NEUROGENIC LESIONS OF THE MYOCARDIUM

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The fact has been widely reported in the literature that the myocardium may be damaged by the action of large doses of adrenalin [1, 6, 8]. We have previously reported [3, 4] that after a single intramuscular injection of a massive dose of adrenalin into rats (0.5-0.8 ml of a 1:1000 solution), significant changes in the ECG develop within a few hours, and at the end of 24-48 hr destructive histological changes appear in the myocardium.

The aim of the present investigation was to cause injury to the myocardium by a neurogenic method, i. e., by the action on the myocardium of adrenalin or some substance closely related to it by structure and mode of action, as an endogenous mediator liberated from the endings of postganglionic sympathetic fibres as a result of stimulation. For this purpose we applied excessive stimulation to the stellate ganglia, through which pass the main nerve connections of the heart.

METHOD

Experiments were carried out on 73 rats weighing from 250 to 350 g. Under light ether anesthesia a midline incision was made, the neurovascular bundle was opened up, and the stellate ganglion was dissected out under a loupe. The ganglion was seized between the blades of a hemostat for 5-15 min, after which the hemostat was removed, streptocide powder sprinkled into the wound and the skin sutured. No case of sepsis of the operation wound was observed. In one group of animals (13) trauma was applied to the left stellate ganglion, in another group (32) to the right, and in a third group (7) to both stellate ganglia. In 6 experiments the region of the stellate ganglion was liberally painted with turpentine and the would was then closed.

The control group consisted of 15 animals. Some of these remained intact, while in others the neurovascular bundle was opened under ether anethesia and the stellate ganglion dissected without subsequent trauma to it. The animals survived for periods varying from 4 hr to 11 days; 11 animals died at various intervals after the operation (from 4 hr to 7 days) and the rest were sacrificed by decapitation. The heart was extracted from the chest, rinsed with physiological saline, fixed in 12% formalin solution and embedded in paraffin wax. Sections were cut in a transverse direction at the level of the papillary muscles, and stained with hematoxylin-eosin, picrofuchsin (by Van Gieson's method) and, in some cases, with iron-hematoxylin (by Heidenhain's method). The ECG was recorded in some animals, using the three standard leads, at different times after operation.

RESULTS

The experiments showed that in 27 of 52 cases using mechanical trauma and in 4 of 6 cases using chemical trauma (painting the ganglion with turpentine) excessive stimulation of the stellate ganglia caused a neurogenic lesion of the myocardium, bearing the character of cloudy swelling. On microscopic investigation swelling

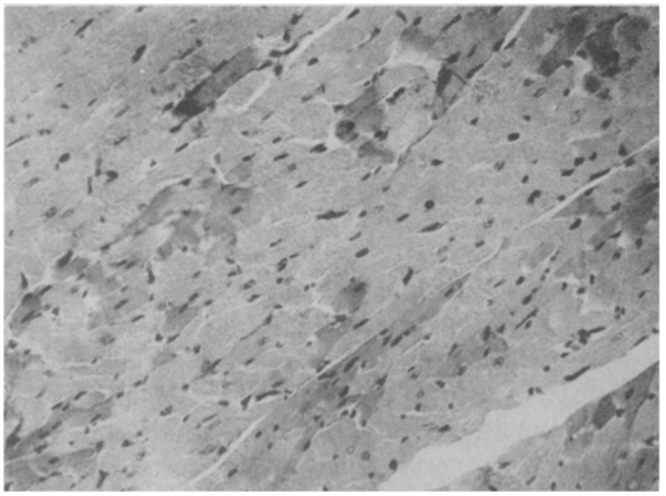

Fig. 1. Dystrophic changes in individual muscle fibers of the rat's heart. Trauma to the stellate ganglion. Stained by Van Gieson's method. Magnification 320 times.

