folia medica

Folia Medica 62(4): 723-9
DOI: 10.3897/folmed.62.e51473

Original Article

The Effect of Chronic Treatment with Lacosamide and Topiramate on Cognitive Functions and Impaired Emotional Responses in a Pilocarpine-induced Post-status Epilepticus Rat Model

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Received: 25 Feb 2020 ♦ **Accepted:** 18 May 2020 ♦ **Published:** 31 Dec 2020

Citation: Shishmanova-Doseva M, Tchekalarova J, Nenchovska Z, Ivanova N, Georgieva K, Peychev L. The effect of chronic treatment with lacosamide and topiramate on cognitive functions and impaired emotional responses in a pilocarpine-induced post-status epilepticus rat model. Folia Med (Plovdiv) 2020;62(4):723-9. doi: 10.3897/folmed.62.e51473.

Abstract

Introduction: Epilepsy and antiepileptic drugs can affect negatively the cognitive abilities of patients.

Aim: The present study aimed to evaluate the effect of topiramate (TPM) and lacosamide (LCM) on the emotional and cognitive responses in naive animals and in animals with pilocarpine-induced status epilepticus.

Materials and methods: Male Wistar rats were randomly divided into 6 groups and status epilepticus was evoked in half of them by a single i.p. administration of pilocarpine (Pilo) (320 mg/kg): Pilo-veh, Pilo-TPM (80 mg/kg) and Pilo-LCM (30 mg/kg). Matched naive rats were treated with the same doses as follows: C-veh, C-TPM, and C-LCM. In a step-down passive avoidance test, the learning session was held for one day, the early retention test was conducted on day 2, and the long-term memory test - on day 7. Motor activity and anxiety were evaluated in an open field test.

Results: The Pilo-TPM and Pilo-LCM groups increased the time spent on the platform compared to Pilo-veh animals while the C-LCM animals decreased the time compared to C-veh animals during short- and long-term memory retention tests. TPM and LCM exerted an anxiolytic effect in naive rats. The two antiepileptic drugs were unable to alleviate the hyperactivity, but they alleviated the impulsivity associated with decreased anxiety level in epileptic rats.

Conclusions: Our findings suggest that LCM and TPM have a beneficial effect on cognition both in naive and epileptic rats. While the two antiepileptic drugs can produce an anxiolytic effect in naive rats, they alleviate the impulsivity after pilocarpine treatment.

Keywords

anxiety, cognition, epilepsy, lacosamide, topiramate

INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by development of spontaneous recurring seizures. Temporal lobe epilepsy (TLE) is the most common form with the highest frequency of drug-resistant patients.[1,2] Epilepsy is often accompanied by disturbed emotional status and cognitive functions[3] that could be associated with impaired amygdala-hippocampal complex function, hippocampal neuronal loss, decreased neuronal density and/or brain lesions.[4,5]

Over the last ten years, there has been a breakthrough in the design and development of many new antiepileptic drugs (AEDs) such as levetiracetam, brivaracetam, lacosamide (LCM), perampanel, etc, some of them having a unique mechanism of action.[6] It is still not entirely clear whether they have only symptomatic effects or can influence the underlying processes of epileptogenesis. Many AEDs, especially the older ones, can produce a high rate of serious side effects additionally or deteriorate existing ones as cognitive and mood decline.[7] Lacosamide is a new third-generation AED that has been approved as monotherapy or adjunctive therapy in adults with partial onset seizures.[8] LCM has a unique mechanism of action through promoting the slow inactivation of sodium channels to more hyperpolarized potentials[9], thus likely to produce 'mood-stabilizing' effect like some other AEDs such as carbamazepine, lamotrigine, and valproate which affect only the fast inactivation of these channels.[10] The effect of LCM on cognitive functions and behaviour is still not well elucidated and data are controversial.

Topiramate (TPM) is a widely used broad-spectrum AED with multiple mechanisms of action, which includes potentiation of GABAergic neurotransmission, inhibition of AMPA glutamate type receptors, voltage-gated sodium and calcium channels.[6] TPM is effective in both partial and generalized seizures and has some additional indications for the treatment of migraine, obesity, and bipolar disorder.[11] There is evidence that TPM impairs cognitive functions by influencing negatively working and long-term memory, slowing psychomotor reaction times[6], although other studies have shown that TPM monotherapy is associated with better cognitive performance than add-on therapy and lack of negative effect on executive functions and learning.[12] Animal models of epilepsy as the pilocarpine model of acquired TLE are widely used to investigate the relationship between epilepsy, behavioural alterations and the effect of applied drug therapy. In this model, the changed excitability of the neurons causes brain damage and neurochemical alterations in experimental animals which are very similar to complexity to those observed in the human brain.[13]

AIM

In the present study, we evaluated the effect of chronic treatment with either LCM or TPM on changed cognitive and emotional responses in a pilocarpine-induced post-status epilepticus (SE) rat model of TLE.

