# DISTURBANCE OF LEARNING AND THE SLEEP STRUCTURE IN RATS WITH COBALT-INDUCED EPILEPTOGENIC FOCUS IN THE SENSOMOTOR CORTEX

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The formation of an epileptogenic focus is accompanied not only by changes in electrical activity reflecting epileptization of brain structures [5, 9], but also by behavioral changes, including changes in motor activity and attention [12], and impairment of learning and memory [2, 8, 14]. Data on the influence of epileptiform discharges on the structure of the waking-sleep cycles are contradictory. Depending on the localizationn of the epileptic focus, various disturbances of the cyclic pattern of sleep have been described, but it is mainly the mechanism of the paradoxical phase that is disturbed, which leads to a sharp reduction of its duration [1, 4, 7]. Meanwhile we know that abolition of the paradoxical phase of sleep (PPS) in experimental animals by various types of deprivation may play the role of amnesic factors [3, 6, 13]. These facts suggest that the mechanisms of disturbance of sleep and memory induced by epileptiform activity are interconnected.

The aim of this investigation was to study possible electrophysiological correlates of the influence of a chronic epileptogenic focus on learning and memory, by comparison with observed disturbances of the sleep structure.

## EXPERIMENTAL METHOD

Experiments were carried out on male rats weighing 180-220 g with a chronic epileptogenic focus in the sensomotor cortex. The epileptogenic focus was created by application of metallic cobalt powder to the cortical surface by the method described previously [9]. Simultaneously with application of cobalt, chronic electrodes were implanted into the rats to record electrical activity of the sensomotor cortex (mirror focus) and dorsal hippocampus and to record myograms of the cervical muscles. Electrical activity was recorded on a 17-channel Neurograf-18 electroencephalograph, and the data were than processed by the BA-161 neurocomputer (Italy).

During the analysis of waking-sleep cycles the duration of falling asleep (the period from the beginning of recording of the EEG to the appearance of the first, slow-wave phase

TABLE 1. Epileptiform Activity on EEG Recorded from Cortex and Dorsal Hippocampus of Rats with a Chronic Epileptogenic Focus (M ± m)

| Structure tested | Duration of discharges, sec/min | Number of discharges in 1 min | Duration of one discharge, sec |
|---|---|---|---|
| Sensomotor cortex (mirror focus) | 12,2±3,7 | 16,2±5,8 | 0,77±0,12 |
| Dorsal hippocampus | 10,8±3,8 | 19,8±7,56 | 0,59±0,18 |

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TABLE 2. Effect of Epileptogenic Focus on Ability of Rats to Learn PACR (M ± m)

| Experimental conditions | Number of visits to dark compartment | Latent periods of visit to dark compartment, sec | |
|---|---|---|---|
| | | before learning | after learning |
| Control | 1,0 | 1,8±0,8 | 57,7±4,2 |
| EA | 2,5±0,96 | 4,5±0,9 | 34,5±8,5 |

