Antiarrhythmic Activity of Phytoadaptogens in Short-Term Ischemia-Reperfusion of the Heart and Postinfarction Cardiosclerosis

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A course of treatment (16 mg/kg orally during 5 days) by *Aralia mandshurica* or *Rhodiola rosea* extracts reduced the incidence of ischemic and reperfusion ventricular arrhythmias during 10-min ischemia and 10-min reperfusion. Extracts of *Eleutherococcus senticosus*, *Leuzea carthamoides*, and *Panax ginseng* did not change the incidence of ischemic and reperfusion arrhythmias. Chronic treatment by aralia, rhodiola, and eleutherococcus elevated the ventricular fibrillation threshold in rats with postinfarction cardiosclerosis. Ginseng and leuzea did not change this parameter in rats with postinfarction cardiosclerosis.

Key Words: *adaptogens; ischemia; reperfusion; cardiosclerosis; arrhythmia*

Treatment and therapy of arrhythmias remain pressing problems. The potentialities of drug correction of this abnormality are confined to classes I-IV antiarrhythmic agents [6], which fact necessitates the creation of effective drugs with a principally new mechanism of action, which would be effective in the treatment of cardiac rhythm disorders, resistant to traditional drug therapy. We think that the new generation antiarrhythmic drugs can be based on phytoadaptogens. Of these, we should like to mention primarily eleutherococcus extract and ginseng glycosides, exhibiting protective effect on experimental ischemia-reperfusion of the heart [7,9] and epinephrine-induced arrhythmias [5]. Previously we showed that a course of rhodiola treatment improved heart resistance to arrhythmogenic effect of epinephrine [5]. We failed to find published data on the effects of ginseng, eleutherococcus, and rhodiola on the electrical stability of the heart in postinfarction cardiosclerosis. Antiarrhythmic effects of leuzea and aralia are not studied.

We evaluated the antiarrhythmic effects of rhodiola, ginseng, eleutherococcus, aralia, and leuzea on the model of short-term ischemia-reperfusion of the heart and postinfarction cardiosclerosis.

MATERIALS AND METHODS

Coronary occlusion and reperfusion were simulated in Wistar rats (250-280 g) narcotized by α-chloralose (50 mg/kg intraperitoneally) [12] under conditions of forced ventilation of the lungs by a modified PO-2 device (Krasnogvardeyets Firm). The duration of coronary occlusion was 10 min, of reperfusion 10 min. The ECG was continuously recorded in the first thoracic lead by computer-aided

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biopotential amplifier (UBF4-03) using original applied software throughout ischemia and subsequent reperfusion. Analysis of ECG included evaluation of the incidence of solitary and multiple ventricular extrasystoles, ventricular tachycardia, and ventricular fibrillation. The severity of arrhythmias was evaluated in points: 1 point: solitary ventricular arrhythmias; 2 points: multiple ventricular arrhythmias; 3 points: ventricular tachycardia (VT); 4 points: reversible ventricular fibrillation (VF); 5 points: repeated VF [11]. The points were not summed up, only the maximum value was taken into consideration. For example, if an animal developed all three arrhythmia types, the status was evaluated by 4 points.

Postinfarction cardiosclerosis was induced by ligature of the left coronary artery [12]. After 45 days, when the formation of postinfarction cardiosclerosis was over according to published data [8], the VF threshold was evaluated by a previously described method [10] using EKSD-01L pacemaker developed by the Biotok Company. The duration of pulses was 10 msec at 2 msec intervals and 83 Hz frequency. The minimum voltage causing ventricular fibrillation at least 10 sec long was taken for fibrillation threshold.

Phytoadaptogens (Biolit Firm) were used as water extracts. Raw plants were dried at a temperature no higher than 50°C on shelf dryers with forced ventilation. Residual humidity was no more than 4%. The plants were then fragmented with a hammer mill to obtain particles of 1-2 mm in size. Fragmented raw material was subjected to extraction by triple maceration at water:material proportion of 50:1. The resultant phytoadaptogen extracts were filtered on a UKF-1.P2 device (Tenzor-Microfilter Firm) with a cartridge for filtration of particles smaller than 10 μ in size and concentrated in a two-step vacuum evaporator at 50°C to 65-70% concentration of extracted substances. Concentrated extracts were put into a VACUCELL 55 laboratory vacuum drier (BMT) and dehydrated till residual humidity of 4% at 60°C.

