The antiepileptic drug lacosamide and memory – A preclinical study

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Abstract

Objective: Lacosamide (LC) belongs to a new generation of antiepileptic drugs (AEDs) and demonstrates unique mechanism of action. The drug also shows neuroprotective activity on the hippocampus. In this study, the impact of LC on learning processes was assessed.

Methods: Adult male Wistar rats (n = 40) were used. Lacosamide was administered p.o. as a single (25 mg/kg or 75 mg/kg) or repeated doses (75 mg/kg). The effect of the drug was assessed in the Morris water maze (spatial memory) and the passive avoidance (PA) (emotional memory).

Results: Lacosamide administered at a single dose or repeatedly did not impair spatial memory in Morris water maze. Higher swimming speed was observed in rats after administration of acute doses of LC. In PA, the disturbance of emotional memory was observed only after the single high dose of LC.

Conclusion: Lacosamide does not impair memory and learning processes. The emotional memory impairment observed after the acute high dose appears to be temporary and did not occur after repeated administration.

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1. Introduction

Lacosamide (LC) is a novel antiepileptic drug (AED) and its mechanism of action distinguishes it from other AEDs. Unlike classical AEDs like phenytoin or carbamazepine which affect fast inactivation, LC enhances sodium channel slow inactivation. This results in stabilization of neuronal membranes and decrease in neuronal firing [1]. It has been suggested that the drug also binds to collapsin response mediator protein 2 (CRMP-2) which plays a role in neuronal differentiation. Collapsin response mediator protein 2 is associated with the development of epilepsy, but its role is not fully clear [2]. Latest study indicates that CRMP-2 is also linked to the addiction-like behavior and LC can reduce the hippocampal CRMP-2 level in ethanol-addicted mice [3]. However, another study indicated that the drug does not specifically bind to human CRMP-2 [4].

An important part of the mechanism of action of LC is its neuroprotective activity. The drug reduced the production of reactive oxygen species by increasing the expression of antioxidant enzymes and inhibiting lipid peroxidation [5]. It has been also shown that LC has a neuroprotective effect on the hippocampus which is a brain structure associated with memory processes [6]. Other studies also indicated the neuroprotective effect of LC on the hippocampus [7,8]. It is an important observation because memory disturbances can be not only a secondary effect of epilepsy or other central disorders but also a side effect of AEDs. Especially, first generation of AEDs may cause a deterioration in cognitive functions thus contributing to a significant reduction in the patient’s quality of life [9]. Due to mechanism of action and pharmacokinetic properties, there is an opportunity to use LC not just in epilepsy [10–13]. It is worth emphasizing, that preliminary preclinical results indicate the possibility of using the drug in Alzheimer's disease [14].

For this reason, the aim of the study was to assess the effect of LC administered at an acute dose or repeatedly on two types of memory: spatial and emotional. Two behavioral models enabling the assessment of memory were used in the study: the Morris water maze and passive avoidance (PA) test.

2. Materials and methods

2.1. Animals

Forty adult male Wistar rats (Mossakowski Institute of Experimental and Clinical Medicine, Warsaw, Poland) weighing 260–310 g were used. The animals were housed in groups of four in cages with free access to water and standard chow. Normal laboratory conditions were maintained in the room (20–22 °C, 12-h light/12-h of dark cycle). Experiments were carried out between 8:00 a.m. and 3:00 p.m. Rats were divided into five groups, 8 rats in each (LC acute high dose; LC acute low dose; LC prolonged...
doses; control for acute experiment; control for prolonged experiment).

The experiments were performed in strict accordance with Polish governmental regulations concerning experiments on animals (Dz.U.05.33.289) and European Union Directive 2010/63/EU. All experimental protocols were approved by the Local Ethics Committee for Experimentation on Animals (resolution no. 66/L B/121/2018).

2.2. Drug

Lacosamide (Vimpat, UCB Pharma S.A, USA) was administered as an oral solution directly into the stomach via an oral gavage. To study the acute effect on memory processes, a single dose of 25 mg/kg or 75 mg/kg was administered about an hour before the trial. Lacosamide was also given repeatedly once a day at a dose of 25 mg/kg for 2 weeks to assess the prolonged effect on memory processes. On the trial days, the animals received the drug after the end of the test to avoid the impact of the acute dose on the results. In the PA, the drug was administered 2 weeks before the test. The animals in the control group received 0.2 ml/100 g of a 1% aqueous solution of methylcellulose.

