

Protective effect of lacosamide and topiramate treatment against Pentylenetetrazole-induced kindling and associated cognitive dysfunction in rats

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Abstract

Cognitive impairment is considered the most common comorbidity in epilepsy. The aim of the present study was to explore the effects of long-term treatment with lacosamide and topiramate on epileptogenesis and related cognitive dysfunction in an experimental model of pentylenetetrazole (PTZ)-induced kindling. The latter was induced by the repeated administration of subconvulsive dose of PTZ (40 mg/kg, s.c.) on every alternate day for 8–9 weeks. Both drugs were applied daily in a dose of 10 mg/kg p.o. 30 min before PTZ injection. To assess behavioral comorbidities all rats underwent one active and one passive avoidance tests. The results show that lacosamide significantly suppressed the progression of kindling, while the effect of topiramate was not so pronounced on seizure development. Long-term treatment with both antiepileptic drugs managed to ameliorate the kindling-associated impairment of learning and memory. Lacosamide and topiramate improved active and passive learning abilities and facilitated the formation of short- and long-term memory traces. Both drugs failed to prevent the hyperactivity associated with epilepsy.

Keywords

lacosamide, topiramate, kindling, seizures, cognition

Introduction

Epilepsy is a chronic neurological disorder characterized by the presence of recurrent unprovoked seizures due to an imbalance between cerebral excitatory and inhibitory pathways. It is one of the most common neurological conditions affecting more than 50 million people of all ages worldwide (Abdullahi and Adamu 2017). Epileptogenesis is the process by which parts of a normal healthy brain are converted into hyperexcitatory ones leading to the occurrence of recurring epileptiform events and the appearance of the first spontaneous seizure (Pitkänen et al. 2015). This process may

be triggered by genetic or different acquired factors. The latter include ischemic stroke, traumatic brain injury, brain tumors or infections, status epilepticus or febrile seizures etc. (Löscher and Brandt 2010). Moreover, epileptogenesis may continue long after the diagnosis of epilepsy and has an impact on seizure severity and frequency (Pitkänen et al. 2015). The most susceptible brain structures to the epileptogenic process are the hippocampus, piriform cortex, and amygdala which are of a great importance for cognitive functions and mood behavior (Aroniadou-Anderjaska et al. 2008).

Different animal models are used to evaluate the epileptogenic process. All of them are associated with synaptic

reorganization, astrogliosis, neurogenesis, and neuronal loss (Gupta et al. 2003). One of the models widely used to evaluate epileptogenesis and related mood and cognitive disturbances is the kindling model (Morimoto et al. 2004). The term “kindling” refers to a process in which the periodic application of an initially sub effective dose of a chemical compound or an electrical stimulus induces progressive intensification of brain excitability leading to a seizure disorder. A widely used chemoconvulsant agent to induce kindling is pentylenetetrazole (PTZ) which leads to significant neuronal loss in the CA1 and CA3 hippocampal subfields (Löscher 2011).

A large number of patients with epilepsy suffer from cognitive dysfunction and behavioural alterations such as depression, anxiety and aggressive behaviour which could be associated with morphological and functional alterations in temporal lobe structures (Marcangelo and Ovsiew 2007). Cognitive complications are very heterogeneous and affect different abilities such as language, attention, learning, memory, problem-solving skills etc. The type of deficits depends on the type and location of the underlying neuropathology (Vrinda et al. 2019). Neurocognitive impairment could be a consequence not only of the epileptogenic process but also of the applied antiepileptic treatment. By decreasing neuronal excitability antiepileptic drugs (AEDs) can affect normal neuronal function and therefore produce cognitive adverse effects (Motamedi and Meador 2004). They are most common for the old generations AEDs with a broad spectrum of action whereas newer AEDs with novel mechanisms of action or acting on specific targets have shown lower incidents of behavioural side effects (Vrinda et al. 2019). Lacosamide in a new AED which has a unique mechanism of action. It selectively enhances the slow inactivation of sodium channels and, thus, decreases neuronal hyperexcitability (Licko et al. 2013). Topiramate is a second-generation AED with multiple mechanisms of action including potentiation of γ -aminobutyric acid (GABA)-mediated chloride influx, modulation of voltage-dependent sodium and L-type calcium channels, and blocking glutamatergic α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainic acid receptors (Frisch et al. 2007). Although the anticonvulsant activity of TPM is well established, its anti-epileptogenic properties and effects on behavioral responses are still controversial. The data about the effect of lacosamide on cognitive performance and epileptogenesis are still insufficient.

