membranotrotic effect of these drugs. The effects of NAID discovered by us may be of importance for understanding the mechanisms of their ulcerogenic effect. When the drugs are taken per os, the local concentration on the stomach wall may be close to or even exceed the membranolytic concentration. Surprisingly, there are no data concerning the ulcerogenic effect of izamben in the literature available.

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Antiarrhythmic Effect of *Rodiola rosea* and Its Possible Mechanism

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UDC 616.12-008.318+615.22

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 116, № 8, pp. 175-176, August, 1993
Original article submitted March 16, 1993

Key Words: *arrhythmias; adaptogens*

Prophylaxis of ventricular arrhythmias is one of the most important problems of modern cardiology [11]. The possibility of preventing arrhythmias in experimental coronary occlusion by adaptation to brief periodic immobilization, physical loads, and high-altitude hypoxia has been shown in recent publications [5,9].

However, the possibility of preventing arrhythmias by administering *R. rosea* extract, which is known to exhibit a milder antistressor effect in comparison with physical means of adaptation [7], has not been discussed in the literature. We have earlier shown that preadaptation of animals, by administering a course of injections of *R. rosea* extract promotes the accumulation of enkephalins and prostacycline, which possess antiarrhythmic activity [4,14,16], in organs and tissues [3,4,8].

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Hence, it seemed of interest to investigate the antiarrhythmic activity of *R. rosea* preparation, as well as to study some possible mechanisms of this effect.

MATERIALS AND METHODS

Experiments were carried out on 183 male Wistar rats weighing 150-200 g. The animals were adapted by administering courses of injections (per os) of officinal preparation of *R. rosea* (8 days, a single dose of 1 ml/kg), which is a known adaptogen [10]. One day after the last session of adaptation, arrhythmias were simulated in the rats by intravenous injections of norepinephrine in a dose of 90 μg/kg [13] or of 10% $CaCl_2$ in a volume of 0.15 ml/100 g body weight [2]. The electrocardiogram (ECG) in the standard lead II was recorded during 5 min postinjection.

In separate series of experiments, 30 min before the simulation of arrhythmias, animals adapted as mentioned above received injections (0.5 mg/kg) of naloxone, which blocks the μ-opioid receptors

0007-4888/93/0008-0974$12.50

TABLE 1. Effect of Preadaptation and Subsequent Injection of Indomethacin or Naloxone on Occurrence of Ventricular Extrasystoles (VE) and $CaCl_2$–Induced Extrasystoles and/or Ventricular Fibrillation (VF)

Experimental conditions	Adrenergic arrhythmias			$CaCl_2$-induced arrhythmias		
	n	without VE	VE	*n*	without VE	VE and/or VF
Control	18	1	17	19	1	18
Adaptation	15	12*	3*	18	12*	6*
Indomethacin + adaptation	18	11*	7*	14	6	8
Naloxone + adaptation	11	2	9	11	2	9

Note. *n* – number of animals in the experiment; an asterisk indicates reliable differences vs. the control (<0.05).

(OR) [15], or of 10% alcohol solution of indomethacin (an inhibitor of prostanoid biosynthesis) in a dose of 10 mg/kg (1 ml/kg), prepared *ex tempore* using 0.9% NaCl [12]. The animals not exposed to any influences before arrhythmia simulation served as the control. All the preparations except *R. rosea* were injected intravenously.

The results were statistically processed using χ^2 test [1].

RESULTS

The results of our findings are presented in Table 1.

The administration of norepinephrine to the control animals caused the development of multiple ventricular extrasystoles (94% of cases) (Table 1), whereas in the adapted animals similar alterations of the ECG were observed in only 20% of individuals. Similar results were obtained for the model of Ca-induced arrhythmias: the development of multiple ventricular extrasystoles and/or ventricular fibrillation was noted in just 33% of adapted animals vs. 95% in the control.

