Pharmaco-EEG-based assessment of interaction between ethanol and topiramate

Bogusława Pietrzak, Elżbieta Czarnecka

Department of Pharmacodynamics, Medical University of Łódź, Muszyńskiego 1, PL 90-151 Łódź, Poland

Correspondence: Bogusława Pietrzak, e-mail: bpietrzak@pharm.am.lodz.pl

Abstract:
Topiramate, an anticonvulsant, has been reported to increase the number of abstinent days and decrease craving in alcohol-dependent individuals. However, maintaining abstinence during the therapy of addicts is a considerable problem. Therefore, it is important to assess the interactions of ethanol with the topiramate. In this study, we have decided to examine this interaction by using pharmaco-EEG method. The influence of topiramate on the effect of ethanol on EEG of rabbits (midbrain reticular formation, hippocampus, frontal cortex) was tested. Topiramate was administered (*per os*) at a single dose (25 and 100 mg/kg) or repeatedly at a dose of 25 mg/kg for 14 days. Ethanol was injected at a dose of 0.8 g/kg 120 min after topiramate treatment. Ethanol caused an increase in the slow frequencies (0.5–4 Hz) in the recording, as well as a marked decrease in the fastest frequencies (13–30 and 30–45 Hz). The above changes in the EEG spectrum composition are associated with a significant depressive effect of high ethanol doses on the central nervous system. Topiramate administered both at single and multiple doses affects EEG recordings from all the investigated structures. The drug administered at a single dose together with ethanol demonstrated marked synergism of action. Topiramate used at multiple doses enhanced the effect of ethanol on EEG recording from the frontal cortex and midbrain reticular formation. The drug reduced the sensitivity of the hippocampus to the effect of ethanol, which may be associated with the effectiveness of topiramate in the therapy of alcoholism in humans. The observed interaction is probably of pharmacodynamic character.

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

Introduction

Substances exerting their effect on various neurotransmitter systems, e.g., opioid, serotoninergic, dopaminergic, GABAergic or excitatory amino acid, play an important role in pharmacological therapy of alcoholism.

Among many different drugs, acamprosate, as well as drugs blocking opioid receptors (naltrexone and nalmefen) have been regarded as effective agents, prolonging the periods of abstinence and reducing the amounts of consumed alcohol [3, 12, 13, 26, 27, 38].

Recent research suggests a role for new generation anticonvulsants in the treatment of alcohol dependence beyond their use in withdrawal syndromes [7, 28, 41, 48]. The results concerning topiramate seem to be especially interesting [17, 29].

Topiramate, an anticonvulsant drug normally used in the treatment of seizure disorders, has recently been reported to help in the treatment of several psychiatric disorders, including alcoholism [4]. Relative to placebo, oral topiramate administration increased the number of abstinent days in alcohol-dependent individuals who received standard medication in a dou-

ble-blind 12-week clinical trial [25]. In the same study, topiramate also decreased daily alcohol consumption, number of heavy drinking days, and alcohol craving. Subsequent analyses showed that topiramate increased overall well-being and quality of life in these alcoholic subjects, while reducing alcohol dependence severity and harmful drinking consequences [24].

However, maintaining abstinence during the therapy of addicts is a considerable problem. Therefore, it is important to assess the interactions of alcohol with the drugs which are or can be used in the treatment of alcoholism. Such interactions are of certain clinical importance because of the possibility of breaches of abstinence both in the course of the therapy of alcoholism with these drugs, and during their use for different indications.

Studies of pharmacodynamic interactions are difficult, especially in the case of complex, multidirectional activity of the investigated agents. They are often identified by exclusion of pharmacokinetic character of the studied interaction. The results of experimental studies are also diverse and may depend on the selected experimental model.

Topiramate and alcohol are characterized by a complex mechanism of action in the central nervous system, influencing the same neurotransmission pathways. This is associated with a potential risk of interactions enhancing the central effect of the studied substances.

In the present study, the pharmaco-EEG method based on recording of bioelectrical activity of the selected rabbit brain structures was used.

The aim of the study was to assess the effect of topiramate administered at single or multiple doses on EEG recordings obtained from rabbits implanted with electrodes located in various cerebral structures.

Materials and Methods

Animals and treatment

Thirty rabbits of both sexes, weighing 3.0–3.9 kg, 5 months old were used. The animals were housed in individual cages under normal laboratory conditions (temperature 20–22ºC, under a 12h light/12 h dark cycle) and they had free access to commercial chow and water. All experiments were performed between 10.00 a.m. and 03.00 p.m. Topiramate (Topamax, Janssen-Cilag International N.V.) was administered *per os (po)* (in the form of suspension in 1% methylcellulose solution) once at a 25 and 100 mg/kg dose or repeatedly at a dose of 25 mg/kg for 14 days. Ethanol was administered into the marginal ear vein by bolus injection (*iv*) at a dose of 0.8 g/kg (40.13% v/v solution) 120 min after topiramate treatment. The dose of ethanol was selected on the basis of our previous studies [32–34].

The doses of topiramate 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 various investigators varied, and fell within a wide range and differed considerably in various experimental models [15, 16, 19]. For acute experiments, we selected the doses of 25 and 100 mg/kg, used in the preclinical studies of the drug and regarded as a low and high dose.

Control rabbits received i*v* isotonic saline solution. The drugs were given in the volume of 0.2 ml/kg.

All the procedures used in these experiments were approved by the Ethics Committee of the Medical University (Łódź, Poland).

