ROLE OF DIFFERENT OPIATE RECEPTORS IN REGULATION OF NOCICEPTIVE ARTERIAL PRESSURE RESPONSES

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KEY WORDS: conscious rate; nociceptive responses; arterial pressure; opiate receptor agonists; intrathecal microinjections.

Recent investigations have shown the existence of several different types of opiate receptors and their varied role in the regulation of nociceptive sensitivity and the analgesic action of opiates and opioids. The differential role of each of these types of receptors has been established in the formation of behavioral responses to nociceptive stimuli of thermal, mechanical, and chemical nature [3, 8, 13], and the receptor characteristics of pain integration at the suprasegmental and segmental levels of the CNS [11, 15]. The existence of subtypes of receptors (for example, μ_1- and μ_2- receptors), with different roles in the mechanism of opiate analgesia, has been suggested [9, 14]. Opioidergic processes also are known to participate in regulation of the circulation and, in particular, in tonic control of the arterial blood pressure (BP) and in the formation of arterial hypertension [1, 5, 10]. However, the receptor mechanisms of realization of hemodynamic responses elicited by pain remain virtually unstudied.

The aim of this investigation was to analyze the receptor organization of opioidergic mechanisms determining BP changes in response to pain, and using antagonists of different types of opiate receptors.

EXPERIMENTAL METHOD

Blood pressure in the carotid artery, and the latent period (in seconds) of withdrawal of the tail in the tail-flick test and the threshold of vocalization (in milliamperes) during electrical stimulation of the base of the tail were recorded in 42 conscious rats [2]. Pharmacological agents were injected intrathecally [7] through previously implanted cannulas at the level of the upper limbar segments and into the lateral cerebral ventricles, in volumes of not more than 5 and 3 µl respectively. Their effect was assessed 5-15 min after the microinjections. The following substances were used: morphine hydrochloride, 1-30 µg; D-Ala^2-Gly-ol^5-enkephalin (DAGO, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR) 0.1-10 µg; D-Ala^2-D-Leu^5-enkephalin (DADL, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR) 0.1-5 µg; bremazocine (Sandoz, Switzerland) 10 µg; pentazocine (Lexir, from Gedeon Richter, Hungary) 10-30 µg; naloxone (from Sigma, USA) 10 µg.

EXPERIMENTAL RESULTS

Morphine (2-5 mg/kg) and pentazocine (5-15 mg/kg), when injected intraperitoneally against the background of distinct inhibition of the vocal response, significantly increased the pressor responses of BP that developed simultaneously with vocalization of the animals (Fig. 1a). After injection of these drugs in analgesic doses (5-30 µg) into the cerebral ventricles the BP responses were unchanged, but after intrathecal microinjections they were enhanced (Fig. 1b, c); the intensity of the activating effect on the autonomic system, moreover, was the same after systemic and intrathecal injection. Comparison of the data obtained by different methods of administration of morphine and pentazocine suggested that potentiation of the nociceptive shifts of BP was due to their action mainly at the segmental level.

Data on changes in the motor and emotional manifestations of pain after intrathecal microinjections of morphine and of agonists of opiate receptors of the µ (DAGO), δ (DADL), and (bremazocine) types in doses evoking the most marked changes in nociceptive responses of BP,

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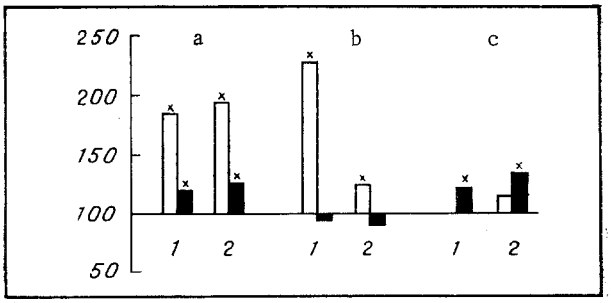

Fig. 1. Effect of morphine and pentazocine in vocalization and BP responses (in %) to electrical stimulation of the tail in rats. a) Intraperitoneal injection of morphine (2-5 mg/kg) and pentazocine (15 mg/kg); b c) intraventricular and intrathecal injection in doses of 5 and 30 μg, respectively. 1) Morphine, 2) pentazocine. Unshaded columns — changes in vocalization threshold; black columns — amplitudes of BP responses. Here and in Figs. 2 and 3: *$p < 0.05$ compared with control.

are summarized in Fig. 2. All substances except DAGO not only had an analgesic action, but also potentiated the BP responses. Naloxone (intrathecally) abolished the analgesic and autonomic effects of morphine and opioids.

