ROLE OF THE OPIOIDERGIC SYSTEM IN REGULATION OF AFFERENT RESPONSES OF DAMAGED MYOCARDIUM

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In the early stages of acute myocardial damage (coronary arterial occlusion, formalin-induced necrosis of an area of myocardium, etc.) a transient and reversible response of "functional deafferentation" of the heart develops [1, 2, 4]. During its development, electrical stimulation of the sinus node zone (SNZ) of the heart, which normally leads to the appearance of evoked potentials (EP) in various parts of the CNS, ceases to be effective because of the appearance of inhibitory processes in the stimulated structures. It has been suggested that this reaction may play an antinociceptive role, including painless and symptom-free forms of myocardial infarction. Inhibition of afferentation during cardiac damage has been linked with the formation of presynaptic depression of neurons of the intracardial nervous system [4, 9]. Endogenous opioid peptides are also known to be modulators of neuronal interactions, and the receptor apparatus of the opioidergic system is widely represented in the heart [3, 7, 8].

The aim of this investigation was to determine the role of the opioidergic system of the heart in modulation of its afferent responses after injury.

EXPERIMENTAL METHOD

There were four series of acute experiments on 29 adult cats weighing 2.5-3 kg, anesthetized with chloralose and immobilized by muscle relaxants. EP in response to single electrical stimulation of SNZ (square pulses, 0.3 msec, 10-15 mA) were recorded in the focus of maximal activity of the first sensomotor area of the cerebral cortex (CC) and in the centrum medianum thalami (CMT). The basic parameters of EP were recorded and analyzed by means of a "Neuroaverager" coherent discrete signal store ("OTE-Biomedica," Italy) and the "Iskra-1256" computer system, programed for analog information input. Differences between results were taken to be significant at the $p < 0.05$ level. During the experiments 0.1 ml of physiological saline containing bradykinin in doses of 1-6, 10-15, and 25-60 μg was injected subepicardially (experiments of series I). Besides this, the following solutions were injected into the pericardial cavity: in series II — naloxone (0.1 and 1.0 mg), in series III — moradol (butarfanol tartrate, 0.1 and 0.3 mg), and in IV — dalargin (D-ala^2-leu-enkephalin, 1-3 μg).

EXPERIMENTAL RESULTS

Single electrical stimulation of SNZ of the intact myocardium led to the appearance of EP in CC and CMT. The total amplitude of the initial positive—negative deflection of potential was 124.8 ± 12.2 μV, whereas in CMT (negative—positive wave) it was 81.6 ± 12.04 μV. Subepicardial injection of bradykinin solution in a dose of 1-6 μg induced a very small increase of amplitudes by the second to third minute: 144.2 ± 14.6 μV in CC and 110.6 ± 14.1 μV in CMT. Injection of 10-15 μg of bradykinin differed in its effects on the amplitude of EP, increasing it in some cases and reducing it in others. Increasing the dose to 25-60 μg caused a consistent decrease of the total amplitude of the initial phases of EP 2-3 min after injection for a period of 20 to 30 min. At the 5th minute the values of the amplitudes were: in CC — 42.6 ± 6.4 μV ($p < 0.01$), in CMT — 39.8 ± 2.4 μV ($p < 0.01$). It can be concluded from this section of the work that reproduction of the "functional deafferentation" reaction is stable when large doses of bradykinin are used, and it was possible to proceed with the next three series of investigations.

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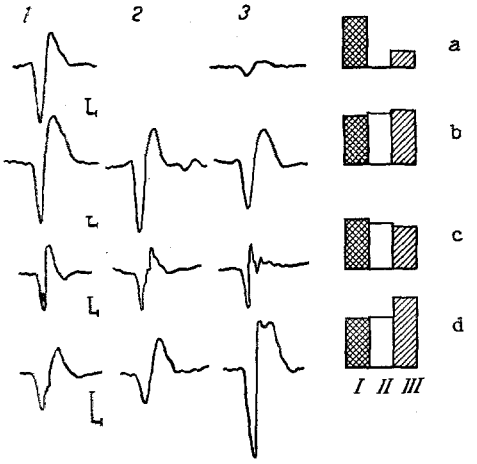

Fig. 1. EP recorded in CC during electrical stimulation of SNZ of intact myocardium (1), 20 min after injection of naloxone (2, b), moradol (2, c), and dalargin (2, d), and 5 min after injection of bradykinin (3). Doses and mode of injection of drugs indicated in text. Columns denote changes in amplitude of initial phases of EP after injection of drugs with opioid activity (II) and after injection of bradykinin (III), in percentages of initial data (I), taken as 100%. Calibration: 60 μV, 20 msec.

