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COMPARATIVE STUDY OF ACTIVATION OF LIPID PEROXIDATION AFTER ELECTRICAL DESTRUCTION OF THE MYOCARDIUM AND DURING EARLY DEVELOPMENT OF ACUTE MYOCARDIAL INFARCTION IN EXPERIMENTS ON DOGS

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KEY WORDS: arrhythmia; ischemia; lipid peroxidation; electrical destruction

Important factors in the etiology and pathogenesis of many cardiovascular diseases and their associated arrhythmias are stress-induced and ischemic lesions of the myocardium, which are accompanied by activation of free-radical lipid oxidation with the release of toxic products of incomplete lipid peroxidation (LPO) into the blood stream [1, 5, 7, 9, 10, 12]. For that reason the level of LPO metabolites in the general blood stream may be a criterion reflecting the degree of injury of biomembranes. Electrical destruction of the conducting pathways of the heart is nowadays used for the treatment of arrhythmias [2], but no research into the effect of electrical stimulation on LPO processes in cardiomyocyte membranes could be found. Knowledge of the possible contribution of several damaging factors of electrical destruction (the shock wave, the polarizing action of the current, the thermal factor) to activation of LPO is extremely important, for in clinical practice electrical destruction has to be undertaken on patients with arrhythmias based on ischemic heart disease and atherosclerosis, an important component of whose pathogenesis is activation of LPO [1, 7, 9].

The aim of this investigation was a comparative experimental study of the dynamics of LPO metabolites, namely conjugated dienes (CD) and malonic dialdehyde (MDA), in the blood serum of dogs after electrical destruction of the myocardium and after acute myocardial infarction (AMI).

EXPERIMENTAL METHOD

Experiments were carried out on 22 mongrel dogs of both sexes weighing 15-25 kg, anesthetized intravenously with thiopental sodium (1% solution, 0.5-1.0 g per animal), undergoing operations with the assistance of artificial ventilation of the lungs by the RO-2 apparatus. Thoracotomy was performed in the fourth right intercostal space, and this was followed by longitudinal pericardiostomy. The control group 1 contained three animals undergoing mock operations. In the animals of group 2 a model of AMI was created by ligation of the posterior interventricular artery (the presence of AMI was confirmed electrocardiographically and morphologically). In 16 dogs of experimental group 3, complete transverse heart block was created through the aorto-atrial groove by electrical destruction by a discharge from the DI-03 defibrillator, with

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TABLE 1. Dynamics of Serum CD and MDA Concentrations after Electrical Destruction and Acute Infarction of the Myocardium (in % of initial values)

Group	Number of observations	Metabolite	Time of taking blood, min			
			1	10	60	120
1-	3	CD	100±1	108±4	97±15	118±6
		MDA	100±1	100±1	100±1	98±15
2-	3	CD	109±54	112±78	160±10	142±15
		MDA	101±1	132±19	151±26	143±18
3-	16	CD	109±24	92±8	87±6	98±21
		MDA	113±2	110±4	94±27	97±1
		CD	$p_1>0,05$	>0,05	>0,05	>0,05
			$p_2>0,05$	>0,05	<0,001	<0,001
			$p_3>0,05$	>0,05	<0,01	<0,05
		MDA	$p_1<0,001$	<0,05	<0,01	>0,05
			$p_2<0,001$	>0,05	<0,001	<0,001
			$p_3>0,05$	<0,05	<0,05	<0,05

Legend. p_1) Significance of differences between groups 1 and 3, p_2) between groups 2 and 3, p_3) between groups 1 and 2.

energy of 200-300 J [2], followed by implantation of an electrocardiostimulator. Heparinized blood was taken from the femoral vein after thoracotomy: 1, 10, 60, and 120 min after ligation of the artery (group 2), or after application of the discharge (group 3). Blood was taken from the animals of group 1 at these same times. Concentrations of CD by the method in [3] and MDA by the method in [6] were determined in the blood serum. Since levels of CD and MDA vary widely in animals after thoracotomy, this level during analysis of the results was taken to be 100% for each animal. The results were subjected to statistical analysis by the sampling method [11, 13]. The significance of the results was assessed by Student's test.

EXPERIMENTAL RESULTS

The results are given in Table 1. In animals undergoing the mock operation, no significant changes were found in blood levels of LPO metabolites. Following electrical destruction the concentration of a primary LPO metabolite, namely CD, in the blood serum did not change significantly during the experiment. The MDA concentration in the dogs' blood was significantly increased by 10-13% 1 and 10 min after application of the discharge, but after 60-120 min the MDA level had returned to its initial value, indicating a sufficiently rapid compensatory reaction of the natural antioxidative systems of the body. Thus the discharge under the chosen conditions (200-300 J) was optimal and relatively atraumatic, for activation of LPO was not significant. Since, under these experimental conditions, we were dealing with a healthy heart, whereas under clinical conditions the arrhythmias were most frequently associated with cardiovascular pathology, and the period of normalization of LPO processes may be increased in patients after electrical destruction of the myocardium, the use of antioxidants and membrane stabilizers can be recommended on prophylactic grounds in the preoperative period.

A serious complication which may follow electrical destruction is the development of AMI, but this may be quite difficult to diagnose, for the electrocardiographic picture in the postoperative period is very changeable and may be difficult to interpret. This study of the dynamics of LPO metabolites on a model of AMI showed that after ligation of the artery the CD concentration in the general blood stream increased as early as after 1 min, to reach 147-160% of its initial level by the 10th-120th minutes of the experiment. The MDA concentration began to rise at the 10th minute, and after 60-120 min it was 1.4-1.5 times higher than initially, in agreement with data obtained by other workers [8-10].

Thus during the development of AMI more prolonged and more intensive activation of free-radical lipid oxidation takes place than after electrical destruction.

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A NEW MOLECULAR MECHANISM OF NEURONAL NICOTINIC ACETYLCHOLINE RECEPTOR BLOCKADE

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KEY WORDS: nicotinic acetylcholine receptor; ionic channel; restorative properties; reducing properties; disulfide bonds

Three basic mechanisms of blocking of neuronal nicotinic acetylcholine (N-Ach) receptors have been described: blocking the open ionic channel, blocking the recognition center (competitive type of blockade), and blocking the closed ionic channel [4]. However, the molecular mechanism proper of ionic channel function has not been adequately studied. We attempted to link this mechanism with oxidation—reduction changes in sulfhydryl and disulfide groups appearing in the N-Ach receptor, and blockade of the receptor with reduction of S—S bonds in its active center.

The basis for the present investigation was, first, that previously we found marked oxidation—reduction properties in central nicotinic cholinolytics, compounds belonging to different chemical groups [3, 6], and second, data in the literature indicating that a functionally important disulfide bond is present in the active center of the N-Ach receptor, and its reduction leads to blockade of the receptor, whereas oxidation abolishes this blocking effect [7, 9].

EXPERIMENTAL METHOD

The central nicotinic cholinolytic activity was assessed in the nicotine test on albino mice and rats [1, 8]. Indices of protection were calculated by computer by probit analysis. Contractions of a segment of isolated rat ileum were recorded under isometric conditions by a 6M × 9B mechanotron [2]. The experimental results were analyzed by comparing mean values of EC_{50} obtained by logit analysis. The concentration of SH-groups was determined in the supernatant of rat brain (3000 × 15 min) spectrophotometrically in medium of the following composition: 50 mM Tris-HCl (pH 7.45), 20 mM KCl, 100 mM NaCl, 60 mM $MgCl_2$, 30 mM ATP. The volume of the sample was 1 ml. Samples were incubated for 30 min at

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