

C nociceptor activity in human nerve during painful and non painful skin stimulation

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SUMMARY Percutaneous recordings from more than one hundred single C fibres have been performed in the radial nerve of conscious human subjects. All these fibres belong to the polymodal C nociceptor group, being excited by mechanical and thermal and also by chemical stimulation. Conduction velocities showed a monophasic distribution with a mean value of 0.86 m/s (SD: 0.17). The mechanical threshold, measured with von Frey hairs, varied between 2.3 and 13.1 g. The receptive field was circular or elliptical; for 33 units the mean axes were 6 mm and 7 mm. Mechanically evoked C fibre discharge even up to more than 10 spikes/s was not necessarily accompanied by pain sensation. Nettle sting evoked an irregular C fibre discharge (maximum 10 spikes/s) accompanied by a pricking and burning sensation; the sensation of itch which was sometimes reported, was not correlated with the discharge frequency. C fibre activation by a chemical irritant (paint remover) also evoked an irregular discharge (maximum 3 to 6 spikes/s), accompanied by pricking and burning pain sensation. The C threshold for radiant heat usually lay below the subject's pain threshold. Increasing skin temperature produced increasing neural firing rate. The mean spike frequency rarely exceeded two spikes/s even with stimuli evoking strong heat pain. The occurrence of subjective heat pain response could be as well predicted from the C fibre spike frequency as from the skin temperature. It is concluded that nociceptive C input provoked by thermal or chemical stimuli correlates well with pain sensation. However, similar C input provided by mechanical stimulation which activates also A beta mechanoreceptors, did not necessarily produce pain sensation.

It has been shown in animal experiments during the past decades that there are several kinds of primary afferent neurons, classified as nociceptors. They are characterised by raised thresholds and are activated by stimuli that are potentially or frankly damaging to the skin.¹ As it is difficult to define a noxious threshold in terms of exact values of stimulus intensities, several authors^{2,3} prefer to define a nociceptor as a receptor whose dynamic properties extend into damaging stimulus intensities, irrespective of its threshold value. The concept of nociception enables neurophysiologists to study the behaviour—and the mechanisms underlying it—of an organism in response to noxious elements of the environment, without dealing with subjective experience. However, the

question of the relationship between nociception and pain sensation inevitably arises. In the literature the assumption is often made that stimuli which evoke pain sensation in man also do so in animals. In addition nociception and pain sensation are sometimes assumed to be the same, and a nociceptor is then freely regarded as a pain receptor.

We have recorded single unit activity of primary cutaneous afferents in conscious human subjects in response to a diversity of natural skin stimuli. The main purpose of these experiments was to establish the links between nociceptor activity and pain perception. The cutaneous input was manipulated in a measurable way while the subjective experience was recorded; experimental conditions were such as to minimise the variable influence of psychological factors on pain perception. In this report we will deal with the nociceptors with unmyelinated C afferents. It will be demonstrated

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that these afferents have similar properties to the animal "polymodal C nociceptors," and that this nociceptive input does not necessarily evoke pain sensation.

Methods

Recording methods

Unitary fibre activity in the superficial radial nerve was recorded percutaneously with tungsten micro-electrodes according to the technique described by Hagbarth and Vallbo.⁴ Details of our recording technique have been described previously.⁵ The subjects were healthy young adults; most of them were medical students or clinical staff assistants who were paid for participating. The experimental techniques were fully explained to them and informed consent was obtained. They were familiarised with the stimulation methods before nerve recording was started.

Stimuli

For quantitative mechanical stimulation, eight calibrated von Frey hairs were used; the forces of these hairs expressed in gram-weight, were as follows: 0.1; 0.9; 2.3; 5.7; 6.9; 13.1; 21.5; 90.

For thermal stimulation the radiation of a bulb was concentrated on the skin by a convex lens; the irradiated area was circular with a diameter of 1.5 cm. Within this area and close to the receptive field a small thermistor was fixed which measured the surface temperature and controlled the current of the bulb. Skin temperatures between 35°C and 55°C could be arranged.

The chemical stimuli used included intradermal injection of histamine and papain, nettle sting (*Urtica urens*), and cutaneous application of a commercially available paint remover containing methylene chloride dissolved in methanol.

