GENERAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

Individual Resistance to Cerebral Ischemia and Negative Effect of Emotional Stress on the Course of This Disorder

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The ratio of low-activity and high-activity rats differed in autumn, winter, and spring litters. Initially more intensive cerebral blood flow in low-active rats and its more pronounced decrease after common carotid artery occlusion determined their higher sensitivity to cerebral ischemia (compared to high-activity animals). After 18-h immobilization stress cerebral blood flow decreased by 10-15%, which abolished the difference in the individual resistance to cerebral ischemia. Independently on emotional resistance, cerebral ischemia was not accompanied by the development of collateral blood flow in the acute period and caused death of 90% rats.

Key Words: *local cerebral blood flow; cerebral ischemia; emotional resistance; emotional stress*

Published data show that animals with different emotional resistance are characterized by different reactions of functional systems to the same factors [7]. Our previous studies showed that albino rats demonstrating high activity in the open-field test (HA rats) are more predisposed to cerebral ischemia produced by common carotid artery occlusion than low-activity animals (LA rats), while in Wistar rats this relationship is inverted [2, 5]. The animals predisposed to cerebral ischemia were characterized by initially higher local cerebral blood flow (LCBF) and its more pronounced reduction during ischemia. These changes determined the development of severe brain injury than in relatively resistant animals. Double testing of albino rats (open field test and 10-min swimming in water for evaluation of their predisposition to depressive states) revealed higher mortality rate in HA rats compared to LA animals. However, HA rats with minimum depression score survived more often than LA animals with high depression score [6]. Probably, repeated testing in water used for evaluation of rat depressiveness is a stress factor that affects their physiological reactions [7,9]. The course of cerebral ischemia in animals exposed to emotional stress remains unknown. This work was designed to solve this problem.

Here we selected Wistar rats prognostically predisposed (LA in the open-field test) and resistant to emotional stress (HA in the open-field test) and determined the weights of the adrenal glands and thymus, specific features of LCBF and EEG, and LCBF/EEG ratio reflecting cerebral blood supply to cortical neurons in animals of both subgroups under control conditions. Changes in these characteristics, severity of neurological deficit, and mortality rate were estimated over the first 24 h of cerebral ischemia. We evaluated changes in the weights of target organs, LCBF, EEG, and LCBF/EEG ratio in HA and LA animals subjected to 18-h emotional stress. Test indexes in HA and LA animals exposed to emotional stress were recorded in the acute period of cerebral ischemia.

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MATERIALS AND METHODS

Experiments were performed on 300 male Wistar rats weighing 250-300 g. Emotional resistance of animals was determined by the index of locomotor activity in the open-field test [5]. Cerebral ischemia was modeled by bilateral occlusion of the common carotid arteries (first the left artery and than the right one) under Nembutal anesthesia (45 mg/kg). The mortality rate and neurological deficit in survivors were determined using the McGrow scale for small laboratory animals. Emotional stress was studied on the model of aggressive conflict behavior (tail fixation for 18 h) [8]. LCBF in cerebral hemispheres and collateral blood supply to the parietal and occipital cortex were measured using needle electrodes (expressed in periflux, Pf). The measurements were performed before, over the first minutes, and by the 20th minute of cerebral ischemia using a Laser-Doppler Flowmeter (Peri Flux-3). EEG was recorded from the surface of metal optical waveguides on a PM-6000 polygraph (Nikon Kohden). Since slow waves (4-8 Hz) dominate in narcotized small laboratory animals, their integral amplitude (μV) [2] and LCBF/EEG ratio were determined at 5-sec intervals. The results were analyzed by Student's *t* test.

RESULTS

LA rats are prognostically predisposed, while HA animals are resistant to this model of emotional stress (Table 1). Our results are consistent with published data [5]. In the population of Wistar rats the ratio between animals prognostically predisposed and resistant to emotional stress differed from that in the population of albino rats [2]. The percentage of LA and HA rats varied in autumn (36 and 25%, respectively), winter (43 and 15%, respectively), and spring litters (56 and 7%, respectively). The LA/HA ratio in autumn, winter, and spring litters was 1.7, 3, and 8, respectively. The number of ambivalent aminals practically did not differ in autumn, winter, and spring (39, 42, and 37%, respectively). The study of cerebral ischemia and stress was performed only on LA and HA animals.

