Human and Animal Physiology

The Dynamics of Basic EEG Characteristics Under the Influence of Carbamazepine

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ABSTRACT. The influence of Carbamazepine (CBZ) was studied regarding the dynamics of characteristics of EEG (absolute value of power, mean frequencies within the standard EEG ranges, epileptiform graphoelements morphology and density) during the treatment of 45 epileptic children (aged 1-16). The findings obtained before and 3-6 months after the commencement of CBZ monotherapy were compared. The most expressed and persistent effect of CBZ was observed in 3 months of therapy and manifested itself in a considerable increase of absolute power value in the low frequency bands of EEG spectrum and in decreased average frequency of alpha waves. The diminution of spontaneous epileptiform graphoelements density (78% average) was seen on EEGs recorded at rest with closed eyes. No interhemispheric peculiarities were revealed. In three cases (with partial frontal and temporal fits) CBZ therapy was marked by worsening of both clinical manifestations and EEG picture. © *2010 Bull. Georg. Natl. Acad. Sci.*

Key words: epilepsy, Carbamazepin, EEG power value.

Introduction

Administration of Carbamazepine (CBZ) counts over half a century of its history. Once included in the arsenal of practitioner physicians in the 1960s as an antiepileptic drug (AED), CBZ has not only sustained its position, but also revealed new properties, allowing to sizably broaden the area of its application. The complex positive action of CBZ, provides not only effective suppression of seizures, but also good thymoleptic result, elimination of concurrent behavioral and psychic disorders. In this connection, CBZ is used in modern medicine as antiepileptic, neurotropic, and psychotropic medication [1].

According to the ILAE recommendations, CBZ is at present considered the first choice medicine in the treatment of partial epileptic paroxysms, including fits with secondary generalization [2]. Taking into account the prevalence of partial, localization-dependent seizeres making up to 60 % of all forms of epilepsy in children and about 80% - in adults [3, 4] the share of CBZ and its derivatives among the total volume of AEM used is not less than 50%. However, in primarily generalized seizures, particularly with atonic, myoclonic and absence fits administration of CBZ requires adequate caution since CBZ was established to be capable of provoking certain types of epileptic paroxysms [2]. The advisability of its administration is being discussed in respect of benign partial epilepsy with central-temporal spikes, Lennox- Gastaut syndrome and Continuous Spike and Waves during Slow Sleep [2].

Obviously, electroencephalographic (EEG) examination of patients placed on CBZ therapy is of special im-

portance due to this ability of medication: the administration of CBZ and its derivates should be scheduled with due regard to the form of epilepsy, specificity of individual EEG, EEG dynamics and clinical manifestation during the treatment. In this light, the aim of the present work was to study the dynamics of EEG characteristics in epileptic children at different stages of CBZ monotherapy.

Material and Methods

Patients. Subjects with partial seizures, with or without secondary generalization were drawn from a pool of patient clinics of the Department of Pediatric Neurology of the Medical University of Tbilisi. The present study included 45 children (details are presented in Table.1).

All patients have the history of partial seizures with or without secondary generalization with at least two seizures in 6 months prior to entry into the study.

The dosage (in monotherapy) was defined by the physician-in-charge, individually reckoned on the basis of mean daily dose 20 mg per 1kg of the body weight.

EEG Recording and Methods of Analysis. All the patients underwent three-fold recording of the EEGs: at first visit, before the administration of AED, in 3-4 and 6-8 months after the commencement of the treatment. In children aged 1-3 the EEG recordings were carried out during natural sleep. In patients over 3 years of age the recordings were performed in relaxed wake state. The rhythmic photostimulation (ranging 3-27 Hz), hyperventilation (3 min), and breath hold (15-25 sec) after hyperventilation being used as functional tests.

Table 1.

Characteristics of the contingent

Age (years)	
Range	1 - 16
Mean (SD)	7.6 ± 3.20
Males	21
Females	24
Seizure types	
Simple partial	9
Complex partial	13
Partial secondarily generalized	23
EEG findings	
Abnormal	11
Focal	28
Generalized	6

EEG signals were recorded using a set of 19 scalp electrodes (according to the International 10–20 system) and amplified and filtered by digital encephalograph ENCEPHALAN 131-03, professional version, "MEDICOM" (Russia). The pass band of the amplifiers 0.5-100 Hz, notch filter- 50 Hz. The signals from each input electrode were digitized in online regime with the frequency discreditation 256 Hz with the resolution of 12 bits. Electrode (Ag/AgCl) specific resistance was not higher than 5KΩ.

