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Differential effects of morphine on pain and temperature perception in human volunteers

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Electrophysiological and behavioral evidence suggests that morphine may have a differential effect on nociceptive and thermal pathways. In this study, we explored the perceptual consequences of these differential actions by examining the effect of a low morphine dose (0.08 mg/kg) on pain and temperature sensations arising from cutaneous thermal stimuli. In a double-blind placebo-controled study, we compared the perceived temperature intensity and perceived pain intensity and unpleasantness of noxious and innocuous heat and cold applied to the face of human subjects, with and without low doses of systemic morphine. The results showed that morphine modified pain-related sensations. In contrast, perceived thermal intensity of both noxious and innocuous heat or cold stimuli was unchanged by low-dose morphine administration. These findings suggest that low doses of morphine have a differential effect on pain and temperature sensations arising from the same stimulus, and thus that these sensations could be subserved by different neuronal populations.

KEYWORDS: morphine, psychophysics, pain, noxious heat, noxious cold, temperature.

INTRODUCTION

Although there is a close anatomical and physiological association in the nervous system between nociceptive and thermal pathways, there is accumulating evidence that morphine exerts a differential effect on these modalities. For example, Craig and Hunsley (1991) showed that systemically-administrated morphine enhances responses of dorsal horn spinothalamic cool-sensitive neurons in cats, which is the opposite effect normally observed for nociceptive neurons (Kitahata *et al.*, 1974; Dickenson & Sullivan, 1986). Further, the local application of morphine to the medullary dorsal horn of monkeys leads to a diminution in the monkey's ability to discriminate noxious cutaneous heat, but not innocuous cool stimuli (Oliveras *et al.*, 1986a,b). Similarly, Schwartz *et al.* (1978) found that systematic morphine disrupts monkeys' ability to detect skin warming but not skin cooling. In humans, cold detection thresholds are not altered by low doses of morphine that alter thresholds for heat detection (Brennum *et al.*, 1993, 1994). This lack of an inhibitory morphine effect on the detection and perception of innocuous cool contrasts sharply

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with the effect of morphine on the painfulness of *noxious* cold. Using the cold pressor model in humans, several investigator have found that morphine increases tolerance to noxious cold (Bromage *et al.*, 1980; Jones *et al.*, 1988).

In addition to the evidence that morphine does not have an inhibitory effect on innocuous cool transmission, other data indicate that innocuous cooling in itself has an inhibitory effect on nociceptive transmission. The application of cold has been reported to reduce pain evoked by electrical stimulation of a peripheral nerve (Bini *et al.*, 1984). Further, a pressure block of peripheral nerve A-fiber conduction, which eliminates the sensation of cool, produces an increase in the threshold for cold pain from about 15 to 24 °C and causes a burning pain sensation to stimuli normally perceived as cool (Wahren *et al.*, 1989; Yarnitsky & Ochoa, 1990). Craig and Hunsley (1991) hypothesized that the dorsal horn lamina I spinothalamic tract cool-sensitive neurons, whose activity is sometimes enhanced by morphine, serve two functions. First, they are sensory transmission neurons underlying the perception of cool, and second their activity serves to modulate pain perception. According to this hypothesis, morphine should have a differential effect on cool perception than on heat pain or cold pain perception. Cool-sensitive neurons continue to discharge into the noxious cold range, and psychophysical evidence suggests that the perception of 'coldness' in the noxious cold range may be subserved by cool-sensitive neurons (Chen *et al.*, 1996).

The current study tests the hypothesis that low-dose morphine has a selective inhibitory effect on the painfulness of thermal stimuli and that temperature perception, even in the noxious range, may be spared by morphine. A preliminary report of these data has been published in abstract form (Morin *et al.*, 1996).

MATERIALS AND METHODS

Subjects

Twenty-one healthy paid volunteers, (10 female and 11 male) aged 18 to 47 years (mean=27) were recruited using announcements placed across the university campus. During a preliminary information session, the general goals of the experiment were explained, subjects practiced rating different stimuli using visual analog scales (VAS) and completed a medical questionnaire. Exclusion criteria included alcohol or drug abuse, chronic disease, psychiatric problems, pregnancy (recent, present or imminent), hypertension, asthma or head injury. In addition, a registered nurse verified that subjects were in good health and had no medical problems contra-indicating morphine administration. Subjects were informed that they would be exposed to innocuous and noxious thermal stimuli, that they would receive either a low dose of morphine or an inactive solution (placebo), and that they could withdraw from the experiment at any time without prejudice. A consent form, approved by the hospital human ethics committee, was signed by all subjects.

Stimuli and rating scales

Throughout the experiment, subjects were asked to evaluate noxious and innocuous thermal, as well as visual stimuli. Cooling (25, 15 and 0°C) or heating (40, 45 and 49°C) stimuli were delivered using a feedback-controled 1-cm-diameter contact Peltier thermode placed on the skin above the upper lip. The baseline temperature was 32°C. The slope of all temperature changes was constant at 5°C/s and stimuli were held at the peak temperature for 5 s. Five-second visual stimuli (5, 40 and 265 Lux) were presented via a 3-cm-diameter opaque white light positioned 100-cm in front of the eyes. Thermal and light stimuli were controled by computer.

