GENERAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

Correction of Cerebral Ischemia in Low-Resistant Animals with an Antistress Drug Deltaran

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Deltaran decreased the amplitude of EEG slow waves and restored neuronal reactivity after carotid artery occlusion in Wistar rats sensitive to cerebral ischemia. Deltaran had no effect on local cerebral blood flow. This drug increased blood supply to a unit of neuronal activity in the brain of intact animals during the acute stage of cerebral ischemia, provided 100% survival rate of rats with cerebral ischemia, and prevented the development of neurological symptoms in survivors. Animal experiments proved the possibility of correcting cerebral ischemia with antistress drug Deltaran.

Key Words: *cerebral blood flow; cerebral ischemia; delta sleep-inducing peptide; Deltaran; emotional resistance*

Under similar conditions of experimental cerebral ischemia, the severity of disorders depends on the deficiency of macroergic substances and strict organization of respiratory metabolism in the brain tissue [2], as well as by high intensity of basal blood flow in the brain and its more drastic impairment during common carotid artery occlusion [1,3]. Wistar rats exhibiting low activity in the open-field test and predisposed to emotional stress are highly sensitive to cerebral ischemia [6,9]. The concentration of catecholamines in the brain tissue and adrenal glands [7,10] and content of neuropeptides in brain structures and blood of these rats [7,8,10,11] are much lower than in stress-resistant animals. An inhibitory amino acid transmitter glycine binds toxic compounds (aldehydes and ketones) intensively formed during acute ischemia [4]. Stress and various diseases are accompanied by a deficiency of endogenous neuroprotectors, including delta sleep-inducing peptide (DSIP).

Here we studied whether a neuroprotective drug Deltaran consisting of glycine and DSIP with stress-protective, nootropic, and adaptogenic properties can be used for reducing the severity of ischemic injury to the brain.

MATERIALS AND METHODS

Experiments were performed on 32 male Wistar rats weighing 350-400 g. The animals were tested in the open field [5]. Experimental rats had locomotor activity index of 0.2-0.6 and were prognostically resistant to cerebral ischemia. The direct effect of Deltaran (Komkon) on local cerebral blood flow (lCBF), electrical activity of the brain (EEG recording), and adequacy of blood supply (lCBF/EEG) was studied on 6 narcotized animals for 120 min. The control group included 18 rats. Cerebral ischemia in intact animals was produced by sub-

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sequent bilateral occlusion of the common carotid arteries under nembutal anesthesia (45 mg/kg). The left carotid artery was ligated first. Treated rats (n=8) received intraperitoneal injections of Deltaran in a dose of 10 μg/300 g body weight (10 μg/ml) 20 min before narcosis and 40 min before common carotid artery occlusion. Periflux lCBF in both cerebral hemispheres was measured in the zone of collateral blood supply to the parietooccipital cortex using needle optical light guides (Laser-Doppler Flowmeter, Peri Flux-3). The measurements were performed before, over the first minutes, and by the 20th minute of cerebral ischemia. EEG was recorded from the surface of metal optical light guides on a PM-6000 polygraph (Nikon Kohden). Since slow waves (4-8 Hz) dominate in narcotized small laboratory animals, the integral amplitude (μV) [1] and lCBF/EEG ratio were determined at 5-sec intervals. The mortality rate and neurological deficit in survivors were determined by the McGrow scale for small laboratory animals [12]. The results were analyzed by paired and unpaired Student's t tests.

RESULTS

Deltaran has no effect in healthy organism [13]. Deltaran injection to intact animals with low emotional resistance was followed by statistically insignificant variations in lCBF. The reaction to the test preparation differed in different animals, which was probably associated with basal emotional reactivity and individual sensitivity to Deltaran. The amplitude of EEG slow waves in both hemispheres decreased 5 min after injection. A 25% decrease was observed 30 min after treatment (p<0.05). Electrical activity of the brain remained low over 120 min after Deltaran administration. The mean blood supply to a unit of neuronal activity in the left and right hemispheres increased by 61 and 67%, respectively, 30 min after treatment with the antistress drug (compared to rats not receiving Deltaran). The improvement of blood supply to the brain probably compensates the deficiency in animals sensitive to cerebral ischemia (compared to resistant rats) [3].

Immediately after common carotid artery occlusion lCBF sharply decreased in low-resistant animals receiving Deltaran and control animals. lCBF progressively increased by the 20th minute after treatment, which was related to collateral blood supply (Fig. 1). No statistically significant differences in lCBF were revealed in control and treated rats. Deltaran had no effect on lCBF under normal conditions and during cerebral ischemia.