For each child, 20 artifact-free EEG epochs (at rest, with open and closed eyes, during functional exertion and 20 sec after their termination) each of 9 s duration were selected for spectral analysis to calculate spectral power.

Visual analysis of EEG for the evaluation of the specificity of the background activity (focal and/or generalized slow waves, morphology of epileptiform elements, the spike density and the number of paroxysmal bursts discharges) was performed before the quantitative assessment.

A fast Fourier transformation algorithm of signal processing was used to obtain the power spectrum of each lead. For the statistical evaluation of the EEG phenomena were calculated within 6 frequency bands: delta (0.5-4.0 Hz), theta-1(4.0-6.0 Hz), theta-2 (6.0-8.0 Hz), alpha (8-13 Hz), beta-1 (13-24 Hz), beta-2 (24-50.8 Hz). The following quantitative characteristics of EEGs were analyzed: absolute values of the power spectra (AVP), the limits of the spectrum, median values of the frequency power.

Statistical analysis. Wilcoxon's test was applied to determine the probabilities in all the groups in power spectra. Each of the frequency bands was analyzed separately. Statistical calculations were preformed using Biostat. For all the analyses, we took the two-tailed significance ($p < 0.05$).

Results

The main results obtained from the qualitative analysis of the EEG dynamics at different stages of CBZ administration are demonstrated in Fig.1.

The analysis of total AVP dynamics reveals a reliable elevation of this index in parietal and, especially, occipital recordings 3 months after the beginning of the treatment. The frontal and central regions showed a similar picture, though it was less expressed and did not reach the reliability level. This elevation remained even 6 months after the beginning of CBZ consumption, having a slight tendency to decrease mainly in occipital recordings. However, at all the stages of the treatment

AVP indices preserved higher values than those before the therapy.

The spectral analysis of AVP dynamics showed that the increase in total values of this index is caused mainly by the growth proportion of low frequency wave ranges in the common EEG pattern. Increase in the activity of both delta and theta ranges was observed, being better pronounced in the theta frequency range. In turn, the analysis of the activity dynamics in theta sub-ranges (Table 2, theta-1, theta-2) revealed the primary augmentation of the quantity of waves in theta-2 zone. Similarly to the total AVP, the theta-range indices of AVP tended to decrease in 6 months (compared to those of month 3) of the extension of CBZ consumption, however kept exceeding the initial indices, recorded before the commencement of the treatment. Almost in all the children investigated an obvious increase in the AVP of alpha activity was also found (Table 2, alpha). This increase was particularly demonstrative in occipital zones, however also seen in central, parietal and temporal zones. It reached maximal values in the 3rd month after the commencement of CBZ consumption. The fact has to be emphasized that along with the increase of AVP in alpha range there was also a decrease in mean frequency of alpha rhythm against the background of CBZ therapy. Individual changes of the power and average-frequency alpha activity were rather variable. The decrease in the average alpha frequency > 0.5 Hz was observed in 10 of 32 patients; in the rest of the patients this deceleration did not exceed 0.5 Hz , though remained during the entire course of the investigations, being mostly pronounced in the occipital zone.

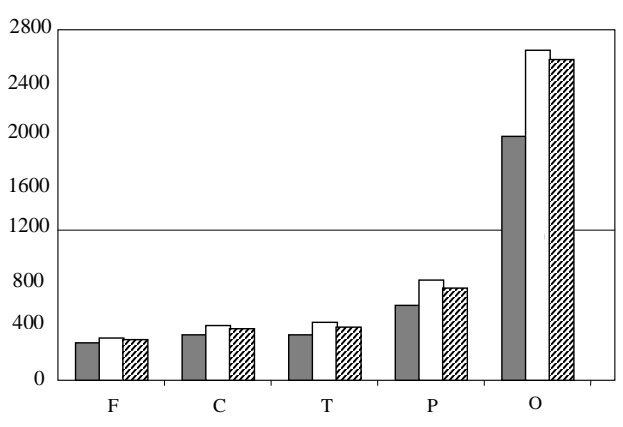Alteration of AVP and frequency characteristics of the activity in beta spectrum (Table 2, beta-1, beta-2)

