side the cell. The action of DAAE and pronase from inside the sarcolemma (Fig. 2, I; Fig. 3) is very similar and evidently directed toward the same site in the membrane.

It can be postulated on the basis of these results that DAAE, compared with ethmozine, has an additional site for its action on the sarcolemma. This feature of DAAE is evidently responsible for its longer and more effective antiarrhythmic action.

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EFFECT OF GUTIMIN ON THE MYOCARDIAL FATTY ACID UPTAKE DURING PROLONGED DISCONNECTION OF THE HEART FROM THE CIRCULATION IN DOGS WITH MODERATE HYPOTHERMIA

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Gutimin (guanylthiourea) is used in medicine as an antihypoxic agent [1, 3, 4, 8]. Experiments have demonstrated its positive effect on ATPase activity in the myocardium, brain, and erythrocytes [1, 6].

Considering that the main sources of energy for heart muscle are fatty acids, in both the free and the bound state [9-11], the effect of preventive administration of gutimin on myocardial fatty acid uptake was studied when the heart was disconnected from the circulation in dogs with moderate hypothermia.

EXPERIMENTAL METHOD

Experiments were carried out on 48 male dogs weighing 12-20 kg, kept on a diet consisting mainly of animal fat. The dogs were not fed for 24 h before the experiments. After premedication (trimeperidine, atropine), under endotracheal ether-oxygen anesthesia (stage III_2) together with relaxants, the animals were cooled by a combination of the Kholod-2F apparatus and ice and snow packs covering the trunk. When the rectal temperature was reduced to 30°C thoracotomy was performed in the sixth right intercostal space, and the heart was disconnected from the circulation by application of tourniquets to the atrial veins (groups 3 and 4). In the experimental series (groups 5 and 6) gutimin was injected intravenously in a dose of 20 mg/kg before cooling and in a dose of 45-50 mg/kg 25-30 min before occlusion under similar experimental conditions. Prolonged disconnection of the heart from the circulation (for 60 min) was carried out in both series. Measures to restore cardiac activity included cardiac-massage, artificial ventilation of the lungs, intra-arterial injection of

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TABLE 1. Effect of Gutimin on Composition and Uptake of Fatty Acids from Blood Lipids by Canine Myocardium during Disconnection of Heart from Circulation for 60 min and Whole-Body Cooling to 30-28°C (M ± m)

Fatty acids	Group 1 (n = 14): intact dogs		Group 2; n = 9, 28°C (THB – SHB)	Group 3 (n = 6); 28°C + occlusion (composition of acids)	Group 4 (n = 7); 28°C + occlusion + rewarming (THB – SHB)	Group 5 (n = 6); 28°C + occlusion + gutimin (composition of acids)	Group 6 (n = 7); 28°C + occlusion + rewarming + gutimin (THB – SHB)
	composition of acids	THB – SHB					
8:0	1,0±0,2	+0,1	–0,3*	0,3±0,1	–0,01	0,2	–0,3±0,1*
9:0	1,5±0,1	–0,5±0,1	–0,9±0,1*	0,2	–0,2	1,25±0,4	–0,2
10:0	1,2±0,3	–0,3	+0,5±0,1*	0,5±0,1	+0,3±0,1*	1,44±0,5	+2,75±0,3*
11:0	1,8±0,4	+0,4±0,1	+0,1	0,7±0,1	–0,9±0,1*	4,2±0,4*	+0,4±0,1
12:0	3,9±0,7	+2,3±0,5	–0,6±0,1*	1,0±0,1	+0,3±0,1	3,7±0,9	+1,8±0,3
13:0	2,3±0,7	+0,8±0,1	–0,2*	2,0±0,3	–0,2	3,7±1,1*	+3,3±0.5*
14:0	3,9±0,4	+1,5±0,2	+1,0±0,1	1,9±,03	+0,1	4,4±0,6	+2,2±0,5*
14:1	0,5±0,1	–0,1	–0,2*	0,3±0,1	–0,4	2,3±0,9*	–0,6±0,1*
15:0	5,5±0,3	+0,6±0,1	+0,6±0,1	2,0±0,4	–0,6±0,1	5,8±0,6	–0,9±0,1*
15:1	0,6±0,2	–0,1	–0,9±0,1*	0,1	–0,2	1,4±0,3	+0,9±0,1*
16:0	14,7±0,8	–2,1±0,4	–0,5±0,1*	18,2±2,2	–1,3±0,3	10,3±0,9*	+1,1±0,1*
16:1	2,6±0,3	–1,3±0,2	–1,5±0,2	5,8±0,8	–2,7±0,6*	2,7±0,3*	–1,0±0,1
17:0	3,7±0,1	–1,0±0,2	–1,1±0,2	0,4±0,1	+1,9±0,5*	4,1±0,5	+0,5±0,1*
17:1	1,4±0,4	+0,6±0,1	+0,6±0,1	1,2±0,3	+0,1	1,4±0,4	+0,4±0,1,
18:0	9,7±1,9	–2,4±0,2	–0,3*	14,0±1,8	+1,2±0,2	14,9±1,9	–0,1
18:1	17,1±2,0	+3,8±0,3	+4,3±0,7	22,6±1,4	+2,2±0,9	11,9±1,4*	+0,4±0,1
18:2	10,1±1,4	–1,0±0,1	–1,5±0,2*	12,0±1,2	+1,1±0,2*	8,7±0,5*	–3,8±0,5*
18:3	1,0±0,1	–0,3	+0.4*	1,9±0,3	+0,1	1,6±0,7	–0,2
20:1	0,9±0,1	+0,1	–0,4±0,1*	0,4±0,1	+0,2	1,1±0,4	+0,2
20:2	1,1±0,1	–0,7±0,1	–0,3*	0,5±0,1	–0,1	2,4±0,3	–0,7±0,1
20:3	0,2	–0,2	+0,1	0,8±0,2	+0,2	0,8±0,2	+0,3*
20:4	4,3±0,4	+0,3	+0,3	7,5±0,9	+0,9±0,1	6,0±0,1	+0,1*

