Comparative Analysis of the Effects of Adapromine, Midantane, and Bromantane on Bioelectrical Activity of Rat Brain

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The adamantane derivatives adapromine, midantane, and bromantane modify bioelectrical activity of brain cortex and subcortical structures. Neurophysiological effects of these preparations indicate that they possess psychostimulating activity. The effect of bromantane on electrical potentials from left and right sensorimotor cortex, dorsal hippocampus, and lateral hypothalamus was stronger than that of adapromine and midantane. This effect was observed as greater quantitative changes in the characteristics of electroencephalogram and changes practically in all characteristics of the power spectrum of electroencephalogram.

Key Words: *bioelectrical activity; EEG Fourier spectra; psychostimulating drugs; adamantane derivatives*

Adamantane derivatives have a broad spectrum of pharmacological activities, including psychostimulating, antidepressant, and nootropic [1,2,4,7,9,10, 13,14]. Some of them produce pronounced effects on the central nervous system and brain biopotentials in intact animals [3]. However, their effects have not been studied in detail and compared.

In the present study we compared the effects of three adamantane derivatives (adapromine, midantane, and bromantane) on bioelectrical activity and Fourier power spectra of electroencephalograms (EEG) recorded from different brain structures in intact nonrestrained rats.

MATERIALS AND METHODS

Experiments were carried out on outbred male albino rats weighting 200-250 g. Adapromine, midantane, and bromantane (20 mg/kg) were administered through a gastral tube. Since bromantane is water-insoluble, it was administered as a 5% solution in polyethylene glycol-400 (PEG-400).

Effects of the preparations on biopotentials from different brain structures were examined in unrestrained rats using Fourier quantitative spectral analysis. Detailed technique of electrode insertion into the sensorimotor cortex, dorsal hippocampus, and lateral hypothalamus, recording and processing of bioelectrical activity, and quantitative spectral analysis were described elsewhere [6]. Electroencephalograms of the studied brain structures were recorded with an MF-Alpha apparatus (W.A.B. Technology or O.T.E. Biomedica) before (background) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 after administration of the preparations. The data were analyzed by paired nonparametrical sign test.

RESULTS

A significant 20-30% decrease in the total power (TP) of left and right cortex EEG predominantly due to a decrease in the absolute power (AP) in the θ and β_1 ranges was observed after administration of adapromine (Table 1). This effect reached the maxi-

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TABLE 1. Effects of Adapromine, Midantane, and Bromantane on Absolute and Total Power and Dominant Peaks on EEG PS from Different Structures of Rat Brain (*M±m*)

Brain structure	Preparation	Time after administration, h	Absolute power of ranges, Hz					Total power 0-32	Amplitude of dominant peak, μV2/Hz	Frequency of dominant peak, Hz
			0-4 δ	4-8 θ	8-13 α	13-20 β_1	20-32 β_2			
Left cortex	A	1	-16.2±17.1	-30.0±23.5*	-21.6±22.2	-23.2±14.3*	-2.4±25.6	-22.2±17.0*	-26.6±20.2*	-1.2±7.3
	M	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
		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
	B	2-3	-42.5±27.8*	-50.8±19.2*	-45.0±24.8*	-45.5±13.8*	-27.8±17.3*	-43.5±18.7*	-51.8±24.3*	-5.5±3.7*
		6-7	-31.2±28.2*	-46.0±17.5*	-34.4±25.2*	-27.6±21.3*	-22.6±16.1*	-33.4±21.2*	-47.8±18.9*	-9.0±6.7*
Right cortex	A		-11.0±7.0*	-32.0±19.7*	-23.5±17.3	-16.6±9.2*	-5.5±8.7	-21.0±12.7*	-36.5±23.2*	+1.2±2.8
	M	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
		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
	B	2-3	-40.6±23.9*	-61.8±14.1*	-54.6±20.9*	-41.8±13.1*	-35.2±14.3*	-49.6±15.8*	-63.6±12.7*	-2.8±6.8
		6-7	-37.8±21.5*	-58.8±8.7*	-49.6±15.5*	-33.6±15.9*	-27.4±21.2	-45.2±13.9*	-65.2±11.7*	-7.4±4.9*
Hippocampus	A	1.5	+0.4±14.7	-19.6±13.5*	-20.0±8.8*	-20.4±18.2	-9.4±17.2	-17.8±10.9*	-26.0±22.6*	-5.4±17.8
	M	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*	-3.2±8.4
	B	2-3	-30.2±8.0*	-41.5±11.0*	-33.3±10.4*	-21.8±14.1*	-15.1±12.3*	-30.6±10.3*	-39.0±14.0*	-2.1±9.9
		6-7	-31.2±11.5*	-47.7±9.3*	-36.2±9.2*	-24.6±8.9*	-20.2±9.9*	-33.8±8.9*	-46.8±10.6*	-8.0±7.9
Hypothalamus	A		-19.2±16.8	-31.0±26.5	-13.5±17.9	-13.2±15.5	-5.7±8.0	-19.2±16.2	-39.8±30.6*	-5.0±3.4
	M	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*
	B	2-3	-19.7±25.7	-33.0±22.1*	-30.5±24.2*	-25.0±16.0*	-25.5±9.8*	-28.5±16.8*	-34.8±15.0*	-4.3±7.5

