EFFECT OF STIMULATION AND INHIBITION OF LIPID PEROXIDATION ON KINETICS OF MYOGLOBIN AND CREATINE KINASE IN UNCOMPLICATED AND COMPLICATED HEALING OF EXPERIMENTAL MYOCARDIAL INFARCTION

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Lipid peroxidation (LPO) has until recently been ascribed an important role in complications of healing of a myocardial infarct (MI), and its products have been regarded as among the principal factors concerned in changes in the ischemic myocardium [3, 10]. In view of the important biological functions of LPO in the maintenance of cell membrane homeostasis under physiological and pathological conditions [5], and also since MI is regarded as a special form of reactive inflammation [1, 11], ensuring uncomplicated healing of the infarct zone by the postinfarct scar, assuming a level of reactivity appropriate for the disease and synchronization of necrotic and reparative processes, but leading to complication of healing through the formation of a postinfarction aneurism for the development of rupture of the heart when reactivity is disturbed due to desynchronization of necrotic and reparative processes [4], reports have been published not only of the destructive, but also of the reconstructive role of LPO in myocardial infarction [8].

Considering the prime importance of the dynamics of necrotic changes in the forms and outcomes of healing of MI and the potential possibility of its optimization by the regulation of these processes, and also considering the links established between necrotic processes and LPO in myocardial infarction, there is an evident need for a goal-directed study of the changes taking place when LPO is influenced by various factors. The absence of any special studies in this direction motivated the present investigation.

EXPERIMENTAL METHOD

Experiments were carried out on 45 dogs weighing 6-18 kg. A model of MI was obtained under general anesthesia after thoracotomy by ligation of the anterior interventricular artery along its course in two regions in its upper and middle third. The animals were divided into three equal groups. In group 1, no drugs disturbing reactivity and, consequently, disturbing the healing of MI were used. In group 2 the animals received pyrogenal daily during the first 7 days in high doses, so that a model of hyperreactive complicated healing of IM was produced [7]. In group 3 the animals were given aminopyrine on a similar schedule, to produce a model of complicated healing of hyporeactive MI [6]. Each group of animals was divided into three equal subgroups. No special effect on LPO was used in the first subgroups of each group In the second subgroups autologous blood/irradiated with ultraviolet light (UVAB) in a volume of 1.5 ml/kg body weight, and with a wavelength of 254 nm and an exposure of 15 min. According to [9], UVAB activates leukocytes and LPO In the 3rd subgroups the antioxidant α-tocopherol acetate was used in the average therapeutic dose of 1.5 mg/kg daily. These procedures directed toward LPO in animals constituting the 2nd and 3rd subgroups were carried out 3-4 h after the beginning of myocardial infarction, and continued daily for 4 days. Ten dogs undergoing mock operations, with thoracopericardiotomy, served as the control.

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TABLE 1. MG Concentration and CK Activity in Blood Plasma of Dogs of different Subgroups with MI and Treated with UVAB and α-Tocopherol Acetate (M; σ)

