

Unmyelinated Afferents Constitute a Second System Coding Tactile Stimuli of the Human Hairy Skin

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Vallbo, Å. B., H. Olausson, and J. Wessberg. Unmyelinated afferents constitute a second system coding tactile stimuli of the human hairy skin. *J. Neurophysiol.* 81: 2753–2763, 1999. Impulses were recorded from unmyelinated afferents innervating the forearm skin of human subjects using the technique of microneurography. Units responding to innocuous skin deformation were selected. The sample ($n = 38$) was split into low-threshold units ($n = 27$) and high-threshold units ($n = 11$) on the basis of three distinctive features, i.e., thresholds to skin deformation, size of response to innocuous skin deformation, and differential response to sharp and blunt stimuli. The low-threshold units provisionally were denoted tactile afferents on the basis of their response properties, which strongly suggest that they are coding some feature of tactile stimuli. They exhibited, in many respects, similar functional properties as described for low-threshold C-mechanoreceptive units in other mammals. However, a delayed acceleration, not previously demonstrated, was observed in response to long-lasting innocuous indentations. It was concluded that human hairy skin is innervated by a system of highly sensitive mechanoreceptive units with unmyelinated afferents akin to the system previously described in other mammals. The confirmation that the system is present in the forearm skin and not only in the face area where it first was identified suggests a largely general distribution although there are indications that the tactile C afferents may be lacking in the very distal parts of the limbs. The functional role of the system remains to be assessed although physiological properties of the sense organs invite to speculations that the slow tactile system might have closer relations to limbic functions than to cognitive and motor functions.

INTRODUCTION

It is well known that mechanoreceptive innervation of the skin in various mammals is dual as it comprises not only myelinated afferents but unmyelinated afferents as well. Thus innocuous skin deformation is coded in A afferents, which are fast conducting, as well as in C afferents, which conduct impulses as slowly as ~ 1 m/s (Bessou and Perl 1969; Bessou et al. 1971; Burgess and Perl 1973; Douglas and Ritchie 1957; Iggo 1960; Iggo and Kornhuber 1977; Kumazawa and Perl 1977a; Lynn and Carpenter 1982; Shea and Perl 1985; Zottermann 1939). Until recently, C-mechanoreceptive afferents from the skin seemed to be lacking altogether in man. Actually, in textbooks of human physiology, it commonly is stated that afferent responses to touch, pressure, and vibration are all carried by large myelinated fibers in the peripheral nerves (e.g., Kandel et al. 1991; Zigmond et al. 1999).

An important basis for the conclusion that human skin

lacked sensitive C mechanoreceptors were microneurography studies, which indicated that appreciable responses in unmyelinated afferents are only produced by noxious stimuli or changes of skin temperature (Schmidt et al. 1995; Torebjörk 1974; Torebjörk and Hallin 1974). In contrast, light mechanical stimuli have been found to be either completely ineffective or to elicit but a few impulses at low rates in some C units. The interpretation that skin deformation is coded exclusively by large afferents in man has been supported by experiments suggesting that tactile sensation is lost when conduction in the large myelinated fibers is blocked (Hallin and Torebjörk 1976; Mackenzie et al. 1975; Sinclair and Hinshaw 1950; Torebjörk and Hallin 1973). Actually Kumazawa and Perl (1977a) suggested that the system of unmyelinated afferents responding to light touch had faded out during evolution. This hypothesis seemed consistent with human studies as well as their own finding that these units were less common in the monkey than in the cat.

However, a few microneurography studies have provided evidence that highly sensitive C-mechanoreceptive units are not lacking altogether in man. Nordin (1990) presented the first description of tactile C units in man, which he found in the face area, while Johansson et al. (1988) had observed them a few years earlier in the same region. Because such units had not been found in other skin areas, it seemed reasonable that the tactile C units in the human face constitute an evolutionary vestige that might have been preserved in a small and specialized skin area alone.

However, evidence of a more general distribution of tactile C afferents in man was provided in a short communication (Vallbo et al. 1993) where we demonstrated that they are present in the hairy skin of the forearm as well.

In the present paper, basic functional properties of human low-threshold mechanoreceptive C afferents will be described to demonstrate that they constitute a separate set of cutaneous sensory units characterized by distinctly different functional characteristics compared with the high-threshold mechanoreceptive C afferents, commonly classified as nociceptors. Moreover, a delayed acceleration of impulse response to sustained indentation, not previously reported, will be described.

METHODS

Material

The present report is based on recordings of 38 cutaneous afferents that responded to innocuous skin deformation and conducted impulses in C range, i.e., ~ 1 m/s. The units were recorded in 17 experiments. The material was collected from 17 subjects: 8 females and 9 males,

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age 21–31 yr. Informed and written consent was obtained from all subjects, and the experiments were performed according to the Declaration of Helsinki. The study was approved by the ethical committee of the Medical Faculty, Göteborg University.

Nerve recording

Nerve impulses were recorded with the microneurography technique from the lateral antebrachial cutaneous nerve, which is a small branch of the musculo-cutaneous nerve. The innervation zone of this sensory nerve comprises a strip of skin on the radial aspect of the forearm from the elbow to the wrist, sometimes extending over the dorsum of the hand.

The microneurography technique has been described in many previous papers (e.g., Vallbo et al. 1979). However, the small size of the nerve exploited in the present study posed particular difficulties in finding and impaling fascicles, and a fair number of experiments failed altogether in this respect.

The ZOOM/SC system, developed at the Department of Physiology, Umeå University, Sweden, was used to sample data to a PC computer and to pursue primary analyses. The nerve signal was recorded using a passive band-pass filter set to 200 Hz to 4 kHz and sampled at 12,800 Hz. Recordings were accepted as originating from a single unit on the basis of impulse size, shape, and relative time of occurrence. These features were examined off-line using a combination of an automatic retrieval system (Edin et al. 1988) and visual inspection of the individual spike on expanded time scale, both facilities being part of the ZOOM/SC system.

The microneurography records presented in the illustrations are displayed in their original form to demonstrate the true signal to noise ratio of the recorded signals.

Search procedure

When the recording electrode tip had attained an intrafascicular position, the experimenter explored the relevant skin area by stroking his finger tips over the skin. Multiunit responses to such stimuli often consisted of preferentially either A or C afferents, as appreciated on the basis of impulse shapes and latencies. Any well-isolated single C unit with a clear and consistent response to these stimuli was studied further. On the other hand, when finger strokings revealed multiunit activity that seemed to include unmyelinated afferents, slightly stronger, but innocuous, mechanical stimuli were applied in search for a single unit.

Mechanical stimuli

A number of tools and means were used to deliver mechanical stimuli in addition to tender finger strokings, glass rods, and wooden sticks. Timing signals to mark the application of stimuli with hand-held instruments were delivered by means of a foot pedal.