MATERIALS AND METHODS

Animals and grouping

A total of 83 mature male Wistar rats with body weights ranging from 150 to 180 g were obtained from the Animal Center of the Medical University, Plovdiv. Rats were housed in plastic cages (5-6 per cage) under 12/12h light/dark cycle and controlled temperature (22±1°C). The animals were allowed to eat and drink *ad libitum*. This study was performed in strict accordance with the guidelines of the European Community Council directives 86/609/EEC. 0.2010/63/EC. Experiments were approved by the Bulgarian Food Safety Agency (No 206/01.10.2018) and by the Ethics Committee on Human and Animal Experimentation of Medical University of Plovdiv.

The rats were randomly divided into 6 groups (n=12 in each group): group 1 – controls (C-veh) treated with saline (1 ml/kg per os); group 2 – the epilepsy group (Pilo-veh) treated with saline (1 ml/kg per os) and with induced SE with pilocarpine 320 mg/kg i.p.; group 3 – the topiramate group (C-TPM), treated with topiramate 80 mg/kg per os; group 4 – epilepsy and topiramate (Pilo-TPM), treated with topiramate 80 mg/kg per os and with induced SE with pilocarpine 320 mg/kg i.p; group 5 – the lacosamide group (C-LCM), treated with lacosamide 30 mg/kg per os, and group 6 – epilepsy and lacosamide (Pilo-LCM), treated with lacosamide 30 mg/kg per os and with induced SE with pilocarpine 320 mg/kg i.p.

Induction of status epilepticus

Rats from the 3 groups with TLE were injected with pilocarpine hydrochloride 320 mg/kg i.p. (Sigma Aldrich), 30 min after administering scopolamine methyl nitrate 1 mg/kg i.p. (Sigma Aldrich), applied to reduce the peripheral cholinergic effects. After the Pilo administration, all animals were placed in separate cages to observe their behaviour, recording the latency to first seizure, the severity of motor SE and the rate of survival animals within 2 hours. The appearance of clonic motor seizures at stage 4/5 according to the Racine scale was considered to be the beginning of the SE.[14] Eleven animals died during the induction of SE. After 2 hours of epilepsy, diazepam (Sopharma, Bulgaria) at a dose of 10 mg/kg was injected intraperitoneally to relieve convulsions and reduce mortality. Approximately 3 hours after the Pilo injection, the rats were given subcutaneously 0.9% of NaCl and glucose in equal volumes (up to 3% of body weight) to restore the volume lost. The two AEDs, TPM (Topamax, Janssen-Cilag, Slovenia) and LCM (Vimpat, USB Pharma, Brussels, Belgium), were administered orally by gavage over a period of 2 months. Matched groups

were treated with vehicle. Eight weeks after Pilo injection, all rats were subjected to behavioural tests, including the passive avoidance test and the open field test. During all these weeks, all animals from the six groups received the drugs and vehicle accordingly.

Behaviour tests

Passive avoidance step-down test

The rats were placed individually in an automatic step-down device (UgoBasile, Italy) for passive avoidance with negative reinforcement, as previously reported.[15] A test chamber (14 cm×33 cm) was used equipped with a vibrating plastic platform (14 cm×19 cm) and the rats were placed on it at the beginning of experiment. They were trained twice at 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 session was conducted in one day, 24 hours later was the test for early retention while the test for long-term memory was performed on day 7. The reaction latency (remaining on the platform for 60 sec) was considered as a measure of learning and retention.

Open field test

The open field (OF) test was used to elucidate the emotional responses, including locomotor activity and anxiety. The test was executed as described in our previous report.[16] In brief, the tested rat was placed at the central zone of the grey polystyrene box (100×100×60 cm). The following parameters were measured: the distance travelled in the periphery (cm), distance and time (sec) in the central aversive zone for a 5-min period. The automatic video tracking system (SMART PanLab software, Harvard Apparatus, USA) was used for measurement.

