EFFECT OF NARCOTIC ANALGESICS ON CONDUCTION OF EXCITATION IN AFFERENT FIBERS OF VISCERAL NERVES

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The effect of morphine and trimeperidine on cortical and subcortical brain potentials arising in response to visceral nerve stimulation was studied in experiments on cats anesthetized with chloralose. Morphine was shown to inhibit potentials evoked by stimulation of the inferior cardiac and vagus nerves in the specific, association, and nonspecific brain structures. Trimeperidine had a similar action. Under the influence of morphine, potentials arising during stimulation of the splanchnic nerve in the association and nonspecific structures also were inhibited; inhibition of responses in the specific pathways was less marked.

KEY WORDS: narcotic analgesics; afferent pathways.

One possible mechanism of the pain-relieving effect of the narcotic analgesics is by disturbance of synaptic transmission in the afferent pathways [4, 6-11, 13, 14].

In the investigation described below the effect of morphine and trimeperidine was studied on cortical, diencephalic, and mesencephalic potentials arising in response to electrical stimulation of visceral nerves.

EXPERIMENTAL METHOD

Cats were lightly anesthetized with chloralose (10-20 mg/kg, intravenously). The animals were immobilized by gallamine triethiodide, given by intravenous drip. During the experiments the animals were artificially ventilated and heated. The inferior cardiac, vagus, and splanchnic nerves were stimulated by supramaximal square pulses 1-4 msec in duration and with a frequency of once every 5 sec. Evoked potentials were recorded by a unipolar method in the projection areas of somatovisceral sensation, in the association and nonspecific areas of the cortex, in the specific (VPL, VPM), association (MD, LD, LP), and nonspecific (CM, NCP) thalamic nuclei, and in the mesencephalic reticular formation and medial lemniscus. The subcortical electrodes were inserted in accordance with the coordinates of the stereotaxic atlas of Jasper and Ajmone-Marsan [12]. The position of the recording electrodes was verified in histological preparations. The test substances were injected intravenously. Altogether 46 experiments were performed.

EXPERIMENTAL RESULTS AND DISCUSSION

After injection of morphine in doses of 5-10 mg/kg the amplitude of potentials in the first zone of somatovisceral sensation and in the coronary gyrus in response to stimulation of the inferior cardiac nerve was reduced by 30-70%. In the association areas of the cortex (Lat. ant., Supr. ant.), and also in the posterior lateral, posterior suprasylvian, and middle ectosylvian gyri, inhibition of the responses after injection of morphine was more marked. In some experiments, after injection of morphine in doses of 2.5-5 mg/kg, some increase in amplitude of the evoked potentials was observed, but after a further injection of the drug the potentials were inhibited. In recordings from the subcortical electrodes the amplitude of the potentials in the specific thalamic relay nuclei (VPL, VPM) and in the medial lemniscus was

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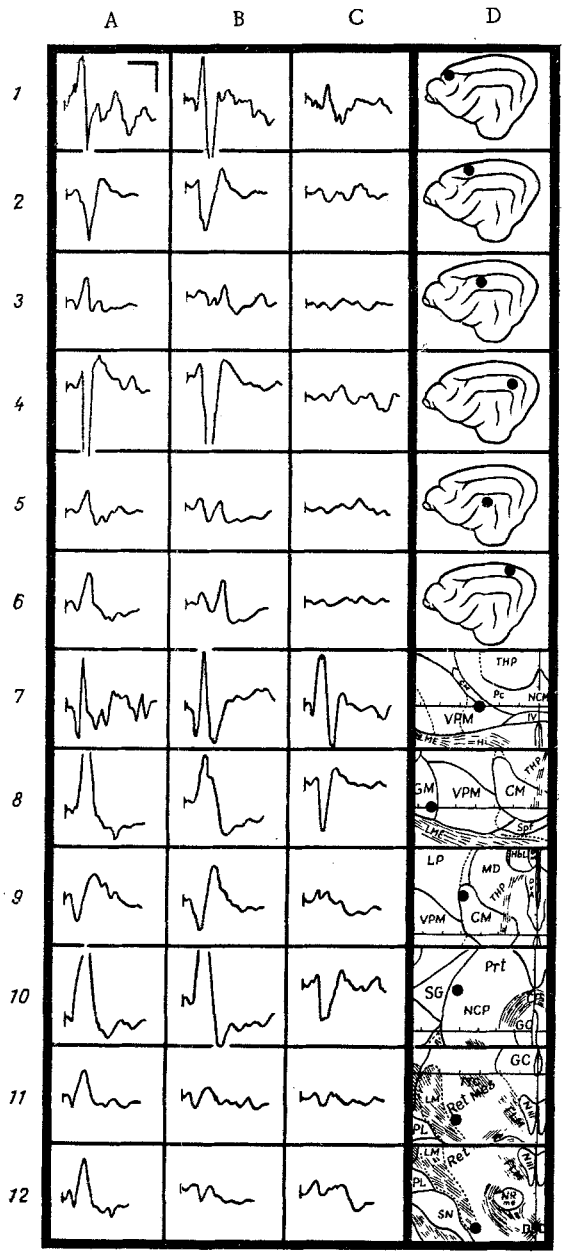

