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# EFFECT OF LAMBDA-CYHALOTHRIN ON MEMORY AND MOVEMENT IN MICE AFTER TRANSIENT INCOMPLETE CEREBRAL ISCHEMIA

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**Abstract:** Lambda-cyhalothrin (LCH) is a synthetic pyrethroid used as an insecticide. The aim of the study was to investigate the effect of LCH on memory, movement activity, and co-ordination in mice exposed to bilateral clamping of the carotid arteries (BCCA). On the first postsurgical day, the examined animals (BCCA/LCH) were injected with LCH *i.p.* and trained in the passive avoidance task 30 min. after the injection. Controls were: sham-operated animals (SHAM), with their carotids exposed but not occluded, animals subjected to BCCA (BCCA), and sham-operated mice injected with LCH (SHAM/LCH). In the following experiments, memory retention, working spatial memory, movement activity, and co-ordination were examined. Neither memory nor movement co-ordination were impaired by BCCA or LCH. Exploratory locomotor activity was significantly reduced in the BCCA/LCH group ($p < 0.01$ *vs* SHAM). Spontaneous movement activity was significantly reduced in the BCCA/LCH group ($p < 0.001$ *vs* SHAM, $p < 0.05$ *vs* BCCA, $p < 0.001$ *vs* SHAM/LCH), as well as in the BCCA group ($p < 0.01$ *vs* SHAM). Exposure to LCH coexisting with BCCA decreased motor activity in the mice in 2 subsequent 30-min. periods of observation. BCCA itself decreased motor activity in the 31–60 min. of observation. These results show that BCCA combined with exposure to a subtoxic dose of LCH does not impair memory; however, they affect behaviour by reducing the horizontal movement activity in mice.

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## INTRODUCTION

Pesticides are widely used in agricultural and horticultural cultivation for crop protection. Among the most commonly used pesticides are organophosphates and pyrethroids [1]. As organophpsphates contaminate groundwaters [1, 8], are able to accumulate in fatty tissue of living organisms [23], and irreversibly damage the hippocampal structure in the central nervous system of mammals [22], manufacturers and farmers pay increasing attention to pyrethroids.

Synthetic pyrethroids are commonly used as potent means for pest control and account for 30% of all insecticides used worldwide for agricultural, domestic and veterinary uses [5]. Pyretyhroids are more hydrophobic than other classes of insecticides [21], and therefore their site of action is the cell membrane. Lambda-cyhalothrin (LCH) is a type II pyrethroid producing choreoatetosis and salivation (the CS-syndrome) due to the presence of the α-cyano group in its' molecule [29]. Its main target sites are sodium channels in the membranes of neurons in the central nervous system. Therefore, it is considered to be a neurotoxin. The mechanism of LCH toxicity produces delay in sodium channel inactivation, which leads to persistent depolarization of the nerve membrane [15]. Some type II pyrethroids were found to decrease open channel probability of calci-

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um-independent voltage-gated maxi-chloride channels in mouse neuroblastoma cells [3, 4]. A recent study by Clark and Symington [6] shows that LCH produces membrane depolarization, calcium ion influx, and neurotransmitter release from rat brain synaptosomes. However, the nature of LCH poisoning syndromes remains partially unclear. Moreover, LCH was found to possess estrogenic properties and an ability to function as a xenoestrogen promoting human breast carcinoma cell proliferation *in vitro* [34].

LCH has found multiple uses in pest (fleas, cockroaches, flies, and ants) control [34]. LCH-soaked hammock nets have proved to be highly effective against the malaria transmitting species of Anopheles [19]. Due to the widespread use of LCH for controlling pest insects in agriculture, public health, and households, its residues are present in agricultural and urban runoff, which have been found to be toxic to aquatic organisms including fish and amphipods [11]. According to data from Belgium [7], the present intake of LCH with fruits and vegetables (for the 97.5$^{th}$ percentile of consumption) is 10% of acceptable daily intake (ADI) for humans, which is safe.