Experimental procedure

Using coordinates according to Sawyer et al. [39], the rabbits had monopolar electrodes implanted (under chloralose 60 mg/kg and urethane 400 mg/kg anesthesia) into the following brain structures: MRF – midbrain reticular formation (P – 8 mm, L – 3 mm, H – 15 mm), Hp – dorsal hippocampus (P – 3 mm, L – 5 mm, H – 5 mm) and C – frontal cortex (A – 3 mm, L – 2 mm). The cortical electrodes were made of silver wiring with a 0.15 mm diameter ball at the tip. The subcortical electrodes were made of Teflon-covered steel wiring (0.11 mm in diameter; Leico Industries New York). Experiments were performed on the rabbits for a period of 4 weeks following the surgery.

EEG recordings were performed with 8-channel electroencephalograph (Medicor-EEG 8S) 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 ($120 \times 60 \times 60$ cm) with a transparent roof and front and with a grid floor. The cage was located in a semi-sound-proof room. A closed-circuit TV system recorded the animals' behavior.

Frequencies	Brain structures		
	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

Two-minute artifact-free EEG recordings (selected by the experimenter) were taken for computer analysis. EEG samples were digitized at the rate of 128 samples/s and the Fourier transform of consecutive 4 s epochs for each channel was calculated. 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 then compressed into six frequency bands as follows: 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) and 30–45 Hz (fast beta rhythm). At the end of the experiment, positioning of the electrode tip was verified histologically. The experiments were carried out on groups of six animals each. EEG was recorded before and 2 h after topiramate application, 15 and 60 min after ethanol and saline (control group) injection.

The results are presented as percentages of a given frequency in the frequency histogram and as a percentage change in relation to the initial value.

Statistical analysis

The normality of distribution was checked by means of Kolmogorov-Smirnov test, with Lillieforse correction. Statistical evaluation was performed by Kruskal-Wallis (ANOVA) test and Mann-Whitney U-test, or Wilcoxon matched pair test, using the Statistica for Windows 5.0 software package.

Results

The mean contribution of particular frequencies to total power spectrum (histogram) in the rabbits has been presented in Table 1.

No changes were found in EEG recordings in rabbits given *iv* 0.9% NaCl (Fig. 1A). Ethanol at the 0.8 g/kg, *iv* dose produced changes in the EEG recordings from the frontal cortex and MRF, and fewer significant changes in the recordings from the hippo-
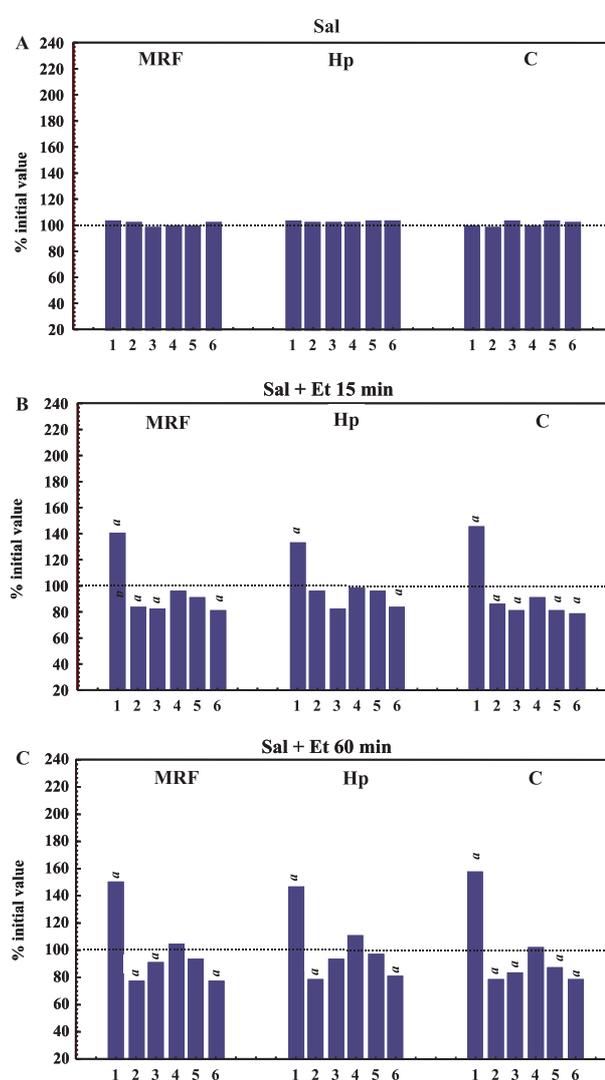

Fig. 1. The mean changes in particular frequencies of EEG rhythms expressed as the percent of initial value after administration of saline (Sal) – (**A**) and ethanol of 0.8g/kg *iv* (Et) – (**B**,**C**); (1) 0.5–4 Hz; (2) 4–7 Hz; (3) 7–10 Hz; (4) 10–13 Hz; (5) 13–30 Hz; (6) 30–45 Hz; MRF – midbrain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

campus (Fig.1B, C). The increase in particular power in the 0.5–4 Hz frequency band and the decrease in 4–7 Hz, 7–10 Hz, 30–45 Hz in the recordings from the frontal cortex and MRF, and in 13–30 Hz band in the frontal cortex recordings only were observed. The power in the 0.5–4 Hz frequency range increased and in 30–45 Hz decreased in hippocampal recordings (Fig. 1B, C).

