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Effects of Morphine Sulfate on Dorsal-horn Neuronal Responses to Graded Noxious Thermal Stimulation in the Decerebrate Cat

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Effects of morphine sulfate upon activity of the neurons of dorsal-horn lamina V as evoked by graded noxious thermal stimuli applied on the receptive field were studied in spinal cord-transected, decerebrate cats utilizing an extracellular microelectrode recording technique. All single units studied (n = 30) responded to noxious thermal as well as to noxious mechanical stimulation. Their spontaneous discharge frequency was 9.7 ± 1.5 (mean ± 1 SE) impulses/sec (IPS), the threshold skin temperature was 44.8 ± 0.2 C, and a linear correlation existed between skin temperature and discharge frequency at 6.7 ± 0.6 IPS/degree C. Morphine, 1 and 2 mg/kg, iv, suppressed spontaneous activity by 53 ± 6 and 84 ± 6 per cent, respectively; increased threshold skin temperature to 46.5 ± 0.3 and 47.9 ± 0.5 C, respectively, and maintained the linear correlation between skin temperature and discharge frequency but depressed the mean slope of the regression line to 4.5 ± 0.7 and to 2.4 ± 0.4 IPS/degree C, respectively. Naloxone, 0.02–0.04 mg/kg, iv, reversed all of these changes produced by morphine. The results of the present study are, to the authors' knowledge, the first demonstration of the suppressive effect of morphine on the spinal nociceptive neurons in Rexed lamina V as they respond to graded noxious thermal stimuli. These results may explain the analgesic action of morphine at the spinal level. (Key words: Analgesics, narcotic: morphine. Antagonists, narcotic: naloxone. Spinal cord: Rexed lamina V.)

DURING THE PAST DECADE, significant advances have been made in the clarification of the mechanisms of morphine analgesia. One of these developments is the elucidation of some spinal mechanisms of morphine analgesia. In 1974, Kitahata *et al.*[1] demonstrated that intravenous administration of morphine sulfate has a significant suppressive effect upon the spontaneous and mechanically evoked single-unit activity of dorsal-horn nociceptive neurons located in Rexed laminae I and V of the feline lumbar spinal cord, without affecting that of dorsal-horn non-nociceptive neurons located in Rexed laminae IV and VI. This suppressive effect of morphine and its derivatives upon spinal nociceptive neurons was confirmed by other investigators.[2–11] Using noxious radiant-heat stimulation, Calvillo *et al.*[4,5] showed that morphine, whether administered intravenously[4] or applied to dorsal-horn neurons by microiontophoresis,[5] suppressed responses of dorsal-horn neurons to noxious-heat stimulation applied to the peripheral receptive field of the cat's skin. Duggan *et al.*[6–8] have also studied the effects of morphine and enkephalins on dorsal-horn neuronal responses to noxious thermal stimulation. However, there have been no quantitative and statistical studies dealing with effects of morphine on responses of dorsal-horn neurons to graded noxious thermal stimuli.

In 1952, Hardy *et al.*[12] found that a skin temperature of 44.3 ± 0.5 C is the threshold for pricking pain sensation elicited on the human forehead when using the Hardy-Wolff-Goodell dolorimeter; this value seems to agree with the response threshold of the deeper dorsal-horn nociceptive neurons of the feline lumbar spinal cord when noxious thermal stimuli are applied.[13,14]

The present investigation was undertaken in decerebrated, spinal cord-transected cats to elucidate further some analgesic mechanisms of morphine at the spinal level by examining its effects on threshold skin temperature, evoked nociceptive neuronal activity, and the slope of the regression line between the skin temperature and the discharge frequency of nociceptive neurons. In addition, the effect of naloxone on the changes produced by morphine was studied.

