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Behavioral perseveration and impairment of long-term memory in rats after intrahippocampal injection of kainic acid in subconvulsive dose

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Abstract

Delayed disturbances of cognitive functions caused by intrahippocampal injection of subconvulsive dose of kainic acid were studied in rats. Animals were behaviorally tested for the presence of cognitive deterioration 1 week after bilateral injection of 0.25 μg kainic acid into the left and right hippocampi. Behavioral tests included the retrieval of a food-procuring task, its experimental extinction, and learning of a new similar task. Kainate-treated rats showed deterioration of performance of the task learned before the treatment: An impairment of the task performance occurred in the first trial of a daily session (each daily session consisted of 10 trials), and beginning from the second trial, the task was performed as rapidly as by control animals. This deterioration of retrieval in the first trial took place during several days, in spite of daily training during the retrieval test. Other disturbances of cognitive functions in kainate-treated rats were revealed in the test of experimental extinction of the response. At the initial step of this test, the rats showed active behavioral perseveration, performing habitual response with short latencies in spite of reinforcement removal. Besides, kainate-treated rats made significantly more responses before full extinction (inhibition of the previously learned response) than the control rats. In the learning test, kainate-treated rats did not exhibit any disturbances: repeated learning was the same as in the control group. Therefore, results showed that hippocampal dysfunctions induced by kainic acid resulted in the following cognitive disturbances: difficulties in memory retrieval and weakening of inhibitory control. These disturbances can be most adequately explained on the basis of the concept, according to which the hippocampus acts as a detector and comparator of new signals, thereby accomplishing selective attention.

Keywords: Kainic acid; Hippocampus; Memory retrieval; Response extinction; Behavioral perseveration

1. Introduction

Kainic acid (KA), the agonist of kainate subgroup of glutamate receptors, is a widespread tool for experimental research. An influence of this drug on neurons ranges from depolarization to severe damage (Lothman and Collins, 1981; Ben-Ari, 1985; Ben-Ari and Cossart, 2000; Farooqui et al., 2001). KA in high doses is used as a neurotoxin to produce brain lesions; intracerebral injections of the drug cause local destruction of neurons and may also result in neuronal death in distant areas, yet sparing afferent fibers and axons (Ben-Ari, 1985). A systemic or intraventricular injection of KA in convulsive doses reproduces most of the morphological characteristics of hippocampal sclerosis (neuronal loss, gliosis, reorganization of neurotransmitter receptors, mossy fiber sprouting and granule cell dispersion) observed in patients with temporal lobe epilepsy (Ben-Ari and Cossart, 2000; Morimoto et al., 2004). These morphological changes are accompanied by various disturbances of cognitive functions. When administered systemically, KA may cause some impairments of spatial memory and learning (Brown-Croyts et al., 2000; Mikati et al., 2001) or memory deteriorations in elevated plus-maze (Mikulecka et al., 2000). In a study of Stubley-Weatherly et al., bilateral injection of KA into the dorsal or ventral hippocampus produced a deficit in the acquisition of water maze task in rats (Stubley-Weatherly et al., 1996). However, effects of KA in subconvulsive doses are poorly investigated, therefore it would be useful to study this question more thoroughly. In the present work we used microinjections of a subconvulsive dose of KA into hippocampus because hippocampal system plays a key

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role in cognitive functions (Squire, 1992; Milner et al., 1998; Vinogradova, 2001; Eichenbaum, 2001; McNaughton and Wickens, 2003). The significance of hippocampus in memory processes was studied for many decades; nevertheless, its specific role in these processes remains unclear. The most popular conception of hippocampal function proposes that the hippocampus of rats and other animals represents their location within environment, thus providing the basis for spatial memory and navigation (O'Keefe and Nadel, 1978). This conception contradicts the hypothesis specifying the hippocampal system as the background for declarative (episodic) memory (Squire, 1992; Eichenbaum, 2001). There is a compromise view, that the right hippocampus is particularly involved in memory for location within an environment, and the left hippocampus is mainly involved in context-dependent episodic memory (Burgess et al., 2002). At any rate, a number of experimental evidence showed, that the role of the hippocampus concludes not only in spatial memory and navigation; the hippocampal system is also necessary for associative learning even without any components of spatial information (Brasted et al., 2003). The hippocampus is also rated as a suppressor of inappropriate associations (McNaughton and Wickens, 2003). In early works the hippocampus was also regarded as a detector of novelty and a comparator of new signals (see Ref. in: Vinogradova, 2001). Therefore, behavioral analysis of hippocampal deterioration is still relevant for study. In the present study local injury of the hippocampus was induced by KA. Akaike et al. showed that after injection of 1 μg of KA into dorsal hippocampus multiple spike discharges initially appeared in the hippocampus, and 60 min after the injection seizures spread to neocortex (Akaike et al., 2001). During ictal EEG the rats showed only immobilization. Two days after KA injection these seizures disappeared and all rats became electrographically and behaviorally normal (Akaike et al., 2001). In the present study we used the dose of KA four times lesser than in the cited paper, behavioral tests started 1 week after the injection. These experimental conditions have been chosen to minimize the influence of injection procedures and seizures. Behavioral tests were intended for the investigation of separate memory processes and involved the retrieval of the response, its experimental extinction, and relearning in the same experimental chamber.