Rectangular electrical pulses (0.3 Hz) delivered by a Grass S88 stimulator through a needle cathode in contact with the skin were used to measure conduction velocity.

Results

More than 100 afferent cutaneous C fibres were studied in the radial nerves. All these fibres belonged to the polymodal C nociceptor group, being excited by mechanical and thermal (fig 1) and also by chemical stimulation. Low threshold mechanoreceptive C fibres could not be demonstrated.

The conduction velocities were measured by percutaneous stimulation and showed a monophasic distribution with a mean value of 0.86 m/s (SD: 0.17) (fig 2). The C fibre terminals did not require intense electrical skin stimulation to be excited; sometimes the suprathreshold single shock stimulus was not even felt by the subject.

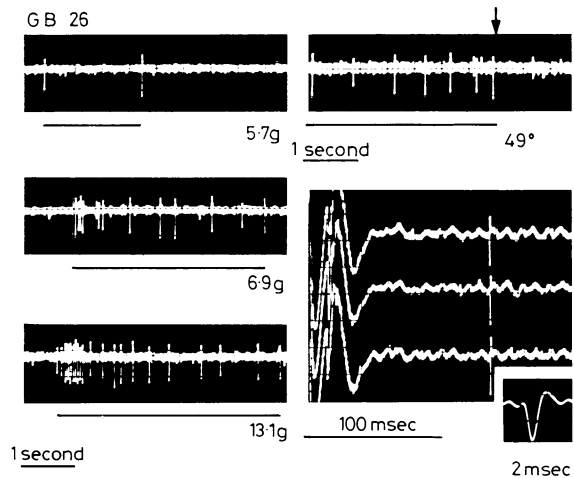


Fig 1 Responses of a single afferent C fibre recorded from the superficial radial nerve. Left: the receptive field was stimulated with three different von Frey hairs; the force exerted by these hairs is expressed in grams. The horizontal bars indicate the duration of the stimulus. These mechanical stimuli were not judged as painful by the subject. Right top: discharge of the same unit during application of radiation heat yielding a skin temperature of 49°C. At the arrow, the stimulus was interrupted because strong pain was reported by the subject. Right bottom: response to repetitive electrical stimulation of the receptive skin area with rectangular negative pulses (0.5 ms, 0.8 mA, 0.3 Hz). The distance between stimulation and recording site was 12 cm. The inset shows the triphasic form of the action potential with a prominent negative phase (negativity is downwards). The amplitude of the spike is about 100 μ V.

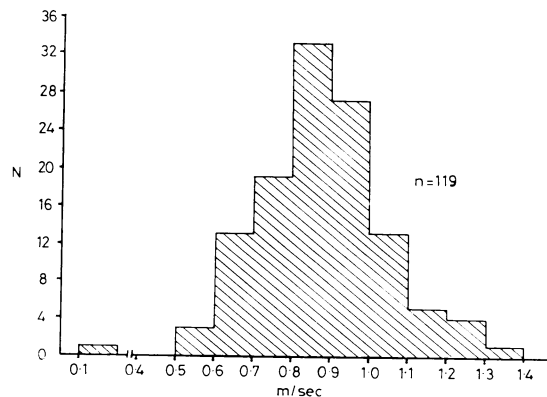


Fig 2 Distribution of conduction velocities of 119 polymodal nociceptive C fibres in the radial nerve. Mean value is 0.86 m/s.

Response to mechanical stimulation

All units studied were easily activated by pinching the skin or by pressure with pointed objects. In contrast they were not responsive to touch or pressure with a finger or rubbing with a cotton wool. The receptive field was circular or elliptical. For 33 units the mean axes were 6 mm and 7 mm; the largest receptive field was 10 mm by 15 mm and the smallest 2 mm by 3 mm. If explored with a fine needle or with a von Frey hair at threshold, a punctiform sensitivity was observed: several receptive spots (two to eight) were separated by unresponsive areas. The mechanical threshold, measured with von Frey hairs, varied between 2.3 and 13.1 g (fig 3). A stimulus-response function could not be achieved with precision since it was impossible to apply different von Frey hairs in exactly the same spot and since the C fibre discharge was variable for the same stimulus applied in different spots of the receptive area (fig 4). It was, however, clear that as a rule the discharge frequency increased with increasing stimulus intensity. Repetitive mechanical stimulation in the same spot provoked fatigue. When the stimulus was prolonged a clear adaptation was seen. The maximal mean spike frequency could be as high as 20 spikes per second when elicited by strong but bearable skin pinching. Stimulation with von Frey hairs even up to 90 g were mostly judged as