Dry phytoadaptogen extracts were dissolved in water and administered intragastrically through a tube. *Eleutherococcus senticosus*, *Rhodiola rosea*, *Panax ginseng*, *Leuzea carthamoides*, and *Aralia mandshurica* were used in a dose of 16 mg/kg. Adaptogens were used according to the following protocol: once daily for 5 days, the last dose given 2 h before coronary occlusion. The adaptogen doses were chosen on the base of published data on cardioprotective activity of toniside, a complex adaptogen [1]. Control animals received the same volume of water through a tube. The study was carried out by the blind method: the drugs and water were administered by one assistant, while coronary occlusion was induced and the results were processed by another experimenter, who did not know which rats were experimental and which were controls.

The results were processed using Student's *t* test and χ^2 test.

RESULTS

A course of *Rhodiola rosea* extract (5 days) caused a 3-fold reduction in the incidence of occlusion VT in comparison with the control group (Table 1). The incidence of ventricular extrasystole (VE) during ischemia in animals treated by rhodiola was 4-fold lower than in the controls. For example, 19% control rats were resistant to arrhythmogenic effect of ischemia, while in the group treated by *Rhodiola rosea* the number of resistant animals was as high as 81%. *Rhodiola rosea* extract promoted an increase of the rat heart resistance to not only ischemia, but also to arrhythmogenic effect of reperfusion. The incidence of reperfusion VT and VE in animals treated by the adaptogen was 3-fold lower than in the controls (Table 1). Evaluation of the severity of ischemic arrhythmias in points showed 2.73 points in the control *vs.* 0.53 (5-fold less) in experimental rats (Fig. 1). Arrhythmia severity index during reperfusion was 1.05 in rats treated by *Rhodiola rosea* extract *vs.* 2.73 points in the controls.

Chronic treatment by *Aralia mandshurica* also promoted improvement of heart resistance to arrhythmogenic effect of ischemia and reperfusion (Table 1). The incidence of occlusion VT in rats treated by aralia was 4-fold lower and of VE 6-fold lower than in the control group. A total of 86%

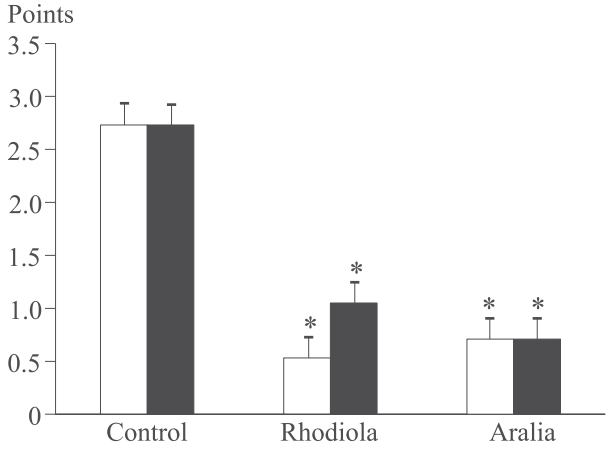

Fig. 1. Effects of courses of treatment by rhodiola and aralia extracts on the severity of arrhythmias. Light bars: ischemia (10 min); dark bars: reperfusion (10 min). *$p<0.001$ *vs.* control.

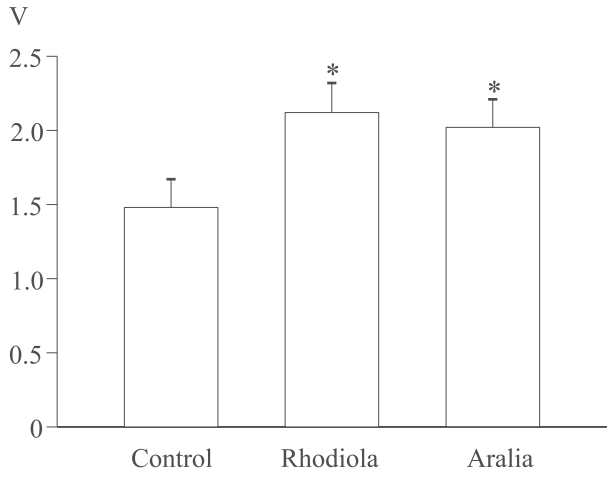

Fig. 2. Antifibrillation effects of courses of treatment by rhodiola and aralia in rats with postinfarction cardiosclerosis. *p<0.01 *vs.* control.

animals which received aralia before coronary occlusion developed no arrhythmias, *vs.* just 19% in the control group. Rats treated by aralia developed reperfusion VT and VE 4-fold less frequently than the controls. Our data indicate that 79% rats treated by *Aralia mandshurica* extract were tolerant to the arrhythmogenic effect of reperfusion, *vs.* just 19% in the control group. The severity of arrhythmia in rats treated by aralia was 3.8 times lower during ischemia and during coronary bloodflow recovery than in the control (Fig. 1). No antiarrhythmic effects of ginseng, leuzea, and eleutherococcus were detected in animals which received curses of treatment by these phytopreparations.

