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Effect of Systemic Morphine on the Responses of Convergent Neurons to Noxious Heat Stimuli Applied over Graded Surface Areas

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Background: **Stimulus intensity is a major determinant of the antinociceptive activity of opiates. This study focused on the influence of the spatial characteristics of nociceptive stimuli, on opiate-induced depressions of nociceptive transmission at the level of the spinal cord.**

Methods: **Anesthetized rats were prepared to allow extracellular recordings to be made from convergent neurons in the lumbar dorsal horn. The effects of systemic morphine (1 and 10 mg/kg) were compared with those of saline for thermal stimuli of constant intensity, applied to the area of skin surrounding the excitatory receptive field (1.9 cm^2) or to a much larger adjacent area (18 cm^2).**

Results: **The responses (mean ± SD) elicited by the 1.9-cm^2 stimulus were not modified by 1 mg/kg intravenous morphine, although they were decreased by the 10-mg/kg dose (to 11 ± 4% of control values compared with saline; $P < 0.05$). In contrast, when the 18-cm^2 stimulus was applied, 1 mg/kg intravenous morphine produced a paradoxical facilitation of the neuronal responses (159 ± 36% of control values; $P < 0.05$) and 10 mg/kg intravenous morphine resulted in a weaker depression of the responses (to 42 ± 24% of control values; $P < 0.05$) than was observed with the smaller stimulus.**

Conclusions: **Doses of systemic morphine in the analgesic range for rats had dual effects on nociceptive transmission at the level of the spinal cord, depending on the surface area that was stimulated. Such effects are difficult to explain in terms of accepted pharmacodynamic concepts and may reflect an opioid-induced depression of descending inhibitory influences triggered by spatial summation. (Key words: Antinociception; morphine; spatial summation; spinal cord.)**

STUDIES of the encoding properties of spinal nociresponsive neurons and their sensitivity to administered opiate have been conducted almost exclusively using stimuli involving punctate areas of their cutaneous receptive fields. Systemic and intrathecal deliveries of morphine have been shown to exert powerful depressive effects on the evoked responses of dorsal horn neurons (see Yaksh[1] and Duggan *et al.*[2] for reviews). During such conditions, stimulus intensity is an important determinant of the magnitude of an opiate's effect.[3,4] Stimulus intensity also critically influences the antinociceptive effect of morphine as inferred from more integrated behaviors, such as withdrawal responses elicited by electric[5,6] or thermal stimuli.[7,8]

The influence of other physical characteristics of the noxious stimulus has not been evaluated systematically. Spatial summation may be an important factor in the processing of nociceptive information, as it is for other cutaneous senses.[9,10] The current study was designed to evaluate the effect of high- and low-dose morphine against stimuli of constant intensities applied over different surface areas. Previous studies showed that the simultaneous activation of a large population of nociresponsive spinal neurons triggers a supraspinally mediated negative feedback loop, modulating the output of convergent neurons.[11,12] We assume that such mechanisms are complementary to segmental influences, either excitatory or inhibitory, which are the main source of modulation of the response of dorsal horn convergent neurons when nociceptive inputs are restricted to small areas.[13,14] As a result of inhibitory mechanisms triggered by spatial summation, increasing the surface being stimulated may have two opposite effects on the spinal transmission of nociceptive information: (1) an increase

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in the overall number of spinal afferent and dorsal horn neurons activated, and (2) a decrease in the individual responses of dorsal horn convergent units. The net result of these opposite effects has not been evaluated yet. Determining how opiates interfere with the ability of convergent neurons to encode the stimulated surface area might provide some clues in this regard. Furthermore, opiates have been shown to enhance inhibitory controls organized within the rostral ventromedial medulla (see Willis and Coggeshall[14] and Fields *et al.*[15] for reviews) and to decrease inhibitory controls originating in more caudal brain stem structures.[16–22] Thus, the current study might provide further information about inhibitory controls triggered by spatial summation and help us to determine what relation they might share with other known modulating systems.

