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Pharmaco-EEG-based assessment of the interaction between ethanol and oxcarbazepine

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Abstract:
Oxcarbazepine is a representative molecule for a new class of anticonvulsant drugs that can treat alcohol dependence in addition to other disorders. Interestingly, the central mechanism of action in oxcarbazepine is very similar to ethanol, suggesting that these two agents may interact and cause enhanced effects in the central nervous system. In this study, we used a pharmaco-EEG method to examine the influence of oxcarbazepine on the effect of ethanol on the EEG of rabbits (midbrain reticular formation, hippocampus, frontal cortex). Oxcarbazepine was administered *po* as a single dose (20 mg/kg or 80 mg/kg) or repeatedly at a dose of 40 mg/kg/day for 14 days. Ethanol was injected *iv* at a dose of 0.8 g/kg 60 min after the administration of oxcarbazepine. Ethanol caused an increase in the low frequencies (0.5–4 Hz) in the recordings, and it caused a marked decrease in higher frequencies (13–30 Hz and 30–45 Hz). Oxcarbazepine altered the EEG pattern in rabbits; this interaction was dependent on the dose of the drug and whether it was administered as a single dose or as multiple doses. Oxcarbazepine administered at a lower dose had a synergistic effect with ethanol in the frontal cortex and midbrain reticular formation, and a similar effect was observed in the hippocampus at a higher dose. Changes in EEG recordings after the administration of oxcarbazepine alone were more pronounced after multiple administrations. The drug decreased the sensitivity of the hippocampus to ethanol, an observation that may be important for the treatment of alcohol addiction.

Key words:
pharmaco-EEG, ethanol, oxcarbazepine, rabbits

Introduction

Alcohol withdrawal syndrome is a serious complication of alcohol dependence, and it often requires intensive medical treatment. Although benzodiazepines are traditionally used to treat alcohol withdrawal syndrome, antiepileptic drugs have been shown to be equally efficacious in relieving alcohol withdrawal symptoms.

Oxcarbazepine is a new anticonvulsive drug created by a structural modification of carbamazepine to improve side effects [38]. As shown by placebo-controlled trials for epilepsy, oxcarbazepine has very good efficacy and beer side-effect profile. Oxcarbazepine dosage should be adjusted according to each patient's need (300–2400 mg/day) [4, 20, 38].

Previous studies have proposed the use of oxcarbazepine for the treatment of alcohol withdrawal syndrome in alcohol-dependent patients [6, 37]. Furthermore, Croissant et al. [7] reported positive clinical results for oxcarbazepine in reducing the risk of relapse in the treatment of alcohol dependence.

Oxcarbazepine and alcohol have complex mechanisms of action in the central nervous system. As both compounds regulate/modulate the activity of the same

neurotransmitter systems, it is possible that they may interact. However, very little is known about the interaction between oxcarbazepine and ethanol. Such an interaction is of clinical importance because of the possibility of relapse during alcoholism therapy and alcohol consumption during oxcarbazepine use.

Studies of pharmacodynamic interactions are difficult, especially for agents such as oxcarbazepine and ethanol, which have complex, multidirectional activities. Indeed, studies have used the exclusion of pharmacokinetic characteristics to study such interactions.

Pharmaco-EEG is a method that can assess interactions between drugs that have effects on the central nervous system. Using this method, we previously demonstrated that tiagabine, gabapentin, topiramate and levetiracetam [25, 27–29] both reduce the effect of ethanol on the bioelectric activity of the hippocampus and enhance its action in the frontal cortex and midbrain reticular formation. The present study investigated whether the interaction between ethanol and oxcarbazepine is similar in character.

Materials and Methods

Animals and treatment

Thirty rabbits (males and females) aged five months and weighing 3.0–3.9 kg were used. The animals were housed in individual cages under normal laboratory conditions (20–22°C, 12 h light/12 h dark cycle) with free access to commercial chow and water. All experiments were performed between 10:00 a.m. and 03:00 p.m.. Oxcarbazepine (Trileptal, Novartis) was given *po* (in the form of a suspension in 1% methylcellulose solution) either at a single dose (of 20 mg/kg or 80 mg/kg) or repeatedly (at a dose of 40 mg/kg) for 14 days. Because of its short half-life, the drug was administered twice a day (at 09:00 a.m. and 04:00 p.m). The doses of oxcarbazepine used in our study were selected on the basis of literature data concerning preclinical studies of the drug. Both single and repeated doses used by investigators varied, fell within a wide range, and differed considerably for various experimental models [1, 18, 41]. For acute experiments, we selected doses of 20 and 80 mg/kg, which were used in preclinical studies of the drug, and we regarded these as the low and high doses, respectively.

