CORRELATION BETWEEN ANXIOLYTIC AND ELECTROENCEPHALOGRAPHIC EFFECTS OF BUSPIRONE

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In order to understand the neurophysiological mechanisms of action of tranquilizers, it is very important to determine the connection between the effects of these drugs at the electroencephalographic and behavioral levels. The results of single investigations suggest the existence of correlation between the anxiolytic effect and reduction of the frequency of the theta-rhythm of the animal brain under the influence of benzodiazepine anxiolytics [1, 6]. However, ability to reduce the frequency of theta-activity has not been described for other types of tranquilizers, including the parent of the anxiolytic drugs, meprobamate [6, 8], and the most recent tranquilizer, buspirone [8]. The reason may be pressure of views which have developed on the effects of tranquilizers at the EEG level, where most attention has been paid to changes in beta-activity [7, 8]. On the other hand, in most investigations meprobamate has been used as the representative of the atypical tranquilizers, and the anxiolytic action of meprobamate is much weaker than that of the benzodiazepines and it also gives rise to marked side effects.

In the modern view buspirone has a basically new mechanism of its anxiolytic action, in which the GABA-benzodiazepine system does not play a key role [9, 10]. Possibly the serotoninergic (buspirone is an agonist of 1A-serotonin receptors) [4, 14] and dopaminergic systems [12, 15] are more important for the anxiolytic effect of this drug. The pharmacologic properties of buspirone also distinguish it essentially from the benzodiazepine tranquilizers. With its distinct anxiolytic effect, buspirone has a weak sedative action, has no muscle-relaxing or anticonvulsant effects, and it is considered that drug dependence to it does not develop [13].

The aim of this investigation was to study the effect of buspirone on the EEG, to compare it with that of diazepam, and to study correlation between the anxiolytic and electroencephalographic effects of buspirone.

EXPERIMENTAL METHOD

Experiments were carried out on male laboratory albino rats weighing 200-240 g whose behavior was unrestrained. Fourier spectral analysis of the EEG of the rats' sensomotor cortex was carried out before (background) and 15, 30, 60, 90, 120, 150, and 180 min after injection of the drugs, by means of a "Berg–Fourier Analyzer" (O.T.E. Biomedica, Italy). The averaging time of the spectrum was 4 min 8 sec. Fuller details of the method were described previously [3]. The anxiolytic action of the drugs was assessed by creating a conflict situation between feeding and defensive motivations [2]. Buspirone (5 and 10 mg/kg, generously provided by "Glaxo," U.K.), and RO 15-1788 (10 mg/kg, from "Hoffman LaRoche," Switzerland) were injected intraperitoneally.

EXPERIMENTAL RESULTS

The power spectrum of the sensomotor cortical EEG of the intact tranquil conscious rat consists of a unimodal distribution with peak activity within the 6-7 Hz range. After a single intraperitoneal injection of physiological saline the spectrum was virtually unchanged (Fig. 1, Ia).

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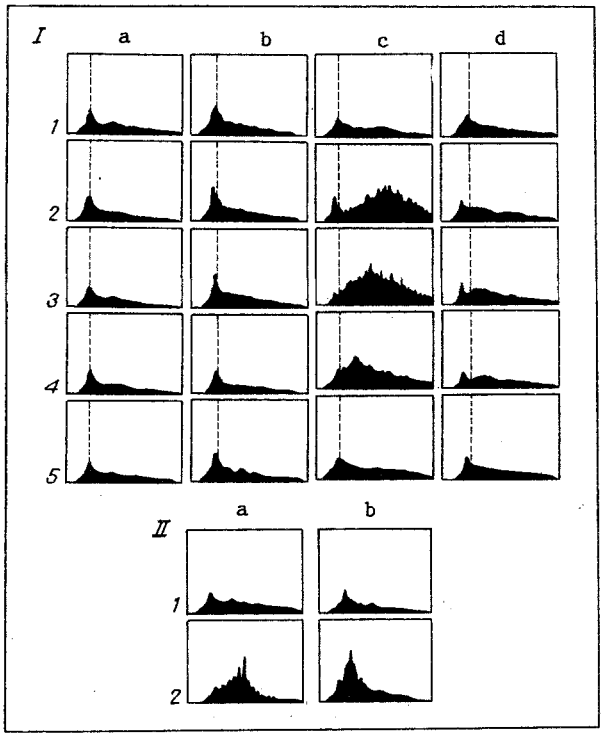

