

---

## Nociceptor Activation and Pain

E. Torebjork

*Phil. Trans. R. Soc. Lond. B* 1985 **308**, 227-234

doi: 10.1098/rstb.1985.0023

---

### Email alerting service

Receive free email alerts when new articles cite this article - sign up in the box at the top right-hand corner of the article or click [here](#)

---

To subscribe to *Phil. Trans. R. Soc. Lond. B* go to: <http://rstb.royalsocietypublishing.org/subscriptions>

---

## Nociceptor activation and pain

BY E. TOREBJÖRK

*Department of Clinical Neurophysiology, University Hospital, S-75185 Uppsala, Sweden*

This paper reviews advances in our knowledge on the physiological properties of human nociceptors and their capacity to signal pain. Conventional microneurography was used in combination with intraneural microstimulation in subjects who estimated the magnitude of pain from nociceptor stimulation. The experimental evidence favours the notion that C polymodal nociceptors can provide a peripheral neuronal basis for determination of heat pain threshold and also an essential peripheral code for suprathreshold magnitude judgements of heat pain. Furthermore, sensitized C polymodal nociceptors can contribute to hyperalgesia after a mild heat injury to hairy skin. Temporal summation is documented for dull, delayed C fibre pain, which is different in quality and less accurately projected than the fast, sharp pain from high-threshold A  $\delta$  nociceptors. A segmental organization is shown for projected and referred pain from deep structures. Examples are given of central inhibition of pain by a prostaglandin synthetase inhibitor, and by physical manoeuvres such as vibration and cooling. Recent reports on microneurographic findings after nerve injury indicate that the technique may be useful for future studies on pathophysiological pain mechanisms.

### INTRODUCTION

Human microneurography (Vallbo & Hagbarth 1968) involves microelectrode recordings of nerve impulses in intact nerves in awake human subjects. The technique has been used to study the response properties of various types of sensory detectors in man (Vallbo *et al.* 1979), and has allowed comparisons with sensory receptors described in animals. The great advantage of the technique is that the subjects will report what they feel when their peripheral sensory units are stimulated. Thus not only can the nerve fibres and their receptors be studied, but also the perceptual capacity of the central nervous system. In particular, the technique of electrical intraneural microstimulation, i.n.m.s. (Torebjörk & Ochoa 1980), takes full advantage of the discriminative capacity of the human brain. Sensations can be dissected into their most elementary components (Ochoa & Torebjörk 1983), thereby allowing new insights into processing of sensory events, including pain.

The following sections include brief descriptions of some physiological properties of human nociceptors. The main emphasis is focused on psycho-physical correlations between nociceptor stimulation and pain.

### METHODS

Microneurography and intraneural microstimulation were performed in awake human subjects by using tungsten microelectrodes coated with epoxy resin, whose tip diameters were of the order of 1–5  $\mu\text{m}$ . These were inserted percutaneously into a peripheral nerve at an accessible site, such as the median nerve at the wrist or above the elbow, the radial or the ulnar

[ 9 ]

nerve at the wrist, or the peroneal nerve at knee or ankle levels. A reference electrode was inserted a few millimetres under the skin nearby. By means of a switch in the preamplifier, the electrodes could be connected to either the input of a storage oscilloscope for microneurographic recording, or to a stimulator delivering rectangular electrical pulses of 0.25 ms duration and intensities ranging from 1 to 3  $\mu\text{A}$ , repeated at frequencies of 1–100 Hz in trains lasting for 2–20 s.

Details of the techniques and the psychological methods have been described elsewhere (Torebjörk & Ochoa 1980; Torebjörk 1981; Vallbo 1981; Ochoa & Torebjörk 1983; Vallbo *et al.* 1984; Torebjörk *et al.* 1984a, c).

