EFFECT OF ACUTE HYPOXIA IN THE ANTENATAL PERIOD ON FUNCTIONS OF THE HIGHER LEVELS OF THE CNS IN RATS

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A decrease in motor activity, depression of the orienting reflex, and its faster extinction than in control animals were observed in sexually mature rats exposed to acute hypoxia in the antenatal period. Disturbances of conditioned reflex activity indicating impairment of fixation of the temporary connection, weakening of inhibition, and lowering of the mobility of nervous processes were discovered in the experimental rats. When tests involving "difficult" tasks were presented the experimental rats developed epiliptiform seizures. An increase in predisposition to seizures also was observed after administration of threshold doses of metrazol.

KEY WORDS: *Intrauterine hypoxia; brain; higher nervous activity.*

There is clinical evidence of the special pathogenetic role of fetal hypoxia in the development of mental backwardness [5-7, 9]. Experimental fetal hypoxia leads to developmental disturbances and pathological changes in the brain [1-4, 10].

In this investigation the functions of the higher levels of the CNS were studied in the postnatal period in rats exposed in utero to acute hypoxia.

EXPERIMENTAL METHOD

On the 14th-16th day of pregnancy female rats were placed in a pressure chamber in which an altitude of 8000-9000 m was simulated for 2 h. The progeny of the experimental and control animals was kept under identical conditions until the age of 2 months. The behavior of the rats was investigated by a method using an "open field" (45×45 cm), divided into 9 squares. Every 5 min the number of times the rats moved into adjacent squares, climbed vertically, sniffed at holes in the center of each square, and defecated was counted.

A conditioned passive avoidance reflex (CPAR) was formed by the single learning method in a special chamber [8]. The latent period from placing the animal in the illuminated compartment of the chamber until the rat moved into the dark compartment, where it was given an electric shock, was recorded. Preservation of the CPAR was tested after 24 h. The length of time that the rats stayed in the illuminated compartment of the chamber was recorded up to a maximal time of observation of 600 sec. A defensive conditioned active avoidance reflex (CAAR) was formed in a Y-shaped maze. A light switched on in one of the passages of the maze served as the conditioned stimulus. The CAAR, in the form of running into the illuminated passage, was produced up to the level of six correct runs out of seven. Preservation of the CAAR was verified after seven days by reconditioning. The index of preservation (IP) was calculated as the ratio, in per cent, between the difference in the number of combinations required to produce the reflex in the original and repeated experiments and the number of combinations in the original experiments.

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TABLE 1. Behavior of Rats in Open Field

Index	Control animals				Experimental animals			
	1—5 min	6—10 min	%	1—10 min	1—5 min	6—10 min	%	1—10 min
Motor activity (number of crossings of boundaries): horizontally	9,1	4,0	43	13,1	7,6	2,1	27*	9,8*
vertically	9,1	4,1	45	13,2	6,8	1,0	14*	7,8*
Sniffing at holes	3,5	3,1	88	6,6	4,3	1,1	25*	5,4
Washing	2,7	2,0	74	4,7	3,8	1,9	50*	5,7
Defecation				2				1

Note. Here and in Tables 2 and 3 values differing by a statistically significant degree from the control are marked by an asterisk.

TABLE 2. Formation and Testing of Preservation of CPAR

Animals	Number of animals	Duration of stay in illuminated compartment, sec	
		during formation of CPAR	during testing of preservation of CPAR
Control	13	7,9	299,2
Experimental	21	22,5*	543,5*

TABLE 3. Conditioned Active Avoidance Reflex

Index	Control animals	Experimental animals
Formation of CAAR (number of combinations)	26	8*
Testing its preservation (number of combinations)	8	4*
Mean IP	51.4	28.7*
Modification of CAAR (number of combinations)	25	21
Testing its preservation (number of combinations)	13	10
Extinction of CAAR (per cent of runs into dark passage)	46	38

To investigate the predisposition of the rats to seizures a 2% solution of metrazol was injected subcutaneously in a dose of 30 mg/kg. Statistical analysis of the results was carried out by the use of the Wilcoxon—Mann—Whitney criterion and by a modified Fisher's method. Altogether 24 experimental and 14 control noninbred rats were used.

EXPERIMENTAL RESULTS

The weight of the animals exposed in the antenatal period to acute hypoxia averaged 173 (116-230) g and that of the control rats 246 (215-310) g at the beginning of the investigation.

Tests by the open field method (Table 1) showed that in the experimental animals motor activity during movements in the horizontal and vertical directions was significantly reduced. Comparison of results obtained during the first and next periods of 5 min revealed a sharp decrease in motor activity in the second period of the test compared with the control animals. Similar results also were obtained by other tests (sniffing the holes, washing movements). The experimental animals defecated only half as often as the controls. These results are evidence of a decrease in motor activity, depression of the orienting reflex, its more rapid extinction in the experimental rats, and a decrease in their emotional response to the new situation.

