MORPHOLOGICAL AND FUNCTIONAL FEATURES OF HEART MUSCLE IN CHRONICALLY DESYMPATHIZED RATS

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It was shown previously that the cardiac output is increased in chronically desympathized animals [2]. Under such conditions the load on the heart is naturally altered and changes may arise in the function and structure of the heart muscle. To examine these problems, in the investigation described below the contractile function of the heart, cardiomyocyte morphology, and the ultrastructure of heart tissue mitochondria were studied.

EXPERIMENTAL METHOD

Experiments were carried out on desympathized and control rats weighing 100 g. Desympathization was carried out by injecting guanethidine into newborn rats for 4 weeks: Under these conditions 0.5% of the normal number of neurons remain in the sympathetic ganglia [1]. The contractile function of the heart was estimated from the curve of pressure in the left ventricle; the pressure was recorded under open chest conditions, during artificial respiration (urethane anesthesia, 160 mg/kg), by means of a cannula introduced into the apex of the left ventricle. The cannula was connected to the transducer of a Mingograph-34 electromanometer (from Elema, Sweden). The systolic pressure and the rate of its rise in the left ventricle were calculated [5, 8]. These parameters were recorded when the animal was in a state of relative physiological rest and also when maximal loading was created by compression of the ascending aorta for 30 sec. To study cardiomyocyte morphology pieces of the left ventricle were fixed in Carnoy's fluid and embedded in paraffin wax; serial sections were cut to a thickness of 7 μ and stained with iron–hematoxylin. To study the ultrastructure of the mitochondria, the tissues were fixed in 5% glutaraldehyde, postfixed with OsO_4, and embedded in Epon-812; sections were stained with lead by Reynold's method [10] and examined in the Hitachi 11-B and Hitachi-12 electron microscopes.

EXPERIMENTAL RESULTS

At relative physiological rest the systolic pressure of the desympathized rats was the same as in the control but the rate of rise of pressure in the left ventricle was increased by 22% ($P < 0.05$) compared with the control (Table 1). The force of contraction of the myocardium, measured as the maximal pressure in the left ventricle [8], 5 sec after the beginning of compression of the aorta was increased in the desympathized rats from 80 to 172 mm Hg, whereas in the control rats it was increased from 88 to 181 mm Hg. i.e., about equally. The maximal rate of rise of pressure in the left venticle (dp/dt_{max}) under these conditions was increased in the desympathized rats from 3164 to 5330 mm Hg/sec, compared with from 2523 to 3880 mm Hg/sec in the control rats. The rate of rise of pressure in the desympathized animals in the initial stage of compression of the aorta was thus 27% greater than in the control ($P < 0.01$). Later, as compression of the aorta continued, the contractile function of the heart was depressed in both desympathized and control animals, but the course of the process differed in the two groups. In the control rats the systolic pressure 25 sec after the beginning of compression of the aorta fell to 107 mm Hg, but it fell more in the desympathized rats (to 59 mm Hg). The value of dp/dt_{max} in the control rats by the 25th second

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TABLE 1. Comparative Cardiac Function in Control and Chronically Desympathized Rats at Relative Physiological Rest and During Compression of the Ascending Aorta

Group of animals	Time of determination of parameter after compression of aorta	Systolic pressure, mm Hg	P	Rate of rise or pressure, mm Hg/sec	P
		Relative physiological rest			
Control rats	—	101±10,6 (n=7)		2812±277 (n=7)	
Desympathized rats	—	90±7,6 (n=9)	$P_3>0,05$	3584±192 (n=9)	$P_3<0,05$
		Compression of ascending aorta			
Control rats	Intially	88±12,3 (n=7)		2523±245 (n=7)	
	After 5 sec	181±21,3 (n=6)	$P_1<0,01$	3880±327 (n=6)	$P_1<0,01$
	After 25 sec	107±8,1 (n=6)	$P_2<0,01$	2660±205 (n=6)	$P_2<0,01$
Desympathized rats	Initially	80±7,4 (n=9)		3164±296 (n=9)	$P_3>0,05$
	After 5 sec	172±16,3 (n=6)	$P_1<0,001$	5330±229 (n=9)	$P_1<0,001$ $P_3<0,01$
	After 25 sec	59±6,4 (n=8)	$P_2<0,001$ $P_3<0,001$	1300±191 (n=8)	$P_2<0,001$ $P_3<0,001$

Legend. P_1) Compared with initial level, P_2) compared with previous state, P_3) compared with control.

