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# Quantitative Pharmaco-Electroencephalographic Analysis of Bromantane

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UDC 615.276.4.015.46.076.9

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol.116, № 11, pp. 515-518, November, 1993
Original article submitted June 8, 1993

**Key words:** *spectral analysis of electroencephalogram; psychostimulators; adamantanes; bromantane; free behavior of rats; excitation*

Special attention in the field of pharmacology has been paid lately to derivatives of aminoadamantane, which is known to influence the monoaminergic processes in the brain [1,4,12,16,17]. Bromantane, a derivative of 2-aminoadamantane, exhibits immunostimulating activity and a pronounced stimulating effect on the central nervous system (CNS) [13,14]. Being a psychostimulator, bromantane significantly inhibits the development of fatigue in animals under conditions of prolonged operant activity and exerts a pronounced adaptogenic effect combined with an immunostimulating and detoxicating action. It is noteworthy that after just a single administration, bromantane manifests its protective effect under conditions of hypoxia, hypo- and hyperthermia, exhausting physical exercise, intoxication, etc. [7,13,14].

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The objective of the present study was to investigate the effect of bromantane on biopotentials of different structures of the brain of intact rats during free behavior, using quantitative spectral analysis of electroencephalograms (EEG) according to Fourier and to make a comparative evaluation of the effect of the drug on the CNS. This method was applied by us in earlier investigations on the effect of different psychotropic drugs such as neuroleptics, nootropics, antidepressants, tranquilizers, and psychic energizers on animals [2,5-7,9-11].

## MATERIALS AND METHODS

The experiments were performed on 18 nonpedigree albino male rats weighing 180-250 g. Chronic implantation of Nichrome electrodes into the sensorimotor cortex of both hemispheres, dorsal hippocampus and lateral hypothalamus of the rat brain, the recording of biopotentials, processing of the experimental data, and quantitative spectral

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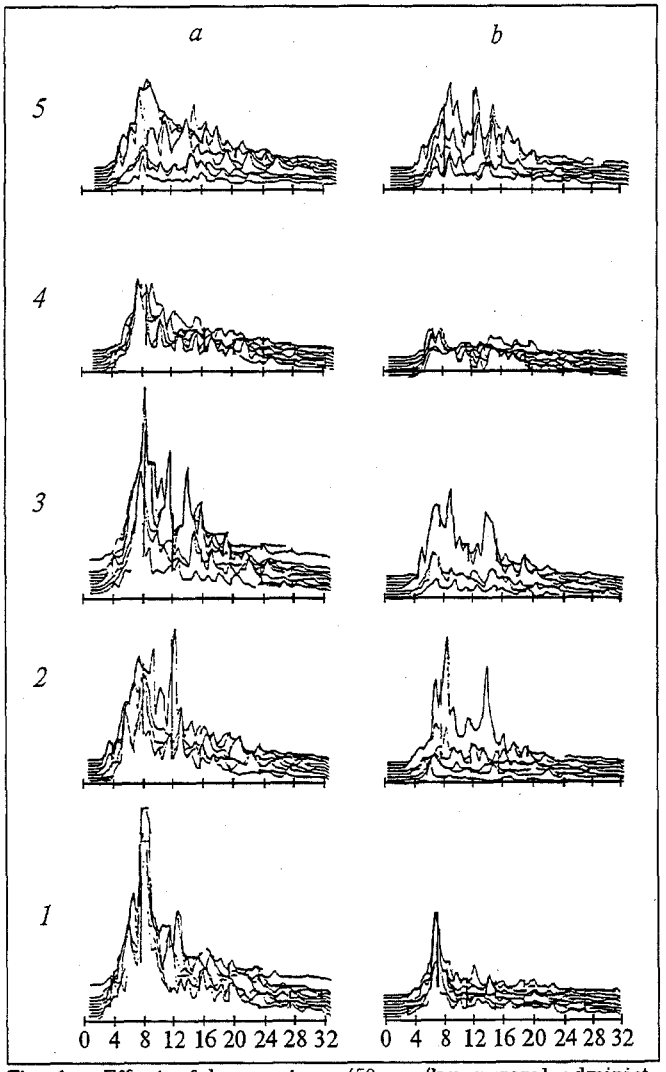


**Fig. 1.** Effect of bromantane (50 mg/kg, peroral administration) on EEG power spectra (after Fourier) of the dorsal hippocampus (*a*) and sensorimotor cortex (*b*) of the rat brain during free behavior. *1*) compressed EEG spectra (each line was recorded for 30 sec) before administration of bromantane (baseline); *2–5*) 2, 4, 6, and 8 h after administration of the drug.

analysis of EEG were carried out as described earlier [2,6,9,11]. The bioelectric activity of the brain was recorded with O.T.E. Biomedica neurophysiological instruments (Italy) before (baseline value) and 1-8 h after peroral administration of bromantane in the optimal effective dose of 20 mg/kg [13,14] dissolved in 1 ml of polyethyleneglycol-400 (PEG-400) [8]. The experimental data were processed using the nonparametric sign test [2,8]. The experiments were performed and the results were processed in an Alpha-M specialized device (W.A.B. Technology, Russia).

