FOCAL METABOLIC MYOCARDIAL LESIONS PRODUCED BY THE ACTION OF ISOPROTERENOL ON THE ISOLATED RAT HEART

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A single injection of 0.5 ml 1% isoproterenol solution into the cannula above the isolated perfused rat heart leads to the development of severe focal necrobiotic changes in the muscle cells of the myocardium. These changes were very similar in character to isoproterenol lesions produced in the myocardium in vivo. No connection was found between the isoproteronal lesions in the myocardium and coronary ischemia. The severity of the isoproteronal lesions in the isolated heart showed definite correlation with the composition of the perfusion fluids.

The harmful action of toxic doses of synthetic catecholamines (especially, of derivatives of isopropylnoradrenalin) on the myocardium has been established by several workers [12, 13]. Changes in the myocardium produced by isopropylnoradrenalin derivatives are usually described as infarct-like, suggesting their connection with coronary ischemia in certain zones of the myocardium [9]. The accumulation of evidence that catecholamines have a direct action on metabolism of the myocardial cells [8, 10, 11, 14] and morphological observations on the early changes in the myocardium under the influence of catecholamines [2, 3, 6] have caused the role of coronary effects in catecholamine lesions of the myocardium to be questioned.

The object of this investigation was to study the action of isoproterenol sulfate on the isolated rat heart by polarization-microscopic and histochemical methods in an attempt to assess the relative importance of metabolic and coronary effects of the catecholamines in the development of the necrobiotic changes in the myocardium.

EXPERIMENTAL METHOD

Retrograde coronary perfusion of 20 isolated rat hearts was set up and a single injection of 0.5 ml 1% isoproterenol solution given into the cannula above the heart 15 min after the beginning of perfusion. The perfusion continued for 3 h after the injection of isoproterenol. After injection of isoproterenol five hearts were perfused with a solution containing Evans' blue dye in a concentration of 1 mg/ml. Isoproterenol was injected subcutaneously into 10 animals in a dose of 0.6 ml of the 1% solution per 100 g bodyweight and the animals were killed 30 min-3 h later. The technique of perfusion, the composition of the perfusion fluids used, and the methods of histological and histochemical investigation of the material were described previously [1].

EXPERIMENTAL RESULTS

Perfusion of the isolated hearts for 3 h with solutions of different composition itself causes certain degenerative and necrobiotic changes in the myocardium [1]. The conclusion that the changes in the myocardium were connected with the action of isoproterenol was drawn while making allowance for this fact.

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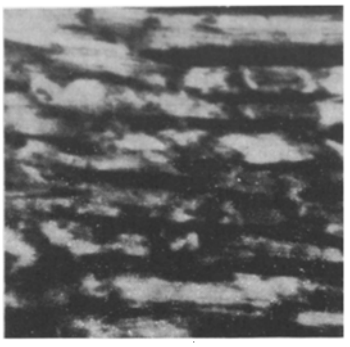

Fig. 1

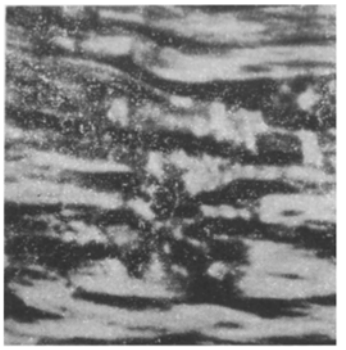

Fig. 2

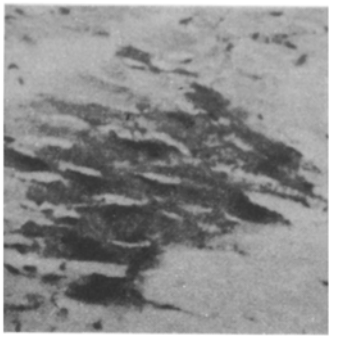

Fig. 3

Fig. 1. Large focus of damage to muscle cells in isolated heart caused by isoproterenol. Here and in Figs. 2 and 3: objective 25, ocular 15. Photographed in polarized light.

Fig. 2. Focus of injury to muscle cells as a result of the action of isoproterenol in vivo.

Fig. 3. Group of muscle cells in a state of contracture. Diffuse sarcoplasmic PAS-reaction, resistant to diastase.

In hearts perfused with Hanks's solution multiple large foci of damage were formed 3 h after a single injection of isoproterenol (Fig. 1). These foci were characterized by marked polymorphism of the changes in the muscle cells. Contractural changes combined within the same cell with local loss of anisotropy in zones lying directly next to the sarcolemma, were predominant. Primary cloudy swelling of the sarcoplasm was common. Characteristically succinate dehydrogenase activity was completely absent in the muscle cells undergoing cloudy swelling. Typical contractures and myocytolysis, so characteristic of adrenalin lesions of the myocardium [4-7], were much less common. A positive reaction for enzymes of the phosphorylase group was found only in muscle cells lying directly beneath the epicardium and in the endothelium of the blood vessels throughout the myocardium. The foci of injury were scattered relatively uniformly in all parts of the heart and showed no tendency toward selective localization or connection with the topography of the coronary vessels.

During the reproduction of isoproterenol lesions in thermocardium after perfusion of the isolated heart with Hanks's solution containing 4×10^{-8} g/ml noradrenalin the foci of injury were much smaller in size and were less frequently found. The foci often contained overstretched muscle cells with greatly widened isotropic disks. After perfusion with medium No. 199 containing 4×10^{-8} g/ml noradrenalin and 0.08 unit/ml insulin, isoproterenol gave rise to less marked damage of the myocardium still. In this case only solitary small foci of injured muscle cells could be found, like those observed in isolated hearts perfused for 3 h with medium No. 199 and not treated with isoproterenol. Characteristically the changes produced by isoproterenol in isolated hearts perfused with solutions of different composition were indistinguishable in the types of injury to the muscle cells. The only difference was in the severity of the injury, as reflected in the size and number of the foci.

Under the influence of a toxic dose of isoproterenol in vivo, foci of injury very similar in severity to those found in the isolated heart were found after 3 h in the myocardium. These were large foci of muscle cells in a state of contracture and of acute cloudy swelling (Fig. 2). Muscle cells with contractural changes gave an intensive diffuse sarcoplasmic PAS-reaction which was not abolished by preliminary treatment with diastase (Fig. 3). This was the only histochemical difference between the lesions found in vivo and those obtained in the isolated heart.

Polarization-microscopic and histochemical investigations thus show that a single injection of a toxic dose of isoproterenol causes well-marked large-focal lesions of muscle cells very similar in severity and in cell forms both in vivo and in the isolated heart. These changes have no selective localization but are distributed uniformly throughout the myocardium of the ventricles and ventricular septum. No correlation could be found between the distribution of the foci and the topography of the coronary vessels. In experiments with vital dye, it entered all the coronary vessels equally. On microscopic examination the dye could be seen in the endothelium of all capillaries and, what is particularly important, in the injured muscle cells. The conclusion [9] that the large focal lesions of the myocardium produced by isoproterenol are connected with constriction of the coronary vessels therefore seems to be incorrect. It was clearly estab-

lished that the foci were formed by a gradual increase in number of injured cells and not by simultaneous injury to all cells of the focus. During the first hour after injection of isoproterenol most of the injured muscle cells in the myocardium were distributed in mosaic fashion and did not form large foci. This type of picture is also characteristic of adrenalin lesions of the myocardium [6]. It can be concluded from these observations that the harmful action of isoproterenol is due to its direct effect on the metabolism of the heart muscle cells and not with any disturbance of the coronary circulation.

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