EFFECT OF TRANQUILIZERS ON THE RAT ELECTROENCEPHALOGRAM

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In the modern view, the most characteristic effect of tranquilizers on the CNS is an increase in fast-wave beta-activity [8, 9, 13, 15, 16]. Meanwhile, investigations on animals have laid special emphasis on reduction of the frequency of the theta-rhythm [11]. However, the connection between the changes described above, on the one hand, and the anxiolytic effect and the widely distributed side effects (muscle relaxation etc.) of the tranquilizers, on the other hand, remains unclear. Accordingly it was decided to study the effect of several known and new tranquilizers on electrical activity of the rat brain during free behavior and to attempt to correlate changes in the EEG power spectrum with the pharmacological profile of a particular drug and to elucidate the neurophysiological mechanisms of action of this group of substances.

This study is a continuation of a series of pharmacoelectroencephalographic investigations on conscious rats conducted at the Research Institute of Pharmacology, Russian Academy of Medical Sciences (Moscow) [2, 5].

EXPERIMENTAL METHOD

Experiments were carried out on 33 noninbred male albino rats weighing 180-250 g. Under pentobarbital anesthesia (50 mg/kg, intramuscularly) chronic nichrome electrodes were inserted stereotactically into the sensomotor cortex and dorsal hippocampus of the left and right cerebral hemispheres of the rats 5-6 days before the neurophysiological experiments. A more detailed description of the procedure can be found in previous publications [4, 5]. In the course of the experiment, for 1-1.5 h the rats were allowed to become accustomed to the experimental setup in the chamber, and the EEG of the above-mentioned brain structures was recorded in the conscious rats for 5 min before (background) and after injection of the drug, and thereafter every 30 min for 3-4 h after the injection, on an electroencephalograph, and simultaneously on a tape recorder ("O.T.E. Biomedica," Italy). Fourier spectral analysis of the power of the EEG was undertaken on a "Berg-Fourier Analyzer" ("O.T.E. Biomedica"). Artefacts connected with sudden movements of the animals were excluded from analysis. The action of diazepam (5 mg/kg), meprobamate (90 mg/kg), trioxazine (100 mg/kg), and mexidol (50 mg/kg), injected intraperitoneally, was studied. The experimental results were subjected to statistical analysis by the nonparametric signs test [7].

EXPERIMENTAL RESULTS

Analysis of the amplitude of the cortical EEG of normal control rats revealed fluctuations from 50 to 120 μV, and in the case of the hippocampal EEG, from 100 to 400 μV. Spectral analysis of the EEG showed that before injection (background) the power spectrum of the cortical EEG of normal rats during free behavior, in the conscious state, is a distribution with a dominant frequency of 6-7 Hz and with a peak power of 5 to 15 μV^2/Hz. The control, in which physiological saline alone was injected, showed that the power spectrum of the cortex and hippocampus was relatively stable for 3-4 h after injection.

