GENERAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

Impairment of Learning and Memory after Photothrombosis of the Prefrontal Cortex in Rat Brain: Effects of Noopept

G. A. Romanova, F. M. Shakova, T. A. Gudasheva*, and R. U. Ostrovskaya*

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Experiments were performed on rats trained conditioned passive avoidance response. Acquisition and retention of memory traces were impaired after photothrombosis of the prefrontal cortex. The acyl-prolyl-containing dipeptide Noopept facilitated retention and retrieval of a conditioned passive avoidance response, normalized learning capacity in animals with ischemic damage to the cerebral cortex, and promoted finish training in rats with hereditary learning deficit. These results show that Noopept improves all three stages of memory. It should be emphasized that the effect of Noopept was most pronounced in animals with impaired mnesic function.

Key Words: *photothrombosis; prefrontal cortex; Noopept; conditioned passive avoidance response*

Disturbances in integrative functions of the central nervous system (CNS) result from damage to the cerebral cortex during ischemic stroke (cerebral infarction)associated with persistent focal morphological changes in brain structures. These disorders are characterized by destructive changes followed by the loss of functions due to interruption of functional relationships, injury, and disintegration of existing physiological systems. Damage to the cerebral cortex is a general pathological process, which violates CNS functions associated with this brain region.

The prefrontal cortex is responsible for spatial orientation. This structure and the hippocampus play a key role in the mechanisms of learning and memory [2, 4,7,8].

Previous studies showed that local photochemical damage to rate prefrontal cortex (photothrombosis) produces amnesia. Pathomorphological assay of the brain performed after behavioral tests revealed focal ischemic necroses in the cerebral cortex separated from intact surrounding tissues [11].

Here we evaluated impairment of conditioned passive avoidance response (CPAR) produced by photochemical damage to the prefrontal cortex, learning deficit in animals with ischemic focuses formed after photothrombosis of vessels in this brain area, and correction of memory disorders with the acyl-prolyl-containing dipeptide Noopept [3].

MATERIALS AND METHODS

Experiments were performed on male outbred rats weighing 180-200 g. Locomotor activity was studied in the open-field test using a computerized RODEO-1 device. Functional state of CNS was evaluated by the latency of transition from the dark to the illuminated compartment. CPAR learning was successful, if the rat stayed in illuminated compartment for 300 sec. The procedure of CPAR learning was described elsewhere [9]. The animals were intraperitoneally narcotized with 300 mg/kg chloral hydrate. Bilateral focal ischemia of the prefrontal cortex was induced by photo-

Institute of General Pathology and Pathophysiology; *Institute of Pharmacology, Russian Academy of Medical Sciences, Moscow. ***Address for correspondence:*** parochial@mtu-net.ru. Romanova G. A.

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stimulation of vascular thrombosis [13], which most adequately reproduces ischemic stroke. This method is based on photostimulation of thrombosis in cerebral vessels during the interaction between the photosensitive stain Bengal rose (3%, 40 mg/kg) administered into the vascular bed and focused beam delivered using a xenon lamp (24 V, 250 W). The reaction led to the release of free oxygen, activation of redox reactions, damage to the vascular endothelium, and platelet aggregation resulting in thrombus formation and occlusion of vessels (ischemic insult) [5].

Light beams were consecutively directed to intact cranial surface above the prefrontal cortex of the left and right hemispheres (15 min each). Noopept was injected intraperitoneally in a dose of 0.5 mg/kg 1 h after bilateral focal ischemic damage to the prefrontal cortex and then daily for 9 days. The last treatment was performed 15 min before testing. When CPAR learning was preceded by photochemical damage to the prefrontal cortex, Noopept was given 1 h after photothrombosis, for 9 days before and during learning, and 15 min before testing.

We performed 3 series of experiments. In series I the rats were learned CPAR and then exposed to photothrombosis of the prefrontal cortex. Retention of CPAR was tested 9 days after surgery. In this series we compared CPAR performance in animals of 3 groups: sham operation and 0.9% NaCl (group 1, n=10); photothrombosis and 0.9% NaCl (group 2, n=9); and photothrombosis and 0.5 mg/kg Noopept (group 3, n=9).