A 40.13% (v/v) solution of ethanol was injected as a bolus into the marginal ear vein at a dose of 0.8 g/kg 60 min after the administration of oxcarbazepine. This dose of ethanol was selected on the basis of our previous studies [25, 29, 30]. Control rabbits received (*iv*) isotonic saline solution or 1% methylcellulose (*po*). The drugs were given in a volume of 0.2 ml/kg.

The experiments were carried out in strict accordance with the Polish governmental regulation concerning experiments on animals (Dz.U. 05.33.289). All of the experimental protocols were approved by the Local Ethical Committee for Experimentation on Animals.

Experimental procedure

Monopolar electrodes were implanted into the following rabbit brain structures: the midbrain reticular formation, MRF (P 8 mm, L 3 mm, H 15 mm); the dorsal hippocampus, Hp (P 3 mm, L 5 mm, H 5 mm); and the frontal cortex, C (A 3 mm, L 2 mm), according to the method of Sawyer et al. [35]. The implantation was done under chloralose (60 mg/kg) and urethane (400 mg/kg) anesthesia. The cortical electrodes were made of 0.15 mm diameter silver wire with a ball tip. The subcortical electrodes were made of 0.11 mm diameter Teflon-covered steel wire (Leico Industries, New York). Pharmaco-EEG experiments were performed four weeks after surgery.

EEG recordings were made with an 8-channel electroencephalograph (Medicor-EEG 8S, Budapest, Hungary) with a time constant set at 0.3 s and the high filter set at 60 Hz. During the recordings, the animals remained in an observation cage (120 × 60 × 60 cm) with a transparent roof and front as well as a grid floor. The cage was located in a quiet room, and a closed circuit TV system was used to record animal behavior.

Two-minute artifact-free EEG recordings (selected by the experimenter) were taken for computer analysis. EEG samples were digitized at a rate of 128 samples/s, and a Fourier transformation of consecutive 4 s epochs for each channel was performed. Each spectrum consisted of 512 terms for a frequency range between 0 and 45 Hz, with each term having a width of 0.25 Hz. For further statistical analysis, the transformed data were compressed into these six frequency bands: 0.5–4 Hz (delta rhythm), 4–7 Hz (theta rhythm), 7–10 Hz (slow-alpha rhythm), 10–13 Hz (fast-alpha rhythm), 13–30 Hz (slow-beta rhythm), 30–45 Hz (fast-beta rhythm), and the absolute power over the

entire frequency bands (0.5–45 Hz) was calculated. The results are presented as a percentage of these frequencies in the histogram. At the end of the experiment, the positions of the electrode tips were verified histologically. Six animals were used for each experimental group. In acute experiments, the EEG was recorded before and 1 h after the administration of oxcarbazepine as well as at 15 min and 60 min after the injection of ethanol. In experiments involving multiple dosing, EEGs were recorded after 7 and 14 days of oxcarbazepine treatment (60 min after last dose) and at 15 min and 60 min after the ethanol injection.

Analysis of results

The results are presented as the percent change of the initial value. The normality of the distribution was checked by the Kolmogorov-Smirnov test with Lilliefors correction. Statistical analysis was done with the Kruskal-Wallis (ANOVA) test and the Mann-Whitney U-test (comparison between groups), or it was done with the Wilcoxon matched pair test (comparison in a group), using the Statistics for Windows 5.0 software package. A p-value of 0.05 or less was considered to indicate a statistically significant difference for all statistical tests.

Results

The mean contribution of particular frequencies to the total power spectrum (histogram) is given in Table 1.

