EFFECT OF GUTIMIN ON LACTIC ACID UTILIZATION

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Experiments on rats and rabbits showed that gutimin in a dose of 100 mg/kg increases the utilization of lactic acid whether formed by anaerobic metabolism (hypoxic hypoxia and traumatic shock) or if administered from outside. The more rapid removal of lactate from animals protected with gutimin takes place without any substantial increase in the oxygen consumption.

Previous investigations [1] showed that gutimin (a substance with a marked protective action in acute forms of hypoxia) increases the intensity of glycolysis in the brain under normal conditions and, in particular, if the partial pressure of oxygen is lowered. The increase in energy production in the course of anaerobic carbohydrate metabolism can be regarded as one component of the mechanism of the antihypoxic action of gutimin. However, if the oxygen supply is considerably restricted, glycolysis cannot support life for any length of time because of the accumulation of incompletely oxidized products, chiefly lactic acid. Consequently, increased resistance of the animal to hypoxia by the activation of glycolysis is possible only if lactate elimination is provided for.

In the investigation described below the effect of gutimin was studied on the lactic acid concentration in various tissues during high-altitude hypoxia and traumatic shock, in whose genesis a leading role is also ascribed to hypoxia. Special experiments also were carried out to test the utilization of lactic acid after administration of sublethal doses of lactate (lactate loading) to animals, and the lactate dehydrogenase (LDH) activity also was determined.

EXPERIMENTAL METHOD

Experiments were carried out on male rats weighing 160-280 g. Gutimin was injected intraperitoneally in a dose of 100 mg/kg 1 h before exposure to hypoxia. High-altitude hypoxia was created in a pressure chamber by taking the rats to an "altitude" of 10 km and exposing them to this altitude for 1.5 h. Traumatic shock was produced by Cannon's method (by crushing the soft tissues of the thigh). The animals were decapitated 30 min after injury. The lactic acid concentration was determined in the blood and organs (frozen with liquid oxygen) by the method of Barker and Summerson [4] in Ström's modification [9]. Lactate loading was produced by means of lithium lactate, which was injected intravenously into the intact rabbits in a dose of 500 mg/kg and intraperitoneally into the rats in a dose of 700 mg/kg. In the experiments on rabbits the dynamics of the fall in the blood lactic acid level (blood taken from the common carotid artery) was studied 10, 20, 30, 60, and 90 min after the injection. Lactic acid was determined in the rats of this series once only, 30 min after the injection of the lactate. The oxygen consumption of these rats under normal conditions, 1 h after the injection of gutimin, and 30 min after lactate loading was measured with a Miropol'skii apparatus. The total LDH activity was determined spectrophotometrically by recording changes in the optical density of the solution, reflecting the decrease in the NAD·H_2 content in the presence of pyruvate. Activity was calculated by the formula: activity = (4820 × E × dilution)/weight of sample (in mg) units, where 4820 is a conversion factor and E the decrease in extinction in 1 min.

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TABLE 1. Effect of Gutimin on Lactic Acid Concentration in the Tissues during Hypoxic Hypoxia and Shock (M ± m)

Conditions	Lactic acid concentration				
	in mmoles/kg wet weight of tissue				in mM
	brain	heart	liver	kidneys	blood
Control	2,80±0,10	5,12±0,19	5,59±0,11	3,49±0,16	1,20±0,08
Gutimin	2,49±0,12	5,47±0,14	6,14±0,27	3,70±0,20	1,20±0,07
Hypoxia	4,71±0,21	6,65±1,47	7,63±0,82	—	10,47±1,01
Gutimin + hypoxia	3,65±0,12	7,37±1,0	6,55±0,69	—	7,53±0,96
Shock	4,86±0,19	6,97±0,34	8,68±0,32	11,85±0,51	9,70±0,65
Gutimin + shock	3,66±0,16	6,86±0,41	7,24±0,38	7,16±0,48	6,55±0,31

TABLE 2. Effect of Gutimin on Total LDH Activity (M ± m)

