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EFFECT OF MICROINJECTION OF MORPHINE AND TRAMADOL INTO THE LOCUS COERULEUS ON NOCICEPTIVE RESPONSES OF SPINAL NEURONS AND ARTERIAL PRESSURE CHANGES

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KEY WORDS: nociceptive stimulation; spinal neurons; locus coeruleus; arterial pressure; opiate analgesics.

It has been shown in recent years that analgesia arising after stimulation of the nuclei raphe, the periaqueductal gray matter, nucleus of the tractus solitarius, and certain other brain zones is accompanied by hypertension, tachycardia, and changes in the regional blood flow [6, 8, 10, 12]. It is considered that antinociceptive structures are involved in the regulation not only of pain, but also of the responses of the cardiovascular system, and that they may be the substrate for realization of both the pain-relieving and the hemodynamic action of narcotic analgesics. A special place in the integration of functional processes of different modalities during pain is played by the locus coeruleus in the medulla, which contains opiate peptides as well as noradrenalin, and which has multiple anatomical connections with antinociceptive and vasomotor structures of the brain, and also with the spinal cord [13]. However, changes in pain after injection of opiate analgesics into the locus coeruleus, their neurophysiological and neurochemical mechanisms, and their association with changes in nociceptive responses of the arterial blood pressure (BP) still remain completely unstudied.

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TABLE 1. Changes in Neuronal Activity in Posterior Horn of Spinal Cord and in BP during Pain, in Response to Microinjection of Morphine and Tremadol into Region of Locus Coeruleus

Parameter	Background	Nociceptive stimulation	Microinjections in control		Microinjections during pain	
			morphine 50 μg	tremadol 100 μg	morphine 50 μg	tremadol 100 μg
Discharge frequency of neurons, spikes/sec	10,5±3,1	63,5±7,2	8,1±3,9	9,5±3,5	42,6±6,1*	48,2±6,1*
BP, mm Hg	106±4	158±6	105±4	105±4	155±7	151±6

Legend. *$p < 0.05$) Changes significant compared with control.

EXPERIMENTAL METHOD

Experiments were carried out on 16 unanesthetized, curarized cats. As a first step, under ether anesthesia, microcannulas were inserted stereotaxically into the region of the locus coeruleus [14] and intrathecally [7] at level L3, 4 for injecting pharmacological agents, and the carotid artery was catheterized to measure BP by a VI6-5MA electromanometer. Spike discharges from neurons of the posterior horn of the spinal cord at level L4, 5 were recorded by glass microelectrodes, filled with 3.5 M KCl, with a resistance of 3-5 M Ω. To amplify bioelectrical activity, to monitor it visually, and for analysis, we used the EPM complex (Research Institute of Experimental Medicine, Academy of Medical Sciences of the USSR), coupled with an "Élektronika-60M" computer. Drugs were microinjected into the locus coeruleus in a volume of 5 μl, and intrathecally in a volume of 0.2 ml, in the following doses: morphine 50 μg, tramadol (Tramal, Grunenthal, West Germany) 100 μg, naloxone (Narcan, Du Pont, West Germany) 20-200 μg; phentolamine 250 μg.

EXPERIMENTAL RESULTS

Altogether 19 neurons, corresponding in their properties to neurons with a wide dynamic range of responses, were recorded. They generated spontaneous spike discharges with a frequency of 7-14 spikes/sec. Tactile stimulation in the region of the receptive field increased spike activity up to 21-30 spikes/sec but did not change BP. Squeezing the skin of the receptive field with toothed forceps, with an intensity inducing a whole range of generalized-affective manifestations of pain in conscious animals, quickened the spike discharges of the neurons to 55-72 spikes/sec, and was accompanied by elevation of BP by 40-60 mm Hg.

Results obtained in response to injection of drugs into the locus coeruleus are given in Table 1. Morphine and tramadol did not change the spontaneous activity of animal neurons, or the background BP and the amplitude of pressor responses of BP to the damaging stimulation, but 5 min after injection, they significantly reduced the neuronal response to nociceptive stimulation. The action of the narcotic analgesics reached a peak 10-15 min after microinjection (Table 1).

The depressant action of morphine and tremadol on nociceptive responses of the neurons was abolished by preliminary injection of naloxone into the region of the locus coeruleus or against the background of intrathecal microinjection of the α-adrenolytic drug phentolamine (Fig. 1). After preliminary intrathecal injection of naloxone the effect of the narcotic analgesics was unchanged. It must be emphasized that if naloxone, in doses of 20 and 200 μg, when injected intrathecally or microinjected into the locus coeruleus, did not affect the nociceptive changes in BP, phentolamine reduced them significantly.

The investigations showed that the antinociceptive effect obtained by injecting morphine and tremadol into the locus coeruleus is realized through selective inhibition of nociceptive responses of relay neurons in the posterior horn of the spinal cord. It is a striking fact that, by contrast with action directed toward other antinociceptive brain zones, in the case of action directed toward the locus coeruleus, analgesia developed without any increase in the background BP. The experiments with naloxone led to the conclusion that descending influences of the locus coeruleus are triggered through opiate receptors, in agreement with data on increased activity of the neurons of that structure after injection of morphine [9]. It was shown previously that preliminary destruction of neurons of the locus coeruleus with monosodium glutamate reduces the pain-relieving action of morphine in the tail withdrawal test, and that correlation is absent between changes in morphine analgesia and the noradrenalin concentration in the brain stem [5]. Meanwhile, the antinociceptive effect is realized at the spinal cord level, as is shown by its development immediately after microinjection or tramadol into the locus coeruleus, but the leading role in this effect belongs to enhancement of adrenergic neurotransmission processes.

