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Narcotics Do Not Alter the Heat Response of Unmyelinated Primary Afferents in Monkeys

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Recent reports of opiate receptors in the peripheral nervous system have led to the hypothesis that the analgesic action of opiates might, in part, result from a reduction in response of peripheral nerve fibers thought to be concerned with signaling pain (nociceptive afferents). The authors examined the effects of the narcotics, fentanyl (up to 30 μg/kg, iv) and morphine (1 mg/kg, iv), on the response of single unmyelinated afferents (C-fiber nociceptors and warm fibers), recorded in monkeys, to heat stimuli applied to their receptive fields. Neither narcotic affected the response of the afferents. In addition, naloxone did not affect their response. Thus, an alteration of cutaneous nociceptor response is unlikely to contribute to the analgesic action of narcotics. (Key words: Analgesics: receptors. Anesthetics, intravenous: fentanyl, morphine. Nerve: C-fibers; nociceptors; primary afferents; unmyelinated afferents.)

THE ANALGESIC EFFECTS of narcotics are thought to be mediated by their actions on specific opiate receptors at spinal and supraspinal sites.[1–5] Opiate receptors have been shown to exist on presynaptic terminals of primary afferents in the dorsal horn[6,7] and are thought to provide presynaptic inhibition of nociceptive signals.[8,9] Recent studies indicate that opiate receptors may be present on peripheral nerve axons as well as on cutaneous primary afferent terminals.[10,11] However, the effects of opiates on cutaneous nociceptors and peripheral nerves are not entirely clear. Conflicting results on the effects of morphine on the electrically evoked compound action potential in peripheral nerves have been reported.[12–14] Several studies suggest that the effects of narcotics on the peripheral part of primary afferent neurons may contribute significantly to their antinociceptive effects.[15–18] The present studies were undertaken to determine whether the narcotic fentanyl alters the response of single unmyelinated (C-fiber) nociceptive afferents and warm fibers to heat stimuli applied to their cutaneous receptive fields.

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Methods

Neural Recording Techniques

Action potential activity from single unmyelinated nociceptive afferents was recorded from the ulnar, median, and medial antebrachial cutaneous nerves of *Macaca fascicularis* monkeys (weight 4–6 kg) using a standard teased-fiber dissection and extracellular recording technique described previously.[19,20] The appropriate nerve was dissected from contiguous connective tissue and placed in a groove next to a small dissection platform. After the epineural and perineural sheaths were opened, small nerve fascicles were cut proximally from the parent nerve. Thus, central connections of the fibers are severed in this technique and only centripetally conducted action potentials are recorded. The cut nerve fascicle was rotated onto the dissection platform and then, with the use of an operating microscope, the nerve fascicle was separated into fine strands suitable for single-unit recording. The strand was wrapped around a platinum recording electrode and single fibers for recording were identified as described in the following. Further details regarding neural recording, data storage, and analysis are shown in figure 1.

Identification of Nociceptive and Warm Fibers

We recorded from two types of unmyelinated afferent fibers: 1) C-fiber nociceptive afferents whose cutaneous receptors are sensitive to both intense mechanical and heat stimuli (CMHs); and 2) C-fiber afferents whose receptors respond to gentle warming but not to mechanical stimuli. These are commonly referred to as warm fibers.[21] The former fiber type is thought to signal pain, whereas the latter fiber type is thought to signal warmth.

Nociceptive Afferents. Nociceptive afferents were initially identified by their response to firm squeezing of the skin. The skin was then mapped with dye at spots where the receptor responded to stimulation with a 0.5-mm diameter nylon monofilament that exerted a force of 20 g. This area was considered the receptive field of the nociceptor.