Bilateral clamping of carotid arteries (BCCA) is an animal model of some age-associated neurodegenerative states occurring in humans at old age, e.g. transient ischemic attacks (TIAs). BCCA in mice produces moderate oligemic hypoxia of the brain, causing no neuronal damage, but increasing GABA content in the frontal cortex, hippocampus and striatum [17].

As the average life span of humans is on the increase, there is a high chance that they remain engaged in numerous activities, including pesticide use, and consume food and water polluted with traces of pesticides. This is of great interest if exposure to low doses of LCH from pesticidal formulas may produce behavioral changes in the elderly undergoing TIAs.

## MATERIAL AND METHODS

**Animals.** Non-gravid female albino Swiss mice weighing 18-24 g, approximately 6 weeks of age purchased from a licensed dealer (T. Górzkowski, Warsaw, Poland) were used in the study. All animals were given a 7-day acclimation period and maintained on a 12 hr light/dark cycle. Food and tap water were provided *ad libitum*. Temperature was maintained at 21 ± 2ºC.

There were 4 groups of 10 animals each: I) BCCA-operated injected 24 hr after surgery with 0.1 $LD_{50}$ LCH *i.p.* (BCCA/LCH); II) BCCA-operated injected 24 hr after surgery with respective volume of 0.9% saline *i.p.* (BCCA); III) SHAM-operated (with their carotids separated, but not clamped) injected 24 hr after surgery with LCH *i.p.* (SHAM/LCH); and IV) SHAM-operated injected 24 hr after surgery with 0.9% saline *i.p.* (SHAM).

**Surgical procedure.** The surgical procedure of bilateral clamping of the carotid arteries (BCCA) was performed under ketamine (100 mg/kg bw) + xylazine (20 mg/kg bw) *i.p.* anesthesia. Ketamine (Ketanest, 50 mg/ml) was purchased from Parke-Davis, Berlin, Germany. Xylazine (Rometar, 20 mg/ml) was purchased from Spofa, Praha, Czech Republic.

Mice were subjected to 30-min. bilateral clamping of the common carotid arteries (BCCA) by wrapping threads around the arteries to occlude blood flow. BCCA was performed under Ketamine (100 mg/kg bw) + Xylazine (20 mg/kg bw) intraperitoneal anesthesia. The two anesthetics were chosen considering their safety and anesthetic effectiveness [2, 28]. The cessation of carotid blood flow was controlled visually. After 30 min. the threads were removed, arteries were inspected for blood re-flow, and the surrounding skin was sutured. Sham-operated mice had their carotids exposed, but not clamped. During the procedure, mice were breathing spontaneously and were kept at a constant temperature of 37°C by a heating pad and a lamp.

**Administartion of lambda-cyhalothrin.** LCH (Karate 025 EC containing 25 g of LCH/l) was purchased from Syngenta Limited, UK. $LD_{50}$ of LCH for mice was calculated with Lichtfield and Wilcoxon's method [16] to be 6.9 mg of LCH/kg of bw [5.6-8.5].

On the first postsurgical day (24 h after the surgery), groups I (BCCA/LCH) and III (SHAM/LCH) were injected with 0.1 $LD_{50}$ of LCH *i.p.* Groups II (BCCA) and IV (SHAM) were injected with respective volumes of 0.9% saline *i.p.*

**Passive avoidance.** A step-through passive avoidance (PA) task was used in the study. The task relies on the innate preference of rodents for dark, enclosed spaces, and is regarded as a measure of long-term memory retention [31]. Avoidance training consisted of a single trial in which each animal was placed in an illuminated box (15 × 12 × 15 cm) adjacent to a darkened one (the same size) with an electric grid floor. A 4 × 5 cm doorway was located at floor level in the centre of the wall separating the boxes. Thirty seconds after placing the animal in the centre of the illuminated box, a passage joining the 2 boxes was opened. After entering the dark box the animal was punished with an electric foot shock (2 mA for 2s). Twenty-four hours after the training trial, memory retention test was conducted in which the same animals were placed in the illuminated box and the latency to enter the darkened box was recorded. The test ended when the mouse entered the darkened box or when 180 sec has elapsed. Mice that did not enter in the time allotted received latency 180 sec. Administration of the tested pesticide before training may impair or improve learning by affecting memory acquisition and/or recalling.

