INTRODUCTION

Epilepsy is a common chronic neurological disorder that affects 1% to 3% of the population (Hauser 1996). Different animal models have been used to investigate epileptic mechanisms (Banerjee et al. 2009). Penicillin-induced epilepsy is one of the most common models. The application of penicillin to the cerebral cortex of animals, such as cats, dogs, and monkeys, induces epileptiform activity. The administration of penicillin locally produces an epileptic focus in many species, including rats. The neurons around the focus try to prevent the spread of the seizure thus, the penicillin acts only regionally at the beginning (Prince and Wilder 1967, Noebels and Pedley 1977). When penicillin is applied locally, focal epileptiform activity is first observed, following by spreading of the epileptiform activity and the appearance of generalized epilepsy (Gerald et al. 1973, Canan et al. 2008).

Penicillin exerts its convulsant activity by means of the gamma-aminobutyric acid (GABA) system (Antoniadis et al. 1980, Hori et al. 1985). GABA is the main neurotransmitter responsible for postsynaptic inhibition in the central nervous system of mammals (Dichter 1980). GABA exerts its effects mainly through two kinds of receptors, GABA$_A$ and GABA$_B$. The GABA$_A$ receptor is a member of the ligand-gated ion channel superfamily, and it plays a major role in inhibitory synaptic transmission in the brain. By the activation of GABA$_A$ receptors, chloride channels are opened, and the flow of chloride ions inward leads to inhibition of neuronal activity (Sakmann et al. 1983, Yasui et al. 1985).

Levetiracetam (LEV) is a new antiepileptic drug, which was shown to be effective against partial and generalized seizures in several animal models of epilepsy. (Gower et al. 1992, Löscher and Hönack 1993, Klitgaard et al. 1998). In the clinic, LEV is used in partial refractory epilepsy treatment (Dooley and Plosker 2000, Shorvon et al. 2000). Since April 2006, LEV has been used in Europe as adjunctive therapy in adults and adolescents with myoclonic epilepsy. The antiepileptic mechanism of LEV is not clear yet, and it is not effective against conventional drug targets, such as the Na$^+$ channel, T-type Ca$^{2+}$ channels, GABA, and glutamate receptors (Zona et al. 2001, Margineanu and Klitgaard 2003). LEV is effective on N-type Ca$^{2+}$ chan-
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nels and binds to (SV2A) which is a presynaptic membrane glycoprotein found in synaptic vesicles (Bajjalieh et al. 1993, Niespodziany et al. 2001, Reigada et al. 2003). The SV2A protein is responsible for the regulation of synaptic vesicle exocytosis and neurotransmitter release. LEV is the only antiepileptic to show binding affinity for the SV2A protein (Lynch et al. 2004). A previous study showed that mice without SV2A suffer strong seizures, do not thrive, and die within three weeks (Crowder et al. 1999).

LEV exhibited anticonvulsant activity against secondarily generalised activity from focal seizures induced by pilocarpine in mice [ED50 value 7 mg/kg intraperitoneally (ip)], pilocarpine and kainic acid in rats (minimum active doses 17 and 54 mg/kg, respectively, ip) (Klitgaard et al. 1998). In different studies LEV had no effect on acute maximal electroshock and pentylenetetrazole (PTZ)-induced seizures (Löscher and Hönack 1993), but it provided potent protection in genetic and chronic epilepsy animal models (Ji-qun et al. 2005).

To our knowledge, no study has evaluated the effect of LEV on penicillin-induced epilepsy. Therefore, in the present study, we examined the anticonvulsive effect of LEV on penicillin-induced epileptiform activity in rats.

METHODS

Animals

Female Wistar albino rats at 12–16 weeks of age and weighing 200–230 g were used in the experiments. The animals were obtained from the Experimental Research Centre of Ondokuz Mayis University (Samsun, Turkey). The rats were maintained on a 12 h light: 12 h dark cycle at a temperature of 21±3°C and 50% humidity. The animals were given food and water ad libitum. During the animal studies, the guidelines of the European Community Council for experimental animal care were applied. Before the experiments, this study was approved by the Ethical Committee for Animal Experiments at the University of Ondokuz Mayis (OMU HADYEK/2009-55).

