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Changes in Learning and Memory in Pentylenetetrazole Induced Amnesia of Rats Treated with Lacosamide

KEYWORDS: Lacosamide, Pentylenetetrazole, learning and memory, shuttle box

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ABSTRACT *Cognitive impairments are frequently observed in epileptic patients. It is known, that not only epilepsy but also antiepileptic drugs can induce cognitive and behavioural abnormalities. Lacosamide (LCM) is a new antiepileptic drug and its effect on cognitive functions is not fully elucidated. The aim of the study was to assess the effect of Lacosamide on the cognitive functions in a drug-induced model of amnesia with pentylenetetrazole (PTZ) in rats. The controls increased avoidances in learning and memory sessions. Lacosamide administration to kindled animals led to a slight increase of the number of active avoidances compared with PTZ controls and restored motor activity suppressed by PTZ. The therapeutic dose of LCM shows a tendency towards a neuroprotective effect on cognitive functions in the PTZ kindling model in rats.*

Introduction

Cognitive impairment is frequently observed in epileptic patients. Clinical reports suggest that not only epilepsy but also therapeutic drugs, used in the treatment of epilepsy, exert negative effect on cognition which affects the quality of life of epileptic patients [1]. Most patients with epilepsy require chronic pharmacological therapy [2], although, approximately 30% of patients are refractory to seizure control by available antiepileptic drug (AED) therapies [3, 4]. In the last decade, several new options for the medical treatment of epilepsy have been introduced, including novel AEDs. The new AEDs differ from older agents in several important ways, including mechanism of action, spectrum of activity, pharmacokinetics, and safety profile [5]. Lacosamide is a new AED which has been recently approved as adjunctive treatment for partial-onset seizures in patients aged ≥16 years by the European Medicines Agency (EMEA; August 2008) and in patients aged ≥17 years by the U.S. Food and Drug Administration (FDA; October 2008). There is little information about the effect of the drug on cognitive functions as well as its effect in different models of drug-induced amnesia. One of these models is "kindling". It causes a relatively permanent alteration of brain functions leading to increased excitability to repeated ineffective electrical or chemical stimuli. Pentylenetetrazole is a very commonly used chemical kindling agent [6, 7], inducing retrograde amnesia, and is used for testing treatments of post-seizure cognitive and emotional problems [8, 9].

Aim

The present study was undertaken to assess the effect of therapeutic doses of Lacosamide on the cognitive functions in a PTZ-induced model of amnesia.

Materials and methods

Male Wistar rats (150-180 g) were used in the study (n=24). 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. The experimental protocol was approved by the Bulgarian Food Safety Agency and the Ethical Committee on Human and Animal Experimentation of Medical University - Plovdiv.

The rats were divided into three groups (n=8): 1st group (controls) was treated with saline p.o. and saline s.c., 2nd (PTZ controls) - saline p.o. and PTZ (40 mg▪kg^{-1}) s.c, 3rd (LCM group) – LCM 3mg▪kg^{-1} p.o. and PTZ (40 mg▪kg^{-1}), s.c. The dose of LCM used is the lowest therapeutic one. It was applied orally 5 days a week, 30 min before sessions.

Kindling was induced by the administration of PTZ on every alternate day for 9–11 weeks or until stage 4 of epileptogenesis was achieved. After each PTZ injection, convulsive behaviour was observed for 30 min. The resultant seizures were scored 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). The PTZ injections were stopped when the animals showed adequate kindling, i.e. seizure score of 4 was achieved after three consecutive injections.

Cognition was assessed after 24 h of the last PTZ injection. We used Shuttle box (Ugo Basile, Italy) for assessment of passive and active avoidances. Learning session was held for 5 consecutive days and consisted of thirty trails (6 sec light and buzzer, 670 Hz and 70 dB, followed within 3 sec 0.4 mA foot electrical stimulation and a 12 sec pause). Retention test for memory trace was performed on the 12th day from the beginning of the training. The behavioural parameters measured were: avoidances (number of correct responses on conditioned stimuli), escapes (number of unconditioned responses) and intertrial crossings.

Statistical analysis

Statistical evaluation of group differences was done by one-way ANOVA and the Tukey *post hoc* test. The intergroup differences were assessed by a paired Sample *t*-test.

Results

The controls increased significantly the number of avoidances on the 2nd, 3rd, 4th, and 5th day of the learning session compared with the 1st day of the trial ($P<0.05$). The PTZ control group had a significantly lower number of avoidances in comparison with those of the controls during the learning session on the 1st ($P<0.01$), 2nd ($P<0.05$) and 3rd day ($P<0.05$). The LCM group decreased significantly their number of avoidances only on the 1st and 2nd day of learning session ($P<0.05$), but on the 3rd day increased them to levels insignificantly different from those of controls (Chart 1).

