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Inhibitory effects do not depend on the subjective experience of pain during heterotopic noxious conditioning stimulation (HNCS): a contribution to the psychophysics of pain inhibition

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Heterotopic noxious conditioning stimulation (HNCS) has been thought to give access to the diffuse noxious inhibitory controls (DNIC) in man, which can be activated in wide-dynamic-range neurons by noxious stimulation from remote areas of the body and form the neurophysiological basis of the phenomenon 'pain inhibits pain'. The latter phenomenon suggests that the subjective experience of pain is a prerequisite for an inhibitory action. The necessity of using painful stimuli as conditioning and as test stimuli to produce inhibitory effects was investigated in the present study, using a HNCS paradigm. Twenty young men received conditioning stimuli created by tonic heat at painful and non-painful levels, using either hot water (hand) or thermode (forearm). The test stimuli were phasic heat stimuli (thermode) at painful and non-painful levels applied to the cheek. Only painful but not non-painful heat as conditioning stimulus increased the heat pain threshold and decreased the ability to discriminate between painful heat of different intensities. These two findings are in accord with an inhibitory effect depending on a painful conditioning stimulus. However, the intensity ratings of the test stimuli indicated inhibitory effects of the conditioning stimuli also upon non-painful levels. Furthermore, non-painful heat as conditioning stimulus also appeared to be capable of decreasing the ratings of the test stimuli at painful levels. The latter two findings suggest: (i) that very strong but subjectively still non-painful stimulation can trigger pain inhibitory effects and (ii) that also subjectively non-painful stimuli are affected by inhibitory influences during HNCS. © 2002 Published by Elsevier Science Ltd on behalf of European Federation of Chapters of the International Association for the Study of Pain.

KEYWORDS: pain inhibition, diffuse noxious inhibitory controls (DNIC), heterotopic noxious conditioning stimulation (HNCS), psychophysics.

INTRODUCTION

The term diffuse noxious inhibitory controls (DNIC) has been used to describe the observation that the activity of pain-signaling neurons in the spinal dorsal horn and in trigeminal nuclei can be inhibited by noxious stimuli applied to body areas far remote from the excitatory fields of these neurons (Le Bars *et al.*, 1979a; Dickenson & Le Bars, 1983; Morton *et al.*, 1988). It appears that wide-dynamic-range (WDR) neurons with non-noxious and noxious input are especially sensitive to this inhibitory effect (Le Bars *et al.*, 1979a,b; Schouenborg & Dickenson, 1985).

To study DNIC in man, an experimental paradigm was developed involving heterotopic noxious

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conditioning stimulation (HNCS). HNCS describes the perceptual effect of a conditioning stimulus, mainly a tonic and clearly painful one, on a test stimulus, mainly a phasic and less painful one, which were applied at sites remote enough from each other to exclude segmental interactions. Since a reduction of pain sensitivity has been reliably observed in HNCS paradigms, HNCS effects have been assumed to be based on the activation of the DNIC (Price & McHaffie, 1988; Willer *et al.*, 1984, 1989, 1990).

Whether the subjective painfulness of the conditioning and the test stimuli forms a prerequisite for the inhibitory action in a HNCS paradigm has not yet been investigated in a systematic fashion although inhibitory effects upon non-painful sensations have been observed. Pertovaara *et al.* (1982) found sensitivity to non-painful warmth and cold to be reduced by tonic ischemic pain. Talbot *et al.* (1987) reported that cold pressor pain decreased the sensitivity to heat at painful and at non-painful levels. Finally, Plaghki *et al.* (1994), also using cold pressor pain, observed a reduction of the ratings and the pain-related evoked brain potentials evoked by laser stimulus intensities above and below pain threshold. To be fair, HNCS has appeared to have at least no inhibitory effects on vibration sensitivity and vision (Pertovaara *et al.*, 1982; Talbot *et al.*, 1989).