Hence, our experiments showed antiarrhythmic effects on the model of ischemia and reperfusion *in vivo* only for aralia and rhodiola extracts in doses of 16 mg/kg. However, it is probable that in higher doses other phytoadaptogens will also increase heart resistance to arrhythmogenic effects of coronary occlusion and reperfusion. These data are in good agreement with our previous data on the capacity of *Rhodiola rosea* extract to improve the rat heart tolerance of arrhythmogenic effect of epinephrine in toxic doses [5]. On the other hand, the present findings disagree with the previous data [7,9] on the antiarrhythmic effects of eleutherococcus and *Panax notoginseng* saponines. This disagreement can be explained by the use of another experimental model (ischemia-reperfusion of isolated heart) and by addition of *Eleutherococcus senticosus* dry extract directly into perfusion solution (but not administered orally as in our study) [9], or by the use of panaxatriol saponines [7], whose biological activity is many-fold higher than that of the extract used in our study.

Antifibrillation activity of some phytoadaptogens was detected on the model of postinfarction cardiosclerosis in rats. A course of treatment by aralia extract elevated the VF threshold by 36%, eleutherococcus by 46%, and rhodiola by 43% *vs.* the control (Fig. 2). The effects of ginseng and leuzea on VF threshold were negligible. However

TABLE 1. Effects of Courses (16 mg/kg×5 days) of Phytoadaptogen Extracts on the Incidence of Ischemic and Reperfusion Arrhythmias on the Model of Short-Term Ischemia (10 min) and Reperfusion (10 min)

Group	Ischemia								Reperfusion							
	NVA		MVE		VT		VF		NVA		MVE		VT		VF	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Control (*n*=44)	6	14	38	86	30	68	11	25	9	20	35	80	33	75	14	32
Aralia (*n*=14)	12***	86	2***	14	2*	14	2	14	11**	79	3**	21	2**	14	2	14
Rhodiola (*n*=16)	13***	81	3***	19	3*	19	1	6	12**	75	4**	25	4*	25	2	13
Ginseng (*n*=14)	3	21	11	79	9	64	4	29	3	21	1	79	1	79	5	36
Leuzea (*n*=15)	4	26.6	11	73	11	73	7	26	4	26	11	73	11	73	6	40
Eleutherococcus (*n*=15)	5	31	11	68	6	37.5	4	25	4	25	12	75	9	56	4	25

Note. *n*: number of animals in a group. Experiments were carried out 2 h after the last dose of phytoadaptogen. NVA: no ventricular arrhythmias; MVE: multiple ventricular extrasystoles. *p<0.025, **p<0.01, ***p<0.001 *vs.* control.

it is probable that in doses higher than 16 mg/kg ginseng and leuzea will exhibit antifibrillation effects, as the antifibrillation effects of, *e.g.*, ginsenosides have been described [13]. Our results indicating eleutherococcus effect on VF threshold seemingly contradict the data on the absence of antiarrhythmic activity of this drug in coronary occlusion and reperfusion. But this discrepancy is just seeming, as the causes of arrhythmias in the two models were not identical: electrostimulation in postinfarction cardiosclerosis and ischemic and reperfusion injuries to cardiomyocytes under conditions of coronary occlusion. In addition, we should like to note that neither rhodiola, nor aralia, possessing antiarrhythmic activity, modified the incidence of VF in coronary occlusion and reperfusion. Presumably, this can be explained by low incidence of VF in the control sample, which prevented the detection of a significant antifibrillation effect of these phytoadaptogens on the ischemia and reperfusion model.

Our pervious data suggest a working hypothesis on the mechanism of antiarrhythmic effect of phytoadaptogens. We found that courses of treatment by extracts of rhodiola, eleutherococcus, and leuzea caused an increase in the plasma levels of β-endorphin in experimental animals [2], while naloxone blocking of opioid receptors almost completely canceled the antiarrhythmic effects of rhodiola and eleutherococcus on the model of epinephrine-induced arrhythmias [4,5]. We demonstrated antiarrhythmic and antifibrillation activities of exogenous opioids in ischemia and reperfusion of the heart and in postinfarction cardiosclerosis [3,10]. For this reason, it will be just to hypothesize that the antiarrhythmic effect of phytoadaptogens is a result of increase of opioid peptide levels in the blood and tissues of rats.

Hence, our findings indicate that *Rhodiola rosea* and *Aralia mandshurica* extracts, administered in a dose of 16 mg/kg by courses, exhibit a pronounced antiarrhythmic effect in experimental ischemia and reperfusion *in vivo*. Chronic treatment by *Aralia mandshurica*, *Rhodiola rosea*, and *Eleutherococcus senticosus* extracts improves significantly the electrical stability of the heart in animals with postinfarction cardiosclerosis.

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