Activity-dependent changes in impulse conduction in a focal nerve lesion

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Summary

The present study was undertaken to determine whether, in patients with a focal nerve lesion, the axonal hyperpolarization produced by conduction of brief trains of impulses would result in conduction block in cutaneous afferents, thus indicating a site of impaired safety margin for impulse transmission. In 25 patients with focal conduction slowing across the carpal tunnel segment of the median nerve, a conditioning train of 10 supramaximal stimuli at 200 Hz resulted in a reduction in amplitude and an increase in latency of the test volley set up by a supramaximal stimulus. These changes exceeded those seen in control subjects, but followed a similar time course, with full recovery within 150 ms. There was a significant correlation between these changes and the severity of the compression neuropathy as indicated by the degree of focal conduction slowing in routine nerve conduction studies. Control data suggested that the measured changes in amplitude could be explained by temporal dispersion of the compound sensory volley. This view was supported by measurements of the changes in amplitude (and latency) in normal subjects during acute compression before conduction block had developed. In addition, there were similar linear relationships between the activity-dependent amplitude reduction and the corresponding change in latency for both the patients and the control subjects, indicating that there was no need to invoke factors additional to those operating in the control subjects to explain the greater amplitude depression in the patients. It is concluded that, although the depression in amplitude was greater in patients than in healthy subjects, the magnitude of this change can be explained by temporal dispersion of the abnormal compound sensory action potential associated with greater conduction slowing. Activity-dependent conduction block may play little role in the pathophysiology of carpal tunnel syndrome.

Keywords: conduction; conduction block; cutaneous afferents; activity

Abbreviations: SNAP = sensory nerve action potential

Introduction

Conduction of brief trains of impulses causes an activity-dependent depression in the excitability of axons, associated with two positive after-potentials (Gasser, 1935). The mechanisms responsible for the hyperpolarization vary with the length of the impulse train: largely activation of a nodal slow $K^+$ conductance following brief trains (Baker et al., 1987; Taylor et al., 1992; Burke, 1993; Miller et al., 1995), and activation of the electrogenic $Na^+/K^+$ pump with longer trains (Bergmans, 1970, 1982; Schoepflie and Katohi, 1973; Raymond, 1979; Barrett and Barrett, 1982; Bostock and Grafe, 1985; Applegate and Burke, 1989; Gordon et al., 1990; Burke, 1993; Morita et al., 1993). The role of sodium-activated $K^+$ channels in these activity-dependent processes is not established, but they are likely to be more important the longer the impulse train and thereby the greater the intraxonial accumulation of $Na^+$ ions (Koh et al., 1994).

The activity-dependent processes activated by short trains of impulses have measurable effects on normal cutaneous afferents of human subjects, affecting both the latency and amplitude of maximal compound sensory action potentials (Miller et al., 1995). However, the amplitude changes can be adequately explained by temporal dispersion of the compound afferent volley and probably do not reflect conduction block. The difficulty in producing activity-dependent conduction block in normal cutaneous afferents through this mechanism is presumably related to the high safety margin for action potential generation at each node of Ranvier. However, if the safety margin is impaired by, for example, focal
demyelination, this normal physiological mechanism could produce conduction block at the site of pathology (Bostock and Burke, 1985).

Carpal tunnel syndrome is a common focal nerve lesion. The pathological changes consist of a mixture of oedema, epineural and intraneurial fibrosis, paranodal demyelination and remyelination, in addition to axonal loss (Aguayo et al., 1971; Ochoa et al., 1972; Ochoa and Marotte, 1973; Gilliatt, 1980; Lundborg et al., 1982; Brown, 1984). The most characteristic lesion is displacement of the myelin from the site of compression, with resultant retraction of myelin from the node, the so-called tadpole appearance (Ochoa and Marotte, 1973; Gilliatt, 1980). There is commonly marked slowing of impulse conduction in affected axons, localized to the carpal tunnel segment (Buchthal and Rosenfalk, 1971; Casey and Le Quesne, 1972; Kimura, 1979; Goadsby and Burke, 1994). The mechanism of this slowing has not been established, but its existence suggests focal pathology and a site of impaired safety margin for impulse conduction.