Tab. 1. Mean share of particular frequencies in the total power spectrum (%) ± SEM, n = 10

Brain structures / Frequencies	MRF	Hp	C
0.5–4 Hz	31.06 ± 5.11	31.38 ± 4.25	28.90 ± 5.32
4–7 Hz	33.48 ± 7.71	34.56 ± 6.25	34.59 ± 7.13
7–10 Hz	15.84 ± 2.15	15.74 ± 1.28	16.23 ± 1.84
10–13 Hz	11.26 ± 2.02	10.81 ± 2.12	11.83 ± 1.56
13–30 Hz	5.67 ± 1.91	5.28 ± 1.06	5.76 ± 1.26
30–45 Hz	2.65 ± 1.10	2.28 ± 0.44	2.67 ± 0.11

MRF – midbrain reticular formation, Hp – dorsal hippocampus, C – frontal cortex

No change was found in EEG recordings from rabbits treated *iv* with 0.9% (w/v) NaCl (Fig. 1A) or 1% methylcellulose (data not shown). *Iv* injection of ethanol (0.8 g/kg) markedly changed EEG recordings in the frontal cortex (C), in the midbrain reticular formation (MRF), and, to a lesser extent, in the dorsal hippocampus (Hp) (Fig. 1B, C). An increase in power in the 0.5–4 Hz frequency band, and a decrease in the

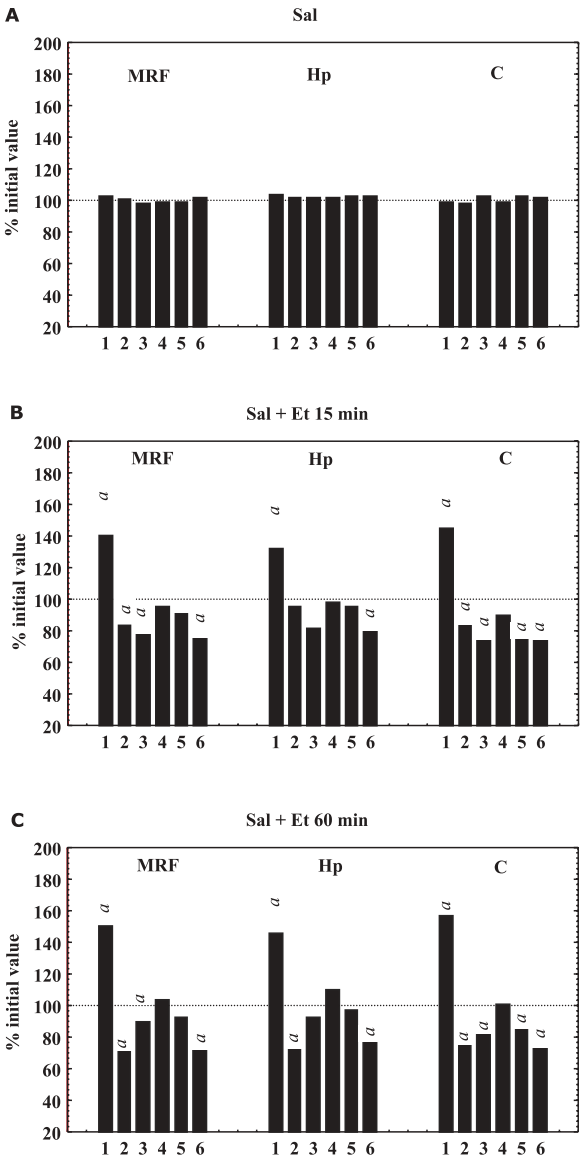

Fig. 1. The mean changes in particular frequencies of EEG rhythms expressed as the percent of initial value ± SD after administration of saline (Sal) – (**A**) and ethanol of 0.8 g/kg, *iv* (Et) – (**B**, **C**); (1) 0.5–4 Hz; (2) 4–7 Hz; (3) 7–10 Hz; (4) 10–13 Hz; (5) 13–30 Hz; (6) 30–45 Hz; (1–6) 0.5–45 Hz; (MRF) midbrain reticular formation; (Hp) hippocampus; (C) frontal cortex. Significant difference *vs.* initial value, *a* – $p < 0.05$, Wilcoxon's test

