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PSYCHOPHYSICAL AND ELECTROPHYSIOLOGICAL APPROACHES TO THE PAIN-RELIEVING EFFECTS OF HETEROTOPIC NOCICEPTIVE STIMULI

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SUMMARY

The nociceptive flexion reflex (R_{III} reflex) and the concurrent subjective pain score elicited by right sural nerve stimulation at random intensities were studied in 10 healthy volunteers. A close relationship was found between the recruitment curves of the reflex and the pain score as a function of stimulus intensity. As a consequence, the threshold of the R_{III} reflex (T_r) and of pain sensation (T_p) were found to be almost identical (mean: 9.8 and 11.3 mA, respectively). Similarly, the threshold for obtaining a maximal reflex response (T_{mr}) was found to be very close to that for intolerable pain (T_{ip}): 33.5 and 35.1 mA, respectively.

These four parameters were studied before and during the immersion of the left hand into a heated thermoregulated waterbath at various temperatures (from 40 to 47.5°C). While nonnociceptive temperatures (40 to 44°C) were without effect, higher conditioning temperatures induced an increase in the four thresholds. In addition, a highly significant linear relationship was observed between the increase in these thresholds and the intensity of the conditioning stimulus in the 44 to 47.5°C range.

These four parameters were also studied before and during three other nociceptive conditioning stimuli: immersion of the left hand into a 6°C waterbath, 10 watts muscular exercise of the left hand performed under ischaemia and a painful (5.5 kg/cm²) pinch applied on the nasal septum. These three conditioning situations induced a very significant increase of the four thresholds considered in this study with the greatest being observed during nociceptive cold applied to the left hand.

During all the conditioning situations, variations in T_r and T_p as well as in T_{mr} and T_{ip} were found to be linearly related. This indicates a close relationship between the effects of the conditioning nociceptive stimuli on the reflex and the related pain sensation.

These results suggest that the modulation of pain by heterotopic nociceptive stimuli can be explained at least in part by a depression in the transmission of nociceptive messages at the spinal level. They are discussed with reference to the counterirritation phenomena and common features with 'diffuse noxious inhibitory controls' (DNIC) are underlined.

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INTRODUCTION

Counterirritation phenomena, that is, the paradoxical pain-relieving effects of pain elicited from heterotopic body areas, have been known for centuries and most popular methods of practising medicine have included and still do include their therapeutic use (Wynn, 1947; Wand-Tetley, 1956; Le Bars *et al.*, 1984). Furthermore, painful electrical stimulation of the skin (Sarlandière, 1825; Trousseau and Pidoux, 1836-1839; Duchenne, 1855) has recently been reintroduced in the treatment of chronic pain (Melzack, 1975; Jeans, 1979) and has been described as 'hypoalgesia by hyperstimulation'. Along the same lines, intense cold ('ice massage') applied to the hand has been reported to relieve dental pain (Melzack *et al.*, 1980*a*) and related methods have been used for the treatment of muscular (Travell, 1952; Grant, 1964; Mennell, 1975) and low back pain (Melzack *et al.*, 1980*b*).

Surprisingly, the phenomena have not given rise to many investigations involving experimental pain in man (Duncker, 1937; Hardy *et al.*, 1940; Gammon and Starr, 1941; Parsons and Goetzl, 1945; Pertovaara *et al.*, 1982).

The first aim of the present study was to attempt to investigate these phenomena in a quantitative fashion. In addition, we have recently proposed (Le Bars *et al.*, 1979*b*) that inhibitory mechanisms occurring at the spinal level could be the neural basis for counterirritation phenomena. This hypothesis was tested in the present study by investigating the effects of heterotopic nociceptive stimuli upon a nociceptive spinal reflex (R_{III} reflex). The sural nerve was stimulated and both the R_{III} reflex and the simultaneously evoked sensation were recorded to allow the study of the effects of various conditioning nociceptive stimuli applied to the contralateral arm or nose of human subjects. This experimental protocol was chosen because the threshold of R_{III} reflex was previously found to be close to the threshold of pain sensation (Willer, 1977). The results demonstrated that both pain sensation and reflex activities can be reduced by all types of conditioning nociceptive stimuli used in this study. A preliminary report of this work has previously appeared (Le Bars *et al.*, 1983).

METHODS

The experiments were performed on 10 healthy volunteers (8 men, 2 women, 26 to 44 years old), carefully briefed and familiar with the experimental procedure. They gave their informed consent, according to the principles of the Helsinki convention. During the sessions, the subjects sat comfortably reclined in an armchair in order to obtain good muscular relaxation. The details of the method for stimulating the sural nerve and recording reflex activity from a knee flexor muscle have previously been fully described (Willer, 1977). In brief, the right sural nerve was stimulated at a rate of 0.25 Hz behind the lateral malleolus through a pair of surface electrodes, 2 cm apart on the degreased skin. The electrical stimulus consisted of a volley of 8 rectangular pulses (1 ms duration) delivered over 20 ms. Their intensity was varied randomly (*see below*) and was permanently monitored. Electromyographic reflex responses were recorded from the ipsilateral biceps femoris muscle, using a pair of surface electrodes on the degreased skin overlying the muscle (fig. 2A). These reflex responses were full-wave rectified, integrated (usual time window 100 ms, 80 ms after the stimulus onset) and expressed as percentages of the maximal control values.