## RESULTS

### *General properties of C polymodal nociceptors in man and monkey*

Recordings, particularly from the radial and peroneal nerves, have shown that human hairy skin has a rich supply of nociceptors with unmyelinated (C) fibres (Torebjörk & Hallin 1970, 1974, 1976; van Hees & Gybels 1972; Torebjörk 1974, 1979). Such nociceptors respond to mechanical, thermal and chemical stimuli of near-painful or painful intensity, and resemble in many respects the C polymodal nociceptors identified in the cat (Iggo 1959; Bessou & Perl 1969) and the monkey (Beitel & Dubner 1976; Kumazawa & Perl 1977). Indeed, the discharge frequencies and response profiles at temperatures ranging from 39 to 51 °C were virtually identical in a population of fairly low threshold C polymodal nociceptors in *Macaca fascicularis* compared with a population of human C polymodal nociceptors with similar thresholds (LaMotte *et al.* 1984).

### *Heat thresholds for C nociceptors and subjective thresholds for heat pain*

Human C nociceptor thresholds for heat stimuli applied to hairy skin have been found to range from about 40 to 47 °C (van Hees & Gybels 1981). These can be compared with heat pain thresholds ranging from 41 to 49 °C in normal subjects (LaMotte *et al.* 1982). Selective blocking of conduction in myelinated (A) fibres by compression or ischaemia did not alter heat pain thresholds (LaMotte *et al.* 1982). These observations suggest that C polymodal nociceptors can provide a peripheral neuronal basis for determination of heat pain threshold, at least in hairy skin.

### *Suprathreshold response functions of C nociceptors and magnitude ratings of pain*

Intensity–response functions have been obtained for 14 C polymodal nociceptors by relating the total number of impulses evoked per stimulus to stimulus temperature in the range 39–51 °C. For most nociceptors the number of impulses increased fairly linearly with increasing temperature, even though a few nociceptor responses saturated at 51 °C. Corresponding scale ratings of pain were obtained in the same experiments in which nociceptor recordings were made. When averages were computed for all 14 tests, a nearly linear relation was found between the mean number of C nociceptor impulses and the median ratings of pain (Torebjörk *et al.* 1984a). The result indicates that C nociceptors can provide an essential peripheral neuronal code for magnitude judgements of heat pain. This notion is supported by the observation that C nociceptors are capable of signalling small increments of the order of 0.1–0.5 °C on an already painful base temperature of 48 °C, and this capacity is matched by the capacities of humans to detect and rate such increments as painful (Robinson *et al.* 1983).

*Sensitization of C nociceptors and hyperalgesia*

Immediately after a mild heat injury (50 °C for 100 s) the C nociceptors in hairy skin exhibited fatigue, and pain ratings were less than before the injury (hypoalgesia). Within 5–10 min after the injury, some nociceptor thresholds were lower and the responsiveness to suprathreshold stimuli were enhanced, characterizing nociceptor sensitization. Pain ratings during this period indicated lowering of pain thresholds and greater than normal rating of suprathreshold stimuli (hyperalgesia). A compression block of conduction in A fibres did not alter these changes in pain ratings. Thus it is concluded that C nociceptors can contribute to hyperalgesia after a mild injury to hairy skin (Torebjörk & Hallin 1977; Torebjörk *et al.* 1984a). However, more intense heat stimuli have been shown to produce sensitization of monkey A  $\delta$  nociceptors, and nociceptors of this type are likely to contribute to cutaneous hyperalgesia after severe injuries, particularly in glabrous skin (Meyer & Campbell 1981).

*Temporal summation of C fibre pain*

While there was fairly good matching between activity in a population of C nociceptors and pain, mismatching was often observed between activity in a single C nociceptor and simultaneous pain ratings. As many as 9 of 14 nociceptors responded with a few impulses to temperatures that were rated as nonpainful (Torebjörk *et al.* 1984a), confirming previous observations that low rates of impulses in a single C nociceptor need not evoke pain (Torebjörk & Hallin 1974; van Hees & Gybels 1981). It was evident that summation of C nociceptor impulses was necessary to evoke pain (Torebjörk 1981). An example of temporal summation of pain is shown in figure 1. The graphs are voltage analogues of pain ratings of an individual subject during 20 s trains of i.n.m.s. at fixed stimulus intensity and various frequencies. At 1 Hz pain was not signalled until 13 s after the beginning of the stimulus train, with progressively shorter latencies at 3, 5 and 10 Hz. Pain also peaked earlier and ratings were higher with higher stimulus frequency. Since the stimulus intensity was not altered it must be presumed that the same number of axons were activated in each trial and that the observed changes in pain ratings were due to the effects of temporal summation of impulses. Also, the duration of pain could outlast the duration of C nociceptor activity by several seconds, even when conduction delays to the central nervous system were compensated for (LaMotte *et al.* 1984). Again, this observation suggests a temporal summation mechanism for C fibre pain at central levels. Such summation may occur already at the dorsal horn. It is known that the discharge of dorsal horn neurons becomes progressively larger in response to repetitive electrical stimulation of C afferent fibres (Mendell & Wall 1965), and that heat-evoked discharge in dorsal horn neurons receiving input from C nociceptors can continue beyond the cessation of C fibre activity (Handwerker *et al.* 1975).

