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EFFECT OF SODIUM HYDROXYBUTYRATE ON BLOOD SUPPLY AND ACTIVITY OF THE INTACT AND ISCHEMIZED MYOCARDIUM

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KEY WORDS: sodium hydroxybutyrate; coronary blood flow; intact and ischemized myocardium.

Because of the experimental and clinical evidence that sodium hydroxybutyrate has a marked antihypoxic action [1, 6, 8, 11, 12] it could be expected that it would also have an antianginal effect. Clinical trials have shown, for example, that the compound abolishes painful episodes in patients with acute myocardial infarction and with severe attacks of angina [7, 10]. However, until recently the problem of the effect of sodium hydroxybutyrate (SHB) on the blood supply and activity of the heart had received little study. The investigation described below was carried out in an attempt to fill this gap.

EXPERIMENTAL METHOD

To judge the effect of SHB on the blood supply of the intact myocardium two series of experiments were carried out on cats weighing 2-3 kg, anesthetized with pentobarbital (30 mg/kg, intravenously). SHB was injected intravenously in a dose of 100 mg/kg in the experiments of series I (five animals) and in a dose of 200 mg/kg in the experiments of series II (six animals). The blood supply of the heart was judged from the flow of blood from the coronary sinus [2]. The uptake of oxygen by the heart was determined simultaneously by measuring the arteriovenous oxygen difference photometrically, using a type 036M oxyhemograph.

In the next two series of experiments on cats anesthetized with pentobarbital the effect of SHB on activity of the intact myocardium was studied. An electromagnetic method was used to measure the blood flow in the ascending part of the arch of the aorta by means of a Soviet RKE-1 flowmeter. The following parameters of cardiac activity and the hemodynamics

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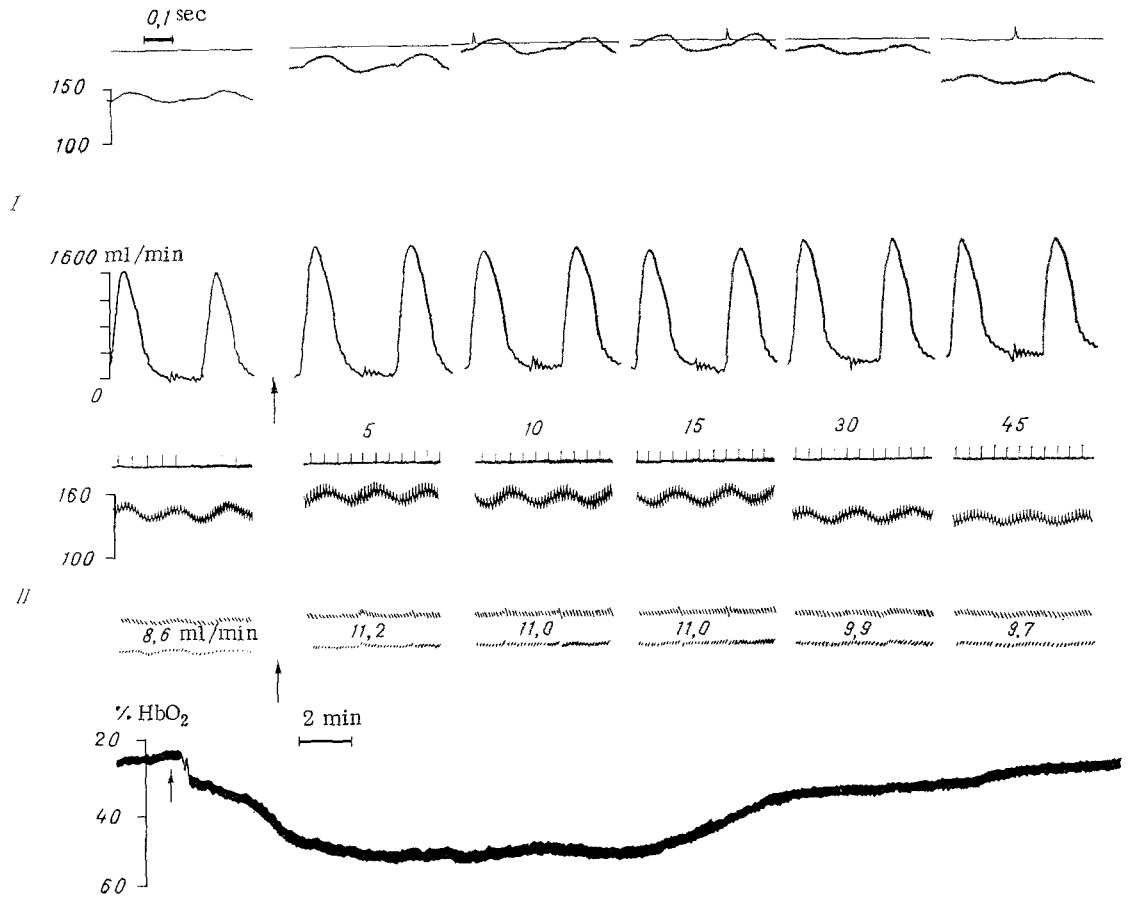

