The Role of Heart Vegetative Nerves in Antiarrhythmic Effect of β-Endorphin in Experimental Myocardial Ischemia

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 123, No. 5, pp. 509-511, May, 1997
Original article submitted March 6, 1996

Acute experiments on narcotized cats showed that premedication with β-endorphin promotes the development of ventricular tachycardia and decreases the occurrence of ventricular fibrillation caused by myocardial ischemia. The antifibrillatory effect of β-endorphin is related to central nervous structures regulating the function of the cardiovascular system and is mediated through the vagus nerves.

Key Words: *β-endorphin; myocardial ischemia; cardiac arrhythmias; vagus nerves; stellate ganglia*

Clinical studies revealed that reduced blood concentration of β-endorphin (BE) in patients with myocardial infarction is characteristic of grave disorders accompanied by marked circulatory insufficiency and cardiac arrhythmias [1]. Moreover, experiments on animals showed that BE injected prior to infarction considerably restricts necrotic zone, preserves myocardial contractility in zones with normal circulation, and reduces mortality [6]. Taking into consideration these data and the important role of changed activity of the bulbar cardiovascular center and sympathetic influences in the development of ischemic cardiac arrhythmias, we decided to estimate the interrelationship between the protective effect of BE and functioning of different cardiac nerves.

MATERIALS AND METHODS

Experiments were carried out on 39 cats of both sexes weighing 2-4 kg narcotized with Nembutal (40 mg/kg, intraperitoneally). Myocardial ischemia was modeled by occluding the circumflex branch of the left coronary artery near the main vessel. Arrhythmias were recorded during a 15-min occlusion and subsequent 15-min reperfusion periods. We showed that under these conditions idioventricular arrhythmia developes in 72% of cases, ventricular tachycardia (VT) in 28% of cases, and ventricular fibrillation (VF) in 55% of cases [8].

β-Endorphin, a nonselective agonist of opiate receptors (Laboratory of Peptide Synthesis, Cardiology Research Center, Russian Academy of Medical Sciences) was injected intravenously (50 μg/kg, bolus) 5 min before occlusion of the coronary artery [6,13]. In some experiments, vagus nerves were cut on the neck, or the lower cardiac nerve and caudal loop were cut near the stellate ganglion. ECG and blood pressure in the femoral artery were recorded with a Biokomb-8 polyphysiograph (Orion/EMG). Statistical significance of differences was evaluated using the Student's t and χ^2 tests.

RESULTS

In 10 experiments, the effects of preliminary BE injection on the development of arrhythmias induced by occlusion of coronary artery were studied. Neither BE, nor subsequent occlusion of the coronary artery (during a 30-sec period) produced considerable shifts of hemodynamic parameters. Myocardial ischemia in these animals was accompanied by cardiac rhythm disturbances (Fig. 1). The occurrence of VT was

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0007-4888/97/0005-0442$18.00

twofold higher than in the control group, VT being observed during the 1st minute of reperfusion. Elevated epinephrine concentration promotes the development of arrhythmias during the recirculation period following a short-term coronary occlusion [5]. Taking into account the fact that BE induces catecholamine release from the adrenals and an up to 60-min elevation of their blood concentration [15], the increased occurrence of VT can be attributed to the elevated catecholamine concentration in the blood. At the same time it should be noted that VF were 2.8-fold less frequent in BE-injected animals in comparison with the control (Fig. 1). Moreover, shifts in the hemodynamic parameters in these animals were less pronounced than in the control (occlusion without BE injection), in whom arterial pressure dropped as follows: systolic and diastolic arterial pressures by 24% and 27%, respectively, mean diastolic pressure by 24% and pulse pressure by 17%, and heart rate decreased by 21% [8]. The latter agrees with the relationship between the arterial pressure reduction during the early stages of myocardial ischemia and the occurrence of VF [3]. Thus, these findings attest to an antifibrillatory effect of BE in myocardial ischemia.

Since functional rearrangement in the bulbar cardiovascular center plays an important role in the development of VF in myocardial ischemia [4], in the next experimental series we studied the effect of restriction of central nervous influences on the heart on the development of arrhythmias in myocardial ischemia against the background of BE. To this end, in 10 experiments bilateral transection of the vagus nerves and cardiac branches of the stellate ganglia preceded BE injection. Neither transection nor BE changed the studied hemodynamic parameters. Coronary occlusion under these conditions also did not change the hemodynamic parameters measured after 30 sec of ischemia. In this group, the occurrence of VT was 2.5-fold lower than in animals with preserved heart innervation and myocardial ischemia against the background of BE (Fig. 1). However, myocardial ischemia under conditions of bilateral transection of vagus nerves and cardiac fibers of the stellate ganglia without BE (n=10) was accompanied by VF in 20% of cases, while VT was absent in all experiments (Fig. 1). Thus, after transection of vagus nerves and cardiac fibers of the stellate ganglia, BE increased the occurrence of VT as it did under conditions of intact heart innervation. However, under conditions of restricted sympathetic and parasympathetic innervation, myocardial ischemia against the background of BE was 2-fold more frequently accompanied by VF compared to animals with preserved innervation (Fig. 1). This suggested the absence of protective effect of