Methods

Experiments were performed on 30 cats weighing between 2 and 4 kg. During anesthesia with halothane, nitrous oxide, and oxygen, animals were prepared with tracheostomy, carotid-artery cannulation to monitor arterial blood pressure, and jugular-vein cannulation for the administration of drugs and intravenous fluids. Both carotid arteries were ligated (ischemic partial decerebration), and electrical lesions were made stereotactically and bilaterally in the midbrain reticular formation (electrolytic decerebration). A laminectomy was performed to expose the lumbar and sacral cord segments, which were covered with a mixture of paraffin and mineral oil maintained at 37 C. The spinal cord was transected at L1. Anesthesia was then discontinued and the animal's lungs were arti-

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ficially ventilated with oxygen using a Harvard® pump. Gallamine triethiodide (2–3 mg/kg/hr) was administered intravenously. End-tidal CO_2 was held at 30–37 torr as measured by an infrared gas analyzer. Care was taken to maintain systolic blood pressure above 80 torr. Rectal temperature was maintained at 37.5 ± 1 C with an infrared heating lamp and by a servocontrolled warm mattress. In some animals, a pneumothorax was instituted to decrease respiratory movement of the spinal cord. The foot pads of the left hind limb, which was immobilized, sole upwards, in a holder, were blackened with India ink and a miniature thermistor was placed adjacent to the center of the receptive field.

Extracellular unit recordings of dorsal-horn neurons were made in each cat near the L7 root entry zone using a glass-rod platinum-sheathed Transidyne Microtrode® microelectrode with 1–2 μm exposed tip, which was inserted by a hydraulic micromanipulator. The input signals were acquired through a differential AC preamplifier, displayed on a cathode-ray oscilloscope, and simultaneously recorded on magnetic tape. Laminar organization of dorsal-horn cells was identified by the depth of the electrode from the cord dorsum, by the spontaneous discharge pattern of unitary activity, and by the characteristic evoked responses to peripheral stimuli of the following types: 1) touch, airpuff, light stroking of hair or skin with a camel's hair brush; 2) pressure, compression of the skin by deep squeezing; 3) pinch, compression of the skin with a forceps; 4) noxious radiant heat (skin temperature above 45 C); 5) application of ethyl chloride (below 15 C).

Units responding principally to high-threshold mechanical and noxious thermal stimulation were sampled. All the units studied progressively increased their discharge frequencies when skin temperature was increased. The center of the receptive field of the units studied was on one of the foot pads. The thermal stimulation was designed to keep the surface of the skin at a constant temperature for 10 sec using the radiation of a bulb (a tungsten-filament lamp, 120V, 100W) in a heat projector with a 3.5-cm^2 aperture. The output voltage of the thermistor was fed back to the summing point of the operational amplifier for negative feedback to control the heating current of the bulb; this took approximately 2.2–2.5 sec to reach the set temperature, and was followed by a 10-sec constant temperature. The center of the aperture of the heat projector was placed at the center of the receptive field of one of the foot pads. The skin temperature at the thermistor location was monitored continuously and recorded on magnetic tape. During the control period, spontaneous activity of each unit was recorded for 10 min. Thermal stimuli in one-degree steps between 42 and 51 C of skin temperature were used to evoke single-unit activity every 60–80 sec. This interstimulus interval was sufficient for the skin temperature to return to the pre-stimulation values (33–34 C).

Following the control study, morphine sulfate, 1 mg/kg (19 cats) and 2 mg/kg (11 cats), was administered intravenously and the responses to a series of graded noxious thermal stimuli were observed during maximal suppression of activity (3–15 min). To study the effect of opiate antagonism, naloxone, 0.02 and 0.04 mg/kg, was then administered intravenously and the responses evaluated again. At the end of the experiment an electrolytic lesion was made by passing direct current through the recording microelectrode. The lesion was verified histologically.

Data recorded on magnetic tape were processed off-line with a digital computer (DEC PDP-11/40). Mean evoked discharge frequency of each unit at each degree of skin temperature was determined by averaging the discharge frequencies observed over 17 sec immediately after each exposure to radiant heat. This period of measurement was chosen because it was the average duration of the evoked responses following thermal stimulation. The relationship between skin temperature and discharge frequency was plotted for each series of thermal stimulations of each unit and its regression line was computed before and after administration of morphine and naloxone. The threshold skin temperature was defined as the skin temperature at which a single-unit discharge frequency increased by 20 per cent over its spontaneous discharge frequency. The significances of the mean values of spontaneous discharge frequency, threshold temperature, and slope of the skin temperature–discharge response regression line obtained during control periods, after administration of morphine and after administration of naloxone, were assessed by the Student t test for paired data. P values of 0.05 or less indicated statistical significance. Data were expressed as means ± one standard error (1 SE).

