ABOLITION OF DISTURBANCES OF ELECTRICAL STABILITY OF THE HEART IN POSTINFARCTION CARDIOSCLEROSIS BY ADAPTATION TO SHORT-TERM STRESS AND ANTIOXIDANT (IONOL) ADMINISTRATION

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Adaptation to short-term stress activates stress limiting [2], including antioxidant, systems of the body [3], and thus limits the stress reaction [4, 9] and various kinds of stress-induced injuries [7]. Adaptation prevents, in particular, lowering of the ventricular fibrillation threshold in stress, fibrillation itself, and various arrhythmias associated with acute ischemia and infarction [5, 6]. Antioxidants, which reproduce to some degree the effect of adaptation to short-term stress [5, 8], have a similar prophylactic effect. Until recently it was still undecided whether adaptation to short-term stress and antioxidant administration can exert an antiarrhythmic effect in established postinfarction cardiosclerosis (PIC), when the factor disturbing the electrical stability of the heart is a scar, and when neither ischemia nor stress is present.

The aim of this investigation was to study the effect of adaptation to short-term stress and of administration of the synthetic antioxidant ionol [2,6-di(tert-butyl-4-methylphenol)] on the ventricular fibrillation threshold and ventricular ectopic activity in animals with PIC.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 300-400 g. There were four series of experiments: I) control; II) animals were used in the experiment 1.5 months after creation of myocardial infarction, i.e., animals with PIC; III) animals receiving ionol; IV) animals with PIC, receiving ionol for 4 days before the experiment; V) animals adapted to short-term stress; VI) animals adapted to short-term stress 30 days after infarction. Myocardial infarction was produced by ligation of the descending branch of the left coronary artery [15]. Adaptation to short-term stress was created by fixing the animals in the supine position for 15 days: on the 1st day for 15 min, on the 2nd day for 30 min, the 3rd day for 45 min, and the remaining 12 days for 1 h each day. Ionol in sunflower oil was administered per os on 4 days before the experiments in a daily dose of 60 mg/kg body weight. In acute experiments on animals anesthetized with pentobarbital (50 mg/kg) the response of the heart to stimulation of the peripheral end of the divided vagus nerve was evaluated (ÉSL-2 stimulator, duration 2 msec, delay 5 msec, frequency 20 Hz). After determination of the threshold value of the stimulus, which was 0.22-0.28 V, the response to stimulation with a strength of 1, 2, 3, and 4 thresholds was evaluated consecutively with intervals of 5 min. The ECG and blood pressure (BP) in the coronary artery were recorded on the Mingograf-34 apparatus (Siemens-Elema, Sweden). The electrical threshold of ventricular fibrillation (VFT) was then determined, for which purpose thoracotomy was performed, and the heart was stimulated by single premature square pulses, 10 msec in duration, from an SEN-3201 stimulator (Nihon Kohden, Japan), triggered by the ECG R wave, and applied through a coaxial electrode, inserted into the apex of the right ventricle. The VFT was estimated as the minimal strength of current, in milliamperes, in response to which fibrillation developed. In these experiments the strength of current inducing fibrillation was recorded simultaneously with the ECG and BP.

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TABLE 1. Effect of Adaptation to Short-Term Stress and the Antioxidant Ionol on Myocardial Ectopic Activity during Vagus-Induced Bradycardia Associated with PIC

Experimental conditions	Total number of animals with extrasystoles	Number of extrasystoles in 30 sec during vagus nerve stimulation of undermentioned strengths (thresholds)				Total number of extrasystoles for whole group
		1	2	3	4	
PIC	9	40	65	194	262	561
PIC + adaptation	5	0	1	85	80	166
PIC + ionol	6	8	24	42	64	138

Note. Extrasystoles during vagus nerve stimulation did not arise in these experiments in control animals or in intact animals receiving ionol or adapted to short-term stress. Each series of experiments was done on 11 rats.

EXPERIMENTAL RESULTS

The absolute weight of the heart in the control animals and also in animals adapted to short-term stress and animals receiving ionol, averaged 1050 mg, whereas in rats with cardiosclerosis it was 1375 mg, and the relative weight of the heart was increased by 40%. The weight of the postinfarction connective-tissue scar varied from 151 to 165 mg and was unchanged by adaptation and ionol.