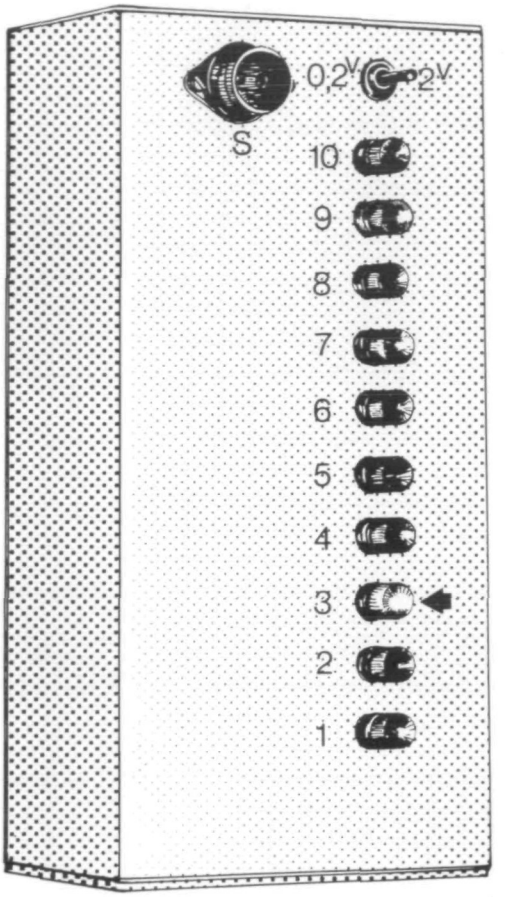

FIG. 1. Device used by the subjects for estimation of sensations elicited by the sural nerve stimulus. The ten-level visual scale consists of ten potentiometers (S = output). The pain threshold is defined as level 3 (arrow) and intolerable pain as level 10 (*see text*). The device was manipulated by the right hand of the subject.

The subjective quality (tactile or painful) and intensity of the sensation elicited by the sural nerve stimulus were estimated by the subjects on a ten-level visual scale consisting of 10 switches (fig. 1). Each of these was connected to a potentiometer delivering a d.c. current from 0.2 V (level 1) to 2 V (level 10) by increasing 0.2 V steps. The pain threshold was defined as level 3. Thus the first two levels represented tactile sensations, while levels 4 to 10 corresponded to increasingly painful sensations from just above threshold to intolerable pain.

The electrical signals (reflex, sensation and stimulus intensity) were fed to a storage oscilloscope to allow the monitoring of the experiments, to a tape recorder, and to a computer for on-line digitization of data. Because of a technical breakdown, some data relating to the reflex responses could not be analysed.

The intensity of stimulation was delivered randomly while both the digitized nociceptive reflex and sensation were plotted against stimulus intensity *via* a computer program. As shown in fig. 2, both the reflex activity and subjective rating score increased linearly as a function of stimulus intensity within a limited range. This allowed the measurement of both pain and nociceptive reflex thresholds. For this purpose at least 20 x-y points were used for calculating the regression curves; for each curve, the significance of the regression coefficient (r) was always at $P < 0.01$.

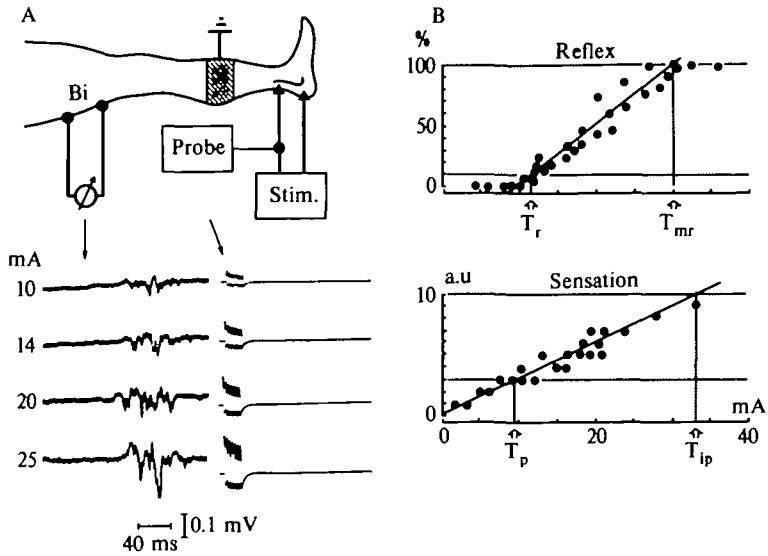

FIG. 2. A. *Upper part*: experimental design for stimulating the sural nerve (Stim.), measuring the stimulus intensity (Probe) and recording reflex activity from the biceps femoris muscle (Bi). *Lower part*: example of recruitment of the nociceptive reflex (R_{III}) activity (*left*) as a function of stimulus intensity (*right*). B. *Upper part*: method for calculating the reflex threshold (T_r) and the threshold for obtaining a maximum reflex response (T_{mr}). *Lower part*: method for calculating the pain threshold (T_p) and the threshold for intolerable pain (T_{ip}) (*see text*; a.u. = arbitrary units).

The reflex threshold (T_r) was defined as the abscissa corresponding to the intersection of the reflex linear regression curve with the 10 per cent ordinate line (upper fig. 2B). The threshold for obtaining a maximal reflex response (T_{mr}) was defined as the abscissa corresponding to the intersection of the reflex linear regression curve with the 100 per cent ordinate line (upper fig. 2B).

The pain threshold (T_p) was defined as the abscissa corresponding to the intersection of the sensation linear regression curve with the level 3 ordinate line (lower fig. 2B). The threshold for intolerable pain (T_{ip}) was defined as the abscissa corresponding to the intersection of the sensation linear regression curve with the level 10 ordinate line (lower fig. 2B).

The general experimental procedure consisted in the repetition of the protocol described above, before and during the application of a heterotopic conditioning stimulus.

The effects of conditioning noxious and nonnoxious heat stimuli applied to the left hand were studied on the pain sensation and nociceptive reflex elicited by stimulation of the right sural nerve. For this purpose, subjects were required to dip the hand, to a depth of 5 cm above the wrist, into an agitated thermoregulated waterbath for a time varying between 2 and 3 min. Several temperatures were tested in random order (40, 42, 44, 45, 46, 47, 47.5°C).

The effects of other modalities of noxious stimuli such as cold, noxious pinch and muscular pain were also studied using the following procedures. (1) For cold stimuli, subjects were required to dip the left hand into an agitated waterbath maintained at 6°C. (2) For muscle pain, subjects had to perform a 10 watts muscular exercise with the left forearm during ischaemic block of the arterial blood flow achieved by a pneumatic cuff placed around the middle of the left arm and inflated to 1.5 times the systolic blood pressure. (3) For a noxious pinch, a pressure of 4.5 kg/cm^2 was applied to a 15 to 20 mm^2 area of the nasal septum using a pair of forceps.