In series II Noopept was administered 1 h after photothrombosis and then daily for 9 days. After this treatment, the animals were trained CPAR. We compared learning ability in animals of 3 groups: sham operation and 0.9% NaCl (group 1, n=15); photothrombosis and 0.9% NaCl (group 2, n=15); and photothrombosis and 0.5 mg/kg Noopept (group 3, n=15).

In our experiments 30-35% animals were unable to learn CPAR. Series I was performed on rats remaining in the light compartment over 300 sec during CPAR retention test. The animals entering the dark compartment earlier than 300 sec after the start of this test ("half-learned rats") were used in series III. These rats were divided into 2 groups. Experimental animals (n=9) received 0.5 mg/kg Noopept for 9 days before and during finish training. Control rats (n=6) received physiological saline for 9 days. CPAR retention was tested on day 9 after finish training.

The results were analyzed by Mann—Whitney U test.

RESULTS

In series I ischemia of the prefrontal cortex markedly decreased the latency of CPAR in group 2 rats on day 9 after photothrombosis. Daily intraperitoneal treatment with Noopept increased this parameter compared to animals receiving physiological saline (Fig. 1, *a*).

Series II showed that chronic administration of Noopept facilitates CPAR acquisition compared to that in untreated animals (Fig. 1, *b*).

In series III Noopept promoted finish training in 62.5% (p<0.05) rats, while control animals did not complete learning.

Our results show that in animals with impaired acquisition and retention of memory traces, Noopept facilitates CPAR retention and retrieval, normalizes learning capacity in animals with ischemic damage to the cerebral cortex, and promotes finish training in rats with hereditary learning deficit. Thus, Noopept improves all three stages of memory. It should be emphasized that the nootropic effect of this preparation was most pronounced in animals with photothrombosis-impaired mnesic functions.

Our findings are consistent with the results of previous experiments with electrical shock-produced damage. Noopept administered before and after training or before testing was effective in the CPAR task. Therefore, Noopept facilitates information processing, storage, consolidation, and retrieval [9].

Noopept decreases infarction area during cortical thrombosis [11] and exhibits anticoagulant, fibrinolytic, and antithrombotic properties [6]. Moreover, Noopept protects brain neurons from damaging factors during cerebral ischemia. Experiments with isolated snail neurons showed that Noopept in doses of 10^{-8}-10^{-9} M blocks potential-dependent Ca^{2+} and K^{+} channels [12]. Studies of cultured granular neurons from rat cerebellum demonstrated that Noopept in a dose of

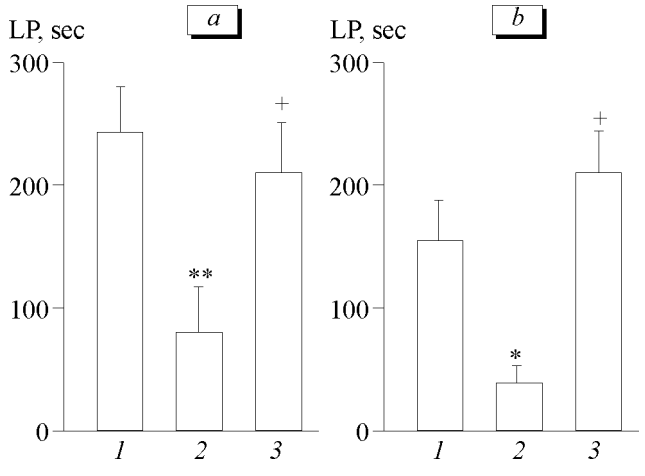

Fig. 1. Effects of Noopept on retention (*a*) and learning (*b*) of conditioned passive avoidance response (LP, latency period) during photothrombosis of the prefrontal cortex: sham operation and 0.9% NaCl (*1*), photothrombosis and 0.9% NaCl (*2*), and photothrombosis and Noopept (*3*). *p<0.001 and **p<0.05 compared to *1*; ^{+}p<0.05 compared to *2*.

10^{-6} M prevents cell death produced by glutamate in a neurotoxic concentration of 75 mM or initiated under conditions of lipid peroxidation induced with $FeSO_4$, sodium ascorbate, and glucose and oxygen deprivation [1].

These data indicate that Noopept possessing various neurochemical properties holds much promise for the therapy of insult and post-insult states. The model of local photochemical damage to the prefrontal cortex in rat brain is suitable and adequate for studying amnesia and learning deficit in the postischemic period.

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