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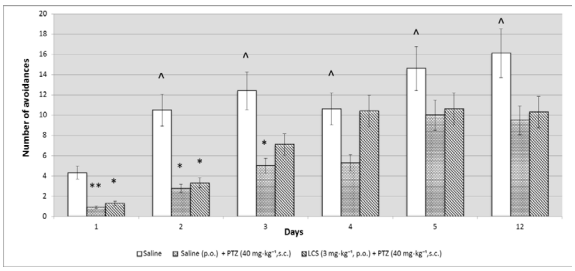
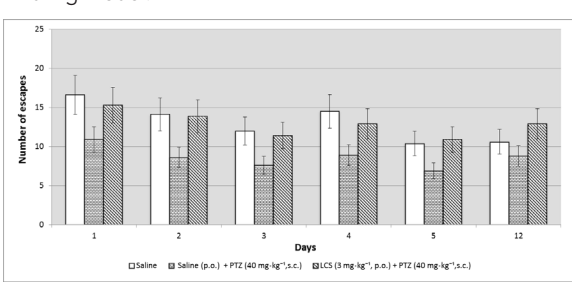
Chart 1. Effects of Lacosamide on number of avoidances in PTZ-kindling model. (*P<0.05, **P<0.01 in comparison with control group; ^P<0.05 of control group compared to the 1st day).



During the retention test the number of avoidances of the control group was significantly higher (P<0.05) in comparison with day 1 (Chart 1). Both groups treated with PTZ decreased insignificantly the number of avoidances in comparison with the control animals (P>0.05).

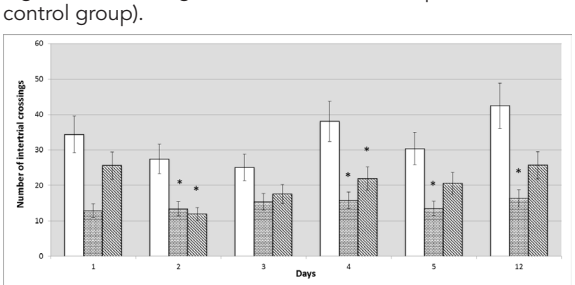
The control group did not change significantly their number of escapes during the learning session and memory retention test in comparison with the first day of the trial (Chart 2). The number of escapes during the learning and memory sessions of the PTZ controls tended to be lower than those of the control animals. The escapes of LCM group tended to be higher than those of PTZ controls, but because of the large interindividual differences these effects were not statistically significant.

Chart 2. Effects of Lacosamide on number of escapes in PTZ-kindling model.



No change was found in the number of intertrial crossings in the controls during the five learning days and on the memory retention test compared with the first day of the trial (Chart 3). The PTZ controls decreased significantly the number of intertrial crossings on the 2nd, 4th and 5th days of the learning session (P<0.05) and on the retention test (P<0.05) in comparison with the control animals. The number of intertrial crossings of the LCM group was significantly lower only on the 2nd and 4th day (P<0.05), but on the 5th day of the learning session and on the retention test it was increased to levels insignificantly different from those of the controls.

Chart 3. Effects of Lacosamide on number of intertrial crossings in PTZ-kindling model. (*P<0.05 in comparison with the control group).



Discussion

It has been shown that not only epilepsy but also antiepileptic drugs can induce cognitive and behavioural abnormalities such as impairment of learning and memory [10]. Lacosamide is a new antiepileptic drug whose mode of action is not fully understood. LCM belongs to the group of sodium channel blockers. Errington et al. (2008) have proposed a novel interaction for Lacosamide which modulates the sodium channels in a novel manner: it enhances selectively the slow inactivation of the voltage-gated sodium channels with no effects on rapid inactivation, resulting in stabilization of hyperexcitable neuronal membranes [11]. Data on the effects of LCM on cognitive function is still scarce and contradictory. In patients with epilepsy LCM can induce memory impairment, but the effect is limited and insignificant [12]. Experimental data show that treatment with LCM with a dose of 30 $mg \cdot kg^{-1}$ causes a significant decrease of attention in intact rats [13], but its effect on learning and memory are still not clear. Our results present that LCM in a therapeutic dose has a slight tendency towards a neuroptotective effect in PTZ-induced models of amnesia in rats.

PTZ is a central nervous system convulsant which is thought to act at the picrotoxin site of the γ-aminobutyric acid type A ($GABA_A$) receptor, blocking the GABA-mediated Cl^- influx through an allocentric interaction in the Cl^-channel, leading to neuronal membrane depolarization and, consequently, the propagation and maintenance of seizure activity. This is the reason, PTZ to be used not only for examining the efficacy of potential anticonvulsants in rats [14], but also for testing post-seizure cognitive and emotional problems [8, 9].

Our results are in agreement with previous experimental data that has clearly shown that PTZ kindling impairs long term memory [15, 16] and can induce retrograde amnesia in the shuttle box and step down avoidance test in rodents [8].

The present results show a tendency towards a neuroprotective effect of the selected dose of Lacosamide on the cognitive function in the PTZ kindling model. The treatment with Lacosamide during PTZ-induced kindling tends to restore the decreased active and passive learning abilities of rats by the convulsant as assessed by the number of avoidances and escapes. Lacosamide had no positive effect on memory during the memory retention test. Lacosamide also restores the motor activity of the rats to the level of the control group on the last day of the learning session and on the retention test and in this way prevents the PTZ negative effect.

Conclusion

The results of this study demonstrate that the PTZ kindling model can produce cognitive problems. Therapeutic dose of Lacosamide induce a slight increase of active learning abilities and motor activity in rats with PTZ-induced amnesia. These results suggest that LCM shows a slight tendency towards a neuroprotective effect in a PTZ kindling model.

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