CHANGES IN BEHAVIORAL AND ELECTROPHYSIOLOGICAL PARAMETERS IN RATS WITH CEREBROVASCULAR DISTURBANCES

Yu. V. Burov, M. Yu. Kosoi, T. S. Gan'shina, G. M. Molodavkin, and R. S. Mirzoyan

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Neurological disturbances caused by ligation of the cerebral vessels have been described in animals of different species [7, 9-11]. According to data in the literature [12, 13] ligation of the right middle cerebral artery in rats causes increased spontaneous motor activity and changes in aggressiveness at various times after the operation. Meanwhile no systematic investigations of the behavior and bioelectrical processes in the CNS during cerebrovascular disturbances could be found in the literature. This line of research seems important in order to understand the connection between cerebrovascular disturbances and brain function.

The aim of this investigation was to study the blood supply of the brain and behavioral and electrophysiological parameters in rats after ligation of both common carotid arteries.

EXPERIMENTAL METHOD

Experiments were carried out on 94 noninbred male albino rats weighing 200-300 g. A disturbance of the cerebral circulaton was produced by bilateral ligation of the common carotid arteries under general anesthesia (pentobarbital, 40 mg/kg). Rats undergoing mock operations, limited to the stage of access to the carotid arteries, served as the control. The cerebral blood flow was recorded by the hydrogen clearance method [5], and platinum electrodes 0.3 mm in diameter were inserted into the parietal cortex of the rats stereotaxially for this purpose. Hydrogen clearance was recorded on an Lp7e polarograph (Czechoslovakia). The animals' behavior was assessed by studying changes in their motor and orientating-investigative activity, and also the ability of the animals to learn by the use of negative reinforcement techniques. Motor and orienting-investigative activity was studied by means of an "Opto-Varimex" recorder (Columbus, USA), and in the open field test (intensity of illumination 25,000 lx). A conditioned passive avoidance reflex (CPAR) was produced by a modified method [6], based on the inborn tendency of rats to seek a confined, darkened space. A conditioned bilateral active avoidance reflex (CAAR) was produced in a shuttle box [1]. The combination of a conditioned acoustic stimulus and painful electrical reinforcement through the electrode floor, 5 sec after the beginning of conditioned stimulation, was used. The animal could avoid painful stimulation by moving to the opposite half of the box during 5 sec after application of the conditioned stimulus, and this was regarded as a correct response, or the animal could avoid stimulation by the same method. The rats were trained for 3 days and 60 combinations were presented each day. The criterion of learning was taken to be seven correct responses out of 10. The number of intertrial responses also was taken into account. The effect of bilaterial ligation of the carotid arteries on recovery cycles of the primary response of the sensomotor cortex of the rat to sciatic nerve stimulation [4] and on the duration of preservation of the EEG after termination of artificial respiration [15] also was evaluated. Acute electrophysiological experiments were carried out 5-7 days after the operation, on the rats simultaneously (one from the experimental and one from the control group). The results were subjected to analysis by Student's test [2] and by means of the nonparametric signs test and Wilcoxon—Mann—Whitney test [3].

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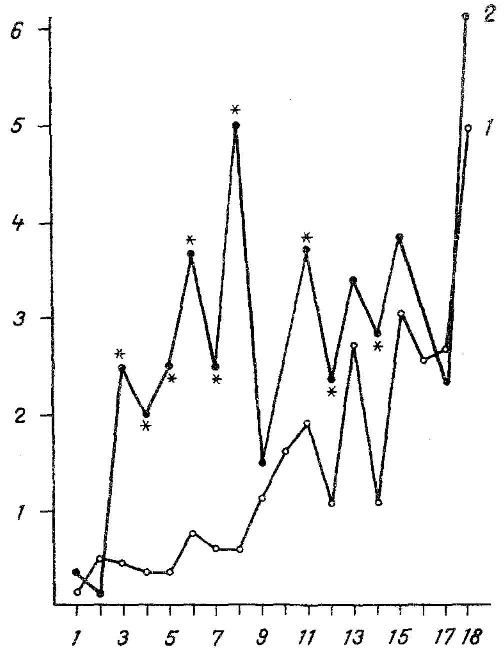

Fig. 1

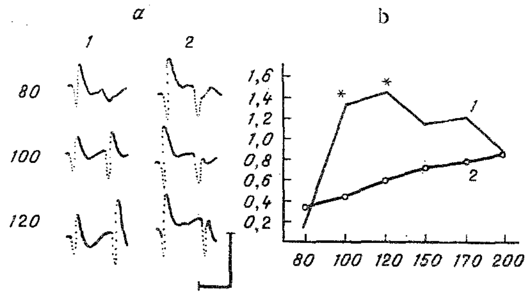

Fig. 2

Fig. 1. Time course of CAAR production in rats in shuttle box. Abscissa, serial number of group of 10 combinations; ordinate, ratio of number of avoidances (correct responses) to number of intertrial responses (in relative units). 1) After ligation of common carotid arteries; 2) after mock operation. *) Differences between curves significant at the $p \leqslant 0.05$ level.

