Effects of Central Opiate and Serotoninergic Structures on Heart Rhythm during Acute Myocardial Ischemia

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Electrostimulation of the central gray matter in the sylvian aqueduct and nucleus raphe magnus produced an antiarrhythmic effect during acute myocardial ischemia. Stimulation and blockade of opiate receptors in the central amygdaloid nucleus and lateral hypothalamus with dalargin and naloxone induced the same effect. Destruction of the central gray matter in the sylvian aqueduct and nucleus raphe magnus decreased electrical stability of ischemic myocardium.

Key Words: *acute myocardial ischemia; arrhythmias; central opiate and serotoninergic structures*

High mortality rate from cardiac arrhythmias developed in the acute stage of myocardial infarction is still a pressing medical problem. Previous studies showed that cardiac arrhythmias are related to hyperactivation of various nervous structures. Destruction of these structures enhances electrical stability of ischemic myocardium [3,6].

It was demonstrated that modulation of opiate and serotoninergic brain structures can prevent arrhythmogenesis [2,4]. However, systemic activation of opiate and serotonin receptors does not allow evaluating the central component of their influence on cardiac rhythmic activity. Here we studied the role of the central gray matter in the sylvian aqueduct (CGM), lateral hypothalamus (LH), central amygdaloid nucleus (CAN), and nucleus raphe magnus (NRM) in the pathogenesis of cardiac arrhythmias during acute myocardial ischemia.

MATERIALS AND METHODS

Experiments were performed on 121 outbred albino male rats weighing 160-220 g and narcotized with 50 mg/kg nembutal under conditions of controlled ventilation (0.2 mg/kg ditilin). Acute myocardial ischemia was induced by ligation of the left descending coronary artery. ECG was recorded using standard leads. We estimated the number of multiple ventricular extrasystoles, episodes of paroxysmal ventricular tachycardia and ventricular fibrillation, and duration of these attacks.

In control rats (n=22), the left coronary artery was ligated without (n=9) or with preliminary bilateral microinjections of 0.9% NaCl (0.2 μl) into CAN (AP=1, L=3.5, H=8, n=6) or LH (AP=0.5, L=1.5, H=8) [9].

In group 1 rats (n=17), the left coronary artery was ligated after stimulation of CGM (AP=6, L=0, H=6) with rectangular pulses for 10 min (2 V, 50 Hz, 0.1 msec, n=8) or CGM destruction with direct cathode current (5 μA, 10 sec, n=9). In group 2 rats (n=17), stimulation (n=8) or destruction (5 μA, 5 sec, n=9) of NRM (AP=10.5, L=0; H=10.5) was performed before ischemia.

Group 3 included 67 rats. Before left coronary artery ligation some animals received bilateral microinjections of 0.2 μl naloxone (80 ng) into CAN (n=13) and LH (n=18), while others were administered with 0.2 μl dalargin (200 ng) into CAN (n=13) and LH (n=21).

Histological verification of microinjections and electrodes was performed on a freezing microtome by routine methods.

The results were analyzed by exact Fischer's test.

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RESULTS

Preliminary studies of arrhythmogenesis in control rats revealed similar reactions of the heart to acute myocardial ischemia, therefore the data were pooled.

Stimulation of CGM before left coronary artery ligation increased the percentage of animals without ischemic arrhythmias (Fig. 1). The incidence of extrasystoles and paroxysmal ventricular tachycardia decreased, while ventricular fibrillation was not observed in these rats.

Precoagulation of CGM produced an opposite effect: multiple extrasystoles and paroxysmal ventricular tachycardia developed in all animals, and ventricular fibrillation was observed in 56% rats.

Stimulation and coagulation of NRM caused similar changes. Hyperactivation of NRM decreased the incidence of arrhythmias, while its destruction promoted arrhythmogenesis (Fig. 2).

Stimulation and blockade of opiate receptors in CAN and LH produced an arrhythmogenic effect: the incidence of multiple extrasystoles in these rats was 2-fold lower than in controls. Microinjections of dalargin into CAN most significantly prevented paroxysmal ventricular tachycardia and ventricular fibrillation. This compound decreased the incidence of paroxysmal ventricular tachycardia (23% animals) and completely prevented the development of ventricular fibrillation (*vs.* 83 and 44% in the control). After microinjections of dalargin the percent of animals without arrhythmias increased by 9-11 times (Fig. 3).

Our results indicate that activation of CGM and NRM neurons produces an antiarrhythmic effect during acute myocardial ischemia. This is probably related to the influence of serotonin released from NRM neurons, whose axons project into sympathetic preganglionic neurons in the thoracic spinal cord [10]. This pathway inhibits sympathetic preganglionic neurons [8]. Previous studies showed that their hyperactivation during acute myocardial ischemia potentiates the development of cardiac arrhythmias [3]. Stimulation of CGM activates NRM neurons [5] and, therefore, inhibits sympathetic preganglionic neurons. Blockade of arrhythmogenesis during CGM stimulation can be related to the inhibition of catecholaminergic brain structures, since endogenous opiates act as their functional antagonists. This hypothesis is confirmed by published data that generator of pathologically enhanced excitation in noradrenergic brain nuclei (*e.g.*, locus coeruleus) initiates cardiac arrhythmias during acute myocardial ischemia [6]. Moreover, dalargin-induced stimulation of δ- and μ-

