Journal of Physiology (1992), **450**, *pp.* 581–592
With 4 figures
Printed in Great Britain

SINGLE C NOCICEPTOR RESPONSES AND PSYCHOPHYSICAL PARAMETERS OF EVOKED PAIN: EFFECT OF RATE OF RISE OF HEAT STIMULI IN HUMANS

BY DAVID YARNITSKY*, DONALD A. SIMONE†, ROSE M. DOTSON‡, MARTHA A. CLINE AND JOSÉ L. OCHOA

From the Departments of Neurology and Neurosurgery, Good Samaritan Hospital and Medical Center, and Oregon Health Sciences University, Portland, 97210, USA

(*Received 16 September 1991*)

SUMMARY

1. Effects of rate of rise of temperature stimuli applied to skin on (i) unitary receptor threshold and frequency response of ten single C nociceptors, and (ii) on magnitude and reaction times of evoked pain were studied in fifteen healthy human volunteers.

2. Temperature ramps of 32 to 45 or 47 °C were applied at three consistent rates of rise to receptive fields of C nociceptors in dorsum of foot ($n = 9$) or hand ($n = 1$). For rates of rise of 0·3, 2·0 and 6·0 °C/s, mean receptor threshold for heat was remarkably uniform: $41·5 \pm 0·57$, $41·5 \pm 0·61$ and $41·9 \pm 0·71$ °C respectively.

3. The mean discharge rate of the ten cutaneous C nociceptors increased with rate of rise of temperature stimuli: $1·22 \pm 0·13$, $4·57 \pm 0·49$ and $13·45 \pm 0·71$ impulses/s, respectively, for stimulus temperature rates of 0·3, 2·0 and 6·0 °C/s.

4. Magnitude estimates of pain for thirteen subjects also increased with rate of rise of temperature stimuli. Mean normalized magnitude estimates of heat pain were: $11·8 \pm 1·55$, $15·1 \pm 0·84$ and $28·0 \pm 1·87$ for stimulus rates of rise of 0·3, 2·0 and 6·0 °C/s, respectively.

5. Results of simultaneous recordings of reaction time for pain and of C nociceptor responses to heat ramps given at 2·0 °C/s, in three subjects, indicate that under those circumstances heat pain messages are exclusively mediated by C nociceptors.

INTRODUCTION

When a stimulus of increasing or decreasing temperature is delivered to the skin, the neural activity evoked in afferent fibres, and consequently the threshold for the perceived sensation, depends not only on stimulus intensity, but importantly, on the rate at which stimulus energy increases. Electrophysiological studies in humans

* Present address: Department of Neurology, Rambam Medical Center, Haifa, Israel.
† Present address: Department of Psychiatry, Division of Neuroscience Research, University of Minnesota, Minneapolis, MN, USA.
‡ Present address: Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, USA.

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(Konietzny & Hensel, 1984) and monkeys (Beitel, Dubner, Harris & Sumino, 1977; Kenshalo & Duclaux, 1977; Duclaux & Kenshalo, 1980; Sumino & Dubner, 1981) have shown that for a given amount of stimulus energy, the discharge rate recorded from warm-specific and cold-specific primary afferents increases as the rate of temperature change increases. In turn, psychophysical threshold measurements for warmth and cold sensations in humans reveal that the higher the rate of temperature change (steeper temperature ramps), the lower the threshold for subjective detection (Hensel, 1952; Kenshalo, Holmes & Wood, 1968).

Psychophysical studies have also demonstrated that detection thresholds for heat pain decrease in response to higher rates of temperature rise (Yarnitsky & Ochoa, 1990). This indicates that nociceptors, in a manner similar to cold- and warm-specific afferents, increase their firing frequency in concert with rates of temperature rise. The present study investigated effects of rate of stimulus rise upon magnitude of heat pain, reaction times and receptor responses of single C polymodal nociceptors supplying hairy skin of the human foot or hand. It was found that magnitude of heat pain and discharge rate of C nociceptors increase with increasing rate of temperature rise, while mean receptor threshold remains unchanged. In addition, we report that reaction time for heat pain detection is appropriately longer than latency for activation of C nociceptors, and disproportionately longer than expected for A nociceptors, suggesting that under the present experimental conditions, heat pain is signalled predominantly by C nociceptors. Preliminary results have been reported (Yarnitsky, Simone, Dotson, Cline & Ochoa, 1989).