Warm Fibers. Warm fibers were distinguished from nociceptive afferents by their exquisite sensitivity to gentle warming, failure to respond to mechanical stimuli, and spontaneous activity that stops with cooling of the receptive field.[21] The receptive field of warm fibers is typically

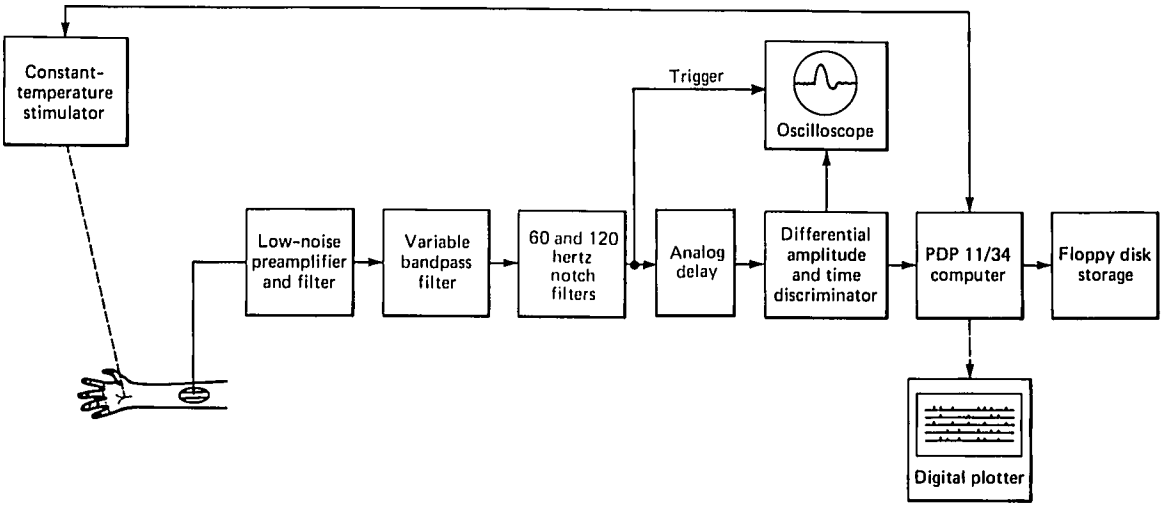

FIG. 1. Block diagram of the neurophysiologic experiment. The dissected nerve filament is looped around a 27-gauge platinum wire electrode for unipolar recording. Action potentials are amplified by a low-noise preamplifier (Princeton Applied Research Corporation) with a 20K variable gain and a passband of 3 Hz to 10 KHz. The output of the amplifier is filtered by 60 and 120 Hz notch filters to minimize "line" noise and is then filtered by a Kronhite variable passband filter to optimize the signal-to-noise ratio for a given action potential. A differential amplitude and time discriminator are used to separate the desired impulses from other fiber impulses or from background noises by providing an adjustable-voltage window and time window to screen out irrelevant signals. Each relevant action potential is monitored both visually on an oscilloscope and aurally *via* a loud speaker. An analog delay allows visualization of the complete action potential waveform (*i.e.*, not just the waveform after the trigger point of the oscilloscope) and helps in precise action potential identification. The discriminator provides a digital pulse to the computer for every neural signal that falls within both the amplitude and time windows. The PDP-11/34® computer stores the time of occurrence of these digital pulses on a floppy disk. On-line programs indicate impulse counts during designated time periods during the run, and thus facilitate decisions with regard to continuing a particular experiment. In addition, off-line programs are used to generate replicas of the nerve impulse train as well as appropriate histograms, which are plotted on a digital plotter.

punctate and is located by observing where an ice-cold probe (2-mm diameter) suppresses the spontaneous activity.

CONSTANT-TEMPERATURE STIMULATOR

A CO_2 laser under radiometer feedback control provided a noncontact, stepped increase in skin temperature to the receptive field of the primary afferents. This laser thermal stimulator was used in previous studies[19,20,22,23] and is described in detail elsewhere.[24] Heat stimuli were delivered to a 7.5-mm diameter test spot within the receptive field of the primary afferent.