*Pain from intraneural stimulation of A  $\delta$  and C nociceptive fibres*

Human subjects could discriminate two types of cutaneous pain elicited by intraneural microstimulation in the median nerve (Torebjörk & Ochoa 1980). One type had a dull aching quality and was projected to diffusely delineated areas of skin 5–10 mm across, often larger in the palm than in the finger tips (figure 2). Microneurographic recordings from intraneural sites where dull pain was felt at liminal stimulus intensity for sensory detection often revealed signals from bundles of C nociceptive fibres close to the electrode tip. The other type of pain

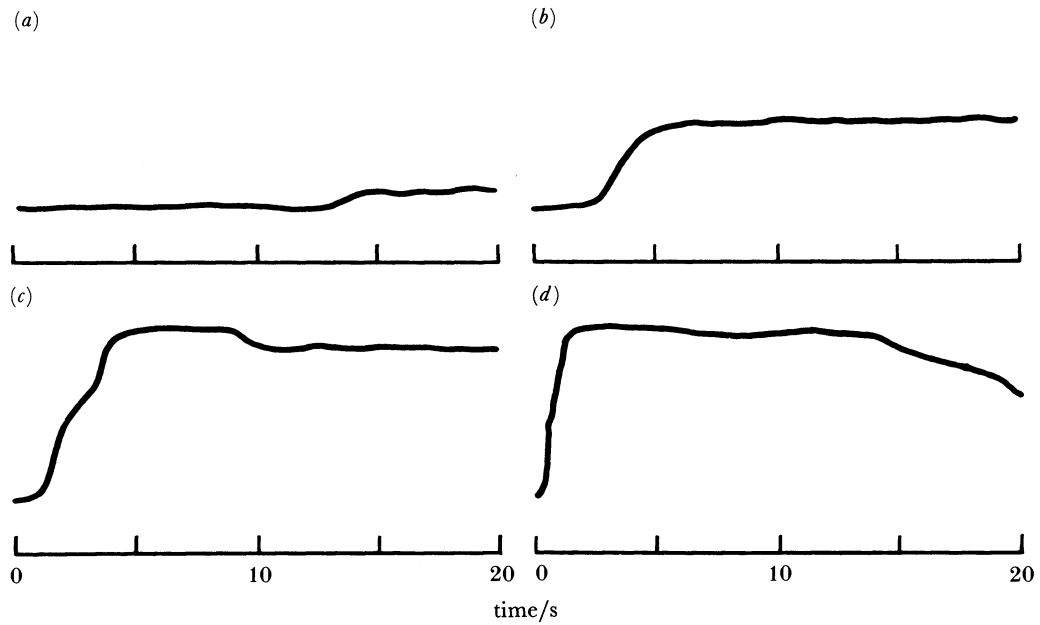


FIGURE 1. Voltage analogue of a subject's pain ratings during intraneural stimulation at constant intensity for 20 s periods at (a) 1 Hz, (b) 3 Hz, (c) 5 Hz and (d) 10 Hz. Note delayed and low pain rating at 1 Hz, in contrast with the shorter latencies and steeper increases in pain ratings at higher frequencies. (Modified from Torebjörk *et al.* (1984c).)

