CHANGES IN ULTRASTRUCTURE OF THE MYOCARDIUM PRODUCED BY TOXIC DOSES OF ADRENALIN IN THE INTACT HEART AND AFTER PHARMACOLOGICAL BLOCKADE OF β-ADRENERGIC RECEPTORS

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A submicroscopic study of the effect of toxic doses of adrenalin on different parts of the intact heart showed damage to the myocardium of the ventricles and atria: overcontraction of the myofibrils (frequently with their rupture), deformation of the mitochondria, destruction of the tubules of the sarcotubular system. Injection of propranolol alone caused no significant changes in the ultrastructure of the ventricular or atrial cells. If propranolol was injected before the toxic dose of adrenalin, it appreciably reduced the harmful action of adrenalin but did not abolish it altogether.

Propranolol is one of a group of substances with selective ability to block β-adrenergic receptors, and it is highly effective in the treatment of tachycardia [7]. Besides its antiarrhythmic action, propranolol also possesses adrenolytic properties. The precise mechanism of action of this substance has not yet been explained [1, 2].

The object of the present investigation was to make a submicroscopic study of various parts of the heart following administration of toxic doses of adrenalin alone or after preliminary blockade of the β-adrenergic receptors by propranolol.

EXPERIMENTAL METHOD

Experiments were carried out on 16 chinchilla rabbits weighing 3-4.5 kg. The rabbits were divided into 4 groups. The animals of group 1 received an intravenous injection of adrenalin (25-30 μg/kg body weight), those of group 2 an intravenous injection of propranolol (1.5 μg/kg body weight), and group 3 propranolol in the same dose, followed after 15-20 min by adrenalin in a dose of 25-30 μg/kg. The animals of group 4 were the controls. The heart was removed 15-20 min after injection of the drugs. Pieces were fixed by Caulfield's method, embedded in methacrylate and Araldite, and examined in the UÉMV-100 V electron microscope.

EXPERIMENTAL RESULTS

Electron-microscopic examination of the myocardium after administration of toxic doses of adrenalin revealed significant changes in the muscle cells of the ventricles and atria. The changes observed in both parts of the heart were similar in character, but the destructive changes in the ventricles were more severe than in the atria. The mosaic pattern of damage to the myocardium was a conspicuous feature: side by side with severely damaged muscle cells, in every case there were cells which had preserved their normal structure.

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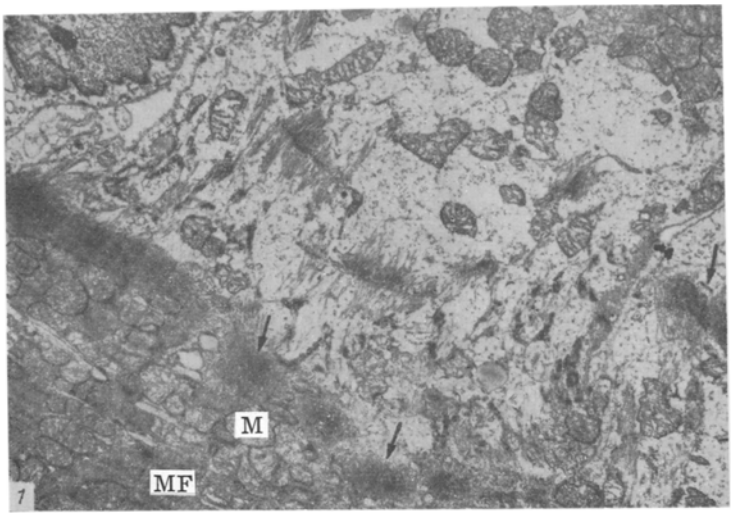

Fig. 1. Myocardium of a rabbit 20 min after injection of a toxic dose of adrenalin: M) mitochondria, MF) myofibrils. Arrow indicates focus of overcontracted myofibrils, 12,000×.

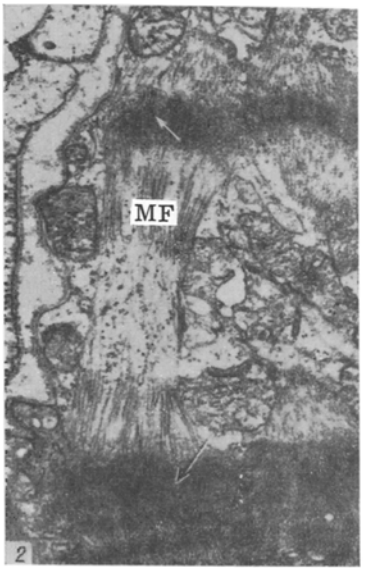

Fig. 2. Focus of overcontraction of myofibrils (indicated by arrow). Fragmentation of sarcomere with rupture of muscle filaments (MF), 20,000×.

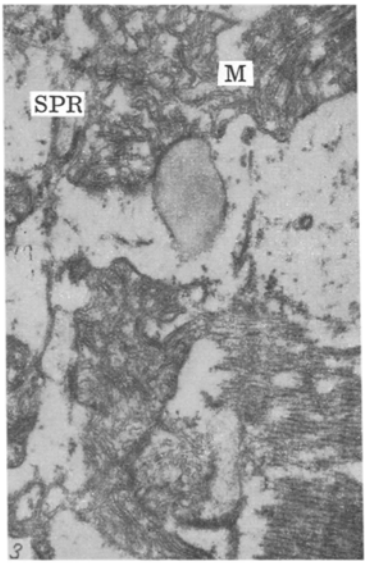

Fig. 3. Deformation of mitochondria (M) with partial destruction of cristae. Destruction of tubules of sarcoplasmic reticulum (SPR), 28,000×.