After each thermal or visual stimulus subjects rated the stimulus intensity, and after thermal stimuli they also rated pain intensity and pain unpleasantness on separate VAS's depicted in Figure 1(A). Subjects were given instructions similar to those used by Rainville *et al.* (1992) for differentiating pain intensity and unpleasantness. Although subjects were asked to rate the sensations on the 100-mm scales, they were allowed to put a mark beyond the right anchor of each

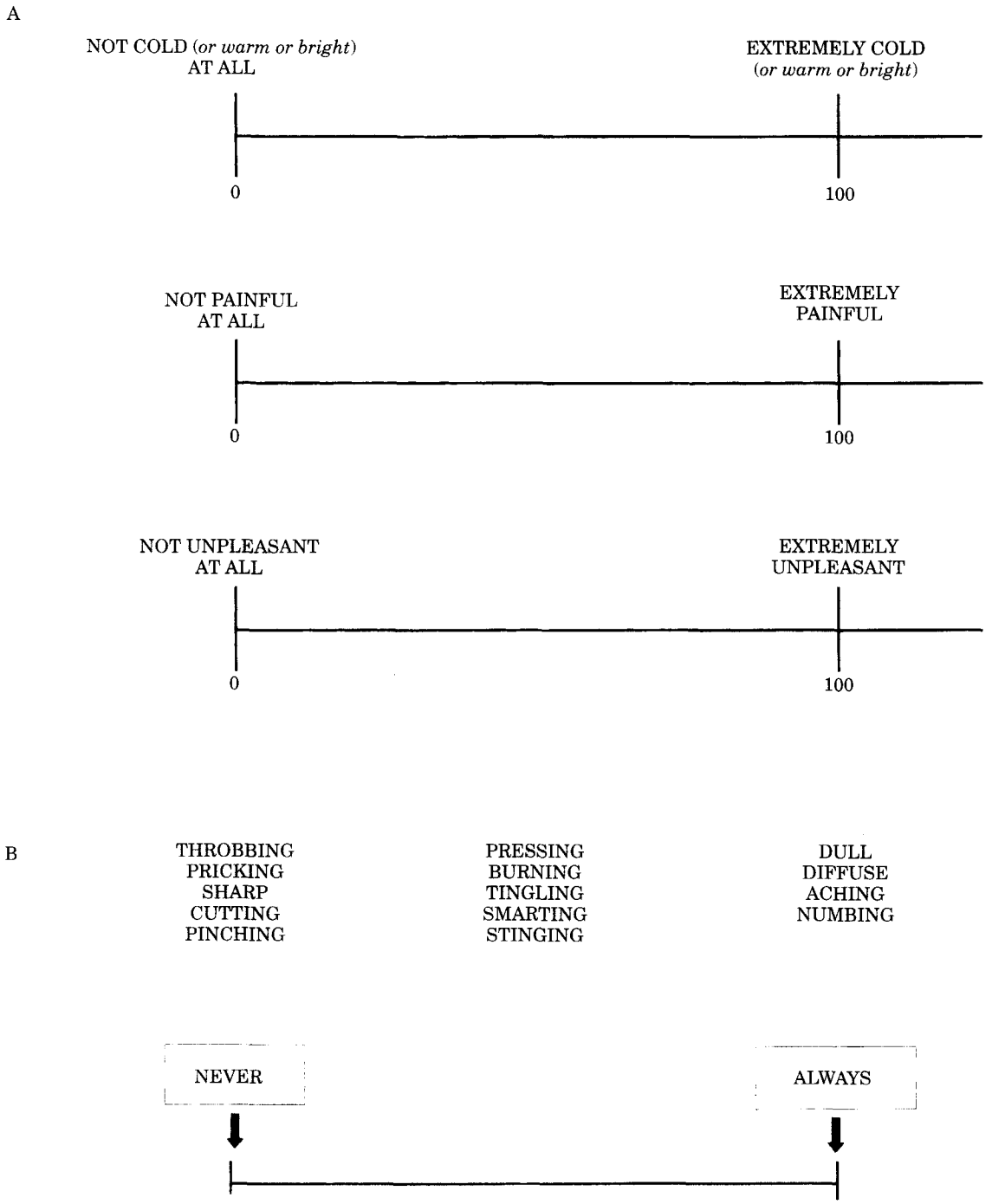

FIG. 1. Visual analogue scales for stimulus intensity, pain intensity, and pain unpleasantness (A). Verbal descriptors extracted from the McGill Pain Questionnaire describing the sensory quality of pain.

scale, in order to avoid ceiling effects observed in VAS ratings (Rainville *et al.*, 1992). Subjects were also asked to rate each sensation on VASs for a variety of verbal descriptors of pain sensation (Melzack, 1975; Morin & Bushnell, 1998), with anchors of 'never' and 'always' [Fig. 1(B)]. Finally, subjects rated the intensity of opiate side-effects on 100-mm VASs for nausea ('none'

