PHARMACOLOGY

SPECTRAL ANALYSIS OF THE EFFECT OF MIDANTANE ON BIOELECTRICAL ACTIVITY OF THE RAT BRAIN

S. V. Krapivin, S. A. Sergeeva, I. S. Morozov, and I. U. Dulpe

UDC 612.822.3.014.46:615.216.32+615.216.32.015.4:612.822.3

KEY WORDS: midantane; spectral analysis of the EEG; psychostimulants

Recently a secure place in the repertoire of drugs for the treatment of Parkinson's syndrome has been occupied by midantane (1-aminoadamantane), which was suggested initially as an antiviral agent. It has been shown that amino derivatives of adamantane. including midantane and gludantane (1-aminoadamantane glucuronide) possess psychostimulant and antidepressive properties [6]. The mechanism of action of midantane is not yet sufficiently clear. Some workers [14, 15] consider that its antiparkinsonian effect is due to its ability to stimulate the CNS, whereas other [1, 2, 13] consider that the efficacy of the compound is connected with its ability to realize the catecholamine reserves of the peripheral and central nervous system and to release catecholamines from their neuronal depots [1, 12]. There is evidence too of the n-cholinolytic activity of midantane and its ability to stimulate dopaminergic and noradrenergic receptors [4, 11].

Meanwhile the electrophysiological effects and mechanism of action of midantane at the neurophysiological level in man and animals has so far received little study. The aim of the present investigation was accordingly to study the effect of midantane on bioelectrical activity of cortical and subcortical brain structures in unrestrained rats.

EXPERIMENTAL METHOD

Experiments were carried out on 17 noninbred male albino rats weighing 180-250 g. Under pentobarbital anesthesia (50 mg/kg, intramuscularly) nichrome electrodes for chronic recording of the EEG were implanted under stereotaxic conditions into the sensomotor cortex of the left and right hemispheres, the dorsal hippocampus, and the lateral hypothalamus of the left hemisphere of the rats 5-6 days before the neurophysiological experiments. A more detailed description of the methods will be found in previous publications [8, 9].

On the day of the experiment, for 1-1.5 h the rats were accustomed to the experimental situation in the chamber, after which electrical activity of the brain structures of the conscious and unrestrained rats was recorded before (background) and after (0.5, 1, 1.5, 2, 2.5, 3, 4, and 5 h) peroral administration of 20 mg/kg of midantane, on a "Neirograf-18" instrument and simultaneously on a tape recorder ("O.T.E. Biomedica" (Italy)). The potentials were recorded during 5-min time cuts. After the experiments, the EEG recorded on tape was subjected to Fourier analysis by means of a "Berg—Fourier Analyzer" (O.T.E. Biomedica). Power spectra (PS) were stored over a period of 4 min 08 sec [8, 9]. For statistical analysis of the data the nonparametric signs test was used [10].

EXPERIMENTAL RESULTS

Spectral analysis of the rat EEG showed that P5 of the sensomotor cortex, the dorsal hippocampus, and the lateral hypothalamus is a distribution with a dominant peak in the theta-band with a frequency of 6-7 Hz and the power of this

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR M. D. Mashkovski.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 112, No. 7, pp. 57-59, July, 1991. Original article submitted November 12, 1990.

0007-4888/91/0007-0975$12.50

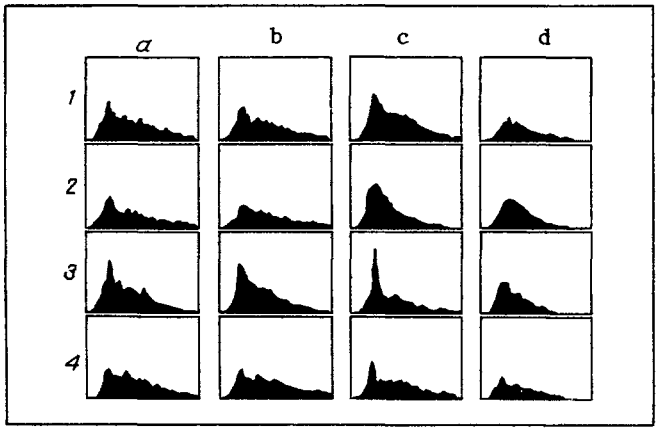

Fig. 1. Effect of midantane (20 mg/kg perorally) on EEG Fourier power spectra of left (a) and right (b) sensomotor cortex, dorsal hippocampus (c), and lateral hypothalamus (d). 1) Before administration of drug (background); 2, 3, 4) 2, 4, and 5 h respectively after administration of midantane. Calibration for each frame: abscissa, from 0 to 32 Hz; ordinate, from 0 to 16 μV^2/Hz (a, b, d) and from 0 to 64 μV^2/Hz (c).

