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PREVENTION OF STRESS AND ANOXIC HEART DAMAGE BY THE GLUCOCORTICOID DEXAMETHASONE

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Severe emotional-painful stress (EPS) is known to cause damage to the cells of the myocardium and to disturb its contractile function [1]. The principal pathogenetic element of this stress injury is an increase, many times over, in the blood catecholamine concentration [9] and, in turn, this leads to the development of the lipid triad and to injury to the cell membranes [2]. However, the fact is worth noting that administration of exogenous catecholamines and their synthetic analogs to animals in doses comparable with those observed during stress causes more severe damage to the myocardium than stress itself, although in a stress situation a high catecholamine level is maintained for a long time [3, 11]. In other words, one of the many factors of stress has a stronger damaging action on the heart than the stress reaction as a whole.

These observations suggest that in stress besides the harmful action of an excess of catecholamines, a cardioprotective effect of other hormones also is exhibited. This action may be exerted above all by glucocorticoids which, according to some data, are stabilizers of biomembranes [10, 12], they reduce the degree of ischemic damage to the myocardium [5, 12], and restrict loss of enzymes accompanying such damage [5].

The object of this investigation was to study the possibility of protection of the heart against stress damage by preliminary administration of the glucocorticoid dexamethasone (DM).

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 220-250 g. The animals were divided into four groups: 1) control rats, 2) rats receiving DM in a dose of 5 mg/kg intraperitoneally 7 h before sacrifice, 3) rats exposed to EPS by the method in [6] for 6 h, and 4) rats receiving DM before stress in the same dose as the animals of group 2.

The heart was removed under urethane anesthesia 1 h after the end of EPS and was perfused with Krebs–Henseleit solution, oxygenated with a gas mixture containing 95% O_2 and 5% CO_2, at 37°C. The contractile function of the left ventricular myocardium was investigated under isovolemic conditions by the method in [7]. In the course of the experiments a definite heart rate was imposed by means of an ESL-1 apparatus. The coronary blood flow was determined at a frequency of 120 beats/min. After perfusion of the heart for 90 min under conditions of normal oxygenation — with minimal release of creatine phosphokinase (CPK) into the perfusion fluid, anoxia was created. The perfusion solution was then aerated with a mixture containing 95% N_2 and 5% CO_2. This anoxic procedure lasted 10 min, and was followed by reoxygenation also for 10 min.

CPK activity was determined in the perfusate which had passed through the coronary system by the method in [4] at the 90th minute of perfusion during normal oxygenation, at the 10th minute of anoxia, and at the 2nd minute of reoxygenation.

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TABLE 1. Effect of EPS and DM on Parameters of Contractile Function of Isolated Rat Heart

Group of animals	Developed pressure, mm Hg	Maximal rate of fall of pressure	Maximal rate of development of pressure	Coronary flow, ml/(g·min)
		mm Hg/sec		
1) control (n=16)	77,8±3,4	1500±96	910±70	9,7±0,3
2) DM (n=9)	82,4±4,1	1556±133	1005±91	10,1±0,4
3) EPS (n=14)	56,7±3,1	1055±72	731±65	6,8±0,3
4) EPS + DM (n=9)	69,5±4,0	1356±81	850±75	8,9±0,4
P_{1-2}	>0,1	>0,1	>0,1	>0,1
P_{1-3}	<0,01	<0,001	<0,05	<0,05
P_{1-4}	>0,1	>0,1	>0,1	<0,1
P_{3-4}	<0,05	<0,05	>0,1	<0,1

Legend. Here and in Table 2, n denotes number of animals in a group.

EXPERIMENTAL RESULTS

The data in Table 1 indicate the principal parameters of contractile function of the isolated hearts. Injection of DM had no effect on myocardial contractility. EPS led to a fall of the developed pressure by 28%, and of the maximal rates of development and of fall of pressure by 30 and 20% respectively. The coronary flow in the hearts of animals exposed to EPS was reduced by 30%.

Preliminary injection of DM considerably abolished the damaging effect of stress on the contractile function of the myocardium. No parameters of the contractile function of the hearts of animals receiving DM before EPS differed significantly from the control.

At the next stage of the experiment the effect of EPS and DM was studied on resistence of the myocardium to anoxia and reoxygenation. Table 2 gives data on CPK release from the myocardial cells during anoxia and reoxygenation. This release of the enzyme is a generally accepted criterion of injury to cardiomyocyte cell membranes [2]. As will be clear from Table 2, during perfusion under conditions of adequate oxygenation the release of CPK from the myocardium was small and was about the same for all groups. Anoxia for 10 min led to a twofold increase in release of the enzyme into the perfusate from the control animals, and at the second minute of reoxygenation the CPK activity in the perfusate was 5 times higher than during aerobic perfusion. EPS potentiates anoxic and, to an even greater degree, reoxygenation damage to the myocardium: At the 10th minute of anoxia and at the 2nd minute of reoxygenation the release of CPK was increased by 2.5 and 7 times respectively.

Injection of DM into intact animals did not affect CPK release during anoxia but substantially reduced it during reoxygenation. Preliminary injection of DM before stress completely prevented the potentiating effect of stress on anoxic and reoxygenation damage. During reoxygenation the level of CPK activity in the perfusate from animals receiving DM before stress was actually lower than in the control.

DM thus considerably reduces the degree of reoxygenation damage to the myocardium, as reflected in CPK release from the cardiomyocytes and completely prevents the decrease in the resistance of the heart to anoxia and reoxygenation arising under the influence of EPS.

