ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN REPARATIVE REGENERATION AND COMPENSATION OF HEART FUNCTION IN EXPERIMENTAL MYOCARDIAL INFARCTION

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The development of myocardial infarction (MI) is accompanied by changes in several parameters of the function, metabolism, and structure of heart muscle. An essential role in the genesis of these disturbances is ascribed to the sympathetic nervous system (SNS). It has been shown that blocking sympathetic influences by chemical desympathization of an animal alleviates the hemodynamic, structural, and functional disturbances in the heart in the acute period of experimental MI [8]. The role of the SNS in compensation of cardiac function and in reparative regeneration after MI is a no less important problem, from both the theoretical and practical points of view, but it has received less study. The investigation described below was accordingly devoted to an examination of this problem.

EXPERIMENTAL METHOD

Chemically desympathized (n = 104) and control (n = 101) male Wistar rats weighing 220-290 g were used. Desympathization was produced by the drug Isobarin (guanethidine), from "Pliva" (Yugoslavia) [9]. Methods based on imposing an increasing frequency of contractions on the heart [6] and creation of a load of maximal resistance by compression of the aorta for 10 sec were used as function tests. Parameters of cardiac contractility were recorded after 2, 5, and 10 sec of compression of the aorta: systolic and end-diastolic (SP and EDP respectively) pressure in the left ventricle, maximal rate of development (dP/dt_{max}) and fall (dP/dt_{min}) of pressure. The intensity of contractile function (ICF) [7] and index of contractility [10] were calculated. Acute experiments were carried out under urethane anesthesia (160 mg/100 g) after thoracotomy with artificial respiration. The pressure in the left ventricle was recorded by a catheter connected to the transducer of a Mingograf-34 electromanometer ("Elema," Sweden). The ECG and first derivative of pressure (by means of a DE-1 instrument) were recorded simultaneously. Noradrenalin (NA) was injected into the right ventricle in a single dose of 0.5 μg/kg. Experimental MI was induced by high ligation of the anterior descending branch of the left coronary artery. The numerical results were analyzed by Student's test. The heart of the experimental and control animals, killed 3, 7, 14, and 30 days after occlusion of the coronary artery, were stained with hematoxylin and eosin, by Van Fieson's method, and by Selye's method for the presence of fuchsinophilic granules.

EXPERIMENTAL RESULTS

Normalization of the contractile function of the heart was not observed 30 days after induction of MI in either the control or the desympathized rats kept in a state of relative physiological rest. It was depressed in both desympathized and control animals, but by a lesser degree in the former (Table 1). A study of the adaptive capacity of the infarcted heart using functional loading tests showed that on imposition of an increasing contraction rate up to 450 beats/min SP in the desympathized heart fell by 16.3% and ICF by 4.5%. Under similar conditions SP in the heart of the control animals fell by 11.3%, whereas ICF rose by 14.3% (Table 1). In the aortic resistance loading test, maximal values of the force of

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TABLE 1. Parameters of Contractility of Left Ventricular Myocardium in Control (I) and Desympathized (II) Rats 30 Days after Ligation of Coronary Artery (M ± m)

Parameter	Group of animals	Before ligation	30 days after ligation	Difference, % of original value	During stimulation 450 beats/min	Difference, % of original value
SP, mm Hg	I	134±2,2	98±7,14*	—26,9	87±17,0	—11,3
	II	92±4,6	86±7,91	—6,5	72±10,0	—16,3
EDP, mm Hg	I	10,0±0,7	4,8±0,37*	—52,0	8,4±1,5	+42,8
	II	7,8±0,6	5,2±0,64*	—33,3	6,6±0,5	+21,2
ICF, mm Hg·min/mg	I	126±10,3	42±4,47*	—66,9	48±5,2	+14,3
	II	95±9,8	45±7,97*	—52,4	43±4,0	—4,4
dP/dt_{max}, mm Hg/sec	I	7747±505	3425±310*	—55,2	2717±359	—20,7
	II	6380±236	3383±322*	—46,9	2330±546	—31,1
dP/dt_{min}, mm Hg/sec	I	3757±224	1857±186*	—50,6	1525±182	—17,9
	II	2877±191	1575±194*	—45,3	1012±148	—35,8
IC, sec^{-1}	I	100±3,5	57±3,3*	—42,5	56±11,0	—1,8
	II	85±4,4	55±8,0*	—34,7	54±7,0	—1,8
Heart rate, beats/min	I	363±15,9	304±13,4*	—16,2	—	—
	II	369±6,7	333±26,2	—9,8	—	—

*P < 0.05.

left ventricular contraction in the infarcted heart at the first, second, and third compressions of the aorta were 63.8, 78.7, and 66.6% higher respectively than the corresponding parameters of intact animals ($P < 0.05$). The increase in SP in the infarcted, desympathized heart in the same loading test was smaller and was 40.0, 48.7, and 30.0% higher respectively than in desympathized rats without infarction ($P < 0.05$). The difference was manifested as a greater decrease in SP than in the control rats at the 10th second of each compression of the aorta. In desympathized animals it fell at the 1st, 2nd and 3rd compressions by 59.8, 44.3, and 41.3% ($P < 0.05$) and in the controls by 35.4, 37.8, and 26.7% ($P < 0.05$) respectively.

