PROTECTIVE ACTION OF LITHIUM HYDROXYBUTYRATE ON THE ISCHEMIC MYOCARDIUM

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It was shown previously that GABA derivatives sodium hydroxybutyrate and pyracetam, which are antioxidants, have a marked anti-ischemic action on models of experimental myocardial ischemia and delay the development of ischemic heart damage [1, 6, 7].

The aim of this investigation was to study the antianoxic and anti-ischemic properties of another GABA derivative, namely lithium hydroxybutyrate (LHB).

EXPERIMENTAL METHOD

To study the antianoxic action of the compound experiments were carried out on noninbred albino mice under anoxic conditions induced by ligation of the trachea [8]. LHB activity was judged by the duration of preservation of cardiac potentials and the number of animals whose cardiac electrical activity was preserved for more than 10 min. The compound was injected intraperitoneally in a dose of 500 mg/kg 15 min before the state of anoxia developed. To assess the anti-ischemic activity of LHB a model of acute coronary insufficiency was created in anesthetized cats. The degree of ischemia was judged from the mean elevation of the ST segment on the epicardial ECG, recorded on the Mingograf 81 instrument [6]. Experiments were carried out on cats anesthetized with pentobarbital sodium (40 mg/kg, intravenously) to study the effect of LHB on the rate of rise of creatine phosphokinase (CPK) activity in blood from the coronary sinus, during occlusion of the anterior descending branch of the left coronary artery in its middle third for 60 min. Blood samples were taken before and 20, 30, 45, and 60 min after occlusion of the coronary artery. The blood plasma CPK activity was determined by means of kits from "Chemapol" (Czechoslovakia). In these same experiments the ATP concentration was determined in the ischemic and conventionally intact myocardium by the method in [12]. LHB was injected immediately after occlusion of the coronary artery in a dose of 200 mg/kg. There were two series of experiments, with six animals in each. To study the effect of LHB on the blood supply of the ischemic myocardium, experiments were carried out on dogs weighing 12-20 kg, anesthetized with pentobarbital sodium (40 mg/kg, intravenously). The retrograde blood supply to the ischemic focus and the blood flow in intact regions of the heart muscle were recorded simultaneously in these animals [7]. The true collateral blood flow in the ischemic zone was calculated by the formula given in [14]. The compound was injected intravenously in a dose of 200 mg/kg 30 min after coronary occlusion, when the systemic arterial pressure (BP) and parameters of the blood supply to the ischemic myocardium had stabilized and remained constant over a long period of time [9, 10]. The experimental results were subjected to statistical analysis by Student's t test, Wilcoxon's test for paired comparisons, Fisher's exact test, and Theil's and Hollander's corner tests.

EXPERIMENTAL RESULTS

LHB protected the myocardium to a considerable degree against the efects of anoxia: the duration of preservation of cardiac potentials was increased under these conditions from 481.3 ± 49.8 to 1032.8 ± 133.1 sec ($p < 0.01$). The number of animals in which cardiac electrical activity continued for more than 10 min was increased also. Whereas this activity was preserved in 3 of 13 animals in the control, in the series receiving prophylactic

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TABLE 1. Effect of LHB (200 mg/kg, intravenously) on Blood Supply of Intact and Ischemic Zones of Myocardium (in % of initial level; M ± m, n = 5)

Parameter	Background	Time after injection of compound, min				
		2	5	10	20	30
Mean BP, mm Hg	96,7±6,7	+10,1±5,8	+15,6±5,1*	+16,2±3,9*	+17,0±5,6*	−0,3±3,5
Retrograde perfusion pressure, mm Hg	35,2±4,8	+13,7±9,4	+14,0±6,7	+15,8±6,4	+13,3±7,6	+0,8±5,6
Blood flow in circumflex branch of left coronary artery, ml/min	18,2±4,8	+32,0±8,8*	+29,2±5,8*	+30,0±5,1**	+6,1±3,1	−12,3±5,0
Retrograde blood flow, ml/min	1,63±0,38	+33,6±6,0*	+36,5±6,2**	+25,0±8,6	+16,4±4,2*	−1,6±5,9
True coronary collateral blood flow, ml/min	0,80±0,12	+27,5±1,7***	+36,6±5,0***	+23,9±6,2*	+16,7±2,4**	−3,0±6,0

Legend. *p < 0.05; **p < 0.01; ***p < 0.001.