The present study was undertaken to determine whether the axonal hyperpolarization produced by brief trains of impulses would result in conduction block in patients with carpal tunnel syndrome at the site of presumed impairment of the safety margin. Such a finding would support the view that the slowing of conduction across the pathological segment was physiologically similar to that in a demyelinated lesion.

Methods

Studies were conducted on 25 patients (seven male, 18 female, aged 30–47 years), who attended a diagnostic neurophysiology clinic. Each had clinical evidence consistent with carpal tunnel syndrome, and electrophysiological evidence of focal slowing of the median nerve at the wrist (Goadsby and Burke, 1994). The data from these patients were compared with data from 25 healthy control subjects (10 male, 15 female, age 21–49 years), published elsewhere (Miller et al., 1996). All patients and healthy subjects gave informed consent to the experimental procedures, which had the approval of the appropriate Institutional Ethics Committee.

All patients complained of paraesthesiae and pain in the affected upper limb, often maximal in the distribution of the median nerve, and worse at night. Nine patients had a clinically detectable deficit of tactile sensation in the median nerve territory (all nine), or weakness of the thenar muscle abductor pollicis brevis (five out of the nine patients). No subject had a history of other medical conditions known to affect nerve function, such as diabetes, thyroid disease or excessive alcohol intake.

All patients underwent routine nerve conduction studies to evaluate median and ulnar nerve function (Goadsby and Burke, 1994). These studies included comparison of the digital sensory potentials from digit II to wrist and elbow and from digit V to wrist, the radial and median sensory potentials for digit I, and the median and ulnar potentials for digit IV. Using the ulnar and radial values, the conduction time for a sensory nerve action potential (SNAP) was calculated for the digit II–wrist conduction distance and, by subtracting this value from the measured latency, the delay in conduction across the carpal tunnel segment was estimated. Palmar stimulation was performed for the median nerve measuring orthodromic conduction from palm to wrist, and antidromic conduction from palm to digit II (Goadsby and Burke, 1994), in order to demonstrate that the conduction slowing was indeed maximal over the carpal tunnel segment. To be included in the study, the amplitude of the compound SNAP from digit II had to exceed 5 µV. Of necessity this excluded patients with severe carpal tunnel syndrome, thus explaining the paucity of clinically detectable median nerve deficits (see above).

The digital nerves of the index finger were stimulated using ring electrodes around the proximal phalanx. The SNAP was recorded using bipolar surface electrodes overlying the median nerve at the wrist, with an inter-electrode distance of 4 cm (Eduardo and Burke, 1988). Skin temperature was recorded at the second metacarpophalangeal joint and the wrist and kept above 32°C at both sites by radiant heat or wrapping the limb in a blanket if necessary. The conditioning stimulus consisted of a train of 10 pulses, each of 0.1 ms duration, delivered at 200 Hz. Stimulus intensity was 10–20% above that necessary to produce a SNAP of maximal amplitude. The test stimulus consisted of a single pulse of 0.1 ms duration, delivered at intervals of 2–200 ms after the last pulse of the conditioning train. The test stimulus was supramaximal in order to factor out the changes in excitability at the site of stimulation and thereby to ensure that all axons were recruited regardless of their excitability. For each conditioning-test interval, recordings of amplitude and onset latency were compared with those of an unconditioned test potential. All results were then normalized. Each recording was the average of 8–16 trials. Latency was measured to the first positive peak. Amplitudes were measured from the negative peak to positive peak (falling phase) to ensure that stimulus artefact did not affect recordings at short conditioning-test intervals, particularly in patients in whom SNAP amplitude was relatively low (see Table 1).