While doubts regarding the necessity of experiencing pain can be based on empirical ground for the test stimulus, doubts regarding the necessity of having a conditioning stimulus of painful quality can only be based on the lack of positive evidence. The conditioning stimuli in HNCS studies were mainly not assessed for their perceptual qualities. Instead, it was taken as given that certain stimulus intensities are noxious (Willer *et al.*, 1984, 1989, 1990; Talbot *et al.*, 1987, 1989). When the perceptual consequences of the conditioning stimuli were assessed, the stimuli were often presented at only one very high and, by that, certainly noxious intensity level (Pertovaara *et al.*, 1982; Chen *et al.*, 1985; Arendt-Nielsen & Gotliebsen, 1992; Watanabe *et al.*, 1996) and compared with only very low level stimuli (Price & McHaffie, 1988; Kakigi, 1994; Graven-Nielsen *et al.*, 1998). These methodological approaches are not very revealing with respect to the question that painfulness is a necessary prerequisite for an inhibitory action of the conditioning stimulus. In one of our studies we utilized two conditioning stimuli both very close to pain threshold, one above and one below (Lautenbacher & Rollman, 1997). Interestingly, these two stimuli did not differ in their inhibitory effects.

Considering the shortcomings of previous studies regarding the experience of pain as a prerequisite for observing inhibition during HNCS, we planned the present study in which: (i) the inhibitory effects of conditioning stimuli upon test stimuli at non-painful and painful levels should be compared and (ii) non-painful and painful levels of the conditioning stimulus are tested for their inhibitory effects upon the test stimulus. We used as conditioning stimuli-like Willer *et al.* (1984, 1989, 1990)—hot water and a new method of applying tonic heat at precisely tailored levels (Lautenbacher *et al.*, 1995; Lautenbacher & Rollman, 1997). The latter method was used to compare stimulus intensities that are close to each other, one being non-painful and one being painful. A shortcoming of some of the previous studies was the low number of subjects, which was frequently not higher than 10 (Pertovaara *et al.*, 1982; Willer *et al.*, 1984, 1990; Chen *et al.*, 1985; Talbot *et al.*, 1987, 1989). It is quite clear that strong effects were found and weak effects were missed by such an experimental strategy. Therefore, we studied 20 subjects although the experiment necessary was time and effort consuming.

METHODS

Subjects

To pick up potentially small experimental effects, which might have been missed in previous studies, we aimed to minimize intra-group variance by investigating only healthy men ($n = 20$) within a limited age range from 24 to 33 years (mean = 27.5 years, SD = 4.4). Exclusion criteria were all kinds of acute and chronic diseases. The diagnostic interview, which was designed for this purpose, aimed especially at the exclusion of cardiovascular diseases, allergies, hyper-responsiveness to stress, mental disorders, neuropathies, disc diseases, endocrine disorders and nerve injuries as well as dermatosis at the upper extremities. All subjects studied were drug-free. The protocol was approved by the local ethics committee; all subjects gave written informed consent and were paid for participation.

APPARATUS AND PROCEDURE

The effects of four types of conditioning stimulus were tested: hot water of 46.5 °C (thought as being a condition with painful heat), hot water of 42.0 °C (thought as being a condition with non-painful heat), thermode at a temperature being tailored to be painful and thermode at a temperature being tailored to be non-painful. The intensities of the conditioning stimulus were selected according to previous experiences in studies on the DNIC for hot water stimulation (Willer *et al.*, 1984) and relative to pain threshold for thermode stimulation as well as monitored by assessing the subjective sensations evoked. The stimuli were applied either at the hand (hot water) or at the volar forearm (thermode). The test stimuli were produced by a second thermode and applied to the cheek. The test stimuli were either applied alone (Baseline) or concurrently with the conditioning stimulus (Treatment) (see Fig. 1). Conditioning stimulus and test stimulus were always applied ipsilaterally.

Each treatment by a conditioning stimulus was preceded by its own baseline, resulting into eight experimental blocks (see Fig. 1). Regarding the conditioning stimulus there was either the sequence painful heat–non-painful heat–painful heat–non-painful heat or the sequence non-painful heat–painful heat–non-painful heat–painful heat. The two sequences were arranged this way to avoid two painful conditioning stimuli following each other and were balanced across subjects. Accordingly, the body side was varied, using either the sequence left–right–left–right or the second one right–left–right–left. The order of the types of stimulator 'hot water' or 'thermode' was random.