Fig. 1. Effect of morphine on cortical, diencephalic, and mesencephalic evoked potentials during vagus nerve stimulation: 1-12) potentials at recording points indicated on brain schemes. A) Initial background; B) 20 min after injection of morphine in a dose of 5 mg/kg; C) 40 min after first and 10 min after second injection of morphine in a dose of 5 mg/kg; D) brain schemes showing location of recording electrodes. Intensity of vagus nerve stimulation 30 V, pulse duration 1 msec. Vertical line represents 100 μV, horizontal line 100 msec. Experiment on cat immobilized with gallamine triethiodide and anesthetized with chloralose (20 mg/kg).

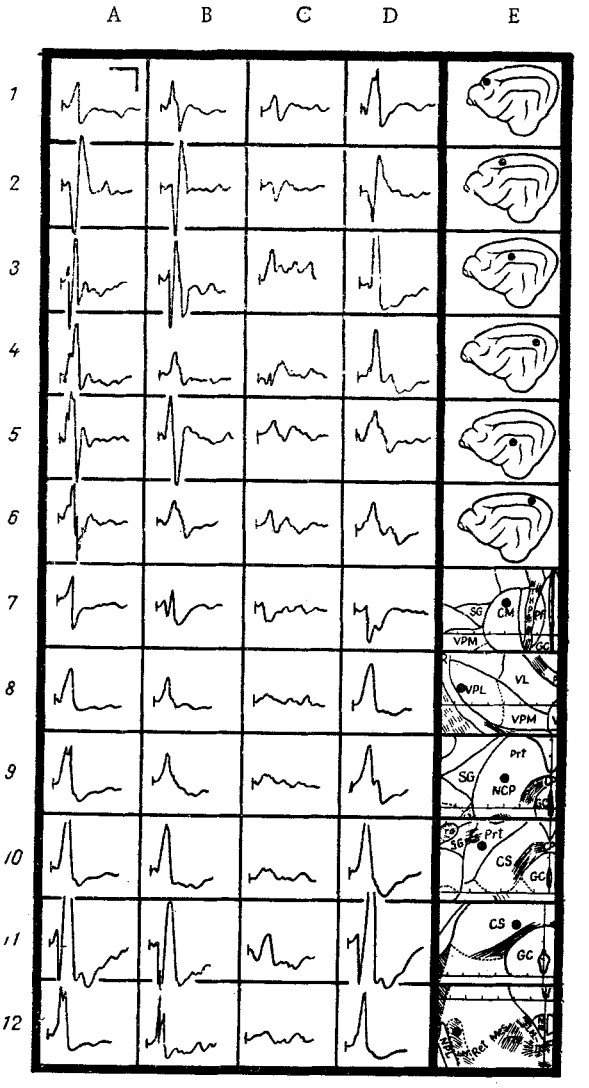

Fig. 2. Effect of trimeperidine on cortical, diencephalic, and mesencephalic evoked potentials during stimulation of inferior cardiac nerve: 1-12) potentials at recording points indicated on brain scheme. A) Initial background; B) 8 min after injection of trimeperidine in a dose of 3 mg/kg; C) 26 min after first and 13 min after second injection of trimeperidine in a dose of 3 mg/kg; D) 1 h 27 min after second injection; E) brain scheme showing location of recording electrodes. Intensity of stimulation of inferior cardiac nerve 30 V, pulse duration 1 msec. Vertical line 100 μV, horizontal line 100 msec. Experiment on cat immobilized with gallamine triethiodide and anesthetized with chloralose (20 mg/kg).

reduced by 30-70% and responses also were inhibited in the centrum medianum, the nucleus of the posterior commissure, the mesencephalic reticular formation, and the central gray matter.

The maximal effect was observed after 15-20 min. A tendency for the potentials to recover was observed after 2-2.5 h.

In the experiments with vagus nerve stimulation similar changes in the potentials were observed (Fig. 1). However, the phase of increase in amplitude of the potentials after injection of morphine in doses of 2.5-5 mg/kg was less marked.

In most experiments (85%) morphine, in doses of 2-8 mg/kg, inhibited the negative phase of the primary responses and potentials in the association areas of the cortex in response to splanchnic nerve stimulation. In some experiments (15%), after injection of morphine the amplitude of the primary responses was increased (mainly on account of the negative component). Potentials in the ventral posterolateral nucleus and medial lemniscus underwent no significant changes. Responses in the thalamic association nuclei (MD, LD), the centrum medianum, and the mesencephalic reticular formation were sharply inhibited or disappeared.