Parameter	Group of animals with different form of MI	Subgroup of animals	Duration of experimental MI, days								
			3/24	7/24	10/24	15/24	18/24	24/24	40/24	3	5
MG,	1	First	64,8	72,0	82,8*	74,1*	68,4	55,1	60,2	45,4	40,3
			20,5	23,9	24,7	21,0	19,2	22,5	25,2	19,4	17,7
		Second	61,8	81,9*	84,9*	79,1*	77,0*	61,5	44,7	35,5	33,0
			6,8	17,0	17,5	14,4	15,3	12,1	7,2	2,4	7,6
ng/ml		Third	45,6	58,6	80,2*	84,2*	72,6	70,6	61,4	54,6	44,5
			6,8	7,5	14,4	15,3	5,5	12,1	6,6	7,2	2,7
	2	First	68,9	87,8*	89,2*	81,8*	75,5*	79,5*	65,2	53,4	42,6
			24,5	24,9	23,5	26,5	19,7	20,5	27,1	19,5	17,3
		Second	64,3	95,3*	96,2*	74,5*	64,6	60,9	52,8	53,1	38,2
			11,5	7,3	7,4	12,1	15,5	13,5	14,7	15,2	14,3
		Third	51,5	68,4	85,7*	85,8*	76,2*	71,6	68,3	69,0	50,4
			16,3	15,2	15,9	19,3	9,4	13,1	15,7	11,6	10,9
	3	First	60,1	71,8	80,6*	75,8*	67,3	66,0	67,2	52,5	47,4
			9,9	15,7	13,3	20,2	15,5	14,9	17,9	26,3	14,9
		Second	59,4	76,6*	79,8*	67,1	63,4	51,2	41,4	39,3	35,8
			9,8	12,3	10,4	16,6	16,3	13,4	5,0	9,1	4,7
		Third	51,6	57,5	67,8	86,9*	93,1*	84,7*	73,8	68,8	62,0
			3,6	17,4	18,5	23,6	24,3	9,5	13,1	12,5	3,1
CK,	1	First	8	12	19	21	65*	68*	25	16	10
			3	5	6	7	17	20	6	5	3
		Second	23	29	30	54*	80*	60*	40	25	20
			7	8	8	15	19	21	20	8	6
U/liter		Third	10	15	20	25	45*	59*	48*	40*	15
			3	9	4	8	13	16	9	10	4
	Second	First	10	14	16	43*	98*	67*	22	12	8
			5	6	4	11	32	28	7	4	4
		Second	25	44	55*	120*	97*	90*	45*	25	10
			7	19	12	40	36	29	13	14	5
		Third	20	25	29	38*	54*	70*	37*	16	7
			4	7	6	5	14	20	9	7	3
	Third	First	8	10	18	24	32*	35*	43*	22	14
			4	8	8	9	13	12	16	8	5
		Second	10	18	25	43*	60*	74*	50*	30	15
			3	9	5	11	16	20	10	15	6
		Third	14	20	27	30	35*	37*	56	42*	25
			5	4	8	11	10	14	20	15	7

Legend. *$p < 0.05$ compared with control.

Blood samples were taken 3, 7, 10, 15, 18, 24, and 40 h and 3 and 5 days after the beginning of the experiments in order to determine the myoglobin concentration (MG), by radioimmunoassay (using a kit from Radiopreparat, Academy of Sciences of the Uzbek SSR), and creatine kinase (CK) activity was determined biochemically (using a kit of reagents from Lachema, Czechoslovakia).

The outcome of healing of MI was monitored at autopsy. The animals were taken from the experiments on the 15th day of myocardial infarction, in full accordance with the rules.

The results of determination of MG and CK were subjected to statistical analysis.

EXPERIMENTAL RESULTS

In animals of all subgroups of group 1 the zone of the MI healed with a postinfarction scar. In the 1st and 2nd subgroups of group 2 and in the 1st and 3rd subgroups of group 3 the experimental MI was complicated by a postinfarction aneurism. The aneurism was larger in the 2nd subgroup of group 2 and in the 3rd subgroup of group 3. The MI in the 3rd subgroup of group 2 and in the 2nd subgroup of group 3 healed by a postinfarction scar despite the initially complicated course. In agreement with these observations, activation and inhibition of LPO in the case of uncomplicated MI had little effect on its healing. During complicated hyperreactive myocardial infarction activation of LPO aggravates the disturbances whereas inhibition of LPO helps to normalize its healing. Conversely, in complicated hyporeactive MI activation of LPO leads to normalization whereas inhibition of LPO aggravates the disturbances of its healing.

The results of the study of the kinetics of MG and CK in the different subgroups of the various groups of animals are in agreement with the outcome of healing of MI (Table 1).

In the control, the plasma MG concentration was 37.3 ± 8.9 ng/ml and CK activity was 8.1 ± 3.2 U/liter.

The qualitative picture of the kinetics of MG and CK was the same in all subgroups of all groups of animals. Initially the MG concentration and CK activity rose, and after reaching a maximum (earlier for MG and later for CK) they fell. The rate of rise of their concentration and activity was greater than their rate of fall.