For a given subject, a maximum of 3 sequences were performed during any one session; the time between sequences consisted of a 20 min relaxation; each session lasted between 60 and 90 min. For each sequence, numerical data concerning the effects of the heterotopic stimuli upon the four parameters defined above were expressed as percentages of the control values. Global mean results were expressed in terms of percentage increases in thresholds. Paired t test and linear regression analysis were used for studying the significance of variations.

RESULTS

As described above, the experimental procedure consisted of sequences during which both the spinal nociceptive reflex (R_{III}) and the related subjective sensation elicited by the random stimulation of the right sural nerve were measured before and during the application of heterotopic conditioning somatic stimulation. The following sections consider in turn the characteristics of the unconditioned (control) response and their modification by conditioning stimuli.

Characteristics of Control Responses

The general characteristics of the control responses are illustrated with a typical individual example in fig. 2B. In this experiment, the threshold of the R_{III} response was 11.8 mA and the threshold of the maximal R_{III} response was 30.0 mA; note the linear nature of the intensity-response curve between these values. The corresponding curve obtained for subjective sensations exhibited a similar trend with 9.8 mA and 32.9 mA as thresholds for pain and intolerable pain, respectively. Such curves were generally very reproducible with minimal variations between sequences (*see* figs. 3 and 5, dotted lines).

The Table summarizes the mean reflex (T_r) and pain (T_p) thresholds for individual subjects and their corresponding thresholds for maximal reflex response (T_{mr}) and intolerable pain (T_{ip}). In 2 subjects, it was not possible to analyse the reflex activity because it was always contaminated with an EMG response related to

TABLE. INDIVIDUAL MEAN (±SEM) CONTROL THRESHOLDS VALUES OBTAINED FOR THE 10 SUBJECTS

	Reflex			*Sensation*			*Reflex/sensation relationships*	
	T_r (mA)	T_{mr} (mA)	T_{mr}/T_r	T_p (mA)	T_{ip} (mA)	T_{ip}/T_p	T_p/T_r	T_{ip}/T_{mr}
Subjects	$\bar{m}$ SEM	$\bar{m}$ SEM		$\bar{m}$ SEM	$\bar{m}$ SEM			
1	10.3 ± 0.3	38.2 ± 2.8	3.7	8.7 ± 1.0	29.5 ± 3.0	3.4	0.84	0 77
2				8.8 ± 0.2	28.9 ± 1.8	3.3		
3	8.5 ± 0.3	30.1 ± 3.1	3.5	10 1 ± 0.7	30.6 ± 1.7	3.0	1.18	1 01
4	10.0 ± 0.4	21.9 ± 2.1	2.2	10 3 ± 1.1	31.9 ± 2.2	3.1	1.03	1.46
5	8.9 ± 0.3	32.0 ± 2.7	3.6	10.4 ± 0.7	29.0 ± 0 9	2.9	1.16	0.90
6	9.6 ± 0.2	31.0 ± 2.9	3.2	10.5 ± 1.0	33.7 ± 2.6	3.2	1.09	1.09
7				12.4 ± 0.3	31.4 ± 1.4	2.5		
8	10.1 ± 0.1	38.8 ± 2.1	3.8	12.4 ± 0 9	38.2 ± 3.3	3.1	1.23	0.98
9	10.4 ± 0.4	37.8 ± 3.2	3.6	13.2 ± 0.8	49.4 ± 5.6	3.7	1.26	1.31
10	10.4 ± 0.4	38.0 ± 3.0	3.5	15.8 ± 0.6	49.0 ± 3 6	3.1	1.51	1.27
$\bar{m}$ ± SEM	9.8 ± 0.3	33.5 ± 2.1	3.4 ± 0.2	11.3 ± 0.7	35 1 ± 2.5	3.1 ± 0.1	1 16 ± 0.07	1.10 ± 0.08

T_r = nociceptive reflex threshold; T_{mr} = threshold of maximal nociceptive reflex response; T_p = pain threshold; T_{ip} = threshold for intolerable pain *See text* for interpretation of ratios (T_{mr}/T_r, T_{ip}/T_p, T_p/T_r and T_{ip}/T_{mr}) Subjects are listed with reference to increasing values of T_p; the overall means are added on the lower line.

a jumping movement. An indication of the variation between sequences and between individuals can be obtained by considering the standard errors of the means (SEM) as indicated in the Table for each individual subject and for the whole group. Note that the variations both between sequences and between individuals were relatively low for T_r, slightly higher for T_p (two- to threefold) and much higher for T_{mr} and T_{ip} (approximately ten-fold). However, the mean intensity-response curves obtained with all the subjects for the reflex responses and the pain sensations were, overall, remarkably similar. On the one hand, the mean values for T_r and T_p were 9.8 ± 0.3 and 11.3 ± 0.7 mA, respectively, while on the other, T_{mr} and T_{ip} were found to be of 33.5 ± 2.1 and 35.1 ± 2.5 mA, respectively.

The similarity in the intensity-response curves can also be seen on the right of the Table which indicates the T_p/T_r and T_{ip}/T_{mr} ratios for individual subjects; note that most of these values are close to 1. The Table also shows that the threshold for obtaining a maximal reflex response was close to three times the reflex threshold (mean $T_{mr}/T_r = 3.4 \pm 0.2$). Similarly, the threshold for intolerable pain was also close to three times the threshold of pain sensation (mean $T_{ip}/T_p = 3.1 \pm 0.1$). Note again the relatively small variations between individuals.

As described in the following section, these intensity-response curves could be markedly influenced by various heterotopic nociceptive conditioning stimuli.

