Effect of Indomethacin on Kainic Acid-Induced Memory Disorders

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Single administration of kainic acid to Wistar rats impaired quenching of the conditioned response and increased the number of perseverative reactions 2 weeks postinjection. Indomethacin prevented behavioral disturbances induced by kainic acid.

Key Words: *memory; kainic acid; indomethacin; cyclooxygenases*

Memory disorders are common symptoms of neurodegenerative diseases (Alzheimer's disease, Korsakoff's syndrome, *etc.*). The search for new methods to prevent and compensate cognitive dysfunction in these patients is important for clinical practice. Such studies will elucidate the mechanism of neurodegenerative processes. The development of approaches to prevention and compensation of memory dysfunction and attention disorders is based on the established mechanisms of neurodegeneration. They include activation of the GABAergic and cholinergic system, dietary modification of the lipid composition of brain cells, prevention of oxidative stress with antioxidants, modulation of nitric oxide synthesis, and treatment with antiinflammatory and immunomodulatory drugs. The kainate model is extensively used in modern studies [1-3,5,10,12]. A specific feature of kainic acid (KA) is its ability to initiate epileptogenesis accompanied by neuronal death in the temporal area of the brain [7,10]. Administration of KA is followed by the development of cognitive dysfunction in animals, which mainly depends on activity of the hippocampal system [2, 3,7]. Our previous studies showed that treatment with the anticonvulsant valproate prevents memory disorders induced by KA [2]. Here we studied protective activity of nonsteroid antiinflammatory drug indomethacin.

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MATERIALS AND METHODS

Experiments were performed on 25 male Wistar rats weighing 170-180 g. During behavioral studies the animals were maintained under normal conditions and specific feeding regimen. The rats were trained in food-procuring behavior in an experimental chamber for 5 days (10 trials per day). During this period the animals learned to run to a target shelf over less than 10 sec. Behavioral tests were described elsewhere [1]. After training the animals were divided into 3 groups. Group 1 rats (n=9) received KA (8 mg/kg intraperitoneally, RBI) and were treated with isotonic NaCl over the next 9 days. Group 2 rats (n=7) received KA (8 mg/kg intraperitoneally) and were treated with indomethacin (4 mg/kg intraperitoneally, Sigma) at 24-h intervals. Control rats (n=12) received physiological saline. In group 2 animals indomethacin was injected 4 h after treatment with KA and then daily for 9 days. The dose of the test drug was selected taking into account the results of our previous experiments and published data on chronic administration of indomethacin to rats [13].

Retention of conditioned behavior was tested 14 days after treatment with KA. The rats were placed in an experimental chamber and the latency of run to the target shelf was measured. The next

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series was conducted to study quenching of the conditioned response. Over 2 days the animals were placed in the chamber, but did not receive food reinforcement. We recorded the latency of the response and number of unreinforced reactions. The animals were placed in the chamber until they stopped to run to the target shelf. The latency of more than 150 sec over 3 successive runs served as the criterion of quenching. We also recorded the number of automatized perseverative reactions during the first day of quenching (number of successive runs with a duration of less than 10 sec over the first day of quenching).

The results were analyzed by Student's *t* test.

RESULTS

Limbic seizures (cessation of normal activity, grooming, and shaking) were observed in some rats 30 min after administration of KA in a dose of 8 mg/kg. All animals exhibited this behavior 1 h after treatment. Limbic seizures lasted 2-3 h, but were not observed in the follow-up period (3 weeks).

Conditioned behavior in rats 14 days after KA administration did not differ from the control. All animals reproduced the response. Behavioral differences were revealed only in quenching of the experimental response. Published data show that this behavior is impaired under the influence of KA [1-3]. Quenching is gradual cessation of its reproduction in the absence of reinforcement. This specific type of inhibitory learning requires replacement of the skill and adaptation to new experimental conditions [8]. After administration of KA group 1 rats exhibited greater number of runs to unreinforced shelf until cessation of skill performance (Fig. 1, Table 1). The number of perseverative reactions in these rats was higher than in controls. The increase in the number of perseverative reactions is associated with impairment of adaptive behavior and manifested in repeated run to the unreinforced shelf. Administration of indomethacin over 9 days after treatment with KA prevented the development of memory disorders (Table 1). In these rats the incidence of perseverative reactions and the number of runs until cessation of skill performance approached the control.