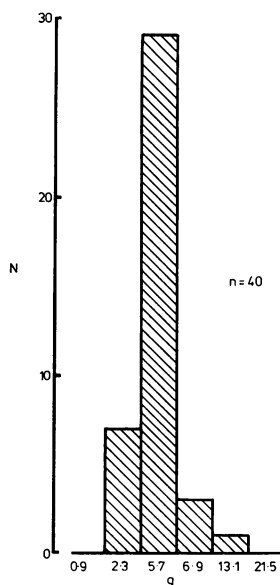


Fig 3 Distribution of thresholds for mechanical stimulation of 40 polymodal nociceptive C units, tested with calibrated von Frey hairs.

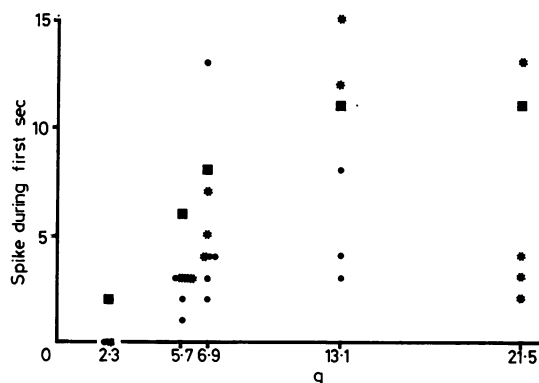


Fig 4 Response of three single C units (represented by different symbols) to different von Frey hairs. In ordinate the number of spikes during the first second of the discharge is given. Successive stimuli were not applied in exactly the same spot of the receptive field. These stimuli were not experienced as painful.

non-painful by the subjects; sometimes a slightly pricking sensation was experienced but commonly a non-painful pressure sensation was reported. These stimuli produced discharges up to 15 spikes per second. In our experience mechanically evoked C fibre discharges even up to more than 10 spikes per second might or might not be accompanied by pain sensation.

Response to chemical stimulation

Afferent C fibres could be activated by intra-dermal injection of histamine or papain; this method was rather inconvenient because the mechanical intervention of the injection itself was painful and could possibly alter the receptor sensitivity. A natural way of injecting histamine was realised by nettle sting (*Urtica urens*). It is known that the hairs of this plant contain histamine and acetylcholine⁶ and also serotonin.⁷ Keele⁸ argues that even the combination of these three products does not fully account for the immediate and long-lasting character of nettle pain and suggests that other components (for example the proteolytic enzyme solanain) are involved.

For our purpose, a leaf was gently cut from the plant and then brought in contact with the receptive skin area until a sting sensation was reported. This sensation started with a sharp pricking pain followed by pricking or burning pain with fluctuating intensity; sometimes itch was reported. Seven C units were tested in this way and they were all activated. After an initial discharge (maximum 10 spikes per second) the

activity usually diminished and became very irregular (fig 5B). Generally, there was a good correlation between C fibre activity and sensation: both started immediately after the sting, both had a fluctuating course with ups and downs. There was however no strict correlation between the intensity of C fibre activity and the quality of the reported sensation: the sensation of itch could be reported very early coinciding with spike rates of 3 to 5 per second, or could appear after a long period of burning and pricking pain, when C fibre activity was dying out (fig 5B).

For chemical skin stimulation we often used a commercially available paint remover. The great advantage of this substance is the gelatinous consistency which allows it to be applied to any area of the skin. After a delay varying from a few seconds to a few tens of seconds, a fairly strong pain is felt with a pricking and burning character; this pain disappears when the substance is removed. The skin remains a little reddish and shiny, but no blister appears. By testing the different components of this industrial preparation we identified methylene chloride dissolved in methanol as the pain producing element. With this product we tested the nociceptive C afferents in 17 experiments; in every case the fibre was responsive. The discharge pattern was irregular with maximal mean spike frequencies of three to six spikes per second. An example of C fibre response is shown in fig 5A; in this experiment the chemical irritant was left on the skin for a long time (almost 7 minutes). The chemical cutaneous stimulations used in our experiments did not apparently activate A beta mechanoreceptors. Nettle stimulation was tested in the receptive field of six mechanoreceptive units with A beta afferents (3 RA, 2 SA, 1 hair follicle receptor); the paint remover was applied to the receptive field of 4 SA and 3 RA units. None of these mechanoreceptors was excited.