Methods

Preparation of the Animals

Experiments were performed on adult male Sprague-Dawley rats (Charles River, Saint-Aubin-Les-Elbeuf, France) that weighed 200–250 g. The animals were housed in groups of six, provided with food and water *ad libitum*, and maintained on a 12-h light–dark cycle.

Surgical preparations were as described before.[11,12] Anesthesia was induced with halothane (2–2.5%) and nitrous oxide (70%) in oxygen. The trachea and left jugular vein were fitted with catheters. The level of mechanical ventilation was adjusted to maintain the end-tidal carbon dioxide level between 3.5 and 4% (Capnomac; Datex Instruments, Helsinki, Finland). Muscle relaxation was achieved by continuous intravenous infusion of gallamine triethiodide. A laminectomy was performed to expose dorsal horn segments L3 and L4. The adjacent vertebrae were clamped and stabilized in a stereotaxic frame. Fluid losses were replaced with lactated Ringer's solution at 4 ml · kg^{-1} · h^{-1}. Heart rate, blood pressure, and end-tidal carbon dioxide and halothane levels were monitored continuously to control the depth of anesthesia. Core temperature was maintained at 37 ± 0.5°C using a homeothermic blanket.

Electrophysiologic Recordings

Extracellular recordings were made from 38 single dorsal horn convergent neurons, 30–45 min after the end of the surgery, with anesthesia maintained by halothane, 0.6%, and nitrous oxide, 70%, in oxygen. The recordings were made using glass micropipettes (10–15 MΩ) filled with NaCl, 5%, and pontamine sky blue. The signal was acquired through a differential AC preamplifier, displayed on an oscilloscope, and gated so only single-unit activity was recorded. The output was fed to a computer data acquisition system (Notocord System, Croissy sur Seine, France) for on-line digitization and storage for further analysis.

Lumbar dorsal horn neurons were classified as convergent based on their responses to innocuous and noxious mechanical stimulation. Convergent neurons are encountered preferentially, albeit not exclusively, in Rexed lamina IV, V, and VI of the dorsal horn. In the current experiments, recordings sites, as marked by dye electrophoresis from the micropipettes at the end of the experiments, were located between 680 and 1,010 mm below the surface of the spinal cord. Light mechanical stimuli produced with a blunt probe and noxious pinch were used to characterize each recorded unit and to delineate its excitatory receptive field, which was taken as the area of skin from which the cell could be activated by such stimuli. The excitatory receptive fields of the cells were located distally on the ipsilateral hind paw and covered mean surface areas of 1.7 ± 0.6 cm^2.

Stimulus Conditions and Treatment Groups

Two types of stimuli having the same intensity but different spatial properties were used. The smaller stimulus involved immersing a 1.9-cm^2 area of skin surrounding the excitatory receptive field of the recorded unit (*i.e.*, one to three digits of the ipsilateral hind paw in 48°C water). The larger stimulus (18 cm^2) involved the immersion of the hind paw to as much as 20 mm below the knee. The duration of these immersions was 15 s. A lag time of 10 min between successive stimuli was used to reduce the possibility of sensitization phenomena resulting from repetitive nociceptive thermal stimulation.[23–25] Previous studies showed that such experimental conditions allow recordings of reproducible nociceptive thermal responses without significant modifications of neuronal excitability.[11,12]

The responses elicited by the 1.9- or 18-cm^2 stimuli were evaluated before and 10 and 20 min after a single intravenous dose of morphine hydrochloride or saline vehicle. Three treatment groups were considered: a control group of rats that received saline (1 ml/kg), an M1 group of rats that received 1 mg/kg intravenous morphine diluted in normal saline, and an M10 group of rats that received 10 mg/kg intravenous morphine. Twenty-five minutes after the drug was injected, naloxone hydrochloride (0.4 mg/kg) was administered intravenously to challenge the effects mediated by opioid receptors.