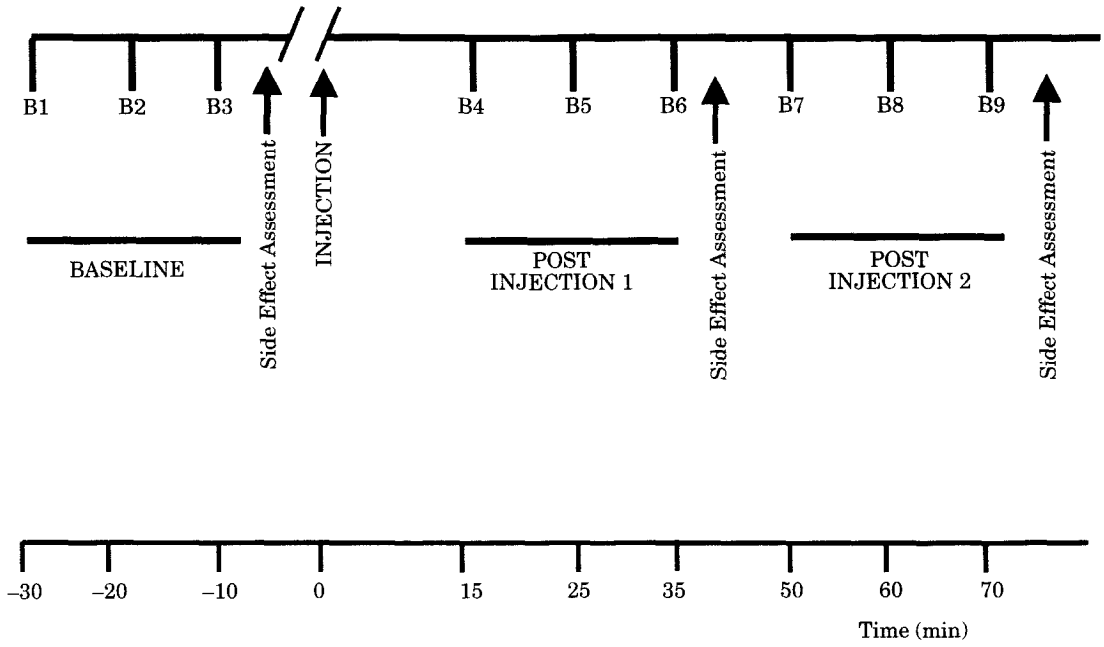

FIG. 2. Experimental procedure. During one block (B) subjects rated stimulus intensity, pain intensity and pain unpleasantness of 5-s pulses of three levels of cooling (25, 15, 0°C) or warming (40, 45, 47°C) stimuli, stimulus intensity of three levels of light intensities (5, 40, 265 Lux) and used verbal descriptors to characterize sensations produced by single cold (22 or 6°C) or hot (40 or 47°C) stimuli.

and 'constant'), alertness ('can't keep my eyes open' and 'wide awake'), itching ('no itch at all' and 'itch as bad as it could possibly be') and mood ('worst I've ever felt' and 'best I've ever felt') (Coda *et al.*, 1993).

Morphine/saline administration and subject monitoring

The experiments were performed in a quiet light-controlled room with resuscitation equipment and the opiate antagonist naloxone (Narcan) available. An intravenous catheter was inserted into the anticubical fossa by the registered nurse at the beginning of the experiment. Blood pressure, oxygen saturation and heart rate were then continuously monitored with a pulse oximeter (Accusat). Under a physician's supervision, the nurse injected a 10-ml volume of either morphine sulfate (0.08 mg/kg) dissolved in NaCl (0.9%) or the placebo (saline vehicle) during 2.5 min. The solution was prepared and encoded by the hospital pharmacist, and neither the experimenter, nurse, physician nor subject knew what was being injected. At the end of the experiment, subjects were allowed to leave the hospital only after the return of normal functioning, were required to be accompanied by an adult, and were instructed not to drive or use dangerous machinery for the remainder of the day.

EXPERIMENTAL PROCEDURE

Subjects were randomly assigned to the morphine or vehicle control group. Each subject participated in two sessions separated by 1 week, with heat stimuli presented in one and cold stimuli in the other. Session order was counterbalanced across subjects, and each subject received the same drug treatment at both sessions. Thermal and visual stimuli were presented during 10-min blocks, with three blocks presented before the injection and six blocks presented after, as shown in Figure 2. Each block consisted of one presentation of three levels of cold or hot stimuli and one presentation of three levels of visual stimuli (Fig. 2). A 5-s stimulus was presented every 30 s, followed by the subjects'

completion of the VASs for stimulus intensity, pain intensity and pain unpleasantness. At the end of each block, a single hot (47 or 40°C) or cold (22 or 6°C) stimulus was presented, and subjects completed the VASs for stimulus quality. Ratings of side-effects were reported immediately before and 45 and 75 min after the injection (Fig. 2).

Data analysis

For each subject, ratings were averaged across three series of stimulus presentations: Baseline (three control ratings), Post-Injection 1 (15, 25 and 35 min post-injection) and Post-Injection 2 (50, 60 and 70 min post-injection). Analysis of covariance (ANCOVA) for repeated measures was performed on the averaged data to describe the effect of injection (placebo *vs* morphine) on post-stimulus injection ratings (Post-Injection 1 and Post-Injection 2). The baseline condition was the covariate, in order to account for individual differences in ratings. Between-subject contrasts were performed for post-injection responses, and homogeneity of slopes was tested between morphine and placebo groups. Light intensity ratings, verbal descriptor ratings (summed across the 14 words) and side-effect ratings were also analysed using ANCOVA. Significance was accepted as $p<0.05$.

RESULTS

Eleven subjects received morphine and 10 received saline. One subject developed a cutaneous rash after the injection in the first session, and an allergic reaction was suspected. At the end of the session, the pharmacist confirmed that morphine was injected; the subject was referred to an allergist and excluded from the second session.