Statistical analysis

Experimental results were presented as mean ± SEM. After testing for assumptions of normality of data distribution and homogeneity of variance, two-way ANOVA with factors epilepsy and treatment was used. Post-hoc comparisons via the Bonferroni test in case of justification was used. If data was not normally distributed, Games-Howell post-hoc tests depending on the homogeneity of the dispersions (found by using the Levene's test) was applied. Statistically significant differences were accepted at $p \leq 0.05$. Analysis was conducted using the SigmaStat® (version 11.0.) statistical package.

RESULTS

Passive-avoidance step-down test

Two-way ANOVA revealed a significant main effect of the TPM treatment [$F(1, 44) = 12.282$, $p=0.001$] and interaction between Epilepsy × TPM treatment [$F(1, 44) = 10.291$, $p< 0.01$] without any effect of Epilepsy factor on the learning session on day 1 in the step-down test. The Games-Howell post-hoc test demonstrated that the Pilo-veh group had a shorter latency reaction than C-veh animals ($p<0.05$) while both groups treated with topiramate C-TPM and Pilo-TPM had a longer time to stay on the platform compared to Pilo-veh animals ($p<0.05$ and $p<0.001$, respectively) **(Table 1)**.

Two-way ANOVA demonstrated a significant main interaction between Epilepsy × LCM treatment [$F(1, 44) = 26.592$, $p=0.001$] without any effect of LCM factor on the learning session at day 1. The Games-Howell *post-hoc* test demonstrated that the C-LCM group had a significantly shorter latency reaction than C-veh animals ($p<0.05$) while the Pilo-LCM group increased the time spent on the platform compared to the Pilo-veh animals ($p=0.001$) **(Table 1)**.

In the early retention test, two-way ANOVA demonstrated a significant main effect of TPM treatment [$F(1, 44) = 5.001$, $p<0.05$], Epilepsy factor [$F(1, 44) = 5.105$, $p<0.05$] and interaction between them [$F(1, 44) = 9.456$, $p<0.01$]. The Games-Howell *post-hoc* test revealed that Pilo-veh group had a shorter latency reaction than C-veh group ($p< 0.01$). Longer time for staying on the platform was demonstrated by both groups treated with TPM, C-TPM and Pilo-TPM, in comparison with the Pilo-veh group ($p<0.05$ and $p<0.01$, respectively) **(Table 1)**.

Table 1. Effect of topiramate (TPM) and lacosamide (LCM) on the latency time (sec) during learning and memory in step-down passive avoidance test

Groups	C-veh (Saline)	C-TPM (80 mg/kg)	C–LCM (30 mg/kg)	Pilo-veh (320 mg/kg)	Pilo-TPM (80 mg/kg)	Pilo-LCM (30 mg/kg)
Day 1	21.3±3.5 s	22.4±4.4 s°	12.5±1.3 s	7.1±0.9 s**	32.0±4.8 s°°°	19.5±1.5 s
Day 2	39.6±4.2 s	35.7±5.3 s°	20.3±3.1 s*∞	14.6±2.4 s***	39.5±6.0 s°°	37.1±3.8 s°°
Day 7	47.5±3.7 s	43.8±4.3 s°°	24.2±5.1 s**∞	21.7±2.6 s***	48.8±4.9 s°°°	51.9±3.0 s°°°

*$p<0.05$, **$p<0.01$, ***$p<0.001$ – in comparison with the saline group; °$p<0.05$, °°$p<0.01$ °°°$p< 0.001$ – in comparison with the Pilo-veh group; ∞$p<0.001$ in comparison with the Pilo-LCM group.

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A significant main interaction was demonstrated between Epilepsy × LCM treatment [$F(1, 44) = 36.636$, $p<0.001$] during the early memory retention test. The Bonferroni *post-hoc* test revealed that the C-LCM group had a shorter latency reaction than C-veh group ($p<0.01$) while Pilo-LCM group had a better performance than that that of the Pilo-veh and C-LCM group ($p<0.001$ and $p<0.01$, respectively) **(Table 1)**.

During the long-term memory retention test, two-way ANOVA showed a significant main effect of TPM treatment [$F(1, 44) = 8.836$, $p<0.01$], Epilepsy factor [$F(1, 44) = 7.00$, $p<0.05$] and interaction between both factors [$F(1, 44) = 15.286$, $p<0.001$]. Analysis of variance demonstrated a significant decrease in the time spent on the platform for the Pilo-veh group compared to the C-veh group ($p<0.001$). Both groups treated with TPM Pilo-TPM and C-TPM increased the latency time in the step-down test compared to Pilo-veh animals ($p<0.001$) **(Table 1)**.

