ELECTROGRAPHIC CORRELATES OF THE ANTIAMNESIC ACTION OF NOOTROPIC AGENTS AFTER DEPRIVATION OF THE PARADOXICAL PHASE OF SLEEP

L. N. Nerobkova, T. A. Voronina,
N. V. Markina, and
I. Kh. Rakhmankulova

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Deprivation of the paradoxical phase of sleep (PPS) leads to a disturbance of a group of interconnected neurochemical, behavioral, and electrophysiological parameters [1]. One of the most important manifestations of these changes is a disturbance of learning and memory [2, 3, 7, 9], which is linked with the basic neurochemical changes observed during deprivation of PPS, and consisting of a disturbance of nucleic acid and protein synthesis [1].

On the other hand hand, drugs with a nootropic type of action abolish amnesia induced by various damaging factors, and neutralize the metabolic disturbances [4, 7, 8, 10]. However, from the electrophysiological aspect, the mechanism of the antiamnesic action of nootropic drugs has virtually not been studied. We know that during PPS electrical activity of the hippocampus is characterized by a well-marked theta-rhythm, which can be subdivided into tonic (4-6 Hz) and phasic (7-12 Hz) components, differing in their functional and neurochemical basis [6, 11-13].

The aim of this investigation was to undertake an electrophysiological analysis of the action of nootropic drugs and to discover the electroencephalographic correlates of their antiamnesic action.

EXPERIMENTAL METHOD

Experiments were carried out on male albino rats weighing 180-220 g with chronically implanted electrodes. Electrical activity of the sensomotor cortex and dorsal hippocampus and the myogram of the neck muscles were studied. The duration of falling asleep (the period from the beginning of recording of the EEG 30 min after injection of the drug until the appearance of the first slow-wave phase of sleep) and the duration of episodes of awakening and of the two phases of sleep – fast (PPS) and slow-wave (SWS) sleep. During PPS, spectral analysis of the EEG was undertaken. Electrical activity was recorded on a "Neirograf-18" electroencephalograph and the data were processed on BAS-161 neurocomputer ("O.T.E. Biomedica," Italy).

The animals were trained in passive avoidance conditioning (PAC) [3]. Preservation of PAC was judged from the time spent by the rats in the lit compartment of the chamber, the maximal duration of observation being 3 min, 24 h after the training session. Immediately after training the rats underwent PPS deprivation, using a technique of small platforms in a basin of water for 24 h [3].

The test substances were injected intraperitoneally 40 min before the training session in the following doses: meclofenoxate 50 mg/kg, cleregil 100 mg/kg, phenazepam 1 mg/kg, the antioxidant 2-ethyl-6-methyl-3-oxypyridine (3-OP) 50 mg/kg. The animals were divided into four groups with six rats in each group: 1) learning without deprivation of PPS; 2)

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TABLE 1. Effect of Drugs on Latent Period of Visit by Rats to Dark Compartment during PAC (M ± m)

Experimental conditions	Latent period, sec	
	during training	during reproduction
Control 1 (without PPS deprivation)	1,8±0,7	57,7±9,1
Control 2 (with PPS deprivation)	2,2±0,3	4,4±1,5
PPS deprivation + cleregil	3,1±0,6	19,7±2,2*
PPS deprivation + meclofenoxate	2,3±0,3	73,3±15,2*
PPS deprivation + 3-OP	2,1±0,4	68,8±2,2*
PPS deprivation + phenazepam	2,3±0,3	3,2±0,4*

Legend. *) Significant differences from control 2 ($p < 0.01$).

