CHANGES IN EEG AND HIGHER NERVOUS ACTIVITY OF RATS RECEIVING ACELIZINE OR ANTI-ISCHEMIC PROTECTION OF THE BRAIN

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Previous investigations showed that the former Soviet water-soluble form of aspirin, known as acelizine (All-Union Research Institute of Chemistry and Technology of Therapeutic Substances, Khar'kov) possesses marked anti-ischemic activity against general total cerebral ischemia [1].

The aim of the present investigation was to study CNS (reflected in EEG data) and higher nervous activity in rats surviving general total cerebral ischemia and receiving the optimal dose of acelizine, elaborated previously, as a prophylactic measure.

EXPERIMENTAL METHOD

Experiments were carried out on 43 Wistar rats weighing 200-250 g. Cerebral ischemia was produced by intraperitoneal general anesthesia (200 mg ketamine/kg body weight), by a method developed by the writers [2], for 25 min. Acelizine was injected intramuscularly in a dose of 150 mg/kg, 30 min before the creation of ischemia.

The EEG was recorded throughout the experiment from gilded electrodes 0.4 mm in diameter, implanted previously (bilaterally and subdurally) at projection points of the somatosensory and motor cortex [3]. The reference electrode was fixed in the nasal bones.

Measurements of the momentary amplitude, in mm (A) from an arbitrarily drawn base line [1] to the point of intersection with the line of the EEG were made on the EEG trace (Fig. 1a). The measurements were made at equal time intervals (t). The data were fed into a computer, with an indication of the calibration signal. The program determined the position of the zero line of the EEG [2] and calculated the area between the latter and the EEG line (shaded regions). The mean sum of the areas during a time interval of 1 sec gave the value of the power index (PI) of the EEG in μV/sec.

Higher nervous activity was assessed on the basis of analysis of the ability of the animals to form an active avoidance reflex in a V maze. The maze consisted of three corridors with electrified floor and with a lamp at the end. Training began 7-8 days after the operation. Up to 100 combinations of light–electric current were given per day and the number of conditioned responses (to light) was recorded. Animals undergoing a mock operation served as the control.

The results were analyzed on an Élektronika BK-0010 personal computer by the spectral analysis method. The significance of differences was calculated by Student's and Cochrane's tests.

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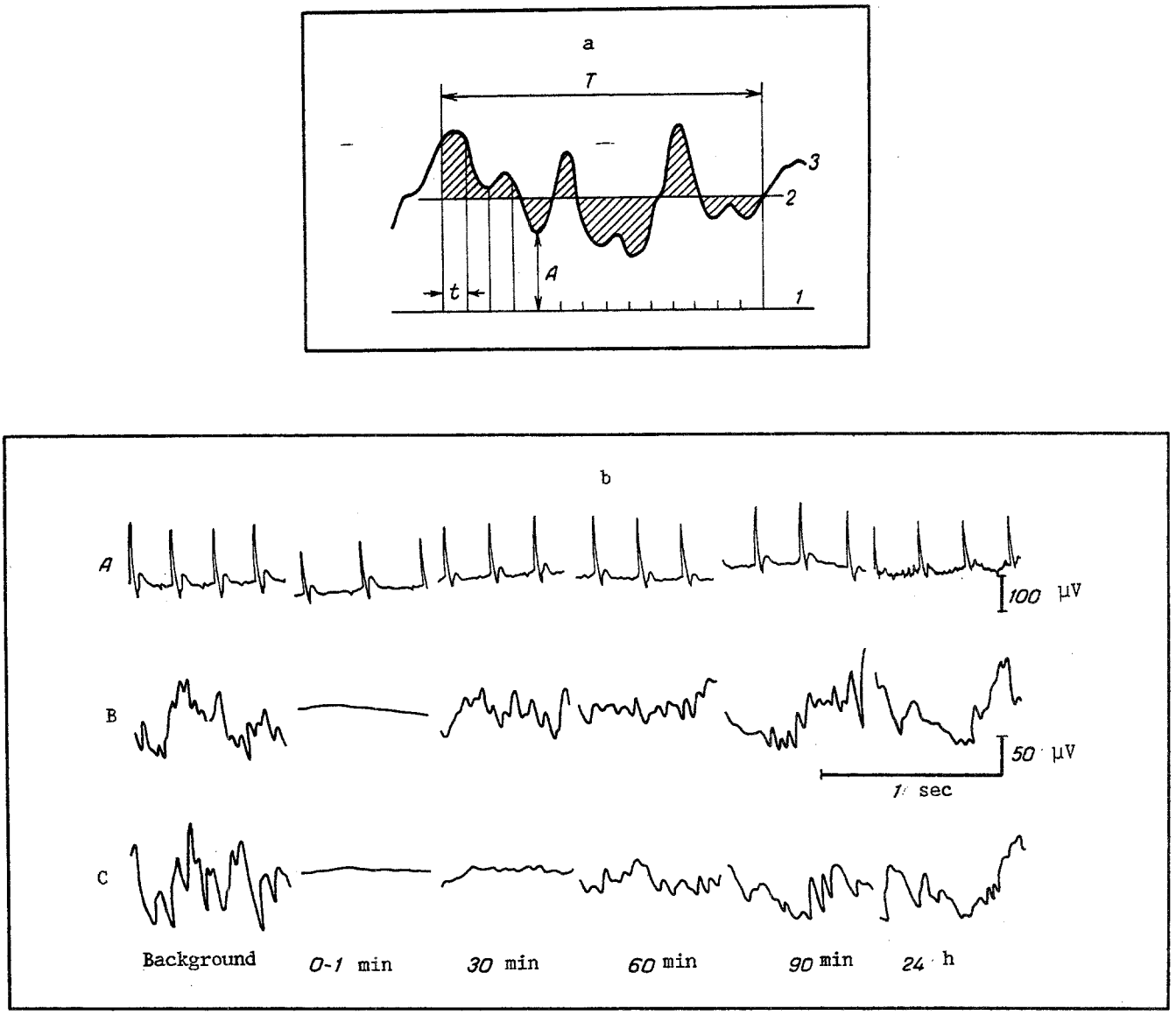