The heart rate of the animals with PIC was unchanged compared with the control (398 ± 12 and 412 ± 9 beats/min) but BP was reduced by 40-45 mm Hg to 100 mm Hg. This fall of pressure was not abolished by adaptation to short-term stress or by administration of ionol. PIC was regularly accompanied by lowering of VFT by more than 50% compared with the control (2.9 ± 0.2 and 6.4 ± 0.2 mA, respectively). This phenomenon was completely abolished both by adaptation and by administration of ionol.

A study of the negative chrootropic action of the vagus nerve revealed that ionol did not change this effect in the control animals or in animals with cardiosclerosis. However, adaptation to short-term stress reduced vagus-induced bradycardia by 33-50% in animals in both groups.

Inhibition of the sinus node pacemaker on stimulation of the vagus nerve is traditionally used to estimate the level of ectopic activity of the heart [14]. In the present experiments vagus nerve stimulation did not cause the appearance of extrasystoles in the control animals or in animals adapted to short-term stress or receiving ionol. Accordingly, data on ectopic activity, i.e., on the number of extrasystoles, are given in Table 1 only in animals of three equal groups with PIC. The total number of extrasystoles in animals with cardiosclerosis and not receiving treatment, for all four periods of vagus nerve stimulation, was 561. This fact, evidence of increased ectopic activity of the heart during PIC, is sufficiently well known [11, 13, 16]. The main conclusion from the data in Table 1 is that adaptation of animals with established PIC to short-term stress, and also administration of ionol to such animals, reduced the ectopic activity of the heart three to fourfold: The total number of extrasystoles in these series was no longer 561, but 166 and 138, respectively. The ECGs, reproduced in Fig. 1, demonstrate this same pattern. This result is particularly significant for ionol which, as was pointed out above, did not change the negative chronotropic effect of the vagus nerve, but nevertheless reduced the number of extrasystoles, i.e., the ectopic activity of the heart, by 75% in cardiosclerosis. In this case, therefore, the effect did not depend on the reduction of the degree of inhibition of the natural cardiac pacemaker, but was due to direct depression of ectopic activity of the heart. The protective effect of adaptations to short-term stress in this case, however, is complex in origin. It is undoubtedly due to the fact that this factor reduces by half the negative chronotropic effects of the vagus nerve, and it may be dependent on direct depression of ectopic activity by regulatory factors activated by adaptation.

When the antiarrhythmic effect of adaptation to short-term stress and of administration of the antioxidant ionol is evaluated, it must be recalled that disturbances of electrical stability of the heart during PIC are connected with the fact that groups of cardiomyocytes, subjected to acute ischemia, are always present in the postinfarction scar and, in particular, in its boundary zone. These cells preserve a near-normal histologic structure [16], and, at the same time, they possess significantly altered bioelectrical activity [12, 16], which may

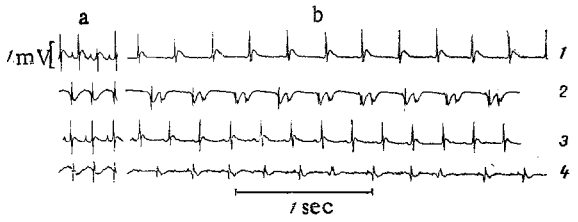

Fig. 1. Effect of antioxidant ionol on level of ectopic activity during vagus-induced bradycardia in the presence of PIC: a, b) ECG before and during vagus nerve stimulation, respectively. 1) Control; 2) PIC; 3) ionol; 4) PIC + ionol.

become the cause of ectopic and recurrent excitation, i.e., of the two chief phenomena that constitute the basis of arrhythmias in animals [13] and humans [11] in association with PIC.

Thus, the antioxidant ionol and adaptation to short-term stress somehow or other block this pathogenetic chain. The possibility cannot be ruled out that the ability of this type of adaptation [7] and of the antioxidant [9] to inhibit central adrenergic mechanisms, and also to depress the reactivity of the heart itself to adrenalin [1, 10], may play a role in the realization of this blockade. At the same time, it will be evident that mechanisms of the antiarrhythmic effect of adaptation to short-term stress and antioxidants require further investigation.

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