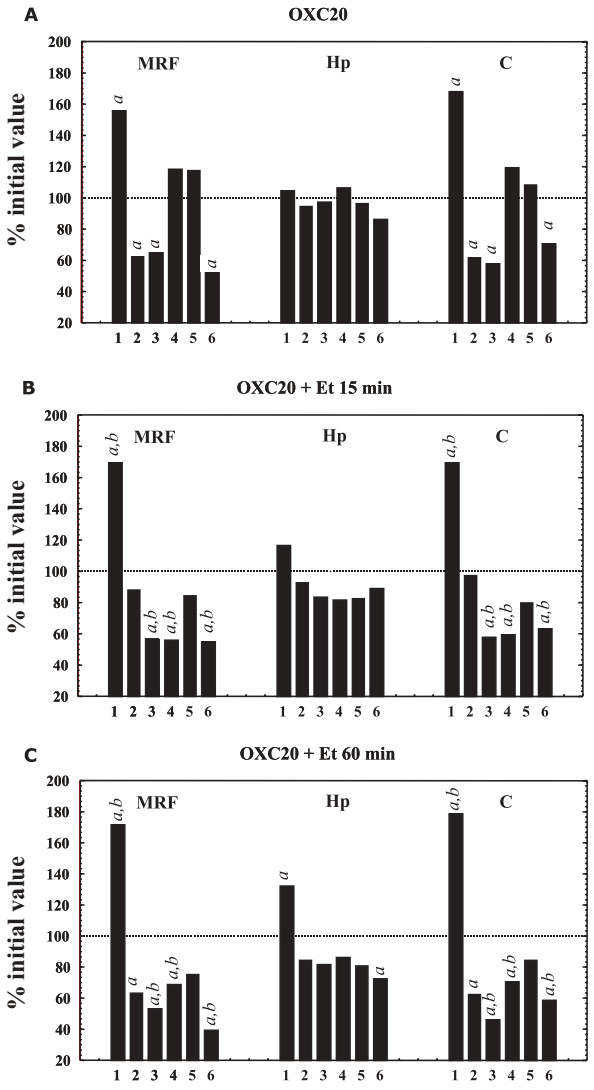

Fig. 2. The mean changes in particular frequencies of EEG rhythms expressed as the percent of initial value ± SD after administration of oxcarbazepine at 20 mg/kg, *po* (OXC 20) – (**A**) and ethanol 0.8 g/kg, *iv* (Et) – (**B**, **C**). Significant difference *vs.* initial value, *a* – $p < 0.05$, Wilcoxon's test. Significant difference *vs.* ethanol-treated group, *b* – $p < 0.05$, Mann-Whitney U-test. For explanation of numbers and brain structure abbreviations, see legend of Figure 1

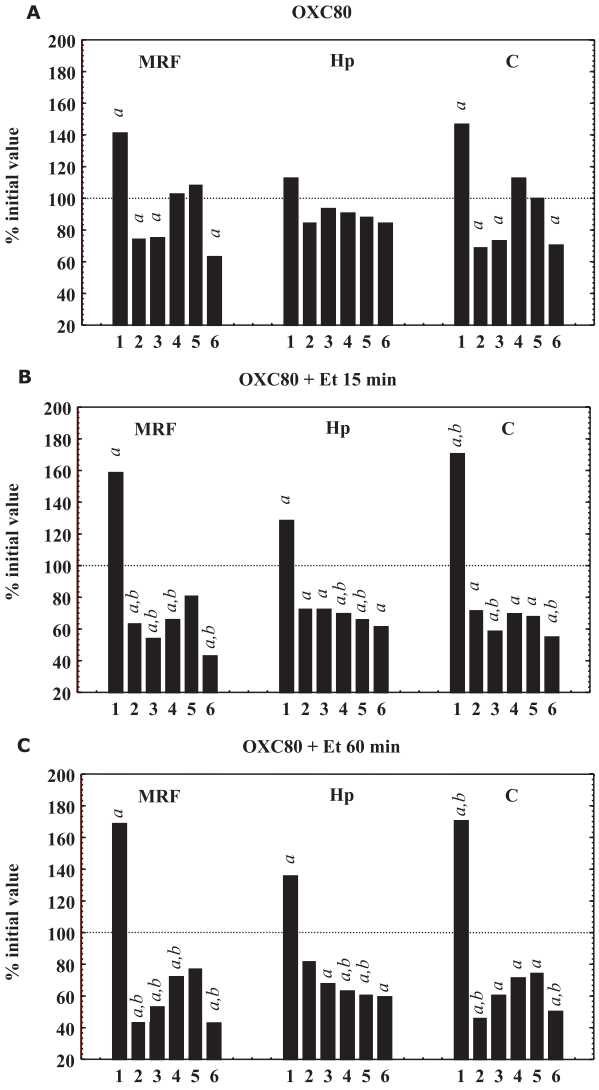

Fig. 3. The mean changes in particular frequencies of EEG rhythms expressed as the percent of initial value ± SD after administration of oxcarbazepine at 80 mg/kg, *po* (OXC 80) – (**A**) and ethanol 0.8 g/kg, *iv* (Et) – (**B**, **C**). Significant difference *vs.* initial value, *a* – $p < 0.05$, Wilcoxon's test. Significant difference *vs.* ethanol-treated group, *b* – $p < 0.05$, Mann-Whitney U-test. For explanation of numbers and brain structure abbreviations, see legend of Figure 1

4–7 Hz, 7–10 Hz, and 30–45 Hz frequency bands for C and the MRF recordings as well as in the 13–30 Hz frequency band (C recording only) were observed. Analysis of the EEG recordings from the Hp revealed an increase in the power in the 0.5–4 Hz frequency range and a decrease in the 30–45 Hz frequency band (Fig. 1B, C).