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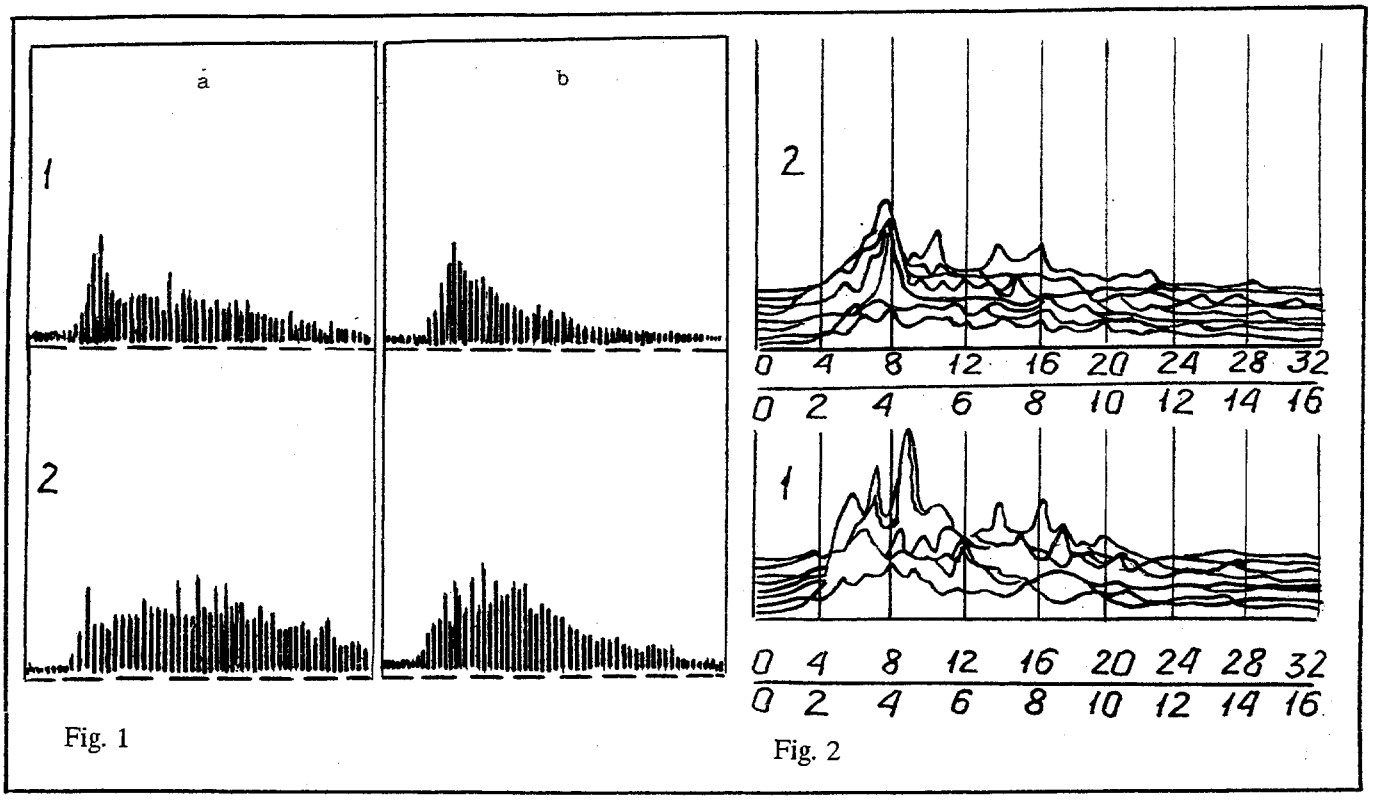

Fig. 1. Effect of meprobamate on power spectrum of EEG of dorsal hippocampus of left (a) and right (b) cerebral hemispheres of a rat: 1) before injection of meprobamate (background); 2) 30 min after injection of meprobamate. Calibration for each square: abscissa, from 0 to 32 Hz; ordinate, from 0 to 64 μV^2.

Fig. 2. Effect of trioxazine on compressed power spectra of EEG (from 0 to 32 Hz) of left sensomotor cortex of a rat: 1) before, 2) 30 min after injection of trioxazine.

Diazepam led to a sharp increase in the different proportion of the absolute power of all frequency bands and of total power (the changes reached a maximum 15-30 min after injection); at first a rise but then a fall of amplitude of the dominant peak were observed. The frequency of the dominant peak was reduced in the region of lower frequencies by 1-1.5 Hz. The changes were more marked in the cortex than in the hippocampus. It was noted that the frequency change was quickly restored (30-60 min after injection of diazepam), but changes in absolute power were observed until 3-4 h after injection of diazepam.

Meprobamate caused a decrease in amplitude of the dominant peak and a decrease in the absolute power of the theta band in the sensomotor cortex, accompanied by a shift of the frequency of the dominant power by 1-2 Hz into the region of lower frequency bands. Besides this, an increase in the $beta_1$- and $beta_2$-frequency bands was observed in the power spectrum of the cortical EEG. Similar changes in the power spectrum of the EEG took place in the hippocampus; in the left hippocampus, moreover, the effect was manifested more strongly than in the right (Fig. 1). The maximum of the effect in the cortex occurred at 15-30 min, in the hippocampus at 45-60 min, and this was followed by the development of gradual restoration of the EEG power spectra close to the background values.

