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ENERGY METABOLISM AND CONTRACTILE ACTIVITY OF THE MYOCARDIUM AFTER CARDIOCYTOTOXIC INJURY

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Experiments on anesthetized dogs with a closed chest showed that injection of anticardiac cytotoxic serum into one of the main branches of the left coronary artery was followed by zonal disturbances of energy metabolism (a decrease in the ATP, ADP, AMP, and glycogen concentrations and contractility of the affected area of the left ventricle). Compensatory hyperfunction of the left and right ventricles and an increase in their noradrenalin concentration were found. The indices of energy metabolism in the unaffected area of the heart showed no significant change.

KEY WORDS: cardiodynamics; myocardial metabolism; injury to the heart.

It was shown previously that injection of anticardiac cytotoxic serum (ACS) into one branch of the left coronary artery led to sharp and prolonged disturbances of the hemodynamics similar to the picture of cardiogenic shock [1] and due to disturbances of the contractile activity of the myocardium [3] and to deposition of blood [5]. Focal injury of the heart muscle developed in the region of direct action of ACS [7].

To shed light on the mechanisms of disturbance of cardiac activity after cytotoxic injury, it was considered important to compare changes in energy metabolism in different parts of the heart with zonal changes in contractile activity of the myocardium.

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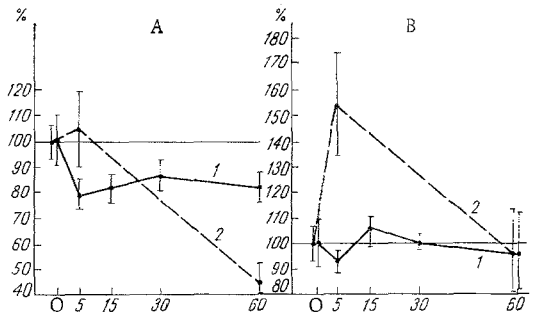

Fig. 1. Changes in contractile activity (1) and noradrenalin concentration (2) in injured (A) and uninjured (B) areas of left ventricle after injection of ACS. Abscissa, zonal changes in contractile activity of myocardium and in noradrenalin concentration in myocardium (in % of initial level); ordinate, time after injection of ACS (O), in min.

EXPERIMENTAL METHOD

The systemic arterial pressure (SAT), the cardiac output (by the thermodilution method), the pressure in the left ventricle, and its first derivative were recorded in acute experiments on dogs weighing 16-21 kg under morphine-chlorolose anesthesia (0.0025 and 0.07 g/kg body weight respectively) without thoracotomy. ACS (titer in the complement fixation test – CFT – 1:400) was injected in a dose of 1-1.5 ml into the circumflex or descending branch of the left coronary artery through a specially made "coronary" catheter, and after indices of the cardiodynamics had been recorded at various times after injection of ACS (5-7 and 60 min) thoracotomy was performed and samples of myocardial tissue taken. In the affected (corresponding to the site of injection of ACS) and undamaged areas of the left ventricle and also in the right ventricle the concentrations of adenine nucleotides (ATP, ADP, AMP) [13], of inorganic phosphorus [2], of oxidized (NAD + NADP) and reduced forms of nicotinamide coenzymes [10], and glycogen [8], activity of cytochrome c-oxidase (CCO) [14] and succinate dehydrogenase [12], and the concentrations of catecholamines [4] were determined.

Zonal changes in contractile activity of the myocardium in the area of direct action of ACS (injured area) and in the uninjured area of the left ventricle were investigated in a special series of experiments on thoracotomized animals by means of strain gauge transducers fixed to the heart (14 experiments). Details of the method were described previously [3]. In control experiments normal rabbit serum was injected into the coronary circulation.

The numerical results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

The most marked disturbances of the circulation were found during the first minutes of intracoronary injection of ACS. SAP fell by 43.2%, the cardiac output by 32.5%, the pressure in the left ventricle by 44.3%, and its first derivative (dp/dt_{max}) by 29.3%. All these indices except the cardiac output showed a tendency to recover 40-60 min later, but the total peripheral resistance (TPR) was a little higher than initially. In the area of direct action of ACS definite weakening of contractile activity was observed (Fig. 1), and it continued throughout the period of observation (1 h). Meanwhile, in an area of myocardium from the left ventricle some distance from the site of injury, no regular changes in the force of contractions as a rule were observed. In most experiments (10 of 14) an increase in the force of contractions was observed in this part: On average by $13 \pm 4.3\%$ ($n = 10$, $P < 0.05$) after 15 min. No significant changes in the indices of energy metabolism of the myocardium were detected in the first 5 min.

