the cardiac contractions was reduced in all experiments with 3-hydroxyanthranilic acid, i.e., a negative inotropic effect was seen on the isolated frog's heart. Under the influence of quinolinic acid, cardiac arrhythmias appeared with concentrations as low as 10^{-6} M, in the form of single extrasystoles and episodes of tachycardia (Fig. 3). The force of the cardiac contractions was virtually unchanged, but during paroxyms the voltage of the ECG of the isolated frog's heart decreased significantly. With quinolinic acid in a concentration of 10^{-3} M bradycardia developed, and against its background cardiac arrest in diastole for 53 sec was observed in some cases, after which the cardiac activity was restored but the bradycardia was more marked than before transient cardiac arrest. The results of this investigation also were confirmed by those of clinical investigations: a raised serum kynurenin level was observed during atrial fibrillation of bradycardic type, sinus node weakness, sinus bradycardia, and chronic AV block [7]. A new pathogenetic pathway of onset of cardiac arrhythmias has thus been discovered.

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NEW ASPECTS OF THE NEUROPHYSIOLOGICAL MECHANISM OF ACTION OF NOOTROPIC DRUGS

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Much experimental material has now been collected on nootropic drugs as agents improving mental working capacity and leaning and memory processes, and suggestions regarding their biochemical mechanism of action have been put forward [8, 12, 13]. Meanwhile the neurophysiological mechanisms of action of nootropic drugs have received little study.

During visual and frequency analysis of the EEG of animals and man, as a rule no action of nootropic drugs can be detected [5, 12]. Spectral analysis of the human EEG reveals definite, but often opposite, changes in the power spectra of the EEG due to these drugs and, in particular, reduction of slow frequencies with an increase of power in the α-band and some increase in β-activity. However, these effects have been observed mainly in complex forms of pathology (aging, ischemia, cerebrovascular disturbances) and during long-term administration of the drugs [7, 9, 10, 14].

The clearest electrophysiological manifestation of the action of nootropic drugs is observed with the use of transcallosal evoked potentials [1, 11, 12]. However, the strengthening of transcallosal responses under the influence of drugs, observed in these investigations, cannot entirely explain the mechanism of their nootropic effect.

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In the present investigation, to obtain some ideas on possible neurophysiological mechanisms of action of nootropic drugs, a Fourier spectral analysis of the power of the cortical and hippocampal EEG of freely behaving rats was undertaken with the aid of a neurocomputer analyzer.

EXPERIMENTAL METHOD

Experiments were carried out on 29 freely behaving noninbred male rats weighing 200-250 g. Under pentobarbital anesthesia electrodes were inserted into the animals' sensomotor cortex and dorsal hippocampus of the left and right cerebral hemispheres, and the reference electrode was located in the nasal bone. Experiments began not less than 5-6 days after the operation. In the course of the experiments the rats were allowed a period of 1-1.5 h to become accustomed to the experimental situation in the chamber, after which the EEG of the above-mentioned brain structures was recorded on a Neurograph-18 electroencephalograph and simultaneously on a tape recorder (O.T.E. Biomedica, Italy) in conscious rats for 5 min before (background) and after injection of the drug, every consecutive 30 min for 3-4 h after the injection. A group of six rats, into which physiological saline was injected under similar conditions, served as an additional control.

Spectral analysis of the power of the EEG, by Fourier transform, was carried out on a Berg Fourier Analyzer (O.T.E. Biomedica) in two channels consecutively, the bioelectrical activity recorded in the course of the experiment being led in from the tape recorder. Artefacts connected with sudden movements of the animals were excluded from analysis in this way. Distributions of EEG power spectra (epoch of analysis 4 min 8 sec), total power and relative powers of frequencies within certain bands were analyzed. The action of the α-pyrrolidone derivative pyracetam (300 mg/kg, from Polfa, Poland), pyritinol (100 mg/kg, from Merck, West Germany), and the antioxidant 2-ethyl-6-methyl-3-hydroxypyridine (3-HP, 100 mg/kg), which were injected intraperitoneally, was studied.

