EFFECT OF PRELIMINARY BLOCKING OF α- AND β-ADRENORECEPTORS ON DISTURBANCES OF MYOCARDIAL EXTENSIBILITY AND CONTRACTILITY IN STRESS

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It was shown previously that depression of cardiac contractility in emotional-painful stress (EPS) is based on reduced myocardial extensibility and reduced efficiency of the Frank—Starling mechanism, associated with a disturbance of relaxation [2, 5]. Considering the probable adrenergic nature of stress injuries [3, 4], it can be postulated that disturbances of myocardial contractility in EPS are due to the harmful action of high blood levels of catecholamines arising during stress [8].

In this investigation the effect of preliminary administration of the α-adrenoblocker phentolamine and the β-adrenoblocker inderal on the parameters of extensibility and the Frank—Starling mechanism of the atria was studied during EPS.

EXPERIMENTAL METHOD

Male Wistar rats weighing 180-200 g were used. EPS was produced in the form of an anxiety neurosis [6] on one occasion only in the course of 6 h. The rats were decapitated 2 h after the end of EPS and the right atrium was removed and placed in a bath containing Krebs—Henseleit solution (95% O_2, 5% CO_2, pH 7.4, 34°C), and attached to the F-50 myograph of the DMP-4B Physiograph (Narco-Biosystems, USA), so that contractions could be recorded under isometric conditions. After spontaneous contractions for 40-50 min the atrium was gradually stretched by means of a load to length L_{max} at which it developed maximal tension in systole during isometric contraction (T_{max}). The change in length of the atrium was recorded while the load stretching the atrium was increased by every 100 mg. The load corresponding to L_{max} was described as the maximal resting tension (T_r). Extensibility of the atria was judged from the increase in length (ΔL) during stretching and the value of L_{max}. Contractility was evaluated from the increase in tension developed by the atrium in systole in the course of stretching (ΔT) and by the value of T_{max}. The contracture effect of hypoxia (with replacement of the oxygenated solution in the bath by unoxygenated solution for 20 min) and of an excess of Ca^{++} (by increasing the Ca^{++} concentration in the solution from 2.5 to 7.5 mM in 5 min) also was determined. This effect, characterizing relaxation, was studied on the plateau of the Frank—Starling curve and was estimated as the index of contracture (IC), calculated as the ratio of the increase in resting tension in response to hypoxia or Ca^{++} (ΔT_r) to the value of T_{max} before the beginning of action of these factors (T_{orig});

$$IC = \frac{\Delta T_r \cdot 100\%}{T_{orig}}$$

Inderal or phentolamine was injected intraperitoneally, 30 min before EPS, in single doses of 1 and 5 mg/kg respectively. The results were subjected to statistical analysis by Student's test.

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TABLE 1. Effect of Preliminary Injection of Inderal and Phentolamine on Length and Contractility of Atria in Rats Exposed to EPS

Experimental conditions	Length of atrium, mm		P_{max}, mg	Index of contracture, %	
	initial	L_{max}		hypoxia (20th min of exposure)	7.5 mM Ca^{++} (5th minute of exposure)
1. Control (n = 10)	10,3±0,3	18,0±0,4	387±17	140±15	72±7
2. EPS (n=10)	10,2±0,3	15,9±0,3	180±23	275±30	130±20
P_{1-2}	>0,5	<0,02	<0,01	<0,01	<0,001
3. Control + inderal (n = 8)	10,2±0,4	17,5±0,15	403±10	119±13	73±14
P_{1-3}	>0,5	>0,5	>0,1	>0,1	>0,5
4. EPS + inderal (n = 8)	10,3±0,3	17,1±0,5	340±18	172±35	76±10
P_{1-4}	>0,5	>0,1	>0,1	>0,5	>0,5
P_{2-4}	>0,5	<0,05	<0,01	<0,01	<0,01
5. Control + phentolamine (n = 9)	10,25±0,2	17,62±0,3	363±17	126±15	59±19
P_{1-5}	>0,5	>0,5	>0,5	>0,1	>0,1
6. EPS + phentolamine (n = 9)	10,2±0,25	16,6±0,2	218±25	282±50	156±15
P_{1-6}	>0,5	<0,05	<0,01	<0,001	<0,01
P_{2-6}	>0,5	>0,05	>0,1	>0,5	>0,1

