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Effect of the administration of tiagabine and gabapentin on rabbit electroencephalogram activity

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Abstract

New generation antiepileptic drugs, including gabapentin and tiagabine, are used in monotherapy or in combination with other drugs for specific seizure types. The multidirectional mechanism of activity and varied pharmacological properties of these drugs suggest that they could also be used in the therapy of other diseases. A possible limitation of new generation antiepileptic drugs is the incidence of CNS-related adverse effects. Few studies have assessed the effect of new antiepileptic drugs on electroencephalogram (EEG) recordings in subjects using these drugs for diseases other than epilepsy. The aim of this study was to determine the effects of tiagabine and gabapentin on EEG recordings from the midbrain reticular formation, dorsal hippocampus and frontal cortex in rabbits. Tiagabine was administered orally at a single dose of 5 and 20 mg kg^{-1}, or repeatedly at a dose of 5 mg kg^{-1} (twice a day) for 14 days. Gabapentin was administered orally at a single dose of 25 and 100 mg kg^{-1}, or repeatedly at a dose of 25 mg kg^{-1} (twice a day) for 14 days. Both tiagabine and gabapentin caused changes indicative of CNS inhibitory properties, which may be associated with the adverse effects of the drugs. After repeated doses of the drugs, the changes in EEG recordings were less pronounced than after single doses, which may indicate adaptive changes. The hippocampus was found to be the least sensitive to the effect of gabapentin.

Introduction

New generation antiepileptic drugs that appeared on the pharmaceutical market during the last decade have extended the possibilities of treating epilepsy. They have greater specific activity and a more favourable pharmacokinetic profile (Blaise & Bourgeois 2000).

Tiagabine and gabapentin are examples of the new generation antiepileptic drugs. Both of these agents enhance GABA-ergic transmission. Tiagabine inhibits GABA reuptake by its effect on the activity of GAT-1, the main transporter of that neurotransmitter. GAT-1 allows neurotransmitter reuptake to the presynaptic regions or glial cells (Borden et al 1994; Soudijn & van Wijngaarden 2000; Czuczwar & Patsalos 2001; Schachter 2001). Inhibition of the reuptake system leads to activation and/or enhancement of GABA-ergic function in the CNS.

Gabapentine was synthesized as a GABA analogue (Borden et al 1994). It easily penetrates the blood–brain barrier owing to the active L-amino acid transport system (Gustavson & Mendel 1995; Snel et al 1997). Despite its structural similarity to GABA and agonistic effect on the GABA-ergic system, it is incapable of binding to known GABA receptors. Recently, Parker et al (2004) concluded that gabapentin selectively activates presynaptic GABA-B heteroreceptors but not GABA-B autoreceptors. Gabapentin has been demonstrated to increase GABA turnover and concentration in some structures of rat brain, primarily by activation of GAD (decarboxylase) and inhibition of GABA-T (aminotransferase) (Herranz 2003). There is no evidence for gabapentin interaction with GABA transporters. The drug can exert an anticonvulsant effect by blocking the $\alpha 2\delta$ subunit of voltage-dependent calcium channels (Gee et al 1996). It can also have an indirect effect on voltage-dependent sodium channels (Herranz 2003). In-vitro studies with labelled gabapentin demonstrated the presence of peptide binding sites in rat brain within the neocortex and hippocampus, which may also be associated with anticonvulsant activity of the drug (Suman-Chauman et al 1993).

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Tiagabine and gabapentin could also be applied in the therapy of other diseases such as neuropathic pain, mental disorders, alcohol addiction, amyotropic lateral sclerosis and multiple sclerosis.

The problem that may impose a limitation on use of new generation antiepileptic drugs is the incidence of CNS-related adverse effects such as somnolence, dizziness, headache, impairment of cognitive functions and, less frequently, depression, tremor and hyperexcitability (Wong & Lhatoo 2000; Genton et al 2001; Schachter 2001; Glauser 2004; La Roche & Helmers 2004). According to many authors, such adverse effects occur most frequently as a result of too rapid an increase of the drug dose (Gustavson & Mendel 1995; Blaise & Bourgeois 2000; Johannessen et al 2003).

Changes in bioelectric brain activity after administration of the drug is one of the methods that allows the profile of its effect to be assesed. Drugs with a specific central effect, as well as diseases associated with CNS dysfunction, are characterized by a specific electroencephalographic profile. The possibility of drawing conclusions regarding the effectiveness of the administered drug is another important advantage of this method. The changes noted by electroencephalogram (EEG) after administration of the drug significantly precede changes in the clinical presentation of the disease and allow evaluation of the efficacy of both the administered dose and the drug selected for the therapy. The method, referred to as pharmaco-EEG, is an accepted therapeutic tool facilitating appropriate selection and dosage of drugs with central effects.

