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

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KEY WORDS: myocardial infarction; arrhythmia; lipid peroxidation; ionol

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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TABLE 1. Effect of Initial Level of Developed Tension on Time of Onset of Arrhythmia after Beginning of Action of H_2O_2 on Atria of Control Animals

Experimental conditions	Initially developed tension, mg	Time of onset of arrhythmia, min
Control 1 (n=4)	400—480	1 3 3 3
Control 2 (n=8)	290—380	3 3 4 4 4 6 6 >11
		$P_{1-2}<0,05$
Normalized control (n=8)	100—300	5 6 >11 >11 >11 >11 >11
		$P_{1,2-3}<0,05$

Legend. n) Number of atria.

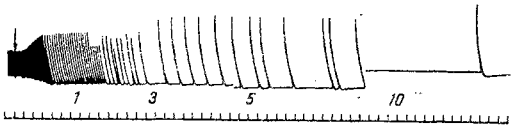

Fig. 1. Mechanogram of spontaneously contracting atrium before and after addition of H_2O_2 to surrounding solution. Numbers represent time after addition of H_2O_2 (in min).

for 3 days before the operation and 6 h after the operation in a dose of 50 mg/kg. The results were subjected to statistical analysis by the nonparametric method of Wilcoxon, Mann, and Whitney, using the U test [1].

EXPERIMENTAL RESULTS

Induction of LPO by addition of H_2O_2 to the surrounding fluid in most experiments of the control series evoked a 3-phase response of the spontaneously contracting atria, which was fully described previously by an initial increase in developed tension, a very small increase in the heart rate, and a decrease in the resting tension. Later, as the process developed regularly, progressive bradyarrhythmia accompanied by characteristic changes in developed tension appeared and increased in degree, and in some cases terminated in cardiac arrest. The sensitivity of the control atria to the LPO inducer, estimated from the time of onset of the arrhythmia, was less under these circumstances in those which had a lower level of developed tension compared with the rest. This is clear from Table 1, in which all atria of the control series are divided into two groups: the first group (control 1) with an initial developed tension of 400-480 mg, the second (control 2) with a tension of 290-380 mg. Thus, if the developed tension was 400-480 mg the time of onset of the arrhythmia did not exceed 3 min (Table 1). In the group of atria with a developed tension of 290-380 mg this time was doubled, and in some cases no arrhythmia occurred during the period of observation (Table 1). Experimental infarction is known to lead to a reduction in developed tension by more than half. Accordingly it was useful to equalize the developed tension in the control with that observed during infarction, and this was done in a special series of experiments.

Experimental MI caused considerable disturbances of pacemaker function in the atria: 60% of atria of the animals of group 3 stopped beating while still during preliminary oxygenation. Addition of ionol reduced this

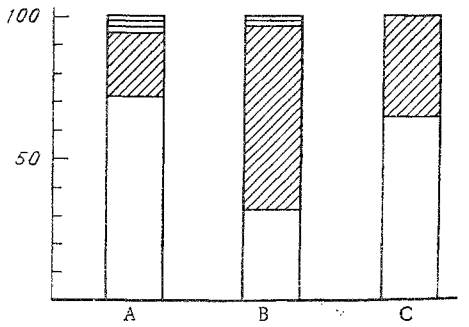

Fig. 2. Effect of experimental MI and preliminary administration of ionol (50 mg/kg) on resistance of the atria and arrhythmia-inducing action of the LPO inducer. Ordinate, period of observation (in percent, 10 min taken as 100%). Unshaded columns – time of regular atrial function during period of observation, oblique shading – time of arrhythmias, horizontal shading – time during which atria did not function. A) Normalized control (n = 8), B) MI (n = 8), C) MI + ionol (n = 12).

proportion by one-third. Atrial arrest during preliminary oxygenation was due to a reversible disturbance of pacemaker function, for the addition of adrenalin (10^{-5} M) to the surrounding solution regularly led to a resumption of contraction.

