Research Article **IJNR (2019) 3:9**

International Journal of Neuroscience Research (ISSN:2572-8385)

The Effect of Nitrendipine and Levetiracetam in Pentylenetetrazole Kindled Rats

Meryem Dilek Karakurt[1], Süleyman Emre Kocacan[2], Cafer Marangoz[3]

[1]Ankara Yıldırım Beyazıt University Medical Faculty, Ankara, TURKEY
[2]Ondokuz Mayıs University Medical Faculty, Samsun, TURKEY
[3]Istanbul Medipol University Medical Faculty, Istanbul, TURKEY

ABSTRACT

We aimed to investigate the efficacy of L-type voltage gated calcium channel blocker nitrendipine and levetiracetam in pentylenetetrazole (PTZ) kindled male rats. In order to establish kindling model, 35 mg/kg PTZ injected intraperitoneally (i.p.) to male wistar albino rats three days a week. Then, screw electrodes were placed in the skulls of the kindled rats. During the experiments, EEG activities and seizure behaviors of kindled rats were recorded. The kindled rats were divided into control (n=6), PTZ (n=6), nitrendipine (2.5 mg/kg (n=6), 5 mg/kg (n=6), 10 mg/kg (n=6)) and levetiracetam (10 mg/kg (n=6), 20 mg/kg (n=6), 40 mg/kg (n=6)) groups. Nitrendipine (5 mg/kg) and levetiracetam (20 mg/kg) were suppressed the spike frequency and the seizure score effectively ($p<0.05$). The effective doses of nitrendipine (5 mg/kg) and levetiracetam (20 mg/kg) were administered consecutively to the kindled animals (n=6). The co-administration of nitrendipine (5 mg/kg) and levetiracetam (20 mg/kg) did not effectively decrease the spike frequency and seizure score ($p>0.05$). The co-administration of nitrendipine and levetiracetam was not more effective than administration of nitrendipine or levetiracetam separately ($p>0.05$).

Keywords: levetiracetam, nitrendipine, kindling model, voltage-gated calcium channels, rat

Abbrevations:
PTZ: Pentylenetetrazol; DMSO: Dimethyl sulfoxide; sc: Second; EEG: Electroencephalography; mV: Milivolt;

***Correspondence to Author:**
Meryem Dilek Karakurt
Ankara Yıldırım Beyazıt University Medical Faculty, Physiology Department, 06010 Ankara, TURKEY

How to cite this article:
Meryem Dilek Karakurt, Süleyman Emre Kocacan, Cafer Marangoz. The Effect of Nitrendipine and Levetiracetam in Pentylenetetrazole Kindled Rats. International Journal of Neuroscience Research, 2019; 3:9.

eSciPub LLC, Houston, TX USA.
Website: https://escipub.com/

1. Introduction

Kindling is the progressive development of seizures in response to administration of a subconvulsant stimulus in a repeated fashion [1, 2] and it produces circuitry seen in complex partial seizures with secondary generalization [3]. The reorganizations which are the responses to excess neuronal activity, includes transcription factors, immediate early genes, protein synthesis, neurogenesis, and synaptogenesis, in addition to activation of glutamate receptors, second messengers, neurotrophic factors, and axon guidance molecules [4]. The electrical kindling and the chemical kindling are two main kinds of the kindling model. Subconvulsant chemical and subconvulsant electrical stimulation appear to activate similar anatomic pathways, however chemical kindling affects the whole brain for a relatively long period. As a chemoconvulsant pentylenetetrazole (PTZ) is one of the most preferred substances used in the development of chemical kindling [3]. *PTZ is a noncompetitive antagonist, which blocks gamma aminobutyric acid (GABA)-mediated Cl- influx through Cl- channels* [5].

Large elevations in neuronal calcium, especially via L-type voltage-gated calcium channels, are mainly responsible for seizure generation and propagation of epileptic discharges [6, 7]. Nitrendipine is a dihidropyridine analog which acts as L-type voltage-gated calcium channel blocker [8]. Nitrendipine binds the α1 subunit of L-type voltage-gated calcium channels [9] responsible for the opening and closing of the channel [10]. Nitrendipine can cross the blood brain barrier because of its highly lipophilic structure [11]. Although, nitrendipine is an antihypertensive drug used for primary hypertension [8, 12], the potential application of dihidropyridine analogs in a range of areas has been studied to determine whether it offers advantages compared to current therapies [13]. Also, the anticonvulsant activity of nitrendipine has been investigated in a variety of seizure models [6, 14-16].

