Cutaneous afferent activity in median and radial nerve fascicles: a microelectrode study

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SYNOPSIS Cutaneous afferent activity was recorded in fascicles of the median and radial nerves of normal subjects using percutaneous microelectrodes. Multi-unit fascicular responses were dominated by activity in large myelinated fibres. Easily tolerated electrical stimuli evoked the full spectrum of fast and slow myelinated fibre activity but more intense levels were required to activate unmyelinated fibres. Correlation of the evoked potentials and the sensations reported by the subject suggested that fast myelinated fibres mediate tactile sensations. Pricking pain appeared with the activation of slow myelinated fibres. The only sensations induced by electrical stimuli were tactile or painful.

Sensory fascicles of peripheral nerves contain large and small myelinated fibres, unmyelinated afferent fibres, and unmyelinated sympathetic efferent fibres. The different modalities of normal cutaneous sensation may be attributed to varying patterns of impulse transmission in afferent fibre groups, and the variable symptoms of peripheral nerve lesions may reasonably be attributed to varying patterns of fibre involvement. An understanding of the function of individual fibre groups in sensory nerves is therefore germane not only to normal sensation but also to pathological states.

Routine neurophysiological studies of peripheral nerve function are necessarily restricted to large myelinated fibres. The function of other fibres must be inferred from clinical data or from histopathological findings on biopsy specimens. Using meticulous techniques, potentials from small myelinated fibres can be recorded by needle macroelectrodes inserted close to the relevant nerve (Buchthal and Rosenfalck, 1966), but even with this method potentials conducted at 17 m/s are the slowest that can be recorded reliably in normal man (Buchthal, 1973). Since action potential amplitude is a function of the square of fibre diameter, it is not unexpected that difficulty is encountered in recording potentials from small fibres even with averaging techniques, particularly since such potentials are more dispersed and must be picked up through the insulating tissue that surrounds the fascicle.

The microelectrode technique described by Vallbo and Hagbarth (1968) allows recording of neural responses from within the fascicle, in which site fascicular insulation becomes a benefit rather than a handicap. The technique has proved suitable in normal subjects for studying mass neural responses to physiological stimuli (Vallbo and Hagbarth, 1968; Hagbarth et al., 1970) and the evoked compound action potential (Hallin and Torebjörk, 1973; Torebjörk and Hallin, 1973). Even the activity of single sensory fibre axons may be recorded, be they myelinated (Hagbarth et al., 1970) or unmyelinated (Torebjörk, 1974; Torebjörk and Hallin, 1974).

The studies to be reported were undertaken with the aim of developing the technique as a diagnostic tool. Of necessity, the findings complement and amplify the earlier studies from Hagbarth’s department. Particular attention has been devoted to the spectrum of conduction velocity that can be recorded reliably in normal

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1 Supported by the National Health and Medical Research Council of Australia.
2 Commonwealth Postgraduate Scholar and Edwin and Daisy Street Research Fellow.
(Received 13 February 1975.)
sensory fascicles and the stimulus levels required to activate these fibres. Attempts have been made to identify the fibres responsible for the sensations evoked by electric stimuli of varying strength. In the accompanying paper (Mackenzie et al., 1975), the technique has been used to monitor the development of preferential fibre blocks in order to elucidate the roles of different fibres in sensations evoked by more physiological stimuli. A preliminary report of some of this work has been presented to the Australian Association of Neurologists (Burke et al., 1974).

**METHODS**

Sensory fascicles of the median nerve were studied in 20 experimental sessions in six normal subjects, aged 24 to 45 years, the microelectrodes being inserted just proximal to the wrist. Fascicles of the superficial branch of the radial nerve were studied in 12 experimental sessions in three of these subjects, the microelectrodes being inserted 5–6 cm proximal to the wrist.