METHODS

Subjects and general procedure

Fifteen healthy, informed volunteers (6 males and 9 females) participated in the experiments. Ages ranged from 19 to 43 years. They gave written consent for a number of test procedures, inclusive of tolerably painful stimuli and invasive intraneural microrecordings and microstimulation. During all experiments, subjects sat in a comfortable reclining position with the tested limb on a padded holder.

Thermal cutaneous stimulation

Heat stimuli were delivered to skin by means of a Peltier type thermode (3×2 cm) using the Marstock Thermotest (Somedic AB, Stockholm) as described by Fruhstorfer, Lindblom & Schmidt (1976). Stimulus ramps to 45 °C were applied from an adapting temperature of 32 °C. In cases where such temperature step did not induce pain, the limit was increased up to 47 °C. Heat stimuli were delivered at three different rates of temperature change; 0·3, 2·0 and 6·0 °C/s. The sites of stimulation were on the skin of the dorsum of the foot in the territory of the peroneal nerve, or on the dorsum of the hand in the territory of the superficial radial nerve. During recordings of identified C nociceptors, the thermode was placed so as to cover their receptive fields.

Intraneural recording and microstimulation

Action potentials were recorded from single afferent nerve fibres using the technique of microneurography (Vallbo & Hagbarth, 1968; Torebjörk & Hallin, 1974). A lacquer-insulated tungsten microelectrode (200 μm in diameter) was inserted into the superficial peroneal nerve or the superficial radial nerve and a similar reference electrode was inserted into subcutaneous tissue 1–2 cm away. A switch on the preamplifier allowed the intraneural electrode to be used alternatively for recording or stimulation by connecting the preamplifier to either the input of the recording system or to the output of a Grass S48 constant voltage stimulator with stimulus isolation unit. Intraneural microstimulation (INMS) was used to identify nerve penetration and to

evoke projected unitary sensations (Torebjörk & Ochoa, 1980; Ochoa & Torebjörk, 1983, 1989). While advancing the electrode manually towards the nerve, square-wave pulses (0·3–0·35 V) of 0·25 ms duration were passed through the electrode at a rate of 10–20 Hz. This stimulation regime produces an immediate sensation of projected paraesthesias when the electrode penetrates a fascicle.

Identification of nociceptors

INMS and natural cutaneous stimulation were used to search for nociceptors following a recommended method (Torebjörk & Ochoa, 1990). During INMS the electrode was gently repositioned until the subject reported a sensation of dull or burning pain referred to a small region of skin. The apparatus was then switched to recording mode and mechanical stimuli were applied to the skin in the region where the pain was projected. Cutaneous stimulation consisted of stroking with a cotton swab, applying pressure with a blunt probe and mildly pinching with the experimenter's fingers. Pressure and moderate pinching were used to search blindly for high threshold afferent units in the absence of INMS. Pinching was kept to the minimum, to avoid sensitization. For measurement of nerve fibre conduction velocity, two intradermal needle electrodes (interelectrode distance = 3 mm) were inserted at the receptive field of the unit and used for electrical stimulation. Latency from stimulus to C nociceptor response recorded at the intraneural electrode was measured on an oscilloscope. Axonal conduction velocities were calculated from latency and distance measured between stimulation and recording sites. The afferent character of recorded C units was verified by demonstrating temporary prolongation of the response latency by intercurrent natural stimulation of the receptor (Torebjörk & Hallin, 1974; Torebjörk & Ochoa, 1990).