To assess the effects produced by acute compression and ischaemia on neural transmission and axonal excitability, the technique of threshold tracking, as described by Bostock and Baker (1988), was used on six healthy subjects. Ischaemia of 12 min duration was produced by inflation of a sphygmomanometer cuff 5 cm in diameter, around the wrist at the level of the flexor retinaculum. Pressure was maintained above 200 mmHg. The effects of ischaemia on neural transmission were assessed by tracking the amplitude and latency of a maximal SNAP produced by supramaximal stimulation of the median nerve proximal to the cuff, and recorded using ring electrodes around digit II. To assess excitability changes in axons underlying the flexor retinaculum, a submaximal test pulse of 0.1 ms duration was
Table 1

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Patients</th>
<th>Significance</th>
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<tbody>
<tr>
<td>Number</td>
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<td>25</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
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<td>30-47</td>
<td></td>
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<tr>
<td>Gender*</td>
<td>10M, 15F</td>
<td>7M, 18F</td>
<td></td>
</tr>
<tr>
<td>Digit II to wrist amplitude</td>
<td>29.4±7.1 μV</td>
<td>14.1±8.2 μV</td>
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<tr>
<td>Digit II to wrist conduction velocity</td>
<td>59.4±3.4 m/s</td>
<td>40.6±8.5 m/s</td>
<td>P &lt; 0.001</td>
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<tr>
<td>Digit V to wrist amplitude</td>
<td>15.2±6.3 μV</td>
<td>15.1±7.2 μV</td>
<td>Not significant</td>
</tr>
<tr>
<td>Digit V to wrist conduction velocity</td>
<td>55.5±3.7 m/s</td>
<td>57.8±3.9 m/s</td>
<td>P &lt; 0.05</td>
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<tr>
<td>Conduction delay</td>
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<td>1.10±0.7 ms</td>
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</table>

Results are expressed as mean±SD. *M = male; F = female.

delivered to the median nerve under the cuff (Bostock et al., 1994). Stimulus intensity was adjusted to produce an antidromic SNAP in digit II of 30-40% of maximum. Excitability was measured using two different paradigms, the computer alternating between measuring the amplitude of the changing SNAP produced by a fixed submaximal stimulus ('amplitude tracking') (see Fig. 5B), or altering stimulus intensity to keep the amplitude of the SNAP constant ('threshold tracking').

Results

The sensory nerve conduction studies on the 25 patients are summarized in Table 1. In all patients, there was evidence of focal conduction slowing across the carpal tunnel segment of the median nerve, with normal conduction in distal and proximal segments. The calculated degree of slowing across the carpal tunnel was 1.1±0.7 ms (mean±SD). It is notable that the amplitude of the SNAP was significantly smaller in the patients (even though an amplitude of >5 μV was a criterion for inclusion in the study).

Brief trains of impulses (10 stimuli at 200 Hz) were delivered to digit II to produce an activity-dependent decrease in excitability along the course of the nerve and, thereby, activity-dependent conduction block at the site of nerve pathology. The excitability changes occurring at sites remote from the site of stimulation are reproduced from Miller et al. (1995) in Fig. 1. Accordingly, if the activity-dependent depression in excitability affected impulse transmission, it would do so with the time course illustrated in this figure.

Activity-dependent changes in amplitude and latency of the compound SNAP

In all patients, the conditioning train of 10 supramaximal stimuli at 200 Hz produced changes in the amplitude and latency of the maximal test potential. These changes lasted <150 ms (Fig. 2), much as in Fig. 1. The time course of these changes was similar to that in the healthy subjects, but the extent was greater at all conditioning-test intervals up to 150 ms. The amplitude and latency changes that occur in normal cutaneous axons have been described in detail elsewhere (Miller et al., 1995), and have been attributed to dispersion of the compound SNAP due to activity-dependent hyperpolarization at each node between the stimulating and recording sites, due to activation of nodal slow K+ conductances.

In both the healthy subjects and patients, there was marked depression in the amplitude of the compound SNAP at the 2-ms conditioning-test interval, corresponding to the refractory period. Amplitude recovered by the 10-ms interval to 92% of the unconditioned control in the patients and to 96% in the healthy subjects. It then returned more slowly to 100% over 100-150 ms. The 'notch' on the recovery of amplitude at 10-15 ms presumably represents supernormality due to the last stimulus in the conditioning train riding on the activity-dependent depression.

The mean activity-dependent increase in latency was greater in the patients than the healthy subjects at all conditioning-test intervals up to 150 ms. The increase in
latency in the healthy subjects largely paralleled the decrease in amplitude (Fig. 2, open circles), but in the patients, the 'notch' due to supernormality was not clear on the latency plot (Fig. 2B, closed circles).

