Role of Glycolysis in the Genesis of Early Postocclusion Arrhythmias

L. N. Sernov, V. P. Balashov, Ya. V. Kostin, D. G. Sedova, and V. V. Gatsura

UDC 616.127-005.4-036.11-06:616.12-008.318-036.4-02:615.273.55]-07

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny,* Vol. 117, № 6, pp. 625-626, June, 1994
Original article submitted November 16, 1993

Antiarrhythmic effects of phosphorylated glycolysis intermediates glucose-1-phosphate, fructose-1,6-diphosphate, and phosphoenolpyruvate in early postocclusion arrhythmias are shown in rat experiments; in contrast to these, D-glucose, sodium pyruvate, and monoiodacetate, a glycolysis inhibitor, exert no appreciable antiarrhythmic effect.

Key Words: *occlusion arrhythmias; glycolysis; glycolysis intermediates*

There is no doubt that prolongation of glycolytic energy production during administration of glycolysis intermediates and electron acceptors has a favorable impact on the course of acute myocardial ischemia, improving the hemodynamic parameters and decreasing the size of the necrosis zone [1,5,6,8]. The contribution of glycolysis to the development of early postocclusion arrhythmias and ventricular fibrillation is still being debated [2,3].

We investigated the effects of monoiodacetate glycolysis intermediates on the course of postocclusion arrhythmias and the incidence of ventricular fibrillation in acute myocardial ischemia.

MATERIALS AND METHODS

Experiments were carried out with Wistar rats weighing 160 to 240 g narcotized with sodium thiopental in a dose of 50 mg/kg intraperitoneally. The descending branch of the left coronary artery was occluded in a single step during artificial ventilation of the lungs. The ECG was continuously recorded in the II standard lead. The following characteristics of arrhythmia were assessed: latent period before the development of occlusion arrhythmias, mean number of ventricular extrasystoles, frequency and duration of paroxysms of ventricular tachycardia, and incidence of ventricular fibrillation. The tested compounds: monoiodacetate (MIA), D-glucose (DGL), glucose-1-phosphate (G-1-P), fructose-1,6-diphosphate (FDP), phosphoenolpyruvate (PEP), and pyruvate (PV) were intravenously injected as a sodium salt solution in 0.5 ml normal saline with a microdosing device according to the following scheme: 25% of the dose in a jet before coronary artery occlusion and 75% by drip infusion for 10 min after the occlusion. MIA was jet-injected 2 min before occlusion. Doses of the compounds are presented in Table 1. The data were statistically processed using Student's t test and χ^2 methods.

RESULTS

In the control the development of early postocclusion arrhythmias lasting for 70±16 sec was observed as soon as 218±39 sec after coronary artery occlusion in 100% of experiments. In 5 of the 13 experiments the animals developed ventricular fibrillation (Table 1).

Department of Antiischemic Agents, Research Center of Bioactive Substances, Staraya Kupavna; Department of Pharmacology, Mordovian University, Saransk. (Presented by P. V. Sergeev, Member of the Russian Academy of Medical Sciences)

0007-4888/94/0006-0629$12.50

TABLE 1. Effect of MIA and Glycolysis Intermediates on the Course of Early Postocclusion Arrhythmias

Experim. conditions	Dose, mg/kg	Number of animals developing				Latent period, sec	VT duration, sec	Number of VE
		total	VE	VT	VF			
Control	–	13	13	13	5	218±39	70±16	90±9
MIA	1.0	8	8	8	4	232±68	24±7*	54±11
	4.0	5	5	4	1	123±58	32±12	81±12
DGL	100.0	12	12	10	1	324±32	18±5*	69±15
G–1–P	100.0	9	9	7	0*	287±46	6±3*	67±16
FDP	50.0	9	8	6*	2	254±53	21±8*	48±12*
	100.0	9	7	5*	1	349±46*	18±10*	71±28
	150.0	9	5*	5*	0*	405±44*	9±4*	29±13*
PEP	0.1	9	9	8	1	262±40	9±3*	65±13
	0.5	8	8	3*	0*	451±27*	7±5*	51±18
PV	10.0	9	9	9	1	240±51	28±11	68±16
	100.0	7	7	6	3	257±69	49±15	128±25

Note. VE: ventricular extrasystole; VT: ventricular tachycardia; VF: ventricular fibrillation. Asterisk shows reliable difference from control ($p<0.05$).

The glycolysis inhibitor MIA in a dose of 1 mg/kg did not affect the incidence of arrhythmias in rats, but it shortened the mean duration of ventricular tachycardia to 24±7 sec vs. 70±16 sec in the control ($p<0.05$) and somewhat decreased the intensity of ventricular extrasystoles. If the MIA dose was increased to 4 mg/kg, its effect was less pronounced. Moreover, a trend toward a shorter latent period before the development of arrhythmias was observed. MIA in a dose of 20 mg/kg caused the death of all experimental animals ($n=6$).

DGL in a total dose of 100 mg/kg had a slight protective effect on the course of early postocclusion arrhythmias, which manifested itself in a shorter ventricular tachycardia, 18±5 sec ($p<0.05$), a trend toward a longer latent period, and less intensive ventricular extrasystoles. G-1-P, a phosphorylated intermediate of the initial stage of glycolysis, had a more marked antiarrhythmic effect if administered in parallel with DGL. The duration of ventricular tachycardia was a mere 6±3 sec and none of the 9 animals developed ventricular fibrillation.