Effects of Heat Applied to the Hand

The responses described above were recorded before and during the immersion of the contralateral hand in a waterbath. As shown in fig. 3, which illustrates an individual example, the responses were modified in direct relationship to the conditioning temperature of the waterbath. At 42°C, neither the reflex nor the sensation recruitment curves were different from the controls. At 44°C there was a slight shift to the right for the reflex response curve while the sensation curve remained unchanged. The shift of the reflex curve is mainly due to a change in the slope, the T_r being unchanged. In contrast with 45, 46 and 47°C, both the reflex and the sensation recruitment curves were shifted to the right, with a maximal effect for the highest temperature. Note both the progressive increase in T_r, T_{mr}, T_p and T_{ip}, and the decrease in the slopes of the curves as a function of the temperature.

Data obtained for all the subjects are summarized in fig. 4, which shows the mean increase in threshold as a function of the conditioning temperature applied to the left hand. Note that moderate (nonnoxious) temperatures, in the 40 to 44°C range did not significantly modify the four parameters considered. In contrast, higher conditioning temperatures clearly induced an increase in the four thresholds. In addition, these increases were very significantly related to the intensity of the conditioning stimuli. This relationship was linear in the 44 to 47.5°C range (dotted lines). Higher temperatures were not tested because 47.5°C was the highest temperature that could be tolerated for a sufficient length of time to obtain the intensity-response curves (*see* Methods).

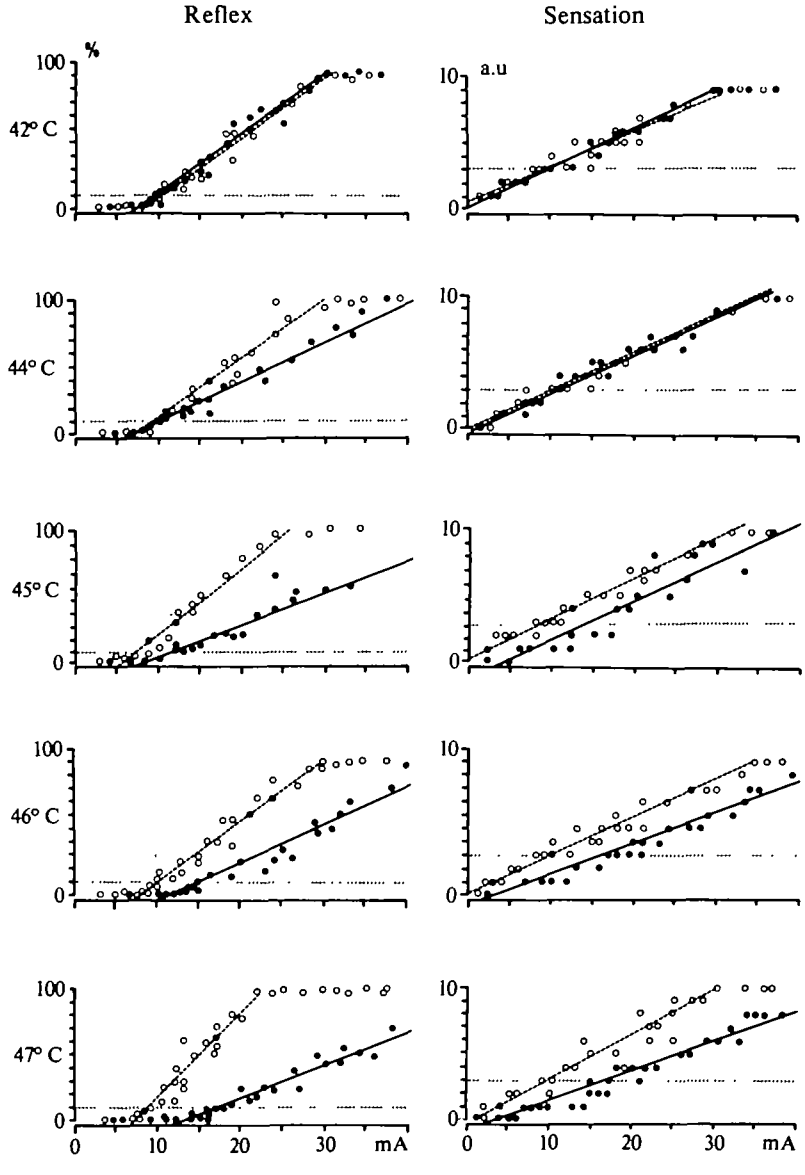

FIG. 3. Individual examples obtained in one subject showing the effects of various conditioning thermal stimuli applied to the contralateral hand (temperatures indicated on the left) on the nociceptive reflex activity (*left*) and the corresponding subjective sensation (*right*) induced by sural nerve stimulation (a.u. = arbitrary units). For each sequence, control (open circle, dotted line) and conditioned (filled circle, solid line) recruitment curves are plotted on the same graph (*see text*).