Further analysis of the experimental data (in accordance with the 3-phase response of the atria to induction of LPO) was based on determination of the duration of regular contraction, of arrhythmia, and of arrest, for each atrium. The period of observation was 10 min.

Atria with MI were found to have much higher sensitivity than the control to the arrhythmia-inducing action of H_2O_2 (Fig. 2). For instance, the duration of the arrhythmias and of atrial arrest was 2.3 times greater than in the control. Administration of ionol to the animals before the operation to produce myocardial infarction reduced this figure almost by half. Previous MI thus left a certain trace in the animals' myocardium which led to potentiation of the action of H_2O_2. This potentiating effect may be largely prevented by preliminary administration of the antioxidant ionol.

When the experimental results are assessed it must be recalled that the decrease in resistance of the atria to the LPO inducer associated with an increase in their developed tension can very probably be explained on the grounds that an increase in the oxygen demand of the contracting muscle leads to activation of LPO in it. In turn, activation of LPO causes a marked arrhythmogenic effect [6]. The potentiating effect of preceding myocardial infarction on the induction of arrhythmia by addition of H_2O_2 is evidently based on the reduction of activity of antioxidative enzyme systems of the myocardium in the nonischemic zone observed by the writers previously in experimental myocardial infarction [2].

The results as a whole indicate that antioxidants may be used to prevent arrhythmias in experimental myocardial infarction.

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COMPARATIVE MORPHOLOGICAL AND FUNCTIONAL STUDY OF INDIVIDUAL RESISTANCE OF ANIMALS TO HYPOXIA

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KEY WORDS: hypoxia; resistance; plastic metabolism

The aim of this investigation was to analyze ways of realization of the adaptive reserve capacity by phylogenetically different brain structures in animals differing in their initial resistance to hypoxia and to look for correlation between resistance to hypoxia and the dynamics of the acid–base balance.

EXPERIMENTAL METHOD

Experiments were carried out on 50 mature male rats weighing 180-200 g. Depending on their individual resistance to hypoxia the animals were divided into rats with low (LRR) and high (HRR) resistance [2]. The animals of each group were then divided into control and experimental, and exposed for 8 h daily in a pressure chamber at an "altitude" of 5000 m for 1 month.

Concentrations of cytoplasmic RNA (by Einarson's method) and total protein [3] were determined in the cerebral cortex and reticular formation (RF). These parameters were determined quantitatively on a scanning microspectrophotometer [1] and also by morphometry and karyometry.

The animals were decapitated and the brain fixed in Carnoy's fluid and embedded in paraffin wax. The acid–base balance of blood taken from the jugular vein was studied on an OP-210/2 microanalyzer.

EXPERIMENTAL RESULTS

Analysis of the results of the histochemical study of protein metabolism in HRR showed that its intensity is higher in RF than in the cortex (Table 1). Long-term adaptation was accompanied by an increase in the RNA and protein concentration both in the cortex and in RF, evidence of activation of protein metabolism. The high intensity of this process in RF is probably attributable to the fact that adaptation in these animals is maintained by high protein metabolism at the medullary level. The stability of the dimensions of the cytoplasm of cortical neurons is explained by their need to maintain a sufficiently high RNA and protein concentration, in order to sustain a high level of metabolism. In RF, against the background of a reduced area of cytoplasm, the total content of RNA and protein was reduced. These findings suggest that adaptation to hypoxia in HRR is effected mainly by subcortical structures. The RNA/protein ratio in the test structures in HRR was unchanged after training in the pressure chamber, evidently as a result of the stability of protein metabolism in the brain tissue. This perhaps also determines the high level of their adaptation to hypoxia.

The RNA content in RF was found to be higher than in the cortex in LRR (Table 1). Long-term pressure chamber training was accompanied by a fall in the RNA level in the cortex and a rise in the total protein level. Changes in protein metabolism in RF were less marked and were characterized by a synchronous fall of the RNA and protein levels in response to long-term exposure to hypoxia. Analysis of changes in protein metabolism showed that the RNA/protein ratio decreased after adaptation to hypoxia in the structures studied: not signifi-

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