According to The Report of the American Epilepsy Society and the Guideline Development as a result of Class I studies, levetiracetam is effective as add-on therapy for treatment of resistant generalize epilepsy with generalize tonic clonic seizures and also add-on therapy for treatment of juvenile myoclonic epilepsy and juvenile absence seizures [17]. It has been known that levetiracetam binds the synaptic vesicle protein 2A [18], the activity of which is related to the exocytosis of transmitter vesicles [19, 20]. Several studies investigated the anticonvulsant effect of levetiracetam via voltage gated calcium channels [21, 22]. To determine the efficacy of nitrendipine and levetiracetam that both have effect on seizure suppression via voltage gated calcium channels the experiments exhibited in awake kindled rats using simultaneous observations of electrophysiological activity and seizure behavior.

2. Materials and Methods

2.1. Animals

Male Wistar albino rats (12–16 weeks, weighing 200 ± 25 g) were used. The rats were housed individually in a 12 h light, 12 h dark cycle at a temperature of 22±2° C and 50–55% moisture. Water and food were provided ad libitum. This study was approved by the local Ethical Committee for Animal Experiments at the University of Ondokuz Mayis in Samsun. All experiments were conducted according to the guidelines of the European Community Council for animal care.

2.2. Kindling

To induce kindling, the rats were injected i.p. with a subconvulsive dose of PTZ (35 mg/kg) three times a week (Monday, Wednesday, and Friday). After the injections the animals were placed individually in transparent boxes (35 (L)×35 (W)×35 (H) cm). Their seizure behaviors were observed for 30 minutes (min) according to Fischer and Kittner's seizure scale of 1–5 and stage 3–5 seizure behaviors were accepted as generalized seizure. Stages were

characterized as follows. Stage 0: no seizure. Stage 0.5: weak nodding. Stage 1: twitching of face, eyelids, and ears. Stage 1.5: mild clonic activity of forelimb. Stage 2: myoclonic body jerks, clonic movement of forelimb without rearing. Stage 2.5: swift clonic seizures of forelimb following partial rearing. Stage 3: robust bilateral forelimb clonus with complete rearing (≥ 10 sec). Stage 3.5: rearing and falling with intense bilateral forelimb clonus. Stage 4: generalized clonic seizures with rearing-falling down episodes or jumping. Stage 4.5: generalized clonic-tonic seizures with failure of righting reflex. Stage 5: generalized clonic-tonic seizures and status epilepticus (≥2 min). The rats were kindled after having five generalized seizures [23]. To induce kindling, injections were performed over a period of four weeks [24]. Nonkindled and dead rats were excluded from the study.

2.3. Surgical Operation

The kindled rats were anesthetized with 90 mg/kg ketamine hydrochloride and 10 mg/kg xylasine (i.p.). Then rats positioned on a stereotaxic apparatus (Harvard). After a midline scalp incision, stainless steel screw electrodes were fixed into the skull by the following coordinates: first electrode: 3 mm lateral to sagittal suture, 4 mm anterior to Bregma (primary motor cortex, M1); and second electrode: 3 mm lateral to sagittal suture, 4 mm posterior to Bregma (medial parietal association cortex, MPtA) [25]. An electrode was identified as a reference and positioned in the skull at 4 mm posterior to the Bregma. Electrodes fixed in the skull were attached to a connecting socket. Except the socket, the electrodes on the surface of the skull were implanted by using cold-cured dental acrylic.

2.4. Electrophysiological Recordings

After the surgery recovery period of a week, awake kindled rats were connected to a computerized EEG recording system (PowerLab/4SP, AD Instruments). The seizure behaviors of the animals were observed at the same time for 30 min. The off-line analysis of the EEG recordings and the spike frequency for each animal were automatically calculated using the Chart v.5.1.1 program.

2.5. Drugs and Routes

Drugs were administered as follows:

PTZ: Dissolved in saline, injected i.p.

Nitrendipine: Dissolved in 3% DMSO, administered i.p.

Levetiracetam: Dissolved in saline, administered i.p.

PTZ, nitrendipine, and levetiracetam were purchased from Sigma-Aldrich Co.

2.6. Experimental Groups

The kindled rats (n=60) were divided into 10 groups. The groups were as follows.

