GENERAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

Different Antiarrhythmic Effects of Dalargin and β-Endorphin in Severe Myocardial Ischemia During Stimulation of the Sensorimotor Cortex

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The effects of the opiate receptor agonists dalargin and β-endorphin on the occurrence of idioventricular arrhythmias, including ventricular tachycardia and fibrillation, are studied in acute experiments on Nembutal-anesthetized cats. Dalargin administered in the dose crossing the blood-brain barrier produces a pronounced antiarrhythmic effect, while β-endorphin is effective only against ventricular fibrillation.

Key Words: *dalargin; β-endorphin; myocardial ischemia; cardiac arrhythmia; stimulation of sensorimotor cortex*

Ischemic damage to the myocardium often results from stress and is accompanied by hyperactivation of the sympatheticoadrenal system leading to serious functional disorders in the cardiovascular system [7]. The damaging sympatheticoadrenal influences on the myocardium can be controlled by opioid peptides which exhibit the highest protective activity upon activation of the sympathetic nervous system [9]. A decrease in blood concentration of opioid peptides in acute myocardial infarction aggravates ischemia and indicative of unfavorable prognosis [2], implying that under conditions of stress the opioid peptide pool should be exogenously replenished.

In the present study we compared the effects of exogenous opioid peptides on the development of ischemic arrhythmias against the background of stimulation of the sensorimotor zone of brain cortex which is involved in realization of stress reactions.

MATERIALS AND METHODS

Experiments were performed on adult cats of both sexes (body weight 2-4 kg) under Nembutal anesthesia (40 mg/kg intraperitoneally) and artificial ventilation. A loose ligature was applied onto the left circumflex coronary artery in its upper third. Ischemia was produced by tying the ligature for 15 min with subsequent reperfusion. In all experiments the sensorimotor zone of brain cortex was stimulated for 20 sec using silver unipolar electrodes (tip diameter 0.8 mm), which were applied onto the sigmoid fissure after craniotomy, and an ESL-1 electrostimulator (rectangular pulses, 1 msec, 30 Hz, 2.5-6.5 mA). The correctness of the stimulating electrode localization was verified after extensive craniotomy. In series I, the cardiac branches arising from the stellate ganglia were cut, and the coronary artery was occluded after 5 min. In series II, the synthetic analog of Leu-enkephalin dalargin (500 μg/kg) was infused via the femoral vein throughout the entire period of ischemia [10]. In series III, a bolus intravenous injection of 50 μg/kg β-endorphin (BE, Cardiology Research Center) was performed 5 min before ischemia [8,12]. The ECG (leads II and III) and blood pressure in the femoral artery were recorded for 15 min of ischemia and 15 min of reperfusion. The following cardiac rhythm disturbances were analyzed: group and polytopic extrasystoles, allorhythmias, and ventricular

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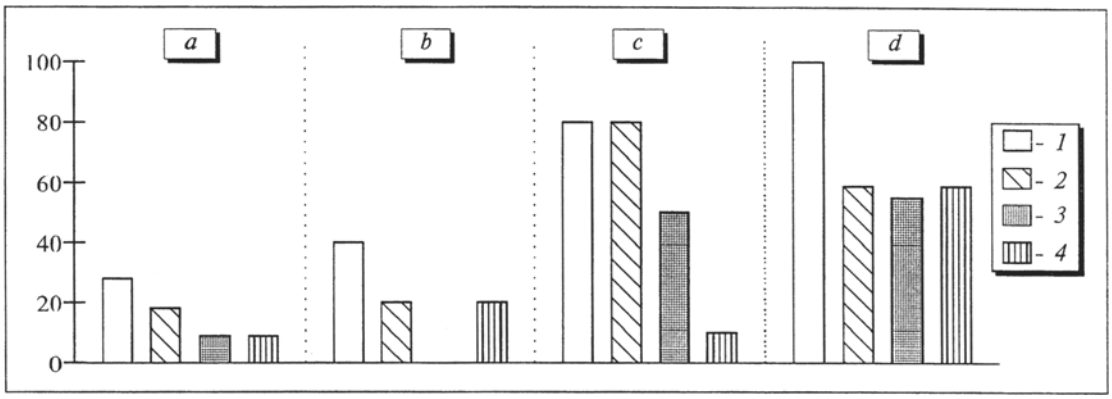

Fig. 1. Effects of dalargin, β-endorphin, and elimination of sympathetic innervation on the occurrence of idioventricular arrhythmias in myocardial ischemia developing upon stimulation of the sensorimotor cortex. Development of arrhythmia upon stimulation of the sensorimotor cortex: *a*) cutting of cardiac branches arising from the stellate ganglion, *b*) administration of dalargin, *c*) administration of β-endorphin, *d*) without drugs. *1*) gross idioventricular arrhythmias, *2*) group extrasystoles, *3*) ventricular tachycardia, *4*) ventricular fibrillation. Ordinate: occurrence of arrhythmias, %.

tachycardia (VT) and fibrillation (VF). The significance of differences was evaluated by χ^2 and Student's *t* tests.