2. Materials and methods

Male Wistar rats ($n=20$), weighting 180–200 g, were used as subjects. Experiments were carried out in accordance with the guidelines of the Institutional Animal Care and Use Commission of ITEB RAN. Rats were kept on 0800 h/2000 h light/dark cycle with free access to water, and a feeding schedule according to which they were fed during training and immediately after the

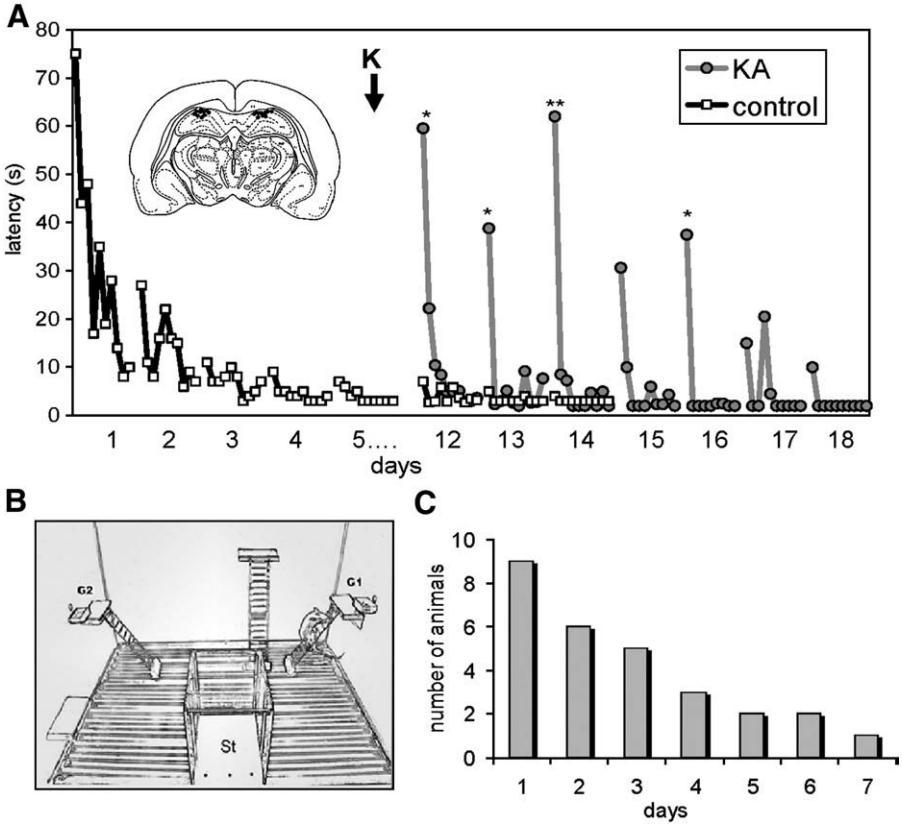

Fig. 1. A. Latencies of trials during learning and retrieval of food-procuring task. The arrow indicates the time of drug or vehicle infusion. Latencies of all trials per day are shown. Control — animals with the injection of saline ($n=10$), KA — a group of animals treated with kainic acid ($n=10$). Top left — schematic representation of the injection sites. *$P<0.01$, **$P<0.001$. B. Experimental chamber for behavioral tests. St — start box; G1 — goal shelf No. 1; G2 — goal shelf No. 2. C. The number of animals with deteriorated retrieval during the test in the KA-treated group.

experiment once a day. The weight of the animals decreased by no more than 20% during the period of adaptation to experimental conditions.