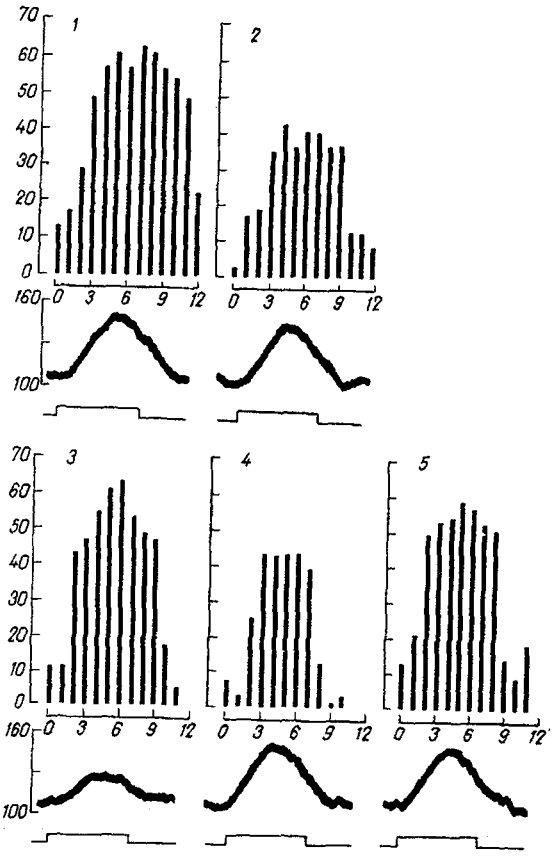

Fig. 1. Pharmacological analysis of effect of morphine, injected into locus coeruleus, during pain. 1) Control; 2) morphine (50 μg) after preliminary intrathecal injection of phentolamine (250 μg); 4) morphine preceded by intrathecal injection of naloxone (200 μg); 5) morphine preceded by injection of naloxone into locus coeruleus. From top to bottom: neurogram: abscissa, time (in sec); ordinate, frequency of spike discharge (spikes/sec); BP; marker of nociceptive stimulation.

It was shown for the first time that the opioidergic system of the locus coeruleus is not involved in the tonic regulation of BP and in the formation of pressor changes of BP brought about by nociceptive stimuli. Dissociation of the regulation of pain and its hemodynamic manifestations was recently postulated, on account of receptor-dependent differences in segmental opioidergic mechanisms, and it is largely responsible for the resistance of nociceptive changes in the circulation in response to opiates and opioids [2, 3]. Our own observations indicate that this dissociation may also be formed at the level of an antinociceptive brain zone such as the locus coeruleus, and also, on the evidence of data in the literature, at the level of the central gray matter and lateral reticular nuclei [4, 8, 11]. This is evidently a common property of opioidergic components of endogenous analgesic systems and it determines their dual function role in pain, namely weakening of the aversiveness of the pain-producing agent and creation of hemodynamic grounds for its avoidance.

The opioidergic component of the locus coeruleus thus plays an important role in descending inhibition of the nociceptive flow of impulses at the spinal cord level, and this mechanism is a component of the pain-relieving action of narcotic analgesics of different chemical structure. The results do not rule out involvement of the locus coeruleus in the regulation of nociceptive hemodynamic reactions, but such regulation is not connected with the opioidergic system of this brain formation, but can take place through its other neurotransmitter components, and above all, through the adrenergic system.

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EFFECT OF DIFFERENT TEMPERATURE CONDITIONS OF REPERFUSION ON RECOVERY OF MYOCARDIAL CONTRACTILITY AFTER HYPOTHERMAL CARDIAC ISCHEMIA

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One cause of acute cardiac failure (ACF) following open heart operations with an assisted circulation is reperfusion [7, 9]. In order to prevent the development of postoperative ACF, a technique of pharmaco-hypothermal cardioplegia is nowadays mainly used for anti-ischemic protection of the myocardium during the period when the heart is by-passed [3]. It must be noted that despite cooling of the heart muscle during the period of ischemia to 8-12°C [2], no attention has yet been paid to the temperature conditions of reperfusion during the first minutes after opening of the aorta.

The aim of the present investigation was to study the effect of various temperature conditions of reperfusion on the restoration of contractility and the cAMP concentration of the myocardium after hypothermal ischemia of its tissues.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male and female rats weighing 180-200 g. Under intraperitoneal pentobarbital anesthesia (25 mg/kg) the heart was removed from intact animals and perfused with oxygenated Krebs—Henseleit solution at 37°C. After perfusion for 15 min the heart was stopped by simultaneous compression of the aorta and external cooling of the myocardium to 8-12°C. Hypothermal ischemia of the heart lasted 90 min. Reperfusion was then commenced with perfusion fluid

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