Threshold assessment

Thresholds to mechanical stimuli were assessed with von Frey bristles calibrated with a high precision electronic balance to give the following amounts of force: 0.1, 0.3, 0.6, 1.3, 2.5, 5, 10, 20, 40, 80, and 160 mN. The bristles were made of nylon wires with the following diameters: 0.11, 0.11, 0.11, 0.12, 0.12, 0.21, 0.21, 0.21, 0.30, 0.35, and 0.4 mm. The force of the weakest bristle that gave a response in at least three tests was taken to the protocol as the threshold of the unit. One or two optimal target points were marked on the skin on the basis of threshold assessments and used as targets for subsequent suprathreshold stimuli.

Strain gauge device

A hand-held strain gauge device was employed to monitor indentation force while perpendicular indentations were delivered. It consists of a handle with a metal bar ending with an exchangeable Perspex probe. Strain gauges glued to the metal bar were connected to a bridge amplifier calibrated in force and the signal was sampled at 400 Hz. Sharp and blunt probes were used to provide either pin-prick type of stimuli or innocuous skin indentations. The blunt probe ended with a hemisphere with a diameter of 1.5 mm, whereas the sharp probe ended with a tip diameter of ~0.1 mm.

Soft brush

To produce an innocuous moving stimulus that covered the sensitive spots of the receptive field, a 2-cm-wide, soft, and flat water-color painting brush was swept manually over the skin (Vang, size 18, type 43718, Oskar Vangerow, Daimlerstrasse 2, D-85521 Ottobrunn, Germany). The total vertical force was ~0.2 N as assessed by pressing the brush against a balance with a similar angle as used in the experiments.

Plotter-controlled moving stimuli

Moving stimuli of more well-controlled characteristics were delivered with a probe connected to an X-Y plotter. This approach, which has been described in detail in a previous study (Vallbo et al. 1995), provided stimuli of constant speed, reasonably uniform indentation force, and controlled spatial localization and extent.

The stimulus probe was held in a nearly vertical position in an arm extending from the X-Y plotter head. The probe was fixed to a light aluminum tube that was allowed to slide up and down in low-friction plastic bushings to minimize variations of indentation force as the probe tip was moving over the skin surface. To obtain desired indentation forces, metal rings were added to the upper end of the aluminum tube. Skin indentation force in milliNewtons was approximated by multiplying by 10 the total weight in grams of tube, probe, and added metal rings.

Probe movements were always along the forearm in strict proximal or distal direction. Timing signals indicating start and stop of the moving probe were sampled at 25.6 kHz.

Two different probes were used for different purposes. To collect data on instantaneous impulse rates to light indentations moving over the skin surface at two different speeds (2 and 10 mm/s), a small probe ending with a hemisphere of 1 mm in diameter was employed with an indentation force of 5 mN. Another probe designed to indent a broader strip of skin was used to analyze fatigue. It ended with a 15-mm-long half-cylinder with a diameter of 4 mm. The long axis of the half-cylinder always was kept at right angle to the direction of probe movement. The surface was covered with a fine-woven fabric (Leukoplast, Hamburg) to give a fair friction against the skin and the probe consistently was loaded to give a vertical force of 80 mN. This probe will be referred to as the wide probe.

Thermal stimuli

Warm and heat stimuli were produced with a halogen light bulb with a gold-coated reflector to provide optimal infrared emission. It was held at a distance of 10 cm from the receptive field. The subject was instructed to press a button as soon as she/he felt the warmth sensation and to keep the button down until she/he noticed a minimal pain sensation. The release of the button automatically turned off the lamp. The skin was cooled with acetone dropped on the receptive field. Saline at room temperature was used as a control. Skin temperature was not measured, nor controlled, in these tests.

Estimation of conduction velocity

Conduction velocity was estimated from the stimulus response latency to electrical or mechanical stimuli. Electrical stimuli were delivered to the receptive field with a constant current stimulator connected to surface electrodes. Two electrode arrangements were used. Either a bipolar cushion electrode with 15 mm interelectrode distance (border to border) (Dantec Medical, Skovlunde, Denmark) or a metal probe with a diameter of 5 mm and a remote metal plate attached to the subject's hand. Stimulus parameters were 0.1 ms duration and ≤ 15 mA intensity depending on subject's tolerance.

To assess the latency to mechanical stimuli, light taps were delivered toward a highly sensitive spot within the receptive field using the strain gauge device (see *Strain gauge device*; Fig. 1). Tests with distinct initial rise of the force record were selected for analysis while the minimal latency measured from the selected tests was used to estimate conduction velocity.

Statistical analysis

To test whether a distribution of observations (von Frey thresholds, Fig. 2) was more likely uni- or bimodal, two statistical models were fitted to the experimental data. The first comprised a simple Gaussian distribution. The second model was a sum of two Gaussian distributions fitted to data more than and < 5 mN von Frey threshold, while the two distributions were weighted relative to each other by the number of observations in each group. Residual errors were used to

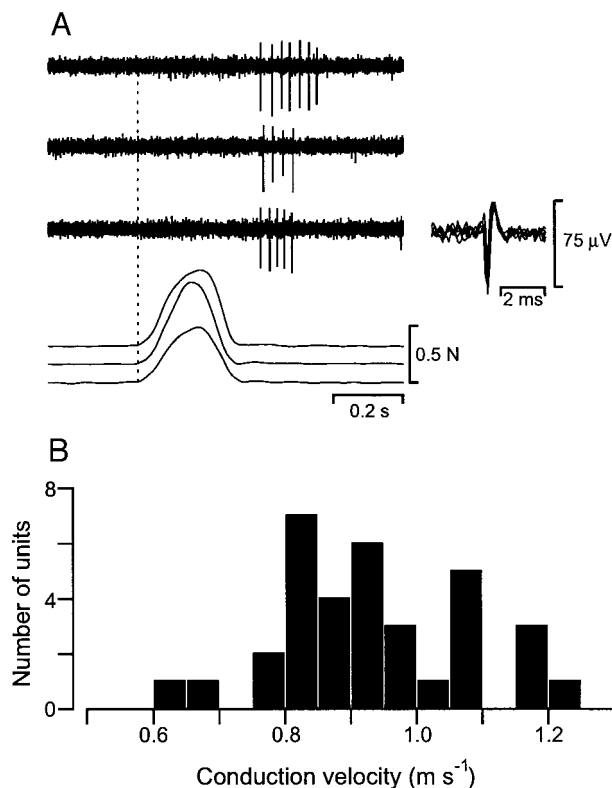


FIG. 1. Conduction velocity of mechanoreceptive C afferents. A: responses of an unmyelinated afferent to 3 tap stimuli delivered toward a highly sensitive spot within the receptive field, illustrating the method of conduction velocity assessment. Hatched line indicates 0 time for latency assessment corresponding to 1st increase in force record. Distance between receptive field and nerve recording site was, in this case, 274 mm yielding a conduction velocity of 0.64 m/s. Unit's threshold to local indentation was 2.5 mN. *Inset*: on expanded time scale, the 5 action potentials of the *bottom trace* superimposed. B: distribution of conduction velocity of 34 C afferents, estimated on the basis of mechanical stimuli as in A. Mean value was 0.9 m/s and the range 0.6–1.2 m/s.