Fig. Dynamics of total AVP at different stages of treatment: gray columns - before treatment, white columns - 3, shaded columns - 6 months after the commencement of the treatment. X-axis - EEG leads: F-frontal, C - central, T - temporal, O - occipital, P- parietal regions of the brain cortex. Y - axis- power spectrum - $\mu V^2 s$.

did not show any steady dynamics, revealing different features at a particular recording. For example, in frontal central and temporal zones, the growth of the activity power was observed after 3 months of CBZ therapy within beta-1 range (Table 2, beta-1). However this index decreased in month 6 of the therapy and reached initial levels, occasionally being even lower. Apparently different was the dynamics of this range of the activity in parietal and occipital zones: in parietal regions AVP continued to elevate during the entire course of the investigation, while in occipital areas after the initial decrease in month 3 the elevation of this index was seen in month 6 of the treatment.

Dynamics of beta-2 range activity (Table 2, beta-2) in frontal, central and temporal zones coincided with that of beta-1 range but, in contrast, revealed a significant decrease in the parietal zone in month 6 of the observation. The functional significance of this type dynamics in this spectrum is not quite clear.

The described AVP dynamics changes were analogous in both hemispheres – i.e. no interhemispheric specificity was seen in the activity dynamics of the analyzed frequency ranges (Table 2).

The qualitative analysis revealed that against the background of CBZ therapy, there was a decrease in the density (78 % average compared to the primary recordings) of spontaneous epileptiform graphoelements as well as spontaneous generalized epileptiform bursts (82% average) in the EEGs recorded at rest with closed eyes. Complete normalization of the EEG at rest was recorded in 39 % of patients after 3 months and in 47 % of patients after 6 months of the commencement of the treatment. A certain decrease in the patients' response to functional tests - i.e. reduction of the number of generalized paroxysmal interictal and especially ictal type bursts against the background of rhythmic photostimulation and hyperventilation - was seen. This decrease was clearly expressed during the comparison of initial data and those recorded in month 3 of the commencement of the treatment. The comparison of the recordings obtained in month 3 and 6 showed that these differences became expressed to a lower degree, not reaching, in a number of cases, the levels of reliability.

It is worth noting that, during CBZ therapy, in three cases (children under 8 with partial frontal seizures - 2, partial temporal seizures - 1) a worsening of clinical and EEG manifestations of the disease was observed: more frequent seizures, appearance of fits with secondary generalization. In all these patients the presence in the initial EEG of periodic spontaneous generalized bursts

Table 2.

Spectral analysis of dynamics   of AVP at   different stages of   treatment.