The effects of gabapentin and tiagabine on EEG recordings have been assessed predominantly in subjects with epilepsy (Kalviainen et al 1996), as well as in experimental animal models of epilepsy (Walton et al 1994; Coenen et al 1995). Only a few studies have assessed the effect of the drugs themselves on EEG recordings. Saletu et al (1986) evaluated the EEG and psychotropic properties of gabapentin in normal subjects. Attenuation of total power augmentation of delta and theta activity and a decrease of alpha activity were demonstrated. Beta activity showed alternating changes.

The aim of the present study was to assess the effect of tiagabine and gabapentin on EEG recordings in the rabbit. Recording and assessment of EEG from selected brain structures could allow more comprehensive analysis of the mechanism of medication effects.

Materials and Methods

Animals and treatment

Thirty-six rabbits of both sexes (5 months old, 2.7–3.0 kg) were used. The animals were housed in individual cages under standard laboratory conditions (temperature 20–22°C, natural day/night cycle) and they had free access to commercial chow food and water. All experiments were performed between 1100 hours and 1400 hours. Tiagabine hydrochloride monohydrate (Sanofi Winthrop, Gentilly Cedex, France) was administered orally (in the form of a suspension in 1% methylcellulose solution) once at a dose of 5 and 20 mg kg^{-1}, or repeatedly at a dose of 5 mg kg^{-1} twice a day for 14 days. Gabapentin (Neurontin; Parke-Davis, Berlin, Germany) was administered orally (in the form of a suspension in 1% methylcellulose solution) once at a dose of 25 and 100 mg kg^{-1}, or repeatedly at a dose of 25 mg kg^{-1} twice a day for 14 days. Multiple dosing was started with lower drug doses, increased gradually after 2 and 4 days of treatment up to the final dose of 5 mg kg^{-1} per day for tiagabine and 25 mg kg^{-1} pre day for gabapentin. Control rabbits received 1% methylcellulose solution orally. The drugs were given in a volume of 0.2 mL kg^{-1}.

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

Experimental procedure

Using coordinates according to Sawyer et al (1954), the rabbits had monopolar electrodes implanted (under 60 mg kg^{-1} chloralose and 400 mg kg^{-1} urethane anaesthesia) into the following brain structures: midbrain reticular formation (P 8 mm, L 3 mm, H 15 mm); dorsal hippocampus (P 3 mm, L 5 mm, H 5 mm); and 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, USA). Experiments were performed on the rabbits over a period of 4 weeks following the surgery.

EEG recordings were performed 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, and a grid floor. The cage was located in a semi-soundproof room. A closed-circuit TV system recorded the animals' behaviour.

Two-minute artefact-free EEG recordings (selected by the experimenter) were taken for computer analysis. EEG samples were digitized at the rate of 128 samples s^{-1} and the Fourier transform of consecutive 4-s epochs for each channel was calculated. Each spectrum consisted of 256 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, the positioning of the electrode tips was verified histologically. The experiments were carried out on groups of six animals each. EEGs were recorded before and 1 h after a single tiagabine or gabapentin administration. In the experiments involving multiple dosing, EEGs were recorded after 7 and 14 days of treatment.

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

Statistical analysis

The normality of distribution was checked by the Kolmogorow–Smirnow test, with Lillieforse correction. Statistical evaluation was performed by the Wilcoxon

matched-pair test, using the Statistica for Windows 5.0 software (StatSoft Poland, Kraków, Poland) package.

Results

Table 1 shows the mean share of particular frequencies before treatment with the drugs in the different brain structures. No changes were found in the EEG recordings after administration of the 1% methylcellulose solution.

Tiagabine administered to rabbits at a single dose of 5 mg kg^{-1} significantly changed the EEG recordings from all the investigated brain structures (Figure 1). The hippocampus was observed to be the most sensitive to the effect of tiagabine. Recordings from the hippocampus revealed a decreased proportion of the 4–7 Hz frequency and high frequencies within the 13–45 Hz range, as well as an increased proportion of the low frequency 0.5–4 Hz (Figure 1).

The changes in EEG recordings from the frontal cortex were slightly less pronounced. The increase of the 0.5–4 Hz frequency and decrease of the 4–7 Hz and the highest frequency range 30–45 Hz in the recording were statistically significant.