Surgical and Experimental procedure

Under urethane (1.25 g/kg, ip) anesthesia, the rats were fixed on a stereotaxic apparatus and an incision (approximately 3 cm long) was made in the rostrocaudal direction. The skull bone of the left somatomotor cortex was removed after thinning with a dental drill. Ag/AgCl ball electrodes were placed on the cortex according to the following coordinates (first electrode, 2 mm lateral to sagittal suture and 1 mm anterior to bregma; second electrode, 2 mm lateral to sagittal suture and 5 mm posterior to bregma). The common reference electrode was fixed on the pinna. Body temperature was monitored using a rectal probe and maintained at 37°C with a homeothermic blanket system (Harvard Homoeothermic Blanket, USA).

After exposing the left cerebral cortex, epileptiform activity was produced by an injection of 500 IU [2.5 μl administered intracerebroventricularly (icv)] of penicillin G potassium (2 mm lateral and 1 mm posterior to bregma, 3.5 mm beneath the brain surface with a Hamilton microsyringe; infusion rate 0.5 μl/min). The coordinates for penicillin injection were derived from the atlas of the rat brain as were the electrode coordinates (Paxinos and Watson 2007). Levetiracetam was applied ip in three different doses (20, 40, 80 mg/kg) 60 min before penicillin injection.

Electrocorticographical (ECoG) recordings

ECoG recording started after the electrodes were placed. Basal activity was recorded in all of the animals for ten minutes at the beginning of the recording. The recording continued for a 180 minutes period after penicillin injection. Serebrocortical activity was recorded by PowerLab 4/SP (ADInstruments, Australia). Analogue signals obtained from cerebral cortex were transported to a computer. Spike numbers and amplitudes for each animal were automatically calculated by using a software program (Chart v5.1.1.)

The chemicals and route

Penicillin G potassium (500 IU) was used to induce epileptiform activity. The penicillin G was dissolved in distilled water (2.5 μl) and applied icv. Three different doses of LEV (20, 40, and 80 mg/kg) were injected ip 60 min before the penicillin application. The LEV was dissolved in 0.9% saline. The application time of LEV was determined according to the half lifetime, peak concentration time, and the current literature (Klitgaard et al. 1998).
Experimental Groups

The rats were randomly divided into six groups (n=7 per group). The first group was the control group. No chemicals were applied to this group. The rats in the second group received an icv injection of saline, and the third group received a penicillin injection via the icv route. The fourth, fifth, and the sixth groups were the LEV groups. Three different doses of LEV (20, 40, and 80 mg/kg) were applied ip before the penicillin injection.

Statistical Analysis

Latency to the first spike, as well as the frequency and amplitudes of the spikes, were analyzed in each experiment by means of Chart v51.1 (ADI Instruments) software. For each of the animals, the mean spike frequencies and amplitudes in every one minute were calculated automatically. The data obtained were analyzed using the SPSS 16.0 package program for Windows.

One-way analysis of variance (ANOVA) and post-hoc Tukey tests were used for the analysis of the spike frequencies and amplitudes. Kruskal-Wallis (ANOVA) followed by post-hoc Tukey tests were used for the latency period analysis. The results were expressed as means ± SEM. A P value less than 0.05 was accepted as statistically significant.

RESULTS

The ECoG activity was recorded for 10 min in the control group (Fig. 1A). In the second group, the ECoG activity was recorded following the administration of 2.5 μl of saline icv. There was no change in the basal

![Fig. 1. ECoG recordings showing spike frequencies and amplitudes 30 minutes after penicillin application. (A) Basal activity; (B) normal saline, (C) penicillin G; (D) levetiracetam 20 mg/kg; (E) levetiracetam 40 mg/kg; (F) levetiracetam 80 mg/kg.](image-url)
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...activity in this group when it was compared with the control group (Fig. 1B). In the penicillin group where 500 IU of penicillin G in a volume of 2.5 μl was administered (icv) to the animals, epileptiform activity began to appear in 2.3±1.1 min following the penicillin injection. The mean spike frequency per minute reached a maximum (200.71±32.67) at about 30 min after the application of the penicillin (Fig. 1C). The epileptiform activity continued for 180 minutes after the penicillin injection and decreased thereafter.