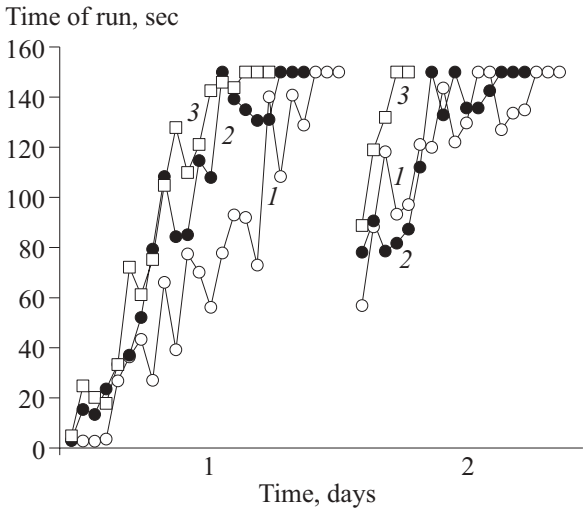

Fig. 1. Quenching in experimental animals of various groups. Administration of kainic acid (*1*); administration of kainic acid and indomethacin (*2*); control (*3*).

Indomethacin is a nonselective inhibitor of cyclooxygenases (COX-1 and COX-2) serving as the key enzymes of prostaglandin synthesis (lipid mediators of preimmune resistance). COX-2 expression depends on synaptic activity and significantly increases during stimulation of glutamate receptors [6]. It was hypothesized that COX-2 and synthesized prostanoids are involved in postsynaptic signal transduction from excitatory neurons and play an important role in normal plasticity of the brain and progression of pathological processes. The inhibition of COX-2 impairs long-term memory [11,14]. Cognitive dysfunction that accompanies aging and neurodegenerative diseases is associated with activity of this enzyme [4]. Expression of COX-2 mRNA increases 4 h after administration of KA and remained high by the 24th hour [9]. However, little is known about the role of cyclooxygenases and prostanoids in the progression of neurodegenerative processes induced by KA. Selective COX-2 inhibitors can potentiate the inducing

TABLE 1. Quenching of Conditioned Behavior after Administration of KA and Indomethacin (*M*±*SD*)

Parameter	Control (*n*=12)	KA (*n*=9)	KA and indomethacin (*n*=7)
Number of perseverations	2.6±0.4	4.90±0.35**	2.3±1.1
Number of runs until the cessation of skill performance, day 1	10.1±0.8	14.7±1.8*	11.2±3.0
Number of runs until the cessation of skill performance, day 2	4.3±1.7	5.6±1.2	4.1±2.3

Note. *p=0.02 and **p=0.001 compared to the control.

effect of KA on seizure activity in mice. Moreover, these agents significantly increase the number of damaged hippocampal neurons [5]. Probably, prostanoid synthesis and cyclooxygenase activation play a protective role in the initial stage of seizure development. The pathogenic influence of these events manifested at late stages. Moreover, the COX-1/COX-2 ratio should be taken into account.

Our results and published data [10,12] suggest that nonsteroid antiinflammatory drugs produce a protective effect on cognitive function under the influence of KA. This action depends on the time of treatment and selectivity of the effect on COX-1 and COX-2. Selective inhibition of COX-2 usually impairs cognitive function in animals [11,14]. Nonsteroid antiinflammatory drugs administered not less than 2 h (4 h in our study) after the start of KA-induced seizure activity have a positive effect [10, 12]. However, administration of these drugs immediately before treatment with KA increases symptoms of seizure activity [5,10].

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