# EFFECT OF NARCOTIC ANALGESICS ON TRANSMISSION OF EXCITATION IN THE SPINAL CORD

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In experiments on unanesthetized, curarized spinal cats, morphine, trimeperidine, and fentanyl caused no change in the amplitude of evoked potentials in the ventrolateral columns in the lumbar region of the spinal cord in response to single or repetitive stimulation of a cutaneous or pelvic nerve. In some experiments these preparations inhibited neurons of the posterior horns of the spinal cord that are activated by nociceptive stimulation of peripheral receptors or by intraarterial injection of bradykinin. It is suggested that a spinal component exists in the action of the narcotic analgesics.

KEY WORDS: spinal cord; morphine; bradykinin.

Several investigators [1, 2, 5, 13] have suggested that narcotic analgesics may disturb the transmission of excitation in tracts responsible for the conduction of nociceptive information actually at the spinal cord level. However, in most cases the action of analgesics on the tramsmission of excitation has been studied in segmental reflex pathways. The effect of these substances on the ascending tracts of the spinal cord has been studied in only a few investigations and the results were highly contradictory. Fujita et al. [11], for instance, postulated a direct inhibitory effect of narcotic analgesics on the transmission of excitation in the afferent tracts of the spinal cord, whereas Saton and Takagi [14] consider that disturbance of synaptic transmission at the spinal level is due to activation of descending inhibitory influences from the higher levels of the CNS through the action of the analgesics.

The object of the present investigation was to study the effect of morphine, trimeperidine, and fentanyl on evoked responses in the ventrolateral columns of the spinal cord (where nociceptive sensation is mainly conducted) in response to stimulation of a cutaneous or pelvic nerve. In a separate series of experiments the action of these drugs on neurons in the intermediate zone of the posterior horns of the spinal cord, activated by nociceptive stimulation following injection of bradykinin into an artery of the hind limb, was evaluated.

## EXPERIMENTAL METHOD

Experiments were carried out on cats weighing 2-3 kg. Tracheotomy, catheterization of veins and arteries, access to the spinal canal, and dissection of the peripheral nerves were carried out under ether anesthesia. In all the experiments the spinal cord of the animals was divided at the level T8-T9. Total immobilization was secured by intravenous injection of anatruxonium. Evoked responses in the ventrolateral columns of the spinal cord at the level L4-L5 were recorded starting 2 h after the end of inhalation of ether, by means of glass electrodes filled with a solution of an electrolyte (diameter of tip 10-15 $\mu$). A contralateral cutaneous or pelvic nerve was stimulated by single, paired (interval 100 msec) or series of (frequency 10 Hz) supramaximal pulses. In a separate series of experiments nociceptive stimulation of the receptors of the hind limb was induced by intraarterial injection of 10 $\mu$g bradykinin by the method of Besson et al. [9]. In these experiments spike discharges from neurons of the intermediate zone of the posterior horn of the spinal cord were recorded by a microelectrode technique before and after injection of bradykinin. Only nociceptive neurons which, in response to this method of stimulation, increased their discharge frequency by 2-5 times were included in the investigation. The results of these experiments were recorded on magnetic tape, after which the frequency (for every 5 sec) of spikes generated by the nerve cells was analyzed on the Neiron-1 computer. All the substances tested were injected intravenously under the control of the blood pressure in the common carotid ar-

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TABLE 1. Effect of Narcotic Analgesics on Spontaneous Activity of Interneurons of the Posterior Horns of the Cat Spinal Cord and on Their Activity Evoked by Intraarterial Injection of Bradykinin

| Drug | Dose mg/kg intravenously | Group of neurons responding by increase in spontaneous discharge frequency to intraarterial injection of bradykinin * | | | | | | | Dose in which drugs inhibit unit activity in posterior horns of spinal cord during stimulation nerve, mg/kg intravenously† | Analgesic doses of drugs for rats when injected intravenously, mg/kg |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | | |
| Morphine | 10 | −/− | −/− | 0/− | 0/− | 0/0 | 0/0 | +/0 | 3—4 | 3,5‡ |
| Trimeperidine | 10 | −/− | −/− | −/− | 0/− | 0/− | 0/0 | +/0 | 4—5 | 2,5‡ |
| Fentanyl | 0,6 | −/− | 0/− | −/0 | 0/0 | 0/0 | 0/0 | 0/0 | 0,6 | 0,013** |

