Antiamnesic Effect of Acyl-Prolyl-Containing Dipeptide (GVS-111) in Compression-Induced Damage to Frontal Cortex

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny,* Vol. 130, No, 9, pp. 272-274, September, 2000
Original article submitted March 15, 2000

Antiamnestic effect of acyl-prolyl-containing dipeptide GVS-111 was demonstrated in rats with bilateral compression-induced damage to the frontal cortex. Both intraperitoneal and oral administration of the dipeptide improved retrieval of passive avoidance responses in rats with compression-induced cerebral ischemia compared to untreated controls.

Key Words: *compression of the cerebral cortex; dipeptides; behavior; nootropics*

Focal cerebral ischemia caused by local superficial compression with subdural hematoma or resulting from neurosurgical intervention (retraction ischemia) leads to cortex destruction and the formation of cortical infarction. Clinical observations are confirmed by experimental studies on animals with cerebral compression ischemia [3,11-13].

Our previous findings showed that bilateral compression of the frontal cortex not only causes focal ischemic necrosis, but also disturbs integrative activity of the CNS [3]. The search of pharmacological agents for prevention of secondary pathological processes is an important aspect in the analysis of the mechanisms of neuronal death and traumatic and ischemic damage to the brain.

The frontal (prefrontal) cortex is a principal structure responsible for spatial orientation; it also plays an important role in learning and memory [7].

The aim of the present study was to investigate the antiamnesic effects of a new nootropic drug GVS-111 in experimental bilateral compression-induced focal damage to the frontal cortex.

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MATERIALS AND METHODS

Experiments were carried out on 64 outbred male albino rats weighing 180-200 g. Before surgery the animals were tested in an open field (recording horizontal activity in a RODEO-1 automatic set for 5 min) and trained conditioned passive avoidance task (PA). The latency of transition from the light to dark compartment in the experimental chamber was evaluated [6]. On day 1 the rat was placed into the compartment illuminated with 100 W bulb and allowed to enter the dark compartment (the mean latency of transition before learning was 10 sec) and stay there for 5 min (the door between the compartments was closed after entry). This procedure was repeated after 1 h, but this time the rat was immediately taken out of the dark compartment. On the next day the procedure was repeated twice with a 1-h interval. During the second session the entry to the dark compartment was punished with an electric shock (1.0 mA, 50 Hz, 4 sec) applied through the metal grid floor. The latency of 300 sec was taken as the criterion of successful learning, the animals with shorter latencies were discarded from further experiments. Bilateral compression of the frontal cortex was modeled under chloral hydrate anesthesia (300 mg/kg, intraperitoneally). The head was fixed in a stereotaxic apparatus, the scull

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TABLE 1. Effect of Bilateral Compression of the Frontal Cortex and Postoperative Treatment with GVS-111 on Horizontal Motor Activity and Latency of Passive Avoidance Response in Rats ($M \pm m$)

Index	Before compression	Day 9 after compression			
		sham-operation+NaCl	compression		
			+NaCl	+GVS-111, i.p.	+GVS-111, *per os*
Motor activity	312.3±28.4	120.6±21.3	186.3±24.0	140.2±30.5	172.8±31.3
PA latency	300	165.50±24.89*	44.20±7.65+	161.20±29.13*	117.20±41.39**

Note. *$p<0.01$; **$p<0.05$ in comparison with compression+NaCl, +$p<0.05$ in comparison with the corresponding parameters before surgery.

over the two frontal regions were drilled with a 3-mm cylinder milling cutter, then the dura mater was cut and a teflon rod (2 mm in diameter) fixed in a stereotaxic manipulator was slowly introduced into the cortex to a depth of 2 mm for 15 min (compression pressure 40 mm Hg). Then the rod was removed and the wound was sutured. The control (sham-operated) rats were anesthetized and underwent cranial trepanation without brain damage. Horizontal activity in the open field and PA performance were evaluated on day 9 after surgery. The animals were divided into 4 groups: sham-operated rats treated with saline (group 1, control); rats with compression damage treated with saline (group 2), intraperitoneal GVS-111, 0.5 mg/kg (group 3), and oral GVS-111, 10 mg/kg (group 4).

The rats received GVS-111 and saline 1 h after surgery and then daily until day 9. On day 9 intraperitoneal GVS-111 was administered 15 min and oral GVS-111 60 min before testing. The data were analyzed statistically using Student's t test.

RESULTS

The studied groups did not significantly differ in horizontal motor activity and PA latency before surgery.

Bilateral compression of the frontal cortex led to necrosis (ischemic infarction) [3]. On day 9 after surgery the rats showed considerable behavioral disorders. Group 2 rats exhibited higher motor activity compared to sham-operated controls ($p<0.05$), and considerably shorter PA latency ($p<0.01$) (Table 1). Daily intraperitoneal injections of GVS-111 (group 3) normalized motor activity, while oral administration (group 4) was had no effect on this parameter (Table 1).

Both intraperitoneal and oral GVS-111 improved PA performance. The PA latency in groups 3 and 4 significantly differed from that in group 2 and approached the control value, which confirmed its pronounced antiamnesic, *i. e.* nootropic effect.

We have previously shown that postoperative administration of piracetam in a dose of 500 mg/kg *per os* improves PA performance after compression ischemia of the frontal cortex [2]. In the present study, orally administered GVS-111 produced similar effect in a much lower dose (10 mg/kg), which attested to its higher nootropic activity compared to piracetam. Previous studies demonstrated that local compression of the cerebral cortex leads to a combined ischemic and traumatic damage [3]. Behavioral disorders caused by this damage can be attributed to a variety of pathogenic mechanisms including destabilization of ionic homeostasis, disturbed transport of Ca^{2+} ions and their accumulation in neurons, activation of lipid peroxidation, enhanced release of glutamate producing a neurotoxic effect, and other metabolic shifts associated with ischemic damage to cell membranes [8,14]. Experiments on animals with impaired cognitive functions showed that GVS-111 prevented or decelerated these pathological processes and exhibited both neuroprotective and nootropic activity [1,4,9,10,15].

GVS-111 is metabolized to cyclo-prolyl-glycine, which is a new endogenous cyclic dipeptide with nootropic activity identified in the brain [6]. It can be assumed that nootropic effects of GVS-111 involve endogenous peptidergic mechanisms. In conclusion, GVS-111 can be considered as a promising drug for the treatment of CNS functional disorders, caused by traumatic and ischemic damage to the cerebral cortex.

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