The most important changes were observed in the contractile elements of the muscle cells. Numerous areas of overcontracted myofibrils (focal contractures) were visible in them. Sometimes several such foci of overcontracted myofibrils apparently joined together to form distinctive nodules of contraction (Fig. 1). These areas were of increased density and appeared homogeneous, and the regular arrangement of their muscle filaments was disturbed. The myofibrils of adjacent areas were in a state of contraction or relaxation, varying in degree. As the result of strong overcontraction, the regular arrangement of the cell organelles was disturbed. The myofibrils and most of the mitochondria were displaced toward the poles of the cell, whereas the central part remained free and contained single mitochondria and fragments of muscle filaments and membranous structures. Rupture and fragmentation of the myofibrils, with their total destruction in the region of the I-disks, were frequently observed (Fig. 2). Elements of the sarcotubular

system were partly destroyed. However, individual tubules of the transverse T system remained intact. In this case they appeared dilated. The content of lipoprotein complexes in the sarcoplasm was increased.

The mitochondria showed changes of a special kind. Most characteristically they underwent marked deformation. The mitochondria appeared to be crushed or shrunken, with an irregularly condensed matrix, and with disarranged and partly destroyed cristae (Fig. 3).

Submicroscopic study of the myocardium of animals receiving propranolol alone showed no significant changes in the ultrastructural organization of the ventricular or atrial muscle cells, in agreement with the results of physiological investigations [6, 11].

After pharmacological blockade of the β-adrenergic receptors by propranolol the same doses of adrenalin did not produce such marked changes in the myocardium. The total number of damaged cells was less than after injection of adrenalin alone. Isolated areas of overcontracted myofibrils were seen in the muscle cells. However, the number of nodules and the degree of their contraction were less than after injection of adrenalin alone. Most mitochondria retained their normal ultrastructural organization under these conditions. Only in some cases was polymorphism of the mitochondria observed, as reflected by variation in the size and arrangement of the cristae. The changes in ultrastructure described above thus show that propranolol appreciably reduces the harmful action of toxic doses of adrenalin but does not abolish it altogether.

Under the influence of toxic doses of adrenalin, the metabolism of the heart is disturbed, and this subsequently leads to degenerative changes in the myocardium [13]. Two types of degeneration take place as the result of the toxic effects of adrenalin: cloudy swelling and fatty degeneration [5]. In the foci of cloudy swelling the muscle fibers appeared homogeneous, they had lost their cross striation, and they were irregular in thickness. Vedeneeva [3] and Danilova [5] confirmed that the damage is mainly confined to the contractile elements, but they were unable to demonstrate the nature of these changes by histological methods. By the use of polarization and phase-contrast microscopes, together with other methods, Tsellarius and co-workers [10] distinguished two types of damage to the myofibrils: contracture and myocytolysis. The contractural changes were expressed as intensified anisotropy of the myofibrils, approximation of the anisotropic disks, and sometimes their total fusion. In myocytolysis, the myofibrils had apparently melted and ceased to be visible. The authors cited consider that an active part in the development of myocytolysis is played by the lysosomal system of the cell. The present authors have shown [8] that mainly one type of damage to the myofibrils is observed in the muscle cells of the myocardium, and this corresponds to the contractural type of changes. Other workers have also reported similar findings [4, 14]. So far as myocytolysis is concerned, no changes of this type could be found. No increase in lysosomal activity could be found in the electron microscope in the damaged cells 20 min after injection of adrenalin. Indeed, it would be hard to imagine that the lysosomal response could play any significant role in this process over a period of a few minutes. There is thus every reason to consider that true liquefaction (myocytolysis) does not take place at this stage. The results of the present investigation show that because of strong overcontraction, the myofibrils in some areas cease to be visible. Simultaneously with contraction and rupture of the myofibrils, some apparent mechanical displacement of the organelles, including fragments of the myofibrils and mitochondria, takes place toward the poles of the cell, as a result of which a pattern of reduced density is produced, and this may be taken as myocytolysis. The mosaic character of damage to the myocardium is evidently connected with differences in the intensity of function of the cells, as is also observed under physiological conditions [8].

The functional activity of the catecholamines is manifested by an increase in the strength and rate of contraction of the myocardium (positive inotropic effect). An important role in the mechanism of this process is played by the ATPase of the sarcotubular system. The ability of adrenalin to block the activity of the ATPase of the sarcotubular system has been demonstrated [12], and this may lead to an increase in the free calcium concentration in the cell. Accumulation of calcium in the sarcoplasm evidently leads initially to overcontraction and subsequently to the changes in the contractile structures described above, leading ultimately to their necrosis.

The changes observed in the ultrastructural organization of mitochondria and the increased content of lipoprotein complexes could be evidence of metabolic disturbances, for not only does adrenalin inhibit oxidative phosphorylation, but it also disturbs the coordination between aerobic and anaerobic metabolism [9].

The mechanism of deformation of the mitochondria is not yet completely clear. There are two possible explanations of this phenomenon. First, as a result of strong overcontraction of the cells the mitochondria may be mechanically compressed. Second, the possibility of a direct effect of adrenalin on the actomyosin present in the mitochondria cannot be ruled out.

The results of the present investigation confirm that after pharmacological blockade of the β-adrenergic receptors the harmful action of toxic doses of adrenalin is considerably reduced.

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