7. L. A. Orbeli, "The nervous system at low pressure," Sov. Nauka, No. 10, 66 (1940).
8. Yu. A. Yakunin, "Epilepsy," in: Neurology and Pathology of Early Childhood [in Russian], Leningrad (1981), pp. 299-315.
9. P. D. Altland and B. A. Rattner, "Age and altitude tolerance in rats: temperature, plasma, enzymes and corticosterone," J. Appl. Physiol., **50**, No. 2, 367 (1981).
10. E. A. Cavalheiro, "The susceptibility of rats to pilocarpine-induced seizures is age-dependent." Develop. Brain Res., **37**, 43 (1987).
11. D. Marcsova and P. Mares, "Ontogenetic development of wet dog shakes accompanying hippocampal epileptic after-discharges in rats," Active Nerv. Sup. (Prague), No. 4, 254 (1988).

ABOLITION OF DISTURBANCES OF ELECTRICAL STABILITY OF THE HEART AND ARRHYTHMIAS A SYNTHETIC ACETYLCHOLINE ANALOG

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KEY WORDS: myocardial infarction; postinfarction cardiosclerosis; cardiac arrhythmias; acetylcholine analog.

The cholinergic regulation of the heart limits excessive adrenergic (stressor) effects on that organ, helps to maintain a sufficiently high resting potential (RP) of the myocardial cells, and thus possesses a stress-limiting, antiarrhythmic action [4]. In many cases, however, strong negative chronotropic effects of the vagus nerve are linked with suppression of automatism of the sinus node and may lead to the realization of foci of ectopic excitation at a lower level, and the appearance of cardiac arrhythmias [1, 5]. Accordingly, the search for new antiarrhythmic factors, which would completely possess the adrenolytic and hyperpolarizing actions of acetylcholine, but which would not have the excessive negative chronotropic effect, characteristic of acetylcholine, and would thus prove to be optimal antiarrhythmics, has become particularly urgent.

The aim of this investigation was to study the effect of ethyl-3/2-ethyl-2,2-dimethylhydrazinium propionate· iodide (EDHPI) (approved invention No. 4217356/31-04) on the disturbance of electrical stability of the heart and arrhythmias associated with acute myocardial infarction and postinfarction cardiosclerosis, and also with acute ischemia and subsequent reperfusion.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 250-400 g. The first stage in the investigation envisaged assessment of the effect of EDHPI on the disturbance of electrical stability of the heart associated with acute myocardial infarction and postinfarction cardiosclerosis, and consisted of the six following series: I) control animals; II) animals receiving EDHPI; III) animals with experimental myocardial infarction; IV) animals with experimental myocardial infarction and receiving EDHPI; V) animals with postinfarction cardiosclerosis; VI) animals with postinfarction cardiosclerosis and receiving EDHPI. In the second stage the effect of EDHPI, atropine, and their combinations were studied on ischemic and reperfusion arrhythmias,

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TABLE 1. Effect of EDHPI on Threshold of Ventricular Fibrillation and Ectopic Activity of the Heart in Myocardial Infarction and in Postinfarction Cardiosclerosis ($M \pm m$)

Series of experiments	Initial HR, beats/min	ΔHR (beats/min) 4 thresholds	Total number of extrasystoles	Threshold of ventricular fibrillation, mA
I – control (n = 9)	387±10	210±23	0	6,0±0,5
II – EDHPI (n = 7)	364±13	146±13	0	6,4±0,4
III – infarct (n = 12)	402±12	268±18	202	1,9±0,2
IV – infarct + EDHPI (n = 12)	392±15	207±27	35	4,1±0,2
V – cardiosclerosis (n = 9)	383±15	209±21	401	2,1±0,2
VI – cardiosclerosis + (n = 9)	352±8	124±27	81	4,3±0,5
$p_{I\ II}$		>0,05		>0,05
$p_{I\ III}$		<0,05		<0,001
$p_{III\ IV}$		<0,05		<0,001
$p_{I\ V}$				<0,001
$p_{V\ VI}$				<0,01

TABLE 2. Effect of EDHPI, Atropine, and a Combination of Both on Disturbance of Rhythm of Isolated Heart during Ischemia and Reperfusion ($M \pm m$)