I – First visit (background), II – 3 and III – 6 months

	DELTA			THETA 1			THETA 2			ALPHA			BETA 1			BETA 2		
	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III	I	II	III
F_1	347.6 ±42.1	466.7 ±38.7	487.1 ±31.4	109.0 ±21.7	115.3 ±19.4	134.5 ±20.2	38.7 ±10.4	86.5 ±18.3	84.8 ±19.8	60.3 ±14.4	44.4 ±12.3	58.8 ±14.2	19.7 ±4.7	12.5 ±4.1	18.4 ±4.9	21.7 ±8.1	6.8 ±2.2	10.1 ±2.5
F_2	319.0 ±38.5	551.1 ±36.4	598.7 ±36.1	99.6 ±20.7	102.3 ±20.8	115.7 ±18.3	41.3 ±11.3	93.0 ±17.6	99.6 ±19.5	55.7 ±15.7	49.8 ±12.8	49.9 ±11.8	17.8 ±4.4	14.9 ±4.7	17.4 ±5.1	20.8 ±7.9	5.8 ±2.0	9.4 ±1.8
F_3	186.8 ±20.3	395.1 ±18.4	398.1 ±19.9	66.8 ±15.1	123.7 ±19.4	124.2 ±22.7	46.1 ±12.3	107.7 ±18.8	103.1 ±17.4	89.2 ±16.4	81.1 ±16.1	90.6 ±17.4	20.4 ±5.5	15.6 ±4.8	18.1 ±5.5	15.6 ±3.3	6.8 ±3.1	7.4 ±2.1
F_4	157.6 ±22.5	441.8 ±21.1	388.5 ±23.8	55.6 ±16.4	108.1 ±21.1	123.1 ±20.4	44.0 ±14.7	105.2 ±17.2	106.9 ±19.1	87.3 ±16.1	75.8 ±17.7	81.4 ±18.3	20.0 ±6.1	14.9 ±3.9	18.8 ±5.6	14.2 ±3.1	5.3 ±2.8	8.1 ±3.1
C_3	130.3 ±19.5	284.2 ±24.4	311.2 ±18.9	57.0 ±11.6	121.7 ±13.4	124.1 ±17.8	42.2 ±9.4	193.6 ±19.4	194.1 ±15.1	86.9 ±17.8	123.2 ±19.4	128.4 ±18.8	19.0 ±9.3	15.7 ±8.8	17.4 ±8.9	13.6 ±3.2	6.4 ±2.1	7.7 ±2.1
C_4	124.9 ±19.7	270.3 ±20.1	300.9 ±19.1	44.3 ±13.2	114.1 ±13.8	132.1 ±15.1	36.5 ±10.3	192.1 ±17.9	198.3 ±21.4	85.3 ±18.1	129.9 ±17.9	122.8 ±19.1	16.6 ±9.8	14.3 ±7.9	16.1 ±9.4	14.0 ±3.3	5.7 ±2.7	7.9 ±2.8
P_3	118.8 ±20.4	397.2 ±23.2	436.1 ±25.4	47.5 ±11.9	100.3 ±15.3	98.8 ±15.8	46.9 ±9.2	239.2 ±19.9	234.7 ±19.9	100.9 ±18.6	113.3 ±18.8	122.2 ±16.4	18.9 ±8.1	22.0 ±8.8	24.1 ±9.9	9.3 ±1.9	6.1 ±1.4	7.7 ±1.9
P_4	115.1 ±25.1	415.7 ±22.8	411.1 ±23.3	39.8 ±13.3	121.8 ±14.7	118.4 ±14.9	48.9 ±10.1	261.6 ±18.9	222.2 ±16.7	107.5 ±19.2	123.3 ±17.3	130.4 ±18.3	18.4 ±7.6	22.7 ±8.1	26.1 ±10.1	10.7 ±1.7	5.9 ±1.3	7.1 ±1.5
O_1	146.4 ±22.6	326.4 ±25.1	334.2 ±28.5	61.5 ±16.1	156.4 ±20.4	166.2 ±20.9	81.6 ±13.8	280.8 ±20.4	220.5 ±25.2	140.5 ±12.5	184.1 ±12.8	189.3 ±13.5	23.4 ±8.4	15.9 ±8.3	20.1 ±7.3	9.3 ±1.1	6.4 ±1.1	7.3 ±1.3
O_2	165.4 ±19.8	352.4 ±26.4	323.9 ±27.2	49.2 ±17.1	144.1 ±18.7	153.1 ±18.1	92.9 ±14.1	284.6 ±18.9	239.6 ±21.6	135.1 ±13.2	195.7 ±13.9	179.8 ±16.4	22.6 ±7.7	15.0 ±8.9	20.4 ±8.3	10.1 ±0.8	5.7 ±1.0	7.3 ±1.4
T_3	110.5 ±13.6	208.8 ±20.1	237.1 ±21.1	47.3 ±13.1	99.4 ±18.5	102.4 ±18.9	37.7 ±10.3	108.4 ±18.8	104.1 ±19.7	61.3 ±11.3	83.7 ±13.2	91.4 ±13.6	18.4 ±6.1	13.8 ±6.6	16.6 ±5.8	8.2 ±0.7	5.9 ±0.8	7.4 ±0.7
T_4	94.9 ±12.8	213.7 ±17.4	278.4 ±23.1	37.4 ±14.4	95.8 ±19.7	115.9 ±10.4	34.5 ±13.1	109.9 ±15.9	102.4 ±16.6	62.9 ±10.9	89.1 ±13.8	89.5 ±11.9	16.6 ±6.9	15.4 ±5.9	16.9 ±6.1	9.6 ±0.8	5.4 ±0.6	8.1 ±0.6
T_5	164.0 ±19.4	264.4 ±22.1	260.9 ±20.8	44.5 ±11.9	92.1 ±16.5	99.4 ±14.8	38.7 ±11.8	110.8 ±15.8	107.9 ±17.5	71.8 ±9.9	83.6 ±10.9	87.4 ±13.3	19.4 ±7.1	15.3 ±6.3	20.1 ±6.7	11.4 ±0.8	5.6 ±0.7	6.3 ±0.6
T_6	157.1 ±17.9	284.9 ±25.1	269.3 ±22.6	31.3 ±12.5	96.3 ±18.2	92.4 ±18.2	29.7 ±13.8	109.2 ±16.0	106.4 ±19.8	75.6 ±10.5	94.1 ±11.2	92.9 ±14.7	18.3 ±7.3	14.7 ±7.1	20.8 ±5.5	12.5 ±0.6	5.2 ±0.8	6.1 ±0.8

of sharp waves and peak-wave discharges was observed.