The animals were trained with a spatial appetitive-motivated task in an experimental chamber (60 × 80 × 60 cm) containing a start box and four shelves placed at different heights and ladders (Fig. 1B). To reach the goal shelf with moistened ball of bread, animals had to climb the ladder. Before the beginning of the training, all animals were habituated including handling and ascending the ladders for 5 days. A daily session of the training consisted of 10 trials. The learning was estimated by the measure of trial time (latency), i.e. the time that took the animals to run the distance from the start box to the goal shelf G1 displayed at a height of 25 cm over the floor. The latency of a trial was limited by 150 s. During the training period the latency decreased and on the fourth day became stabilized to 5–10 s. The details of the learning procedure and properties of used task were described previously (Arkhipov, 1999).

After the training, all rats were divided into two groups: control (saline-treated, $n=10$) and experimental (KA-treated, $n=10$). Animals were anesthetized with pentobarbital (32 mg/kg, i.p.), and injected with saline (control group) or KA (experimental group). Kainic acid (Sigma) was dissolved in sterile saline and injected bilaterally into the dorsal hippocampus (AP: −3.0 mm relative to bregma; ML: ±3.0 mm; V: −2.9) (Paxinos and Watson, 1986) in a dose of 0.25 μg (volume 0.5 μl) in each side. Morphological control of the injection site was carried out after behavioral experiments by the slicing of the frozen brain. After the treatment with KA or saline, the rats were subjected to visual monitoring for 6 h and returned to individual cages. During the week the animals were maintained on a 12/12 h light/dark schedule with free access to food and water. One day before the behavioral test, the food was removed from the cages.

Retrieval of the response was tested 7 days after kainic treatment. This time was chosen in accordance with our previous data, which showed that the behavior of KA-treated animals was nearly normal in this period. During the retrieval test bread pellets were placed on the goal shelf, then the animals were placed to the start box, the door was opened, and the latent period of responses was registered.

The test for experimental extinction of learned task was done at the time when the retrieval of the response by experimental