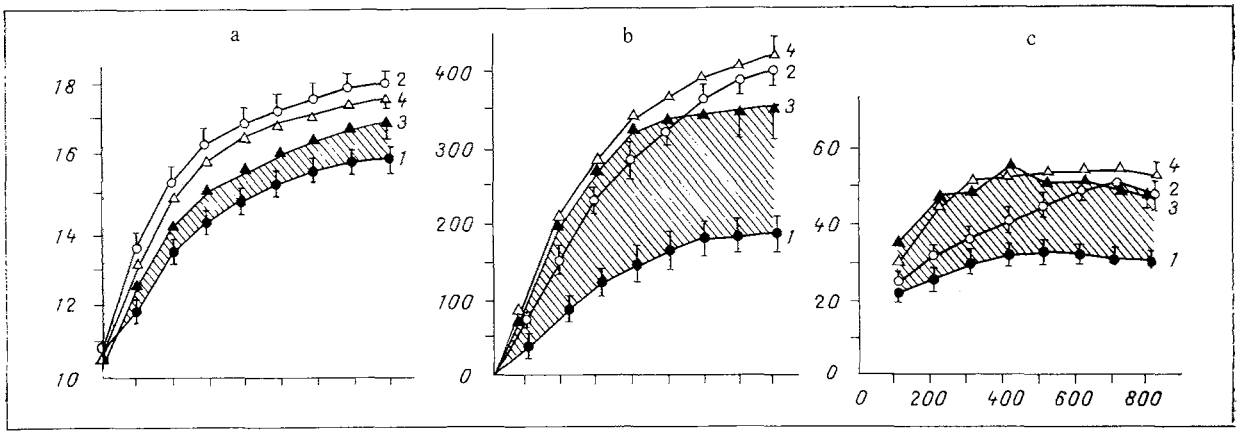

Fig. 1. Effect of preliminary injection of inderal on extensibility (a), developed tension (b), and efficiency of the Frank–Starling mechanism (c) of right atrium of rats exposed to stress. Abscissa, stretching load (resting tension, in mg); ordinate: a) length of atrium (in mm), b) developed systolic tension (in mg), c) increase in developed tension in response to increase in length of atrium by 1 mm ($\Delta T/\Delta L$, in mg/mm). 1) EPS, 2) intact control, 3) EPS + inderal, 4) control + inderal. Shaded zone denotes protective effect of inderal.

EXPERIMENTAL RESULTS

The results (Table 1, Fig. 1) show that the decrease in atrial extensibility and in the value of L_{max}, usually produced by stress, was largely prevented by preliminary administration of inderal. As a result, in rats exposed to stress after receiving inderal, L_{max} (17.1 ± 0.5 mm) did not differ significantly from the control (18.0 ± 0.4 mm). Inderal also prevented the stress-induced depression of developed tension and the fall in efficiency of the Frank–Starling mechanism. In rats exposed to EPS, for instance, the increase in developed tension in response to stretching by a standard load was 33-50% less than in the control (Fig. 1). Inderal prevented this phenomenon almost completely. In rats exposed to EPS the increases in developed tension in response to every millimeter increase of length of the atrium during stretching ($\Delta T/\Delta L$) were less than in the control. This decrease was not observed in rats exposed to stress after receiving inderal, and their $\Delta T/\Delta L$ curve almost coincided with that of the control animals receiving this β-blocker. Ultimately the value of T_{max} in rats exposed to EPS after inderal did not differ from the control (Table 1). EPS potentiated the contracture effect of hypoxia and excess of Ca^{++}. In animals exposed to EPS, for instance, IC of the atrium under the influence of hypoxia (275 ± 30%) and of Ca^{++}

excess (130 ± 20%) was approximately doubled compared with the control (140 ± 15 and 72 ± 7% respectively). Preliminary injection of inderal almost completely prevented this poststress relaxation defect of the cardiomyocytes. In rats exposed to EPS after receiving inderal the atrial IC during hypoxia (172 ± 40%) and Ca^{++} excess (76 ± 10%) did not differ from the control.

The use of phentolamine in similar experiments had no such protective effect. As Table 1 shows, the parameters of extensibility and contractility of the atria and also the effects of hypoxia and Ca^{++} in rats exposed to EPS after receiving phentolamine were indistinguishable from those in rats exposed to EPS without injection of the blockers.

On the whole these results confirm the view that disturbances of cardiac structure and function during stress are catecholamine dependent and they are evidence that the harmful action of catecholamines on the myocardium is realized through the β-adrenoreceptors of the cardiomyocytes. This is in agreement with views expressed by a majority of workers, who consider that the influence of the adrenergic system on cardiac function and metabolism is effected through β-adrenoreceptors and the adenylate cyclase system, whereas α-adrenoreceptors in the myocardium are located mainly presynaptically and have no direct functional role [1, 7, 9, 10].

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