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Ultrastructural Changes in Myocardium of Hypertensive Rats Treated with Nifedipine

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Spontaneously hypertensive rats (SHR) with high systolic pressure received calcium antagonist nifedipine in medium therapeutic doses for 2 weeks. Electron microscopy of the myocardium revealed considerable changes in the sarcoplasmic reticulum manifested in dramatic dilation of tubules, destruction of membranes, and appearance of amorphous matter of medium electron density in tubules in animals treated with nifedipine. Since sarcoplasmic reticulum plays an important role in calcium-dependent excitation-contraction coupling, the observed structural changes can underlie the negative inotropic effect of long-term nifedipine therapy.

Key Words: *myocardium; arterial hypertension*; *nifedipine*; *sarcoplasmic reticulum*

At present, slow calcium channel blockers are widely used for antihypertensive therapy. Calcium ions play an important role in regulation of the vascular tone. Factors increasing the intracellular Ca^{2+} concentration induce blood pressure rise: free calcium ions appeared in the sarcoplasm in concentration above 10^{-6} M bind to calmodulin and induce transformation of light myosin chains resulting in conversion of chemical into mechanical energy, *i.e.* contraction. This calcium-calmodulin mechanism increases Na^{+} influx into the cell, enhances sensitivity of smooth muscle cells to growth factors, and stimulates their proliferation. Calcium antagonists, inhibitors of slow calcium channels, block Ca^{2+} entry into the cell and produce a pronounced hypotensive effect. However, some authorities recently reported a negative inotropic effect of slow calcium channel blockers on the myocardium [3-5]. Calcium ions participate in the excitation-contraction coupling on membranes of the sarcoplasmic reticulum (SPR) and the blockade of calcium channels inevitably affects this mechanism. Our aim was to study the state of SPR in the myocardium of hypertensive rats, which received hypotensive therapy (calcium antagonists).

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MATERIALS AND METHODS

Experiments were carried out on 20 spontaneously hypertensive (SHR) rats. Ten Wistar—Kyoto rats ser-

TABLE 1. Effect of Nifedipine on Blood Pressure (mm Hg) in Rats (*M*±*m*, *n*=10)

Observation period, weeks	Control	SHR	SHR+ nifedipine
1	139.0±3.5	161.0±5.4	160±6
2	148.0±3.1	177±6	163.0±5.5
3	147.0±1.9	192.0±3.5	173.0±3.5
4	144.0±2.8	198.0±4.1	183.0±7.6
5	161±3	220±5	188.0±5.4
6	153.0±2.7	233±5	202.0±6.3
7	144.0±3.1	218±5	205.0±4.7
8	149.0±4.2	222±6	188.0±4.9

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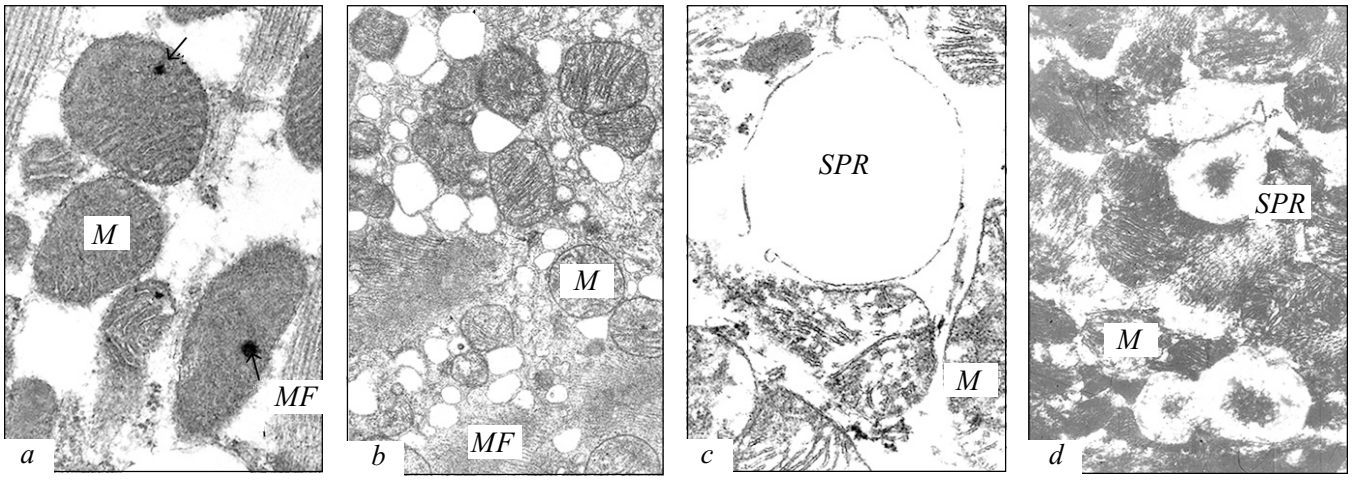

Fig. 1. Ultrastructural changes in the left ventricular myocardium of spontaneously hypertensive rat treated with nifedipine. ×30,000 (*a*, *c*); ×20,000 (*b*, *d*). *a*) electron-dense calcium inclusions (arrows) in mitochondria (*M*); *b*) numerous dilated tubules of sarcoplasmic reticulum (*SPR*); *c*) drastic dilation of the SPR tubule with signs of membrane damage; *d*) amorphous matters of moderate electron density in dilated cisterns and tubules. *MF*: myofibrils.

ved as the control. Some SHR rats (n=10) were intramuscularly injected with nifedipine in a daily dose of 0.5 mg/kg (medium therapeutic dose for humans) for 8 weeks. Systolic blood pressure in the caudal artery was measured weekly in all rats. After 8 weeks the experimental and control animals were sacrificed by cardiac extirpation. The hearts were perfused with 2.5% glutardialdehyde. Papillary muscles were isolated, postfixed in OsO_4 (pH 7.2-7.4), and embedded in Epon-Araldite. Ultrathin sections (Reicher-Jung-Ultracut ultramicrotome) were contrasted with lead hydroxide and uranyl acetate, and examined under a Zeiss-10 electron microscope. Electron microscopy was performed at the Laboratory of Electron Microscopy (head Dr. P. Rieger) of the Institute of Pathology, University of Heidelberg, Germany.

RESULTS

Nifedipine produced a statistically significant hypotensive effect in rats (Table 1).

In SHR rats, mitochondria contained electron-dense inclusions (Fig. 1, *a*), which were probably calcium deposits [2]. This assumption was confirmed by analytical electron microscopy allowing identification of some ions on ultrathin sections.

The most pronounced ultrastructural phenomenon was the appearance of a large number of SPR cisterns (Fig. 1, *b*); drastic enlargement of SPR tubules with signs of membrane destruction (Fig. 1, *c*); and the presence of amorphous matter of medium electron density in dilated SPR tubules and cisterns (Fig. 1, *d*).

Thus, long-term treatment with calcium antagonist nifedipine induces destructive ultrastructural modifications in SPR in the myocardium of SHR rats. These changes inevitably affecting the excitation-contraction coupling are most probably responsible for reduced contractility of both ventricles observed after long-term administration of nifedipine to hypertensive animals [1].

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