The conditioning stimulus as produced by hot water was administered either at a temperature of 46.5 °C (thought as being painful) or at a temperature of 42 °C (though as being non-painful), following the results of Willer *et al.* (1984). The subject immersed his hand up to 10 cm above the wrist in a hot waterbath held at one of the two temperatures. The water temperature was controlled by a thermostat (Variostat, Huber), and the water was stirred by a force and suction pump to avoid regional temperature difference within the

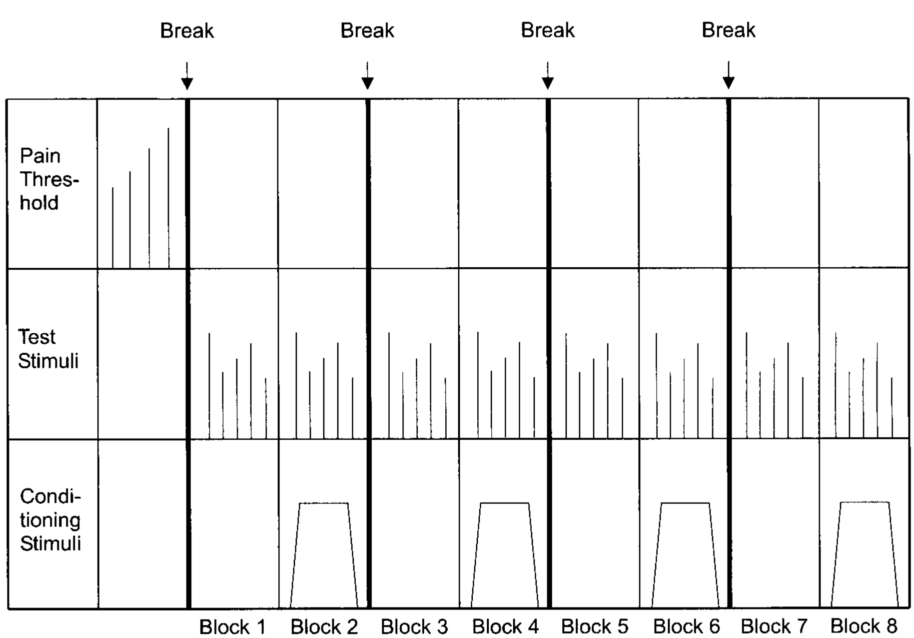

FIG. 1. Schematic illustration of a session.

waterbath. The immersion time was as long as necessary as to apply all test stimuli, which took on the average 10 min.

The conditioning stimulus produced by the thermode was administered either at painful or at non-painful temperatures. This was done, using a tonic heat pain model (Lautenbacher *et al.*, 1995) and a Peltier stimulator (PATH-Tester, Galfe *et al.*, 1990) both described in detail elsewhere. In brief, small heat pulses with an amplitude of 1.3 °C were administered at a constant frequency of 30 pulses per minute by a contact thermode of 6 cm^2 at the middle of the volar forearm. In the condition with painful heat, the pulses were tailored to have a base of 0.3 °C below the individual pain threshold and a peak temperature of 1 °C above it. In the condition with non-painful heat, the procedure was the same with the exception that the peak was 0.3 °C below and the base 1.6 °C below pain threshold. This approach allowed a comparison of the effects of tolerable tonic heat pain with the effects of very strong but still non-painful tonic heat. The individual pain thresholds were assessed for both forearms at the beginning of each session, using the method of adjustment in seven trials. The average pain threshold with no differences between body sides was 45.2 °C (SD = 0.85). The duration of the conditioning stimulation by thermode was also around 10 min for each of the two conditions.

The test stimuli were applied by the same type of Peltier stimulator (PATH-tester). The thermode was placed against two sites at each cheek, resulting in four stimulation sites at both cheeks. Consequently, the effect of each of the four conditioning stimuli could be assessed by test stimuli applied at different sites to control for effects due to local sensitization. Conditioning stimulation and test stimulation were always applied ipsilaterally.

Twenty-two test stimuli were administered in each experimental block. Each stimulus has a saw-tooth shape, started at a temperature of 36 °C and changed at a rate of 1.5 °C/s from baseline to maximum and reverse. The 22 stimuli were arranged in two sequential series of 11 stimuli. The first series ranged from 37 to 47 °C with stimulus intensity intervals of 1 °C and the second series from 36 to 46 °C. The same random order of stimulus intensities was presented in each series. The temperature difference between series 1 and 2, namely 1 °C on average, was scheduled to allow assessment of the discrimination ability for such a temperature difference. The stimulus time interval and the subsequent rating time interval (10 s) were signaled by visual and acoustic cues. The length of the rating interval did not allow to start the next test stimulus earlier than 10 s after the end of the preceding test stimulus.