Results

All the units studied responded to noxious thermal stimulation when skin temperature was increased to more than 45 C and when it was lowered to less than 15 C. Among the neurons studied, 12 of 30 units responded to pressure and pinch, and 18 of 30 units responded to touch, pressure and pinch. These neurons responded to noxious thermal stimulation with radiant heat with an initial burst of spike activity, followed by prolonged discharges (fig. 1). Following morphine administration, the evoked activity at 45 C

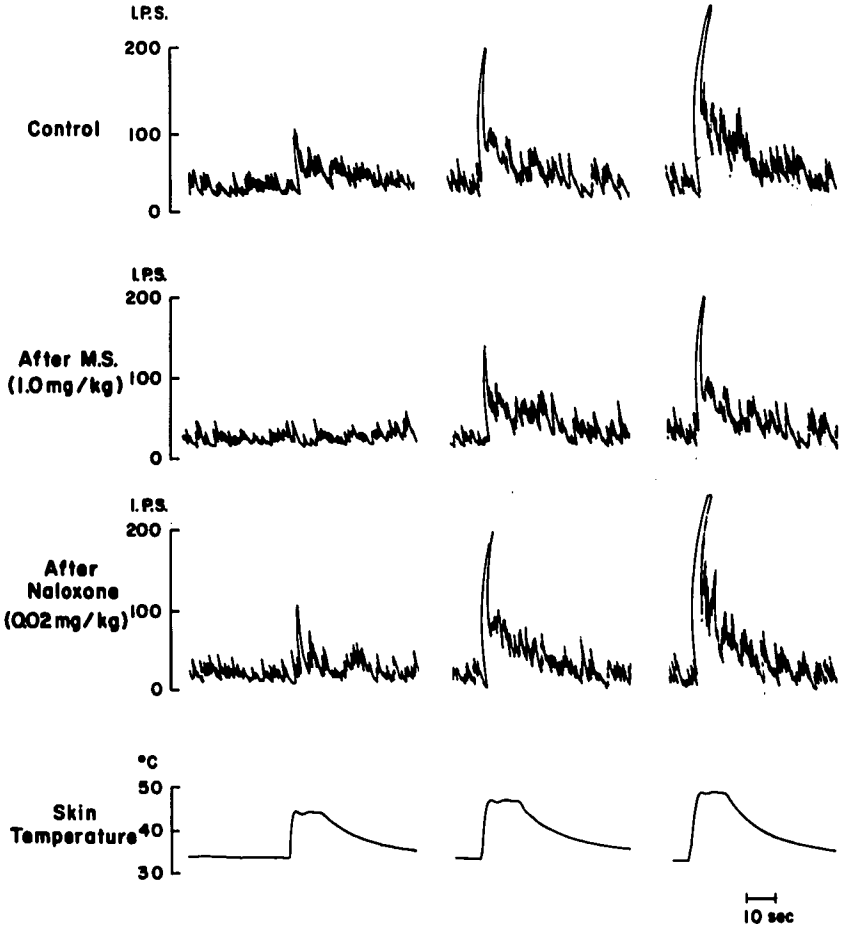

FIG. 1. Examples of polygraph tracings of impulses/sec (IPS) of lamina V neurons as they respond to graded noxious thermal stimulation (from left to right, 45, 48 and 50 C). *Top*: control study; *middle*: after morphine administration; *bottom*: after naloxone administration.

was completely suppressed, while some activity remained at 48 and 50 C. Naloxone reversed morphine-induced suppression.

A linear relationship between skin temperature and discharge frequency was observed with each unit. The slopes of the regression lines varied somewhat among individual units. Threshold skin temperatures, spontaneous firing rates, and the slopes of regression lines changed following morphine, and the changes were reversed by naloxone (fig. 2). The mean frequency of spontaneous activity of 30 units was 9.7 ± 1.5 (mean ± 1 SE) impulses/sec (IPS). The mean threshold skin temperature for 30 single units studied was 44.8 ± 0.2 C (table 1). During stimulation below the threshold temperature, the discharge frequency remained at the level of spontaneous activity. Above the threshold temperature, there was a progressive increase in single-unit discharge frequency, which was correlated with a graded increase in skin temperature. The mean value of the slope of the regression line was 6.71 ± 0.63 IPS/degree C.