A marked increase in amplitude was found after visual assessment of post-ethanol recordings. The changes persisted during the length of the 1 hour-long observation.

No changes in behavior were observed after acute or chronic administration of oxcarbazepine. In contrast, immediately after ethanol injection, the rabbits exhibited a considerable disturbance in body balance that subsided gradually, and finally disappeared after 45–60 min.

Oxcarbazepine given *po* to rabbits at a single dose of 20 mg/kg markedly changed EEG recordings MRF

and C. An increase in 0.5–4 Hz frequencies with decreased 4–10 Hz and 30–45 Hz frequencies were observed (Fig. 2A). Oxcarbazepine (20 mg/kg) did not significantly affect the spectrum of EEG recording from the Hp (Fig. 2A).

Oxcarbazepine (20 mg/kg) administered to rabbits 60 min before ethanol (0.8 g/kg) exacerbated the ethanol-induced increase in 0.5–4 Hz frequencies and decrease in 7–13 Hz and 30–45 Hz frequencies recorded from the C and MRF. No ethanol-induced changes were observed in EEG recordings from the Hp (Fig. 2B, C).

The change in EEG recordings from oxcarbazepine administered to rabbits at the high dose of 80 mg/kg was similar to the change in EEG recordings from the low dose (Fig. 3A).

Oxcarbazepine (80 mg/kg) administered to rabbits 60 min before ethanol treatment (0.8 g/kg) enhanced the effect of ethanol on the EEG recordings. When compared to ethanol alone, a significant increase in 0.5–4 Hz frequencies in the C and a decrease in 7–10 and 30–45 Hz frequencies in the C and 4–13 Hz and 30–45 Hz frequencies in the MRF were observed. An enhanced effect of ethanol on higher frequencies (10–30 Hz) was observed in hippocampal EEG recordings (Fig. 3B, C).

Oxcarbazepine administered at a dose of 40 mg/kg/day for seven days markedly affected the EEG recordings obtained from the MRF (increased the proportion of 10–30 Hz frequencies) (Fig. 4A).

In rabbits treated for seven days, oxcarbazepine prevented the ethanol-induced increase in low frequencies in Hp recordings. No effect of oxcarbazepine on ethanol-induced EEG changes was observed in the other structures studied (Fig. 4B, C).

After 14 days of oxcarbazepine administration, changes in EEG recordings were more pronounced (Fig. 5A). In recordings obtained from the MRF, an increase in 0.5–4 Hz, 10–30 Hz frequencies, accompanied by a decrease in 4–7 Hz and 30–45 Hz frequencies, was observed. EEG recorded from the C demonstrated an increased proportion of 0.5–4 Hz and a decreased proportion of 4–7 Hz frequencies. In the Hp, a decreased proportion of 13– 45 Hz range was observed (Fig. 5A).

Oxcarbazepine administered for two weeks prevented ethanol-induced alterations within the low frequency range in recordings obtained from the Hp. No increase in the proportion of 0.5–4 Hz frequencies was observed in the recordings. However, the effect