Compared to control HA rats (n=17), LA animals (n=20) had higher levels of LCBF (106.00±5.81 and 121.25±6.48 Pf, respectively, p<0.05) and amplitude of EEG (12.30±1.00 and 15.17±1.20 μV, respectively, p<0.05). However, blood supply to neurons in LA rats was 7% lower than in HA animals.

LCBF was reduced in rats immediately after common carotid artery occlusion. After 20 min LCBF increased due to collateral blood supply. However, during the acute period lCBF in LA (n=18) and HA rats (n=10) was below the control by 30 and 20%, respectively (Fig. 1, *a*). The amplitude of EEG progressively increased immediately after occlusion (particularly in HA animals) and decreased to the control level 20 min later (Fig. 2, *a*). The LCBF/EEG ratio decreased by 25-35% over the first 20 min of ischemia. The reduction of lCBF was most pronounced in LA rats, which determines high predisposition of these animals to ischemia. The mortality rate for LA rats (38%) 2-fold surpassed that for HA animals (20%). In HA rats the decrease in LCBF was less pronounced due low initial value of this index.

LCBF in rats exposed to emotional stress was 10-15% lower than in the control. It was most pronounced in LA animals (Fig. 1, *b*). EEG remained unchanged after stress (Fig. 2, *b*). These peculiarities determined a decrease in the LCBF/EEG ratio, which was most pronounced in LA rats.

LCBF progressively decreased in LA (n=14) and HA rats (n=8) over the first 20 min of ischemia. No signs of collateral blood supply were observed (Fig. 1, *b*). After stress, electrical activity of the brain did not differ from the control. However, we did not reveal an increase in the amplitude of EEG in stressed animals immediately after common carotid artery occlusion (as differentiated from unstressed rats). The amplitude of EEG decreased in both cerebral hemispheres after 20 min. These changes were most pronounced in HA animals (Fig. 2, *b*). Blood supply to neurons progressively decreased. The emotional reaction to stress was so potent that differences in the individual resistance of animals to cerebral ischemia were abolished. The mortality rate increased to a similar level in rats of both groups. After 1 day the morta-

TABLE 1. Effect of Various Stress Factors on Weights of the Thymus and Adrenal Glands (mg/100 g body weight) in Rats with Different Emotional Resistance

Group	Target organ	Control	Ischemia	18-h stress	Stress and ischemia
LA rats	Thymus	64.6±1.8	52.3±1.4	44.5±3.6	37.7±1.3
	Adrenal glands	6.9±0.4	7.2±0.6	7.6±0.8	8.5±0.6
HA rats	Thymus	71.3±2.1	68.6±2.6	66.7±4.2	45.4±1.7
	Adrenal glands	6.4±0.6	6.6±0.4	6.9±0.3	7.2±0.7