Note. Here and in Table 2: A) adapromine, M) midantane, B) bromantane. Each value before drug administration was taken as 100%. *p<0.05.

mum 1 h after administration. The initial bioelectrical activity and power spectra (PS) were restored by the 4th-5th h.

Similar changes in TP predominantly due a decrease in the AP in the α-, β_1- and β_2- (sometimes θ) EEG ranges were observed 1-3 h after administration of midantane. Interestingly, after 4-5 h this effect was replaced by an opposite one: significant increase in the θ-range occurred in the left cortex and in the δ- and α-ranges in the right cortex, against the background of the tendency toward an increase in all ranges except β_2-range: its AP significantly decreased in both hemispheres.

In comparison with these preparations, bromantane caused a greater decrease (40-50%) in the TP of EEG spectra due to a decline in all ranges. It should be noted that the effect of bromantane was longer: it lasted 8 h and consisted of two phases — a 40-50% decrease in TP after 2-3 h followed by certain normalization (phase 1) and a 30-40% decrease in TP of all ranges in cortex EEG spectra after 6-7 h (phase 2).

Adapromine caused similar changes in PS of hippocampal EEG (a decrease in TP due to decline in θ- and α-ranges), which lasted 4-5 h. Midantane increased AP of only θ-range dominating in hippocampal PS, which reflects enhanced organizavion of the main rhythm. These effects reached the maximum 1-3 h after administration of the drug and lasted 5 h. The effect of bromantane on the hippocampus was similar to its effect on the cortex: it caused a two-phase decrease (after 2-3 h and 6-7 h) in TP due to a decline in AP of all ranges.

The effects of adapromine on the hypothalamus were similar to those on the cortex and hippocampus, but statistically insignificant. The effects of midantane on PS EEG were the same as in the cortex and in the hippocampus, namely, an appreciable increase in δ-, θ-, α-ranges and in the amplitude of dominant peak and a slight increase in dominant frequency. Bromantane also caused a two-phase decrease in AP in all ranges and, consequently, decreased TP of EEG spectra, although to a lesser degree than in the cortex and hippocampus; this effect being more pronounced than that of adapromine.

In addition to analysis of absolute parameters of EEG spectra, important information can be obtained from analysis of changes in the structure of EEG spectra reflected as modified powers of the ranges and ratios between the frequencies of these ranges (Table 2).

Adapromine increased the relative power of β_2-range, which was statistically significant in the right cortex and hippocampus at reduction of the $\theta/(\beta_1+\beta_2)$ ratio (Table 2).

In none of the studied brain structures, midantane increased the proportion of $\beta_{1,2}$-ranges, which often decreased under the action of this drug.

Interestingly, midantane increased the proportion of the θ-range in the cortex and hippocampus of the left hemisphere. This effect was most pronounced in the hippocampus: all ratios — θ/δ; θ/α; $\theta/(\beta_1+\beta_2)$, were increased.

Bromantane increased the proportion of β_1=(15-20 Hz) and β_2=(20-35 Hz) ranges in the cortex (the increase being greater in the right hemisphere), in the hippocampus, and partially in the hypothalamus. This effect was equally high in both phases of bromantane action and surpassed the effect of adapromine. It is noteworthy that this increase in the proportion of the fast-wave activity occurs predominantly due a significant decrease in the proportion of θ-range of frequencies. Accordingly, the $\theta/(\beta_1+\beta_2)$ index decreases in all structures. Bromantane decreased the frequency of the dominant peak in EEG spectra by 0.2-0.4 Hz in all studied brain structures. This may be explained by specific effect of PEG-400 on bioelectrical activity of the brain: it causes a small delay of dominant activity. Unilateral, but quantitatively diverse, effect on the left and right cortex was typical of bromantane, as evidenced by different quantitative changes in TP parameters, amplitude, and frequency of dominant peak (Table 1).