Control group: EEGs and seizure stages recorded without administration of any drug for 30 min (n=6).

PTZ group: PTZ 35 mg/kg (n=6).

Nitrendipine groups: Nitrendipine 2.5 mg/kg (n=6), 5 mg/kg (n=6), and 10 mg/kg (n=6) 30 min before PTZ injection.

Levetiracetam groups: Levetiracetam 10 mg/kg (n=6), 20 mg/kg (n=6), and 40 mg/kg (n=6) 30 min before PTZ injection.

Nitrendipine-Levetiracetam group: Nitrendipine at a dose of 5 mg/kg and levetiracetam at a dose of 20 mg/kg were injected consecutively (i.p.) into rats 30 min before PTZ injection (n=6).

DMSO group: 3% DMSO (a volume of 0.1 ml) was injected (i.p.) into rats 30 min before PTZ injection (n=6).

2.7. Statistical Analysis

The data obtained were assessed using the SPSS package program. Shapiro–Wilk and Kolmogorov–Simirnov tests were used for determining the normal distribution of the variables. A one-way analysis of variance (ANOVA) and the post-hoc Tukey test were used for comparing the spike frequency data among the groups. The seizure stage data were analyzed with the Kruskal–Wallis test, and

the Mann–Whitney U Test was used for binary comparison. P value less than 0.05 was considered statistically significant.

3. Results

3.1. Effects of PTZ on PTZ-kindled rats

After the PTZ (35 mg/kg, i.p.) injection, EEG activities of the kindled rats were recorded, and their seizure stages were scored for 30 min. Generalized seizures were observed in all animals of the PTZ group (Figure 1, 2; Table I).

Table 1 Average seizure stage in the PTZ group and treatment groups; Data are shown as mean ± standard deviation of the mean (SD). The Mann–Whitney U test was used. *p<0.05 compared to the PTZ group.

Group	Average Seizure Stage ± SD
PTZ 35 mg/kg	3,7 ± 0,5
NITR 2,5 mg/kg	3,1 ± 0,7
NITR 5 mg/kg	2,8 ± 0,4*
NITR 10 mg/kg	3,1 ± 0,7
LEV 10 mg/kg	2,6 ± 0,7*
LEV 20 mg/kg	2,2 ± 1,1*
LEV 40 mg/kg	3,3 ± 0,3
NITR 5 mg/kg - LEV 10 mg/kg	3,7 ± 0,9

3.2. Effects of Nitrendipine on PTZ-kindled rats

Nitrendipine at doses of 2.5 and 10 mg/kg did not effectively suppress the spike frequency ($p>0.05$) or the seizure stage ($p>0.05$) (Figure 1, 2; Table I) compared with the PTZ group. Nitrendipine (5 mg/kg) reduced the spike frequency ($p<0.05$) and the seizure stage in kindled rats compared with the PTZ group ($p<0.05$) (Figure 1, 2; Table I).

3.3. Effects of Levetiracetam on PTZ-kindled rats

Levetiracetam at the dose of 10 mg/kg did not effectively suppress the spike frequency in kindled rats ($p>0.05$) (Figure 1, 2) but diminished the seizure stage ($p<0.05$) (Table I). Levetiracetam (20 mg/kg) suppressed the spike frequency ($p<0.05$) and the seizure stage significantly compared with the PTZ group ($p<0.05$) (Figure 1, 2; Table I). Levetiracetam (40 mg/kg) did not change the spike frequency ($p>0.05$) or the seizure stage significantly compared with the PTZ group ($p>0.05$) (Figure 1, 2; Table I).

3.4. Effects of Nitrendipine-Levetiracetam on PTZ-kindled rats

The anticonvulsant doses of nitrendipine (5 mg/kg) and levetiracetam (20 mg/kg) were

administered consecutively to kindled rats. The nitrendipine (5 mg/kg)- levetiracetam (20 mg/kg) combination did not change the spike frequency ($p>0.05$) or the seizure stage significantly ($p>0.05$) compared to the PTZ group (Figure 1, 2; Table I).

3.5. Effects of DMSO on PTZ-kindled rats

%3 DMSO in % 0.9 NaCl did not change seizure parameters compared with the PTZ group ($p>0.05$) (Figure 1).