The response of the heart to adrenalin on the 30th day of MI was increased in both control and desympathized animals. The pressor response of the heart of the desympathized rats exceeded that in the control animals: 20 sec after injection of NA, SP, and ICF of the left ventricle of the desympathized heart were 51.5 and 66.6% higher ($P < 0.01$) and in the control rats 44.9 and 58.2% higher ($P < 0.05$) respectively. Analysis of the data reflecting changes in the response to adrenalin under the influence of infarction showed that the initially enhanced responsiveness of the desympathized heart [5] showed no tendency to rise further after occlusion of the coronary artery. For instance, before occlusion of the coronary artery in these animals, SP rose by 64.1% ($P < 0.01$) in response to injection of NA, but on the 30th day of MI it rose by 51.5%. By contrast, the development of MI in the control rats was accompanied by increased responsiveness of the heart to adrenalin; the degree of increase of SP after injection of NA was 21.6% greater than this response in intact rats. An essential factor determining the increased response of the desympathized heart to adrenalin is an increase in the number of active adrenoreceptors (AR) [5]. The absence of any further increase in the response of the infarcted heart of desympathized rats to adrenalin, and the presence of such an increase in the control rats may therefore be evidence that the number of AR in the desympathized heart remains unchanged during development of MI, whereas in the control rats, on the contrary, the zone of active AR is widened. In the latter case this is also evidently due to a fall in catecholamine concentration in the heart in MI and is a manifestation of the compensatory reaction of the body as a whole in order to maintain the function of cardiovascular system when the mediator of the SNS is present in reduced concentration in the myocardium.

Analysis of the morphological data obtained 3, 7, 14, and 30 days after creation of MI showed that in desympathized rats infarct formation takes place within a shorter time than in the control rats. In desympathized rats, for instance, the initial signs of organization of the infarct (the appearance of many macrophages and thin connective-tissue fibers in the zone of necrosis) were found as early as the 3rd-7th day, on the 14th day the zone of infarction was completely occupied by a scar consisting of coarse connective-tissue fibers, and on the 30th day the scar tissue was undergoing collagenization. In the control rats initial signs of organization of the infarct did not appear until the 14th day, and a scar formed of coarse fibers was observed on the 30th day (Fig. 1). Changes in the peri-infarct and extrainfarct zone of the left ventricular myocardium also differed (Fig. 2). In desympa-

