Extinction of Operant Behavior as the Test for Cognitive Disorders Induced with Kainic Acid

V. I. Arkhipov and N. A. Shevchenko

Translated from *Byulleten' Eksperimental'noi Biologii I Meditsiny*, Vol. 133, No. 6, pp. 640-642, June 2002
Original article submitted February 12, 2002

Wistar rats were trained food-procuring task for 5 days and then extinction of the operant behavior was studied for 6 days after injection of an epileptogen (kainic acid, 8 mg/kg, intraperitoneally). Kainic acid induced long-term impairment of inhibitory processes in the brain, which impeded extinction of a conditioned response. This effect was prevented by daily injections of anticonvulsant sodium valproate (300 mg/kg for 4 days).

Key Words: *anticonvulsant activity*; *kainic acid*; *respiratory rate*; *sodium valproate*; *memory*

Epileptiform activity, specifically its recurrent form, leads to various morphofunctional changes in the brain and disturbs cognitive processes. The temporal cortex playing a major role in memory processes [7,10] are very sensitive to convulsive activity (CA) [8]. However, even potent CA inducing pronounced structural changes leads to only minor disturbances in long-term memory, which can be compensated with time. On the other hand, CA of low intensity and duration producing no visible morphofunctional changes in the brain could lead to considerable cognitive deficiency in animals [2].

We previously found that partial picrotoxin-induced kindling in rats had no effect on learning and retrieval of food-procuring conditione response, but substantially disturbed extinction processes [1]. The aim of this work was to elucidate whether other CA inducers, in particular kainic acid, can produce such impairment. We also studied whether anticonvulsant sodium valproate can compensate for the effects of kainic acid.

Laboratory of Synaptic Transmission Mechanisms, Institute of Theoretical and Experimental Biophysics, Russian Academy of Sciences, Puschino, Russia. ***Address for correspondence:*** arkhipov@iteb.serpukhov.su. Arkhipov V. I.

MATERIALS AND METHODS

Experiments were carried out on male Wistar rats (n=25) weighing 170-180 g. The animals were kept under normal conditions with a special dietary regimen on days of behavioral experiments.

The rats were trained to find the target shelf within 10 sec in a special experimental chamber [3]. Training was carried out for 5 consecutive days; each session consisted of 10 runs.

Trained rats were divided into three experimental groups. Group 1 rats (n=8) were injected with kainic acid (RBI; 8 mg/kg, intraperitoneally) immediately after completion of training and 0.9% NaCl for subsequent 4 days. Group 2 rats (n=7) received kainic acid and then anticonlvusant (sodium valproate, RBI; 300 mg/kg, intraperitoneally) daily for the next 4 days. Control rats (n=10) were injected intraperitoneally with 0.9% NaCl.

Retention of the conditioned behavior was tested 5 was days after injection of kainic acid. To this end the rats were placed in the experimental chamber and the time of finding the target shelf was recorded.

During the next two days the rats were placed in the experimental chamber, but received no reinforcement. The number of visits to the target shelf without reward was scored and the corresponding latencies were measured. This experimental series was con-

