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EFFECT OF A TERRILYTIN—NICOTINIC ACID MIXTURE ON THE STRUCTURAL AND FUNCTIONAL STATE OF THE MYOCARDIUM IN EXPERIMENTAL ISCHEMIA

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Research is currently in progress into the therapeutic properties of the Soviet preparation terrilytin, obtained from the culture fluid of *Aspergillus terricola* [2]. The writers showed previously that terrilytin, in conjunction with nicotinic acid, prevents hypercoagulation in the lymph and blood and has a favorable influence on the course of experimental myocardial infarction [1, 3-5].

The aim of this investigation was to study the effect of a terrilytin—nicotinic acid mixture (TNA) on the state of the ischemic myocardium.

EXPERIMENTAL METHOD

Two series of experiments were carried out on 35 rabbits. The animals of series I served as the control, and in series II, 30 min after ligation of the anterior interventricular branch of the left coronary artery a mixture of TNA was injected intravenously in the following doses: terrilytin 50 proteolytic units/kg, nicotinic acid 5 mg/kg. Tests were carried out before and 1, 3, and 7 days after the experiment (five rabbits at each time). Several oxidation-reduction enzymes and carbohydrates were studied by histochemical methods in the necrotic, perinecrotic, and intact zones of the myocardium.

EXPERIMENTAL RESULTS

One day after the production of an acute myocardial infarct (AMI) the diformazan concentration in the zone of necrosis was increased, but under these circumstances signs of "enzymic diffusion" were observed, in the form of precipitation of a homogeneous histochemical reaction product. A change in its standard parameters was observed on demonstration of glucose and, in particular, of glycogen. The increase in the cytophotometric density of cardiomyocytes in the necrotic zone must be regarded as most probably due to dissociation of the enzymes and substrates studied from the corresponding ultrastructures on which they function. This was confirmed by the subsequent sharp fall (by more than half) of the concentration of the histochemical reaction products after the third and, in particular, the seventh day (Table 1).

In the perinecrotic zone after 1 day the cardiomyocytes showed increased activity of NADPH and lactate dehydrogenases. The small increase in the glycogen and glucose concen-

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TABLE 1. Histochemical Parameters of Cardiomyocytes Normally and at Various Times of Experimental AMI Based on Spectrophotometric Data

Zone tested	Times of investigation, days	Parameter, conventional units								NADH oxidoreductase	NADPH oxidoreductase
		glycogen	glucose	NAPS	LDH	SDH	CCO	IDH	MDH		
Cardiomyocytes of intact animals											
		9,7±0,82	16,1±1,24	8,0±0,72	19,1±1,19	18,4±1,27	20,9±1,36	23,7±1,30	25,8±1,48	23,7±1,42	9,2±0,67
Cardiomyocytes of animals with myocardial infarction											
Necrotic	1	19,7±1,12	22,8±1,24	12,1±0,85	27,6±1,47	21,7±1,34	23,8±1,36	28,4±1,51	28,9±1,46	25,3±1,56	14,2±1,02
	2	10,1±0,86	19,5±1,62	10,1±0,82	12,1±1,16	10,1±1,06	9,17±0,84	15,7±1,22	9,75±0,82	10,1±1,42	18,5±1,36
	3	4,3±0,64	27,5±1,58	7,5±0,69	4,2±0,65	3,7±0,49	5,29±0,63	4,9±0,58	4,91±0,61	6,34±0,51	6,12±0,71
Perinecrotic	1	14,3±1,16	19,7±1,38	16,2±1,39	20,4±1,26	17,1±1,20	18,3±1,16	21,2±1,46	22,3±1,34	19,1±1,30	10,4±0,93
	2	7,21±0,76	14,3±1,19	13,8±0,92	17,5±1,21	11,2±0,93	15,2±1,05	13,6±0,98	17,1±1,28	13,1±1,19	19,5±1,25
	3	5,1±0,45	12,8±0,98	12,9±1,12	15,8±0,95	13,6±0,98	14,1±1,21	14,5±1,20	19,3±1,44	17,5±1,51	26,3±1,4[illegible]
Intact	1	12,7±0,86	10,5±0,97	19,1±1,28	17,8±1,18	14,3±1,00	15,1±1,11	18,3±1,47	18,0±1,35	16,8±1,42	8,1±0,96
	2	10,2±0,97	8,31±0,64	17,8±1,41	15,3±1,29	10,5±1,17	16,2±1,36	22,4±1,56	24,8±1,61	23,7±1,58	13,5±1,18
	3	8,13±0,73	6,29±0,56	16,0±1,23	14,8±1,36	15,9±1,41	14,7±1,25	20,1±1,35	28,6±1,49	29,5±1,75	16,2±1,36
Cardiomyocytes of animals with myocardial infarction and receiving TNA mixture											
Necrotic	1	14,3±1,28	13,5±1,16	17,5±1,25	24,8±1,62	22,7±1,50	20,1±1,68	24,8±1,75	23,6±1,44	28,3±1, 1	22,7±1,46
	2	9,5±0,87	15,8±1,25	22,1±1,36	19,3±1,46	16,2±1,18	11,3±0,96	12,3±1,29	12,2±1,19	11,36±1,07	14,2±1,26
	3	6,9±0,72	26,1±1,52	14,8±1,28	9,5±1,00	7,9±0,79	6,3±0,88	5,7±0,70	6,3±0,76	5,1±0,68	6,4±0,82
Perinecrotic	1	9,2±1,30	12,7±1,41	7,1±0,86	21,7±1,28	19,1±1,20	18,7±1,37	27,1±1,56	28,3±1,68	24,4±1,48	19,7±1,48
	2	10,8±1,22	14,7±1,36	8,9±0,92	22,9±1,36	18,6±1,29	19,6±1,26	24,3±1,51	26,7±1, 4	21,0±1,32	20,8±1,36
	3	13,2±1,36	9,75±0,86	11,5±1,00	26,5±1,59	19,5±1,31	19,3±1,19	24,8±1,53	25,8±1,48	22,7±1,40	17,2±1,2[illegible]
Intact	1	13,8±1,29	11,9±0,92	14,3±0,99	23,8±1,64	20,3±1,17	21,5±1,44	22,1±1,42	22,9±1,31	26,5±1,39	17,9±1,42
	2	8,6±0,79	14,3±1,19	12,1±1,08	24,2±1,42	18,7±1,26	22,7±1,27	20,5±1,35	23,6±1,58	24,3±1,56	18,1±1,28
	3	7,1±0,64	12,2±1,33	13,2±1,16	21,7±1,35	19,5±1,49	22,0±1,42	21,7±1,27	22,7±1,46	15,9±1,66	18,4±1,51