In the previous study on healthy subjects (Miller et al., 1995), it was demonstrated, first, that the excitability changes responsible for these changes in amplitude and latency occurred at sites remote from the site of stimulation (see Fig. 1) and, secondly, that the increase in latency was proportional to conduction distance. Those findings supported the view that the overall increase in latency represented the cumulative effect of small latency changes at each node of Ranvier in the conduction pathway. Furthermore, it was shown that the depression of amplitude could be accounted for by temporal dispersion of the compound SNAP, both during the refractory period and the phase of activity-dependent depression. Assuming that the distal segment of the nerve (digit to palm) was indeed quite normal in the patients, the greater change in latency and the greater depression of amplitude in the patients can be attributed to focal changes at the site of pathology. Amplitude was depressed during the refractory period to 72.3% in the patients and 79.7% in the healthy subjects; latency was increased by 0.47 ms in the patients and by 0.29 ms in the healthy controls. Amplitude was depressed to 90% in the patients and 94.6% in the control subjects at the 20-ms conditioning-test interval, associated with latency increases of ~0.18 ms and 0.11 ms, respectively.

**Correlation with the severity of the pre-existing conduction abnormality**

For each patient, the degree of slowing across the carpal tunnel segment was estimated by comparing (i) the measured latency for the compound SNAP from digit II with the latency predicted for that conduction distance given the conduction velocity of the ulnar SNAP from digit V; (ii) the radial and median SNAPs from digit I; and (iii) the ulnar and median SNAPs from digit IV. It should be stressed that the calculated ‘mean delay’ does not equate with the severity of carpal tunnel syndrome, but it is a measure of the severity of the focal conduction abnormality due to the median nerve compression.

Figure 3A is a plot of this estimate of conduction delay against the maximal depression in amplitude of the conditioned test potential occurring at the conditioning-test intervals 20–50 ms. Figure 3B is a plot of the change in latency for the conditioning-test interval associated with maximal amplitude depression against the ‘mean delay’. Both relationships have significant linear correlations, even when the outlier with a mean delay of 3.5 ms is omitted. It is notable that the regression lines intercept the vertical axes at an amplitude reduction of 6.7% and a latency change of 0.054 ms, values which are well within the range seen in normal subjects who have no such ‘delay’ (see Fig. 2).

**Mechanisms of the greater activity-dependent decrease in amplitude of the compound SNAP in patients**

There was a significant correlation between the maximal depression of amplitude of the test potential at the 20–50 ms conditioning-test intervals and the change in latency that occurred at that interval (Fig. 4, P = 0.0008). This suggests that, as in normal subjects, the amplitude depression may be due to temporal dispersion of the compound SNAP.

In the patient data of Fig. 2, the mean amplitude depression recorded for the 20–50 ms conditioning-test intervals (<10%) was associated with a mean increase in latency of 0.15–0.18 ms. These values are consonant with the effects of increasing conduction distance reported by Miller et al. (1995): an
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Fig. 3 Correlation of the decrease in amplitude (A) and the increase in latency (B) caused by conditioning trains of impulses with the unconditioned conduction delay across the carpal tunnel segment. For each patient the plotted datum point represents the greatest amplitude reduction occurring at the conditioning-test intervals of 20–50 ms and the corresponding latency increase.

Fig. 4 Relationship between the maximal depression in amplitude of the test potential at the 20–50 ms conditioning-test intervals, and the corresponding change in latency for each patient. Same data as in Fig. 3.

increase in mean latency of 0.09±0.01 ms was produced by increasing conduction distance by ~6 mm, and an increase in latency of 0.3±0.01 ms was produced by an increase in conduction distance of ~18 mm. These changes were associated with amplitude reductions of the compound SNAP of 7±1.8% and 23.9±2%, respectively, presumably due to greater temporal dispersion of the compound volley over the longer conduction distance.