0007-4888/02/1336-0553$27.00

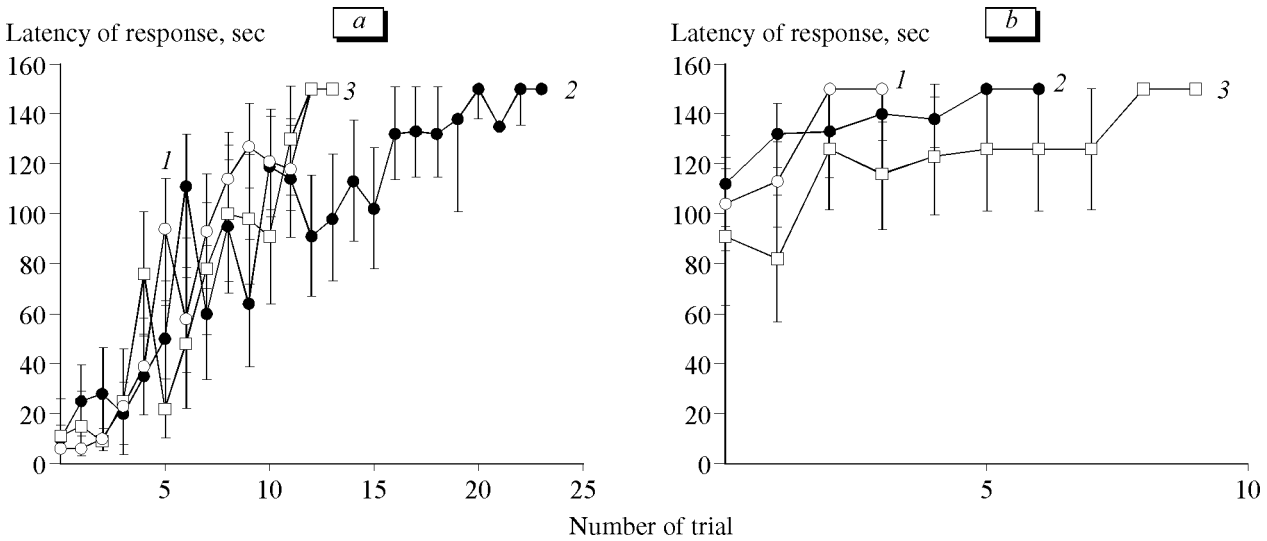

Fig. 1. Extinction of conditioned response in Wistar rats on days 1 (*a*) and 2 of the test without food reinforcement. Controls (*1*); kainic acid (*2*); kainic acid+sodium valproate (*3*).

tinued until extinction (rats do not run to the target shelf, *i. e*. the latencies in three successive trials were >150 sec).

The results were statistically analyzed by the Student's t test at $p<0.05$.

RESULTS

In some animals, kainic acid (8 mg/kg) induced convulsive reactions (they stopped moving and started grooming and shakings) as soon as 30 min after the injection. One hour postinjection CA was observed in all rats and after 2 hours it disappeared.

All three groups of animals demonstrated good retention of the conditioned response. Only in group 1 rats, the latency of reaching the target shelf in the first run was more than 10 sec. In other trials, the rats quickly and confidently run to the target shelf. Thus, kainic acid in a dose that does not induce status epilepticus caused no appreciable effect on long-term memory responsible for retention and retrieval of conditioned behavior. Nevertheless, delayed aftereffects of CA on the cognitive function were revealed in other behavioral test (extinction of the conditioned response).

On day 1 the dynamics of extinction differed in three groups of rats (Fig. 1). Kainic acid impaired the inhibitory processes in the brain. This manifested in increased number of runs in group 1 rats. These animals demonstrated enhanced exploratory activity, actively moved over the experimental chamber, and extinction in this group was attained after a greater number of runs (Fig. 2). In group 2, the dynamics of extinction did not differ from the control (Fig. 1), which confirmed the efficiency of the anticonvulsant.

Thus, kainic acid in a dose producing no appreciable memory deficiency impaired the inhibitory processes in the brain. This impairment can be revealed 6 days after administration of the convulsant. Kainic acid is a glutamate analog and potent agonist of kainate receptors, a subtype of endogenous glutamate receptors. Kainic acid exhibits selective toxicity to the hippocampus both after local and systemic administration [9]. The data on the effects of kainic acid on learning and memory are disputable. Some authors showed that systemic injection or local application of kainic acid to brain structures impairs learning and memory, while other scientists revealed no long-term memory deficiency under similar conditions [2].