TABLE 1. Quantitative Analysis of PS of EEG of Brain Structures of Unrestrained Rats after Administration of Midantane (20 mg/kg, perorally)

Brain structure	Time after administ.	Band of spectrum, absolute power					Total power 0-32	Amplitude of dominant peak	Frequency of dominant peak
		0—4 δ	4—8 θ	8—15 α	13—20 β_1	20—32 β_2			
Left cortex	1—3	−12,5±16,8	−28,5±14,9*	−33,5±9,5*	−30,3±6,6*	−24,8±7,5*	−28,1±8,5*	−31,3±12,6*	+5,3±12,6
Left cortex	4—5	+18,0±33,9	+27,2±21,4*	+20,7±31,8	+7,2±22,8	−18,2±3,9*	+8,3±14,9	±16,5±12,1*	−1,5±12,3
Right cortex	1—3	−4,0±50,1	−22,6±26,5	−29,7±12,6*	−29,1±9,3*	−16,8±5,8*	−30,0±5,8*	−26,6±33,2	+5,6±14,2
Right cortex	4—5	+34,7±10,2*	+14,6±13,6	+27,6±24,0*	+11,3±16,2	−17,0±4,0*	+10,3±7,0*	+4,6±38,1	−9,3±10,0
Hippocampus	1—5	+6,2±16,5	+38,3±21,3*	+26,0±25,8	+7,3±10,2	−1,0±7,1	+17,3±12,5	+33,2±21,1*	3 −3,2±8,4
Hypothalamus	1—5	+35,5±23,8*	+44,3±29,7*	+64,0±29,8*	+11,2±16,5	−7,7±23,4	+30,7±22,5	+75,8±50,1*	+16,7±12,3*
		Band of spectrum, relative power					Ratio of indices		
		0—4 δ	4—8 θ	8—13 α	13—20 β_1	20—32 β_2	θ/δ	θ/α	θ/(β_1+β_2)
Left cortex	1—3	+22,0±25,9	+2,6±9,3	−5,0±3,0*	−3,1±6,0	+6,2±5,4*	−14,6±8,6*	+11,0±9,0*	−2,3±22,0
Left cortex	4—5	+20,7±37,7	+18,7±5,6	+10,0±11,7	−2,7±6,3	−38,8±27,7*	+12,0±42,7	+7,2±10,9	+34,7±14,8
Right cortex	1—3	+21,8±45,8	+0,8±14,5	−7,5±4,8*	−4,1±6,6	+13,7±16,7	−8,6±32,3	+7,0±17,4	0,0±26,6
Right cortex	4—5	+19,3±17,2	+5,0±17,3	+14,7±10,9*	+0,7±8,0	−24,3±4,1*	−15,0±4,0*	−7,3±25,0	+17,6±22,6
Hippocampus	1—5	−7,2±7,6	+24,2±6,1	+0,2±15,0	−12,2±6,9*	−6,8±15,9	+33,2±11,3*	+25,6±19,6*	+38,2±14,4*
Hypothalamus	1—5	+3,8±10,5	+7,6±10,6	+21,1±9,3*	−14,4±4,9*	−21,4±17,9	+3,9±7,5	−10,8±10,0	+40,7±19,8*

Legend. Level of each value in background (before administration of midantane) taken as 100%. Mean values ± standard deviation are shown. *p < 0.05 (nonparametric signs test).

maximum of the distribution averages 5-15 μV^2/Hz in the cortex, 20-50 μV^2/Hz in the hippocampus, and 5-10 μV^2/Hz in the hypothalamus.

