PATHOLOGICAL PHYSIOLOGY AND GENERAL PATHOLOGY

Disturbances in the Integrative Activity of the Rat Brain after Bilateral Focal Compression Ischemia of the Frontal Cortex

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Pathomorphological changes and disturbances in the integrative activity of the central nervous system of rats are studied after bilateral compression ischemia of the frontal cortex. Bilateral compression of the frontal cortex is shown to result in the formation of limited foci of ischemic necroses in the cortex, which are surrounded by the perifocal zone. This is attended by reduced horizontal motor activity in the "open field" test, as well as by a reduced latency of the conditioned passive avoidance response. The motor activity of operated animals is restored on day 14 postoperation, correlating with regeneration of some damaged neurons in the perifocal zone, whereas the latency of the conditioned passive avoidance response remains markedly reduced.

Key Words: *focal ischemia of the cortex; frontal cortex; conditioned passive avoidance response*

Focal compression ischemia, due to compression of confined areas of the brain surface, is associated with subdural hematomas or complications following neurosurgical intervention (retraction ischemia) and is attended by cortex destruction and cortical infarction. Clinical observations have been corroborated by data obtained for experimental compression ischemia of the brain in animals [6-9,14,15].

Our previous studies [3-5] showed that after frontal lobectomy the conditioned behavior of rats (active and passive avoidance responses) is disturbed and the motor activity of animals in the "open field" test increases. It is also well known that the prefrontal cortex is one of the major structures regulating spatial orientation and, along with the hippocampus, playing an important role in learning and memory [13,16]. Some findings have demonstrated that a 5-min occlusion of the common carotid arteries attended by cerebral ischemia markedly disturbs the elaboration of conditioned passive avoidance responses (CPAR) and increases the motor activity in the "open field" [10-12]. The integrative activity of the brain following local ischemic damage to the frontal cortex has not been studied. In this connection a complex study of pathomorphological changes and the functional sequelae of focal compression ischemia of the cerebral cortex is of indubitable interest and of practical importance in clinics.

In the present study performed on rats using a model of compression ischemia of the brain we

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compared the time course of destructive processes in the ischemic focus with the time course of disturbances in the integrative activity of the central nervous system (CNS) during 14 days after the frontal cortex had been damaged.

MATERIALS AND METHODS

The experiments were carried out on 27 male random-bred albino rats weighing 200-250 g. Prior to the operation the motor activity of animals was assessed in the "open field" test on a RODEO-I device; we recorded the horizontal (the number of squares crossed), vertical (postures), and exploratory (investigation of the upper and lower holes in the test chamber) activity. CPAR was then elaborated in animals and the latency of movement from the light to the dark compartment of the chamber was determined [1].

Bilateral symmetrical foci of compression ischemia of the frontal cortex were reproduced after Barskov *et al.* [9]. The head of a rat anesthetized with chloral hydrate (300 mg/kg, i.p.) was fixed in a stereotaxic clamp and holes were made with a cylindrical bore (3 mm in diameter) above the frontal cortex, without damaging the dura mater. A Teflon rod (2 mm in diameter) was fixed in a manipulator and slowly inserted into the cortex to a depth of 2 mm, where it was left for 15 min, after which the rod was removed and the wound was sutured. The motor activity and CPAR were assessed on days 4, 9, and 14 postoperation. Sham-operated animals, which underwent bilateral skull trephanation without damage to the cerebral cortex, served as the control. The results were statistically processed using Student's *t* test. Upon completion of the experiments the animals were killed with a toxic dose of ether, the brain was isolated, fixed in a Formalin-acetic acid-ethanol mixture (2:1:7), and then embedded in paraffin.

