EFFECT OF MORPHINE AND OPIATE RECEPTOR AGONISTS ON BLOOD PRESSURE AND ELECTRICAL ACTIVITY IN THE RENAL NERVE IN RESPONSE TO STIMULATION OF THE PERIAQUEDUCTAL GRAY MATTER

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UDC 615.31:547.95:547.943].015.4:]616.12-008.331.1-02:616-009.7]-092.9

Key Words: endogenous analgesic system; nociceptive reactions; sympathetic mechanisms; blood pressure; opioidergic mechanisms.

Experimental and clinical observations have shown that opiates and ophoids, in analgesic doses, do not change nociceptive hemodynamic reactions or potentiate them. One of the mechanisms of the pharmacologic resistance of circulatory changes during pain is the activating effect of morphinelike analgesics on the propriospinal system for generalization of sympathetic reflexes [3]. Interneurons of the propriospinal system also are involved in the conduction of nociceptive impulsation and they are under the modulating control of the "analgesic zones" of the midbrain [4]. However, the effect of the antinociceptive systems of the brain on sympathetic segmental mechanisms of formation of the sympathetic-activating action of analgesics and pharmacologic resistance of nociceptive hemodynamic reactions has virtually not been studied.

In the investigation described below, the effect of morphine and of opiate receptor agonists was studied on sympathetic mechanisms regulating nociceptive circulatory changes under conditions of stimulation analgesia, induced by electrical stimulation of the periaqueductal gray matter of the midbrain.

EXPERIMENTAL METHOD

Experiments were carried out on 38 unanesthetized curarized cats and five conscious animals. The central periaqueductal gray matter was stimulated in the region *A* +2 to −2; *L*, *R* 0.5 [5] by square pulses with parameters of 1-8 V, 0.1-0.5 msec, 100 pulses/sec for 30-120 sec.

In chronic experiments painful stimulation was applied by electrical stimulation of the spinal muscles through spherical electrodes (15-20 V, 1-5 msec, 5-10 Hz, for 2-5 sec). The blood pressure (BP), intersystolic intervals (ISI), and emotional–affective manifestations of pain, on a special scale of features (in points) were recorded [2].

In acute experiments nociceptive stimulation was applied by stimulating the peroneal nerve by pulses exciting A- and C-afferent fibers (10-15 V, 1-2 msec, 10-20 Hz). Electrical activity in the renal nerve was derived by bipolar electrodes in the usual way. Parameters of sympathetic electrical activity, BP, and ISI were recorded simultaneously and subjected to statistical analysis by a specialized computer system of our own design, based on the "Élektronika DZ-28" microcomputer.

Morphine hydrochloride was injected intravenously in doses of 1 and 5 mg/kg. D-Ala^2-Gly-ol^5-enkephalin (DAGO), in doses of 10, 50, and 100 μg, and D-Ala^2-D-Leu^5-enkephalin (DADL) in doses of 10, 100, and 200 μg (All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR), and also serotonin (100 μg) and parachloramphetamine (500 μg) (from "Sigma," USA) were injected intrathecally, into the spinal cord at the level of L1-2 [7].

Department of Pharmacology, I. P. Pavlov First Leningrad Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Val'dman.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 108, No. 9, pp. 309-311, September, 1989. Original article submitted December 26, 1988.

TABLE 1. Effect of Stimulation of Periaqueductal Gray Matter on Sympathetic Activity in Renal Nerve, BP, and their Changes during Nociceptive Stimulation of Peroneal Nerve ($M \pm m$)

Experimenteal conditions	Parameter			
	amplitude of sympathetic activity, μV	frequency of sympathetic activity, Hz	initial BP, mm Hg	increase in BP, mm Hg
Stimulation of midbrain with intensity of:				
1—3 V	52,5±10,2	65,6±10,3	118±4	9±2
4—8 V	83,4±8,2	115,7±9,0	118±4	58±8
Nociceptive stimulation of personeal nerve (control)	94,8±5,5	126,8±14,7	118±4	44±4
Nociceptive stimulation after stimulation of midbrain with intensity of:				
1—3 V	83,0±7,7	106,8±13,4	124±6	45±5
4—8 V	64,8±5,2*	115,0±14,8	137,0±10*	25±5*

Legend. Here and in Table 2: *$p < 0.05$ compared with control.

