Role of Sympathetic Nervous System in Protective Effects of Selective κ-Opiate Receptor Agonist Dynorphin A_{1-13} on the Incidence of Cardiac Arrhythmia during Myocardial Ischemia

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Preliminary administration of dynorphin A_{1-13} to narcotized cats with myocardial ischemia attenuated cardiac fibrillation, but increased the incidence of ventricular tachycardia. Protective effect of dynorphin A_{1-13} was observed only under conditions of intact sympathetic cardiac innervation.

Key Words: *dynorphin A_{1-13}; κ-opiate receptors; myocardial ischemia; cardiac arrhythmia; stellate ganglion*

Recent studies demonstrated the presence of μ-,δ-, and κ-opiate receptors in the heart. Dynorphin A_{1-13} (DYN) is a selective agonist of κ-opiate receptors [6]. Agonists of μ- and δ-opiate receptors posses considerable antiarrhythmic properties in myocardial ischemia [7, 12], but the role of κ-opiate receptors and the effects of DYN on heart rhythm received little attention. Experiments on the isolated heart showed that DYN increased the incidence of cardiac arrhythmia and cAMP concentration in the heart, while naloxone completely abolished these effects [11]. Neurogenic mechanisms play an important role in the pathogenesis of ischemic cardiac arrhythmias [3]. Moreover, κ-opiate receptors were found in brain regions involved in the regulation of the cardiovascular system and in sympathetic postganglionic fibers innervating coronary vessels and cardiomyocytes [14]. Here we studied the effects of DYN on the development of cardiac arrhythmias and possible sympathetic mechanisms of this action.

MATERIALS AND METHODS

Experiments were performed on 49 male and female cats weighing 2-4 kg and narcotized with Nembutal (40 mg/kg intraperitoneally). Myocardial ischemia was induced by occlusion of circumflex branch of the left coronary artery. The development of arrhythmia was monitored over 15-min myocardial ischemia and 15-min reperfusion. Our previous studies showed that under these conditions, idioventricular rhythm, ventricular tachycardia, and ventricular fibrillation were observed in 72, 28, and 56% observations, respectively [8]. Electrocardiogram and blood pressure in the femoral artery and left ventricle were recorded on a Biokomb-8 polyphysiograph (Orion/EMG).

The selective κ-opiate receptor agonist DYN (Laboratory of Peptide Synthesis, Russian Cardiology Research Center) in a dose of 40 μg/kg was intravenously infused for 15 min from the moment of coronary occlusion.

In series I (n=12), coronary occlusion (CO) was performed against the background of DYN administration and intact cardiac innervation. In series II (n=10), CO and infusion of DYN was preceded by bilateral vagotomy and transection of cardiac branches of the stellate ganglia (5 min before CO). In series III, cardiac branches of stellate ganglia were transected 5 min before CO in animals with (n=10) or without (n=10) DYN infusion. In series 4 (n=7), DYN effects on adrenergic properties of the heart were studied by

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analyzing cardiac reactions (changes in left ventricular pressure, heart rate (HR), and Opie index) to 1 μg/kg norepinephrine [5] in animals with or without DYN infusion. The results were analyzed by Student's t and χ^2 tests.

RESULTS

In series I, the effect of DYN on the development of arrhythmia during CO was studied under conditions of intact cardiac innervation. The initial systolic, diastolic, pulse, and mean pressures were 121.4±9.5, 94.4±10.1, 27±1.26, and 103.6±9.92 mm Hg, respectively, and HR was 136.6±16.1 beats/min. These hemodynamics parameters slightly varied soon after the onset of myocardial ischemia (30 sec postocclusion) and then progressively decreased. Systolic, pulse, and mean pressures decreased by 35.5 ($p<0.01$), 25 ($p<0.01$), and 34% ($p<0.05$), respectively, to the 3rd minute of ischemia. Hemodynamic parameters retuned to normal after 5-10 min and did not differ from the initial values during reperfusion. In untreated animals these parameters considerably decreased by the 30th second of acute myocardial ischemia [8], hence DYN prevents the decrease in blood pressure at the initial stages of myocardial ischemia, which was demonstrated to represent a good prognostic sign [4]. CO against the background of DYN infusion was accompanied by the appearance of idioventricular rhythm in 42% animals. Multiple ventricular extrasystoles and ventricular tachycardia were observed in 16 and 33% cats, respectively (Fig. 1, *a*). It should be emphasized that myocardial ischemia was never complicated by ventricular fibrillation. Idioventricular rhythm and ventricular fibrillation were observed in 72 and 56% cats not treated with DYN, respectively (Fig. 1, *b*) [8]. Therefore, DYN prevents the development of ischemic cardiac arrhythmia including ventricular fibrillation.