Response to thermal stimulation

All C units studied could be activated by thermal radiation. Usually the threshold for activation was just below pain threshold; exceptionally, high temperatures were needed for C activation. As a rule increasing skin temperature also produced increasing neural firing rate (fig 6). The discharge pattern was rather irregular and with prolonged stimulation spikes tended to group themselves. The mean spike frequency was rather low even with strong painful stimuli; we never registered values in excess of 10 spikes per second. The possible role of the polymodal C nociceptors in

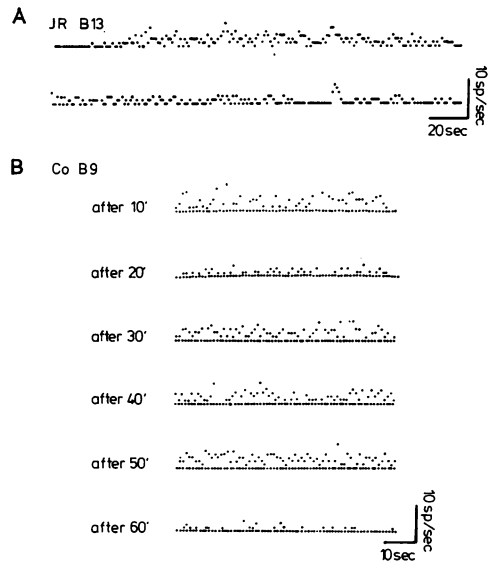


Fig 5 A. Afferent C fibre activity during application of an irritant chemical (a paint remover containing methylene chloride and methanol) on the receptive field. Both discharge and burning sensation started after 20 s. Maximal firing rate was 5 to 6 spikes per second. During the second half of application time the discharge was somewhat diminished and appeared discontinuously. This paralleled the pain sensation which was only slight and fluctuated during the second half. B. Afferent C fibre activity in response to stimulation with nettles. Six samples from a 1 hour observation are shown. The discharge started immediately after nettle application (not shown), accompanied by a pricking and burning sensation. Several weals developed at the border of and outside the receptive field. After 20 minutes both neural activity and sensation diminished temporarily; however the sensation remained burning and pricking in character until after 60 min itch was reported, at that time the fibre activity was of low frequency.

evaluating painful heat stimuli and in contributing to heat pain sensation was studied in a series of eight experiments on eight different C units. The question we tried to answer by these experiments was the following: is heat-pain sensation better correlated with C fibre activity or with skin temperature? In other words: can the occurrence of a pain response be predicted better from the skin temperature or from the single C fibre discharge?

Stimuli from 40°C to 55°C were given in a random order; between two stimuli the skin temperature was let to cool down to 30°C (resulting in a stimulus interval from 20 to 40 seconds). In addition to the signalling of the first pricking or

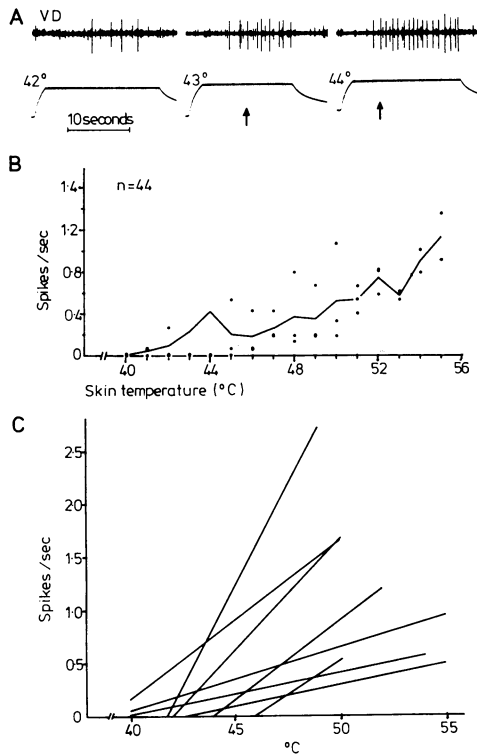


Fig 6 A. Examples of single C fibre response to radiant heat stimulation with different skin temperatures. Arrows indicate pain report. B. Responses of the same unit as in A to 44 radiant heat stimuli with skin temperatures between 40° and 55°C. C fibre activity is measured as mean frequency per second during the stimulus plateau. Points represent individual trials; the curve joins the mean values. C. Linear regression lines computed from the discharges of eight different C nociceptors. The number of stimuli in the individual experiments varied from 6 to 44, with a total of 183.