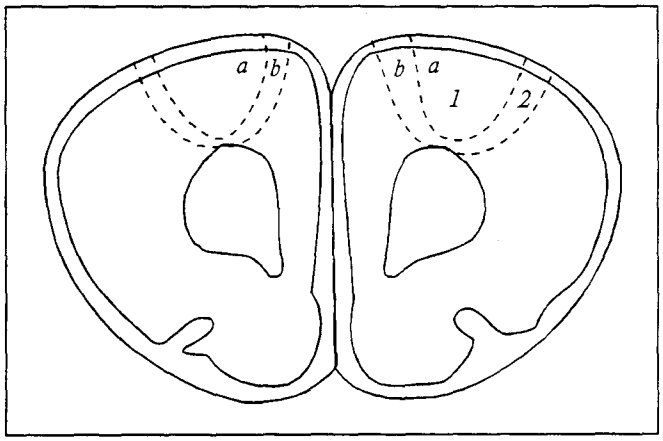

Fig. 1. Localization of foci of ischemic necroses in frontal cortex of rat brain. Frontal section at a level of 3.3 mm anterior to the bregma. At this level the subcortical white substance is found in the frontal lobes in the central part of the section [17]. *a*) zone of necrosis; *b*) perifocal area (penumbra). Areas *1* and *2* of the frontal cortex are presented in Fig. 2 as *a* and *b*, respectively.

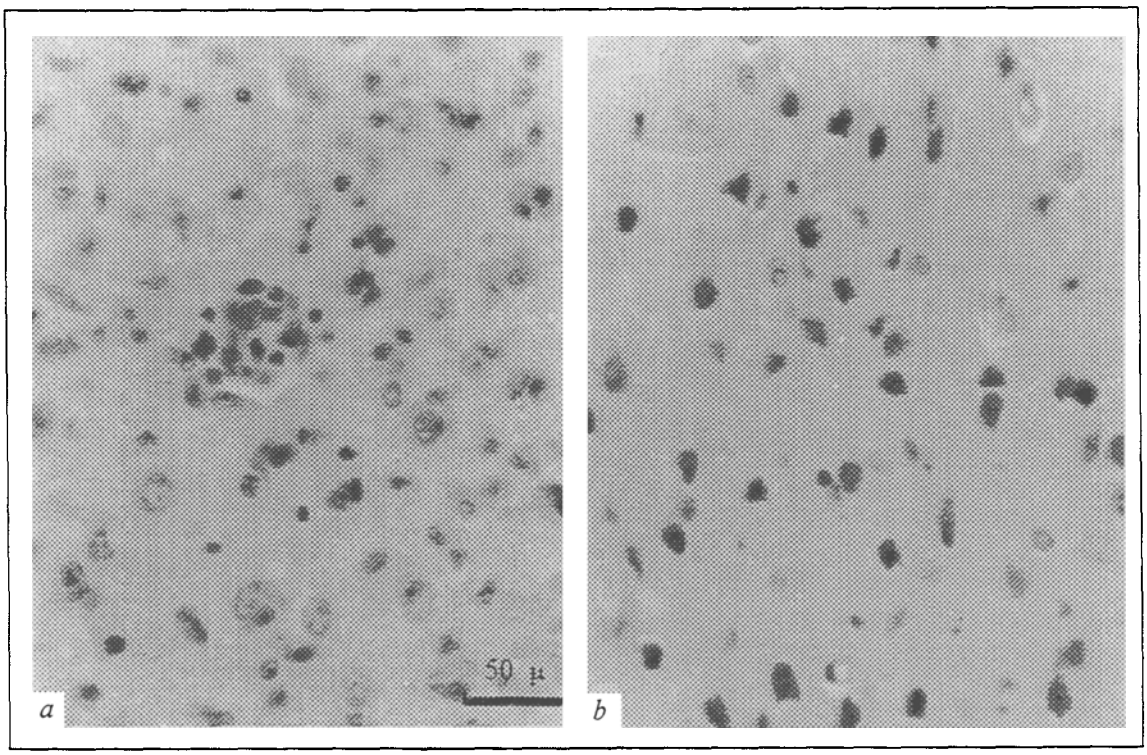

Fig. 2. Histopathological changes in focus of compression ischemia in frontal cortex on day 4 postoperation. Hematoxylin–eosin staining. Scale 50 μ. *a*) necrotic focus; *b*) perifocal area.

