MECHANISM OF ACTION OF DALARGIN IN EXPERIMENTAL MYOCARDIAL ISCHEMIA

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KEY WORDS: dalargin; myocardial ischemia; ventricular fibrillation.

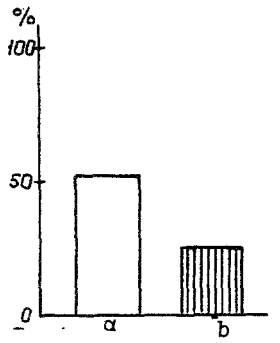
Administration of the synthetic Leu-enkaphalin analog dalargin lowers the frequency of development of ischemic arrhythmias of the heart, including ventricular fibrillation [3]. The antiarrhythmic effect of opioid peptides is associated mainly with inhibition of the peripheral action of catecholamines due to a fall in the cAMP level and adenylate cyclase activity [7, 8]. Meanwhile enkephalins also possess a central action, for they modify spontaneous and evoked neuronal activity in different parts of the CNS, including the brain stem, in which the bulbar cardiovascular and respiratory centers play an important role in the development of ischemic cardiac arrhythmias [2, 5, 6, 13, 14]. However, dalargin circulating in the blood in low concentrations does not pass through the blood–brain barrier and is quickly destroyed by the plasma peptidases [9]. Under these conditions its antiarrhythmic effect can be limited only by peripheral action on the functional state of various types of cells, including afferent nerve endings. Setting out from data on the wide distribution of opiate receptors, both in the myocardium itself and in nervous structures regulating its activity [1, 11, 12], it was decided to study the role of neurogenic mechanisms in the protective action of dalargin against myocardial ischemia.

EXPERIMENTAL METHOD

Experiments were carried out on 47 male and female cats weighing 3-4 kg, under pentobarbital anesthesia (40 mg/kg body weight intraperitoneally). After tracheotomy the animals were artificially ventilated, thoracotomy performed, the pericardium divided, and a dederon thread was introduced under the circumflex branch of the left coronary artery close to the site of its origin from the main trunk. Myocardial ischemia was induced by compression of the circumflex branch of the left coronary artery for 15 min. During 15 min of myocardial ischemia and 15 min of reperfusion the character of development of disturbance of the cardiac rhythm was analyzed. In this model of myocardial ischemia, ventricular fibrillation arises in 55% of cases [4]. In some experiments, before the model of myocardial ischemia was created, bilateral vagotomy was performed. In different series of experiments dalargin was given in the following doses: 2 μg to the heart, 10 μg/kg intravenously, and 500 μg/kg intravenously. The ECG in standard lead II and BP in the femoral artery were recorded on a "Biokomb" recording system. The significance of the results was estimated by the chi-square and signs tests.

Russian National Medical University, Moscow. (Presented by Academician of the Russian Academy of Medical Sciences B. T. Velichkovskii.) Translated from Byulleten Éksperimental'noi Biologii i Meditsiny, Vol. 114, No. 10, pp. 345-347, October, 1992. Original article submitted March 18, 1992.

 0007-4888/92/0010-1400$12.50



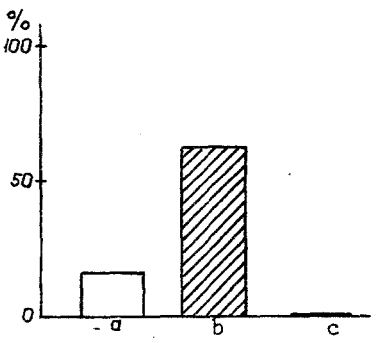


Fig. 1 Fig. 2

Fig. 1. Frequency of development of ischemic ventricular fibrillation during application of dalargin to the heart: a) frequency of development of ischemic ventricular fibrillation in control; b) frequency of development of ischemic ventricular fibrillation on application of dalargin to the heart.

Fig. 2. Development of ischemic ventricular fibrillation in response to intravenous injection of dalargin in doses not passing through (10 μg/kg) and passing through blood-brain barrier (500 μg/kg). a) Frequency of development of ischemic ventricular fibrillation after intravenous injection of dalargin in a dose of 10 μg/kg with vagus nerves intact; b) frequency of development of ischemic ventricular fibrillation after vagotomyand intravenous injection of dalargin in a dose of 10 μg/kg; c) absence of development of ventricular fibrillation after vagotomy and intravenous injection of dalargin in a dose of 500 μg/kg.