Injection of bradykinin in the experiments of series II was preceded by application of naloxone solution into the pericardial cavity in the experiments of series II, of moradol in series III, and of dalargin in series IV (each in a volume of 0.1 ml). Bradykinin (25-60 μg) was injected 20 min later, at the peak of action of the other drugs. Injection of the morphine antagonist naloxone had no significant effect on the total amplitude of the initial phases of EP in CC but significantly increased it in the thalamus. Application of moradol (a ligand of μ-opioid receptors) had no significant effect on values of EP amplitude, and the same was true of injection of dalargin (a ligand of δ-opioid receptors). Injection of bradykinin against this background did not lead to the development of a "functional deafferentation" reaction of the heart (Fig. 1). Moreover, against the background of moradol, the total amplitude of the initial phases of EP increased significantly in CMT, whereas after injection of dalargin, it did so both in CMT and in CC (see Table 1).

After intravenous injection of the test drugs in the same dose as by intrapericardial injection, the development of the "functional deafferentation" of the heart reaction was not impeded. Essentially, the amplitude of EP recorded in CC and CMT to stimulation of the sciatic nerve did not change significantly throughout the experiments. Application of naloxone to the SNZ in a dose of 1 mg led to some increase in the total amplitude of the initial phases of EP in CC and CMT after injection of bradykinin. A similar effect was found when the dose of moradol injected into the pericardial cavity was increased (up to 0.3 mg). The dose of dalargin effectively increasing the total activity of the initial phases of EP after administration of bradykinin was not less than 1 μg.

When the results are analyzed it will be recalled that the drugs were applied to SNZ in doses not causing changes in afferent responses when injected intravenously, and in all cases when EP were recorded to sciatic nerve stimulation. These results ruled out any central resorptive effect and enabled all the changes in cardiac afferentation observed to be linked with the local action of the drugs. It also seems important that afferent flows induced by stimulation of the intact myocardium showed significant changes only after injection of naloxone into the thalamic (CMT), traditionally regarded as a pathway for conduction and processing of nociceptive spike trains. However, these doses of the drugs, when injected intrapericardially, were sufficient to rule out completely the development of a "functional deafferentation" reaction of the heart.

It had been suggested that an important role in the development of cardiac pain is played by kinins. This determined the choice of experimental model in the present investigation [5, 6]. Small doses of bradykinin were found to lead to an increase of excitability of the stimulated structures of the heart, whereas large doses reduced it. Reduction of excitability under

TABLE 1. Changes in Total Amplitude of Initial Phases of EP in Response to Intrapericardial Injection of Bradykinin, against the Background of the Action of Drugs with Opioid Activity

Series of experiments	Zone of recording	Initial data	At 20th minute after injection of drug		At 5th minute after injection of bradykinin	
		Total amplitude of initial phases of EP, μV				
II	CC	124,8±12,2	129,6±10,3	(104%)	134,4±4,4	(108%)
	CMT	81,6±12,04	134,4±4,4*	(165%)	95,6±9,6	(117%)
III	CC	167,6±16,9	156,0±16,1	(93%)	148,0±8,4	(88%)
	CMT	136,8±16,8	136,8±13,9	(100%)	182,4±12,1*	(133%)
IV	CC	85,2±8,4	86,4±7,2	(101%)	141,2±5,2*	(142%)
	CMT	81,6±8,02	97,2±5,9	(119%)	147,2±2,9*	(160%)

*Significant differences from initial data. Percentages of initial value shown in parentheses.

these circumstances is a "functional deafferentation" reaction of the heart, and according to our data it depends on activity of the opioid system of that organ. It is logical to suggest that in cases of mild nutrional disturbances of the myocardium, not involving any risk or infarction, the accumulation of small quantities of algogenic substances is manifested by an increase (not significant, according to our data) in cardiac afferentation, and possibly accompanied by the formation of a perceptual component of nociceptive excitation. In the presence of marked coronary insufficiency the algogenic substances trigger the opioidergic system modulating the afferent "output" from the heart, which in the early stages of myocardial ischemia may play an antinociceptive role. It has been shown that frequent repetition of experimental coronary occlusions completely exhausts the "functional deafferentation" reaction of the heart as early as after presentation of the second or third episode of ischemia, and this is shown by an attack of coronary pain [2]. Injection of drugs with opioid activity (agonists or antagonists) induces their competition with endogenous opioids, facilitating the development of a "deafferentation" reaction accompanied by damage to the heart. The development of this reaction was prevented most effectively by intrapericardial injection of dalargin. This fact suggests that δ-opioid receptors play a key role in the modulation of afferent flows of the pathological myocardium.

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