Administration of physiological saline to the control rats led to no significant change in PS of the EEG. Spectral analysis of PS of the EEG after administration of midantane revealed significant changes in the potentials (Fig. 1). In the right and left sensomotor cortex midantane led to biphasic changes in PS of the EEG. In the first phase (the maximum of the effect occurred 1-3 h after administration) there was a decrease in nearly all frequency bands (except delta) (Fig. 1a, b). In the second phase (maximum of the effect 4-5 h after administration), which was observed in about 70% of the animals, the effect was partly reversed: there was an increase in the theta and alpha frequency bands (Fig. 1a, b). Until 5 h after administration of midantane, there was no sign of recovery of PS of the cortical EEG. In the hippocampus and hypothalamus no biphasic effect was present. In the hippocampus an increase was observed in the theta frequency band, whereas in the hypothalamus there was an increase in the slow-wave delta, theta, and alpha frequency bands (Fig. 1c, d). The maximum

of this effect occurred 1-3 h after administration of midantane and the effect was maintained for a long time, up to 5 h after administration of the drug.

Quantitative analysis of PS of the EEG gave a more complete picture of the changes observed after administration of midantane (Table 1). In the first phase more marked changes were observed in the left cortex than in the right: all frequency bands were reduced, leading to a fall of the total power, and the amplitude of the dominant peak was significantly reduced. In the right cortex the absolute power of the theta-band and the amplitude of the dominant peak were not significantly changed. In neither structure was the frequency of dominant activity altered. In the second phase, in the left cortex, the absolute power of the theta-band was significantly increased, and this was accompanied by a decrease in absolute power of the $beta_2$-band; in the right cortex the absolute power of the delta and alpha-bands was increased. whereas the power of $beta_2$-activity was reduced. In the second phase the frequency of the dominant peak of PS of the cortical EEG likewise was unchanged. In the hippocampus the absolute power of the theta-band was increased statistically significantly, and this was accompanied by an increase in amplitude of the dominant activity in this band (Table 1). In the hypothalamus, more marked changes were observed in PS of the EEG: besides an increase in the absolute power of the slow-wave frequency bands, on account of which the total power was increased, an increase in amplitude of the dominant peak and its shift into the region of higher frequencies by about 1-1.5 Hz were observed.

On the basis of the relative power and indices, changes in structure of the spectra of the brain formations tested can be characterized (Table 1). It will be seen that in the left cortex, in the first phase there was a not very great, but statistically significant, change in the relations between the frequency bands on account of a decrease in the alpha-band and an increase in the $beta_2$ frequency band (indices). In the right cortex the changes were in the same direction but were even less in magnitude than in the left cortex. In the second phase, changes in PS of the cortical structures were directed toward an increase in the relative power of the theta- and alpha-bands, accompanied by a decrease in the relative power of the $beta_2$ frequency band (Table 1). In the hippocampus there was a marked change in the ratio between the dominant theta frequency band, which was significantly increased, and the other frequency bands. Predominance of the theta band over the others also was expressed as a significant increase in the indices (Table 1). In the hypothalamus changes also were noted in PS of the EEG, namely an increase in the alpha-band and a decrease in the $beta_1$ frequency band (Table 1).

Thus, after administration of midantane initially activation of the EEG is observed in the cortex, but later this is replaced by synchronization of the potentials, in the hippocampus the dominant theta activity is increased, but in the hypothalamus the slow-wave activity is increased.

The results described evidently suggest that midantane has a psychostimulant action on the CNS, for it has been noted that adapromine, sydnocarb, and amphetamine have a similar effect on the EEG in animals [3]. Data obtained on rabbits after injection of gludantane, the glucuronide derivative of adamantane – are very interesting [5]. The authors cited showed that gludantane has a neurotropic action, which is characteristic of drugs with antidepressive and psychostimulant activity. In particular, it causes significant activation of the EEG: a biphasic effect was noted, similar to the results of the present investigation, with comparatively long restoration of the initial EEG activity (270 min or more). The suggested mechanism of action of gludantane is the same as that of amantadine (midantane): it promotes release of catecholamines from their depots [7]. The therapeutic action of midantane and gludantane is associated with their effect on dopamine metabolism [4], to which great importance is currently attached as a neurotransmitter regulating emotional-behavioral activity of mammals, changes in which are probably reflected in restructuring of bioelectrical activity of the cerebral cortex and deep brain structures.