Here we evaluated minor disturbances in cognitive functions induced by CA. The dose of kainic acid

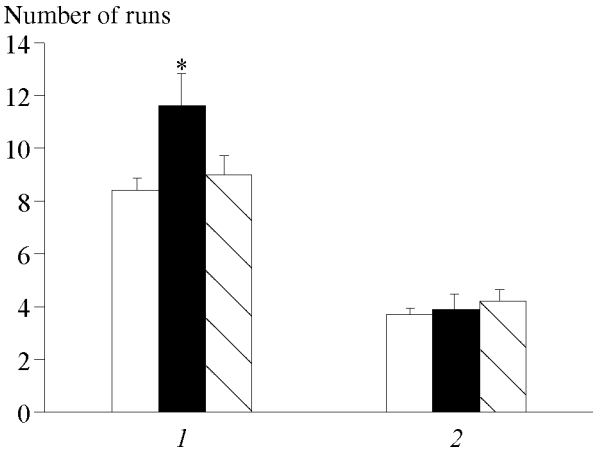

Fig. 2. Number of runs before extinction of the response in the test without food reinforcement on days 1 (*1*) and 2 (*2*). Light columns: control; dark columns: kainic acid; dashed columns: kainic acid+ sodium valproate. *$p<0.05$ compared to the control.

we used in this work was chosen so that it little affected animal behavior. However, the test on extinction of the conditioned response revealed some cognitive abnormalities. Memory extinction depends on protein synthesis and, hence, it can be inhibited by anisomycin [4]. This process is a special inhibitory type of learning characterized by some peculiarities, which manifest not only in behavior, but also in specific neural and molecular mechanisms. In contrast to the formation of conditioned taste aversion, its extinction does not depend on muscarinic receptors and mitogen-activated protein kinases [4]. Our experiments also revealed peculiarities of this inhibitory form of learning: extinction of a conditioned response can be influenced by a slight epileptogenic stimulus that has no effect on other memory mechanisms. This is true for both pharmacological kindling [1] and kainic acid models.

In many cases anticonvulsant prevent memory disorders induced by epileptogenic stimuli, but can interfere memory processes themselves. Thus, their effects are diverse and depend on various factors. In our study, sodium valproate abolished the negative effects of kainic acid on cognitive function. It was established that CA and memory deficiency induced by kainic acid could be effectively prevented with sodium valproate, but not with phenobarbital [5].

Thus, impairment of inhibitory processes in the brain is the early manifestation of cognitive disturbances occurring during epileptogenesis. A possible mechanism of impairment of inhibitory process is the dysfunction of temporal regions of the brain most vulnerable to epileptiform activity, specifically of hippocampus [8]. It is assumed that the hippocampus controls orientation and exploratory behavior acting as a novelty acceptor [10]. Therefore, damage to the hippocampus will impair behavioral responses to repetitive stimuli and their inhibition. It was established that hippocampal injury affects memory extinction processes in behavioral experiments [6]. Weakened inhibition of behavioral responses in these animals is associated with perseveration and enhanced orientation activity similar to that induced by kainic acid in our experiments.

The work was supported by Regional Program "Podmoskov'e" (grant No. 01-04-97008).

REFERENCES

1. V. I. Arkhipov and D. G. Sochivko, *Byull. Eksp. Biol. Med.*, **128**, No. 7, 32-34 (1999).
2. V. I. Arkhipov, D. G. Sochivko, and O. V. Godukhin, *Uspekhi Sovremen. Biol.*, **121**, No. 2, 211-222 (2001).
3. V. I. Arkhipov, *Behav. Neural Biol.*, **57**, 244-247 (1992).
4. D. E. Berman and Y. Dudai, *Science*, **291**, 2417-24197 (2001).
5. A. R. Bolanos, M. Sarkisian, Y. Yang, *et al.*, *Neurology*, **51**, No. 1, 41 (1998).
6. T. S. Brown, P. G. Kauffmann, and L. A. Marco, *Brain Res.*, **12**, No. 1, 86-98 (1969).
7. H. Eichenbaum, *Nature Rev. Neurosci.*, **1**, No. 1, 41 (2000).
8. J. O. McNamara, *Nature*, **399**, Suppl., A15-A22 (1999).
9. J. W. Olney, V. Rhee, and O. L. Ho, *Brain Res.*, **77**, No. 3, 507-512 (1974).
10. O. S. Vinogradova, *Hippocampus*, **11**, 578-598 (2001).