INTERACTION BETWEEN BRADYKININ, MORPHINE, AND NALOXONE AT THE SENSOMOTOR CORTICAL UNIT LEVEL

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UDC 615.212.7:547.943+615.357:577.175.853/.015.4:612.822

The effects of bradykinin, morphine, and naloxone applied by microiontophoresis on sensomotor cortical neurons were studied in waking rabbits. Bradykinin increased the discharge frequency of most neurons. Morphine inhibited unit activity. Against the background of morphine, bradykinin had no activating action. Naloxone abolished the depriming effect of morphine and restored the response of the neurons to bradykinin. It is concluded that bradykinin interacts with opiate receptors in the brain.

KEY WORDS: opiate receptors; neurons; sensomotor cortex; bradykinin; morphine; naloxone.

Experimental data now available indicate that the endogenous oligopeptide bradykinin participates in the formation of the pain response. Bradykinin, if administered locally or systemically, induces pain in man and animals [3, 6, 11]. The most objective manifestation of the pain response in animals is vocalization [8, 10], which is observed after intra-arterial injection of bradykinin. Bradykinin induces vocalization also when injected into the cerebral ventricles of waking rabbits [4]. Intra-arterial injection of bradykinin also evokes a sharp increase in the discharge frequency of neurons in the posterior horns of the spinal cord, brain stem, and sensomotor cortex [1, 5, 15]. Activation of unit activity also is observed after iontophoretic application of bradykinin to, for example, spinal and sensomotor cortical neurons [12, 13]. Correlation thus exists between the ability of bradykinin to evoke a pain response in animals after intra-arterial and intraventricular injection, and its ability to increase the discharge frequency of neurons when injected intra-arterially or applied by microiontophoresis to single brain neurons.

The object of this investigation was to study interaction of bradykinin with morphine and with naloxone, an antagonist of the narcotic analgesics, at the single sensomotor cortical unit level. The sensomotor cortex is known to participate in the response to nociceptive stimulation [2], including to injection of bradykinin [1, 9].

EXPERIMENTAL METHOD

Experiments were carried out on unanesthetized unimmobilized rabbits weighing 2.5-3.0 kg. For extracellular recording of unit activity and microiontophoretic application of the drugs, four-barreled glass microelectrodes with a tip 2-5 μ in diameter were used. The potentials derived were amplified by means of an MZ-4 microelectrode amplifier (Nihon Kohden) and U7-2 measuring amplifier, transformed by a vibrator into square pulses 3 msec in duration, and then recorded on an N327-5 automatic pen writer. Meanwhile the number of pulses was recorded on the same writer by means of a simple integrator in the form of an integral curve. The recording barrel of the microelectrode was filled with 2.5 M NaCl. The other barrels were filled with freshly prepared aqueous solutions of the following substances: bradykinin triacetate (Reanal, 0.8×10^{-3} M, pH 6.0), morphine hydrochloride (0.6×10^{-2}M, pH 5.0), and naloxone hydrochloride (Endo, 0.3×10^{-2}M, pH 5.0). The substances were applied by a positive current of 30-75 nA for a period which varied for the different substances from 10 to 60 sec.

EXPERIMENTAL RESULTS

After microiontophoretic application of bradykinin, morphine, and naloxone to sensomotor cortical neurons the following results were obtained (Fig. 1). Of 80 neurons tested, an increase in discharge frequency

Laboratory of Molecular Neurophysiology and Biochemistry, P. K. Anokhin Institute of Normal Physiology, Academy of Medical Sciences of the USSR, Moscow. Laboratory of Pharmacology of the Nervous System, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 88, No. 12, pp. 683-685, December, 1979. Original article submitted May 16, 1979.

0007-4888/79/8812-1431 $07.50

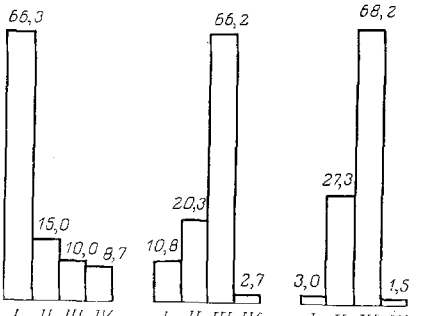

Fig. 1. Types of responses of sensomotor cortical neurons to microiontophoretic application of bradykinin, morphine, and naloxone. I) Increase in unit activity; II) no response; III) inhibition of unit activity; IV) phasic response. Numbers above columns show percentage of neurons giving corresponding response; number of neurons tested shown in parentheses.