Discriminable action potentials from single nerve fibres were amplified, displayed on an oscilloscope and on an electrostatic chart recorder (Gould), audiomonitored and stored on magnetic tape for off-line analysis.

Psychophysical methods

All fifteen subjects were suitably trained in the method of *magnitude estimation* (Stevens, 1975) by having them assess the amount of pain produced by a spectrum of intensities of heat stimuli applied to the dorsum of the foot. Subjects were instructed to assign a number of their own choosing to the maximum magnitude of pain produced by each stimulus, while judging the magnitudes of successive evoked painful sensations in proportion to each other. Three of the volunteers also participated in studies of *reaction time* for heat pain.

Test protocol

Electrophysiological responses of C primary afferent nociceptors and psychophysical measurements of pain evoked by heat stimuli were recorded simultaneously or separately.

Stimulus–response behaviour of C nociceptors. Seven of the fifteen subjects participated in microneurography and psychophysical studies. Once a single nociceptor unit was isolated, the mechanical threshold of its receptor was determined using calibrated nylon monofilaments (von Frey hairs). A standard suprathreshold monofilament with a bending force of 25 g was then used to map the area of the receptive field. After measuring conduction velocity, the thermode was centred on the receptive field. The actual experiment was initiated with five heat ramps of 32 to 45 or 47 °C, applied at a constant rate of 2 °C/s. Stimuli were delivered every 40 s to ensure that such a regime would not result in undue elevation or depression of the receptor threshold for heat. Following these pre-test trials, fifteen test stimuli (five at each of three rates) were presented in random order. Again, an interval of at least 40 s was allowed between successive stimuli to avoid sensitization of nociceptors, and hyperalgesia. C nociceptor threshold and discharge rate were determined for each heat ramp stimulus.

Psychophysical studies. The thermode was placed on the dorsum of one foot and each subject judged the magnitude of pain produced by heat stimuli of 45 or 47 °C applied using parameters identical to those described above. Five adaptation trials were obtained under a constant rate of temperature change (2·0 °C/s) followed by the series of test stimuli. Magnitude estimates of pain and electrophysiological responses were obtained simultaneously in five subjects. Reaction time measurements for heat pain were additionally obtained in three of these subjects while recording from a C nociceptor (see below). Eight of the fifteen subjects participated only in the psychophysical

experiments. Comparisons were made between magnitude of heat pain and evoked nociceptor activity. All subjects were prevented visual or auditory cues emerging from their recorded electrophysiological responses.

Comparison of reaction time for pain and activation of C nociceptors. Reaction time for heat pain and evoked response of C nociceptors were recorded simultaneously in three subjects. Reaction time was measured by having each subject signal the instant a painful sensation was perceived, by pressing a switch. Each subject's latency for pain detection was displayed on a storage oscilloscope and chart recorder, measured, and compared to the corresponding evoked C nociceptor discharge to determine when the signalled reaction to pain occurred relative to onset of recorded C nociceptor discharge.

Data analysis

Receptor threshold and firing frequency. One-way analysis of variance with repeated measures was applied to determine effects of rate of temperature rise on mean unitary response frequency, and mean receptor threshold of identified C nociceptors. Heat threshold was taken as the point along the temperature ramp where the first action potential was elicited. Calculations were made to correct for artifact in threshold temperature measurement since determination of firing onset was based on intraneural recordings with the electrode placed a few centimetres away from the receptor. By the time the action potential had reached the recording electrode, temperature of the stimulating probe had increased to slightly above the actual temperature at firing onset. Therefore, conduction time along the afferent (from receptor to recording electrode) was subtracted from the time the first evoked action potential was recorded. Data were pooled for stimulus ramps to 45 or 47 °C. Pairwise comparisons between mean discharge frequency and mean threshold for the different rates of temperature change were made using the Newman–Keuls procedure.