The midbrain reticular formation, where changes were observed with respect to low frequencies only, seems to be the least sensitive structure to the effect of tiagabine. An increased proportion of low frequency 0.5–4 Hz and a decrease of the 4–7 Hz frequency was observed in the EEG recordings (Figure 1).

Tiagabine administered to rabbits at a single dose of 20 mg kg^{-1} caused considerable changes in the EEG recordings. The changes were more pronounced compared with those observed after the lower dose but were similar in nature, involving a marked shift towards the slow frequency 0.5–4 Hz, as well as reduced proportion of the 4–10 Hz frequency range in all the investigated structures (Figure 1).

Tiagabine administered to rabbits for 7 days caused changes in the recordings from the midbrain reticular formation and from the frontal cortex (Figure 2). A reduced proportion of the 4–7 Hz and 30–45 Hz frequencies in the histogram was observed, as well as an increase of the low 0.5–4 Hz frequency proportion, and, in recordings obtained from the midbrain reticular formation, also an increase of the 10–13 Hz frequency. No statistically significant changes were observed in recordings from the hippocampus (Figure 2).

Table 1 Mean share of particular frequencies before drug treatment in different brain structures

Frequencies (Hz)	Midbrain reticular formation	Dorsal hippocampus	Frontal cortex
0.5–4	31.06 ± 5.11%	31.38 ± 4.25%	28.90 ± 5.32%
4–7	33.48 ± 7.71%	34.56 ± 6.25%	34.59 ± 7.13%
7–10	15.84 ± 2.15%	15.74 ± 1.28%	16.23 ± 1.84%
10–13	11.26 ± 2.02%	10.8 ± 2.0%	11.83 ± 1.56%
13–30	5.67 ± 1.91%	5.28 ± 1.46%	5.76 ± 1.26%
30–45	2.65 ± 1.1%	2.21 ± 0.84%	2.67 ± 1.11%

Data are mean ± s.e.m., n = 12.

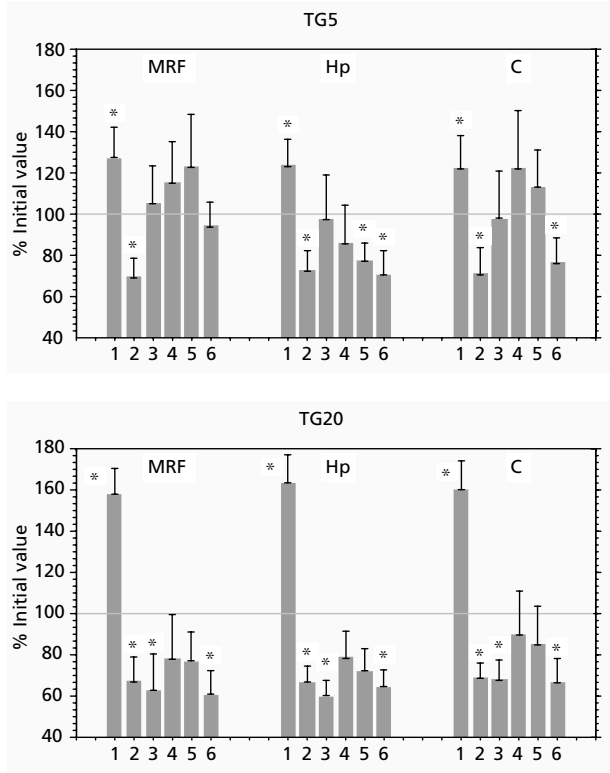

Figure 1 Mean changes in particular frequencies of electroencephalogram rhythms expressed as a percentage of the initial value ± s.d. after administration of tiagabine at a dose of 5 mg kg^{-1} (TG5) or 20 mg kg^{-1} (TG20). 1, 0.5–4 Hz; 2, 4–7 Hz; 3, 7–10 Hz; 4, 10–13 Hz; 5, 13–30 Hz; 6, 30–45 Hz. MRF, midbrain reticular formation; Hp, dorsal hippocampus; C, frontal cortex. *$P < 0.05$, significant difference compared with the initial value (Wilcoxon test).

Tiagabine administered to rabbits for 14 days affected the EEG recordings only slightly. The effect involved only an increase of the low 0.5–4 Hz frequency proportion in the recordings obtained from the midbrain reticular formation and the frontal cortex. No statistically significant differences were observed in recordings from the hippocampus (Figure 2).

