EFFECT OF MYOCARDIAL INFARCTION ON CHOLINERGIC REACTIVITY OF THE ATRIA AND THEIR ACETYLCHOLINE CONCENTRATION

M. G. Pshennikova, M. V. Shimkovich, and K. B. Vinnitskaya

UDC 616.127-005.8-07:616.125-008.931:577.164.184

KEY WORDS: myocardial infarction; acetylcholine; cholinergic reactivity.

An important role in the development of stress-induced and ischemic arrhythmias and fibrillation of the heart is played by the formation of a focus of excitation in the frontal region of the cerebral cortex and associated strengthening of both adrenergic and cholinergic influences on the heart [10, 13]. It has been shown, for instance, that stimulation of the vagus nerve in infarction leads to the onset of arrhythmias, which is evidently due to the manifestation of ectopic foci of excitation in the heart on account of depression of the normal pacemaker [3, 5, 11]. It has also been shown that in myocardial infarction the chronotropic effect of vagus nerve stimulation increases [3]. This suggests that a change in the cholinergic regulation of the pacemaker in infarction takes place not only outside the heart, but also at the level of the pacemaker itself.

The aim of this investigation was to study the effect of myocardial infarction on cholinergic reactivity of the right atrium, in which the pacemaker is located, and also on the acetylcholine concentration in the atria.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 250-350 g. An infarct was produced by the standard method [12] by ligation of the left coronary artery, which led to an infarct of the left ventricle. The animals were used in the experiments 24 h after ligation of the coronary artery and were killed by decapitation. Some rats were used in a physiological experiment to determine cholinergic reactivity. For this purpose, immediately after decapitation the right atrium was removed and transferred into a thermostatically controlled bath containing oxygenated (95% O_2, 5% CO_2) Krebs–Henseleit solution (pH 7.4, 34°C). The base of the atrium was fixed immovably, and the apex of the auricle was attached to the transducer of an apparatus recording isometric contractions (F-60 transducer, DMP-4B physiograph, Narco-Biosystems, USA). After 40-50 min of spontaneous contractions the atrium was gradually stretched by means of a weight to its maximal physiological length, at which it developed its maximal force of contraction. Under these conditions, i.e., on the plateau of the Starling curve, the chronotropic and inotropic responses of the atrium were determined to acetylcholine which was added to the fluid in the bath in increasing concentrations, on the cumulative principle: 10, 30, 60, and 100 ng/ml. Cholinergic reactivity of the pacemaker was judged from the chronotropic response, cholinergic reactivity of the contractile myocardium of the atrium from the inotropic response. These responses were evaluated on the basis of the change in frequency and maximal force of atrial contraction respectively. Changes in the parameters were calculated both in absolute values and as percentages of the initial data. Some animals were used to determine the acetylcholine concentration in both atria by a biological test on the longitudinal muscle of the guinea pig ileum [4] in the modification in [1].

EXPERIMENTAL RESULTS

The chronotropic effect of acetylcholine, namely a decrease in the frequency of contractions, was significantly greater in animals with infarction than in the controls (Table 1). The threshold concentration of acetylcholine to give a marked chronotropic effect (reduction

Research Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow. Problem Laboratory for Tissue Hormone Biochemistry, I. M. Sechenov First Moscow Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR G. N. Kryzhanovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 106, No. 7, pp. 5-7, July, 1988. Original article submitted October 23, 1987.

 0007-4888/88/0007-0916$12.50

TABLE 1. Chronotropic and Inotropic Responses of Isolated Right Atrium to Acetylcholine in Myocardial Infarction (M±m)

Indicator of atrial conductivity	Control (n = 12)	Myocardial infarction (n = 13)
Initial frequency of contractions	236,7±7,5	246,0±9,2
Reduction of frequency of contractions in response to acetylcholine, ng/ml		
10	4,0±2,0	11,25±2,7*
30	11,5±1,3	23,9±4,8**
60	15,5±1,6	34,0±3,0*
100	18,7±2,9	37,8±5,0*
Initial maximal force of contraction, mN	456,5±35,0	264,3±10,0*
Reduction of maximal force of contraction in response to acetylcholine, ng/ml		
10	30,8±2,3	26,7±2,2
30	50,4±1,9	46,6±2,5
60	59,9±1,3	53,9±3,6
100	62,3±2,6	59,8±2,8

Legend. Reduction of parameters due to acetylcholine given as a percentage of their initial value, taken as 100%. Frequency of contraction shown as their number per minute. *$p < 0.001$, **$p < 0.01$ compared with control.

of the frequency of contractions by not less than 10% of the initial value) in the majority of animals with infarction was approximately half (22 ± 6 ng/ml) of that in the control (49 ± 4 ng/ml; $p<0.001$). It follows from the results that infarction leads to reduction of the maximal force of atrial contraction almost by half (Table 1); this is in agreement with previous data on depression of the contractile function of nonischemic zones of the heart in myocardial infarction [2]. Meanwhile infarction did not give rise to significant changes in the inotropic response of the atrium to acetylcholine. The threshold acetylcholine concentration for this reaction in infarction (0.26 ± 0.06 ng/ml) was also found not to differ from the control (0.36 ± 0.12 ng/ml). On the whole the data are evidence that infarction for 24 h increases the cholinergic reactivity of the pacemaker but does not affect reactivity of the contractile myocardium to acetylcholine. These differences are perhaps connected with the fact that the pacemaker region has a cholinergic innervation of much greater density than the contractile myocardium [9], and for that reason changes in the control apparatus in this area may be more marked than in other parts of the atrium.