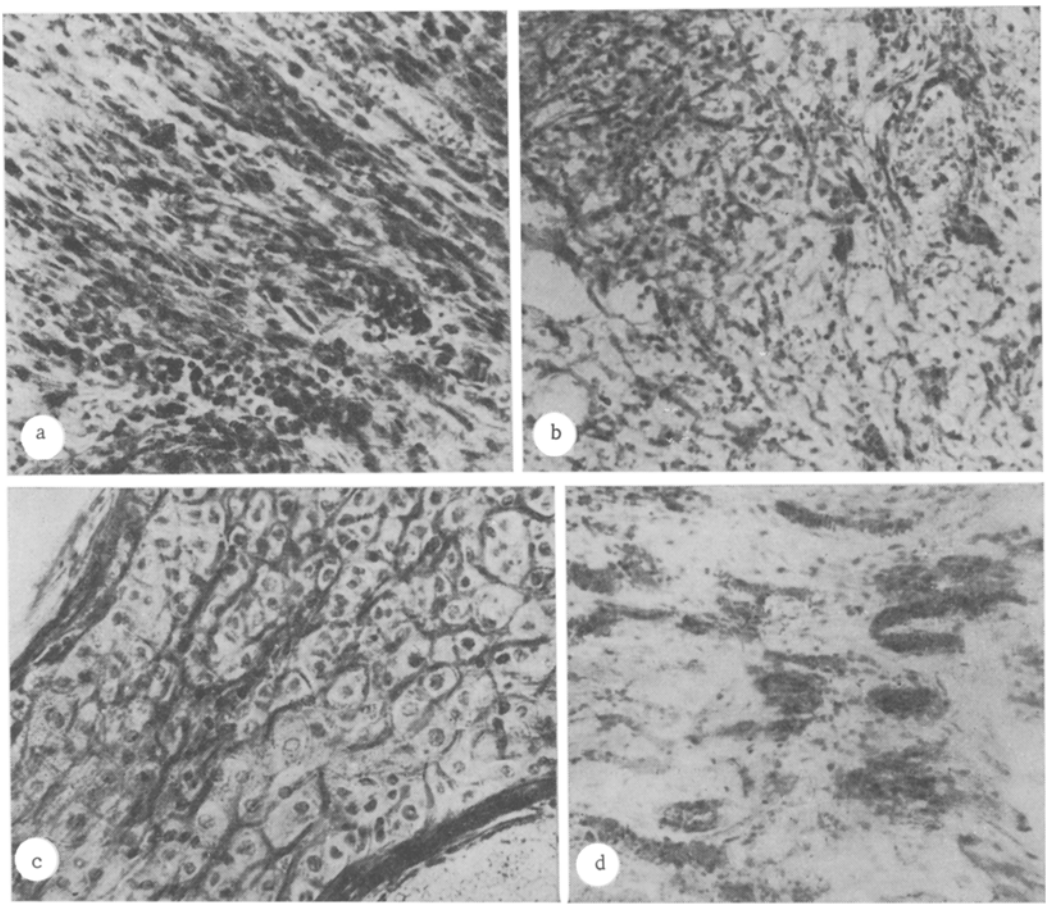

Fig. 1. Morphological changes in zone of MI in desympathized and control rats. a) Experiment, 3 days; macrophages and fibroblasts in zone of necrosis (hematoxylin and eosin, 100×); b) experiment, 7 days; thin fibers of young connective tissue and cells at site of necrosis (Van Gieson's stain, 70×); c) experiment, 30 days; masses of collagen visible among connective tissue fibers (Van Gieson, 140×); d) control, 30 days; area of scar formation in infarct with islands of preserved muscle fibers (hematoxylin and eosin, 70×).

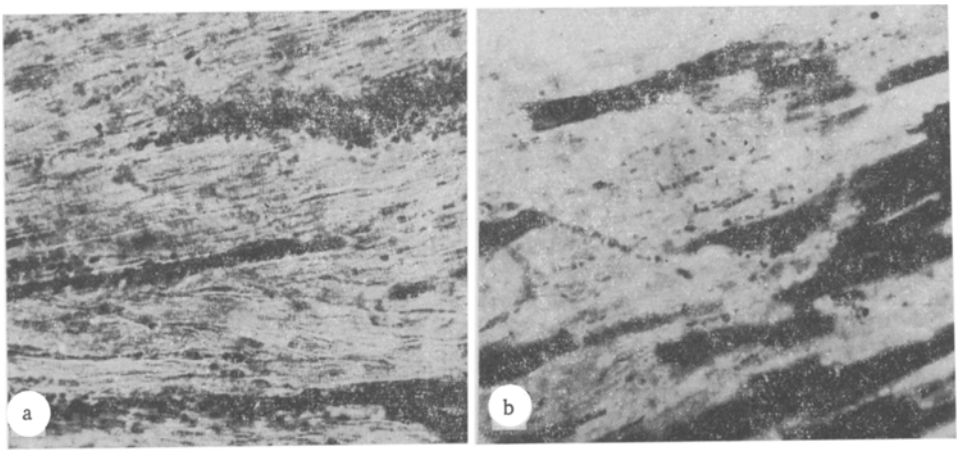

Fig. 2. Morphological changes in peri-infarct and extrainfarct zones of myocardium in desympathized and control rats. a) Experiment, 14 days; dilated vessels congested with blood, hemorrhages in extrainfarct zone (Selye's stain, 100×); b) control, 14 days; fuchsinophilia of fibers in peri-infarct zone (Selye's stain, 120×).

thized rats, by contrast with the controls, there was no clearly defined peri-infarct zone: Changes were observed throughout the muscle and consisted of dilatation and congestion of the vessels with blood, the appearance of foci of infiltration, and fuchsinophilia of individual muscle fibers. These changes did not differ essentially in character from those observed in the desympathized myocardium and they were the result of desympathization. The changes mentioned above were not related to the time of infarction. In the control rats the peri-infarct zone differed sharply from the remaining muscle: It contained large hemorrhages, fibers with marked fuchsinophilia (7-14 days), and hypertrophy of muscle fibers adjacent to the scar (30 days). The extrainfarct zone of the control hearts was characterized mainly by acute vascular disorders [8], which disappeared completely in the later stages.

Comparison of the morphological data showed that the faster formation of scar tissue in the desympathized rats compared with the control is linked with increased phagocytic activity of the macrophages in them, with the early fibroblast response, and a sharp increase in fiber-forming function, combining to produce rapid absorption of foci of necrosis (3rd day), early maturation of connective tissue (7th day), and scar formation. Consequently, blocking the SNS by chemical desympathization contributes to the more rapid healing of the myocardial infarct. The data are in agreement with those of other workers who note that division of sympathetic nerves accelerates regeneration, promotes wound healing, and encourages the liquidation of inflammation in the tissues [4], whereas blockade of fibers of the autonomic nervous system and, in particular, of its sympathetic division, leads to rapid and early differentation of connective tissue [1].

A probable cause of the absence of compensatory hypertrophy of the muscle fibers in the juxtainfarct zone in desympathized heart is a disturbance of protein metabolism in the desympathized myocardium [3].

The results of this investigation thus revealed a twofold influence of the SNS on compensation and adaptation of heart function and on reparative regeneration in MI. When sympathetic influences are blocked, connective tissue cells were found to be activated, so that the infarct healed in a shorter time. At the same time, desympathization was shown to inhibit the development of compensatory reactions and to limit the adaptive powers of the heart. One factor determining the reduced adaptive power of the desympathized heart is degenerative changes in the myocardium associated with desympathization itself [2].

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