PHARMACOLOGY AND TOXICOLOGY

Nootropic Correction of Disturbances in Learning and Memory Caused by Superhigh Frequency Electromagnetic Radiation

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Superhigh frequency electromagnetic radiation of low intensity produces retrograde amnesia in rats tested for passive avoidance conditioning. Oxiracetam and aniracetam completely prevent the amnestic action of electromagnetic radiation, while nooglutil, piracetam, and centrophenoxine markedly weaken it. It is postulated that pyrrolidone-derived nootropics can be used for the pharmacological correction of disturbances in learning and memory caused by superhigh frequency electromagnetic radiation.

Key Words: *nootropics; nonthermal superhigh frequency electromagnetic radiation; amnesia*

We showed previously [4,5] that after one hour of electromagnetic radiation (EMR) of superhigh frequency (SHF) and low intensity retrograde amnesia develops in rats, a condition which is prevented by piracetam, the classic representative of nootropic drugs. The present study was undertaken to clarify if the other nootropics (oxiracetam, aniracetam, centrophenoxine, nooglutil, etc.) are able to prevent the amnestic effect of nonthermal SHF EMR. Since the hippocampus plays a key role in executing memory mechanisms [2,8], being, together with the hypothalamus, the part of the brain most sensitive to EMR [10], the effect of SHF EMR was assessed by the extracellular concentration of potassium ions as well as the total electrical activity of the CA1 hippocampal area for ortho- and antidromal stimulation.

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MATERIALS AND METHODS

Behavioral experiments were carried out on male Wistar rats weighing 160-230 g. Animals were conditioned to elaborate the passive avoidance response (CPAR) [12] and immediately thereafter they were subjected to SHF EMR for 1 h (wavelength 12.6 cm, frequency 2375 MHz, power flux density 1 mW/cm^2). The parameters of SHF EMR were metrologically monitored. During the irradiation, animals in individual cages made of radio-transparent materials were placed inside a screened chamber in a uniform electromagnetic field. The control animals underwent conditioning followed by sham irradiation. The method has been described in detail previously [4]. The nootropic drugs (injected i.p. 45-60 min prior to CPAR training) used in the study were as follows: piracetam (Latvbiofarm), oxiracetam, N-acetylglycinamide (both compounds synthesized at the Research Center of Biomedical Technology, Russian Ministry of Health,

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TABLE 1. Influence of Nootropic Drugs and the Serum Protein Fraction on the Amnestic Effect Induced by SHF EMR in Rats

Preparation	Total number of rats	Number of CPAR-trained rats	Number of rats with retrograde amnesia after irradiation (CPAR test)		
			0 h	after 1 h	after 24 h
NaCl + CPAR training (control 1)	30	27 (90)	–	–	–
NaCl + sham irradiation (control 2)	30	28 (93)	5 (17)	6 (20)	8 (27)
NaCl + SHF EMR (control 3)	30	26 (87)	23 (77)°°°	19 (63)°°°	15 (50)°
Piracetam, 100 mg/kg + SHF EMR	20	16 (80)	9 (45)*	7 (35)*	7 (35)
Piracetam, 200 mg/kg + SHF EMR	20	17 (85)	6 (30)*	6 (30)*	5 (25)*
Oxiracetam, 10 mg/kg + SHF EMR	20	17 (85)	8 (40)*	7 (35)*	7 (35)
Oxiracetam, 100 mg/kg + SHF EMR	10	10 (100)	1 (10)***	2 (20)*	1 (10)*
Aniracetam, 50 mg/kg + SHF EMR	10	10 (100)	2 (20)**	1 (10)*	1 (10)*
N–acetylglycinamide, 1 mg/kg + SHF EMR	10	8 (80)	7 (70)	7 (70)	5 (50)
N–acetylglycinamide, 10 mg/kg + SHF EMR	10	9 (90)	8 (80)	7 (70)	5 (50)
Centrophenoxine, 50 mg/kg + SHF EMR	16	14 (87)	5 (31)**	5 (31)*	4 (25)
Nooglutil, 50 mg/kg + SHF EMR	18	17 (94)	6 (33)**	5 (28)*	4 (22)*
Serum Protein fraction, 2 mg/kg + sham irradiation	10	1 (10)°°°	9 (90)°°	9 (90)°°	9 (90)°°
Serum Protein fraction, 2 mg/kg + SHF EMR	16	2 (12)***	5 (31)**	5 (31)*	5 (31)

Note. One asterisk or a circle denotes $p<0.05$, two symbols $p<0.01$, and three symbols $p<0.001$; the reliability of differences as compared to control 3 is designated by asterisks and to control 2 by circles. Figures given in parentheses are percentages.

and made available by Dr. S. M. Dudkin), aniracetam (Ro 13-5057, Hoffmann-La Roche), centrophenoxine (meclofenoxate, Germed), and the novel nootropic nooglutil, created recently at the Research Institute of Pharmacology, Russian Academy of Medical Sciences [9] (the last two drugs were made available by Prof. T. A. Voronina). Also administered i.p. was the protein fraction of seal blood serum, which, while not possessing nootropic activity, is able to protect the organism in different stress situations [1,11].

