2. N. Ya. Lukomskaya and M. I. Nikol'skaya, The Search for Remedies Against Motion Sickness [in Russian], Leningrad (1971).
3. L. A. Radkevich, Kosm. Biol., No. 6, 50 (1977).
4. K. V. Sudakov, Vopr. Med. Khimii, No. 3, 15 (1984).
5. E. A. Yumatov, K. Hecht, and Yu. G. Skotselyas, Zh. Vyssh. Nerv. Deyat., No. 2, 345 (1979).
6. V. V. Yasnetsov, O. P. Vakulina, V. S. Shashkov, et al., Byull. Éksp. Biol. Med., No. 8, 164 (1985).
7. V. V. Yasnetsov, Yu. V. Drozd, and V. S. Shashkov, Experimental and Clinical Pharmacology of Pain-Relieving Substances [in Russian], Leningrad (1986), pp. 64-66.
8. V. V. Yasnetsov, Yu. V. Drozd, and V. S. Shashkov, Byull. Éksp. Biol. Med., No. 5, 586 (1987).
9. G. H. Crampton and N. G. Daunton, Brain Behav. Evol., 23, 36 (1983).
10. D. De Wied, G. L. Kovacs, B. Bohus, et al., Eur. J. Pharmacol., 49, 427 (1978).
11. D. De Wied, J. M. Van Ree, and H. M. Greven, Life Sci., 26, 1575 (1980).
12. I. Kiraly and J. M. Van Ree, Neuropharmacology, 23, 511 (1984).
13. R. S. Snider and W. T. Niemer, A Stereotaxic Atlas of the Cat Brain, Chicago (1961).
14. K. B. Suri, G. H. Crampton, and N. G. Daunton, Aviat. Space Environ. Med., 50, 614 (1979).
15. J. M. Van Ree, A. R. Caffe, and G. Wolterink, Neutopharmacology, 21, 1111 (1982).

NEUROPHYSIOLOGICAL ANALYSIS OF NOOTROPIC CORRECTION OF ABNORMAL EEG FINDINGS DURING CHRONIC ADMINISTRATION OF ETHANOL TO ANIMALS

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KEY WORDS: ethanol; nootropic drugs; EEG.

Nootropic drugs are used in the modern treatment of alcoholism for the correction of functional and intellectual disturbances [5, 6, 8, 9]. Meanwhile, the manifestations and mechanisms of the protective action of nootropic drugs at the neurophysiological level have not yet been explained.

The aim of the present investigation was accordingly to study abnormalities of the EEG of the sensomotor cortex (SMC) and dorsal hippocampus (DH) of rats receiving ethanol by long-term administration, and the effect of drugs with nootropic activity on these changes.

EXPERIMENTAL METHOD

Experiments were carried out on 28 noninbred male rats weighing 300-350 g, divided into four groups: group 1) control (six intact rats); 2) six rats receiving daily intraperitoneal injections of 25% ethanol solution in a dose of 1.2 g/kg; 3) eight rats receiving daily injections of ethanol in the same dose + pyracetam (from Polfa, Poland) in a dose of 300 mg/kg, intraperitoneally, 50 min before injection of ethanol; 4) eight rats receiving an intraperitoneal injection of 2-ethyl-6-methyl-3-hydroxypyridine (3-HP), a substance with nootropic activity [1, 3, 10], in a dose of 100 mg/kg 30 min before the injection of ethanol. All substances were injected for 40 days. The animals were kept under animal house conditions on a standard diet. The experiments were carried out between 9 a.m. and 1 p.m.

Nichrome electrodes were implanted under sterotaxic conditions, under pentobarbital anesthesia (50 mg/kg, intramuscularly), into SMC and DH [14] 5-6 days before the electrophysio-