However, in patients with a focal nerve lesion, the pre-existing conduction slowing and, presumably, the abnormal increase in activity-dependent slowing occur at the site of pathology, not at each node of Ranvier between the stimulating and recording sites. The effects of ischaemia and focal compression were modelled using a 5-cm wide sphygmomanometer cuff inflated around the wrist to 200 mmHg for 12 min in six healthy subjects. Skin temperature was monitored at wrist and first metacarpophalangeal joint and was maintained at >32°C. During ischaemia, there was a progressive reduction in the amplitude of the compound SNAP recorded antidromically from digit II in response to supramaximal stimuli delivered to the median nerve immediately proximal to the cuff (Fig. 5A). This amplitude reduction was associated with a parallel increase in latency to the positive peak of the compound SNAP. After ischaemia for 12 min, the amplitude reduction was 19.5±3.6% and the increase in latency was 0.31±0.04 ms (mean±SEM). These values are similar to those reported above from the study of Miller et al. (1995) who produced dispersion of the compound SNAP by increasing conduction distance slightly.

To determine whether the amplitude decrease in Fig. 5A was due to conduction block rather than dispersion of the compound volley, the excitability of axons underneath the cuff was measured in each of the six subjects in the same experiment as the measurements of the effect of cuff inflation on impulse conduction, but after full recovery from the effects of that episode of ischaemia, as judged by the return of threshold to its pre-ischaemic level (Fig. 5B). Excitability changes are maximal under the cuff (Bostock et al., 1991), and conduction failure first appears at that site (Brown, 1984). In each subject, axonal excitability was determined using two methods simultaneously: (i) tracking the changes in amplitude of the compound SNAP produced by a constant submaximal stimulus; (ii) tracking the changes in stimulus intensity required to produce a SNAP of constant amplitude. In each case, the control SNAP was set to be 30–40% of maximum. As in Fig. 5B, the excitability of cutaneous axons innervating digit II was enhanced for the full 12-min duration of ischaemia. There was no evidence of conduction block, a finding consistent with the view that the amplitude decrease in Fig. 5A was due, not to conduction block but, presumably, to dispersion of the compound volley. During ischaemia there was a linear relationship between the amplitude reduction of the compound SNAP produced by supramaximal stimulation, and the corresponding changes in latency (Fig. 6), as would
Fig. 5 The changes in impulse transmission (A) and axonal excitability (B) produced by inflating a sphygmomanometer cuff around the wrist to 200 mmHg for 12 min. The SNAP was recorded antidromically from digit II in response to stimulation immediately proximal to the cuff (A) or under it (B). (A) The reduction in amplitude and prolongation in latency of the SNAP produced by a supramaximal test stimulus. (B) The changes in excitability of axons under the cuff using submaximal test pulses, alternating between two different paradigms: adjusting stimulus intensity to produce a SNAP of 40% maximum ('threshold tracking') and tracking the changes in amplitude of the SNAP produced by a constant stimulus intensity ('amplitude tracking'). The two paradigms provide complementary evidence indicating that excitability was increased throughout the 12-min period of cuff inflation. Note that latency increases during the 12-min period of ischaemia in both A and B, the difference in latency being due to the different conduction distances.

Fig. 6 Relationship between the reduction in the amplitude of the SNAP produced by a supramaximal test stimulus and the corresponding change in latency during the 12-min period of ischaemia. Data obtained from Fig. 5. The discrete latency intervals result from the computer’s sampling rate.

Fig. 7 Relationship between the mean reduction in amplitude and the corresponding mean increase in latency for the patients (filled circles) and control subjects (open circles) at each conditioning-test interval. Data replotted from Fig. 2. The regression line is for all data, combining those for controls and patients.

be expected if the decrease in amplitude was due to temporal dispersion. Together with the previous data, the experiments illustrated in Figs 5 and 6 suggest that the abnormally large activity-dependent decrease in amplitude of the compound SNAP of patients in Fig. 2 can be explained by temporal dispersion of an already pathological volley.

