SPECTRAL ANALYSIS OF THE EFFECT OF NOMIFENSINE ON THE EEG IN RATS

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Nomifensine possesses antidepressive and psychostimulant activity. In the spectrum of its action nomifensine closely resembles imipraminelike preparations: it has an antireserpine and adrenopotentiating action and it reduces the hypothermic effect of apomorphine and the cataleptogenic action of neuroleptics, etc. [5, 13]. Unlike the tricyclic antidepressants, nomofensine does not potentiate the narcotic action of hexobarbital and alcohol and has no cholinolytic action [6].

Brain tissue has been shown to be highly sensitive to nomifensine, and its concentration in the cerebral cortex is higher than in other parts of the brain [12]. Nomifensine is a powerful blocker of neuronal dopamine uptake, but at the same time it inhibits noradrenalin reuptake more strongly. An assessment of the blocking action of nomifensine on dopamine uptake must take account of the fact that it has a dopamine-releasing action. Since nomifensine potentiates noradrenergic and, in particular, dopaminergic transmission in synapses, it can be used in parkinsonism, especially if parkinsonism is combined with depression. This aspect of the action of nomifensine distinguishes it from other antidepressants [6].

The psychotropic profile of nomifensine is reflected in its antidepressive and psychostimulant action. Its thymoleptic action is weaker than that of imipramine, but stronger than that of the psychostimulants, and it can therefore be given to patients with depression, when the disease pattern is dominated by inertia, passiveness, and diminished working capacity. The drug exerts a stimulating action on patients, improves their working capacity, and does not disturb the speed and accuracy of psychomotor reactions [6].

Meanwhile the electrophysiological correlates of the action of nomifensine on the CNS have received only little study. Accordingly, it was decided to study the effect of nomifensine on the brain electrical activity of unrestrained animals.

EXPERIMENTAL METHOD

Experiments were carried out on 19 nonibred male albino rats weighing 180-250 g. Under pentobarbital anesthesia (150 mg/kg, intramuscularly) nichrome electrodes for long-term recording of potentials were implanted stereotactically into the left and right sensomotor cortex, and the dorsal hippocampus and lateral hypothalamus of the left cerebral hemisphere. A more detailed description of the methods can be found in previous publications [3, 4]. On the day of the experiment, the rats were accustomed to the experimental situation in the chamber for 1-1.5 h, after which the electrical activity of the rats' brain structures was recorded on a "Neirograf-18" instrument, and simultaneously on a tape recorder ("O.T.E. Biomedica," Italy), in the conscious, unrestrained animals before (background) and 0.5, 1, 1.5, 2, 2.5, and 3 h after peroral administration of 10 mg/kg nomifensine. Recordings were made during time intervals of 5 min, After the experiments the electroencephalogram (EEG) recorded on tape was subjected to Fourier analysis on a Berg–Fourier Analyzer ("O.T.E. Biomedica"). Power spectra were averaged over a period of 4 min 08 sec [3, 4]. The results were subjected to statistical analysis by the nonparametric signs test [7].

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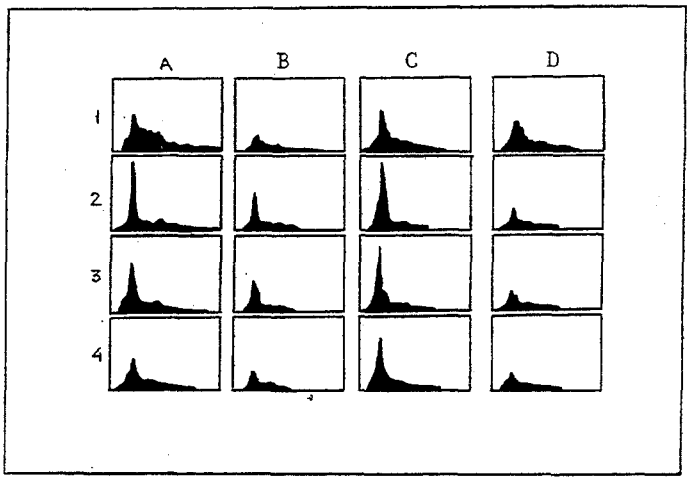

Fig. 1. Effect of nomifensine on EEG power spectra in sensomotor cortex of left (A) and right (B) cerebral hemispheres, and of left dorsal hippocampus (C) and lateral hypothalamus (D) of a rat. 1) Before (background), and 2, 3, 4) 1, 2, and 3 h respectively after administration of nomifensine Calibration of 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).