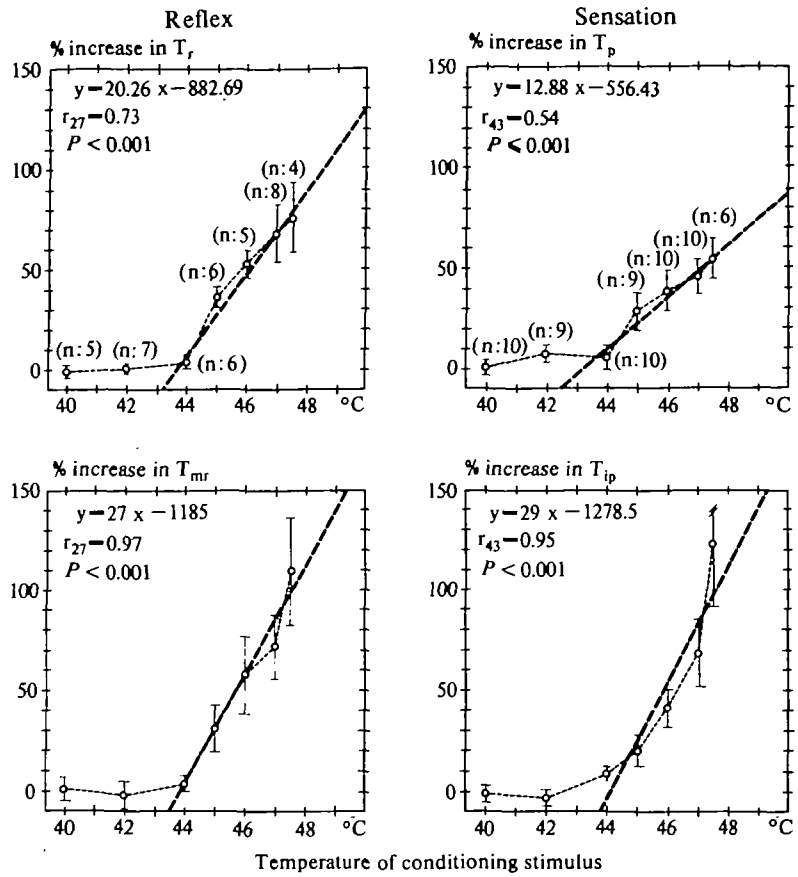

FIG. 4. Effects of conditioning thermal (40 to 47.5°C) stimuli applied to the contralateral hand (abscissa) on the four thresholds, as defined in fig. 2B (ordinates). Each point indicates the mean (±SEM) percentage increase in threshold (n = no. of subjects). Statistical analysis of regression lines is indicated in the upper left hand corner of each graph.

On considering the curves related to the reflex response (left part of fig. 4), it is seen that the T_r and T_{mr} curves are quite superimposable. From these curves, it can be estimated that the conditioning temperatures which induced a 50 per cent increase in T_r and T_{mr} thresholds were 46.1 and 45.8°C, respectively. On the other hand, by considering the curves related to sensation (right part of fig. 4), it is obvious that the T_p curve is less steep than the one for T_{ip}, the latter resembling those related to the reflex. The estimates of the temperatures which could induce an increase of 50 per cent in T_p and T_{ip} were 47.1 and 45.8°C, respectively. To summarize this section, both the nociceptive reflex and painful sensation evoked by stimulating the sural nerve were similarly affected by heating the contralateral hand in the 44 to 47.5°C range, in a peculiarly close fashion for suprathreshold responses (T_{mr} and T_{ip}).

Effects of Other Conditioning Stimuli

From the results described in the preceding section, it appears that nociceptive flexion reflexes and painful sensations were very significantly depressed by heterotopic heat stimuli in the nociceptive range (*see* Discussion). For further evidence that heterotopic nociceptive stimuli were able to influence both a nociceptive reflex and the related pain sensation, other modalities of noxious conditioning stimuli were tested. The effects of noxious cold, muscular pain and noxious pinch were studied on the four parameters described above.

As shown in fig. 5, which illustrates an individual example, the intensity-reflex and intensity-sensation recruitment curves were substantially shifted to the right by these three conditioning stimuli. The immersion of the contralateral hand into a 6° C waterbath, muscle pain induced by forearm muscular exercise during ischaemia and strong pressure applied to the nasal septum, all resulted in a shift of the curves to

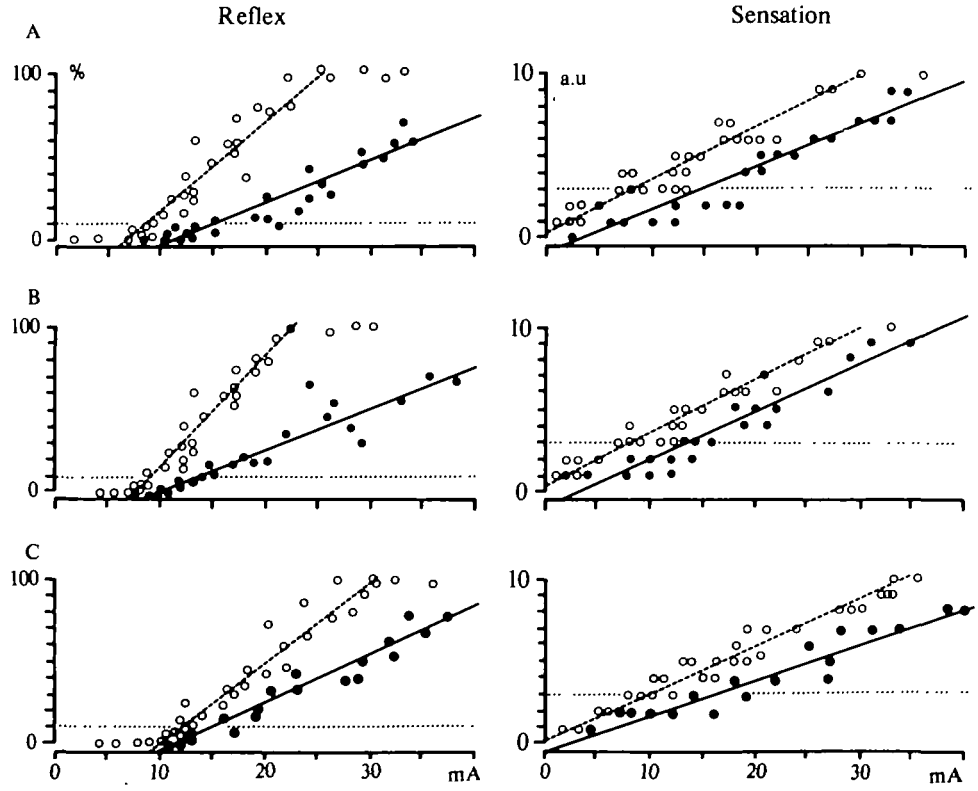

FIG. 5. Individual examples obtained in one subject (same as in fig. 3) showing the effects of three heterotopic nociceptive conditioning stimuli (presentation and symbols as in fig. 3). A, immersion of the left hand in an agitated waterbath maintained at 6°C. B, 10 watts muscular exercise with the left forearm during an ischaemic block of arterial blood flow achieved using a pneumatic cuff placed around the middle part of the left arm and inflated to 1.5-fold the systolic blood pressure. C, application of a pair of forceps (15 to 20 mm^2; 4.5 kg/cm^2) to the nasal septum.

the right, similar to those obtained when the same subject immersed his hand in the 47° C waterbath (*see* lower part of fig. 3).