Morphine significantly suppressed both spontaneous and evoked activity in a dose-related fashion in all neurons studied. Morphine, 1 mg/kg (n = 19), caused 53 ± 5.8 per cent suppression of spontaneous activity and increased the mean threshold skin temperature to 46.5 ± 0.3 C. In response to stimulation above the threshold skin temperature, a progressive increase in evoked single-unit discharge frequency correlated well with the increase in the stimulus skin temperature. This correlation was maintained even after the administration of morphine. The mean slope of the stimulus skin temperature *vs.* single-unit discharge frequency regression line was, however, significantly diminished to 4.53 ± 0.72 IPS/degree C after administration of morphine, 1 mg/kg.

When the dose of morphine was increased to 2 mg/kg (n = 11), the suppression of spontaneous activity was 84.4 ± 6.1 per cent. The mean threshold skin temperature was increased to 47.9 ± 0.5 C and the mean slope of the regression line was diminished to 2.38 ± 0.35 IPS/degree C. These values were significantly different from control values or those obtained with morphine, 1 mg/kg.

The changes produced by morphine at both doses were reversed within a few minutes by naloxone, 0.02

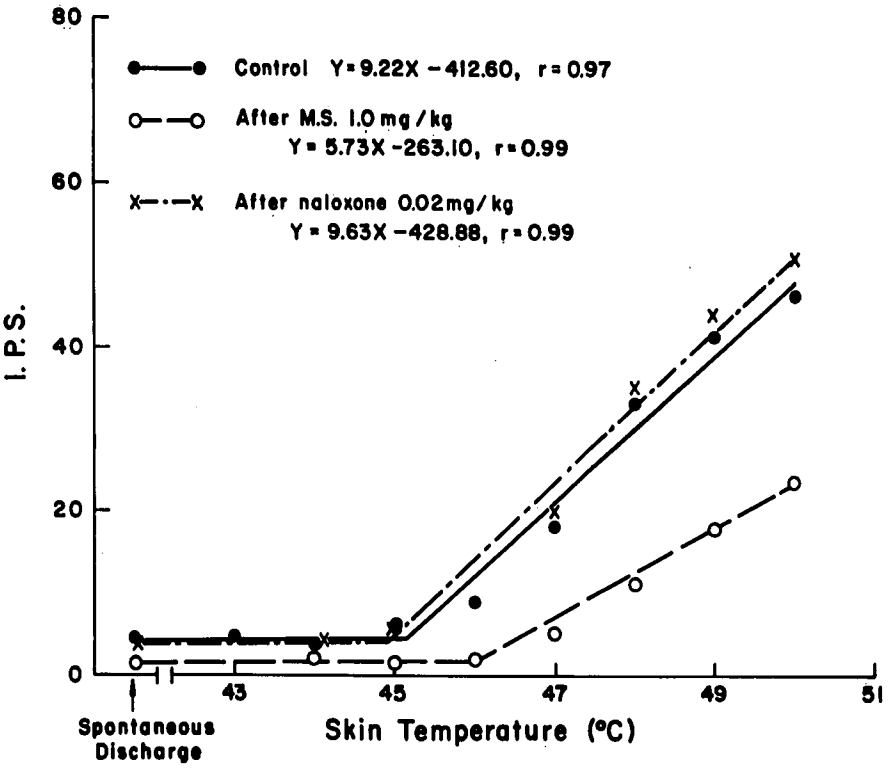

FIG. 2. An example of stimulus skin temperature *vs.* single-unit discharge frequency relationship, with regression lines computed during the control study, after administration of morphine, and after naloxone reversal.

and 0.04 mg/kg. Naloxone, 0.02 mg/kg (n = 11) reversed the suppression caused by morphine, 1 mg/kg, to 94 ± 7 per cent of the control values, and naloxone, 0.04 mg/kg (n = 10), reversed the suppression caused by morphine, 2 mg/kg, to 91 ± 9 per cent of the control values. The mean values of the slopes of the regression lines following naloxone, 0.02 and 0.04 mg/kg, were 5.86 ± 0.58 and 5.79 ± 0.74 IPS/degree C respectively. Likewise, threshold skin temperature was restored to 44.7 ± 0.3 and 44.6 ± 0.2 C, respectively (table 1).