In the LEV group administered 20 mg/kg of LEV ip, spike waves of epileptic activity began in 4.1±0.2 min after the penicillin injection. The average spike frequency reached a maximum level (72±37) at the 20th min after the penicillin injection. After that, epileptiform activity continued for 180 min and decreased thereafter. Analysis of the average spike frequencies in this group at the 30th (56.33±9.14) (Fig. 1D) and 60th (41.83±16.21) min revealed a significant decrease compared with those of the penicillin group (P<0.01). In the group administered 40 mg/kg of LEV ip 60 min before the penicillin injection, spike waves began to appear 4.6±0.3 min after the penicillin injection. The average spike frequency reached a maximum (42.00±7.04) at the 30th min after the penicillin injection. There was a significant decrease in the average spike frequencies of this group at the 30th (Fig. 1E) and 60th min when compared with the time points in the penicillin group (P<0.01). In the group administered 80 mg/kg of LEV ip 60 min before the penicillin injection, epileptic discharges began in 2.8±0.2 min. The average spike frequency reached a maximum 20 min after the penicillin injection (138±32.92). The epileptic activity continued during all the recordings for 180 min. After the penicillin injection, the decrease in the average spike frequencies (101.83±39.67) was not significant at the 30th min (P>0.05) (Fig. 1F) when compared with the penicillin group. The decrease in the average spike frequencies (54.83±10.86) at the 60th min after the penicillin injection was significant (P<0.05).

The analysis of the latency period to the first spike after the penicillin injection revealed no significant difference between the LEV groups and the penicillin group (P>0.05). In the LEV groups, the mean amplitude of the epileptiform activity was not different compared to the penicillin group (P>0.05).

The most effective dose of LEV was 40 mg/kg. At this dose, LEV reduced the average spike frequencies at the 30th and 60th min after the penicillin injection (P<0.01). The mean spike frequency reached a maximum at the 30th min after the penicillin injection. The decrease at the 90th min was not significant (P>0.05). When the means of the spike amplitudes were compared with those of the penicillin group at the same minutes, there was not a significant difference (P>0.05). The percentage changes in the mean spike frequencies of LEV (20, 40, and 80 mg/kg doses) compared with those of the penicillin group is shown in Figure 2.

DISCUSSION

To the best of our knowledge, this is the first study to investigate the effects of LEV on penicillin-induced...
epilepsy in the literature. In the present study, we demonstrated the effect of LEV on penicillin-induced epileptiform activity and tried to determine the effective dose of LEV. The administration of LEV at doses of 20, 40, and 80 mg/kg 1 h before seizure induction significantly decreased the spike frequencies of epileptiform activity.

The penicillin model is one of the most common models in experimental epilepsy research. Penicillin blocks GABA\(_A\) receptors and prevents the inhibitor effect of GABA (Avanzini and Franceschetti 2003, Jefferys 2003). Impaired inhibition causes spike waves in EEG and these waves are converted to ictal discharges. As a result of GABA\(_A\) receptor antagonism, low doses of penicillin selectively block inhibitory postsynaptic potentials (Wong and Prince 1979, Dingledine and Gjerstad 1980). Higher doses of penicillin may have some nonspecific effects (Ayala et al. 1970). When successive doses of penicillin were injected ip to the rats, it was seen that the amount of the convulsive activity decreased but the number of SWD bursts increased by the repetitive doses (Stankiewicz et al. 1995). The authors suggested that the central nervous system (CNS) may develop tolerance to the convulsive effect of penicillin by increasing GABA receptor sensibility or GABA availability.

Rats are more sensitive to penicillin epilepsy when compared with other laboratory animals. The minimum intracortical effective dose of penicillin to produce generalized convolution in rats is 200 IU (Edmonds et al. 1974). It has been found that local penicillin injection elevates brain temperature in rats and this elevation is correlated with the intensity of the seizures (Tokiwai et al. 2013). Focal ischemia occurring at the beginning of the epilepsy has been thought to be responsible of this increase in the brain temperature (Karaszewski et al. 2006). In our laboratory, penicillin G was administered to rats at a dose of 400 IU, and epileptiform activity was analyzed (Canan et al. 2008). In a different study, Yildirim and coauthors (2011) investigated the influence of nitric oxide (NO) and adenosine on penicillin (200 IU) induced epilepsy. Also Bostanci and Bağirici (2006, 2007a,b) administered penicillin G icv and investigated the effects of octanol, carbenoxolone, and quinine on epileptiform activity. The results of these studies showed that these substances reduced penicillin-induced epileptiform activity.