EXPERIMENTAL RESULTS

Administration of physiological saline to the control rats did not lead to any significant change in the Fourier spectra of the EEG. As routine analysis of the EEG traces showed, electrical activity of the brain structures was unchanged after administration of nomifensine.

Clear changes were observed in the power spectra of the EEG of various brain structures after administration of nomifensine. For instance, in the cortex of the left and right hemispheres the dominant peak of the EEG power spectra grew in size and stability, while the remaining frequency bands decreased (Fig. 1). The effect reached a maximum 1 h after administration of nomifensine. Later all frequency bands decreased in power (until 3 h after administration of the drug). An increase in the dominant power also was observed in the theta frequency band in the hippocampus (maximum after 1-1.5 h), whereas the other bands decreased; after 3 h the original structure of the EEG power spectra was restored. In the hypothalamus the effect was the opposite: all frequency bands decreased (maximum of the effect after 2 h), and this lasted throughout the 3 h of EEG recording.

Quantitative Fourier analysis of the EEG power spectra gives the most complete picture of the changes observed after administration of nomifensine (Table 1) In the left cerebral cortex the absolute power of all frequency bands (except theta) was reduced, and the total power of the EEG spectra fell accordingly. A similar, and equally marked effect also was observed in the cortex of the right hemisphere, except that a tendency was noted for the power of the theta-band to increase. The increase in power of this band was connected with an increase in amplitude of the dominant peak, which took place in the cortex of the right and left cerebral hemispheres, although it was much more marked in the right hemisphere. In the hippocampus a tendency was noted for the absolute power of all frequency bands except theta to decrease; the decrease in power of the alpha and $beta_2$-bands was significant. A sharp increase also was observed in the amplitude of the dominant power. In the hypothalamus there was a tendency for the power of all frequency bands to decrease; the decrease in absolute power of the theta-band and the total power and amplitude of the dominant peak was significant. Unlike in other brain structures, in the hypothalamus there was a certain shift of the frequency of the dominant peak into the region of slower waves.

The relative power of the frequency bands and the indices (the ratio between values for the individual power bands) provides a measure of the change in structure of the EEG power spectra (Table 1). In all structures except the hypothalamus there was an increase in the relative power of the theta-band, which became more marked against the background of a fall in power of the remaining bands. In the cortex of the left hemisphere there was a marked

TABLE 1. Quantitative Analysis of EEG Power Spectra of Various Brain Structures of Unrestrained Rats after Administration of Nomifensine (10 mg/kg)

Brain structure	Parameters of power spectra							
	absolute power of spectral band (Hz)					total power 0.32 Hz	amplitude of dominant peak, μV^2/Hz	frequency of dominant peak, Hz
	0—4 delta	4—8 theta	8—13 alpha	13—20 beta$_1$	20—32 beta$_2$			
Left cortex	−21,6±7,6*	−20,3±23,7	−51,7±5,1*	−44,7±11,5*	−26,3±1,2*	−35,7±7,8*	+37,3±32,1*	−2,6±4,6
Right cortex	−12,3±35,3	+12,3±26,6	−48,0±12,2*	−39,3±29,2*	−27,0±6,1*	−26,7±18,7*	+84,3±45,0*	−2,7±4,6
Hippocampus	−8,6±11,5	+44,3±39,5*	−48,3±15,5*	−27,0±25,5	−15,0±10,5*	−10,7±20,5	+105,0±51,2*	−6,0±10,3
Hypothalamus	−10,0±17,3	−24,0±12,1*	−18,0±18,5	−11,8±18,3	+5,3±9,2	−12,0±11,8*	−40,0±11,0*	−11,0±3,6*
Brain structure	Relative power of spectral bands (Hz)					Ratio of indices		
	0—4	4—8	8—13	13—20	20—32	Theta/delta	Theta/alpha	Theta/beta$_1$ + beta$_2$
Left cortex	−23,0±12,0*	+23,0±26,1	−23,3±16,0*	−13,0±12,1*	+42,7±26,3*	+0,4±24,0	+70,3±64,6*	+26,0±35,0
Right cortex	+17,7±35,2	+53,3±19,5*	−28,0±5,3*	+20,7±18,3*	+8,0±36,0	+36,7±32,3*	+115,0±16,7*	+88,7±50,6*
Hippocampus	+7,0±34,6	+61,0±13,1*	−43,3±10,7*	−20,0±11,8*	−4,3±9,3	+62,0±46,1*	+191,0±71,9*	+85,7±5,0*
Hypothalamus	+3,3±7,0	−14,3±4,9*	−7,0±9,8	−1,0±7,9	+22,7±29,8*	−15,3±9,5*	−5,7±8,3	−21,0±7,8*