Trimeperidine (3-6 mg/kg) caused changes in potentials evoked by stimulation of the inferior cardiac (Fig. 2) and vagus nerves that were similar in direction and intensity to the changes recorded after injection of morphine. At the mesencephalic level trimeperidine also caused inhibition of potentials on the superior colliculus, pretectal region, and central tegmental tract. Unlike morphine, after injection of trimeperidine no phase of increased amplitude of the potentials was observed.

The results show that morphine and trimeperidine disturb the transmission of impulses in afferent pathways of the visceral nerves. The drugs studied inhibit responses to stimulation of the inferior cardiac and vagus nerves in the classical ascending pathways (medial lemniscus, ventral posterolateral thalamic nucleus, first cortical area of somatovisceral sensation). These results suggest that morphine and trimeperidine disturb synaptic transmission in the afferent pathways of these nerves at the medullary level. Potentials in the specific conducting pathways of the splanchnic nerve were modified by a much lesser degree by morphine: responses in the medial lemniscus and ventral posterolateral nucleus remained unchanged and the negative phase of the primary responses in the cortex was inhibited. Unlike potentials evoked by stimulation of the visceral nerves, the amplitude of responses to stimulation of the somatic nerves is increased in these same structures [9, 10].

According to the results of morphological and electrophysiological investigations, the principles of central organization of the visceral and somatic afferent systems are similar in their general features [5]. However, the composition of the fibers of the visceral and somatic pathways is different. In particular, the somatic nerves contain many more of the thick, type A–β myelinated fibers than the visceral nerves. At the same time, evoked potentials arising in response to stimulation of nerves of different composition are known to differ in their sensitivity to drugs [1]. The stability of responses to sciatic nerve stimulation in the classical pathways may perhaps be due to the high safety factor of the somatic afferent system.

Morphine and trimeperidine inhibit responses in the nonspecific and association structures of the brain during visceral nerve stimulation. The narcotic analgesics have a similar effect on potentials in the same structures during somatic stimulation [9, 10]. Inhibition of potentials in the association and nonspecific brain structures may be the result of the action of the drugs on synaptic transmission in those structures, on the transmission of impulses along collaterals from the specific pathways, and also at the spinal cord level. This last suggestion is confirmed by the observations of Bulaev [2, 3], who showed that morphine inhibits evoked activity of interneurons of the posterior horns of the spinal cord during somatic stimulation. The inhibitory effect of the narcotic analgesics may accordingly be attributed both to their action directly at the spinal cord level and to the strengthening of supraspinal inhibitory influences [15, 16].

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ANTIARRHYTHMIC ACTIVITY OF THE β_2-ADRENOBLOCKER ALPRENOLOL

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Experiments on dogs, cats, and rats with various disturbances of the cardiac rhythm showed that the β_2-adrenoblocker alfeprol, the Soviet analog of alprenolol, has a marked antiarrhythmic action. The substance abolishes atrial arrhythmias induced by electrical stimulation of the atria or by application of aconitine, it controls ventricular arrhythmias arising as a result of occlusion of a branch of the coronary artery or of ouabain poisoning, and it prevents lethal ventricular fibrillation in rats after calcium chloride poisoning. The antiarrhythmic effect of alprenolol is ascribed not only to blocking of β-adrenoreceptors but also to the quinidine-like action of the compound.

KEY WORDS: cardiac arrhythmias; catecholamines; β-adrenoblockers; alfeprol (alprenolol).

β-Adrenoblockers differing from propranolol (Inderal, Anapriline) by their weaker cardiodepressive action have recently been obtained. They include alfeprol, the Soviet analog of alprenolol or aptin, synthezied by Simon [6]. The characteristic effects produced by this β-adrenoblocker have been explained by its adrenomimetic activity [8] or by its predominant action on β_2-adrenoreceptors [4].

Considering that the adrenoreceptors of the myocardium are of the β_1 type it was decided to study the degree of antiarrhythmic action shown by alprenolol in experimental arrhythmias.

EXPERIMENTAL METHOD

Experiments were carried out on 21 dogs (7-13 kg), 38 cats (1.9-3.1 kg), and 63 rats (150-200 g). Atrial arrhythmias in the acute experiments on dogs were induced by mechanical injury to the region of the opening of the venae cavae followed by stimulation of the right atrium with dc pulses, and in cats by application of a swab soaked in 0.05% aconitine nitrate solution to the auricle of the right atrium. Ventricular tachyarrhythmias were induced in dogs by ligation of the descending branch of the left coronary artery and in cats by poisoning

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