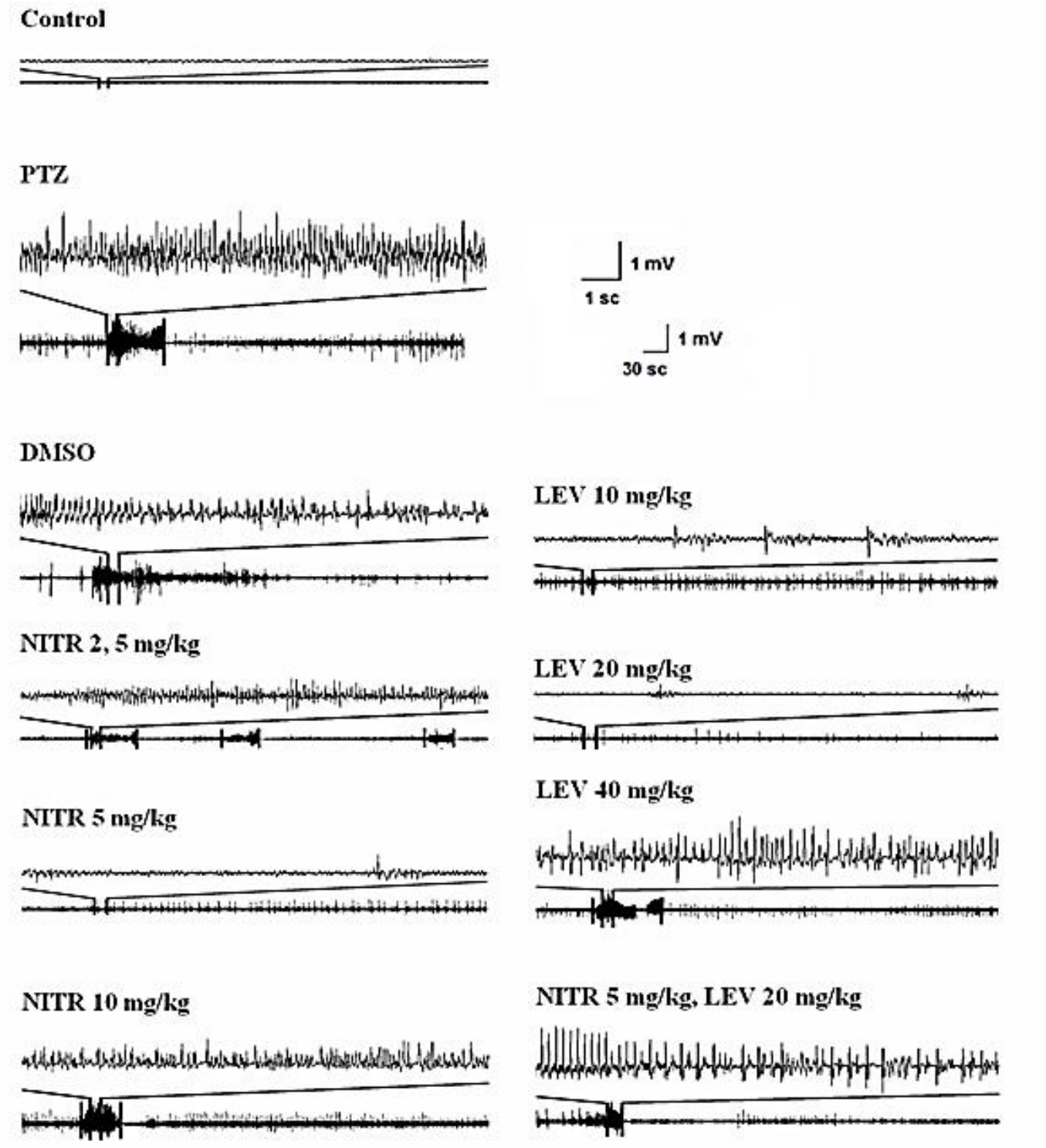

Figure 1-EEG recordings and seizure stage observed simultaneously in the PTZ group, DMSO group, and treatment groups. X-axis represent time in seconds (sc), and Y-axis represent amplitude in millivolts (mV).