In visual assessment of post-ethanol recordings, a marked increase in the amplitude was notable. The changes persisted during 1-h observation. Immediately after the administration of this dose of ethanol, the rabbits revealed great disturbances of equilibrium.

In our previous studies, we assessed ethanol levels after a single dose of ethanol identical with that used in the present study. Ethanol level was estimated at 106.8 ± 5.54 mg% 15 min, and 86.1 ± 1.54 mg% 60 min after ethanol administration [11].

Topiramate administered to rabbits at a single dose of 25 mg/kg, significantly altered EEG recordings from all the investigated structures. Increased proportion of slow frequency activity (0.5–4 Hz) and decreased proportions of 4–7 and 30–45 Hz, was observed, and in the hippocampus there was additionally a decrease in 7–10 Hz frequency (Fig. 2A).

Ethanol at a single dose (0.8 g/kg) administered 120 min after topiramate (25 mg/kg) caused considerable enhancement of changes in EEG recordings in comparison with those observed after ethanol alone (Fig. 2B, C).

Fifteen minutes after administration of ethanol, in the MRF and frontal cortex a higher increase in proportion of slow (0.5–4 Hz) frequency recordings and decrease in 4–7, 7–10 and 30–45 Hz frequencies were observed in comparison with the recordings obtained after ethanol alone, whereas in the hippocampus there was a more significant decrease in the recordings of 4 to 45 Hz frequency range (Fig. 2B).

Sixty minutes after ethanol administration, the changes were similar in character, but less pronounced. MRF recordings demonstrated a decreased proportion of 4–7 Hz and 30–45 Hz frequencies, hippocampal of 10–13 Hz, and cortical of 4–7 Hz in comparison with the effect of ethanol alone. The latter structure still exhibited an increased proportion of the slowest frequency 0.5–4 Hz (Fig. 2C).

Topiramate administered to rabbits at a single high dose (100 mg/kg) significantly altered EEG recordings from all the investigated structures. The changes were similar in character to those observed after the
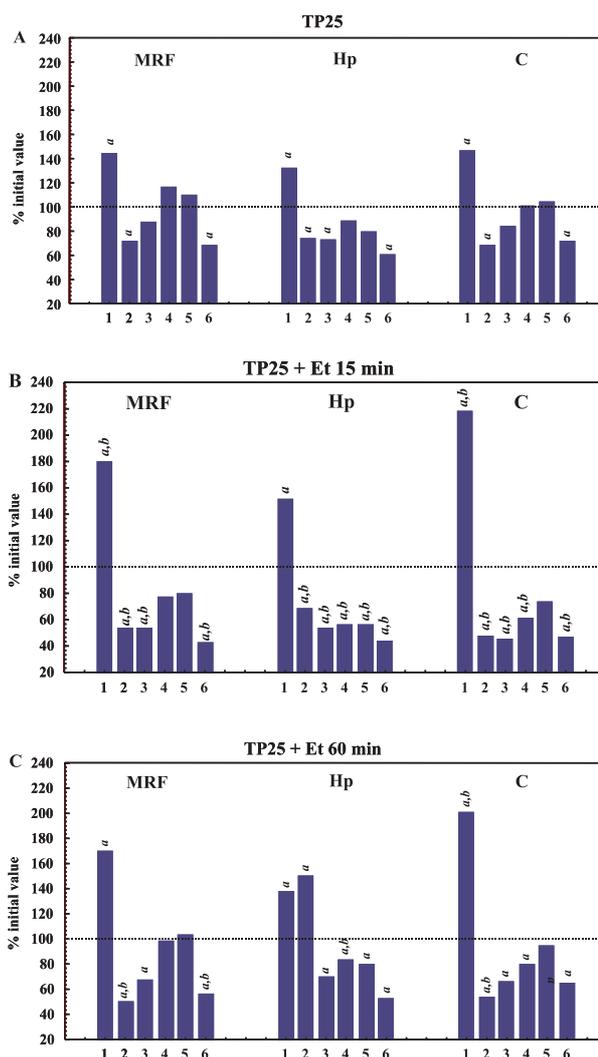

Fig. 2. The mean changes in particular frequencies of EEG rhythms expressed as the percent of initial value after administration of topiramate at 25 mg/kg *po* (TP25) – (**A**) and ethanol 0.8 g/kg *iv* (Et) – (**B**,**C**). Significant difference *vs.* initial value, [a] $p < 0.05$, Wilcoxon's test. 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

lower dose of the drug, but additionally other frequencies were affected (Fig. 3A).

In all the investigated structures, the proportion of slow frequency (0.5–4 Hz) was increased, whereas that of 4–7 and 7–10 Hz frequencies was decreased. Recordings from the MRF demonstrated an additional increase in 13–30 Hz and decrease in 30–45 Hz frequency ranges, and those from the hippocampus – in 30–45 and 10–13 Hz frequencies, respectively (Fig. 3A).

