ELECTRICAL INSTABILITY OF THE HEART IN EXPERIMENTAL MYOCARDIAL INFARCTION AND POSTINFARCTION CARDIOSCLEROSIS ABOLISHED BY A BENZODIAZEPINE RECEPTOR AGONIST

F. Z. Meerson, N. A. Abdikaliev, and M. G. Pshennikova

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Disturbance of the inhibitory effect of the GABA-ergic system of the brain on autonomic centers regulating cardiac activity can lead to the onset of arrhythmias [2]. Activation of the GABA-ergic system by means of sodium valproate, on the other hand, limits arrhythmias in acute ischemia and reperfusion of the heart and abolishes disturbances of electrical stability of the heart associated with acute infarct and postinfarction cardiosclerosis [4]. These data are evidence that a search for the most effective drugs to activate the GABA-ergic system, for use in the prevention and treatment of arrhythmias, is well worthwhile. One possible way of conducting such a search is to use agonists of benzodiazepine receptors, which potentiate effects of the GABA-ergic system at the GABA–receptor complex level [8, 9].

The aim of this investigation was to study the effect of the tranquilizer, phenazepam, an agonist of benzodiazepine receptors, on disturbances of electrical stability of the heart in acute myocardial infarction and postinfarction cardiosclerosis.

EXPERIMENTAL METHOD

Male Wistar rats weighing 250-350 g were used. The first stage of the investigation was aimed at assessing the effect of phenazepam on electrical instability of the heart in acute myocardial infarction and consisted of four series of experiments: I) control; II) animals receiving phenazepam; III) animals with experimental infarction; IV) animals with experimental myocardial infarction receiving phenazepam. The second stage of the investigation had the aim of assessing the effect of phenazepam on electrical instability of the heart in post-infarction cardiosclerosis and also consisted of four series of experiments: I) control; II) animals receiving phenazepam; III) animals with postinfarction cardiosclerosis; and IV) animals with postinfarction cardiosclerosis, receiving phenazepam. Experimental myocardial infarction was induced by Selye's method by ligating the descending branch of the left coronary artery. The animals were used in the experiments 1 day after ligation of the coronary artery. In the experiments with postinfarction cardiosclerosis the animals were used 1.5 months after creation of the acute myocardial infarct, by the same method. The threshold of fibrillation during electrical stimulation of the apex of the heart and ectopic activity of the heart against the background of vagal bradycardia were assessed by the usual method. Phenazepam was injected twice into animals with acute myocardial infarction: the first injection before coronary occulusion, the second 1 h before the beginning of the experiment to determine parameters of electrical stability of the heart, intraperitoneally in a dose of 1 mg/kg. In postinfarction cardiosclerosis phenazepam was injected 3 times 2 days before the experiment to determine the parameters of electrical stability; the last injection was given 1 h before the experiment, in a dose of 1 mg/kg intraperitoneally.

EXPERIMENTAL RESULTS

The results in Table 1 show that acute myocardial infarction in these experiments was accompanied by disturbances of electrical stability of the heart, as was the case in previous investigations [3]: an increased degree of inhibition of sinus pacemaker activity during

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TABLE 1. Effect of Phenazepam on Threshold of Ventricular Fibrillation and Ectopic Activity in Acute Myocardial Infarction

Series of experiments	Initial heat rate, beats/min	Threshold voltage of current, V	ΔHR/min				Total number of extrasystoles	Mean number of extrasystoles per animal	Threshold of ventricular fibrillation, mA
			one threshold	two thresholds	three thresholds	four thresholds			
I. Control	393±12	0,4±0,05	75±21	143±21	190±18	220±22	2	0,2±0,1	6,3±0,5
II. Phenazepam	402±9	0,22±0,01	42±3	146±21	203±20	226±20	0	0	6,9±0,2
III. Myocardial infarction	403±16	0,17±0,02	88±18	221±27	274±20	286±26	325	32,5±12,0	1,5±0,2
IV. Infarction + phenazepam	398±18	0,17±0,02	52±13	165±22	242±20	271±17	59	5,9±2,7	4,0±0,5
p_{III-IV}								<0,05	<0,001

Legend. In each series of experiments n = 10.

