EFFECT OF MALATE AND NAD ON LOCAL MYOCARDIAL CONTRACTILITY DURING ACUTE CORONARY ARTERIAL OCCLUSION

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When the protective action of drugs on the ischemic myocardium is assessed, very often recovery of electrophysiological, biochemical, and histologic parameters are regarded as equivalent to manifestation of viability of the myocardium. However, as Hearse [5] has rightly pointed out, we can hardly speak of the protective action of drugs unless the contractile function of the "rescued" myocardium recovers. The present writer showed previously that malate and NAD increase contractility and the pumping function of the acutely ischemic heart. However, it is not yet clear whether these substances can restore myocardial contractile function in an ischemic focus, for the effects observed may have been due to their action on intact zones of the affected heart.

In the investigation described below the effect of malate, NAD, and a combination of both on contractility of the myocardium ws studied in the central ischemic zone, the boundary zone, and an intact zone of the left ventricle during acute coronary arterial occlusion.

EXPERIMENTAL METHODS

Altogether four series (including one control) of acute experiments were carried out on 37 cats weighing 2-3.7 kg, under pentobarbital sodium anesthesia (35 mg/kg, intraperitoneally). The local function of areas of myocardium was studied by the impedance method [3, 11]. For this purpose, three pairs of electrodes were implanted into the tissue of the left ventricle in the region of the supposed zone of ischemia, in the boundary zone, and at distance from it. The change in the distance between the electrodes a result of contraction of the muscle fibers was accompanied by a proportional change in impedance of the region of the myocardium studied. Active systolic shortening of the myocardial segment was estimated from the amplitude of the impedance curve [8]. Acute myocardial ischemia was induced by ligation of the anterior interventricular branch of the left coronary artery. The ischemic zone was defined as the segment of myocardium located immediately below the site of occlusion. The region located in the zone of blood supply of the left circumflex coronary artery was regarded as intact myocardium. The boundary zone was defined as the segment of myocardium on the boundary between cyanotic and normal tissue, active systolic shortening of which was less than initially [8]. If the location of the electrodes did not satisfy these demands, the results of the corresponding experiments were disregarded. The pressure in the left ventrile, and its maximal rate of rise and fall were recorded. The index of contractility (IC) was calculated: $IC = \frac{dp/dt\ max}{P_p}$ [10]. The blood pressure (BP) was measured in the left carotid artery by means of a mercury manometer. The animals were heparinized (1000 U/kg body weight, intravenously). The test preparations – malate in a dose of 100 mg/kg and NAD in a dose of 0.2 mg/kg – were given as a single intravenous injection 20 min after occlusion. These same doses were used to study the combined effects of the two compounds. The results were subjected to statistical analysis by Student's t test and by the Wilcoxon–Mann–Whitney nonparametric U test.

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TABLE 1. Changes (in %) in Parameters of Cardiohemodynamics after Injection of Malate, NAD, and a Combination of Both (M ± m)

Parameter	Control (n = 8)		Malate (n = 10)		NAD (n = 9)		Malate + NAD (n = 10)	
	initial data	20th minute	initial data	20th minute	initial data	20th minute	initial data	20th minute
BP, mm Hg	91,3±6,7	−11,6±4,5	110,5±5,9	+13,8±3,8*	91,7±6,1	+3,7±1,5*	86,0±4,8	+10,9±6,1*
Pressure in left ventricle, mm Hg	110,6±7,2	−5,8±6,9	116,7±8,9	+12,5±3,0*	101,2±9,3	+12,3±3,2*	98,0±5,4	+14,9±5,1*
Index of contractility, sec^{-1}	24,5±2,1	−11,2±3,9	28,0±2,8	+23,3±3,6*	33,9±1,8	+13,1±3,6*	25,9±1,7	+25,7±4,2*
Maximal rate of fall of pressure in left ventricle, mm Hg/sec	1065±105	−2,7±8,3	990±77	+27,8±6,9*	1076±100	+20,5±4,7*	1007±87	+24,1±5,9*
HR, beats/min	170±5	−0,3±2,6	148±11	+1,5±2,6	140±10	−1,5±3,4	139±7	−4,4±4,5

Legend. Values of parameters found 20 min after occlusion of coronary artery taken as initial data. *P < 0.05 compared with control.