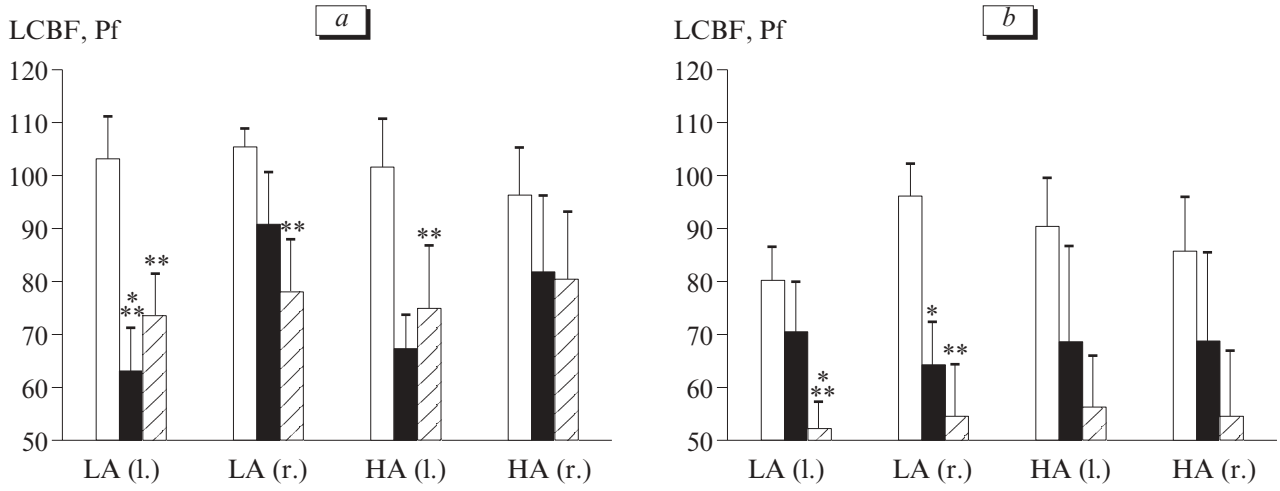

Fig. 1. Collateral cerebral blood flow (LCBF) in the left (l.) and right (r.) cerebral hemispheres of rats with different emotional resistance after common carotid artery occlusion: control rats (*a*) and animals exposed to 18-h emotional stress (*b*). Here and in Fig. 2: light bars, baseline level; dark bars, ischemia; shaded bars, after 20-min ischemia. LA: low-activity animals (predisposed to emotional stress). HA: high-activity animals (resistant to emotional stress). *$p<0.02$, **$p<0.01$, and ***$p<0.001$ compared to the control.

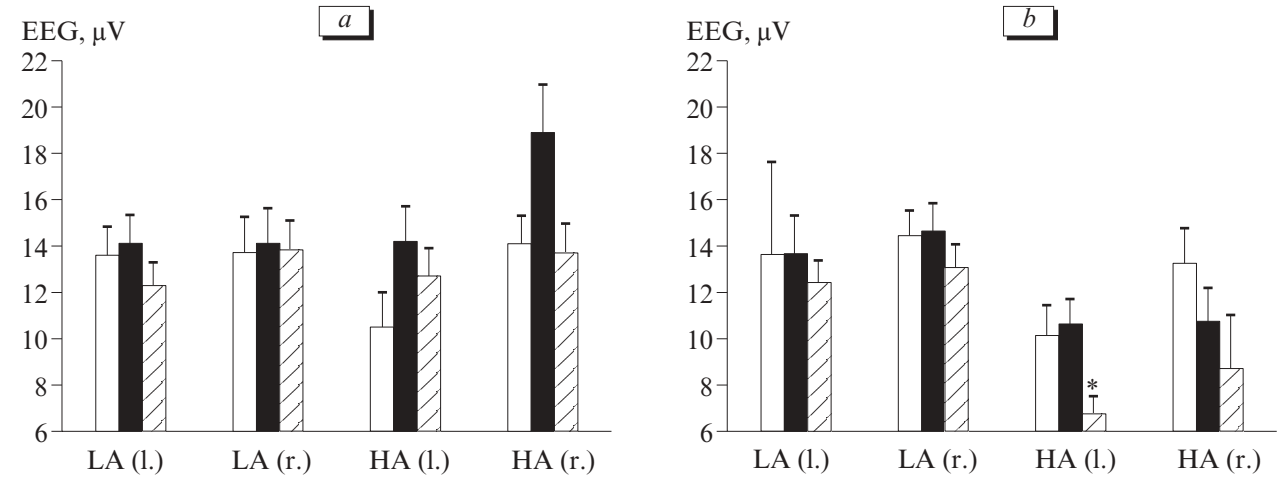

Fig. 2. Electrical activity of the left and right cerebral hemispheres in rats with different emotional resistance after common carotid artery occlusion: control rats (*a*) and animals exposed to 18-h emotional stress (*b*). *$p<0.05$ compared to the control.

lity rate for LA and HA animals was 91 and 88%, respectively.

Our results show that emotional stress (but not pain stress) is accompanied by reduction of LCBF. These changes are probably related to a neurogenic increase in cerebral vascular tone resulting from activation of the sympathoadrenal system [7]. After stress exposure, cerebral ischemia was not accompanied by the onset of collateral blood supply. Occlusion of cerebral arteries is followed by a decrease in intravascular pressure and development of metabolic changes. Under normal conditions these changes decrease the tone and cause pronounced dilation of cerebral vessels, which contributes to the increase in collateral blood supply to the basin of occluded arteries [1]. This response is observed during the loss of autoregulatory function in cerebral vessels that accompanies bilateral occlusion of the common carotid arteries [1]. We assume that the negative effect of stress exposure on the course of cerebral ischemia depends on inhibition of normal vasodilatory reaction in cerebral arteries. This reaction compensates for deficiency in collateral blood supply during occlusion of cerebral arteries. The results of previous experiments allow us to hypothesize the existence of this mechanism. Intravenous injection (before carotid artery ligation) of a polymer reducing hydrodynamic resistance of blood flow is followed by autoregulatory vasoconstriction of cerebral vessels [3] and sharply decreases collateral blood supply [4], which increases the mortality rate of animals.

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