Fig. 1. Changes in power spectrum of sensomotor cortical EEG of rats under the influence of diazepam and buspirone. I: a) Power spectrum after injection of physiological saline, b, c) after injection of 1 and 5 mg/kg diazepam, and d) 5 mg/kg buspirone respectively. 1) Before injection of substances (background), 2-5) 15, 30, 60, and 120 min respectively after injection. II: a) Power spectrum after injection of 5 mg/kg diazepam (other type of response), b) 10 mg/kg buspirone. 1) Before, 2) 15 min after injection of drugs. Calibration, here and to Fig. 2: abscissa for each frame, from 0 to 32 Hz; ordinate for each frame 0-16 μV^2/Hz. No marked changes in power of the spectrum were observed likewise under the influence of diazepam in a dose of 1 mg/kg. The most characteristic manifestation of the effect was a shift of the peak of the theta-band into the region of lower frequencies, on average by 1.0 Hz (Fig. 1, Ib). Under the conditions of the conflict situation diazepam (1 mg/kg) had a distinct anxiolytic effect: the number of punishable takings of water under the influence of the drug was 6.3 ± 0.43, compared with 1.86 ± 0.22 ($p < 0.05$) in the control.

In a dose of 5 mg/kg diazepam caused considerable changes in the power spectrum. The dominant peak of the spectrum 15 min after injection of the drug was enlarged and shifted by 1.0-1.5 Hz toward lower frequencies, with the result that the power of the delta (0.5-4.5 Hz) and theta (5-9 Hz) bands was increased. Additionally, a sharp increase in power of the high-frequency bands (12-32 Hz, see Fig. 1, Ic) was observed. In 50% of animals the power of the theta-band 30 min after injection of the drug was significantly reduced, and during the next 2 h the background level of power of the alpha (9.5-13 Hz) and beta (13.5-32 Hz) bands gradually recovered (Fig. 1, Ic). In the other half of the animals, after 30 min a peak appeared in the 12-16 Hz region of the spectra. The appearance of this peak led to a sharp increase in power of the beta-1 band (13.5-20 Hz) and of the total power of the spectrum. The power spectrum returned to its initial state 2-2.5 h after injection of the drug. In one-third of animals diazepam in a dose of 5 mg/kg caused the appearance of a peak in the 12-16 Hz band as early as 15 min after the injection, and in this case no changes could be observed in the peak in the theta-band (Fig. 1, Ia).

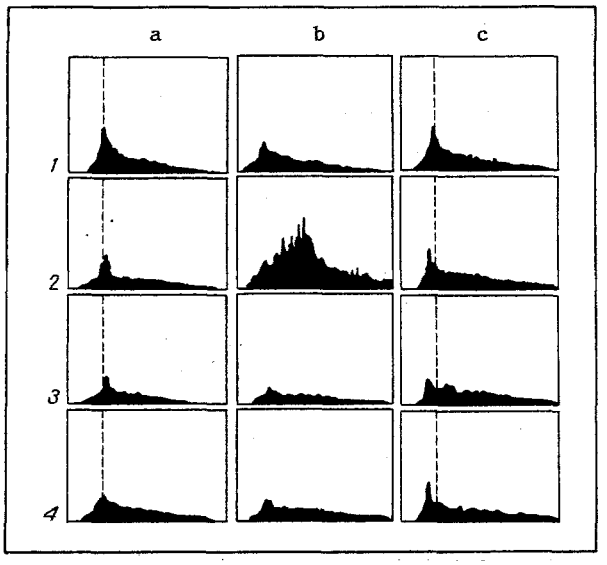

Fig. 2. Effect of benzodiazepine receptor antagonist Ro 15-1788 on EEG effects of diazepam and buspirone. a) Changes in power spectra of rat sensomotor cortex under the influence of Ro 15-1788 (10 mg/kg). 1) Before injection of substances (background), 2-4) 15, 30, and 60 min respectively after injection; b, c: 1) before injection of drugs (background), 2) 15 min after injection of 5 mg/kg diazepam and 5 mg/kg buspirone respectively, 3, 4) 5 and 20 min respectively after injection of Ro 15-1788 (10 mg/kg).

The effect of buspirone (5 mg/kg) on the power spectrum of the rat cerebral cortex was close to the action of diazepam in small doses (1 mg/kg): in the absence of any marked changes in spectral power, only a shift of the dominant peak on average by 1.0 Hz toward lower frequencies was observed (Fig. 1, Id). The presence of the anxiolytic effect of buspirone in a dose of 5 mg/kg was demonstrated during the conflict situation, in which case the drug significantly increased the number of punishable takings of water compared with the control (8.6 ± 1.06 and 3.15 ± 0.25 respectively, $p < 0.05$).

