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Cardioprotective Effects of Adaptogens of Plant Origin

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Adaptogenic preparations of plant origin (henceforth termed adaptogens) are finding increasingly wide application in the systematic treatment of various diseases [1,5]. It is known that the preadaptation of experimental animals (their exposure to certain physical effects) can to a considerable extent prevent stress-induced and ischemic damage to the heart [3,4]. There are grounds for assuming that adaptogens of plant origin can effectively protect the heart from stress-induced damage [1,5]. This subject, however, has been little studied.

In the present investigation the effect of plant adaptogens (extracts of *Rhodiola rosea, Eleuterococcus,* and *Leuzea carthamoides,* and p-hydroxyphenethyl alcohol) was studied on animals subjected to stress. Since stress-induced damage to the heart is adrenergic in nature, we studied the effect of the above-mentioned preparations with respect to cyclic nucleotides (CN) as markers for determining the state of the autonomic innervation of the heart.

MATERIALS AND METHODS

Experiments were carried out on 200 male rats weighing 180-200 g. The cardioprotective effect of the above-mentioned preparations, which were given to the experimental animals before they were subjected to stress, was investigated with the aid of an emotional-painful stress model (EPS) [8]. Officinal extracts of *Rhodiola rosea, Eleuterococcus,* and *Leuzea carthamoides* were administered through a gastric tube (course of treatment 8 days; a single dose of 1 ml/kg) [1,5]. p-hydroxyphenethyl alcohol (a biologically active substance isolated from *R. rosea*) was injected intramuscularly (a single dose of 20 mg/kg) [5]. For purposes of comparison we used a widely known adaptation method whereby the animals were subjected to brief periods of immobilization according to the following scheme [3]: the animals were made to

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TABLE 1. Effect of Adaptogenic Preparations and of a Series of "Training" Immobilization Sessions on ^{99m}Tc–PP Accumulation in the Myocardium During Stress ($M \pm m$)

Experimental conditions	^{99m}Tc-PP in myocardium, % of dose per g tissue
Intact animals	0.071±0.001
6 h EPS	0.257±0.036 ***
Rhodiola rosea	0.075±0.001
Rhodiola rosea + 6 h EPS	0.101±0.004 * +++
Eleuterococcus	0.077±0.006
Eleuterococcus + 6 h EPS	0.118±0.006 * +++
Leuzea carthamoides	0.071±0.007
Leuzea carthamoides + 6 h EPS	0.175±0.014 ** +
p–Hydroxyphenethyl alcohol	0.083±0.007
p–Hydroxyphenethyl alcohol + 6 h EPS	0.102±0.007 * +++
Series of immobilization sessions	0.118±0.002 *
Series of immobilization sessions + 6 h EPS	0.140±0.005 ** ++

Note: Here and in Table 2 the number of experimental animals in each group was not less than 10. EPS – emotional–painful stress. Statistically reliable difference with respect to the group of intact animals: * – $p<0.05$, ** – $p<0.01$, *** – $p<0.001$. Statistically reliable difference with respect to the stress–control animals: + – $p<0.05$, ++ – $p<0.01$, +++ – $p<0.001$.

lie still on their backs for 15, 30, and 45 min on the 1st, 2nd, and 3rd days, respectively, and for 1 h on the 4th, 5th, 6th, 8th, 10th, 12th, and 14th days. The degree of stress-induced damage to the heart was assessed on the basis of the amount of pyrophosphate (Tc-PP) labeled with radioactive technetium (99 m Tc) that was entrapped by the myocardium [2,11].

The myocardium was frozen in liquid nitrogen immediately after it was removed. The concentration of CN was determined by radioimmunoassay (with equipment made by the firm Amersham, England). The CN were extracted with a 0.01 M solution of HCl in ethanol in accordance with the instructions accompanying the equipment. The data obtained were subjected to Student's t test.

RESULTS

The modeling of EPS for a period of 6 hours induced a 3.6-fold increase in the Tc-PP concentration in the heart (as compared with the intact animals) (Table 1). These changes indicate an accelerated intake of calcium ions by the cardiac myocyte, which could have been the result of stress-induced damage to the cell membranes [2,11].

The introduction of the above-mentioned adaptogens during an eight-day period had no effect on the Tc-PP concentration in the cardiac muscle in rats not subjected to stress (Table 1). In animals that underwent an eight-day course of treatment with *R. rosea* extract before being subjected to stress, the Tc-PP concentration in the myocardium was 2.5 times lower as compared with the stress-control group of animals, although it was 42% higher than in the intact animals (Table 1). In animals given *Eleuterococcus* extract during an eight-day period before being subjected to stress the Tc-PP concentration was 30% lower as compared with the stress-control animals. In animals given p-hydroxyphenethyl alcohol before being subjected to stress the Tc-PP concentration in the myocardium was 61% lower as compared with the stress-control animals. Preadaptation of the animals (their immobilization for brief periods) decreased the Tc-PP concentration by 48% (Table 1).

Thus, judging from their cardioprotective effect, the adaptogens (with the exception of *L. carthamoides*) were as efficacious as, or even more efficacious than, adaptation by brief periods of immobilization. The most effective was *R. rosea* extract, which was used in further experiments.

We found that after 6 hours of EPS the cAMP concentration increased two times, while the cGMP concentration decreased 1.5 times in the myocardium (Table 2); most likely this resulted from an activation of CAC and a lowering of the tonus of the vagus nerve, respectively [14]. Such an intensification of control by the sympathetic nerves and decrease of the parasympathetic effect on the myocardium can

TABLE 2. Effect of *Rhodiola rosea* Extract and of Adaptation on CN Concentration in Myocardium during Stress ($M \pm m$)

Experimental conditions	Heart	
	cAMP	cGMP
	ppm/g tissue	
Intact animals	562±44.9 ***	34.5±4.2 **
6 h EPS	1045.0±105.2	21.3±3.2
Rhodiola rosea	621.7±92.4 **+	30.0±2.3
Rhodiola rosea + 6 h of EPS	780.7±54.2 ***	27.4±3.3
Course of immobilization	858.7±62.5	25.1±2.3
Course of immobilization + 6 h EPS	734.9±68.8	30.5±1.6

lead to damage to the membraned of the cardiac myocytes [4,10,13].

The administration of *R. rosea* extract during an eight-day period had no effect on the CN concentration in the heart as compared with the intact animals. However, the administration of this extract helps considerably to prevent stress-induced change in the CN concentration in the cardiac muscle.

Sufficient information has been amassed which clearly indicated that stress-induced damage to the heart is due basically to hyperactivation of CAC [4,10,13]. The role of the parasympathetic nervous system in stress-induced damage to the myocardium needs further investigation. It has been reported in the literature, however, that an increase in the tonus of the vagus nerve weakens the influence of the sympathetic nerves on the myocardium. Thus, for example, agonists of the M-cholinoreceptors limit the release of norepinephrine from the sympathetic nerve endings [9] and inhibit adenylate cyclase [12].

Our findings lead us to assume that the cardioprotective properties of the above-mentioned adaptogenic preparations are probably due to their effect on the state of the autonomic nervous system and consequently on the CN concentration.

Thus, adaptogens of plant origin, and, above all, of *Rodiola rosea* extract and p-hydroxyphenethyl alcohol can be used for helping to prevent stress-induced damage to the myocardium. The cardioprotective effect of *Rhodiola rosea* extract is evidently related to its ability to prevent stress-induced changes in the CN concentration in the myocardium.

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