The curves in Fig. 1 reflect the time course of systolic and diastolic pressure in the left ventricle of the isolated heart during anoxia and reoxygenation. It will be clear from Fig. 1 that anoxia for 10 min led to a fall of systolic pressure in the control animals and to the development of anoxic contracture, manifested as elevation of the diastolic pressure. As a result, the developed pressure (the shaded zone) fell catastrophically. During reoxygenation the systolic pressure rose and the diastolic fell, but at the 10th minute of reoxygenation they had not yet reached their initial levels. The time course of systolic and diastolic

TABLE 2. Effect of EPS and DM on CPK Release from Myocardium (units/liter)

Group of animals	Perfusion for 90 min	Anoxia for 10 min	Reoxygenation for 2 min
1) control (n=16)	12,0±1,5	28,0±3,0	71,0±6,1
2) DM (n=9)	13,0±1,5	27,0±2,7	46,0±3,2
3) EPS (n=14)	18,0±1,0	43,1±3,4	129,0±11,4
4) EPS + DM (n=9)	13,0±1,3	29,0±2,5	56,1±4,1
P_{1-2}	>0,1	>0,1	<0,001
P_{1-3}	<0,05	<0,001	<0,001
P_{1-4}	>0,1	>0,1	<0,05
P_{3-4}	<0,05	<0,001	<0,001

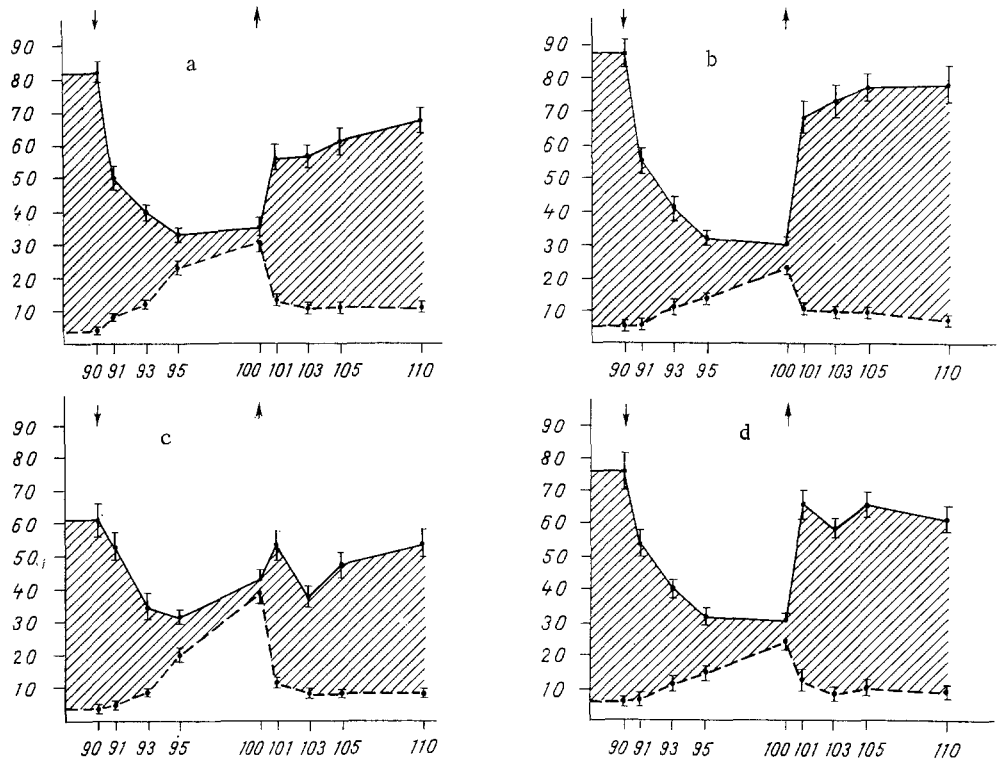

Fig. 1. Effect of DM and EPS on systolic and diastolic pressure in isolated hearts of rats during anoxia and reoxygenation. a) Control, b) DM, c) EPS, d) EPS + DM. Abscissa, time after beginning of perfusion (in min); ordinate, pressure (in mm Hg). Continuous line — systolic pressure, broken line — diastolic pressure. Arrow pointing downward — beginning of anoxia, arrow pointing upward — beginning of reoxygenation.

pressure in the hearts of animals subjected to EPS were the same during anoxia and reoxygenation as in the control, but at the 10th minute of anoxia contracture was more marked.

DM in the control animals considerably reduced anoxic contracture and led to more complete recovery of the contractile function during reoxygenation. Injection of DM before exposure to stress not only prevented the reduction in myocardial contractility during aerobic perfusion, but also reduced the degree of anoxic contracture compared with that both in animals exposed to stress and in the control animals.

On the whole the results are evidence that, first, DM prevents stress disturbances of myocardial contractility under aerobic conditions and the potentiating effect of stress on anoxic and reoxygenation damage to heart muscle; second, DM reduces hypoxic contracture and facilitates full restoration of myocardial contractility during reoxygenation, and also reduces the degree of reoxygenation damage to the myocardium, assessed according to the criterion of CPK loss.

When the protective effect of the synthetic glucocorticoid DM is assessed it must be remembered that the cardiomyocyte membranes are damaged during stress as a result of activation of lipid peroxidation [1, 3] and labilization of lysosomes [2]. Glucocorticoids stabilize lysosomal membranes [12] and, according to the latest data, they have an antioxidant action [13]. It can be tentatively suggested that this is the explanation of their cardioprotective effect against stress injury to the heart.

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