The experimental technique was essentially similar to that of Hagbarth et al. (1970). Insulated tungsten microelectrodes tapered to a tip of diameter 1–5 μm were inserted manually through the skin into the relevant nerve. Penetration of an appropriate fascicle was facilitated by stimulating through the microelectrode tip at a stimulus level sufficient to produce paraesthesiae in the distribution of the fascicle. Using the severity of the paraesthesiae as a guide, the electrode was advanced until the voltage necessary to induce paraesthesiae was minimal, always less than 1.0 V and usually close to 0.5 V. At these levels the microelectrode was invariably intrafascicular. The electrical stimuli were delivered at 1/s but at times more precise adjustments could be made using frequencies of 5–10/s. When the microelectrode was intrafascicular, minute adjustments of position could be made by recording through the microelectrode and monitoring on a loudspeaker the intensity of the neural activity induced by scraping the skin of the fascicular innervation zone.

Recordings were ‘monopolar’, the indifferent electrode being a similar microelectrode with a bared tip of length 2 mm inserted subcutaneously at a transverse distance of 2 cm from the active electrode. Two different amplification systems were used. The most satisfactory consisted of a preamplifier of fixed gain of 1 000 coupled to an amplifier of variable gain, usually 50, occasionally 100. In some experiments the first stage amplifier consisted of a PAR low noise amplifier model CR-4 coupled to a modified Tektronix 122 preamplifier, the total gain of the system being 33 000 or 330 000. This latter system proved less satisfactory for short conduction distances due to the recovery time of the initial stage. For both amplification systems the bandwidth (−3 dB) was set at 0.2 or 0.3 to 3 kHz. The relatively high low-frequency filter was found necessary to minimize movement artefact and 50 Hz interference, which sometimes proved a problem when averaging multiple sweeps and using high gains. Even so, in some experiments an earthed metal shield was necessary to eliminate vestiges of 50 Hz interference. The filtering system did not affect the results significantly, since the shape of individual action potentials was not a factor under study.

The amplified neural activity was monitored on a loudspeaker and a Tektronix 564 storage oscilloscope and was recorded on tape (Electrodata Model 6300-2). An amplitude discriminator (cf. Hagbarth et al., 1970) was used in some experiments to improve signal-to-noise ratio of gross multi-unit responses to physiological stimuli and additionally the treated multi-unit neurogram was then integrated using a R–C low pass filter with a time constant of 0.1 s. The evoked compound action potential was elicited using electrical stimuli usually of 0.4 ms duration, although in some experiments, particularly in the radial nerve, the duration of 0.1 ms was preferred because this reduced stimulus artefact for short conduction distances. Stimuli were delivered by a Devices Stimulus Isolation Unit through a pair of uninsulated needle electrodes inserted subcutaneously into the richest site in the fascicular innervation zone. The evoked activity was amplified, monitored, recorded on tape, and averaged on a fixed programme averaging computer (ND 801 Enhancetrion 1024). The amplitude discriminator was not used in studies of the evoked compound action potential.

The stimulus voltage delivered through the electrodes in the fascicular innervation zone was adjusted until just perceived by the subject—that is, perceptual threshold, Tp. At different stimulus intensities, expressed as multiples of Tp, the responses to 100, occasionally 200, consecutive stimuli were averaged in order to highlight low amplitude slowly conducting potentials. Stimulus current was monitored in control experiments using a Tektronix Type P6016 Current Probe and, under the experimental conditions, a linear relationship was found between stimulus current and applied voltage. During the recording of A fibre potentials stimuli were delivered at 1.0/s, but, for C fibre responses, a stimulus repetition rate of one every 3 s was used. The slower stimulation rate was found necessary because C fibres sometimes failed to respond to the higher rate and also because more intense stimuli
were usually necessary to activate unmyelinated fibres. For experiments in which the perceptual correlates accompanying repetitive stimulation were studied, stimuli were delivered at frequencies of 50–500 Hz. In control experiments, it was found that stimulus current did not change significantly during brief trains at these frequencies.