If temporal dispersion was responsible for the activity-dependent reduction in amplitude of the compound SNAP in the patients as well as in the control subjects, then prolongation in latency may be sufficient to explain the measured reductions in amplitude for both groups. To examine this further, the mean reduction in amplitude was plotted against the change in latency at each conditioning-test interval for the data in Fig. 2. There were significant linear relationships for both the patients and the control subjects ($P < 0.0001$ for patients and controls). The slopes of the relationships did not differ significantly ($P = 0.33$), and the relationship remained as well described by linear regression when the data from both groups were combined (Fig. 7; $r = 0.976$, $P < 0.0001$). Accordingly there is no need to postulate additional mechanisms in the patients to explain their greater amplitude reduction, over and above the mechanism(s) operating in controls. The correlation coefficient indicates that 95% of the variance of amplitude can be explained by the variability of latency (or by a factor directly related to latency).

Discussion
The results reported in this paper establish that activity produces a greater decrease in amplitude and increase in latency of the compound SNAP in patients with carpal tunnel syndrome than in normal subjects, and that these changes are correlated to the severity of the pre-existing abnormality of conduction. However, the changes in amplitude were surprisingly small, and could be explained by temporal dispersion of the compound volley associated with the greater
conduction slowing. As a result, while the extent of the activity-dependent amplitude depression was greater in the patients than in healthy subjects, there seems to be no compelling reason to invoke activity-dependent conduction block as the cause for the pathologically large amplitude depression. A conclusion of the present findings might be that activity-dependent conduction block occurs in few if any axons in this disorder, too few to produce a significant change in the compound SNAP. Accordingly, it is possible that the history of preceding axonal activity plays little role in symptoms of patients with this disorder.

Previous studies have suggested that, in carpal tunnel syndrome, there is prolongation of the refractory period of transmission (Tackmann and Lehmann, 1974; Gilliatt and Meer, 1990), and an impairment of the ability to conduct trains of impulses (Lehmann and Tackmann, 1974). Our findings are consistent with these studies, in so far as there was a greater activity-dependent amplitude reduction in the patients. However, the possibility that temporal dispersion of the compound afferent volley could explain the amplitude reduction was not addressed by these earlier studies. In addition, the protocol adopted by Lehmann and Tackmann (1974) did not define the time course of the changes and so did not allow attribution of the activity-dependent depression to a specific biophysical mechanism.

Before discussing the implications of the present results for the pathophysiology of carpal tunnel syndrome, it is necessary to address potential limitations of the study and conclusions. First, the study required that a SNAP of >5 μV could be recorded and was therefore restricted to patients with mild and moderate carpal tunnel syndrome: it is likely that additional factors may become important in patients with more prominent clinical deficits. Secondly, it is possible that the activity-dependent hyperpolarization created by a train of 10 impulses was an inadequate stress to impulse conduction sufficiently to jeopardize transmission across sites of lowered safety margin. This issue is considered below. Thirdly, it is possible that activity-dependent conduction block developed, but in only a few critically affected axons, too few to produce a significant decrease in amplitude of the SNAP. However, this alternative would still be compatible with two major conclusions of the present study: that activity-dependent changes in impulse transmission may play little role in the symptomatology of carpal tunnel syndrome, and that nerve conduction techniques do not reveal significant activity-dependent conduction failure in this disorder.

Adequacy of the stress produced by conducting short trains of impulses
As detailed in the Introduction, the hyperpolarization produced by short trains of impulses is probably due to activation of nodal slow K⁺ conductances. The resulting depression in excitability reaches a maximum with the trains used in the present study, 10 impulses at 200 Hz (Taylor et al., 1992). Accordingly, it is unlikely that greater activity-dependent changes would be produced through this mechanism using longer trains. Other mechanisms that also result in axonal hyperpolarization are mobilized by longer trains: activation of the electrogenic Na⁺/K⁺ pump (Bostock and Grafe, 1985; Gordon et al., 1990; Morita et al., 1993), and possibly Na⁺-dependent K⁺ channels (Koh et al., 1994). The greater hyperpolarization produced by these additional mechanisms would jeopardize conduction at sites of impaired safety margin more profoundly than would the conditioning stimulus train used in the present study, and might lead to the conduction failure not seen with the present stress.

