ADAPTATION TO STRESS INCREASES THE RESISTANCE OF THE HEART TO ADRENOTOXIC DAMAGE

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Recent investigations have shown that adaptation to repeated damaging stress involves activation of the so-called stress-limiting systems [9], viz.: the GABA-ergic [8], opioidergic [2], antioxidative [6], and other systems, leading to increased resistance of the body to many different harmful environmental factors [6, 9]. With respect to the heart it has been shown that such adaptation can considerably reduced disturbances of contractility and electrical stability and arrhythmias of the heart associated with stress-induced damage [1], acute ischemia [2, 6], myocardial infarction [4], and postinfarction cardiosclerosis [3].

More recently it was shown that the protective and, in particular, the antiarrhythmic effect of adaptation is clearly manifested during ischemic and reperfusion arrhythmias, reproduced in isolated hearts, and consequently, it must be largely formed at the level of the heart itself [7]. The question of whether similar protection is realized during the cardiotoxic action of catecholamines, and if so, due to what local systems, have not been studied. One such local mechanism responsible for adaptive antiarrhythmic protection may be a decrease in the number of β-receptors in the heart, which Torda et al. [11] found during repeated immobilization stress.

The aim of this investigation was to assess the effect of preliminary adaptation to short-term immobilization stress on resistance of the heart to adrenergic damage and to compare the effects obtained with the cardioprotective action of the β-blocker propranolol (Obsidan).

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 250-300 g. In the first stage the animals were adapted to stress by short-term fixation in the supine position for 15 days: 15 min on day 1, 30 min on day 2, 45 min on day 3, and 60 min on each subsequent day. At the end of adaptation, the control and adapted animals were heparinized (200 U/100 g, intraperitoneally), the animals were anesthetized with pentobarbital (50 mg/100 g intraperitoneally), and the heart was quickly removed and placed in a Langendorff's perfusion system. Standard Krebs–Henseleit solution (11 mM glucose) was used for perfusion. The solution was aerated with a gas mixture of 95% O_2 + 5% CO_2 at 37°C; the pH range was 7.3-7.4. The perfusion pressure was 9.5 kPa. Mechanical activity of the isolated heart was recorded by means of a TD-112S isotonic transducer, attached to the apex of the heart. The ECG, amplitude of contraction, and its first derivative were recorded by means of specialized modules of the RM6000 polygraph and NC-9 oscilloscope (Nihon Kohden, Japan). Electrodes for recording the ECG were applied one to the aorta, at the base of the heart, the other to the left ventricle. Models of adrenergic arrhythmias were produced by injecting adrenalin in a concentration of $5 \cdot 10^{-5}$ M into the perfusion solution. Equal groups of adapted and unadapted animals were formed. The results were subjected to statistical analysis by the usual methods and the significance of differences was determined by Student's test.

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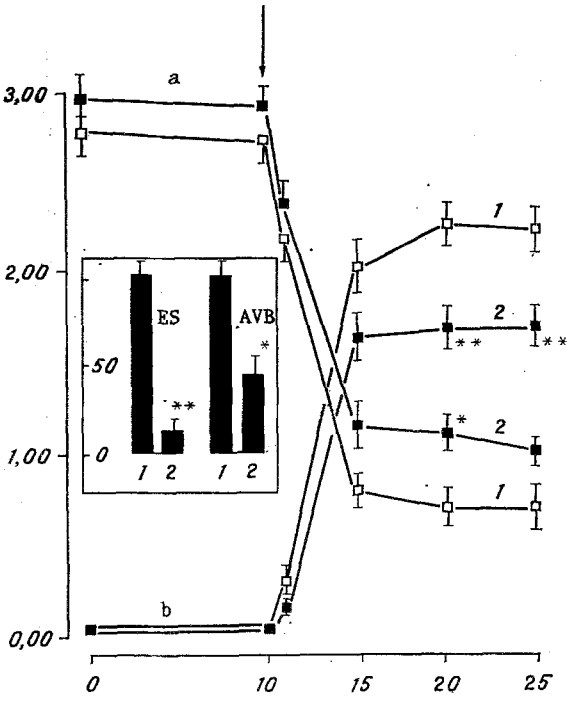