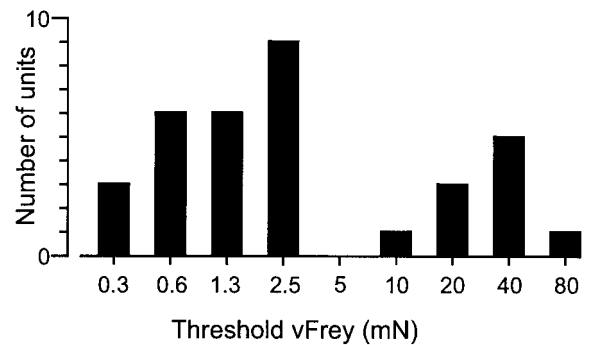


FIG. 2. Distribution of thresholds to von Frey bristle stimuli of 34 mechanosensitive C afferents. Bimodal distribution suggests that the sample consists of 2 different unit types, i.e., low-threshold or tactile units and high-threshold units (see text).

assess goodness of fit when the two different models were tried. The appropriate *F* test was applied to evaluate statistically the difference in residual errors between the more complex bimodal model compared with the unimodal model (Johnson and Wichern 1992).

RESULTS

Unit sample

Thirty-eight afferents from the forearm skin with conduction velocities in the C range were studied to explore their responses to mechanical stimuli. They all responded to innocuous skin deformation although the size of the response varied considerably. Qualitative observations in 12 of them demonstrated no or very little response to temperature changes, including heating up to noxious threshold. On the basis of their sensitivity to skin deformation, using a variety of stimuli, the units were split into two groups. The larger group ($n = 27$) had low mechanical thresholds and were highly sensitive to innocuous skin deformation, whereas a smaller group ($n = 11$) had high thresholds and were assumed to be nociceptors. The arguments for this split will be exposed in the following text in relation to the presentation of the units' responses to mechanical stimuli.

Conduction velocity

Figure 1A shows responses of a low-threshold mechanoreceptive afferent to perpendicular skin indentations. Three distinct tap stimuli, aimed toward a highly sensitive spot within the receptive field, were delivered with a hand-held strain gauge device. It may be appreciated that distinct responses with high impulse rates appeared at a long latency, amounting to several hundred milliseconds, after the onset of the stimulus. Because the unit had a low threshold, i.e., 2.5 mN as assessed with von Frey stimuli, the sense organ was very likely excited by the initial part of the indentations. Hence it seemed reasonable to infer an estimate of conduction velocity from the latency between initial rise of force and the first nerve impulse.

Invariably, the slow conduction velocity of the unmyelinated afferents was evident already during the experiment because it was easy to appreciate from the loudspeaker output that the latency was much longer than with myelinated afferents. In fact, preliminary assessment on-line during the experiment of the conduction velocity falling in the C or A range never failed as confirmed in off-line analysis of records.

The *inset* of Fig. 1A shows the five nerve impulses of the lower trace on expanded time scale to demonstrate the di- or triphasic shape with the most prominent phase in the negative direction; this is typical of impulses in unmyelinated fibers as recorded with the microneurography technique. This shape invariably was found with the C fibers, whereas it may be encountered only occasionally with myelinated fibers (e.g., Vallbo 1976).

Conduction velocity was inferred for 34 C afferents on the basis of their responses to mechanical stimulation, yielding a mean of 0.9 m/s. The distribution of estimated conduction velocities is shown in Fig. 1B. The remaining four units were classified as C afferents on the basis of qualitative estimates of latency to mechanical stimuli during the experiment and impulse shape as detailed in METHODS.

A subset of nine units also were stimulated electrically with surface electrodes to estimate conduction velocity. There was a close relation between data obtained with the two approaches ($r = 0.8$, $P < 0.02$), although mechanical stimuli yielded systematically slightly lower conduction velocities, i.e., 0.9 versus 1.0 m/s (means). This is expected considering that the delay with mechanical stimuli includes time for mechanoelectrical transduction, encoder processes as well as propagation through terminals, which might be bypassed by the electrical stimuli. The high correlation between the two data sets seems to justify our approach to infer conduction velocities from mechanical stimuli as described in METHODS. Still, these estimates should be regarded as approximations, adequate to classify the units as C afferents but probably not to justify further analyses.

Thresholds to mechanical stimuli

Thresholds to mechanical stimuli were assessed with calibrated von Frey bristles. Care was taken to hit one of the highly sensitive spots within the receptive field. Figure 2 shows a histogram of the thresholds presented with a logarithmic x axis to compress the scale. It is obvious that there is a marked trough in the range ~ 5 mN, separating the units in two groups; i.e., the plot suggests a bimodal distribution of thresholds. This impression was analyzed statistically, first, by fitting a simple unimodal normal distribution to the whole data set, and second, by fitting two separate normal distributions, one to the data set below and one to the data set >5 mN. In these procedures, the logarithm of the von Frey thresholds was used. The bimodal model gave a significant improvement in goodness of fit over the unimodal ($F = 19.47$, $P < 0.001$). Indeed, the fit of the bimodal model is surprisingly good, given the sparsity of the data.

On the basis of the observations presented in the histogram of Fig. 2 and the statistical analysis, the units were split into two groups. The left-hand units with thresholds <5 mN were denoted low-threshold mechanoreceptive or tactile C afferents, whereas the right-hand units with thresholds >5 mN were classified as high-threshold mechanoreceptors, assumed to be nociceptors. The median threshold of the tactile units was 1.3 mN ($n = 24$) which is similar to the values reported by Nordin (1990) for the unmyelinated afferents from the facial skin. Our high-threshold units, on the other hand, had ~ 30 times higher thresholds (40 mN, $n = 10$), which values fall in the same range as recently found with human mechanosensitive noci-

ceptors (Schmidt et al. 1997). Further support for the interpretation that these two groups represent two different types of sense organs will be presented later in this paper.

The proportion of tactile afferents was large in the present sample (71%), suggesting that such units are fairly common in the nerve, although it is difficult to make a more definite inference on the basis of the present data because the search stimuli probably gave a bias against high-threshold units.

A previous analysis of a smaller sample of C afferents from the same skin area did not yield a bimodal threshold distribution (Vallbo et al. 1993). However, it seems reasonable that the present data are more reliable because, successively, we have become more aware of the high precision required in aiming the von Frey hair toward the small highly sensitive spots within the field to assess the true threshold. Actually, detailed analyses of the receptive field geography suggested that maximal sensitivity might be limited to a very small point while sensitivity decreases very steeply with distance (J. Wessberg, H. Olausson, K. Wiklund Fernström, and Å. B. Vallbo, unpublished data).