It is generally known that the hemodynamic effect of reflex stimulation of any modality is determined by activation of sympathetic preganglionic neurons and by modulating influences of suprasegmental vasomotor mechanisms. Comparison of the results obtained in the various tests after intrathecal and intraventricular injection of ligands sheds light on the role os suprasegmental and segmental opioidergic processes in the formation of BP shifts during pain. It has been shown that the tail withdrawal response in the tail-flick test is a segmental motor reflex, whereas the vocal response characterizes the suprasegmental level of closing of the reflex chain for nociceptive stimuli [6]. Analgesia, which develops in the vocalization test immediately after intrathecal injection of the agonists, is thus due to limitation of the intensity of the ascending flow of nociceptive impulses. Changes in the latent period of tail withdrawal after intraventricular microinjections of the compounds depend on their action on descending influences from the suprasegmental systems. It will be clear from Fig. 2 that DAGO and DADL, injected intrathecally, inhibited the vocalization response equally or, in other words, they inhibited the spread of nociceptive impulses to suprasegmental structures equally. According to their strength of action on processes of descending inhibition of segmental nociceptive reflexes in the tail-flick test, the agonists were distributed as follows: DAGO > DADL = morphine > bremazocine. No correlation was thus found between the direction of the hemodynamic action of the opioids and their effect on the intensity of the ascending nociceptive flow and the character of descending control of segmental mechanisms. Consequently, it is the spinal opioidergic systems which play the leading role in the realization of the action of morphine and opioids on pain-determined changes in BP.

The results not only confirmed the hypothesis [4] that opioidergic regulation of behavioral and hemodynamic manifestations of pain are effected separately, but they also showed that this separation is determined at the level of δ- and κ-opiate receptors of the spinal cord already. At the same time, the autonomic depressant action of DAGO, a μ-receptor agonist, cannot be explained by simple reduction in the intensity of the combined flow of nociceptive impulses in neuronal structures at the segmental level, manifested as lengthening of the latent period of tail withdrawal. For instance DADL, an agonist of δ-opiate receptors, inhibited the response of tail withdrawal much more strongly than DAGO (Fig. 2), but it potentiated the response of BP.

As already mentioned, functional heterogeneity of the various types of opiate receptors at suprasegmental and segmental levels of the CNS in the regulation of nociceptive sensitivity has recently been postulated [3, 8, 11, 13, 15]. Our data show directly that the role of the different opiate receptors in the regulation of nociceptive hemodynamic responses is dissimilar. Evidently μ-opiate receptors can be regarded as the basis of autonomic depressant opioidergic mechanisms of the spinal cord. Analgesic effects of morphine can be realized, as we know, not only through μ-receptors, but also through δ- and κ-opiate receptors [12]. It is evident from this standpoint that the action of morphine on μ-opiate receptors does not play the leading role in its hemodynamic effect. Meanwhile morphine, DADL, and bremazocine potentiated the nociceptive shifts of BP about equally. Consequently, the autonomic activat-

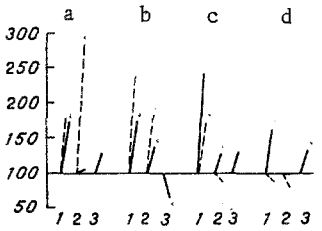

Fig. 2

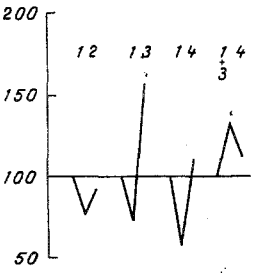

Fig. 3

Fig. 2. Changes in emotional-behavioral and hemodynamic nociceptive responses (in %) after intrathecal injection of morphine and opioids. a) Morphine (10 μg); b) DAGO (0.5 μg); c) DADL (1 μg); d) bremazocine (10 μg). 1) Latent period of tail withdrawal; 2) vocalization threshold; 3) amplitude of BP response. Broken lines show data following intraventricular injection of ligands. *$p < 0.05$ compared with control.

