EFFECT OF SHORT-TERM ADAPTATION TO HYPOXIA ON THE DEVELOPMENT OF ACUTE CEREBRAL CIRCULATORY DISORDERS IN RATS GENETICALLY PREDISPOSED TO EPILEPSY

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At the present stage in the treatment and prevention of cerebrovascular diseases special attention is being paid to the search for ways of increasing the resistance of nerve tissue to hypoxia and ischemia through the use of drugs or other methods. We know that long-term adaptation to high-altitude hypoxia for 15-55 days can increase the general resistance of the body to oxygen insufficiency arising through the action of various extremal factors, and under experimental conditions it may have a prophylactic effect in acute heart failure, ischemic myocardial necrosis, spontaneous hereditary hypertension, and DOCA-salt hypertension [2, 8, 9, 14], and can also reduce the intensity of the seizure manifestations arising through acoustic stress in rats genetically predisposed to epilepsy [4, 7], or induced by the action of metrazol [8], strychnine, and penicillin [1, 11]. At the same time, there is evidence that not only long-term, but also short-term preliminary exposure for a few hours to hyperbaric hypoxia can increase the resistance of animals to subsequent severe hypoxia [3].

The aim of this investigation was to study the possibility of prevention of acute disturbances of the cerebral circulation arising during acoustic stress by means of short-term (2 h) adaptation of animals to hypoxia in a pressure chamber.

EXPERIMENTAL METHOD

Experiments were carried out on 25 Krushinskii–Molodkina (KM) rats. Previous experiments on rats of this line showed that prolonged interrupted acoustic stimulation induces intensive excitation of the brain in the animals, with motor and autonomic disturbances, epileptic fits, hypoxia of nerve tissue, functional changes in the cerebral vessels with an increase in their permeability, and the development of diapedetic hemorrhages [6]. Animals of the same sex, age, and equal sensitivity to acoustic stimulation were strictly divided into experimental and control groups.

In experiments with adaptation to hypoxia rats of the experimental group were placed beforehand in a pressure chamber, in which the air pressure was reduced to correspond to an altitude of 5000 m above sea level. The capacity of the pressure chamber was 50 liters and the ventilation was 7 liters of air per minute; two animals were kept in the chamber at the same time.

After the end of adaptation to hypoxia for 2 h the animals of the experimental group and the control unadapted rats were subjected to acoustic stimulation in a Plexiglas chamber measuring 45 × 50 × 60 cm, by the method described previously [7]. After exposure for 1.5 min to the action of a loud electric bell (100-120 dB) a series of alternate loud and soft acoustic stimuli was applied for 10 sec, with intervals of 10 min between them. After 15 min of this type of stimulation there was a pause of 3 min, after which the loud sound was again applied for 1.5 min. During exposure of the experimental and control rats to sound the following parameters were determined: the latent period, character, and intensity of the convulsion, and the severity of the motor disturbances, distinguishing between a mild degree (slight disturbances of muscle tone, not limiting the animal's movement in the cham-

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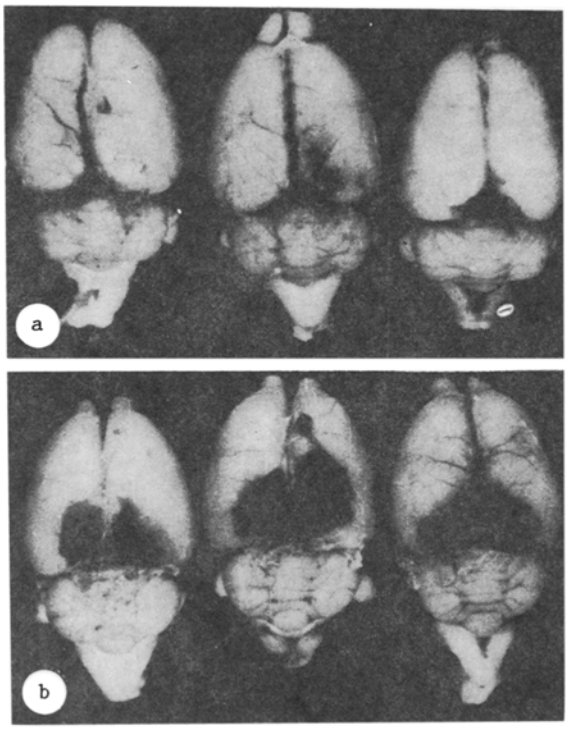