DISCUSSION

On the whole, our results are in agreement with those obtained by other authors studying the influence of CBZ on EEG characteristics [5, 6]: during the treatment of children suffering from partial epilepsy with CBZ EEG undergoes a number of regular changes, the most consistent being the deceleration of the background EEG activity and decrease in the mean frequency of the alpha rhythm. According to the results shown in Table 2 this deceleration arises at the expense of the augmentation of mean- and high- amplitude activity of the low frequency range, predominantly in the parietal and occipital zones of the brain cortex. No interhemispheric differences in CBZ action were revealed.

This fact is interest-inducing, since CBZ is the only medication, among the variety of the AEDs currently used, to act on the baseline EEG characteristics in such a way [7, 8]. The neurophysiological mechanisms underlying this effect (especially, as regards the effect of alpha rhythm deceleration) are not known. The inference may be made that in this aspect this drug shows some resemblance to the benzodiazepine group preparations [9]. Such a special feature of CBZ allows to suggest that its anti-epileptic effect happens via neurophysiological and molecular mechanisms that at least partly differ from the action mechanisms of other pharmacological groups of AEDs - and from Valproate Acid derivatives in the first place. This suggestion may be favored by the study results of Liu et al., 2006 [10] showing that at the thalamic level CBZ can activate GABAa receptors of neuronal membranes, which has not been seen during the treatment with other anti-epileptic drugs. It was shown also that lamotrigine, carbamazepine and phenytoin differentially alter extracellular levels of 5-hydroxytryptamine, dopamine and amino acids [11].

Apparently, it is not inconceivable that these traits are plausible reasons of the worsening effect of CBZ in certain forms of epileptic fits. In our investigations we also observed exacerbation of the disease in three

patients (6.6% of the cases). It is supposed that with absence seizures, where the basic mechanism is the thalamic pacemaker, CBZ is capable of acting on neuronal structures of the thalamic ventro-basal nucleus [10]. In this connection, we have to underline that we observed worsening of the course of the disease in patients with partial frontal and temporal seizures. Patients with absence seizure were not involved in the study for the clear reason that CBZ is not recommended for absence epileptics [2]. Therefore the mechanism proposed by Liu et al., 2006 [10] could hardly account for the effect we have observed. Kochen et al., 2002 [12] also doubt that this mechanism explains exacerbation of the fits in some cases during CBZ therapy. These authors report that intensity of the fits increased not only in the patients with generalized forms of epilepsy but also in adults and children suffering from partial fits, which complies with our results. Thus, it only can be established at present that in cryptogenic frontal epilepsy with generalized bursts of peak-wave discharges and benign rolandic epilepsy with diffuse interictal sharp waves and the discharges of the "sharp wave-slow wave complexes" there is a risk of a negative effect of CBZ. The issue whether the negative effect of CBZ is largely related to the types of seizures (generalized or partial) , or whether the main significance should be ascribed to the morphology of dominating epileptiform elements (i.e. spike discharges, peak-wave complexes) remains topical [13]. Thereupon it is significant that in three of our patients with aggravation of the epileptic attacks the presence in the initial EEG of periodic spontaneous generalized bursts of sharp waves and peak- wave discharges was observed.

On the other hand, it has to be remembered that the cases with exacerbation in the course of the disease are observed not only with CBZ therapy: in an approximately comparable number of cases this effect was described under the administration of all currently widely used AEDs [14]. Apparently, we have to admit that our knowledge of pharmacological and neurophysiological mechanisms of the antiepileptic action of AEDs is far from being complete.

A certain interest may lie in the fact found in our studies – the lack of reliable enough slowing down of baseline EEG rhythmicity and decrease in the intensity of epileptiform EEG elements (the spike density , and the number of paroxysmal bursts discharges) when we compared the results obtained after 3 and 6 months of CBZ administration in the examined patients. Taking into account that all the patients were treated with standard doses of CBZ, this fact is likely to suggest that in the cases where no clear clinical and/or EEG – effect is observed after three months of the start of CBZ therapy, alteration of further treatment strategy (CBZ dosage as well as shifting from mono to complex therapy or even replacement of AED) should be discussed.