LEV is an enantiomer of the ethyl analogue of the nootropic agent piracetam. LEV has some neuroprotective properties besides its antiepileptogenic effects (Shetty 2013). Neuroprotective effects of LEV were investigated in the rat middle cerebral artery occlusion model. Following cerebral artery occlusion, LEV induced a significant protection by reducing the infarct volume in the brain but did not change the body temperature (Hanon and Klitgaard 2001).

In the previous studies, it was shown that LEV was not effective against maximal electroshock and subcutaneous PTZ- induced epileptic seizures tests in mice and rats in doses up to 500 mg/kg, but it increased the thresholds for tonic electroconvulsions and myoclonic and clonic seizures induced by iv infusion of PTZ (Löscher and Hönack 1993). Luszczki and Czuczwar (2005) estimated the threshold-increasing dose (TID20) of LEV (44 mg/kg) for maximal electroconvulsions in mice using least-squares linear regression analysis. They determined that the TID50 was 150 mg/kg for LEV in the same study. Their findings are in agreement with those of Löscher and Hönack (1993).

LEV was found to have no effect on seizures evoked by icv injection of the excitatory amino acids N-methyl-D-aspartate (NMDA) and 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid (AMPA) (Klitgaard et al. 1998). On the other hand, Löscher and colleagues (1998) reported that LEV has protective effects against some experimental seizures evoked by sound and pilocarpine and that it has preventive effects in many kindling models of epilepsy. LEV prevented the progression of convulsions in a genetic epilepsy model (Yan et al. 2005). LEV also showed a protective effect against seizures induced by methyl-6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate (DMCM), which is a reverse agonist of benzodiazepine receptors (Rigo et al. 2002).

LEV prevents epileptic seizures by a new mechanism. In 1995, the binding site for LEV has been identified in brain membranes (Noyer et al. 1995). This binding side is an integral protein that is localized on neurons’ synaptic membrane fraction and is widely distributed. This binding protein was named as synaptic vesicle protein (SV2A) (Lynch et al. 2004) SV2A is a member of a small gene family consisting of three isoforms SV2A, SV2B and SV2C (Bajjalieh et al. 1993). Only SV2A binds to LEV. SV2A is essential for survival and for normal nervous system functioning. Experimental research demonstrated that the brain and
the synapse morphology were normal in SV2A knockout mice (Crowder et al. 1999). Another study showed that SV2 proteins are not essential for synaptic transmission, neurotransmitter current or storage but they are important during synaptic activation (seizure activity) by regulating Ca\(^{2+}\) dynamics in releasing Ca\(^{2+}\) (Janz et al. 1999). In a different study, LEV reduced the generation of the repetitive action potential and affected the single action potential in hippocampal CA1 neurons from rat in a patch-clamp study. LEV also decreased the voltage-operated potassium currents (Madeja et al. 2003).

LEV is the first drug to directly target the synaptic releasing mechanism. Using this mechanism, it protects against seizures. Studying different epilepsy models may reveal the exact mechanism by which LEV exerts its action.

In an experimental model of self-sustaining status epilepticus in rats induced by electrical stimulation of the perforant path, pre-treatment with LEV (30 mg/kg intravenously) decreased self evoked seizures and 50–100 mg/kg administered intravenously prevented seizures. After beginning of the seizures, 200 mg/kg of LEV decreased the seizures and 500–1000 mg/kg of LEV stopped the seizures (Mazarati et al. 2004). In our study, we applied LEV ip before the penicillin injection at doses of 20, 40, and 80 mg/kg. LEV was effective in decreasing frequencies of spike waves at these doses. In a different study of spontaneously epileptic rats (SER), the authors compared the preventive effect of LEV against seizures with that of other antiepileptics (Ji-qun et al. 2005). LEV was administered in single doses of 40, 80 and 160 mg/kg /day and 80 mg/kg for five days. Air was blown on the animal’s head to induce a tonic convulsion. At single doses, LEV (80–160 mg/kg) inhibited absence-like seizures, but no effect was observed with 40 mg/kg of LEV. When LEV was applied at a dose of 80 mg/kg for five days, the inhibitor effects on seizures increased proportionally with the given dose. The study concluded that LEV is effective against tonic convulsions and absence-like seizures in SER. We applied LEV at single doses of 20, 40, and 80 mg/kg before the administration of penicillin. We observed that the frequencies of spike waves decreased compared with the control group.

