Our results may explain why nonachlazine possesses partial β-adrenoblocking properties together with its physiologically manifested β-stimulating activity. As was noted previously [1], this mechanism of self-limitation of its own sympathomimetic activity may perhaps play a role in the realization of some positive properties of nonachlazine and, in particular, its ability to potentiate the inotropic function of the heart without the development of tachycardia or an increase in the oxygen consumption of the heart.

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EFFECT OF MORPHINE ON SUPRASEGMENTAL AND SEGMENTAL MECHANISMS OF BLOOD PRESSURE REGULATION DURING PAIN

Yu. D. Ignatov, A. A. Zaitsev, and E. G. Bogdanov

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KEY WORDS: sympathetic activity; blood pressure; nociceptive responses; morphine; segmental mechanisms

Morphine-like compounds, which effectively inhibit emotional and motor manifestations of pain, have virtually no effect on nociceptive hemodynamic responses [2, 7, 9]. It has been suggested that the uncoupling of these effects is based on dissociation in the action of opioids on modulating influences of the analgesic systems of the brain relative to emotions and autonomic activities, and increased resistance to analgesics of neuronal structures in the spinal cord – the final component of vasomotor regulation [3]. The resistance of nociceptive responses of the circulation may also be due to the central activating action of morphine on the sympathetic system, discovered by the writers previously [1]. However, the neurophysiological processes and brain levels responsible for the formation of this effect of morphine have not been investigated.

For the reason given above, it was decided to study the role of the segmental and suprasegmental structures in the realization of the activating effect of morphine on sympathetic mechanisms of vasomotor regulation.

EXPERIMENTAL METHOD

Unanesthetized curarized cats with an intact brain (30 animals) and with the spinal cord divided at the T7-T8 level (five animals) were used. The common peroneal and splanchnic

Department of Pharmacology, I. P. Pavlov First Leningrad Medical Institute.

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TABLE 1. Effect of Morphine (100 μg) on BP, ISI, and Sympathetic Activity in Renal Nerve during Nociceptive Stimulation of Peroneal Nerve (M ± m)

Experimental conditions	Background values of parameters					Maximal values of parameters during nociceptive stimulation				
	BP, mm Hg	ISI, msec	amplitude, μV	duration, msec	frequency, spikes/sec	BP, mm Hg	ISI, msec	sympathetic activity: amplitude, μV	sympathetic activity: duration, msec	sympathetic activity: frequency, spikes/sec
Control	128±14	335±21	39±7	1,1±0,4	44±8	163±11	385±24	80±12	3,2±0,9	91±8
Morphine										
into cerebral ventricles	125±11	304±18	35±6	1,2±0,6	47±7	164±12	348±21	78±9	2,8±0,7	87±11
intrathecally	150±16	305±16	62±5*	2,2±0,2*	71±6*	197±16	399±20	89±13	3,6±0,6	102±7

Legend. *p < 0.05 compared with control.

nerves were stimulated by pulses with an amplitude of 10-15 V, duration 1 msec, and frequency 10-20 Hz, activating A- and C-afferent fibers [5]. Sympathetic electrical activity in the renal nerve was derived by bipolar silver electrodes (UBP 2-04 amplifier). By means of a specialized computer system based on the Elektronika D 3-28 microcomputer, designed by ourselves, the amplitude and duration of each spike, their frequency, and also the blood pressure (BP) and intersystolic intervals (ISI) were recorded and analyzed statistically. Morphine hydrochloride was injected into the lateral ventricles of the brain and also intrathecally [8] at the level L1-L2 in doses of 5, 10, 20, 50, and 100 μg and in a volume of not more than 10-50 μl.

EXPERIMENTAL RESULTS

The initial BP of animals with an intact brain was 128 ± 14 mm Hg and ISI was 335 ± 21 msec. Discharges of sympathetic activity in the renal nerve were synchronized with pulse waves of BP. In response to repetitive stimulation of the peroneal nerve pressor reactions of BP and tachycardia developed, and the amplitude, duration, and frequency of the spikes increased (Table 1). Stimulation of this nerve with single pulses with an amplitude of 10 V was accompanied by the appearance of a short-latency (80-100 msec) A-response in the renal nerve. The late C-response appeared after a latent period of 400-500 msec, but it was weak and was recorded in 60% of observations (Fig. 1a).

