Morphology of Cortical Structures in Cerebral Ischemia and its Combination with Audiogenic Seizures

E. N. Popova and F. A. Yakhin

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Studies of the sensorimotor and auditory areas of the brain in rats after ligation of the left common carotid artery reveal polymorphous alterations in cortical vessels, neurons, and glial cells. Compensatory reversible alterations constitute the largest group. In cerebral ischemia combined with audiogenic seizures dystrophic and destructive alterations in cortical elements become more significant. Alterations in cortical structures after bilateral ligation of the common carotid arteries are more pronounced than those occurring after unilateral occlusion. During the postseizure period after ligation of both arteries, dystrophic and destructive alterations become more severe, while reparative processes are inhibited.

Key Words: *cerebral ischemia; audiogenic seizures; sensorimotor and auditory cortex*

The high incidence of cardiovascular diseases and increasing frequency of their combination with epileptic seizures have sparked interest in the pathogenesis of so-called vascular epilepsy. However, postmortem material does not provide an answer to a number of important questions regarding the morphogenesis of epileptic seizures occurring against the background of cerebrovascular disorders. Therefore, experimental studies are of particular interest.

Animal experiments have shown alterations in cortical structures after damage to the carotid arteries; these alterations are regarded as hypoxic [1], reversible [12], reactive [13], and reflecting stimulation of individual neurons [4].

The use of the model of audiogenic epilepsy developed by L. V. Krushinskii [6], which well approximates the physiological and clinical reality, has shown acute and largely reversible alterations in cortical vessels, neurons, their dendrites, and glial cells during the tonic phase of an epileptic seizure and during the postseizure period [7,10,11].

As far as we are aware, alterations in cortical structures in audiogenic epilepsy against the background of ischemic damage to the brain have not been studied in experiments.

Our objective was to investigate the changes occurring in cortical structures in cerebral ischemia combined with audiogenic seizures.

MATERIALS AND METHODS

Seizures were provoked by hyperstimulation of the brain with sound stimuli. The animals were placed in a 42×26×50 cm Plexiglass chamber with an electric bell attached to one of the walls. A sound stimulus (101 dB, mixed frequencies) was applied and stopped immediately after the development of seizures; in the absence of a seizure the stimulation was continued for 1.5 min. In order to individualize the responses of rats to the stimulus, the intensity of seizures was assessed according to a 5-point scale [6]. After the baseline reaction to the stimulus had been determined (3 or 4 stimulations every other day), two-step ligation of the carotid

Laboratory of Brain Ultrastructure, Institute of the Brain, Russian Academy of Medical Sciences, Moscow; Chair of Nervous Diseases, Medical Institute, Kazan. (Presented by O. S. Adrianov, Member of the Russian Academy of Medical Sciences)

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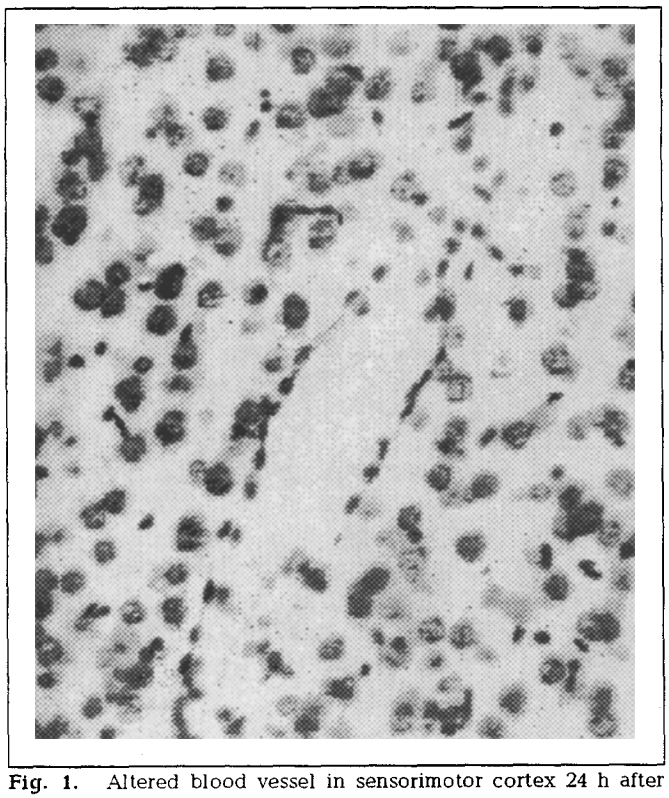

