13% less collagen (61.8±3.4 *vs.* 71.4±2.9%, $p<0.05$).

Thus, restriction of FRO by α-TPH even at the initial stage of inflammation leads to the suppression of the vascular reaction in the inflammatory focus, inhibition of the leukocyte phase and of the proliferative activity of fibroblasts, and stimulation of fibroblast differentiation; however, it lowers the rate of fibroblast capsule formation.

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