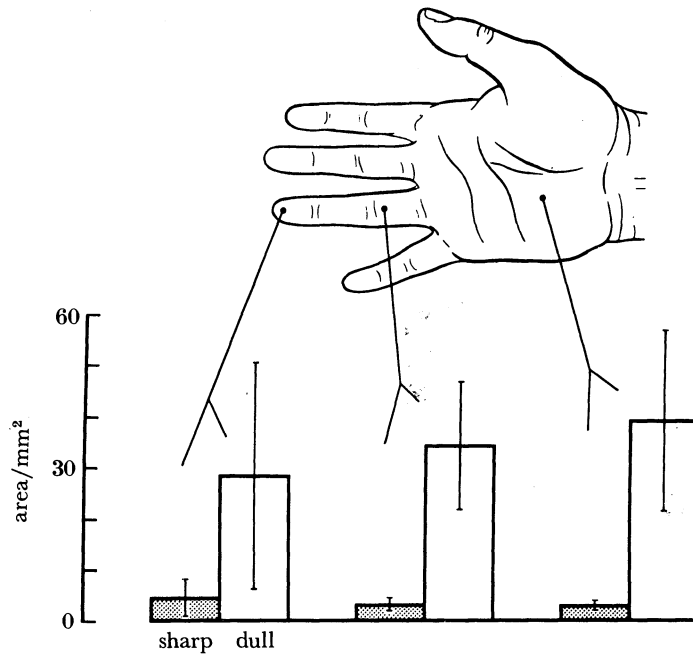


FIGURE 2. Areas of projected fields of pain from intraneural stimulation in the median nerve. Sharp pain (filled columns) was projected to significantly smaller areas than dull pain (open columns) both in finger tips, fingers and palm. (Data compiled from Schady *et al.* (1983).)

was sharp pricking or stinging and was projected to small, punctiform areas of skin, significantly smaller than the projection areas of dull pain (figure 2). Recordings from such sites where stinging pain was felt at liminal stimulus intensity for detection sometimes revealed single unit impulses from A  $\delta$  nociceptive fibres with receptive fields located at the site of projected sharp pain. Typically, such A  $\delta$  nociceptors in the glabrous skin of the hand had very high mechanical thresholds and did not respond to noxious heat. The receptive fields were small but difficult to map in detail because of the high-intensity stimuli that had to be used to elicit responses. Such very high-threshold nociceptors probably would not have been detected in conventional microneurographic recordings without microstimulation. However, it was not uncommon for i.n.m.s. to induce stinging pain projected to a skin region where no receptor could be identified. This is perhaps not surprising in view of the known difficulties involved in recording activity from single A  $\delta$  fibres in man (Adriaensen *et al.* 1983).

In conclusion, the results from intraneural microstimulation support previous reports of a role of C nociceptive fibres in dull delayed pain and of A  $\delta$  nociceptive fibres in fast sharp pain (Zotterman 1933; Collins *et al.* 1960; Torebjörk & Hallin 1973; Mackenzie *et al.* 1975). Furthermore, the A  $\delta$  nociceptive system seems more accurate in localizing and delineating pain than the C nociceptive system.

#### *Referred pain*

Superficial pain from intraneural stimulation in cutaneous fascicles of the median nerve was typically projected to skin areas within the innervation territory of the median nerve (Schady *et al.* 1983; Torebjörk *et al.* 1984*b*). By contrast, deep pain projected to muscle could be referred to regions outside those supplied by the impaled nerve (Torebjörk & Ochoa 1980). In a study on 26 median nerve muscle fascicles, it was found that pain was projected not only to muscles in the forearm, but in 7 cases was also referred to the upper arm and chest wall, sometimes mimicking angina pectoris. In these cases, projected and referred pain involved muscles supplied by the same spinal segment (Torebjörk *et al.* 1984*b*). This suggests convergence of nociceptive inputs at the level of the dorsal horn. The fact that referred pain was observed only when muscle fascicles were stimulated implies that such convergence is more common for nociceptive fibres from muscle than from skin.