Fig. 1. Effect of adaptation of amplitude of contraction, contracture, and arrhythmia of the isolated heart exposed to the action of cardiotoxic doses of adrenalin ($5 \cdot 10^{-5}$ M). Abscissa, time (in min) after beginning of experiments; arrow indicates beginning of action of adrenalin. Ordinate, amplitude of contraction (a) and contracture (b, in mm); 1) control (n = 10), 2) adaptation (n = 10). Inset: reduction of mean number of extrasystoles (ES) and mean duration of atrioventricular blockade (AVB) in isolated heart of preadapted animals. Corresponding values in control taken as 100%. All parameters shown in the form of M ± m. Significance of differences: *p < 0.05, **p < 0.01.

EXPERIMENTAL RESULTS

The data shown in Fig. 1 indicate that perfusion of the isolated heart with toxic doses of adrenalin against the background of sinus tachycardia leads to depression of contractile function. The amplitude of contraction and the rate of contraction and relaxation were reduced by 75% after 15 min of action of adrenalin, whereas contracture amounted to 80% of the initial amplitude of contraction. Marked disturbances of rhythm also developed, in the form of extrasystoles (233 in a group) and atrioventricular blockade (duration 385 sec in a group).

Preliminary adaptation increased the resistance of the isolated heart to adrenalin-induced arrhythmias. For instance, the number of extrasystoles fell by 6.5 times and the duration of atrioventricular blockade in the group of adapted animals was only half of that in the control (Fig. 1).

Thus during adrenergic heart damage, just as during ischemia and reperfusion, a marked antiarrhythmic effect of adaptation was observed. It is very important to note that this effect was accompanied by reduction of adrenotoxic contracture by 25%. Moreover, the amplitude of contractions of the isolated heart of the adapted animals after 10-15 min of action of adrenalin was 57% greater than in the control (Fig. 1).

When an attempt is made to explain this direct cardioprotective antiarrhythmic action of adaptation it must be recalled that cardiotoxic damage associated with the action of large doses of adrenalin can be realized by at least two mechanisms. First, through the β-receptor adenylate cyclase system, i.e., due to the action of cAMP and an increase in the inflow of Ca^{++}; second, adrenalin may modify the membrane bilayer due to activation of lipid perioxidation without involvement of β-receptors [1]. The mechanism of activation in this case is oxidation of the excess of adrenalin to adrenochrome; the semiquinone of adrenalin thus formed "sheds" an electron to oxygen and in that way gives rise to a superoxide

radical ($O_2^{\cdot}$), activating lipid peroxidation. Our experiments showed that the β-blocker propranolol, in concentrations effectively blocking β-receptors (10^{-6} M), but too small to exert a nonspecific action on the membrane [10], abolish virtually completely both the arrhythmias and the depression of contractility under the influence of toxic doses of adrenalin. The important conclusion can thus be drawn that the basic role in the pathogenetic chain of adrenotoxic damage is played by interaction between catecholamines and receptors, and not by their direct effect on the membrane. Otherwise the β-blocker would be ineffective.

When the results are analyzed, it must be recalled that the antiarrhythmic effect of adaptation was comparable with that of well-known anti-arrhythmic and β-blocker propranolol; however propranolol, like preadaptation, limited depression of the contractile function of the heart.

The facts described above emphasize on the whole that the protective antiarrhythmic effect of the β-adrenoblocker was similar in many respects to the cardioprotective effect of adaptation to stress.

The view that a decrease in the number of β-receptors of the heart during adaptation to stress can play an important role in the formation of adaptive antiarrhythmic protection, as was demonstrated by Torda and co-workers [11], will therefore probably be substantiated.

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