The aim of the present study was to investigate the effects of lacosamide and topiramate treatment on epileptogenesis, cognitive impairment and motor performance in a rat model of PTZ-induced kindling.

Material and methods

Reagents

Lacosamide (Vimpat, USB Pharma, Brussels, Belgium); Topiramate (Topamax, Janssen-Cilag,); Pentylenetetrazole was purchased from Sigma Aldrich.

Animals

Male Wistar rats (160–180 g) were used in the study ($n = 48$). They were housed in cages and fed standard rat chow and water ad libitum. The rats were maintained at an ambient temperature of 21–25 °C with a 12/12-h dark-light cycle. This study was performed in strict accordance with the guidelines of the European Community Council directives 86/609/EEC. 0.2010/63/EC. The experimental protocol was approved by the Bulgarian Food Safety Agency (№ 50/30.06.2011) and the Ethical Committee on Human and Animal Experimentation of Medical University – Plovdiv (№ 3/26.06.2014).

Induction of kindling

Kindling was induced by the administration of PTZ at a sub convulsive dose (40 mg/kg s.c.) on every alternate day for 8–9 weeks or until all animals from the vehicle control group reached stage 5 seizures after three consecutive injections. PTZ solution was prepared freshly every day through the dissolving of PTZ in saline. After each PTZ injection, all rats were placed individually into Plexiglas cages and convulsive behavior was observed for 30 min. The intensity of seizures was scored according to modified Racine's scale as follows: Stage 0 (no response); Stage 1 (hyperactivity, restlessness, and vibrissae twitching); Stage 2 (head nodding, head clonus and myoclonic jerks); Stage 3 (unilateral or bilateral limb clonus); Stage 4 (forelimb clonic seizures); Stage 5 (generalized clonic seizures with falling) and stage 6 (death).

Experimental protocol

The rats were randomly divided into six groups ($n = 8$) as follows: 1) C-veh group (controls treated with saline 1 ml/kg p.o. and saline s.c.), 2) PTZ-veh group (rats were treated with 1 ml/kg saline p.o. and injected with PTZ 40 mg/kg s.c.), 3) LCM group (treated with lacosamide 10 mg/kg p.o.), 4) LCM-PTZ group (treated with lacosamide 10 mg/kg p.o. and PTZ 40 mg/kg s.c.), 5) TPM group (treated with topiramate 10 mg/kg p.o.) and 6) TPM-PTZ group (treated with topiramate 10 mg/kg p.o. and PTZ 40 mg/kg s.c.). Drugs were applied orally 30 min before PTZ injection. All tests for assessment of cognitive function and motor performance were started 24 h after the last PTZ injection. During this period both drugs were applied orally 30 min before sessions.

Activity cage

The activity cage apparatus (Biological Research Apparatus, Ugo Basile, Italy) was a clear plastic box 40 cm² with 40-cm high walls. A printer automatically recorded the number of movements in two categories, horizontal and vertical, captured by the infrared sensor array located on either side of the cage. The animals were individually tracked for 180 sec in each session, which was conducted under identical conditions. This testing was performed to

measure the spontaneous locomotor activity on days 1, 8, and 15 from the beginning of the behavioural tests.

Active avoidance test

The active avoidance test was performed in a shuttle box (Automatic Reflex Conditioner, UgoBasile, Italy) as previously described (Shishmanova-Doseva et al. 2018, 2019). Learning session was held for 5 consecutive days and consisted of thirty trails each. During each trail, the subject was given a conditioned light stimulus (6 sec) and sound stimulus (buzzer 670 Hz and 70 dB) which were followed within 3 sec by a foot electrical stimulation (0.4 mA) and a 12-sec pause. Retention test for memory trace was performed on day 12 from the beginning of training. The behavioural parameters measured were: number of avoidances (number of correct responses on conditioned stimuli), number of escapes (number of unconditioned responses).

Passive avoidance test

An automatic step-down device (UgoBasile, Italy) was used for passive avoidance with negative reinforcement as previously reported (Shishmanova-Doseva et al. 2018). A standard cage was used equipped with a vibrating plastic platform and the rats were placed on it at the beginning of the experiment. They trained twice with a 60-min interval between the sessions. The reaction latency was measured when the rats attempted to climb down from the platform with three or all four paws and, at the same time, they were given an electric foot – shock (0.4 mA for 10 s) through the grid. The learning sessions were conducted in two consecutive days. The short-term memory retention test was conducted 24 hours after the last learning session while the test for long-term memory was performed on day 7. The reaction latency (remaining on the platform for more than 60 sec) in 2 consecutive training sessions was considered as a measure of learning and retention.