Histologic studies verified the units to be in the Rexed lamina V of the feline lumbar spinal cord, except for three units of 30, which were located in the dorsal portion of lamina VI.

Discussion

The results of the present study indicate that intravenously administered morphine significantly suppresses spontaneous single-unit activity in a dose-related manner, increases the threshold skin temperature for response to noxious thermal stimuli, and decreases the slopes of regression lines of single-unit responses to various stimulus skin temperatures. Others have shown a linear relationship between stimulus skin temperature above threshold and single-

TABLE 1. Percentage Suppression of the Frequency of Spontaneous Discharge, Threshold Skin Temperature, and Slope of Skin Temperature *vs.* Response Regression Line during Control Conditions and after Intravenous Administration of Morphine Sulfate and Naloxone (Means ± SE)

	Suppression of Spontaneous Discharge Frequency (Per Cent) $\bar{x}$ ± 1 SE	Threshold Skin Temperature C	Slope of Temperature–Response Regression Line Impulses/Sec/Degree C
Control (n = 30)	—	44.8 ± 0.2	6.71 ± 0.63
After morphine sulfate, 1.0 mg/kg (n = 19)	53.0 ± 5.8*	46.5 ± 0.3*	4.53 ± 0.72*
Followed by naloxone, 0.02 mg/kg (n = 11)	6.4 ± 6.9	44.7 ± 0.3	5.86 ± 0.58
After morphine sulfate, 2.0 mg/kg (n = 11)	84.4 ± 6.1*	47.9 ± 0.5*	2.38 ± 0.35*
Followed by naloxone, 0.04 mg/kg (n = 10)	9.1 ± 9.2	44.6 ± 0.2	5.79 ± 0.74

The mean value of each after administration of morphine sulfate, 2.0 mg/kg, iv, was significantly different from each of those after morphine sulfate, 1.0 mg/kg, iv (t test for unpaired data, $P < 0.05$).

* Significantly different from control, $P < 0.01$ (t test for paired data).

unit discharge frequencies of C-fibers and small myelinated fibers of the peripheral nerves of anesthetized cats[15,16] and of spinal-cord neurons of cats with transected spinal cords.[13,14] When skin temperature was kept at a constant noxious level for 10 sec, Beck *et al.*[16] found that the thresholds of the majority of the C-fiber heat receptors were between 40 and 45 C and the discharges in C-fibers were related linearly to the level of skin temperature between 40 and 60 C. Price and Browe[14] found 66 spinal cord neurons that responded to radiant heat applied to blackened skin using the Hardy-Wolff-Goodell dolorimeter among 154 neurons that responded to mechanical noxious or non-noxious stimulation. These 66 heat-responding neurons were classified into three groups; warming units (10), which had threshold skin temperatures between 35 and 42 C and responded maximally below 43 C; warming–noxious units (14), which had threshold responses between 35 and 42 C, maximum responses above 43 C, and tended to plateau at or below 45 C of skin temperature; and noxious thermal units (42), which had thermal thresholds between 43 and 50 C (mean 44.5 C) and discharge frequencies that were linearly related to the level of the skin temperature between 43 and 49 C. They verified histologically that warming–noxious units and noxious thermal units were distributed evenly throughout Rexed laminae V, VI, and VII, whereas warming units were mainly located in lamina IV and, to a lesser extent, in lamina V. The 42 noxious thermal neurons studied by Price and Browe,[14] which responded to pressure and pinch stimulation or to touch, pressure and pinch stimulation, were similar to the neurons we studied. This is substantiated further by the fact that the spontaneous frequencies of neuronal discharges and the rates of increase of neuronal discharges per degree of skin temperature increase seem to have been similar in the two studies.