Stratton and coworkers (2003) investigated antiepileptic effects of LEV in an electrical kindling model. In this study, 50 mg/kg of LEV prevented the progression of kindling seizures in a dose-dependent manner in rats. The ED50 value for LEV was determined as 32 mg/kg in this study. The preventive effects of LEV have been studied in mice including acute maximal electroshock and a PTZ model (Klitgaard et al. 1998). LEV had no effect in this model until 540 mg/kg ip, but it had protective effects in electrical kindling and PTZ kindling models (ED50 values of 7–36 mg/kg respectively, ip). LEV also showed a strong effect on seizures induced by pilocarpine in mice (ED50 =7 mg/kg), and it was effective against pilocarpine- and kainic acid-induced epilepsy in rats (minimum active dose of 17–54 mg/kg) (Klitgaard et al. 1998). In the pilocarpine and kainic acid models, the seizure activity was evaluated according to the Racine (1972) scale. The penicillin model that we used in our study was an acute experimental epilepsy model, and epileptiform discharges were estimated by ECoG recordings. The effective doses of LEV in our study were concordant with the doses used in the pilocarpine and kainic acid rat models.

Van Vliet and others (2009) investigated the development of tolerance with antiepileptic use. In an electrical kindling rat model where LEV and valproic acid (VPA) were alternatively used, tolerance of LEV was not prevented, but seizures were inhibited for a longer period compared to monotherapy.

In a tetanus toxin model, spontaneous and intermittent generalized seizures were initiated that imitated human complex partial epilepsy (Doheny et al. 2002). Carbamazepine and LEV were injected in doses of 8–16 mg/kg ip for seven days. Spike frequencies of generalized and non generalized seizures decreased significantly in a dose dependent manner when LEV was administered. Carbamazepine exhibited no significant anticonvulsant effect during the seven day study period. Tetanus toxin is a neurotoxin, which blocks the synthesis or release of GABA. Both penicillin and tetanus toxin models induce seizures through the neurotransmitter GABA. As LEV showed significant efficacy in both these epilepsy models, these data further suggest an indirect effect of LEV on GABA.

In a study of cultured rat cortical neurons and pyramidal neurons from rat hippocampal slices, LEV had no effect on the voltage-activated tetrodotoxin-sensitive inward Na\(^{+}\) current and on the low-voltage-activated (T-type) Ca\(^{2+}\) current (Zona et al. 2001). This suggests that the inhibition of voltage-operated Na\(^{+}\) or T-type Ca\(^{2+}\) channels is not responsible for the antiepileptic mechanism of LEV.
There is some evidence that LEV may play a role in potentiating GABAergic inhibition (Löschner et al. 1996). Conflicting results were found in studies of the interaction between the antiepileptic effects of LEV and GABAergic mechanisms (Margineanu and Wülfer 1995). Binding studies have demonstrated the presence of a specific site for LEV in synaptic membranes in various structures of the rat brain, including the hippocampus, but no specific binding was observed in peripheral tissues. GABA and GABA-related compounds demonstrated any affinity for LEV-binding site but two convulsants pentylenetetrazole and beme- grid, which were reported to act at the picrotoxin site of the GABA_α receptor, inhibited LEV (Noyer et al. 1995). As a result, it was concluded that some interactions could exist between LEV and an undefined site on the GABA_α receptor.

LEV reduced the calcium current through high voltage activated N-type Ca^{2+} channels of CA1 pyramidal hippocampal neurons of Wistar rats, thus reducing seizure activity (Lukyanetz et al. 2002). The authors suggested that a subtype of N-type channels sensitive to LEV might exist and that this subtype might be involved in the molecular basis of the antiepileptic action of LEV.

