BEHAVIORAL FEATURES AND PROTEIN SYNTHESIS IN THE BRAIN OF RATS RECEIVING ETHANOL WITH MATERNAL MILK

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KEY WORDS: brain; behavior; protein synthesis; ethanol; lactation.

The effect of ethanol on the developing brain may be manifested in the course of its administration not only in the antenatal, but also in the early postnatal period, before development of the brain is complete. The principal mode of entry of ethanol into the neonate is with the maternal milk during lactation. Ethyl alcohol, administered during lactation, has been found in an amount of 0.25-0.65% of the administered dose in the milk of goats, cows, sheep, and dogs, as well as of lactating women [6]. Due to the low activity of alcohol-degrading enzymes in the tissues [7] and to its slow excretion in the newborn [8], ethanol administered with milk may have a long-term action on the recipient. Observations have shown delayed development of the brain, functional disturbances, and structural changes in the CNS of animals receiving ethanol in the early postnatal period [3-5].

The aim of this investigation was to study the effect of ethanol, administered to lactating female rats on behavioral reactions, parameters of conditioned-reflex activity, and protein synthesis in the brain of the progeny in late ontogeny.

EXPERIMENTAL METHOD

Female rats were given a 10% solution of ethanol instead of drinking water from the 3rd through the 20th days after giving birth; in addition, they were given 2 ml of 40% ethanol by gastric tube 3 times a week. The total daily dose was 5-8 g/kg body weight. Behavioral responses were studied in the progeny of these animals, starting with the age of 2 months. Horizontal and vertical motor activity, investigative activity, the grooming reflex, and defecation were recorded by the open field method in two consecutive periods, each of 2 min, in a darkened room and also in bright light. Formation and preservation of passive defensive conditioned reflexes (CPAR) also were studied by the single learning method with maximal testing time of 300 sec, and by the active avoidance method (CAAR) in a shuttle box (the conditioned stimuli were interrupted light and sound). The sensitivity to an audiogenic stimulus (a bell, 100 dB) also was determined. Protein synthesis in the brain was studied with the aid of ^{35}S-methionine, injected intraperitoneally, and the intensity of its incorporation (relative specific activity — RSA) into water-insoluble and water-soluble proteins was determined in six brain structures. Altogether 55 noninbred rats were used in the experiments. The significance of differences between the results was estimated by Student's and the Wilcoxon–Mann–Whitney tests.

EXPERIMENTAL RESULTS

The behavioral characteristics of the animals in the open field test are shown in Fig. 1. Male rats of the experimental group showed no significant changes in their motor activity. Under different experimental conditions (with diffuse and bright light) their behavior was characterized by a significant increase in the number of groomings and defecations. In the experimental female rats under ordinary lighting conditions motor and investigative activity was sharply reduced ($p < 0.05$) and the number of defecations was increased. Under stress conditions, when animals of the control group were exposed to bright light, their motor and

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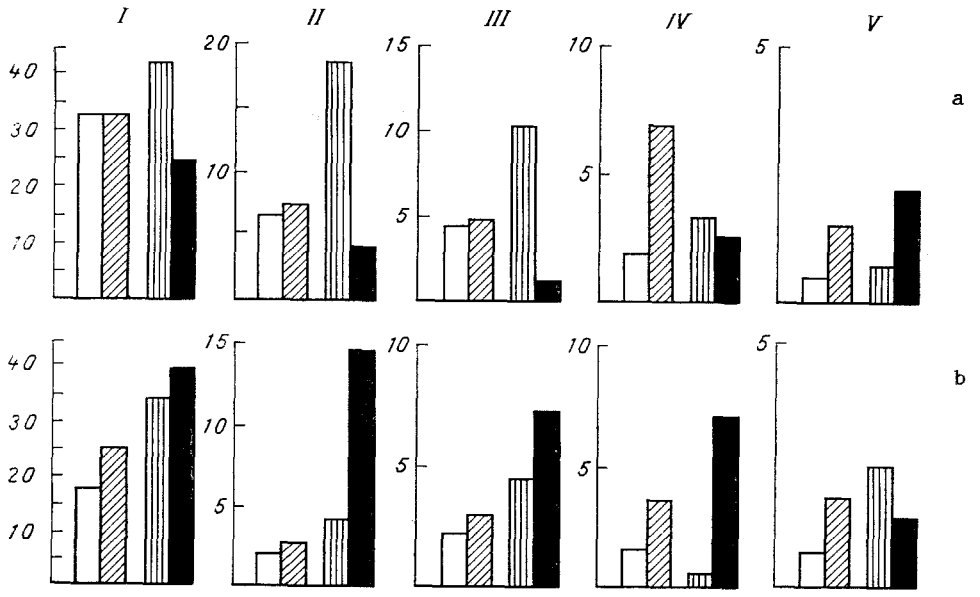

Fig. 1. Parameters of open field behavior in rats. I) Horizontal, II) vertical motor activity, III) investigative activity, IV) grooming, V) defecation. a) Diffuse light, b) bright light. Unshaded columns and obliquely shaded columns — control and experimental males; horizontally shaded and black columns — control and experimental females.

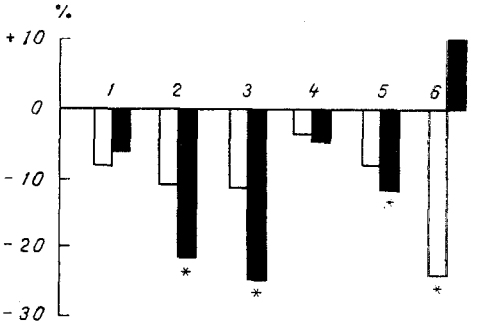

Fig. 2. Changes in incorporation of ^{35}S-methionine into proteins in different parts of the brain (in % of control). 1) Cerebral cortex, 2) hippocampus, 3) corpus striatum, 4) cerebellum, 5) medulla, 6) hypothalamus. Unshaded columns — water-insoluble proteins, black columns — water-soluble proteins.

investigative activity and the number of groomings were reduced. Meanwhile, motor activity and the number of specialized responses (groomings) in the experimental animals increased, i.e., the changes were opposite in direction. Changes in the number of defecations also were opposite: an increase in the control, a decrease in the experimental group.