Topiramate administered to rabbits at a single high dose (100 mg/kg) 120 min before ethanol injection, enhanced significantly its effect on EEG (Fig. 3B,C).
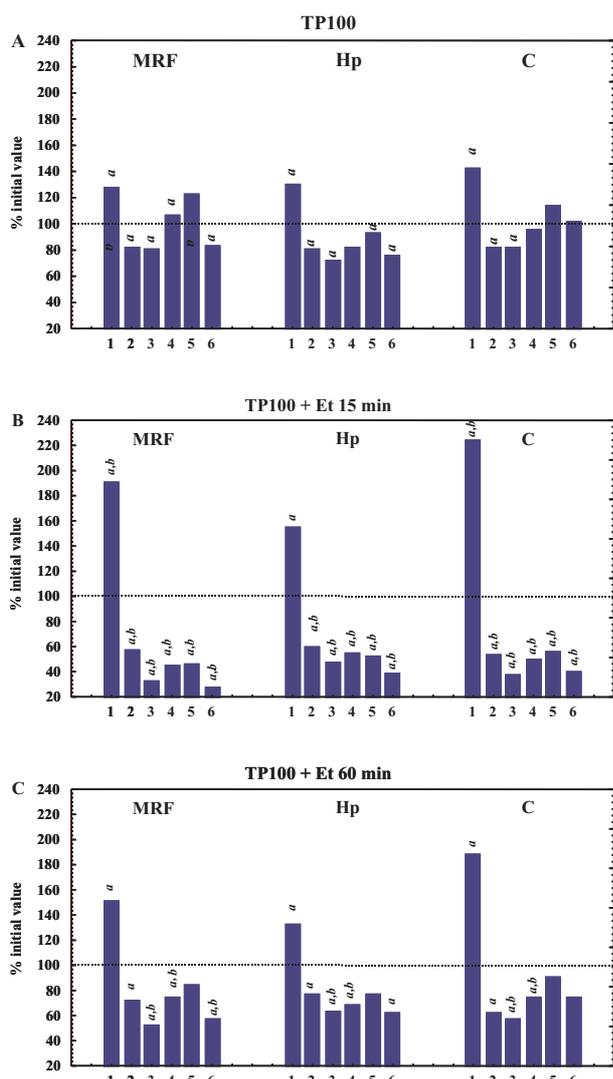
Fig. 3. The mean changes in particular frequencies of EEG rhythms expressed as the percent of initial value after administration of topiramate at 100 mg/kg *po* (TP100) – (**A**) and ethanol 0.8 g/kg *iv* (Et) – (**B**,**C**). Significant difference *vs.* initial value, [a] $p < 0.05$, Wilcoxon's test. 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

Fifteen minutes after ethanol administration, the decrease in 4 to 45 Hz frequency proportion was enhanced in all the investigated structures. Additionally, recordings from the MRF and frontal cortex demonstrated enhanced post-ethanol changes involving the increased proportion of slow frequency (0.5–4 Hz). In the hippocampus, the increase in 0.5–4 Hz frequency was not more pronounced than after ethanol alone (Fig. 3B).

In the recordings obtained 60 min after ethanol administration, the changes were less significant and in-

cluded reduced proportion of 7–10 and 10–13 Hz frequencies in all the investigated structures and additionally in 30–45 Hz frequency in the MRF (Fig. 3C).

After 7-day treatment with topiramate (25 mg/kg /day), the recordings from all the investigated structures demonstrated increased proportion of the lowest frequency (0.5–4 Hz) and decreased proportions of 4–7 and 30–45 Hz frequencies. Additionally, increased proportion of 10–13 and 13–30 Hz frequencies was observed in the MRF, and decreased proportion of 7–10 Hz frequency was seen in the hippocampus (Fig. 4A).

Topiramate administered for 7 days reduced post-ethanol changes in hippocampal EEG recordings associated with increased proportion of the lowest frequency (0.5–4 Hz). On the other hand, the post-ethanol changes in the MRF and frontal cortex were enhanced and involved the increased proportion of the lowest frequency recordings and the decrease in 4–7, 7–10 Hz frequencies, and in MRF also 30–45 Hz (Fig. 4B).

Sixty minutes after ethanol administration, recordings from the MRF and frontal cortex did not differ from those obtained after ethanol alone. In hippocampal recordings, no ethanol effects were still seen (Fig. 4C).

After 14 days of topiramate treatment (25 mg/kg /day) EEG changes were similar to those observed after 7 days (Fig. 5A).

In all the investigated structures, the proportion of the slowest frequency (0.5–4 Hz) was increased and that of 4–7 Hz was decreased. In the MRF, the proportion of 10–30 Hz frequency in the spectrum increased as well, whereas reduced proportion of 30–45 Hz frequency was observed both in the MRF and in the hippocampus (Fig. 5A).

When a single dose of ethanol was injected after 14-day topiramate treatment, the recordings from the hippocampus demonstrated (like after 7-day topiramate treatment) inhibition of ethanol-induced changes with respect to the increased 0.5–4 Hz frequency proportion. In the MRF and frontal cortex, post-ethanol changes were enhanced and included an increase in 0.5–4 Hz frequency proportion in the recording with a decrease in 4–7 and 7–10 Hz frequency ranges, and additionally 30–45 Hz in the MRF (Fig. 5B).