Under the influence of buspirone in a dose of 10 mg/kg a marked increase in power of the alpha-band and in the total power of the spectrum was observed, in connection with the appearance of a peak in the 9-11 Hz band (the time of the effect was 15-30 min after injection; Fig. 1, IIb). The response of the remaining animals did not differ from the changes in the power spectrum under the influence of buspirone in a dose of 5 mg/kg.

By contrast with diazepam, the benzodiazepine receptor antagonist Ro 15-1788 in a dose of 10 mg/kg caused a decrease in power of the sensomotor cortical spectra in all bands and a shift by 0.5-1.0 Hz of the theta-wave peak toward higher frequencies (Fig. 2a). Although the power of the peak of the theta-band (natural frequency 1.5 Hz) was not increased, as a result of these changes in the power spectrum the ratio of the power of the peak to the total power of the theta-band was increased by 28%. This type of effect of Ro 15-1788 on the EEG has common features with the action of nootropic drugs studied previously under similar conditions [3]. However, nootropic drugs cannot induce an increase in frequency of theta-activity in intact animals. The results suggest that changes in the power spectrum of the rat EEG under the influence of Ro 15-1788 reflect not only the higher level of wakefulness, but may also be connected with the weak anxiogenic effect described by several workers for this drug [5]. The results are in agreement with those obtained by Schapf and co-workers [11], who showed that Ro 15-1788 reduces the power of the low-frequency bands and the total power of the EEG spectrum in healthy volunteers, and increases the frequency of the basic rhythm of the EEG, whereas beta activity in this case is unchanged.

Ro 15-1788 differed in its influence on the effects of diazepam and buspirone. In a dose of 10 mg/kg Ro 15-1788 abolished all the effects of diazepam (5 mg/kg) at both electroencephalographic (Fig. 2b) and behavioral levels (Fig. 3). Conversely Ro 15-1788 (10 mg/kg) did not change the effect of buspirone (5 mg/kg) on the power spectrum of the EEG (Fig. 2c) and had no effect on its anxiolytic action under conflict situation conditions (Fig. 3).

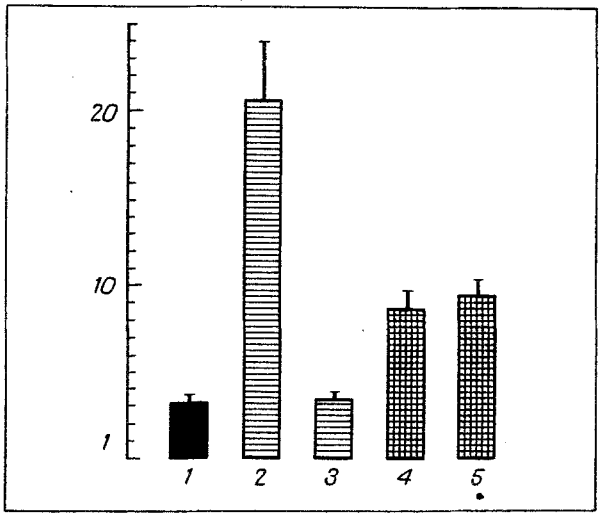

Fig. 3. Effect of Ro 15-1788 on effects of diazepam and buspirone under conflict situation conditions. 1) Control, 2) diazepam (5 mg/kg), 3) diazepam (5 mg/kg) and Ro 15-1788 (10 mg/kg, 15 min after injection of diazepam), 4) buspirone (5 mg/kg), 5) buspirone (5 mg/kg) and Ro 15-1788 (10 mg/kg, injected 15 min after buspirone). Ordinate, number of punishable takings of water.

The results of the behavioral investigation thus indicate that the most important effect at the EEG level for both buspirone and diazepam is reduction of the frequency of the theta-rhythm. The character of the effect of buspirone in a dose of 5 mg/kg on the EEG corresponds to the currently held views of this drug as a nonsedative anxiolytic [13].

The results confirm the previous suggestion [1] that the correlate of the anxiolytic effect of tranquilizers at the EEG level is slowing of the theta-rhythmic activity of the animals' brain. The absence of an effect of the benzodiazepine receptor antagonist Ro 15-1788 on the EEG and on the behavioral manifestations of the action of buspirone is evidence that the anxiolytic effect of buspirone and benzodiazepines at the receptor level is realized by different mechanisms.

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