Electrical activity of the brain increased over the first minutes after common carotid artery occlusion against the background of Deltaran treatment. EEG remained practically unchanged in animals not receiving Deltaran (Fig. 2). Electrical activity in treated rats returned to normal by the 20th minute, but was lower than in animals not receiving Deltaran. Thus, in low-resistant rats receiving Deltaran we observed a reactive increase in neuronal activity of the brain during the acute postischemic period after carotid artery occlusion followed by its decrease by the 20th minute to a level typical of animals resistant to cerebral ischemia.

Blood supply to a unit of neuronal activity in rats receiving Deltaran was higher than in animals not receiving antistress therapy (Fig. 3). The lCBF/EEG ratio significantly decreased over the first minutes of ischemia after common carotid artery oc-

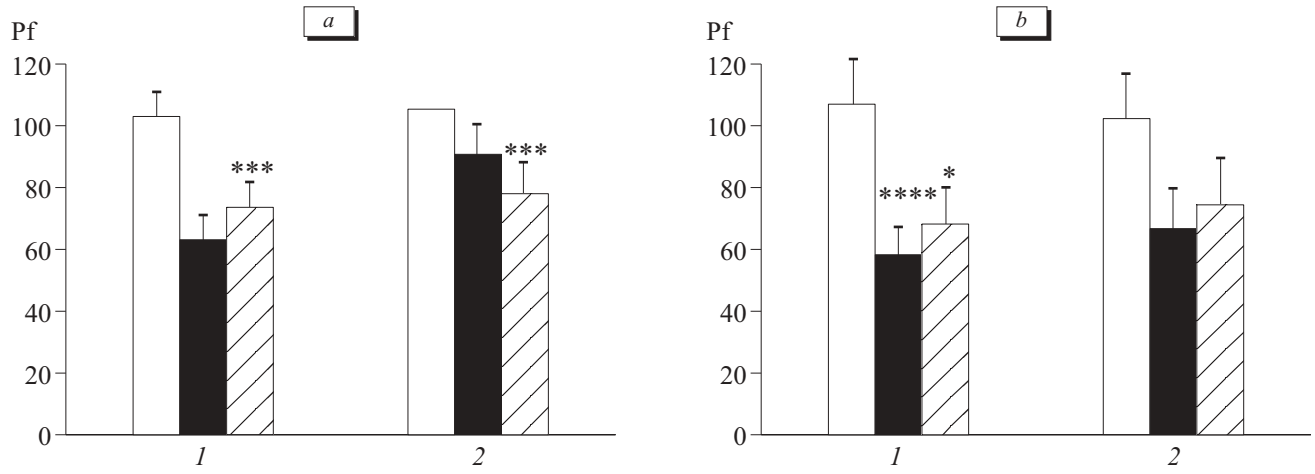

Fig. 1. Collateral cerebral blood flow in the left (*1*) and right hemispheres (*2*) of control (*a*) and Deltaran-treated rats low resistant to cerebral ischemia (*b*) after bilateral occlusion of the common carotid arteries. Pf, periflux. Here and in Figs. 2 and 3: light bars, basal level; dark bars, 1-2 min after ischemia; shaded bars, 20 min after ischemia. *p<0.05, **p<0.02, ***p<0.01, ****p<0.001 compared to the basal level.