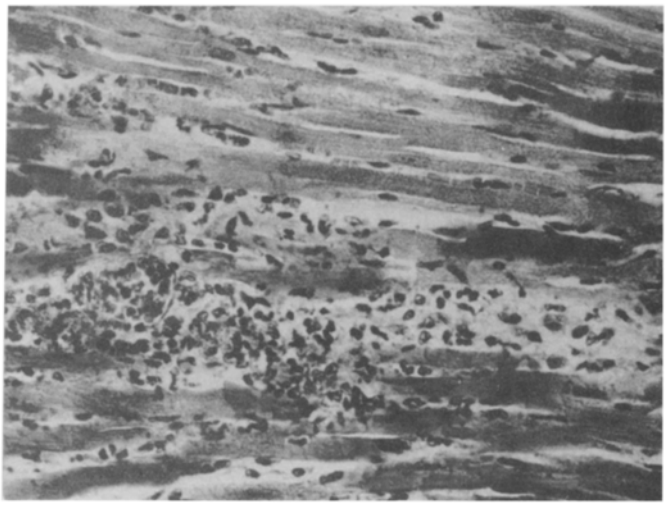

Fig. 2. Destruction of muscle fibers with considerable cellular reaction. Trauma to the stellate ganglion. Stained by Van Gieson's method. Magnification 320 times.

of individual muscle fibers was found, with homogenization of the sarcoplasm and disappearance of the cross-striation. By comparison with the unchanged fibers, these were more darkly stained, so that in some cases the sections had a variegated appearance (Fig. 1). As a rule the manifestations of cloudy swelling were focal in character and affected only individual muscle fibers or groups of fibers, mainly in the left ventricle and the papillary muscles. Subsequently, depending on the time after infliction of the trauma, the patches of cloudy swelling either underwent resolution or, on the contrary, grew, leading to destruction of the muscle fibers and the formation of small foci of necrosis of the myocardium. The muscle fibers either melted away and dissolved (myolysis) or broke up into small fragments (plasmorrhexis). In the latter case a weak or moderately intensive cellular reaction was observed. Only occasionally (in 5 experiments) was considerable myocardial dystrophy observed, accompanied by intensive destruction of individual groups of muscle fibers and by well marked cellular infiltration (Fig. 2).

The blood vessels and capillaries were grossly dilated in some cases and filled with blood cells; sometimes small extravasations of blood from small vessels were seen. The ECG, taken at various times after operation, usually showed very slight voltage changes of the P, R, S, and T waves, with a small displacement of the ST interval from the isoelectric line.

Comparison of the results obtained after stimulation of the right, left or both stellate ganglia simultaneously showed no particular difference in the pattern of the myocardial lesion. For instance, of the 32 rats subjected to the trauma of the right stellate ganglion, dystrophic changes were observed in 18, and of the 13 rats in which trauma was applied to the left ganglion-in 4, and of the 7 rats in which both ganglia were injured-in 5. As regards the 6 cases of stimulation of the stellate ganglia with turpentine, dystrophic changes were observed in all three cases in which the left ganglion was treated and in one of the three cases in which the right was stimulated. The animals usually tolerated simultaneous bilateral trauma to the stellate ganglia and the application of turpentine to the region of the exposed ganglion very badly. Of the 7 animals undergoing operation, 5 died in the course of the first 24 hr in the first case, and 3 of the 6 in the second.

In order to induce experimental adrenalin myocarditis, most workers use the simultaneous injection of adrenalin and caffeine or theophyllin. It is considered that the latter increase the load on the myocardium and thereby predispose the heart to the development of destructive changes after the injection of toxic doses of adrenalin. In our experiments the subcutaneous injection of 1 ml of 10% caffeine solution at the same time as the trauma was applied to the stellate ganglia had no significant effect on the course or character of the cloudy swelling of the myocardium (19 experiments). Nor was any appreciable effect observed from the use of cortisone (20 mg/kg body weight, in a single dose or daily for one week), which, according to our experiments and reports in the literature [9], considerably aggravates lesions of the myocardium caused by adrenalin and noradrenalin (7 experiments).

In the discussion of the results obtained, the first question which arises is: to what extent may the changes in the myocardium brought about by a neurogenic mechanism be compared with the changes arising as a result of large doses of adrenalin or noradrenalin? Analysis of the findings showed that they have features in common. In adrenalin myocarditis, destruction of muscle fibers and the pronounced cellular reaction appear only at the end of the first 24 hours of the investigation. During the first few hours after the injection we observed nothing more than dystrophic changes in the myocardium: irregularity of staining, swelling, homogenization and fragmentation of individual muscle fibers, with loss of their cross-striation (Fig. 3), i. e., the same picture as in the