Subjects rated the intensity of the test stimuli on a horizontal visual analog scale (VAS) of 100 mm. The scale anchors were 'no sensation' and 'strongest imaginable sensation'. Furthermore, the subjects gave a categorial rating with the categories 'not painful' and 'painful'. The latter rating allowed determination of the pain threshold according to the method of constant stimuli. The subjective intensity of the conditioning stimuli was rated by the subjects after the 2nd, 6th, 10th, 14th, 18th, and 22nd presentation of the test stimulus. For this purpose, a second horizontal VAS of 100 mm was used with an anchor of 'faintly painful' just in the middle so that all non-painful sensations were smaller than 50 and all painful ones greater than 50.

During the whole session, which took around 3 h, subjects sat upright at a small table. Each time after two blocks (baseline and treatment) a break of 10 min was scheduled to prevent carry-over effects and to keep the subjects vigilant (see Fig. 1). Before 'heterotopic noxious conditioning stimulation' (HNCS) started and after determination of the pain threshold, various practice trials were conducted to familiarize the subjects both with the stimuli and the ratings.

Statistics

Pain thresholds for the test stimuli were determined by assessing the temperature at which 50% of the categorial ratings were 'not painful' and 50% 'painful'. Furthermore, the intensity ratings on the visual analog scale (VAS) for the test stimuli were grouped into four ranges: ratings for temperatures from 36° to 38 °C, ratings for temperatures from 39 to 41 °C, ratings for temperatures from 42 to 44 °C and ratings for temperatures from 45 to 47 °C. The

VAS ratings within each of these four ranges were averaged. This was done to get more reliable measures because the resulting average ratings were based on 5 or 6 single VAS ratings. Finally, a score for discrimination ability was computed by using the difference of 1 °C between stimulus series 1 and stimulus series 2. More precisely, the differences between the VAS ratings for those pairs of stimuli from series 1 and series 2 with a temperature difference of 1 °C were determined, e.g. VAS $\text{rating}_{37\,°C}$–VAS $\text{rating}_{36\,°C}$, VAS $\text{rating}_{38\,°C}$–VAS $\text{rating}_{37\,°C}$, etc. Then, these VAS rating differences were averaged over two ranges 36–41 °C and 42–47 °C. Consequently, discrimination ability could be estimated within a low temperature range and within a high temperature range.

Means and standard deviations were computed for the basic descriptions of the data. The differences between conditions were assessed by *t* tests for dependent samples (one-tailed testing). α was set to 0.05 throughout. Such a liberal statistical approach, which avoids type-II errors rather than type-I errors, was preferred to catch any inhibitory effect of HNCS if present at all.

RESULTS

The visual analog scale (VAS) ratings for the conditioning stimuli are illustrated in Fig. 2. Both 'hot water' and 'thermode' stimulation produced very similar time courses of the ratings for the conditioning stimulus as regards painful heat. The ratings started on the average slightly above pain threshold (VAS rating of 50), increased steadily over the six trials (roughly 10 min) and never differed between the types of stimulation (all six tests: $p > 0.05$). Within each type of stimulation the conditioning stimulus designed to reflect painful heat differed significantly at all times from that designed to reflect non-painful heat (all 12 tests: $p < 0.05$). However, non-painful heat as produced by hot water led consistently to lower ratings than non-painful heat as produced by thermode (all six tests: $p < 0.05$). The ratings for non-painful heat as produced by thermode were not only higher from the onset but even passed pain threshold (VAS rating of 50) by the last trial. Consequently, the design of a conditioning stimulus, using tonic heat delivered by a thermode, which was as strong as