EXPERIMENTAL RESULTS

To study the neurogenic mechanisms of the protective action of dalargin on the frequency of development of cardiac arrhythmias associated with myocardial ischemia, it was essential to study the possibility of a direct effect of dalargin on the heart. For this purpose, in 11 experiments occlusion of the coronary artery was performed during application of 2 μg dalargin in 0.1 ml physiological saline to the heart. In this series of experiments myocardial ischemia was accompanied by the development of single extrasystoles in 72% of experiments, grouped extrasystoles developed in one experiment, allorhythmia and ventricular tachycardia in 27% of experiments, and ventricular fibrillation in 27% of experiments (Fig. 1). In almost half (45.5%) of experiments myocardial ischemia was not accompanied by the development of gross disturbances of the cardiac rhythm. Comparative analysis of these results with the development of ischemic arrhythmias without application of dalargin showed that even a single application of dalargin to the heart is accompanied by a reduction by half of the frequency of development of ventricular fibrillation, possibly due to its interaction both with the opiate receptors of the heart itself and with opioid receptors of afferent fibers of the vagus nerves.

Accordingly, in the next series of experiments the possible role of the vagus nerves was studied in the decrease in frequency of development of ischemic cardiac arrhythmias following injection of dalargin. For this purpose the frequency of development of ischemic arrhythmias was studied after bilateral vagotomy and intravenous injection of dalargin in a dose insufficient to pass through the blood-brain barrier (10 μg/kg). Division of the vagus

nerves in the control series of experiments (13 experiments) did not lead to any significant change in the frequency of development of fibrillation of the heart during myocardial ischemia ($p < 0.5$). Intravenous injection of dalargin in a dose of 10 μg/kg, with the vagus nerves intact, significantly lowered the frequency and development of ventricular fibrillation in myocardial ischemia, so that it developed in only 18% of experiments. Analysis of the results obtained in 12 experiments showed that after bilateral vagotomy and intravenous injection of 10 μg/kg dalargin, as a rule myocardial ischemia was complicated by the development of arrhythmia. Fibrillation of the heart developed in 66% of cases (Fig. 2). Thus division of the vagus nerves abolishes the protective effect of dalargin in a dose of 10 μg/kg on the frequency of development of ischemic myocardial fibrillation ($p < 0.02$), evidence of the presence of a reflex mechanism in the antiarrhythmic action of dalargin during myocardial ischemia.

To examine the action of dalargin on the CNS in myocardial ischemia, in the next series of experiments (11 experiments) the frequency of development of ischemic cardiac arrhythmias was studied against the background of bilateral vagotomy and intravenous injection of dalargin in a dose passing through the blood-brain barrier (500 μg/kg body weight) [10]. Under these conditions grouped ventricular extrasystoles were observed in 27% of cases and ventricular tachycardia in 18% of experiments. Fibrillation of the heart did not develop in even a single experiment (Fig. 2). Thus dalargin, in a dose passing through the blood-brain barrier, prevents the development of ischemic myocardial fibrillation even after division of the vagus nerves ($P < 0.01$), possible evidence of its direct effect on central structures involved in regulation of cardiac activity.

If the antiarrhythmic effect of dalargin, preceded by vagotomy, is compared when injected in doses passing and not passing through the blood-brain barrier, it can be tentatively suggested that dalargin can modify the functional state of the nervous centers involved in the regulation of cardiac activity either by a reflex mechanism or directly. Considering that neuronal spike activity in the bulbar cardiovascular center is modified in the presence of myocardial ischemia even before ventricular fibrillation develops, and that opioid peptides exert their own modulating effect on the regulatory systems of the body mainly when their activity is changed, it can be postulated that exogenous Leu-enkephalins facilitate compensatory reorganization of the activity of the bulbar cardiovascular center. Thus the protective effect of dalargin is evidently due not only to its antiadrenergic action but also to its effect on nervous structures maintaining optimal conditions of cardiac activity in myocardial ischemia.

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