EFFECT OF PROSTAGLANDINS, CYCLIC NUCLEOTIDES, AND IONS ON THE ANALGESIC EFFECT OF ENKEPHALIN ANALOGS

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Evidence that certain endogenous substances belonging to the group of intracellular modulators weaken the analgesic effect of opiates has recently been published. For example, this property is exhibited by prostaglandins (PG), cyclic nucleotides, and calcium ions. The first data on antagonism between opiates and PG were obtained by Ferri et al. [5], who showed that PGE, when injected into the cerebral ventricles, weaken analgesia induced in rats by morphine. There is evidence that adenine, adenosine, cyclic AMP, and dibutyryl cAMP, when injected in different ways, reduce the analgesic effect of morphine [6]. Calcium ions, if injected into the cerebral ventricles or intraperitoneally, weaken morphine analgesia [7, 9].

The writers showed previously that the chlorides of lithium, rubidium, and cesium weaken the analgesic effect of morphine [1]. Considering the similarity in the spectrum of pharmacologic activity of opiates and opioid peptides, and also the absence of data on the influence of intracellular modulators on the effect of opioid peptides, it was decided to make a comparative study of the influence of some PG, cyclic nucleotides, and calcium, lithium, cesium, and rubidium ions on the analgesic effect of two enkephalin analogs: Tyr-D-Ala-Gly-Phe-NH_2 and Tyr-D-Ala-Gly-Phe(–NO)NH_2.

EXPERIMENTAL METHOD

A pain reaction in rats, estimated in terms of vocalization, was induced by electrical stimulation of the skin of the tail. The threshold of the pain reaction (in volts) was determined every 15 min after intravenous injection of the tetrapeptide-amide or its nitro analog in doses of 10 and 2 mg/kg respectively. PG, cyclic nucleotides, and calcium chloride were injected intravenously 15 min after injection of the enkephalin analogs. Lithium, rubidium, and cesium chlorides were injected intraperitoneally as aqueous solutions 1 h before injection of the enkephalin analogs in doses of 210, 150, and 210 mg/kg respectively. The PGE_1, PGE_2, $PGE_{2\alpha}$, dibutyryl cAMP, cAMP, and cGMP used in the experiments were from Sigma.

EXPERIMENTAL RESULTS AND DISCUSSION

The tetrapeptide-amide in a dose of 10 mg/kg induced a more than twofold increase in the threshold of pain reaction, and the mean duration of this effect was 90-100 min. The maximal rise of threshold was observed 30 min after injection of the peptide. The nitro analog of the tetrapeptide-amide gave a similar effect in a dose of 2 mg/kg. In the strength of their analgesic action these enkephalin analogs, in the doses used, were not inferior to morphine in a dose of 2.5 mg/kg (intravenously). PGE_1, PGE_2, and $PGE_{2\alpha}$, in a dose of 240 μg/kg, considerably weakened the analgesic effect of tetrapeptide-amide (Fig. 1) and of its nitro analog. cAMP in a dose of 50 mg/kg and dibutyryl cAMP in a dose of 20 mg/kg also reduced the analgesic effect of the enkephalin analogs considerably. Unlike cAMP, cGMP in a dose of 50 mg/kg had no distinct effect on the analgesic action of the enkephalin analogs.

Cesium and rubidium salts considerably weakened analgesia induced by the enkephalin analogs, for they lowered the threshold of the pain reaction and also shortened the duration of

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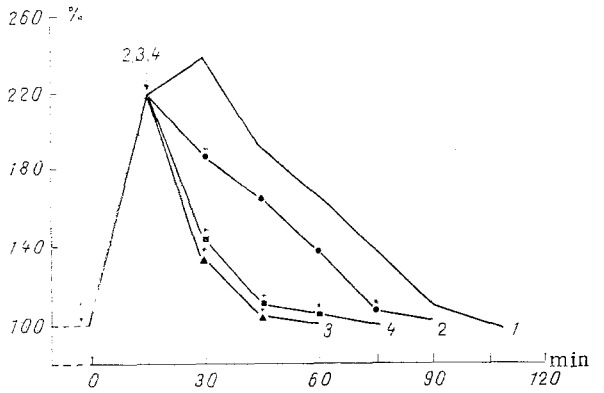

Fig. 1. Effect of PG on analgesic action of tetrapeptide-amide (T). Arrows indicate time of injection of tetrapeptide-amide (1) and PG (2, 3, 4). 1) T; 2) T + PGE_1; 3) T + PGE_2; 4) T + $PGE_{2\alpha}$. Abscissa, time (in min); ordinate, threshold of pain reactions (in %). Asterisk indicates difference from control statistically significant.