## RESULTS

The experiments demonstrated that bromantane produces a pronounced effect on the CNS, which is reflected in significant changes in many indexes of the EEG spectra of the brain structures studied.

Two to three hours after administration of bromantane the absolute power of all frequency ranges in the EEG spectra and the total power decreases (Fig. 1). The effect of bromantane has a biphasic and unidirectional nature: the first maximum was recorded after 2-3 h, when the total power dropped to 40-50%; later on the power tended to revert to its background level, but 6-7 h after administration of bromantane the second maximum of the drug effect was observed, when we recorded a decrease in the power of all spectral ranges in the cortex of both hemispheres, hippocampus, and hypothalamus (Fig. 2). It should be noted that bromantane produces a prolonged (stable) action on the EEG so that during 8 h of recording we did not observe a complete restoration of the EEG indexes to the baseline values.

Quantitative pharmaco-EEG-analysis of bromantane makes it possible to differentiate and characterize the changes in the EEG spectra

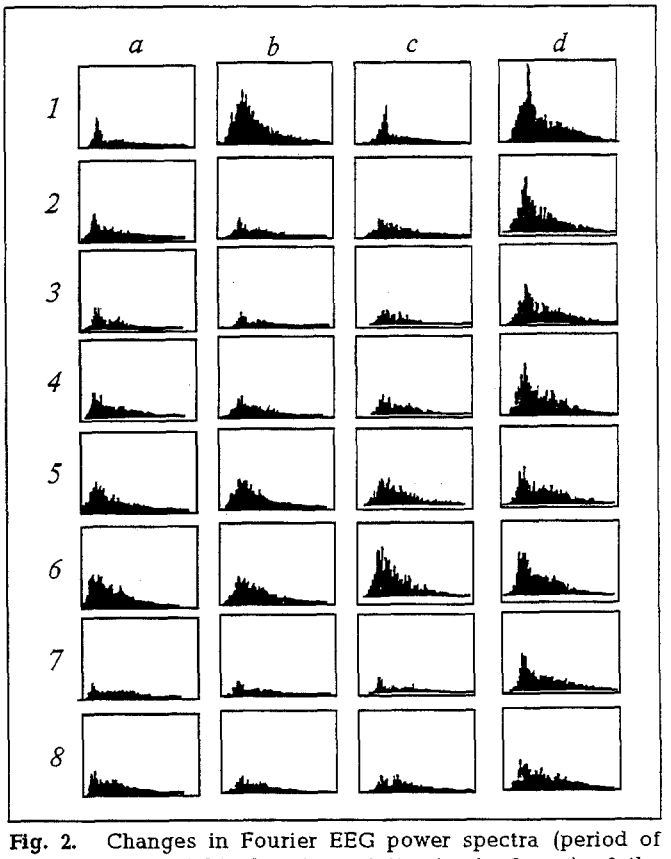


**Fig. 2.** Changes in Fourier EEG power spectra (period of accumulation of bioelectric activity 4 min 8 sec) of the sensorimotor cortex of the left (*a*) and right (*b*) hemispheres of the rat brain, lateral hypothalamus (*c*), and dorsal hippocampus (*d*), under the action of bromantane (50 mg/kg, peroral administration). *1*) baseline (before administration of the drug), *2–8*) 1–7 h after administration of bromantane. Calibration of each cell, abscissa: 0–32 Hz, ordinate: 0–16 $\mu V^2$/Hz (*a, b, c*) and 0–64 $\mu V^2$/Hz (*d*).

evoked by injection of the drug (Table 1). It should be noted that PEG-400 is not a completely neutral agent with respect to the CNS [6,9]. In the EEG of the cortex, hippocampus and hypothalamus it induces a decrease in the amplitude of the dominating peak and a shift of its frequency toward the lower frequency range. Administration of PEG-400 leads to a reduction of the absolute power of the θ, α and $\beta_1$ ranges in the cortex; of the δ, θ and $\beta_2$ ranges in the hippocampus, and of all frequency ranges in the hypothalamus. At the same time, PEG-400 practically does not alter the spectral structure, i.e., does not influence the relative power of any of the frequency ranges and their ratio. The quantitative characteristics of the effect of PEG-400 on EEG were decribed earlier [8].