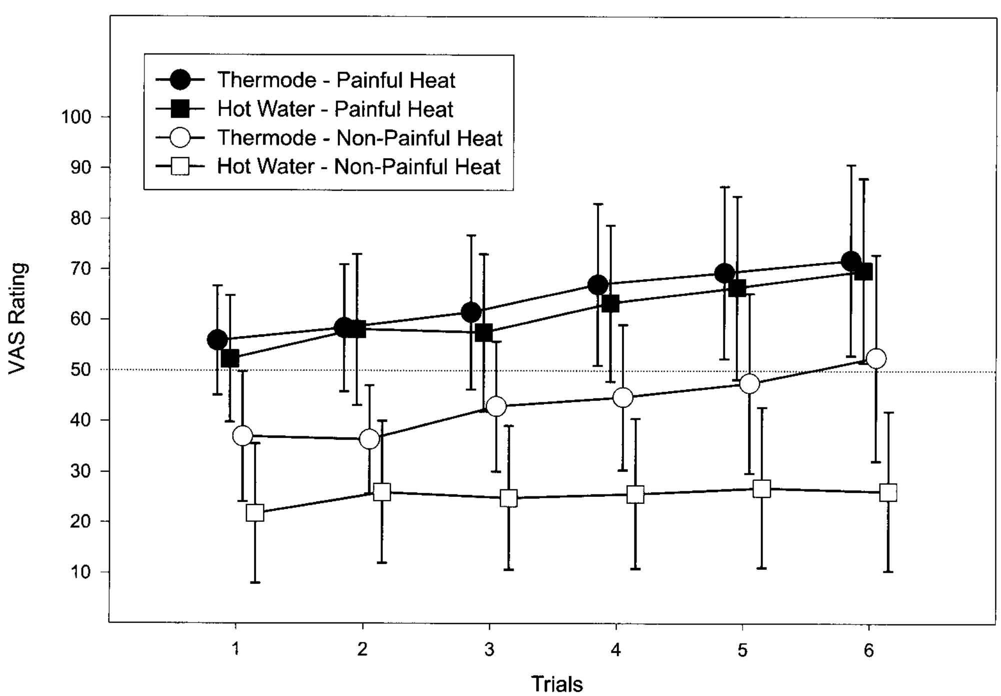

FIG. 2. Mean (±SD) VAS ratings for intensity of the conditioning stimuli; the dotted line at a rating of 50 indicates a level of a faintly painful sensation.

possible but consistently not painful, was generally but not entirely successful.

The effects of the conditioning stimuli on the pain thresholds for the test stimuli are presented in Fig. 3. Only the conditioning stimuli scheduled to be painful increased the pain thresholds significantly compared to the preceding baseline condition (hot water: $p = 0.003$, thermode: $p = 0.004$).

The effects of the conditioning stimuli on the VAS intensity ratings are presented in Fig. 4. The 'painful heat' conditioning stimulus produced by the thermode reduced the ratings of the test stimuli only at temperatures between 45 and 47 °C ($p < 0.001$). Given the fact that the average pain threshold for the test stimulus was around 45 °C (see Fig. 3), the inhibitory effect of HNCS was obvious mainly at painful levels of the test stimulus. In contrast, the 'painful heat' conditioning stimulus produced by hot water reduced the ratings of the test stimulus at temperatures between 39 and 41 °C ($p = 0.009$), between 42 and 44 °C ($p = 0.001$) and between 45 and 47 °C ($p = 0.024$). Furthermore, 'non-painful heat' conditioning stimuli produced by both hot water and thermode significantly reduced ratings of the test stimulus at temperatures between 45 and 47 °C, that is at painful levels (hot water: $p = 0.050$, thermode: $p = 0.001$).

The effects of the conditioning stimuli on the scores for discrimination ability are shown in Fig. 5. Only the 'painful heat' conditioning stimulus produced by the thermode reduced the discrimination ability in the high temperature range, which contained the painful temperatures ($p = 0.036$).

DISCUSSION

The question to be answered by the present study was whether the inhibitory effects depend on the subjective experience of pain during heterotopic noxious conditioning stimulation (HNCS). The major findings in this respect were: (i) that non-painful levels of the conditioning stimulus produced by hot water and by thermode had clearly inhibitory effects upon the intensity ratings of the test stimuli at painful levels and (ii) that painful levels of the conditioning stimulus produced by hot water had clearly inhibitory effects upon the intensity ratings of the test stimuli at non-painful levels.