EXPERIMENTAL PROTOCOL

Table 1 summarizes the experimental protocol. Monkeys were initially sedated by intramuscular injection of ketamine (10 mg/kg). Anesthesia was induced with an iv bolus of 6 mg/kg of pentobarbital and maintained with a continuous infusion of pentobarbital (4–6 $mg \cdot kg^{-1} \cdot h^{-1}$). After tracheal intubation, the monkeys were artificially ventilated. Continuous CO_2 monitoring was used, and ventilation was adjusted to maintain end-

TABLE 1. Summary of Experimental Protocol

Animal	Macaque monkeys
Nerves	Ulnar, median, and medial antebrachial cutaneous
Preparation	Pentobarbital-anesthetized animal Brain-dead, unanesthetized
Types of afferents	Unmyelinated nociceptive afferents (CMHs, n = 16) Warm fibers (n = 4)
Skin Type	Hairy or glabrous
Drugs and doses	Fentanyl: 5–30 μg/kg iv Morphine: 1 mg/kg iv Halothane: 2% inspired concentration
Stimulus parameters (Repeat presentation of heat stimulus)	CMHs: 46–48° C, 1-s (for hairy skin) or 3-s (for glabrous skin) duration at 30- or 60-s intervals Warm fibers: 39–43° C, 3 s at 30- or 60-s intervals
Time course of drug administration	Stable baseline response, at least 5 min iv bolus fentanyl (5 μg or 10 μg/kg) or single bolus of morphine (1 mg/kg) Further fentanyl iv (5–10 μg/kg) at 5-min intervals 5–10 min after last narcotic dose, 0.8 mg naloxone administered iv in 10/16 CMHs In some (n = 6) units, 2% halothane (inspired concentration) was administered for 10 min

tidal P_{CO_2} at 32–40 mmHg. The electrocardiogram, heart rate, and blood pressure were continuously monitored to ensure that adequate anesthesia was maintained throughout the experiments. Blood pressure was recorded *via* a catheter in the femoral artery. There was an interval of at least 4 h between the administration of ketamine and the first neurophysiologic recording.

Dextrose (5%) in normal saline was infused intravenously throughout the experiment to maintain hydration. The animals were paralyzed with pancuronium bromide to facilitate respiratory control. Core temperature, measured *via* a rectal probe, was maintained near 38° C with the use of circulating water heating pads.

In addition to the studies in the anesthetized preparation, the effects of fentanyl on CMHs were also determined in unanesthetized monkeys rendered brain-dead. This was done to exclude confounding interactive effects of pentobarbital and the narcotic. Brain death was achieved under halothane anesthesia by ligating both common carotid arteries in the neck and by transection of the brain at the midcollicular level.

To determine the effects of fentanyl, we recorded responses to repeated suprathreshold heat stimuli (39–43° C for warm fibers and 46–48° C for CMHs) before, during, and after the administration of intravenous doses of fentanyl (cumulative dose of 15–30 μg/kg). Stimulus duration was 1 s (hairy skin) or 3 s (glabrous skin), and stimuli were repeated at 30- or 60-s intervals. After a stable baseline response to the repeated heat stimulus was observed for at least 5 min in a given fiber, a 5 or 10 μg/kg iv bolus of fentanyl was administered. Additional doses of fentanyl (5–10 μg/kg) were administered at 5-min intervals. In some fibers, naloxone (0.8 mg, iv) was given 5–10 min after the highest dose of fentanyl to reverse the effect of fentanyl. In some of the CMHs, at varying intervals after naloxone administration (6–20 min), 2% inspired halothane was delivered for 10 min. This was done to confirm that the CMHs, which did not change in response after the fentanyl administration, could increase in response after halothane administration, as was observed in our earlier study.[25] At the end of the experiment, conduction velocity was estimated from measurements of the latency of response to suprathreshold electrical stimuli applied to the receptive field with intradermal electrodes and from measurements of conduction distance. In some studies, morphine sulphate (1 mg/kg, iv) was given in place of fentanyl.