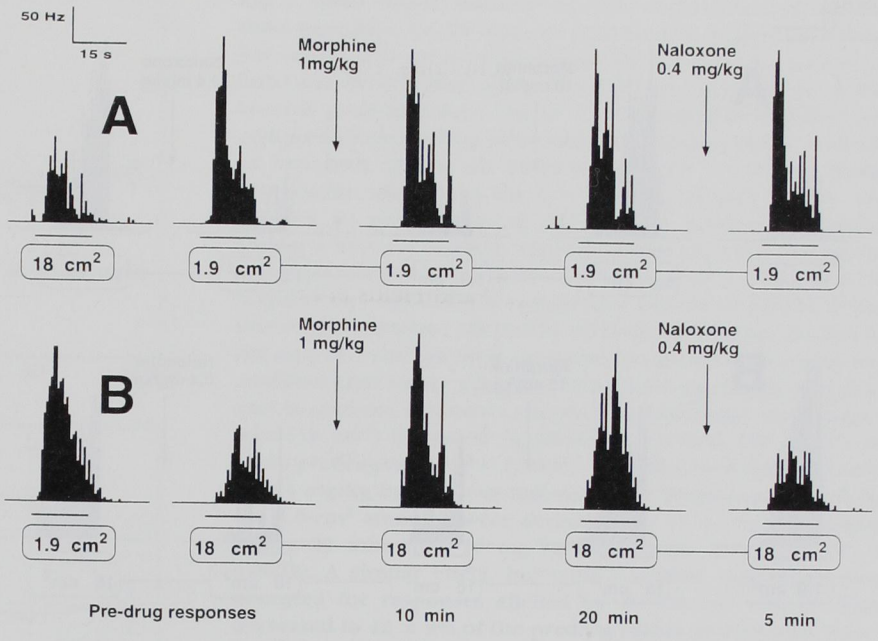

Fig. 1. Ratemeter recordings show individual examples of the effects of 1 mg/kg intravenous morphine on the noxious heat (48°C) responses of convergent neurons. Histograms represent the number of action potentials per unit of time (bin width = 500 ms). The timing of the stimulus (15 s) is indicated by the horizontal bars below the histograms. The two stimuli are presented before drug administration. Afterward, only one size of stimulated surface area is used to assess the effects of morphine. Before drug administration, neuronal responses display typically a 40–50% slower firing rate when the stimulated surface area increased from 1.9 to 18 cm^2 (see also the predrug responses in fig. 2). Such a feature is fully in keeping with previous findings regarding supraspinally mediated inhibitory controls triggered by spatial summation.[11,12] Animal A (*A*) was randomly assigned to receive the 1-mg/kg dose and the 1.9-cm^2 stimulus. The evoked response was not modified after morphine or naloxone, which was injected 25 min after morphine. In contrast, the same dose of morphine induced a large, naloxone-reversible increase in the response to the 18-cm^2 stimulus (*B*).

Data Analysis

The study was designed to evaluate the influence of the stimulated surface area and the dose of systemically administered morphine on the thermal responses of dorsal horn convergent neurons. The animals were assigned randomly to one of the three treatment groups and one of the two stimulus conditions (1.9 or 18 cm^2) in a counterbalanced design. The other stimulus was applied only once, before drug injection, to analyze differences between the 1.9- and 18-cm^2 predrug responses (fig. 1).

Neuronal responses are counted as the total number of action potentials for 15 s, beginning with the onset of the heat stimulus and corrected for background activity. Background activity is counted during the 10 s preceding each stimulation period. Neuronal responses are expressed as a percentage of mean predrug responses, which are derived from the two last stimulations preceding drug administration. All data are expressed as the mean ± SD. Analyses of variance and *post hoc* Fischer least-significant difference test were used for relevant comparisons. According to Bonferroni correction, the level of significance was set at 0.008 for multiple comparisons.

Results

Extracellular recordings made from 38 single dorsal horn convergent neurons (with 10–14 animals per treatment group) are presented. Before drug administration, the firing frequencies evoked by the 1.9-cm^2 thermal stimuli was 107 ± 28, 116 ± 27, and 107 ± 32 action potentials/s in the control group, the M1 group, and the M10 group, respectively. The corresponding responses elicited by the 18-cm^2 stimulus were 60 ± 21, 70 ± 22, and 56 ± 19 action potentials/s. Thus, the paradigm of constant intensity stimuli with different spatial properties induced a 40–50% slowing of the firing rate of dorsal horn convergent neurons in all three groups (see the predrug responses in figs. 1 and 2).