Legend. *P < 0.05 compared with group 1. THB – SHB) Difference between concentrations of acids in lipids in blood flowing to and from the heart.

donors' blood with adrenalin, and heating of the animals. At different stages of the experiments the pericardium was divided and samples were taken successively from blood flowing toward the heart (THB), from the orifice of the aorta, blood flowing from the heart (SHB) from the coronary sinus when the dogs were cooled to 30-28°C at the 60th minute of ischemia and at the height of reheating of the animals (rectal temperature 35-36°C). The control series (intact dogs) consisted of animals from which blood for investigation was taken under normothermic conditions, and with the same anesthesia as was used in the previous series. The blood gutimin concentration was determined by a method developed by the writers themselves [5]. Blood for subsequent determination of fatty acids in the composition of total lipids was treated by the method of Sinyak et al. [7]. Acids were analyzed by gas chromatography [2], with temperature programming from 75 to 185°C with intervals of 6°C/min. The results were expressed in percent.

The experimental results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

Altogether 27 acids were found in the blood of the intact dogs, of which six together accounted for more than 70% of the total (15:0, 16:0, 18:0, 18:1, 18:2, and 20:4), another seven acids together accounted for 20% of the total (saturated acids with from 10 to 14 carbon atoms, 17:0, and a monoenic acid, 16:1). Analysis of the composition of the fatty acids in THB and SHB revealed assimilation of four acids (12:0, 14:0, 16:0, and 18:1) by the dogs' myocardium and an increase in the excretion of acids 16:1, 17:0, 18:3, and 20:2 (group 1) with the venous blood (Table 1).

The absolute content of fatty acids in THB and SHB of dogs cooled to 30-28°C was increased, as a result of activation of lipolysis which accompanies hypothermia. However, the over-all level of fatty acid uptake was unchanged and there was no difference in the arteriovenous difference between the total fatty acid concentrations in THB and SHB. The result of cooling of the animals was reorganization of more than 50% of the fatty-acid composition of lipids in THB and SHB: the quantity of certain monoenic and polyenic acids was increased, the relative percentage of saturated acids with between 8 and 14 carbon atoms (i.e., those rapidly synthesized and most mobile in metabolism, mainly with an active role in cell bioenergetics) was reduced. Meanwhile the acids taken up by the heart were mainly the same as in the control, but other acids were not excreted in large amounts with the SHB, namely 8:0, 9:0, and 12:0. Less of the 14:1, 15:1, and 18:2 acids was retained in the heart, although their absolute levels remained high, and more of the 18:3 acid was retained, due to its assimilation (group 2).

