Activity-dependent conduction block in multifocal motor neuropathy

Ryuji Kaji,1 Hugh Bostock,2 Nobuo Kohara,1 Nagako Murase,1 Jun Kimura1,3 and Hiroshi Shibasaki1

1Department of Neurology, Kyoto University Hospital, Kyoto, Japan, 2Sobell Department of Neurophysiology, Institute of Neurology, Queen Square, London, UK and 3Department of Neurology, University of Iowa Hospitals and Clinics, Iowa City, USA

Summary

Patients with multifocal motor neuropathy may complain of muscle fatigue, even though the degree of conduction block assessed at rest has improved with treatment. To explore the mechanism involved, we examined changes in muscle force during maximum voluntary contraction (MVC) and monitored conduction block before and after MVC in five patients with multifocal motor neuropathy. The results were compared with those for the contralateral unaffected homonymous muscles. For one patient, who had bilateral involvement, a normal subject of a similar age and stature served as the control. Results of conduction studies were also compared with those from six patients with amyotrophic lateral sclerosis (ALS) with similar compound muscle action potential (CMAP) amplitudes after proximal stimulation. During MVC for 60 s, the affected muscles developed prominent fatigue; the force at the end of contraction compared with the initial force was significantly lower for the affected muscles [42 ± 19% (mean ± standard deviation) of the initial force] than for the control muscles (94 ± 9%; P = 0.01). After MVC, the amplitude ratio of CMAPs after proximal versus distal nerve stimulation transiently decreased to 19 ± 14% of that before MVC in the affected muscles, but not in the control muscles (94 ± 3.8% of that before MVC) and in patients with ALS (95 ± 6.7%). In one patient with a focal lesion in the forearm, nerve excitability was monitored at the lesion site before and after MVC for 120 s. There were significant increases in axonal threshold (~48%) and supernormality (~135%) immediately after MVC, suggesting that the axonal membrane had undergone hyperpolarization and, by extrapolation, that this had precipitated the conduction block. This study is the first to show that activity-dependent conduction block plays a role in human disease by causing muscle fatigue.

Keywords: activity-dependent conduction block; multifocal motor neuropathy; fatigue; membrane hyperpolarization; threshold tracking

Abbreviations: AAEM = American Association of Electrodiagnostic Medicine; ADM = abductor digiti minimi; ALS = amyotrophic lateral sclerosis; APB = abductor pollicis brevis; CMAP = compound muscle action potential; MMN = multifocal motor neuropathy; MVC = maximal voluntary contraction; P/D ratio = proximal-to-distal CMAP amplitude ratio

Introduction

Multifocal motor neuropathy (MMN) is a treatable condition, often associated with high anti-GM1 antibody titres (Parry and Clarke, 1988; Pestronk et al., 1988; Kaji et al., 1992). Its diagnosis rests upon the demonstration of focal motor conduction block in multiple nerves (Sumner, 1997), with normal sensory conduction across the lesion (Kaji et al., 1993). This peculiar sparing of sensory axons remains an enigma, and frequently causes difficulties in differential diagnosis from motor neuron disease (Parry and Clarke, 1988).

The mechanism of conduction block is best understood by analysing saltatory conduction in myelinated axons (Kaji and Kimura, 1991). Saltation is made possible by the successive activation of inward sodium currents, which generate the outward driving current at the node to be excited. For conduction to be successful, the driving current must exceed the threshold current at the node. The safety factor of transmission is defined as the ratio of the driving current to the threshold current (Tasaki, 1953). It is normally >5 and, if it falls below 1 conduction will fail. Demyelinating conduction block is considered a physiological consequence of altered cable properties of the axon (Kaji and Kimura,
Increased nodal capacitance due to demyelination results in slowing of conduction through prolongation of the internodal conduction time, because it takes longer for the driving current to charge the extra capacitance. If the driving current available at the node falls short of the threshold current, so that the safety factor is reduced below unity, conduction block will occur.