Trioxazine led to a decrease in the absolute power of the theta-frequency band in the cortex, a decrease in amplitude of the dominant peak, and a shift of that peak by 0.5-1 Hz into the region of lower frequencies. The maximum of the changes took place at 15-30 min in the cortex and 60 min in the hippocampus. Unlike the previous drugs thioxazine did not lead to any considerable increase in absolute power of the fast-wave frequency bands (Fig. 2).

TABLE 1. Quantitative Analysis of Changes (in %) of Relative and Total Power of Fourier EEG Spectra of Sensomotor Cortex and Dorsal Hippocampus under the Influence of Tranquilizers in Rats

Brain structure	Drug (dose, mg/kg)	Time of maximum of effect, min	Relative power of frequency bands of spectrum, Hz					Total power of spectrum 0-32 Hz
			0—4 δ	4—8 θ	8—13 α	13—20 β_1	20—32 β_2	
Cortex	Diazepam (5)	15	−47±11**	−40±9*	−48±7*	+18±5*	+63±13**	+145±21**
	Meprobamate (90)	30	−48±12*	−47±9*	−5±4	+41±13*	+83±8**	+134±167
	Trioazine (100)	30	−37±5*	+6±6	−5±17	−9±13	+27±11*	−14±8
	Mexidol (50)	120	−20±10	+10±2	+3±5	−13±3*	−15±4*	+11±10
Hippo-campus	Diazepam (5)	15	−30±18	−27±7*	−32±9*	+23±7*	+58±11**	+130±19**
	Meprobamate (90)	45	−18±14	−35±7*	−3±5	+29±4*	+35±7*	+4±23
	Trioazine (100)	60	+47±6*	−7±8	−3±8	−1±8	+14±10	−23±6*
	Mexidol (50)	60	−7±8	−2±2	−1±3	+7±2	+6±8	+10±5

Legend. Level of each parameter in background (before injection of drug) is 100%. Mean values ± standard deviation are shown. *$p < 0.05$, **$p < 0.01$.

Under the influence of mexidol stabilization and potentiation of the dominant peak of the EEG power spectrum of the cortex (maximum of effect 2-2.5 h) and hippocampus (maximum of effect 1-1.5 h) were observed. A tendency was noted for the absolute power of the slow-wave part of the spectrum to decrease in the delta-band and for the absolute power to increase in the alpha- and beta-frequency bands of the EEG power spectrum.

Quantitative analysis of the relative and total power enables changes in the structure of the EEG Fourier spectrum under the influence of the test drugs to be assessed (Table 1). Clearly, under the influence of diazepam a change took place in the structure of the EEG power spectra, due to a decrease in power of the slow-wave and an increase in power of the fast-wave components of the frequency bands, and by a greater degree, moreover, in the cortex than in the hippocampus. A characteristic feature of diazepam was a marked increase in the total power of the EEG spectra, compared with the other preparations. Meprobamate also changed the structure of the spectra in the brain structures tested, leading to a decrease in the slow-wave and an increase in the relative power of the $beta_{1,2}$-frequency bands. Trioxazine did not give rise to such considerable restructuring of the EEG spectra, and under its influence a decrease could be observed in the delta-band and strengthening of the relative power of the $beta_2$-frequency band in the cortex, but a decrease in total power in the hippocampus (Table 1). Mexidol did not affect the EEG spectra of the hippocampus, but in the cortex it increased the relative power of the theta-band, while decreasing the fraction of the $beta_{1,2}$-frequency bands.