Statistical analysis

Experimental results were presented as mean \pm S.E.M. The results were analysed using parametric tests because of normally distributed data, as assessed by the Kolmogorov-Smirnov test. The tests were repeated several times during the experiment and the results were assessed by the mixed between-within subject design of two-way-ANOVA for repeated measures where the within-subject factor was time while the Drug treatment and Epilepsy were the between-subject factors. The main effects of time, Drug treatment, Epilepsy and interaction between them were examined. For within-subject factor Mauchly's test of sphericity was applied to examine whether the assumption of sphericity was met ($p > 0.05$) or was violated ($p < 0.05$). In the second case a Greenhouse-Geisser adjustment factor, ϵ – was applied. The between-group differences were assessed by Tukey's or Games Howell post-hoc tests depending on the homogeneity of the dispersions (found by using the Levene's test). Data of seizure score severity were analyzed by one-way ANOVA. Statistically significant differences were accepted at $p \leq 0.05$. The analysis was conducted by using the SPSS (version 19) statistical package.

Results

Effect on seizure severity score

All animals from each kindled group survived till the end of the whole experiment. In the PTZ-veh group repeated administration of PTZ at a subconvulsive dose of 40 mg/kg s.c. on every second day (for 63 days) 32 injections in total led to an increased convulsive activity presented with generalized tonic-clonic seizures (Fig. 1). Pre-treatment with lacosamide significantly suppressed the progression of kindling evidenced by the decrease in seizure

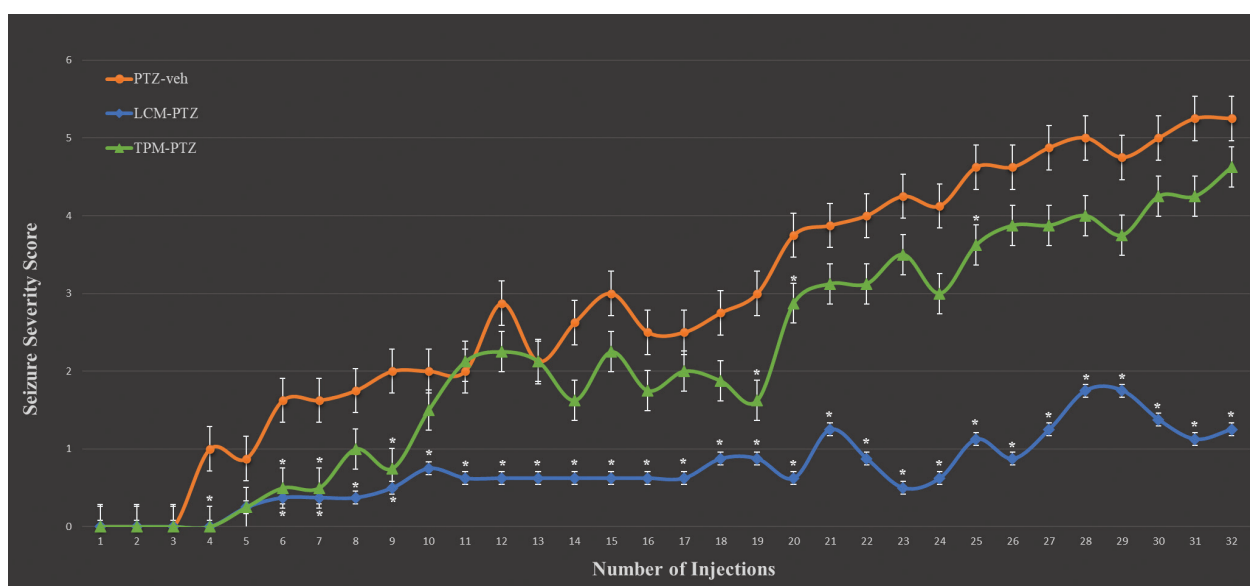


Figure 1. Effect of lacosamide (LCM) and topiramate (TPM) treatment on seizure severity score in a PTZ-kindling model. * $p < 0.05$ compared to the PTZ-veh group.

severity score when compared to the PTZ-veh group from 4th till last PTZ-injection ($p < 0.05$). Topiramate treatment had a tendency to decrease the seizure severity score and only during the 6th, 7th, 9th and 25th injections the result was significant.