Gabapentin administered to rabbits in a single dose of 25 mg kg^{-1} significantly affected the EEG recordings obtained from the midbrain reticular formation and frontal cortex. A marked increase in the proportion of the 0.5–4 Hz frequencies, with a parallel decrease in the proportion of the 4–7 and 30–45 Hz frequencies was observed (Figure 3). The structure that was the least sensitive to the effect of the drug was the hippocampus, where only the proportion of the high frequency 30–45 Hz was significantly decreased (Figure 3).

After a high dose of gabapentin (100 mg kg^{-1}) was administered to rabbits, the nature of the EEG changes was similar to that observed after the low dose. In the midbrain reticular system and the frontal cortex, a marked decrease in the proportion of the 4–7 Hz and 30–45 Hz frequencies, as well as an increase of the low 0.5–4 Hz frequency, was observed. The hippocampus demonstrated low sensitivity also to the higher dose of the drug (Figure 3).

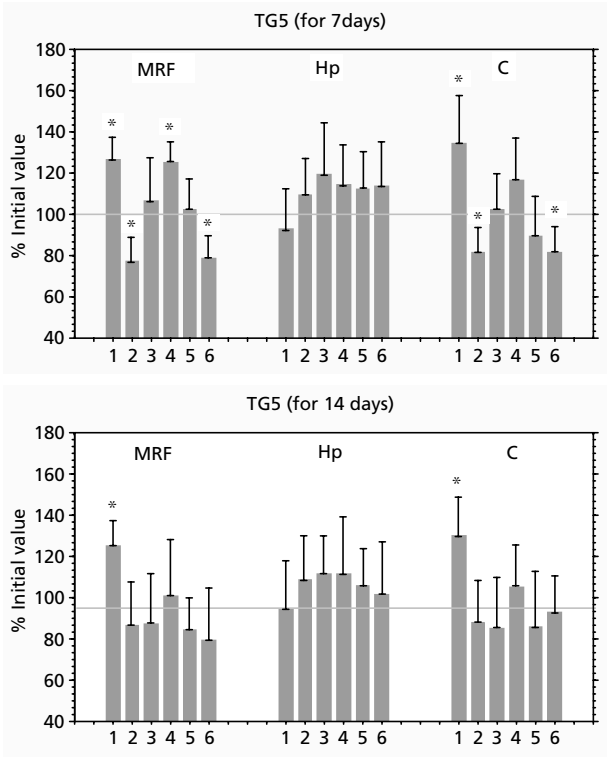

Figure 2 Mean changes in particular frequencies of electroencephalogram rhythms expressed as a percentage of the initial value ± s.d. after prolonged administration of tiagabine at a dose of 5 mg kg^{-1} (TG5) for 7 or 14 days. See Figure 1 for explanation of numbers and brain structure abbreviations. *$P < 0.05$, significant difference compared with the initial value (Wilcoxon test).

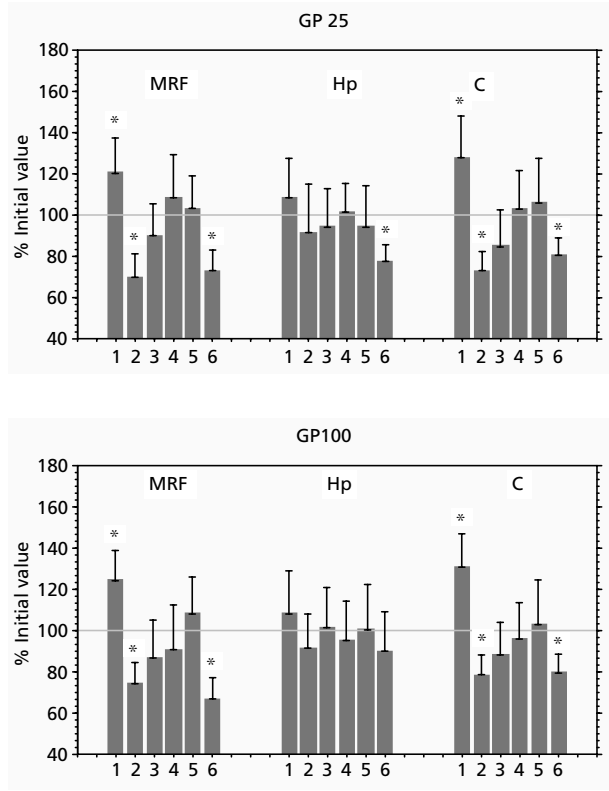

Figure 3 Mean changes in particular frequencies of electroencephalogram rhythms expressed as a percentage of the initial value ± s.d. after administration of gabapentin at a dose of 25 mg kg^{-1} (GP25) or 100 mg kg^{-1} (GP100). See Figure 1 for explanation of numbers and brain structure abbreviations. *$P < 0.05$, significant difference compared with the initial value (Wilcoxon test).