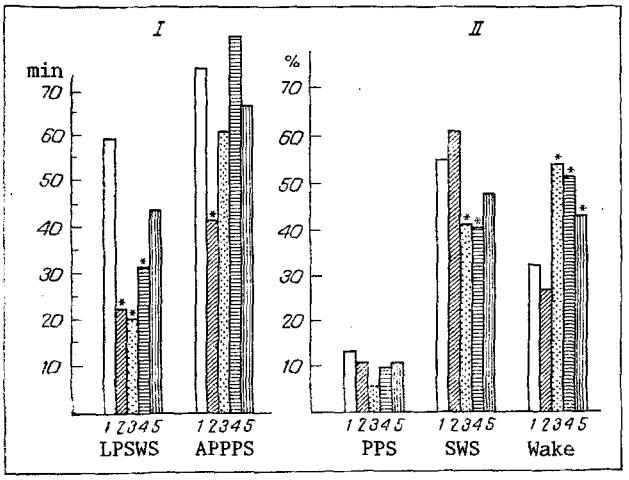

Fig. 1. Effect of drugs on sleep cycles of rats. Vertical axis, time, min (I) and fraction of phases of sleep, in % (II). 1) Control; 2) phenazepam; 3) cleregil; 4) meclofenoxate; 5) 3-OP. LP) Latent period; AP) active period; Wake) wakefulness. *$p < 0.05$ compared with control.

learning followed by deprivation of PPS; 3) learning preceded by administration of drugs and without deprivation of PPS; 4) learning preceded by administration of drugs and followed by PPS deprivation.

EXPERIMENTAL RESULTS

Deprivation of PPS induced amnesia of PAC, confirming results obtained by other workers [2, 7, 9]. When the response was reproduced after 24 h, a marked increase in the latent period of the rats' visit to the dark compartment was observed in group 1, evidence of reinforcement of the habit. In the rats of group 2, exposed to 24 h of PPS deprivation immediately after the traning session, the duration of the latent period of the visit to the dark compartment was the same as in the untrained rats, i.e., they completely lost their acquired skill (Table 1). Administration of the nootropic drugs abolished the amnesia: cleregil, in the dose tested, partially abolished the reproduction deficit, whereas meclofenoxate and 3-OP restored the control level of reproduction (training without deprivation). Unlike the nootropic drugs, phenazepam had no antiamnesic action and did not change the latent period of the visit to the dark compartment (Table 1). The electrophysiological control showed that under conditions of PPS deprivation the fraction of fast sleep fell from 13.5% in the control to 1.72%. THe test substances in this experiment did not affect these parameters, due to the experimental conditions, which presupposed interruption of PPS at its beginning due to the animal falling into the water immediately after relaxation of its

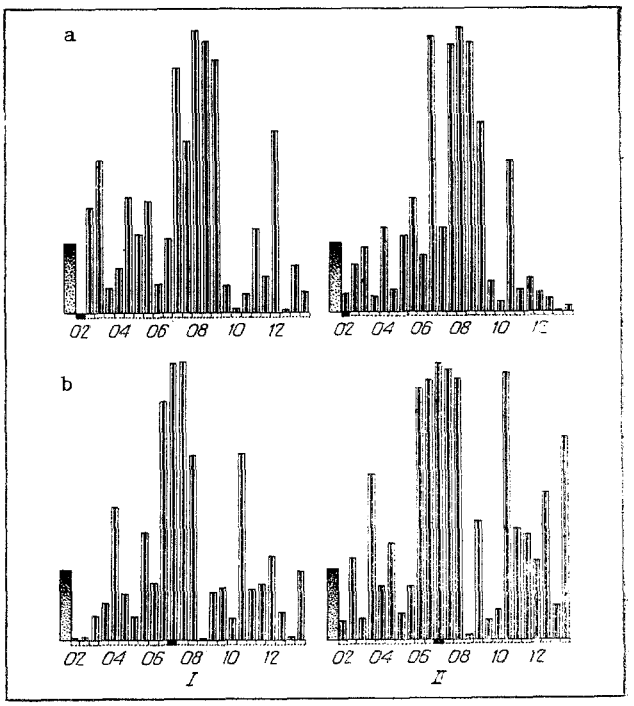

Fig. 2. Effect of learning on frequency spectra of EEG of sensomotor cortex (I) and dorsal hippocampus (II) recorded during PPS. a) Before learning PAC; b) after learning. Abscissa, frequency range from 0 to 22 Hz; ordinate, power of spectrum (in μV^2).

muscles. In the intact animals (without PPS deprivation) all the substances tested shortened the latent period of onset of SWS, but the time of onset of PPS was shortened only by phenazepam (Fig. 1). Following administration of meclofenoxate, cleregil, and 3-OP the fraction of both PPS and SWS was reduced and the fraction of the periods of wakefulness was increased; phenazepam, on the other hand, caused a decrease in the periods of wakefulness and an increase in the SWS fraction, while not significantly changing the relative contribution of PPS (Fig. 1).