Taking into account the important role of the autonomic nervous system in the development of ischemic cardiac arrhythmia, in series II we studied the development of arrhythmias during myocardial ischemia against the background of DYN infusion and bilateral transection of the vagus nerves and cardiac branches of the stellate ganglia. Hemodynamic parameters and HR practically did not change by the 30th second of myocardial ischemia. CO provoked multiple ventricular extrasystoles, allorhythmia, ventricular tachycardia, and ventricular fibrillation in 30, 20, 40, and 40% cats, respectively (Fig. 1, *a*). Multiple ventricular extrasystoles and ventricular fibrillation were observed in 20 and allorhythmia in 10% cats receiving no DYN (Fig. 1, *b*) [9]. Thus, DYN produced an arrhythmogenic effects on denervated heart 2-fold increasing the incidence of ventricular fibrillation.

Extracardial nervous mechanisms, in particular sympathetic influences, play an important role in the pathogenesis of ischemic cardiac arrhythmia. The highest sympathetic activity of cat inferior cardiac nerve was recorded immediately before ventricular fibrillation [2]. Clinical observations indicate that the incidence of ventricular arrhythmia in patients with coronary diseases markedly decreased after excision of the stellate ganglion [13]. Therefore, in series III we studied the role of the sympathetic nervous system in the protective effects of DYN on the development of ischemic cardiac arrhythmia. Cardiac branches of both stellate ganglia were cut before CO and DYN infusion. Ventricular tachycardia and ventricular fibrillation were noted in 20 and multiple ventricular extrasystoles in 20% cats (similarly to control animals receiving no DYN; Figs. 1, *a* and *b*). Therefore, DYN did not prevent the development of ischemic arrhythmia after bilateral transection of cardiac branches of the stellate ganglia.

Hyperactivation of the sympathoadrenal system plays the major role in the pathogenesis of cardiac arrhythmia during myocardial ischemia [2]. Opioids can modulate activity of this system under various conditions, including myocardial ischemia [1]. There-

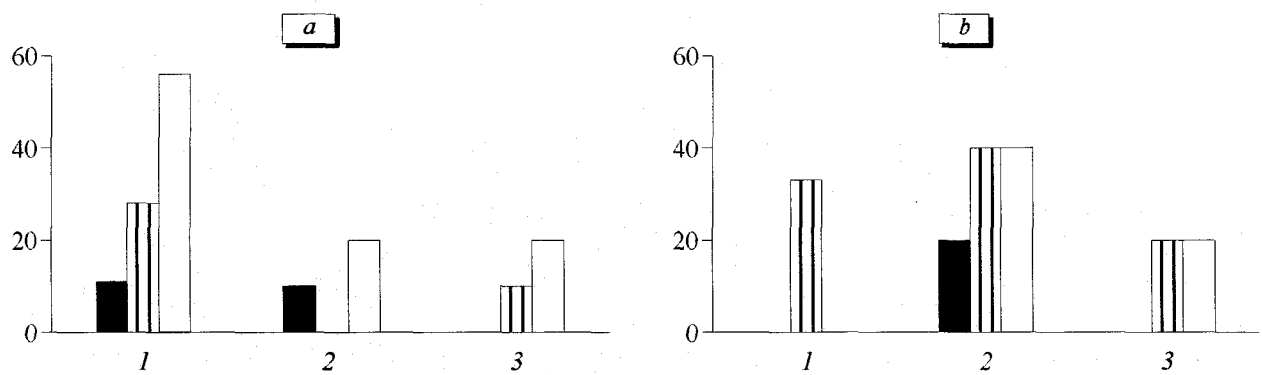

Fig. 1. Incidence of ischemic cardiac arrhythmias (%) at various cardiac innervation (*a*) and after infusion of dynorphin A_{1-13} (*b*): intact cardiac innervation (*1*), transection of vagus nerves and cardiac branches of stellate ganglia (*2*), and transection of cardiac branches of stellate ganglia (*3*). Dark bars: allorhythmia; shaded bars: ventricular tachycardia; and light bars: ventricular fibrillation.

fore, in series IV we studied the ability of DYN to affect adrenoreactivity of the heart by analyzing cardiac reactions (changes in left ventricular pressure, HR, and Opie index) to norepinephrine in animals with or without DYN administration. Cardiac reactions to standard norepinephrine dose in animals administered with Ringer's solution served as the control.

Adrenoreactivity of the heart in control animals remained unchanged: responses to norepinephrine before and after infusion of Ringer's solution were similar.

Cardiac reactions to norepinephrine were enhanced in animals receiving DYN: left ventricular pressure and Opie index increased by 34 and 46%, respectively. The number of β-adrenoceptors determining cardiac adrenoreactivity is inversely related to norepinephrine concentration in the heart [13]. A considerable increase in cardiac adrenoreactivity induced by DYN is probably associated with inhibition of sympathetic influences on the myocardium and represents a mechanism of its effects on ischemic cardiac arrhythmia.

Thus, the selective κ-opiate receptor agonist DYN produces a strong antiarrhythmic effects and prevents the development of ischemic cardiac arrhythmia via inhibition of the sympathetic nervous system, which is confirmed by the fact that DYN modulates cardiac adrenoreactivity and decreases norepinephrine content [10].

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