Pain ratings

Temperatures of 49 and 0°C were consistently rated as painful, whereas 15, 25, 40 and 45°C were rarely rated above pain threshold. Pain intensity and unpleasantness ratings of noxious heat (49°C) and noxious cold (0°C) are displayed in Figure 3. For noxious heat, post-injection ratings of both pain intensity [Fig. 3(A)] and pain unpleasantness [Fig. 3(B)] were significantly reduced from baseline ratings by morphine, but not by placebo [ANCOVA, repeated measures, $F(1, 18)=7.03$, $p=0.016$ and $F(1, 18)=7.97$, $p=0.011$, respectively]. A contrast analysis revealed that pain intensity ratings [Fig. 3(A)] were significantly lower in the morphine than in the placebo group at Post-Injection 1 and 2 assessment periods [$F(1, 18)=5.7$, $p=0.028$ and $F(1, 18)=6.8$, $p=0.018$, respectively]. Likewise, unpleasantness ratings were also lower in the morphine group, compared with those of the placebo group, both at Post-Injection 1 [$F(1, 18)=6.1$, $p=0.024$] and at Post-Injection 2 [$F(1,18)=8.1$, $p=0.011$]. For noxious cold (0°C), unpleasantness ratings [Fig. 3(D)] were significantly reduced after morphine, but not placebo [$F(1, 18)=9.75$, $p=0.006$]. A contrast analysis showed that unpleasantness ratings of the morphine group were significantly lower than those of the placebo group at Post-Injection 1[$F(1, 18)=11.2$, $p=0.004$] and tended to be lower at Post-Injection 2 [$F(1,18)=3.7$, $p=0.07$]. Nevertheless, no significant morphine-related reduction in pain intensity was found for noxious cold ($p=0.16$).

Stimulus intensity ratings

In contrast to the effects on pain ratings, morphine had no significant effect on perceived stimulus intensity. Figure 4 shows that the perceived stimulus intensity of noxious heat (49°C) and noxious cold (0°C) were not altered by morphine ($p=0.13$ and 0.61, respectively) [Figs 4(A) and 4(B)]. Ratings of stimulus intensity for innocuous warm (45 and 40°C) and cool (15 and 25°C) were also not altered by morphine [Figs 4(C)–(F)] (p from 0.1 to 0.6). Although there was a general decrease in stimulus intensity ratings over time for innocuous temperatures, this effect was independent of treatment received and thus was probably related to habituation.