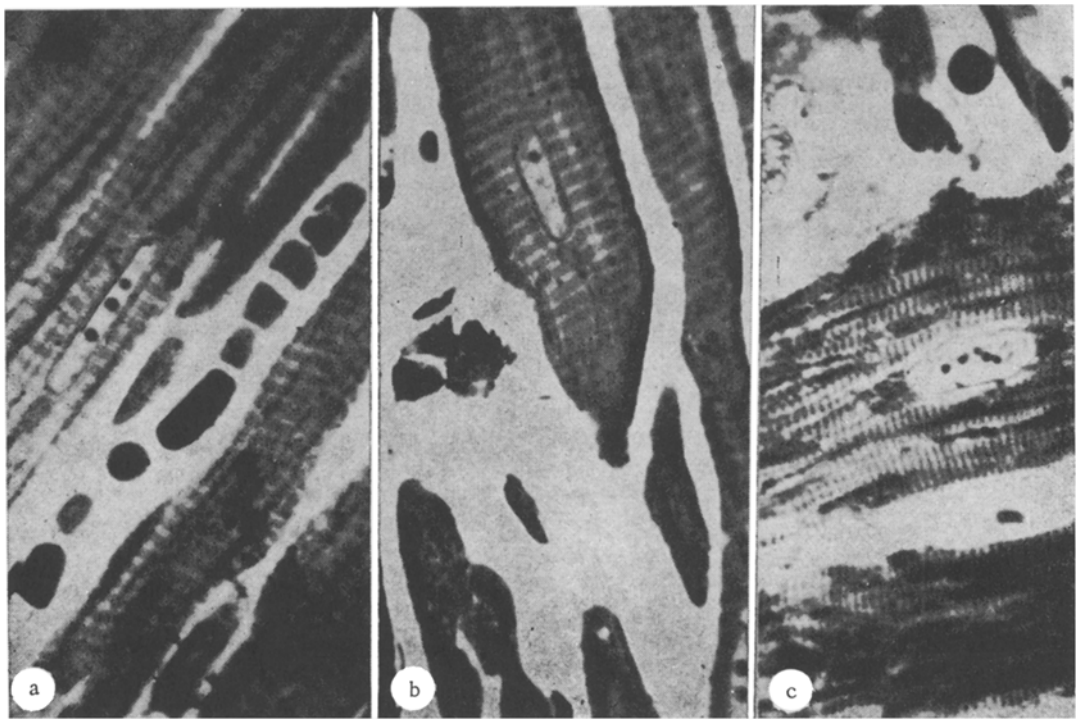

Fig. 1. Morphology of left ventricular cardiomyocytes from control (a) and chronically desympathized (b, c) rats. Iron-hematoxylin. Magnification 900 ×.