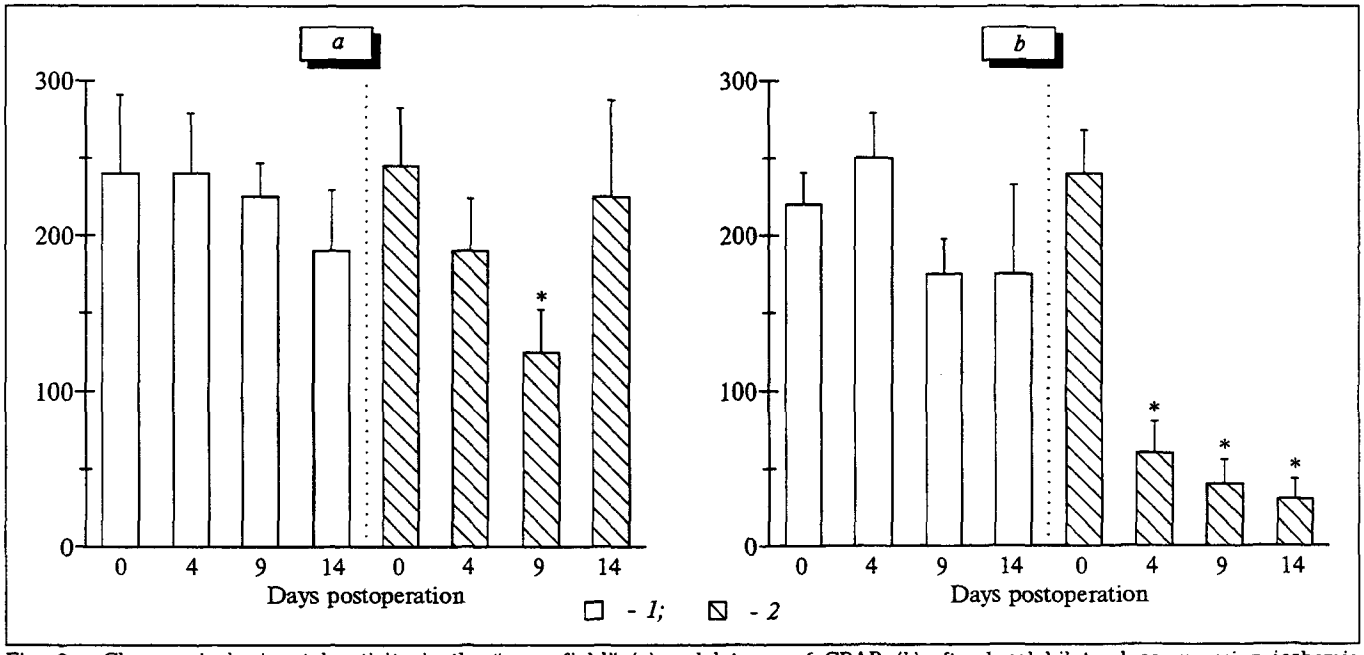

Fig. 3. Changes in horizontal activity in the "open field" (*a*) and latency of CPAR (*b*) after local bilateral compression ischemia of frontal cortex. Ordinate: *a*) number of squares crossed during 300 sec; *b*) latency of CPAR, sec. *1*) sham-operated animals; *2*) local compression ischemia of frontal cortex. Asterisk indicates $p<0.05$ *vs.* the preoperational values.

Paraffin sections were stained with hematoxylin-eosin and vanadium-acidic fuchsin [2].

RESULTS

A study of histological preparations showed (Fig. 1) that 1-2 days after local compression a necrotic focus formed in the frontal cortex (ischemic infarction). The necrotic zone was surrounded by a perifocal area (penumbra), which, along with chromatophilic and irreversibly damaged necrotized (acidophilic) neurons, contained normal neurons (Fig. 2). Solitary small hemorrhages could be observed in both the cortex and the underlying white substance. In addition to the main focus of ischemic necrosis, a few small exofocal lesions predominantly containing solitary chromatophilic neurons were found in the primary olfactory cortex, hippocampus, striatum, and thalamic reticular and anterior-medial nuclei. By the end of the first week postoperation, a gliomesodermal scar started to form in the zone of cortical infarction; the number of chromatophilic neurons decreased in the perifocal area, which may be due to both death and regeneration of these cells.