TABLE 2. Effect of Phenazepam on Threshold of Ventricular Fibrillation and Ectopic Activity in Postinfarction Cardiosclerosis (M ± m)

Series of experiments	Initial heart rate, beats/min	Threshold voltage of current, V	ΔHR/min				Total number of extrasystoles	Mean number of extrasystoles per animal	Threshold of ventricular fibrillation, mA
			one threshold	two thresholds	three thresholds	four thresholds			
I. Control	367±11	0,22±0,03	75±10,0	167±17	205±17	220±13	5	0,5±0,3	5,5±0,3
II. Phenazepam	347±10	0,28±0,04	37±3,3	120±13	189±18	221±9	0	0	6,4±0,1
III. Postinfarction cardiosclerosis	352±10	0,25±0,02	69±7,8	168±23	202±16	207±17	249	27,7±14,0	2,0±0,2
IV. Cardiosclerosis + phenazepam	338±10	0,22±0,02	47±7,0	138±23	175±21	170±17	15	1,7±0,9	4,0±0,3
p_{III-IV}								<0,01	<0,001

Legend. In each series of experiments n = 9.

vagus nerve stimulation, the appearance of multiple extrasystoles against the background of vagal bradycardia, which were virtually absent in the control and, finally, lowering of the electrical threshold of fibrillation of the heart by 75% (from 6.3 ± 0.5 to 1.5 ± 0.2 mA). Phenazepam, when injected into the control animals, had no effect on the parameters of electrical stability of the heart and, at the same time, significantly limited disturbances of electrical stability of the heart associated with myocardial infarction. In fact, the number of extrasystoles, calculated per animal, was 5.9 ± 2.7 in rats receiving phenazepam compared with 32.5 ± 12.0 in unprotected animals with myocardial infarction; the threshold of fibrillation against the background of phenazepam was 4.0 ± 0.5 mA compared with 1.5 ± 0.2 mA in unprotected animals with myocardial infarction. In other words, injection of phenazepam reduced by several times the fall of the electrical threshold of fibrillation and the number of extrasystoles in animals with acute myocardial infarction, i.e., limited these disturbances of electrical stability of the heart.

To assess the true significance of this protective effect of phenazepam, attention must be paid to data on mortality from experimental myocardial infarction obtained in these experiments. Altogether, to create acute myocardial infarction and postinfarction cardiosclerosis, which will be discussed below, we performed coronary occlusion on 70 unprotected rats. The mortality among these animals in the next 24 h was 47%. Coronary occlusion was performed on 20 animals after they had received a single injection of phenazepam in the dose mentioned above. Only one of these rats died during the next 24 h. Thus by limiting disturbances of electrical stability of the heart in the acute period of experimental myocardial infarction, phenazepam under our experimental conditions reduced the mortality of the animals sharply.

The data in Table 2 reflect the results of treatment of electrical instability of the heart in postinfarction cardiosclerosis with phenazepam. In postinfarction cardiosclerosis marked ectopic activity of the heart was observed: against the background of vagal bradycardia multiple ventricular extrasystoles occurred (27.7 ± 14.0 per animal). The electrical threshold of fibrillation was lowered by two-thirds. These disturbances correspond to the high probability of arrhythmias and fibrillation of the heart in patients with postinfarction cardiosclerosis, familiar in clinical cardiology. Phenazepam, as shown by the data in Table 2, abolished ventricular extrasystoles associated with vagal bradycardia virtually completely,

i.e., suppressed ectopic activity of the heart and caused a twofold rise in the threshold of fibrillation and thus reduced the probability of its onset.

It is essential to note that the antiarrhythmic effect in acute myocardial infarction and postinfarction cardiosclerosis was obtained by the use of doses of phenazepam which had no significant effect on blood pressure.

Any attempt to evaluate the antiarrhythmic effect of the benzodiazepine receptor agonist, phenazepam, in the present experiments must take into account the fact that phenazepam, when added to the perfusion fluid, as we showed in a separate series of experiments, does not affect ischemic and reperfusion arrhythmias produced in the isolated heart, i.e., it has no local antiarrhythmic action. Consequently, the antiarrhythmic effect described above is attributable to the action of phenazepam, as benzodiazepine receptor agonist, at the central level.

An important function of benzodiazepine receptors, which are widely distributed in synaptic structures of the cortex [1] and other parts of the brain, is to potentiate the effects of the GABA-ergic system at all levels of the CNS [5-7]. A decisive role of activation of central adrenergic mechanisms has been proved in disturbances of the electrical stability of the heart in acute ischemia, and for that reason ischemic arrhythmias can be prevented both by the intracisternal injection of a β-blocker [10] and by removal of the stellate ganglion [11]. It can be tentatively suggested that benzodiazepines, including phenazepam, potentiate the tonic inhibition, exerted by GABA-ergic neurons, of those neurons which realize adrenergic influences on the heart. As a result, the excessive activation of these neurons, which usually arises in response to acute cardiac ischemia, remains limited after administration of phenazepam, and the antiarrhythmic effect demonstrated above thus takes place at the central level.

Consequently, agonists of benzodiazepine receptors, like other activators of the GABA-ergic system, possess not only traditional psychotropic properties, but also marked antiarrhythmic activity, so that a detailed study of them in clinical cardiology is essential.

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