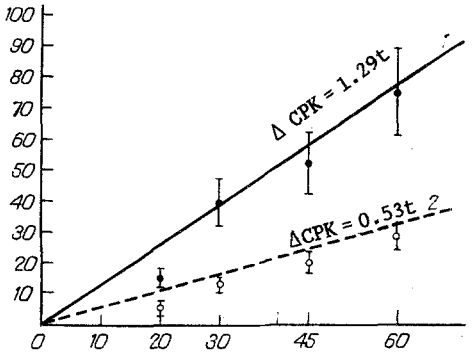

Fig. 1. Effect of LHB (200 mg/kg, intravenously) on rate of rise of CPK level in blood from coronary sinus during occlusion of coronary artery for 60 min in anesthetized cats. Abscissa, duration of coronary occlusion (in min); ordinate, increase of CPK activity (in U/liter). 1) Control, 2) experiment.

LHB it was preserved in 8 of 10 animals ($p < 0.05$). These data are in agreement with observations of other workers [2, 3], who also showed on other models of anoxic states that LHB possesses quite strong antianoxic properties.

However, the fact that a substance possesses antianoxic properties still does not mean that it must also have an anti-ischemic action in a situation of coronary arterial occlusion. To study this question, experiments were carried out on a model of acute coronary insufficiency in anesthetized cats. They showed that LHB, only 5 min after injection, reduced the average rise of the ST segment on the epicardial ECG during occlusion of the coronary artery for 5 min. Whereas in the control the mean rise of the ST segment 1, 3, and 5 min after the beginning of coronary occlusion was 7.1 ± 1.1, 10.9 ± 2.0, and 11.8 ± 2.3 mV respectively, 5 min after injection of LHB it was reduced to 5.7 ± 1.1, 8.7 ± 1.4, and 9.1 ± 1.4 mV respectively ($p < 0.05$). The action of the compound lasted 25-30 min.

The electrophysiological data were confirmed by biochemical tests. LHB considerably reduced the rate of rise of CPK activity in blood from the coronary sinus during occlusion of the coronary artery for 60 min in cats. In the control and experimental series (Fig. 1) the linear regression coefficients were 1.29 and 0.53 respectively ($p < 0.05$).

We know that elevation of the ST segment on the epicardial ECG and a rise of CPK activity in blood flowing from an ischemic focus are significant indicators of the severity of ischemic damage. Considering the results of the present investigations, it can be concluded that LHB improves the functional state of an ischemic focus in the myocardium and delays the transition from reversible into irreversible ischemic damage. This conclusion is confirmed by the results of our experiments in which the ATP concentration was recorded in the cat myocardium after occlusion of the coronary artery for 60 min. Under these conditions LHB was found to increase the ATP concentration both in the conventionally intact (from 2.72 ± 0.06 to 4.83 ± 0.21 μmoles/g; $p < 0.001$) and in the ischemic (from 1.25 ± 0.07 to

1.76 ± 0.11 μmoles/g; $p < 0.01$) zone of the myocardium. Lowering of the ATP reserves is the chief determinant of irreversible ischemic damage and is used as a criterion of the severity of the process [11, 13]. Taking this into account, it can be postulated that LHB improves the functional state of the cardiomyocytes in the ischemic zone.

The writers showed previously that an important role in the anti-ischemic effect of antianoxic agents is played by their influence on the blood supply directly to the focus of myocardial ischemia [7]. An increase in the blood supply of the ischemic zone permits the more rapid removal of metabolic products from it, and thereby abolishes the inhibitory effect of these products on energy formation [4, 5]. Our own experiments on dogs showed that LHB considerably increases the blood supply to both the intact and the ischemic zone of the myocardium. Under these circumstances it is very important that the true collateral blood flow in the ischemic focus is increased for a long time (Table 1).

The antianoxic agent LHB thus has a protective action on the ischemic myocardium, and an important role in this effect is evidently played by its ability to strengthen the coronary collateral circulation.

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