Significant zonal disturbances of energy metabolism were found in the myocardium 1 h after injection of ACS. The level of adenine nucleotides fell considerably in the injured part of the left ventricle: ATP by 36.7%, ADP by 41.1%, and AMP by 35.5%. The concentrations of glycogen and noradrenalin (by 37.6 and 55% respectively) showed significant decreases at the same time. In the injured part of the myocardium of the left ventricle and in the right ventricle no such changes were observed (except a decrease in CCO activity). Meanwhile in the uninjured part, 1 h later there was an increase in the total nicotinamide coenzymes (by 34.8%), mainly on account of oxidized forms. The noradrenalin concentration was increased in the early period of the reaction, but 60 min later in the uninjured part of the left ventricle it was virtually unchanged and showed a definite tendency to rise in the right ventricle.

TABLE 1. State of Myocardial Energy Metabolism in Cytotoxic Injury to the Heart

Indices	Left ventricle						Right ventricle		
	Injured area			Uninjured area					
	control 1	5 min* 2	60 min* 3	control 4	5 min* 5	60 min* 6	control 7	5 min* 8	60 min* 9
Adenine nucleotides, μmoles/g tissue:									
ATP	3,35±0,18	3,48±0,22	2,2±0,15 $P_{3-6}<0,001$	3,8±0,25	3,84±0,38	3,48±0,16	3,14±0,42	3,15±0,28	3,0±0,3
ADP	1,36±0,1	1,36±0,27	1,03±0,12 $P_{3-6}<0,01$	1,52±0,1	1,35±0,28	1,75±0,15	1,16±0,14	1,4±0,28	1,3±0,1
AMP	0,69±0,09	0,74±0,22	0,4±0,06 $P_{3-6}<0,01$	0,64±0,11	0,77±0,16	0,62±0,1	0,44±0,12	0,76±0,19	0,5±0,1
Total	5,4±0,3	5,33±0,48 P_{2-5} 0,002	3,63±0,22 $P_{3-6}<0,001$	5,98±0,34	6,12±0,5	5,85±0,45	4,75±0,52	5,32±0,64	4,8±0,5
Inorganic phosphorus, mg%	40,11±3,18	38,87±3,18	35,38±3,1	40,34±7,5	42,58±2,87	42,15±2,5	38,34±3,93	38,83±3,89	38,3±1,9
Glycogen, mg%	631,5±54,44	544,3±107,5	376,7±47,6 $P_{3-6}<0,02$	614±35,7	613,1±27,5	604,2±69	645,7±74,86	504,6±38,35	711,9±68,9
Nicotinamide coenzymes, μg/g tissue:									
NAD + NADP	210±37,5	238,6±31,75	229,16±14,1 $P_{3-6}<0,02$	216,8±28,7	273,3±32,5	316,4±26,5	218,7±28,73	250,4±52,1	302,14±19,7
NADH + NADPH	94,6±16,18	89,5±6,65	68,2±9,4	84,5±13	104±10,73	89,7±8,9	76,8±10,43	82,9±7,77	80,88±10
total	271,2±47,9	337,1±32,36	297,4±19,3 $P_{3-6}<0,01$	301,3±31,1	377±35,2	406,1±27,3 $P_{4-6}<0,05$	295,6±23,44	333,3±51,6	383,02±28
NAD + NADP / NADH + NADPH	2,49±0,53	2,4±0,3	3,49±0,35	2,9±0,5	2,7±0,42	3,6±0,3	3,13±0,6	3,1±0,7	3,97±0,5
CCO, ind. units / mg protein/sec	1,03±0,113	0,754±0,12	0,343±0,08	0,792±0,072	0,848±0,148	0,440±0,07	0,83±0,196	0,566±0,114	0,406±0,07
Noradrenalin concentration, μg/g	0,91±0,07	0,94±0,14	0,40±0,04 $P_{1-3}<0,01$ $P_{3-6}<0,01$	0,91±0,07	1,41±0,16	0,89±0,14	1,24±0,11	1,1±0,12	1,63±0,24 $P_{7-9}<0,05$

*Time of taking samples from the myocardium measured after the time of intracoronary injection of ACS. Where the difference between the arithmetic means is significant, this is shown by the corresponding level of significance of P. In other cases differences between indices are not significant.