A significant main interaction was revealed by two-way ANOVA between Epilepsy × LCM treatment [$F(1, 44) = 52.352$, $p<0.001$] during the long term memory retention test. The Bonferroni *post-hoc* test showed that Pilo-LCM increased the latency time in the step-down test compared to the Pilo-veh animals ($p<0.001$). A significant decrease in the time spent on the platform was detected for the C-LCM group in comparison with Pilo-LCM and C-veh ones ($p<0.001$) **(Table 1)**.

Open field test

For TPM treatment, two-way ANOVA revealed a significant main effect of Epilepsy [$F(1, 44) = 19.024$, $p<0.001$] without Epilepsy × Treatment interaction ($p>0.05$) on the distance travelled in the peripheral zone of the OF apparatus. The *post-hoc* test demonstrated that the epileptic group treated with vehicle (Pilo-veh) displayed increased distance in the periphery compared to the control group (C-veh) ($p=0.0067$) while TPM was unable to correct epilepsy-induced response ($p=0.0105$ Pilo-TPM compared to C-veh group; $p=0.046$ Pilo-TPM compared to C-TPM group) **(Fig. 1A)**.

For the parameters for measurement anxiety, a main Epilepsy effect [$F(1, 44) = 7.436$, $p=0.009$] with Epilepsy × Treatment interaction [$F(1, 44) = 17.793$, $p<0.001$] was detected for the distance travelled in the aversive central zone, as well as Epilepsy × Treatment interaction [$F(1, 44) = 18.523$, $p<0.001$] for the time spent in the center for chronic treatment with TPM. Pilocarpine enhanced the impulsive-like behaviour in vehicle-treated group (The Games-Howell *post-hoc* test: distance in center: $p<0.001$ Pilo-veh compared to C-veh group; time in center: $p=0.0002$) The chronic treatment with TPM produced an anxiolytic effect in naive controls with increased distance travelled ($p<0.001$ C-TPM compared to compared to C-veh) and time spent in the center ($p=0.0024$ C-TPM compared to compared to C-veh) **(Fig. 1 B, C)**. The treatment with TPM alleviated the epilepsy-induced increased impulsive-like behaviour (distance in the center: $p=0.0019$ Pilo-TPM com-