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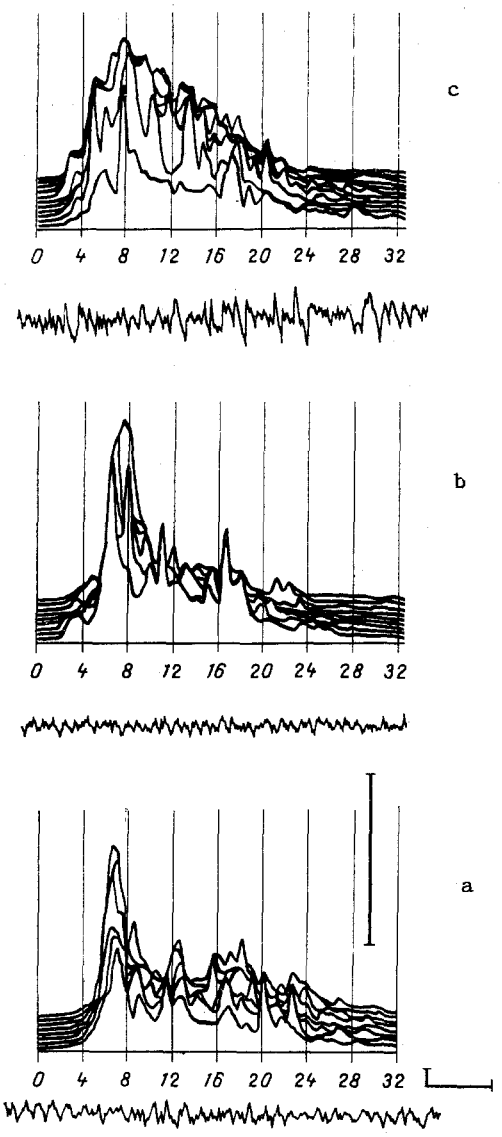

Fig. 1

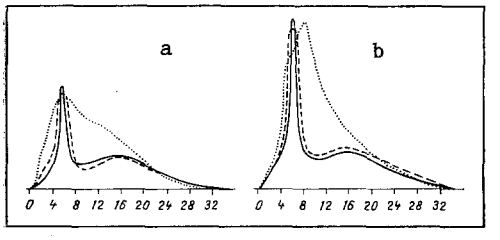

Fig. 2

Fig. 1. Effect of long-term administration of ethanol and its discontinuation on EEG of SMC of unrestrained rats and its PS. a) EEG of cortex and its PS in control; b) the same 30 min after last injection of ethanol; c) the same after discontinuation of ethanol. Calibration for EEG 50 μV, 1 sec. Calibration for PS of EEG: 5 $\mu V^2/Hz$, 0-32 Hz. Consecutive curves of PS, averaged for every 30 sec, shown.

Fig. 2. Diagram of changes in PS of EEG of SMC (a) and DH (b) of rats after discontinuation of long-term administration of ethanol. Continuous line — PS of EEG in control; broken line — the same, 30 min after last injection of ethanol; dotted line — the same after discontinuation of ethanol. Abscissa, frequency bands of spectrum (in Hz).

logical investigations. The EEG was recorded in unrestained rats. In the course of the experiments the animals were first accustomed to the experimental situation (1-1.5 h), after which the electrical activity of the above-mentioned structures of the animals' brain was recorded for 10 min in the conscious animals on an electroencephalograph and tape recorder. EEG changes in the brain structures were analyzed after long-term administration of ethanol (30 min after the last injection) and also 24 h after discontinuation of ethanol or of the combination of ethanol and the drug.

Visual and spectral Fourier analysis of the EEG was carried out by means of the Neurograph-18 electroencephalograph and the Berg-Fourier Analyzer (O.T.E. Biomedica, Italy), which

TABLE 1. Changes in Relative Power of Ranges of PS of EEG by Fourier Analysis (total power 100%) for Rat SMC and DH, during Long-Term Administration of Ethanol Alone, Ethanol with Pyracetam, and Ethanol with 3-HP

Brain structure	PS of EEG	Frequency band, Hz	Control	Ethanol	Discontinuation of		
					ethanol	ethanol and pyracetam	ethanol and 3-HP
Cortex	δ	0—4	1	2	3*	1	1
	θ	4—8	30	30	23*	24*	30
	α	8—13	29	26	32	28	30
	β_1	13—20	24	26	27	28	22
	β_2	20—32	16	16	15	19	17
Hippocampus	δ	0—4	1	1	1	1	1
	θ	4—8	37	36	32*	33	36
	α	8—13	30	30	36*	32	35
	β_1	13—20	22	22	21	22	18
	β_2	20—32	10	11	10	12	10

Legend. Here and in Table 2: *$p<0.05$ compared with control.

incorporates a computer. Artefacts connected with sudden movements of the rats were excluded from analysis (averaging time 4 min 0.8 sec), and for this purpose an additional low-frequency filter in the Berg-Fourier Analyzer (reduction of 6 dB within the 0-4 Hz range) was used.

