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EFFECT OF MORPHINE AND AZIDOMORPHINE ON CORTICAL UNIT ACTIVITY

V. M. Bulaev and O. N. Chichenkov

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In acute experiments on unanesthetized curarized cats and rats morphine and azidomorphine, in analgesic doses, inhibited spontaneous and bradykinin-evoked unit activity in the sensomotor cortex. The depriming action of both drugs was abolished by nalorphine. It is suggested that the inhibitory action of morphine and azidomorphine is due to their direct action on the cerebral cortex.

KEY WORDS: morphine; azidomorphine; single unit activity; sensomotor cortex.

New drugs (fentanyl, etorphine, and azidomorphine), with an analgesic activity several orders of magnitude higher than that of morphine, have recently been obtained. The effect of fentanyl and etorphine on the nervous system has received little study and no data are available on the direction of action of azidomorphine [4] in the CNS in general. The role of the sensomotor cortex in the response to nociceptive stimulation in cats and rats has been established in investigations by many workers [1, 3, 8]. It is also known that injury to the somatosensory cortex in man leads to the loss of pain sensation [5].

In this investigation the effect of azidomorphine* and morphine on spontaneous single unit activity of the sensomotor cortex and activity evoked by nociceptive stimulation was studied. The effect of nalorphine, an antagonist of the narcotic analgesic, on the effects of morphine and azidomorphine also was investigated.

EXPERIMENTAL METHOD

Experiments were carried out on 15 cats weighing 2-3 kg and 10 rats weighing 250-300 g. Tracheotomy and catheterization of the veins and arteries were performed under ether anesthesia. The animal was then fixed in a special frame, immobilized with anatruxonium (0.1-0.2 mg/kg), and artificially ventilated. Unit activity in the sensomotor cortex was derived by glass microelectrodes with a tip 1-3 μ in diameter and recorded continuously throughout the experiment on the PP-15 scaler–printer. Intraarterial injection of bradykinin (10 μg) was used as a method of specific nociceptive stimulation [6]. Morphine, azidomorphine, and nalorphine were injected intravenously. Control experiments showed that the drugs tested, in the doses used, caused virtually no change in the arterial pressure.

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Laboratory of Pharmacology of the Nervous System, Institute of Pharmacology, Academy of Medical Sciences of the USSR. Department of Pharmacology, Faculties of Therapeutics and Environmental Health, I. M. Sechenov First Moscow Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 83, No. 6, pp. 698-699, June, 1977. Original article submitted January 14, 1977.

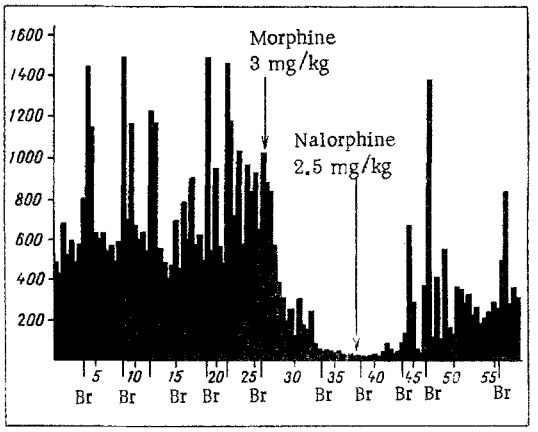

Fig. 1

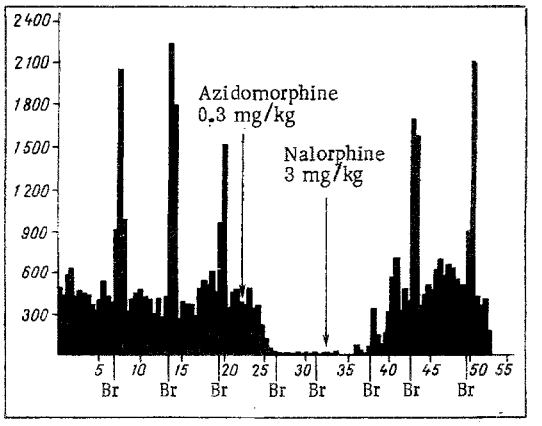

Fig. 2

Fig. 1. Effect of morphine and nalorphine on spontaneous and bradykinin-evoked single unit activity of the sensomotor cortex. Columns represent number of spikes in 30-sec intervals. Br) Intraarterial injection of 10 μg bradykinin. Abscissa, time (in min); ordinate, number of spikes.

Fig. 2. Effect of azidomorphine and nalorphine on spontaneous and bradykinin-evoked single unit activity of the sensomotor cortex. Legend as in Fig. 1.