Magnitude estimates of pain. These were normalized as follows. For each subject, the mean of magnitude estimates for all temperature stimuli was calculated. Then, a grand mean of the estimates across all subjects was determined. A correction factor was calculated for each subject by dividing the grand mean by the subject's mean estimate. Normalized magnitude estimates for each subject were then obtained by multiplying each subject's magnitude estimate by the correction factor. A one-way analysis of variance with repeated measures was used to determine the effect of rate of temperature rise on the magnitude of pain. Comparisons between mean magnitude estimates of pain were made using the Neuman–Keuls procedure.

RESULTS

General receptor characteristics of C nociceptors

Evoked neural responses to heat were obtained from ten C polymodal nociceptor afferents (nine from the superficial peroneal nerve and one from the superficial radial nerve) in seven subjects. The mean conduction velocity was 0·83 m/s (range 0·5–1·5). Mechanical receptor thresholds, as determined using von Frey monofilaments, ranged from 0·52–25 g (median 1·94 g). None of the C fibres studied was spontaneously active prior to or during the experiment.

Effect of rate of temperature rise on receptor threshold

Table 1 shows the mean receptor threshold for all ten nociceptors as a function of slope of stimulus temperature ramp. Receptor thresholds did not change significantly as rate of stimulus rise increased. Mean receptor thresholds for stimulus rates of 0·3, 2·0 and 6·0 °C/s were 41·5±0·57, 41·5±0·61 and 41·9±0·71 °C respectively. Thresholds remained relatively stable throughout the fifteen stimulus

Fig. 1. Discharge of a single C nociceptor in response to heat stimulus ramps between 32 and 47 °C, at three rates of temperature rise. Note different time bases for each of three graphs. Discharge rate recorded and peak magnitude estimate of evoked pain are given.