A definite role in the change in the tissue response to a mediator is known to be played by the concentration of that mediator in it. The results of determination of the acetylcholine concentration in the atria showed that infarction causes a sharp decrease of this parameter. The acetylcholine concentration in the atria averaged 162.2 ± 22.0 ng/g in the control and 34.3 ± 11.0 ng/g in infarction, i.e., it was about 4 times less. This phenomenon is evidently due to the above-mentioned activation of the cholinergic component of regulation of the heart in infarction, leading to an excessive growth of the "release" of mediator from cholinergic fiber endings, which is not compensated by increased mediator synthesis. By analogy with desensitization of muscarinic receptors in the presence of an excess of mediator, when depression of cholinergic reactivity of the tissue is due to reduction of the number of binding sites [6], it can thus be tentatively suggested that a fall in the acetylcholine concentration may lead to unmasking of reserve receptors and thus to an increase in the number of active acetylcholine receptors. However, another explanation of the increase in cholinergic reactivity seems probable. Some of the muscarinic receptors may be able to switch from a state of low affinity for acetylcholine to a state of high or of very high affinity [9]. An important role in this switch is played by Mg^{++} ions which, in conjunction with guanyl nucleotides, modulate the properties of muscarinic receptors [7]. In infarction the concentration of free Mg^{++} ions in the myocardium rises due to breakdown of the Mg-ATP complex; it can thus be postulated that a definite role in the increased cholinergic reactivity of the pacemaker in infarction is played by an increase in the affinity of the muscarinic receptors of the pacemaker for acetylcholine.

Simultaneous studies of the response of the right atrium to noradrenalin showed that the changes in cholinergic reactivity of the pacemaker described above are not accompanied by any significant changes in adrenergic reactivity during infarction lasting 24 h. Consequently, the increase in cholinergic reactivity of the pacemaker in infarction leads to relative predominance of its cholinergic over its adrenergic reactivity. The cause of this change is difficult at present to understand. However, data in the literature [8] indicating that the number of muscarinic receptors in the rat atria is 20 times greater than the number of β-adrenoreceptors suggests that the observed shift may be to some extent linked with this numerical predominance of acetylcholine receptors.

On the whole the results of this investigation are evidence that the increase in sensitivity of the pacemaker to vagus nerve stimulation during infarction for the first 1-2 days, which was demonstrated previously [3], is due to increased cholinergic reactivity of the pacemaker and its relative predominance over adrenergic reactivity. These changes depress the resistance of the pacemaker to cholinergic influences, and this may facilitate the manifestation of ectopic foci of excitation and, consequently, the development of arrhythmias.

LITERATURE CITED

1. K. B. Vinnitskaya, E. B. Tezikov, T. D. Bol'shakova, and N. K. Khitrov, Scientific Publications Lodged with the All-Union Institute of Scientific and Technical Information, No. 9, 29 (1985).
2. F. Z. Meerson and R. S. Dosmogambetova, Kardiologiya, 23, No. 3, 20 (1983).
3. F. Z. Meerson, L. M. Belkina, S. S. Dyusenov, et al., Kardiologiya, No. 8, 19 (1986).
4. H. A. Dieterich and K. Löffelholz, Naunyn-Schmiederberg's Arch. Pharmacol., 296, 143 (1977).
5. N. El-Sherif, R. Mehra, W. Gough, and R. H. Zeiler, Circulat. Res., 51, 152 (1982).
6. S. W. Halvorsen and M. M. Nathanson, J. Biol. Chem., 256, 7941 (1981).
7. Y. Kurachi, T. Nakajima, and T. Sugimoto, Pflügers Arch., 407, 572 (1986).
8. J. Linden, C. H. Hollen, and A. Patel, Circulat. Res., 56, 728 (1985).
9. K. Löffelholz and A. J. Pappano, Pharmacol. Rev., 37, 1 (1985).
10. B. Lown, R. A. Desilva, P. Reich, and B. J. Murawski, Am. J. Psychiat., 137, 1325 (1980).
11. B. Scherlag, N. El-Sherif, R. Hope, and R. Lazzara, Circulat. Res., 35, 372 (1974).
12. H. Selye, E. Bajusz, S. Grasso, and P. Mendell, Angiology, 11, 398 (1960).
13. J. E. Skinner, Stress and Heart Disease, ed. by R. E. Beamish et al., Boston (1985), pp. 44-59.