Fig. 1. Calculation of power index of EEG (a). Time course of EKG and EEG changes in reperfusion period after cerebral ischemia for 25 min and against the background of acelizine, given 30 min before ischemia (b): a) explanation in text; b: A) EKG, B) EEG of sensory cortex, C) EEG of motor cortex.

EXPERIMENTAL RESULTS

Analysis of the EEG of rats with cerebral ischemia showed that in both control and experimental animals a progressive decrease in the amplitude of the EEG began after compression of the brachiocephalic vessels for about 10-13 sec. After 20-22 sec, against the background of a continuing fall of amplitude, the continuous EEG tracing disintegrated into periods of electrical silence of the cortex, short periods of rhythmic low-frequency activity, and separate high-amplitude waves. Later the rhythmic activity was completely suppressed, and after 30 sec the amplitude of the separate, infrequent waves fell below 2 μV (Fig. 1b).

After removal of the ligatures from the cervical arteries in the control experiments the EEG was not completely restored. Toward the 90th minute of the postischemic period the power index had reached only 30% of its initial values. Spikes and pointed waves were recorded on the EEG (Fig. 3, Table 1).

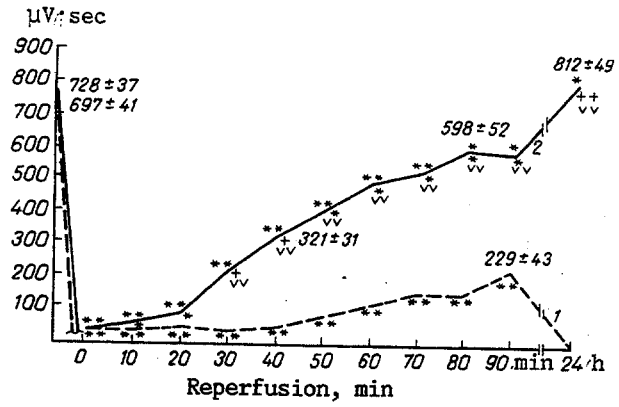

Fig. 2

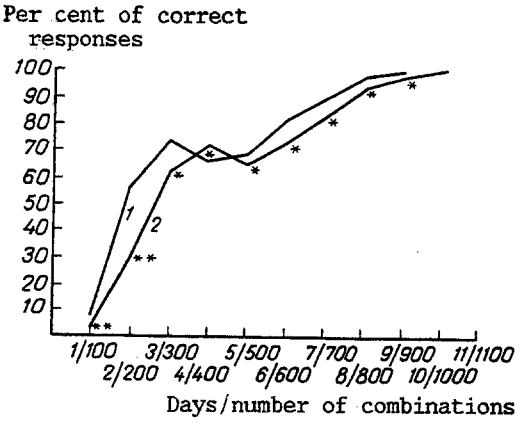

Fig. 3

Fig. 2. Time course of restoration of EEG power index after cerebral ischemia for 25 min, and against the background of acelizine, given in a dose 150 mg/kg 30 min before ischemia: 1) control, 2) experiment. *p < 0.05, **p < 0.01: Significance of differences from background values. +p < 0.05, ++p < 0.01: Significance of differences from previous values. p < 0.05, p < 0.01: Significance of differences from control.