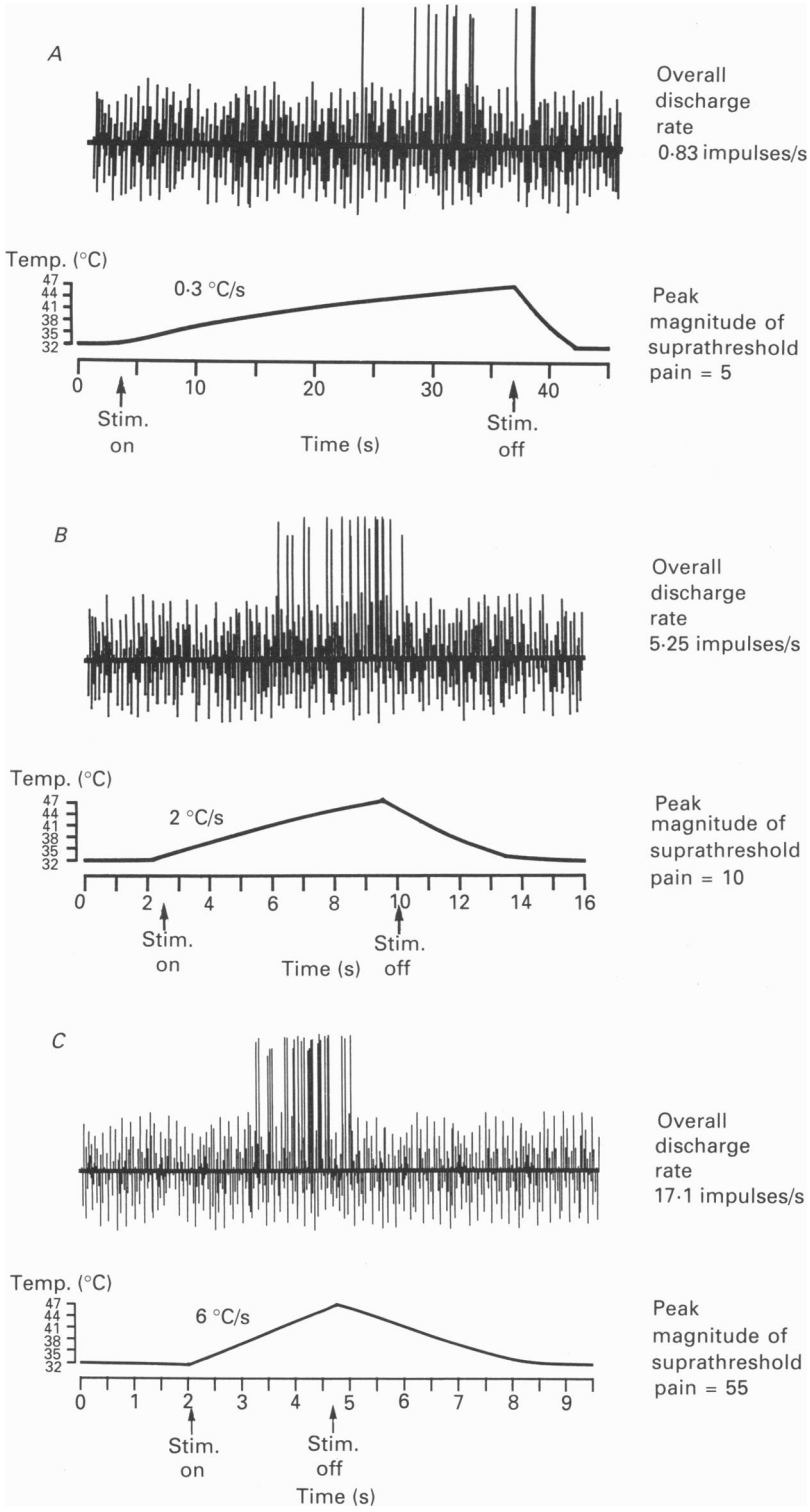

Fig. 1. For legend see facing page.

presentations. Further, receptor thresholds measured during each temperature slope were unaffected by repeated trials of stimulation. Table 2 shows stability of the mean firing threshold obtained for each of the five trials for the three rates of stimulus rise.

Effect of rate of temperature rise on pain magnitude and firing frequency of C nociceptors

The magnitude of heat pain sensation and the mean firing frequency of C polymodal nociceptors increased significantly with increasing rates of stimulus temperature rise. Figure 1 shows simultaneously recorded evoked responses of a single C nociceptor and magnitude of pain produced by stimulus ramps of 32–47 °C, delivered at the three different rates of temperature change, as observed in one subject. As the rate of temperature rise increased, firing frequency and peak magnitude estimates of pain also increased.

TABLE 1. Mean (±S.E.M.) receptor threshold for heat of C nociceptors

Rate of temperature rise (°C/s)	Threshold (°C)	Range
0·3	41·5 (0·57)	38·3–44·6
2·0	41·5 (0·61)	38·2–43·6
6·0	41·0 (0·71)	37·2–44·2

TABLE 2. Mean receptor threshold for heat (°C, ±S.E.M.) of C nociceptors as a function of successive trials

Rate of temperature rise (°C/s)	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5
0·3	41·3 (0·69)	40·9 (0·55)	41·2 (0·66)	41·4 (0·43)	42·5 (0·87)
2·0	41·9 (0·82)	41·3 (0·78)	41·9 (0·64)	41·0 (0·81)	40·7 (0·76)
6·0	41·3 (0·65)	41·3 (0·85)	42·6 (0·96)	41·9 (0·94)	42·0 (1·03)

Mean evoked responses of each nociceptor for the three rates of stimulus temperature rise are shown in Fig. 2. The mean impulse discharge frequency of each nociceptor increased with increasing rate of temperature change. A one-way analysis of variance with repeated measures revealed a highly significant effect of rate of stimulus rise on response frequency ($P > 0{\cdot}001$). Mean response frequencies evoked by stimulation rates of 0·3, 2·0 and 6·0 °C/s were $1{\cdot}22 \pm 0{\cdot}13$, $4{\cdot}57 \pm 0{\cdot}49$ and $13{\cdot}45 \pm 0{\cdot}71$ impulses/s, respectively. These response frequencies differed significantly from each other ($P < 0{\cdot}05$) and are illustrated on the left panel in Fig. 3.