Electrophysiological experiments were carried out on hippocampal sections obtained from male Wistar rats weighing 50-100 g. The preparation and incubation of sections (450-500 μ thick) were performed routinely. The perfusion medium contained 126 mM NaCl, 3 mM KCl, 1.2 mM $MgSO_4$, 1.25 mM NaH_2PO_4, 2 mM $CaCl_2$, 26 mM $NaHCO_3$, and 10 mM glucose. The solution was saturated with a gas mixture of 95% O_2 and 5% CO_2, pH 7.4, at 35±0.5°C. The flow rate was 2 ml/min. The extracellular concentration of K^+ ions was determined using potassium-selective glass microelectrodes [3]. The tip of one channel of the double micropipette was filled with potassium ion-exchange resin (Corning, 477317) and the rest of the space was filled up with a 0.5 M KCl solution. The other channel, used as a comparison electrode, was filled with 150 mM NaCl solution. The resistance of the K^+-sensitive electrode was 300-500 MΩ. The total electrical activity was recorded in the CA1 area using the reference channel of the ion-selective electrode. Ortho- and antidromal stimulation was performed with platinum bipolar electrodes (rectangular pulses lasting 0.1-0.4 msec, amplitude 3-8 V, single or with a frequency of 20 Hz). Data were processed using Fisher's exact method.

RESULTS

As is evident from Table 1, SHF EMR causes retrograde amnesia in rats according to the CPAR test. The majority of the studied nootropics manifested marked antiamnestic properties. Thus, for instance, pyrrolidone derivatives, oxiracetam at 100 mg/kg and aniracetam at 50 mg/kg, completely prevented the development of the amnestic effect in animals during the whole period of observation. The action of nooglutil (50 mg/kg), piracetam (200 mg/kg), and centrophenoxine (50 mg/kg) was somewhat weaker. In contrast, N-acetylglycinamide at 1 and 10 mg/kg, reported to exhibit marked nootropic properties on different models [6,7], did not display antiamnestic activity in our case when used in the indicated range of doses.

It is to be noted that the protein fraction of the blood serum, which itself produces the marked

amnestic effect in a dose of 2 mg/kg, significantly weakens the amnestic effect of SHF EMR (Table 1).

The electrophysiological studies found that the extracellular baseline concentration of K^+ ions at a depth of 150-180 u in the CA1 area is 3.0±0.25 mM and 3.0±0.28 mM in the control (sham irradiation) and test (SHF EMR) animals, respectively. The control and test groups also showed no differences in the changes of the extracellular content of K^+ ions induced by ortho- and antidromal stimulation. Moreover, the focal responses did not reliably differ in latency, amplitude, or shape in these groups of animals.

Thus, a number of nootropics (namely, oxiracetam, aniracetam, nooglutil, piracetam, and centrophenoxine) and the serum protein fraction are able to block or markedly weaken the amnestic effect of SHF EMR, which is reportedly [13] a stressor activating the endogenous opioid system. We showed [4,5] that various neurochemical systems including the opioid-, choline-, and GABA-ergic as well as the benzodiazepine receptors are involved in the genesis of the SHF EMR-induced retrograde amnesia. These components may also play a certain role in the mechanism of the protective action of nootropics [5,9]. The serum protein fraction probably possesses antistress properties and may interact with the μ-opioid and benzodiazepine receptors [11].

Therefore, the pyrrolidone-derived nootropics nooglutil and centrophenoxine can be used for the pharmacological correction of SHF EMR-induced disturbances in learning and memory.

REFERENCES

1. Zh. K. Aslanyants, G. R. Melik-Eganov, A. V. Evstratov, *et al., Byull. Eksp. Biol. Med.*, **112**, № 11, 503-505 (1991).
2. O. S. Vinogradova, *The Hippocampus and Memory* [in Russian], Moscow (1975).
3. L. Vyklitskii and E. Sikova, *Integrative Function of the Brain* [in Russian], Moscow, (1981), pp. 193-202.
4. I. N. Krylova, A. S. Dukhanin, A. B. Il'in, *et al., Byull. Eksp. Biol. Med.*, **114**, № 11, 483-484 (1992).
5. I. N. Krylova, V. V. Yasnetsov, A. S. Dukhanin, and Yu. P. Pal'tsev, *Ibid.*, **115**, № 3, 260-262 (1993).
6. A. I. Machula, V. I. Naumova, Yu. I. Bashnin, *et al., Eksp. Klin. Farmakol.*, № 4, 55-57 (1993).
7. V. I. Naumova, I. N. Krylova, Yu. V. Drozd, *et al., Byull. Eksp. Biol. Med.*, **107**, № 6, 711-713 (1989).
8. T. N. Oniani, *Specific Physiology of the Nervous System* [in Russian], Leningrad (1983), pp. 412-449.
9. S. B. Seredenin and T. A. Voronina, *Eksp. Klin. Farmakol.*, № 1, 4-10 (1992).
10. Yu. A. Kholodov and M. A. Shishlo, *Electromagnetic Fields in Neurophysiology* [in Russian], Moscow (1979).
11. V. V. Yasnetsov, A. N. Gromov, N. M. Kiseleva, *et al., Byull. Eksp. Biol. Med.*, **117**, № 4, 444-445 (1994).
12. R. Cumin, E. F. Bandle, E. Gamzu, *et al., Psychopharmacology*, **78**, 104-111 (1982).
13. H. Lai, A. Horita, and A. W. Guy, *Proc. 11th Ann. Int. Conf. IEEE Eng. Med. and Biol. Soc.*, New York (1989), pp. 1161-1162.