Involvement of Central and Peripheral Cannabinoid Receptors in the Regulation of Heart Resistance to Arrhythmogenic Effects of Epinephrine

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Intravenous injection of the selective cannabinoid receptor agonist HU-210 in doses of 0.05 and 0.25 mg/kg increased heart resistance to arrhythmogenic effects of epinephrine, while intracerebroventricular infusion of this substance had no effect on the incidence of epinephrine-induced arrhythmia. The selective antagonist of type I cannabinoid receptors SR141716A in a dose of 3 mg/kg and ganglion blocker hexamethonium in a dose of 10 mg/kg did not modify the antiarrhythmic effect of HU-210. This effect of HU-210 is probably related to activation of type II peripheral cannabinoid receptors.

Key Words: *cannabinoid receptors; epinephrine-induced arrhythmia*

The search for new antiarrhythmic drugs causing no side effects is the topical medical problem. The mechanisms underlying heart resistance to arrhythmogenic factors are of considerable importance in this respect. The endogenous cannabinoid (CB) system is of particular interest, because CB receptor agonists display high cardiovascular activity [2,7,12,13] and modulate the state of the autonomic nervous system [6,13] determining the electrical stability of the heart. Marijuana containing CB as the active components was reported to induce ventricular extrasystoles (VE) in healthy volunteers [7] and to decrease exercise tolerance in patients with coronary heart disease [2]. However, the role of CB receptors in the pathogenesis of arrhythmia remains unclear.

Here we studied the involvement of central and peripheral CB receptors in the regulation of heart resistance to arrhythmogenic effects of epinephrine.

MATERIALS AND METHODS

Experiments were performed on Wistar rats weighing 150-200 g. Arrhythmias were induced by intravenous injection of 120 mg/kg epinephrine under ether anesthesia. Electrocardiogram (ECG) was recorded (lead I) for 5 min after epinephrine administration, and the incidence of VE, ventricular tachycardia (VT), and ventricular fibrillation (VF) was estimated using a UBF4-03 amplifier and original computer software.

The selective agonist of CB_1 and CB_2 receptors HU-210 (Prof. R. Mechoulam, Jerusalem University) [9] and selective CB_1 receptor antagonist SR141716A (Dr. M. Mosse, Sanofi Recherch) [3,11] were used. Both preparations were dissolved in Cremophore EL: ethanol:distilled water mixture (1:1:18) immediately before intravenous injection. HU-210 was injected 30 min before epinephrine administration. SR141716A was injected 30 min before HU-210 administration. Hexamethonium (10 mg/kg, Sigma) was injected intravenously 10 min before HU-210 and then 10 min before epinephrine administration. HU-210 was injected intracerebroventricularly (i.c.v.) to other rats weighing 250-300 g. Five-seven days before the experiment, cannulas were stereotactically implanted (AP +1.5 mm, L +2.0 mm, V -3.5 mm) into the lateral cerebral ventricle of amobarbital-anesthetized rats (50 mg/kg intraperitoneally) using a SEZh-5 stereotactic device (Konstruktor) [10]. CB was dissolved in

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10 μl dimethyl sulfoxide and infused i.c.v. at a flow rate of 5 μl/min 30 min before epinephrine administration. Doses of CB receptor ligands, methods for their dissolution, and time of injection were selected on the basis of previous studies [3,9,11,13,14]. The animals injected with the corresponding solvent (intravenously or i.c.v.) before epinephrine administration served as the control. The results were analyzed by χ^2 test.

RESULTS

The selective CB receptor agonist HU-210 infused i.c.v. in doses of 0.5 and 5 μg/rat had no effect on the incidence of arrhythmia. However, intravenous injection of 0.05 and 0.25 mg/kg HU-210 produced a dose-dependent antiarrhythmic effect (Table 1). Inefficiency of HU-210 administered i.c.v. was not related to its low dose. The weight of rat brain does not exceed 2 g [1]. The dose of HU-210 infused i.c.v. (5 μg) corresponded to that injected intravenously (2.5 mg/kg). Thus, central CB receptors are not involved in the regulation of heart resistance to arrhythmogenic effects of epinephrine.

The ganglion blocker hexamethonium in a dose of 10 mg/kg and selective CB_1 receptor antagonist SR141716A in a dose of 3 mg/kg did not modify antiarrhythmic properties of HU-210 and had no effect on epinephrine-induced arrhythmias (Table 1). Therefore, antiarrhythmic effects of HU-210 were not associated with changes in the state of the autonomic nervous system or activation of CB_1 receptors.

The antiarrhythmic effect of HU-210 in epinephrine-induced arrhythmias is probably associated with

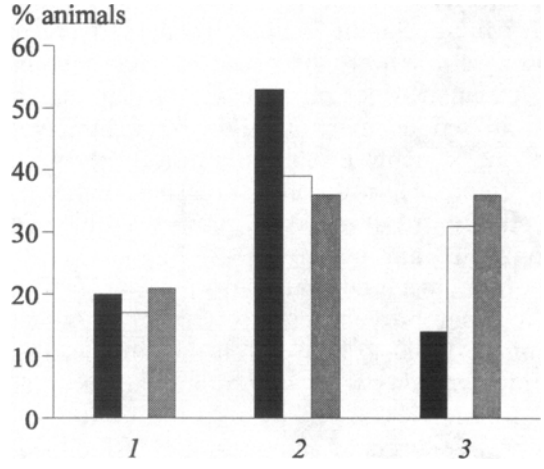

Fig. 1. Effects of HU-210 injected intracerebroventricularly in doses of 0.5 (light bars) and 5 μg/rat (shaded bars) on the incidence of epinephrine-induced arrhythmias: ventricular tachycardia (*1*), multiple ventricular extrasystoles (*2*), and without ventricular arrhythmias (*3*). Control: dimethyl sulfoxide (dark bars).

TABLE 1. Effects of CB Receptor Ligands on Incidence of Epinephrine-Induced Arrhythmias

Type	Control (n=15)		Hexamethonium (n=15)		SR141716A (n=14)		HU-210, mg/kg									
							0.05 (n=14)		0.25 (n=13)		0.5					
											+hexamethonium (n=14)		+SR141716A (n=14)			
	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%		
Without ventricular arrhythmias	0	0	1	7	2	14	4***	29	6**	46	6**	43	4***	29		
Ventricular extrasystoles single	1	7	2	14	1	7	1	7	2	15	2	14	4	29		
multiple	14	93	12	80	11	79	9	64	5*	38	6**	43	5	36		
Ventricular tachycardia	8	53	7	47	6	46	1**	7	2***	15	3	21	2***	14		
Ventricular fibrillation	4	47	6	40	5	35	0**	0	0**	0	1***	7	0**	0		

Note. *p<0.001, **p<0.01, and ***p<0.05 compared to the control (χ^2 test).

activation of CB_2 receptors in the myocardium. Nonspecific antiarrhythmic effects can be excluded, because HU-210 was effective even in a concentration of 0.05 mg/kg, i.e. 20-30-fold below the minimum effective doses of other antiarrhythmic drugs (lidocaine, procainamide, and flecainide) [4]. Activation of adenylate cyclase and increase in cAMP level underlie the arrhythmogenic effect of epinephrine [8]. At the same time, CB were reported to inhibit adenylate cyclase via G_i proteins [5]. Thus, antiarrhythmic effects of HU-210 are probably related to activation of cardiac CB_2 receptors and inhibition of cAMP synthesis.

Our findings suggest that peripheral CB receptors play an important role in the regulation of heart resistance to arrhythmogenic effects of epinephrine.

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