Similarly, the peak magnitude of burning pain significantly increased with the rate of temperature rise ($P < 0{\cdot}001$). Mean magnitude estimates of pain produced by stimulus rates of 0·3 and 2·0 °C/s did not differ significantly, although the magnitude estimates increased for eight of thirteen subjects. For all subjects, the greatest magnitude estimates of pain were produced by the highest rates of stimulation. Indeed, mean magnitude estimates of pain produced by the 6·0 °C/s ramp differed significantly from those evoked by the shallower temperature ramps ($P < 0{\cdot}05$). Mean magnitude estimates of pain for all subjects are shown in Fig. 3 (right panel). Firing frequency of a single C nociceptor and the magnitude of heat pain for a single subject are illustrated in Fig. 4. It is clear that, for this subject, both magnitude of

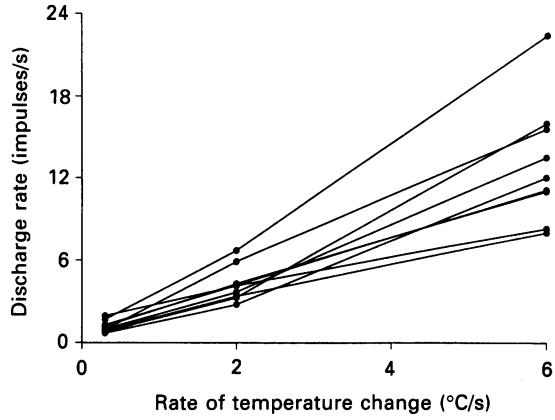

Fig. 2. Discharge rate for ten C nociceptors evoked by three rates of temperature rise (to 45 or 47 °C). Each data point represents the mean of five trials.

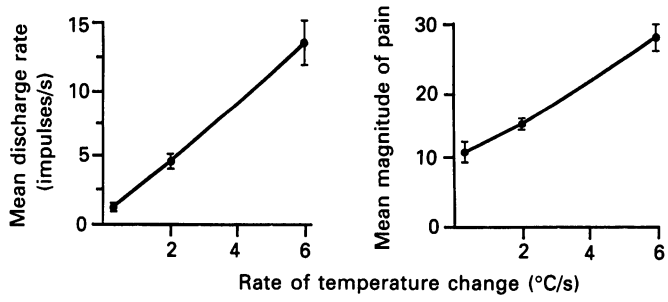

Fig. 3. Comparison of mean (±S.E.M.) firing frequencies for all C nociceptors (left panel) and mean (±S.E.M.) magnitude of heat pain for all subjects (right panel) as a function of rate of temperature change.

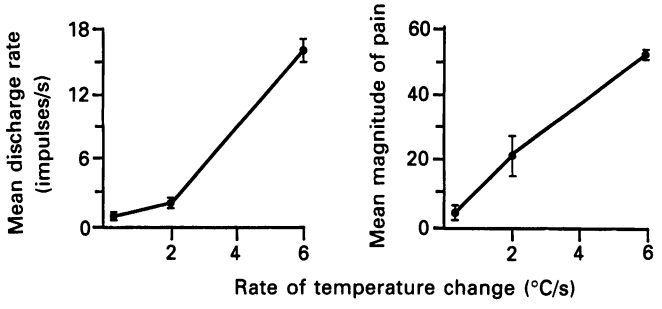

Fig. 4. Comparison of mean (±S.E.M.) firing frequencies for a single C nociceptor (left panel) and mean (±S.E.M.) magnitude of heat pain (right panel) obtained simultaneously from a single subject.

pain and simultaneously recorded firing frequency response of a C nociceptor increased with each increase in rate of stimulus temperature rise.

