Mechanism of Protective Effect of Dalargin Against Ischemic Arrhythmias

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Acute tests on cats with altered sympathetic innervation of the heart show that the protective action exerted by dalargin against the development of ischemic ventricular fibrillation is due to a modulating influence of this leu-enkephalin analog on both the sympathetic and parasympathetic regulation of cardiac activity.

Key Words: *dalargin; ischemic arrhythmias; stellate ganglia*

The sympathetic nervous system is known to play an important role in the development of ischemic arrhythmias [3,13]. Therefore, the search for agents capable of modulating this system's activity is important. Of interest in this respect are opioid peptides, because they alter excitation transmission in sympathetic ganglia by inducing slow inhibitory postsynaptic potentials and restrict norepinephrine release from sympathetic nerve endings by acting on presynaptic opiate receptors [9,12]. We found previously that dalargin (DG), a synthetic leu-enkephalin analog, can protect against the development of ventricular fibrillation in myocardial ischemia (MI) [4]. DG has also been shown to modulate the activity of the sympathoadrenal system [1,2,8]. In view of this, and also considering the important contribution of the sympathetic nervous system to ischemic arrhythmias, in the present study we tested DG for its effect on the development of ischemic arrhythmias in animals with altered sympathetic innervation of the heart.

MATERIALS AND METHODS

The tests were performed on 26 Nembutal-anesthetized (40 mg/kg intraperitoneally) and artificially ventilated cats of both sexes weighing 2-4 kg. MI was produced by occluding, using a controllable loop, the circumflex branch of the left coronary artery near its orifice. The development of ischemia in the myocardium was recorded over 15 min of coronary artery occlusion and 15 min of the reperfusion period. ECG and pressure in the femoral artery were recorded with a BIOKOMB-8 recorder (ORION/EMG). The events considered in the analysis were solitary and grouped extrasystoles, ventricular tachycardia, and ventricular fibrillation. Sympathetic nerve supply to the heart was altered by cutting, 5 min prior to coronary artery occlusion, the inferior cardiac nerve and caudal subclavicular loop at the site of their exit from the stellate ganglion. The synthetic leu-enkephalin analog DG (produced by the Laboratory of Peptide Synthesis at the Cardiology Research Center, Moscow) was infused dropwise intravenously in a dose of 10 μg/kg (which does cross the blood-brain barrier) throughout the period of coronary artery occlusion [10]. The statistical significance of differences was estimated by Student's *t* test and the sign test.

RESULTS

In the first series, DG in a dose of 10 μg/kg known not to penetrate the blood-brain barrier was tested for its effect on the incidence of ischemic arrhythmias under conditions of disrupted sympathetic nerve supply to the MI zone. Since myocardial excitability in the ischemic zone resulting from compression of the circumflex branch of the left coronary artery is

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influenced by small cardiac nerves given off by the left stellate ganglion [14], coronary artery occlusion was preceded in 10 cats by transection of these cardiac nerves. After this left-sided sympathectomy, the heart rate remained unchanged (116.1±13.1 beats/min), while the systolic arterial pressure decreased by 6.5% relative to its initial value of 132.6±10.1 mm Hg (Fig. 1, *a*), the decrease being significant in 70% of the cases. Under these circumstances, the MI in cats administered DG was complicated by the development of grouped ventricular extrasystoles in 30% of the animals and by ventricular fibrillation in 20%; no gross abnormalities of cardiac rhythm were observed in the remaining cats. In tests where no DG was given after nerve branches of the left stellate ganglion were cut, MI was accompanied by grouped extrasystoles in 20% of the cats, by ventricular tachycardia in 10%, and by ventricular fibrillation in 10%, while no gross cardiac rhythm abnormalities were noted in the remaining cats. These results indicate that DG administered in a dose that does not cross the blood-brain barrier fails to decrease the incidence of arrhythmias in animals with impaired sympathetic influences in the MI zone.