Sixty minutes after the administration of ethanol, the previously observed changes were attenuated, and undetectable in the hippocampus. Moreover, recordings from the MRF demonstrated increased proportion of high frequency (13–30 Hz), and those from the frontal cortex – decreased proportion of 4–7 Hz frequency (Fig. 5C).
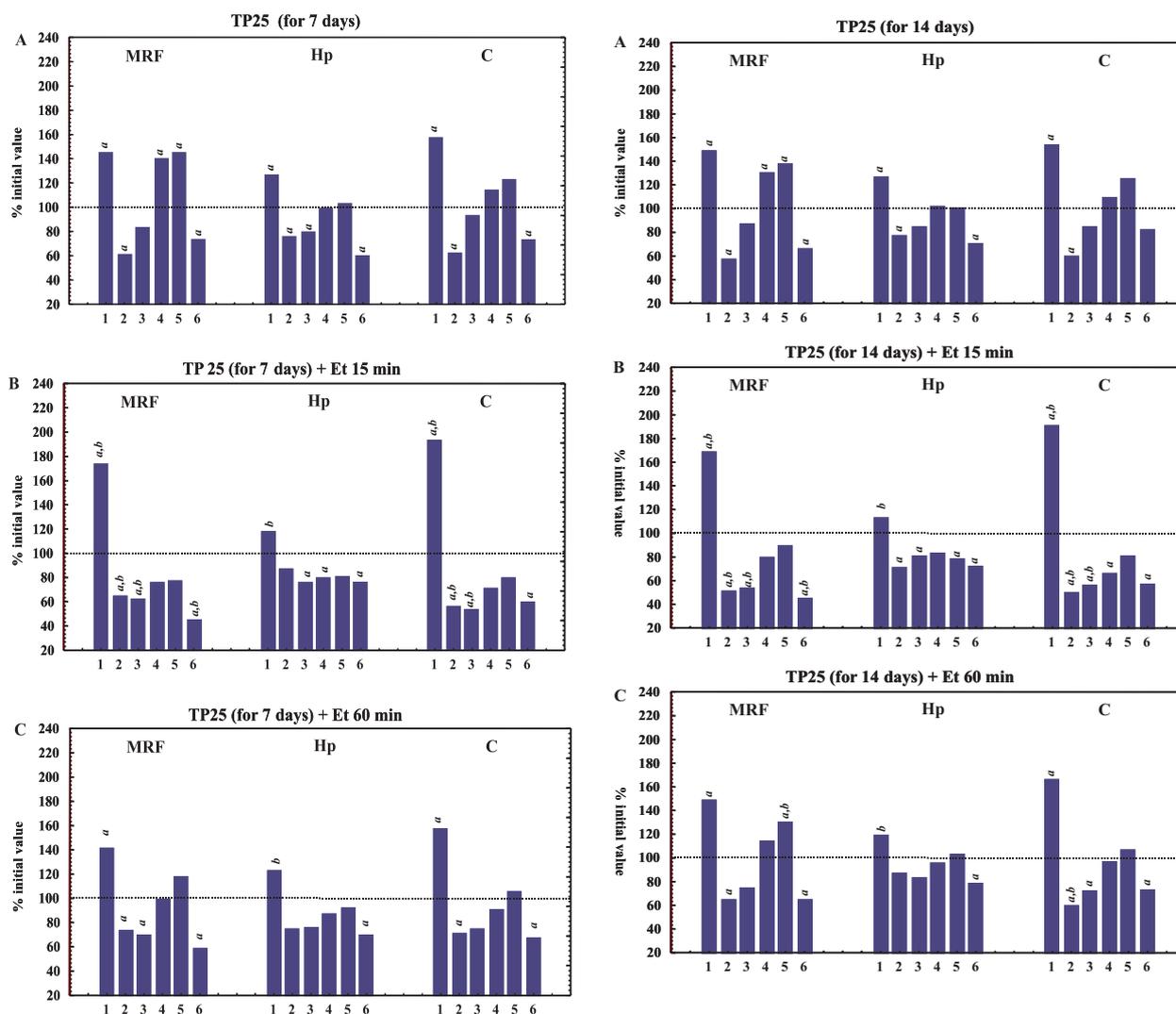
Fig. 4. The mean changes in particular frequencies of EEG rhythms expressed as the percent of initial value after administration of topiramate at 25 mg/kg, *po* (TP25 for 7 days) – (**A**) and ethanol at 0.8 g/kg, *iv* (Et) – (**B,C**). Significant difference *vs.* initial value, [a] p < 0.05, Wilcoxon's 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 Figure1

Fig. 5. The mean changes in particular frequencies of EEG rhythms expressed as the percent of initial value after administration of topiramate at 25 mg/kg, *po* (TP25 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 the study was an attempt to answer the question whether topiramate can interact with ethanol and what is the character of this interaction. The study was based on the pharmaco-EEG method, used in order to assess the effects of topiramate and ethanol on bioelectrical activity of the brain in rabbits.

Ethanol causes characteristic changes in EEG recordings. They depend on the administered dose of ethanol and are more evident when its blood concentration rises rapidly. In our studies, we found that high doses of ethanol administered to rabbits affected EEG recordings from the frontal cortex to the largest extent, and slightly less significantly those from midbrain reticular formation and hippocampus. The observed changes were associated with an increased proportion of low frequencies 0.5–4 Hz (delta rhythm) in the recordings, and a decreased proportion of the beta rhythm, and in the frontal cortex also of

the alpha rhythm. The above changes in the EEG spectrum composition are associated with a significant depressive effect of high ethanol doses on the central nervous system.

Topiramate alone also altered considerably the EEG recordings obtained from rabbits. The observed changes were dependent on the investigated structure, drug dose and its single or repeated use. Single doses influenced to similar extent the changes in recordings obtained from the MRF and frontal cortex, and the observed changes indicated inhibitory character of this influence. It was demonstrated by increased proportion of low frequency waves, i.e. delta rhythm, and decreased proportion of theta rhythm and the highest frequency beta rhythm, whereas in hippocampal recordings an additional reduction in alpha rhythm was observed. This inhibitory effect of topiramate correlates with its central adverse effects observed in the patients during the initial period of treatment or after overdose [23, 43].