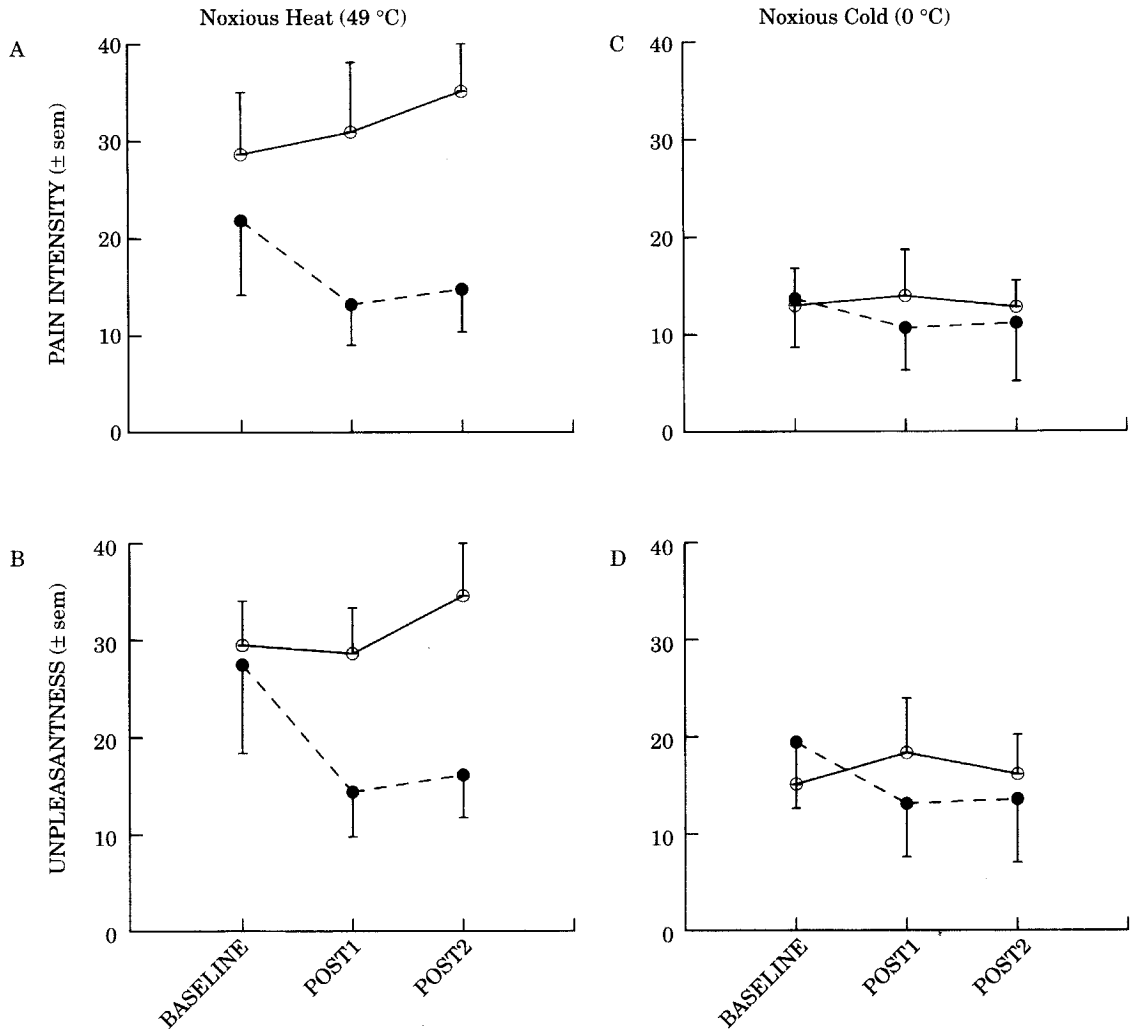

FIG. 3. Pain intensity (top), pain unpleasantness (bottom) ratings for noxious heat (left column) and noxious cold (right column) before (BASELINE) and after (POST1 and POST2) morphine (●) or placebo (○) injection. Morphine but not placebo significantly reduced heat pain intensity (A), heat pain unpleasantness (B) and cold pain unpleasantness (D).

Subjects' evaluations of the three levels of light intensities are shown in Figure 5. Neither morphine nor placebo significantly affected subjects' ratings of visual stimulus intensity (p >0.18). Suggesting that subjects' ability to perform the evaluation task did not change throughout the experiment and was not altered by morphine.

Verbal descriptor ratings

Verbal descriptor rating of pain sensations, averaged across the 14 words, are shown in Figure 6. There was a large variation among subjects in the number of words chosen and the score given to each word, as reflected by the large standard error bars. Nonetheless, averaged verbal descriptor ratings of noxious heat [Fig. 6(A)] and noxious cold [Fig. 6(B)] were significantly reduced by morphine but not by placebo [$F(1, 18)=7.2$, $p=0.015$ and $F(1, 18)=6.6$, $p=0.02$, respectively]. Contrast analysis revealed that post-injection ratings were significantly lower for the morphine group than for the placebo group at Post-Injection 1 and Post-Injection 2 for noxious heat [$F(1, 18)=8.4$, $p=0.01$ and $F(1,18)=5.8$, $p=0.027$,

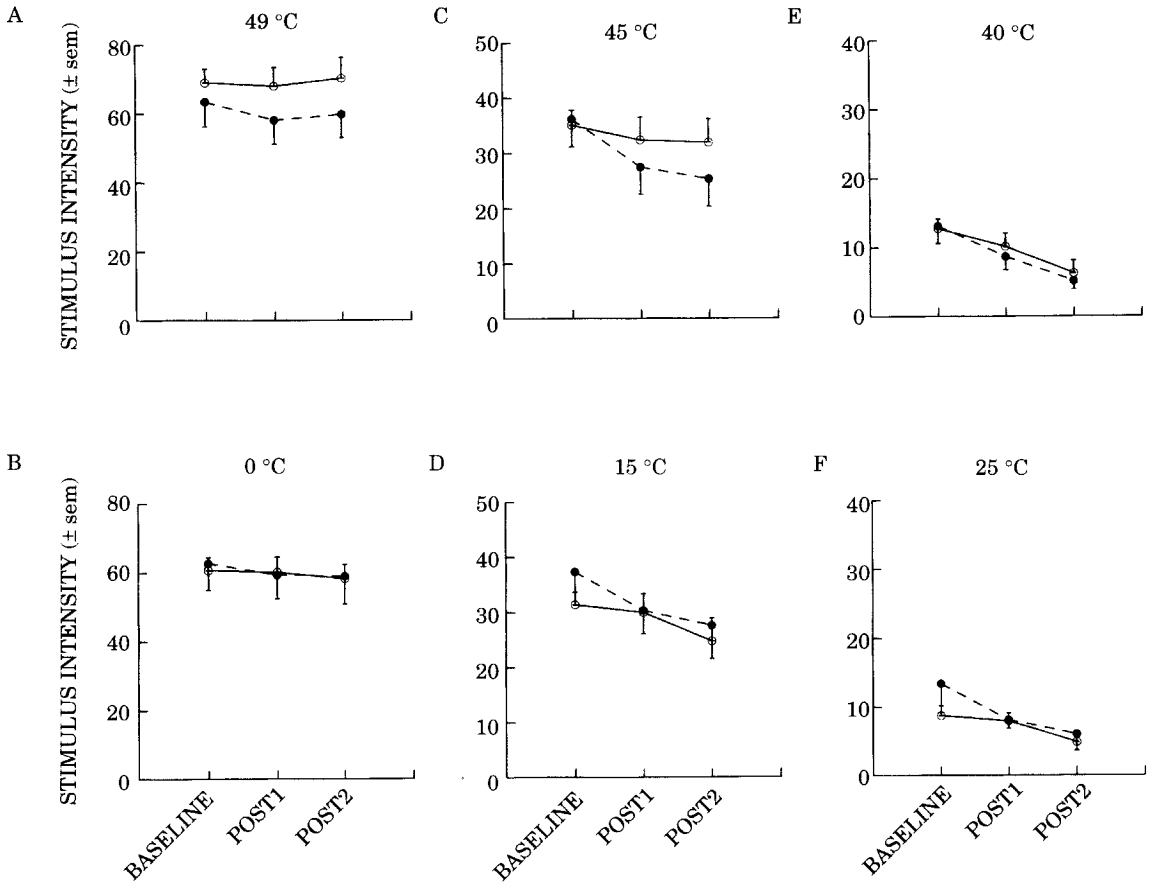

FIG. 4. Temperature intensity ratings of noxious and innocuous thermal stimuli before (BASELINE) and after (POST1 and POST2) morphine (●) or placebo (○) injection. Neither morphine nor placebo significantly modified noxious (A, B) or innocuous (C-F) temperature intensity ratings.

respectively] and noxious cold [$F(1,18)=4.6$, $p=0.047$ and [$F(1, 18)=6.3$, $p=0.022$, respectively]. Averaged verbal descriptor scores for innocuous thermal stimuli (not shown) were low and were not modified by either morphine or saline injection ($p>0.2$).