Fig. 2. Changes in recovery cycles of primary response of rat sensomotor cortex after ligation of common carotid arteries. a) Averaged responses to stimuli separated by intervals of 80, 100, and 120 msec. 1) After ligation of carotid arteries; 2) after mock operation. Numbers on left of traces indicate intervals between stimuli (in msec). Calibration: 80 msec, 500 μV; b) recovery cycles of primary response plotted from results of the same experiment. Abscissa, intervals between stimuli (in msec); ordinate, ratios of amplitudes of testing and conditioning responses (in relative units). *) Differences between curves are significant at the $p = 0.05$ level.

EXPERIMENTAL RESULTS

The cerebral blood flow in the parietal cortex of the rats 24 h after ligation of the carotid arteries was reduced on average by 61 ± 7.8% (39-83%). After the 3rd day partial recovery of the cerebral blood flow was observed in the majority of animals. During the 24 h after ligation of the carotid arteries 20% of the animals died. Some animals also died during the next 3 weeks. After the operation a progressive loss of body weight was observed in all the rats during the first 5-7 days, on average by 25 ± 2% (21-29%). Clear correlation was found between the survival rate of the animals and changes in their body weight.

In rats with a disturbed cerebral hemodynamic apathy, lethargy, and disturbances of movement coordination were observed. On the first day spontaneous motor activity, recorded automatically, was reduced in the experimental rats by a greater degree (by 1.7 times) than in the control. It must be noted that later motor activity of the experimental rats was increased. This is evidence of the absence of extinction of the orienting-investigative reflex, unlike in the control and intact animals.

When the rats were investigated by the CPAR method 24 h after ligation of the carotid arteries a disturbance of their instinctive behavior was observed: 48% of the animals did not rush into the darkened compartment of the box from the lighted compartment. On the 2nd day this behavioral disturbance was observed in 26%, and on the 7th day in 18% of rats. Among the control and intact animals, reversal of preference for the darkened compartment instead of the lighted compartment occurred in 2% of the rats. The behavioral disturbance in the experimental group cannot be explained by a reduction of motor activity, for no correlation was observed between this disturbance and horizontal activity in the open field test. However, with respect to ability to form and preserve CPAR, the experimental rats with undisturbed instinctive behavior did not differ significantly from the control.

Meanwhile, during CAAR formation differences were found between animals of the experimental and control groups. Both learning to avoid painful stimulation and the formation of avoidance skill took place more slowly in rats with disturbed cerebral hemodynamics than in animals undergoing the mock operation. On the 1st day of the experiment no animal reached the criterion of trained. On the 2nd day the number of rats reaching this criterion was 31% in the experimental and 57% in the control group, whereas on the 3rd day the proportions were 50 and 73%, respectively. Parallel with acquisition of avoidance skill, the number of intertrial changes of compartments increased, to reach a maximum by the end of the 2nd day, and it fell to the original values toward the end of the 3rd day, in the course of stabilization of CAAR. The number of intertrial moves during the first 2 days was significantly greater than in the control. To evaluate the goal-directedness of the rats' behavior during CAAR formation, the ratio between the number of correct responses and the number of intertrial moves was used as the indicator. It clearly demonstrates differences in the time course of the responses to the conditioning stimulus in the animals of both groups. These differences were manifested most clearly in the first 2 days (Fig. 1).

The large number of intertrial moves made by rats with cerebrovascular disturbances may indicate the reduced ability of the animals to form temporary connections between the conditioned and unconditioned stimuli, and also disturbance of the balance between excitation and inhibition in the CNS. To solve this problem, recovery cycles of primary responses in the somatosensory cortex were investigated. The phase of depression of the test response (a decrease in amplitude) was most marked both in intact animals and those undergoing the mock operation when the intervals between stimuli measured 80-125 msec. After bilateral ligation of the carotid arteries depression of the test response weakened compared with the control, and the effect was most marked and stable when intervals between stimuli measured 80-100 msec (Fig. 2). When artificial respiration was discontinued, the EEG was observed to disappear first in rats with a disturbed cerebral hemodynamics, and later in the control animals. Recovery of the EEG when the breathing apparatus was restarted took place in the opposite order.

The phase of depression of the test response is known to reflect activity of the cortical recurrent inhibition system [14], for which the mediator is GABA [8]. Changes observed in this parameter after ligation of the carotid arteries are evidence of depression of the functional activity of the GABA-ergic system. We also know that GABA is an inhibitory mediator, largely responsible for determining the level of excitability of the brain. Weakening of inhibitory processes as a result of disturbance of the cerebral circulation thus probably is largely responsible for the high level of random motor activity during the use of the conditioned active avoidance reflex method.

Disturbance of the cerebral circulation in rats thus gives rise to disorders of the vital functions and of inborn behavior and also impairs the ability to learn in association with weakening of inhibition in the CNS.

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