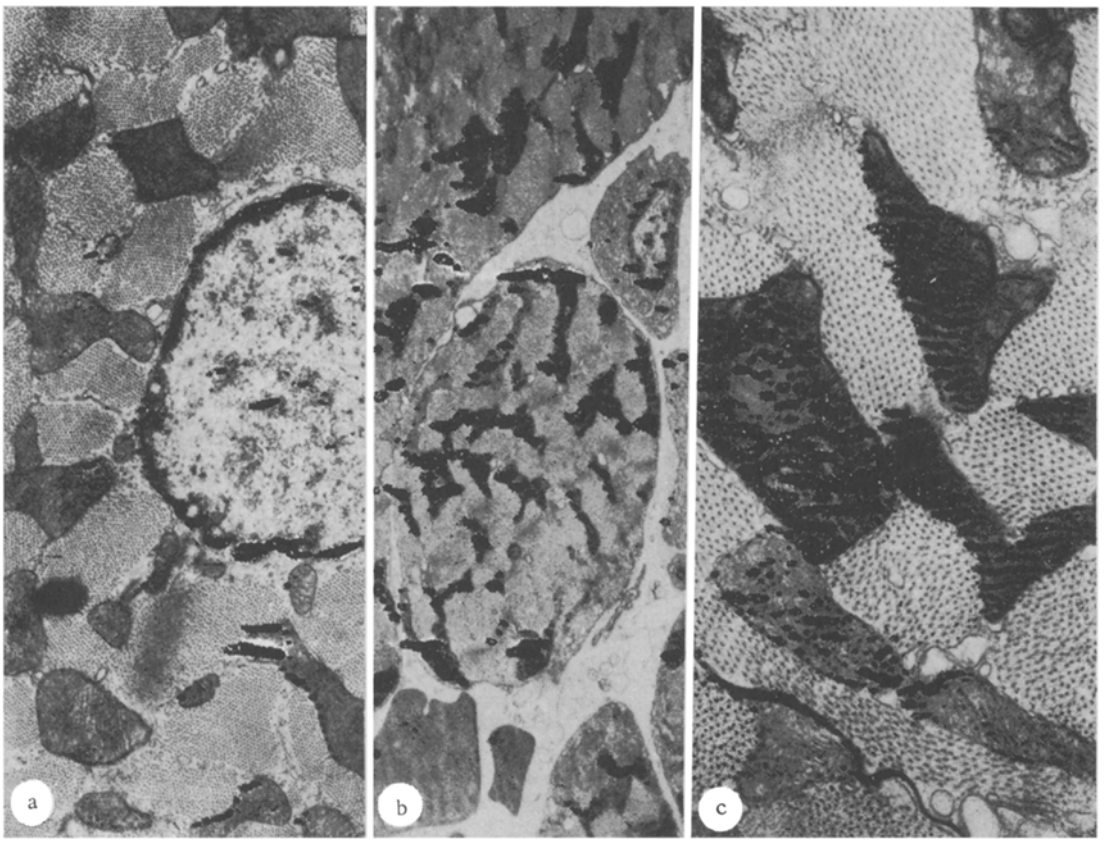

Fig. 2. Ultrastructure of mitochondria in left ventricular cardiomyocytes of control (a) and chronically desympathized (b, c) rats. Magnification: a) 16,100, b) 7300, c) 38,000 ×.

was down to 2660 mm Hg/sec, but in the desympathized rats it reached 1300 mm Hg/sec. The force and velocity of contraction of the left ventricle in the desympathized animals thus fell by a greater degree during long-term loading than in the control.

Investigation of the morphology of left ventricular cardiomyocytes showed that their mean diameter in the desympathized rats was 20.73 ± 0.12 conventional units and in the control rats 18.83 ± 0.18 conventional units ($P < 0.001$). The percentage of cardiomyocyte nuclei containing two or more nucleoli was 58.3 ± 3.1 in the experiment and 32.9 ± 1.7 in the control ($P < 0.001$). The diameter of the nuclei was increased to 5.92 ± 0.08 (5.53 ± 0.11 in the control). Besides the evidence of myocardial hypertrophy signs of interstitial edema also were observed (Fig. 1): The space between neighboring groups of fibers was enlarged, with no corresponding increase in the amount of connective tissue. Changes also were observed in the blood vessels of the heart: The capillaries were greatly dilated and contained many more cells than normally (Fig. 1).

These results are evidence of hypertrophy of the heart in the desympathized animals. This is confirmed also by weighing the heart. The mean absolute weight of the heart was 407 ± 3.7 mg in the desympathized rats ($n = 51$) but 316 ± 2.6 mg in the controls ($n = 35$; $P < 0.001$). The increase in weight of the heart in the experimental animals was accounted for mainly by the left ventricle. Its weight in the desympathized animals was 300 ± 8.1 mg but in the controls it was only 225 ± 3.1 mg ($P < 0.001$). The weight of the right ventricle also was increased a little in the desympathized rats (107 ± 6.7 mg in the experiment, 91 3.8 mg in the control; $P < 0.05$).

The ultrastructure of the mitochondria of the heart tissue in the desympthazied animals differed sharply from the control. First, two morphologically distinct populations of mitochondria appeared in the heart muscle of the desympathized rats: mitochondria with an electron-dense matrix and with more electron-dense outer and inner membranes, and mitochondria indistinguishable in their morphology from those of control animals (Fig. 2). Yet another

difference was found when serial sections were studied. Mitochondria of the cardiomyocytes in the experimental group, unlike the control, were single and oval or elongated in shape (Fig. 2). Intermitochondrial contacts, characteristic of the cardiomyocytes of the control rats [7], were extremely rare in the experimental animals. This particular morphological feature of the mitochondria is evidence that all the many mitochondria in the cell do not belong to the same mitochondrial system.