Fig. 1

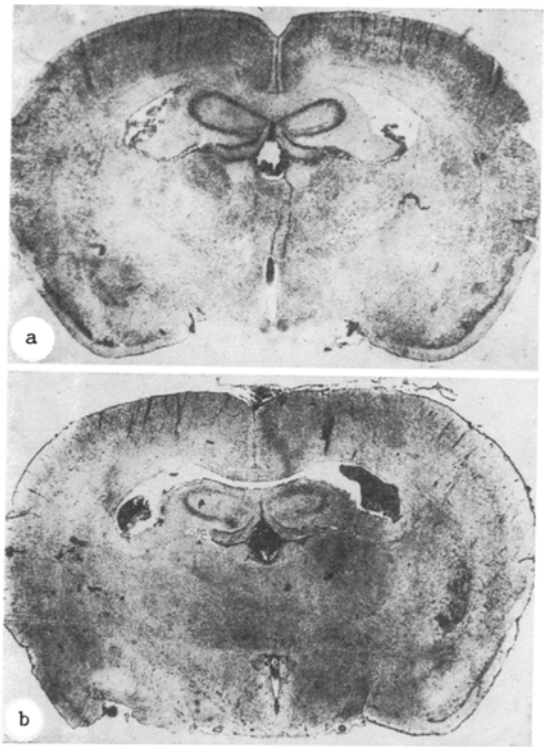

Fig. 2

Fig. 1. Subdural and subarachnoid hemorrhages are smaller in rats adapted to hypoxia (a) than control rats (b) of the KM line after exposure to acoustic stress.

Fig. 2. Ventricular hemorrhages are smaller in rats adapted to hypoxia (a) than in control rats (b) of the KM line after exposure to acoustic stress. Hematoxylin-eosin, Microplanar system.

ber), an average degree (paresis of the limbs, most frequently the hind limbs, impairing mobility), and a severe degree (the animal is virtually unable to move about).

The effect of short-term adaptation to hypoxia on the development of intracranial hemorrhages during acoustic stress was studied. Immediately after the end of the experiments with exposure to the acoustic stimulus the animals were decapitated and the brain fixed in 10% formalin solution. The area of the subdural hemorrhages (in square millimeters) was calculated on photographs with the aid of a Pericolor-1000 system (France); a microscopic study of the brain was undertaken, using the following staining methods: hematoxylin and eosin, Nissl's thionine, and Van Gieson's picrofuchsine. Mortality and disturbances of motion were analyzed statistically by Fisher's test, the frequency of hemorrhages by the Chi-square test, and the severity of the homorrhages by Student's test.

EXPERIMENTAL RESULTS

Preliminary adaptation to hypoxia for 2 h reduced the mortality and the number of severe disturbances of motion in animals of the experimental group during acoustic stress by two-thirds compared with the control (25 and 85.6%, respectively; $P < 0.01$). The severity of the clinical manifestation in the animals was determined by the extent of the acute cerebral circulatory disturbances.

Parameters characterizing the general level of excitability of the CNS did not differ significantly in rats of the experimental and control groups.

Macroscopic investigation of the brain revealed subdural and subarachnoid hemorrhages of different sizes, mainly in the parieto-occipital regions of the brain, in all rats of the control group and in some rats of the experimental group.

The frequency of subdural and subarachnoid hemorrhages discovered on external inspection of the brain in rats adapted to hypoxia after acoustic stimulation was only one-third of that in animals of the control group: hemmorhages were observed in all rats of the control