Morphine in doses of 5 to 100 μg, if injected into the lateral cerebral ventricles, and in doses of 5 to 100 μg, given by intrathecal injection, did not effect nociceptive responses and did not change the background values of the parameters of the systemic hemodynamics or of spike activity (Table 1). Morphine (5-20 μg, injected intrathecally), likewise did not affect the A-reflex response to single stimulation of the somatic nerve, but increased the amplitude and duration of the C-response (Fig. 1b). After microinjection of morphine in a dose of 100 μg BP rose to 150 ± 16 mm Hg, the mean amplitude, duration, and frequency of the spikes increased, the synchronization of sympathetic activity with the pulse waves of BP was disturbed. Spontaneous spike discharges appeared, accompanied by hypertensive shifts of BP and by tachycardia. However, the changes in BP, ISI, and sympathetic activity induced by nociceptive stimulation were not reduced by morphine in this dose. Moreover, in response to single stimulation of the peroneal nerve a prolonged high-frequency discharge appeared in the renal nerve, without any separation into short- and long-latency components (Fig. 1c).

The results suggested that this activating action of morphine on the sympathetic system was due to its effect directly on the sympathetic vasomotor mechanisms at the segmental level. To test this hypothesis morphine was injected intrathecally into spinal animals, in which BP was 89 ± 11 mm Hg and ISI was 380 ± 24 msec. Sympathetic activity in the renal nerve, with an amplitude of 24 ± 7 μV, a duration of 1.1 ± 0.6 msec, and a frequency of 12 ± 4 spikes/sec in these animals was not synchronized with the pulse waves of BP, and repetitive stimulation of the splanchnic nerve was accompanied by pressor response to BP with an amplitude of 20 ± 6 mm Hg and increased the parameters of sympathetic activity to 50 ± 12 μV, 2.2 ± 0.9 msec, and 25 ± 6 spikes/sec. During stimulation of the visceral nerve with single pulses, marked reflex responses were clearly seen in the renal nerve with a latent period of 50-60 msec.

Morphine in a dose of 100 μg increased the background level of sympathetic activity, increased BP and, at the same time, increased the spike discharge and hypertensive shifts caused by repetitive stimulation of the splanchnic nerve (Fig. 2). In response to single stimulation of the nerve, as a rule the amplitude and duration of the reflex response increased.

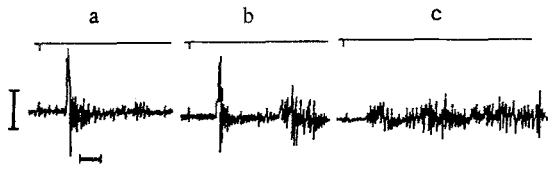

Fig. 1

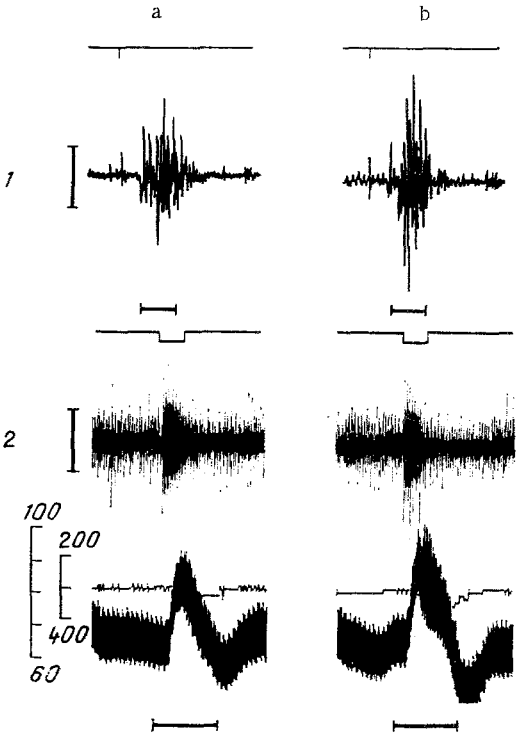

Fig. 2

Fig. 1. Effect of morphine given by intrathecal injection into unanesthetized cats on reflex responses in renal nerve to single stimulation of peroneal nerve. a) Control; b, c) morphine in doses of 5 and 100 μg, respectively. From top to bottom: marker of stimulation, spike discharge in renal nerve, time marker (100 msec). Calibration of spike amplitude 100 μV.