burning sensation the subjects were asked to interrupt the stimulus by saying "stop" when pain became strong; this was done to avoid lesions due to burning. If the stimulus was tolerated the temperature plateau was maintained for 15 seconds. C fibre activity was measured as the mean firing frequency per second during the stimulus plateau. The relation between skin temperature and C fibre discharge is represented by the regression lines computed for each of the eight experiments, shown in the lower part of fig 6. From the total of 192 stimuli about one half (91) were judged as painful; from these 91 painful stimuli 37 were considered as very painful.

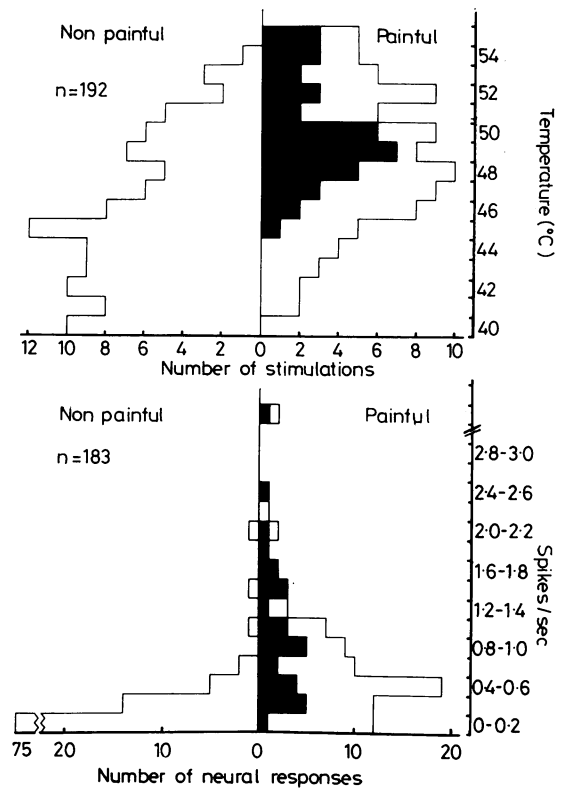


Fig 7 Upper diagram: distribution of 192 heat stimuli (from eight experiments) in the classes of judgment in function of the skin temperature. Black compartment represents strong pain. All stimuli of 55°C were judged as painful, all stimuli of 40°C as non-painful. Between these two extreme values the percentage of pain response increased with the temperature. The 50% value was at 46°C. Lower diagram: distribution of 183 C fibre responses (from the same eight experiments) according to the subject's judgments. C fibre activity higher than 0.4 spikes/s is mostly (86%) accompanied by report of pain.

The distribution of the stimuli in the classes of judgment in function of the skin temperature is shown in fig 7 (upper diagram). All stimuli of 55°C were judged as painful and all stimuli of 40°C as non-painful; between these two extreme values, the percentage of pain response increased with the temperature; the 50% value was at 46°C. In a similar way the stimuli were classified and distributed as a function of the neural responses (fig 7, lower diagram). For convenient arrangement the neural responses were divided into the same number of classes (16) as the number of temperature values. In nine stimulations the "stop"

answer occurred before the temperature plateau was reached, resulting in a total number of 183 stimuli that could be analysed. C fibre activity of more than 0.4 spikes per second was accompanied by pain response in 86% of the trials; stimuli giving rise to discharges of less than 0.2 spikes per second were mostly (also 86%) judged as non-painful.

In order to answer the question if subjective response correlated better with the skin temperature or with the unitary C fibre activity, the point-biserial correlation was computed (table). All correlation values were significantly different from zero ($p < 0.01$). The correlations between C fibre activity and subjective response were slightly better than those between skin temperature and subjective response, but these differences were not significant. It must be realised that by pooling the data from the eight experiments, the correlations are obscured compared with those in a single individual, but on the other hand pooling takes into account the different thresholds of the C nociceptors. From the data it can be concluded that a pain response can be predicted as well from the skin temperature as from the C fibre discharge; therefore it may well be that the subjective judgment is based on C nociceptor input.

