ROLE OF α- AND β-RECEPTORS IN THE GENESIS OF EXPERIMENTAL MYOCARDIAL NECROSIS

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The authors previous investigations have shown that following a single intramuscular injection of sympathomimetic amines, of both the catecholamine (adrenalin, noradrenalin, isoprenaline) and the phenylalkylamine (ephedrine, amphetamine) type into rats, foci of necrosis are observed in the myocardium, the severity of which in these experiments was greatest after injection of adrenalin and isoprenaline and least after injection of noradrenalin and amphetamine. It was concluded from a pharmacological analysis that the injurious effect of the sympathomimetic amines is independent of their effect on the blood vessels of the heart, and is a result of direct action on the adrenergic structures of the myocardium [1, 3].

This analysis was continued in the present investigation. Its object was to determine whether the adrenergic structures of the myocardium, excitation of which with large doses of sympathomimetic drugs leads to the production of foci of myocardial necrosis, belong to the α- or β-receptors [6].

EXPERIMENTAL METHOD

Experiments were carried out on male rats weighing 200-250 g. The test substances were injected intramuscularly. Two days later the animals were decapitated, the heart was removed and fixed in 12% formalin solution, and then embedded in paraffin wax. Sections were cut transversely at the level of the papillary muscles and stained with hematoxylin-eosin or with picrofuchsin (by Van Gieson's method).

To obtain experimental myocardial necrosis adrenalin, noradrenalin, and isoprenaline were used. The substances were injected at a single dose of 0.5-0.8 ml of the 1:1000 solution per animal. To act on the myocardium with endogenous adrenergic substances secreted at the endings of the cardiac sympathetic fibers during excessive stimulation, methods were developed for obtaining neurogenic degenerative changes by the stellate ganglion [2] and the arch of the aorta [4].

Sympatholytin was used as the α-blocking agent and dichloroisoproterenol as the β-blocking agent.

EXPERIMENTAL RESULTS AND DISCUSSION

The experiments showed that injection of adrenalin and isoprenaline in the above doses caused necrosis of the myocardium in 100% of cases, stimulation of the arch of the aorta in 85%, and stimulation of the stellate ganglion in 52% of cases.

The use of α- and β-blocking agents during development of necrosis of the myocardium produced by various methods and substances gave different results.

Experiments with the α-Blocking Agent Sympatholytin

Sympatholytin was injected intramuscularly in a dose of 10 mg/kg 30-50 min before injection of harmful doses of sympathomimetics or application of excessive stimulation to the sympathetic nervous system. Sympatholytin was injected in good time, because according to data obtained by R. A. Khaunina [5], the sympatholytic effect of this drug developed slowly and persists for several days.

Experiments with Adrenalin. The results of these experiments (see table) showed that sympatholytin noticeably prevents development of adrenalin necrosis of the myocardium. In only 4 of 11 cases were solitary collections of cells observed, concentrated mainly in the papillary muscles, whereas in the animals receiving adrenalin alone, massive and multiple collections of cells were observed in all the

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Effect of Agents Blocking α- and β-Receptors on Development of Experimental Myocardial Necrosis

	No. of expts.	Necrosis		
		severe	slight	absent
Experiments with sympatholytin blocking α-receptors				
Adrenalin	11	11	0	0
Sympatholytin + adrenalin	11	0	4	7
Sympatholytin	11	0	0	11
Noradrenalin	10	2	4	4
Sympatholytin + noradrenalin	21	7	3	11
Sympatholytin	11	0	0	11
Stimulation of stellate ganglion	8	0	4	4
Sympatholytin + stimulation of stellate ganglion	12	0	0	12
Sympatholytin	7	0	0	7
Stimulation of arch of aorta	19	7	8	4
Sympatholytin + stimulation of arch of aorta	16	2	3	11
Sympatholytin	5	0	2	3
Experiments with dichloroisoproterenol, blocking β-receptors				
Isoprenaline	15	15	0	0
Dichloroisoproterenol + isoprenaline	14	1	8	5
Dichloroisoproterenol	4	0	0	4
Dichloroisoproterenol + adrenalin	7*	0	0	1
Stimulation of arch of aorta	9	3	6	0
Dichloroisoproterenol + stimulation of arch of aorta	7	5	2	0

*6 rats died a few minutes after injection of adrenalin from pulmonary edema.

experiments throughout the thickness of the myocardium. In the animals receiving sympatholytin alone, in the dose given above, no visible morphological changes were found in the myocardium.