Thus, the investigations performed provide evidence of a pronounced arrhythmia-preventing effect of the natural adaptogen (*R. rosea*) in the model of adrenergic and calcium-induced arrhythmias.

According to Meerson's concept, so-called stress-limiting systems (to which he refers, in particular, the opioidergic and prostanoid systems) play the leading role in the mechanisms of the antiarrhythmic effect of adaptation [9].

A logical assumption was that during the course of injections of *R. rosea*, activation of the above-mentioned systems, which enables the adaptogen to produce an antiarrhythmic effect, occurs. In fact, we showed in previous studies that a course of injections of the extract of *R. rosea* causes an increase in the blood plasma and tissues of the levels of opioid peptides and prostacycline [4,6,8], these substances possessing antiarrhythmic activity [4,14,16].

Therefore, in order to elucidate the possible contribution of opioid peptides and prostanoids to the mechanisms of the antiarrhythmic effect of the test adaptogen preparation, a series of experiments was performed where the inhibitor of cyclooxygenase indomethacin or the nonselective OR blocker naloxone was injected directly before arrhythmia simulation.

It was established that the injection of indomethacin did not affect the occurrence of adrenergic and Ca-induced arrhythmias either in the controls or in the adapted animals (Table 1) as compared to the corresponding rat groups not given the blocker of prostaglandin synthesis. This fact obviously indicates that prostanoids are not the messengers of the antiarrhythmic effect of *R. rosea*. On the contrary, the administration of naloxone completely leveled the antiarrhythmic effect of *R. rosea*, this suggesting an opioidergic nature of the latter.

We showed earlier that naloxone is capable of inhibiting the antiarrhythmic effect of enkephalins [4]. On the other hand, as we have already pointed out, a course of injections of *R. rosea* is able to raise the level of opioid peptides in organs and tissues [3,8]. One may assume that it is the effect of precisely these peptides which is inhibited by naloxone in the animals given *R. rosea*.

Thus, our findings provide reliable evidence of the possibility of preventing arrhythmias by a course of injections of adaptogen (*R. rosea*). The mechanisms of this effect are still to be studied. However, the participation of the endogenous opioid system in the realization of the antiarrhythmic effect of *R. rosea* is an indisputable fact.

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Dynorphin A (1-17), Met-Enkephalin-Arg^6-Phe^7 and Substance P (1-11) Levels in the Brain of Mice with Different Levels of Ethanol Consumption

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UDC 612.822-06.012.82.015.2:547.943

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 116, № 8, pp. 177-178, August, 1993
Original article submitted February 26, 1993

Key Words: *dynorphin; Met-enkephalin-Arg^6-Phe^7; substance P (1-11); ethanol consumption; brain*

There are several hypotheses connecting the development of ethanol dependence with the activity level of the endogenous opiate system. According to some of these hypotheses, a deficiency in this system provokes ethanol consumption and the formation of alcohol dependence [2,3]. In particular, such a deficiency may include disorders of the synthesis or processing of opioid peptides and acceleration of their hydrolysis. An alternative assumption is that the development of ethanol dependence is due to activation of the opiatergic system [10,11]. In the present study we determined the concentration of some opiates in the brain of three strains of mice, one of which, C57Bl10/D1, exhibits a high level of ethanol consumption in a free choice situation, whereas the other two, A/Sn and A.CA, practically do not consume ethanol under the same regime. Earlier, we used the same approach to measure the content of Met- and Leu-enkephalins and β-endorphin in rats with different levels of ethanol consumption [1,5]. Taking into account the fact that Met-enkephalin may be accumulated in the brain as a result of the processing of both proopimelanocortin and proenkephalin, while Leu-enkephalin may be a product of either proenkephalin or prodynorphin, we focused on measuring the levels of dynorphin and Met-enkephalin-Arg^6-Phe^7, which are formed only in the processing of prodynorph in and proenkephalin, respectively. In addition, we measured the concentration of substance P (1-11), the secretion and synthesis of which are controlled by

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0007-4888/93/0008-0976$12.50