Activity cage

Two-way repeated-measures ANOVA revealed a significant main effect of time on the number of horizontal movements [$F(2, 88) = 29.818, p < 0.001$]. The post-hoc test showed that the PTZ-veh group had a significantly

higher number of movements in comparison with the C-veh group during the 2nd ($p < 0.01$) and 3rd ($p < 0.05$) time of testing. Analysis of variance demonstrated that the LCM-PTZ group had a significantly higher number of horizontal movements compared to the LCM-group during the 1st ($p < 0.05$), 2nd ($p < 0.01$) and 3rd ($p < 0.001$) training session (Fig. 2A). Increased number of horizontal movements was also observed for the TPM-PTZ animals compared to the TPM group during 2nd ($p < 0.05$) and 3rd ($p < 0.01$) training session.

On the number of vertical movements a significant main effect of time [$F(2, 88) = 4.682, p < 0.05$] and time

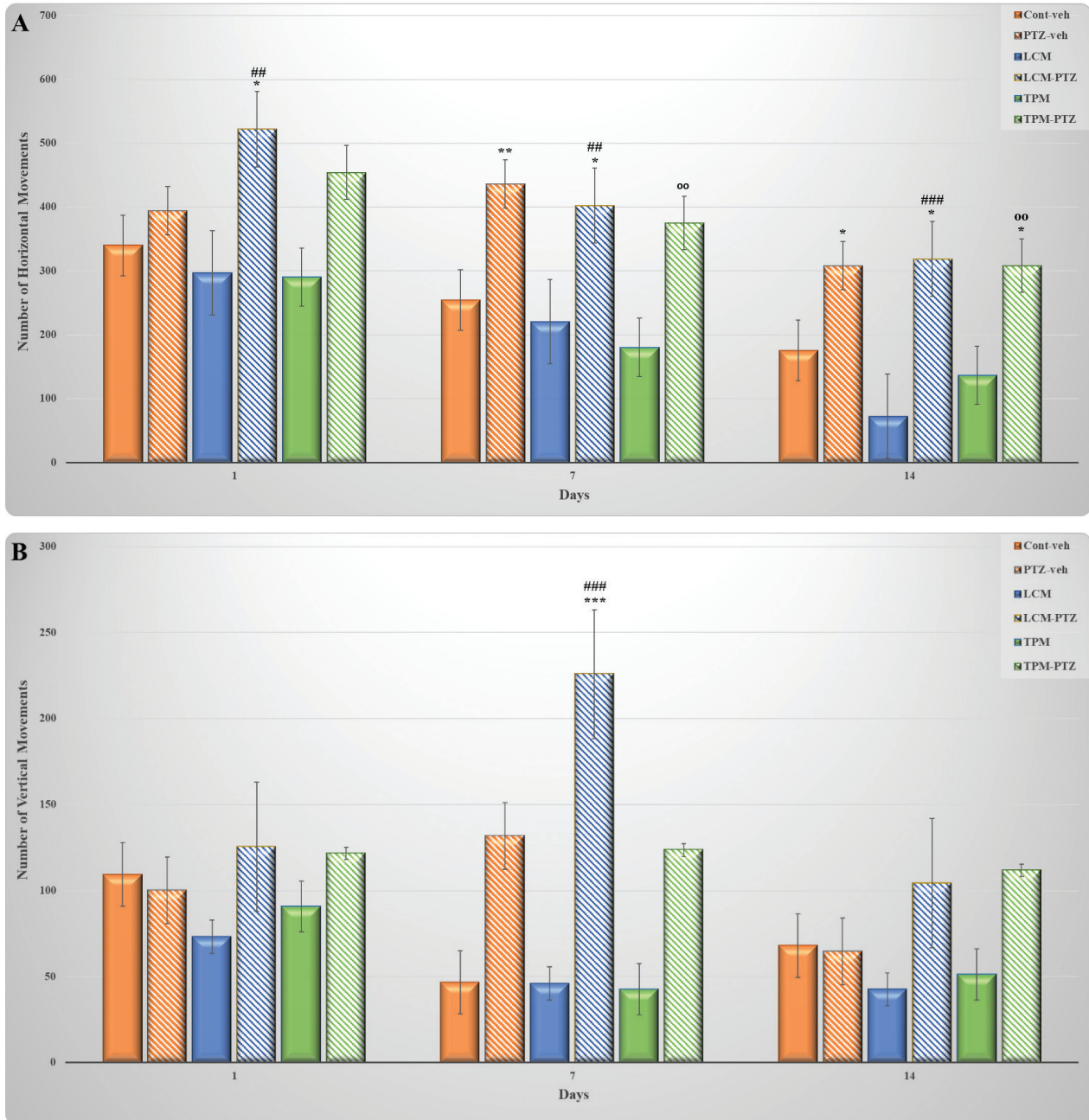


Figure 2. A. Effect of lacosamide (LCM) and topiramate (TPM) treatment on the number of horizontal movements in a PTZ-kindling model. * $p < 0.05$, ** $p < 0.01$ compared to the C-veh group; ## $p < 0.01$, ### $p < 0.001$ compared to the LCM group; oo $p < 0.01$ compared to the TPM group. **B.** Effect of lacosamide (LCM) and topiramate (TPM) treatment on the number of vertical movements in a PTZ-kindling model. *** $p < 0.001$ compared to the C-veh group; ### $p < 0.001$ compared to the LCM group.

× Epilepsy interaction [$F(2, 88) = 9.673, p < 0.001$] were observed. The post-hoc test showed that the PTZ-veh group had a tendency for a higher number of movements compared to the C-veh group ($p = 0.070$) but lower than that of the LCM-PTZ animals ($p < 0.05$) during 2nd training session. Moreover, the LCM-PTZ rats increased the number of movements compared to the C-veh and LCM groups, $p < 0.001$ (Fig. 2B).

Active avoidance test

Two-way repeated-measures ANOVA revealed a significant main effect of the time [$F(5, 220) = 54.259, p < 0.001$] as well as the time × Drug treatment × Epilepsy interaction [$F(5, 220) = 11.416, p = 0.001$] on the number of avoidances. Tukey's post-hoc test showed that the PTZ-veh group had a significantly lower number of avoidances than had the C-veh group during all days of the learning session ($p < 0.01, \text{resp.