Response to touch and pin-prick stimuli

Figure 3A contrasts responses of a low- and a high-threshold unit when two different kinds of stimuli were delivered, i.e., indentations with a rounded probe and pin-prick stimuli. In these tests, the experimenter tried to adjust stimulus force to produce near maximal impulse rates. Responses of the low-threshold unit were intense and about the same with both stimuli, which perceptually were quite different. The high-threshold unit, on the other hand, failed to respond altogether to the innocuous stimulus while it gave a substantial response to the pin-prick stimulus.

To what extent it was a general feature of the sample that low- and high-threshold units responded differently to innocuous touch and pin-prick stimuli is shown in the scatter plot of Fig. 3B. Peak rates elicited by pointed and blunt-probe stimuli of all tested units are plotted against their von Frey thresholds. \circ indicate units that were tested with only one of the two stimuli, whereas \bullet represent units tested with both stimuli. As expected the tactile C afferents, i.e., those with thresholds <5 mN, responded more strongly than the high-threshold units to blunt-probe stimulus. Actually there was no overlap in peak rates between the two groups, and the difference in medians was highly significant (Wilcoxon, $P < 0.001$). Moreover, the low-threshold units ($n = 23$) did not discriminate between innocuous and pin-prick stimuli because the impulse rates were largely the same (Wilcoxon, $P > 0.25$). In contrast, the high-threshold units responded with considerably higher rates to pin-prick stimuli than to blunt-probe stimuli. The difference between medians of their peak rates was statistically significant in spite of the small sample ($n = 5$) (Wilcoxon, $P < 0.01$). A similar lack of discrimination between blunt and sharp stimuli was described by Nordin (1990) for one face unit.

These findings suggest two different unit types rather than a continuum, as does the bimodal distribution of von Frey thresholds (Fig. 2). Moreover, the borderline between the two unit groups as separated by pin-prick and smooth-probe stimuli coincides with the trough in the distribution of von Frey thresholds. Hence the two analyses agree and converge toward the conclusion that the sample consists of two distinct unit

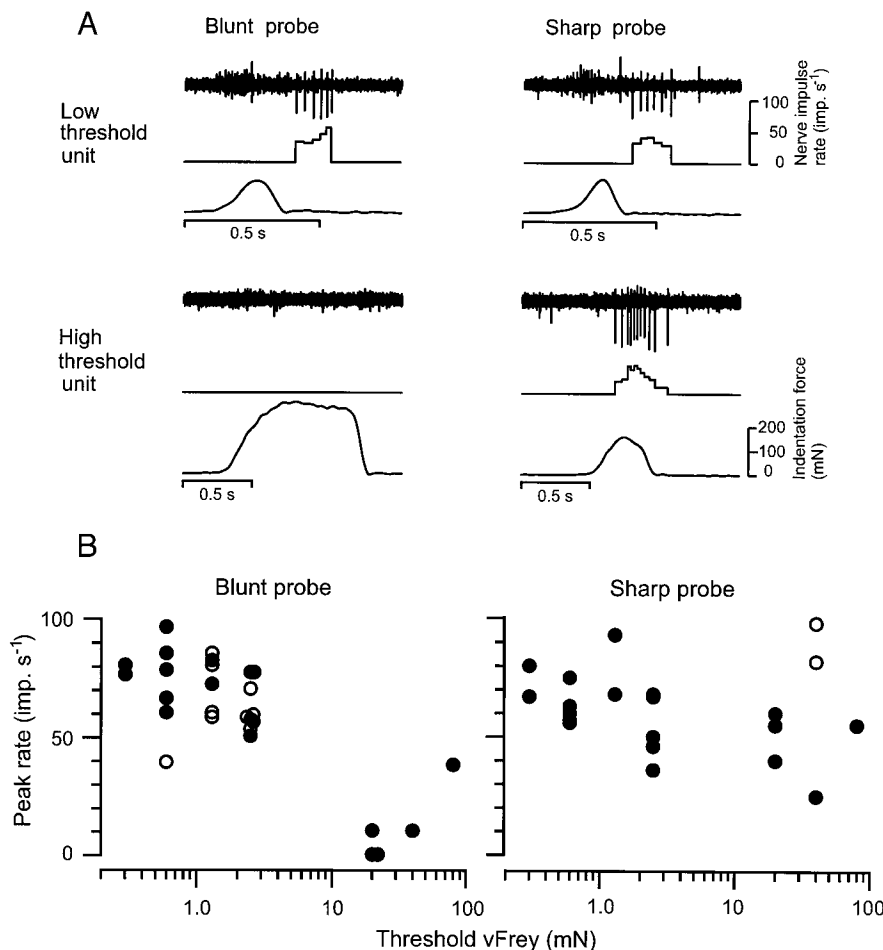


FIG. 3. Differential responses of low- and high-threshold C afferents to smooth and pin-prick stimuli. *A*: responses to blunt and sharp probes of a tactile C-afferent unit (*top*, von Frey threshold 2.5 mN) and a high-threshold unit (*bottom*, von Frey threshold 20 mN). Note different time scales for *top* and *bottom*. Scales for impulse rate and indentation force apply to both panels. Note early bursts of low amplitude impulses from myelinated afferents in 2 *top* records illustrating the marked difference in delay between A and C afferents. *B*: scatter plots of peak impulse rates of 30 mechanoreceptive C afferents to blunt- and sharp-probe stimuli as in *A* vs. the units' von Frey thresholds. ●, units tested with both stimuli ($n = 19$); ○, units tested with blunt ($n = 9$) or sharp probe alone ($n = 2$). Overlapping symbols have been slightly shifted along the x axis.

types, i.e., afferents coding some feature of tactile stimuli and high-threshold mechanoreceptive afferents, generally assumed to code nociceptive stimuli.

Responses to moving tactile stimuli

In previous studies it has been shown that low-threshold C mechanoreceptors are particularly responsive to tactile stimuli that are slowly moving over the skin surface (Bessou et al. 1971; Nordin 1990; Shea and Perl 1985). This was found to be true with the human tactile C afferents as well. Figure 4

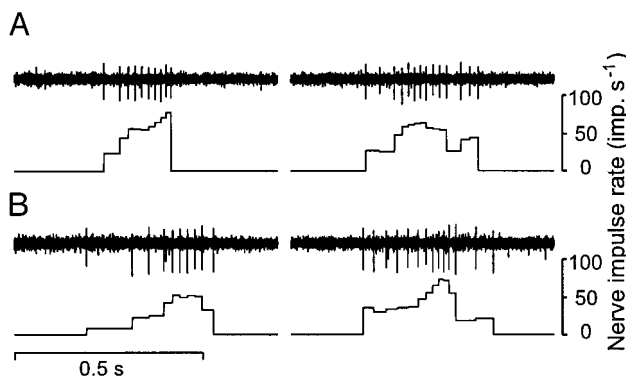


FIG. 4. Responses of tactile C afferents to light touch. *A* and *B*: responses of 2 separate units to the experimenter stroking his finger tip over the receptive field. Peak impulse rates were 78 and 64 imp/s (*A*) and 52 and 73 imp/s (*B*).

illustrates the high impulse rates elicited with two tactile C afferents when the experimenter slowly moved his finger tip over the receptive fields.