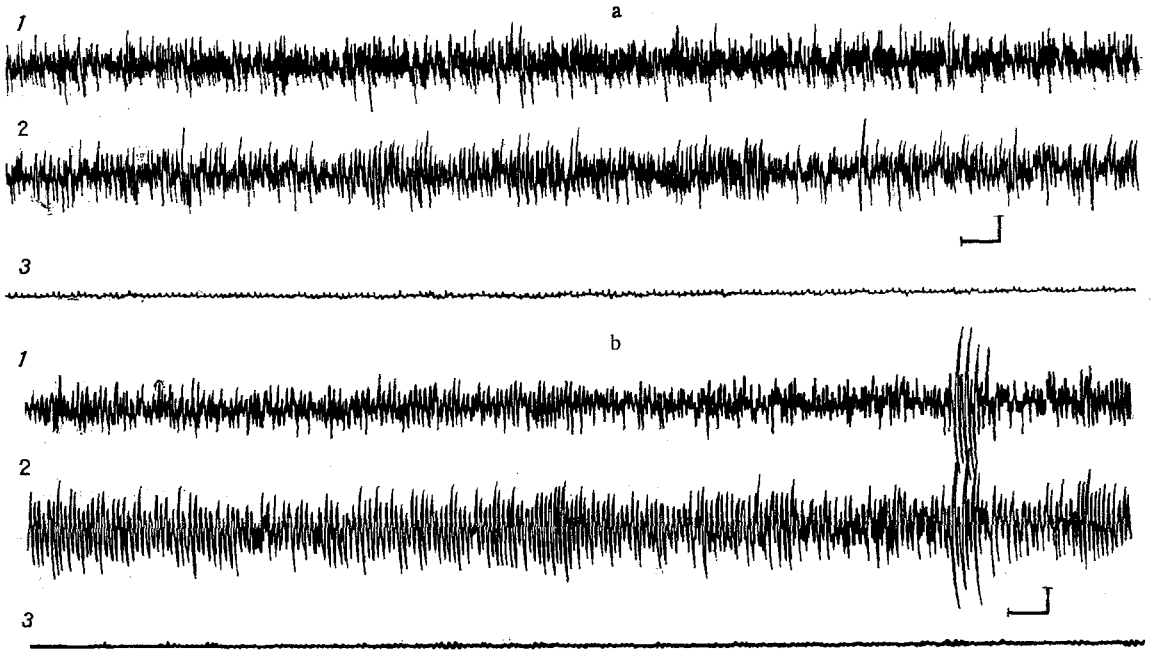


Fig. 1. Electrical activity of the sensomotor cortex (1) and dorsal hippocampus (2) and electromyogram of the cervical muscles (3) during PPS. a, b) Traces recorded in rats found to have a defect of recall of PACR and rats with normal recall of PACR, respectively. Calibration: 50 μV, 1 sec.

of sleep), and the duration of episodes of waking and of two phases of sleep, namely fast (paradoxical) and slow-wave sleep (SWS), were evaluated. Spectral analysis of the EEG was carried out during PPS.

The animals were trained by the passive avoidance conditioned reflex (PACR) method in a chamber with an electrode floor, divided into two compartments: dark (punishable) and light (safe) [6]. The reflex was reproduced 24 h after learning. The degree of preservation of the skill was judged from the change in the length of the rat's stay in the dark compartment.

Two groups of animals (six rats in each group) were used in the experiments: 1) control animals, undergoing a mock operation; 2) rats with a chronic epileptogenic focus. The experiments were carried out in accordance with the following scheme: recording of the background EEG and control recording of sleep cycles, 24 h before training, and recording a second time from the same animals immediately after a training session in PACR, and recording immediately after the session of PACR recall.

## EXPERIMENTAL RESULTS

The method of application of cobalt used in this investigation revealed epileptiform activity (EA) in the EEG recorded in rats with no motor fits. The EA was characterized by high-amplitude paroxysmal discharges of pointed and slow waves, peaks, and spike and wave