In cytotoxic injury to the myocardium a decrease in contractile activity and disturbances of energy metabolism are thus observed mainly in the area of direct action of ACS, and changes in contractility are detectable before metabolic changes.

Zonal changes in the activity of the heart and in the indices of its metabolism, similar in character and direction, have been described in local myocardial ischemia [9, 11].

Just as in myocardial ischemia, in cytotoxic injury the decrease in myocardial contractility preceding metabolic disturbances is evidently due not to a fall in the ATP concentration, but to disturbance of the supply of this energy substrate from the mitochondria to the contractile elements and disturbance of its utilization in the contraction process [6]. At the same time, the substantial decrease in the concentration of adenine nucleotides 1 h after injection of ACS is the result of the harmful action of cytotoxins on the mitochondria and contractile elements of the myocytes [7]. The evident tendency toward an increase in the contractile function of the myocardium of the injured parts of the heart can be interpreted as a manifestation of their compensatory hyperfunction. The increase in the noradrenalin concentration in the uninjured parts of the myocardium may be evidence of involvement of the sympathetic nervous system in compensatory reactions.

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CHANGES IN ACTIVITY OF THE HISTAMINE AND SEROTONIN SYSTEMS IN ACUTE MESENTERIC VASCULAR OBSTRUCTION

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Experiments on 24 dogs showed that acute occlusion of the cranial mesenteric artery, depending on its duration, leads to biphasic changes in the activity of the histamine and serotonin systems. In the stage of intestinal ischemia the liberation of histamine and serotonin from mast cells is increased, with activation of enzymes responsible for their inactivation (diamine and monoamine oxidases). In the state of intestinal infarction, the enzyme component of the histamine system is considerably inhibited and serotonin activity reduced as the result of progressive intoxication of the animal by substances of microbial and metabolic genesis.

KEY WORDS: mesenteric vessels; occlusion; histamine; serotonin.

Many investigators [4-6, 11] attach great importance to biologically active substances in the pathogenesis of irreversibility in the case of acute obstruction of the mesenteric vessels. Meanwhile data on the role of vasoactive amines such as histamine and serotonin are few in number and at times contradictory in nature [4, 7, 10]. A shortcoming of many investigations is the absence of information on the dynamics of changes in vasoactive substances in different stages of the disease (ischemia, necrosis of the intestine, peritonitis), and also on dependence of their blood levels on the state of inactivation enzymes.

EXPERIMENTAL METHOD

Considering the comparative rarity of the disease, activity of the histamine and serotonin systems was studied in experiments on 24 adult mongrel dogs of both sexes weighing 10-25 kg. Acute mesenteric vascular obstruction was produced by application of a tourniquet to the trunk of the cranial mesenteric artery (CMA) after laparotomy after intravenous hexobarbital (0.03 g/kg) anesthesia.

The animals were divided into four groups with six dogs in each group. In group 1 (control) the effect of anesthesia, operative trauma, and the prolonged enforced position of the animal on the operating table on indices of histamine and serotonin metabolism was studied. In the three main groups, giving rise to occlusion of CMA of different duration, three successive stages of acute mesenteric vascular obstruction were simulated: The stage of ischemia (3 h), infarction of the intestine (6 h), and peritonitis (12 h of occlusion). Blood for investigation was taken by cannulation of one femoral vein before the operation, 1, 3, 6, and 12 h after the beginning of occlusion, and 60 min after revascularization at each time of occlusion. Activity of the histamine and serotonin systems was judged from the blood concentrations of the amines and activity of their inactivation enzymes in the plasma. The histamine [8] and serotonin [9] levels in the blood were determined fluorometrically. Activity of diamine oxidase (DO) [2] and monoamine oxidase (MAO) [1] was determined from the decrease in the substrate concentration.

EXPERIMENTAL RESULTS

Data showing changes in the activity of the histamine and serotonin systems are given in Tables 1 and 2. No sharp changes in the histamine and serotonin concentration in the systemic blood stream could be found

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