Experiments with Noradrenalin. These experiments were carried out on 41 rats: 10 rats were used as controls for injection of noradrenalin, 11 for injection of sympatholytin, and 21 rats received an injection of sympatholytin before one of noradrenalin (see table). Of the 10 animals receiving noradrenalin alone, necrotic changes in the myocardium were observed in 6, but only in 2 of these was the necrosis severe, and in 4 animals only solitary collections of cells and disintegration of individual groups of muscle fibers were observed. In 4 cases no morphological changes were found in the myocardium. In the group of animals receiving sympatholytin first, well marked necrosis was observed in 7 cases, slight necrosis in 6, and no necrosis in 8 cases. When sympatholytin alone was given, no changes were found in the myocardium.

Experiments with Stimulation of the Stellate Ganglion and Arch of the Aorta. These experiments showed that the preliminary injection of sympatholytin 20-50 min before trauma to the stellate ganglion had a marked preventive effect on development of degeneration in the myocardium usually observed after this procedure (see table).

Similar results were obtained in experiments in which the arch of the aorta was stimulated. Sympatholytin has a marked preventive action on the development of reflex degeneration of the myocardium.

Experiments with the β-Blocking Agent Dichloroisoproterenol

Experiments with Isoprenaline. As shown above, the α-sympathomimetic drug isoprenaline, in a dose of 0.5-0.8 mg per animal, caused extensive necroses of the myocardium in 100% of cases in these experiments. Preliminary injection of the β-blocking agent dichloroisoproterenol (3-10 mg/kg) largely prevented or reduced the severity of the necrosis produced by isoprenaline. The results obtained are given in the table.

Experiments with Adrenalin. In this series of experiments dichloroisoproterenol was injected in a dose of 1-3 mg per animal 15-20 min before injection of an injurious dose of adrenalin (0.5 mg). Of 7 animals receiving preliminary injection of dichloroisoproterenol, 6 died a few minutes after injection of adrenalin from pulmonary edema. One rat was killed two days later, and microscopic examination revealed no changes in the myocardium. Injection of dichloroisoproterenol alone, even in large doses (up to 10 mg) had no appreciable effect either on the behavior of the animals or on the morphological picture of the myocardium (see table). Because of this sharp increase in mortality following combined administration of dichloroisoproterenol and adrenalin, it was impossible to test a wider range of doses and to draw conclusions regarding the preventive effect of dichloroisoproterenol on the production of myocardial necrosis by adrenalin.

Experiments with Electrical Stimulation of the Arch of the Aorta. Preliminary injection of dichloroisoproterenol in a dose of 5-10 mg/kg 30-50 min before the beginning of electrical stimulation of the aortic arch, and then again in the same dose during stimulation had no protective action on the myocardium (see table).

When summarizing the results of the series of experiments with the β-blocking agent dichloroisoproterenol, it has a marked protective effect on lesions of the myocardium produced by the α-sympathomimetic drug isoprenaline, but has no protective action against myocardial damage produced by the endogenous sympathomimetic mediator amine.

As these experiments showed, myocardial degeneration may be obtained by the action of sympathomimetic drugs—noradrenalin, affecting α-receptors, and isoprenaline, affecting β-receptors—on the myocardium. Adrenalin acts on both α- and β-receptors. In these experiments the strongest and most constant injurious effect was observed when adrenalin and isoprenaline were injected, suggesting that excessive stimulation of α-receptors causes injury to the myocardium. Injection of noradrenalin or exposure of the myocardium to the action of endogenous mediator catecholamines liberated at the endings of the cardiac sympathetic nerve fibers in response to excessive stimulation, also lead to changes in the myocardium, although of a less severe degree. Bearing in mind the accepted view that noradrenalin is the mediator of sympathetic nervous impulses in the heart, in either case evidently influences acting on α-receptors are predominant, so that the effects obtained are similar in their end results. On the other hand, the α-blocking agent sympatholytin has a marked preventive action on adrenalin- and noradrenalin- induced and neurogenic lesions of the myocardium, or as the β-blocking agent dichloroisoproterenol gives an effect in the case of lesions produced by the α-sympathomimetic drug isoprenaline but has little effect on reflex damage to the myocardium. These results suggest that myocardial necrosis may result from excitation of both the α- and the β-receptors of the myocardium.

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