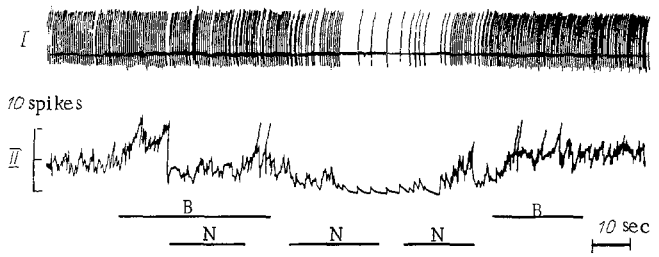

Fig. 2. Responses of sensomotor cortical neuron of rabbit to microiontophoretic application of bradykinin (B), morphine (M), and naloxone (N). I) Spike activity of neuron; II) integral curve of frequency of spike discharge of same neuron. Horizontal lines mark injection of test substances. Drugs applied by currents of 60 nA.

(on average by 50-60%) was observed in 66% during application of bradykinin. No response to bradykinin was given by 15% of neurons. In 10% of neurons bradykinin inhibited spike activity, and in 9% of neurons the responses to bradykinin were biphasic. Unlike bradykinin, morphine and naloxone inhibited spontaneous unit activity (by 66 and 68% respectively); in some neurons morphine and naloxone suppressed spontaneous activity virtually completely. About 20% of neurons did not respond to application of morphine and 27% to application of naloxone. Activation of spontaneous unit activity and phasic responses were observed in 13% of neurons to application of morphine and in about 5% of neurons to application of naloxone.

The action of morphine on excitatory responses to bradykinin was studied in 40 neurons. Morphine weakened or completely inhibited existing bradykinin activation in 80% of neurons. Against the background of depression of unit activity by morphine, bradykinin had no activating action.

Naloxone had a similar action to morphine on the activating effect of bradykinin and weakened or completely inhibited activation in 78% of neurons. Against the background of naloxone, bradykinin caused no increase in the discharge frequency of the neurons.

Morphine and naloxone were applied consecutively to 39 neurons which responded by an increase in discharge frequency to bradykinin. Morphine depressed spontaneous unit activity and abolished bradykinin activation. Naloxone caused a gradual increase in spontaneous activity and restored the original responses of the neurons to bradykinin (Fig. 2).

The analgesic action of morphine is known to be due to its ability to bind with opiate receptors, which are distributed heterogeneously in the spinal cord and brain [14]. Naloxone, an antagonist of the narcotic analgesics, with greater affinity for opiate receptors, displaces morphine and abolishes its analgesic action.

The results suggest that bradykinin also interacts with opiate receptors. This hypothesis is based on the fact that bradykinin had no activating action when given after morphine, evidently because the opiate receptors were already occupied by the analgesic. When application of morphine was followed by that of its specific antagonist, naloxone, the response of the neurons to bradykinin was restored.

At the level of opiate receptors of single neurons interaction thus takes place between the endogenous oligopeptide bradykinin, inducing pain, and morphine and naloxone. Confirmation that opiate receptors may be the substrate of the pain response is given by observations showing that naloxone potentiates nociceptive responses in animals [7].

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EFFECT OF AMPHETAMINE AND CAFFEINE ON BEHAVIORAL CHANGES FOLLOWING ELECTRICAL STIMULATION OF THE CAUDATE NUCLEUS IN CATS

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UDC 615.214.32.015.4:612.826.1

Low doses of amphetamine (0.1-0.5 mg/kg), not affecting the spontaneous behavior of cats, prevent the appearance of behavioral depression after repetitive low-frequency stimulation of the caudate nucleus. Activation phenomena observed after the end of stimulation are considerably potentiated, sometimes with stereotype formation. Caffeine (10-80 mg/kg), which may even activate spontaneous behavior in cats, does not prevent the development of caudate inhibition.

KEY WORDS: amphetamine; caffeine; caudate nucleus; behavioral depression; caudate depression.

Psychostimulation by drugs may depend, among other things, on changes in function of the caudate nucleus [2]. This view is based on the results of a study of caudate responses arising actually during brain

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(Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 88, No. 12, pp. 685-688, December, 1979. Original article submitted January 16, 1979.