Fig. 1. Altered blood vessel in sensorimotor cortex 24 h after ligation of the left common carotid artery. Nissl staining. ×150.

arteries was performed under urethane anesthesia (800 mg/kg intraperitoneally): the arteries were ligated at the level of the thyroid gland below the bifurcation of the internal and external arteries.The second operation was performed 8 days after the first. The audiogenic epileptic reaction was determined one day after the ligation each artery. The sensorimotor and auditory areas of the cortex were taken for morphological studies, which were performed with the use of the Nissl, Golgi, and Miagawa-Aleksandrovskaya methods.

RESULTS

One day after ligation of the left common carotid artery not complicated by audiogenic seizures, reversible alterations with elements of a compensatory nature prevailed in the cortex. These were dystonia of some vessels, swelling and pycnosis of endothelial nuclei, increased permeability of the vascular wall, and perivascular edema (Fig. 1). Numerous swollen neurons in a state of peripheral chromatolysis were seen in the cortex. In some of them strong indications of reparative processes were observed, such as enlargement and ectopia of nucleoli and the presence of a hyperchromic band in the cytoplasm around the nucleus. Signs of reversible ultrastructural shifts in chromatolytically changed neurons were seen in the hippocampus 20 h after a 15-min occlusion of the left carotid artery in rats [13].

The studied areas of the cortex also contained hyperchromic cells, which were more frequent in the sensorimotor area. At the ultrastructural level, chromatolytically altered and dark cortical neurons were seen in rat sensorimotor cortex after a uni-