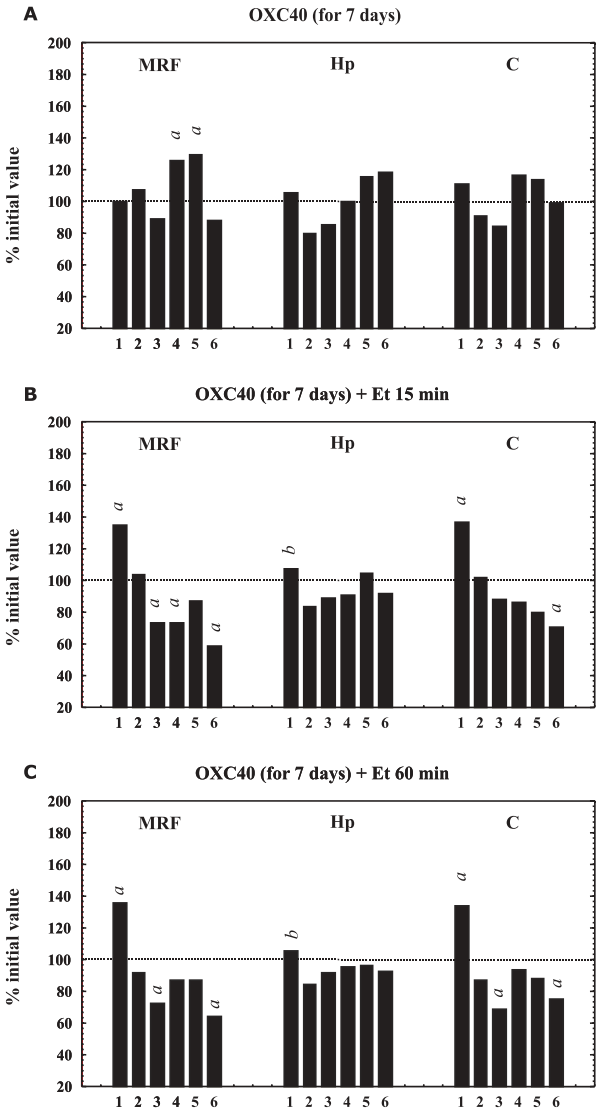

Fig. 4. The mean changes in particular frequencies of EEG rhythms expressed as the percent of initial value ± SD after administration of oxcarbazepine at 40 mg/kg/day *po* (OXC 40 for 7 days) – (**A**) and ethanol at 0.8 g/kg, *iv* (Et) – (**B**, **C**). Significant difference *vs.* initial value, *a* – $p < 0.05$, Wilcoxon's test. Significant difference *vs.* ethanol-treated group, *b* – $p < 0.05$, Mann-Whitney U-test. For explanation of numbers and brain structure abbreviations, see legend of Figure 1

of ethanol on 10–30 Hz frequencies was enhanced. In recordings obtained from the C, oxcarbazepine enhanced the effect of ethanol on 0.5–4 Hz frequencies (only 15 min after ethanol administration) and 7–10 Hz frequencies. A decrease in the proportion of 7–10 and 30–45 Hz frequencies, which was more significant than after treatment with ethanol alone, was observed in the MRF (Fig. 5B, C).