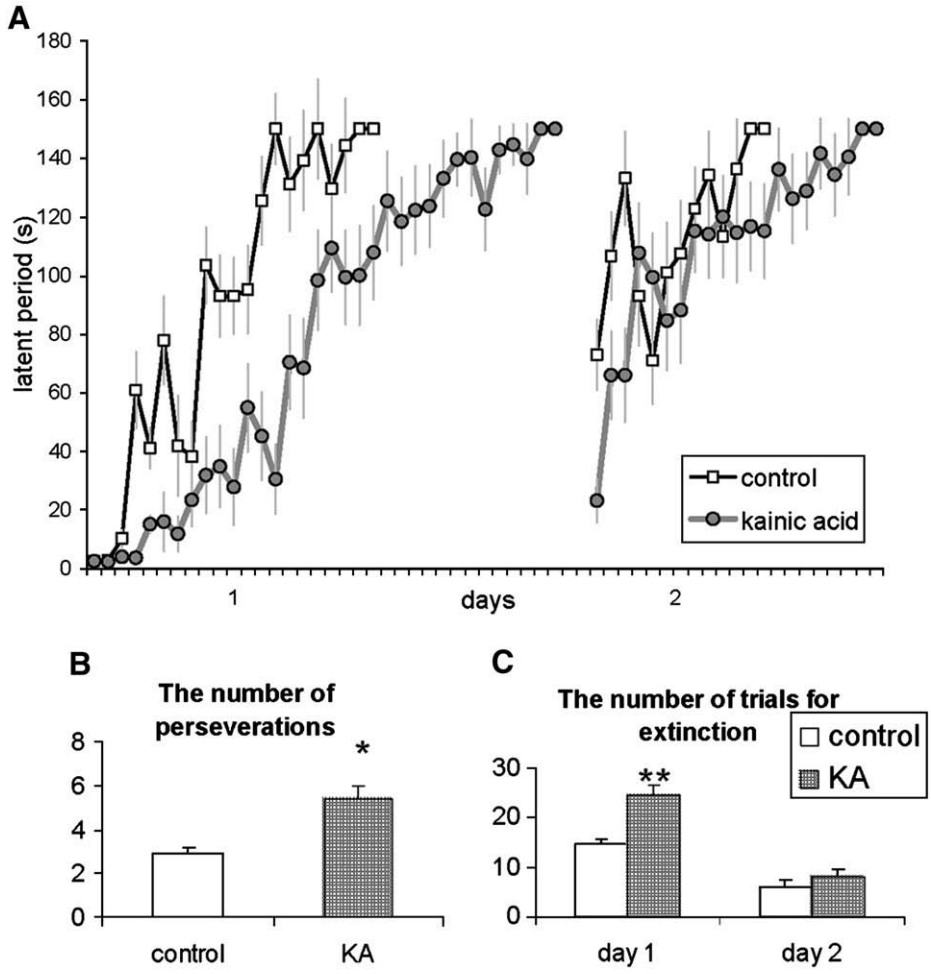

Fig. 2. A. Dynamics of latencies during experimental extinction (results are Means ± SEM). Control — animals with the injection of saline ($n=10$), KA — a group of animals treated with kainic acid ($n=8$). B. The number of perseverations in control and KA-treated groups. C. The number of trials performed by the rats in control and KA-treated groups on the first and the second days of experimental extinction. Error bars indicate SEM. *$P=0.004$; $F=19.4$; $df=16$. **$P=0.002$; $F=14.0$; $df=16$.

animals was on the control level. During the extinction procedure, the goal shelf was available for animals but food reinforcement was absent. The trial time (latency) was registered and the number of trials made by the rats during the daily session was calculated. The daily session of the test continued until animals stopped running to the goal shelf, and the latency of two subsequent trials exceeded 150 s. The mean number of trials that was necessary for the extinction was calculated in each group. Besides, perseverative reactions performed by the animals at the beginning of the extinction procedure (the number of trials with the latent period less than 10 s in succession on the first day of extinction test) were calculated also.

After the response extinction, which lasted 2 days, the animals were repeatedly trained to run for food reinforcement to the shelf G2 (Fig. 1A) displayed on the left side in the same experimental chamber. The time required for reaching the goal shelf (latent period) was registered for each rat during this relearning procedure. Mean latency during learning and relearning procedures were calculated in control and KA-treated groups. The mean numbers of trials and perseverative reactions in the experimental extinction test were calculated and analyzed using one-way ANOVA.

3. Results

During learning, latencies for the running to the goal shelf G1 gradually decreased and reached the stable level on the 4th day of the training (Fig. 1A). After completion of the learning phase all rats were treated with saline (saline-treated group) and KA (KA-treated group). An intrahippocampal injection of KA resulted in a short-term tremor of vibrissae, forelimb clonus, and eye protruding in rats. Manifestations of limbic convulsions in KA-treated rats continued less than 4 h and were not detected during the next 10 days. Therefore, the KA treatment used in the present study can be considered as a weak convulsive influence.

The test for the retrieval of learned response carried out 7 days after KA treatment or saline. During this test control animals run to the shelf G1 with short latent periods, demonstrating intact memory (Fig. 1A). In contrast, KA-treated animals showed deteriorations in memory: Latencies of several initial trials in this group were significantly longer than in the control group. A typical feature of KA-treated rats in retrieval test was a prolonged first trial in the daily session, and beginning from the second trial (all animals made 10 trials in each daily session), animals responded as rapidly as saline-treated rats (Fig. 1A). Surprisingly, such character of the retrieval (increased latency of the first trials during daily session) occurred for a few days, in spite of daily training of the rats. Three from ten rats in the KA-treated group showed a prolonged first trial during 5 successive days. While performing the first of ten daily trials, these rats behaved as habituated but unlearned animals, exhibiting a marked exploratory activity in the experimental chamber. The number of the animals with deteriorated response diminished from day to day (see Fig. 1C), and 1 week after beginning of the retrieval test all animals in the KA-treated group performed the task as in the control group. Equal performance of the task in control and KA groups gave possibility to carry out the test of extinction.