However, the stress produced by the short trains used in the present study probably approximates the stress produced by normal activity. The discharge of cutaneous mechanoreceptors in glabrous skin may reach high instantaneous frequencies for a few impulses (Knibestol and Vallbo, 1970; Edin and Abbs, 1991), but it is then poorly maintained, subsiding completely with RA units (Meissner corpuscles) and Pacinian corpuscles or continuing at a much lower rate with SA I and II units (Ruffini endings and Merkel discs, respectively). Accordingly, if activity-dependent conduction block played a significant role in symptom production in patients with carpal tunnel syndrome, it would have been reasonable to expect greater change in the present study.

All patients complained of positive sensory symptoms, worse at night. It is conceivable that the findings might have been different if the patients had been studied at night or suffered from a greater degree of median neuropathy. The exclusion of patients with very small sensory potentials and the absence of clinical signs in the majority (16 out of 25) imply that the findings are biased by patients with relatively mild compression neuropathy. However, all patients had evidence of nerve conduction slowing across the carpal tunnel, and a marked decrease in amplitude of the compound SNAP, as shown in Table 1. The present study was primarily concerned with whether the pre-existing conduction slowing was associated with an impairment of the safety margin for impulse conduction, as would be expected if it were due to demyelination.

At first sight, the smaller SNAP in the patients (mean 14.1 μV) than control subjects (mean 29.4 μV) suggests that there was a significant loss of conducting axons, due either to baseline conduction block or to axonal fallout in the patients. However, given the large effects that temporal dispersion can have on compound afferent potentials, it is possible that much of the baseline amplitude loss was due to temporal dispersion. There are neurophysiological criteria for conduction block in motor axons (though their validity can be debated) but there are no good criteria for conduction block in sensory axons. In this respect it is worth noting that the degree of amplitude loss attributed to dispersion of the SNAP in the present study and that of Miller et al. (1996) is greater than expected from previous reports (Kimura et al., 1986; Olney et al., 1987). Two factors could explain this: (i) the conditioned SNAP was recorded orthodromically not
antidromically (because the conditioning stimulus train would not have been acceptable to volunteers if delivered at wrist level); (ii) the falling phase of the SNAP was measured rather than the rising phase (because it would be less affected by stimulus artefact and would allow more accurate measurement of the relatively small SNAPs of patients). Either way, the results of the present study emphasize the importance of temporal dispersion and raise questions about baseline conduction block in patients with carpal tunnel syndrome.

Pathophysiology of carpal tunnel syndrome

While it remains to be seen whether more profound hyperpolarization would produce conduction block in patients with carpal tunnel syndrome, it is appropriate to question the premises underlying the present study.

The pre-existing conduction slowing could be the result of paranodal demyelination. Current studies using microneurography to record from single large-myelinated axons as they develop conduction block indicate that conduction time across single internodes can be prolonged from the normal 20–40 µs to >600 µs, at which level intermittent conduction failure may ensue (J. T. Inglis, J. B. Leeper, S. C. Gandevia and D. Burke, unpublished observations). It would take only a couple of affected internodes to produce the degree of conduction slowing seen in patients with carpal tunnel syndrome, and this accords with physiological and pathological data indicating that compression is not uniform across the 4-cm length of the tunnel (Brown et al., 1976; Kimura, 1979; Brown and Yates, 1982).

Demyelination is not the only mechanism that will slow impulse conduction, though it is generally considered to be an important factor when the degree of slowing is great (Brown, 1984). Slowing can result from tapering of axons and remyelination with short internodes. Both of these factors may occur in carpal tunnel syndrome and would not result in a markedly impaired safety margin for impulse conduction, but they would probably be minor factors in patients with mild-to-moderate disorders, symptomatically of short duration. However, in addition, inactivation of the Na⁺ conductance, as occurs in depolarized axons, will result in conduction slowing, and is probably the mechanism responsible for the slowing in Fig. 5. The data in Fig. 5 indicate that impulse conduction can slow not only in the absence of demyelination but, paradoxically, when axons are hyperexcitable. It may seem superfluous to conclude that carpal tunnel syndrome is a compressive neuropathy, but the mechanism through which chronic or recurrent compression produces conduction slowing remain uncertain. One possibility is that the conduction slowing is more analogous to the conduction slowing produced by acute compression (Fig. 5) than demyelination.

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