In each of six CMHs (three in hairy skin and three in glabrous skin), the effects of three different cumulative doses of fentanyl (5, 10, and 20 μg/kg) were studied. The responses before and after the different fentanyl doses were analyzed with a two-way analysis of variance, between–within/split-plot design.[26]

The responses of the CMHs before and after morphine or halothane administration were analyzed by a paired *t* test, with $P < 0.05$ considered significant.

Results

We recorded from 11 CMHs in pentobarbital-anesthetized monkeys and five CMHs in decerebrated, unanesthetized monkeys. In the pentobarbital-anesthetized monkeys, five of the CMHs had receptive fields on the glabrous skin of the hand and six CMHs had receptive fields on the hairy skin of the forearm. Unmyelinated nociceptors with receptive fields located in hairy and glabrous skin were both studied because they differ significantly with regard to their propensity to sensitive to noxious heat stimuli.[20] Results from two typical fibers, one that innervated the hairy skin of the forearm and another that innervated the glabrous skin of the hand, are shown in figure 2. The receptive field of the first CMH (fig. 2*A*) was exposed to a 1-s, 46° C stimulus delivered every 60 s. The receptive field of the second CMH (fig. 2*B*) was exposed to a 3-s, 47° C stimulus delivered every 60 s. The response was greater in the first trial compared with subsequent trials, and a stable baseline response was usually observed within 5–8 trials. This temporal suppression of response to repeated heat stimuli has been reported previously for CMHs.[22,27] After a stable baseline response to the stimulus was achieved, doses of fentanyl were administered at 5-min intervals. The total cumulative dose administered was 20 μg/kg and 30 μg/kg, respectively, in the first and second fiber. There was no change in the response of the CMH to repeated heat stimuli, although a pronounced effect on blood pressure was usually observed (fig. 2*B*). In addition, naloxone hydrochloride (0.8 mg, iv) given after the fentanyl did not alter the response of the CMH, whereas the expected reversal of the blood pressure depression did occur. In contrast, the response of the CMH (fig. 2*B*) increased markedly (sensitization) after the administration of halothane (2% inspired concentration) for 10 min, which is consistent with our previously reported results.[25]

The total response to heat on a CMH during each 5-min drug manipulation was normalized by dividing by the control response of that CMH during the 5 min before the first drug administration. The mean normalized response of the 11 CMHs, studied under pentobarbital anesthesia at the 5, 10, 20, and 30 μg/kg doses of fentanyl, was 93 ± 3%, 96 ± 2%, 99 ± 4% and 100 ± 5% (mean ± SEM) of control, respectively. The mean response after the administration of naloxone hydrochloride (0.8 mg iv) was 100 ± 4% of control. Analysis of the effects of fentanyl on the response of the six CMHs in which three different doses of fentanyl were studied (5, 10, and 20 μg/kg), showed no statistically significant effects at the different doses ($P > 0.05$; F = 0.96; DF (fentanyl doses) = 3; DF

(no. of fibers) = 12). Fentanyl had no significant effects on CMHs with receptive fields located in either hairy or glabrous skin ($P > 0.05$; F = 0.003; DF (skin type) = 1; DF (no. fibers) = 4).

We recorded from five CMHs in decerebrated unanesthetized monkeys. Fentanyl, in dosages ranging from 20 to 50 μg/kg, also did not affect the heat responses of these CMHs recorded in brain-dead, unanesthetized monkeys. The mean response was 95 ± 2% of control at the maximum doses of fentanyl (*t* test for paired samples, $P > 0.05$). Thus, the failure of fentanyl to affect significantly the response of nociceptors was not due to a confounding interactive effect of pentobarbital in the anesthetized preparations.

