EFFECT OF SANOTENSIN ON THE ULTRASTRUCTURE OF RABBIT HEART MUSCLE CELLS

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A study of left heart function showed that a two-week course of sanotensin reduces the contractility of the left ventricle. Electron-microscopic investigation of heart muscle cells revealed considerable accumulation of glycogen and lipid droplets in the myocytes of the atria and ventricles after a dose of sanotensin of 1 mg/kg. With an increase in the dose to 2 mg/kg the tendency toward the accumulation of glycogen was increased, distinctive "buds" containing only mitochondria and glycogen were formed, and destructive changes occurred in the mitochondria. The results are evidence of a disturbance of the energy metabolism of the muscle cells, which is evidently one cause of the decreased contractility of the heart muscle.

KEY WORDS: sanotensin; ultrastructure of myocardiocytes; glycogen.

Sanotensin [β-(N-azacyclo-octyl)-ethylguanidine sulfate] is an antiadrenergic compound with a selective sympatholytic action. This compound is widely used in clinical practice for the treatment of hypertension. Sanotensin inhibits adrenergic influences on the cardiovascular system, as shown by a decrease in the peripheral resistance and the cardiac output, slowing of the heart beat, and a decrease in the venous pressure [1, 2, 10]. The essential nature of the processes taking place in heart muscle cells during sanotensin treatment has not yet been adequately explained.

The object of this investigation was to study the fine structure of the heart muscle cells during administration of sanotensin.

EXPERIMENTAL

Experiments were carried out on 20 chinchilla rabbits weighing 2-2.5 kg. Sanotensin was injected subcutaneously as a 0.1% solution for 14 days in doses of 1 mg/kg (series I) and 2 mg/kg (series II) daily. In the course of the experiment the contractility of the heart was determined from the maximal pressure developed by the ventricles during isometric contraction with the ascending aorta occluded for 5 sec. The pressure was measured electromanometrically by catheterization of the open heart. The results were compared with those of the control group (30 animals) and subjected to statistical analysis by Student's method. The level of significance for the difference of the means was $P \leq 0.05$. The animals were killed on the 15th day after the first injection of sanotensin by rapid extraction of the heart.

The myocardium of the left atrium and ventricle was used as the material for electron-microscopic investigation. Pieces of tissue measuring 1 mm$^3$ were fixed in 1% OsO$_4$ solution by Caulfield's method, dehydrated, and embedded in Araldite. Electron micrographs were obtained on the JEM-100V electron microscope.

RESULTS

Administration of sanotensin for 2 weeks in the therapeutic dose (1 mg/kg) or a double dose led to
Fig. 1. Myocardium of a rabbit receiving sanotensin in a dose of 1 mg/kg: a) accumulation of glycogen granules in perinuclear zone between myofibrils and mitochondria in muscle cell from the left atrium (22,000 ×); b) glycogen granules inside a mitochondrion (46,000 ×); c) cluster of lipid droplets between mitochondria and myofibrils in muscle cell of the left ventricle (45,000 ×). Here and in Figs. 2 and 3: N) nucleus, G) glycogen, M) mitochondria, MF) myofibrils, L) lipids.

Fig. 2. Myocardium of left ventricle after injection of sanotensin in a dose of 2 mg/kg: a, b, c, d) dynamics of structural changes in mitochondria – accumulation of dense osmiophilic granules on mitochondrial cristae (50,000 ×).

Some decrease in the contractility of the left ventricle. The maximal pressure in the control was 238 ± 5 mm Hg, but in the experimental group it fell to 215 ± 9 and 213 ± 8 mm Hg (in series I and II, respectively).

Electron-microscopic investigation of the myocytes from the ventricles and atria of rabbits receiving sanotensin in a dose of 1 mg/kg revealed numerous glycogen granules and lipid droplets. Glycogen granules measuring 300–400 Å, round or polygonal in shape, were distributed diffusely between the myofibrils and myofilaments, sometimes forming large clusters in the perinuclear (Fig. 1a) and subsarcolemmal zones. Sometimes glycogen granules were found in the cisterns of the T-system of the sarcoplasmic reticulum and in the mitochondria (Fig. 1b). The number of microparticles in the perinuclear zones of the atrial myocytes was reduced, or they were completely absent. As well as the accumulation of glycogen, there was a sharp increase in the content of lipids in the muscle cells of the atria and, in particular, of the ventricles (Fig. 1c). Lipid droplets measuring 0.3–1 μ, with a characteristic periodic alternation of osmiophilic density, surrounded by a single membrane, lay in close contact with the mitochondria. The structure of most mitochondria, myofibrils, and nuclei was indistinguishable from normal.