Thirty min. after LCH or saline injection, animals from all the groups (I-IV) were trained in the passive avoidance task (PA). On the second postsurgical day they were examined in PA for 180 sec.

**Y-maze task.** Spontaneous alternation was assessed in a Y-maze, which is used as a measure of working spatial memory [20]. The total number of arm entries in the Y-maze was considered a measure of exploratory locomotor activity. The Y-maze consists of three 10 × 10 × 10 cm compartments without a floor, joined together by 4-cm long corridors at 120° in such a way that each corridor opens to one compartment only. The maze was placed on a clean sheet of paper on a table-top. In order to prevent odour cues, the maze was cleaned between the trials of different mice and a clean sheet of paper used for each animal. Mice naturally tend to explore the maze by systematically entering each arm. The ability to alternate requires that the animals know which arm they had already visited. In the task, each mouse was placed at the end of one arm and allowed to move through the maze for 8 min. The percentage of alternation, defined as consecutive entries into all 3 arms without repetitions in overlapping triplet sets, to all possible alternations × 100% was counted. For example, if the arms were marked as X, Y and Z, and the animal entered the arms in the following order XYZXZYZXYXYZXZ, the actual alternation would be 7, the total number of arm entries would be 14, and the percent alternation 58.33%.

On the second postsurgical day, after LCH or saline injection, the mice were examined in the Y-maze for 8 min.

**Movement activity.** Horizontal spontaneous locomotor activity was assessed with an automated device consisting of a circular box (32 cm in diameter) with 2 photocells mounted horizontally 2 cm above the floor at an angle of 90°. The photo-beam was activated when the mouse interrupted the beam. In the task, the animals were not habituated for the apparatus, therefore they were placed individually in the actometers for 1 h (2 subsequent 30-min periods: 0–30 min., 31–60 min.). The number of impulses was recorded after 30 and 60 min. The first period was considered as the rate of exploratory locomotor activity. The second period was considered as the rate of spontaneous locomotor activity.

On the second postsurgical day, after LCH or saline injection, locomotor activity of the mice was measured within 2 subsequent 30 min. periods.

**Movement co-ordination.** Movement co-ordination was examined on a rod rotating at the rate of 10 cycles per min. The animals were placed on the rod (1 cm diameter) 50 cm above the ground for 120 sec. The trial ended when the mouse fell off the rod or 120 sec. had elapsed, whichever occurred first.

On the second postsurgical day, after LCH or saline injection, mice were placed on a rotating rod for 120 sec. to test their movement co-ordination.

**Statistical analysis.** A Kruskal-Wallis non-parametric ANOVA test was used to analyze the data from passive avoidance task, as well as for analysis of the number of arm entries recorded in the Y-maze. PA and locomotor activity in the Y-maze results were expressed as median values with the 25$^{th}$ and 75$^{th}$ percentiles. The results of spontaneous alternation in the Y-maze task, movement co-ordination test and spontaneous motor activity test were shown as means ± SEM, and evaluated by one-way analysis of variance ANOVA followed by Student-Newman-Keuls test. The p value $< 0.05$ was considered statistically significant.

After the experiments the animals were decapitated while under ketamine and xylazine anesthesia. The local Ethics Committee for Animal Experiments in Lublin approved the experiment (Opinion No. 30/2000, dated 24.11.2000).

## RESULTS

**Effect of LCH and BCCA on memory retention in passive avoidance task.** No statistically significant differences were observed in memory retention among groups I-IV. Median values of latency (with the 25$^{th}$ and 75$^{th}$ percentiles) were: 180 sec. (180, 180) in group I (BCCA/LCH), 180 sec. (105, 180) in group II (BCCA), 180 sec. (20, 180) in group III (SHAM/LCH), and 180 sec. (180, 180) in group IV (SHAM). Post tests were not calculated; $p > 0.05$.