Analysis of the results shows that cooling animals to 30-28°C causes reorganization of fatty acid metabolism in the heart muscle.

The continuing cardiac contractions, with a frequency of 45 ± 7 beats/min, for 13-19 min after disconnection of the heart from the circulation in dogs with moderate hypothermia and the subsequent asystole led primarily to mixing of THB and SHB, as a result of which the composition of the fatty acids in these two types of blood became the same, but they also caused changes in the composition of the fatty acids. Compared with data obtained before occlusion, there was an increase in the content of acids 11:0, 13:0, and 20:4 in the blood, and a decrease in the content of seven acids: the saturated acid 17:0, the monoenic acids 14:1, 15:1, 17:1, and 20:1, and the polyenic acid 20:2 (group 3).

Restoration of cardiac activity after 60 min of ischemia and rewarming of the animals led to assimilation of acids 10:0, 17:0, and 18:0 and to an increase in the excretion of acids 11:0 and 16:1 with the SHB (group 4). Compared with results obtained at the end of occlusion, the composition of the fatty acids in THB and SHB was characterized by an increase in the content of four saturated acids – 8, 9, 10, and 17, of three monoenic acids – 14, 15, and 20, and of the essential polyenic acids 18:2 and 20:4. The content of acids 16:0, 17:1, 18:1, and 18:3 was reduced. The level of essential acids 18:2 and 20:4 in the blood was raised much more than in the control, but their uptake by the heart was not observed. The absolute content of fatty acids in the dogs' blood at the height of rewarming was higher than during cooling of the animals to 30-28°C. There were substantial differences from the control in the uptake of fatty acids by the myocardium during rewarming of the dogs, and the control values of uptake were observed in the case of only two acids (15:1 and 18:1, group 4).

Consequently, myocardial ischemia (60 min) under conditions of moderate hypothermia, and rewarming of the animals were accompanied by fatty acid metabolism (uptake) in the heart muscle that was inappropriate for those conditions. An attempt was accordingly made to influence fatty acid metabolism by means of the antihypoxant gutimin, whose effect on several parameters of metabolism proved to be highly positive in the corresponding experiments [6].

Preventive administration of gutimin to the dogs prolonged the period of work of the heart after application of tourniquets to the atrial veins compared with the control. According to our observations the maximal gutimin concentration in the blood of the dogs (3.55 mg/liter) was observed 15.5 min after its injection. Only traces of gutimin were detected in the blood after 60 min. As a result of administration of gutimin the concentration of 11 acids in the blood were increased (group 5). Meanwhile the levels of acids 16:0, 16:1, and 18:1 fell (to 50%), as also did the concentrations of acids 18:2 and 20:4. At the height of rewarming in animals receiving gutimin (group 6) the quantity of acids with between 8 and 15 carbon atoms increased considerably (by 2-3 times), the levels of acids 18:3 and 20:2 rose, whereas the concentrations of acids 14:1, 17:0, 18:2, and 20:4 decreased compared with the control at the same stage of the investigation. The heart assimilated more of seven acids, of which those taken up by the greatest degree were the saturated acids 10, 12, 13, and 14, and the monoenic acid 15:1. Large quantities of five acids (group 6) were excreted with SHB. Compared with the control, assimilation or excretion was found to be in the same direction for 10 of the 27 acids detected in the blood, and the data for five of these acids were close to the control values – 11:0, 12:0, 16:1, 17:1, and 20:2.

Preventive administration of gutimin to dogs before disconnection of the heart from the circulation thus activated fatty acid metabolism in the animals and in the heart itself. The content of saturated fatty acids with a small number of carbon atoms in the blood was increased, active uptake of several acids by the myocardium was observed, and the blood levels and assimilation of several polyenic acids, some of them essential, were reduced. This last fact is of great importance for the present experiments, for the appearance of linoleic (18:2) and arachidonic (20:4) acids in the blood in large quantities points to a profound reorganization of lipid metabolism in the body, destruction of cell membranes, disturbances of prostaglandin metabolism, and so on [12].

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