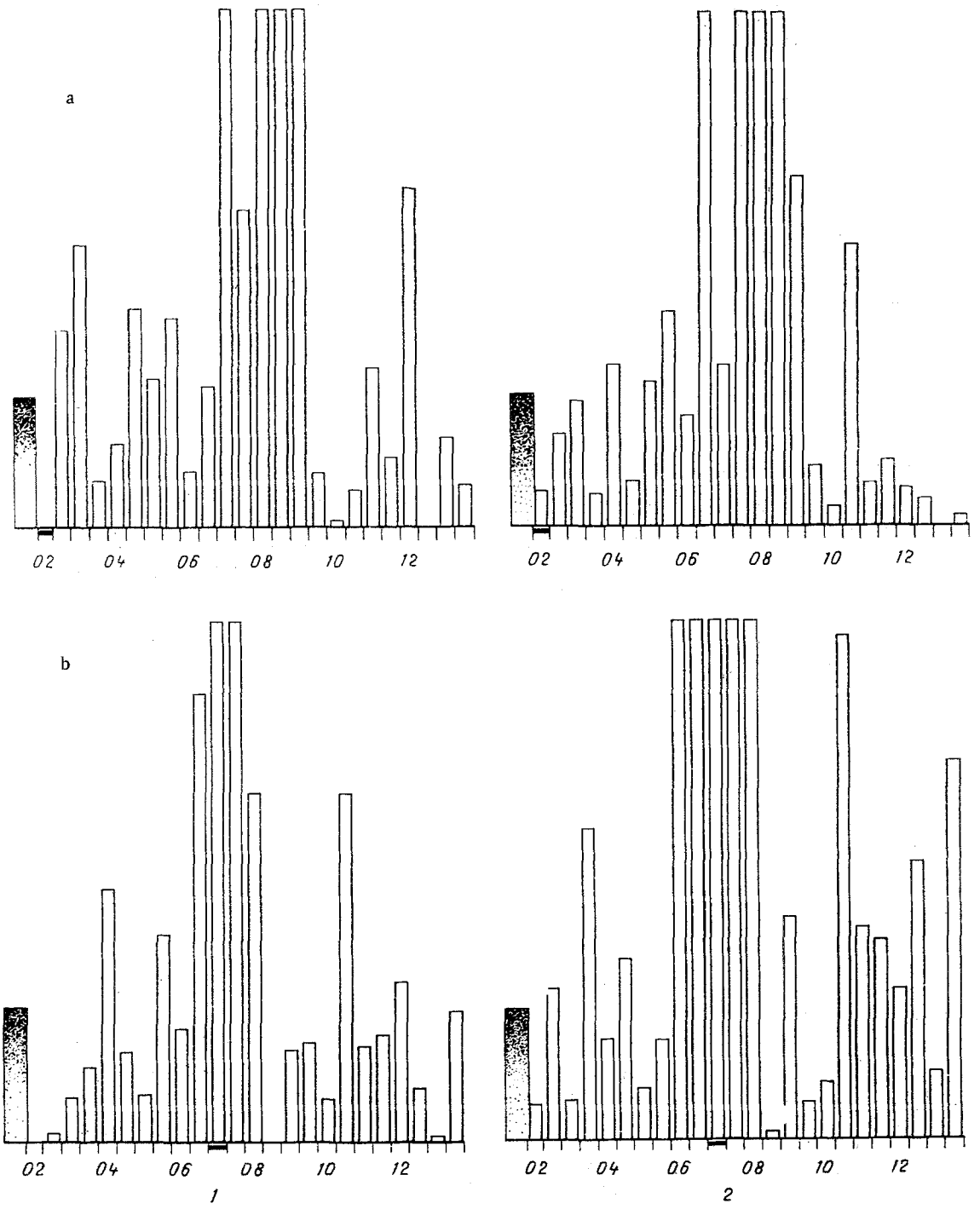


Fig. 2. Frequency power spectra of EEG recorded from sensomotor cortex (1) and dorsal hippocampus (2) during PPS. Abscissa, frequency of EEG; ordinate, power of individual components of spectrum (in $\mu V^2$). Remainder of legend as to Fig. 1.

complexes. The EA appeared as early as 24-48 h after application of the epileptogram and lasted for 2-3 weeks. On the 5th-6th day generalized EA developed, and was expressed both in the mirror focus and in the hippocampus (Table 1).

The ability of the epileptized rats to learn at this period was reduced, as shown by an increase in the number of visits necessary to form a PACR (Table 2).

During recall of the PACR after 24 h the control animals showed a considerable increase in the latent period of visiting the dark compartment, evidence that the reflex was well

TABLE 3. Effect of Learning on Duration of Individual Phases of Waking–Sleep Cycle (in % of total duration) in Rats with Cobalt-Induced Epileptogenic Focus in Sensomotor Cortex (M ± m)

| Experimental conditions | Waking | PPS | SWS |
|---|---|---|---|
| Control | 31,0±12,9 | 13,05±4,25 | 53,97±9,45 |
| EA | 57,85±54,18 | 2,58±1,36 | 39,47±27,7 |
| Control after learning | 64,25±10,8 | 7,85±3,36 | 27,75±9,23 |
| EA after learning | 65,41±7,92 | 1,13±0,22 | 33,61±9,24 |

formed (Table 2). In rats with a chronic epileptogenic focus, a clear deficit of recall of the reflex was found, as shown by a decrease in the latent period of visiting the dark compartment by the experimental rats compared with the same parameters in the control animals (Table 2); the latent period of visiting the dark compartment by two of the rats in this case did not differ from the control parameters for untrained rats (about 2 sec), indicating a complete disturbance of the skill, whereas two rats reproduced the response with recall, but on the second time of placing. Thus the existence of generalized EA in rats with a chronic epileptogenic focus not only reduces their ability to learn, but also leads to a defect of reproduction of the passage avoidance reflex.