#### *Central inhibition of pain*

Because intraneural microstimulation bypasses peripheral receptors, the technique can be used to study central effects of analgesic agents or manoeuvres on intraneurally induced pain (Torebjörk *et al.* 1984*c*). In this way it was shown that a prostaglandin synthetase inhibitor, zomepirac sodium, has a central analgesic action in addition to possible peripheral inhibitory effects on nociceptor sensitization (Schady & Torebjörk 1984). Furthermore, vibration and cooling of skin produced analgesia at central levels (figure 3), quite separate from any conceivable additional effects on receptor sensibility (Bini *et al.* 1984).

#### *Pathological pain*

So far, most experiments have been performed in normal subjects to obtain solid facts about the normal physiology of pain. It is expected that this collection of normal data will serve as a valuable reference for pathophysiological studies on patients with pain. A few studies have been published on the influence of the sympathetic system on causalgic pain (Wallin *et al.* 1976;



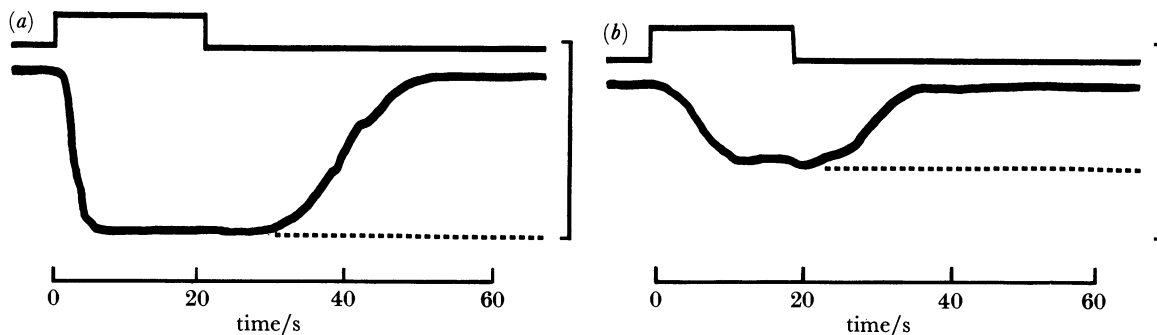


FIGURE 3. Effects on a subject's rating of intraneurally evoked pain when vibration (*a*) and cooling (*b*) were applied to the skin area to which pain was projected. Periods of natural skin stimuli are indicated in upper traces and pain ratings in lower traces (no pain at lower ends of vertical bars). The reduction of pain can be explained only by central inhibitory mechanisms. (Modified from Bini *et al.* (1984).)

Torebjörk & Hallin 1979), and on ectopic impulse generation in neuromas and other nerve disorders with paresthesiae (Torebjörk *et al.* 1979; Ochoa & Torebjörk 1980; Nyström & Hagbarth 1981; Ochoa *et al.* 1982; Nordin *et al.* 1984). However, relevant data are fragmentary, and much more work is needed to increase our understanding of the difficult problems of pathological pain.

#### CONCLUSION

The combined use of microneurography and intraneural microstimulation in psychophysiological experiments performed in awake human subjects has provided new insights into peripheral and central pain mechanisms under normal conditions. It is a challenge for the future to apply these techniques to the study of pathological pain.

This work was supported by grants from the Swedish Medical Research Council (nos 5206 and 6153).

#### REFERENCES

- Adriaensen, H., Gybels, J., Handwerker, H. O. & Van Hees, J. 1983 Response properties of thin myelinated (A- $\delta$ ) fibres in human skin nerves. *J. Neurophysiol.* **49**, 111–112.
- Beitel, R. E. & Dubner, R. 1976 The response of unmyelinated (C) polymodal nociceptors to thermal stimuli applied to the monkey's face. *J. Neurophysiol.* **39**, 1160–1175.
- Bessou, P. & Perl, E. R. 1969 Response of cutaneous sensory units with unmyelinated fibers to noxious stimuli. *J. Neurophysiol.* **32**, 1025–1043.
- Bini, G., Cruccu, G., Hagbarth, K.-E., Schady, W. & Torebjörk, H. E. 1984 Analgesic effect of vibration and cooling on pain induced by intraneural electrical stimulation. *Pain* **18**, 239–248.
- Collins, W. F. Jr, Nulsen, F. E. & Randt, C. T. 1960 Relation of peripheral nerve fiber size and sensation in man. *Arch. Neurol., Chicago* **3**, 381–385.
- Handwerker, H. O., Iggo, A. & Zimmerman, M. 1975 Segmental and supraspinal actions on dorsal horn neurons responding to noxious and non-noxious skin stimuli. *Pain* **1**, 147–165.
- Iggo, A. 1959 Cutaneous heat and cold receptors with slowly conducting (C) afferent fibers. *Q. Jl exp. Physiol.* **44**, 362–370.
- Kumazawa, T. & Perl, E. R. 1977 Primate cutaneous sensory units with unmyelinated (C) afferent fibers. *J. Neurophysiol.* **40**, 1325–1338.
- LaMotte, R. H., Thalhammer, J. G., Torebjörk, H. E. & Robinson, C. J. 1982 Peripheral neural mechanisms of cutaneous hyperalgesia following mild injury by heat. *J. Neurosci.* **2**, 765–781.