Throughout an experiment, frequent checks were made to ensure that the microelectrode remained in the same site in the fascicle, and additionally that perceptual threshold remained constant. It was consistently found that perceptual threshold for single shocks was lowered after trains of stimuli at fast rates. As a routine the responses to singleshocks at the slow standard rates were studied fully before stimuli at fast rates were given. All experiments were performed in an air-conditioned laboratory. Skin temperature was measured using an Ellab Electronic Thermometer and maintained at 32°C using radiant heat when necessary.

In all experiments appropriate antiseptic precautions were taken. Untoward reactions have been limited to transient paraesthesiae in the distribution of the penetrated fascicle on percussion over the penetration site and occasional dysesthesiae on stroking the fascicular innervation zone. These symptoms commonly developed within 48 hours of the experiment and usually lasted a few days, never more than two weeks. There have been no permanent sequela. In most cases six weeks elapsed between experiments on the same nerve but occasionally this was reduced to three weeks for the radial nerve.

Conduction velocities were calculated by dividing the distance between stimulating and recording electrodes by the latencies of the recorded potentials. The values obtained are approximate only, since in all probability they underestimate the true conduction velocity because of the inaccuracies of surface measurement of fibre length. This is particularly so when stimulating small terminal ramifications of sensory axons. For this reason, the myelinated A fibre spectrum has been divided into fast and slow conducting components, above and below 15–20 m/s respectively. The latter group contains the so-called A-delta fibres of other authors (Collins et al., 1960; Dyck et al., 1972).

**FIG. 1** Multi-unit responses to cutaneous stimuli (median nerve). a. Responses to moderately heavy touch stimuli. Note the 'on' and 'off' responses. b. Responses to scraping the skin with sandpaper. Lower traces illustrate the raw neurogram and upper traces the 'integrated' neurogram. In a the amplitude discriminator has been used to eliminate most of the noise, while in b the neurographic activity is not so treated. As in subsequent figures the neural responses have been retouched.

**RESULTS**

Responses to Physiological Stimuli After penetration of a sensory fascicle, stroking of the fascicular innervation zone evoked a profuse multi-unit discharge accompanied by a characteristic sound on the loudspeaker (Fig. 1). Such activity could not be recorded when the micro electrode was extrafascicular even if it was immediately adjacent to the fascicle. In both median and radial nerves the fascicular area was usually confined to that of a digital nerve, with corresponding extension onto palm or dorsum of the hand. In many experiments the full extent of the fascicular area could not be mapped, since it appeared that the microelectrode picked up activity from only part of the fascicle. Minor adjustments of the microelectrode at times brought other parts of the fascicular area into better focus. With median nerve fascicles digital pulp skin usually provided the richest neural activity.

Fascicular responses to a range of physiological stimuli were tested, but only tactile stimuli produced a consistent response. The multi-unit neural discharge was most intense when an abrasive stimulus was used, particularly if applied transversely across the dermal ridges. Thermal sensations induced by cold or warm
metal and pain sensations induced by a pin prick produced no greater discharge than could be achieved with a similar tactile stimulus. Cooling produced by the evaporation of ether and warmth, heat and pain induced by radiant heat failed to evoke any consistent discharge. Typically, the multi-unit response to a touch

FIG. 3 The effects of fascicular insulation (median nerve). a. The neurographic response to a stimulus voltage of 5.0 Tp showing a complex potential with components conducting down to 10 m/s. b. The response to the same stimulus after withdrawal of the microelectrode to a site which was just extrafascicular. The response consists of a simple triphasic potential. Average of 200 sweeps at each site.

FIG. 4 Myelinated A fibre activity (radial nerve). a. Five sweeps have been superimposed. A few slow potentials can be discerned but signal to noise ratio is poor. b. Average of 100 sweeps using input gain of 33 000. Slow myelinated potentials are more obvious. c. Average of 100 sweeps using input gain of 330 000. Multiple slow potentials are visible but the voltage of the fast potentials exceeds the input levels of the averager so that their details are lost.