Multiple doses of topiramate also affected significantly EEG recordings obtained from all the investigated structures. Changes observed after 7- and 14-day treatment were similar in character, but different from those observed after a single dose of the drug. The MRF and the frontal cortex demonstrated increased proportion of delta rhythm, and decreased proportion of theta rhythm. Additionally, fast alpha rhythm and slow beta rhythm proportions were significantly increased in the MRF. Changes of similar character were also observed in recordings from the frontal cortex, although they did not reach statistical significance. This spectrum shift towards alpha and slow beta rhythm indicated gradual attenuation of the inhibitory effect of the drug, which may correlate with the transient character of adverse effects observed in the patients. Changes in the hippocampus were of slightly different character, similar to those observed after a single dose of the drug. Recordings from that structure demonstrated increased proportion of delta rhythm and decreased proportion of theta, slow alpha and fast beta rhythms.

A high single dose of topiramate (100 mg/kg) administered together with ethanol enhanced post-ethanol changes in EEG recordings from the MRF and frontal cortex, especially in the acute phase of its activity (within 15 min after administration). In hippocampal recordings, the proportion of delta rhythm was not higher than after ethanol alone. Interaction after a 4-fold lower dose of the drug was similar in char-

acter, although the observed changes were transient and less pronounced.

Ethanol administered after 7- and 14-day topiramate treatment caused more pronounced changes in delta rhythm as well as a decrease in proportion of theta and slow alpha rhythm in recordings from the MRF and frontal cortex. In the MRF, enhancement of ethanol-induced changes included also reduced proportion of fast beta rhythm in the recordings. In hippocampal recordings, ethanol did not increase the proportion of delta rhythm, that was characteristic of the effect of high alcohol doses.

Thus, we observed a bidirectional, brain region-dependent, character of interaction between topiramate administered at multiple doses and ethanol. MRF and frontal cortex recordings exhibited marked synergism of these agents, whereas in the hippocampus topiramate significantly reduced the response to ethanol, which is a favorable aspect of the observed interaction.

The observed interaction is difficult to assess, because the mechanism of action of topiramate has not been elucidated in detail yet. Its action associated with inhibition of calcium channels, which consequently leads to a decrease in intraneuronal calcium level and inhibition of glutamatergic transmission, has been emphasized [35, 47]. In experimental studies, topiramate was found to modulate the activity of the glutamatergic systems by antagonizing the AMPA and kainate receptors [1, 2, 20].

Electrophysiological studies on animals demonstrated that single doses of alcohol also inhibited the function of excitatory amino acid receptors, e.g., glutamate and voltage-dependent calcium channels [21, 22, 37, 44]. These mechanisms may be the basis of the observed interaction of synergistic character, leading to enhancement of the effect of acute ethanol doses administered together with topiramate.

The interaction observed in the hippocampus, associated with inhibition of ethanol-induced changes in the low frequency range, seems to be especially important. We observed similar effect in our previous studies focused on the interactions of ethanol with tiagabine and levetiracetam [30, 31]. These drugs, administered at multiple doses (and levetiracetam also at a single dose) inhibited the typical effect of ethanol, namely, the increase in the proportion of delta rhythm in EEG recordings. Reducing hippocampal sensitivity to the effect of ethanol manifested as inhibition of ethanol-induced changes within the slow frequency

range seems to be an important and beneficial aspect of the observed interaction. Such mechanism may contribute to a favorable effect of new generation antiepileptic drugs in the treatment of abstinence syndrome in alcoholics.

The main role in the reinforcement mechanism leading to the development of addictions has been attributed to the mesolimbic system, including also the hippocampus. The effectiveness of topiramate in the treatment of alcoholism is considered to be associated probably with the enhancement of endogenous GABA effect on $GABA_A$ receptors, which results in suppression of mesolimbic dopaminergic neurons responsible for reinforcement in addictions [8, 9]. This mechanism, however, may be more complex and associated also with the influence on glutamatergic transmission.

An impediment to our understanding of the mechanism of topiramate action is the paucity of animal studies examining the drug impact on behavioral measures related to addictive properties of alcohol. In laboratory tests, it has been shown to attenuate withdrawal signs in kindling models of ethanol dependence in rats [8], as well as to reduce the ethanol preference in C57BL/6J mice in a free-choice study [17].

There are also several reports indicating the neuroprotective effect of new antiepileptic drugs, including topiramate [10, 14, 40, 42]. Yang et al. [45, 46] demonstrated that topiramate reduced the extent of ischemic area during the treatment of ischemic brain damage. In other studies utilizing animal models of ischemia, topiramate has been found to inhibit degeneration of pyramidal cells in the hippocampus [36].

The effect observed in the hippocampus in our study might also have been due to some extent to the neuroprotective activity of topiramate.

The analysis of the obtained results indicates an interaction between ethanol and topiramate with respect to their effect on rabbit EEG. The course of this interaction may be dependent to some extent on the dose of the drug, single or multiple dosing schedule and the investigated structure.

The pharmacokinetic character of this interaction is difficult to envisage. Twenty percent of topiramate is known to be metabolized in the liver, and with the simultaneous use of enzymatic indicators this metabolism may reach even 50% [6, 18]. *In vitro* studies have demonstrated that the drug is an inhibitor of CYP2C19 [5]. Ethanol is metabolized by various pathways, however, the oxidation pathway is predominant, and the factors influencing the oxidation rate include enzymatic activity and hepatocytic capability of NADH reoxidation.