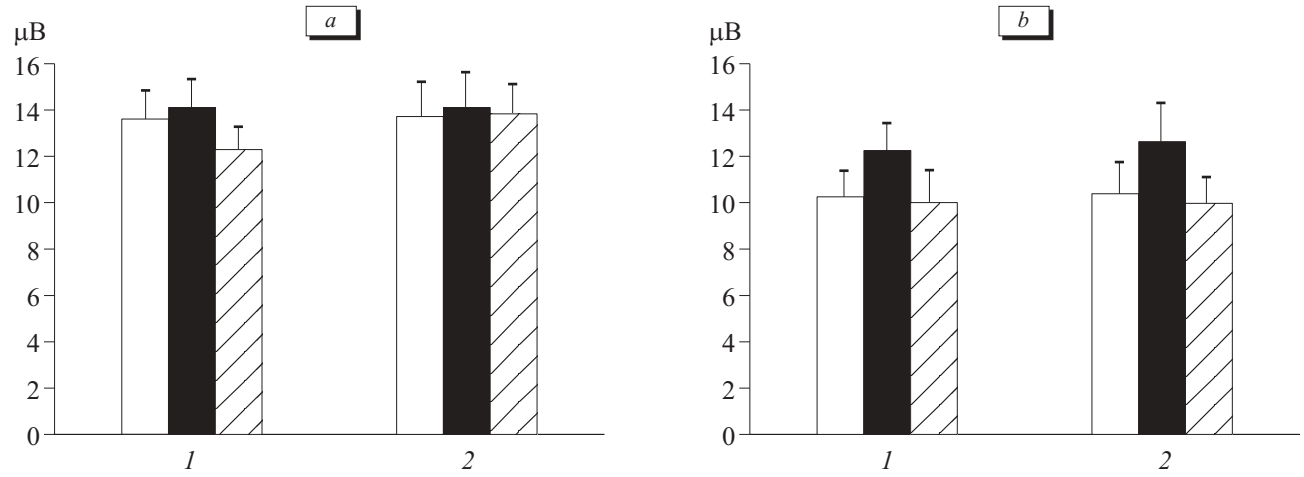

Fig. 2. Electrical activity of the left (*1*) and right hemispheres (*2*) in control (*a*) and Deltaran-treated rats low resistant to cerebral ischemia (*b*) after bilateral occlusion of the common carotid arteries.

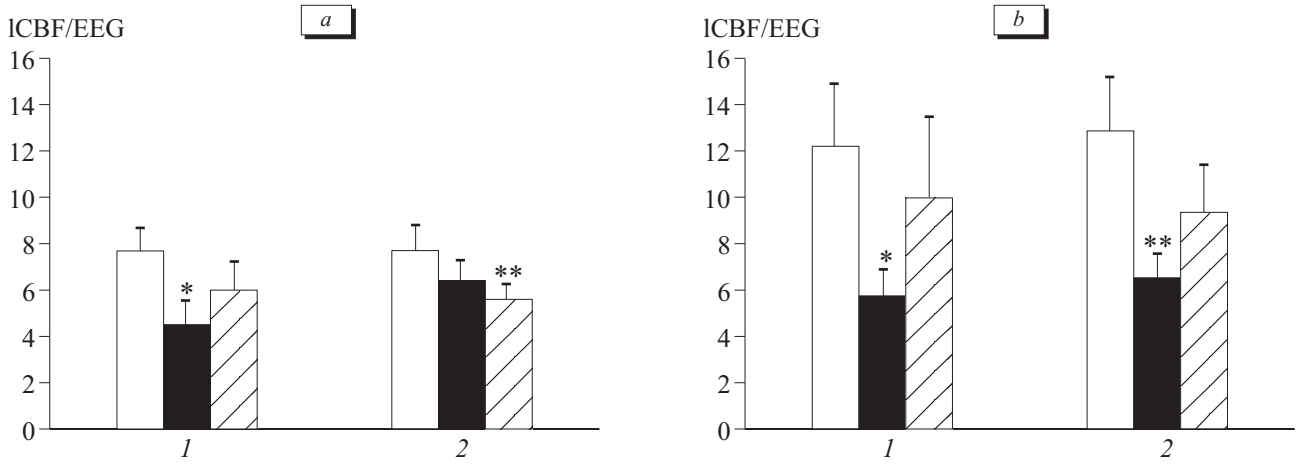

Fig. 3. Ratio of local cerebral blood flow to the amplitude of slow waves of electrical activity of the brain (lCBF/EEG) in control (*a*) and Deltaran-treated rats low resistant to cerebral ischemia (*b*) after bilateral occlusion of the common carotid arteries: left hemisphere (*1*) and right hemisphere (*2*). **p*<0.05 and ***p*<0.02 compared to the basal level.

clusion. During this period the lCBF/EEG ratio did not differ from that in animals not receiving Deltaran. The lCBF/EEG ratio increased by the 20th minute of ischemia. The lCBF/EEG ratio was 35% below the background values, but still surpassed the corresponding level in animals not receiving Deltaran, in whom blood supply to a unit of neuronal activity in the brain decreased over the first minutes and remained practically unchanged during the follow-up period. These data indicate that Deltaran produces a sedative effect on the nervous system, inhibits neuronal activity, and normalizes reactivity during ischemia. The test drug has no effect on lCBF, but increases blood supply to a unit of neuronal activity in the brain tissue. The survival rate of Deltaran-receiving animals with cerebral ischemia reached 100%. The mortality rate of rats not receiving the antistress drug was 38%. Neurological symptoms were not observed in 5 survived rats (62%). Mild neurological deficit was revealed in 3 animals (38%).

Our results suggest that antistress drug Deltaran compensating for a deficiency of endogenous neuroprotectors reduces the severity of ischemia, prevents the stress component of pathological processes, and normalizes electrical activity of the brain due to an increase in the mean blood supply to a unit of neuronal activity. The antistress neuroprotector Deltaran can be recommended as a prophylactic drug to patients with high risk of ischemic stroke and can be used in the therapy of this condition.

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