Fig. 1. Effect of SHB on activity and blood supply of intact myocardium. I) Effect of SHB on cardiac activity and hemodynamics. From top to bottom: time marker, blood pressure in carotid artery, phasic blood flow in ascending part of arch of aorta. From left to right: before injection, 5, 10, 15, 30, and 45 min after injection of SHB in a dose of 200 mg/kg; II) effect of SHB on coronary blood flow and oxygen uptake of the heart. From top to bottom: time marker, blood pressure in carotid artery, oxyhemoglobin (HbO_2) concentration in blood of coronary sinus. Arrow indicates injection of SHB in a dose of of 200 mg/kg.

TABLE 1. Effect of SHB (200 mg/kg intravenously) on Activity of Intact Myocardium and State of Hemodynamics (changes in %; M ± m, n = 6)

Parameter of hemodynamics	Background level	Time after injection of SHB, min				
		5	10	15	30	45
Arterial pressure, mm Hg	114,6±9,7	+11,2±4,3*	+11,3±3,9*	+5,3±2,4	−6,2±8,1	−12,4±7,6
Heart rate, beats/min	178,2±7,4	−3,0±2,4	−1,8±4,8	−0,1±5,2	+0,8±6,8	−1,5±5,9
Systolic ejection, ml	2,2±0,24	+43,6±5,5†	+29,3±5,0†	+16,4±7,2	+13,1±4,2*	+1,9±7,6
Cardiac output, ml/min	402,0±23,9	+39,2±6,1†	+26,4±6,4†	+16,0±8,3	+13,2±6,7	−0,6±6,2
Maximal acceleration of blood flow, cm/sec²	1172,5±112,4	+27,1±11,4	+21,3±9,3	+29,0±12,2	+40,2±13,2*	+27,4±10,0*

*P < 0.05.
†P < 0.01.