RESULTS

Changes in the functional state of cortical centers play an important role in genesis of cardiac arrhythmias [13]. Stimulation of these structures under conditions of myocardial ischemia markedly increases the occurrence of gross idioventricular arrhythmias [3]. At the same time, in stress, which is realized predominantly via the central nervous system, ischemic damage to the myocardium and development of arrhythmias are associated with increased activity of the sympatheticoadrenal system [7]. Therefore, in the first series of experiments we have evaluated the role of sympathetic system in the development of ischemia-induced cardiac rhythm disturbances upon stimulation of the sensorimotor cortex. In 11 cats, the cardiac branches arising from the stellate ganglia were cut 5 min prior to coronary occlusion, after which reduction in systolic (21.2%, $p<0.05$, 139.1± 6.6 mm Hg) and diastolic (26.6%, $p<0.05$, 104.1±6.4 mm Hg) pressure were observed in all animals, while a 26.6% decrease in heart rate (143.2±7.4 beats/min) was recorded in 72% and a 21.9% decrease in pulse pressure (36.21±2.4 mm Hg) in 54% of the animals. A slight (12.4%) increase in pulse pressure was observed 30 sec after coronary occlusion upon stimulation of the sensorimotor cortex, while other hemodynamic parameters remained unchanged. Myocardial ischemia was accompanied by VT in 9% and VF also in 9% of experiments (Fig. 1, *a*, *d*). These findings indicate that myocardial ischemia against the background of stimulation of the sensorimotor cortex and interrupted sympathetic innervation was not accompanied by any considerable decrease in arterial pressure 30 sec after coronary occlusion and was not aggravated by VT ($p<0.05$) and VF ($p<0.02$) in comparison with results obtained under the same conditions, but with intact sympathetic innervation. Thus, the sympathetic nervous system plays substantial role in myocardial ischemia developing upon stimulation of the sensorimotor cortex, and elimination of sympathetic influences has an antiarrhythmic effect.

Bearing in mind the role of sympathetic nervous system in the pathogenesis of ischemic arrhythmias and the ability of opioid peptides to modulate its activity [9], in the second series of experiments we examined the effect of the synthetic analog of Leu-enkephalin dalargin, an agonist of δ- and μ-receptors, on the occurrence of ischemic arrhythmias upon stimulation of the sensorimotor cortex. Dalargin was intravenously infused into 10 cats throughout the entire period of ischemia in a dose of 500 μg/kg, which provides its crossing the blood-brain barrier. Similar to series I, we observed no changes in hemodynamic parameters compared with baseline level (130.7±5.2 mm Hg, 100.9±4.7 mm Hg, 155.2±10 beats/min, 28.8±2.4 mm Hg, respectively). Twenty percent of the animals developed VF. Ventricular tachycardia was not observed in this series (Fig. 1, *b*), which may be associated with the ability of dalargin to reduce the release of catecholamines from the adrenals [1]. These results indicate that administration of dalargin in the doses crossing the blood-brain barrier prevents considerable hemodynamic alterations at the early stages of myocardial ischemia, significantly ($p<0.001$) reduces the occurrence of gross idioventricular arrhythmias, and decreases the occurrence of VF 3-fold compared with animals given no dalargin; they also confirm the relationship between reduction in blood pressure and occurrence

of VF [3]. Administration of dalargin under similar conditions but in the dose that does not cross blood-brain barrier (10 μg/kg) produces a weaker antiarrhythmic effect: myocardial ischemia is complicated by VT in 14% and by VF in 28% of cats. Thus, upon stimulation of the sensorimotor cortex dalargin displays the highest antiarrhythmic activity in the dose crossing the blood-brain barrier. This effect is probably mediated by δ- and μ-opiate receptors of cardiovascular and respiratory centers of the medulla oblongata, which are involved in the development of ischemic arrhythmias [4,5].

In series III (n=10), we studied the effect of the opioid peptide β-endorphin, an agonist of μ-, δ-, ε-, and κ- opiate receptors, on the occurrence of ischemic arrhythmias upon stimulation of the sensorimotor cortex. It was reported that this peptide is a component of the stress-limiting system [8,15]. The peptide was administered intravenously (bolus injection) in the dose crossing the blood-brain barrier (50 μg/kg) 5 min before clamping the coronary artery. The preparation produced no appreciable changes in hemodynamic parameters compared with baseline level: 129.2±5.8 mm Hg, 97.6±5.7 mm Hg, 160.2± 8.2 beats/min, 31.57±1.9 mm Hg, respectively). Coronary occlusion had no appreciable effect on hemodynamic parameters, indicating that BE precludes a decrease in hemodynamic parameters. The occurrence of VF was observed in 10% and VT in 50% of the animals (Fig. 1, *b*). The absence of protective effect of BE under these experimental conditions on the occurrence of VT and other arrhythmias may be associated with the ability of this peptide to modulate the release of catecholamines from adrenals [14]. The antifibrillatory effect is probably due to the central action of BE: this peptide acts on the bulbar centers and other brain structures that participate in the regulation of cardiovascular system and are involved in the development of VF [4,5,11].

From our results it can be concluded that both BE and dalargin administered is doses crossing the blood-brain barrier reduce arterial pressure at the early stages of myocardial ischemia developing against the background of the sensorimotor cortex stimulation, thus preventing ventricular fibrillation. This is consistent with the relationship between a drop in arterial pressure after 30 sec of coronary occlusion and the occurrence of VF, which may be associated with rearrangements in the function of the bulbar cardiovascular center that is involved in the development of VF. At the same time, the different effects of these peptides on the occurrence of gross idioventricular arrhythmias, including VT, may be due to increased blood catecholamine content. The antiarrhythmic effect of dalargin is probably associated both with a decrease in blood catecholamines and the ability of dalargin to interact with only d and m-opiate receptors, which is consistent with the higher antiarrhythmic activity of selective agonists [6]. Thus, dalargin is a more prospective anti-ischemic drug than BE.

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