TABLE 4. Number of Animals Responding by Seizures at Different Stages of the Investigation

Index	Control animals			Experimental animals		
	total No. rats	seizures		total No. rats	seizures	
		absolute	%		absolute	%
Formation of CAAR to light	14	0	0	24	0	0
Testing preservation of CAAR	14	0	0	24	3	12,5
Reversing CAAR to running into dark passage	14	0	0	21	9	43
Testing preservation of CAAR	14	0	0	12	3	25
Restoring CAAR to light	14	0	0	21	7	33
Extinction of CAAR	12	0	0	12	5	41
Metrazol (30 mg/kg)	15	5	33	19	17	90

During formation of the CPAR the experimental rats stayed longer (almost 3 times) in the illuminated compartment of the chamber than the controls. The IP of the CPAR in the experimental rats was significantly higher than in the controls (Table 2).

During formation of the CAAR the experimental rats required fewer combinations than the controls (Table 3). Indeed a CAAR was formed in five of the 24 experimental animals after the first combination, but in other rats the CAAR was more difficult to form. In 15 experimental animals IP after 7 days was negative, but in nine animals it was positive. Meanwhile, a negative IP was observed in only three of the 14 control animals. On the average, IP for CAAR in the experimental animals was reduced to almost half its value in the controls, indicating marked disturbance of fixation of the temporary connection. During reversal of the CAAR — so that the rats ran into the dark passage, the rate of formation and preservation of the new conditioned reflex in the experimental animals differed only a little from in the controls. The original reflex of running into the illuminated passage was later restored and then extinguished by presenting 50 combinations without reinforcing electric shock. Under these circumstances it was difficult to extinguish the CAAR in the experimental rats (Table 3).

On the presentation of "difficult" experimental tasks (reversal of the reflex, testing its preservation, extinction of the CAAR) to the experimental animals 80% of them developed generalized seizures (Table 4). Seizures occurred particularly often during reversal of the CAAR and during its extinction (41-43% of animals). In the control group under the same experimental conditions, no rat showed convulsions.

Most rats which developed convulsions were eliminated from further experiments and the results for testing the preservation of the reflex of running into the dark passage, restoration of the original reflex to light, and its extinction were accordingly obtained with a relatively small number of animals, too small to be significant. In nearly all the experimental animals (in 17 of 19) seizures developed after subcutaneous injection of 30 mg/kg metrazol. In the control group this dose of metrazol caused convulsions in only one-third of the animals.

The results suggest that whereas there was a general lowering of tone of the higher levels of the CNS in the experimental animals, inhibition was disturbed to a greater degree, so that there was a relative predominance of excitation. This is shown by the more rapid formation and the less easy extinction of the conditioned reflex, and also by the increased predisposition to seizures. The lowering of the mobility of the nervous processes in the experimental animals was revealed during reversal of the role of the conditioned stimuli, which proved to be beyond the ability of nearly half of the experimental animals and led to the development of severe excitation and convulsions. Other facts which merit mention include the lengthening of the latent period of formation of the CPAR and the more rapid formation of the CAAR to light (after the first combination in 20% of rats), so that a disturbance of the ecologically determined preference of darkness to light can be presumed to have taken place in half of the experimental rats.

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DYNAMICS OF DENDRITIC AND TRANSCALLOSAL CORTICAL POTENTIALS DURING HYPERTHERMIA

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Dendritic and transcallosal potentials in the course of hyperthermia and after restoration of temperature homeostasis were investigated in experiments of waking rabbits exposed in a heat chamber to an air temperature of 45°C. The effect of the high temperature was accompanied by marked depression of the amplitude of the dendritic potential, although by a lesser degree than the transcallosal response. The results are evidence of the direct inhibitory effect of heat on neurons in the various layers of the cortex. Restoration of the function of the cortical neurons after a high degree of hyperthermia is observed 24 h after normothermia is reached.

KEY WORDS: *Hyperthermia; cerebral cortex; evoked potentials.*

Experimental and clinical evidence have now been obtained to show that during hyperthermia the rhythm of the global electrocorticogram (ECoG) is slowed and its amplitude increased [3-5, 7, 10, 13, 15] and evoked potentials in specific cortical projection zones in response to adequate stimulation of receptors are sharply inhibited [4, 8]. However, it is impossible from these data to assess objectively the effect of a high temperature directly on cortical neurons, for the changes recorded largely reflect the functional state of subcortical structures also.

In the investigation described below the method of recording dendritic and transcallosal potentials was used in a direct study of cerebral cortical function in the course of hyperthermia and after restoration of temperature homeostasis.

EXPERIMENTAL METHOD

Experiments were carried out on 15 adult rabbits without the use of anesthetics or muscle relaxants. In most cases two experiments were carried out on each rabbit at an interval of 1 week. Two days before the experiment, under superficial pentobarbital anesthesia, stainless steel needle electrodes with an active tip 100 μ in diameter and an interelectrode

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