- LaMotte, R. H., Torebjörk, H. E., Robinson, C. J. & Thalhammer, J. G. 1984 Time-intensity profiles of cutaneous pain in normal and hyperalgesic skin: a comparison with C-nociceptor activities in monkey and human. *J. Neurophysiol.* **51**, 1434–1450.
- Mackenzie, R. A., Burke, D., Skuse, N. F. & Lethlean, A. K. 1975 Fibre function and perception during cutaneous nerve block. *J. Neurol. Neurosurg. Psychiat.* **38**, 865–873.
- Mendell, L. M. & Wall, P. D. 1965 Responses of single dorsal cord cells to peripheral cutaneous unmyelinated fibres. *Nature, Lond.* **206**, 97–99.
- Meyer, R. A. & Campbell, J. N. 1981 Myelinated nociceptive afferents account for the hyperalgesia that follows a burn to the hand. *Science, Wash.* **213**, 1527–1529.
- Nordin, M., Nyström, B., Wallin, U. & Hagbarth, K.-E. 1984 Ectopic sensory discharges and paresthesiae in patients with disorders of peripheral nerves, dorsal roots and dorsal columns. *Pain*. (In the press.)
- Nyström, B. & Hagbarth, K.-E. 1981 Microelectrode recordings from transected nerves in amputees with phantom limb pain. *Neurosci. Lett.* **27**, 211–216.
- Ochoa, J. L. & Torebjörk, H. E. 1980 Paresthesiae from ectopic impulse generation in human sensory nerves. *Brain* **103**, 835–853.
- Ochoa, J. L. & Torebjörk, H. E. 1983 Sensations evoked by intraneural microstimulation of single mechanoreceptor units innervating the human hand. *J. Physiol., Lond.* **342**, 633–654.
- Ochoa, J. L., Torebjörk, H. E., Culp, W. J. & Schady, W. 1982 Abnormal spontaneous activity in single sensory nerve fibers in humans. *Muscle Nerve* **5**, S74–S77.
- Robinson, C. J., Torebjörk, H. E. & LaMotte, R. H. 1983 Psychophysical detection and pain ratings of incremental thermal stimuli: a comparison with nociceptor responses in humans. *Brain Res.* **274**, 87–106.
- Schady, W. & Torebjörk, H. E. 1984 Central effects of zomepirac on pain evoked by intraneural stimulation in man. *J. clin. Pharmac.* (In the press.)
- Schady, W., Torebjörk, H. E. & Ochoa, J. L. 1983 Peripheral projections of nerve fibres in the human median nerve. *Brain Res.* **277**, 249–261.
- Torebjörk, H. E. 1974 Afferent C units responding to mechanical, thermal and chemical stimuli in human non-glabrous skin. *Acta physiol. scand.* **92**, 374–390.
- Torebjörk, H. E. 1979 Activity in C nociceptors and sensation. In *Sensory functions of the skin in humans* (ed. D. R. Kenshalo), pp. 313–321. New York: Plenum Press.
- Torebjörk, H. E. 1981 Human microneurography and the problems of pain. *Jap. J. EEG EMG (Suppl.)*, pp. 169–175.
- Torebjörk, H. E. & Hallin, R. G. 1970 C-fibre units recorded from human sensory nerve fascicles in situ. *Acta soc. med. ups.* **75**, 81–84.
- Torebjörk, H. E. & Hallin, R. G. 1973 Perceptual changes accompanying controlled preferential blocking of A and C fibre responses in intact human skin nerves. *Expl Brain Res.* **16**, 321–332.
- Torebjörk, H. E. & Hallin, R. G. 1974 Identification of afferent C units in intact human skin nerves. *Brain Res.* **67**, 387–403.