2.3. Morris water maze test (MWM)

The Morris water maze test is carried out in a circular tank (diameter, 180 cm; walls, 50 cm high) which was filled with water at 22–24 °C and placed in a room with several extra-maze cues. The pool was virtually divided into four sections: N, S, W, and E, and a transparent circular platform (diameter, 8 cm) was placed in the center of one of them. The platform was hidden about 2 cm below the surface of water and was invisible for animals during swimming. Trials were recorded with a camera located above the pool which allowed to monitor the swimming phase in real-time without eye contact between the animal and the experimenter. Rat position, swimming, and entrance to the platform were detected using ANY-maze software (ANY-maze, USA).

Rats were tested across five days [15]. During the first four days of the experiment (acquisition tests), the rats swam in the pool with the platform which was placed in a selected quadrant and remained the same throughout the experiment. Rats were placed into the pool in a different quadrant, facing the wall and allowed to swim for 60 s. If the rat found the platform, it was allowed to stay on it for 15 s before being removed and dried off. When the animal could not find the platform at the end of the 60 s, it was placed onto the platform manually by the experimenter for 15 s to observe the room. Each animal had four trials per day (16 trials total). On the fifth day, the platform was removed and a probe trial was performed in which the animals were allowed to swim freely for 60 s.

2.4. Passive avoidance test (PA)

The PA test allows to assess memory retention. Animals learn to avoid specific compartment associated with an aversive stimulus (foot shock). A step-through, light–dark apparatus (Gemini Avoidance System, San Diego, USA) consists of two similar compartments with grid floor (25 x 20 x 17 cm). Between them a movable gate is located and it closes automatically when the animal passes into another compartment.

The PA test is a two-day study [16]. On the first day, an acquisition trial is performed. Each rat was put into a selected compartment and initially allowed to freely explore for 60 s. The light was off and the gate was closed. After this period, the light was turned on and the gate was opened, simultaneously. The animal was able move freely to the dark compartment. When the rat entered into the dark compartment, the gate automatically closed and an electric foot shock (0.5 mA) was delivered through the grid floor for 3 s. Then the animal remained in the apparatus for approximately an additional 15 s after the shock to allow to form the association between an aversive stimulus and the dark compartment.

Twenty-four hours after the acquisition trial, each rat was subjected to a retention trial which consists of one trial carried out identically to the acquisition trial except delivering foot shock after entering the dark compartment. The latency to enter the dark compartment was measured. The duration of the trial was a maximum of 300 s and if the animal did not enter into the dark compartment within this time, it was returned to its home cage, and a latency of 300 s was recorded.

2.5. Statistical analysis

The Statistica 13 was used in statistical analysis. The normality of each distribution was checked by the Kolmogorov–Smirnov test, with Lilliefors correction. Statistical analysis was performed with the Mann–Whitney U-test (comparison between groups) and post hoc Friedman test (comparison within a group) in the MWM. Moreover, the Mann–Whitney U-test was also used to compare groups in the PA test. A p-value of 0.05 or less indicated a statistically significant difference for all statistical tests. Due to use of non-parametric test, data are presented as median (horizontal bar), first and third quartiles (vertical column), and minimum and maximum (vertical line). Outliers and extreme values are represented by circles and asterisks.

3. Results

3.1. The effect of lacosamide administered at low dose on the spatial memory in rats in Morris water maze

Lacosamide administered at a single dose of 25 mg/kg p.o. did not affect learning processes in rats. Time needed to find the platform did not differ between groups on particular test days (Fig. 1A).

Studied time was gradually shortened during the experiment and significant differences in this time were observed between first and last experimental days in both studied groups. Significant reduction in this time was also observed between first and third days in the control group. As shown in Fig. 1B, distance needed to find the platform was also similar in both studied groups, and gradually decreased during the experiment. Compared to the initial values, statistically significant differences were observed on third and fourth days in both groups. On the other hand, the swimming speed achieved by the rats receiving LC was higher on all experimental days compared to that in the control group (Fig. 1C). However, a significant difference was observed only on the first day of the experiment. Fig. 1D shows that LC did not affect the percentage of time spent by rats in the platform zone, compared to the control group. Studied parameter significantly increased on the third and fourth experimental days in both groups. However, significant increases were observed only between second and fourth days in the LC group and on third and fourth days in the control group, compared to the initial values.

