Effect of Dopamine on the Plasma Glucose Level and Glycogen Phosphorylase Activity in Experimental Coronary Occlusion

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Dopamine agonists express dissimilar effects on the blood glucose level. It is supposed that the influence of dopaminergic agents on the blood glucose level is mediated via α- and β-adrenoreceptor-dependent regulation of insulin and glucagon secretion. The detailed mechanism of the influence is unclear; moreover, pharmacological analysis of the effect of dopaminemimetics on the glucose level have yielded different results in different experiments [12]. The dissimilar pattern of dopamine agonist influence on the blood glucose level is apparently determined mainly by the dose used and the resulting difference in the degree of dopamine and adrenergic receptor stimulation.

The aim of this work was a study of the effect of dropwise administration of a low dose of dopamine on the glucose level and glycogen phosphorylase activity in the plasma of dogs with coronary-occlusive injury of the myocardium. The glycogen phosphorylase activity was studied keeping in mind not only the participation of this enzyme in carbohydrate metabolism, but also its role as a marker of ischemic damage of the myocardium.

MATERIALS AND METHODS

Experiments were performed on outbred dogs of both sexes under pentobarbital sodium anesthesia (40 mg per kg intrapleurally) on the opened chest under conditions of forced pulmonary ventilation. Myocardial ischemia was modeled by ligation of the median third of the anterior interventricular branch of the left coronary artery. The surgical procedures were carried out by E.V. Katkov. Dopamine (Dopmin, Finland) was administered intravenously in a dose of 5 μg per kg per min during the interval 21-80 min after ligation of the coronary artery, it was followed by the administration of saline during the 81st-110th min. Control animals received saline only from the 21st to the 110th min following artery ligation. Blood samples were taken prior to coronary occlusion (initial state) and 20, 25, 30, 80, and 110 min thereafter. Plasma was assayed for the glucose content, using the ortho-toluidine method, and for the activity of glycogen phosphorylase *a* and *b* (E.C. 2.4.1.1) [4]. The possibility of dopamine interference with the plasma products of the enzymatic reaction or glucose is excluded *in vitro* according to the recommendations of the International Federation of Clinical Chemistry [1]. The results were statistically evaluated.

RESULTS

During the whole period of the experiment the glucose content in the plasma of animals of both groups remained at the initial level. The only statistically reliable difference in the glucose levels between the control and experimental groups, observed 25 min after the

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TABLE 1. Effect of Dopamine on Glucose Level in Dog Plasma (mM per Liter, $M \pm m$).

Group of animals	Glucose level in ischemia					
	0 min	20 min	25 min	35 min	80 min	110 min
Control	(7) 10.0±2.7	(7) 9.0±1.7	(6) 13.7±2.6	(7) 8.4±2.0	(6) 10.0±2.3	(4) 10.4±3.2
Experimental (dopamine infusion from 21st to 80th min)	(7) 6.9±1.2	(8) 7.9±2.1	(4) 7.0±0.9*	(6) 6.2±1.3	(7) 8.2±1.3	(6) 10.8±2.6

Note: here and in Table 2 an asterisk indicates significant differences from the control ($p<0.05$); the number of animals is given in parentheses.

onset of ischemia, is related to a slight (negligible in comparison with the initial level) rise in the glucose content in the control group at this time (Table 1); this rise was not seen in the animals receiving dopamine. The rise of the plasma glucose level in the control animals 25 min after the onset of coronary occlusion is consistent with the activation of glycogen phosphorylases *a* and *b* at this time. The glycogen phosphorylase activity significantly exceeded both the initial activity ($p<0.001$ for both enzyme variants) and the 20-min-ischemia activity ($p<0.001$). On the other hand, at the 35th min the activity of both enzyme forms in the control group decreased ($p<0.05$ when compared with the initial and 20-min-ischemia level), while subsequently (at 80-110 min) it returned to the initial level. In the course of dopamine infusion, glycogen phosphorylase activity did not vary from the initial level at any time, this explaining the differences between the control and experimental groups 25-35 min following the onset of ischemia (Table 2).