The effects of intravenous morphine were assessed after at least two consecutive stable control responses were obtained with a variation of less than 10% in the discharge rate. A transient (60–120 s) bradycardia associated with a decrease in the end-tidal carbon dioxide level was observed immediately after the injection in 6 of 14 animals in the M1 group and in all but one animal in the M10 group. Individual examples of the effects of 1 and 10 mg/kg intravenous morphine in the two stimulus conditions are presented in figures 1 and 2. Morphine given in a low dose did not change the responses elicited by the 1.9-cm^2 stimulus. In contrast, when the 18-cm^2 stimulus was applied, the same dose of morphine induced a paradoxical, naloxone-reversible acceleration of the firing rate of the recorded convergent neuron. The high dose of morphine exerted a strong depressant effect on both 1.9- and 18-cm^2 responses.

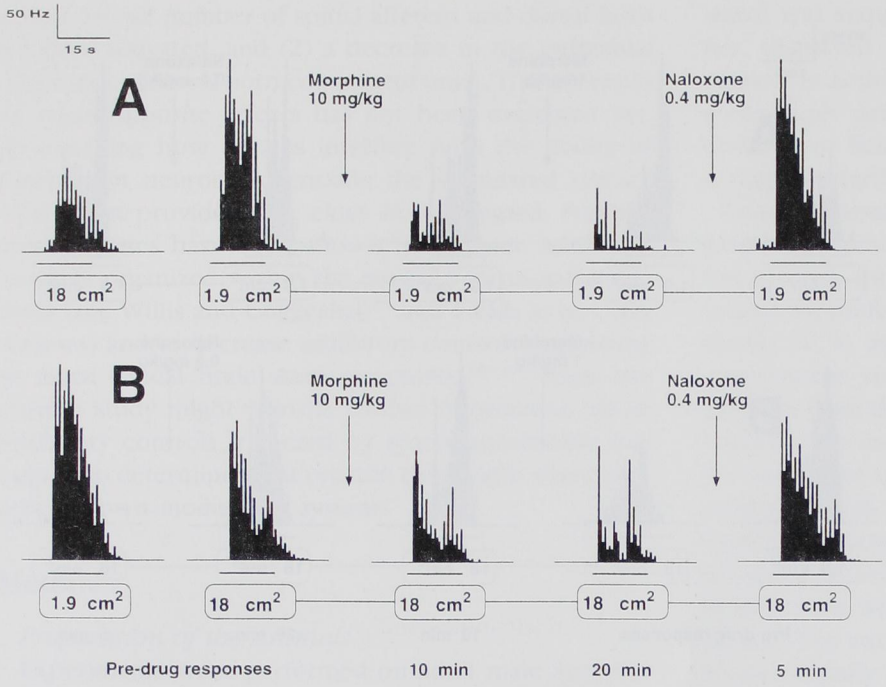

Fig. 2. Ratemeter recordings show individual examples of the effects of 10 mg/kg intravenous morphine on the noxious heat (48°C) responses of convergent neurons. The same scale and presentation are used as shown in figure 1. The 10-mg/kg dose of morphine induced a large, naloxone-reversible decrease in the responses elicited by the 1.9- (*A*) and the 18-cm² (*B*) stimuli.

Figure 3 presents the time courses of the effects observed under the six sets of conditions. At the time of the maximum effect of 1 mg/kg intravenous morphine, the neuronal responses elicited by noxious stimulation limited to the area (1.9 cm^2) of the excitatory receptive fields were not different from those observed in the control group. In contrast, responses elicited by stimulating a much larger area (18 cm^2) were significantly greater after morphine than in the control group ($P = 0.0001$). The paradoxical, naloxone-reversible facilitatory effect of the 1-mg/kg dose was observed consistently for all neurons observed. The 10-mg/kg dose induced a nearly complete suppression of the 1.9-cm^2 response and a partial suppression of the 18-cm^2 response. Twenty minutes after injection, the firing frequencies elicited by the 1.9- and the 18-cm^2 stimuli were significantly less in the M10 group than in the control group ($P < 0.0001$ for both stimulus conditions). The magnitude of the effect differed significantly between stimulus conditions ($P = 0.0066$).

