EFFECT OF SODIUM HYDROXYBUTYRATE ON LACTATE AND PYRUVATE CONCENTRATIONS IN ANOXIA

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Sodium hydroxybutyrate prevented the increase in lactate content developing in the brain and heart under anoxic conditions and also lowered the predominance of lactate over pyruvate characteristic of anoxia.

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Substances minimizing disturbances of tissue respiration under anoxic conditions are of considerable interest in modern anesthesiology. Reports have been published that sodium hydroxybutyrate has a protective action in oxygen deficiency [5, 7]. However, the mechanism of this effect has not yet been studied. The compound was synthesized in 1963 in the Institute of Pharmacology and Chemotherapy, AMN SSSR in 1963. Zakusov and Ostrovskaya [3] showed that this compound increases the survival period of mice kept in an atmosphere with a sharply reduced oxygen concentration.

Against this background we investigated the effect of sodium hydroxybutyrate on the concentration of lactate and pyruvate in the brain and heart tissues of animals under anoxic conditions.

EXPERIMENTAL METHOD

Experiments were carried out on albino mice weighing 20 g. The 22 mice of series I, not exposed to anoxia and not receiving sodium hydroxybutyrate, acted as controls. The 9 animals of series II received sodium hydroxybutyrate intraperitoneally in a dose of 500 mg/kg. The mice of series III and IV (13 and 17

TABLE 1. Effect of Sodium Hydroxybutyrate on Lactate and Pyruvate Concentrations (in mg%) in the Brain and Myocardium of Mice under Anoxic Conditions (M ± m)

Organ	Conditions	Lactate	Pyruvate	Anoxic excess of lactate
Brain	Control (I)	21,0±0,67	4,1±0,16	
	Hydroxybutyrate (II)	18,0±0,9 $P_{I-II} < 0,02$	5,3±0,31 $P_{I-II} < 0,001$	
	Anoxia (III)	59,7±2,0 $P_{I-III} < 0,001$	8,6±0,24 $P_{I-III} < 0,001$	14,4±2,2 6,3±0,46 $P_{III-IV} = 0,001$
	Hydroxybutyrate + anoxia (IV)	20,8±0,47 $P_{II-IV} < 0,01$ $P_{III-IV} < 0,001$	4,18±0,18 $P_{II-IV} < 0,01$ $P_{III-IV} < 0,001$	
Heart	Control (I)	21,7±0,54	3,74±0,19	
	Hydroxybutyrate (II)	25,3±1,17 $P_{I-II} = 0,01$	6,2±0,29 $P_{I-II} < 0,001$	
	Anoxia (III)	60,8±3,5 $P_{I-III} < 0,001$	6,8±0,44 $P_{I-III} < 0,001$	21,9±3,0 9,7±1,2 $P_{III-IV} < 0,001$
	Hydroxybutyrate + anoxia (IV)	26,0±1,5 $P_{II-IV} > 0,5$ $P_{III-IV} < 0,001$	4,18±0,12 $P_{II-IV} < 0,001$ $P_{III-IV} < 0,001$	

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animals respectively) were exposed to anoxia. For this purpose the mice were placed in exsiccators, which were filled with nitrogen from a cylinder (to the extent of 95% of the volume of the exsiccator) and then hermetically sealed. Since previous observations had shown that the mean life span of mice under these conditions is 21 ± 0.95 min, the animals of both series were kept in the exsiccator for 20 min (the time immediately preceding the onset of anoxic convlusions). No further determinations were made on those animals which developed convulsions before 20 min, because the convulsions themselves cause accumulation of lactic acid. The mice of series III received no premedication before anoxia, but the mice of series IV were given sodium hydroxybutyrate (500 mg/kg) 30 min before being placed in the exsiccator. This was based on the previous observation that the protective action of sodium hydroxybutyrate, in the dose given, against anoxia reaches a maximum between the 30th and 60th minutes. All the animals were decapitated, and the heart and brain were frozen in liquid nitrogen and homogenized. Proteins were precipitated with trichloroacetic acid. Lactate concentration was determined by the method of Barker and Summerson [6], and the pyruvate concentration by the method of S. D. Balakhovskii and I. S. Balakhovskii [1].

EXPERIMENTAL RESULTS AND DISCUSSION

Comparison of the lactate and pyruvate contents in the animals of series I and II showed that sodium hydroxybutyrate causes some decrease in the lactate content and a slight increase in the pyruvate content in brain tissue. In heart tissue the content of both substances was slightly increased (Table 1).

Anoxia (series III) caused a marked increase in the lactate level and a less marked increase in the content of pyruvate. After the preliminary administration of sodium hydroxybutyrate, despite the fact that the animals were kept under anoxic conditions (series IV), their lactate concentration hardly increased at all, while their pyruvate concentration fell slightly. Elevation of the lactate level is known to be the result of an inadequate supply of oxygen to the tissues [2, 4], because of which the pyruvate, which in the presence of oxygen is included in the Krebs' cycle, under anaerobic conditions is converted into lactate, forming what Huckabee [8] has called the anoxic lactate excess. To calculate the anoxic lactate excess, this worker suggested the following formula:

$$xL = (L_{20} - L_0) - (P_{20} - P_0) \cdot \frac{L_0}{P_0},$$

where xL represents the anoxic lactate excess, L_{20} the lactate concentration (in mg%) at the 20th minute of inhalation of the anoxic mixture, L_0 the initial lactate level during inhalation of air, and P_{20} and P_0 the corresponding values for pyruvate.

According to this formula, the value of xL for animals exposed to anoxia (series III) was 14.4 ± 2.2 mg% for the brain tissue and 21.9 ± 3 mg% for the heart tissue. Meanwhile, for animals kept under anoxic conditions after administration of sodium hydroxybutyrate, the value of xL for the brain tissue was only 6.3 ± 0.46 mg% and for the heart tissue 9.7 ± 1.2 mg%. These calculations show that the preliminary administration of sodium hydroxybutyrate reduced the accumulation of an anoxic lactate excess to less than half. The resulting decrease in the degree of metabolic acidosis is perhaps one cause of the protective action of sodium hydroxybutyrate under anoxic conditions.

The other possible mechanisms of the protective effect of this compound require further study.

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