EFFECT OF TRASYLOL ON PERMEABILITY OF THE TISSUE–BLOOD BARRIERS OF THE ISCHEMIC MYOCARDIUM

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Ligation of the descending branch of the left coronary artery caused an increase in the permeability of the tissue–blood barriers of the myocardium in the ischemic zone and in the boundary zone for sulfacetamide sodium. Trasylol reduced the permeability of the myocardial tissue–blood barriers in these zones and did not affect permeability in the intact zone. The use of a fluorescein test revealed the presence of a membranotropic effect of trasylol; the compound did not affect the osmotic resistance of the erythrocytes *in vitro*.

KEY WORDS: myocardial ischemia; permeability; trasylol.

An early manifestation of acute myocardial ischemia is increased permeability of the tissue–blood barriers (TBB) of the heart [2, 4] and of the membranes of the intracellular organelles, especially the mitochondria and lysosomes. Labilization of the lysosomal membranes leads to liberation of proteases, and through the intervention of tissue mediators [1], these not only produce intracellular autolysis [9] but also affect the permeability on the myocardial vessels. There would therefore appear to be a good case for using protease inhibitors, notably trasylol, in acute ischemia.

The object of this investigation was to study the membranotropic action of trasylol and its effect on permeability of the myocardial TBB during acute ischemia.

EXPERIMENTAL METHOD

Changes in permeability of the ischemic myocardium under the influence of trasylol were studied in acute experiments on rabbits and on rabbit hearts isolated by Langendorff's method. Acute experiments were carried out on 24 rabbits of both sexes (2-3 kg) under general anesthesia with pentobarbital sodium in a dose of 30 mg/kg intraperitoneally. Myocardial ischemia was produced by occlusion of the descending branch of the left coronary artery in its middle third for 30 min, followed by removal of the ligature and intravenous injection of sulfacetamide sodium in a dose of 200 mg/kg (as an indicator of the permeability of TBB [6]). Temporary disturbance of the coronary blood flow was preferred to permanent disturbance so as to create identical conditions for the entry and distribution of the indicator in the ischemic, boundary, and intact zones. Trasylol was injected intravenously 5 min after ligation of the coronary artery in doses of 200 and 1000 units/kg. The animals were killed 30 min after the injection of sulfacetamide sodium and that compound was determined in tissue samples (0.5 g) taken from the ischemic, boundary, and intact zones, and also in the blood serum [7]. The state of permeability of the myocardial TBB was judged from the coefficient of permeability (the ratio between the concentrations of sulfacetamide sodium in the tissue and in the serum, in %) [6]. In 20 experiments on isolated hearts ischemia was produced by the same method. Trasylol perfusion (1 and 10 units/ml) began 5 min after ligation of the coronary artery. Perfusion with sulfacetamide sodium in a concentration of $2 \cdot 10^{-5}$ began immediately after removal of the ligature. The content of indicator in the tissues taken from the ischemic, boundary,

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TABLE 1. Effect of Trasylol on Permeability of TBB of Ischemic Rabbit Myocardium *in vivo* and *in vitro* (M ± m)

Experimental conditions	Control or experiment	Number of experiments	Dose or concentration of trasylol	Coefficient of permeability for sulfacetamide sodium	Concentration of sulfacetamide sodium (in mg %)
Experiments in vivo					
intact myocardium	Control	8		42,2± 2,3	
	Experiment	8	200 units/kg	43,0± 2,2	—
		8	1000 "	41,2± 1,8	
myocardium of boundary zone	Control	8		49,3± 1,8	
	Experiment	8	200 "	48,7± 2,5	—
		8	1000 "	45,2± 1,7	
myocardium of ischemic zone	Control	8		58,6± 2,8	—
	Experiment	8	200 "	55,6± 2,9	
		8	1000 "	50,8± 1,8*	
Experiments in vitro					
intact myocardium	Control	8			112,3± 8,5
	Experiment	6	1 units/ml	—	99,1± 6,7
		6	10 "		101,3± 5,8
myocardium of boundary zone	Control	8			164,2± 13,0
		6	1 "		166,4± 12,1
	Experiment	6	10 "		144,2± 10,0
myocardium of ischemic zone	Control	8			200,1± 15,7
		6	1 "	—	191,1± 13,6
	Experiment	6	10 "		157,7± 9,1*

Legend. Values differing by a statistically significant degree ($P < 0.05$) from the control are marked by an asterisk.

and intact zones was estimated quantitatively 30 min after the beginning of perfusion with sulfacetamide sodium. The direct effect of trasylol on the membranes was studied on rabbit erythrocytes by a fluorometric method [5] and by the osmotic resistance method. The trasylol concentration in these experiments was 20 and 100 units/ml.

EXPERIMENTAL RESULTS AND DISCUSSION

The experimental results are given in Table 1. Acute myocardial ischemia in the control experiments *in vivo* was accompanied by increased permeability of the myocardial TBB in the ischemic and boundary zones compared with the intact zone, in agreement with previous observations [2]. Higher values of the coefficient of permeability in the present experiments can evidently be attributed to the temporary nature of ligation of the coronary artery. Trasylol in a dose of 1000 units/kg definitely reduced permeability in the zone of ischemia. In a dose of 200 units/kg the effectiveness of the compound was very low. In the intact zone of the myocardium no changes in permeability of TBB were found under the influence of trasylol.

The results of the experiments on the isolated hearts also provided evidence of increased permeability of the myocardial TBB in the ischemic and boundary zones. A marked decrease in permeability of the myocardial TBB was recorded only in the ischemic zone if trasylol was given in a concentration of 10 units/ml.

Trasylol did not affect the parameters of erythrocyte resistance in a hypotonic medium. The fluorometric investigation revealed a significant decrease in erythrocyte permeability to fluorescein under the influence of trasylol in a concentration of 100 units/ml from 29.3 ± 2.1 μA in the control to 13.6 ± 1.0 μA in the experimental series. This suggests that trasylol may have a membrane-stabilizing effect. This hypothesis is in agreement with data showing the decrease in permeability of the TBB of the ischemic myocardium under the influence of trasylol. However, when the effect of trasylol on permeability is assessed allowance must also be made for the possibility of its indirect action. For example, the antiedematous action of trasylol [9] and its inhibition of kallikrein [10] the activity of which is increased in acute myocardial ischemia [3], may also play an important role in the mechanism of the effect of trasylol on permeability. This conclusion is supported by the absence of changes in permeability of TBB in the intact zone of the myocardium following administration of trasylol and the marked effect of the preparation in the ischemic zone, where the kallikrein–kinin system, of which trasylol is a powerful inhibitor, undergoes activation.

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