Gabapentin administered to rabbits for 7 days affected the EEG recordings obtained from all the investigated structures. Recordings from the midbrain reticular formation and the frontal cortex demonstrated marked changes associated with an increased proportion of the 0.5–4 Hz and reduced proportion of 4–7 and 7–10 Hz frequencies, and, additionally, the 30–45 Hz frequency in the midbrain reticular formation (Figure 4).

As with the single dose, the changes observed in hippocampal recordings were the least significant. There was only a reduced proportion of the 30–45 Hz frequency in the recordings (Figure 4).

Changes in EEG recordings obtained from rabbits administered gabapentin for 14 days were different compared with those observed after 7 days of drug administration. Frontal cortex recordings demonstrated only a significant increase in the proportion of low frequency 0.5–4 Hz, and hippocampal recordings showed an increase of 7–10 and 10–13 Hz frequencies (Figure 4).

After single and multiple doses of tiagabine and gabapentin, no changes were observed in the behaviour of the animals.

Discussion

The effect of single and multiple doses of tiagabine and gabapentin on bioelectric brain activity in rabbits was assessed by pharmaco-EEG. The rabbit is a good experimental model because the frequency ranges constituting the particular rhythms in the EEG recordings are analogous to those found in humans. Moreover, implantation of the recording electrodes to specific brain structures allows precise and reproducible recordings of the bioelectric activity of these structures to be obtained.

The drugs selected for this study are characterized by their multidirectional mechanism of action, which extends their clinical position by their potential usefulness for indications other than epilepsy.

The tiagabine and gabapentine doses used in our study were selected on the basis of literature data from preclinical studies of the drugs. The doses used by various authors, both single and repeated, were differentiated within a wide range of values, and differed significantly in various experimental models (Coenen et al 1995; Suzdak & Jansen 1995; Cleton et al 2000a, b; Yang et al 2000; La Roche & Helmers 2004). We selected two doses of each drug for single administration (5 and 20 mg kg^{-1} for tiagabine, and 25 and 100 mg kg^{-1} for gabapentin) used in preclinical studies of these drugs and regarded as low and high doses, respectively.

In our study, single administration of tiagabine affected the EEG recordings obtained from all the evaluated structures. The hippocampus was found to be the most sensitive to the effect of tiagabine. The observed changes, indicating the

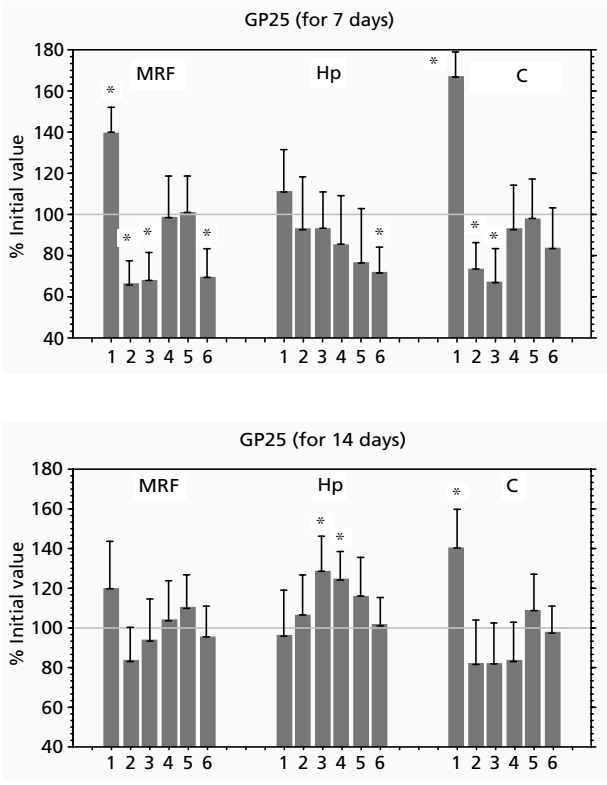

Figure 4 Mean changes in particular frequencies of electroencephalogram rhythms expressed as a percentage of the initial value ± s.d. after prolonged administration of gabapentin at a dose of 25 mg kg^{-1} (GP25) for 7 or 14 days. See Figure 1 for explanation of numbers and brain structure abbreviations. *$P < 0.05$, significant difference compared with the initial value (Wilcoxon test).