In six of the 16 CMHs (four in pentobarbital-anesthetized and two in decerebrate monkeys), 2% halothane was administered for 10 min following the administration of naloxone. The response of the CMHs during the last 5 min of halothane administration was significantly increased to 146 ± 12% of control (*t* test for paired samples, $P < 0.02$).

The effects of fentanyl, at the 5–30 μg/kg iv doses, on the mean normalized response of CMHs recorded in pentobarbital-anesthetized monkeys (n = 11) were compared with CMHs recorded in decerebrated, unanesthetized monkeys (n = 5). Because the two groups were not significantly different ($P > 0.4$, *t* test for unpaired samples), the data were pooled into one group. The mean normalized response of all CMHs studied after 5, 10, 20, and 30 μg/kg of fentanyl, after naloxone administration, and after halothane administration is expressed as a per cent of control in figure 3. The only significant change was the increased response after halothane administration.

To determine if fentanyl altered action potential generation and conduction time, a comparison was made of the time interval from the onset of the heat stimulus to the recording of the first action potential (latency of response) before and after the administration of fentanyl. The latency of response is the sum of the transduction time at the cutaneous receptor (*i.e.*, time for initiation of an action potential following the onset of heat stimulus) and the conduction time from the receptor to the recording site. For each CMH, the latency of response after the maximal iv dose of fentanyl (15–50 μg/kg) was calculated as a per cent of the latency of response prior to the administration of fentanyl. The latency of response after fentanyl administration was 115 ± 9% (mean ± SEM) of control (*t* test for paired samples, $P > 0.3$). Thus, it is unlikely that fentanyl has any major effect on the transduction mechanism or the conduction of impulses in C-fiber nociceptors. In addition, after the administration of fentanyl, we did not observe any change in the configuration of the extracellularly recorded action potential.

The normalized mean response of the four warm fibers following the administration of fentanyl (10–50 μg/kg, iv) was 100 ± 2% (mean ± SEM) of control, indicating that the narcotic had no significant effect on the response to heat of warm fibers as well (*t* test for paired samples, $P > 0.8$).