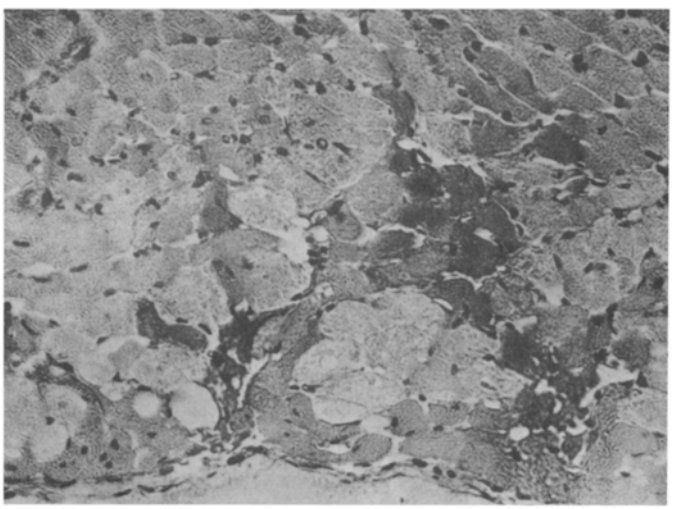

Fig. 3. Dystrophic changes in individual muscle fibers of the rat's heart 3 hours after intramuscular injection of 0.6 ml of 1:1000 adrenalin. Stained by Van Gieson's method. Magnification 320 times.

neurogenic lesions of the myocardium (see Fig. 1). After the action of toxic doses of adrenalin or noradrenalin on the myocardium, destruction of muscle fibers was more in evidence than dystrophy and was accompanied by intensive cellular infiltration; in neurogenic lesions of the myocardium the pathological process was more sluggish in its course and only in isolated cases was destruction of many muscle fibers an obvious cellular reaction (see Fig. 2).

In this case the picture of the myocardial lesion was little different from that caused by adrenalin. This gives grounds for the belief that in both cases the cause of the damage was the same: in one case adrenalin injected from an extrinsic source in a large dose, and in the other-adrenalin or some substance closely resembling it in structure and mode of action, liberated by the endings of the postganglionic sympathetic fibers during excitation.

If this is so, then a second question arises: what is the nature of the injurious action of adrenalin? Is it the result of the direct action of adrenalin on the adrenergic systems of the myocardial tissue, or is it primarily the result of changes in the blood supply of the myocardium and the consequent impairment of its nutrition [2], or is the principal role in the development of "adrenalin myocarditis" played by the nervous system and, in particular, by the functional state of the spinal centers of innervation of the heart [7]?

We are inclined to think that the destructive changes in the myocardium are the result of the action of adrenalin on the adrenergic systems of the myocardium. This hypothesis is supported by our experiments on the injection of large doses of pituitrin and nicotine. In these experiments we did not cause destructive changes in the myocardium, although the pressor effect was undoubtedly very pronounced, and the conditions were consequently right for the development of acute anoxia of the myocardium. Of the series of neurotropic drugs which we tested previously, affecting the reflex arc in different points (central, ganglionic and peripheral), only those possessing a well marked sympathicolytic and adrenolytic action were able to prevent the development of "adrenalin myocarditis"[3, 4]. Finally, the dystrophic changes arising in the myocardium after trauma to the stellate ganglia also support the view that a leading part is played by biochemical processes taking place in the adrenergic systems of the myocardium both during the injection of exogenous adrenalin in large doses and during the action of the endogenous adrenalin functioning as mediator.

SUMMARY

This investigation was aimed at obtaining myocardial lesions by a neurogenic route, i. e., by acting upon the myocardium with adrenalin and noradrenalin (mediators, appearing at the ends of postganglionic fibers of the cardiac sympathetic nerves after their stimulation). For this purpose very strong stimulation, either mechanical or chemical, was applied to the stellate ganglia. Myocardial lesions, of the character of cloudy swelling (swelling of individual muscular fibers homogenization of the sarcoplasm, disappearance of the cross-striation) appear after stimulation of the stellate ganglia. These phenomena of cloudy swelling are focal in character. Later, depending upon the stage of the disease, they either resolve or, on the contrary, are enhanced, leading to the formation of small foci of necrosis in the myocardium with mildly or moderately cellular reaction. Pronounced disintegration of separate groups of muscular fibers and considerable cellular reaction were recorded in individual cases.

Myocardial lesions, provoked by parenteral administration of massive doses of adrenalin, are compared to those resulting from the stimulation of the stellate ganglia, the mechanism of the action of these agents being discussed.

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