Legend. Background level of each value (before administration of nomifensine) is 100%. Mean values ± standard deviation shown *$p < 0.05$ (By nonparametric signs test).

increase in the relative power of the beta$_2$-band, and in the cortex of the right hemisphere, in the power of the beta$_1$-frequency band, which was not observed in the hippocampus In the hypothalamus, due to the decrease in power of the theta-band, the power of the beta$_2$-band increased. It was also noted that the ratio of the power of the theta band to that of the delta-, alpha-, and beta$_{1,2}$-bands increased in the cortex and hippocampus; in the 1st case this was associated with an increase in power of the theta-band, in the 2nd case with an increase in power of the theta-band and a decrease in power of the alpha-band, and in the 3rd case with an increase in power of the theta-band and a decrease in the contribution of beta$_{1,2}$-activity Changes in the indices in the hypothalamus were opposite in character.

Thus changes in the EEG spectra suggest that the most characteristic feature of the action of nomifensine in the cortex and hippocampus is reduction of the absolute power of all frequency bands except theta-activity, an increase in amplitude of the dominant power in the theta-frequency band, and an increase in the relative power of the beta$_{1,2}$ frequency bands. The changes taking place reach their maximum after 1-1.5 h, and mainly terminate 3 h after administration of the drug.

The results so far as the character of the effect of nonifensine on the EEG spectrum is concerned, coincide with those obtained by other workers who studied the effect of amphetamine and showed that it leads to a predominant increase in the theta-band (4-9 Hz) in the EEG spectra, accompanied by reduction of the power of the remaining frequency bands in different structures of the animal brain [2, 9, 10, 11]. This is directly connected with the fact that nomifensine has a beta-phenylethylamine structure, which is characteristic of amphetaminelike stimulants [8]. One of these studies characteristically showed that nonhallucinogenic amphetamine derivatives caused a general decrease in power of all frequency bands of EEG spectra in rats, whereas hallucinogenic derivatives lead to an increase in power within the 7-9-Hz band, and in particular, in the striatum, but to a lesser degree in the hippocampus and cerebral cortex of rats while the remaining frequency bands are depressed [10].

It can be concluded that the pattern of change of the EEG spectra observed under the influence of nomifensine is evidence that it causes a rise in the level of wakefulness and excitability of animals [2, 3, 4]. In order to respond flexibly and effectively to signals from the environment, the brain must possess a high level of wakefulness, This is regarded as the basis on which the whole complex construction of the mental state is supported. With a rise of the level of wakefulness (up to optimal limits) the brain is more able to respond adequately to external stimuli [1]. Elevation of the level of wakefulness and enhancement of the functional state of the brain evidently lie at the basis of the neurophysiological mechanisms of optimization of behavior under the influence of psychostimulants, including nomifensine.

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OLEOFERROTRAST, A RADIO-OPAQUE MAGNETIC MEDIUM: ITS RADIOSPECIFICITY AND TOXICITY

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Artificial contrasting of organs and systems with the aid of substances absorbing x-rays is a technique used in nearly every branch of clinical medicine. Water-soluble and oily radio-opaque substances (ROS) containing iodine, and an aqueous suspension of barium sulfate are the most widely used in medical practice. Despite their many positive properties these substances have one common failing: when introduced into the body they undergo physiological processes linked with the blood and lymph flow and the contractility of hollow organs, and they cannot be stored for the necessary length of time in the region of concern to the investigator. One way out of this difficulty is to create a new class of ROS containing magnetic substances in their composition.

In the scientific literature there are publications devoted to magnetic ROS and attempts to contrast various organs and systems with them [2-6].

Disadvantages of known radio-opaque magnetic media include the possibility of absorption of the carrier liquid in a hollow organ during contrasting and their low stability with time in gravitational and magnetic fields because of the large particle size.

The aim of this investigation was to obtain and study the possibility of using a magnetic ROS on an oily base to contrast various hollow organs under experimental conditions, and possessing the following essential qualities: pharmacologic inertia, i.e., harmlessness for the recipient; chemical and physical stability; a high degree of dispersion; homogeneity; sufficient saturation magnetization to be directed by an external magnetic field; optimal viscosity and optimal radio-opacity. We studied the physicochemical and radiospecific properties of a newly developed preparation, conventionally called oleoferrotrast.

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