CONCLUSION

The results obtained allow us to conclude that the use of any type of AED should be accomplished with maximal caution and under regular EEG control. The necessity of such control is due to the fact that in some cases worsening of EEG findings was revealed before the onset of clinical signs of exacerbation of the patient's state. Based on our results, such a control must be performed not rarer than once in three months.

At the same time the cases with negative effect of CBZ should not be considered as a reason for unconditional rejection of this drug, since, as noted in the Introduction, its positive influence in many respects outweighs the probability of its negative action.

ადამიანისა და ცხოველთა ფიზიოლოგია

ეეგ-მახასიათებლების დინამიკა კარბამაზეპინით მკურნალობის ფონზე

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** თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი

ეპილეფსიით დააავადებული 1-16 წლის ასაკის ბავშვების მკურნალობისას შესწავლილია კარბამაზეპინის ზეგავლენა ეეგ-მახასიათებლების (სიმძლავრეების აბსოლუტური და შეფარდებითი სიდიდეები, ეპილეპტიფორმული აქტივობის სიმკვრივე, საშუალო სიხშირეები ეეგ-ს სტანდარტული დიაპაზონის ფარგლებში, ეპილეპტიფორმული მაჩვენებლების მორფოლოგია და მათი რაოდენობა) დინამიკაზე. წარმოდგენილი მონაცემები მიღებულია კარბამაზეპინის მონოთერაპიამდე და მისი მიღებიდან 3-6 თვის შემდეგ.

კარბამაზეპინის ზემოქმედების ყველაზე თვალსაჩინო და მყარი ეფექტი გამოვლინდა ეეგ სპექტრის დაბალსიხშირიანი აქტივობის აბსოლუტური სიდიდეების გაზრდაში. ამასთანავე, აღრიცხულია ალფა- ტალღების საშუალო სიხშირის და სპონტანური ეპილეპტიფორმული გრაფოელემენტების რაოდენობის (78%-მდე) შემცირება ეეგ-ს რეგისტრაციისას მშვიდ მდგომარეობაში. 3 შემთხვევაში (2 ფრონტალური და ტემპორალური წილის ეპილეფსია) კარბამაზეპინის თერაპიამ აჩვენა უარყოფითი შედეგები როგორც კლინიკური, ისე ეეგ მაჩვენებლების მიხედვით.

REFERENCES

1. *J. Sramek, V. Zarotsky, N.R. Cutler* (2002), Drugs, **62**(3):1635-1648.
2. *T. Glauser, E. Ben-Menachem, B. Bourgeois, et al.* (2006), Epilepsia, **47**(7): 1094-1120.
3. *P. Goodridge, S.D. Shorvon* (1983), Brit. Med., **1** (287): 645-647.
4. *Y.M. Hart, J. Sander, L. Johnson, S.D. Shorvon* (1990), Lancet; **1**(336): 1271-1274.
5. *J.D. Frost, R.A. Hrachovy, D.G. Glaze, G. Rettig* (1995), Clin. Neurophysiol. **12**(1): 57-63.
6. *X. Wu, C.H. Xiao* (1996), Clin. Electroencephalogr., **27**(1): 40-45.
7. *I. Khachidze, V. Maloletnev, M. Mamukashvili* (2006), Bulletin of the Georgian Acad. Sci. **5**(32): 1109-1114.
8. *M.C. Salinsky, L.M. Binder, B.S. Oken, et al.* (2002), Epilepsia, **43**(5): 482-490.
9. *D. Garcia-Borreguero, T. Bronisch, S. Apelt, A. Yassouridis and H. Emrich* (1991), European Arch. Psychiatry. Clin. Neurosci. **241**(3): 145-150.
10. *L. Liu, T. Zheng, M. Morris et al.* (2006), J. Pharmacol. Exp. Ther., **2**(319): 790-798.
11. *S. Ahmad, L. Fowler, P. Whitton* (2005), Epilepsy Res., **63**(2/3): 141-149.
12. *S. Kochen, B. Giagante, S. Oddo* (2002), European Journal of Neurology, **9**(1): 41-47.
13. *R. Guerrini, A. Belmonte, P. Genton* (1998), Epilepsia, **39** (Suppl. 3): 2-10.
14. *E. Perucca, L. Gram, G. Avanzini, O. Dulac* (1998), Epilepsia, **1**(39): 5-17.