}$) and on day 12 ($p < 0.001$) (Fig. 3). The LCM-PTZ group increased significantly the number of conditioned stimulus responses compared to the PTZ-veh group on days 3 ($p < 0.01$), 4 ($p = 0.01$) and 5 ($p < 0.01$) as well as on the retest ($p < 0.05$) while the TPM-PTZ group led to this effect only on day 5 ($p < 0.01$) and had a tendency to reach it on day 12 ($p = 0.084$). Both groups LCM-veh and TPM-veh decreased the number of avoidances compared to the control animals from day 2 of the learning session till day 5 ($p < 0.05, \text{resp.}$) and on the memory retention test ($p < 0.001$).

Two-way ANOVA for repeated-measures showed that there was only a significant main effect of the time

factor [$F(5, 220) = 5.411, p < 0.001$] on the number of escapes. The post-hoc analysis showed that the PTZ-veh group had a significantly lower number of escapes in comparison with the C-veh group during days 3 ($p < 0.05$), 4 ($p = 0.001$) and 5 ($p < 0.05$) of the learning session and on day 12 ($p < 0.05$) (Fig. 4). The LCM-PTZ group had a significantly higher number of unconditioned responses on days 3 ($p < 0.01$), 4 ($p < 0.01$) and 5 ($p < 0.05$) and on the memory retention test ($p < 0.01$) in comparison with the PTZ-veh animals. The TPM-PTZ group significantly increased the number of escapes only on day 4 ($p < 0.01$) of the learning session and on day 12 ($p = 0.05$).

Passive avoidance test

Two-way ANOVA for repeated measures revealed a significant main effect of the time [$F(3, 132) = 14.222, p < 0.001$], and a significant interaction between time × Drug treatment × Epilepsy [$F(3, 132) = 2.376, p = 0.05$] on the step-down latency time. The post-hoc test confirmed that the PTZ-veh rats had a shorter latency reaction than that of the C-veh animals on day 2 of the learning session ($p < 0.05$) and during the short-term and long-term memory retention tests ($p < 0.001, \text{resp.}$) (Fig. 5). The LCM-PTZ group increased the latency time in comparison with the PTZ-veh rats during day 2 of the learning session ($p < 0.05$) while during the short-term ($p < 0.001, \text{resp.}$) and long-term ($p < 0.001, \text{resp.}$) memory retention tests both groups LCM-PTZ and TPM-PTZ managed to stay longer on the platform compared to the PTZ-veh group.