The formation of an epileptic focus in the rat brain due to application of cobalt to the surface of the sensomotor cortex was shown to lead to marked changes in the structure of sleep: the contribution of periods of wakefulness increased by comparison with the control animals, but the contribution of the different phases of sleep was reduced. PPS was greatly reduced — from 13% in the control animals to 2.5% in animals with an epileptic focus (Table 3).

In intact animals training in PACR caused a very small decrease in the latent period of onset of sleep. A tendency was observed for the contribution of both PPS and SWS to decrease and for the contribution of the period of wakefulness to the sleep-waking cycle to increase. In rats with marked EA, training in PACR led to a decrease in the contribution of PPS to the sleep-waking cycle but did not affect SWS (Table 3).

Analysis of the EEG traces recorded in the cortex and hippocampus showed that in epileptized rats, besides changes in the sleep structure, disturbance of the hippocampal ν-rhythm was observed in the PPS period. We know that in intact animals a well-marked modulated ν-rhythm is recorded at this time, with the presence of tonic (4-6 waves/sec) and phasic (8-12 waves/sec) components. In epileptized rats with a defect of PACR recall, a varied degree of disturbance of the phasic component of the ν-rhythm was observed, or even its complete reduction (Figs. 1a and 2a). In rats with normal PACR recall, despite the presence of paroxysmal activity, the hippocampal ν-rhythm remained intact with alternation of tonic and phasic components (Figs. 1b and 2b). Disturbance of the sleep structure with shortening of PPS was observed in our investigations in all epileptized rats, whereas a defect of learing and memory was discovered only in rats in whom the phasic component of the ν-rhythm was disturbed.

Integrity of the ν-rhythm, with both its components present, probably reflects the level of activation of brain structures necessary for learning and recall. In the light of the hypothesis on the existence of two generators, located in the septum and hippocampus, responsible for the genesis of the different components of the ν-rhythm [11, 15], and data indicating that cholinergic neurons of the septohippocampal tract form two functionally and morphologically different systems, modulated by different neurotransmitter systems [10], it can be postulated that the disturbance of the phasic components of the ν-rhythm observed in epileptized rats is the result of a disturbance of one of these systems.

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# USE OF 2-DEOXYGLUCOSE TO ANALYZE THE HUMORAL COMPONENT OF THE CARDIOVASCULAR RESPONSE TO STRESS

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Various types of stressors, inducing marked responses of the cardiovascular system, are widely used as models of neurogenic experimental hypertension [2]. One typical response of the endocrine system to stress is the release to catecholamines (mainly adrenalin) from the adrenals [7], which is accompanied by elevation of the blood glucose level [3]. The role of increased adrenalin concentrations in the realization of stress-induced circulatory reactions is not yet clear. The discovery of β-adrenoreceptors on sympathetic nerve endings provided a basis for the hypothesis that release of noradrenalin (NA) from endings can take place, and the hypertensive responses can thereby be increased, leading to the development of hypertension [8]. A gap in the experimental proof of the hypothesis is that elevation of the blood pressure (BP) takes place only after prolonged administration of exogenous adrenalin in large doses [13].

The aim of this investigation was to analyze the role of raised concentrations of endogenous adrenalin in the regulation of the cardiovascular system in waking animals. For this purpose a model of "metabolic stress," induced by 2-deoxyglucose (2-DG) was used. 2-DG and glucose utilized the same transport system during passage through the blood–brain barrier and nerve cell membranes [14]. Unlike glucose, 2-DG inhibits the isomerase reaction and induces intracellular glucopenia in the CNS, which is accompanied by activation of hypothalamic structures, by potentiation of the flow of impulses in the sympathetic nerve of the adrenals, and by adrenalin release from the adrenals [6, 11]. Thus under the influence of

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