A Mechanism of Antiarrhythmic Effect of *Rhodiola Rosea*

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It is shown that autonomic nervous system participates in the preventive antiarrhythmic effect of *Rhodiola rosea*. The effect of the preparation is presumably mediated through modulation of the sympathetic nervous system.

Key Words: *Rhodiola rosea; epinephrine-induced arrhythmias; autonomic nervous system*

The search for effective antiarrhythmic drugs without negative inotropic effect is an important problem of cardiology [8,10]. The natural adaptogen *Rhodiola rosea* is a prospective preparation of this type [7]. We have previously demonstrated that *Rhodiola rosea* extract (RRE) exerts positive inotropic [6], cardioprotective [3], and antiarrhythmic [4] effects. However, the mechanism of its antiarrhythmic effect remains unstudied.

Taking into account the incontestable role of the autonomic nervous system in arrythmogenesis, we attempted to evaluate the role of sympathetic and parasympathetic systems in realization of preventive antiarrhythmic effect of RRE.

MATERIALS AND METHODS

Experiments were carried out on male Wistar rats weighing 180-200 g. The animals (except controls) received RRE (officinal *Extr. Rhodiola fluidum*) for 8 days in a daily dose of 1 ml/kg *per os*. The dose and the scheme of administration were chosen on the basis of experimental data obtained by Prof. A. S. Saratikov [7]. Prior to induction of arrhythmia, RRE-treated rats received one of the following agents:

1) the inhibitor of monoamine storage in peripheral and central neurons reserpine (5 mg/kg, intraperitoneally, 24 h before experiment [2]);

2) the muscarinic receptor antagonist atropine (1 mg/kg, intravenously, 15 min before experiment [1]);

3) the peripheral muscarinic receptor antagonist methylatropine (0.5 mg/kg intravenously 15 min before experiment [12]);

4) the ganglioblocker hexamethonium (10 mg/kg intravenously 15 min before experiment [1]).

Arrhythmia was modeled with epinephrine (220 μg/kg, intravenously [9]) under light ether narcosis. ECG in standard lead II was recorded during 5 min.

Intact animals served as the control.

The data were processed using χ^2 test.

RESULTS

As seen from Table 1, preadaptation with RRE reduced the occurrence of epinephrine-induced arrhythmias: the percentage of animals without arrhythmias increased 4-fold, while the occurrence of ventricular tachycardia decreased 2.5-fold. These findings are in conformity with our previous observations [4].

Injection of hexamethonium to RRE-preadapted rats (switching off the autonomic cardiac innervation) practically abolished the antiarrhythmic effect of RRE. The percentage of animals without arrhythmias decreased in comparison with RRE-treated rats (Table 1). However, hexamethonium slightly potentiated the antiarrhythmic effect of RRE with respect to ventricular fibrillation, the most malignant arrhythmia (Table 1). This effect of the ganglioblocker can be attributed to its intrinsic antiarrhythmic activity [5].

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TABLE 1. Effect of Hexamethonium, Atropine, and Methylatropine on Antiarrhythmic Effect of RRE in Modeled Epinephrine-Induced Arrhythmias (Dose of Epinephrine 200 μg/kg)

Group	Without ventricular arrhythmias		Ventricular extrasystoles		Ventricular tachycardia		Ventricular fibrillation	
	n	%	*n*	%	*n*	%	*n*	%
Control (*n*=25)	2	8	23	92	13	52	7	28
Rhodiola (*n*=22)	7*	32	15*	78	4**	18	2	9
Rhodiola+hexamethonium, 10 mg/kg (*n*=20)	3	15	16	80	5	25	1*	5
Rhodiola+atropine, 1 mg/kg (*n*=20)	11***	55	9***	45	4*	20	—	—
Methylatropine 0.5 mg/kg (*n*=17)	3	18	13	77	7	41	1	6
Rhodiola+methylatropine 0.5 mg/kg (*n*=19)	11**	58	8*	42	2	11	—	—

Note. Here and in Table 2: *$p<0.05$, *$p<0.025$, and *$p<0.001$ compared with the control.

TABLE 2. Effect of Reserpine on Antiarrhythmic Effect of RRE in Modeled Epinephrine-Induced Arrhythmias (Dose of Epinephrine 140 μg/kg)

Group	Without ventricular arrhythmias		Ventricular extrasystoles		Ventricular tachycardia		Ventricular fibrillation	
	n	%	*n*	%	*n*	%	*n*	%
Control (*n*=18)	3	17	15	83	7	39	1	6
Rhodiola (*n*=18)	9*	50	9*	50	4	22	—	—
Reserpine, 5 mg/kg (*n*=19)	1	5	17	89	5	26	1	5
Rhodiola+reserpine, 5 mg/kg (*n*=21)	5	24	16	76	6	29	2	10

To evaluate the role of the parasympathetic system in realization of the antiarrhythmic effect of RRE, special experiments were performed with blockade of muscarinic cholinergic receptors with atropine or methylatropine, an atropine analog, which does not cross the blood-brain barrier. Atropine did not abolish the antiarrhythmic effect of RRE and even insignificantly increased the number of animals without arrhythmias (Table 1). Methylatropine produced a similar effect.

If *n. vagus* is involved into realization of the antiarrhythmic effect of RRE, blockade of muscarinic cholinergic receptors should diminish this effect. However, atropine [5] and methylatropine had no effect on the pattern of epinephrine-induced arrhythmias (Table 1). These data allow one to exclude the vagal component of antiarrhythmic activity of RRE.

In this context it should be mentioned that increased tone of the sympathetic nervous system facilitates the development of electrical instability in the myocardium [11]. Bearing in mind the above-mentioned facts and the observed diminution of the antiarrhythmic effect of RRE after injection of hexamethonium, it can be hypothesized that improvement of electrical stability of the heart in RRE-treated rats involves a decrease in the tone of the sympathetic nervous system.

To verify this assumption we analyzed antiarrhythmic effect in RRE-preadapted rats after reserpine-induced depletion of endogenous catecholamine pool.

Taking into account the fact that this agent increased myocardial sensitivity to epinephrine [2], the dose of this arrhythmogenic drug was decreased to 140 μg/kg. The arrhythmogenic effect of this dose against the background of RRE preadaptation was also weakened: the occurrence of ventricular extrasystoles decreased 1.7-fold, while the number of animals absolutely resistant to toxic dose of epinephrine increased 3-fold (Table 2).

As seen from Table 2, reserpine-disturbed deposition of catecholamines in adrenergic neurons completely abolished the antiarrhythmic effect of RRE, which is in conformity with our previous data on antagonistic effects of reserpine and glycosides from *Rhodiola rosea* on the central nervous system [7]. Reserpine had no effect on epinephrine-induced arrhythmias.

Thus, our findings suggest that the autonomous nervous system plays an important role in the realization of preventive antiarrhythmic effect of RRE. The positive effect of RRE on electrical stability of the heart is mediated through modulation of adrenergic innervation of the myocardium. However,

the involvement of other mechanisms not related to the autonomic nervous systems cannot be excluded.

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