The above-described bilateral ischemic damage to the frontal cortex was attended by marked changes in the motor activity and conditioned behavior of rats. For instance, on day 4 postoperation the number of squares crossed in the "open field" test decreased by 22%, on average, of the initial level; on day 9 it remained decreased and

TABLE 1. Motor Activity of Rats in the "Open Field" Test ($M\pm m$)

Days	Sham-operated rats (8 rats)				Local ishemia of frontal cortex (19 rats)			
	HA	VA	EAU	EAL	HA	VA	EAU	EAL
Before operation	238.4±38.7	14.4±2.9	10.6±0.9	46.1±8.5	239.7±21.6	14.6±2.4	6.8±1.5	43.5±4.7
Day 4 post-operation	225.3±36.3	20.3±5.2	10.4±1.8	61.1±19.4	187.9±26.9	9.6±2.1	4.9±1.1*	31.6±4.7
Day 9 post-operation	218.0±18.8	16.3±6.2	10.9±2.4	31.3±6.7	128.9±19.3**	8.6±2.1°	3.2±0.8**	18.4±5.5°
Day 14 post-operation	178.0±12.7	11.8±2.9	4.0±0.9	23.2±4.2	226.6±59.9	16.0±4.0	8.8±4.1	34.0±9.9

Note. HA: horizontal activity (number of squares crossed); VA: vertical activity (postures); EAU and EAL: exploratory activity of the upper and lower holes of the chamber. One asterisk and one circle denote reliability ($p<0.05$) of differences *vs.* sham-operated animals and preoperational level, respectively.

did not normalize until days 14-16 postoperation (Fig. 3, *a*). During this period, the motor activity of sham-operated animals was slightly reduced, but these changes were not statistically reliable. Meanwhile, it should be mentioned that the most profound changes in the motor and exploratory activity were observed in rats on day 9 after local ischemia of the frontal cortex, all the parameters studied being markedly reduced as compared to the preoperational level (Table 1). On day 14 postoperation the motor and exploratory activity of animals approached the initial level.

In operated animals ischemic damage to the frontal cortex markedly disturbed memory trace preservation, this manifesting itself in a reduced latency of CPAR. On day 4 after cortical ischemia the latency of CPAR decreased by 72% vis-a-vis the initial level, remaining reduced on days 9 and 14 by 78 and 85%, respectively (Fig. 3, *b*). During these periods, the latency of CPAR in sham-operated animals did not markedly change.

Our findings and the results of similar experiments show that the formation of a confined necrotic zone (infarction) after compression of the cortex is primarily due to the formation of an ischemic focus resulting from the reduced local arterial blood flow [7,8,14]. When the pressure at the surface of the rat brain is equal to or exceeds 40 mm Hg for more than 15 min, ischemic lesions of the cortex are formed in virtually 100% of cases [15].

Studies of the behavior and conditioned responses of rats at different stages after local compression of the frontal cortex demonstrated temporal changes in the motor activity and marked disturbances of memory in operated animals. It may be assumed that as reparative processes develop in the zone of cortical lesions, changes in the motor activity of rats resulting from ischemic infarction of the frontal cortex are compensated. On the other hand, the disturbances of memory, which did not normalize until after the end of the follow-up (2 weeks), are evidently due not only to lesions in the frontal cortex, but also to secondary (exofocal) foci of lesions in the limbic and subcortical structures of the forebrain.

To sum up, this experimental model may provide a basis for designing methods of pharmacological stimulation of the regenerative processes in the focus of ischemic lesions of the cerebral cortex and for promoting the recovery of disturbed CNS functions.

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