Deltaran Prevents an Adverse Effect of Emotional Stress on the Course of Cerebral Ischemia in Low-Resistant Animals

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Local cerebral blood flow in the left hemisphere decreased most significantly in low-resistant Wistar rats preexposed to emotional stress. Deltaran selectively increased blood flow in the left hemisphere and improved blood supply to neuronal activity unit of the brain in these animals. This drug prevented progressive decrease in local cerebral blood flow in both hemispheres during the acute stage of ischemia. The effect of Deltaran was related to modulation of collateral blood flow and adequate blood supply to neuronal activity unit in the brain tissue. Deltaran decreased the mortality rate (by 62%) and alleviated the symptoms of cerebral ischemia. The positive effect of Deltaran was more pronounced in the left hemisphere.

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

An important point regarding the history of patients with ischemic insult is exposure to emotional stress. Emotional stress can cause transitory ischemia, which results in circulatory hypoxia due to vasoconstriction and deceleration of cerebral blood flow in the gray matter of brain contex and in other brain structures. Neurosis is accompanied by an increase in individual variations of local cerebral blood flow (lCBF) in animals. These changes reflect the development of neurocirculatory dystonia in the brain [1,5]. Stress-induced activation of metabolism is followed by a 5-fold increase in production of hydroxyl radicals and imbalance of hormones, neurotransmitters, oxidants, and other stress mediators. Metabolic changes result in the prevalence of catabolic processes. Prior exposure to emotional stress increases the severity of cerebral ischemia and eliminates individual differences in the resistance to ischemia [2,3]. The described changes cause a variety of complications and increase the mortality rate. Inhibitory aminoacidergic neurotransmitter glycine protects the brain from excitotoxic injury. Glycine plays an important role under conditions of increased release of glutamate [6,8] and endogenous antioxidants or neuroprotectors, including delta sleep-inducing peptide (DSIP). DSIP deficiency accompanies age-related disturbances, stress, and various diseases [11].

This work was designed to evaluate whether metabolic protector Deltaran can prevent adverse effects of emotional stress on the course of cerebral ischemia. This drug possesses stress-protective, nootropic, and adaptogenic properties of glycine and DSIP.

MATERIALS AND METHODS

Experiments were performed on 36 male Wistar rats weighing 350-400 g. The animals were tested in the open field [7]. The rats had locomotor activity index of 0.2-0.6 and were prognostically predisposed to cerebral ischemia. The control group included 14 rats preexposed to emotional stress.

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Cerebral ischemia in control animals was produced by successive bilateral occlusion of the common carotid arteries (CCAO, the left carotid artery was ligated first) under nembutal anesthesia (45 mg/kg). Emotional stress was studied on the model of aggressive-conflict behavior (tail fixation for 18 h) [9]. Treated rats (n=22) were preexposed to emotional stress and received intraperitoneal injections of Deltaran in a dose of 10 μg/300 g body weight (10 μg/ml, Komkon) 20 min before narcosis and 40 min before CCAO. Periflux lCBF in both cerebral hemispheres was measured in the zone of collateral blood supply to the parietooccipital cortex using needle optical waveguides (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 waveguides on a PM-6000 polygraph (Nikon Kohden). The integral amplitude (μV) and lCBF/EEG ratio were estimated at 5-sec intervals. The mortality rate and neurological status of survivors were determined 24 h after occlusion using the McGrow scale for small laboratory animals [10]. The stress response was monitored by changes in the weights of the thymus and adrenal glands. The results were analyzed by paired and unpaired Student's t test.

