PREVENTION OF STRESS-INDUCED DEPRESSION OF NATURAL KILLER CELL ACTIVITY BY A β-ADRENOBLOCKER AND VITAMIN E

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A decisive role in the mechanism of the stress-induced depression of function and of injury to many internal organs is known to be played by the action of an excess of catecholamines on β-adrenergic receptors with subsequent activation of lipid peroxidation (LPO), which lead to injury to the cell membranes [1, 3]. In full agreement with this explanation, stress-induced lesion of the heart, stomach, and portal vein can be regularly prevented by preliminary administration of adrenoblockers and antioxidants [2, 10]. In relation to natural killer (NK) cells, which play an essential role in the system of antitumor protection of the organism, stress-induced depression of their activity was demonstrated by the writers previously [5]. However, the possibility of preventing this depression by means of adrenoblockers and antioxidants has not hitherto been studied.

In the investigation described below activity of NK cells was depressed by stress and the problem whether this phenomenon could be prevented by preliminary administration of a β-adrenoblocker (propranolol) and a natural antioxidant (vitamin E) was studied.

EXPERIMENTAL METHOD

Inbred male CBA mice weighing 16-18 g were used. There were two series of experiments, with four experiments in each series. Series I consisted of: group 1) control intact mice, group 2) intact mice + propranolol, group 3) mice exposed to stress, group 4) animals receiving propranolol and then exposed to stress; the experiments of series II consisted of the same groups, but vitamin E was used instead of propranolol.

Propranolol (Inderal, England) was injected intraperitoneally into the mice in a single dose of 1 mg/kg body weight, 30 min before the beginning of exposure to stress. An oily solution of vitamin E (D,L-α-tocopheryl acetate, from Serva, USA) was given to the mice daily for 3 days per os in a dose of 5 IU. The last dose of the vitamin was given 1 h before exposure to stress. Immobilization stress was produced for 6 h by keeping the animals on their back with their limbs fixed.

The animals were decapitated 24 h after the end of immobilization, the splenocytes were isolated, and NK cell activity was determined by incubating effector cells (mouse splenocytes) with target cells (T-cell mouse lymphoma YAC-1, labeled with radioactive chromium) in a 4-hour test. Details of the technique of determining NK cell activity were described by the writers previously [4].

The significance of differences between the experimental results was estimated by Student's t test.

EXPERIMENTAL RESULTS

Prolonged immobilization stress, just as in earlier investigations [4, 5], induced marked depression of NK cell activity and reduced their ability to cause lysis of the target cells by 50% compared with the control (Table 1). Propranolol, a β-adrenoblocker, which itself did not increase NK cell activity, prevented stress-induced depression of NK cells.

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TABLE 1. Effect of Preliminary Administration of Propranolol on Depression of NK Cell Activity in Stress

Group of animals	Experimental conditions	NK cell activity, % ratio of NK cells to target cells		
		100:1	50:1	25:1
1	Control	19,8±1,7	15,0±1,5	13,6±0,9
2	Control + propranolol	18,1±1,5	15,9±1,8	12,7±1,2
3	Stress	9,8±0,8	8,1±0,7	5,2±0,3
4	Propranolol + stress	15,8±1,7	13,6±1,1	9,8±0,6
	P_{1-2}	>0,05	>0,05	>0,05
	P_{1-3}	<0,01	<0,01	<0,01
	P_{3-4}	<0,01	<0,05	<0,05

TABLE 2. Effect of Preliminary Administration of Vitamin E on Stress-Induced Depression of NK Cell Activity

Group of animals	Experimental conditions	NK cell activity, % ratio of NK cells to target cells		
		100:1	50:1	25:1
1	Control	25,6±2,0	17,2±1,9	9,3±0,7
2	Control + vitamin E	27,5±3,0	19,2±1,8	10,2±0,9
3	Stress	12,9±1,8	7,3±0,9	3,7±0,6
4	Vitamin E + stress	19,7±1,7	12,6±1,5	7,8±0,9
	P_{1-2}	>0,05	>0,05	>0,05
	P_{1-3}	<0,01	<0,01	<0,001
	P_{3-4}	<0,05	<0,05	<0,05

Legend. Here and in Table 1, each group contained not less than 10 mice.

