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EFFECT OF PHOSPHOENOLPYRYVATE ON THE COURSE OF THE ACUTE PERIOD OF EXPERIMENTAL MYOCARDIAL INFARCTION

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The compounds 1,3-diphosphoglycerate and phosphoenolpyruvate (PEP) belong to the category of very high-energy substrates of glycolysis, involved in the phosphorylation of ADP. However, despite evident preference for these compounds as potential agents supplying energy for survival of the myocardium under conditions of acute ischemia, there is virtually no information on research in this direction. The only exceptions are a few publications [4-7] describing the results of the use of PEP during cardioplegia and total ischemia of the rat heart.

The aim of this investigation was to study the effect of PEP on some parameters of bioenergetics, blood supply, cardiohemodynamics, and the formation of the zone of necrosis in experimental myocardial infarction.

EXPERIMENTAL METHOD

Experiments were carried out on mongrel male and female dogs weighing 6-17 kg and noninbred male albino rats weighing 250-300 g, anesthetized with pentobarbital sodium (40 mg/kg, intraperitoneally). In experiments on dogs the regional vein of the heart was catheterizod, and after ligation of the coronary artery, its distal segment also was catheterized by the method described previously [1]. Concentrations of lactate and glucose were determined by enzymic methods in samples of blood flowing from the ischemic zone, and the pH of the blood also was monitored. The blood supply to the ischemic region of the heart muscle was judged from the retrograde pressure (RP) and the collateral coronary blood flow (CCBF) in the distal part of the coronary artery. The first derivative of the intraventricular pressure (dp/dt) was recorded by means of a differentiator, and the average blood pressure (ABP) was measured in the femoral artery by means of "Bentley" pressure transducers. PEP ("Sigma") was injected intravenously in fractions of a total dose of 1 mg/kg (25% of the dose every 15 min) 5 min after occlusion of the coronary artery (OCA). A model of a myocardial infarct was produced in the rat by ligation of the descending branch of the left coronary artery at the level of the lower border of the auricle of the atrium. After the end of the manipulation the wound was closed in layers and the rats were artificially ventilated. The experimental animals were killed 4 h after OCA and the dimensions of the zone of ischemia and zone of necrosis were determined by the differential indicator method [2]. PEP was injected immediately after OCA in doses of 10, 1, and 0.1

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TABLE 1. Effect of PEP on Some Parameters of Bioenergetics, Blood Supply, and Cardiohemodynamics of Ischemic Myocardium After Occlusion of the Coronary Artery in Dogs (in percent of initial level)

Experimental conditions	Time after OCA, min	ΔpH	Lactate	Glucose consumption	dp/dt	ABP	RP	CCBF
Control	15	−0,23±0,04	+189±38,3	+370±50,0	−24±4,5	−22±4,5	−4±3,2	−6±2,3
	30	−0,36±0,06	+214±39,0	+370±90,0	−28±4,5	−25±3,6	−12±3,4	−16±3,2
	60	−0,40±0,05	+245±43,2	+490±70,0	−40±5,6	−35±4,3	−23±3,6	−26±5,4
PEP	15	−0,24±0,03	+95±11,4*	−20±2,5*	+3±3,9*	+6±7,5*	+21±3,7*	+36±9,4*
	30	−0,20±0,03*	+142±24,0*	+170±10,0*	+11±4,9*	+8±5,6*	+25±5,6*	+60±11,3*
	60	−0,20±0,04*	+148±20,9*	+180±20,0*	−15±4,1*	−12±4,9*	−8±4,0*	−2±4,2*

Legend. Initial level for RP and CCBF corresponded to values obtained 5 min after OCA. Asterisk – differences from control significant at $p < 0.05$.

mg/kg (0.04, 0.004, and 0.0004 mmole/kg respectively) in a volume of 2 ml (25% of the dose was injected rapidly, the remaining 75% slowly, in the course of 1 h, from a micropump). In these experiments the comparison preparation was the glycolysis intermediate fructose-1,6-diphosphate (FDP), whose cardioprotective activity was established previously [3]. FDP ("Serva") was injected in doses of 300 and 100 mg/kg (0.545 and 0.182 mmole/kg respectively) by a similar method to that used with PEP. Each series included at least 7 experiments.

EXPERIMENTAL RESULTS

The investigation showed that in dogs in the control series of experiments progressive acidification of the blood was observed after OCA, as it passed through the zone of ischemia, and this was accompanied by a sharp increase in the degree of excess lactate and the glucose consumption by the infarcted area of the myocardium (Table 1). Injection of PEP inhibited the further development of regional metabolic acidosis, and changes in pH of the venous blood flowing from the zone of ischemia did not exceed 0.20 ± 0.04 unit. The antiacidotic effect of PEP was realized against the background of a considerable decrease of excess lactate and a sharp decrease, especially in the first 15 min, of glucose consumption by the ischemic region of the myocardium.