- Torebjörk, H. E. & Hallin, R. G. 1976 Skin receptors supplied by unmyelinated (C) fibres in man. In *Sensory functions of the skin in primates* (ed. Y. Zotterman), pp. 475–485. Oxford: Pergamon Press.
- Torebjörk, H. E. & Hallin, R. G. 1977 Sensitization of polymodal nociceptors with C fibres in man. *Proc. int. Un. physiol. Sci.* **13**, 758.
- Torebjörk, H. E. & Hallin, R. G. 1979 Microneurographic studies of peripheral pain mechanisms in man. In *Advances in pain research and therapy* (ed. J. J. Bonica, J. C. Liesbeskind & D. Albe-Fessard), vol. 3, pp. 121–131. New York: Raven Press.
- Torebjörk, H. E., LaMotte, R. H. & Robinson, C. J. 1984a Peripheral neural correlates of magnitude of cutaneous pain and hyperalgesia: simultaneous recordings in humans of sensory judgements of pain and evoked responses in nociceptors with C-fibers. *J. Neurophysiol.* **51**, 325–339.
- Torebjörk, H. E. & Ochoa, J. L. 1980 Specific sensations evoked by activity in single identified sensory units in man. *Acta physiol. scand.* **110**, 445–447.
- Torebjörk, H. E., Ochoa, J. L. & McCann, F. V. 1979 Paresthesiae: abnormal impulse generation in sensory nerve fibres in man. *Acta physiol. scand.* **105**, 518–520.
- Torebjörk, H. E., Ochoa, J. L. & Schady, W. 1984b Referred pain from intraneural stimulation of muscle fascicles in the median nerve. *Pain* **18**, 145–156.
- Torebjörk, H. E., Schady, W. & Ochoa, J. L. 1984c A new method for demonstration of central effects of analgesic agents in man. *J. Neurol. Neurosurg. Psychiat.* **47**, 862–869.
- Vallbo, Å. B. 1981 Sensations evoked from the glabrous skin of the human hand by electrical stimulation of unitary mechanosensitive afferents. *Brain Res.* **215**, 359–363.
- Vallbo, Å. B. & Hagbarth, K.-E. 1968 Activity from skin mechanoreceptors recorded percutaneously in awake human subjects. *Expl Neurol.* **21**, 270–289.
- Vallbo, Å. B., Hagbarth, K.-E., Torebjörk, H. E. & Wallin, B. G. 1979 Somatosensory, proprioceptive and sympathetic activity in human peripheral nerves. *Physiol. Rev.* **59**, 919–957.
- Vallbo, Å. B., Olsson, K. A., Westberg, K. G. & Clark, F. 1984 Micro-stimulation of single tactile afferents from the human hand: sensory attributes related to unit type and properties of receptive fields. *Brain*. (In the press.)



- Van Hees, J. & Gybels, J. M. 1972 Pain related to single afferent C fibres from human skin. *Brain Res.* **48**, 397–400.
- Van Hees, J. & Gybels, J. M. 1981 C nociceptor activity in human nerve during painful and non-painful skin stimulation. *J. Neurol. Neurosurg. Psychiat.* **44**, 600–607.
- Wallin, B. G., Torebjörk, H. E. & Hallin, R. G. 1976 Preliminary observations on the pathophysiology of hyperalgesia in the causalgic pain syndrome. In *Sensory functions of the skin in primates* (ed. Y. Zotterman), pp. 489–499. Oxford: Pergamon Press.
- Zotterman, Y. 1933 Studies in the peripheral nervous mechanism of pain. *Acta med. scand.* **80**, 185–242.