Data obtained from all the subjects are summarized in fig. 6. Note that the three conditioning stimuli induced a very significant increase in the four thresholds considered in this study (i.e. T_r, T_{mr}, T_p and T_{ip}). The greatest variation observed was induced by the noxious cold applied to the contralateral hand.

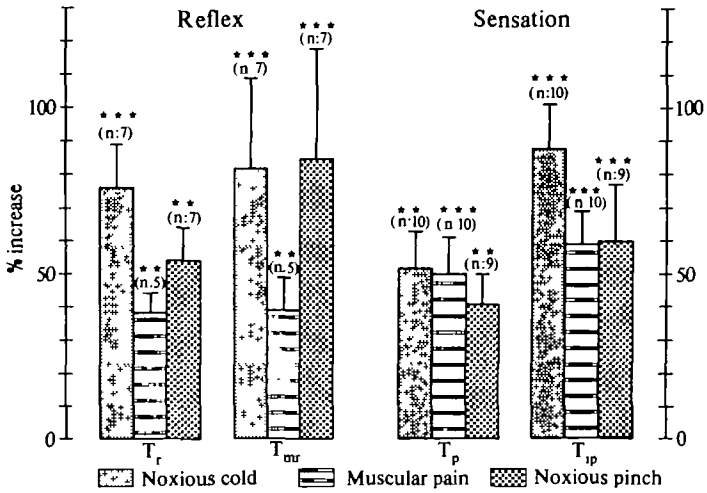

FIG. 6. Effects of three heterotopic nociceptive conditioning stimuli on the four thresholds, as defined in fig. 2B. Each column indicates the mean (±SEM) percentage increase in threshold (n = no. of subjects; $^{**}P < 0.01$; $^{***}P < 0.001$, paired t test).

Relationships between the Nociceptive Reflex and the Related Painful Sensation during Conditioning Stimulation

In the first paragraph, we have demonstrated that the mean intensity-response recruitment curves were almost identical to the reflex and the sensation. This indicates a close relationship between these parameters in the control situation, as has been described previously (Willer, 1977; Willer *et al.*, 1980). The relationships between the nociceptive reflex and pain sensation during the 10 conditioning situations detailed above will now be considered. In the left part of fig. 7, the mean increases in T_r (abscissa) are plotted against the mean increases in T_p (ordinate) for each conditioning situation; note the linear relationship between the increases of T_r and T_p. On the right of fig. 7 such a relationship can also be observed between the increases of T_{mr} (abscissa) and T_{ip} (ordinate). However, the slopes of these two regression lines are quite different. The slope of the left linear regression line is less steep (tg alpha = 0.63) than a 45 deg line (tg alpha = 1), indicating that T_r was, overall, more sensitive than T_p to the conditioning stimulation. On the other hand,

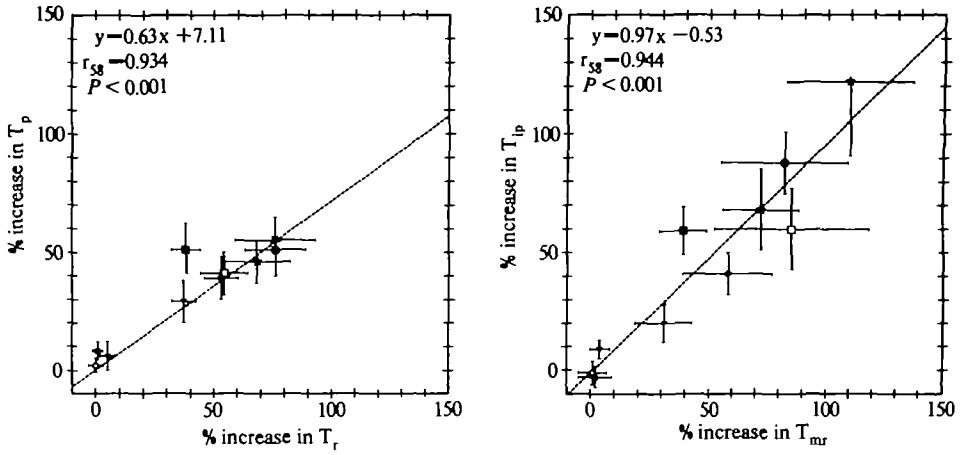

FIG. 7. Correlation between the increases in pain and reflex thresholds obtained during all the conditioning stimuli for all subjects. Left graph: T_r-T_p relationship; right graph: T_{mr}-T_{lp} relationship. Statistical analysis of regression lines is indicated in the upper left hand corner of each graph. o: 40° C; ●: 42° C; ▵: 44° C; ▲: 45° C; ◆: 46° C; ☆: 47° C; ★: 47.5° C; ⊛: noxious cold; ■: muscular pain; □: noxious pinch.

an almost 45 deg regression line (tg alpha = 0.97) can be observed on the right of fig. 7, clearly indicating that T_{mr} is, overall, as sensitive as T_{lp} to the conditioning stimuli.

DISCUSSION

The present results demonstrate that experimentally-induced pain can be profoundly modified by nociceptive stimuli applied to heterotopic body areas: pain elicited by electrical stimulation of the sural nerve could be lowered by various nociceptive stimuli applied to the contralateral hand or the nose. In addition, these conditioning nociceptive stimuli were found to depress the simultaneously recorded nociceptive spinal reflex (R_{III}). With regard to the sensation or the reflex, both threshold and suprathreshold responses were similarly affected. These results will be discussed from several points of view. In the first section the methods which we have used for investigating experimentally-induced pain will be considered. In the second we will consider the relevance of our results to the counterirritation phenomena. The involvement of spinal functions in these phenomena will be discussed in a third section, while hypotheses concerning the underlying mechanisms will be considered in the last.