FIG. 2 Myelinated A fibre activity (median nerve). The range of myelinated fibre potentials recorded in a median nerve fascicle with a reasonably intense stimulus. Input gain 50 000. Average of 200 sweeps.
nerve velocities being conduction potentials commonly recorded were resultant blocking (Fig. 4b, identification accurate so great visible in fast rose fascicle produce paraesthesiae) and unmyelinated fibres were myelinated fibres appeared more sparse and were found, often with difficulty, in only approximately 50% of fascicular penetrations. However, a systematic search for C fibre potentials by stimulating at multiple sites within the innervation zone was not attempted. As a general rule, when unmyelinated fibre potentials were recorded, the microelectrode was in a suitable site for recording sympathetic efferent activity. These latter potentials were heard after unexpected or intense stimuli and produced a blowing sound audible at a long and variable latency of 0.5–1.0 s after the stimulus. The intensity of this sympathetic discharge varied with the subject’s state of preparedness, could be elicited by strong stimuli delivered to the opposite limb, and could be accentuated by alterations in the rate and depth of respiration independent of stimuli. An unexpectedly severe stimulus evoked a shower of sympathetic discharges.

The unmyelinated fibre potentials could have arisen from antidromically activated sympathetic efferent fibres as well as from afferent C fibres (Hallin and Torebjörk, 1973), but no

**FIG. 5 Unmyelinated C fibre potentials (radial nerve). a. Single sweep. A cluster of potentials with velocity up to 1.4 m/s. b. Average of 50 consecutive sweeps. Note that the potentials are not identical in a and b because of latency changes and, occasionally, because of failure to activate individual fibres during repetitive stimulation. Stimulus was delivered using surface electrodes, the stimulus being approximately 7–10.0 Tp. Such profuse C fibre discharges were not found in median nerve fascicles.**
attempt was made to distinguish between these possibilities. Potentials time-locked to the stimulus with these velocities will be considered predominately afferent C fibre activity.

The results obtained from stimulation through needle electrodes were compared with those obtained with surface electrodes (a pair of lead discs of 1.0 cm diameter). Such stimuli were more readily tolerated but were felt to be more diffuse and heavy. Presumably because of the larger fascicular area stimulated with surface electrodes, the evoked neurogram often contained more intense neural activity for a comparably painful stimulus. The less discrete stimulus proved unsuitable for studies of perception. Stimulation of the radial nerve trunk was attempted in addition to stimulation of the skin of the fascicular innervation zone, but proved unsatisfactory because it resulted in a very large fast myelinated fibre response which masked the slower components. Stimulation of the nerve trunk was therefore limited to studies involving long conduction distances.

PERCEPTUAL CORRELATES

Detailed correlations of stimulus voltage (expressed in multiples of perceptual threshold, Tp), the resultant neurographic activity and the sensation reported by the subject were made for the median nerve. Since a brief electric pulse represents a most unphysiological stimulus, the sensations elicited by repetitive stimulation at frequencies within the physiological range (50–500 Hz) were also checked. Few perceptual differences were noted at the different frequencies in this range.

The subthreshold stimulus of 0.75 Tp evoked a low amplitude response due to activity in fast myelinated fibres (Fig. 6). This neural activity was not perceived, despite maximum mental concentration and the provision of visual and auditory cues. With repetitive stimulation at this level a light fluttering sensation was perceived. When the stimulus voltage was decreased to a level at which repetitive shocks were just imperceptible, an evoked compound action potential could not be recorded despite averaging. Thus, although these low threshold potentials were not perceived when activated in an un-
physiological way, repetitive firing reached consciousness.