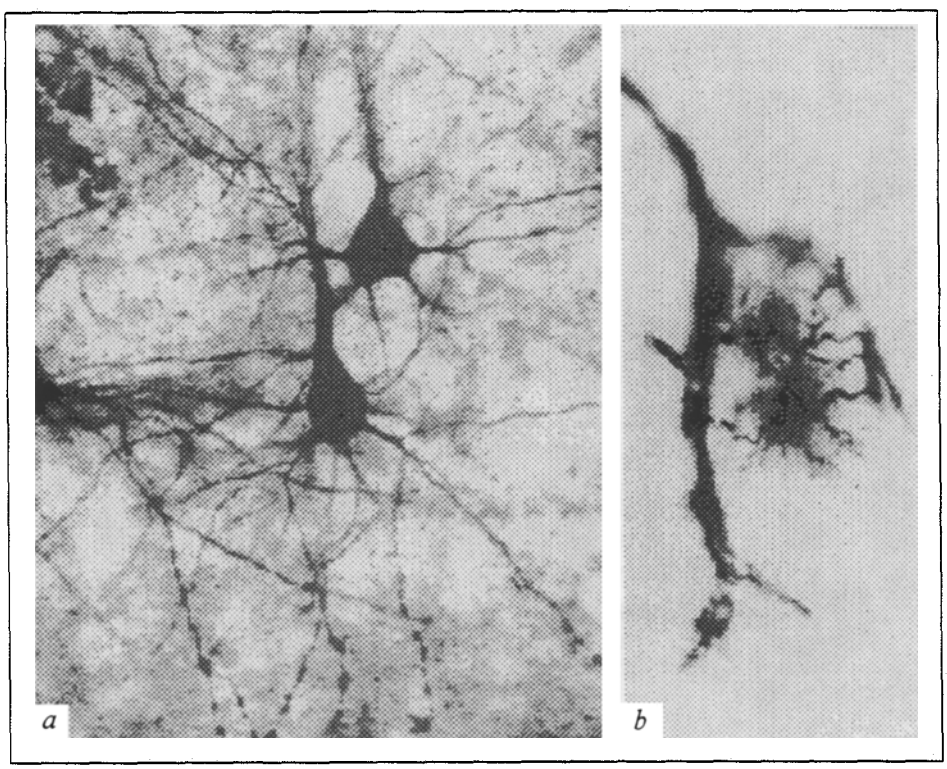

Fig. 2. Varicose alterations in basal dendrites of large neurons in layer V (*a*), clasmatodendrosis and hypertrophy of "vascular peduncles" (*b*) in sensorimotor cortex 24 h after audiogenic seizures induced in rats with ligated left carotid artery. Golgi staining. ×300.

lateral ligation of the common carotid artery and 5-7 days afterwards [1].

Various alterations were observed in the dendrites of cortical neurons. The basal dendrites of some neurons had fewer spikes, in other neurons they lacked all or some spikes and were varicose. These alterations went along with proliferation and dystrophic alterations in the glia (swelling of astrocytes, hyperkaryochromia and clasmatodendrosis, and an increase in the size of drainage oligodendrocytes). On the one hand, the proliferation of glial cells is of a compensatory nature (maintenance of nerve cell viability) and, on the other, it is aimed at replacing dead neurons.

The prevalence of reversible alterations in cortical structures observed after unilateral ligation of the common carotid artery may be attributed to the partial cerebral ischemia and the fact that the collateral circulation takes over.

One day after audiogenic seizures against the background of cerebral ischemia caused by carotid artery ligation, the number of altered cortical neurons and the degree of alterations increased. Common occurrences were pronounced swelling of neurons combined with almost total chromatolysis of the basophilic substance, vacuolization of the cytoplasm (sometimes of the nucleus and nucleolus), cytolysis and karyocytolysis, ghost cells, and foci of missing neurons. Hyperchromatic cells were seen, usually in the lower cortical layers. Especially in the upper cortical layers, dendrites had fewer spikes, and the dendrites of large neurons of the lower layers were varicose (Fig. 2, *a*). In addition to hyperplasia of glial cells, astrocytes with clasmatodendrosis and hypertrophied "vascular peduncles" (Fig. 2, *b*) were seen, these providing compensatory stimulation of the flow of nutrients from blood vessels to nerve cells under conditions of impaired oxidative-reductive metabolism.

The alterations in cortical structures after bilateral ligation of the carotid arteries were more pronounced than those occurring after unilateral ligation. While chromatolytic alterations in cortical neurons prevailed, the number of hyperchromic cells increased, particularly in the sensorimotor cortex (Fig. 3). Cytolysis and karyocytolysis, ghost cells, and foci of missing neurons were seen. Signs of nucleus activation were also revealed, which at the ultrastructural level (enlargement and ectopia of the nucleolus and the appearance of paranucleolar bodies) have been detected just 15 min after bilateral ligation of the carotid arteries in rats [9].

During the postseizure period after bilateral ligation of the arteries, dilation and plethora of some vessels, pycnosis of endothelial cell nuclei, erythrocyte stases, and occasional hemorrhages were observed together with vascular dystonia,