Discussion

Systemic morphine in doses that are analgesic in rats had dual effects on nociceptive transmission at the level of the spinal cord, depending on the dose of the drug and the stimulated surface area. When stimuli were limited to the area of skin surrounding the excitatory receptive field, the thermal responses of the convergent neurons were not modified by 1 mg/kg intravenous morphine, although they were depressed at the higher dose (10 mg/kg). In contrast, when stimuli were applied to a much larger area, 1 mg/kg intravenous morphine produced a paradoxical facilitation of neuronal responses, whereas 10 mg/kg intravenous morphine resulted in depression of the responses, albeit less than that observed with the smaller stimuli.

Thermal stimuli applied on large surface areas of the body have been shown to trigger potent inhibitory mechanisms acting on the firing rate of dorsal horn convergent neurons. Such inhibitory mechanisms are supraspinally mediated, as evidenced from electrophysiologic recordings in spinal- and brain stem–transected rats.[11,12] In the current study, a low dose (1 mg/kg) of intravenous morphine, which had no effect on the thermal responses elicited by the 1.9-cm^2 stimulus, paradoxically enhanced the thermal responses of convergent neurons when the nociceptive stimulus covered a large surface area. Although it has been suggested that μ receptors may mediate direct facilitatory effects *in vitro*,[26–28] little evidence exists that opiates may exert receptor-mediated excitatory actions *in vivo*. At the spinal cord level, morphine has been shown to produce a naloxone-reversible excitation of Renshaw cells[29] and of