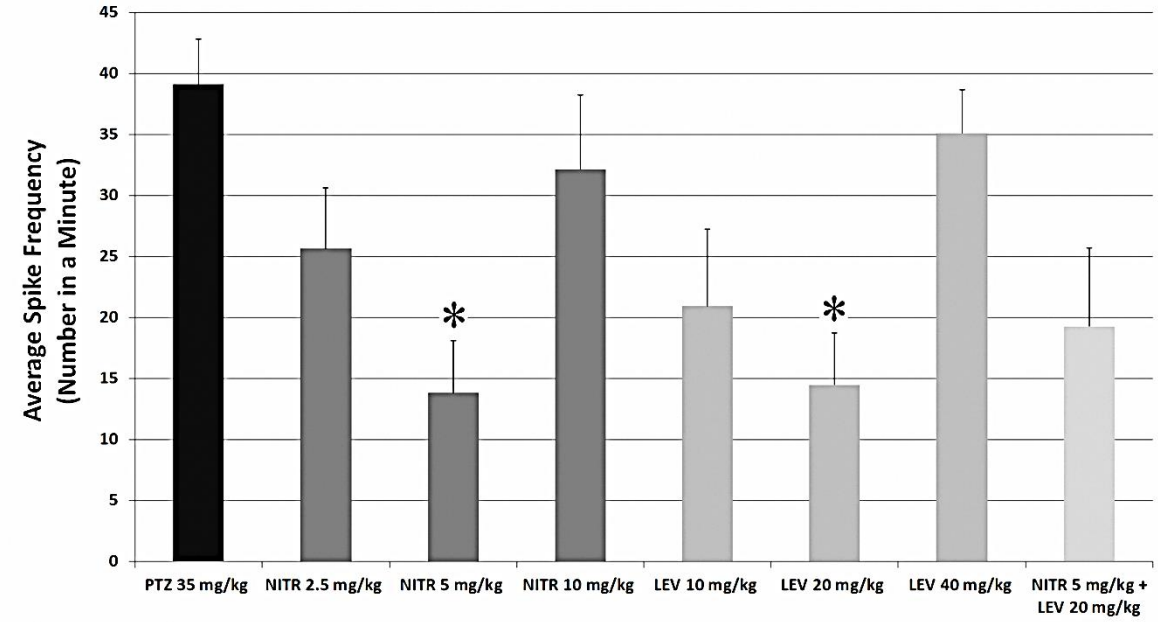

Figure 2- Average spike frequency in the PTZ group, DMSO and treatment groups; Data are expressed as mean ± standard error of the mean (SEM). One-way ANOVA, post hoc Tukey test used. ✻ $p < 0.05$ compared to the PTZ group.

4. Discussion

The anticonvulsant effects of nitrendipine and levetiracetam were dose-dependently determined in awake kindled rats using simultaneous observations of electrophysiological activity and seizure behavior. In this study, the dose of 5 mg/kg of nitrendipine showed anticonvulsant activity by reducing the spike frequency and the seizure stage in PTZ-kindled rats. However, the doses of 2,5 mg/kg and 10 mg/kg of nitrendipine did not effectively reduce the spike frequency or the seizure stage in PTZ-kindled rats. In vitro auto radiographic techniques have been used to localize [3H] nitrendipine binding sites in the rat brain. These sites contain many synaptic connections in the cerebral cortex [26]. The experimental studies have shown that the L-type voltage-gated calcium channel blocker nitrendipine is an effective anticonvulsant in several seizure models when administered at different doses and via different methods [6, 14-16]. Also, Doyle et al. indicated that nitrendipine inhibits central nervous system excitation in a dose-dependent manner [9]. Neuronal L-type voltage gated calcium channels ($Ca_v1.2$ and $Ca_v1.3$) play a role in excitation and transcription coupling. $Ca_v1.3$ is more effective than $Ca_v1.2$ to induce phosphorylation of cAMP-responsive element-binding protein (CREB) phosphorylation [27]. The Ca^{2+} rises provided by $Ca_v1.3$ channels also, trigger epileptogenesis [28]. Paroxismal depolarization shifts (PDSs) depend largely on Ca^{2+}-influx via $Ca_v1.3$ channels [29, 30]. Therefore, $Ca_v1.3$ channels is target for suppression of PDSs and also attenuate epileptogenesis at an early stage [28].