Thus, in the course of coronary-occlusion ischemia, dopamine (5 μg per kg per min) prevented glycogenolysis activation and the related rise of the glucose content in the plasma. The changes in the glycogen phosphorylase activity in the dogs with myocardial ischemia are a feature characterizing the degree of ischemic injury of the cardiomyocytes [7]. The appearance of each new ischemic focus in the myocardium is followed by a rise in the glycogen phosphorylase activity. Here, the rise of glycogen phosphorylase *b* is related to the decrease in the tissue ATP content and increase of orthophosphate, while glycogen phosphorylase *a* is primarily activated by the ischemia-recruited fraction of the heart-residing catecholamines [2].

Earlier we showed that in dogs with coronary-occlusive ischemia dopamine in a dose of 10 μg per kg per min caused, together with an improvement of the blood supply to the ischemic focus and an increase of the minute volume of circulation, an in-

TABLE 2. Effect of Dopamine on Glycogen Phosphorylase Activity in Dog Plasma (μM Inorganic Phosphate per min per Liter of Plasma at 37°C, $M \pm m$).

Duration of ischemia, min	Group of animals	
	Control	Experimental (dopamine infusion from 21st to 80th min)
Glycogen phosphorylase *a*		
0	(9) 178.3±30.8	
20	(11) 189.4±39.3	
25	(4) 498.5±31.1	(3) 229.4±48.7*
35	(3) 60.6±15.9	(3) 175.1±52.0*
80	(4) 150.4±52.1	(5) 307.4±74.1
110	(4) 108.9±19.7	(3) 115.2±52.6
Glycogen phosphorylase *b*		
0	(9) 192.6±52.7	
20	(10) 259.9±107.7	
25	(4) 789.2±116.7	(4) 135.0±44.7*
35	(4) 36.0±0.25	(4) 263.0±116.0*
80	(5) 164.8±42.6	(4) 193.0±78.3
110	(3) 54.6±15.9	(4) 138.6±57.2

crease in the activity of plasma glycogen phosphorylases *a* and *b* in comparison to the initial level [3]. We assumed that the boosted enzymatic activity might be a consequence of the prolonged increase of myocardial contractile activity under the influence of dopamine in a dose stimulating the β-adrenoreceptors in the sinoatrial node and myocardium.

According to Evtanave *et al.* [8], the pharmacodynamics of dopamine administered in a dose of 5 μg per kg per min is also governed by the predominance of β-adrenergic effects. However, a change in the functional state of an organ under pathological conditions (including myocardial ischemia) is known to alter the parameters of adrenergic regulation (the number and affinity of adrenoreceptors, the degree of receptor coupling to intracellular structures) [5,6]. Therefore, the noted effect of dopamine preventing a rise of the plasma glycogen phosphorylase activity can be attributed to a weak expression (or even absence) of the β-adrenomimetic effect of the given dose of preparation on the ischemic myocardium and to the predominance of stimulation of the presynaptic D-2 dopamine and postsynaptic D-1 dopamine receptors of the coronary arteries. The result of such a predominance is inhibition of norepinephrine release, dilation of the coronary arteries, and prevalence of oxygen delivery over its consumption in the myocardium [9-11].

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The Effect of Myelopide and Tactivine on Bone Marrow

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Immunoactive peptides in the thymus and bone marrow play an important role in hemopoiesis. It is known that these peptides can alter the proliferation, differentiation, and migration of hemopoietic cells [1,4,5]. The peptides can also correct disturbances of hemopoiesis following irradiation and thymectomy [7,9]. However, the action of these peptides on hemopoietic tissue has not yet been definitively investigated.

This is a comparative study of the influence of tactivine and myelopide (two preparations of this group widely used in clinical practice) on the clon-

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