In the model of uncomplicated MI, with no attempt to influence LPO (1st subgroup of group 1), the MG concentration and CK activity at different times of the experiment and the time taken by them to reach their peak values were smaller and later respectively than in the model of complicated hyperreactive MI (the 1st subgroup of group 2), but larger and earlier than in the model of complicated hyporeactive MI (1st subgroup of group 3). In accordance with these data, in experimental complicated hyperreactive MI the necrotic processes were accelerated, whereas in the hyporeactive type they were delayed, in agreement with the results of earlier investigations [4].

In the experiments with UVAB (2nd subgroup of groups 1-3) activation of necrotic changes was observed by comparison with the corresponding experiments with no attempt to influence LPO (1st subgroup of groups 1-3), as was reflected in higher values of MG concentration and CK activity, and also their earlier maxima. In the model of uncomplicated MI, under UVAB conditions (subgroup 2 of group 1) the degree of the disturbances of MG and CK kinetics was lower than with the hyperreactive MI model, excluding any effect on LPO (subgroup 1 of group 2), which explains healing of the infarction zone by a postinfarction scar in these cases. In the hyporeactive MI mode with UVAB (subgroup 2 of group 3) changes observed in MG and CK kinetics closely resembled those in uncomplicated MI, disregarding any effect on LPO (subgroup 1 of group 1) which also explains healing of the infarct zone by a postinfarction scar. In the hyperreactive MI model with UVAB (subgroup 2 of group 2) disturbances of MG and CK kinetics were more marked than in the same MI model, disregarding any effect on LPO (subgroup 1 of group 2), which led to more severe disturbances of healing of the infarct and to a larger aneurism.

In the experiments with α-tocopherol acetate (subgroup 3 of groups 1-3), compared with the corresponding experiments with no attempt to influence LPO (subgroup 1 groups 1-3) necrotic changes were weaker, as shown by the lower values of MG concentration and CK activity, and also by the later appearance of their maxima. In uncomplicated MI treated with α-tocopherol acetate (subgroup 3 of group 1) the degree of disturbances of MG and CK kinetics was less than in hyporeactive MI (subgroup 1 of group 3), leading to healing of the infarct by a scar. In the model of hyperreactive MI, in which α-tocopherol acetate was used (subgroup 3 of group 2) the changes observed in MG and CK kinetics were similar to those in uncomplicated MI with no action directed toward LPO (subgroup 1 of group 1), and this also explains healing of the infarct by a scar. In the model of hyporeactive MI in which α-tocopherol acetate was used (subgroup 3 of group 3) disturbances of MG and CK kinetics were more marked than in the same model of MI with no action directed toward LPO (subgroup 1 of group 3), causing more severe disturbances of healing of the infarct zone and a larger aneurism.

The results indicate the importance of LPO in the time course of necrosis and the ultimate outcome of healing of MI. The effect of intervention in LPO on the development of necrotic changes in MI is essentially determined by its form. In normoreactive MI activation and stimulation of LPO lead to moderate changes in MG and CK kinetics without any disturbances of the healing processes. In hyperreactive MI activation of LPO aggravates, whereas inactivation normalizes the kinetics of MG and CK, with optimization of healing of MI. In hyporeactive MI, on the other hand, inhibition of LPO aggravates whereas activation normalizes the MG and CK kinetics with optimization of healing of MI. These results confirm the value of both antioxidants and LPO activators in MI [2, 3], but the use of the corresponding methods of treatment and medication must be differentiated depending on the form of the disease. Uncomplicated MI does not require intervention in LPO. In complicated hyperreactive MI antioxidants are indicated, but stimulation of LPO in complicated hyporeactive MI.

The investigations thus showed that the time course of the necrotic changes can be controlled through regulation of LPO, and the healing of MI can thereby be optimized. With a more rapid course of necrosis antioxidants are indicated, but stimulation of LPO is beneficial if necrosis takes place slowly. α-Tocopherol acetate and UVAB are effective means of inhibition and stimulation of LPO.

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