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PREVENTION OF DISTURBANCES OF CARBOHYDRATE AND OXYGEN METABOLISM OF THE BRAIN AND DEVELOPMENT OF CEREBRAL EDEMA BY ISOTHIOBARBAMINE IN THE EARLY PERIOD AFTER INTRACEREBRAL HEMORRHAGE

M. B. Plotnikov, T. M. Plotnikova, T. V. Yakimova, and A. S. Saratikov

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The pathogenesis of the early posthypoxic period of intracerebral hemorrhage (ICH) is characterized by accumulation of lactate in the brain, with its discharge into the venous blood, and also by the onset and progressive development of edema and swelling of the brain [7, 8]. Lactacidosis of brain tissue is one of the foremost damaging factors in acute cerebrovascular disturbances; it stimulates autolysis, it severely restricts activity of enzymes of brain energy metabolism, and promotes the development of edema [5, 13, 14]. In patients with a cerebrovascular accident, computed tomography has revealed the presence of close correlation between the degree of lactacidosis of the CSF and the magnitude of the edema [9]. In view of the facts described above it is interesting to assess the effects of drugs with an antiacidotic action on the brain against the development of edema. Among substances which limit lactate formation in the hypoxic brain, the most important are sodium hydroxybutyrate and barbiturates [10, 12]. However, these drugs exert their antiacidotic action on brain tissue only in doses inducing anesthesia. Moreover, in severe forms of ischemia and hypoxia, the antihypoxic properties of sodium hydroxybutyrate are not exhibited [10]. The use of the thiobarbituric acid derivative isothiobarbamine, which has a protective action and greatly reduces lactate accumulation in the cerebral cortex under hypoxic conditions, would seem to be more promising [3, 4].

We studied the effect of isothiobarbamine on the blood supply to the brain and on the oxygen, glucose, and lactate utilization of the organ and compared them with the antiedematous effect of the compound in cats after ICH.

EXPERIMENTAL METHOD

Experiments were carried out on 17 anesthetized and 13 conscious cats weighing 2.5-3.5 kg. ICH was reproduced by the method in [4]. The total cerebral blood flow was recorded in anesthetized cats (pentobarbital, 40 mg/kg), by means of an RKÉ-2 flowmeter in both carotid arteries after ligation of all the higher branches up to the internal maxillary arteries; values of pO_2, pCO_2, and pH were measured in samples of cerebral arterial and venous blood (on a "Godart" gas analyzer), concentrations of glucose and lactate were determined [6], and the oxygen, glucose, and lactate consumption of the brain was calculated as the product of the total

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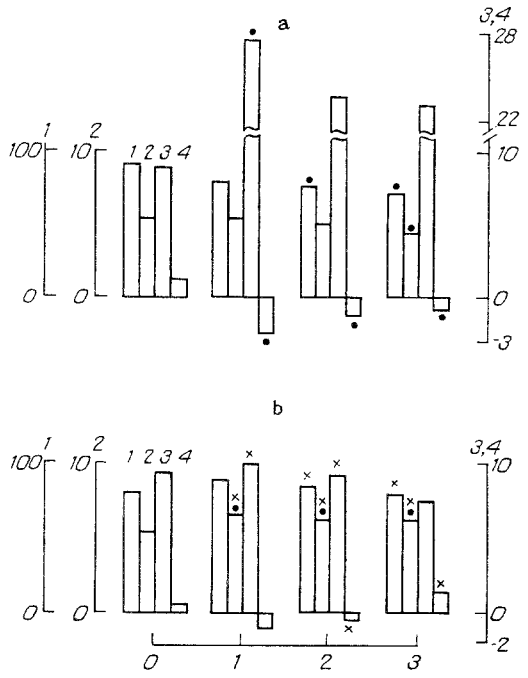

Fig. 1. Changes in total cerebral blood flow (1) and in oxygen (2), glucose (3), and lactate (4) utilization by the brain after ICH. a) ICH; B) ICH + isothiobarbamine; dots indicate significant differences compared with initial level, crosses — the same, with control. Ordinate, value of parameter (in ml or in mg/100 g tissue/min); ordinate, time (in h).

cerebral blood flow and the arteriovenous difference in concentration of the corresponding substance. Edema and swelling of the brain tissue were determined by impedansometry [7]. Isothiobarbamine was injected intravenously in a dose of 50 mg/kg 30 min after ICH into six anesthetized and six conscious cats; 17 animals served as the control. The significance of changes in these parameters was evaluated: in each series of experiments relative to the initial background by the method of direct differences, and relative to the control by means of the Wilcoxon—Mann—Whitney nonparametric test [2].