Fig. 3. Results of pharmacological analysis of receptor mechanisms of activating effect of opioids on the autonomic system following intrathecal injection. Ordinate, changes in amplitude of nociceptive responses of BP (in %). 1) DAGO (0.5 μg); 2) morphine (10 μg); 3) DADL (1 μg); 4) bremazocine (10 μg).

ing action of opioids can be mediated through δ- and/or κ-opiate receptors. For a more detailed analysis of the receptor mechanism of the potentiation of BP responses, δ- and κ-agonists were injected intrathecally after preliminary injection of DAGO. It was postulated that during interaction between the ligand and the μ-receptors, differentiation of the receptor basis of the autonomic activating action of other ligands would be possible.

It was found that the intensity of the autonomic activating effect of the compounds was proportional to their affinity primarily for δ-opiate receptors (Fig. 3). Whereas bremazocine nearly restored the responses of BP, when reduced by DAGO, to the control values, DADL, under conditions of interaction of DAGO with μ-opiate receptors, led to marked potentiation of the nociceptive hemodynamic changes. After preliminary microinjection of DAGO and DADL, bremazocine was ineffective. Characteristically morphine, against the background of DAGO, likewise had no significant effect on BP responses. Evidently the autonomic activating effect of the various opiate ligands during pain is realized predominantly through δ-opiate receptors of the spinal cord.

Thus separation of the opioidergic regulation of manifestations of pain belonging to different modalities is determined by functional heterogeneity of the different types of opiate receptors; the opposite effect of ligands of the opiates on emotional-behavioral and hemodynamic responses, moreover, is established as early as in the initial stages of integration of nociceptive signals — at the level of the spinal cord. Functional differentiation within the population of opiate receptors controlling the BP level during nociceptive stimulation also was found. Autonomic depressant effects of opiates and opioids are realized through μ-opiate receptors, whereas δ-receptors and, to a much lesser extent, κ-receptors participate in the formation of the autonomic activating effect against the background of opiate analgesis. It is perhaps this inadequate δ-receptor selectivity and ability to act on opiate receptors of other types, characteristic of the narcotic analgesics used in clinical practice (morphine, trimeperidine, etc.) that are responsible for the weakness of their normalizing effect on the autonomic system.

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PLASMA β-ENDORPHIN AND STRESS HORMONE LEVELS DURING ADAPTATION AND STRESS

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It is stated in recent publications that activity of the system of opioid neuropeptides is increased during stress [8, 13], but the physiological significance of this phenomenon still remains unclear. The writers showed previously that exogenous administration of analogs of opioid peptides has a positive action on the course of stress [3, 4], so that their role in adaptation can be postulated.

This paper describes a comparative study of β-endorphin and stress hormone levels in the blood plasma of rats during stress and adaptation.

EXPERIMENTAL METHOD

Experiments were carried out on 80 male albino rats weighing 160-180 g. Stress was induced by the method in [9], the essence of which is the existence of a conflict between established conditioned avoidance reflex and unconditioned electrical stimulation at random time intervals.

Some animals were adapted to stress by means of several short sessions of immobilization [5] or by a course (8 days, sessional dose 1 ml/kg) of injections of the pharmacopoeial preparation *Rhodiola rosea* extract, which is a recognized adaptogen of plant origin [7].

The following groups of experimental animals were formed: control — intact rats, group 1) stress (4 h), 2) immobilization, 3) stress after a course of training in immobilization, 4) receiving a course of the adaptogen, 5) stress after a course of the adaptogen.

Immunoreactive β-endorphin in the blood plasma was assayed by means of a kit (Immunonuclear Corp., USA) after preliminary isolation of the β-endorphin fraction by affinity chromatography on sepharose; ACTH was assayed with a kit (CEA IRE Sorin, France), and cortisol, insulin, thyroxine (T_4), and tri-iodothyronine (T_3) by means of kits from "Izotop" (USSR).

The ratio, in percent, between the cortisol and insulin levels (C/I ratio) also was calculated, and its initial level was taken to be 100%.

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