On the fifth day of the experiment, the platform was removed from the pool. The time in which rats would find it was slightly longer in rats receiving LC. However, this difference was not statistically significant in the control group (Fig. 2A). As depicted in Fig. 2B, there is also no difference between groups in the percentage of time spent in the zone where previously the platform was located.
3.2. The effect of lacosamide administered at high dose on the spatial memory in rats in Morris water maze

The animals receiving LC at the single dose of 75 mg/kg p.o. and the control group learned to find the platform faster. The time needed to find it was similar in both groups and it decreased in the following days of the experiment (Fig. 3A). In comparison to the initial values, significant differences were observed in third and fourth test days in both groups. No differences were noted between groups in the traveled distance. It was shortened in the consecutive days of the experiment and statistically significant differences were observed in both groups on the third and fourth days, in relation to the initial values (Fig. 3B). Fig. 3C shows that the swimming speed achieved by the rats receiving LC was higher on all test days in comparison to the control group. However, significant differences between the groups occurred on the first, second, and fourth days of the experiment. The percentage of time spent in the platform zone did not differ between groups and increased in the following test days. In both groups, statistically significant differences were observed on third and fourth days compared to the first day of the test (Fig. 3D).

On the last day of the Morris test when the platform was removed from the pool, the time to find the virtual platform was similar in both groups (Fig. 4A). No difference was observed in the percentage of the time spent in the zone where the platform used to be located (Fig. 4B).

3.3. The effect of lacosamide administered at prolonged dose on the spatial memory in rats in MWM test

Prolonged administration of LC at the dose 25 mg/kg p.o. did not affect learning processes in rats. As shown in Fig. 5A, the time
needed to find a platform was comparable in the following days of the study in both groups and was gradually shorter during the experiment. Statistically significant differences were observed between first and fourth days in both groups and between first and third days in the control group. Lacosamide also did not affect the traveled distance, and studied parameter decreased in the following test days in both groups. Same as time, significant distance reductions were observed between first and last days in both groups and between first and third days in the control group (Fig. 5B). Moreover, swimming speed was similar in both groups (Fig. 5C). The percentage of time spent in the platform zone did not differ between groups in the following days of the study. Increases in time were observed in LC and control groups on third and fourth days, and significant differences were noted in these days in comparison to the first day. Significant decrease was also observed between first and third test days in animals receiving LC (Fig. 5D).

The time in which rats would find the platform if it was still in the pool, slightly increased in the LC groups (Fig. 6A) as the percentage of time spent in the proper zone was decreased (Fig. 6B). However, these differences were not significant in relation to the control group.

3.4. The effect of acute doses of lacosamide on emotional memory in the passive avoidance test

Lacosamide administered at a single dose of 25 mg/kg did not significantly affect step-through latency to enter the dark compartment (Fig. 7A). However, animals receiving the high dose of LC (75 mg/kg) passed significantly faster to the dark compartment than those of the control group on the retention day (Fig. 7B).
3.5. The effect of prolonged administration of lacosamide on emotional memory in the passive avoidance test

As shown in Fig. 7C, LC administered at the dose of 25 mg/kg p.o. for 2 weeks did not cause the disturbance in the step-through latency. Studied parameter was comparable in both groups.

4. Discussion

Lacosamide is a promising drug with unique mechanism of action [1,2]. The drug is considered a relatively safe AED and psychiatric symptoms are rare [17,18]. Moreover, it has been shown in preclinical study that LC protects neuronal cells in the hippocampus from death and injury from ischemic stroke [6]. In another study, the drug reduced hippocampal neuronal loss following status epilepticus [19]. Hence, the aim of this study was to evaluate the effects of LC administered alone at a single or repeated doses on hippocampal-dependent spatial memory and emotional memory.

The results of present study demonstrate that LC does not adversely affect spatial memory in rats. In our study, the drug administered at a low (25 mg/kg p.o.) or high dose (75 mg/kg p.o.) did not impair learning processes in the Morris water maze test. The time needed to reach the submerged platform as well as the traveled distance gradually decreased in the following days of the study. There was also no effect of LC on the percentage of time spent by animals in the zone with the platform. In subsequent trials, the animals swam longer in the appropriate zone. In contrast, the swimming speed achieved by the rats receiving the drug was higher than in the control group on all days of the experiment. Statistically significant differences were observed on all test days.
except the third day for the high dose, but only on the first day for the low dose. On the fifth day of Morris test, the platform was removed from the pool. The time in which the rats find the platform if it would still be in the tank and the time spent in the area where the island was previously located were comparable between the groups. This indicates undisturbed memory in the animals.

