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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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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TABLE 1. Effect of Zinc Sulfate in a Dose of 50 μg/kg on Formation of Alcohol-Directed Motivation in HA and LA Rats (M ± m)

Group of rats	Experimental conditions	Mean daily consumption of water and 15% enthanol solution, ml/kg		Coefficient of ethanol preference	
		1st-10th Days	11th-20th Days	1st-10th Days	11th-20th Days
HA	Control	31,2±7,5 33,1±5,6	34,4±10,0 49,0±4,6	0,51±0,04	0,59±0,03
	Injection of zinc sulfate	45,2±6,8 16,4±4,4	67,1±11,0* 21,8±5,5**	0,31±0,03***	0,27±0,03***
LA	Control	39,6±6,3 37,9±5,0	58,9±7,7 34,5±5,1	0,49±0,02	0,37±0,03
	Injection of zinc sulfate	37,7±7,0 26,7±5,9	53,7±7,1 33,0±6,4	0,43±0,03	0,46±0,04

Legend. Consumption of water above the line, consumption of ethanol below the line. *p<0.05, **p<0.01, ***p<0.001 compared with control.

sibility of preventing an alcohol-directed motivation from developing with the aid of biotic doses of zinc sulfate.

EXPERIMENTAL METHOD

Experiments were carried out on 64 noninbred male rats weighing 200-300 g. At the beginning of the experiment the animals' tendency to develop experimental alcoholism was estimated by studying their behavior under forced swimming conditions, as described previously [4]. For this purpose the rats were kept for 600 sec in a plastic basin 32 cm in diameter and 50 cm high, with a water level of 20 cm (water temperature 20°C). The total time of immobilization (TTI) was recorded, when the rats swam passively in a vertical position, slightly inclined forward, with the head only just projecting above the water surface. Highly active rats (HA), with TTI of under 130 sec, evidence of a low level of alcohol-directed motivation initially, and rats with low activity (LA), with TTI of over 300 sec, classed as animals inclined to develop experimental alcoholism, were distinguished. After testing, the rats were placed in a heated (30°C) cage for 30 min and then returned to the animal house. After 24 h the procedure was repeated. On the 2nd day some of the HA and LA rats were decapitated and organs (liver, kidneys, brain, heart, testes, femur, muscle tissue) were taken for analysis for their zinc content by atom-absorption spectrophotometry [6]. The samples were subjected to dry incineration by the method in [1]. The remaining 47 animals were kept in isolation cages, equipped with feeding bowl and graduated vessels with water and 15% ethanol solution. The rats were divided into two groups: experimental, consisting of 11 HA and 11 LA rats, and control, consisting of 10 HA and 15 LA rats. Rats of the experimental group were given an aqueous solution of zinc sulfate ($ZnSO_4 \cdot 7H_2O$) in a dose of 50 μg/kg (calculated as metal) intraperitoneally once daily for 10 days. Control rats received injections of distilled water by the same schedule. The quantity of ethanol solution and water drunk by each rat was recorded daily both during administration of zinc sulfate and for the 10 days after its discontinuation. The coefficient of ethanol preference (K) was calculated by the formula:

$$K = \frac{E}{W + E},$$

where E denotes the average daily consumption of ethanol solution and W the consumption of water (in ml/kg).

The results were subjected to statistical analysis by the Fisher–Student parametric test. Differences were considered statistically significant at the $p<0.05$ level.

EXPERIMENTAL RESULTS

Chemical analysis showed that the zinc concentration in the brain of HA rats was lower (1.70 ± 0.10 mg % wet weight of tissue) than in LA rats (2.32 ± 0.19 mg %, $p<0.02$), whereas in the other organs studied no difference in the zinc concentration was found.

Intraperitoneal injection of zinc sulfate in a dose of 50 μg/kg into HA rats kept under conditions of free choice between water and 15% ethanol solution led to a lasting reduction of their alcohol consumption, both during and after administration of the compound. The water

consumption of these animals had a tendency to increase during zinc sulfate administration, and this became statistically significant when administration of the compound was discontinued (Table 1).

As Table 1 shows, HA of the experimental and control groups differed especially in their coefficient of ethanol preference.

No differences in ethanol consumption between the experimental and control groups of the LA rats could be found throughout the period of the experiment.

These results indicate that biotic doses of zinc sulfate can prevent the onset of alcohol-directed motivation in HA rats under conditions of isolation stress. The absence of effect of this compound in LA rats, in which the appearance of a tendency to drink ethanol under these conditions can be prevented only by administration of psychotropic drugs [2, 3], may be evidence of differences in the mechanisms lying at the basis of addiction of LA and HA rats to alcohol.

The effectiveness of zinc in small, biotic doses, thus revealed, in our opinion may indicate fresh prospects for the prevention of alcoholism.

LITERATURE CITED

1. G. O. Babenko, Determination of Trace Elements and Metalloenzymes in Experimental and Clinical Medicine [in Ukrainian], Kiev (1968).
2. Yu. V. Burov, A. B. Kampov-Polevoi, and L. N. Nikitina, Byull. Éksp. Biol. Med., No. 3, 289 (1986).
3. A. B. Kampov-Polevoi, Byull. Éksp. Biol. Med., No. 9, 306 (1978).
4. A. B. Kampov-Polevoi, The Pharmacology of Experimental Alcoholism [in Russian], Moscow (1982), pp. 130-135.
5. A. V. Skal'nyi, Enzymes, Metals, Metalloenzymes, in Diagnosis and Treatment [in Russian], Ivano-Frankovsk (1982), pp. 188-189.
6. I. Khavezov and D. Tsalev, Atom-Absorption Analysis [Russian translation], Leningrad (1983).
7. P. J. Collipp, V. K. Kris, M. Castro-Magana, et al., Alcoholism, 8, 556 (1984).
8. E. J. Kasarsakis, W. L. Mantou, J. B. Devenport, et al., Exp. Neurol., 90, 81 (1985).
9. C. C. Pfeiffer and H. R. Brewerman, Biol. Psychiat., 17, 513 (1984).
10. H. H. Sanstead, Nutr. Rev., 43, 129 (1985).
11. K. Weissmann, E. Christensen, and D. Dreyer, Acta Med. Scand., 205, 361 (1979).