Parameter	Control	EDHPI	Ischemia			Reperfusion		
			EDHPI + atropine	atropine	control	EDHPI	EDHPI + atropine	atropine
Extrasystoles (ES)								
number of animals with ES	7	8	2	3	8	8	10	9
total number of ES per group	400	435	90	310	310	375	825	315
mean number of ES per animal	40±18,5	43,5±23,2	9,0±5,0	31±1,7	31±2,1	37,5±2,1	82,5±5,0	31,5±3,2
Ventricular tachycardia (VT):								
number of animals with VT	1	0	0	3	10	9	9	10
total duration of VT per group, sec	28	0	0	26	535	412	133	325
mean duration of VT per animal, sec	2,8±2,8	—	—	2,6±2,0	53,5±22	41,2±12	13,3±5,0	32,5±8,0
Ventricular fibrillation (VF):								
number of animals with VF	0	0	0	0	8	7	5	8
total duration of VF per group, sec	0	0	0	0	1516	978	82**	1987
mean duration of VF per animal, sec	—	—	—	—	151,6±29	97,8±22	8,2±3,2**	198,7±28
Total duration of severe arrhythmias (VT + VF):								
per group, sec	28	0	0	26	2051	1390	215	3212
per animal, sec	2,8±2,8	—	—	2,6±2,0	205±14	139±11,5*	21,5±3,2**	231±15
Number of contracting hearts after 5 min of reperfusion					3	5	10	2

Legend. Ten preparations were used in each group; concentrations: EDHPI 10^{-4} M, atropine 10^{-7} M; significant differences compared with control — $*p < 0.01$, $**p < 0.001$.

induced on the isolated heart. An experimental myocardial infarct was created by Selye's method, by ligating the descending branch of the left coronary artery. In the experiments with postinfarction cardiosclerosis, the animals were studied 1.5 months after creation of an acute myocardial infarct. The electrical threshold of fibrillation of the heart and its ectopic activity were

determined by the method in [1]. Experiments on the isolated heart, perfused by Langendorff's method, were carried out as in [3]. EDHPI was given to animals with myocardial infarction and postinfarction cardiosclerosis perorally in a single dose of 25 mg/kg 2 h before the acute experiment began. This dose is 80 times less than LD_{50}, which we determined in special experiments. Under isolated heart conditions EDHPI was injected into the perfusion fluid in a concentration of 10^{-7} M, and atropine also in a concentration of 10^{-7} M.

EXPERIMENTAL RESULTS

The data in Table 1 show that in acute myocardial infarction, just as in many other published articles [2], an increase was observed in the bradycardia arising in response to the vagus nerve stimulation, with the appearance of multiple ventricular extrasystoles and a more than threefold lowering of the threshold of fibrillation of the heart against this background. EDHPI abolished all these disturbances: compared with untreated animals which developed infarction, bradycardia took the form of reduction of the heart rate by only 207 ± 27 compared with 268 ± 18, the threshold of fibrillation was increased from 1.9 ± 0.2 to 4.1 ± 0.2 and, finally, the number of estrasystoles fell from 202 to 45. In other words, peroral administration of a single dose of EDHPI 24 h after creation of a myocardial infarct largely abolishes disturbances of electrical stability of the heart characteristic of myocardial infarction.

Data showing that postinfarction cardiosclerosis, as demonstrated previously [1], leads to the appearance of very marked extrasystoles against the background of vagal bradycardia, and to approximately the same lowering of the fibrillation threshold as myocardial infarction, also are given in Table 1. Administration of EDHPI reduced the lowering of the fibrillation threshold by half and the number of extrasystoles by 5 times.

Thus a single nontoxic dose of EDHPI against the background of myocardial infarction or postinfarction cardiosclerosis abolishes or significantly weakens disturbances of electrical stability of the heart. This positive result of experimental treatment was realized in the absence of any changes in heart rate and, accordingly, it could be achieved as a result of the primary action of EDHPI on the myocardium.

At the next stage of the investigation, the aim was to assess the mechanism of action of EDHPI at the heart level, for which purpose the effect of EDHPI, atropine, and a combination of both was studied on ischemic and reperfusion on arrhythmias, produced under isolated heart conditions. It was discovered that with a high concentration 1×10^{-4} M EDHPI possesses a marked negative chronotropic effect, reducing the heart rate by 90-100 beats/min. In combination with atropine (1×10^{-7} M) this negative chronotropic action of EDHPI was absent and, consequently, it was due to the acetylcholine-like action of the compound on the cardiac pacemaker.