To explore this aspect using more uniform stimuli with regard to indentation force and speed of movement, moving stimuli also were delivered with a soft water-color brush. Figure 5*A* shows sample records from a low- and a high-threshold unit, whereas *B* is a scatter plot of peak rates elicited by such stimuli for 19 units, plotted against their von Frey thresholds. Although some of the high-threshold units produced faint responses to this soft and innocuous moving stimulus, impulse rates of the low-threshold C afferents were much higher. The close relationship between peak rates and thresholds indicates that these two modes of stimulation yielded mutually consistent data, suggesting that either may be used to broadly characterize unit sensitivity.

To further substantiate the observation of high impulse rates to innocuous skin deformation, a light (5 mN) and small probe with a rounded tip (1-mm diam) was moved with an X-Y-plotter at low speed (2 mm/s) over the receptive field (see METHODS). Data from nine low-threshold units yielded peak rates between 33 and 72 imp/s with a mean of 55 imp/s. Data from these as well as other stimuli (Figs. 3 and 4) indicate that the peak rates represent the upper end of continuous interspike interval distributions, but not outliers, supporting the justification of using peak rates to schematically characterize unit responses as in Figs. 3*B* and 5*B*.

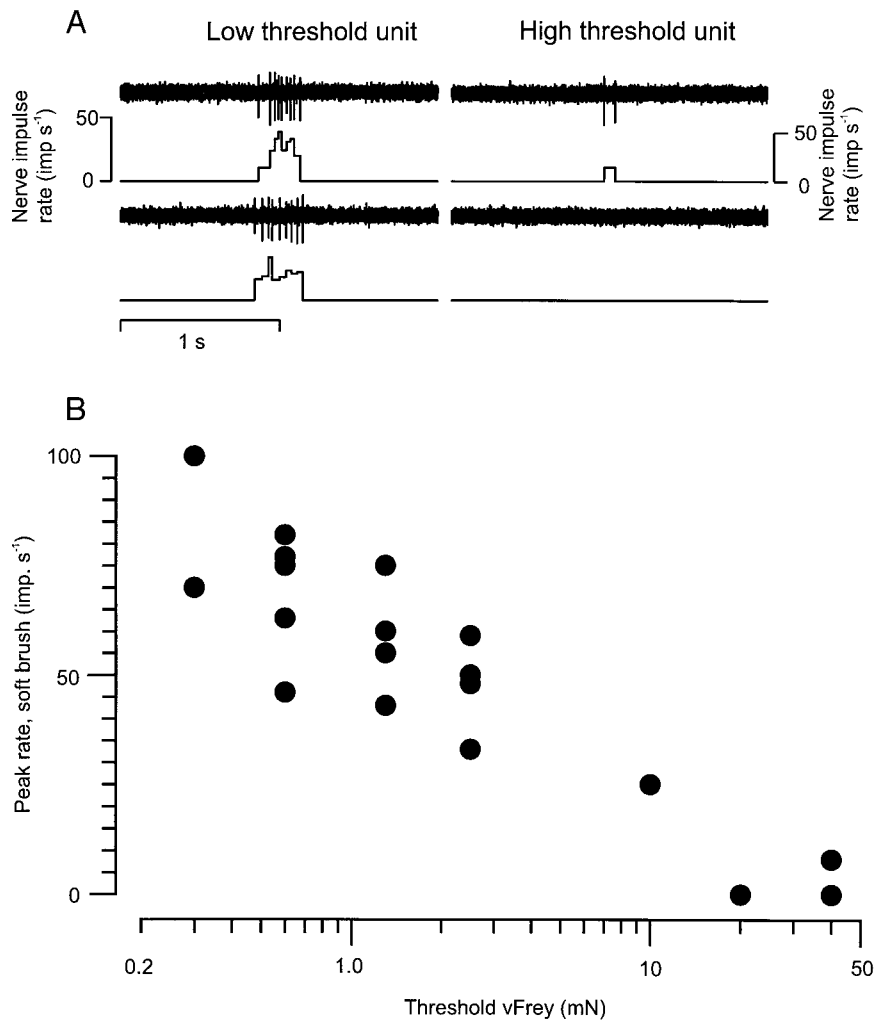


FIG. 5. Responses to moving touch stimuli of mechanoreceptive C afferents. Stimulus was delivered with a soft water-color brush slowly swept over the receptive fields. *A*, left and right: responses of a tactile C-afferent and a high-threshold unit. *B*: peak rate of impulse discharge of 19 units to stimuli as in *A* vs. their von Frey thresholds. Linear correlation coefficient between logarithm of threshold and peak rate was highly significant ($r = -0.91$, $P < 0.001$).

Considering that 100 imp/s is about the maximal rate recorded from unmyelinated afferents to natural stimuli (Iggo 1960), it is obvious that the responses to these light stimuli cover a substantial part of the units' working range. On the other hand, it should be noted that we did not attempt to define the maximal rates that natural stimuli might evoke in the low-threshold C afferents.

The high impulse rate to light mechanical stimuli as illustrated in Figs. 3–5 is a key argument for the identification of the low-threshold C afferents as a separate group of units. They are characterized by distinctly different response properties compared with the high-threshold C afferents collected in the present study as well as various types of high-threshold mechanoreceptive C afferents described in other reports (Bessou and Perl 1969; Bessou et al. 1971; Burgess and Perl 1973; Kumazawa and Perl 1977a; Lynn and Carpenter 1982; Perl 1984; Schmidt et al. 1995; Torebjörk 1974; Torebjörk and Hallin 1974).

RESPONSE DEPENDENCY ON SPEED OF MOVEMENT. A prominent characteristic of the fast conducting tactile system supplied by myelinated afferents is that many units exhibit a high dynamic sensitivity, evident as higher impulse rates, the faster the stimulus is changing. Their dynamic response mostly has been studied with perpendicular indentations but their high dynamic

sensitivity seems to hold for tangential movements as well (Bessou et al. 1971; Essick and Edin 1995).

Studies of low-threshold C-mechanoreceptive units, on the other hand, have demonstrated that their response is poor to rapidly moving stimuli, but still they responded strongly to slowly moving stimuli, indicating a high dynamic sensitivity (Bessou et al. 1971; Nordin 1990; Shea and Perl 1985). Similar response features were found in the present study as illustrated in Fig. 6 where discharge of a representative unit to slow and fast movements are shown. It may be appreciated that the impulse rate was roughly similar with movements at 2 and 10 mm/s. On the other hand, the total number of impulses was much larger with the slow movements. Altogether nine test series with two to four different speeds were pursued with six units yielding similar results, i.e., rates did not increase with higher speed of movement in the range 2–15 mm/s except marginally in two test series.