Fig. 2. Effect of morphine, given by intrathecal injection to spinal cats, on responses of BP and ISI and on changes in spike activity in the renal nerve in response to nociceptive stimulation of the splanchnic nerve. a) Control; b) morphine 100 μg. 1 (from top to bottom) — marker of single stimulation of splanchnic nerve, spike activity in renal nerve, time marker (100 msec); 2 (from top to bottom) — marker of repetitive stimulation of splanchnic nerve, spike activity in renal nerve, ISI, BP, time marker (20 sec). Calibration: of spike discharge 100 μV, of ISI 100 msec, of BP 10 mm Hg.

These results suggest that the activating effect of morphine on the sympathetic system, which in the writers' view is one cause of resistance of nociceptive hemodynamic responses to opiates, may be realized through vasomotor mechanisms in the spinal cord. Comparison of our own results with data in the literature suggests a possible neuronal substrate for the activating effect on the sympathetic system. Considering the marked temporal dispersion of the volley of the C-afferent fibers and the extensive spread of impulses along the spinal cord as far as bulbar structures [5, 10], it can be tentatively suggested that morphine acts primarily on the propriospinal system of generalization of sympathetic reflexes. This suggestion is confirmed by our own data, showing that morphine, injected intrathecally in a dose of 5 and 20 μg, selectively increases the amplitude and duration of the C-reflex response, but in a larger dose (100 μg) it leads to the appearance of a high-frequency prolonged discharge in the renal nerve in response to single stimulation of the somatic nerve. Support for this suggestion is given also by the results of experiments on spinal animals. Under these conditions, when descending modulating influences are abolished and the functional capacity of the propriospinal system is reduced [4], morphine potentiates responses of sympathetic activity and pressor shifts of BP induced by nociceptive stimulation. It can thus be postulated that the effect of morphine, in analgesic doses, on the system of propriospinal neurons is of essential importance in the realization of its activating effect on the sympathetic system, and determines one mechanism of the phenomenon of pharmacologic resistance of nociceptive hemodynamic responses.

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EFFECT OF TAGEFLAR, A SYNTHETIC L-ENKEPHALIN ANALOG, ON MORPHOGENESIS OF EXPERIMENTAL PANCREATITIS

A. S. Kanayan, N. K. Permyakov, G. P. Titova, G. M. Golovleva, and K. P. Arabadzhyan

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Much clinical and experimental evidence has now been obtained to show that, despite the existence of a wide range of drugs, the effectiveness of conservative treatment of pancreatitis is not yet sufficient to meet the demands of clinical medicine. In the last decade research workers have paid close attention to natural neuropeptides and to their synthetic analogs, which have a broad spectrum of biological action. The enkephalins and their synthetic analogs, notably dalargin, are known to be able to inhibit basal and stimulate pancreatic secretion [3, 5], to inhibit activity of the pancreatic enzymes and kinins, potentiate the inhibitory system of proteolytic enzymes [1], and to limit and prevent progression of the pathological process in the pancreas during pancreatitis under both clinical and experimental conditions [1, 4].

The aim of this investigation was to test a new synthetic enkephalin analog — tageflar (synthesized in the Laboratory of Peptide Synthesis, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR) as an agent for the pathogenetic treatment of experimental pancreatitis.

EXPERIMENTAL METHOD

Pancreatitis was produced in 197 noninbred albino rats weighing 180-200 g by cooling the splenic segment of the pancreas with ethyl chloride. Of this total number of rats, tageflar was injected intraperitoneally in a dose of 0.1 mg/kg into 70 rats, immediately after injury to the pancreas, and also 2 and 24 h later. The remaining animals served as the control. Rats of both groups were killed by decapitation 1, 3, 6, and 24 h and 3, 7, 14, 21, and 30 days after injury to the pancreas. The pancreas was fixed in 10% formalin, buffered by Lillie's method, and embedded on paraffin wax. Paraffin sections 4 μ thick were stained with hemotoxylin and eosin, by the Jenner–Giemsa and Gram–Weigert methods. Amylolytic activity of the blood was determined by Caraway's method, and trypsin-like activity and the trypsin inhibitor level in the blood by Shaternikov's method.

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