A potentially important factor contributing to conduction block is the development of membrane hyperpolarization when an axon conducts a train of impulses (Bostock and Grafe, 1985). This activity-dependent hyperpolarization is due to the activation of slow potassium channels when the impulse train is brief, but long-lasting hyperpolarization due to activation of the electrogenic sodium–potassium pump occurs after long impulse trains. At demyelinated nodes, the pump is more activated than in normal axons, to compensate for increased sodium entry into the axon caused by the prolonged action current. When the safety margin is critically impaired, membrane hyperpolarization may block conduction transiently because the driving current fails to reach the elevated threshold.

Activity-dependent conduction block has been documented in experimental CNS demyelination, and it has been suggested that it impairs the neural coding of information in CNS tracts by affecting the timing and frequencies of impulses transmitted (McDonald and Sears, 1970; Kaji et al., 1988; Kaji and Sumner, 1989a). These observations led to the hypothesis that it may play a role in the pathophysiology of multiple sclerosis (Waxman, 1981) and the central fatigue frequently seen in these patients (Waxman, 1988). In fact, conduction block precipitated by natural activity has been demonstrated in single human axons damaged by impalement amplitudes either at the abductor pollicis brevis (APB) (0.24, 0.11 and 0.98 mV) muscle after cervical magnetic stimulation (Vagg et al., 1998). They also found that peripheral motor axons are more susceptible to activity-dependent hyperpolarization than sensory axons, a finding that may result from the more pronounced inward rectification in sensory fibres counteracting the hyperpolarization (Bostock et al., 1994; Burke et al., 1997). The safety factor of sensory axons is also likely to be higher than that of motor axons even at rest, because of their lower rheobase (Mogyoros et al., 1996), which is attributed to low-threshold persistent sodium channels (Bostock and Rothwell, 1997). It has been postulated that these motor–sensory differences in membrane properties may account for the selective motor conduction block in MMN (Vagg et al., 1998).

Recently, Vagg and colleagues showed that hyperpolarization in response to the voluntary activation of human motor axons could be recorded by threshold tracking (Vagg et al., 1998). They also found that peripheral motor axons are more susceptible to activity-dependent hyperpolarization than sensory axons, a finding that may result from the more pronounced inward rectification in sensory fibres counteracting the hyperpolarization (Bostock et al., 1994; Burke et al., 1997). The safety factor of sensory axons is also likely to be higher than that of motor axons even at rest, because of their lower rheobase (Mogyoros et al., 1996), which is attributed to low-threshold persistent sodium channels (Bostock and Rothwell, 1997). It has been postulated that these motor–sensory differences in membrane properties may account for the selective motor conduction block in MMN (Vagg et al., 1998).

The present study was undertaken to examine whether activity-dependent conduction block occurs in MMN and, if so, to test whether it can be precipitated by membrane hyperpolarization. In addition, we compared the muscle force and development of conduction block to determine whether a peripheral conduction abnormality can cause muscle fatigue.

Methods

Subjects

Five male patients with MMN (age 27–72 years, mean 47 years) entered the study after giving informed consent to the protocol. The patients were selected from those attending the outpatient clinics at Kyoto University Hospital and Takeda General Hospital on the criterion of having definite conduction block [according to American Association of Electrodiagnostic Medicine (AAEM) criteria] (Sumner, 1997) in the median or ulnar nerve of an upper limb. Patient 1 had lesions in both median nerves, at the forearm on the left, at the brachial plexus on the right, and patients 2–5 had unilateral lesions in the brachial plexus. The unaffected limb served as an intrasubject control for the fatigue and conduction studies. For patient 1, a normal man of similar age (44 years) and stature served as the control. Diagnosis of MMN was based on the AAEM criteria (Sumner, 1997). Detailed histories and clinical findings for patients 1 and 2 have been reported previously (Kaji et al., 1992, 1993) and only brief descriptions are given below.

We also performed force measurement in one patient and conduction studies in six patients with amyotrophic lateral sclerosis (ALS) (age 42–67 years, mean 51 years) diagnosed by El Escorial criteria (Brooks, 1994) for comparison. They all had decreased compound muscle action potential (CMAP) amplitudes either at the abductor pollicis brevis (APB) (0.24 and 0.54 mV) or the abductor digiti minimi (ADM) (0.28, 0.12, 0.11 and 0.98 mV) muscle after cervical magnetic stimulation.