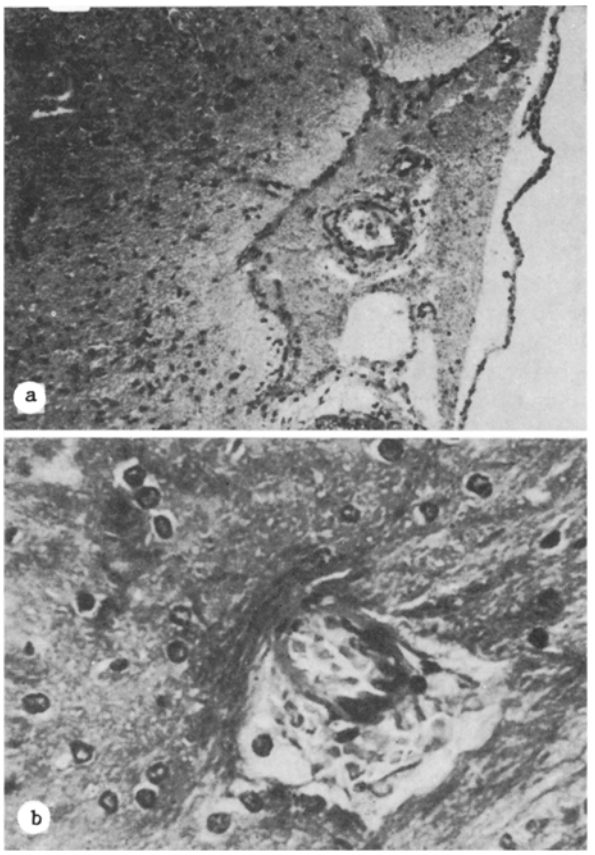

Fig. 3. Disturbance of cerebral circulation in KM rats during exposure to acoustic stress. a) Circumscribed subarachnoid hemorrhage on ventral surface of brain; Van Gieson (here and in Fig. 3b), 100 ×; b) small perivascular hemorrhage in deep brain formations. 400 ×.

group, whereas in the experimental group they were present in only four of 12 animals ($P < 0.01$). The mean area of the subdural and visible subarachnoid hemorrhages in adapted animals was 8.5 times less than in the control (7.846 ± 3.8 and 66.633 ± 12.9 mm^2, respectively; $P < 0.01$; Fig. 1).

On histological examination of the brain marked congestion, dilatation of the veins on the brain surface and of the intracerebral capillaries, especially in the subependymal regions, and signs of cerebral edema were observed in animals of the experimental and control groups. Against this background some animals were observed to have hemorrhages into the lateral, third, and fourth ventricles (Fig. 2a, b), which varied in size from localized perivascular to massive hemorrhages, accompanied by dilatation of the ventricular system of the brain and by injury to the ventricular ependyma; subarachnoid hemorrhages (Fig. 3a) in the region of the cerebral hemispheres, brain stem, and cerebellum, and also solitary perivascular hemorrhages in different parts of the brain — deep brain formations, cortex, brain stem, and cerebellum (Fig. 3b).

Comparison of the extent of the intracerebral hemorrhages in the control and experimental groups showed that preliminary adaptation of the animals to hypoxia reduced by half the frequency of intraventricular hemorrhages, and also appreciably affected their extent. In animals of the experimental group adapted to hypoxia the hemorrhages were localized, perivascular, and unaccompanied by damage to the ventricular ependyma. In the control group, hemorrhages into the ventricles were accompanied in most cases by significant dilatation of the ventricles with a tamponade effect due to blood.

The morphological study of the brain thus showed that adaptation of the animal to hypoxia for 2 h in a pressure chamber has a protective action, reducing the severity of cerebrovascular disturbances accompanying acoustic stress.

The protective effect of short-term adaptation to hypoxia was not due to a change in the level of excitability of the CNS, for the latent period, character, and intensity of the audiogenic fit did not differ significantly in animals of the experimental and control groups.

The mechanism of the protective effect of short-term adaptation to high-altitude hypoxia on acute disturbances of the cerebral circulation arising during acoustic stress has not been adequately explained. In our view, keeping animals at an "altitude" of 5000 m is accompanied by processes leading to reduced permeability of the vascular wall, an increase of the cerebral blood flow in the initial period of adaptation [12], and a consequent improvement in the oxygen supply to the brain tissue. We know that the increase in the cerebral blood flow in hypoxia is an important mechanism maintaining energy homeostasis in the brain [13]. Gradual long-term adaptation to high-altitude hypoxia leads to structural changes in the vascular network of the brain, aimed at ensuring an adequate blood supply to the nerve tissue, together with an increase in density of the capillaries [10] and also with changes in the cell membranes and an increase in the ability of the cell to utilize oxygen [18].

Preliminary exposure to hypobaric hypoxia for 2 h thus has a protective effect on acute disturbances of the cerebral circulation arising during acoustic stress in KM rats, and it significantly reduces the frequency of development and the area of subdural and subarachnoid hemorrhages and the extent of hemorrhages into the cerebral ventricles.

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