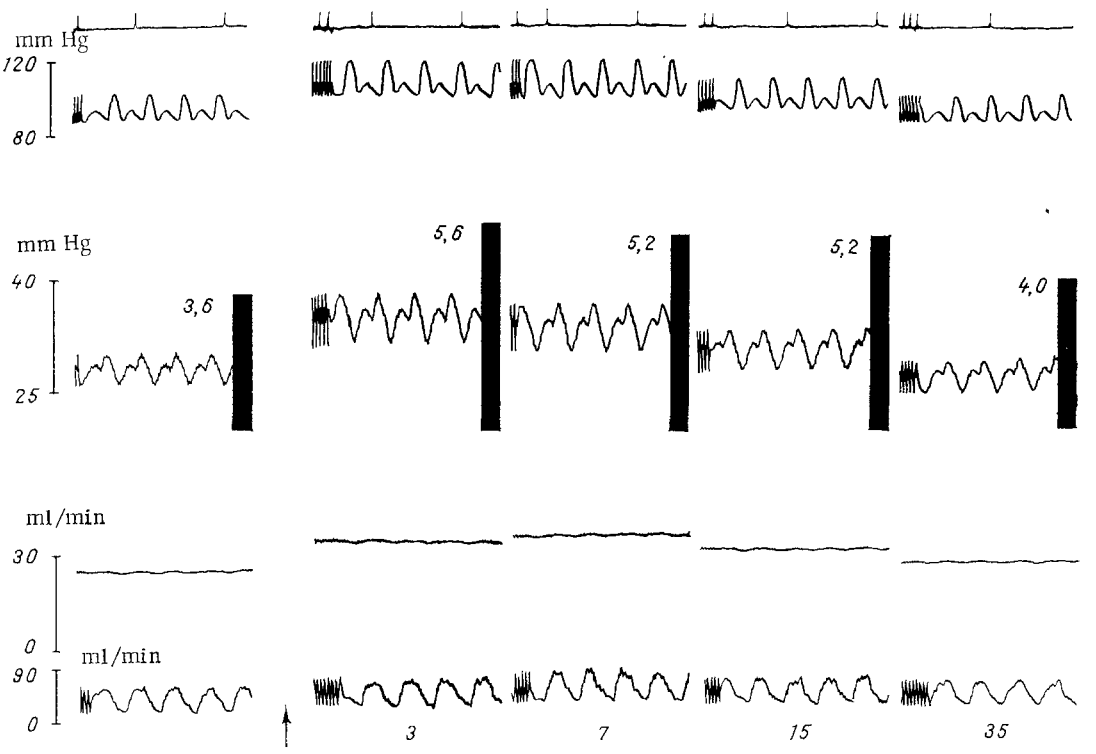

Fig. 2. Effect of SHB on blood supply to focus of ischemia and redistribution of blood flow in myocardium. From top to bottom: time marker, blood pressure in carotid artery, columns denote retrograde blood flow in territory supplied by ligated anterior descending branch of left coronary artery (in ml/min), retrograde perfusion pressure, averaged blood flow in circumflex branch of left coronary artery, phasic blood flow in circumflex artery. From left to right: before injection, 3, 7, 15, and 35 min after injection of SHB in a dose of 200 mg/kg. Arrow indicates time of injection of SHB.

TABLE 2. Effect of SHB (200 mg/kg intravenously) on Activity of Ischemized Myocardium and State of Hemodynamics (changes in %; M ± m, n = 4)

Parameter of hemodynamics	Background level	Time after injection of SHB, min				
		5	10	15	30	45
Arterial pressure, mm Hg	100,6±9,1	+12,9±2,3†	+11,8±1,6†	+9,2±2,0*	+4,7±2,3	+2,6±1,5
Heart rate, beats/min	144,5±5,1	−2,8±2,7	−1,8±1,3	+3,0±3,4	+3,7±3,1	−1,0±1,5
Systolic ejection, ml	10,2±0,05	+35,7±8,3*	+29,3±3,6†	+20,4±5,1*	+11,4±4,0	+3,9±1,9
Cardiac output, ml/min	1390,7±87,8	+27,9±7,9*	+26,1±2,12†	+19,1±3,0†	+10,5±2,6*	+2,6±1,9
Maximal acceleration of blood flow, cm/sec^2	983,3±60,9	+26,9±4,6†	+15,3±4,6*	+10,1±3,4*	+7,1±4,2	3,6±2,3

*P < 0.05.
†P < 0.01.

were recorded: the arterial blood pressure, pulse rate, systolic ejection, cardiac output, and the maximal acceleration of the blood flow caused by the contracting left ventricle [9].

To judge the effect of SHB (200 mg/kg, intravenously) on the blood supply and activity of the ischemized myocardium experiments were carried out on nine dogs in which the anterior descending branch of the left coronary artery was ligated in its middle third. The retrograde coronary blood flow and retrograde pressure in the territory supplied by the ligated artery were recorded. In five dogs the volume velocity of the coronary blood flow was measured in the circumflex branch of the left coronary artery, supplying blood to intact zones of the myocardium, simultaneously with recording of the retrograde blood flow by an ultrasonic method

[3, 4]. In this way the effect of SHB could be judged on the redistribution of blood between the focus of ischemia and the intact zones of the myocardium. In four dogs simultaneously with measurement of the retrograde blood supply to the focus of ischemia, the blood flow in the ascending part of the arch of the aorta was recorded by an electromagnetic method, to enable the effect of SHB on cardiac activity to be determined.

The parameters of cardiac activity under hemodynamics and also of the blood flow were recorded on a Minograph 81 apparatus.

EXPERIMENTAL RESULTS

The experiments showed that the SHB causes a marked increase in the volume velocity of the coronary blood flow in the intact myocardium. The effect of SHB was manifested immediately after injection and was observed for 20-40 min. The maximal increase in the coronary blood flow after injection of SHB in doses of 100 and 200 mg/kg was observed at the 5th-10th minute and amounted to 30.4 ± 7.6% ($P < 0.05$) and 45.1 ± 4.7% ($P < 0.001$) respectively. The increase in the coronary blood flow during the first 10-20 min was accompanied by slight hypertension (on average by 16.2 ± 2.8 mm Hg; $P < 0.01$), after which the systemic arterial pressure gradually returned to normal although the coronary blood flow remained high. In both series of experiments, incidentally, the increase in the coronary blood flow under the influence of SHB was accompanied by an increase in the oxyhemoglobin concentration in blood from the coronary sinus. After administration of SHB in a dose of 100 mg/kg it was 8.2 ± 3.4% ($P < 0.05$), and in a dose of 200 mg/kg it was 13.7 ± 3.5% ($P < 0.05$). For 20-30 min after its injection SHB increased the myocardial oxygen uptake, but by a much lesser degree than the velocity of the coronary blood flow. For instance, in doses of 100 and 200 mg/kg SHB increased the oxygen uptake of the heart by 17.1 ± 5.4% ($P < 0.05$) and 14.3 ± 9.8% ($P < 0.05$) respectively. Consequently, sodium hydroxybutyrate creates a definite oxygen reserve for the heart. In this respect SHB has an action similar to that of typical antianginal agents. The data given above agree with observations of other workers who showed that SHB protects the heart muscle against hypoxia and anoxia [1, 6, 8, 11].