Side-effects

Opiate side effects were minimal, as shown in Figure 7. Only alertness [Fig. 7(A)] was significantly reduced by morphine [$F(1, 18)=10.8$, $p=0.004$]. Nausea [Fig. 7(B)], mood [Fig. 7(C)] and itching [Fig. 7(D)] were not affected by morphine or placebo administration ($p>0.3$). Additionally, when subjects were asked to guess which treatment they had received, they did not guess significantly better than chance, with only 66% of the morphine group accurately guessing their treatment.

DISCUSSION

The present results show that a low dose of morphine selectively modulated pain-related sensations, without significantly altering the perception of temperature intensity, even in the noxious range. Because subjects experienced few morphine-related side-effects and were not able to reliably guess their treatment, the observations of this study cannot be accounted for by subject expectancy. These results support our hypothesis that temperature perception and pain perception are at least partially subserved by separate

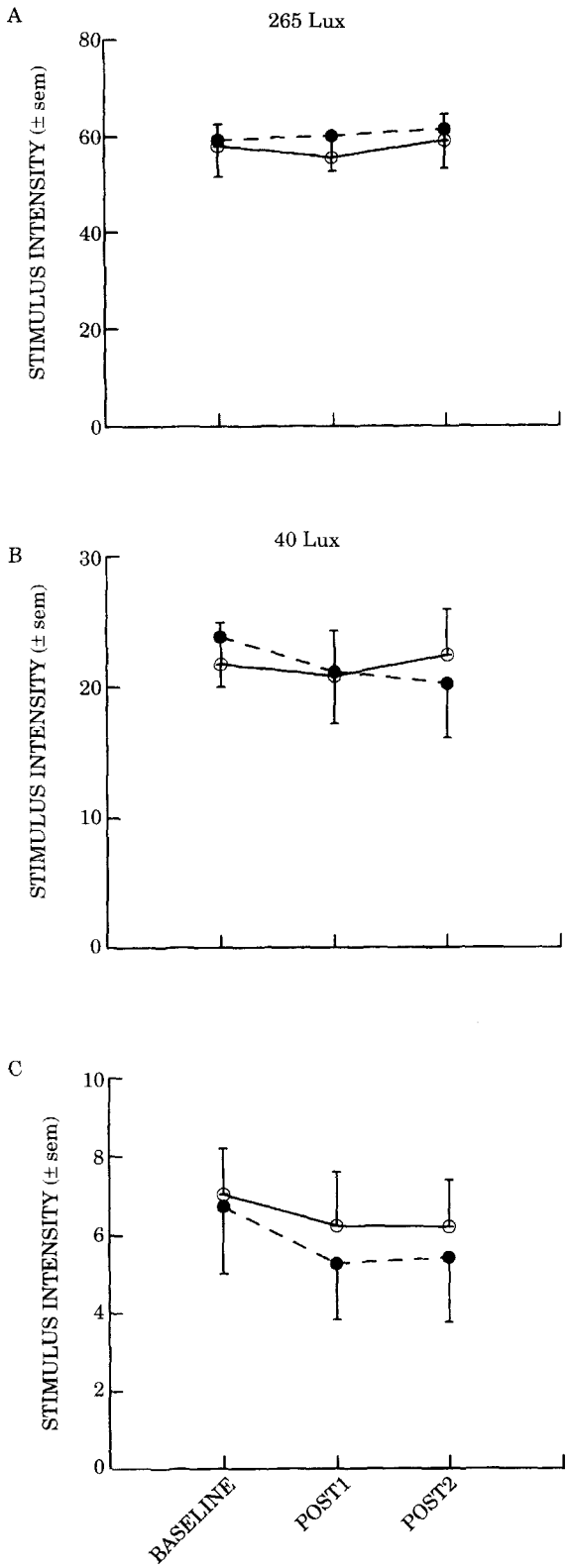

FIG. 5. Ratings of high (A), medium (B) and low (C) visual stimulus intensity. Evaluations of visual stimuli were not affected by the systemic morphine (●) or saline (○) injection.

