Peculiarities of Ischemic Cardiac Arrhythmias in Cats against the Background of Stimulation of Sensorimotor Cortex and Administration of Selective Opiate Receptor Agonists

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In acute experiments on Nembutal-anesthetized cats, the effect of opiate receptor agonists DAGO, DSLET, and dinorphin A_{1-13} on the incidence of idioventricular rhythm disturbances, including ventricular tachycardia and fibrillation, was studied under conditions of occlusion of circumflex branch of the left coronary artery and stimulation of the sensorimotor cortex. The most pronounced effects were observed with DSLET and dinorphin A_{1-13}. These preparations completely prevented ventricular fibrillation. DAGO produced a less pronounced protective effect probably because of parallel increase in plasma catecholamine concentration.

Key Words: *DAGO; DSLET; dinorphin A_{1-13}; opiate receptors; myocardial ischemia; cardiac arrhythmias*

Electrical stimulation of the sensorimotor cortex in animals with myocardial ischemia increases the incidence of all types of ventricular arrhythmias [1]. Parenteral administration of nonselective opioid peptides β-endorphin (agonist of μ-, δ-, κ-, and ε-receptors) and dalargin (agonist of μ- and δ-receptors) produces an antiarrhythmic effect [2,3], but the contribution of various types of opiate receptors into this effect remains unclear. Our aim was to compare the effects of selective opiate peptides: DAGO (μ-receptor agonist), DSLET (δ-receptor agonist), and dinorphin A_{1-13} (κ-receptor agonist) on the development of ischemic cardiac arrhythmias during stimulation of the sensorimotor cortex.

MATERIALS AND METHODS

Experiments were carried out on 26 cats of both sexes weighing 2-4 kg. The animals were anesthetized with Nembutal (40 mg/kg intraperitoneally) and artificially ventilated. The pericardium was opened, and a 0.1-mm doderone thread was passed under the circumflex branch of left coronary artery at the site of its orifice from the main trunk. Myocardial ischemia was produced by 15-min occlusion of the circumflex branch of the left coronary artery followed by restoration of the blood flow. Craniotomy and durotomy were performed over the sigmoid sulcus. The sensorimotor cortex was stimulated for 20 sec with rectangular pulses (1 msec, 30 Hz, 2.5-6.5 mA) delivered via a silver electrode (tip diameter 0.8 μ) from an ESL-1 electrical stimulator. The time between coronary occlusion and the start of stimulation was 10 sec. Stimulation current was determined by a voltage drop on a calibrated resistance using an S1-48B oscilloscope. The position of the electrode was verified by extensive craniotomy after the end of the experiments. In all experiments, ECG in standard leads I or II was recorded. Blood pressure (BP) in the femoral artery was recorded with an EMT-35 electromanometer (Elema). The results were analyzed statistically using Student's t and χ^2 tests.

Three experimental series were carried out. μ-Receptor agonist DAGO (20 mg/kg, series I, n=9), δ-receptor agonist DSLET (20 μg/kg, series II, n=9), and κ-receptor agonist dinorphin A_{1-13} (40 μg/kg, series III, n=8) were administered intravenously in drops during coronary occlusion.

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TABLE 1. Effects of Opiate Receptor Agonists on Hemodynamic Parameters (*M*±*m*, *n*=8-9)

Parameter		DAGO		DSLET		Dinorphin A_{1-13}	
		initial	Δ, %	initial	Δ, %	initial	Δ, %
Blood pressure, mm Hg	systolic	116.4±7.9	-9	119.9±4.9	—	138.1±16.6	-10
	diastolic	86.7±9.8	-11	84.0±6.1	—	124.3±12.1	-11
	mean	91.3±9.6	-8	96.0±5.3	—	95.9±14.3	-10
	pulse	28.3±2.6	—	35.9±4.3	—	27.6±5.3	-8
Heart rate, bpm		132.2±6.5	-5	136.0±13.6	—	123.8±15.2	-4

TABLE 2. Effects of Opiate Receptor Agonists on Incidence (%) of Heart Rhythm Disturbances

Type of arrhythmia		Control	DAGO	DSLET	Dinorphin A_{1-13}
Idioventricular rhythm disturbances		100	56	11	38
including:	grouped extrasystoles	59	11	11	24
	tachycardia	55	11	0***	13
	fibrillation	59	22*	0**	0

Note. *p<0.002, **p<0.01, ***p<0.02 compared to the control.

All peptides were synthesized at the Laboratory of Peptide Synthesis in Russian Cardiology Research-and-Production Complex.

The dropwise injection was chosen, because DAGO and DSLET are the analogues of short-lived enkephalins with half-life of about 2 min, while dinorphin A_{1-13} decays in the plasma during 1 min [4,6].

RESULTS

In series I, all hemodynamic parameters (except pulse pressure) decreased as soon as after 30-sec coronary occlusion (Table 1). Myocardial ischemia against the background of electrical stimulation of the sensorimotor cortex without DAGO produced more pronounced changes in hemodynamic parameters. In all animals, BP decreased by 20-60% 30 seconds after coronary occlusion [1]. Thus, DAGO prevents the drastic drop of BP at the early period of myocardial ischemia.

DAGO reduced the occurrence of cardiac rhythm disturbances, including ventricular fibrillation (Table 2).

In series II (stimulation and infusion of DSLET), no changes in hemodynamic parameters were observed at the early period of myocardial ischemia (Table 1). The incidence of the grouped ventricular extrasystoles was 5-fold lower than in myocardial ischemia without DSLET; ventricular tachycardia and fibrillation were absent (Table 2).

In series III, an insignificant decrease of hemodynamic parameters was observed at the early stages of myocardial ischemia (Table 1). Dinorphin A_{1-13} produced a pronounced antiarrhythmic effect and decreased the incidence of ischemic arrhythmia, including ventricular fibrillation (Table 2).

Thus, selective opioid peptides DAGO, DSLET, and dinorphin A_{1-13} produce a more pronounced antiarrhythmic effect on cardiac function during ischemia against the background of stimulation of the sensorimotor cortex than nonselective peptides dalargin and β-endorphin. The agonists of κ- and δ-opiate receptors completely prevented ventricular fibrillation. This effect is probably related to modulation of sympathetic nerve activity and metabolism in ischemic myocardium by selective opioid peptides [7,8]. A less pronounced protective effect of μ-receptor agonist DAGO can be explained by its capacity to increase blood catecholamine level [6].

REFERENCES

1. G. I. Kositskii, S. D. Mikhailova, S. L. Gorozhanin, *et al.*, *Vestn. Akad. Med. Nauk SSSR*, No. 12, 67-69 (1985).
2. S. D. Mikhailova, G. I. Storozhakov, and A. V. Kudinova, *Byull. Eksp. Biol. Med.*, **122**, No. 10, 375-377 (1996).
3. S. D. Mikhailova, G. I. Storozhakov, and A. V. Kudinova, *Ibid.*, **124**, No. 7, 28-32 (1996).
4. K. N. Yarygin, *Oligopeptides as Regulators of Physiological Functions* [in Russian], Moscow (1987).
5. R. J. A. Kiritsy and N. M. Appel, *J. Pharmacol. Exper. Ther.*, **239**, No. 3, 814-817 (1986).
6. S. Muller and G. Hochaus, *Pharm. Res.*, **12**, No. 8, 1165-1170 (1995).
7. K. Wegener and W. Kummer, *Acta Anat. Basel.*, **151**, No. 2, 112-119 (1994).
8. R. S. Zukin, A. Tempel, and E. L. Gardner, *Natl. Inst. Drug Abuse Res. Monogr. Ser.*, **54**, 146-161 (1984).