Naloxone, whether administered intravenously[2–4,10,11] or microiontophoretically,[5–7] has been shown to reverse the suppressive effects of morphine on both spontaneous[11] and evoked[2–7,10] activity of spinal-cord nociceptive neurons. This reversal of action of morphine by naloxone was further substantiated by us. The extent of reversibility of the action of morphine by naloxone may be related to the dosages of the two drugs.[2–7,10,11] Although there has been no quantitative study concerning the dose of naloxone necessary to reverse the effects of morphine on spinal-cord neurons, 0.02 and 0.04 mg/kg, used in the present study, seem to be adequate for the reversal of the effects of morphine, 1 and 2 mg/kg, respectively.

It has been reported that the sensitization of peripheral nociceptors due to repeated thermal stimulation could occur in polymodal C-fiber units[16,17] and high-threshold mechanoreceptors with myelinated axons.[18] With regard to spinal-cord neurons, Price and Browe[14] also mentioned that their warming–noxious units became sensitized after repeated exposures to skin temperatures above 45 C. This sensitization due to repeated heat stimulation was manifested by a lower threshold, an increased responsiveness over the same temperature range, and the appearance of background discharge.[14,16–18] However, Price and Browe[14] did not find the sensitization phenomenon in noxious thermal neurons. In the present study, stimulation with radiant heat was limited to skin temperatures below 51 C in order to minimize the sensitization of nociceptors[17] and possible skin damage such as blister formation.[19]

More than three decades ago, Hardy *et al.*[20] demonstrated, in a psychophysical study, that morphine, 8 mg, given subcutaneously, increased the threshold temperature for responses to pain elicited by radiant heating of the skin in man. Others did not find that morphine increased the threshold level for responses to pricking pain in man following radiant-heat stimulation.[21,22] Although there are differences in methods and doses between the psychophysical studies in man done by Hardy *et al.*[20] and the present animal study, the results of the present study indicate that morphine increases the noxious thermal threshold for activation of lamina V cells, supporting the observation of Hardy *et al.*[20] in man.

To test the effects of morphine on evoked activity of spinal nociceptive neurons, various investigators have used experimental pain elicited by several means, such as mechanical stimulation,[1,9] electrical stimulation,[2,3,10] and hot-plate[9] and radiant-heat stimulation.[4–6,8] It is interesting that responses to noxious thermal stimuli are seen only in A-delta[16] and C fibers[15,16,23] of peripheral nerves, while responses to noxious mechanical and electrical stimuli could include inputs from large myelinated fibers. In addition, there is evidence that the spinal-cord neurons aroused by an input in thermal nociceptive (C-fiber heat receptor) units could be suppressed by a concurrent input from cutaneous mechanoreceptors with large myelinated axons.[24] This suppression by large myelinated fibers has also been recognized in the spinal-cord neurons that responded to C-fiber electrical stimulation.[25] Since impulse transmission along peripheral nerves is not impaired by morphine,[2,26,27] the effect elicited by mechanical stimuli or by electrical stimuli may affect the suppressive effect of morphine on dorsal-horn neurons. It would appear, therefore, that the study of the effects of morphine on dorsal-horn neuronal activation by noxious thermal stimuli

is more appropriate, since suppression by input from large myelinated afferents is unlikely.

The significance of the present study is the demonstration of a dose-dependent effect of morphine upon the responses of neurons of Rexed lamina V to graded noxious thermal stimuli. To our knowledge, this is the first demonstration of the effect of morphine on the regression line of the stimulus skin temperature *vs.* single-unit discharge frequency of neurons of Rexed lamina V.

These results provide an experimental basis for the explanation of some of the analgesic mechanisms of morphine at the spinal level. It is important, however, to emphasize that these effects at the spinal level were seen in decerebrate, spinal cord-transected animals. Responses to morphine at the spinal level may be influenced by impulses from higher in the neuraxis, as shown by Satoh and Takagi (1971),[28] Takagi *et al.* (1976),[29] and Hanaoka *et al.* (1978),[30] although Le Bars, Menetrey and Besson (1976),[31] were not able to demonstrate this effect in decerebrate cats.

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