During the first 30 min after injection of PEP the negative effect of OCA on the systemic blood pressure and myocardial contractility, RP, and CCBF was completely abolished. In the control series of experiments RP and CCBF had a clear tendency to fall, and at the end of the period of observation they were reduced by 23 ± 3.6 and 26 ± 5.4% respectively. PEP considerably improved the blood supply of the ischemic region of the myocardium, especially 30 min after the beginning of injection, when RP was 25 ± 5.6% higher and CCBF 60 ± 11.3% higher than initially.

The results are evidence of the positive action of PEP on the course of acute myocardial ischemia, an action which correlates with the results of assessment of its effect on the size of the necrotic zone.

The investigations showed (Fig. 1) that PEP, in a dose of 10 mg/kg, reduced by more than 50% the area of the zone of necrosis, which corresponded to 30 ± 4.3% of the zone of ischemia, whereas in the control series of experiments the region of infarction amounted to 68 ± 4.3%. Reduction of the dose of PEP by 10 and 100 times did not significantly weaken its cardioprotective effect.

The comparison substance FDP, in a dose of 300 mg/kg, also had a cardioprotective action, reducing the size of the zone of necrosis to 28 ± 5.5% of the ischemic zone, i.e., it was similar in its effect to PEP.

The investigations indicate that PEP has a significantly stronger cardioprotective action than FDP, for their isoeffective doses, expressed in molar units, are in the ratio of 1:1360. This phenomenon is probably connected with the fact that incorporation of FDP into the glycolytic cycle at the stage of glyceraldehyde-3-phosphate formation, although theoretically should lead to the saving of two ATP molecules, which would be utilized for phosphorylation of glucose, subsequent transformation of FDP in the chain of reactions of glycolysis depends on the activity of a whole series of enzymes, and most important, it is limited by a deficit of oxidized forms of NAD, observed under ischemic conditions. Conversely, the transition from PEP into pyruvic acid, accompanied by phosphorylation of ADP, is the final stage of glycolysis and is distinguished by high reactivity, and is not limited by the presence of oxidized forms of NAD.

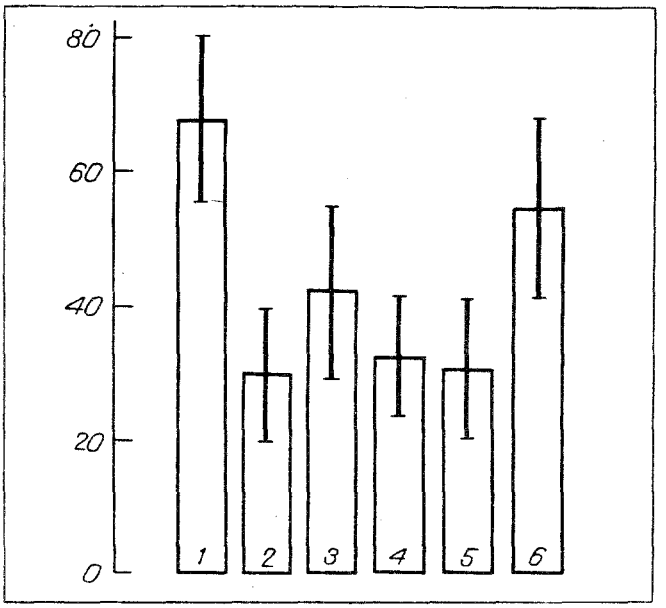

Fig. 1. Effect of PEP and FDP on size of necrotic zone 4 h after occlusion of coronary artery in rats. Ordinate, dimensions of zone of necrosis (in percent of ischemic zone). 1) Control; 2, 3, 4) PEP in doses of 10, 1, and 0.1 mg/kg; 5, 6) PDP in doses of 300 and 100 mg/kg. Confidence interval given at $p = 0.05$ level.

Thus PEP has a positive effect on the course of the acute period of myocardial infarction, as reflected in a decrease in the degree of regional metabolic acidosis, improvement of the bioenergetics and blood supply of the ischemic zone, stabilization of the cardiohemodynamics, and a decrease in size of the zone of necrosis. The high cardioprotective activity of PEP in the presence of a deficit of oxidized forms of NAD suggests that PEP can be regarded as an effective potential anti-ischemic agent if its therapeutic form can be stabilized.

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