Heat stimuli did not activate mechanoreceptors with A beta afferents. On the contrary, the spontaneous activity which was present in some of these afferents was suppressed by radiation heat (fig 8A). It is against this depressed background of large fibre activity that the C nociceptors start firing when the skin temperature reaches their activation threshold (fig 8B).

Table Point-biserial coefficients of correlation (with standard error (s) for testing differences from zero)

Sensory categories	Skin temperature	C fibre discharge
Painful-non painful	0.44 (s: 0.07) (n=192)	0.52 (s: 0.07) (n=183)
Weak pain-strong pain	0.28 (s: 0.10) (n=91)	0.30 (s: 0.11) (n=82)

Discussion

In the unmyelinated afferent fibre population of human cutaneous nerves, warm receptive fibres⁹ and a majority of high threshold afferents responsive to mechanical, thermal and chemical stimuli, have been demonstrated.¹⁰⁻¹³ As the latter have the same functional properties as in sub-human species, the terminology of "polymodal C nociceptor" used by physiologists has been adopted. The average threshold for mechanical

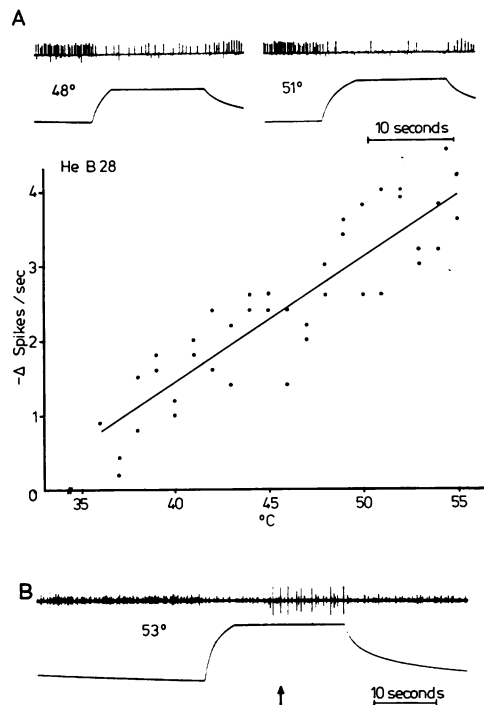


Fig 8 Suppression by radiation heat of spontaneous activity in slowly adapting A beta mechanoreceptors. A. Recording was made from a SA mechanoreceptor (threshold for mechanical stimulation: < 0.1 g; conduction velocity: 42 m/s) with an irregular spontaneous activity of three to eight spikes per second. The receptive field was heated 39 times with temperatures from 36° to 55°C. At the top two examples are given of suppression of the spontaneous activity. In the diagram the data are represented together with the linear regression line. In ordinate the suppression is expressed as the difference between the mean firing frequency per second during the first 5 s of the stimulus plateau and the mean firing frequency during the last 5 s before stimulation. B. In this recording the background activity of low amplitude was mechanoreceptive activity distant from the electrode tip. Heating the skin at 53°C diminished this activity. It is against this depressed background of large fibre activity that a C nociceptor started firing. The arrow indicates report of pain.

stimulation is about 5 to 6 g in both animal²⁻¹⁴ and man. The threshold of these fibres for radiation heat is usually between 40° and 45°C in the cat¹⁵ and in the monkey;¹⁴ this agrees well with the values we obtained in man. These values lay below the pain threshold in man. The discharge rate evoked by quantified heat stimuli is also similar in man and in animal. Both in the

cat¹⁵ and in the monkey,¹⁴ a rather low mean firing rate below 3 spikes per second is found with a stimulus of 50°C. LaMotte and Campbell¹⁴ found in the monkey that the heat-evoked discharge varied inversely with the intensity of a preceding stimulation: this "temporal position effect" could also be demonstrated for human C fibres.⁵ This similarity is stressed as it shows that combined neurophysiological animal work and psychophysical measurements in human subjects are useful for the investigation of the role of nociceptive C fibres.