According to the results of the experiments, the low dose of levetiracetam (10 mg/kg) did not statistically affect the spike frequency data we acquired by determining electrophysiological records. Therefore, levetiracetam (10 mg/kg) did not accepted as an effective dose even decreased the seizure stage data that we simultaneously obtained by behavioral observation. In a previous study, the anticonvulsant activity of levetiracetam determined within a 15 min observation period on PTZ (37 mg/kg, i.p.) kindled mice and, the dose of levetiracetam (10 mg/kg) inhibited seizure behavior [31]. In another study, Cifelli et al. indicated that the differentially expression of $GABA_A$ receptor subunits between the epileptic

cortex and hippocampus results with the different use dependent decrease of $GABA_A$ receptor activity. Also, Cifelli et al. indicated that the use dependent decrease of $GABA_A$ receptor activity did not affected in hippocampus but diminished in the cortex by using levetiracetam in pilokarpin model [32]. And in the present study, probably differentially expression of $GABA_A$ receptor subunits between the epileptic cortex and hippocampus we observed the seizure stage suppression but not sufficient the spike frequency attenuation with low dose of levetiracetam. Further study is needed to better define the mechanism. However, levetiracetam (20 mg/kg) suppressed the spike frequency and the seizure stage in the PTZ-kindled rats. The high dose of 40 mg/kg of levetiracetam did not change the spike frequency or the seizure stage significantly compared with the PTZ group. Also, Rigo et al. indicated that high concentrations of levetiracetam above the therapeutic dose reverse its effect on extending GABA-dependent currents [33]. According to a study of isolated neocortical neurons, levetiracetam decreases the activation of N- and partially P/Q-type voltage-gated calcium channels, and levetiracetam reduces intracellular calcium increase in a dose dependent fashion [21]. Lee et al. reported that levetiracetam decreases the release of glutamate via P/Q-type voltage-gated calcium channels. Also, levetiracetam inhibits calcium currents by inhibiting L-type voltage-gated calcium channels in the spontaneously epileptic rat [22].

Levetiracetam (10 mg/kg) effect in the spike frequency of PTZ kindled rats and nitrendipine (5 mg/kg) effect did not statistically different ($p>0.05$). The consecutive administration of L-type voltage-gated calcium channel blocker nitrendipine (5 mg/kg) and levetiracetam (20 mg/kg) did not effectively depress the spike frequency or the seizure stage of the kindled rats. It is known that the voltage-gated channels regulate intracellular signaling pathways, such as neurotransmitter release by affecting calcium influx [34]. L-type voltage-gated calcium channels are crucial for neuronal excitability and synaptic transmission [35]. In dorsal root ganglion neurons from rats L-type voltage-gated calcium channel blocker nitrendipine inhibits GABA-activated currents. However, the inhibition is concentration dependent [36]. Probably, L-type voltage gated calcium channel inhibition with two effective drugs also inhibited GABA-activated currents. As a result, nitrendipine and levetiracetam did not effectively suppressed the epileptic discharges and also epileptic behavior in kindled rats. Further investigations need to better define the indicated event.

Acknowledgement

This study was supported by the Ondokuz Mayis University Research Foundation (PYO.TIP.1904.09.022). Prof. Dr. Yüksel Bek provided assistance in the statistical analysis.

References

1. Graham V. Goddard, Don C. McIntyre, Curtis K. Leech. A permanent change in brain function resulting from daily electrical stimulation. Experimental Neurology, 1969; 25(3): 0295−0330.
2. Rahim Golmohammadi, Akbar Pejhan, Hassan Azhdari-Zarmehri, Mohammad Mohammad-Zadeh. The role of ethanol on the anticonvulsant effect of valproic acid and cortical microvascular changes after epileptogenesis in mice. Neurol Sciences, 2013; 34(7): 1125-1131.
3. Mary E. Gilbert, Jeffrey H. Goodman. Chemical Kindling. In, Pitkänen A, Philip A, Solomon LM (Ed): Models of Seizures and Epilepsy. Elsevier Academic Press, 2006.
4. Kiyoshi Morimoto, Margaret Fahnestock, Ronald J Racine. Kindling and status epilepticus models of epilepsy: rewiring the brain. Prog Neurobiol, 2004; 73(1): 0001−0060.
5. Axel Becker, Holger Braun, Helmut Schröder, Gisela Grecksch, Volker Höllt. Effects of enadoline on the development of pentylenetetrazole kindling, learning performance, and hippocampal morphology. Brain Research, 1999; 823(1-2): 0191−0197.
6. Gene C. Palmer, Mary L. Stagnitto, Ranjit K. Ray, Marilyn A. Knowles, Rosemary Harvey, George E. Garske. Anticonvulsant properties of

calcium channel blockers in mice: N-methyl-D-, L-aspartate- and Bay K 8644-induced convulsions are potently blocked by the dihydropyridines. Epilepsia, 1993; 34(2): 0372−0380.