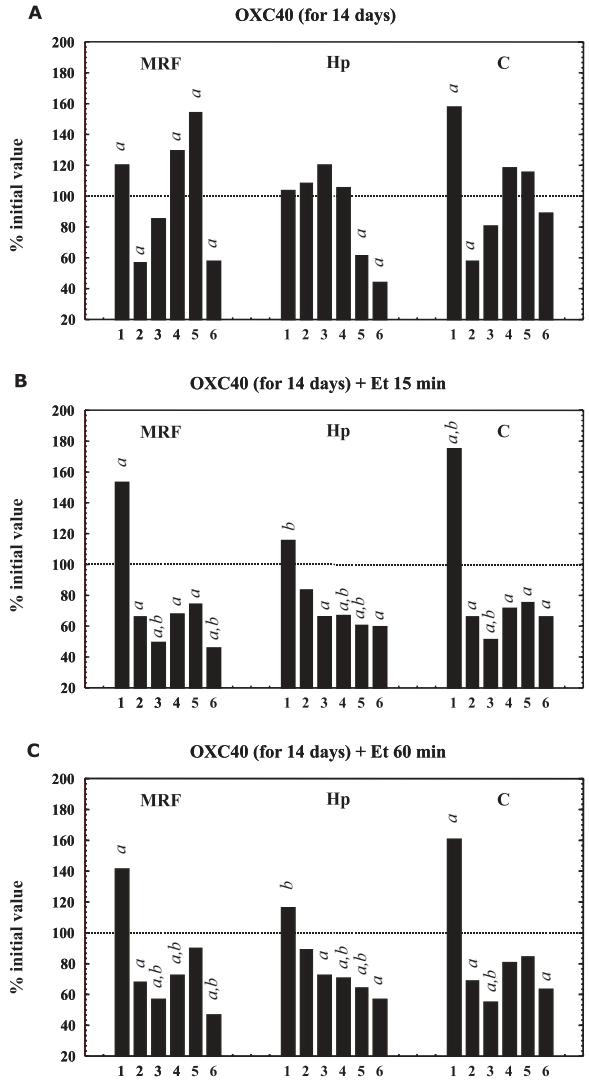

Fig. 5. The mean changes in particular frequencies of EEG rhythms expressed as the percent of initial value ± SD after administration of oxcarbazepine at 40 mg/kg/day *po* (OXC 40 for 14 days) – (**A**) and ethanol 0.8 g/kg, *iv* (Et) – (**B**, **C**). Significant difference *vs.* initial value, *a* – $p < 0.05$, Wilcoxon's test. Significant difference *vs.* ethanol-treated group, *b* – $p < 0.05$, Mann-Whitney U-test. For explanation of numbers and brain structure abbreviations, see legend of Figure 1

Discussion

The aim of this work was to determine whether oxcarbazepine can interact with ethanol to elucidate the characteristics of this interaction. This study used a pharmaco-EEG method to assess the effects of oxcarbazepine and ethanol on the bioelectric activity of the brains of rabbits.

Ethanol produces characteristic, dose-dependent changes in EEG recordings, which are more pronounced when blood concentrations of ethanol rise rapidly. The present study demonstrated that ethanol administered to rabbits as a single high dose potently alters EEG patterns recorded from the frontal cortex and, to a smaller extent, from the midbrain reticular formation and the hippocampus. The observed changes were associated with an increase in the proportion of delta rhythm in the recordings, and they were associated with a reduced proportion of fast-beta rhythm, theta rhythm, slow-alpha rhythm, and slow-beta rhythm. These changes in the EEG spectrum were associated with the potent depressive effect of ethanol on the central nervous system.

Oxcarbazepine administered in single 20 to 80 mg doses changed the recordings obtained from the MRF and C without having a significant effect on Hp recordings. The changes observed after both doses were similar and not dose-dependent. These changes indicate the inhibitory activity of the drug on the central nervous system as evidenced by the shift in the recording spectrum towards low frequencies. Oxcarbazepine in single doses enhanced the effect of ethanol on EEG recordings from the MRF and C, and it enhances this effect in the Hp at a higher dose. from the However, this change was only observed within the high frequency range.

Alterations of EEG recordings after multiple doses of oxcarbazepine were dependant on the duration of treatment and were more pronounced after two weeks of administration. The MRF recordings were most affected, whereas C and Hp were altered to a lesser extent. A characteristic feature of MRF recordings was the increase in the proportion of delta rhythms and 10–30 Hz frequencies. Similar changes in delta and alpha frequency ranges have been observed in clinical studies [4, 32, 33].

Oxcarbazepine administered in multiple doses decreased Hp sensitivity to the effects of ethanol. After 7-day and 14-day treatments with oxcarbazepine, no increase in the proportion of low-frequency delta rhythm, which is a characteristic of ethanol treatment, was observed in EEG recordings. On the other hand, an additional decrease in the proportion of high frequencies, which were more pronounced than with ethanol alone, was observed in recordings after 14 days of treatment.

Oxcarbazepine is a prodrug that is rapidly metabolized into the pharmacologically active monohydroxy

derivative (MHD). *In vitro* studies with rodents have shown that this drug blocks voltage-sensitive sodium channels, thereby stabilizing neuronal membranes, inhibiting repetitive neuronal firing, and reducing synaptic activity. In addition, the monohydroxy derivate of oxcarbazepine reduces activity high-voltage-dependent calcium channels in striatal and cortical neurons, thus reducing glutamatergic transmission [43]. This effect on NMDA glutamatergic transmission due to alcohol discontinuation can cause withdrawal symptoms, withdrawal-related seizures, delirium tremens [11] and craving, which are mechanisms that can contribute to alcohol relapse. Croissant et al. [7] demonstrated that oxcarbazepine reduces craving and facilitates the maintenance of abstinence, whereas in another study by Croissant et al. [6], the time to a severe relapse and time to first consumption of ethanol was similar in patients receiving oxcarbazepine and acamprosate.

Martinotti [19] demonstrated that oxcarbazepine administered at high doses (1500–1800 mg/day) is more effective than naltrexone in the prevention of relapses. The authors emphasized that oxcarbazepine may be used as an alternative to acamprosate or naltrexone, especially in patients with a high level of fear, anxiety and aggression.