In the second series carried out on 6 cats with preserved sympathetic innervation of the MI zone, DG was tested for its effect on the incidence of ischemic arrhythmias after the cardiac nerve branches given off by the right stellate ganglion were cut. This right-sided sympathectomy, unlike the left-sided, led to a 18.2% reduction in heart rate (from its initial value of 198.3±13.3 beats/min) and to a 9.4% decrease in systolic pressure (from its initial value of 148.8±13.2 mm Hg) (Fig. 1, *b*). The fall in heart rate was significant in all cats, while blood pressure significantly decreased in 66% of them. In these cats, DG injection led to idioventricular disturbances of cardiac rhythm in 33.3% of the cases. Grouped extrasystoles developed in 16.6% of the animals and ventricular tachycardia in 33.3%. None of the cats developed ventricular fibrillation. MI occurred without gross abnormalities of cardiac rhythm in 66.7% of the cases, which contrasts with tests where no DG was administered after nerve branches of the right stellate ganglion were cut and where gross cardiac rhythm abnormalities were absent in only 18% of the cases, while grouped extrasystoles occurred in 54% and ventricular tachycardia and ventricular fibrillation in 36%. The results of this test series show that DG in a dose not penetrating the blood-brain barrier exerts a marked antiarrhythmic effect, preventing the development of ventricular fibrillation ($p<0.05$). Since the right-sided sympathectomy resulted in decreased heart rate and arterial pressure, the protective effect of DG appears to have been due not only to inhibition of sympathetic nervous system activity, but also to enhancement of myocardial electrical stability [6,11]. This hypothesis is supported both by our finding that DG failed to decrease the incidence of ventricular fibrillation in MI after bilateral transection of the vagi [5] and by the reported ability of DG to inhibit acetylcholinesterase activity [7].

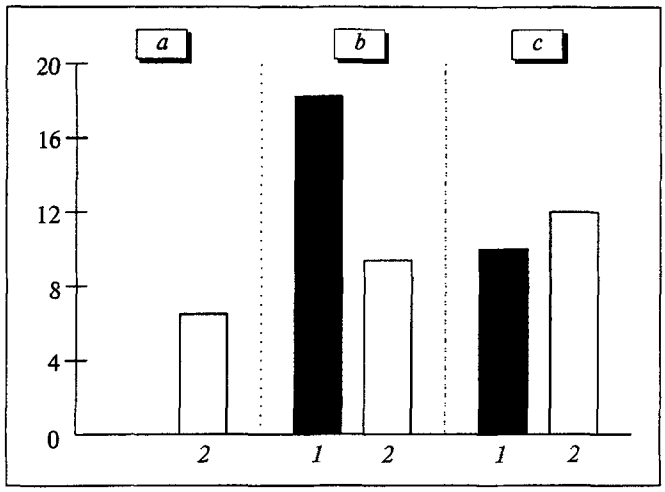

Fig. 1. Percent changes in heart rate (*1*) and systolic pressure (*2*) after left-sided (*a*), right-sided (*b*), and bilateral (*c*) transections of cardiac nerve twigs given off by the stellar ganglion.

Given the reported evidence for an important role the sympathetic nervous system plays in the protection afforded by DG, the aim of our third test series, carried out on 10 cats, was to see how DG would influence the incidence of arrhythmias in MI after the nerve branches of both the right and left stellate ganglia were cut. This bilateral sympathectomy resulted in a 10% decrease in heart rate (from its initial value of 127.5±9.0 beats/min) and a 12% decrease in systolic pressure (from its initial value of 129.7±8.9 mm Hg) (Fig. 1, *c*), the fall in heart rate being significant in 60% of the cases and that in systolic pressure in 80%. Under these conditions, DG administration led to idioventricular disturbances of cardiac rhythm in 20% of the cats and to ventricular fibrillation in 10%; grouped extrasystoles and ventricular tachycardia also developed in 10% of the cats. In tests where no DG was given, MI after bilateral sympathectomy was accompanied by grouped extrasystoles and ventricular tachycardia in 10% of the cases and by ventricular fibrillation in 20%, while no gross cardiac rhythm abnormalities occurred in 60%. These findings indicate that DG administration during MI development after bilateral sympathectomy decreased the incidence of ventricular fibrillation by half. It should be noted, however, that the protective effect of DG against ventricular fibrillation was less pronounced than in animals with preserved nerve supply to the MI zone.

Taken as a whole, the results of this study show that the mechanism by which DG protects against ventricular fibrillation in MI is due to its modulating effects on both the sympathetic and parasympathetic regulation of cardiac activity. Its effect on the latter regulation results in increased electrical stability of the myocardium in animals with impaired coronary blood flow.

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