Force measurement

Muscle fatigue was assessed with a force transducer (Takei, Tokyo, Japan) during maximal voluntary contraction (MVC) for 30, 60 or 120 s. The surface EMGs were also recorded simultaneously using an amplifier bandpass of 100–3000 Hz (Neuropack, Nihonkohden, Tokyo, Japan or Viking IV; Nicolet, Madison, Wis., USA). The output was fed into a computer (Macintosh Quadra 650) for subsequent analysis (AcqKnowledge III, Biopac Systems, Santa Barbara, Calif., USA). Recordings were made from the APB of patients 1 and 4 and from the ADM of patients 2, 3 and 5, all on the affected side. We also measured force from the ADM in a patient with ALS (Fig. 1C). The subject was seated in a reclining chair with the forearm fixed on the arm-rest. The force probe was secured to the distal end of the arm-rest, and the abduction of digit I for APB or digit V for ADM was tested with the hand pronated for the APB and in the neutral position for ADM recordings.
Repetitive stimulation
To exclude a neuromuscular transmission defect as a cause of fatigue, all the patients were examined by repetitive stimulation (3 Hz) of the affected nerve at the wrist using a standard technique (Kimura, 1989) and equipment (Viking IV). The test was repeated after MVC for 60 s.

Monitoring of conduction block
The degree of conduction block was assessed by recording CMAPs after proximal and distal nerve stimulation (proximal and distal responses). Distal responses were recorded from the APB or ADM by stimulating the median or the ulnar nerve at the wrist with electric pulses (0.2 ms duration) using standard equipment (Viking IV).

In patients 2–5 it was not always possible to obtain maximal responses by stimulating at Erb’s point, the lesion site, because the threshold was higher at that point. Proximal responses were therefore recorded by stimulating the C8/T1 roots using a magnetic stimulator (Magstim 200; Magstim, Sheffield, UK) with the maximum output (100%) and a circular coil (12 cm in diameter) placed over the T1 spinous process. The coil was held firmly at a fixed position during the entire study by one of the examiners. The same procedure was carried out in six patients with ALS for comparison. In a patient with MMN (patient 1), the lesion was confined to the forearm, and proximal responses were obtained by stimulating at the elbow with electric pulses.

The response after magnetic stimulation was judged to be maximal if it did not change when the stimulator output was increased from 70 to 100%. All proximal responses used for analysis in patients 2–5 fulfilled this criterion. The response after elbow stimulation in patient 1 met the published criteria for a supramaximal response (Sumner, 1997).

The proximal and distal responses were recorded three times before MVC of the test muscle, immediately after MVC and then at intervals of 30, 60, 90 and 120 s. Responses immediately after MVC were obtained within 5 s of the cessation of the contraction. The three sets of responses before the MVC served as controls to ensure reproducibility.

To assess the degree of conduction block, the proximal-to-distal CMAP amplitude ratio (P/D ratio) was calculated, using baseline-to-negative peak measurements. In MMN patients, distal CMAP amplitudes after stimulating the median or ulnar nerve at the wrist were 4.90 ± 2.57 mV (mean ± standard deviation), and proximal amplitudes were 0.39 ± 0.08 mV after root stimulation in patients 2–5 and 7.54 mV after elbow stimulation in patient 1. The proximal response amplitudes after root stimulation were similar to those in ALS patients (0.38 ± 0.33 mV). The area ratio was not used because analysis of the individual components of the CMAP was not possible using the area in patient 1. Statistical analysis was performed on the last control response and that immediately after MVC, because these data would have been affected minimally by displacement of the stimulating electrodes or coil.

Monitoring of nerve excitability
Nerve excitability was tested in patient 1, whose lesion was localized to the distal median nerve in the forearm. Since
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the method employed was the same as in the previous study (Vagg et al., 1998), it is described here only briefly.