EXPERIMENTAL RESULTS

Morphine, in a dose of 1.5 mg/kg, reduced the spontaneous sensomotor cortical unit activity by 80-90% and also completely abolished the activation of those neurons evoked by bradykinin. At this stage nalorphine, in doses of 1.5-2 mg/kg, restored both the frequency of the spontaneous discharges and also the response of the neurons to bradykinin. With an increase in the dose up to 3 mg/kg, morphine depressed spontaneous unit activity almost completely. Nalorphine (2-3 mg/kg) partly restored the response of the neurons to bradykinin after 5-6 min and increased the spontaneous firing rate (Fig. 1). The inhibitory action of morphine was clearly manifested in experiments on both cats and rats. It is important to note that morphine, in the above-mentioned doses (1.5-3 mg/kg), causes analgesia in rats on intravenous injection [4].

Azidomorphine in most experiments also inhibited spontaneous and bradykinin-evoked unit activity of the sensomotor cortex, but in much smaller doses. For instance, in a dose of 0.02-0.03 mg/kg, which is analgesic for rats [4], azidomorphine in some experiments depressed the spontaneous firing rate by about half and totally abolished the response to bradykinin. In a dose of 0.3 mg/kg it inhibited both spontaneous and bradykinin-evoked activity practically completely. Nalorphine, in doses of 1.5-3 mg/kg, abolished the depriming effect of azidomorphine (Fig. 2). In some experiments, azidomorphine (in doses of between 0.03 and 0.3 mg/kg) had no marked inhibitory action on spontaneous and evoked unit activity.

These results agree with those obtained for other narcotic analgesics. For instance, etorphine, in analgesic doses, inhibits the response of cortical neurons to stimulation of peripheral nerves [2].

These results are evidence of possible correlation between the analgesic activity of the drugs and their ability to depress cortical unit activity. It is important to note that the depriming action of morphine and azidomorphine in these experiments was abolished by nalorphine, a specific antagonist of narcotic analgesics.

Although the disturbance of transmission of excitation in afferent pathways arising under the influence of narcotic analgesics can take place at different levels of the CNS, the possibility that the effect of morphine and azidomorphine described above is connected with their direct action on the cortex cannot be ruled out. The depriming action of the narcotic analgesics on unit activity and its abolition by antagonists have in fact been observed also after iontophoretic application of the drugs to cortical neurons [2, 7].

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CHANGES IN LARGE DENSE-CORE VESICLES IN SYMPATHETIC NERVE ENDINGS CAUSED BY CERTAIN DRUGS

P. A. Motavkin, V. M. Chertok, and G. G. Bozhko

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An electron-microscopic investigation of the large dense-core vesicles of adrenergic nerve endings in the middle cerebral arteries of vertebrates showed that 60-70 min after injection of iproniazid (3 mg/kg) and dopamine (40 mg/kg) significant changes (compared with the control) were observed in the vesicles, the number of which was increased statistically significantly. The participation of the large dense-core vesicles in the accumulation and conversion of noradrenalin and (or) its precursors is postulated.
KEY WORDS: cerebral vessels; innervation; iproniazid and dopamine.

Numerous investigations have shown that the terminal expansions of the sympathetic nerve fibers contain not only small osmiophilic vesicles, but also large dense-core vesicles (DCV), about 80-110 nm in diameter. The view is held [4, 10] that DCV are formed in the perikaryon of adrenergic neurons, from which they are transported along the axon to the nerve ending. These vesicles can take up noradrenalin or other monoamines [1, 5] and not infrequently they are transformed in the axon terminals of sympathetic nerves into small synaptic vesicles [3, 7] or they are extruded from the nerve ending by a process of exocytosis [10, 11]. Studies of the effect of certain drugs capable of modifying the catecholamine reserves in the tissue depots (6-hydroxydopamine, reserpine, protriptyline) have shown [2, 6, 8, 9] that a few hours after administration of the drugs many modified DCV appear in the adrenergic terminal expansions of the axons and the number of these vesicles increases. This phenomenon has been interpreted as a compensatory reaction to a deficiency of catecholamines in the axon terminals. The appearance of modified vesicles, moreover, has been interpreted either as the result of the direct effect of the drug on the DCV [12] or an an indication of increased activity of the DCV as a result of conversions of noradrenalin in the mobile catecholamine depots [9].

The object of this investigation was to study the responses of DCV in the terminal expansions of sympathetic axons to drugs promoting the accumulation of biogenic amines in the tissue depots.

EXPERIMENTAL METHOD

The middle cerebral arteries of 10 hens and 12 cats were investigated. Five animals from each group were used as controls and the rest received intraperitoneal injections of iproniazid (3 mg/kg), followed 6 h later by dopamine (40 mg/kg). The aminals were killed 60-70 min after the last injection of the drugs. Pieces of the vessels were fixed in 2.5% glutaraldehyde and then stained with osmium in Millonig's mixture, dehydrated in alcohols of increasing concentration, and embedded in Epon 812. The sections were examined in the electron microscope. The results were assessed on the basis of changes in the large vesicles in 100 cross sections of adrenergic axon terminals of the control animals and 125 expansions of axons obtained from experimental tissue samples. The large dense-core vesicles were measured in two mutually perpendicular directions.

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