in these parameters in LR rats, whose resistance to the oxygen deficit sharply increased, allow us to conclude that the first enzymatic complex of the respiratory chain, which helps regulate its activity, is of fundamental importance for the formation of the brain's resistance to hypoxia.

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The Effect of Extract from *Rhodiola rosea* on the Level of Inducible HSP-70 in the Myocardium during Stress

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It is demonstrated that the cardioprotective activity of extract from *Rhodiola rosea* in stress reaches the maximum 5 days after the first dose. Heat shock proteins appear in the myocardium 3 days after an 8-day administration of the extract. It is believed that these proteins are not an important factor in the cardioprotective effect of the extract.

Key Words: *adaptation; Rhodiola rosea; heat shock proteins*

Rapid synthesis of heat shock proteins with a molecular weight of 70 kD (hsp-70) is a metabolic manifestation of the stress reaction [9,10]. Undoubtedly, generalized activation of hsp-70 synthesis plays an important role in the development of the cardioprotective effects induced by adaptation to stress [2]. It has been shown that *Rhodiola rosea* possesses marked antistressor and adaptogenic activities [3].

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There is good reason to believe that the cardioprotective effect, which is probably realized with the involvement of hsp-70, is a manifestation of the adaptogenic effect of rhodiola during stress. The present study was designed to test this hypothesis.

MATERIALS AND METHODS

Experiments were performed on male Wistar rats weighing 150-200 g. The animals were adapted by administering the conventional preparation of rhodiola extract for 8 days in a daily dose of 1 ml/kg *per os.*

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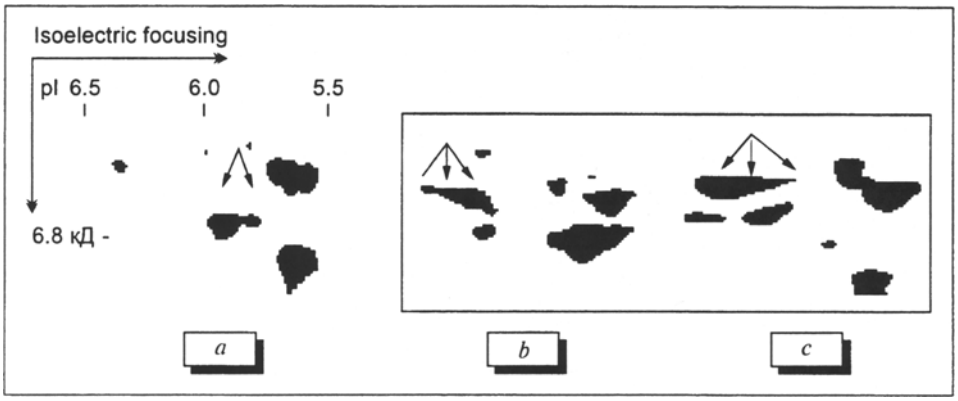

Fig. 1. Electrophoregram of cytosolic proteins of intact rats (*a*); effect of heat shock (48 h after the shock) on the content of hsp-70 in the cardiomyocyte cytosol (*b*) and effect of 8-day administration of extract from *Rhodiola rosea* (*c*, 96 h after the last administration). The localization of hsp-70 is indicated by the rectangle.

Previously, we showed that this schedule provides for the maximum antistressor and cardioprotective effects of the preparation [1].

For the identification of hsp-70 in the cytosolic fraction of cardiomyocytes, the heart was thoroughly washed free of blood by Langendorff perfusion, placed for 10 min at 4°C in a hypotonic buffer containing 10 mM Tris (pH 7.4), 10 mM KCl, and 1 mM PMSF, and then homogenized. The homogenate was filtered and centrifuged at 8000 g for 15 min. Two-dimensional electrophoresis of the supernatant was performed as described elsewhere [8]. Isoelectric focusing was carried out for 18 h at 500 V. The second dimension electrophoresis was done in 9% polyacrylamide gel by Laemmli's method [5]. Carbomoylirated carbanhydrase (LKB Pharmacia) was used as a marker for electrofocusing. Pure proteins (Sigma) were used as molecular markers. Gels were stained with $AgNO_3$ [7]; hsp-70 were identified by their molecular weight and isoelectric point (pI) [9,11].