7. Dong-Yun Han, Bo-Jhih Guan, Ya-Juan Wang, Maria Hatzoglou, Ting-Wei Mu. L-type Calcium Channel Blockers Enhance Trafficking and Function of Epilepsy-associated α1 (D219N) Subunits of GABA (A) Receptors. ACS Chem Biol, 2015; 10(9): 2135-2148.
8. Michael B Gatch, Cleatus J Wallis, Harbans Lal. Effects of calcium channel blockers on pentylenetetrazole drug discrimination in rats. Alcohol, 2001; 23(3): 0141−0147.
9. Karen M. Doyle, Brian P. Kirby, Desiree Murphy, Graham G.Shaw. Effect of L-type calcium channel antagonists on spermine-induced CNS excitation in vivo. Neuroscience Letters, 2005; 380(3): 0247−0251.
10. Ricardo Felix. Voltage-dependent Ca^{2+} channel α2δ auxiliary subunit: structure, function and regulation. Recept Channels, 1999; 6(5): 0351−0362.
11. Daniel Paris, Corbin Bachmeier, Nikunj Patel, Amita Quadros, Claude-Henry Volmar, Vincent Laporte, Jim Ganey, David Beaulieu-Abdelahad, Ghania Ait-Ghezala, Fiona Crawford, Michael J Mullan. Selective Antihypertensive Dihydropyridines Lower Aβ Accumulation by Targeting both the Production and the Clearance of Aβ across the Blood-Brain Barrier. Mol Med, 2011; 17(3-4): 0149−0162.
12. Praveen Kumar Gaur, Shikha Mishra, Suresh Purohit. Nanovesicles of nitrendipine with lipid complex for transdermal delivery: pharmacokinetic and pharmacodynamic studies. Artif Cells Nanomed Biotechnol., 2016; 44(7): 1684-1693.
13. Arnold M. Katz, Nancy M. Leach. Differential effects of 1, 4-dihydropyridine calcium channel blockers: therapeutic implications. J clin Pharmacol, 1987; 27(11): 0825−0834.
14. Simon J. Dolin, Anthony B. Hunter, Michael J. Halsey, Hilary J. Little. Anticonvulsant profile of the dihydropyridine calcium channel antagonists, nitrendipine and nimodipine. Eur J Pharmacol, 1988; 152(1-2): 0019−0027.
15. HJ Little, SJ Dolin, MA Whittington. Calcium channel antagonists prevent adaptive responses to ethanol. Alcohol, 1993; 2, 0263−0267.
16. WP Watson, JJ Little. Effect of dihydropyridines on the distinct components of the ethanol withdrawal syndrome: Evidence for changes in potassium as well as calcium? Alcohol Clin Exp Res, 1997; 21(3): 0409−0416.
17. Andres M. Kanner, Eric Ashman, David Gloss, MPH&TM, Cynthia Harden, Blaise Bourgeois, Jocelyn F. Bautista, Bassel Abou-Khalil, Evren Burakgazi-Dalkilic, Esmeralda Llanas Park, John Stern, Deborah Hirtz, Mark Nespeca, Barry Gidal, Edward Faught, Jacqueline French. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy. Epilepsy Curr, 2018; 18(4): 0269–0278.
18. Berkley A. Lynch, Nathalie Lambeng, Karl Nocka, Patricia Kensel-Hammes, Sandra M. Bajjalieh, Alain Matagne, Bruno Fuks. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. Proc Natl Acad Sci, 2004; 101(26): 9861–9866.
19. Tao Xu, Sandra M. Bajjalieh. SV2 modulates the size of readily releasable pool of secretory vesicles. Nat Cell Biol, 2001; 3(8): 0691−0698.
20. Rafal M. Kaminski, Alain Matagne, Karine Leclercq, Michel Gillard, Philippe Michel, Benoit Kenda, Patrice Talaga, Henrik Klitgaard. SV2A protein is a broad-spectrum anticonvulsant target: functional correlation between protein binding and seizure protection in models of both partial and generalized epilepsy. Neuropharmacology, 2008; 54(4): 0715–0720.
21. Antonio Pisani, Paola Bonsi, Giuseppina Martella, Cristiano De Persis, Cinzia Costa, Francesco Pisani, Giorgio Bernardi, Paolo Calabresi. Intracellular calcium increase in epileptiform activity: modulation by levetiracetam and lamotrigine. Epilepsia, 2004; 45(7): 0719−0728.
22. Hai-Dun Yan, Kumatoshi Ishihara, Takahiro Seki, Ryosuke Hanaya, Kaoru Kurisu, Kazunori Arita, Tadao Serikawa, Masashi Sasa. Inhibitory effects of levetiracetam on the high-voltage-activated L-type Ca2+ channels in hippocampal CA3 neurons of spontaneously epileptic rat (SER). Brain Res Bull, 2013; 90: 0142−0148.
23. W Fischer, H Kittner. Influence of ethanol on the pentylenetetrazole-induced kindling in rats. J Neural Transm, 1998; 105(10-12): 1129−1142.
24. Christine Rauca, Renate Zerbe, Hannelore Jantze. Formation of free hydroxyl radicals after pentylenetetrazole-induced seizure and kindling. Brain Res, 1999; 847(2): 0347-0351.
25. George Paxinos, Charles Watson**,** The Rat Brain in Stereotaxic Coordinates. Elsevier, Amsterdam, NL, 2007.
26. Robert J. Gould, Kenneth M. Murphy, Solomon H. Snyder**.** Autoradiographic localization of