Legend. Numerator: −) depression of response to injection of bradykinin by 75-100%; +) intensification of response to bradykinin by 30-40%; denominator: −) reduction of spontaneous discharge frequency by 50% or more; 0) no effect.

*Seven groups of neurons were tested with each drug.

†Data from Bulaev [1].

‡Data from Mashkovskii and Ishchenko [6].

**Data from Jansen et al. [12].

tery. After the end of the experiments the location of the tip of the recording electrode was identified in serial sections from the regions of the spinal cord studied.

## EXPERIMENTAL RESULTS AND DISCUSSION

According to the existing views, the ventrolateral columns (spinothalamic tract) are the main conductors of nociceptive sensation. It can accordingly be postulated that narcotic analagesics disturb the transmission of excitation in this conducting system actually at the spinal cord level, and specifically in the posterior horns, where the first synaptic relay occurs in the ascending tract. When the effect of morphine (0.1-15 mg/kg), trimeperidine (0.1-12 mg/kg), and fentanyl (0.013-0.6 mg/kg) on the amplitude and configuration of evoked responses in the ventrolateral columns of the spinal cord was studied, no marked changes could be observed. At the same time, the narcotic analgesics are known to depress the activity of those units of the posterior horns which participate in the formation of polysynaptic pathways [1]. It can tentatively be suggested that selective inhibition of the activity of certain neurons by analgesics is masked by the continued activity of most of the cells, so that when the combined response is recorded from a large number of axons in the ventrolateral columns no changes can be detected in the amplitude and configuration of the potentials. In order to restrict attention to neurons involved in the transmission of nociceptive impulses, selective nociceptive stimulation of the peripheral receptors by bradykinin was used. The resulting increase in the discharge frequency of the cells was assessed as the specific response to nociceptive stimulation. The results of investigation of the effect of morphine, trimeperidine, and fentanyl on nociceptive neurons of the intermediate zone of the posterior horns of the spinal cord are given in Table 1. General disturbances of unit activity arising under the influence of narcotic analgesics can be characterized by two effects: a) by a change in the spontaneous discharge frequency and b) by the change in the response evoked by nociceptive stimulation. As Table 1 shows, the results of this series of experiments were equivocal. In half of the experiments (11 of 21) in which these drugs were tested the frequency of spontaneous spike discharges was reduced by 50% or more. In some experiments (7) this effect was accompanied by depression of the response to nociceptive stimulation and repeated injections of bradykinin caused no change in the discharge frequency of the nociceptive neurons. In two experiments the responses of the neurons to nociceptive stimulation were intensified by 30-40% after injection of morphine and trimeperidine. In the other experiments no appreciable disturbances of unit activity could be detected. This variation of the responses evoked by narcotic analgesics in the activity of the nociceptive neurons is evidence in support of the view that cells participating in the formation of the ascending nociceptive signal exhibit functional heterogeneity. This conclusion is also confirmed by the results of the experiments by Ignatov [4], who demonstrated the functional heterogeneity of cells of the substantia gelatinosa. The work of Calvillo et al. [10] showed that morphine, given by iontophoretic application, depressed nociceptive neurons of the intermediate zone of the posterior horn of the spinal cord, activated by nociceptive cutaneous stimulation, in half of the cases. However, in some cells activity remained unchanged or was even increased considerably. Similar results were obtained by Takagi et al. [15] after intravenous injection of morphine.

On the basis of the experimental results described above and of data in the literature it can accordingly be postulated that a spinal component exists in the action of the narcotic analgesics and probably supplements their inhibitory effect on interneuronal transmission in the region of the thalamus [3, 7, 8].

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