LITERATURE CITED

1. D. A. Berzinya and A. A. Kimenis, Éksp. Klin. Farmakoter., No. 10, 66 (1981).
2. D. A. Berzinya and A. A. Kimenis, Éksp. Klin. Farmakoter., No. 15, 50 (1986).
3. Ya. L. Briede and A. A. Kimenis, Éksp. Klin. Farmakoter., No. 15, 38 (1986).
4. A. V. Val'dman and M. M. Kozlovskaya, Éksp. Klin. Farmakoter., No. 15, 22 (1986).
5. S. K. Germane, Ya. L. Briede, and M. M. Krima, Éksp. Klin. Farmakoter., No. 11, 37 (1982).
6. S. K. Germane, M. M. Krima, D. A. Berzinya, and Ya. L. Briede, The Goal-Directed Search for New Neurotropic Preparations [in Russian], Riga (1983), pp. 42-49.
7. I. M. Kamyanov and R. A. Andrezinya, Zh. Nevropatol. Psikhiat., No. 6, 910 (1975).
8. S. V. Krapivin and T. A. Voronina, Farmakol. Toksikol., No. 6, 17 (1987).

9. S. V. Krapivin and T. Iosifov, Pharmacology of Nootropics: Experimental and Clinical Study [in Russian], Moscow (1989), pp. 53-57.
10. R. Runyon, Handbook of Nonparametric Statistics [Russian translation], Moscow (1982).
11. D. B. Appleton, M. J. Eadie, and J. M. Sutherland, Med. J. Australia, **2**, 707 (1971).
12. P. E. Cook, S. W. Dermer, and T. McGurk, Can. J. Psychiat., **31**, 757 (1986).
13. C. Penders, Rev. Med. Liege, **37**, 835 (1972).
14. R. S. Schwab and D. C. Poshanzer, J. Am. Med. Assoc., **20**, 1168 (1969).
15. A. C. Schwieger and A. C. Jenkins, Med. J. Australia, **2**, 630 (1970).

REPARATIVE ACTION OF NUCLEIC ACID PREPARATIONS IN EXPERIMENTAL GASTRIC ULCER

A. S. Loginov, Yu. P. Vainberg, P. A. Kol'tsov, L. S. Aronov, N. Sh. Amirov, M. E. Shabanova, B. Z. Chikunova, and I. E. Trubitsyna

UDC 616.33-002.44-092.9-085.31-547.963.32

KEY WORDS: nucleic acids; gastric ulcer; regeneration.

The search for new drugs for the treatment of peptic ulcer is an urgent task in gastroenterology. Of the many different preparations used to treat this disease, preference is still attached to H_2-blockers and to preparations alleged to stimulate regeneration.

This paper describes the results of a study of the effect of nucleic acid preparations on the healing of experimental gastric ulcers in rats: DNA (the sodium salt of native DNA), and ENKAD (yeast RNA hydrolysate), obtained by a method developed at the Institute of Biophysics, Ministry of Health of the USSR and the All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR [1].

EXPERIMENTAL METHOD

Experimental gastric ulcer was produced by Okabe's method [2] by application of acetic acid to the serous membrane of the stomach. The preparations were injected intramuscularly, starting with the 2nd day of experimental gastric ulcer. On the 14th day the animals were killed under ether anesthesia. The stomach was removed, divided along the greater curvature, and the area of the defect was measured; healing of the ulcer defect was determined by calculation of the ulcer index (UI), equal to the area of the lesion (in cm^2). Control animals were given physiological saline (K_1) or solcoseril intramuscularly (K_2) in a dose of 0.2 ml. The DNA preparation was injected in a dose of 30 mg/kg body weight (0.5 ml), The ENKAD preparation was injected in a dose of 30 mg/kg body weight intramuscularly once a day starting with the 2nd day of experimental gastric ulcer.

EXPERIMENTAL RESULTS

The experimental results are given in Table 1.

Central Research Institute of Gastroenterology, Moscow. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 112, No. 7, pp. 59-60, July, 1991. Original article submitted February 1, 1991.

 0007-4888/91/0007-0978$12.50