FDP, an intermediate of the median phase of glycolysis in a dose of 50 mg/kg reliably ($p<0.05$) reduced the incidence and duration of ventricular tachycardia and reduced the intensity of ventricular extrasystoles. Increasing the FDP dose to 100 mg/kg enhanced the above antiarrhythmic effects of the compound. FDP in the maximal tested dose, 150 mg/kg, reliably lowered the incidence of early postocclusion disorders of heart rhythm, completely prevented the development of ventricular fibrillation, noticeably reduced the duration of ventricular tachycardia and the intensity of ventricular extrasystole, and prolonged the latent period.

PEP, an intermediate of the terminal stage of glycolysis, administered in a dose of 0.1 mg/kg, markedly shortened the duration of ventricular tachycardia to 9±3 sec. If the dose was increased fivefold, the agent significantly reduced the incidence of ventricular tachycardia, completely prevented ventricular fibrillation in the experimental animals, maximally prolonged the latent period (to 451±27 sec), and sharply reduced the duration of ventricular tachycardia.

PV, the final product of Embden-Meyerhoff's cycle, injected in doses of 10 and 100 mg/kg, had no appreciable effect on the characteristics of postocclusion arrhythmias.

The theoretical essence of glycolysis inhibition thus boils down to the prevention of a glycolytic "outburst" which represents one of the triggering factors in the genesis of postocclusion arrhythmias in the early stages of myocardial ischemia [2,3]. Our studies, however, demonstrated that an attempt to inhibit the Embden-Meyerhoff cycle at the level of glyceraldehyde dehydrogenase by MIA did not result in a noticeable improvement in the course of early postocclusion disorders of the heart rhythm.

Use of glycolysis intermediates which may be ranked by their antiarrhythmic activity with due consideration for isomolar doses in the following order: G-1-P < FDP < PEP proved to be more effective. It is therefore possible to propose that glycolysis intermediates are capable of partially inhibiting the active course of preceding reactions according to the "substrate-enzyme" principle, that is, they may "mildly" inhibit the development of the glycolytic "outburst" phenomenon, with energy production preserved at a certain level. The latter

circumstance is fundamentally important, for it helps maintain the functional activity of energy-dependent mechanisms of ionic homeostasis in cardiomyocytes and determines the gradation of glycolysis intermediates by their antiarrhythmic activity as a function of the energetic value of the substrate.

Of course, this hypothesis does not exhaust all the aspects in the mechanism of the antiarrhythmic effect of glycolysis intermediates during early postocclusion arrhythmias. For instance, the antiacidotic effect of FDP and PEP [4] may be of importance, because metabolic acidosis is one of the key components in the pathogenesis of arrhythmias occurring in acute myocardial ischemia [3,7].

REFERENCES

1. V. V. Gatsura, *Usp. Fiziol. Nauk,* **12**, № 1, 97-118 (1981).
2. M. E. Raiskina, *Byull. Vsesoyuzn. Nauch. Kardiol. Tsentra, Akad. Med. Nauk SSSR,* № 2, 85-99 (1980).
3. M. E. Raiskina and B. N. Fel'd, *Usp. Fiziol. Nauk,* **15**, № 3, 108-135 (1984).
4. L. N. Sernov and V. V. Gatsura, *Byull. Eksp. Biol. Med.,* **112**, № 11, 461-462 (1991).
5. L. N. Sernov, Yu. B. Rozonov, and V. V. Gatsura, *Eksp. Klin. Farmakol.,* № 4, 13-15 (1992).
6. I. E. Hassinen, E. M. Nuutinen, K. Ito, *et al., Circulation,* **83**, № 2, 584-593 (1991).
7. R. Lazzara and B. J. Scherlog, in: *Physiology and Pathophysiology of the Heart,* ed. by N. Sperelakis, Kluwer Acad. Publ. (1989).
8. G. Lazzarino, B. Tavazzi, M. Nuutinen, *et al., Ital. J. Biochem.,* **38**, № 4, 251-253 (1989).

Effect of Polycation Based on Alkaloid Lupinin-Antihepolin and Its Complex with Heparin on DNA Synthesis in Rat Hepatocytes

G. T. Makhsudova, V. A. Golenchenko, and V. S. Efimov

UDC 616.36-018.1-008.939.633.2-02:615.273.52]-092.9-07

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny,* Vol. 117, № 6, pp. 627-629, June, 1994
Original article submitted November 16, 1993

The effect of the antiheparinate antihepolin on the intensity of replication processes in rat hepatocytes was studied. A single intravenous infusion of polycation caused an approximately 6-fold increase in the intensity of DNA synthesis on day 2 postinjection followed by a drop to thebaseline level on days 5-6. If antihepolin was injected in parallel with heparin, DNA synthesis was intensified after just 24 hours.

Key Words: *polycations; heparin; antihepolin; polycomplex; hepatocytes; DNA synthesis*

Among synthetic polymers characterized by antiheparin activity linear ionenes are known, such as polybrene [4,3], quaternary ammonium salt of oligomer 25 conidine (QAS-O-25 conidine) [7], and other substances of polycationic structure [2]. Synthetic polycations deserving special attention are those in which natural substances are used as quaternized nitrogen carriers in their construction. For example, a systematic series of polymers that are quaternary salts of polymethacryloil lupinin (poly-MACL) [5] was synthesized on the basis of an alkaloid of *Anabasis aphylla,* lupinin, whose tertiary nitrogen atoms may be easily transformed into quaternary atoms [6]. A characteristic feature of

Department of Hemostasis Pharmacology, Russian State Medical University, Moscow. (Presented by B. T. Velichkovskii, Member of the Russian Academy of Medical Sciences)

0007-4888/94/0006-0631$12.50