In order to check the validity of the method employed in the present study, rats were exposed to heat shock (60-65°C, 20 min) under Barbamyl anesthesia. Emotional pain stress was modeled as described elsewhere [4]. Stress-induced damage to the myocardium was assessed by the accumulation of ^{99m}Tc-pyrophosphate [6]. Intact animals served as a control. The results were analyzed using the χ^2 test.

TABLE 1. Effect of 8-Day Administration of Extract from *Rhodiola rosea* on the Accumulation of ^{99m}Tc-pyrophosphate in the Myocardium during Stress [4] ($M \pm m$)

Group	Accumulation of ^{99m}Tc-pyrophosphate (% of total dose/g tissue)
Intact rats	0.071±0.001
6-h stress (stress control)	0.257±0.036**
6-h stress+administration of rhodiola on:	
day 1	0.219±0.007**+
day 3	0.126±0.009**+
day 5	0.091±0.004**+
day 8	0.101±0.004**+

Note. *$p<0.05$, **$p<0.001$ compared with intact animals; +$p<0.001$ compared with the stress control.

RESULTS

Administration of the extract from *Rhodiola rosea* for 8 days resulted in a significant decrease in the accumulation of ^{99m}Tc-pyrophosphate in the myocardium of experimental animals on days 3-8 of the study (Table 1), which indicates an increased resistance of rat heart to the stress-induced damage. The table shows that the cardioprotective effect of the extract reached the maximum by the 5th day after the first dose and remained unchanged after subsequent administrations.

A typical fragment of an electrophoregram of heart cytosol from intact animals is shown in Fig. 1, *a*. Forty-eight hours after heat shock, several isoforms of stress-induced hsp with a molecular weight of about 71 kD and pI ranging from 6.0 to 6.3 are seen to have accumulated in the myocardium (Fig. 1, *b*). In contrast to the case with intact animals, similar electrophoregrams were obtained for all rats exposed to heat shock. These results agree with previous data [2].

Twenty-four and forty-eight hours after the end of the 8-day administration of rhodiola extract, hsp-70 were not detected in rat myocardium (data not shown). It was not until after 96 h that the proteins appeared (Fig. 1, *c*).

From our results it can be assumed that stimulation of the synthesis of stress proteins in cardiomyocytes by extract from *Rhodiola rosea* does not play any significant role in the increased resistance of the heart to the stress-induced damage, since the effect of the adaptogen on the accumulation of ^{99m}Tc-pyrophosphate in the myocardium was elicited much earlier than hsp-70 was detected electrophoretically.

From a comparison of our findings with those of other researchers who have established a relationship between the accumulation of hsp-70 in the myocardium and the cardioprotective effect of adaptation to stress it can be concluded that the molecular mechanisms of adaptation with the use of plant adaptogens

and the mechanisms involving physical factors are fundamentally different.

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The Effect of Etimyzol on the Development of the Deafferentation Pain Syndrome

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Administration of etimyzol in a dose of 4 mg/kg to rats with deafferentation pain syndrome reduces the incidence of the syndrome and its severity. This effect is associated with activation of the hypothalamic-hypophyseal-adrenal system. Systematic administration of the preparation models repeated stress, thus developing adaptation.

Key Words: *pathological pain; etimyzol; stress, adaptation*

Previously, it was demonstrated that repeated or long-term weak stressors (injection of normal saline or handling) alleviate chronic deafferentation pain syndromes or slow its development as a result of stress analgesia [10-13].

The Russian-manufactured drug etimyzol has been shown to activate the hypothalamic-hypophyseal-adrenal system [8,9], which is involved in the development of the stress reaction.

Our goal was accordingly to test the possibility of preventing the development of the deafferentation pain syndrome (DPS) induced in rats by cutting the sciatic nerve.

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MATERIALS AND METHODS

Experiments were performed on 92 male Wistar rats weighing 150-180 g. DPS was induced by cutting the sciatic nerve at the level of the popliteal fossa, after which the central segment of the nerve was firmly ligated and placed in a polyethylene capsule [4]. Etimyzol was injected intramuscularly as follows: 15 days before and 15 days after surgery (schedule I) and during a 30-day period starting from the first day after surgery (schedule II). The control animals were given normal saline (0.1 ml intramuscularly in the intact paw) according to the two schedules.

The animals were divided into 6 groups: group 1 rats (n=10) were injected with etimyzol in a dose of 4 mg/kg according to schedule I, group 2 rats (n=21) were injected with normal saline according to sched-

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