Potentiation of fast-wave beta-activity under the influence of diazepam and other benzodiazepine tranquilizers has been established by many investigators on different species of animals [9, 13, 15, 16]. Only in certain investigations was particular attention drawn to a decrease in frequency of the theta-rhythm [8, 11]. In its pharmacological properties meprobamate is close to the benzodiazepines [1], and the pattern of its effect on the EEG, similar to the action of diazepam [13], is therefore not surprising. Like diazepam, meprobamate causes muscle relaxation and, although meprobamate has now been almost completely abandoned in clinical practice, this drug is of particular interest because its tranquilizing action is realized, not through the GABA-benzodiazepine system, but through other, little studied mechanisms [9, 14]. Trioxazine, as we know, possesses an extremely weak action on conflict behavior, it does not prevent metrazol seizures [1], and has no muscle relaxant action [6]. From the electrophysiological standpoint trioxazine differs from meprobamate in the absence of any inhibition of the "arousal reaction," and also in the synchronization arising simultaneously in cortical and subcortical regions [6]. Because of the absence of any significant effects of trioxazine on fast-wave activity of brain structures it can be tentatively suggested that potentiation of $beta_1$- and $beta_2$-activity is connected with the myorelaxant action exhibited by these drugs, whereas the decrease in frequency of the theta-rhythm is connected with the anxiolytic properties which they exhibit.

As regards the action of mexidol, which is different from that of the other drugs, it can evidently be postulated that if a single dose of mexidol is given it has predominantly a nootropic action, as may be assumed from the pattern of its effect on the power spectra of the cerebral cortical EEG [2]. Meanwhile, its prolonged administration (100 mg/kg, intraperitoneally, daily for 5 months) leads to an increase in the fast-wave frequency bands of the EEG

power spectra, evidence that in this case mexidol exhibits tranquilizing activity, which in all probability is not without side effects.

It can thus be concluded that a common feature of the action of the tranquilizers studied is a decrease in frequency of the dominant activity, which can probably be attributed to the anxiolytic effect possessed by these drugs, whereas a characteristic feature of the effect of some of them is strengthening of the absolute and/or relative power of the fast-wave beta-activity, which in turn, may be connected with the presence of muscle-relaxing manifestations in the pharmacological profile of these drugs.

LITERATURE CITED

1. Yu. I. Vikhlyaev and T. A. Klygul', Progress in Science. Series: Pharmacology. Chemotherapeutic Agents. Toxicology [in Russian], Moscow (1966), pp. 38-93.
2. T. A. Voronina and S. V. Krapivin, Byull. Éksp. Biol. Med., No. 12, 21 (1986).
3. T. A. Voronina, S. V. Krapivin, and N. N. Bogdanov, Vestn. Akad. Med. Nauk SSSR, No. 2, 17 (1987).
4. S. V. Krapivin and T. A. Voronina, Farmakol. Toksikol., No. 6, 17 (1987).
5. S. V. Krapivin and T. Iosifov, Pharmacology of Nootropic Drugs (Experimental and Clinical Study) [in Russian], Moscow (1989), pp. 53-57.
6. I. Magyar, Venger. Med. Zh., No. 3, 29 (1962).
7. R. Runyon, A Guide to Nonparametric Statistics [Russian translation], Moscow (1982).
8. H. Depoortere, Pharmacopsychiatry, **18**, 17 (1985).
9. H. Depoortere, M. Decobert, P. Granger, and F. Rion-Merle, Neuropsychobiology, **16**, No. 2-3, 157 (1986).
10. M. Fink, Neuropsychobiology, **12**, 173 (1984).
11. F. Gekier, G. Allegre, F. Brindean, and P. Borenstein, Path. Biol., **28**, No. 1, 63 (1980).
12. W. M. Herrmann, EEG In Drug Research, New York (1982), pp. 249-351.
13. F. Krijzer and R. van der Molen, Neuropsychobiology, **18**, 51 (1987).
14. H. Möhler and T. Okada, Science, **198**, 849 (1977).
15. E. Ongini, C. Barzagi, and M. Marzanatti, Eur. J. Pharmacol., **95**, 125 (1983).
16. J. Yamamoto, Jpn. J. Pharmacol., **47**, 123 (1988).