**Influence of LCH and BCCA on working spatial memory in Y-maze task.** There was no significant differences in working spatial memory observed among the examined groups. Results obtained were (% of logical alternation behaviour expressed as mean ± SEM): I (BCCA/LCH) 56.3 ± 1.8, II (BCCA) 59.1 ± 3.8, III (SHAM/LCH) 61.9 ± 1.8, IV (SHAM) 62.0 ± 2.7, $p > 0.05$.

**Influence of LCH and BCCA on exploratory locomotor activity in Y-maze.** The exploratory locomotor activity of the examined animals was not significantly impaired, neither by BCCA nor LCH within the 8 min. examination in the Y-maze. No statistically significant differences in the numbers of arm entries in Y-maze were observed among the examined groups I–IV (Tab. 1).

Data are expressed as the median values with the 25$^{th}$ and 75$^{th}$ percentiles, n-number of mice. NS ($p > 0.05$ *vs* SHAM), Kruskal-Wallis test.

**Table 1.** The effect of LCH and BCCA on exploratory locomotor activity in the Y-maze.

| Total number of arm entries | | | |
|---|---|---|---|
| BCCA + LCH n=10 | BCCA n=10 | SHAM + LCH n=10 | SHAM n=10 |
| 36 (33, 47) | 38 (32, 50) | 37 (35, 51) | 43 (34, 53) |

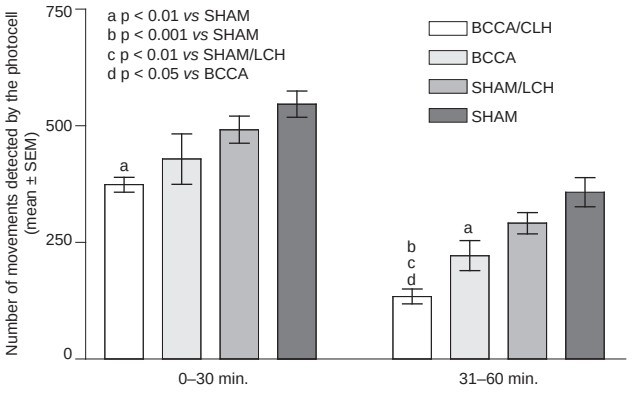


**Figure 1.** Movement activity measured within 2 subsequent 30 min. periods: I 0–30 min., II 31–60 min. One-way Analysis of variance (ANOVA) Student-Newman-Keuls Multiple Comparisons Test.

**Effect of LCH and BCCA on movement activity in the actometer.** The movement activity assessed within the first 30 min. (0–30 min.) of observation differed significantly among groups: I (BCCA/LCH) *vs* IV (SHAM) ($p < 0.01$). Mean values (± SEM) were: I (BCCA/LCH) 373.9 ± 15.9, II (BCCA) 429 ± 54, III (SHAM/LCH) 491.8 ± 28.9, IV (SHAM) 546.8 ± 28.1.

In the subsequent 30 min. (31–60 min.) of observation statistically significant differences were found among the examined groups (Fig. 1). and the mean values of spontaneous locomotor activity (± SEM) were: I (BCCA/LCH) 134.3 ± 16, II (BCCA) 221 ± 32, III (SHAM/LCH) 291.4 ± 22.9, IV (SHAM) 357.8 ± 31.4.

**Influence of LCH and BCCA on movement coordination.** There were no significant differences among the examined groups of animals in movement co-ordination, and the mean times of fully co-ordinated gait on the rotating rod (± SEM) were: I (BCCA/LCH) 100.1s ± 11.9, II (BCCA) 90.2s ± 15.1, III (SHAM/LCH) 107.6s ± 9.4, IV (SHAM) 120s ± 0, $p > 0.05$.