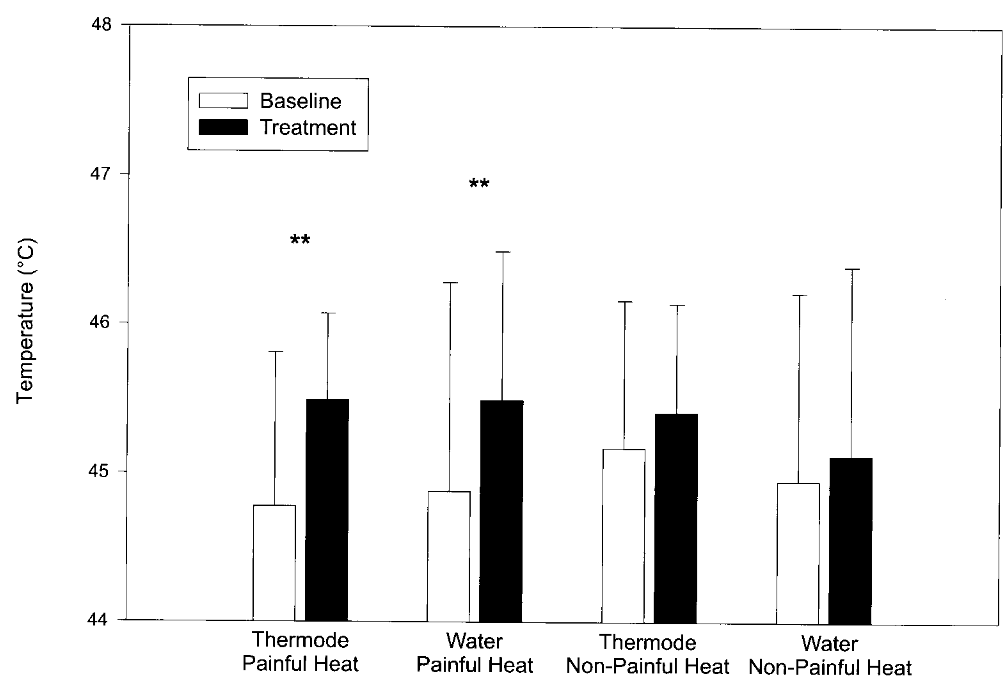

FIG. 3. Mean (±SD) pain thresholds for the test stimuli while being administered alone (Baseline) or concurrently with the conditioning stimuli (Treatment); ** for differences between conditions of $p \leqslant 0.01$.

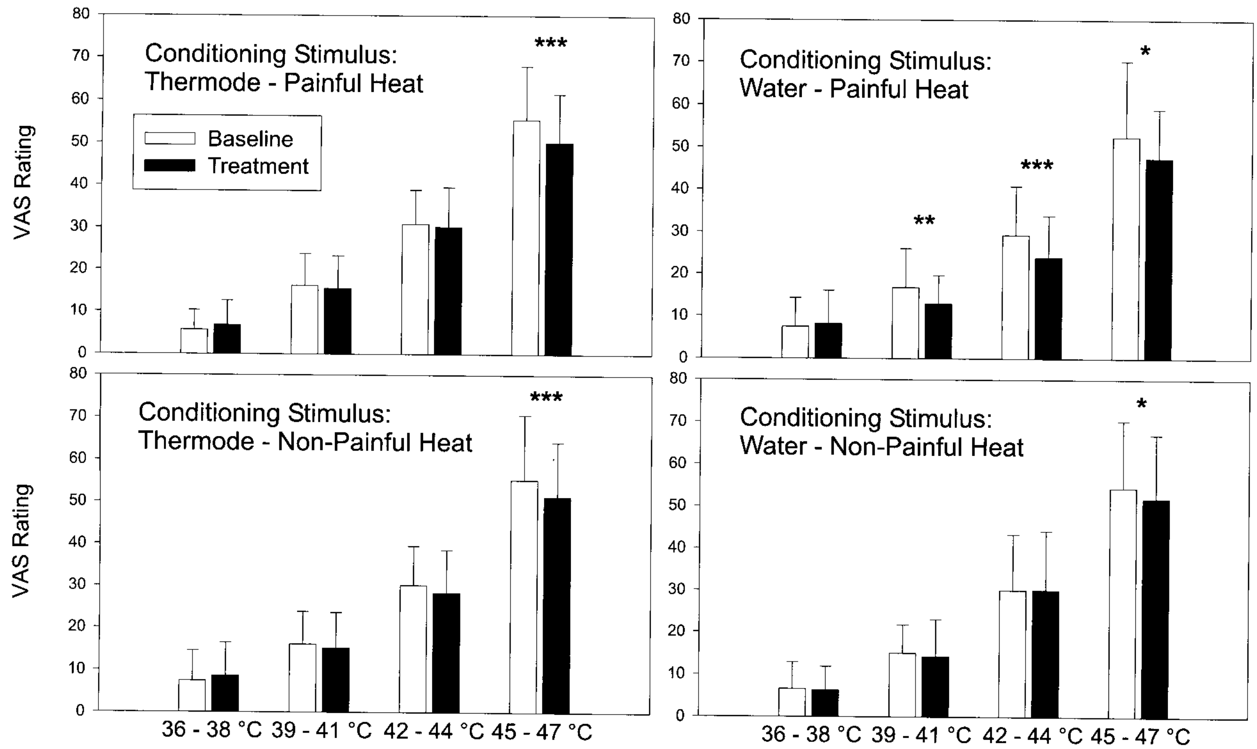

FIG. 4. Mean (±SD) VAS ratings in four temperature ranges for intensity of the test stimuli while being administered alone (Baseline) or concurrently with the conditioning stimuli (Treatment); *, **, *** for differences between conditions of $p \leqslant 0.05$, $p \leqslant 0.01$, $p \leqslant 0.001$.