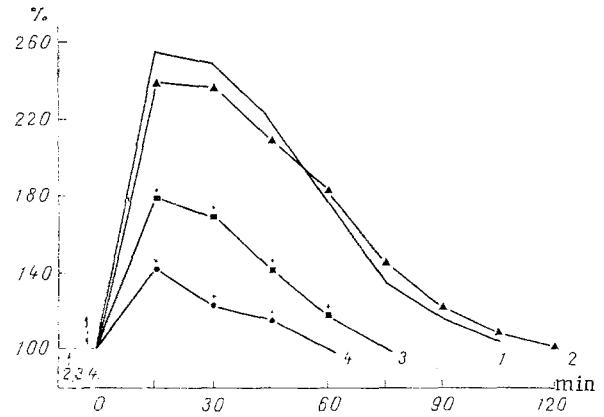

Fig. 2. Effect of lithium, rubidium, and cesium chlorides on analgesic effect of nitro analog of tetrapeptide-amide. Arrows indicate time of injection of lithium, rubidium, and cesium salts (2, 3, 4) and of tetrapeptide-amide nitro analog (NT). 1) NT; 2) LiCl + NT; 3) RbCl + NT; 4) CsCl + NT. Remainder of legend as to Fig. 1.

analgesia (Fig. 2). The ability of cesium to weaken the analgesic action of the enkephalin analogs was greater than that of rubidium. Lithium, in the dose specified, did not weaken the analgesic effect of the enkephalin. In some animals the intensity of this effect was actually increased a little. Calcium caused slight weakening of analgesia (in doses of 125 mg/kg and above), which was less marked than that of rubidium and, in particular, of cesium.

Comparison with data in the literature mentioned above and also with data obtained by the writers previously [1] shows that morphine and analogs of endogenous peptides exhibit distinct similarities. Some PG, cyclic nucleotides, and ions which weaken the analgesic effect of morphine also weaken analgesia induced by the tetrapeptide-amide studied. Some intracellular modulators are known to participate in the formation of the pain reaction. It has been shown that during nociceptive stimulation the concentration of PG in the CNS rises. PG of the E group induces pain in animals when administered in various ways and potentiate the effect of various analgesia-inducing agents, especially bradykinin. The hyperalgesia caused by PGE is weakened by morphine and potentiated by naloxone [4].

By analogy with the suggestion put forward regarding morphine [2] it can be postulated that PG and opioids have opposite effects on subreceptor structures which are common to both. One possible stage at whose level interaction takes place between PG and opiates is adenylate cyclase. Morphine-like preparations have been shown to inhibit PGE-stimulated cAMP formation in rat brain homogenate as a result of inhibition of adenylate cyclase activity [2]. Enkephalins and β-endorphin also inhibit PGE-stimulated cAMP formation.

It can be tentatively suggested that the marked ability of cesium and rubidium to weaken analgesia induced by morphine and enkephalin analogs depends on elevation of the basal cAMP level by these ions [3].

It may be that the antagonism of these three ions toward the effect of enkephalin analogs is connected with their direct action on individual components of opiate receptors. For example, there is evidence that lithium and rubidium can modify binding of ligands of opiate receptors with cerebroside sulfate, a component of opiate receptors [7].

The data obtained in this investigation on the ability of PG, cAMP, dibutyrl cAMP, and lithium, rubidium, and cesium ions to weaken analgesia induced by enkephalin analogs obtained in the present investigation suggests the existence of a complex type of regulation of the functional state of opiate receptors.

The tetrapeptide-amide and its nitro analog were obtained in the Laboratory of Peptide Synthesis, All-Union Cardiologic Scientific Center.

LITERATURE CITED

1. V. M. Bulaev and R. U. Ostrovskaya, Byull. Éksp. Biol. Med., No. 7, 42 (1978).
2. H. O. I. Collier and A. C. Koy, Nature, 248, (1974).
3. R. P. Ebstein, M. Hermoni, and R. H. Belmaker, J. Pharmacol. Exp. Ther., 213, 161 (1980).
4. S. H. Ferreira and M. Nakamura, Prostaglandins, 18, 179 (1979).
5. S. Ferri, A. Santagostino, P. Braga, et al., Psychopharmacologia, 39, 231 (1974).
6. I. Ho, H. Loh, and E. L. Way, J. Pharmacol. Exp. Ther., 185, 336 (1973).
7. T. Kakunaga, H. Kaneo, and K. Hano, J. Pharmacol. Exp. Ther., 153, 134 (1966).
8. P. Y. Law, R. A. Harris, H. H. Loh, et al., J. Pharmacol. Exp. Ther., 207, 458 (1978).
9. M. Lujan, T. Chan-Pham, M. D. Aceto, et al., Life Sci., 23, 1431 (1978).

EFFECT OF OPIOID PEPTIDES, MORPHINE, AND ELECTROACUPUNCTURE ON UNIT ACTIVITY IN THE SENSOMOTOR CORTEX AND BRAIN-STEM RETICULAR FORMATION

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KEY WORDS: opioid peptide; electroacupuncture; naloxone; microiontophoresis.

Most workers nowadays associate the phenomenon of electroacupuncture analgesia mainly with the endogenous opioid system, for it is naloxone-dependent in character [8, 9, 12]. This view has also been confirmed by our own experiments [1, 4]. However, naloxone abolishes the analgesic effect of all opioid peptides without exception, and it is therefore not completely clear which substances — enkephalins, endorphins, or both together, are responsible for the analgesia with electroacupuncture (EA). The results of radioimmunologic investigations are contradictory: some workers observed an increase in the concentration of met-enkephalin but not of β-endorphin in the CSF and blood after electroacupuncture [5], whereas others observed the contrary [7, 11].

With these facts in mind it was decided to study, by the method of microiontophoresis, responses of single neurons in the sensomotor cortex and brain-stem reticular formation to application of enkephalins and endorphins and to compare it with the neuronal effects of EA. Morphine, as the classical representative of the opiates, was used.

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