A bidirectional response of the hippocampus was observed in our studies. On one hand (with respect to low frequencies), oxcarbazepine prevented the action of ethanol, while, on the other hand (with respect to high frequencies), it potentiated ethanol-induced changes in hippocampal bioelectric activity. However, the varied (or synergistic) influence on fast frequencies observed in our study likely does not have clinical significance, unlike that on slow frequencies.

The mechanisms underlying the synergistic interaction between oxcarbazepine and ethanol on brain bioelectrical activity remain to be elucidated. Among various hypotheses, the modulation of glutamatergic transmission and calcium channels by both compounds in the brain seems particularly likely [6, 10, 39]. Furthermore, electrophysiological studies performed on animals revealed that single doses of alcohol inhibit the function of excitatory amino acid receptors and voltage-dependent calcium channels [5].

The ability of oxcarbazepine to prevent the ethanol-induced changes within the low-frequency range deserves special attention. This effect, although difficult to interpret, may be associated with the favorable action of several new generation antiepileptic drugs for the treatment of alcohol addiction [3, 16, 17, 21, 22, 40, 45]. It should be noted that the mesolimbic system, which includes the hippocampus, has been postulated to be involved in the reinforcement mechanism leading to the development of addiction [23, 31].

Activation of GABA-A receptors by a new generation of antiepileptic drugs has been shown to enhance the inhibitory effect in dopaminergic neurons (nucleus accumbens), which reduces the reward system response and, consequently, causes the stimulus to be perceived as pleasant. In clinical studies of alcohol addicts, topiramate (new antiepileptic drug) was demonstrated to both significantly reduce alcohol intake during the initial period of treatment and prolong the administration of the drug that suppresses the urge to drink [12–15]. The action of oxcarbazepine is not readily associated with an effect on GABA-A receptor activity [34, 44] but, in the context of the present results, its potential use for the treatment of alcohol addiction cannot be excluded.

Using the same experimental model, we previously demonstrated reduced hippocampal sensitivity to ethanol after administration of tiagabine, gabapentin, topiramate and levetiracetam [25, 27–29]. These drugs, topiramate in particular, are already under investigation for their potential use in the treatment of alcoholism [12–14].

Since a pharmacokinetic interaction between ethanol and oxcarbazepine can be excluded, ethanol levels were not measured in this study. In previous studies in which we used the same breed of rabbits as in the present experiments, we measured blood ethanol levels following its *iv* injection of ethanol at a dose of 0.8 mg/kg. Its blood level reached 106.8 (± 5.54) mg%, and 86.1 (± 1.54) mg% 15 min and 60 min after the administration of ethanol, respectively [8]. We have no reason to believe that this concentration differs significantly from our previous study. The metabolism of ethanol is associated with various pathways, but the oxidative pathway is dominant, and the factors determining the oxidation rate include enzymatic activity and hepatocytic ability of NADH reoxidation. Oxcarbazepine is metabolized only to a low extent by cytochrome P-450 enzymes, and therefore the possibility that compounds (inductors/inhibitors) exert their effects on the pharmacokinetics of this drug is limited. Oxcarbazepine is an inhibitor of CYP 2C19 and an inductor of CYP 3A4, whereas CYP 2E1 is involved in the metabolism of ethanol [2, 20, 42]. The pharmacokinetic properties of oxcarbazepine and

the metabolism of ethanol do not seem to have common elements, and this excludes a pharmacokinetic explanation for their interaction. Thus, it seems that the underlying mechanisms are pharmacodynamic in nature.

However, studies concerning the pharmacokinetics of oxcarbazepine in animals have reported species-related differences [36]. Moreover, a number of other factors affecting drug interactions should be taken into consideration (hepatic failure, renal failure, taking various drugs). Thus, this does not allow one to completely exclude the possibility that the observed interaction is partly pharmacokinetic in character.

In summary, the interaction between ethanol and oxcarbazepine altered EEG patterns in rabbits. The nature of this interaction was dependant on the dose of the drug and on whether it was administered as a single dose or as multiple doses. Oxcarbazepine administered at a lower dose in combination with ethanol had a markedly synergistic effect on the frontal cortex and the midbrain reticular formation; at a higher dose, it also had this kind of effect in the hippocampus. Changes in EEG recordings after administration of oxcarbazepine alone were more pronounced after repeated administration. The drug decreased the sensitivity of the hippocampus to ethanol, which is an observation that may be important for the treatment of alcohol addiction.

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