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EFFECT OF BRADYKININ AND MORPHINE ON SENSOMOTOR CORTICAL NEURONS IN RATS

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Acute experiments on rats showed that bradykinin, injected by microiontophoresis, activates sensomotor cortical neurons in rats. Morphine, administered in the same way, prevents the development of the bradykinin effect. Bradykinin, it is suggested, acts on opiate receptors in cerebral cortical neurons.

KEY WORDS: bradykinin; morphine; cerebral cortex; opiate receptors.

Bradykinin, if injected intra-arterially or intraperitoneally, induces a sensation of pain in man [4, 8] and a nociceptive response in animals [6]. The sensation of pain after intra-arterial injection of bradykinin is connected with stimulation of paravascular receptors [9] and efferent fibers [2], i.e., it is peripheral in origin. However, recent investigations have shown that bradykinin acts directly on the CNS, by activating interneurons in the posterior horns of the spinal cord after iontophoretic application [7, 11], and it has accordingly been postulated that bradykinin participates in impulse transmission in the spinal cord.

The writers showed previously that bradykinin, when injected intra-arterially, causes activation of sensomotor cortical neurons in rats and that morphine, when injected intravenously, abolishes this effect [1]. However, on the basis of the available results it has not proved possible to determine whether bradykinin and morphine have a direct action on cortical neurons, for the drugs in these investigations were injected systemically.

The object of the present investigation was to ascertain if bradykinin and morphine affect cortical neurons; the method of microiontophoresis, whereby drugs to be tested can be applied directly to single cortical neurons, was used for this purpose.

EXPERIMENTAL METHOD

Rats were anesthetized with urethane (1 g/kg). Sensomotor cortical unit activity was recorded extracellularly by means of multibarreled microelectrodes, filled with aqueous solutions of NaCl (3M), bradykinin (10 mM; pH 4.5), and morphine (0.05 M; pH 5). Bradykinin and morphine were applied to the neurons by cationic currents with a strength of 10-40 nA. The duration of injection varied from 20 to 200 sec. Unit activity was amplified by the MZ-4

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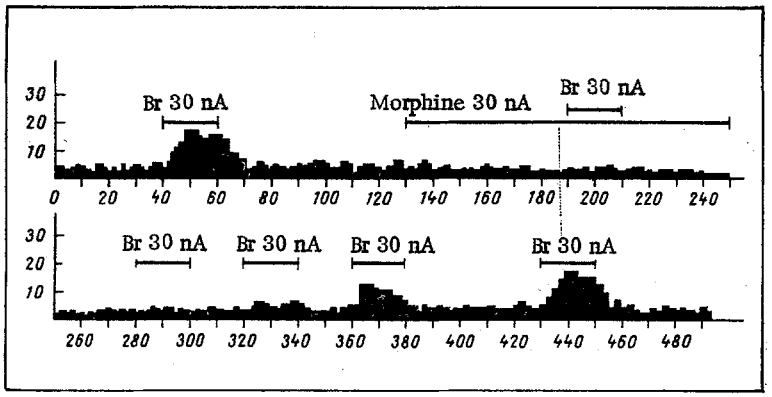

Fig. 1. Effect of bradykinin and morphine on sensomotor cortical unit activity. Histogram of distribution of number of spikes: abscissa, time, in sec; ordinate, number of spikes per second. Horizontal lines below histograms denote time of administration of bradykinin (Br) and morphine.

amplifier and recorded on the S1-17 oscilloscope and Jupiter-20 two-channel tape recorder, and subsequently transcribed on an automatic writer.

EXPERIMENTAL RESULTS

Microiontophoretic application of bradykinin to the sensomotor cortical neurons gave the following results. Of 135 neurons tested 80 did not respond to application of bradykinin, the activity of 10 neurons was reduced, and that of 45 increased. The frequency of the spike discharges increased by 4-5 times compared with the initial level 0.5-1.0 sec after the beginning of bradykinin application. This activation lasted throughout the period of administration of the drug. To be assured of the stability of the unit response to bradykinin, 2-4 min after the end of activation bradykinin was applied a second time. In all 45 neurons recorded, the second application of bradykinin also induced definite activation, indistinguishable in its intensity from the first response.

Morphine, when applied by microiontophoresis, caused a small (by 10-15%) decrease in frequency of the spike discharges. Microiontophoretic application of bradykinin after morphine was not accompanied by any changes in unit activity (Fig. 1). After the application of morphine ceased, the response of the cortical neurons to microiontophoretic application of bradykinin gradually recovered. For instance, in the experiment whose results are illustrated in Fig. 1, an increase in the frequency of the spike discharges by 30-40% was observed after 50-70 sec. Complete recovery of the unit response to bradykinin occurred after 2-2.5 min.

The results of this investigation are evidence of the predominantly activating action of bradykinin, when applied by microiontophoresis to sensomotor cortical neurons in rats, and of the abolition of this effect by morphine in much the same way as these substances act when injected systemically. Morphine prevents the activating effect of bradykinin, evidently because it occupies the receptors which serve to bind bradykinin.

It has now been established that the point of application of morphine in the CNS consists of what are known as opiate receptors, located in the pre- and postsynaptic membrane of neurons [3, 12]. Opiate receptors are irregularly distributed in different parts of the CNS: they are found mostly in the substantia gelatinosa of the spinal cord and thalamic formations, and they are rather less numerous in the cerebral cortex [10]. Since morphine binds with opiate receptors in the CNS, and having regard to the results of the present investigation showing that, if applied directly to a neuron, it abolishes the effect of bradykinin, it can be postulated that bradykinin also reacts with opiate receptors. Considering that bradykinin is a polypeptide in structure, further evidence in support of the above hypothesis is given by the fact that the endorphines (endogenous polypeptides with morphine-like properties) also bind with opiate receptors [5].

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