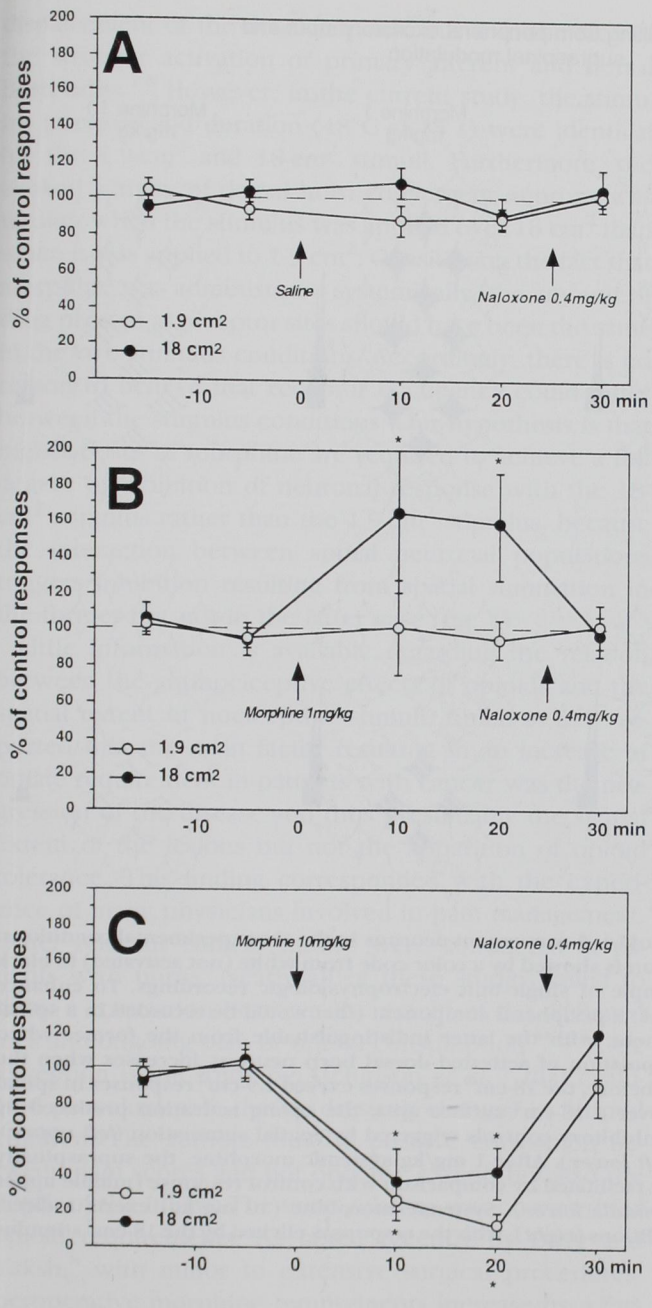

Fig. 3. Mean curves illustrate the differential effects of intravenous morphine on the noxious heat-evoked responses of lumbar convergent neurons for stimulated areas of 1.9 (open symbols) and 18 cm^2 (filled symbols). Ordinate = percentages of the control predrug values (mean ± SD). *Significant difference compared with predrug values (repeated-measurement analysis of variance). (*A*) In the control group (n = 10), the firing frequencies elicited by the 1.9- and the 18-cm^2 stimuli, expressed as percentages of the control predrug responses (mean ± SD), did not vary significantly at any time during the experiments after either saline or naloxone (P = 0.84 and 0.78, respectively). (*B*) In the M1 group (n = 14), the responses of the convergent neurons, elicited by noxious stimulation limited to the area (1.9 cm^2) of their excitatory receptive fields, were not modified after either 1 mg/kg intravenous morphine or naloxone. In contrast, responses elicited by stimulating a much larger area (18 cm^2) increased significantly to reach 159 ± 13% of mean predrug values (P = 0.0006). This effect was fully reversed by 0.4 mg/kg intravenous naloxone. (*C*) Responses elicited by the 1.9-cm^2 stimulus were decreased to 11 ± 1% of predrug values 20 min after 10 mg/kg intravenous morphine (P < 0.0001). A similar effect, but with a smaller magnitude, was observed for responses elicited by the 18-cm^2 stimuli: This decreased to 42 ± 9% of the predrug values 20 min after injection (P < 0.0001). In both cases, the responses returned to the predrug values after naloxone.

some nociceptive specific neurons.[30–32] Such effects also have been reported after spinal application.[33] However, there is strong evidence that in the latter case, the main mechanism is an inhibition of dorsal horn inhibitory interneurons by opioids rather than a direct excitatory effect.[34] Therefore, the possibility that we are dealing with indirect, supraspinally mediated opioid effects must be considered. Such a hypothesis is in keeping with a large body of evidence that indicates that systemic opioids in low doses exert their effects largely by a supraspinal route (see Yaksh[1] and Reisine and Pasternak[35] for reviews). This proposal is also supported by the findings of electrophysiologic studies that compared the effects of systemic opiate injections in intact and spinal preparations.[18,21,36,37]

Therefore, we propose that an opioid-mediated removal of the inhibitory influences triggered by spatial summation account for the paradoxical facilitation observed after the 1-mg/kg dose (fig. 4). The current results thus may confirm and extend previous findings that indicate that some supraspinally mediated inhibitory influences are lifted by morphine administered in low systemic doses or intracerebroventricularly in the rat and in humans.[17–22,38] Such findings do not exclude the possibility that other modulating systems organized within more rostral brain stem structures, namely the system formed by the periaqueductal gray and the rostral ventromedial medulla, are reinforced by opiate administration (for reviews, see Willis and Coggeshall,[14] Fields *et al.*,[15] and Fields and Basbaum[39]).

The functional significance of such a phenomenon remains to be determined. As far as we know, systemic doses of morphine in the 1-mg/kg range have never been reported to induce behavioral indices of hyperalgesia in rats. In contrast, these doses have produced antinocicep-