RESULTS

Exposure to emotional stress for 18 h reduced lCBF in rats predisposed to emotional stress and cerebral ischemia (by 15% compared to intact animals). These changes were most pronounced in the left hemisphere (p<0.05). lCBF in the left and right hemispheres of these animals decreased by 22 and 9%, respectively. The absence of changes in EEG contributed to an 18% decrease in blood supply to neuronal activity unit. These changes were most pronounced in the left hemisphere (-22 and -13% in the left and right hemispheres, respectively). Our results are consistent with published data [2,3]. Cerebral ischemia was accompanied by a progressive decrease in lCBF in the left and right hemispheres (by 37±6 and 46±9%, respectively) without signs of collateral blood flow develorment in the acute stage (Fig. 1). The mortality rate reached 91%. Survivors exhibited mild or moderate neurological symptoms. Reactive increase in the amplitude of EEG was not observed immediately after CCAO. The amplitude of EEG decreased by the 20th minute of ischemia (Fig. 2).

Administration of Deltaran increased lCBF (most affected after stress) in the left hemisphere of animals preexposed to emotional stress. lCBF was similar in animals of this group and rats not receiving the drug (Fig. 1, basal levels). Immediately after CCAO, reduction of lCBF in rats of the Deltaran group was less pronounced compared to control animals (by 2 times). lCBF in the left and right hemispheres of these rats decreased by 20±5 and 28±5%, respectively. lCBF in Deltaran-treated rats remained high during the acute period of ischemia. Therefore, Deltaran prevents progressive decrease in lCBF to a very low level observed in animals not receiving this drug.

Administration of Deltaran decreased the amplitude of electrical activity of the cerebral cortex in animals preexposed to emotional stress (by 24% compared to the basal level, Fig. 2). The described changes were most pronounced in the left hemi-

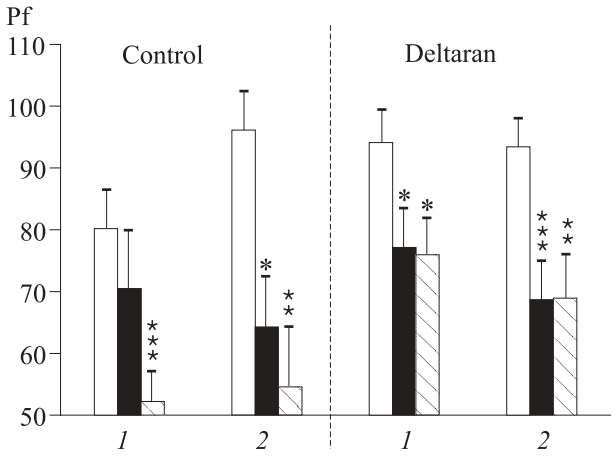

Fig. 1. Collateral blood flow in the left (*1*) and right cerebral hemispheres (*2*) of rats low resistant to cerebral ischemia and preexposed to 18-h emotional stress after common carotid artery occlusion (CCAO). Here and in Figs. 2 and 3: light bars, basal level; dark bars, 1-2 min of ischemia; shaded bars, 20 min of ischemia. *p<0.05, **p<0.01, and ***p<0.001 compared to the basal level.

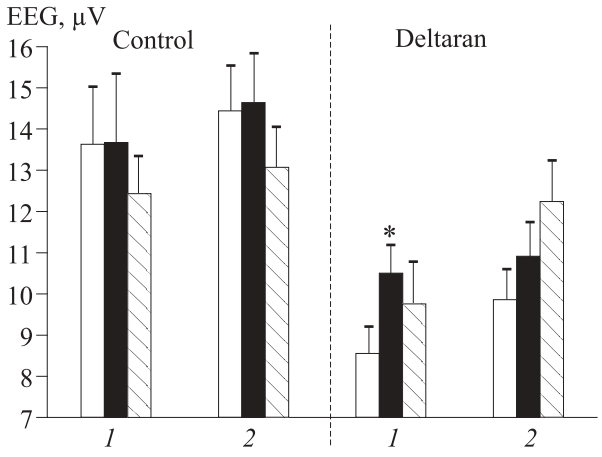

Fig. 2. Electrical activity of the left (*1*) and right cerebral hemispheres (*2*) in rats low resistant to cerebral ischemia and preexposed to 18-h emotional stress after CCAO.