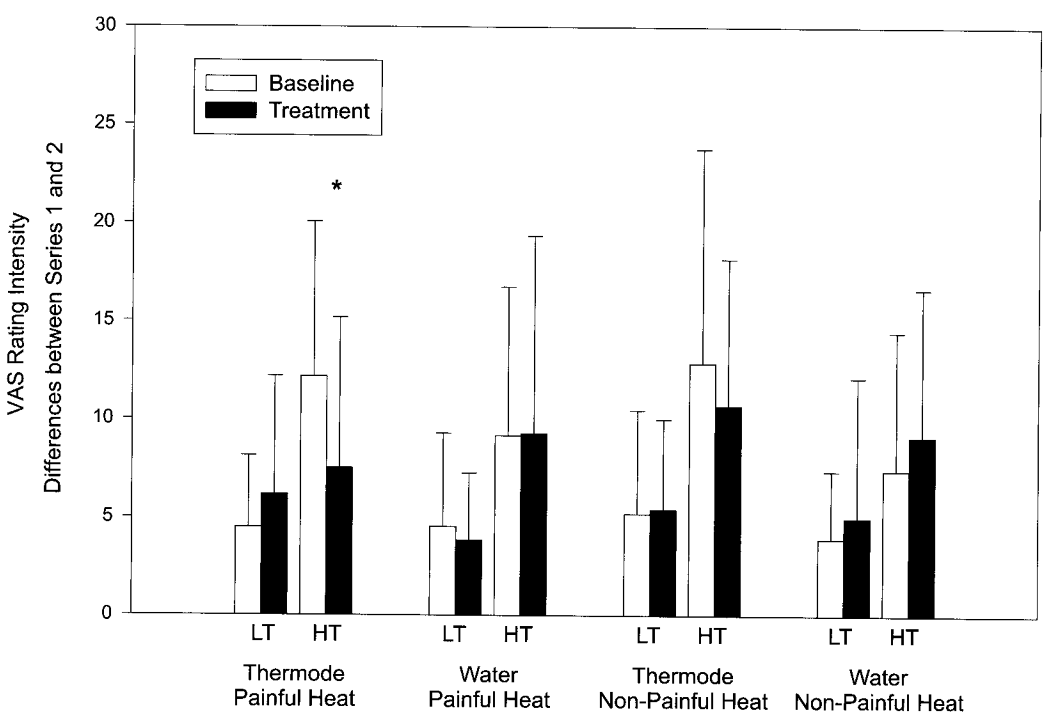

FIG. 5. Mean (±SD) scores of discrimination ability in a low temperature range (LT: 36–41 °C) and a high temperature range (HT: 42–47 °C) for the test stimuli while being administered alone (Baseline) or concurrently with the conditioning stimuli (Treatment); * for differences between conditions of $p \leqslant 0.05$.

Consequently, heterotopic noxious conditioning stimulation (HNCS) does not result solely in pain specific inhibitory interactions between conditioning and test stimuli. Rather, the findings suggest that strong and sustained somatosensory stimulation reduces sensitivity to additional slightly weaker and brief somatosensory stimuli in a heterotopic fashion. The subjective experience of pain appeared to be neither necessary for the conditioning stimulus to induce inhibition nor necessary for the test stimulus to be affected by inhibition. Evidence from studies on nociception has been accumulated (e.g. Dickenson *et al.*, 1980; Ellrich & Treede, 1998), suggesting such an outcome. The activation of the DNIC has appeared to be dependent on nociceptive input, leading not necessarily to painful sensations. The DNIC influence wide-dynamic-range (WDR) neurons, which can be activated by non-painful mechanical stimulation. However, present study offers additional insights because: (i) psychophysical methods were used, which can directly assess the necessity of painfulness for inhibitory effects, and (ii) inhibition was observed for non-painful heat, which does not activate WDR neurons.