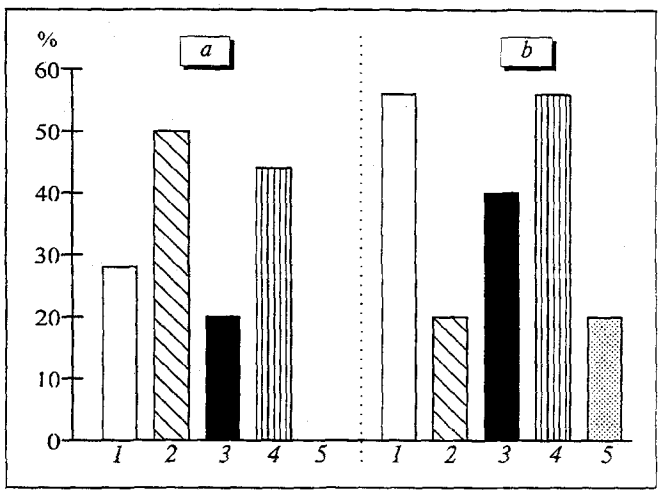

Fig. 1. Effect of β-endorphin on the occurrence of ventricular tachycardia (*a*) and ventricular fibrillation (*b*). *1*) ischemia without BE (n=18); *2-5*) ischemia against the background of BE under conditions of intact heart innervation (*2*, n=10); bilateral transection of vagus nerves and cardiac fibers of the stellate ganglia (*3*, n=10); vagotomy (*4*, n=9); transection of cardiac fibers of the stellate ganglia (*5*, n=10).

BE against VF. Since BE can cross the blood-brain barrier and modulate neuron activity in various brain areas, it can be hypothesized that BE prevents the development of VF through modulation of neuron activity in the cardiovascular and respiratory center of the brainstem [2,11,13].

In next experimental series we studied the role of the sympathetic and parasympathetic systems in the protective effect of BE against VF caused by myocardial ischemia. In 9 experiments BE was injected after bilateral vagotomy. Vagotomy did not affect considerably the recorded hemodynamic parameters. Similar to experiments with intact myocardial innervation, neither BE injection, nor coronary occlusion (by the 30th sec of ischemia) changed considerably the hemodynamic parameters. In this group, the occurrence of VT did not differ from that in animals with preserved innervation (Fig. 1), whereas the occurrence of VF was 2.8-fold higher than in animals with intact innervation and differed little from that observed in vagotomized animals with myocardial ischemia without BE [9].

Thus, these results suggest that bilateral vagotomy abolishes the protective effect of BE against VF caused by myocardial ischemia. The protective effect of BE under conditions of preserved cardiac innervation can be attributed to activation of parasympathetic influences improving electrical stability of the myocardium [14].

The role of sympathetic nervous system in the antifibrillatory effect of BE was studied in 10 experiments with bilateral transection of cardiac fibers of the stellate ganglia. This operation led to a consider-

able decrease in arterial pressure (by 12%, $p<0.001$) and heart rate (by 12%, $p<0.05$). Neither injection of BE nor occlusion of the coronary artery induced reliable shifts in the hemodynamic parameters. Under these conditions no cases of VT were recorded (Fig. 1). This was probably due to activation of parasympathetic regulation of the myocardium resulting in a reduction of its β-adrenergic stimulation [12]. The occurrence of VF in this group did not differ from that in animals with intact innervation (Fig. 1). Thus, the antifibrillatory effect of BE is preserved in this experimental group. This can be attributed to both restricted sympathetic and enhanced parasympathetic influences on the myocardium. This assumption is consistent with the results of other experimental series (vagotomy abolished the protective effect of BE) as well as with published data on depression of parasympathetic influences on the heart in VF [7,10].

Thus, BE elicits an antifibrillatory effect in myocardial ischemia apparently through modulation of the central nervous structures regulating the function of the cardiovascular system, in particular, parasympathetic nervous system, since vagotomy abolished the protective effect of BE. Apart from the antifibrillatory effect, BE considerably increases the occurrence of VT in myocardial ischemia due to elevated catecholamine release from the adrenals. The last phenomenon can limit the use of BE for the treatment of ischemic heart disease.

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