Fatigue

Another characteristic feature of low-threshold C afferents, in contrast to myelinated tactile afferents as described in previous studies, is a high dependency on previous history. Suprathreshold stimuli leave an aftereffect or fatigue, lasting seconds or minutes, which makes the unit less responsive to a

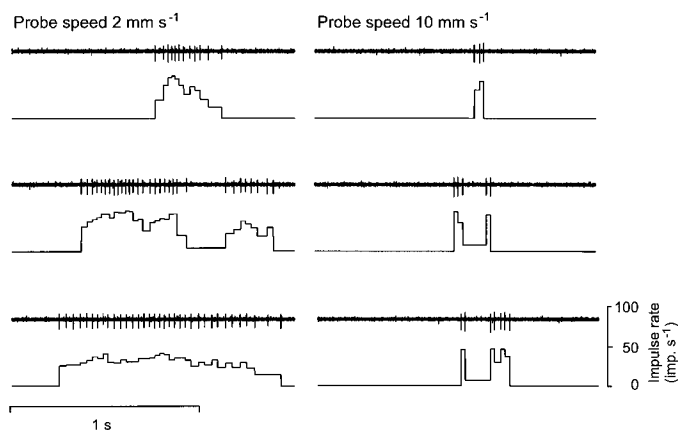


FIG. 6. Responses of a tactile C afferent to touch stimuli moving at 2 different velocities. Small and light probe (1.0-mm diam, indentation force 5 mN) was moved over the central part of the receptive field at 2 different velocities, i.e., 2 and 10 mm/s.

following test stimulus (Bessou et al. 1971; Iggo 1960; Iggo and Kornhuber 1977; Nordin 1990).

The fatigue aspect was analyzed in five units by repetitively moving a probe (wide probe, see METHODS) slowly over the skin along the same track. A representative example is shown in Fig. 7 displaying data from the first 4 and the last 4 of 20 moving stimuli. It may be appreciated that the unit exhibited some fatigue because repeated stimuli resulted in shorter response durations and lower instantaneous impulse rates toward the end of the response. In contrast, the high impulse rates during the first part of the individual test remained largely unchanged throughout the test series. Similar fatigue characteristics have been described in detail in the cat (Iggo and Kornhuber 1977). Fatigue of similar degree as in Fig. 7 or somewhat smaller were present in another 19 test series with four other units. These findings seem to suggest that the dependency of previous history is not quite as prominent as in other mammals.

Adaptation and delayed acceleration

The present study was not focused on a detailed analysis of stimulus response relationship to perpendicular indentations, something that has been much explored in previous studies with other species (e.g., Bessou et al. 1971; Iggo and Kornhuber 1977). However, qualitative observations suggested that human tactile C afferents exhibit roughly similar properties in these respects as previously described for low-threshold C-mechanoreceptive units. These observations include a number of features, e.g., fairly poor response to rapidly changing stimuli, failure to follow vibratory stimuli except at low rates, the need of a relatively prolonged skin contact to elicit responses with weak stimuli, prominent off-responses, and an intermediate adaptation to sustained indentation (Bessou et al. 1971; Burgess and Perl 1973; Iggo 1960; Iggo and Kornhuber 1977; Kumazawa and Perl 1977a; Lynn and Carpenter 1982; Nordin 1990; Shea and Perl 1985).

The intermediate adaptation to sustained indentation is illustrated in Fig. 8A, where it may be appreciated that the impulse rate decreased to zero within 4 s. However, an unexpected response feature was identified in some of the tactile C afferents. When an innocuous skin indentation, e.g., a sustained

pressure with a finger was kept for 10–30 s or more, the firing rate of the unit exhibited a biphasic response. After an initial phase of adaptation to silence or nearly silence, firing resumed and successively built up to considerable rates. An example of such delayed acceleration is illustrated in Fig. 8B, which shows a longer sequence of the recording of Fig. 8A on a more compressed time scale. The initial adaptation phase may be identified in the two panels. In this case, the stimulus was a sustained indentation delivered with a hand-held strain gauge device.

It may be appreciated in Fig. 8B that impulse rate started to increase again ~12 s after the initial phase of adaptation. For a following period of ~30 s, firing was very irregular with recurring short interspike intervals separated by much longer intervals, while the mean rate gradually increased. Then followed a period of more regular firing that climbed to a peak of ~40 imp/s and then successively declined during a period of ~40 s.

Although the details of the delayed acceleration varied to some extent among units, a period of very irregular impulse rate invariably was seen. This period usually included very short interspike intervals, in doublets and sometimes triplets, intercalated with very long intervals, whereas at the same time the units were largely unresponsive to moderate changes of stimulus parameters. It deserves emphasis that similar pattern of irregular firing was not seen during the initial adaptation phase as illustrated in Fig. 8A.

Delayed acceleration was found in 3 of 10 low-threshold units tested in the present sample, while it has been observed, although not reported, in another 3 units in a previous sample (Vallbo et al. 1993). Repeated tests indicated that delayed acceleration was present consistently in units which exhibited this feature. So far we have not been able to identify other unique properties of the units that exhibited delayed acceleration. Rather they seem to conform with the other tactile C afferents.

On direct interrogation, the subjects denied unique or

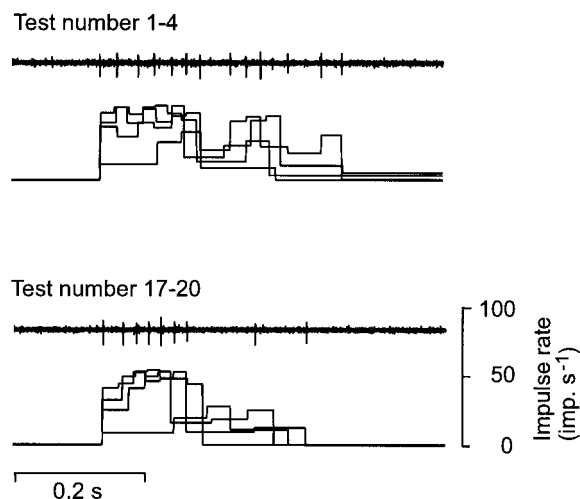


FIG. 7. Fatigue in a tactile C afferent to repeated touch stimuli. Extracts from a series of 20 identical tests. Nerve recordings show impulses from the very 1st and the very last test. *Top*: instantaneous rate records of the initial 4 tests; *bottom*: rates of the last 4 tests. Test stimulus was a computer controlled movement of a 15-mm-wide probe across the receptive field. Indentation force was 80 mN, probe speed 10 mm/s (see text). Stimuli were delivered each 3rd second.