To elucidate the mechanism of action of the drugs under conditions of PPS deprivation, spectral analysis of electrical activity of the sensomotor cortex and dorsal hippocampus under conditions of PPS deprivation was undertaken. During PPS in intact animals, a well-marked theta-rhythm was recorded on the hippocampal EEG, characterized by the presence of low-amplitude rhythmic activity (4-6 Hz) and by discharges of regular waves of higher amplitude (8-11 Hz). The cortical EEG revealed low-amplitude desynchronized activity with the presence of irregular fast and slow waves. After the training session, intensification of the phasic component of the theta-rhythm and an increase in the frequency of its two components were observed on the hippocampal EEG during PPS (Fig. 2).

Phenazepam caused stabilization of the theta-rhythm within the 6-7 Hz range and increased its amplitude (Fig. 3, 1). Cleregil and meclofenoxate, on the other hand, reduced the tonic component of the theta-rhythm. Under the influence of these drugs, and against the background of desynchronized electrical activity, bursts of high-frequency theta-rhythm (9-10 Hz) were recorded (Fig. 3: 2, 3). 3-OP caused intensification of the synchronized theta-rhythm, which was recorded not only in the hippocampus, but also in the cortex, with abundance of both components (Fig. 3: 4).

The investigations showed that deprivation of PPS by the small platforms method induces various behavioral and electrophysiological changes: besides the almost complete abolition of PPS, depression of the hippocampal theta-rhythm, especially of its phasic component, was observed and reproduction of PAC was considerably disturbed. An adverse effect of deprivation on learning has been obtained by many investigators, but the mechanism of this phenomenon has been interpreted differently [1, 2, 7, 9]. In this investigation a deficit of reproduction of PAC, disturbed by deprivation of PPS, correlated not only with shortening of the duration of PPS and SWS, but also with disappearance of the phasic component of the theta-rhythm,

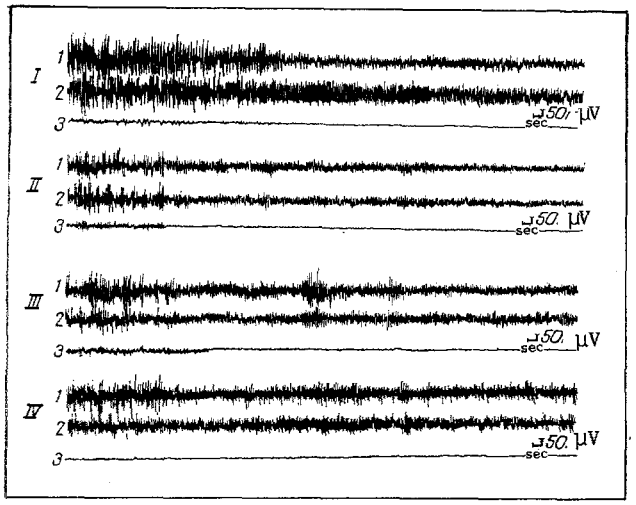

Fig. 3. EEG of sensomotor cortex (1), and dorsal hippocampus (2) during PPS against the background of action of drugs, myogram of cervical muscles (3). I) Phenazepam; II) cleregil; III) meclofenoxate; IV) soluble salt of 3-OP.

characteristic of PPS. Depression of the theta-rhythm is probably directly connected with the behavioral effects, and the abundance of its two components reflects the necessary level of activation of the structures for learning and recall. In Simonov's opinion [5] the theta-rhythm is characteristic of all processes connected with the abstraction of information from the memory.

The electrophysiological analysis yielded evidence that under the influence of both nootropic drugs and phenazepam the relative role of PPS is reduced. However, spectral analysis of the EEG revealed qualitative differences in their effects: substances with a nootropic type of action enhanced the phasic component of the theta-rhythm whereas phenazepam depressed it. It can be tentatively suggested that the electrophysiological correlates of the antiamnesic effect are preservation of a normal two-component theta-rhythm and enhancement of its phasic component, whereas disturbance of the structure of sleep, including reduction of PPS, is not a leading factor in the action on learning and memory.

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