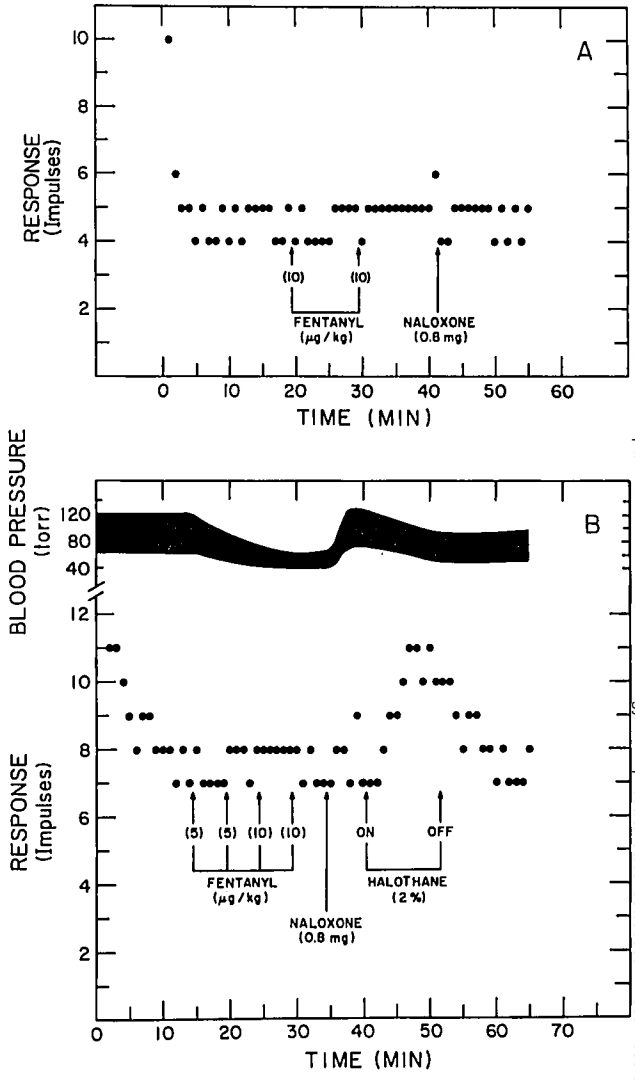

FIG. 2. Effects of fentanyl on the response to heat of CMHs. *A*. The cutaneous receptive field of this CMH located in hairy skin of the forearm was exposed to a 1-s, 46° C stimulus delivered every 60 s. When a stable baseline was observed, fentanyl (10 μg/kg iv) was administered twice at 5-min intervals. No change in response of the CMH was observed. Naloxone (0.8 mg iv) also failed to alter the response of the CMH to heat stimuli. *B*. The cutaneous receptive field of this CMH located in glabrous skin of the hand was exposed to a 3-s, 47° C stimulus delivered every 60 s. Fentanyl (iv) was administered at 5-min intervals to a cumulative dose of 30 μg/kg. No change in response of the CMH was observed, although a pronounced decrease in blood pressure occurred. Naloxone (0.8 mg iv) given after the fentanyl did not alter the response of the CMH significantly, whereas the blood pressure returned to normal. In contrast, the CMH was markedly sensitized after the administration of halothane.

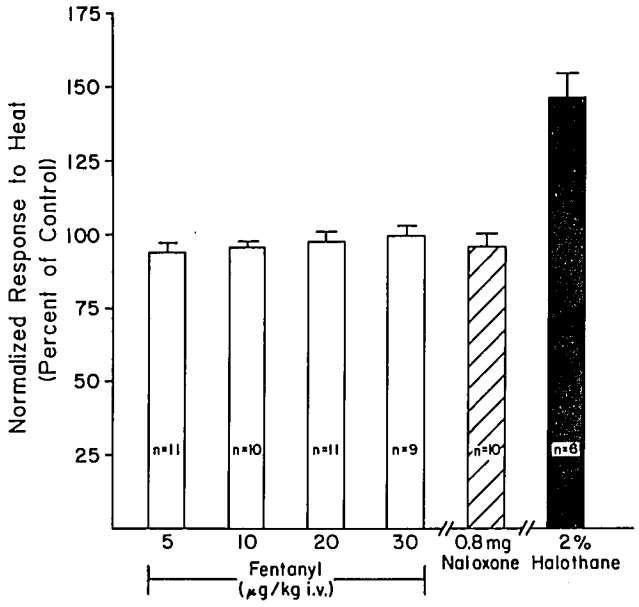

FIG. 3. Effects of fentanyl, naloxone, and halothane on the heat response of CMHs. The total response to heat of a CMH during the 5 min following a drug manipulation was normalized by dividing by the control response of the CMH during the 5 min before the first dose of fentanyl was administered. The mean normalized response of the CMHs did not change for cumulative doses of fentanyl up to 30 μg/kg. Naloxone, administered 5–20 min after the last dose of fentanyl, also did not change the response, whereas the blood pressure depression was reversed as expected. In contrast, the responses of the CMHs were significantly increased ($P < 0.02$) after halothane administration.

In five additional CMHs, the effects of morphine sulfate (1 mg/kg) were studied on the response to repeated heat stimuli. The mean normalized response after morphine administration (94 ± 5% of control, mean ± SEM) was not significantly different from control (*t* test for paired samples, $P > 0.2$).