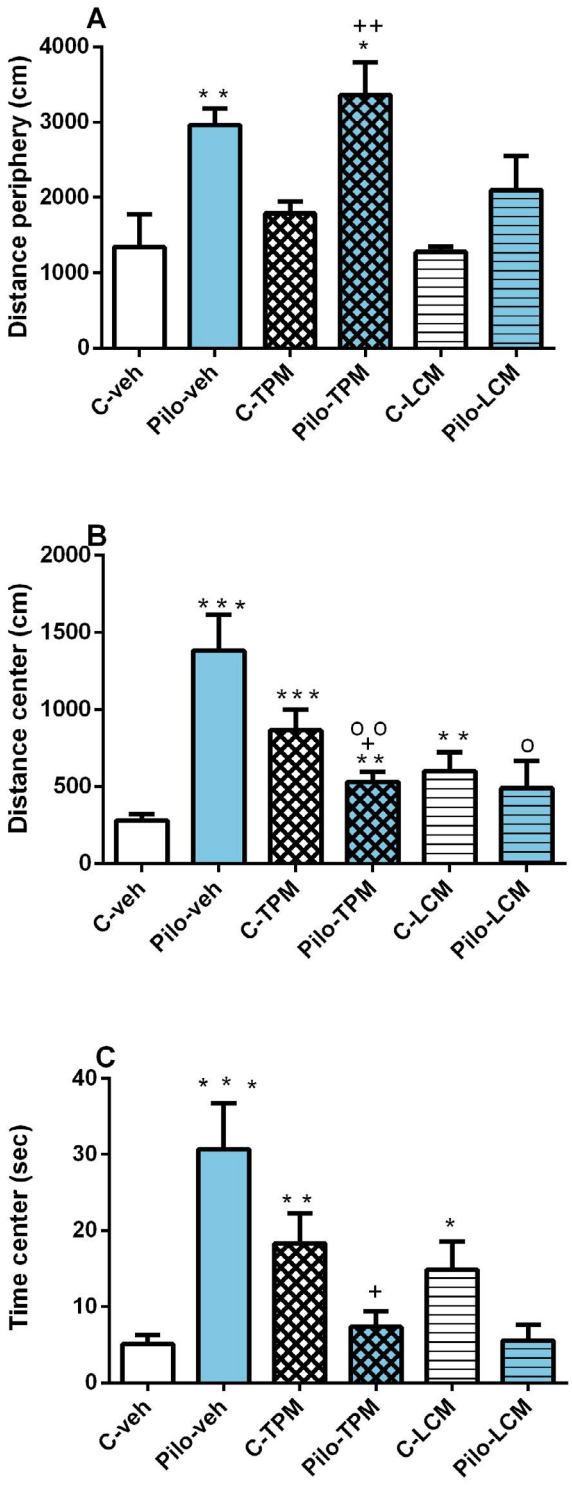

Figure 1. Effect of topiramate (TPM) and lacosamide (CLM) on distance in periphery (cm) (**A**), distance in center (cm) (**B**) and Time in center (sec) (**C**) in naive rats treated with vehicle (C-veh), TPM (C- TPM) and LCM (C-LCM) and epileptic rats treated with vehicle (Pilo-veh), TPM (Pilo-TPM) and LCM (Pilo-LCM). $^{*}p<0.05$, $^{**}p<0.01$; $^{***}p<0.001$ in comparison with the vehicle; $^{o}p < 0.05$, $^{oo}p<0.01$ in comparison with the Pilo-veh group; $^{+}p<0.05$, $^{++}p<0.01$ in comparison with the C-TPM group.

pared to C-veh; p= 0.0034 Pilo-TPM compared to C-TPM; p=0.0053 Pilo-TPM compared to Pilo-veh group; time in center: p=0.0346 Pilo-TPM compared to C-TPM).

For the LCM treatment, two-way ANOVA revealed a significant main effect of Epilepsy factor [$F(1, 44) = 11.624$, p=0.002] on the distance travelled in the peripheral zone of the OF. The long-term LCM administration during epileptogenesis showed a tendency to alleviate the epilepsy-induced increased motor activity **(Fig. 1A)**. A significant main effect of Epilepsy [$F(1, 44) = 11.043$, p=0.002], Treatment [$F(1, 44) = 5.621$, p=0.022] as well as Epilepsy × Treatment interaction [$F(1, 44) = 7.729$, $p<0.01$] was shown for the distance travelled in the central zone. The chronic treatment with LCM in the control group demonstrated an anxiolytic effect (p=0.003 C-LCM compared to C-veh group; p=0.024 for distance and time in the center, respectively) **(Fig. 1 B, C)**. In epileptic rats, chronic LCM treatment mitigated impulsivity with decreasing to control level the distance travelled in the aversive central zone (p=0.04 Pilo-LCM compared to Pilo-veh group).

DISCUSSION

The findings in this study suggest that TPM can influence some domains of cognitive performance positively via improving learning and memory abilities especially in epileptic rats. Although experimental and clinical data considering the effect of TPM on neuropsychological factors is very controversial, our findings support the suggestion that TPM does not affect attention[17] while it improves spatial learning and memory in rats with postoperative cognitive dysfunction due to suppressed neuronal apoptosis in the hippocampal tissues and decreased level of expression of tumor-necrosis-factor, interleukin-1β, and interleukin-6.[18] However, our results appear to differ from clinical findings, which suggests that TPM may produce a relatively more cognitive impairment and/or psychomotor slowing as well as language problems than other AEDs.[19]

In the present study, we have demonstrated that LCM can produce different effects on inhibitory avoidance performance in intact rats and pilocarpine-treated rats. LCM adversely affected passive learning as well as the formation of short- and long-term memory traces in naive rats which is consistent with our previous studies[15,20] while in the epileptic animals, LCM improved the long-term memory performance suggesting that these AEDs exert a disease-modifying effect. As a new AED, there is little evidence for the side effects of LCM on different cognitive domains.[21] In agreement with our results, experimental and clinical data have shown that LCM decreased attention in intact rats[22] and cause cognitive deficits in healthy individuals.[23] Our data are consistent with recently published evidence suggesting a favourable cognitive profile of the treated with LCM epileptic patients who significantly increase their EpiTrack scores[8], a validated system for cognitive assessments under AED therapy.[24] The observed effects of LCM could be due to anti-ictogenic properties accompanied by decreased interictal spike rates and high-frequency oscillations in the hippocampus of rats with TLE.[25] LCM exhibits a cognitive improving effect similar to those of lamotrigine and levetiracetam and better one than carbamazepine and topiramate[21,24] although there is an analysis from randomized controlled trials suggesting a dose-dependent increase in memory problems in patients with epilepsy.[26]