Single stimuli up to twice perceptual threshold produced a discrete light tactile sensation usually reported as a ‘tap’, a ‘flutter’, or a ‘pulse’. Repetitive stimulation produced a vibrating sensation which increased in intensity with the stimulus. Pain was never reported. The components of the evoked compound action potential remained in the fast myelinated fibre range (Fig. 6). At 3.0 Tp, single stimuli were sometimes reported to evoke a pricking sensation, sharp but definitely not painful, and at this level slow myelinated fibre potentials began to appear (Fig. 7). Repetitive stimulation at 3.0 Tp was invariably reported as painful. Even at the fastest stimulus frequencies, subjects reported that the sensation was always maximal early in the stimulus train but eased over the ensuing seconds.

At 5.0 Tp, single stimuli were felt to be sharp and pricking, sometimes mildly painful. Repetitive stimulation was more painful than at 3.0 Tp but was qualitatively similar. Potentials conducting at around 10 m/s were more apparent in the neurogram (Fig. 7). Single stimuli at 7.0 Tp and 10.0 Tp were invariably felt as painful pricking sensations of greater severity, and repetitive stimulation was intolerable to all but well-motivated subjects. The sensation was most intense early in the train but subsequently eased. This stimulus level activated more slow myelinated fibres, the slowest potentials in the evoked neurogram conducting at 4–7 m/s (Fig. 8). In only two experiments have further increases in stimulus voltage resulted in additional components conducted within the myelinated fibre range. Thus, stimulus levels of 10.0 Tp are adequate to activate the full spectrum of myelinated fibres in cutaneous fascicles, and with a well-positioned microelectrode a full spectrum of myelinated fibres has always been recorded.

At 15.0 Tp, single stimuli were reported to produce a heavy sharp jabbing pain, unlike a pin prick. This sensation increased in severity up to 50.0 Tp. An aching lingering ‘after-pain’ persisted between stimuli, particularly at the higher stimulus levels. Over 50.0 Tp, the perceived sensation reached a plateau. Further increases in stimulus voltage produced little change, so that if 50.0 Tp could be tolerated so could 100.0 Tp. Repetitive stimulation at 20.0 Tp on three occasions was intolerable. Afferent C fibre potentials were recorded with these stimulus levels in approximately 50% of fascicular penetrations (Fig. 9). Such activity usually appeared at 15.0–20.0 Tp but on two occasions C fibre potentials were recorded at 10.0 Tp. They have not been recorded in median nerve fascicles at lower stimulus levels.

Less detailed observations on the radial nerve were essentially similar, there being a similar order of recruitment of myelinated fibres with increasing stimulus level. Occasionally, a less intense sensation was reported than expected from the stimulus level and the recorded neural activity. In radial nerve fascicles, afferent C fibre potentials were recorded regularly at 5.0–7.0 Tp and occasionally the sensation reported with this activity was sharp but not painful. Repetitive stimulation at these levels always proved painful.
DISCUSSION

The findings of the present study largely confirm the earlier observations of Vallbo and Hagbarth (1968), Hagbarth et al. (1970), and Hallin and Torebjörk (1973) on the nature of the multunit responses recordable in cutaneous fascicles. A major purpose of the present study was to reassess the degree of reliability with which the different components of the evoked compound action potential could be recorded in normal nerve fascicles and to attempt to correlate fibre activity with stimulus level as a prelude to studies in patients with peripheral neuropathy. Potentials from afferent A fibres covering the full spectrum of fibre size can be recorded reliably with a well-positioned intrafascicular microelectrode. The required stimulus levels are tolerable. Afferent C fibre potentials present more of a problem, at least in the median nerve, because high intensity stimulation is usually required and C fibres may be located in the fascicle only after some searching. Thus pain could prove a limitation to investigations of C fibre function in unsophisticated patients. A further limitation to the microelectrode technique is that quantitative observations on fibre groups cannot be made. The components of the evoked neurogram depend on the site of the microelectrode within the penetrated fascicle. Even with high gains, the recording field of the microelectrode is limited, particularly for low amplitude potentials from small fibres. The field varies with the size of the fibre action potential, and thus the number and size of the different components of the averaged evoked neurogram do not reflect the absolute numbers or proportions of different fibres in the fascicle.