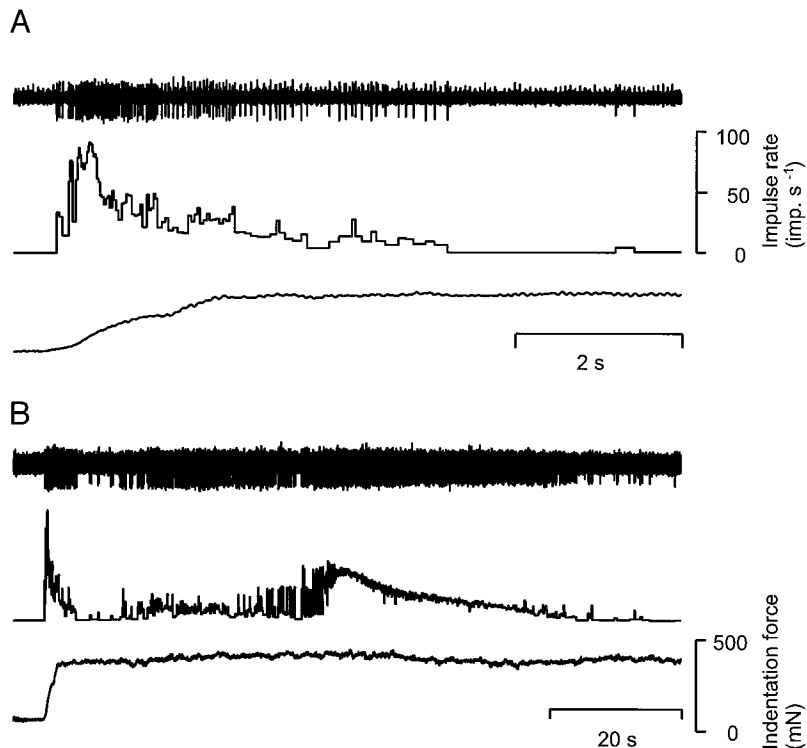


FIG. 8. Adaptation and delayed acceleration of a tactile C afferent. Stimulus was a sustained indentation with a blunt probe (see text). A: initial part of the test; B: longer recording of the same test.

strange sensation from the skin area during the period of delayed acceleration.

DISCUSSION

Two types of mechanosensitive C afferents

The present sample of cutaneous afferents conducted impulses at a speed of ~ 1 m/s, indicating that they were unmyelinated, i.e., C fibers. The units were all mechanoreceptors in the sense that they responded to skin deformation, while limited qualitative observations indicated poor response to temperature changes. Their sensitivity to skin deformation varied considerably and analyses of thresholds as well as suprathreshold responses suggested that the sample was made up of two separate unit types.

First, the distribution of thresholds to skin deformation is bimodal with no overlap between the high- and the low-threshold group (Fig. 2). Second, the low-threshold group responded strongly to innocuous tactile stimuli, whereas the high-threshold units gave a faint response or none at all to such stimuli (Fig. 5). Third and most significant, the low-threshold units did not discriminate between pin pricks and smooth-probe indentations but gave similar responses to these two kinds of stimuli, whereas the high-threshold units responded much stronger to pin-prick stimuli (Fig. 3). Moreover, the borderlines in terms of von Frey threshold coincide with the three separate reasons for splitting the sample, i.e., bimodality of thresholds, strong or weak response to innocuous indentations, and discrimination between pin-pricks and smooth-probe stimuli.

A reasonable assumption is that our high-threshold afferents belong to the group of units commonly denoted nociceptors. However, our analyses are not adequate to firmly assess their true nature nor to define their relation to the separate kinds of high-threshold mechanoreceptive C afferents described in other studies,

i.e., mechanoreceptive nociceptors, mechano-heat-responsive or polymodal nociceptors, and mechano-cold-responsive units (Baumann et al. 1991; Bessou and Perl 1969; Burgess and Perl 1973; Iggo 1960; Kumazawa and Perl 1977a,b; Perl 1984; Schmidt et al. 1995; Shea and Perl 1985; Torebjörk 1974).

The main group of units in our sample had low thresholds to mechanical stimuli (0.3–2.5 mN). These values fall in the same range as the thresholds of tactile A units in human hairy skin (Edin and Abbs 1991; Johansson et al. 1988; Nordin and Hagbarth 1989; Vallbo et al. 1995) and as the thresholds of low-threshold mechanosensitive C afferents studied in various species (Bessou et al. 1971; Iggo and Kornhuber 1977; Kumazawa and Perl 1977a; Lynn and Carpenter 1982; Nordin 1990). Moreover, the responses of our low-threshold C afferents to light tactile stimuli were intense, sometimes approaching maximal rates previously reported for C-fiber afferents to natural stimulation (Iggo 1960). For example, sweeping a soft water-color brush over the receptive field often elicited impulse rates in the range $50\text{--}100\text{ s}^{-1}$. It seems difficult to escape the conclusion that the role of these afferents is to code some feature of innocuous skin deformation. The alternative that they would have a role in nociception is even more unlikely considering that they fail to discriminate between pin-prick stimuli and smooth-probe stimuli, particularly because it was shown that, in contrast, the group of high-threshold units gave a distinctly differential response to these two kinds of stimuli (cf. Bessou and Perl 1969; Torebjörk and Hallin 1974).

Thus it seems justified to provisionally denote our low-threshold units tactile C afferents. It should be emphasized, however, that the term “tactile” as used in this context strictly refers to their response properties and exquisite sensitivity to light tactile stimuli, while their effects within the CNS and their perceptive role remain to be defined.

Functional properties of tactile C afferents

As pointed out in RESULTS, a number of response features strongly suggest that our tactile units belong to the same family as the low-threshold mechanoreceptors described in other species (Bessou and Perl 1969; Bessou et al. 1971; Burgess and Perl 1973; Douglas and Ritchie 1957; Iggo 1960; Iggo and Kornhuber 1977; Kumazawa and Perl 1977a; Lynn and Carpenter 1982; Shea and Perl 1985).

DYNAMIC RESPONSE RANGE. Functional characteristics matching low-threshold C afferents in other mammals include intermediate rate of adaptation (Fig. 8), a clear fatigue to repeated stimuli (Fig. 7), and strong response to slowly moving stimuli but poor sensitivity to fast moving stimuli (Fig. 6). The latter feature has been advanced as particularly distinguishing between myelinated and nonmyelinated low-threshold mechanoreceptive units because the impulse rates of the former regularly increase with speed of stimulus movement (Bessou et al. 1971; Essick and Edin 1995; Nordin 1990; Shea and Perl 1985).

It might appear as a paradox that the tactile C afferents have a high dynamic sensitivity when tested with slowly moving stimuli but still fail to code rapid events. This paradox may be resolved by the assumption that the tactile C units in fact do possess a fair sensitivity to dynamic events but only within a low-frequency range of skin deformations. In contrast, the myelinated tactile system altogether covers a much larger range, i.e., from static skin deformations coded by Ruffini and Merkel units to high-frequency components up to ~300 Hz coded by Pacinian units.

