GENERAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

Role of Vagus Nerves in Antiarrhythmic Effect of DAGO in Acute Myocardial Ischemia

S. D. Mikhailova, G. I. Storozhakov, N. A. Bebyakova, and T. M. Semushkina

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Acute experiments on cats show that DAGO, a selective μ-opiate receptor agonist, elicits a pronounced antiarrhythmic effect in ischemia-induced arrhythmias. The protective effect of DAGO is observed only under conditions of intact parasympathetic innervation of the heart and apparently depends on the *n. vagus* activity and stimulating effect of DAGO on acetylcholine release.

Key Words: *DAGO; μ-opiate receptors; myocardial ischemia; cardiac arrhythmias; vagus nerves*

Antiarrhythmic effect of enkephalins in myocardial ischemia is mediated through specific receptors of different types. Since nonselective agonists of opiate receptors (OR) are usually used in experiments, there is no need to identify these receptors. On the other hand, arrhythmogenic effect of enkephalins depends on functional activity of vagus nerves [7]. In light of this, of particular interest is the role of selective agonists of OR in the development of ischemic arrhythmias. It has been shown that the selective μ-OR agonist DAGO exhibits antiarrhythmic effect on the development of adrenaline-induced arrhythmias [3,13]. Moreover, DAGO possesses an analgesic activity, inhibits lipid peroxidation and improves organism's resistance to hypoxia [1,8,9,14]. Taking into account these pharmacodynamic effect of DAGO and the fact that antiarrhythmic activity of enkephalins depends on functional activity of the autonomous nerve system, this study was aimed at elucidating the effect of the selective μ-OR agonist DAGO on the development of arrhythmias in myocardial ischemia and the role of the autonomous nerve system in this process.

Russian State Medical University, Moscow

MATERIALS AND METHODS

A total of 57 experiments were performed on cats of both sexes weighing 2-4 kg under Nembutal narcosis (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 15-min occlusion and subsequent 15-min reperfusion periods. We have shown that under these conditions idioventricular arrhythmias develop in 72% of cases, ventricular tachycardia in 28% of cases, and ventricular fibrillation in 55% of cases [5]. Electrocardiogram and blood pressure in the femoral artery were recorded with a Biokomb-8 polyphysiograph (ORION/EMG). DAGO, a selective μ-OR agonist (synthesized at the Laboratory of Peptide Synthesis, Russian Cardiology Research Center) were infused over the occlusion period in a dose of 20 μg/kg. The following interventions were performed: group 1 (n=11) — coronary occlusion (CO) and injection of DAGO under conditions of intact innervation; group 2 (n=8) — CO and injection of DAGO under conditions of bilateral transection of the vagus nerve on the neck and sym-

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pathetic cardiac branches near the stellate ganglia (5 min before coronary occlusion); group 3 (n=10) — CO and denervation as in group 2 without DAGO; group 4 (n=9) — CO and DAGO injection under conditions of a cold conduction blockade of myelinated fibers of the vagus nerve. To this end vagus nerves on the neck were separated from sympathetic nerves and placed into a special device with a build-in thermistor recording the temperature of the nerve and carefully isolated from adjacent tissues. The nerves were cooled to 6°C (cold conduction block of myelinated fibers [12]) by perfusing the nerve with a cooling fluid using a vacuum pump 5 min before and over the CO period and during 15-min reperfusion; group 5 (n=10) — CO and denervation as in group 4 without DAGO; group 6 (n=9) — CO and injection of DAGO under conditions of bilateral transection of vagus nerves (5 min before CO).

RESULTS

In group 1 animals we studied the effect of DAGO on the development of CO-induced cardiac rhythm disturbances under conditions of preserved cardiac innervation. Initial systolic and diastolic pressures were 140.9±5.0 and 95.8±4.0 mm Hg, respectively, pulse pressure was 45.2±3.4 mm Hg, mean pressure was 110.8±4.1 mm Hg, and heart rate was 151.4±8.6 beats/min. The early stage of myocardial ischemia (30 sec after CO) in this group was characterized by insignificant shifts of hemodynamic parameters, while in the control group (myocardial ischemia without DAGO) these shifts were more pronounced [5]. Thus, DAGO prevented the ischemia-induced drop of hemodynamic parameters in the early occlusion period, which is regarded as a good prognostic sign [2]. Our experiments showed that injection of the selective μ-OR agonist DAGO in myocardial ischemia reduces the occurrence of idioventricular arrhythmias and ventricular fibrillation 2- and 5-fold, respectively (p<0.05) in comparison with the control group (Fig. 1, *a*, 2, *a*).

