Effect of Fructose-1,6-Diphosphate and Phosphoenolpyruvate on the Course of Early Stage Occlusion and Reperfusion Arrhythmia in Rats

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An important role in the genesis of early postocclusion and reperfusion arrhythmias is played by the changes of electrophysiological parameters, as well as by the disturbances of energy supply in ischemized cardiomyocytes [3-5]. Therefore, the use of energy-supplying drugs can help prevent these threatening complications in the acute period of myocardial infarction. From this point of view, the intermediates of glycolysis fructose-1,6-diphosphate (FDP) and phosphoenolpyruvate (PEP), whose anti-ischemic activity has previously been established [6-8], are very promising.

The aim of the present work was to examine the antiarrhythmic activity of FDP and PEP on the models of early occlusion and reperfusion arrhythmia in rats and also to assess the efficacy of combining energy-supplying drugs with "classical" antiarrhythmics.

MATERIALS AND METHODS

Experiments were carried out on female Wistar rats weighing 180-240 g narcotized with sodium thiopental (50 mg/kg, intraperitoneally). Occlusion (10 min) and reperfusion (5 min observation) of the descending branch of the left coronary artery was performed on open-chest animals placed on controlled respiration. For assessing the antiarrhythmic effect of the drugs studied, the occurrence, the beginning of postocclusion and duration of reperfusion arrhythmias, the average duration of paroxysms of ventricular tachycardia (VT), the mean number of ventricular extrasystoles (VE), as well as their occurrence and the occurrence of ventricular fibrillation (VF) were registered. FDP was administered intravenously according to the following schedule: 25% dose continuously, before the coronary occlusion (CO); 50% dose slowly, during overall period of ishemia, with the aid of a microbatcher; the rest of the dose continuously, directly before the reperfusion. PEP and the comparison preparation, lidocaine, were injected intravenously, continuously, directly before the CO. Doses of the test preparations are presented in the tables. The results were processed statistically using Student's t test and χ^2.

RESULTS

During the first stage of the investigation, we studied the effect of FDP and PEP on the course of early postocclusion arrhythmia (Table 1). In the control series of experiments, the development of VE and paroxysms of VT were observed 249±33

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TABLE 1. Antiarrhythmic Effect of FDP and PEP for Early Postocclusion Arrhythmia in Rats

Experimental conditions	Dose, mg/kg	Number of animals				Latent period, sec	Duration of VT, sec	Number of VE
		total	VE	VT	VF			
Control	–	12	12	12	5	249±33	60±16	82±14
FDP	150.00	9	5	5*	0*	405±45*	10±4*	29±3*
	50.00	9	8	6*	2	254±53	21±8*	48±12*
PEP	0.50	8	8	3*	0*	451±27*	7±5*	51±18
	0.10	9	9	8	1	262±40	9±3*	65±13
Lidocaine	2.50	8	7	3*	0*	313±44	1±0.3*	55±19
	0.25	14	14	11	1*	366±21	9±3*	83±11
	0.10	7	7	7	2	278±41	65±15	62±13
FDP +	50.00							
+ lidocaine	0.10	8	8	7	1	386±15*	7±3*	64±3*

Note. Here and in Table 2 an asterisk indicates reliable differences vs. the control ($p<0.05$)

sec after ligation of the coronary artery. FDP in a dose of 150 mg/kg demonstrated a high antiarrhythmic activity, which manifested in a decreased occurrence of VT and VF, a drop of the intensity of VE, and an extension of the latent period and duration of VT episodes. When the dose of the preparation was reduced to 50 mg/kg, the antiarrhythmic effect of FDP was markedly reduced. In this series of experiments, FDP just affected the occurrence and duration of VT, as well as the intensity of extrasystoles in the experimental animals.

On this model of arrhythmia, the intensity of the antiarrhythmic effect of the other intermediate of glycolysis, PEP, was no less than that of FDP, although the ratio of their isoeffective doses was 1:300. PEP also exhibited a dose-dependent antiarrhythmic activity, the effect of the preparation markedly declining when the dose dropped to 0.1 mg/kg.

The antiarrhythmic effect of the intermediates of glycolysis tested in effective doses was similar to that of the comparison preparation, lidocaine, when used in a dose of 2.5 mg/kg. Decreasing the dose of lidocaine to 0.25 mg/kg markedly reduced its antiarrhythmic activity, and when injected in a dose of 0.1 mg/kg, the preparation failed to produce any statistically significant effect on the course of early postocclusion arrhythmia.