A good correlation was found between activity in fibres of different size and the evoked sensation. Similar correlations have been reported by Collins et al. (1960) who recorded from the exposed sural nerve of patients who had been allowed to wake up fully from general anaesthesia during the course of a cordotomy operation for intractable pain. Dyck et al. (1972) studied sensation with quantitative methods in normal subjects and in patients with polyneuropathy, and then related these measurements to the evoked compound action potential obtained in biopsy specimens of sural nerve. To date the only non-traumatic in vivo human studies to relate perception and the different components of the evoked neurogram have been those of Hallin and Torebjörk (1973) and Torebjörk and Hallin (1973). The primary emphasis of these papers, however, was to contrast the function of myelinated and unmyelinated fibres. Relatively little attention was devoted to differences within the myelinated fibre spectrum, and ‘no serious attempts were made to get a precise measure of the stimulus strength used’ (Hallin and Torebjörk, 1973). A correlation of stimulus level with different fibre thresholds was not made. Repetitive stimulation was studied only in the radial nerve using low frequencies of up to 5 Hz.

That stimuli just below perceptual threshold may evoke a low amplitude neural response has been reported previously (Buchthal and Rosenfalck, 1966), although no definite function was
attributed to the responsible fibres. Single electric shocks represent most unphysiological stimuli, but repetitive stimulation probably parallels normal circumstances a little more closely. In the present experiments, a light tactile sensation was reported when such 'subthreshold' stimuli were delivered repetitively. There was no evidence of truly subthreshold neural activity—of potentials which when activated repetitively failed to evoke any sensation.

Tactile sensations appear to be mediated by fast conducting myelinated fibres of low threshold. Pricking pain is reported with the recruitment of slow myelinated fibres. Hallin and Torebäck (1973) reported that C fibre potentials were recorded in some experiments at stimulus levels which evoked the sensation of pricking pain. This was noticed in a couple of the present experiments at 10.0 Tp, a stimulus level which evoked a reasonably strong pricking pain but which only activated a few C fibres. It might have been noticed more often if a systematic search had been made within each fascicle for C fibres, as was done by Hallin and Torebäck. However, their conclusions were also based on data from the radial nerve, in which C fibres appear to be more abundant and of lower threshold. In the present paper, the results of repetitive stimulation support the belief that pricking pain arises from activity in small myelinated fibres irrespective of the activity in unmyelinated fibres. When delivered repetitively, a stimulus previously felt to be only mildly pricking evokes a definite pain sensation, the stimulus level being far below threshold for unmyelinated fibres. The severity of pain evoked by repetitive stimulation at 7.0–10.0 Tp attests to the potency of this myelinated fibre pain. A qualitatively and quantitatively different pain sensation was reported with single shocks which consistently activated unmyelinated fibres. Thus, two different pain sensations may be felt on activation of small myelinated and unmyelinated afferent fibres. Which pain is of greater importance in normal human experience remains uncertain. The unmyelinated fibre pain is presumably responsible for causalgic and burning pains but, certainly, activation of small myelinated fibres may be accompanied by a pain of at least equal severity.

Only tactile and painful sensations have been evoked by electrical stimulation, despite activation of afferent fibres which under different conditions produce thermal sensations. The present experimental method must be considered inadequate for more detailed studies of such cutaneous sensations because the limitations of electrical stimulation require that activation of high threshold afferent fibres be accompanied by activation of low threshold afferent fibres.

The authors would like to thank Mr and Mrs Edwin Street for their wholehearted support of this project and Professor Karl-Erik Hagbarth for help in setting up the microelectrode technique. They are also grateful to Dr David Gillies for assistance with equipment and to Professor James W. Lance for support and criticism throughout the study. Figures were photographed by the Department of Medical Illustration, University of New South Wales.

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D Burke, R A Mackenzie, N F Skuse and A K Lethlean

*J Neurol Neurosurg Psychiatry* 1975 38: 855-864
doi: 10.1136/jnnp.38.9.855

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