EXPERIMENTAL RESULTS

Analysis of the ampli-ude of the cortical EEG of the normal control rats revealed fluctuations from 50 to 120 μV, and that of the hippocampal EEG from 100 to 300 μV. Visual analysis of the EEG after injection of the preparations showed no definite effect of the nootropic drugs, in agreement with data obtained by other investigators [5, 12].

Spectral analysis of the EEG showed that before injection (background) the power spectrum of the cortical EEG of normal freely behaving rats is a distribution with a dominant frequency of 6-7 Hz and with a peak power on average of 8.22 ± 1.51 $\mu V^2/Hz$. The power spectrum of the hippocampal EEG also is a distribution with a clearly dominant peak of power in the region of the ϑ-rhythm, with peak frequency 6-7 Hz and peak power on average of 37.94 ± 17.64 $\mu V^2/Hz$. The control with a single injection of physiological saline showed that the power spectrum of the cortex and hippocampus was relatively stable, but a small deviation from the background value was observed 30 min after injection (Fig. 1a).

Injection of pyracetam caused a definite change in the EEG power spectra of structures in both cerebral hemispheres (Fig. 1b). Stabilization took place in the spectrum of the cortical EEG 1-1.5 h after the injection, and the dominant peak in the ϑ-band increased on average by $22.79 \pm 4.79\%$; at the same time the power of the spectrum decreased in the bands from 0.5 to 4 and from 8 to 13 Hz. A similar effect, with a maximum 1.5-2 h after the injection, was observed in the hippocampus, with an increase in power of the dominant peak by $58.00 \pm 7.00\%$ and with a decrease in power of neighboring bands of the spectrum.

Pyritinol also caused stabilization and strengthening of the dominant peak of the power spectrum in the cortex by $26.23 \pm 18.90\%$, but this effect reached a maximum at 2.5-3 h. Maximal enlargement of the peak by $31.00 \pm 22.39\%$ took place in the hippocampus after 1 h, and this effect was less than that of pyracetam. Moreover, under the influence of pyritinol there was a tendency for the node of the principal maximum of the EEG power distribution to shift to the left by 1 Hz (Fig. 1c).

Under the influence of 3-HP similar changes took place: stabilization and enlargement of the dominant peak of the EEG power spectrum in the cortex by $21.33 \pm 3.21\%$ (maximum of effect about 2-2.5 h) and in the hippocampus by $64.00 \pm 32.87\%$ (maximum of effect 1-1.5 h, Fig. 1d), were observed.

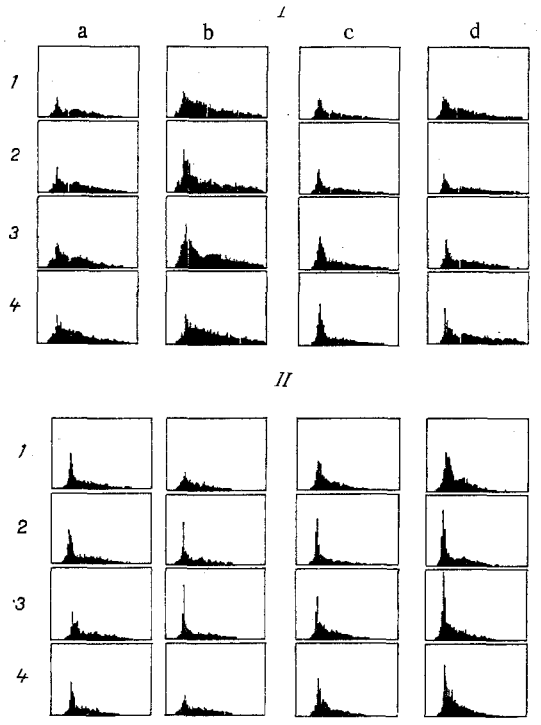

Fig. 1. Changes in power spectra of EEG of sensomotor cortex and dorsal hippocampus of freely behaving rats after injection of physiological saline (a), pyracetam (b), pyritinol (c), and 3-HP (d). I) Cortex; II) hippocampus. 1) Before injection (background); 2-4) 1, 2, and 3 h, respectively after injection. Calibration of abscissa of each window of the memory cell from 0 to 32 Hz, calibration of ordinate: I) 20 μV^2/Hz, II) 60 μV^2/Hz.