Bearing in mind the important role of the autonomous nervous system in the development of ischemic cardiac arrhythmias [4], we evaluated the contribution of this system into the protective effect of DAGO. To this end, the effect of DAGO on the development of ischemic arrhythmias was studied under conditions of bilateral transection of the vagus nerves and cardiac branches of the stellate ganglia. Denervation did not change the studied hemodynamic parameters in these animals. Myocardial ischemia under these conditions was 2-fold more frequently accompanied by idioventricular arrhythmias, coupled extrasystoles, and ventricular fibrillation than

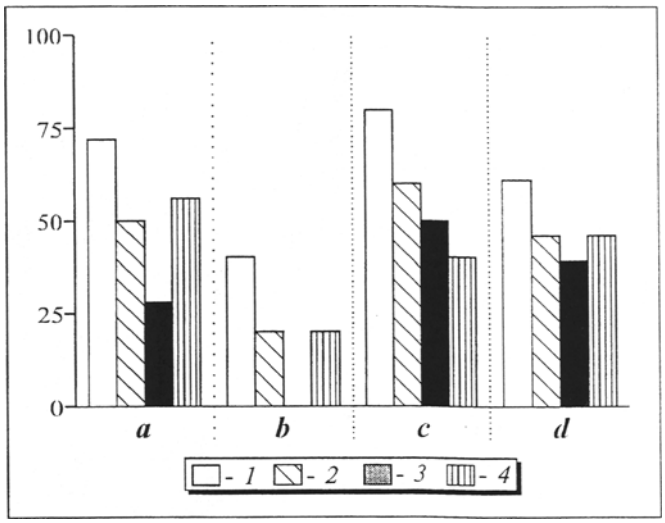

Fig. 1. Occurrence of ischemic arrhythmias under different innervation of the heart. Here and in Fig. 2: *a*) intact innervation; *b*) bilateral transection of vagus nerves and cardiac fibers of the stellate ganglia; *c*) blockade of myelinated vagal fibers; *d*) vagotomy. *1*) idioventricular arrhythmias (%); including: 2) coupled extrasystoles; 3) ventricular tachycardia; *4*) ventricular fibrillation.

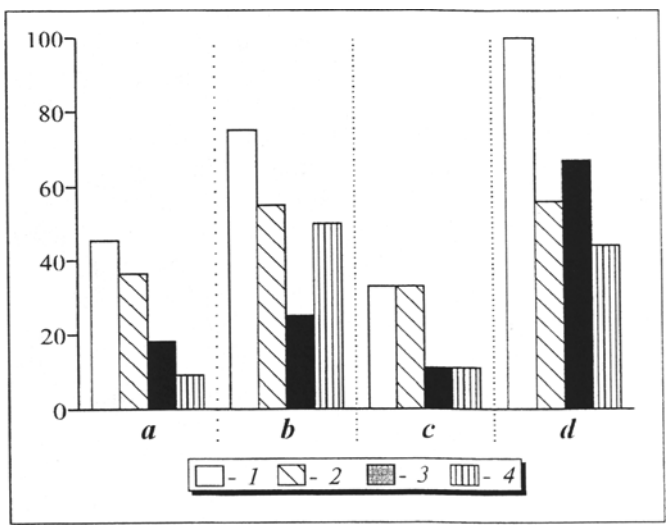

Fig. 2. Effect of DAGO on the occurrence of ischemic arrhythmias under conditions of different innervation of the heart.

in myocardial ischemia under conditions of heart denervation without DAGO injection (group 3, Fig. 1, *b*, 2, *b*). Ventricular tachycardia was observed in 25% animals of group 2 and was absent in group 3. Thus, it can be concluded that transection of vagus and sympathetic nerves in myocardial ischemia against DAGO pretreatment promotes the development of cardiac arrhythmias.

Since μ-OR are concentrated mainly in vagal fibers [15], we explored the involvement of myelinated (afferent projections from the cardiovascular system) and nonmyelinated vagal fibers in the antiarrhythmic effect of DAGO. In group 4, CO and

injection of DAGO were preceded by blockade of myelinated vagal fibers. The blockade of myelinated vagal fibers led to a insignificant rise of blood pressure. In cats treated with DAGO, coronary occlusion under these conditions 2-fold less frequently induced idioventricular arrhythmias and coupled extrasystoles than in animals with myocardial ischemia without DAGO injection (group 5, Fig. 1, *c*, 2, *c*), while the occurrence of ventricular tachycardia and ventricular fibrillation was 5- and 4-fold lower than in untreated animals, respectively. These data suggest that blockade of myelinated vagal fibers does not abolish the protective effect of DAGO on the development of ischemic arrhythmias.

In group 6 animals, CO and injection of DAGO were preceded by bilateral transection of the vagus nerve. Bilateral vagotomy did not change significantly the studied hemodynamic parameters. Under these conditions the occurrence of coupled extrasystoles and ventricular fibrillation induced by myocardial ischemia was the same in animals injected and not injected with DAGO, while the occurrence of ventricular tachycardia against DAGO pretreatment 2-fold surpassed that in vagotomized animals receiving no DAGO (Fig. 1, *d*, 2, *d*) [6]. The latter is probably due to the fact that DAGO increases blood catecholamine level 20 min postinjection [10]. Thus, cold blockade of afferent vagal fibers practically did not alter the antiarrhythmic effect of DAGO, whereas complete transection of the vagus nerves promoted the development of cardiac arrhythmias, in particular ventricular tachycardia. This points to a relationship between the protective effect of DAGO and functional state of the vagus nerves (primarily their efferent portion) and explains the absence of protective effect of DAGO under conditions of not only vagotomy, but also combined transection of the sympathetic and parasympathetic nerves of the heart.

It can be concluded that the selective μ-OR agonist DAGO exerts a pronounced protective effect against ischemic arrhythmias. This effect is observed under preserved parasympathetic innervation and probably depends on the activity of vagus nerves and on the stimulating effect of DAGO on acetylcholine release [11].

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