Administration of bromantane evokes a significant decrease in the absolute power of all frequency ranges (δ, θ, α, $\beta_1$, and $\beta_2$) in the EEG spectra of all structures of the rat brain studied. These changes are much more pronounced than when only the solvent is administered (Table 1). The total power and the amplitude of the dominating peak drastically drop in the θ range (4-8 Hz). Moreover, we observed a slight shift of the dominating peak towards the range of lower frequencies in the cortex of the right and left hemispheres. However, this shift may be attributed to the effect of the solvent [8]. It is noteworthy that in the hypothalamus, during the first phase of the drug effect the absolute power of the δ range and during the second phase the absolute power of the $\beta_1$ range remained at the baseline level (Table 1).

Analysis of the relative power, or the share, of different frequency ranges and their ratio allowed us to characterize the structural changes in the EEG of different regions of the rat brain. Under the action of bromantane the spectral structure (the share of the different rhythms) undergoes fundamental rearrangement: the share of the θ-range drastically reduces, while the share of the $\beta_{1,2}$ range increases. Altogether this leads to a significant decrease in the $\theta/(\beta_1+\beta_2)$ ratio. The θ/α ratio also falls, mainly due to a drastic decrease in the power of the θ-range. It is interesting that such a structural rearrangement of the spectra is more pronounced in the cortex and hippocampus than in the hypothalamus (Table 1).

Although the action of bromantane on the sensorimotor cortex of the right and left hemispheres is of the same direction, the quantitative effect of the drug is different in the two hemi-

TABLE 1. Quantitative Analysis of EEG Power Spectra (PS) of Different Structures of the Rat Brain during Free Behavior after Administration of Bromantane (20 mg/kg, $M \pm m$)

| PS index / Brain structure | Period after administration, h | Absolute power of spectral ranges, Hz | | | | | Total power, 0-32 Hz | Amplitude of dominating peak, μV²/Hz | Frequency of dominating peak, Hz |
|---|---|---|---|---|---|---|---|---|---|
| | | δ, 0-4 | θ, 4-8 | α, 8-13 | $\beta_1$, 13-20 | $\beta_2$, 20-32 | | | |
| Left cortex | 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 |
| Left cortex | 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 | 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 |
| Right cortex | 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 | 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 |
| Hippocampus | 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 | 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 |
| Hypothalamus | 6–7 | −30.0±20.2 | −47.3±17.0 | −40.3±24.5 | −26.0±24.5 | −22.0±6.9 | −33.0±18.6 | −46.3±30.0 | −3.3±8.9 |

*Continued*

| PS index / Brain structure | Period after administration, h | Relative power (Hz) of ranges | | | | | Index ratios | | |
|---|---|---|---|---|---|---|---|---|---|
| | | δ, 0-4 | θ, 4-8 | α, 8-13 | $\beta_1$, 13-20 | $\beta_2$, 20-32 | θ/δ | θ/α | $\theta/(\beta_1+\beta_2)$ |
| Left cortex | 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* |
| Left cortex | 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 | 2–3 | +18.2±35.4 | −25.2±7.8* | −12.4±14.1 | +18.8±12.1* | +33.8±26.4* | −27.8±32.5 | −12.8±8.4* | −38.4±8.3* |
| Right cortex | 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 | 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* |
| Hippocampus | 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 | 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 |
| Hypothalamus | 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* |

**Note.** The baseline value of each index before administration of bromantane is taken as 100%. Asterisk designates the differences with significance $p<0.05$ according to the nonparametric sign test. The indexes of the absolute and total power, amplitude, and frequency of the dominating peak are significant.

spheres (Fig. 2, *a, b*). In particular, this is reflected in different values of the total power and in the amplitude and frequency of the dominating peak, which may either have different dynamics or achieve the same level in different periods (Fig. 2; Table 1). On the basis of the results, we conclude that bromantane exerts a strong and stable effect on the EEG of the cortex, hippocampus, and, to a lesser degree, the hypothalamus, which significantly exceeds the effect of PEG-400.

The observed changes in the EEG under the action of bromantane such as the lessening of the absolute power of all frequency ranges and of the total power, occurring when the share of the $\beta_{1,2}$ ranges in the spectra increases, correlate with a drop in the amplitude of biopotential fluctuations for the build-up of high-frequency oscillations in different structures of the brain. These changes correspond to desynchronization of the EEG and support the assumption that bromantane produces an activating psychostimulating effect on the CNS in animals [6,9,10,13,14]. The results of the quantitative analysis testify that the stimulating effect of bromantane is more pronounced and stable in comparison with the effect of other psychostimulating agents of the adamantane series such as adapromine, midantane, gludantane, and memantine [3,6,9,15]. The biphasic nature of the neurophysiological effect of bromantane may reflect important peculiarities, which, in turn, are most likely determined by the biochemical mechanisms of its action. Therefore, the pharmacokinetics of bromantane may also show some peculiarities.

The different quantitative effect of bromantane on the right and left hemispheres may lead to a smoothing of the asymmetry and facilitation of information transfer between the hemispheres [2]. Elucidation of the mechanisms of action of bromantane is awaiting further studies.

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