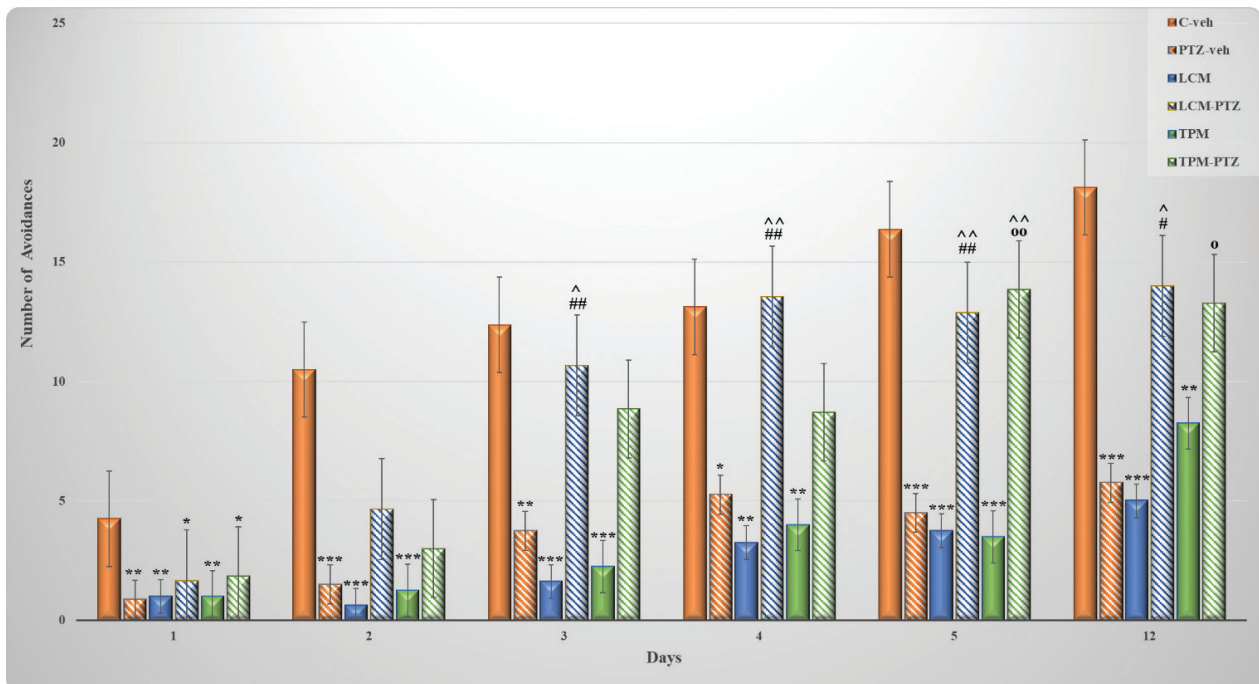


Figure 3. Effect of lacosamide (LCM) and topiramate (TPM) treatment on the number of avoidances in a PTZ-kindling model. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared to the C-veh group; ^ $p < 0.05$, ^^ $p < 0.01$ compared to the PTZ-veh group; # $p < 0.05$, ## $p < 0.01$ compared to the LCM group; ° $p < 0.05$, °° $p < 0.01$ compared to the TPM group.