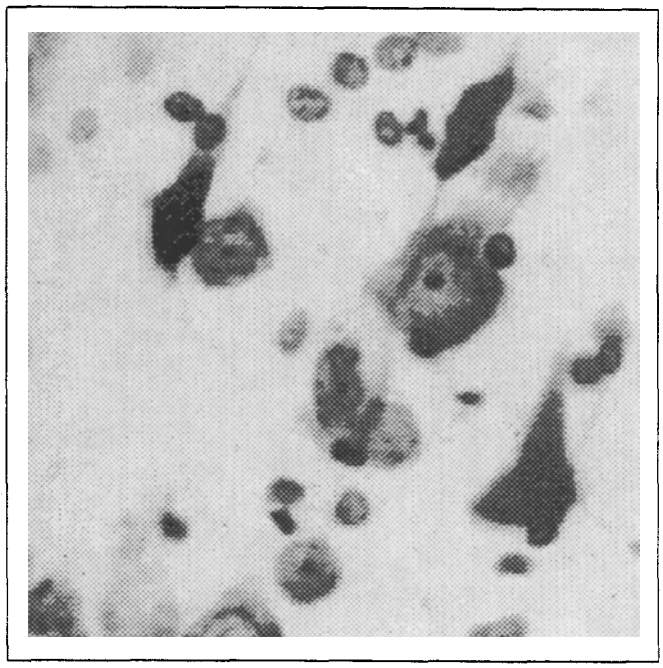

Fig. 3. Hyperchromic cells, foci of missing neurons, and hyperplasia of glial cells 24 h after bilateral ligation of carotid arteries. Nissl staining. ×400.

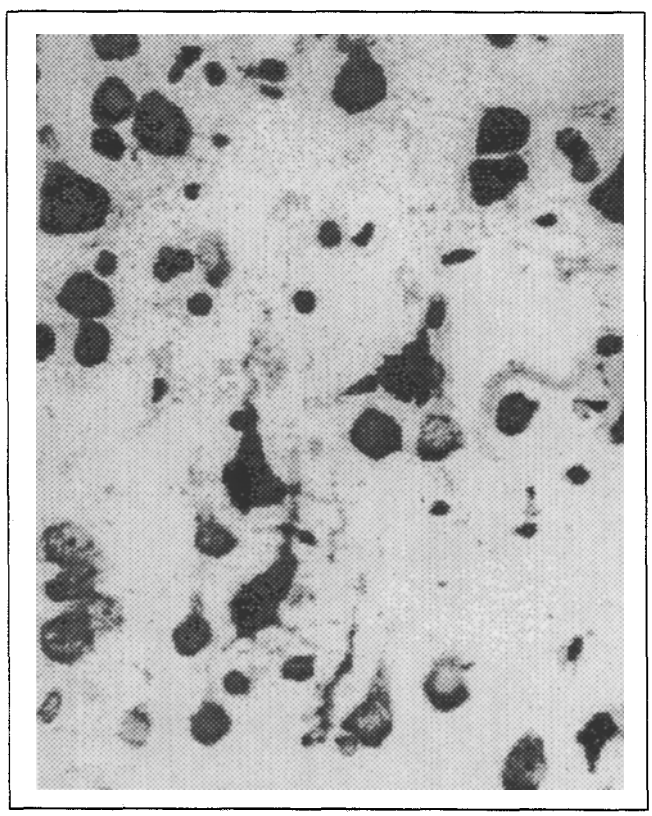

Fig. 4. Hyperchromic and wrinkled neurons in layer V of sensorimotor cortex during postseizure period after bilateral ligation of carotid arteries. Nissl staining. ×400.

swelling of nuclei, and perivascular edema. The number of both hypochromic and hyperchromic neurons and of foci of missing neurons increased. Wrinkled neurons with a corkscrewlike apical dendrite were encountered among the hyperchromic cells of layer V of the sensorimotor cortex (Fig. 4). Since hyperchromophilia is equivalent to an inhibited state [8], their presence during the postseizure period can be regarded as a morphological basis for other seizures because initial inhibition of the motor cortex is known to be a favorable background for the development of a convulsive seizure [2,3].

Reparative processes were inhibited after bilateral ligation of the common carotid arteries. The small number of binuclear cortical neurons rich in basophilic substance implies that this morphological shift is not as important for the compensation of impaired function as neuronal hypertrophy [5].

Thus, morphofunctional disorganization of cortical structures occurs in cerebral ischemia induced by a two-stage ligation of the common carotid arteries. Against the background of this disorganization sensory sound stimulation and the breakdown of compensatory mechanisms facilitate the development of seizures.

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