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EFFECT OF OPIATE RECEPTOR BLOCKADE BY NALOXONE ON DEVELOPMENT OF ISCHEMIC CARDIAC ARRHYTHMIAS

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UDC 616.127-005.4-06:616.12-008.318]-092:[612.822.1:547.94:547.95].064-092.9

KEY WORDS: myocardial ischemia; opioid peptides; naloxone

Under certain conditions a change in activity of the higher levels of the brain, and, in particular, of the sensomotor cortex, complicates the course of acute myocardial ischemia. This effect is manifested as an increase in the frequency of onset of severe cardiac arrhythmias, including ventricular fibrillation [1, 2, 6, 9]. On the other hand, it has been shown [8] that CNS activity during the development of coronary insufficiency may be aimed at overcoming the consequences of myocardial ischemia, by giving rise to its own kind of adaptation to this pathological process and promoting survival. It has been suggested [5] that the prevention of disturbances of cardiac activity in acute myocardial ischemia by preliminary adaptation of animals to repeated stress may be associated with an increase in concentrations of opioid peptides (endorphins and enkephalins) in certain parts of the CNS and, in particular, in the cerebral cortex; the role of these substances in regulation of activity of the cardiovascular system is well known and has been widely studied [4, 7, 12-14].

Data on the role of opioid peptides in the pathogenesis of disturbances of cardiac activity during myocardial ischemia are conflicting. In this situation it is essential to use administration of naloxone, an antagonist of opiate receptors, as a way of evaluating the role of endogenous peptides in the mechanisms of disturbances of cardiac activity. The aim of the present part of the work was to study the pattern of development of cardiac arrhythmia in acute myocardial ischemia after preliminary administration of naloxone.

EXPERIMENTAL METHOD

Experiments were carried out on adult cats, male and female, weighing 2.5-4 kg, under pentobarbital anesthesia (30-40 mg, intraperitoneally). With artificial ventilation of the lungs with the "Vita-1" volume-frequency respirator thoracotomy was performed, the pericardium was opened, and a ligature was passed beneath the circumflex branch of the left coronary artery, close to its origin from the main trunk. Myocardial ischemia was induced by compressing the circumflex branch of the left coronary artery for 15 min. Naloxone hydrochloride

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N. I. Pirogov Second Moscow Medical Institute. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 107, No. 5, pp. 528-530, May, 1989. Original article submitted June 23, 1988.

 0007-4833/89/0005-0598$12.50

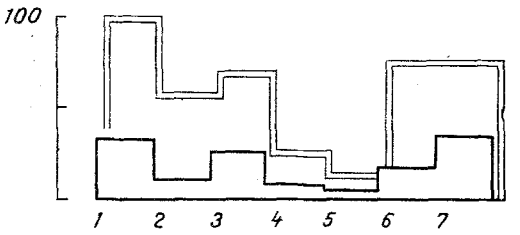

Fig. 1. Effect of preliminary injection of naloxone on frequency of development of cardiac arrhythmia in myocardial ischemia. Abscissa: 1) single ventricular extrasystoles, 2) early, 3) grouped, 4) polytopic ventricular extrasystoles, 5 allorhythmias, 6) ventricular tachycardia, 7) ventricular fibrillation; ordinate, per cent of experiments. Continuous line — control ischemia; double line — ischemia preceded by injection of naloxone.

was injected intravenously into the animals in a dose of 0.2-0.4 mg/kg, 2-6 min before compression of the coronary vessels [4]. The ECG in standards leads II and III, and the blood pressure by the direct method in the femoral artery, by means of an EMT-35 electromanometer ("Elema") were recorded in all experiments. All the parameters were recorded on a "Biocomb-8" Polyphysiograph ("Orion"). The character of disturbances of the cardiac rhythm was analyzed during 15 min of myocardial ischemia and during subsequent perfusion. The statistical significance of differences was assessed by Student's t test and the chi-square test.

EXPERIMENTAL RESULTS

During occlusion of the circumflex branch of the left coronary artery for 15 min, irreversible ventricular fibrillation developed in 10 of the 29 control experiments. As a rule, it appeared (8 of 10 experiments) 1-2 min after release of the ligature on the coronary vessel ($p < 0.05$). In 11 experiments (38%) idioventricular arrhythmias were absent and the rhythm disturbances were limited to supraventricular extrasystoles. Injection of naloxone into 16 intact animals had no effect either on their blood pressure or on their heart rate. This is evidence against a possible role for tonic activation of opiate receptors, blocked by naloxone, in the regulation of the systemic hemodynamics. These data agree to some degree with the results of investigations in [10, 11, 14], although Medvedev and co-workers [3], in experiments on cats anesthetized with urethane and chloralose, observed an increase in cardiac ejection and myocardial contractility after injection of naloxone, without any change in the regional vascular resistance.

After opiate receptor blockage by naloxone the course of myocardial ischemia in the control and experimental series differed significantly (Fig. 1). Whereas in the control animals idioventricular arrhythmias were not found in 38% of the experiments, after preliminary injection of naloxone into the animals they were observed in 100% of cases. Irreversible ventricular fibrillation occurred twice as often as in the control series (the frequency of its development increased from 34 to 75%; $p < 0.01$). Under conditions of opiate receptor blockade, the development of arrhythmias heralding fibrillation also was observed more frequently, especially ventricular tachycardia ($p < 0.001$), which was observed four times more often than in the control series of experiments, and also early ($p < 0.01$) and grouped ($p < 0.05$) ventricular extrasystoles. The significant increase in the number of combined disturbances of the cardiac rhythm — a combination of two or more types of malignant extrasystoles in the same animals, which also is accompanied by increased risk of ventricular fibrillation, also will be noted. Combined arrhythmias of this kind were observed in only 3 of the 29 control experiments and in 10 of the 16 experiments with preliminary injection of naloxone ($p < 0.001$).

Preliminary blockage of opiate receptors with naloxone thus significantly increases the frequency of development of severe idioventricular disturbances of the cardiac rhythm in acute

myocardial infarction, including the onset of ventricular fibrillation and its precursors. This is evidence that the system of endogenous opioid peptides may be involved in the response of the body to acute myocardial ischemia. One of the adaptive, corrective mechanisms preventing the onset of lethal arrhythmias when the blood supply to the heart muscle is disturbed may evidently be connected with this possibility. It is not impossible that the increase in the frequency of development of ischemic cardiac arrhythmias after preliminary injections of naloxone is also connected with the blockage of opiate receptors mediating the antinociceptive action of opioid peptides at the spinal cord level [15] and with activation of sympathetic influences on the myocardium.

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TRANSIENT ISCHEMIA EVOKED BY PARTIAL CORONARY ARTERIAL OCCLUSION IN CONSCIOUS IMMOBILIZED RABBITS

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UDC 616.132.2-007.272-031.84-092.9-07:616.127-005.4

KEY WORDS: myocardial ischemia; occlusion of the coronary artery

It is usually considered that in the presence of marked myocardial ischemia the coronary reserve is exhausted. However, recent experiments on dogs [3, 5] have shown that in the presence of functionally significant ischemia and a low perfusion pressure, the coronary dilatation reserve is preserved and may be detected by means of adenosine. The aim of the present investigation was to study changes in the coronary blood flow and vascular resistance during partial occlusion of a large coronary artery in conscious immobilized rabbits.

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(Presented by Academician of the Academy of Medical Sciences of the USSR V. N. Smirnov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 107, No. 5, pp. 530-532, May, 1989. Original article submitted March 28, 1988.

0007-4888/89/0005-0600$12.50