Thus, from changes in EEG spectra it can be concluded that the major effect of adapromine is a considerable reduction in AP of the dominant θ-activity in the cortex and hippocampus, which lowers the amplitude of EEG signal and TP, and an increase in the proportion of the fast-wave β_2-activity.

Midantane first activates EEG, lowering the amplitude of biopotentials due to a decrease in the AP of θ-, α-, and $\beta_{1,2}$-ranges. This activation did not occur in the hippocampus and hypothalamus and was not accompanied by increase in the proportion of fast-wave fluctuations, which are typical of some classical psychostimulating drugs (phenamine and sidnocarb) [6]. It should be noted that this activation of EEG declines with time and is replaced by an increase in the proportion of θ-range.

In comparison with adapromine and midantane, bromantane produces stronger effect on biopotentials of all studied brain structures, which is reflected by greater quantitative changes in EEG parameters and modifications of all PS characteristics. Bromantane produces qualitatively homogeneous two-phase effects on different brain structures and changes of EEG structure by increasing the proportion of fast-wave $\beta_{1,2}$-ranges.

From our results it can be concluded that bromantane produces stronger and longer stimulating

TABLE 1. Effects of Adapromine, Midantane, and Bromantane on Absolute and Total Power and Dominant Peaks on EEG PS from Different Structures of Rat Brain (*M±m*)

Brain structure	Preparation	Time after administration, h	Absolute power of ranges, Hz					Ratios between parameters (indices)		
			0-4 δ	4-8 θ	8-13 α	13-20 β_1	20-32 β_2	θ/δ	θ/α	α/(β_1+β_2)
Left cortex	A	1	+26.0±48.8	-12.4±17.6	0.0±9.4	-0.6±18.1	+28.2±32.9	-17.8±19.5	-12.0±17.8	-31.8±21.7*
	M	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
		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
	B	2-3	+6.8±24.8	-12.0±6.0*	-3.4±17.3	-0.2±6.9	+24.4±18.6*	-13.0±18.2	-12.2±6.1	-16.6±15.7*
		6-7	+2.6±22.4	-19.4±3.9*	-3.9±10.7	+13.6±12.0*	+21.4±15.5*	-17.2±20.2	-15.2±10.2	-27.4±9.3*
Right cortex	A		+15.0±11.8	-15.5±10.1*	-2.5±11.8	+7.3±14.7	+21.5±15.1*	-25.0±16.0*	-11.6±19.3	+17.6±95.0
	M	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
		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
	B	2-3	+18.2±35.4	-25.2±.8*	-12.4±14.1	+18.8±12.1*	+33.8±26.4*	-27.8±32.5	-12.8±8.4	-38.4±8.3*
		6-7	+12.6±32.2	-24.0±8.1*	-12.2±15.9	+22.8±11.6*	+35.8±24.4*	-13.0±32.8	-25.0±31.4	-40.2±8.0*
Hippocampus	A	1.5	35.6±27.1*	-2.0±11.1	-1.4±6.9	-3.2±11.8	+13.0±7.6*	-19.0±15.2*	0.0±17.1	-4.4±16.9
	M	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*
	B	2-3	+0.3±13.7	-17.1±6.9*	-5.0±8.1	+11.5±6.0*	+21.8±14 5*	-16.2±11.7*	-12.3±11.2*	-27.8±9.9*
		6-7	+4.3±18.4	-20.2±6.2*	-3.0±8.5	+16.0±4.1*	+21.3±13.3*	-22.7±15.3*	-18.0±11.7*	-33.2±7.4*
Hypothalamus	A		+15.5±17.9	-16.7±20.3	+3.7±13.6	+4.3±3.6	+15.5±21.7	-20.7±31.4	-18.5±24.7	-21.5±28.1
	M	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*
	B	2-3	+17.8±50.3	-7.5±9.5	-5.5±12.5	-6.1±7.0	+6.5±23.9	-11.7±32.5	-3.0±8.2	-12.3±19.5
		6-7	+5.0±29.0	-18.3±9.2*	-10.0±13.1	+14.3±9.8*	+24.0±23.5	-18.0±27.6	-9.0±5.5*	-33.3±11.2*

effect than adapromine, midantane, gludantane, memantane, and adaphenoxate [1,3,5,7,8,11,12,14, 15]. These properties of bromantane and its different influences on EEG spectra of the left and right cortex allow one to outline prospective directions in the investigation of the mechanism of action of this preparation.

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