EXPERIMENTAL RESULTS

In the early posthypoxic period of ICH (the first 3 h after injection of blood into the brain) metabolism switched to the hypoxic type, and the total cerebral blood flow and oxygen utilization by the brain fell progressively (Fig. 1). Isothiobarbamine prevented reduction of the cerebral blood flow, inhibition of oxygen consumption, and hyperactivation of glucose utilization by the brain, and reduced the severity of the disturbance of lactate metabolism in brain tissue. For instance, after ICH utilization of lactate by the brain ceased and it was discharged into the cerebral venous blood. In animals treated with the compound, lactate release by brain tissue was less than in the control, but by the 3rd hour of observation (unlike in the control) lactate utilization by the brain was resumed. In our opinion, the primary effect of isothiobarbimine, which determines its influence on the parameters of carbohydrate and oxygen metabolism of the brain, is reduction of excessive activation of glycolysis by the compound during the first few hours after ICH. Marked activation of glucose utilization by the brain takes place in response to acute compressive hypoxia, arising during the period of effusion of blood into the brain parenchyma [8]. The hypoxic state of the brain tissue in patients with intracerebral hemorrhage is accompanied by a marked rise of the cAMP level in the brain [15]; cAMP, which activates phosphofructokinase, leads to stimulation of glycolysis in brain tissue [14]. Isothiobarbamine has a normalizing effect on the cAMP level during hypoxia [3], facilitating inhibition of excessive activation of glycolysis and of lactate accumulation in the brain.

The use of isothiobarbamine had a positive effect on oxygen metabolism of the brain during ICH. In the first few hours after injection of blood into the brain of the control animals a marked increase in the intensity of glycolysis in the nerve tissue did not cause a corresponding increase in the intensity of aerobic oxidative processes, probably on account of realization of the Crabtree effect: The oxygen utilization of the brain showed a tendency to

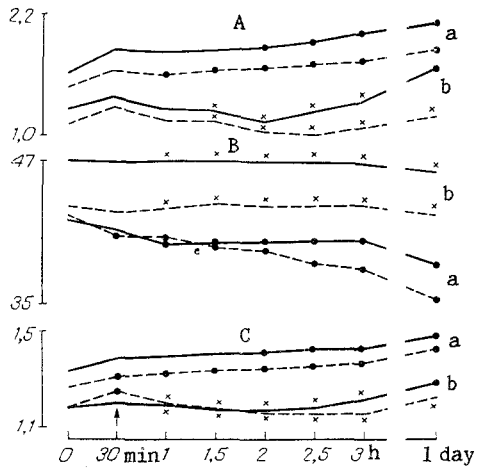

Fig. 2. Change in active impedance (A), interelectrode capacity (B), and total impedance of brain tissue (C) of left (continuous line) and right (broken line) subcortical brain regions of conscious cats after ICH. a) ICH; b) ICH + isothiobarbamine. Ordinate, value of parameter (in kΩ — A, nF — B, and kΩ — C); abscissa, time after ICH.

decline, reaching the level of significance by the 3rd hour of the experiment (Fig. 1). This evidently led to limitation of aerobic oxidation of glycolysis products and to even greater accumulation of excess of lactate in the brain. In turn, lactate closes the "vicious circle" of pathological reactions, inhibiting activity of aerobic enzymes of brain energy metabolism [13]. Isothiobarbamine, limiting an excessive increase in glucose utilization by the brain during ICH, probably inhibits the manifestation of the Crabtree effect and leads to a moderate increase in oxygen utilization by the brain, reflecting activation of aerobic oxidative processes. A combination of prevention of the excessive increase in glucose utilization by the brain and activation of oxygen consumption leads to limitation of lactate accumulation in the brain tissue until 1-2 h after ICH (judging by the amount of it released by the brain) and even to restoration of utilization of the substrate toward 3 h of the experiment.

Weakening of the disturbance of carbohydrate and oxygen metabolism of the brain by isothiobarbamine after ICH was clearly manifested as inhibition of the development of cerebral edema by the compound. In the control, we found the early and progressive development of edema and swelling of the subcortical regions surrounding the hematoma, soon involving also the symmetrical contralateral structures (Fig. 2). In the experimental group, toward the time of injection of isothiobarbamine an increase of impedance and a bilateral tendency toward an increase in the active component of the total impedance, characterizing edema and swelling with compression of the intercellular spaces, were found in the regions of the affected hemisphere studied. Injection of the compound led to preservation of impedance and of its active component at close to the original level (Fig. 2). The absence of a progressive decrease in interelectrode capacity in animals treated with isothiobarbamine when the impedance of the brain tissue was recorded in the subcortical nuclei surrounding the hepatoma and in the contralateral regions is evidence of the stabilizing action of the compound on nerve cell membranes. Consequently, in animals protected by isothiobarbamine, virtually no edema developed during the first hours after ICH; not until 24 h after injection of blood into the cerebral parenchyma did a significant increase in the active resistance and impedance of the left subcortical region begin to develop. However, in the structures of the affected right hemisphere which were studied these parameters did not differ significantly from normal.

It must be particularly emphasized that all the treated animals in the experimental group remained alive, whereas in the control group two of the seven cats died during the first day.

It is interesting to note that under these conditions glycerol, one of the most active agents against edema, exhibited a very moderate antiedematous action and did not lower the mortality of the animals after ICH [7]. Unlike glycerol, isothiobarbamine is evidently an agent for the pathogenetic pharmacoprophylaxis of edema and swelling of brain tissue.

Thus isothiobarbamine in the early posthypoxic period of ICH inhibits the development of edema and swelling of brain tissue. This effect is evidently due to prevention of disturbances of the oxygen and carbohydrate metabolism of the brain and, in particular, of excessive accumulation of lactate in the brain tissue, by the compound.

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