Discussion

Recent anatomic, biochemical, and behavioral studies have reported evidence for the presence of opiate receptors in the peripheral nervous system. Light microscopic, autoradiographic studies have demonstrated that opiate receptors are associated with rat vagus nerve fibers and with other small-diameter nerve fibers.[28–30] Opiate receptors have been shown to be transported peripherally in axons of the rat vagus nerve.[31,32] It is not clear whether these receptors are localized on afferent or efferent fibers. Biochemical investigations have indicated the presence of presynaptic opiate receptors on primary afferent terminals in the dorsal horn.[6,7] In a behavioral study in mice, morphine was found to have a potent antinociceptive effect when injected intraperitoneally.[15] The maximum effect of morphine was seen within 1–2 min following injection of the drug in doses far too low to be effective when given by subcutaneous or intravenous injection. Based on these observations, the authors suggested that the narcotic may be interacting with one or more types of opioid receptors situated on sensory nerve endings in the peritoneum. These observations raise the possibility that part of the analgesic effects of narcotics could be secondary to an effect on cutaneous nociceptors or the peripheral nerve.

Several investigators have studied the effects of narcotics on impulse transmission in peripheral nerves elicited by electrical stimulation. The results of these studies have been conflicting. Kosterlitz and Wallis[12] performed experiments on nerves *in situ* and observed that systemic morphine (up to 3 mg/kg iv) did not alter the compound action potentials of myelinated or unmyelinated nerve fibers. In contrast, Jurna and Grossman,[13] studying the effects of morphine (2 mg/kg iv or intraarterial) on the sural nerve *in situ*, reported that the narcotic had a differential effect on the electrically induced compound action potential. Morphine increased the height of the A-beta fiber wave in the compound action potential, but reduced the height of A-delta and C-fiber waves.

Yuge *et al.*[14] found that morphine (0.1 mg/kg) and fentanyl (25 μg/kg) applied directly on the peripheral nerves produced no significant change in the A-beta, A-delta, or C-components of the compound action potential. Kosterlitz and Wallis[12] and Yuge *et al.*[14] observed no effect of morphine on the conduction velocity or the excitability of peripheral nerve fibers. Compound action potentials provide an estimate of nerve function, but fail to reveal information regarding receptor function, because the electrical stimulation used to elicit the compound action potentials bypasses the receptor.

The most precise means of identifying effects on primary afferent function is to record from single nerve fibers, as was done in this study. This model allows one to study the effects of drugs on cutaneous receptor mechanisms and on conduction along nerve fibers. Any effect on presynaptic mechanisms at the level of the spinal cord, however, cannot be studied. Because narcotics did not alter the receptor transduction mechanism or action potential conduction significantly, the effects on the compound action potential reported by Jurna and Grossman[13] are not due to either a block of cutaneous C-fiber afferents or an alteration of the cutaneous receptor response. Small changes in the conduction velocity of the unmyelinated fibers, however, cannot be excluded by our study. Perhaps a small dispersion of conduction velocity does occur, resulting in a decrease in height of the C-fiber wave in the compound action potential.

The disparity between the observations in the behavioral study by Bentley *et al.*[15] and this study possibly could be explained by differences in the type of noxious stimulus (chemical *vs.* heat) used and the type of receptors studied (intraperitoneal *vs.* cutaneous). Thus, an effect of narcotics on other types of afferents cannot be excluded at present.

This study was of particular interest in light of our recent finding that the general anesthetic halothane enhances the response of cutaneous nociceptors to heat stimuli in a reversible, dose-dependent manner.[25] More recently, we observed that other anesthetics, including nitrous oxide and isoflurane, also alter the responses of CMHs (unpublished observation). At present, the mechanism by which general anesthetics augment the responsiveness of nociceptors is unclear. Studies are in progress to gain further insight into the effects of anesthetics on primary afferents in the hope that it may provide clues to the mechanisms by which anesthetics affect the nervous system.

Studies on the physiology of nociceptor function have been performed in animals anesthetized with different general anesthetics. The interpretation of the results from these studies may be misleading, because the anesthetics themselves may have had an effect on nociceptor function. Because, in the present study, fentanyl had no effect on nociceptive primary afferent function, narcotics may be ideal anesthetic agents for studies of the physiology of the peripheral nervous system in experimental animals.

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