The first question concerns the spinal origin of the nociceptive reflex R_{III}. Although we cannot formally exclude the possibility of the involvement of a spinobulbospinal component in our recordings (*see e.g.*, Shimamura *et al.*, 1964), there is no doubt that this reflex is mainly, if not entirely, organized in the spinal cord since it can be fully observed in paraplegic patients (Hugon, 1973; Willer and Bussel,

1980). The methods used in these investigations followed on from an earlier study (Willer, 1977) in which it was found that there was a close relationship between the threshold of the R_{III} reflex and the threshold of pain elicited by sural nerve stimulation. We have further shown here that the reflex and pain recruitment curves are also closely correlated with suprathreshold stimuli. Of special interest was the observation of a linear relationship for both pain sensation and the reflex response with stimulus intensities over a limited range. As a consequence, the response thresholds (T_r and T_p) and the maximal response thresholds (T_{mr} and T_{ip}) were very similar with the T_{mr}/T_r and T_{ip}/T_p ratios being close to 3 (*see* Table). These findings suggest that, with our experimental conditions the mechanisms for the development of pain, including intolerable levels, have already largely occurred at the periphery and in the spinal cord with few subsequent modifications. We believe that these methods are suitable for pain studies particularly, as discussed below, those related to the modulation of spinal mechanisms.

Our results confirm earlier reports showing that pain thresholds can be increased by a conditioning nociceptive stimulus applied to other areas of the body. Using devices allowing mechanical stimulation of the right and the left forearms, Duncker (1937) reported that the pain sensation induced by the stimulation of one forearm was lowered by the simultaneous nociceptive stimulation of the contralateral forearm in all 40 subjects tested; interestingly, the pressure component elicited by mild stimuli was not affected. Parsons and Goetzl (1945) observed a rise in the threshold to dental pain during the application of a spray of ethyl chloride (nociceptive cold) to the anterior surface of the subject's tibiae. Hardy *et al.* (1940) observed that the progressive pain sensation resulting from ischaemia of the arm was associated with a parallel increase in the threshold for pain elicited by means of thermal radiation of the forehead. More recently, Pertovaara *et al.* (1982) confirmed that pain resulting from ischaemia of the arm associated with muscular exercise strongly increased the dental pain threshold. We have further shown here that suprathreshold pain sensations (T_{ip}) can also be depressed by pain induced by mechanical stimuli, cold or ischaemia. The large reduction in experimental pain observed during the application of nociceptive cold gives experimental support for the use of intense cold for the treatment of clinical pain (Travell, 1952; Grant, 1964; Mennell, 1975; Melzack *et al.*, 1980*b*), such as ice massage of the hand for the relief of dental pain (Melzack *et al.*, 1980*a*).

To our knowledge there are no available data on the use of heat as a conditioning stimulus or on the relationship between the intensity of stimulation and the resultant conditioned pain response. We found here a direct relationship between the conditioning temperature in the nociceptive range (45 to 47.5° C) and the decrease of the conditioned pain sensation. For obvious reasons, higher temperatures were not tested but from fig. 4, it can be presumed that they would readily be effective in lowering pain responses. These observations could explain the efficacy of moxibustion and cautery as drastic pain-relieving methods many years ago.

All these observations are probably relevant to counterirritation phenomena, as

defined as the paradoxical pain relieving effect of pain elicited from other regions of the body (*see* Le Bars *et al.*, 1984). In this respect, it is interesting to note that intolerable pain was more sensitive to the counterirritants tested than threshold pain.

Effects of heterotopic nociceptive conditioning stimuli were also found on the R_{III} reflex activity: indeed both T_r and T_{mr} were increased by all conditioning situations. For thermal stimulation, the increase was directly related to the temperature of the waterbath, within the nociceptive range.

The strong relationship between the R_{III} reflex activity and the related pain sensation observed during control responses (*see above*) was also found during the conditioning periods. This was particularly clear for the supramaximal responses to sural nerve stimulation since, when considering all the conditioning situations, the threshold for obtaining a maximal R_{III} reflex and the threshold for intolerable pain were similarly affected (*see* fig. 7, right). It must be noted, however, that the liminal reflex responses were more affected than pain threshold (*see* fig. 7, left). These observations clearly suggest that the inhibitory effects we have described, and most probably the related counterirritation phenomena, would seem to originate mainly from a depression in the transmission of nociceptive messages at spinal level.

The question arises as to whether attentional phenomena related to the conditioning situations could explain our results. Indeed it has been shown that some attentional states can result in a reduction of R_{III} reflexes (Willer *et al.*, 1979) and pain responses (*see* Beecher, 1957). Such a hypothesis seems unlikely in our experimental situation for the following reasons. The immersion of the right hand in a 40, 42 or 44° C waterbath had no effect on the parameters studied (*see* fig. 4). In addition, in a pilot study (unpublished data), we found that the muscular exercise used in the present work was without effect in the absence of ischaemia. Finally, a mental calculation test was also without effect on the R_{III} reflex. Thus it can be concluded that the observed inhibitory effects were not due to the experimental situation but rather to the nociceptive nature (*see below*) of the conditioning stimuli.

It might be argued that the nociceptive nature of the conditioning stimuli could have induced a state of stress, which in turn could be responsible for the inhibitory effects. Indeed various stressful factors have been shown in animal studies to induce a rise in the threshold of nociceptive reactions ('stress-induced analgesia', *see* references in Tricklebank and Curzon, 1984). In man, a progressive increase in R_{III} reflex threshold takes place when a repeated anxiety-provoking situation occurs, as from anticipation of a severe pain (Willer *et al.*, 1981). This increase requires at least 30 min to become significant. By contrast, in the present study, the inhibitory effects were observed as soon as the conditioning stimuli were applied; furthermore we have no evidence for an increased efficacy of the conditioning stimuli over the 2 to 3 min test period. In addition, we have deliberately excluded intolerable conditioning stimuli (e.g. $> 47.5°$ C) for which stressful reactions would be obvious. Finally, with a paradigm similar to one of those we have used, Pertovaara *et al.* (1982) reported that the pain resulting from 15 min ischaemia associated with controlled

muscular exercise of the arm did not change the ACTH plasma concentration. Therefore, while we cannot formally exclude stress factors, it seems likely that they played a minor role, if any, in the inhibitory effects observed.