## DISCUSSION

Little is known about the influence of LCH on the memory processes and movement in mammals subjected to oligemic brain hypoxia. BCCA in mice is used as a model of transient incomplete cerebral ischemia [30]. BCCA was used in experiments on animals to test the mechanisms of organ ischemia and reperfusion [32]. BCCA was shown to affect the cholinergic system in the rat's brain [12], cause free radical formation, produce changes in the glutaminergic system [13], and increase GABA content in vulnerable brain areas controlling memory processes, movement activity and coordination [10]. In agreement with the present results, in Jóźwiak's studies, BCCA itself was shown not to impair the motor co-ordination in mice (examined on the rod rotating at the rate of 4 cycles per min.), and not to affect the memory processes: neither long-term (examined in the step-through passive avoidance task) nor spatial, working memory (examined in the Y-maze) [14]. Data obtained in the present study show that the exposure to a low dose of an LCH-containing formula coexisting with BCCA significantly decreased exploratory (0–30 min. of observation in the actometer) and spontaneous motor activity (31–60 min. of observation in the actometer) in the mice. Even though no statistically significant differences in exploratory locomotor activity were seen among the examined groups, within the 8 min. period of examination in the Y-maze, slight activity impairment could be seen in the BCCA + LCH group in comparison with the SHAM group. Longer examination in actometers (total of 60 min.) allows a statistically significant differences in the BCCA + LCH group to be seen, in comparison with the SHAM group. Our data are consistent with earlier observations that motor function is a part of behaviour affected by all pyrethroids independent of the route of administration or species exposed, and it is the most extensively characterized neurobehavioral endpoint of pyrethroid intoxication [33]. The vast majority of pyrethroids of type I and II produce a dose-related decrease of general motor activity in mammals [33]. Our previous study has shown that exposure to cypermethrin, an α-cyano pyrethroid, coexisting with BCCA, significantly reduced locomotor activity in mice [25]. Another study of ours evidenced that fenpropathrin, another α-cyano pyrethroid, which does not fit into the traditional classification of pyrethroids, having some properties of type I and type II pyrethroids, impairs memory in mice after BCCA without altering their motor activity [26]. Cypermethrin, fenpropathrin and the R-isomers of LCH are known to act by reducing open chloride channel probability, whereas the S-isomers of LCH antagonize the action of the R-isomers [3].

Ketamine, used as an anesthetic for BCCA in the experiment, might also be discussed as the factor influencing animal behaviour and movement. Ketamine is a non-competitive NMDA receptor antagonist [24]. It affects neurotransmitter levels in the rat brain. It was found to increase prefrontal acetylcholine (ACh) release and impair performance in attention tasks [24]. However, it was used in experiments on animals for testing the mechanisms of organ ischemia and reperfusion [32] considered benign. Ketamine was formerly used for BCCA anesthesia followed by behavioural studies in mice, and was found not to influence locomotor activity and memory processes: neither memory acquisition nor retention or fresh spatial memory [17, 18].

LCH was found to have a cytotoxic effect on rabbit erythrocytes inducing oxidative damage, evidenced by El-Demerdash [9] as a significant decrease in the content of sulfhydryl groups (SH-groups), inhibition of acetylcholinesterase (AChE) and superoxide dismutase (SOD), as well as catalase (CAT) and glutathione S-transferase (GST) activity [9]. It can be hypothesized about LCH's interference with redox processes in mice brains. Studies have been published proving that antioxidant (vitamin C and E,

melatonin) administration provides free radical avoidance, thus protecting the most vulnerable tissues from the detrimental actions of agents having a high oxidizing potential [9, 27].

In conclusion, transient incomplete cerebral ischemia combined with exposure to subtoxic dose of LCH-containing formula do not impair memory; however, it affects behaviour by reducing horizontal movement activity in mice. Therefore, care must be taken to avoid unnecessary exposure of elderly people undergoing TIAs to LCH.

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