The presented pharmacokinetic properties of topiramate and the metabolism of ethanol seem to have no elements in common, which rather excludes a pharmacokinetic explanation for their interaction. Thus, it seems that the underlying mechanisms are pharmacodynamic in nature.

Conclusion

Summing up the obtained results, it can be concluded that: Topiramate administered both at single and multiple doses affects EEG recordings from all the investigated structures.

The drug administered at a single dose together with ethanol demonstrates marked synergism of action.

Topiramate used at multiple doses enhances the effect of ethanol on EEG recording from the frontal cortex and midbrain reticular formation.

The drug reduces the sensitivity of the hippocampus to the effect of ethanol, which may be associated with the effectiveness of topiramate in the therapy of alcoholism in humans.

The observed interaction is probably of pharmacodynamic character.

References:

1. Angehagen M, Ben-Menachem E, Shank R, Ronnback L, Hansson E: Topiramate modulation of kainate-induced calcium currents is inversely related to channel phosphorylation level. J Neurochem, 2004, 88, 320–325.
2. Angehagen M, Ronnback L, Hansson E, Ben-Menachem E: Topiramate reduces AMPA-induced Ca(2+) transients and inhibits GluR1 subunit phosphorylation in astrocytes from primary cultures. J Neurochem, 2005, 94, 1124–1130.
3. Anton RF, Pettinati H, Zweben A, Kranzler HR, Johnson B, Bohn MJ, McCaul ME et al.: A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence. J Clin Psychopharmacol, 2004, 24, 421–428.
4. Arnone D: Review of the use of Topiramate for treatment of psychiatric disorders. Ann Gen Psychiatry, 2005, 4, 5.

5. Benedetti MS: Enzyme induction and inhibition by new antiepileptic drugs: a review of human studies. Fundam Clin Pharmacol, 2000, 14, 301–319.

6. Bialer M, Doose DR, Murthy B, Curtin C, Wang SS, Twyman RE, Schwabe S: Pharmacokinetic interactions of topiramate. Clin Pharmacokinet, 2004, 43, 763–780.

7. Book SW, Myrick H: Novel anticonvulsants in the treatment of alcoholism. Expert Opin Investig Drugs, 2005, 14, 371–376.

8. Cagetti E, Baicy KJ, Olsen RW: Topiramate attenuates withdrawal signs after chronic intermittent ethanol in rats. Neuroreport, 2004, 15, 207–210.

9. Chester JA, Cunningham CL: GABA(A) receptor modulation of the rewarding and aversive effects of ethanol. Alcohol, 2002, 26, 131–143.

10. Costa C, Martella G, Picconi B, Prosperetti C, Pisani A, Di Filippo M, Pisani F et al.: Multiple mechanisms underlying the neuroprotective effects of antiepileptic drugs against in vitro ischemia. Stroke, 2006, 37, 1319–1326.

11. Czarnecka E, Pietkiewicz B, Skrętkowicz J: Investigations of central interaction of ethanol and clonidine. Pol J Pharmacol Pharm, 1986, 38, 157–166.

12. Drobes DJ, Anton RF, Thomas SE, Voronin K: A clinical laboratory paradigm for evaluating medication effects on alcohol consumption: naltrexone and nalmefene. Neuropsychopharmacology, 2003, 28, 755–764.

13. Drobes DJ, Anton RF, Thomas SE, Voronin K: Effects of naltrexone and nalmefene on subjective response to alcohol among non-treatment-seeking alcoholics and social drinkers. Alcohol Clin Exp Res, 2004, 28, 1362–1370.

14. Edmonds HL Jr, Jiang YD, Hang PY, Shank R: Topiramate as a neuroprotectant in a rat model of global ischemia-induced neurodegeneration. Life Sci, 2001, 69, 2265–2277.

15. Frau R, Orru M, Fa M: Effects of topiramate on the prepulse inhibition of the acoustic startle in rats. Neuropsychopharmacology, 2007, 32, 320–331.

16. Frisch C, Kudin AP, Elger CE, Kunz WS, Helmstaedter C: Amelioration of water maze performance deficits by topiramate applied during pilocarpine-induced status epilepticus is negatively dose-dependent. Epilepsy Res, 2007, 73, 173–180.

17. Gabriel KI, Cunningham CL: Effects of topiramate on ethanol and saccharin consumption and preferences in C57BL/6J mice. Alcohol Clin Exp Res, 2005, 29, 75–80.

18. Garnett WR: Clinical pharmacology of topiramate: a review. Epilepsia, 2000, 41, Suppl 1, 61–65.

19. Gremel CM, Gabriel KI, Cunningham CL: Topiramate does not affect the acquisition or expression of ethanol conditioned place preference in DBA/2J or C57BL/6J mice. Alcohol Clin Exp Res, 2006, 30, 783–790.

20. Gryder DS, Rogawski MA: Selective antagonism of GluR5 kainate-receptor-mediated synaptic currents by topiramate in rat basolateral amygdala neurons. J Neurosci, 2003, 23, 7069–7074.

21. Hendricson AW, Thomas MP, Lippmann MJ, Morrisett RA: Suppression of L-type voltage-gated calcium channel-dependent synaptic plasticity by ethanol: analysis of miniature synaptic currents and dendritic calcium transients. Pharmacol Exp Ther, 2003, 307, 550–558.

22. Izumi Y, Nagashima K, Murayama K, Zorumski CF: Acute effects of ethanol on hippocampal long-term potentiation and long-term depression are mediated by different mechanisms. Neuroscience, 2005, 136, 509–517.