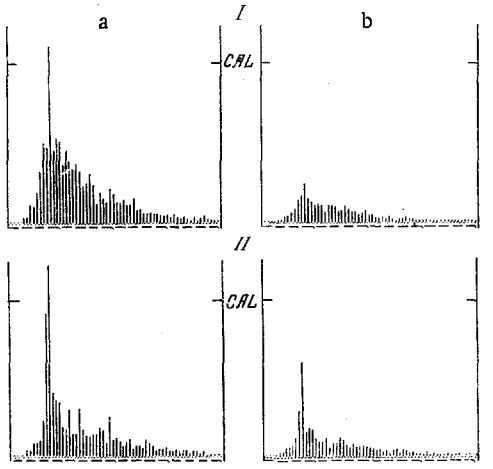

Fig. 2. Change in interhemispheric asymmetry for EEG power spectra of left (a) and right (b) dorsal hippocampus of rats before (I) and 1.5 h after (II) injection of pyracetam. Calibration: abscissa, from 0 to 32 Hz; ordinate, 40 μV^2/Hz.

An important special feature of the action of nootropic drugs is their ability to cause diminution of interhemispheric differences in power of the dominant peak of the distribution, and of total power (Fig. 2) in the cortex and hippocampus. Under these circumstances, these changes took place to the greatest degree under the influence of pyritinol, and in some cases hemispheric asymmetry was reversed.

The drugs studied thus act in the same direction on the EEG power spectra, causing stabilization and increasing the dominant peak of power in the ϑ-band (with a decrease in power in the δ- and α-bands) of the EEG in the cortex and hippocampus of the left and right cerebral hemispheres of rats.

According to the results of spectral analysis, under the influence of the nootropic drugs the organization of the basic rhythm of the animals' EEG was strengthened. This is in agreement with the results of studies of the effect of nootropic drugs on the transcallosal evoked potential in animals [1, 11, 12], which showed that these drugs increase the primary positivity and negativity of the evoked potentials, evidence of their activating influence on excitatory and inhibitory neurons, the precise and synchronous functioning of which is essential for the organization of rhythmic activity [2].

Reorganization of the power spectra and, correspondingly, of the EEG rhythms under the influence of drugs with nootropic action, similar to that observed in the present investigation, also has been discovered in man under certain pathological conditions [7, 14]. This suggests that the nootropic effect is linked with improvement of the organization of rhythmic brain activity.

In the modern view [4, 6], stabilization and strengthening of the peak of the dominant frequency of the cortical EEG spectrum of animals are linked with strengthening of spatial synchronization of biopotentials. On the basis of these views and of the results of the present investigation it can be postulated that the neurophysiological mechanism of the action of nootropic drugs consists of optimal improvement of the organization of rhythmic brain activity and elevation of the level of spatial synchronization of cortical biopotentials. Under these circumstances irradiation of excitation processes within and between the cerebral hemispheres is facilitated, as is confirmed by data on augmentation of transcallosal evoked potentials under the influence of nootropic drugs [1, 12].

This hypothesis concerning the neurophysiological mechanism of the nootropic effect is supported also by the fact that when mental activity is intensified, during difficult problem solving, for instance, in man the level of spatial synchronization is raised. It is also known that chlorpromazine, in doses impairing mental working capacity, appreciably weakens spatial synchronization of cortical biopotentials and the dominant peak of α-activity in the EEG spectrum [3, 4], whereas pyracetam abolishes the side effects of this drug.

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