GENERAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

Effects of Opioid Peptides on the Development of Ischemic Cardiac Arrhythmias under Conditions of Partial Sympathetic Denervation and Laser Irradiation

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The effects of intravenous administration of different opioid peptides on the development of ischemic cardiac arrhythmias under conditions of intraatrial laser irradiation (λ=632.8 nm) were studied in cats with transected cardiac branches of the right stellate ganglion and preserved sympathetic innervation of the ischemized area. Ischemia was caused by occlusion of the circumflex branch of the left coronary artery. It was found that the protective effects of dalargin were most powerful when sympathetic influences on the ischemic area were intensified by laser irradiation. Under these conditions DAGO showed more pronounced antiarrhythmic effects than DSLET.

Key Words: *myocardial ischemia; cardiac arrhythmias; opioid receptors; laser irradiation; sympathetic regulation of the heart*

Autonomic innervation of the heart plays an important role in protective effects of laser irradiation (LI) in ischemic cardiac arrhythmias [5]. It remains unclear whether these effects are due to modified release of neurotransmitter from autonomic nerve terminals or to enhanced synthesis and release of opioid peptides, which exert an antiarrhythmic effect in myocardial ischemia [3,4]. The purpose of this study was to investigate the effects of different opioid peptides on the development of ischemic arrhythmias after intraatrial LI in animals with disturbed sympathetic innervation of the myocardium.

MATERIALS AND METHODS

Experiments were carried out on 85 male and female cats (2.5-4.5 kg) under Nembutal anesthesia (40 mg/kg, intraperitoneally). Myocardial ischemia was caused by 15-min occlusion of the circumflex branch of the left coronary artery. Arrhythmias were monitored during occlusion and for the following 15 min of reperfusion. The right auricle was irradiated with an ILGN-120 He-Ne laser with 3-5 mW power at the end of the light guide (λ=632.8 nm). Under these conditions, idioventricular cardiac arrhythmias have been previously observed in 31% of cases, ventricular fibrillations in 7.7%, and no cases of ventricular tachicardia were recorded [5]. LI was performed 5 min after transection of the inferior cardiac nerve and caudal anastomosis at the level of the right stellate ganglion. Opioid peptides were intravenously infused with a dropper during the ischemia period. The following peptides synthesized at the Laboratory of Peptide Synthesis of the Russian Cardiology Research-and Production Complex were tested: dalargin, μ and δ opioid receptor (OR) agonist (10 μg/kg), DAGO, a selective μ-OR ago-

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nist (20 μg/kg), and DSLET, a selective δ-OR agonist (20 μg/kg). ECG and blood pressure (BP) in the femoral artery were recorded with a P4Ch-02 polygraph connected to a computer via an analog-to-digital convertor. The incidence of grouped ventricular extrasistole, tachycardia and fibrillations was analyzed. Statistical significance was assessed by Student's, Pearson's, and Fisher's tests for 2×2 matrices.

RESULTS

In 10 experiments, transection of the inferior cardiac nerve (ICN) preserving sympathetic innervation of the ischemic area lowered BP by 3% (146±6.2 mm Hg) and decreased the heart rate (HR) by 12.6% (188.29± 17 beats/min, $p<0.01$). Laser irradiation applied to the right atrium induced a 10% elevation of BP ($p<0.05$) without changing the HR. Thirty seconds after coronary occlusion BP remained above the initial level. Myocardial ischemia induced grouped extrasystoles and ventricular tachicardia in half of the animals and irreversible ventricular fibrillation in all animals (Fig.1, *a*).

The increased incidence of idioventricular arrhythmias under these conditions can be attributed to both LI-induced enhancement of myocardium contractility [1,6] and hyperactivation of sympathetic nerves projecting to the ischemic area [13].

Taking into account that opioid peptides modulate sympathetic influences on the myocardium, we studied the effects of different opioid peptides on the development of ischemic cardiac arrhythmias in LI-treated animals with transected ICN. In 10 experiments with dalargin, coronary occlusion caused ischemic arrhythmias in 40% of animals, 30% of them exhibited ventricular tachicardia and 10% ventricular fibrillation (Fig. 1, *b*). These data show that dalargin reduces the occurrence of idioventricular ischemic arrhythmias, including irreversible ventricular fibrillation.

At the same time, in 6 additional experiments with dalargin without LI, coronary occlusion induced ventricular tachycardia in 33% of animals and caused no ventricular fibrillation (Fig. 1, *b*). When neither dalargin nor LI were given (13 experiments), the coronary occlusion resulted in idioventricular arrhythmias in 85% of cases with ventricular tachycardia and fibrillation in 38% of them (Fig. 1, *a*).

Thus, irrespective of laser treatment the δ- and μ-OR agonist dalargin prevented the development of ischemic cardiac arrhythmias under conditions of partial sympathetic denervation of the myocardium.

In 11 experiments with DSLET infusion during coronary occlusion, ischemic arrhythmias were observed in 91% of LI-treated animals with transected ICN (36% of ventricular tachicardia and 55% of ven-