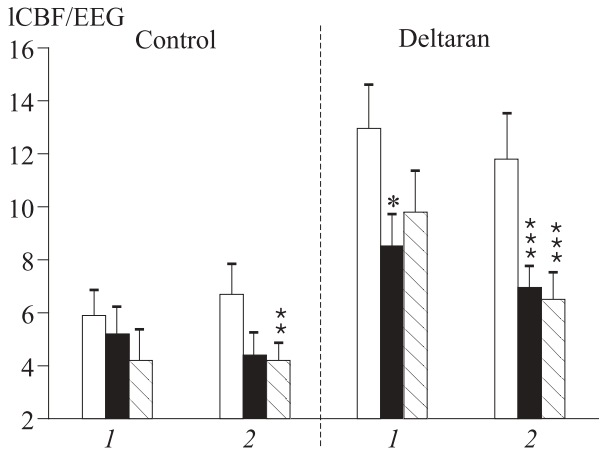

Fig. 3. Blood supply to neuronal activity unit (lCBF/EEG) in the left (*1*) and right cerebral hemispheres (*2*) of rats low resistant to cerebral ischemia and preexposed to 18-h emotional stress after CCAO.

sphere. Deltaran-treated rats exhibited a reactive increase in electrical activity of the brain immediately after CCAO (particularly in the left hemisphere). These changes were not revealed in control animals. The amplitude of slow waves in the left and, especially, in the right hemisphere remained high by the 20th minute of ischemia (12±6 and 25±8% above the basal level, respectively).

Blood supply to neuronal activity unit in the left and right hemispheres of Deltaran-treated rats was higher than in control animals (by 119 and 76%, respectively, compared to the basal level, $p<0.01$; Fig. 3). Immediately after CCAO, the lCBF/EEG ratio decreased more significantly in Deltaran-treated rats (by 21±5%). However, the lCBF/EEG ratio in these rats was higher than in control animals. The lCBF/EEG ratio in the left and right hemispheres of Deltaran-treated rats remained low by the 20th minute of ischemia (17±6 and 24±6% below the basal level, respectively). It should be emphasized that the lCBF/EEG ratio in the left and right hemispheres of Deltaran-treated rats was higher than in animals not receiving the antistress drug (by 63 and 16%, respectively, $p<0.01$).

Only 29% rats of the Deltaran group died after ischemia. Survivors had no neurological symptoms. The mortality rate of rats not receiving antistress therapy was 91%. Neurological deficit of different severity was revealed in survivors of this group.

The data show that Deltaran has no effect on blood flow in low-resistant animals preexposed to emotional stress, but selectively increases lCBF in the left hemisphere, which decreases most significantly after stress. Deltaran inhibits neuronal activity in brain tissue and, therefore, increases blood supply to neuronal activity unit in both cerebral hemispheres. lCBF in Deltaran-treated rats decreases less significantly during the acute period of cerebral ischemia (by 2 times compared to control animals). These rats exhibit a reactive increase in the amplitude of EEG immediately after CCAO. The amplitude of EEG in animals of the Deltaran group exceeds the basal level over the first 20 min of ischemia. Deltaran produces a more potent positive effect in the stress-reactive left hemisphere. Our findings are consistent with clinical data that glycine is most effective under conditions of left-sided carotid ischemic insult [6]. The mortality rate of Deltaran-treated rats with cerebral ischemia was lower compared to control animals (by 3 times, by 62%) and ischemic specimens not exposed to emotional stress (by 9%) [2]. Survivors had no or exhibited only mild neurological symptoms. It was probably associated with adequate blood supply to neuronal activity unit in the brain during the acute stage of ischemia. This drug contributes to compensatory collateral blood flow in the damaged region of the brain. We conclude that Deltaran compensates for a deficiency in endogenous neuroprotectors under conditions of emotional stress. Deltaran prevents the development of negative consequences, decreases the mortality rate, and alleviates symptoms of cerebral ischemia in low-resistant specimens preexposed to emotional stress. Our results suggest that Deltaran holds promise as a prophylactic drug for patients with high risk of ischemic stroke and individuals preexposed to severe emotional stress.

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