Experimental extinction of the response pursued with 8 animals; two rats with most deteriorated retrieval of the response were excluded. Since retrieval test lasted for 1 week, experimental extinction of the response began 2 weeks after the treatment and performed during 2 days. During this test the food reinforcement was absent, nevertheless in several trials animals performed habitually with a small latency and stereotypic trajectory of running. These behavior perseverations were the first step of the extinction test, after that the rats showed exploratory activity around the experimental chamber. The dynamics of the response extinction in control and KA-treated groups was significantly differed: Latency in the KA-treated

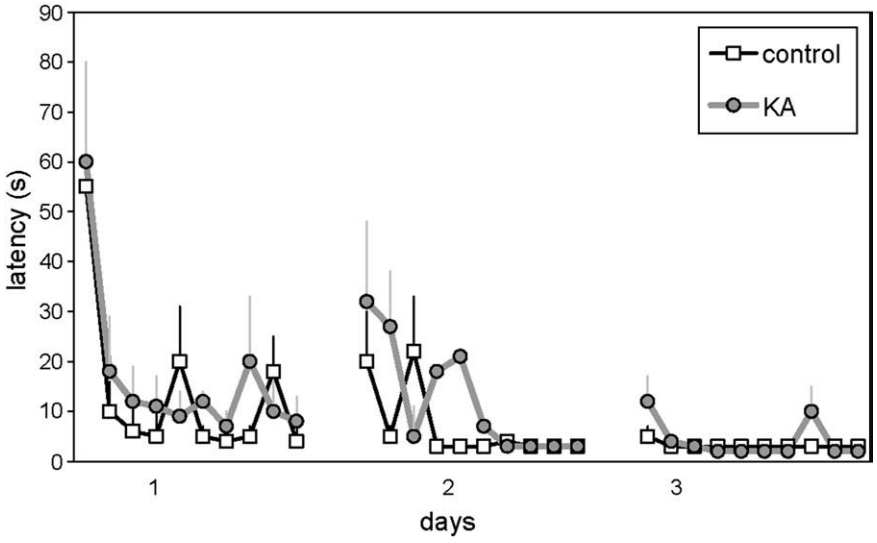

Fig. 3. Dynamics of latencies during the repeated learning. Control — animals with the injection of saline ($n=10$), KA — a group of animals treated with kainic acid ($n=8$).

group increased slower than in control (Fig. 2A). Animals in KA-treated group on the first day of the extinction test made significantly more trials until stoppage of unreinforced responses than in the control group (Fig. 2C). Behavioral perseveration at the initial stage of the test differed between groups also (Fig. 2B).

After the response extinction, all animals were trained to run towards another goal shelf in the same experimental chamber, G2 (Fig. 1B). The task in control and experimental groups was learned more quickly than during initial learning, latencies stabilized to the third day. The learning was not distinct between the KA-treated and control groups (Fig. 3).

4. Discussion

In spite of intensive investigation of KA influence on the brain, not all properties of the drug are comprehensible, thus it is not clear what changes in the brain occur 1 week and more after acute treatment with subconvulsive doses of KA. Apparently, changes of the hippocampus induced by this treatment are insignificant, because more intensive and long-lasting seizures are needed for cell death (Ben-Ari, 1985; Arkhipov et al., 2001). Nevertheless, epileptiform activity is capable to produce delayed deteriorations of memory processes by influencing on parameters of neuronal circuits (Ben-Ari, 2001). For example, a single injection of picrotoxin in a convulsive dose has delayed influence on cognitive processes in rats when the test of experimental extinction is used (Arkhipov, 2002). There is evidence that single brief epileptic seizures can lead to neuronal death signal (Bengzon et al., 1997), but compensatory processes seem to disrupt this signal without additional seizures. As for neurochemical changes, they are very diverse (Bing et al., 1997; Kato et al., 1999; Farooqui et al., 2001); gene expression analysis revealed a lot of upregulated and downregulated genes in the hippocampus of rats after KA treatment (Hunsberger et al., 2005), but it is not clear how these changes can modify cognitive functions. The dose of KA used in the present work is subconvulsive, therefore, the effects of KA could be also conditioned by the property of the drug to activate the glutamatergic neurotransmitter system, which is essential for memory processing (Myhrer, 2003).

The hippocampus is well-studied and much is known about its function in behavioral control (O'Keefe and Nadel, 1978; Squire, 1992; Milner et al., 1998; Vinogradova, 2001; Eichenbaum, 2001; Burgess et al., 2002; McNaughton and Wickens, 2003). Several behavioral tests capable of detecting dysfunction of the hippocampus have been designed. Most of these tests are associated with spatial learning and/or exploratory behavior (Gerlai, 2001). In the present study, we used appetitive-motivated spatial task which is quite complex for rats, and some days of learning were needed for subsequent confident performance. In our previous works, an analysis of response retrieval and experimental extinction of this task revealed some specific features of various pharmacological agents (Arkhipov, 1999, 2002; Arkhipov and Shevchenko, 2005). The study of the retrieval after intrahippocampal injection of KA in the present work also showed an unusual effect. After 1 week of KA treatment, memory defect appeared as specific deterioration of task performance. For several successive days in which the retrieval test was carried out, KA-treated animals could not perform the first trials of daily session correctly in spite of daily training. Obviously, the first trial played the role of the reminding procedure, after which the task was performed perfectly. This memory defect seems to be the result of the deterioration of retrieval rather than of consolidation process, because the animals retained the intact ability to learn and recall a new task (see Fig. 3).