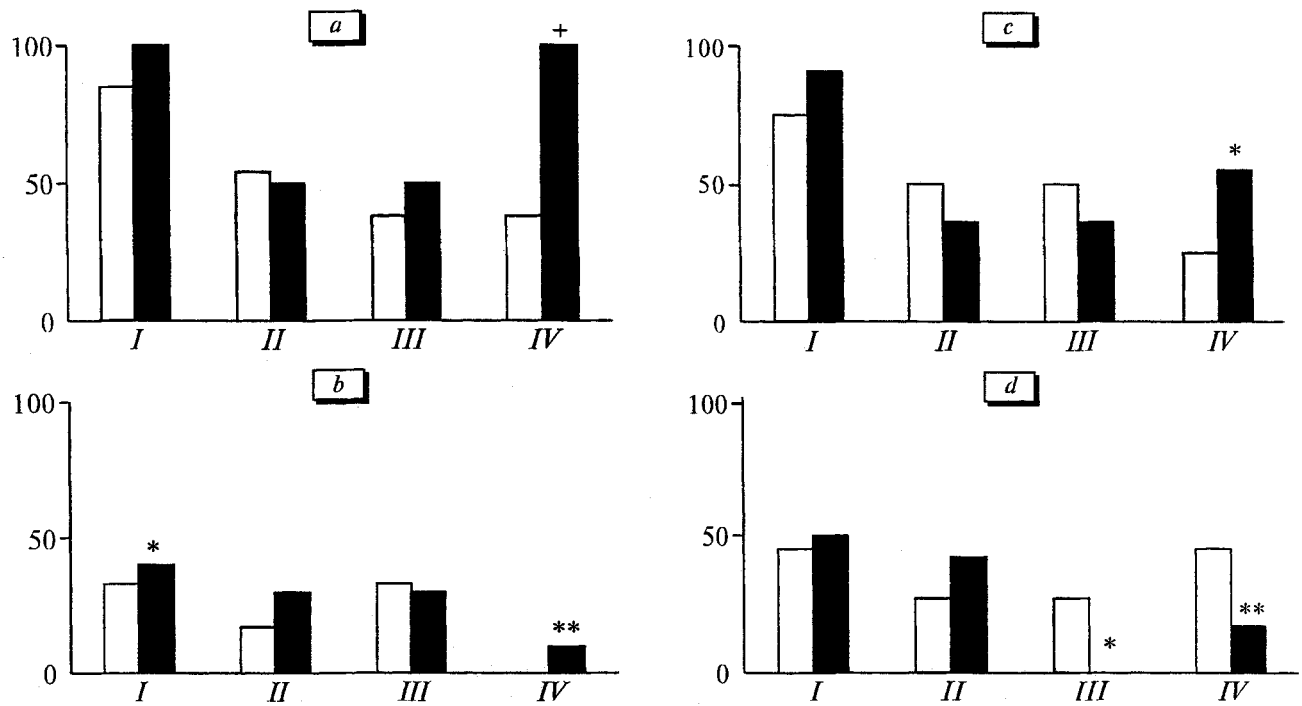

Fig. 1. Development of ischemic cardiac arrhythmias after coronary artery occlusion in animals with transected cardiac branches of the right stellate ganglion in control (*a*) and after administration of dalargin (*b*), DSLET (*c*), and DAGO (*d*). The total number of severe idioventricular arrhythmias (*I*), extrasystoles (*II*), ventricular tachycardia (*III*), and ventricular fibrillation (*IV*). $^{+}p<0.05$ in comparison with experiments without laser irradiation, $^{*}p<0.05$, $^{**}p<0.01$ in comparison with experiments with laser irradiation and without opioid peptide administration. Open and filled bars correspond to experiments without and with laser irradiation, respectively.

tricular fibrillation, Fig. 1, *c*). In 12 experiments with DSLET administration without LI, coronary occlusion caused arrhythmias in 75% of animals with transected ICN with ventricular tachicardia in 50% of the cases and fibrillation in 25%. These results are similar to those observed in experiment without DSLET, which indicates that under conditions of disturbed sympathetic innervation of the myocardium the antifibrillatory effect of DSLET is relatively weak. In the experiments with LI, administration of the peptide induced a nearly 2-fold decrease in the occurrence of ventricular fibrillations in animals with transected ICN in comparison with cats receiving no DSLET.

In 12 experiments with DAGO occlusion of the coronary artery was accompanied by ischemic arrhythmias in 50% of LI-treated animals with transected ICN. Ventricular tachycarida was not observed, while ventricular fibrillation occurred in 17% of cases (Fig. 1, *d*). In experiments with DAGO without LI (n=11) ischemic arrhythmias were observed in 45% of animals (ventricular tachycardia in 27% and ventricular fibrillations in 45%). Hence, DAGO was almost ineffective with respect to severe cardiac rhythm disturbances, but induced an almost 2-fold decrease in the occurrence of idioventricular arrhythmias. DAGO exerted a pronounced antiarrhythmic effect under conditions of impaired sympathetic innervation and LI.

In summary, it can be concluded that the μ-OR agonist DAGO produces more potent antiarrhythmic affect than the δ-OR agonist DSLET in situations when myocardial ischemia is combined with LI treatment and sympathetic innervation of the ischemized area is preserved. Agonists of μ- and δ-OR via their peripheral effects can modulate cardiac activity by reducing sympathetic influences [9,11]. DAGO penetrating the blood-brain barrier interacts with both the peripheral and central μ-OR, thus potentiating parasympathetic influences on the myocardium [12].

Dalargin due to activation of both μ- and δ-OR produces a more powerful antiarrhythmic effects in animals with impaired sympathetic innervation, both treated and untreated with LI. However, potentiation of parasympathetic influences results from activation of the central receptors via μ- and d-OR located on the afferent fibers of the vagus nerve [4,14].

Proceeding from published data on LI-induced activation of the endogenous opioid system, it can be suggested that long-term LI depletes the sympathetic stores of opioid peptides inhibiting the release of noradrenaline [2,7,8,10]. Under conditions of partial denervation of the myocardium and hyperactivation of the remaining sympathetic innervation, LI can produce temporary local depletion of endogenous opioids, which aggravates occlusion-induced ischemia and facilitates the development of cardiac arrhythmias. Under these conditions administration of opioid peptides produces pronounced protective effects.

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