In other studies, the impact of LC on spatial memory was also assessed after various cerebral damages but the results are mixed. In an experiment by Wang et al. [20], neuroprotective activity of LC in a mouse murine model of closed head injury was investigated. The drug was administered in two doses (6 mg/kg or 30 mg/kg i.p.) 30 min after the head injury, and then treatment was continued for 3 days. About a month after the injury, memory processes were assessed in Morris water maze. Improvement of memory was observed in animals given high doses of LC. In other study, memory function was assessed after hypoxic-ischemic brain injury in neonatal rats. Lacosamide was given before the brain injury at the dose of 100 mg/kg p.o. The Morris water maze test was performed after 7 weeks from hypoxia-ischemia. The spatial memory improved in the LC-pretreatment group and a mean escape latency was shorter for these animals [21]. In turn, the results obtained by Pitkänen et al. [22] indicate the lack of protective effect of LC on cognitive functions in rats. The impact of the drug was assessed after traumatic brain injury which occurs as a result of epileptic seizures or status epilepticus. Lacosamide was given at a dose of 30 mg/kg i.p. at 30 min post-injury and 3 times per day for the next 3 days. Spatial memory and learning were examined with the Morris water maze on day 12 after the injury. Brain-injured animals that received the drug needed longer time to find the submerged platform, and traveled for this purpose longer distance than healthy rats treated with LC alone. The observed cognitive impairment was similar to that noted in animals that received saline after brain injury. However, there were no differences in the swimming speed between the studied groups. In our study, the swimming speed was higher in LC-treated groups, but more expressed differences were observed after administration of acute high dose.

In our study, we also assessed the learning processes after 2-week administration of LC at a dose of 25 mg/kg. In these animals, higher swimming speed has not been anymore seen which indicates that it may be a transient effect after an acute dose of LC. As with single doses, no disturbances in spatial memory were observed. The time needed to find the platform and traveled distance were shorter with each subsequent test day. The percentage of time spent by the rats in the zone with the platform gradually increased in the following days of the study and was similar in both groups. On the last day of the test in which the platform was removed from the pool, both time of probable finding the platform and the time in the zone with it were comparable in LC-treated and control groups.

The effect of LC on memory was also assessed using behavioral models other than the Morris water test. Bang et al. demonstrated the influence of LC on memory and the level of histone deacetylase in the rat brain. The amnesia was induced by scopolamine (3 mg/kg i.p.) and then behavioral tests were performed. Lacosamide administered at a dose of 30 mg/kg i.p. significantly increased the time spent near a familiar object in the object recognition test and reduced the transfer latency in the elevated plus maze. The beneficial effect in elevated plus maze was also observed after administration of lower dose of LC (10 mg/kg i.p.). In radial arm maze, reduction in the number of errors was noted in tests carried out after 1, 3, and 24 h from drug administration at the dose of 30 mg/kg i.p. A decrease in the histone deacetylase level was also observed in the cerebral cortex. The authors suggest that the beneficial effect of the drug on memory processes makes opportunity to use it in the treatment of amnesic symptoms of Alzheimer's disease.

In this study, the effect of LC on emotional memory was also observed in the PA test. Lacosamide administered at a single low dose did not affect the latency for entering the dark compartment. However, animals receiving the drug at a high dose spent less time in the lighted compartment, which indicates a negative effect of the drug on memory and a disturbance in associating the dark room with the aversive stimulus. On the other hand, LC administered at a dose of 25 mg/kg for 14 days did not impair cognitive function in the PA test.

In recent years, the influence of LC on memory processes has also been assessed by other researchers. Shishmanova-Doseva et al. [23] assessed the effect of LC at a dose of 3, 10, or 30 mg/kg on learning and emotional memory in rats. The drug was administered intraperitoneally to the animals for 4 weeks. As in our study, cognitive disturbances were observed in rodents given the drug at a high dose (30 mg/kg). The latency time in these animals was reduced during the training learning and also in the short- and long-term memory retention tests. The same authors also evaluate the effect of LC on the emotional memory in animals with pilocarpine-induced status epilepticus. Lacosamide were adminis-

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**Fig. 7.** Effect of low dose (A), high dose (B) and prolonged administration of lacosamide (C) on learning and memory in PA. *p* < 0.05, Mann—Whitney U test.
tered orally for 2 months after status epilepticus. The step-down PA test was used to assess early- and the long-term memory. Rats which obtained LC after status epilepticus spent more time on the platform, which indicate the beneficial effect. However, naïve animals receiving LC had memory impairment associated with decreasing of the time spent on the platform. This adverse effect was observed in short- and long-term memory tests [24].

To summarize, the results of this study demonstrate that LC does not impair memory and learning processes. The only adverse effect was seen in the emotional memory study after administration of the single high dose of LC. However, this effect seems to be transient because during repeated administration it was no longer demonstrated. These results are also relevant from the clinical point of view and confirm the safety of the drug which is drug's advantage, especially compared to the older generation of AEDs.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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