EFFECT OF SODIUM HYDROXYBUTYRATE ON OXIDATION IN BRAIN TISSUE DURING HYPOXIA

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Experiments on mice showed that sodium hydroxybutyrate increases the intensity of oxidation in the brain tissue during normal respiration and prevents the depression of tissue respiration developing in animals under hypoxic conditions. In this respect sodium hydroxybutyrate differs from typical narcotics and transquilizers. Neither nembutal nor chlorpromazine reduced the degree of depression of tissue respiration due to hypoxia.

A previous investigation [1] showed that sodium hydroxybutyrate, unlike typical narcotics and tranquilizers, stimulates the intensity of oxidation in different parts of the brain. In addition, some of us [2] have shown that administration of sodium hydroxybutyrate increases the survival rate of animals in hypoxia.

It was therefore decided to determine whether the depression of tissue respiration characteristic of hypoxia can be prevented by means of sodium hydroxybutyrate.

EXPERIMENTAL

Four series of experiments were carried out on male albino mice weighing 18-20 g. Series I was the control, and the animals were not exposed to hypoxia and did not receive sodium hydroxybutyrate. Series II included mice receiving sodium hydroxybutyrate intraperitoneally in a dose of 500 mg/kg. As previous investigations showed, this dose of sodium hydroxybutyrate produces the greatest increase in absorption of oxygen [1] and exhibits a protective effect in hypoxia [2].

In the experiments of series III and IV, the mice were exposed to hypoxia. Details of the method used to produce hypoxic conditions were described previously [4]. The mice of series III were controls, and to assess the effect of hypoxia they did not receive sodium hydroxybutyrate, while the animals of series IV were injected with sodium hydroxybutyrate 30 min before being placed in an exsiccator containing a hypoxic mixture. The mice of these series were kept in the exsiccator for 20 min each. After removal from the exsiccator they were immediately decapitated and the brain removed. The intensity of oxidation was studied in the cerebral cortex and brain stem of the mice of all series. The determination was carried out by a manometric method in a Warbug apparatus in Chetverikova's modification [5]. The composition of the incubation mixture was as follows (in mmoles/liter): α-ketoglutaric acid 20, neutralized with NaOH, $MgCl_2$ 10, KCl 13.4, ATP 1, K_2HPO_4 15.

The brain tissue was placed in the incubation mixture in the outer receiver of the Warburg apparatus. The central container was filled with alkali (0.1 ml). The apparatus was placed in an incubator for 30-40 min with constant agitation.

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EXPERIMENTAL RESULTS

The study of oxidation in the control animals showed that the absorption of oxygen by the cerebral cortex was 21 ±2.3 μatoms, compared with 19 ±3.1 μatoms by the brain stem. In mice receiving sodium hydroxybutyrate, the oxygen consumption was considerably increased: in the cerebral cortex to 34 ±4.1 μ atoms and in the brain stem to 27.4 ±3.3 μatoms.

The absorption of oxygen in mice exposed to hypoxia was 9.9 ±1.4 μatoms in the cortex and 7.9 ±1.2 μatoms in the brain stem, i.e., less than half the values obtained during normal respiration.

In the experiments of series IV the intensity of oxidation was investigated during hypoxia after preliminary administration of sodium hydroxybutyrate. Despite the fact that the animals were under hypoxic conditions, the oxygen absorption, although depressed slightly, was not depressed so severely as in the mice of the preceding series, which did not receive sodium hydroxybutyrate. Under these experimental conditions the quantity of oxygen absorbed reached 17 ±1.4 μatoms in the cortex and 18.9 ±2.4 μatoms in the brain stem, i.e., it was close to the control level.

Since sodium hydroxybutyrate, in certain doses, shows features of similarity with narcotics and tranquilizers, comparative tests were carried out to study the effect of nembutal and chlorpromazine on oxidation in brain tissue. These showed that nembutal (50 mg/kg) causes a marked decrease in the absorption of oxygen by brain tissue compared with the control: in the cortex to 6.3 ±1.2 μatoms and in the brain stem to 6.2 ±1.1 μatoms. In mice receiving 50 mg/kg nembutal 30 min before exposure to hypoxic conditions, the depression of respiration in the brain tissue not only was not reduced, as it was after administration of sodium hydroxybutyrate, but it was actually more severe than in the control series. Its value was 6.1 ±0.8 μatoms in the cortex and 5.4 ±0.7 μatoms in the brain stem. After preliminary administration of chlorpromazine, no difference could be found in the oxygen absorption by the brain tissue in animals of series III and IV. Consequently, neither nembutal nor chlorpromazine can prevent the depression of tissue respiration produced by hypoxia. Sodium hydroxybutyrate differs significantly in this respect both from barbiturates and from neuroplegics, for it improves tissue respiration and reduces its depression developing as a result of prolonged hypoxia.

Considering the competitive relationships between aerobic and anaerobic processes of tissue respiration, it is interesting to compare the above results with those described by Ostrovskaya and co-workers [3], who studied the effect of sodium hydroxybutyrate on the content of lactic and pyruvic acids. They found that sodium hydroxybutyrate, under conditions of normal respiration, reduces the latic acid concentration and increases the pyruvic acid concentration, indicating an improvement of aerobic respiration, while under hypoxic conditions it prevents the accumulation of lactic acid, i.e., it reduces the amount of hypoxic excess lactate determined by means of Huckabee's formula [6].

It can be postulated on the basis of these results that one of the causes of the increased survival rate produced by sodium hydroxybutyrate in animals under hypoxic conditions is the prevention of disturbance of oxidative processes in the brain tissue.

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