Conditions	LDH concentration			
	in units/mg wet weight of tissue			in units/ml
	brain	heart	muscles	blood serum
Control	713,2±81,2	3689,2±240,5	5192±287,1	366,5±21,5
Hypoxia	586,5±63,5	3821,6±272,0	5378,1±306,0	988,1±91,7
Gutimin + hypoxia	1428,3±161,1	4327,1±291,5	5892,1±321,9	525,7±58,6

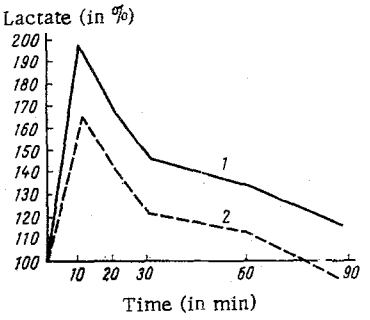

Fig. 1. Effect of gutimin on utilization of lactic acid by rabbits after receiving sublethal doses of lactate: 1) lactic acid consumption by control animals; 2) lactic acid consumption by animals previously receiving gutimin.

EXPERIMENTAL RESULTS AND DISCUSSION

As Table 1 shows, during procedures such as hypoxia for 1.5 h and traumatic shock a marked increase in the lactic acid concentration was observed in all tissues. In the animals protected with gutimin there was a much smaller accumulation of lactate. This decrease was most marked ($P < 0.001$) in the brain, kidneys, and blood, but no significant changes were found in the heart and liver.

The dynamics of lactic acid utilization after intravenous injection of lithium lactate intc rabbits is shown in Fig. 1. In rabbits previously given gutimin the removal of the excess of lactate took place much more rapidly.

The experiments on rats also showed that 30 min after lactate loading the lactic acid concentration in the control animals was 230% of its initial level (from 1.2 ± 0.12 to 2.76 ± 0.3 mg%), whereas in animals previously receiving gutimin the blood lactic acid concentration was increased by only 166% of its initial level (from 1.2 ± 0.12 to 1.99 ± .21 mg%). Whereas in the control animals the utilization of lactate was accompanied by a marked increase in the oxygen consumption – on the average from 33.2 ± 2.4 to 42.3 ± 2.7 ml/100 g in 10 min (by 28%) – under the influence of gutimin the more rapid lactate utilization led to virtually no increase in the oxygen consumption. The general level of oxygen consumption, lowered by gutimin from 33.2 ± 2.4 to 23.1 ± 1.6 ml/100 g in 10 min, rose to only 26.1 ± 1.8 ml/100 g in 10 min (by 11%).

Comparison of the changes in total LDH activity (Table 2) showed that under the influence of hypoxia it was reduced in the brain and significantly increased in the blood serum, in agreement with data in the literature on the disturbance of permeability of the cell membranes in hypoxia and the massive outpouring of cytoplasmic enzymes into the blood [2, 6]. In the animals previously given gutimin, on the other hand, there was a large increase in LDH activity in the brain, heart, and muscles, but a smaller increase in its activity in the serum; these observations evidently indicate stabilization of the cell membranes and a reduced outpouring of enzymes into the blood.

Gutimin thus increased the utilization of lactic acid whether formed by anaerobic metabolism or injected from outside. A similar conclusion has been drawn from the results of experiments with ischemia of the isolated liver for 2 h [3].

The results suggest that gutimin not only increases the rate of glycolysis, but also helps to remove its end products, especially lactate, from the body through its more intensive utilization in the Krebs'

cycle. The increased LDH activity in the organs contributes to this process. It is stated in the literature that oxidative phosphorylation can be maintained, even during complete anoxia, either by reversal of the reactions in the dicarboxylic part of the Krebs' cycle (in the succinate–fumarate–malate system) with the accumulation of succinate or by activation of the conversion of ketoglutarate into succinate with substrate phosphorylation during its course [5, 7, 8]. The second pathway of lactate utilization consists of its conversion into glucose and glycogen. This process takes place chiefly in the liver and kidneys where special enzymes of the Cori cycle exist. Evidently gutimin activates this cycle. This hypothesis is confirmed by the results of the experiments on rats, in which the more rapid lactate clearance after administration of gutimin took place without any significant increase in the oxygen consumption.

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