The study of parameters of CPAR (Table 1) showed that the latent period of formation of the reflex (the time until the animal went into the dark compartment) in the experimental male rats was virtually unchanged compared with the control, whereas in females it was reduced ($p < 0.05$). On testing preservation of CAAR in the experimental animals, significant disturbance of preservation of the reflex was discovered: The males left the safe area of the chamber 2.6 times faster and the females 1.8 times faster than the control rats. Thus the main components of preservation of CAAR in the experimental animals of both sexes were significantly disturbed.

Investigations of CAAR formation and preservation (Table 2) showed that during primary training and retraining of the experimental rats no significant changes were found with respect

TABLE 1. Parameters of Formation and Preservation of CPAR in Rats Receiving Ethanol during Lactation

Group of animals	Number of animals	Duration of stay in lit compartment, sec	
		CPAR formation	testing CPAR preservation
Males			
Control	10	14,50±2,80	228,80±30,65
Experimental	16	18,44±5,27	88,25±30,87*
Females			
Control	14	16,62±2,44	220,23±32,72
Experimental	15	9,27±0,78*	124,13±32,51*

Legend. Here and in Table 2: *p < 0.05.

TABLE 2. Parameters of Formation and Preservation of CAAR in Rats Receiving Ethanol during Lactation

Group of animals	Appearance of		Number of escapes
	first avoidance	first escape	
	combination	combination	
CAAR formation			
Males			
Control	17,8	22,8	11,1
Experimental	10,7	24,8	12,2
Females			
Control	15,4	31,5	4,0
Experimental	10,5	22,1*	6,3
CAAR preservation			
Males			
Control	12,1	24,0	13,9
Experimental	4,8	11,5	17,45
Females			
Control	3,4	22,7	13,8
Experimental	7,68	23,4	7,9

to the majority of parameters of CAAR compared with the controls. Nevertheless, during CAAR formation training of the experimental animals was rather faster, especially in female rats, which showed more rapid appearance of the first avoidance and the first escape, as well as an increased number of escapes. However, consolidation of the temporary connection was disturbed in this group of animals. The number of escapes was reduced almost by half, and appearance of the first avoidance was delayed to the same degree. In male rats preservation of CAAR was not affected.

The results show that administration of ethanol during lactation is reflected only in certain types of conditioned-reflex activity. Besides significant disturbances of preservation of CPAR the basic parameters of CAAR, especially in male rats, remained relatively intact. No differences could be found between control and experimental animals when the response to an audiogenic stimulus was studied. Thus in almost an equal number of experimental rats in each group motor excitation was observed. Generalized seizures did not occur in the experimental and control animals.

To detect differences in the pattern of protein metabolism in the brain of the experimental and control male rats, incorporation of ^{35}S-methionine into the water-soluble and water-insoluble fractions of proteins from different parts of the brain was determined in experimental and control rats aged 3 months. The results of these experiments (Fig. 2) show that incorporation of amino acids into the brain proteins was reduced in animals receiving ethanol with the maternal milk. Changes in synthesis of water-insoluble and water-soluble proteins

differed in degree. Significant inhibition of synthesis of water-insoluble proteins, to the greatest degree, was observed in the hypothalamus, and in the other structures it was less marked. Incorporation of ^{35}S-methionine into water-soluble proteins of the experimental animals was significantly reduced in the hippocampus, subcortical formations and the medulla, and it was reduced by a lesser degree in the cerebral cortex and cerebellum. Some degree of activation of protein synthesis was observed in the hypothalamus. Comparison of the results with data on the action of ethanol administered in the antenatal period on brain protein synthesis [1, 2] reveals definite similarity: inhibition of incorporation of precursors into brain proteins. Some differences were found in the effect of ethanol during each of these periods. Whereas with intrauterine exposure to ethanol synthesis of water-insoluble proteins was disturbed by a greater degree, mainly in the hippocampus and neocortex, postnatal administration of ethanol was accompanied in late ontogeny by marked inhibition of synthesis of water-soluble proteins in several brain structures. Meanwhile, changes of this kind in water-insoluble proteins were observed mainly in the hippocampus.

Disturbances of metabolism of individual groups of proteins in certain brain structures may lie at the basis of changes in behavioral responses and may be reflected in integrative activity of the brain. As was shown above, the action of ethanol in the early postnatal period led to disturbances of certain forms of learning (CPAR) but had no significant effect on CAAR, i.e., it was selective in character. Antenatal alcoholization gave rise to more marked changes in various forms of behavioral reactions than exposure to ethanol in the lactation period. These results are evidently linked both with the action of ethyl alcohol on different stages of ontogenetic maturation of the CNS and with its smaller doses transmitted with maternal milk.

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STAGE OF INHIBITION OF LIPID PEROXIDATION DURING STRESS

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One result of exposure of the body to stress is activation of free-radical lipid peroxidation (LPO), leading to damage to cell membrane structures [2, 7]. However, the question of the pathogenetic role of different stages of stress and of their particular features remains unexplained; in particular, it is not clear what changes in LPO take place during the little-studied early stage of stress.

The aim of this investigation was to study the state of LPO in the brain and blood of rats during exposure to acute stress and to compare it with changes in the parameters of LPO during a pain syndrome.

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