Interestingly, Bouhassira and colleagues observed in two studies (Bouhassira *et al.*, 1994, 1998) that heterotopic inhibition of the RIII reflex is induced, not only by nociceptive visceral stimuli, but also by non-painful visceral stimuli. They attributed this to the specific organization of the sensory receptors involved in visceral pain. However, our findings suggest no fundamental difference between somatic and visceral conditioning stimulation because in our study non-painful somatic stimuli also induced pain inhibition in a heterotopic fashion.

The finding that very strong but still non-painful stimuli are capable to induce pain inhibition in a heterotopic fashion can be explained by the divergence of the nociceptive pathways responsible for the subjective experience of pain and for the activation of the diffuse noxious inhibitory controls (DNIC). According to the findings of De Broucker *et al.* (1990) nociceptive signals, which evoke the subjective experience of pain, are transmitted on a spinothalamic route whereas the signals, which activate the DNIC, are transmitted on spinoreticular pathways. Under the assumption that there are likely different activation thresholds in the two systems a lack of concurrence of the experience of pain and the induction of pain inhibition is a plausible finding. Another and not exclusive explanation can be differing degrees of spatial and temporal summation required for triggering the subjective sensation of pain and for activating DNIC.

The finding that there are inhibitory effects on the perceived intensity of non-painful stimuli can probably be best explained by the additional influence of attentional distraction in HNCS. The conditioning stimulus in a HNCS paradigm is definitely a potential source of distraction. The question arises why this source of distraction has been operative in some experimental setups including the present one (Pertovaara *et al.*, 1982; Talbot *et al.*, 1987; Plaghki *et al.*, 1994) but not in others (Pertovaara *et al.*, 1982; Talbot *et al.*, 1987). The perceptual similarity of the conditioning and test stimuli might be of critical importance. Riley and Levine (1988) demonstrated, in an elegant study, that attentional distraction from pain occurs more easily when a stimulus very similar in perceptual quality to that pain was used as a distracter. Hence, we should have observed, as we did, attentional distraction because both the conditioning stimulus and the test stimulus were heat. This idea of perceptual similarity as an influence on the potency of a distracter might help to explain why certain forms of clinical pain appeared to have no effects on experimentally induced pain (Ekblom & Hansson, 1987; Sigurdsson & Maixner, 1994) whereas others have (Willer *et al.*, 1987a,b).

Some minor findings deserve some comment:

(i) The conditioning stimuli for painful heat as produced by hot water and by thermode were felt equally intense. However, their inhibitory effects differed. The conditioning stimulus produced by the thermode triggered true pain specific effects: an increase in pain threshold, a decrease in intensity ratings only for painful stimuli and a decrease of discrimination ability only in the pain range. The conditioning stimulus produced by hot water not only increased pain threshold and decreased intensity ratings for painful stimuli but also decreased the same ratings for non-painful stimuli and had no effect on discrimination ability in the pain range. Hence, besides subjective intensity there are clearly other factors that determine the inhibitory effect of a conditioning stimulus in HNCS. In the present study the degree of spatial summation ought to be mentioned because there were big differences in the body surface area exposed to the conditioning stimuli when the hot waterbath and the thermode were used for stimulation.

(ii) The conditioning stimulus for non-painful heat produced by the thermode became painful at the very end of stimulation even though stimulation was tailored to the individual pain threshold to be non-painful. It might be that repeated stimulation at intensities slightly below pain threshold activates enough nociceptors and, consequently, triggers temporal summation in a way that pain develops out of a non-painful stimulation (Treede *et al.*, 1995; Price *et al.*, 1977). Future studies should take this into account if very strong but still non-painful stimuli are required for conditioning in HNCS. However, the internal validity of the stimulation paradigm using the thermode was only partially questioned because the conditioning stimulus was on the average 80% of the time non-painful as it was scheduled to be. Although subjectively stronger and at the end even painful the 'non-painful' conditioning stimulus produced by the thermode did not affect the test stimuli much differently than that produced by hot water suggesting again that the inhibitory potency of a conditioning stimulus depends on additional factors besides its subjective intensity.

In summary, the present study provided evidence that in HNCS painful conditioning stimuli have inhibitory effects upon the perception of non-painful test stimuli and that non-painful conditioning stimuli have inhibitory effects upon the perception of painful test stimuli. Consequently, inhibitory effects do not depend on the subjective experience of pain during HNCS. This finding can be best explained by the assumptions: (i) that the nociceptive pathways, which lead to the subjective experience of pain and to the activation of the DNIC, differ and (ii) that in addition to DNIC attentional distraction can become operative and affect the perception of stimuli at painful and non-painful levels during HNCS.

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