Comparison between reaction time for heat pain and latency to C nociceptor activation

Three subjects signalled the time of pain onset in response to additional heat ramps of 2·0 °C/s while evoked responses of a single C nociceptor were recorded from the superficial peroneal nerve. Latency to pain detection was timed relative to recorded receptor response in order to determine which class of primary afferents subserve the message induced by this stimulus. In all three subjects, detection of heat pain always occurred 1–2·5 s after onset of slowly conducted evoked responses in C nociceptors.

DISCUSSION

The peripheral neural mechanisms intervening between natural stimulus parameters and perceived sensation can be advantageously investigated by correlating these two with activity recorded in identified primary afferents in awake human subjects. The present study demonstrates that for heat ramps between two fixed temperature points, magnitude of heat pain and frequency discharge of C nociceptors increase with increasing rates of temperature rise, while receptor threshold for heat remains relatively stable. Further, with heat ramps of 2·0 °C/s, latency to pain detection relative to time activation of C nociceptors suggest that under those circumstances the pain sensation is mediated by C and not by A fibres.

Stimulus energy–receptor frequency response relationship

For thermal stimuli, firing frequency of primary afferents seems to depend on two stimulus parameters, stimulus intensity and the rate at which stimulus energy is delivered. A direct relation between stimulus intensity and evoked firing frequency of primary afferents has been shown for both non-noxious and noxious thermal stimuli in humans (Gybels, Handwerker & van Hees, 1979; Konietzny & Hensel, 1984; Torebjörk, LaMotte & Robinson, 1984) and animals (Beitel & Dubner, 1976; Beitel *et al.* 1977; Kenshalo & Duclaux, 1977; Darian-Smith, Johnson, LaMotte, Shigenaga, Kenins & Champness 1979; Duclaux & Kenshalo, 1980; Sumino & Dubner, 1981), and recently for noxious chemical stimuli in humans (Handwerker, Forster & Kirchoff, 1991). The rate at which stimulus temperature is applied also affects the frequency of firing in primary afferents. Animal studies have shown that higher firing frequencies are evoked by higher rates of temperature change in warm- and cold-specific afferents (Beitel *et al.* 1977; Kenshalo & Duclaux, 1977; Duclaux & Kenshalo, 1980; Sumino & Dubner, 1981). A similar relation between rate of stimulus change and firing frequency of primary afferents has been observed for rapidly adapting mechanoreceptors in humans (Franzén, Thompson, Whistel & Young, 1984). Data for nociceptor behaviour in response to rates of temperature stimulus rise have not been reported in humans before the present study.

Rate of temperature rise and receptor threshold

Conflicting data is available regarding the effect of rate of temperature rise on receptor threshold of single C nociceptors. Bessou & Perl (1969), studying

unmyelinated nociceptors in cat, noted: 'Slow increases in temperature evoked the first impulses at somewhat lower temperatures than more rapid changes'. In rabbits, Lynn (1979) found lower thresholds for rates of 0·2 than for 2·0 °C/s and Treede, Oakland, Meyer & Campbell (1990) recently reported that the receptor threshold of C nociceptors in monkeys increased with rate of stimulus rise, using ramps of 0·1, 1·0 and 10·0 °C/s. It was suggested that for higher rates of temperature rise, skin surface temperature increased to a greater degree during the time required for heat penetration through the skin to receptor depth.

On the other hand, no change in nociceptor threshold was found between rates of 0·2 and 1·5 °C/s in monkey (Croze, Duclaux & Kenshalo, 1976), and neither could we find any change in human C nociceptor firing threshold between the three rates of temperature rise used (0·3, 2·0 and 6·0 °C/s). A possible explanation relates to the size of the area stimulated. Bessou & Perl (1969), Lynn (1979) and Treede *et al.* (1990) used small stimulating probes (areas 0·05, 0·28 and 0·64 cm^2, respectively) while Croze *et al.* (1976) used an 8 cm^2 probe and we a 6 cm^2 probe. It is suspected that heating larger surfaces might induce greater skin warming, through higher energy input and lesser heat dissipation.