DELAYED ACCELERATION. A notable response feature not previously identified in low-threshold C units was found in the present sample, i.e., a delayed acceleration during long-lasting indentations (Fig. 8). After the initial few seconds of adaptation and a following silent period, the unit started to fire again for a period that might last ≤ 1 min. It seemed justified to exclude that delayed acceleration was due to unintentional variations in stimulus characteristics because the units were largely unresponsive to moderate changes of indentation after the initial adaptation period. Moreover, delayed acceleration was consistently present with repeated tests in the units that had it, whereas it was consistently lacking in the other units.

Several characteristics of this response suggest that the functional state of the sense organ is fundamentally different during the phase of delayed acceleration than during the initial response phase: first, the time course with a successive increase of impulse activity after a period of silence, second, the complete lack of relationship between impulse rate and stimulus parameters, and finally the widely and rapidly varying interspike intervals. It is reasonable to ask whether the delayed acceleration represents a truly physiological response or rather is a manifestation of a distorted state of the sense organ. One might speculate that ischemia or sustained mechanical deformations have markedly altered the functional state of the transducer and/or encoder system.

However, even if the response appears odd and unphysiological, it should be emphasized that the test was by no means extreme, neither with regard to physical characteristics of the stimulus nor in its perceptive effects. The stimulus was just a long-lasting pressure with the experimenter's finger, and the delayed acceleration was not associated with any unique sen-

sation from the local area. Obviously this finding has some bearing on the question of perceptual power of the low-threshold C afferents, suggesting that they lack the potential to elicit distinct and unique conscious sensations at least in a situation when one or a few of them are activated.

A separate question is whether delayed acceleration has a functional significance or not. It may be speculated that it might signal a state of circulatory and/or mechanical strain in the skin that would warrant an action, e.g., to change the limb position to remove a local pressure.

On the functional role of tactile C afferents

Over the years only a few comments and hypotheses have been advanced in the literature on possible functional roles of low-threshold unmyelinated C afferents. This seems remarkable considering that the system has been known to exist in other mammals for several decades (Douglas and Ritchie 1957) and a number of reports have described their physiology. Actually, in a comprehensive review Darian-Smith (1984) stated "it must be concluded that single unmyelinated mechanoreceptive fibers relay little information to the CNS about most commonly encountered touch stimuli: the physiological role of these fibers remains unknown."

Their response properties strongly suggest a role in coding some feature of touch stimuli rather than pain and temperature changes. On the other hand, it deserves emphasis that central projections of the tactile C afferents are not known. In considering their functional role, it seems relevant, however, that tactile C units appear to be fairly common in the human forearm skin. In the present sample, the tactile afferents constituted 71% of the C afferents that responded to innocuous skin deformation. In a previous series of experiments with the aim to collect data on myelinated as well as unmyelinated afferents responding to light touch, it was found that as many as 40% of the units sampled from the forearm skin were unmyelinated C afferents (Vallbo et al. 1993). These data seem to militate against the interpretation that the tactile C units are an insignificant vestige in man, as might be suggested by previous studies (Kumazawa and Perl 1977a), but rather suggest that they have a functional role in the human skin.

APPARENT LACK OF PERCEPTIVE EFFECTS. A fundamental aspect is whether impulses in low-threshold C afferents are used or not in the construction of conscious percepts. A number of blocking experiments suggest that they do not, because when impulse propagation in myelinated afferents is impaired in man, subjects report that touch sensibility is lost (Hallin and Torebjörk 1976; Mackenzie et al. 1975; Sinclair and Hinshaw 1950; Torebjörk and Hallin 1973). A caveat might be justified when blocking experiments are interpreted, however, because in most of these studies the very distal parts of the limbs were explored and there is evidence that low-threshold C afferents are scarce or lacking altogether in these skin regions. First, human tactile C afferents have not been clearly demonstrated in distal parts of the limbs in spite of numerous microneurography studies focused on C afferents from these skin regions. Second, Kumazawa and Perl (1977a) demonstrated a proximo-distal gradient in the monkey with fewer tactile C afferents in the peripheral parts of the arm.

Reports that patients with large fiber neuropathy lack touch sensibility seem to further support the view that distinct per-

cepts are not induced by C afferents (e.g., Cole et al. 1995). On the other hand, it might be reasonable to reconsider these analyses with due attention to the particular response properties of the low-threshold C afferents, e.g., their strong response to slowly moving stimuli, as well as the possibility that substantial spatial summation might be required.

Finally the possibility might exist that a perceptual role of the low-threshold C afferents is conditional on activity in the myelinated afferents, i.e., the low-threshold C afferents may add some particular quality or tint to sensations elicited by innocuous skin deformation.

TICKLE. Long ago it was proposed that the low-threshold C afferents might have an essential role in the sensation of tickle (Zotterman 1939). The idea was based on their high sensitivity to skin deformation, their prominent response to slowly moving stimuli, and their tendency to produce afterdischarge as demonstrated in animal experiments. This idea was reiterated in a few later studies without significant additional support (Bessou et al. 1971; Nordin 1990). Qualitative observations in the course of the present study provide no support for the view that human tactile C afferents would be more responsive to tickling stimuli than the myelinated tactile afferents. Nor did our subjects report tickling sensations when the low-threshold mechanoreceptive afferents fired at high rates.

MOTOR AND COGNITIVE VERSUS LIMBIC FUNCTIONS. The functional properties of the low-threshold C afferents, particularly their limited dynamic range, invite speculations regarding their possible functional role. It commonly is held that the high temporal resolution of the myelinated system is of paramount importance in relation to cognitive aspects of tactile sensibility as well as motor functions. For instance, high temporal resolution would be important to characterize surface structure as well as form of external objects and to trigger reflexes and shape motor actions (Johansson 1996; Johnson and Hsiao 1992). Such considerations would suggest that the main role of the tactile C system might fall outside the cognitive and motor realms.

On the other hand, slowly moving and innocuous skin deformations are common in skin-to-skin contact between individuals as part of affiliative behavior (Carter et al. 1997). A role of the low-threshold C afferents in this context might be reasonable to consider. Craig (1996) recently has suggested that unmyelinated thermoreceptive and nociceptive units have the function in common to contribute information to "a larger limbic network involved in homeostatic and behavioral maintenance of the integrity of the self" and "provide the underpinnings for basic emotional and motivational states." It may be asked whether the tactile C afferents might be part of a subsystem within the same family as the nociceptive and thermosensitive afferents in having particularly close connections with limbic structures, possibly with a role in affiliative behavior in relation to skin-to-skin contact (Carter et al. 1997; Nerem et al. 1980; Uvnäs-Moberg 1997).

In relation to such speculations, further analyses of projections within the CNS of low-threshold C-mechanoreceptive afferents would be of great interest (Kumazawa and Perl 1977b). If projections similar to those of the other C-afferent systems were found, this would support the hypothesis of close functional connections with the limbic system. Moreover, functional brain imaging techniques might be rewarding as well as the combina-

tion of microneurography and psychophysical approach to elucidate the functional role of the tactile C system.

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