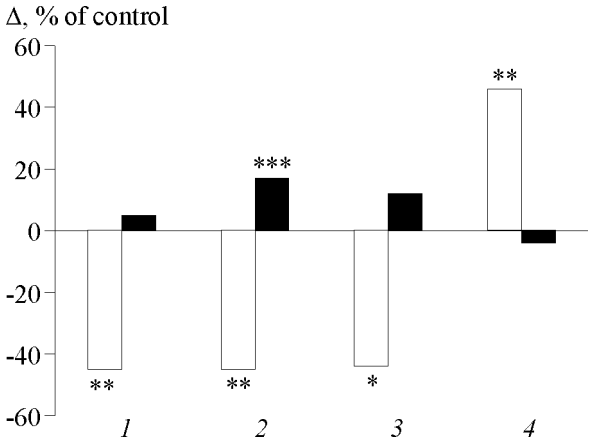

Fig. 1. Effects of stimulation (light bars) and coagulation (dark bars) of the central gray matter in the sylvian aqueduct on the incidence of arrhythmias. Here and in Figs. 2 and 3: *1*) multiple extrasystoles, *2*) paroxysmal ventricular tachycardia, *3*) ventricular fibrillation, *4*) without arrhythmias. **p*<0.001, ***p*<0.01, and ****p*<0.05 compared to the control.

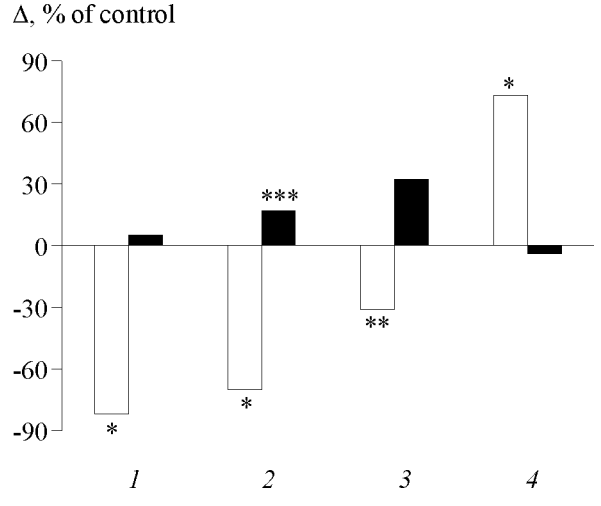

Fig. 2. Effects of stimulation (light bars) and coagulation (dark bars) of the nucleus raphe magnus on the incidence of arrhythmias.

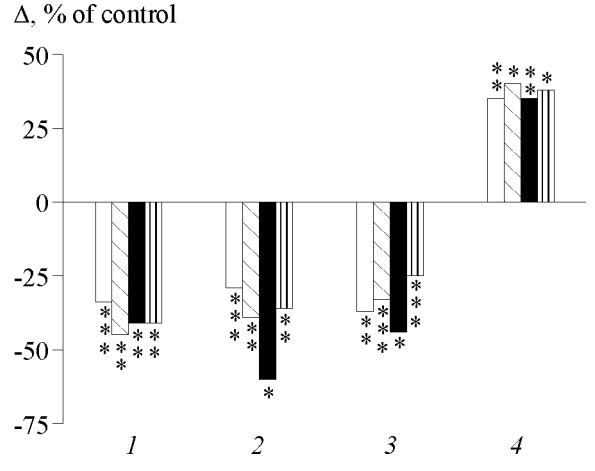

Fig. 3. Effects of naloxone and dalargin on the incidence of arrhythmias. Microinjections of naloxone and dalargin into the central amygdaloid nucleus (light and dark bars, respectively) and lateral hypothalamus (slant and vertical shading, respectively).

opiate receptors in CAN and LH increases electrical stability of ischemic heart. The decrease in the incidence of arrhythmias after administration of the nonselective opiate receptor blocker naloxone into these brain structures is probably associated with its influence on κ-opiate receptors, whose activation aggravates the symptoms of cardiac arrhythmias [7].

REFERENCES

1. E. V. Gubler, *Computational Methods for Studies and Recognition of Pathological Processes* [in Russian], Leningrad (1978).
2. G. I. Kositskii, S. D. Mikhailova, S. L. Gorozhanin, and T. M. Semushkina, *Byull. Eksp. Biol. Med*., **107**, No. 5, 528-530 (1989).
3. S. A. Lebedev, *Effects of Hyperactivated Sympathetic Preganglionic Neurons in the Spinal Cord on Cardiac Rhythmic Activity*, Abstract of Cand. Med. Sci. Dissertation, Irkutsk (1984).
4. Yu. B. Lishmanov, D. S. Ugdyzhekova, and L. N. Maslov, *Byull. Eksp. Biol. Med.*, **124**, No. 9, 286-288 (1997).
5. V. A. Mikhailovich and Yu. D. Ignatov, *Pain Syndrome* [in Russian], Leningrad (1990).
6. Yu. I. Pivovarov, *Central Mechanism Underlying Generation of Cardiac Arrhythmias*, Abstract of Doct. Med. Sci. Dissertation, Irkutsk (1984).
7. D. S. Ugdyzhekova, L. N. Maslov, and Yu. B. Lishmanov, *Byull. Eksp. Biol. Med*., **123**, No. 6, 656-658 (1997).
8. *Physiology of the Autonomic Nervous System* [in Russian], Leningrad (1981).
9. E. Fifkova and Dzh. Marshala, *Electrophysiological Assays*, Eds. Ya. Buresh *et al*. [in Russian], Moscow (1997).
10. R. A. L. Dampney, *Phys. Rev*., **74**, No. 2, 323-359 (1994).