TABLE 2. Effect of Opiate Receptor Agonists, Serotonin, and Parachloramphetamine on Sympathetic Activity in Renal Nerve and BP during Stimulation of Periaqueductal Gray Matter ($M \pm m$)

Parameter	Experimental conditions							
	control	DAGO (100 μg)	control	DADL (200 μg)	control	serotonin (100 μg)	control	parchloramphetamine (500 μm)
Amplitude of sympathetic activity, μV	66,8±14,6	73,0±14,7	75,6±18,2	75,5±3,1	58,5±7,7	34,0±4,2	36,5±6,1	54,5±4,0*
Frequency of sympathetic activity, Hz	94,6±15,8	141,2±12,0	119,0±24,2	149,0±31,0	51,7±7,1	70,3±2,5*	73,0±6,0	92,4±6,1
Increase in BP, mm Hg	48±9	65±2*	28±3	53±14*	26±3	51±10*	35±2	57±2*

EXPERIMENTAL RESULTS

BP in conscious animals was 106 ± 3 mm Hg and IMI 302 ± 23 msec. Stimulation of the periaqueductal gray matter (PGM) was accompanied by hypertensive changes of BP with a maximal amplitude of 55 ± 3 mm Hg, accompanied by tachycardia (108 ± 25 msec) and analgesia. Emotional-affective manifestations of pain were significantly reduced but nociceptive responses of RP were virtually unchanged. Morphine, in analgesic doses of 1 and 5 mg/kg, increased the amplitude of pressor responses of BP to stimulation of PGM to 75 ± 4 mm Hg.

Similar stimulation of PGM in unanesthetized, curarized animals had a sympathetic-activating action. The amplitude and frequency of sympathetic activity in the renal nerve increased significantly and pressor responses of BP developed (Table 1). Electrical stimulation of the peroneal nerve was accompanied by an increase in frequency and amplitude of sympathetic activity and by a rise of BP. After stimulation of the "analgesic zones" of the midbrain, a significant decrease of the nociceptive changes in sympathetic electrical activity and BP did not take place. Only when the intensity of stimulation of PGM was increased to 5-8 V was the amplitude of the hypertensive changes in BP reduced during pain. In this case, however, the initial BP reached 150-160 mm Hg.

The results showed that activation of PGM, inducing analgesia, virtually did not reduce nociceptive hemodynamic responses and had a sympathetic-activating and hypertensive action. Morphine, in analgesic doses, potentiated the sympathetic-activating action of the antinociceptive brain structures.

DAGO, a selective μ-agonist of opiate receptors, when injected intrathecally in doses of 10 and 50 μg, had no effect on the background parameters of sympathetic activity, BF, or ISI and their changes in response to nociceptive stimulation and to electrical stimulation of the midbrain. With an increase in the dose of DAGO to 100 μg the frequency of sympathetic activity and BP increased (Table 2). Meanwhile, pressor responses of BP induced by stimulation of PGM increased significantly. DADL, an agonist of delta-opiate receptors, had no effect over the whole dose range on the initial parameters of sympathetic electrical activity, BP, and ISI or on their changes in response to pain, but in a dose of 200 μg, like DAGO, it potentiated the descending sympathetic-activating action of the "analgesic structures" of the midbrain (Table 2).

The modulating effect of the "analgesic zones" of the midbrain is known to be targeted on structures of the segmental afferent input and it is realized not only through opioidergic, but also through serotoninergic mechanisms of the spinal cord [6]. In the present experiments serotonin (100 μg), injected intrathecally, did not change the background parameters of the hemodynamics and bioelectrical activity in the renal nerve, but significantly potentiated the changes in sympathetic activity and the hypertensive changes in BP in response to stimulation of the midbrain (Table 2). Parachloramphetamine (500 μg) had a similar action 2-4 h after intrathecal injection, at a time when the drug stimulates secretion of serotonin from its presynaptic depots.

These investigations showed that stimulation of PGM induces analgesia, does not affect nociceptive hemodynamic responses, and has a sympathetic-activating action, which is realized with the participation of opioidergic and serotoninergic mechanisms of the spinal cord. Thus not only narcotic analgesics and opioid peptides, but also endogenous antinociceptive systems of the brain may have an activating influence on sympathetic vasomotor mechanisms. This is responsible for the preservation of nociceptive circulatory responses under conditions of analgesia, when the intensity of the nociceptive afferent flow is reduced, and for the formation of stability of the hemodynamic responses to morphinelike analgesics during pain.

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