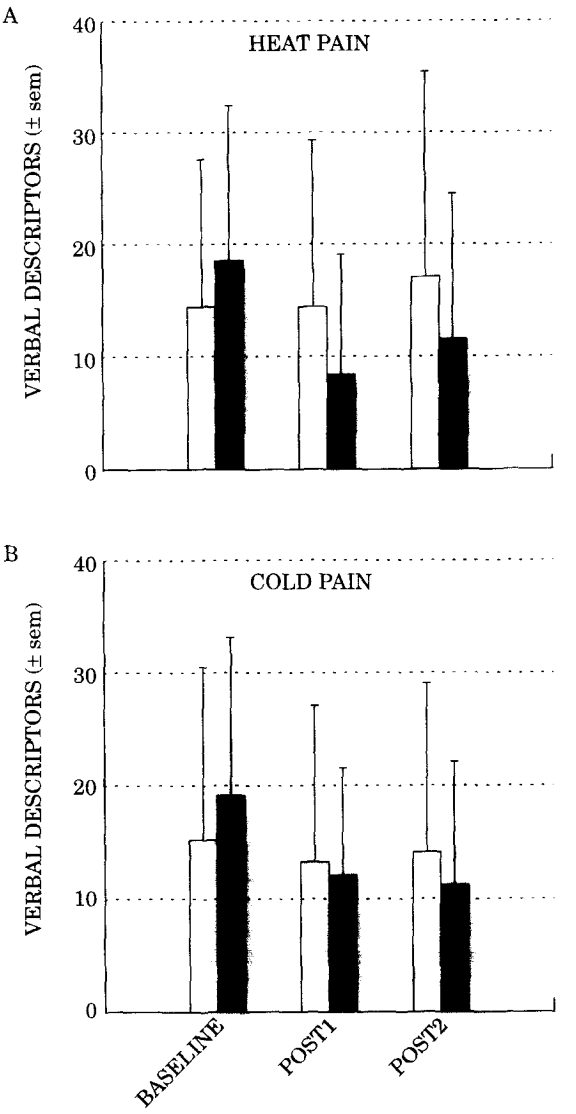

FIG. 6. Mean qualitative ratings of heat pain (A) and cold pain (B). For each subject, verbal descriptor ratings were summed across the 14 words. Morphine (black bars), but not placebo (white bars), decreased these scores for both heat (A) and cold (B) pain.

afferent channels, even for temperatures in the noxious range.

Accumulating evidence from human psychophysical and animal neurophysiological studies strongly supports the idea that low-dose morphine has a preferential effect on sensations mediated by C-fiber activity. Cooper and Vierck (1986) showed, using painful heat in human volunteers, that first pain, which is mediated by Aδ fibers, was unaffected by intramuscular morphine, whereas second pain, which is mediated by

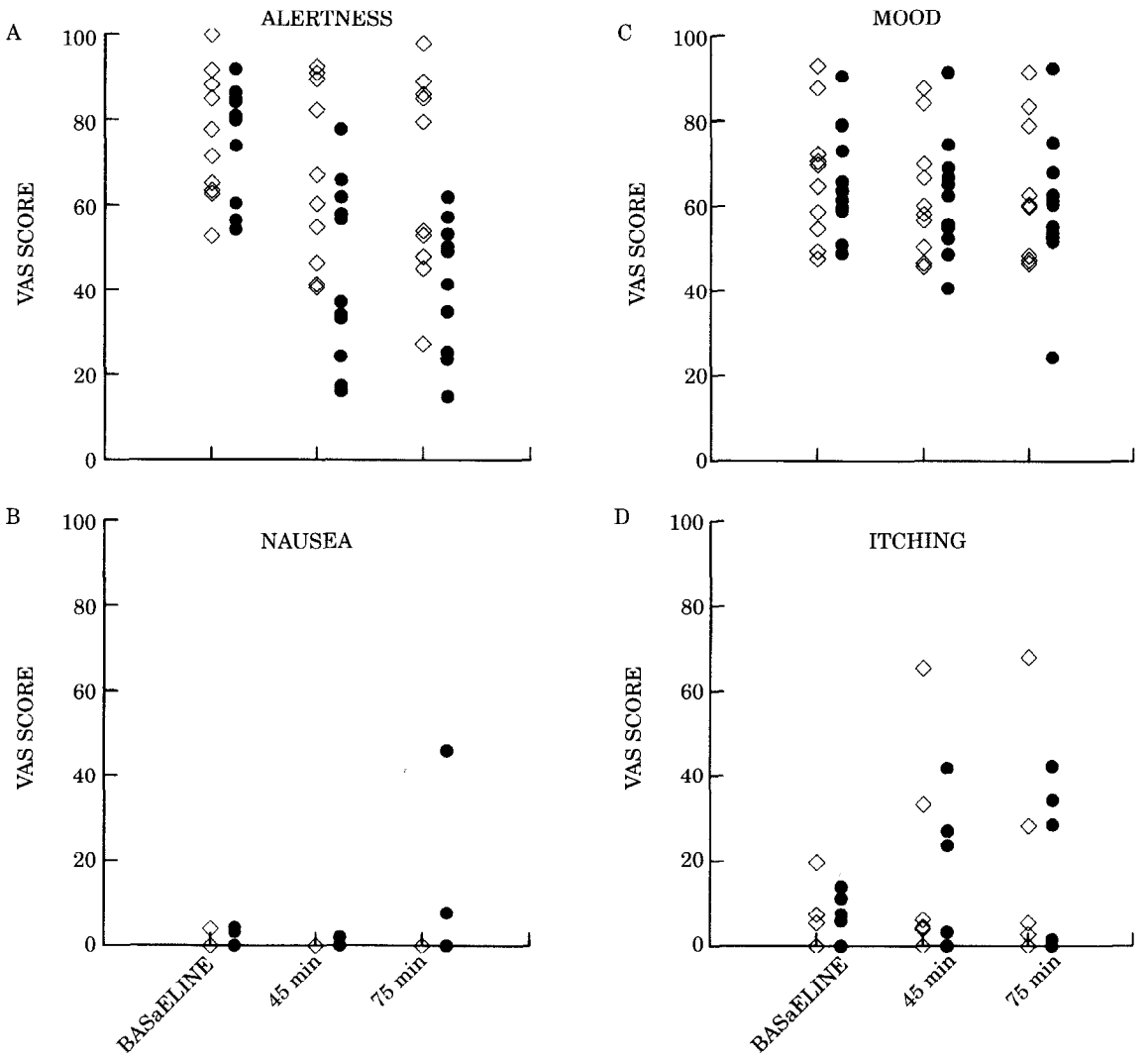

FIG. 7. Side effect ratings. Only alertness was significantly reduced by morphine (A). Nausea (B), Mood (C) and Itching (D) were not affected by morphine (●) or placebo (◇) administration.