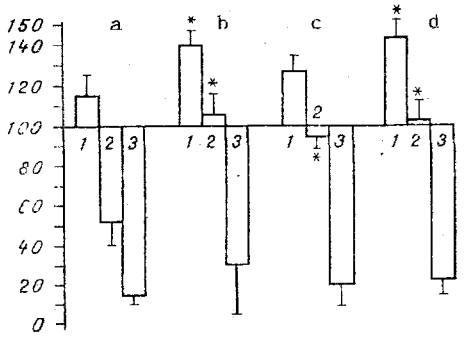

Fig. 1. Changes in degree of systolic shortening of different segments of myocardium 20 min after injection of compounds (in % of level before occlusion): a) control; b) malate (100 mg/kg); c) NAD (0.2 mg/kg); d) malate + NAD. 1) Intact zone; 2) boundary zone; 3) central ischemic zone. *P < 0.05 compared with control.

EXPERIMENTAL RESULTS

Ligation of the coronary artery caused severe disturbances of the mechanical function of the myocardium in the central ischemic zone. Systolic shortening either disappeared or was consistently reduced by 80% of its initial level or more. In some experiments systolic stretching was observed. Depression of contractile function in the boundary zone was less marked. Systolic shortening 40 min after coronary occlusion was reduced on average by 47.8 ± 12.3%. Meanwhile systolic shortening of the intact segment of myocardium was increased in most experiments. Hyperfunction of intact portions of the myocardium during acute ischemia was mainly connected with activation of the Frank–Starling mechanism and was observed in both anesthetized and conscious animals [8, 9]. Contractility of the left ventricle on the whole was moderately reduced. Changes in BP and heart rate (HR) were not significant. Disturbances of myocardial contractility in the control animals later gradually increased.

Malate, NAD, and a combination of both increased contractility of the acutely ischemic heart as a whole and of its separate zones (Table 1, Fig. 1). A particularly marked increase of myocardial function was observed in the boundary zone. Meanwhile the central ischemic zone responded only weakly to pharmacologic intervention. Maximal changes in the parameters studied occurred 20-30 min after injection of the compounds and they differed statistically significantly from the control during 40-50 min of observation. The combined use of malate and NAD, incidentally, did not lead to potentiation of their effects.

The degree of active systolic shortening of the ischemic myocardium can be increased either by a decrease in the after-load [6] or by an increase in the pre-load [12]. However, in the present experiments the after-load was unchanged because the compounds tested did not lower BP. Meanwhile malate and NAD significantly increased IC, which is virtually independent of changes in the pre-load [2]. Accordingly the participation of a primary hemodynamic mechanism in the realization of the positive effect of the compounds on function of the ischemic myocardium can be ruled out. Improvement of contractility of the boundary and intact zones of myocardium was evidently connected with the beneficial effect of malate and NAD on metabolism of the affected heart [4, 7] and also with their ability to increase the blood supply to the ischemic focus in the myocardium [1]. The weak effect of the compounds on myocardial function in the central ischemic zone can be explained either by their inadequate penetration into this zone or by the fact that tissue changes there were already irreversible.

Malate and NAD can thus restore the contractile function of the myocardium in the boundary zone, and this can be interpreted as a manifestation of their antiischemic action.

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LIPOSOME TRANSPORT TO TARGET ANTIGENS AS A POSSIBLE WAY OF STANDARDIZING TARGETED DRUG TRANSPORT

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Targeted drug transport, a field of intensive research in biomedicine, is currently regarded as a promising method of prevention and treatment of several cardiovascular diseases caused by disturbance of integrity of the layer of endothelial cells of the blood vessels [9]. Exposure of the antigenic structures of the intima as a result of this process means that a container containing a drug can be targeted there by antibodies against the corresponding specific structures of the damaged vessel. On the basis of these considerations systems of targeted drug transport to damaged regions of the vascular bed, using liposomes [5], erythrocytes [11], and anticollagen antibodies immobilized on their surface, have been teted both in vitro and in vivo.

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