Fig. 3. Time course of formation of conditioned active avoidance reflex in rats subjected to cerebral ischemia for 25 min, against the background of acelizine given in a dose of 150 mg/kg 30 min before ischemia (experiments) and in animals undergoing mock operation (control). 1) Reflex formation 8 days after operation in control; 2) reflex formation 8 days after exposure to ischemia. *p < 0.05, **p < 0.01: Significance of differences from control.

TABLE 1. Power Index of EEG in Reperfusion Period for Animals Exposed to Cerebral Ischemia for 25 min and Receiving Acelizine in a Dose of 150 mg/kg 30 min before Ischemia

Time af. beginning of reperfusn.	Control	Experiment	p
Background	697±41	738±41	
0—1 min	32±8**	37±12**	
10 min	35±7**	46±13**	
20 »	37±11**	78±21**	
30 »	28±8**	218±26**,+	<0,01
40 »	41±7**	321±31**,+	<0,01
50 »	79±6**	405±34**	<0,01
60 »	109±17**	491±38**	<0,01
70 »	150±23**	523±47**	<0,01
80 »	156±47**	598±52	<0,01
90 »	229±43**	586±57	<0,01
12—24 h	20±4**,++	812±49++	<0,01
n	12	11	

Legend. *p < 0.05, **p < 0.01: Significance of differences from background values; +p < 0.05, ++p < 0.01: Significance of differences from previous values. p) Significance of differences compared with control; n) number of experiments.

TABLE 2. Ability of Animals Exposed to Cerebral Ischemia for 25 min and Previously Given Acelizine in a Dose of 150 mg/kg 30 min before Ischemia (experiment) and in Animals Undergoing Mock Operation (control) to Form Active Avoidance Reflex. Estimates of 10% of Positive Responses to 100 Combinations of Stimuli Light–Electric Current Presented on 1 Day

Group of animals	Days of training										
	1	2	3	4	5	6	7	8	9	10	11
Control	8,5±1,5	55,4±3,8	74,3±8,5	66,7±8,1	68,3±7,9	82,1±5,3	90.1±3,7	97,8±2,7	99,7±0,5	99,7±0,3	
Experiment	3,2±0,2**	29,8±3,1**	62,3±7,9	72,3±8,6	65,8±7,4	73,1±7,4	84,5±6,8	94,9±4,8	97,7±1,1	99,7±0,3	99,7±0,3

Legend. *$p < 0.05$, **$p < 0.01$: Significance of differences from control. n) Number of experiments.

In the experiments with acelizine, the EEG began to recover on average at the 30th minute of reperfusion, and virtually simultaneously in all parts of the cerebral cortex studied (Fig. 1b, Fig. 2, Table 1). By the 40th minute a continuous EEG was recorded, and PI was 50% of the initial value. By the 90th minute of the postischemic period the complex composition of the EEG was virtually fully restored and PI had returned close to its initial value. However, the amplitude–frequency characteristic curve was not completely restored until 24 h after the end of ischemia, and components indicating the presence of pathological processes in the CNS (spikes, pointed waves, paroxysmal activity, etc.) were absent from the EEG, whereas they were clearly defined in the control experiments.

Evaluation of higher nervous activity showed that ability to learn was fully restored 8 days after the operation in animals exposed to cerebral ischemia for 25 min and receiving preliminary acelizine. Just as in the control experiments (animals undergoing a mock operation), to obtain stable reinforcement of the active avoidance reflex, about 900 combinations of light – electric current had to be presented (Fig. 2, Table 2).

Differences in the responses to stimulation were exhibited only for the first 2 days, evidently due to the more severe course of the postoperative period in the experimental series.

Thus acelizine, in a dose of 150 mg/kg, injected into rats 30 min before creation of total complete cerebral ischemia lasting 25 min, promotes complete recovery of CNS function and of higher nervous activity 8 days after exposure to ischemia.

LITERATURE CITED

1. M. V. Bilenko, P. G. Komarov, V. I. Tel'pukhov, et al., Contemporary Aspects of the Clinical Use of Acetylsalicylic Acid [in Russian], Khar'kov (1990), pp. 8-9.
2. V. D. Rozvadovskii, S. O. Trenin, and V. I. Tel'pukhov, "A method of modeling cerebral ischemia," Inventor's Certificate No. 1057979; Otkrytiya, No. 44 (1983).
3. G. Paxinos and C. Watson, The Rat Brain in Stereotaxic Coordinates, New York (1982).