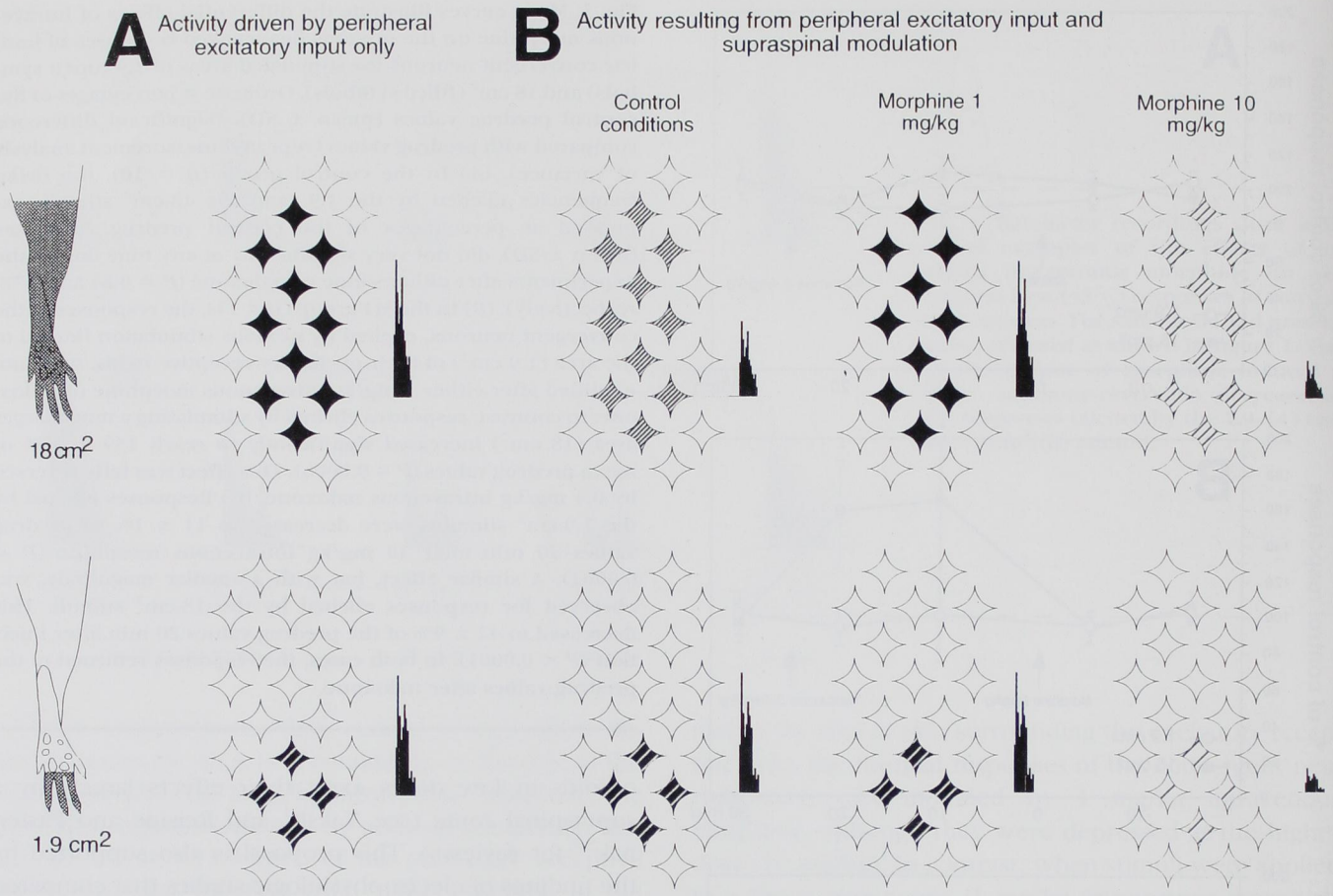

Fig. 4. Representation of the hypothetized behavior of a population of L4–5 convergent neurons in the six experimental conditions. Individual neurons are depicted as diamonds. Their level of activation is showed by a color code from white (not activated) to black (strongly activated). Assumptions are made from a coherent sample of single-unit electrophysiologic recordings. To enhance understanding, the activation of cells was divided artificially into (*A*) a peripheral component (that would be recorded in a spinal preparation, for example) and (*B*) a central modulatory component, with the latter indistinguishable from the former when experiments are performed in intact animals. (*A*) The overall population of activated dorsal horn neurons increases when the stimulus is applied over 18 rather than 1.9 cm^2. However, as shown before, the 18-cm^2 responses exceed 1.9-cm^2 responses in spinal rats.[11] (*B*) In control conditions, when the stimulus is applied over a 18-cm^2 surface area, the strong activation produced by peripheral inputs is counterbalanced by supraspinally mediated inhibitory controls triggered by spatial summation (*left upper*). Such a phenomenon does not occur with the 1.9-cm^2 stimulus (*left lower*). After 1 mg/kg systemic morphine, the supraspinally mediated inhibitory influences are lifted: The 18-cm^2 responses are facilitated by comparison with control response (middle upper panel), and the responses elicited by 1.9 cm^2 are unchanged (*middle lower*). Systemic morphine (10 mg/kg) exerts a direct depressant effect on nociceptive transmission in both stimulus conditions (*right*), with the responses elicited by the 18-cm^2 stimulus again exceeding those elicited by the 1.9-cm^2 stimulus.