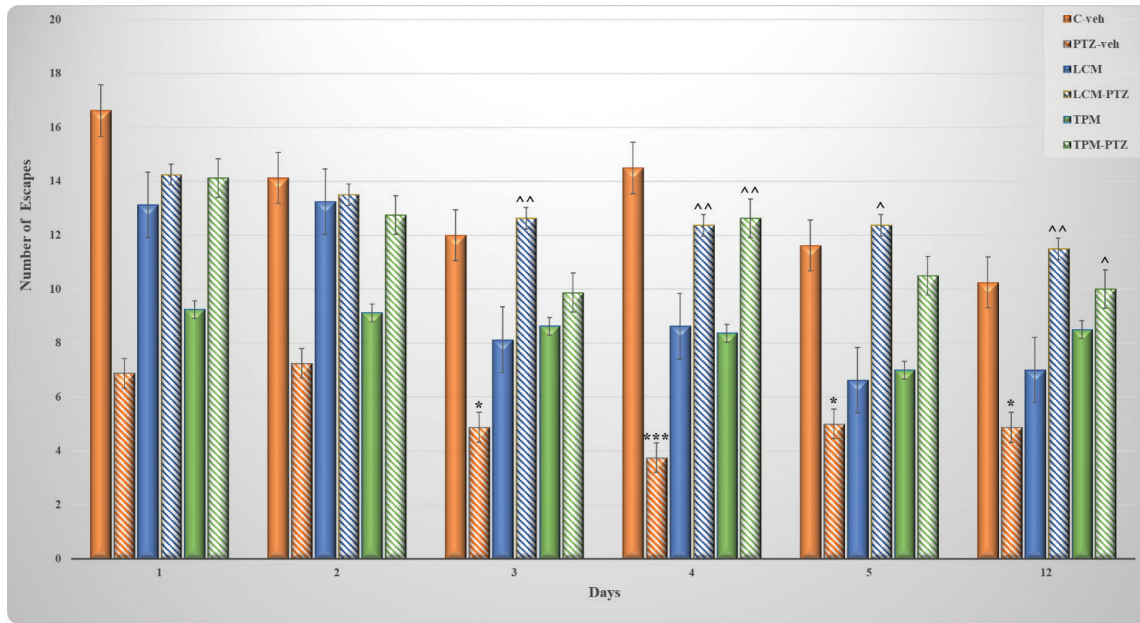


Figure 4. Effect of lacosamide (LCM) and topiramate (TPM) treatment on the number of escapes in a PTZ-kindling model. * $p < 0.05$, *** $p < 0.001$ compared to the C-veh group; ^ $p < 0.05$, ^^ $p < 0.01$ compared to the PTZ-veh group.

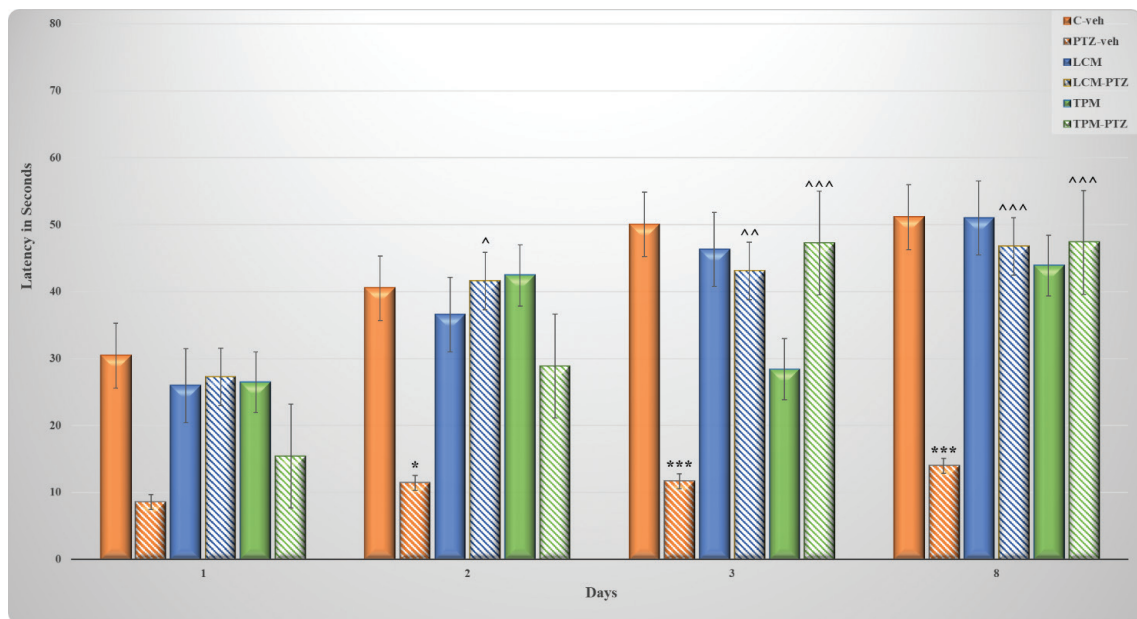


Figure 5. Effect of lacosamide (LCM) and topiramate (TPM) treatment on the step-down latency time (sec) in a PTZ-kindling model. * $p < 0.05$, *** $p < 0.001$ compared to the C-veh group; ^ $p < 0.05$, ^^ $p < 0.01$, ^^ $p < 0.001$ compared to the PTZ-veh group.

Discussion

PTZ-induced kindling is a widely applied experimental model used for the understanding of epileptogenesis, seizure mechanisms, and associated behavioral comorbidities. It is based on repeated subconvulsant brain stimulation which leads with time to the appearance of tonic-clonic seizures (Zhao et al. 2014). In accordance with other authors, in the present study, we found that repeated administration of subconvulsive doses of PTZ for 63 days (32 injections in total) led to the development of kindling in the control animals evidenced by the presence

of convulsions with seizure severity score 5 during three consecutive applications (Agarwal et al. 2011).