Behavioral peculiarities in KA-treated rats were also revealed in the test of experimental extinction of the response. Two stages in the behavior of animals were observed during this test. The first stage was active perseverative behavior: The animals retrieved the response habitually with a short latent period. The number of perseverative trials indicates the ability of rats to inhibit inadequate response. Perseverations caused by the injury of the prefrontal cortex are in the highlight now (Clarke et al., 2004; Morgan et al., 2003), nevertheless, injury of the hippocampal system also results in perseverative behavior (Maruki et al., 2001; Whishaw and Tomie, 1997), and is well-documented in early works (Richard, 1970; Dalland, 1976; Manning and Mcdonough, 1974; Buzsaki et al., 1982). It is important that persevering repetition of the response by rats with hippocampal injury is inconsistent with the notion that the exclusive role of the hippocampus consists in spatial mapping or storing of recent memories. Deterioration of the spatial map should result in decreased performance of the task including a spatial component. Besides, the intact ability of KA-treated rats to learn and recall a new task (see Fig. 3) confirms the view, that spatial memory in rats is not deteriorated. Perhaps, hippocampal injury by subconvulsive doses of KA is not enough for deterioration of this kind of memory.

The second stage of the extinction test is the expression of orienting-exploratory activity, when the animals completed the running toward the unreinforcement shelf G1 and moved actively around the experimental chamber. This stage of behavior was prolonged in KA-treated rats as can be seen from the dynamics of extinction (Fig. 2A, C). It is well known, that rats with hippocampal lesions show elevated behavioral activity particularly in behavioral tasks with food reward (for references see Chan et al., 2001; McNaughton and Wickens, 2003). The strengthening of exploratory activity after KA treatment was noted elsewhere (Bardgett et al., 1997). The orienting reaction is an adaptive form of behavior providing the optimal conditions for perception and analysis of novel information, and this reaction is principally dependent on hippocampal function (Vinogradova, 2001). This form of behavior differs significantly from free locomotion, the orienting-exploratory activity is motivated and provides for an analysis of stimuli and their relations, which is absolutely necessary for any kind of learning. All changes of the established pattern of learning normally occur through the phase of reappearance of the orienting response, with renewal of analysis and temporary suppression of the previously established behavior (Vinogradova, 2001). Nevertheless, strengthened exploratory activity in KA-treated animals is not evidence of improved cognitive ability. On the contrary, long-lasting exploratory activity in rats with hippocampal dysfunction shows excessive sensitivity to distractive stimuli (Oswald et al., 2002), that is defect of selective attention.

The pattern of behavior deteriorations, which we observed after KA treatment, is most adequately explained by the assumption, that the hippocampus is a novelty detector and comparator of signals in its afferent inputs (see Ref. in: Vinogradova, 2001). According to this conception, the hippocampus accomplishes two interconnected functions: selective attention with inhibitory control, which protects the processing of information from interference, and global function of the selected information transfer into the cortical memory storage. Selected information could be of various categories: temporal, spatial, relational, and so on. Perseverations and prolonged oriented-exploratory activity revealed during experimental extinction of the response could be explained by defects in these hippocampal functions. Besides, the hippocampus participates in memory retrieval process by comparing retrieved memory traces with information required for the current task (Arkhipov, 1999). The deterioration of retrieval process can be apparently explained by a defect of this hippocampal function.

In conclusion, the results of the present work suggest that intrahippocampal injection of KA leads to deterioration of long-term memory retrieval and defects of inhibitory control, whereas the ability of animals for learning of a new appetitive task is retained. These data partly explain a lack of learning disturbance after the treatment with subconvulsive doses of KA shown in some studies (Mikulecka et al., 2000). The pattern of cognitive defects revealed in present work agrees with the conception, according to which the hippocampal system accomplishes the functions of a novelty detector and a comparator of signals in its afferent inputs.

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