tion in models involving prolonged tissue injury, such as experimental arthritis,[40,41] intraperitoneal injections of algogenic agents,[42–44] or intraplantar injection of formalin.[43–45] Morphine in low systemic doses also has been reported to depress strongly the vocalization elicited by electric stimuli at intensities that are supramaximal for the activation of C fibers.[46]

The second finding of the current study was that the effects of a large systemic dose of morphine were reduced when the stimulus was applied over 18 cm^2 rather than 1.9 cm^2 of skin. Such a result is difficult to explain based on accepted pharmacodynamic concepts. Indeed, although many studies using electrophysiologic[3,5,6] and behavioral approaches[7,8] support the existence of a strong relation between the strength of the stimulus and the magnitude of the antinociceptive effects of opiates, little is known about the influence of other stimulus parameters. When stimulus intensity increases, higher doses of morphine are required to achieve a given degree of agonist effect. It is assumed to reflect a rightward

displacement of the dose–response curve in the face of the stronger activation of primary afferent and dorsal horn units.[1,8] However, in the current study, the stimulus intensity and duration (48°C at 15 s) were identical for the 1.9-cm^2 and 18-cm^2 stimuli. Furthermore, the evoked activity of dorsal horn convergent neurons was weaker when the stimulus was applied over 18 cm^2 than when it was applied to 1.9 cm^2. Considering the fact that morphine was administered systemically, the amount of drug present at receptor sites should have been the same in the two stimulus conditions. Accordingly, there is no reason to believe that receptor occupancy could differ between the stimulus conditions. Our hypothesis is that higher doses of morphine are required to achieve a full degree of inhibition of neuronal response with the 18-cm^2 stimulus rather than the 1.9-cm^2 stimulus, because the interaction between spinal neuronal populations triggers inhibition resulting from spatial summation in the former but not in the latter case (fig. 4).

Little information is available regarding the relation between the antinociceptive effects of opioids and the spatial extent of nociceptive stimuli. Collin *et al.*[47] reported that the main factor resulting in an increase of opiate requirement in patients with cancer was the progression of the disease and thus presumably the spatial extent of the lesions but not the apparition of opioid tolerance. This finding corresponded with the experience of many physicians involved in pain management. Other relevant clinical studies were conducted in patients with burns. Nearly all of these studies failed to show a correlation between the extent of the damaged area and ongoing pain or opioid consumption.[48–52] One exception is the study by Atchinson *et al.*[53] that evaluated provoked pain during dressing changes in burned children. The authors found a positive correlation between pain scores and not only the extent, but also the depth of the injury. The same relation was observed for opioid requirements. As noted recently by Dirig and Yaksh,[8] with minor to extensive surgical procedures, peroperative morphine requirements increase by a factor of 100, whereas sufentanil doses need to increase only by a factor of 20 to provide the same level of control over autonomic responses. Our finding of a diminished effectiveness of morphine in the face of an increase in the stimulated surface area suggests that not only stimulus intensity, but also the spatial extent of the surgical trauma, might be involved in these conditions. Such a proposal obviously requires further investigation.

In conclusion, the surface area of a noxious stimulus appears to exert a critical influence on the antinociceptive action of opiates at the level of the dorsal horn. Our results suggest that these effects depend on complex interactions between direct and indirect mechanisms, the latter involving supraspinally mediated inhibitory controls triggered by spatial summation.

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