It is worth pointing out the contrast between (1) the phasic nature of the conditioned stimulus (20 ms electrical train) and the long duration (2 to 3 min) of the nociceptive conditioning stimuli; (2) the relatively restricted central input (part of S1) of the sural nerve compared with the wide distribution of the central input evoked by our conditioning stimuli; and (3) the larger central somatotopic representation of the hand and the nose compared with that of the foot. There was therefore a clear imbalance between the afferent volleys triggered by the conditioning and the conditioned stimuli. Previous studies (Willer *et al.*, 1978) have shown that the stimulation parameters used in the present work for eliciting a R_{III} reflex activate predominantly the myelinated fibres of the peripheral nerve. The nociceptive conditioning stimuli we have used, most probably involved Aδ and C fibre nociceptive afferents. This seems particularly clear for thermal conditioning stimuli since 40 to 44° C were ineffective whereas inhibitory effects were found for 45 to 47.5° C in a direct relationship with these temperatures (*see* fig. 4). In man, the pain threshold for thermal stimulation is achieved when skin temperature reaches approximately 45° C (Hardy *et al.*, 1951) and pain scaling is possible only in the 44 to 50° C range (Adair *et al.*, 1968; LaMotte and Campbell, 1978). In addition, pain scaling has been shown to be correlated with the firing of polymodal nociceptors during thermal noxious stimulation (Gybels *et al.*, 1979; Adriaensen *et al.*, 1983). Taken together, these data suggest that the observed inhibition induced by heterotopic thermal conditioning stimuli parallel both the pain sensation and the response of peripheral nociceptors.

In summary, our data show that, whether induced by heat, cold, mechanical or chemical procedures, a painful conditioning stimulus strongly depresses, at spinal level, the nociceptive messages elicited from remote localized body areas. The site of application of the effective conditioning nociceptive stimuli could be far from the site of origin of the conditioned pain response, thus excluding segmental mechanisms and the involvement of trigger points (Travell and Rinzler, 1952).

The close relationship between the effects of the conditioning stimuli on the reflex and the related sensation argues against a mechanism of inhibition acting on the motoneuronal pool. Instead, such a relationship suggests that these inhibitory mechanisms modulate a common spinal interneuronal pool responsible for both nociceptive reflex and ascending pain pathways. The question arises as to the identity of the pathways mediating such inhibitory mechanisms and, more particularly, whether they are confined to the spinal cord or whether they extend to supraspinal structures.

If intraspinal pathways are postulated, very long pathways must be implicated since the responses elicited by stimulation of the sural nerve (S1 dermatome) could be modified by conditioning stimuli applied on the hand (D1 to C6 dermatomes) or on the nose (trigeminal area). Anatomical studies in animals (*see* Cadden *et al.*,

1983) and in man (*see* Nathan and Smith, 1959) have revealed the existence of propriospinal pathways which might be able to mediate remote effects of nociceptive stimuli. In the spinal cat, the flexor reflex of the hindlimb can be inhibited by contralateral nerve stimulation (Eccles and Sherrington, 1931) and forelimb polysynaptic reflexes can be inhibited by nociceptive stimulation of the hindlimb (Miller *et al.*, 1973). In addition, there is evidence in both rat (Fitzgerald, 1982; Cadden *et al.*, 1983) and monkey (Gerhart *et al.*, 1981) that some dorsal horn neurons involved in the transmission of nociceptive information can be inhibited by heterotopic nociceptive stimuli *via* a propriospinal mechanism. However, these inhibitions appear to be relatively weak, to adapt rapidly and to be more marked for conditioning stimuli applied to structures proximal to the excitatory receptive field of the neurons under study than for stimuli applied more distally (Cadden *et al.*, 1983). In any case, if these mechanisms might partly explain our results obtained by conditioning the hand, they do not explain the inhibitions triggered from the nose.

The observations reported in the present study seem more relevant to the 'diffuse noxious inhibitory controls' (DNIC) which have recently been described in the rat (Le Bars *et al.*, 1979*a*, 1982). These controls affect dorsal horn convergent neurons and most of their features can be observed during recordings from neurons driven from receptive fields located on the hindpaw. The following points appear common with the inhibitions described above. (1) The responses of convergent neurons to electrical stimulation of their receptive fields can be inhibited by various noxious stimuli applied to parts of the body distant from the excitatory receptive field, including trigeminal areas (e.g. pinching the nose). (2) The distance between conditioned and conditioning sites of stimulation is not a critical factor for the strength of inhibition. (3) All types of conditioning nociceptive stimuli, whether mechanical, thermal or chemical, are effective. (4) The conditioning stimulus requires spatial and temporal summation much greater than the duration and strength of the conditioned stimulus to be fully effective. (5) In these conditions the inhibitory effects are very powerful, affecting responses to both threshold and suprathreshold electrical shocks. (6) DNIC are directly related to the strength of conditioning stimulation. Of special interest are the observations on DNIC triggered by heat conditioning stimuli: the threshold for obtaining an inhibitory effect was found between 40 and 44° C and, above this, a very significant correlation was observed between the conditioning temperature and the degree of inhibition (Le Bars *et al.*, 1981). (7) Finally, DNIC have been shown to affect both the responses of spinothalamic convergent neurons (Dickenson and Le Bars, 1983) and the polysynaptic reflex discharges evoked in the common peroneal nerve following electrical stimulation of the sural nerve (Schouenborg and Dickenson, 1984). These observations indicate the ability of DNIC to modulate nociceptive information transmitted by ascending pain pathways and also by nociceptive reflex pathways.

These parallels lead us to believe that the inhibitory effects observed here in man and DNIC in the rat share common mechanisms. Since DNIC has been shown to be sustained by a complex loop ascending from and redescending to the spinal cord

(Le Bars *et al.*, 1979*b*), further investigations are needed to substantiate our hypothesis. It will be crucial to know whether the type of inhibitory effects reported here can be observed in patients with paraplegia following complete spinal cord transection. If they are absent, our experimental approach would then seem to be appropriate for the further investigation in man of descending inhibitory controls triggered by nociceptive inputs.

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