PATHOLOGICAL PHYSIOLOGY AND GENERAL PATHOLOGY

EFFECT OF ADAPTATION TO STRESS AND PERIODIC HYPOXIA ON CARDIOMYOCYTE RESTING AND ACTING POTENTIALS IN THE ISOLATED HEART DURING ISCHEMIA AND REPERFUSION

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Adaptation to periodic hypoxia [4] and to a completely different factor, namely repeated exposure to stress [5], have a marked cardioprotective effect. It has been shown that adaptation to repeated stress, and the phenomenon of adaptive stabilization of structures [7, 12] developing under these circumstances, induces a much more marked protective effect against total ischemia and the subsequent reperfusion paradox, as reflected in parameters of cardiac contractility, than adaptation to hypoxia [8].

The aim of this investigation was to compare the cardioprotective effect of adaptation to hypoxia and to repeated stress, using an important criterion, namely the resting and action potentials of cardiomyocytes of the isolated heart in the course of the reperfusion paradox.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 250-300 g. Adaptation to short-term immobilization stress was effected through fixation of the rats in the supine position for 1 h on alternate days (eight immobilizations altogether) [3]. Adaptation to periodic hypoxia was carried out by daily 'ascents' in a pressure chamber, with a gradually increasing altitude up to 4000 m. Each exposure to hypoxia lasted 5 h and the course of adaptation consisted of 40 sessions of hypoxia. Electrical parameters were studied on isolated hearts perfused by Langendorff's method, as described previously [1, 6]. Transmembrane potentials of cardiomyocytes on the subepicardial surface of the left ventricle were recorded by "floating" microelectrodes [11, 14], filled with 3 M KCl solution, and a type MEZ-8201 amplifier ("Nihon Kohden," Japan). A signal from the output of the amplifier was led to a VC-9 oscilloscope with RLG-6201 camera and to an RAT-1100 memory unit ("Nihon Kohden," Japan) for recording and subsequent analysis. The values of the resting potential (RP), the amplitude of the action potential (AP), and the duration of AP at the 50% repolarization level were measured. Parameters of EP were recorded at the height of the period of total ischemia, when spontaneous electrical activity of the heart had disappeared, by the use of short (20-25 sec) periods of electrical stimulation of the preparations by square pulses with a frequency of 0.5 Hz and a duration of 5 msec (SEN-3201 stimulator, "Nihon Kohden"). The period of stabilization of the hearts under aerobic conditions was 25 min, after which total normothermic ischemia was created by stopping the perfusion for 15 min, and this was followed by reperfusion and a study of cardiomyocyte function during 15 min of reperfusion. The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

The results of the study of cardiomyocyte electrical activity of the isolated hearts under aerobic conditions, and during ischemia and reperfusion, in control and adapted animals are given in Fig. 1 and can be summarized as follows.

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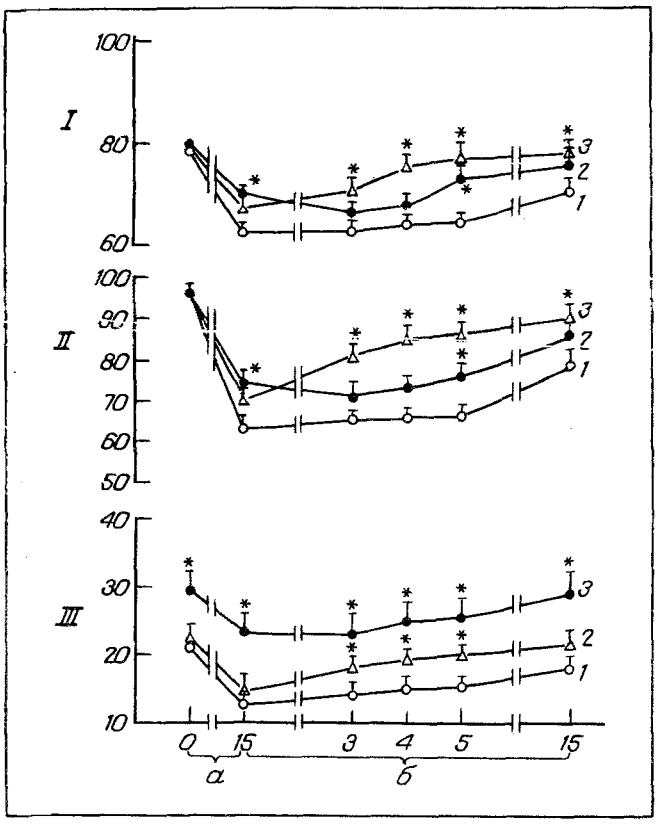

Fig. 1. Effect of adaptation to periodic hypoxia and to repeated stress on cardiomyocyte electrical activity of the isolated heart during total ischemia (a) and reperfusion (b). Abscissa, time (in min); ordinate: I) magnitude of resting potential (in mV); II) amplitude of action potential (in mV); III) duration of action potential at 50% repolarization level (in msec). 1) Control, 2) adaptation to hypoxia, 3) adaptation to stress; asterisk indicates values differing significantly from control.

First, under aerobic conditions the magnitude of RP and AP remained the same in all three series, since the forms of adaptation which we used did not affect these parameters. Meanwhile, the duration of AP during adaptation to hypoxia increased by 40%. This change was evidently caused by some delay of the repolarization process, which is usually explained by slowing of the outflow of K^+ from the intracellular space through the potassium current channels (I_k) of the sarcolemma [2, 10]. Special investigations with separate determination of the mass of the ventricles showed that this phenomenon in the present experiments did not depend on hypertrophy of the cardiomyocytes, because the mass of the left ventricle, the electrical activity of whose cardiomyocytes was recorded, remained normal when the technique of adaptation to hypoxia was used. Consequently, an increase in the duration of AP during adaptation to hypoxia was most probably due to changes in K^+ transport through the sarcolemma, but this requires further study.

Second, at the 15th minute of ischemia marked depression of the amplitudes of RP and AP and also of the duration of AP was observed in all three series. However, during adaptation to hypoxia, this well known combination of arrhythmogenic changes [9, 13] was significantly less marked than in the control: during adaptation to stress this cardioprotective effect was manifested only as a tendency. This result can be understood because it is natural that adaptation to hypoxic hypoxia will protect against ischemic hypoxia by a greater degree than adaptation to stress.

Third, in the early stages of reperfusion (3rd-4th minute) the effect of the types of adaptation used in relation to the amplitude of RP and AP differed: these parameters of cardiomyocyte electrical activity in animals adapted to stress were significantly higher than the control values, whereas in the series of adaptation to hypoxia, the degree of difference from the control was smaller and below the level of significance. During adaptation to hypoxia values of RP and AP were significantly higher than in the control only by the 5th minute of reperfusion. Thus during reperfusion, adaptation to stress

gives more effective protection against arrhythmogenic changes such as depression of RP and AP. This corresponds to a fact established previously: preliminary adaptation to stress has a powerful antiarrhythmic action during reperfusion after total ischemia, whereas adaptation to hypoxia has no such effect [8].

Fourth, both types of adaptation accelerate recovery of the duration of AP during reperfusion, but the quantitative comparison of these two effects is difficult, for the duration of AP in animals adapted to hypoxia is considerably increased under aerobic conditions already, i.e., before creation of the reperfusion paradox.

Thus during ischemia preliminary adaptation to hypoxia limits the arrhythmogenic changes in cardiomyocyte electrical activity more effectively than adaptation to stress, whereas during reperfusion the opposite situation is observed.

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