SHB increased the systolic ejection and cardiac output of the intact myocardium and significantly increased the maximal acceleration of the blood flow in the aorta, evidence of strengthening of the contractile function. Under these circumstances the heart rate was slowed, but not statistically significantly. In a dose of 200 mg/kg SHB had a more marked and prolonged effect (Fig. 1; Table 1). These data are in agreement with experimental and clinical observations made by other workers, who also showed that SHB leads to some slowing of the pulse and elevation of the arterial pressure, especially when the pressure was initially low [1, 5, 7].

The increase in the contractile function of the heart muscle under the influence of SHB was not connected with stimulation of β-adrenergic structures, for practolol, injected in a dose of 15 mg/kg, did not prevent strengthening of the contractile function of the myocardium induced by SHB. Bilateral vagotomy likewise did not abolish the potentiating action of SHB on contractility of the heart muscle. Consequently, the positive inotropic action of SHB was not connected with its effect on the autonomic innervation of the heart.

SHB had a significant effect on the blood supply and activity of the ischemized myocardium. It increased the retrograde inflow of blood to the ischemic focus (on average by 49.4 ± 9.0%; $P < 0.01$) and the retrograde perfusion pressure (on average by 26.1 ± 3.5%; $P < 0.01$). The effect reached a maximum 5-10 min after injection of SHB and lasted 30-40 min. Simultaneously with an increase in the retrograde blood flow, under the influence of SHB the blood flow also was significantly increased in intact zones of the myocardium (Fig. 2). This increase averaged 65.3 ± 7.6% ($P < 0.01$).

Just as in experiments on the intact heart, under conditions of myocardial ischemia SHB raised the arterial pressure, caused virtually no change in the heart rate, and increased the systolic ejection and cardiac output. In particular, it should be noted that SHB strengthened the contractile function of the myocardium when affected by ischemia. This was shown by the increase in the maximal acceleration of the blood flow in the aorta (Table 2).

SHB thus has a positive action on the blood supply and activity of the intact and ischemized myocardium. These findings must be taken into account when sodium hydroxybutyrate is used clinically.

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EXPERIMENTAL STUDY OF THE EFFECT OF NONACHLAZINE ON METABOLISM OF THE ISCHEMIZED MYOCARDIUM

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KEY WORDS: nonachlazine; experimental myocardial infarction; metabolism; treatment.

The influence of nonachlazine on myocardial metabolism is linked with its antianginal effect [1, 2]. Meanwhile no data are available on the effect of the drug on energy metabolism in the myocardium when given repeatedly over a long period of time. In view of the practical importance of such information, the investigation described below was undertaken.

EXPERIMENTAL METHOD

The anterior interventricular branch of the left coronary artery was ligated in the middle third of its course under aseptic conditions under pentobarbital anesthesia in 73 noninbred dogs of both sexes weighing 8-14 kg. Nonachlazine was injected intravenously in a dose of 1 mg/kg body weight into 35 animals 10 min before this ligation, and daily thereafter. The remaining animals served as the control. The dogs were killed after 2 h, 1, 3, and 6 days, and 3 weeks under pentobarbital anesthesia (40 mg/kg, intrapleurally), and samples of myocardial tissue were taken from the central (infarcted), boundary (transitional), and intact (posterior wall of the left ventricle) zones. Activity of Mg-dependent ATPase and creatine phosphokinase [13] of the tissue homogenates was judged from the increase in the concentration of inorganic phosphorus in the incubation medium; activity of glycogen phosphorylases *a* and b was determined by Ramenskii's method [6]. Succinate dehydrogenase [11] and cytochrome c oxidase [15] activity was investigated in a suspension of mitochondria. Protein was determined by the biuret reaction. Samples of myocardium were fixed in liquid nitrogen; adenine nucleotides were determined by high-voltage electrophoresis on paper [14], and the concentrations of glycogen, creatine phosphate, and inorganic phosphorus were determined by known methods [7]. The energy charge was calculated by Atkinson's formula [12]. The results were subjected to statistical analysis by Student's t test.

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