EXPERIMENTAL RESULTS

Investigation of the EEG of SMC and DH of the conscious animals of groups 1 and 2, and its power spectra, showed that long-term administration of ethanol for 40 days caused no marked changes in brain electrical activity compared with intact rats, when recorded 30 min after injection of ethanol (Fig. 1a, b). There was only some increase in the relative power of the δ-band (0-4 Hz) of the power spectrum (PS) of the EEG in SMC (Table 1).

Meanwhile, after discontinuation of ethanol for 24 h after its long-term (40 days) administration revealed considerable changes in the EEG of SMC, with an increase in slow-wave high-amplitude activity with a frequency of 1-4 waves/sec and potentiation of irregular activity with a frequency of 9-13 waves/sec. To correspond with this, distinct "destructuring" of PS of the EEG of SMC was observed, as shown by an increase in the relative power in the δ-bands (0-4 Hz) and the α-bands (8-13 Hz), and also by a decrease in power of the narrow-band peak of the dominant activity (Δθ) in the θ-bands (4-8 Hz) of frequencies of the EEG PS (Fig. 1c). Many spectral ratios showed significant changes: $\frac{\Delta\theta}{\Sigma\theta}$, $\frac{\theta}{\delta+\alpha}$, $\frac{\theta}{\beta_1}$ etc. Table 2).

In addition, 24 h after discontinuation of ethanol potentiation of interhemispheric asymmetry was observed, especially with respect to the amplitude of the dominant peak of PS of the EEG of SMC in the left and right hemispheres (on average by 2.3 times), compared with the control group (the level of interhemispheric differences is taken as 1).

Changes in the EEG of DH were rather different in character. When chronic administration of ethanol had been discontinued for 24 h, α-activity on the hippocampal EEG was intensified and the power of the α-frequency band was increased, so that it began to exceed activity in the θ-band (Tables 1 and 2); under these circumstances the dominant peak of PS of the EEG of DH shifted into the region of higher frequencies (α-band; Fig. 2b).

Pyracetam and 3-HP, after chronic administration (40 days), had a distinct protective action on the EEG disturbances in SMC of the rats connected with discontinuation of chronic alcohol administration. When a combination of ethanol and pyracetam was used, no gross changes in the EEG could be found in association with discontinuation of ethanol for 24 h, and in particular, there were no high-amplitude low-frequency waves. PS of the EEG of SMC of this group of animals had a structure similar to that of PS of the EEG of intact rats; no increase in power of the δ- and α-bands of PS of the EEG was observed (Fig. 3a, b). Many quantitative relationships of the spectral parameters, characterizing the structure of PS of the EEG, were

TABLE 2. Changes in Spectral Parameters of EEG of SMC and DH of Rats against the Background of Chronic Administration of Ethanol, of Ethanol with Pyracetam, and of Ethanol with 5-HP

Brain structure	Parameter of PS of EEG	Control	Ethanol	Discontinuation of		
				ethanol	ethanol and pyracetam	ethanol and 3-HP
Cortex	Relative $\Delta\theta$	17	17	12*	16	18
	$\frac{\Delta\theta}{\Sigma\theta}$	0,57	0,57	0,52*	0,67*	0,68*
	$\frac{\theta}{\delta+\alpha}$	1,00	1,01	0,66*	0,82	0,98
	$\frac{\theta}{\delta}$	30,00	15,00*	7,66*	24,00	30,00
	$\frac{\theta}{\alpha}$	1,03	1,15	0,72*	0,86	1,00
	$\frac{\theta}{\beta_1}$	1,25	1,15	0,85*	0,86*	1,36
	$\frac{\theta}{\beta_2}$	1,88	1,88	1,53	1,26*	1,76
Hippocampus	Relative $\Delta\theta$	25	23	22	21	26
	$\frac{\Delta\theta}{\Sigma\theta}$	0,68	0,64	0,69	0,64	0,72
	$\frac{\theta}{\delta+\alpha}$	1,19	1,16	0,86*	1,00	1,00
	$\frac{\theta}{\delta}$	37,00	36,00	32,00*	33,00	36,00
	$\frac{\theta}{\alpha}$	1,23	1,20	0,89*	1,03	1,03
	$\frac{\theta}{\beta_1}$	1,68	1,64	1,52	1,50	2,00*
	$\frac{\theta}{\beta_2}$	3,70	3,27	3,20	2,75	3,60

Legend. $\Delta\theta$) Narrow-band peak of δ-band (width 1.5 Hz); $\Sigma\theta$) total power of θ-band.

restored to their level in intact animals (Table 2). However, a shift of the peak of the dominant activity by 1-1.5 Hz will be noted into the region of higher frequencies by comparison with PS of the EEG of intact rats (Fig. 3b).