Frequency response of C nociceptors, and pain threshold and magnitude

When a ramp of increasing temperature is delivered to the skin, the physiological sequence of events includes nociceptor firing at its threshold, followed by subjective response at detection threshold when sufficient firing frequency is reached in a sufficient population. Higher frequencies result in greater intensities of pain (van Hees & Gybels, 1981; Torebjörk *et al.* 1984), the magnitude of perceived heat pain sensation being almost linearly related to firing frequency of nociceptor afferents. Therefore, if response frequency of nociceptors increases with rate of temperature change, higher rates should evoke pain of increased magnitude.

If steeper slopes of temperature rise produce increased frequency response of nociceptors, then the minimum afferent input required for psychophysical detection of pain will be attained earlier, that is, at a lower temperature. Results of the present study do show that higher rates of temperature rise along a finite temperature step evoke higher firing frequencies in C nociceptors, and higher magnitudes of perceived pain. This is in keeping with the demonstration that increasing rates of temperature rise result in decreasing psychophysical pain threshold (Yarnitsky & Ochoa, 1990). The present work thus provides a reasonable physiological explanation for a previous psychophysical observation.

It is suspected that the absence of difference in pain magnitude produced by rates of stimulation of 0·3 and 2·0 °C/s is due to compensation by longer temporal summation of the lower firing rate associated with the slowest rate of stimulus rise. At 0·3 °C/s stimulus duration was relatively long (over 30 s). Although subjects were instructed to estimate magnitude of pain only, the longer pain experience may have influenced their subjective pain judgements. However, for eight of thirteen subjects, a stimulus ramp rate of 2·0 °C/s evoked greater magnitude of pain than a ramp rate of 0·3 °C/s.

Role of C and Aδ nociceptors in signalling heat pain

In addition to C nociceptors, small myelinated (Aδ) nociceptors are involved in the mediation of heat-induced pain (Georgopoulos, 1976; Campbell & LaMotte, 1983). The present sample of nociceptors did not include Aδ afferents, and therefore whether these nociceptors contribute to the pain produced by heat stimuli, as presented in this study, cannot be ascertained. However, a major role for these nociceptors is unlikely for several reasons. First, psychophysical studies of first and second pain produced by heat have shown that first pain (presumably mediated by A fibres) is quickly suppressed with repeated heating (Price, Hu, Dubner & Gracely, 1977). Second, activity of C nociceptors recorded in monkeys and in humans (LaMotte, Thalhammer & Robinson, 1983; Torebjörk *et al.* 1984) best correlates with psychophysical measurements of heat pain threshold and magnitude. Third, heat pain threshold, magnitude of suprathreshold heat pain, and reaction time for heat pain are not altered significantly by conduction block of A fibres (Torebjörk *et al.* 1984; Jørum, Lundberg & Torebjörk, 1989; Yarnitsky & Ochoa, 1991). Fourth, psychophysical studies in which reaction time was used to determine peripheral conduction velocity at threshold for heat pain indicate that, for low rates of temperature rise ($< 2{\cdot}0$ °C/s), pain threshold is signalled by C fibre activity (Yarnitsky & Ochoa, 1990). Finally, in the present study, for temperature ramps of 2·0 °C/s the time to pain onset was signalled after initiation of afferent discharge in recorded C nociceptors. Had the pain been conducted by Aδ afferents, given their faster conduction velocity, the perception would have preceded recorded onset of firing of C nociceptors. It is possible, however, that for higher rates of temperature rise, there may be contribution to the pain experience by activity in human Aδ nociceptors.

It is concluded that magnitude of heat pain and discharge rate of C nociceptors evoked by ramps of heat stimuli between fixed limits increase with increasing rates of stimulus temperature rise. This positive correlation, together with the temporal relationship between onset of firing of C nociceptors and pain response, support previous observations, that under normal conditions, cutaneous heat pain is signalled primarily by activity in C fibres.

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