These results agree with data showing that NK cells, like other lymphoid cell populations, possess α- and β-receptors [6, 8, 9]. Stimulation of β-adrenoreceptors by isoproterenol led to an increase in the cAMP concentration in these cells and reduced their cytostatic activity. Preliminary injection of the β-adrenoblocker propranolol prevented this effect [7]. A similar situation evidently was observed also in the present experiments, when an excess of catecholamines, which is characteristic of stress, depressed NK cell activity, whereas propranolol prevented the stress-induced depression of activity of the cells of this type, which are able to cause lysis of target tumor cells.

Immediately after the action of an excess of catecholamines, activation of LPO is known to develop regularly in the heart, blood vessels, and other organs during stress, and this leads to certain disturbances of function which can be regularly prevented by antioxidants [2].

Accordingly, in the next stage of the work the effect of preliminary administration of the natural antioxidant vitamin E on stress-induced depression of NK cell activity was studied. The data in Table 2 show that vitamin E itself did not cause increased NK cell activity in intact animals, but at the same time, it significantly prevented depression of activity of the natural cytotoxicity system, arising in the animals on account of exposure to immobilization stress. This fact is in agreement with evidence showing that vitamin E is an inhibitor of LPO and has a protective action against stress-induced injuries of various organs [3].

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POSSIBLE ROLE OF LIPID PEROXIDATION IN THE PATHOGENESIS OF ARRHYTHMIAS IN MYOCARDIAL INFARCTION

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Intensification of lipid peroxidation (LPO) in ischemic and stress-induced lesions of the heart is well known [2, 4, 5]. There is also evidence indicating that arrhythmias of the spontaneously contracting atrium may arise during induction of LPO in vitro, on the potentiating effect of previous stress on this process, and on the antiarrhythmic action of antioxidants [6]. Meanwhile the role of activation of LPO in the pathogenesis of disturbances of the rhythm of contraction in myocardial infarction (MI) has remained unstudied until recently.

The aim of the present investigation was to determine the effect of MI in animals on the resistance of the atria, taken from them, to H_2O_2, an inducer of LPO, and to determine whether the arrhythmia-inducing action of H_2O_2 can be prevented by means of an antioxidant.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 180-200 g. Experimental MI was induced by the method in [7]. Isolated right atria, containing the sinoatrial node, the cardiac pacemaker, were used in the experiments. Contractility of the isolated atrium was recorded under isometric conditions of contraction in oxygenated Krebs–Henseleit solution by means of a system from "Narco Biosystems" (USA). The spontaneously contracting atrium was gradually stretched to a length at which it developed maximal systolic tension, i.e., until the Starling curve flattened out on a plateau. It was essential for the purpose of this investigation that the maximal tension developed by the atria of animals subjected to Selye's operation to produce myocardial infarction was less than half of that developed in intact animals, and that the resting load required for the plateau on the Starling curve to be reached in this case was equally lower [3]. Since it may happen that the resistance of the contracting myocardium to the arrhythmia-inducing action of LPO may depend to some extent on the level of developed tension, control atria in a special series were stretched to resting load levels close to the average in the group of "infarct" atria and the developed tension in this case did not differ from values observed in the series of animals with an infarct. This "equilibration" of the control and postinfarct atria with respect to developed tension and resting load was an essential condition for correct comparison of the different series of experiments. The atria functioned for 20 min before the addition of H_2O_2 in order to stabilize spontaneous contractile activity, after which the LPO inducer H_2O_2 was added in an amount ensuring an active concentration of H_2O_2 of 1 mM. The animals were divided into four groups: 1) control; 2) control with normalization for developed tension and resting load; 3) animals with MI; 4) rate with MI receiving ionol.* Ionol was given per os

*2,6-Di(tert-butyl-4-methylphenol).

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