C fibers, was reduced. Similarly, Van der Burght *et al.* (1994) demonstrated that morphine failed to affect laser-induced pinprick pain, which is primarily subserved by Aδ fibers. In contrast, morphine has been shown to reduce cold pressor pain (Posner *et al.*, 1985; Jones *et al.*, 1988; Abbott *et al.*, 1992) and contact-thermode heat pain (Price *et al.*, 1985; Brennum *et al.*, 1994), both of which activate C fibers in addition to Aδ fibers. Animal neurophysiological studies further support this differential effect by showing that low and moderate doses of systemic morphine reduce C-, but not Aδ-evoked responses in the spinal cord (LeBars *et al.*, 1976; Dickenson & Sullivan, 1986) and subnucleus reticularis dorsalis (Bing *et al.*, 1989).

Results of Yeomans *et al.* (1996) suggest that at least some of the pain arising from our heating stimulus is mediated by Aδ fibers. These investigators measured foot withdrawal latencies in rats to low (<1–2°C/s) and high (>2°C/s) skin heating rates before and after a capsaicin injection or low doses of systemic morphine, both of which selectively desensitize C fibers. They found that only response latencies to low rates of skin heating were modified, suggesting that the first pain arising from high-rate skin heating is subserved by Aδ fiber activity. Nevertheless, during noxious

heat stimulation of hairy skin in primates, both Aδ and C fibers have been shown to be active (LaMotte & Campbell, 1978; Gybels *et al.*, 1979; VanHees & Gybels, 1981; Adriaensen *et al.*, 1983; Robinson *et al.*, 1983; Yarnitsky *et al.*, 1992). Similarly, evidence suggests that during noxious cold stimulation both Aδ cold-sensitive fibers and C fibers with lower temperature thresholds are active (Dubner *et al.*, 1975; Chatt & Kenshalo 1979; LaMotte & Thalhammer, 1982; Wahren *et al.*, 1989; Yarnitsky & Ochoa, 1990).

Given the preferential effect of low-dose morphine on C-fiber-mediated pathways, our current findings of reduced pain perception after low-dose morphine for both noxious heat and noxious cold presented at onset rates of 5°C/s suggest that C-fiber activity at least partially subserves pain perception, even when stimuli are presented at a fairly high rate. This conclusion is consistent with numerous results of other human studies showing that C-fiber activity is important for the perception of both cold pain (Chen *et al.*, 1996) and heat pain (Price *et al.*, 1977; Robinson *et al.*, 1983; Yarnitsky *et al.*, 1992).

Our data show that for cold stimuli the perception of *temperature* intensity, even for noxious temperatures, is unaffected by a low dose of morphine that alters pain perception. Although we also observed a similar dissociation between the effect of morphine on temperature and pain perception for heat stimuli, there was a slight tendency toward an effect of morphine on heat temperature perception in the noxious range (p=0.16). These data suggest that temperature and pain perception for noxious cold, and maybe for noxious heat, are at least partially subserved by different afferent channels. In the noxious cold range, these findings are consistent with the differential effects of morphine on two populations of cells that respond to noxious cold. Craig and Hunsley (1991) showed that cold specific lamina 1 STT cells are enhanced while multireceptive nociceptive cells are suppressed after systemic morphine administration in the cat. Our findings are also consistent with psychophysical observations of Chen *et al.* (1996), who found that although at steady state temperatures as low as 0°C the predominant sensation is of cold, small *decreases* in temperature from baselines below 10°C produce mainly prickling or tickling sensations. Chen *et al.* (1996) proposed that the cold sensation is probably mediated by Aδ input into the central nervous system (CNS), and the prickling, tickling sensation is probably mediated by pathways with C-fiber input. The finding that perceived temperature intensity in the noxious heat range was not significantly altered by low-dose morphine has no clearly identified physiological correlate. Nevertheless, there was a non-significant tendency for an effect of morphine on noxious heat temperature perception that might represent a real effect with a larger data set. Alternatively, morphine effects on warm perception may have contributed to subjects' ratings of temperature perception in the noxious range, that is, subjects may have combined perceived warmth and perceived pain into these ratings.

Our observation that morphine did not alter warm perception differs from results of Schwartz *et al.* (1978), who demonstrated that systemic doses of morphine from 1–10 mg/kg impaired monkeys' capacity to detect warming stimuli. The differences in these results may due to differences in doses in these studies. Consistent with our current findings, Van de Burght *et al.* (1994) did not observe changes in laser-evoked warm thresholds in human subjects who received 0.15 mg/kg intravenous morphine. Nevertheless, our observations of effects of 0.08 mg/kg morphine on pain perception, but not warmth perception, suggests more profound effects of morphine in pain pathways than in low threshold innocuous thermal pathways. It is possible that peripheral actions of morphine (Hassan *et al.* 1993; Stein, 1995; Stein *et al.*, 1996; Likar *et al.*, 1998) may include effects on warm fibers, which could account for the observation that warm thresholds are sometimes altered by morphine.

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