Low threshold C mechanoreceptors could not be demonstrated in the human radial nerve. This is in contrast with the cutaneous nerve of the cat where they form 36% of the afferent C fibre population.² This difference becomes less important if we compare man with monkey where this fibre type is rare in distal skin regions.¹⁶ The absence of this receptor type in human skin could explain the absence of touch sensation in partial nerve block when only C fibres are conducting.

The main purpose of this study on single C fibres in human subjects was to find out if activity in this type of nociceptive afferent could be related to pain sensation. Our findings show that there is a rather good correlation between nociceptive C fibre discharge and pain sensation if the discharge is evoked by chemical or thermal stimulation. In the latter case the occurrence of subjective pain response can be as well predicted from the C fibre spike frequency as from the skin temperature. In another study⁵ it was concluded that polymodal C nociceptors might also be responsible for the quantitative aspects of heat pain sensation. From these studies one may not state that heat pain is necessarily based on C fibre activity, since afferent delta fibres may also play a role in both chemical and heat pain sensations.

The finding that very low frequencies of C fibre discharge in response to heat stimulation is not necessarily accompanied by pain sensation suggests that some summation mechanism is necessary for conscious pain experience. This is in contrast to the mechanoreceptive system where the generation of a single action potential in a RA mechanoreceptor at the finger-tip coincides with the subjective detection of the stimulus.¹⁷

An important finding in our experiments is that simultaneous excitation of A beta mechanoreceptors and polymodal C nociceptors by mechanical stimulation does not necessarily provoke pain even in the presence of rather high frequency C fibre discharge. C fibre activity up to 10 spikes per second evoked by von Frey hairs or by pinch-

ing the skin often was accompanied by sensation of pressure without any pain. Bearing in mind that strong heat pain was only rarely accompanied by C fibre discharge above 2 spikes per second, it is evident that we are actually dealing with a strong activation of a peripheral nociceptive system without evoking pain sensation. Single fibre recording experiments in man demonstrate that C fibres can easily be excited by mechanical stimuli without any discomfort for the subject, for example by squeezing the skin or by gentle pressure with the finger nails or with von Frey hairs. It is not claimed that these stimuli are not threatening the skin, probably they do; but they are not painful. One could argue that von Frey hair or skin folding activated a far smaller number of C nociceptors than the heat stimulus (irradiating a skin surface of about 1.75 cm²) that we used, and that the pain sensation evoked by heat could in part be the result of a greater degree of spatial summation. However, stimulating with several von Frey hairs at the same time at neighbouring points does not change the sensation of pressure into a sensation of pain, although in this condition as many C fibres can be excited as by the heat stimulus.

Supporters of the specificity theory of pain generally claim that afferent impulses in nociceptive C or A delta fibres are both necessary and sufficient, as regards peripheral input, to evoke pain sensations in conscious man. Such a statement is not fully supported by our findings. Afferent impulses in nociceptive C fibres apparently only evoke pain sensations if other peripheral conditions are satisfied. Our experience about the mechanical excitability of C nociceptors has forced us to realise that considerable activation of cutaneous nociceptors takes place in many conditions of daily life that are not experienced as painful, such as combing the hair, using scissors, eating with knife and fork, playing the guitar etc. Nociceptors are also excited when the patient's sensation is tested by examining two-point discrimination of graphesthesia. Mechanical stimulation above C fibre threshold excites both A beta mechanoreceptors and C nociceptors. Chemical or heat stimulation does not activate A beta mechanoreceptors; a heat stimulus can even suppress their activity. It is a likely hypothesis that the co-activation of A beta mechanoreceptors has an inhibitory influence somewhere in the central nervous system on the nociceptive input. This hypothesis was put forward by Noordenbos,¹⁸ by Melzack and Wall¹⁹ in their gate-control theory, and by other investigators of cutaneous sensibility.

This inhibitory influence of beta input on nociceptive C input could be interpreted as a way of subordinating the function of nociception to the explorative role of the skin. Cutaneous exploration is served in the first place by mechanoreception. It would be impaired if every mechanical stimulus which threatens the skin gave rise to pain sensation. Of course, nature could have raised the mechanical threshold for cutaneous nociceptors, but by keeping the threshold to the strictly noxious level and providing at the same time a pain inhibitory system, another function of the C nociceptors remained possible, namely a contribution to the repair process by means of the axon reflex-induced vasodilatation.

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