Combining antiarrhythmic drugs acting by different mechanisms is one of the methods for improving pharmacological therapy of disturbances of the heart rhythm [2]. Hence, the findings on the antiarrhythmic effect of FDP in a low-efficacy dose (50 mg/kg) combined with lidocaine in a deliberately ineffective dose (0.1 mg/kg) are undoubtedly interesting. As seen from Table 1, combining FDP with lidocaine resulted in an increase of the antiarrhythmic effect according to tests of the latent period and duration of VT.

In the control series of experiments, reperfusion of the coronary blood flow led to the development of VE and VT in 100% of cases, and in 9 out of 12 rats VF occurred (Table 2).

Under the given experimental conditions, FDP and PEP in doses of 150 and 0.5 mg/kg, respectively, increased the electrical stability of the myocardium, although their antiarrhythmic activity on the whole was less pronounced than at the early stages after CO.

On this model of arrhythmia, the preparation serving for comparison, lidocaine, reduced the occurrence and duration of paroxysms of VT to a greater degree than FDP. However, under conditions of reperfusion, in contrast to the case with occlusion arrhythmia, lidocaine in a dose of 0.25 mg/kg did not exert any pronounced effect on the course of heart rhythm disturbances.

TABLE 2. Antiarrhythmic Effect of FDP and PEP during Reperfusion Arrhythmia in Rats

Experimental conditions	Dose, mg/kg	Number of animals				Duration, sec		Number of VE
		total	VE	VT	VF	arrhythmia	VT	
Control	–	12	12	12	9	199±22	71±11	58±14
FDP	150.00	9	7	7	1*	225±35*	23±8*	35±14*
	50.00	8	8	7	3	230±32	71±23	77±26
PEP	0.50	8	8	6	2*	73±28*	14±4*	23±10
	0.10	9	9	9	6	128±30	23±5*	35±12
Lidocaine	2.50	8	8	4*	2*	112±48	6±3*	35±20
	0.25	14	14	14	3*	146±28	41±11	44±12
FDP +	50.00							
+ lidocaine	0.25	8	8	7	0*	101±21*	26±6*	21±8*

Differently from the effect of separate components, FDP and lidocaine combined in subthreshold doses (Table 2) caused an almost twofold decrease of reperfusion arrhythmias, a significant shortening of VT paroxysms, and a statistically reliable decrease of the intensity of ventricular extrasystoles.

The above experimental data provide evidence of a high antiarrhythmic activity of intermediates of glycolysis under conditions of acute myocardial ischemia, this obviously being associated with their ability to prolong the production of glycolytic energy [1]. The additional energy facilitates maintenance of the functional activity of the energy-dependent mechanisms of ion transport and the stabilization of the electrophysiological parameters of ischemized cardiomyocytes, thereby preventing the development of electrical destabilization of the heart.

Hence, pharmacological correction of energy metabolism in the myocardium is a promising way of improving pharmacological therapy of heart rhythm disturbances; intermediates of glycolysis, in particular, may be used both in monotherapy and in combination with "classical" antiarrhythmics.

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Characterization of Erythrocyte Na,K-ATPase in Rats with Different Attitudes to Ethyl Alcohol in Health and after Chronic Alcoholization

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Na,K-ATPase (E.C.3.6.1.4), an enzyme transforming the energy of ATP hydrolysis to perform transmembrane transfer of monovalent cations against their electrochemical potential, is an integral protein of the plasma membranes of all body tissues. It has been shown that the chronic action of ethanol leads to an increase in Na,K-ATPase in the brain [4, 6, 9], erythrocytes [8, 10], skeletal muscles [8], and liver [11]. At the same time, the effect of chronic alcoholization on Na,K-ATPase of animals with different attitudes to ethyl alcohol has been analyzed.

In order to obtain new data on plasma membrane function of animals preferring and rejecting alcohol, we made a study of erythrocytes Na,K-ATPase in rats with different attitudes to alcohol before and after chronic alcoholization.

MATERIALS AND METHODS

Experiments were carried out with 48 male Wistar rats weighing 350-400 g. Alcohopl attitude was

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