The experiments showed that chronic absence of the sympathetic nervous system leads to substantial changes in the structure and function of the heart tissue. The absolute weight of the heart in the desympathized animals was 22% greater than in the control. The increase in weight of the heart takes place chiefly on account of the left ventricle: It is 25% larger than in the control. Morphological investigation of the left ventricle showed an increase in diameter of the cardiomyocytes in desympathized rats by 9.2% compared with the control. The number of nuclei of cardiomyocytes containing two or more nucleoli was 44% greater than in the control, evidence of increased synthetic activity of the cardiomyocytes, which is a characteristic feature of the development of hypertrophy. The increase in number of polynucleolar nuclei is a phenomenon found under normal conditions in the developing myocardium. Its presence is evidently associated in the experimental rats with delay in their development, but in the writers' opinion a combination of this feature with the other changes observed is evidence of hypertrophy.

The contractile function of the myocardium of the hypertrophied hearts of the desympathized rats differed from that in the control. The differences were greatest at the 25th second after loading caused by compression of the ascending aorta. The force of contraction of the left ventricular myocardium in the desympathized animals was reduced under these conditions by 45% compared with the control level, whereas the maximal rate of rise of pressure was reduced by 51%. These results are evidence of depression of the contractile function of the heart in desympathized animals in response to long-term loading. There is evidence to suggest that this phenomenon is connected with a disturbance of the energy supply to the hypertrophied myocardium. We know that the ATP content in hypertrophied myocardium (hypertrophy caused by coarctation of the abdominal aorta) per unit weight of tissue is less than in the control. During maximal isometric loading the ATP concentration in the myocardium is reduced by approximately two-thirds compared with the control [4]. Some workers also have found irregularly shaped mitochondria, containing osmiophilic deposits in the matrix, in hypertrophied human myocardium. In their opinion, these changes in the mitochondria may lead to a decrease in the energy supply of the myocardium [9]. Our own data agree in principle with the results obtained by these workers. We also observed changes in mitochondrial ultrastructure indicating disturbances of the mitochondrial system of the cell. This system is responsible for ensuring the most economical and regular transport of electrical potential during ATP synthesis [7]. The changes observed in the mitochondrial system of the desympathized animals may thus, in our opinion, lead to a disturbance of the energy balance of the myocardium. If this hypothesis regarding a disturbance of the energy balance of the heart in desympathized animals is true, the more rapid depression of the contractile function of the heart after compression of the aorta than in the control may be one stage in the manifestations of a response indicating that these individuals have lower endurance under conditions of stress. The lower endurance of chronically desympathized animals in stress situations was established by previous studies [3, 6].

Profound changes in the structure and function of heart tissue are thus observed in chronically desympathized animals. We do not yet know the primary cause of these changes — whether it is the absence of a direct sympathetic influence on the heart or changes in the state of the cardiovascular system resulting from desympathization. Further research is necessary to shed light on these problems.

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COMPARISON OF THE SYSTEMIC HEMODYNAMICS IN NORMOTENSIVE AND HYPERTENSIVE RATS

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Spontaneously hypertensive rats of the Wistar-Kyoto line (SHR) and rats with renovascular hypertension (RVHR) are regarded as experimental models of essential and symptomatic hypertension in man and are widely used in medical and biological research [1, 6, 7, 9]. Many studies of hypertension have been carried out by the use mainly of only one of these models of hypertension.

The aim of the present investigation was accordingly to study and compare the basic parameters of the systemic hemodynamics and function of the baroreceptor reflex (the cardiac component) in normotensive rats (NR) and in animals with the two different models of hypertension: SHR and RVHR.

EXPERIMENTAL METHOD

Male rats weighing 250-300 g were divided into three groups (15 rats in each group): 1) control, noninbred NR, 2) SHR, 3) RVHR.

The last group consisted of noninbred rats in which a coil with internal diameter of 0.35 mm had been wound around the left renal artery and the right kidney completely removed 28-30 days before the experiment.

All the rats were anesthetized with a mixture of urethane (600 mg/kg) and chloralose (40 mg/kg). The blood pressure was measured by an EMT-34 electromanometer in the femoral artery. Momentary values of the heart rate were determined by a digital pulsotachometer, triggered by the arterial pressure pulse wave. All parameters of the hemodynamics measured were recorded in analog form on a Mingograph-81 apparatus and numerical values of the arterial pressure and pulse rate were recorded on a digital printer. The cardiac output was determined by the tetrapolar rheography method on an RPG2-02 instrument [3]. The formula used for the calculation was:

$$\Delta V = Kp\frac{L2}{Z2}AdT_{ej},$$

where ΔV is the stroke volume of the heart (in cm^3); K a coefficient, with the value 0.7; p the specific resistance of rat blood, which is 165 Ω/cm; L the distance between the chest

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