CNS inhibitory properties of the drug on the investigated structures, were more pronounced after the high dose of 20 mg kg^{-1} than after the 4-fold lower dose. The dose-dependent nature of the effect of the drug on EEG recordings indicates the need for caution when tiagabine doses are increased, in order to avoid adverse events.

After 7 days of treatment with the drug, changes in the EEG recordings obtained from the midbrain reticular formation and frontal cortex were observed. Their character was similar to those occurring after a single dose. After 14 days of tiagabine treatment, the changes were considerably less pronounced and involved only the increased proportion of the low 0.5–4 Hz frequency in the recordings. Hippocampal recordings, after both 1 and 2 weeks of treatment, demonstrated a shift in the recording spectrum towards alpha and beta rhythms. However, these changes did not reach statistical significance. The decreased effect of tiagabine on EEG recordings after multiple doses of the drug may reflect the development of adaptive changes. Studies in mice indicate that tolerance to the anticonvulsant effects does not develop with chronic treatment up 21 days (Karbon et al 1991; Suzdak at al 1994). Cleton et al (2000a) in a pharmacokinetic–pharmacodynamic modelling of tiagabine CNS effects in rats (14 days treatment with an osmotic minipump) did not observe functional adaptation to tiagabine-induced GABA-ergic inhibition. The increase in the beta frequency band of the EEG as a measure of the pharmacological response was used. In the in-vitro [^{3}H]GABA uptake assay, no changes in affinity or functionality for the GABA uptake transporter were observed. In a similar experiment, these authors studied the mechanism of functional adaptation upon chronic treatment with midazolam. It was concluded that midazolam causes functional adaptation unrelated to changes in benzodiazepine receptor function (brain synaptoneurosomal preaparation) (Cleton et al 2000b). According to the hypothesis of Costa (1998), which states that the degree of enhancement of the GABA-ergic tone determines whether or not tolerance development occurs, the differences in the results obtained by us may be associated with species-related variations of sensitivity to tiagabine, specific sensitivity of particular cerebral structures to the drug, and the dosing method.

Gabapentin also caused remarkable changes in the EEG recordings obtained from rabbits. The observed changes were dependent on the assessed structure and on the mode of drug administration (single dose or multiple dose). The changes observed in EEG recordings indicated significant CNS inhibitory properties, reflected by an increase in the proportion of the lowest frequency waves corresponding to the delta rhythm, with a parallel decrease in beta activity. This effect is probably associated with adverse effects involving the CNS, occurring predominantly in patients using gabapentin (Schachter 2001; Bozikas et al 2002; Moretti et al 2003; Bennet & Simpson 2004). The hippocampus, where the drug effect was reflected only by a decreased proportion of the high frequency in the recording, was found to be the least sensitive to gabapentin.

The reactions to multiple doses of gabapentin observed in the EEG recordings were significantly different after 1 and 2 weeks of treatment. After 7 days, the inhibitory CNS effect of the drug was observed in the recordings obtained from all the assessed structures, including the hippocampus. Such changes were not observed after 14 days of gabapentin treatment. At that time, a less pronounced but statistically significant increase of the low frequency proportion was observed only in the recordings obtained from the frontal cortex. It could be supposed that the observed effects are due to adaptation changes. The observed effects correlate with clinical reports concerning the central adverse effects of the drug, which are very severe at the initial stage of treatment and gradually subside in most patients during further therapy (Johannessen et al 2003; Moretti et al 2003; Bennet & Simpson 2004). The hippocampal recordings demonstrated changes connected with an increase of the 7–10 and 10–13 Hz frequency proportions (excitatory response), which was not observed after the 7-day treatment with gabapentin, as well as after an acute dose of the drug.

The results obtained can be summarized as follows. (i) Both tiagabine and gabapentin cause changes in rabbits EEG activity indicative of CNS inhibitory properties, which may be associated with adverse effects of the drugs. (ii) Changes in EEG recordings after a single dose of tiagabine are dose-dependent, whereas after multiple doses they are less pronounced, which may indicate the development of adaptive changes. (iii) After 14 days of gabapentin treatment, changes in EEG recordings obtained from the frontal cortex and midbrain reticular formation are less pronounced, which may indicate the development of adaptive processes after long-term

use of the drug. (iv) The hippocampus was found to be the least sensitive structure to the CNS inhibitory effect of gabapentin. After 14 days of drug treatment an excitatory response was observed in this structure.

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