The data given in Table 2 show how blocking the negative chronotropic action of the compound by atropine affected its antiarrhythmic action. The data in Table 2 also show that under isolated heart conditions EDHPI itself does not possess any reliable antiarrhythmic action on ischemia and reperfusion, relative to the majority of parameters. Atropine itself likewise does not affect ischemic and reperfusion arrhythmias. A combination of EDHPI with atropine has a marked antiarrhythmic effect against both ischemia and reperfusion. In ischemia, for instance, EDHPI combined with atropine reduced the number of hearts in which extrasystoles were observed by 3.5 times, but the number of extrasystoles, calculated per heart, was 3-5 times greater than in other series. During reperfusion this antiarrhythmic effect was even more definite. The average duration of fibrillation, calculated per animal, was 10-20 times less in the EDPHI atropine series than in the other series.

These experiments thus demonstrate unequivocally that the protective (antiarrhythmic) effect of EDHPI on the isolated heart is realized only in combination with atropine and in the absence of bradycardia, and consequently it is not connected with the acetylcholine-like action of the compound, but is a result of its primary action on the myocardium. This fact is in full agreement with data given above on the antiarrhythmic action of EDHPI under intract animal conditions, and in the presence of myocardial infarction and postinfarction cardiosclerosis. In all these cases, abolition of disturbances of electrical stability of the heart observed under the influence of EDHPI was realized when parasympathetic regulation was preserved, i.e., against the background of the action of acetylcholine, the natural agonist of muscarinic receptors, which is known to possess greater affinity for muscarinic receptors than EDHPI. Binding of EDHPI with muscarinic receptors under these conditions and its negative chronotropic effect evidently could not be realized, so that bradycardia did not develop. In experiments on the isolated heart, in the absence of the tonic cholinergic effect, bradycardia was realized but was not accompanied by any antiarrhythmic effect. An antiarrhythmic and, in particular, an antifibrillatory effect appeared only as a result of the action of EDHPI against the background of muscarinic receptor blockade by atropine.

Taken as a whole this means that the powerful antiarrhythmic effect of EDHPI can be realized in the absence of its negative chronotropic effect on muscarinic receptors, it is a primary effect of the compound on the myocardium, and it requires further study by methods of molecular pharmacology.

LITERATURE CITED

1. F. Z. Meerson, L. N. Belkina, S. S. Dyusenov, et al., Kardiologiya, No. 10, 29 (1985).
2. F. Z. Meerson, L. M. Belkina, S. S. Dyusenov, et al., Kardiologiya, No. 8, 19 (1986).
3. F. Z. Meerson, I. Yu. Malyshev, L. M. Belkina, and V. A. Saltykova, Kardiologiya, No. 1, 70 (1988).
4. J. C. Baily, R. J. Kovacs, and D. P. Rardon, in: Mechanisms and Treatment of Cardiac Arrhythmias: Relevance of Basic Studies to Clinical Management, H. J. Reiser and L. N. Horowitz (eds.), Baltimore and Munich (1985), p. 370.
5. M. A. Hofer, Psychosom. Med., **32**, 633 (1970).

ROLE OF THE PROSTACYCLINE-THROMBOXANE SYSTEM IN MECHANISMS PREVENTING ARRHYTHMIAS INDUCED BY CORONARY OCCLUSION IN ADAPTED RATS

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The possibility of prevention of arrhythmias induced by acute myocardial ischemia (AMI) by preliminary adaptation to the periodic action of short periods of immobilization, physical exercises, and high-altitude hypoxia has been demonstrated [1-3]. According to Meerson's concept, an important role in the mechanism of the effect of adaptation is played by activation of the stress-limiting systems (SLS), to which it belongs and, in particular, to the prostaglandin system [2]. The opinion is held that, of all the prostaglandins, the most important role in the pathogenesis of cardiac arrhythmias in AMI is played by thromboxane A_2 ($T \times A_2$) [5, 8, 9]. Meanwhile, it has been shown that the physiologial antagonist of TxA_2 is prostaclcyline (PC), which dilates the coronary vessels and prevents the onset of arrhythmias after coronary artery occlusion [5]. TxA_2, on the other hand, induces coronary spasm and a disturbance of the cardiac rhythm [5, 9]. These observations have led many investigators [5, 8, 9] to consider that the PC/Tx ratio plays, if not the chief, then at least a leading role in the development of arrhythmias associated with AMI.

The aim of this investigation was to analyze the effect of different types of adaptation on the value of the PC/Tx ratio and the frequency of arrhythmias in experimental coronary arterial occlusion.

EXPERIMENTAL METHOD

Experiments were carried out on 60 male Wistar rats weighing initially 200-250 g. The animals were divided arbitrarily into four groups: 1) intact, 2) adaptation to cold, 3) to physical exercise (swimming), 4) to a combination of exposure to cold and

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