The relationship between epilepsy and psychiatric disorders is well established, but the effect of the AEDs on these comorbidities is not well elucidated. Behaviour effects from the OF which we applied in the present study are used to measure locomotion and anxiety-like behaviour. We found that the two drugs produce an anxiolytic effect in naive rats as they increased the travelled distance and the time spent in the central zone, while in epileptic animals, these AEDs alleviated the impulsive behaviour, which is reported earlier in models of TLE, induced by kainate[16,27] and pilocarpine.[28,29] Hyperactivity and decreased anxiety level in pilocarpine-treated rats compared to naive rats is suggested to be associated with a disinhibited hyperactive state probably as a result of disrupted interconnections of important limbic structure involved in the regulation of fear reactions and misevaluation of a threat such as the amygdala, ventral hippocampus and the entorhinal cortex.[30,31] Our results are in accordance with other studies where TPM alleviated the anxiety levels in naive rats[32] while in corneal-kindled mice a favourable effect was not observed.[33] The positive effect is possibly due to the elevation of γ-aminobutyric levels and inhibition of AMPA receptors in the brain by TPM. Our findings are consistent with prior research which showed that LCM improved symptoms of anxiety and decreased the negative mood symptoms states in naive rats and this positive effect was observed in epileptic patients as well.[34,35]

CONCLUSIONS

The present findings reveal that chronic treatment with TPM and LCM improves cognitive performance through amelioration of passive learning and the formation of short- and long-term memory traces. While the two AEDs exert an anxiolytic effect in naive rats, they mitigate the impulsive response in rats with epilepsy.

Acknowledgments

This research was supported by Medical University – Plovdiv, Bulgaria (Grant No. 6/2018).

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Влияние хронического лечения лакозамидом и топираматом на когнитивные функции и ослабленные эмоциональные реакции в модели постстатусного эпилептического ответа на крысах, вызванной пилокарпином

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Дата получения: 25 февраля 2020 ♦ **Дата приемки:** 18 мая 2020 ♦ **Дата публикации:** 31 декабря 2020

Образец цитирования: Shishmanova-Doseva M, Tchekalarova J, Nenchovska Z, Ivanova N, Georgieva K, Peychev L. The effect of chronic treatment with lacosamide and topiramate on cognitive functions and impaired emotional responses in a pilocarpine-induced post-status epilepticus rat model. Folia Med (Plovdiv) 2020;62(4):723-9. doi: 10.3897/folmed.62.e51473.

Резюме

Введение: Эпилепсия и противоэпилептические препараты могут отрицательно влиять на когнитивные способности пациентов.

Цель: Настоящее исследование направлено на оценку влияния топирамина (ТПМ) и лакозамида (ЛЗМ) на эмоциональные и когнитивные реакции здоровых животных и животных с эпилептическим статусом, вызванным пилокарпином.

Материалы и методы: Самцы крыс линии Wistar были случайным образом разделены на 6 групп, и в половине из них был вызван эпилептический статус однократным внутрибрюшинным введением пилокарпина (Pilo) (320 мг / кг): Pilo-veh, Pilo-TPM (80 мг / кг). кг) и Pilo-LCM (30 мг / кг). Крысам с такими же параметрами вводили такие же дозы, как указано ниже: C-veh, C-TPM и C-LCM. При тесте step-down passive avoidance тренировочная сессия проводилась в день 1, тест раннего удержания – на второй день и тест долговременной памяти – в день 7. Двигательная активность и тревожность оценивались с помощью теста открытого поля.

Результаты: Группы, обработанные Pilo-TPM и Pilo-LCM, увеличили время пребывания на платформе по сравнению с животными, обработанными Pilo-veh, в то время как животные, обработанные C-LCM, уменьшили время по сравнению с животными, обработанными C-veh. время тестирования краткосрочной и долгосрочной памяти. TPM и LKM оказывали анксиолитическое действие на здоровых крыс. Оба противоэпилептических препарата не смогли снизить гиперактивность, но они уменьшили импульсивность, связанную с низким уровнем тревожности у эпилептических крыс.

Заключение: Наши результаты показывают, что ТПМ и ЛЗМ благотворно влияют на когнитивные функции как у здоровых, так и у эпилептических крыс. Хотя оба противоэпилептических препарата могут вызывать анксиолитический эффект у здоровых крыс, они снижают импульсивность после лечения пилокарпином.

Ключевые слова

тревога, когнитивные способности, эпилепсия, лакозамид, топирамат