5.

Legend. Values given are arithmetic mean of general series (x) and its confidence limits (α). p = 0.05, n = 35.

trations must be regarded as the result of lowering of the redox potential of the dehydrogenases of the isocitrate cycle. After 3 and 7 days, reduced activity of these enzymes were observed.

In the intact zone activity of NADH-dependent dehydrogenases of glycolysis and of the isocitrate cycle [lactate (LDH), NADH, malate (MDH), and isocitrate (IDH) dehydrogenases] was reduced after 1 day. Activity of terminal oxidation enzymes [cytochrome oxidase (CCO), succinate dehydrogenase (SDH)] and the glucose concentration were reduced. Under these circumstances there was a significant increase in the concentration of glycogen and, in particular, of neutral aminopolysaccharides (NAPS). Later the activity and concentrations of the above enzymes stabilized and regained their initial levels.

The behavior of the enzymes studied in the zone of necrosis after injection of the TNA mixture into animals with experimental AMI was virtually indistinguishable from the corresponding parameters of cardiomyocytes in the analogous zone of the control myocardium.

In the perinecrotic zone 3 days after injection of the mixture, activity of IDH, SDH, and MDH remained high. Activity of NADH dehydrogenase and CCO was close to its initial value. The glycogen and NAPS concentrations showed a tendency to rise. Thus the average histochemical parameters in cardiomyocytes of the perinecrotic zone were almost back to normal, by contrast with the situation in the control. Toward the end of the 7th day activity of all the intramitrochondrial enzymes was close to normal again, evidence of the optimal level of energy formation in the composition of cardiomyocytes adjacent to the zone of destruction.

In the intact zone, by contrast with the control, 1 day after injection of the mixture there was an appreciable increase in activity of several enzymes (LDH, CCO, SDH). The greatest increase was observed in NADPH dehydrogenase activity. After 3 days the activity of the various enzymes and substrates showed a tendency toward normalization.

The facts described above are evidence that under the conditions of experimental AMI three zones are formed, in which the cardiomyocytes differ in behavior with respect to carbohydrate metabolism and activity of a group of oxidoreductases responsible for energy formation in the myocardium. In the control, the intracellular topography and activity of the enzymes studied were disturbed both in the zone of necrosis and in the perinecrotic zone. As we know, the outcome of AMI, which depends on the functional state of the perinecrotic zone, is largely connected with this observation. Intravenous injection of a TNA mixture prevents gross disturbances of the energy formation process in the cardiomyocytes of the perinecrotic zone around the infarct, and thus ensures an optimal level of their functional activity and improves the prognosis of AMI.

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