calcium channel antagonist receptors in rat brain with [3H] nitrendipine. Brain Research, 1985; 330(2): 0217−0223.

27. Hua Zhang, Yu Fu, Christophe Altier, Josef Platzer. Ilya Bezprozvanny $Ca_v1.2$ and $Ca_v1.3$ neuronal L-type calcium channels: differential targeting and signaling to pCREB. Eur J Neurosci, 2006; 23(9): 2297–2310.
28. Victoria Stiglbauer, Matej Hotka, Manuel Ruiß, Karlheinz Hilber, Stefan Boehm, Helmut Kubista $Ca_v1.3$ channels play a crucial role in the formation of paroxysmal depolarization shifts in cultured hippocampal neurons, 2017; 58 (5): 0858-0871.
29. Kevin Staley, Jennifer L. Hellier, F. Edward Dudek. Do interictal spikes drive epileptogenesis? Neuroscientist, 2005; 11(4): 0272–0276.
30. Kevin J Staley, Andrew White, F Edward Dudek. Interictal spikes: harbingers or causes of epilepsy? Neurosci Lett 2011; 497(3): 0247–0250.
31. Jesper F. Bastlund, David Berry, William P. Watson. Pharmacological and histological characterization of nicotine-kindled seizures in mice. Neuropharmacology, 2005; 48(7): 0975−0983.
32. Pierangelo Cifelli, Eleonora Palma, Cristina Roseti, Gianluca Verlengia, Michele Simonato. Changes in the sensitivity of $GABA_A$ current rundown to drug treatments in a model of temporal lobe epilepsy. Cellular Neuroscience, 2013; 7, 108.
33. JM Rigo, G Hans, L Nguyen, V Rocher, S Belachew, B Malgrange, P Leprince, G Moonen, I Selak, A Matagne, H Klitgaard. The anti-epileptic drug levetiracetam reverses the inhibition by negative allosteric modulators of neuronal GABA- and glycine-gated currents. Br J Pharmacol, 2002; 136(5): 0659-0672.
34. Stuart M Cain, Terrance P Snutch. Voltage gated calcium channels in epilepsy. In, Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV (Ed): Jasper's Basic Mechanisms of the Epilepsies 4th ed., (Bethesda (MD): National Center for Biotechnology Information), 2012.
35. Shiyi Wang, Ruslan I. Stanika, Xiaohan Wang, Jussara Hagen, Mary B. Kennedy, Gerald J. Obermair, Roger J. Colbran and Amy Lee. Densin-180 Controls the Trafficking and Signaling of L-Type Voltage-Gated $Ca_v1.2$ Ca^{2+} Channels at Excitatory Synapses. J Neurosci. 2017; 37(18): 4679-4691.
36. L Li, Y Wang, KT Ma, HJ Cheng, L Zhao, JQ Si. The effect of niflumic acid and blocker of calcium channel on the desensitization of gamma aminobutyric acid-activated current. Zhongguo Ying Yong Sheng Li Xue Za Zhi, 2013; 29(2): 0128−0132.