The action of 3-HP was similar to that of pyracetam, for its long-term administration also prevented the onset of pathological changes in the EEG of SMC of the rats (Tables 1 and 2; Fig. 3c).

The protective action of pyracetam and 3-HP also was manifested as obliteration of interhemispheric differences, which was characterized by clear structuring of PS of the EEG in both the left and the right cerebral hemispheres, and by a decrease of the differences in amplitude of the dominant power on the average by 48 ± 11%.

At the level of DH, the drugs tested had no evident protective action. Only a small decrease in power of the α-band of PS could be detected in the group of animals receiving ethanol together with pyracetam, and an increase in power of the θ-band in the group of animals receiving ethanol with 3-HP (Table 1).

The data obtained in this investigation, showing changes in the EEG and the level of interhemispheric differences against the background of discontinuation of ethanol after its long-term administration, agree with data in the literature [7, 11] and, on the whole, they reflect a change in the normal relations between excitation and inhibition processes in the brain structures tested, and, correspondingly, a change in the normal functioning of the CNS [15]. The EEG disturbances revealed correlate with behavioral changes observed under similar experimental conditions. Against the background of discontinuation of ethanol after its long-term administration, learning in a shuttle box was impaired and the relevance of the response of the rats to a conflicting situation was disturbed. The changes in behavior and brain electrical activity observed under the influence of ethanol are perhaps linked with the memory impairment, disturbance of attention, orientation, and so on, observed in the clinical picture of alcoholism [8, 9].

A single dose of pyracetam is known not to abolish EEG disturbances induced by chronic ethanol consumption [11]. Long-term administration of pyracetam, and also of 3-HP, as the

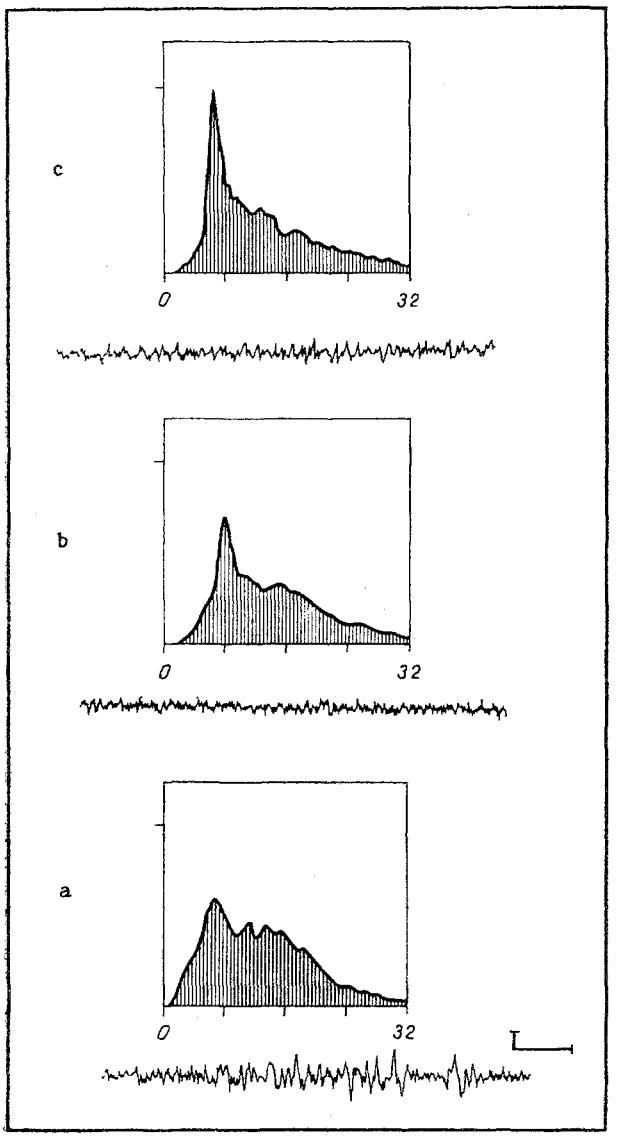

Fig. 3. Effect of drugs with nootropic activity on EEG and its PS against the background of discontinuation of chronic administration of ethanol. a) EEG of SMC and its PS during discontinuation of ethanol; b) the same, but discontinuation of ethanol with pyracetam; c) the same, but discontinuation of ethanol with 3-HP. Cumulation time 4 min 0.8 sec. Calibration of PS) 10 $\mu V^2/Hz$, 0-32 Hz. Calibration of EEG 50 μV, 1 sec.

present investigation shows, can correct the EEG disturbances in SMC associated with discontinuation of long-term injections of ethanol and improves the structure of PS of the EEG through enhancement of the dominant peak and other EEG changes, which correspond to the direction of action of nootropic drugs, administered in a single dose [1].