In our study, only lacosamide managed to retard the kindling-induced epileptogenesis observed by the reduction of seizure severity score compared to control animals while topiramate failed to fully suppress the development of kindling. Our results regarding lacosamide are in agreement with previous researchers who have found that the drug is effective in the suppression of amygdala kindling at doses 10 and 30 mg/kg while the lowest dose of 3 mg/kg was ineffective (Brandt et al. 2006). In addition, there is data that lacosamide reduces the maximal intensity of PTZ-induced

seizures and produces modulatory effects on the GABAergic system (Gáll et al. 2020). The results from the current study complete our previous result where we found that lacosamide at a dose of 30 mg/kg has a pronounced antiepileptogenic effect in a model of temporal lobe epilepsy induced by a single injection of pilocarpine (Shishmanova-Doseva et al. 2021). Data about the effects of topiramate in different kindling models are still contradictory. Topiramate treatment with a higher than our dose of 80 mg/kg decreases the seizure duration and after-discharge duration in electrical kindling of the basolateral amygdala (Chen et al. 2009) while the drug (200 mg/kg) leads to age-dependent disease-modifying effects under conditions of rapid kindling but failed to block fully epileptogenesis (Mazarati et al. 2007). These data complete our previous research where we found that topiramate has a pronounced antiepileptogenic effect in a model of TLE but the dose was much higher (80 mg/kg) than the one applied in the current experiment (Shishmanova-Doseva et al. 2022).

PTZ-kindling model also provides opportunities to study the progression of cognitive dysfunction associated with epilepsy. Impairment of learning and memory is one of the most frequently observed comorbidities of epilepsy (Mishra and Goel 2012, 2019). In the current experiment, epileptic animals had impaired active and passive learning abilities, as well as difficulties in the formation of short- and long-term memory traces. These results are in agreement with previous studies which show that PTZ-kindling is represented by loss of spatial and recognition memory and by pronounced impairment of learning and memory consolidation (Mishra and Goel 2012; Ahmadi et al. 2017). All these negative effects on cognition are associated with a significant neuronal loss in the hippocampus, increased acetylcholine esterase activity, and modulation of serotonergic receptors (Siddharth et al. 2013; Mishra and Goel 2015, 2019; Taiwe et al. 2015). Moreover, recent evidence shows that excessive production of reactive oxygen species and subsequent neuroinflammation play a crucial role not only in the development of epileptogenesis but also have a determining role in the pathogenesis of observed behavior deficits (Ravizza and Vezzani 2018; Kitov et al. 2020; Singh et al. 2021).

In our experiment, we found that both drugs produced different effects in epileptic and naïve rats. Lacosamide and topiramate affected adversely cognitive functions in naïve an-

imals while in the kindled rats they managed to restore them. Both drugs led to improved cognitive performance during epilepsy by improving active and passive learning abilities. Moreover, they facilitated the formation of short- and long term memory traces in both tests - passive and active ones. Lacosamide and topiramate treatment failed to suppress the hyperactivity which was observed with increased number of horizontal and vertical movements in the epileptic animals.

Lacosamide is a new AED and data about its effects on cognitive performance is still insufficient. Our results are consistent with other researchers who have found that the drug improves cognitive performance by decreasing oxidative stress in different brain structures such as the cerebellum and cortex (Abraham et al. 2014). Moreover, a recent study shows that lacosamide has a significant neuroprotective effect against oxidative damage, bioenergetics dysfunction, and DNA damage in a model of PTZ-kindling (Lazzarotto et al. 2021).

Topiramate is a widely used in the clinical practice AED which effects on cognitive functions are still controversial. Our data is in agreement with other studies showing that topiramate improve spatial learning and memory in an experimental model of postoperative cognitive dysfunction (Su et al. 2019). Its neuroprotective effects are related with reduced expression of caspase-3 in the hippocampus, and decreased neuroinflammation as well (Chen et al. 2009; Ye et al. 2014; Su et al. 2019). Contrary, our results differ from other studies showing that topiramate can cause cognitive problems in epileptic patients and some of these effects are related to its pro-oxidant properties (Donegan et al. 2015; Sarangi et al. 2016).

Conclusion

The results from the present study demonstrate that repeated administration of lacosamide managed to mitigate seizure development and produce antiepileptogenic effect in PTZ-kindled rats. Repeated treatment with low doses of either lacosamide or topiramate managed to overcome the cognitive dysfunction associated with epilepsy through improving of passive and active learning abilities and facilitating memory consolidation.

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