Binding sites for LEV were shown to be present at a high concentration in synaptic plasma membranes (Noyer et al. 1995). LEV reversed the inhibitory effects induced by negative modulators of the GABA_α receptor. The GABA_α receptor blocker, bicuculline, produced epileptiform activity \textit{in vivo} and \textit{in vitro}. LEV prevented the GABA_α receptor blocking action of bicuculline and gabazine in guinea-pig hypothalamic neurons (Poulain and Margineanu 2002). Data obtained from GABA\textsubscript{A}-gated currents recorded on cultured hippocampal neurons support this idea (Rigo et al. 2000). Using \textit{in vivo} recordings from rat hippocampus, Margineanu and Wülfer (1995) showed that LEV prevents increases in CA3 neuronal excitability by bicuculline through a non-GABAergic mechanism. This report conflicts with the study by Löschner and coauthors (1996), which demonstrated changes in GABA metabolism and turnover in some parts of the brain following the administration of high doses of LEV. In a different study involving zinc and beta carbolines, LEV reversed the inhibitory effects of these substances on both GABA- and glycine-mediated responses (Rigo et al. 2002). It is still unclear whether LEV acts on GABA receptors.

In a recent study carried out with patients with focal epilepsy treated with LEV, GABA/Cr levels increased significantly in the patient’s brain (Doelken et al. 2010). The authors suggested that this points a complex and indirect effect of LEV on GABAergic system.

Extensive experiments of the receptor binding site of LEV and T type calcium channels indicated that LEV was inactive at more than 30 neurotransmitter receptors and ion channel sites (Noyer et al. 1995). The results showed that the binding site of LEV in the brain is not the same as the binding region of standard antiepileptic drugs. As a result, LEV shows antiepileptic activity against many kinds of seizures, such as partial and secondarily generalized kindled seizures in animal models at low doses, without inducing adverse effects (Gower et al. 1992, Löschner and Hönack 1993).

Another study reported apparent changes in GABA metabolism and turnover in several brain regions following the administration of LEV, in addition to functional alterations in neuronal activity that may be related to LEV’s mechanism of anticonvulsant action (Löschner et al. 1996). LEV did not interact with GABA-transaminase (GABA-T) and glutamic acid decarboxylase (GAD) \textit{in vitro}. Thus, the authors attributed the observed changes in GABA metabolism and turnover to the postsynaptic effects of this drug at brain synaptic membranes.

There is a striking difference between the doses of LEV that suppress seizures and those that provoke adverse events in the preclinical profile of LEV. The neurotoxic adverse effects of LEV have been evaluated in standard tests for motor impairment, such as the rotarod test. LEV had minimal effects on behavior, such as slight hyperactivity, and it did not impair muscle activity in a rotarod test of normal, non epileptic rodents administered doses of LEV up to 1700 mg/kg ip (Löschner and Hönack 1993). Klitgaard and colleagues (1998) reported that the median toxic dose (TD50) value of LEV was 1036 mg/kg in cornally kindled mice in the rotarod test. In a different study, Luszczki and others (2005) reported that the TD50 value of LEV with respect to the impairment of motor coordination in mice was 1601 mg/kg. In that study, the authors used a rotarod test to determine the acute neurotoxic effect of LEV when administered singly and in combination with other antiepileptic drugs. LEV considerably enhanced the acute neurotoxic effects produced by topiramate and carbamazepine,
but it had no influence on the acute neurotoxic effects produced by phenytoin, valproic acid, and phenobarbital. A pharmacodynamic interaction was suggested between these antiepileptic drugs. Such experimental studies can be useful in the selection of the most useful combinations in the treatment of epilepsy.

In the present study, the administration of LEV for 60 min before the penicillin injection at doses of 20, 40, and 80 mg/kg reduced spike frequencies significantly compared to penicillin group at 30th min after the penicillin injection. When the spike amplitudes of the LEV groups were compared with the penicillin group, there was not a significant difference ($P > 0.05$).

Based on the analysis of the data, the most effective dose of LEV in penicillin-induced epilepsy was 40 mg/kg.

CONCLUSION

In light of these results, we conclude that LEV may be an effective antiepileptic in a penicillin model of epilepsy. Our results are consistent with the findings of different epilepsy models treated with LEV in the literature (Klitgaard et al. 1998, Doheny et al. 2002, Stratton et al. 2003). The antiepileptic mechanism of LEV is not yet clear. GABAergic mechanisms may possibly play a role, in addition to the SV2A protein. To further illuminate the antiepileptic mechanisms of LEV, more detailed studies are needed.

REFERENCES


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