23. Johannessen SI, Battino D, Berry DJ, Bialer M, Kramer G, Tomson T, Patsalos PN: Therapeutic drug monitoring of the newer antiepileptic drugs. Ther Drug Monit, 2003, 25, 347–363.

24. Johnson BA, Ait-Daoud N, Akhtar FZ, Ma JZ: Oral topiramate reduces the consequences of drinking and improves the quality of life of alcohol-dependent individuals: a randomized controlled trial. Arch Gen Psychiatry, 2004, 61, 905–912.

25. Johnson BA, Ait-Daoud N, Bowden CL, DiClemente CC, Roache JD, Lawson K, Javors MA, Ma JZ: Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. Lancet, 2003, 361, 1677–1685.

26. Mason BJ: Rationale for combining acamprosate and naltrexone for treating alcohol dependence. J Stud Alcohol, 2005, 15, 148–156.

27. Morley KC, Teesson M, Reid SC, Sannibale C, Thomson C, Phung N, Weltman M et al.: Naltrexone versus acamprosate in the treatment of alcohol dependence: A multicentre, randomized, double-blind, placebo-controlled trial. Addiction, 2006, 101, 1451–1462.

28. Nguyen SA, Deleon CP, Malcolm RJ, Middaugh LD:. Tiagabine reduces ethanol reward in C57BL/6 mice under acute and chronic administration regimens. Synapse, 2005, 56, 135–146.

29. Nguyen SA, Malcom R, Middaugh LD: Topiramate reduces ethanol consumption by C57BL/6 mice. Synapse, 2007, 61, 150–156.

30. Pietrzak B, Czarnecka E: Effect of combined administration of ethanol and levetiracetam on rabbit EEG activity. Alcohol, 2007 (in press)

31. Pietrzak B, Czarnecka E: Effect of combined administration of ethanol and tiagabine on rabbit EEG. Pharmacol Rep, 2006, 58, 890–899.

32. Pietrzak B, Czarnecka E: Effect of the combined administration of ethanol and acamprosate on rabbit EEG. Pharmacol Rep, 2005, 57, 61–69.

33. Pietrzak B, Czarnecka E: The effect of combined administration of ethanol and sertraline, fluoxetine and citalopram on rabbit EEG. Pharmacol Res, 2003, 47, 527–534.

34. Pietrzak B, Kubik-Bogucka E: Influence of mianserin on some central effects of ethanol. Pharmacol Res, 2002, 46, 47–54.

35. Poulsen CF, Schousboe I, Sarup A, White HS, Schousboe A: Effect of topiramate and dBcAMP on expression of glutamate transporters GLAST and GLT-1 in astrocytes cultured separately or together with neurons. Neurochem Int, 2006, 48, 657–661.

36. Rekling JC: Neuroprotective effects of anticonvulsants in rat hippocampal slice cultures exposed to oxygen/glucose deprivation. Neurosci Lett, 2003, 335, 167–170.

37. Roberto M, Schweitzer P, Madamba SG, Stouffer DG, Parsons LH, Siggins GR: Acute and chronic ethanol alter glutamatergic transmission in rat central amygdala: an in vitro and in vivo analysis. J Neurosci, 2004, 24, 1594–1603.

38. Rubio G, Jimenez-Arriero MA, Ponce G, Palomo T: Naltrexone versus acamprosate: one year follow-up of

alcohol dependence treatment. Alcohol Alcohol, 2001, 36, 419–425.

39. Sawyer CH, Everett JW, Green JD: The rabbit diencephalon in stereotaxic coordinates. J Comp Neurol, 1954, 101, 801–824.

40. Schubert S, Brandl U, Brodhun M, Ulrich C, Spaltmann J, Fiedler N, Bauer R: Neuroprotective effects of topiramate after hypoxia-ischemia in newborn piglets. Brain Res, 2005, 1058, 129–136.

41. Soyka M, Roesner S: New pharmacological approaches for the treatment of alcoholism. Expert Opin Pharmacother, 2006, 7, 2341–2353.

42. Willmore LJ: Antiepileptic drugs and neuroprotection: current status and future roles. Epilepsy Behav, 2005, 7, Suppl 3, 25–28.

43. Wong IC, Lhatoo SD: Adverse reactions to new anticonvulsant drugs. Drug Saf, 2000, 23, 35–56.

44. Xu M, Woodward JJ: Ethanol inhibition of NMDA receptors under conditions of altered protein kinase A activity. Neurochem, 2006, 96, 1760–1767.

45. Yang Y, Li Q, Shuaib A: Enhanced neuroprotection and reduced hemorrhagic incidence in focal cerebral ischemia of rat by low dose combination therapy of urokinase and topiramate. Neuropharmacology, 2000, 39, 881–888.

46. Yang Y, Shuaib A, Li Q, Siddiqui MM: Neuroptrotection by delayed administration of topiramate in a rat model of middle cerebral artery embolization. Brain Res, 1998, 804, 169–176.

47. Zhang X, Velumian AA, Jones OT, Carlen PL: Modulation of high-voltage-activated calcium channels in dentate granule cells by topiramate. Epilepsia, 2000, 41, Suppl 1, 52–60.

48. Zullino DF, Khazaal Y, Hattenschwiler J, Borgeat F, Besson J: Anticonvulsant drugs in the treatment of substance withdrawal. Drugs Today (Barc), 2004, 40, 603–619.