It must be specially noted that during long-term administration of pyracetam accompanied by long-term alcoholization, its protective action is manifested chiefly at the cerebral cortical level, in agreement with Giurgea's view [12, 13] that nootropic drugs act mainly at the cortical level.

As was shown previously [1, 2], nootropic drugs are able to improve the organization of the basic rhythmic activity of the brain and to raise the level of spatial synchronization of the EEG; this may perhaps determine the effect of nootropic drugs, including in the presence of disturbances arising after discontinuation of ethanol when administered for the long term. On the basis of the results of this investigation it can be postulated that the protective

action of pyracetam and of 3-HP on PS of the EEG and on electrical activity of the animals' brain under conditions of alcoholic intoxication may lie at the basis of the improvement of working capacity and memory functions observed in alcoholic patients under the influence of pyracetam [4, 8, 9].

LITERATURE CITED

1. T. A. Voronina and S. V. Krapivin, Byull. Éksp. Biol. Med., No. 12, 721 (1986).
2. T. A. Voronina, S. V. Krapivin, and N. N. Bogdanov, Vestn. Akad. Med. Nauk SSSR, No. 2, 17 (1987).
3. K. M. Dyumaev, T. A. Voronina, L. D. Smirnov, and A. V. Val'dman, Vestn. Akad. Med. Nauk SSSR, No. 11, 3 (1984).
4. N. N. Ivanets and A. L. Igonin, The Clinical Importance of the Drug Nootropil [in Russian], Moscow (1976), pp. 133-143.
5. N. N. Ivanets, A. L. Igonin, L. M. Savchenko, and T. P. Nebarakova, Antidepressants and Nootropic Drugs [in Russian], Leningrad (1982), pp. 135-140.
6. A. M. Krasil'nikov and T. G. Rybakova, Antidepressants and Nootropic Drugs [in Russian], Leningrad (1982), pp. 131-135.
7. I. A. Lapina, I. K. Yaichnikov, P. D. Shabanov, and Yu. S. Borodkin, Fiziol. Zh. SSSR, 70, No. 1, 3 (1984).
8. G. M. Rudenko, I. S. Romanova, and S. D. Boyarintseva, The Clinical Importance of the Preparation Nootropil [in Russian], Moscow (1976), pp. 35-45.
9. G. M. Rudenko, Nauch. Trud. Vses. Nauch.-Issled. Khim.-farm. Inst., 9, 121 (1982).
10. L. D. Smirnov and K. M. Dyumaev, Khim.-farm. Zh., No. 4, 28 (1982).
11. E. Czarnecka and E. Stanislawska, Pol. J. Pharmacol. Pharm., 35, 451 (1983).
12. C. Giurgea and F. Moyersoons, Arch. Int. Pharmacodyn., 199, 67 (1972).
13. C. Giurgea, Drug Dev. Res., 2, 441 (1982).
14. L. J. Pellegrino, A. S. Pellegrino, and A. J. Cushman, A Stereotaxic Atlas of the Rat Brain [in Russian], New York (1979).
15. B. P. H. Poschel, P. M. Ho, and F. W. Ninteman, Experientia, 41, 1433 (1985).

PREVENTION OF ALCOHOL-DIRECTED MOTIVATION IN RATS BY ZINC SULFATE

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KEY WORDS: zinc sulfate; biotic dose; alcohol-directed motivation; brain; zinc concentration.

An important role in the mechanisms of formation of various mental diseases such as schizophrenia and manic-depressive psychosis is ascribed to disturbances of zinc metabolism in the CNS, which is connected with the part played by this trace element in neurochemical processes in the brain [9, 10]. In patients with chronic alcoholism the zinc concentration in various parts of the brain also has been shown to be depressed by 15-30% [8], and this is accompanied by characteristic symptoms of zinc deficiency [5, 11]. Other evidence of the important pathogenetic role of zinc in the formation of alcohol-directed motivation is given by experimental data on a significant increase in ethanol consumption by animals kept on a diet deficient in zinc [7].

The aim of this investigation was to study the zinc concentration in the brain of rats variously predisposed to the development of experimental alcoholism, and to study the pos-

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