THE EFFECT OF HYPOXIA AND ACTH ON THE CARBOHYDRATE RESERVE IN TISSUES OF THE WHITE RAT

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A number of investigations [1, 2] have shown that when an organism's oxygen supply becomes inadequate, the role of the carbohydrates is the most important, and for some organs the only source of energy increases markedly. Changes that occur in carbohydrate metabolism under these conditions often result in disturbances of other types of metabolism, which may promote fatty infiltration of tissues, accumulation of various incompletely oxidized metabolic products, and even reduction of the potential of high-energy compounds. Metabolic disturbances accompanying oxygen insufficiency continue to remain for some time even after the influences of the reduced partial pressure of oxygen has been removed from the organism. The degree of reversibility of these disturbances largely determines the reaction of the whole organism, as well as of individual organs, to hypoxia. This problem, however, and especially the problem of the state of tissue carbohydrate reserves have been extremely inadequately studied, since the majority of investigations have been concerned with the dynamics of the carbohydrate reserve in only the blood and brain, neglecting the reserves of other tissues.

In addition, such investigations have been conducted, as a rule, in chronic experiments, in which the animals were subjected to the action of hypoxia for many hours and even for several days, and the development of adaptation under these conditions did not permit estimation of early changes in the state of the tissue carbohydrate reserve.

Studies of shifts in metabolism during hypoxia are intimately related to the search for agents and methods capable of stopping these shifts and elevating the organism's resistance to oxygen hunger. Data have recently appeared [4] which indicate that preliminary administration of adrenocorticotropic hormone from the anterior lobe of the pituitary (ACTH) sharply increases the percent survival of animals under conditions of acute oxygen hunger. The causes of this phenomenon are still unclear in many respects.

In the present study, we investigated the degree and persistence of shifts occurring in the carbohydrate reserve of liver, skeletal muscle, and heart of rats, as well as the effect of preliminary injection of ACTH on the dynamics of the carbohydrate reserve in these tissues, under conditions of acute oxygen hunger and afterward.

METHOD

The work was done in a 64-liter pressure chamber on sexually mature male rats weighing 220-250 gm. The animals were subjected to experimentation one at a time, on an empty stomach. The pressure chamber was equipped with inflow - outflow ventilation and a mercury manometer. The pressure within the chamber was held at a level of 180 mm Hg, corresponding to a "height" of 10,500 meters, for an hour. "Ascent" and "descent" were brought about at a rate of 2100 meters per minute. The animals were killed by decapitation under light ether anaesthesia. Tissues to be analyzed were removed as quickly as possible, fixed in liquid oxygen, and ground in a mortar, after which appropriate portions were taken. Glycogen content was determined by means of a color reaction with concentrated sulfuric acid [5], and lactic acid content by means of a color reaction with p-hydroxydiphenyl [6]. In studies of the recovery period (posthypoxic period), after one hour in the pressure chamber the rats were transferred to an environment in which the partial pressure of oxygen was normal. Finally, in a third series of experiments the animals were first injected subcutaneously with two units of ACTH per day for six days. On the seventh day, the animals were subjected to experimentation. The total dose of hormone was 12 units per rat.

RESULTS

In view of the fact that there were sizable individual variations in glycogen and lactic acid content in the tissues, all the numerical material was treated statistically. The mean values obtained are summarized in the table.

Distinctive changes are observed in the state of the tissue carbohydrate reserve in rats preliminarily injected with ACTH. As may be seen from the data in the

Glycogen and Lactic Acid Concentrations in Rat Tissues Under Various Physiological Conditions

Group No.	Experimental conditions	Liver				Skeletal muscle				Heart			
		number of determinations	amount of glycogen (mg %)	number of determinations	amount of lactic acid (mg %)	number of determinations	amount of glycogen (mg %)	number of determinations	amount of lactic acid (mg %)	number of determinations	amount of glycogen (mg %)	number of determinations	amount of lactic acid (mg %)
1	Control	24	4213±252	21	33±2	24	701±21	22	48±3	22	440±15	21	110±4
2	Oxygen hunger ("height" of 10 500 meters; time 60 minutes)	14	987±106	13	90±6	14	540±27	15	124±7	15	426±17	15	160±6
3	Posthypoxic period	15	2301±311	15	25±1	15	590±39	15	40±3	15	456±19	14	114±6
4	Injection of ACTH, normal conditions	10	4240±321	10	36±2	10	745±19	10	44±4	10	429±12	10	96±6
5	Injection of ACTH, oxygen hunger	10	2381±353	10	40±2	10	621±37	10	55±5	10	425±34	10	120±7
6	Injection of ACTH, post-hypoxic period	5	3478±205	5	38±3	5	753±21	5	40±3	5	443±22	5	91±5

Note: Each figure is the mean of values obtained in two parallel experiments.

table, under normal conditions the effect of the hormone on the state of the tissue carbohydrate reserve was almost imperceptible. We observe only a slight increase in the glycogen of skeletal muscle of experimental rats in comparison with the controls. The sensitivity of the animals to injection of hormone under normal conditions is apparently small; in every instance it has no noticeable effect on the tissue carbohydrate reserve. There is only a

slight degree of elevation of lactic acid utilization in skeletal muscles and myocardium, where a tendency toward reduction of lactic acid content is observed. A different picture is seen in oxygen hunger, where preliminary injection of ACTH results in a considerably smaller loss of glycogen by the liver and skeletal muscle, in comparson with animals that did not receive the hormone. But accumulation of lactic acid in this case is markedly reduced. One has the impression that the hormone promotes the preservation of tissue carbohydrate reserves. It is possible that under conditions of oxygen hunger gluconeogenesis from proteins and fats is enhanced in the tissues under the influence of ACTH, and that an inhibitory effect of ACTH on the hexokinase reaction also appears in these circumstances. As a result, the glycogen reserve in liver and skeletal muscle increases. It should be noted, however, that the hormonal effect influences the level of the glycogen reserve in only liver and skeletal muscle, and has no effect on its level in the heart, where only the reduced lactic acid accumulation is seen.

The normalizing effect of the hormone can also be noted in the posthypoxic period, when a considerably greater degree of restoration of the glycogen reserve in the liver and skeletal muscle is clearly displayed. At the same time, the content of lactic acid in liver, skeletal muscle, and heart returns to normal. Thus, preliminary injection of ACTH has a favorable effect on the state of the tissue carbohydrate reserve, reducing depletion of it in hypoxia and hastening restoration of it in the posthypoxic period. In both cases it causes increased utilization of lactic acid by the tissues. Apparently, the typical adaptive effect of this hormone on metabolism is manifested in this case.

It is possible that the increased percent survival of rats preliminarily given ACTH is connected with the normalizing effect of ACTH on tissue carbohydrate reserves, which porbably causes more complete mobilization of tissue compensatory mechanisms that increase the organism's resistance to oxygen hunger.

SUMMARY

The author studied the effect of preliminary ACTH administration of glycogen and lactic acid concentrations in liver, skeletal muscle, and myocardium of male white rats during oxygen deficiency resulting from reduced barometric pressure and in the posthypoxic period. It was shown that preliminary administration of ACTH (with a total dose of 12 units) to rats later subjected to acute oxygen deficiency markedly reduces the fall in glycogen content in liver and skeletal muscle and simultaneously inhibits the accumulation of lactic acid in these organs. It also leads to more rapid restoration of liver and skeletal muscle glycogen reserves, and more complete elimination of excess lactic acid, during the posthypoxic period. Under conditions of hypoxia and posthypoxia, preliminary administration of ACTH has no significant effect on the cardiac glycogen reserve.

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