A computerized threshold tracking procedure (QTRAC, Institute of Neurology, London) (Bostock et al., 1998) was used to follow the excitability of motor axons in the median nerve innervating the thenar muscles before and after maximal voluntary thumb abduction. The location of the cathode was 5 cm proximal to the wrist crease, over the distal edge of the lesion as identified by MRI (Kaji et al., 1993) (Fig. 4). The anode was placed on the radial side of the forearm. The exact site of stimulation and the current intensity was adjusted to elicit an all-or-none single motor unit response in the APB, after confirming that the unit did not undergo conduction block after MVC for 120 s. The threshold of this unit was tracked with 0.2 ms pulses to establish the unconditioned control threshold.

Supernormality (or superexcitability) reflects the phase of increased axonal excitability that follows immediately after the refractory periods obtained when the test stimulus is preceded by a single supramaximal conditioning stimulus, and was sampled at a conditioning-test interval of 7 ms (Bostock and Grafe, 1985; Burke et al., 1997; Bostock et al., 1998). Because the maximal CMAP produced by the supramaximal conditioning stimulus was superimposed on the test CMAP, the conditioned potential was measured by the computer after on-line subtraction of the CMAP produced by the conditioning stimulus alone. Tracking the threshold for the conditioned response provided a measure of the changes in supernormality; if the tracked threshold was reduced relative to the control threshold, the degree of supernormality was increased. The combination of an increase in the control threshold and an increase in supernormality indicates that the axon has undergone hyperpolarization (Bostock and Grafe, 1985). In addition, the degree of conduction block was assessed by stimulating the wrist (distal response) and the elbow (proximal response). Each parameter was monitored every 6 s, with a stimulation interval of 1 s between measurements. Because of this time interval, the measurements may sometimes lag behind the actual threshold changes (Fig. 5A).

Room temperature was controlled at 25°C.

The entire protocol was approved by the Institutional Review Board of Kyoto University School of Medicine.

Case histories

Patient 1

A 46-year-old man was diagnosed as having MMN in 1991. Muscle weakness was found in the territories of both median nerves, both peroneal nerves and the left ulnar nerve, with no sensory deficits. The lesion in the left median nerve was localized to the distal forearm, sparing the anterior interosseous nerve. MRI showed focal nerve enlargement from 3 to 11 cm proximal to the wrist crease (Fig. 4). Motor conduction studies revealed complete conduction block at a point between 4 and 6 cm proximal to the crease, with normal sensory conduction along the entire nerve.

During the following 4 years, he was on oral cyclophosphamide (50–100 mg/day for 10 months in total) and then on three courses of intravenous immunoglobulins (400 mg/kg/day for 5 days per course). These treatments significantly improved the weakness of the left APB from 0/5 to 4+/5 on the MRC (Medical Research Council) scale. The degree of conduction block also improved greatly (the P/D ratio increased from 0 to 0.3). In 1998 he returned to our clinic because of excessive fatigue in the left hand.

On examination, there were occasional fasciculations and myokymia in the left thenar eminence. Manual muscle testing revealed mild weakness in the left APB (MRC 4+/5), much as on the last visit. The degree of motor conduction block was also similar (P/D ratio = 0.3).

Patient 2

A 57-year-old male architect noticed weakness in the right upper extremity in 1987. The diagnosis of MMN was made in 1990, when the muscle weakness involved the territories of the right median, ulnar, radial, musculocutaneous and axillary nerves, with prominent fasciculations. Motor conduction block was found in the left ulnar nerve between the axilla and Erb’s point, and surgical exploration disclosed multifocal nerve enlargements along the distal lower trunk and the medial and posterior cords of the brachial plexus. There were no sensory deficits, and sensory conduction was normal. After five courses of intravenous immunoglobulin therapy (25–400 mg/kg per day, 3–5 days per course), the weakness of the right ADM improved from 2/5 to 4+/5 on the MRC scale, and the motor conduction block improved (P/D ratio increased from 0.05 to 0.2).

In 1998, he was seen at the clinic complaining of easy fatigability of the right hand when drawing with a pen. The strength of his right hand had not changed, but muscle fatigue was evident on physical examination, by asking him to perform MVC for 30 s. Occasional myokymia was found over the ADM and the first dorsal interosseous muscle on the right.

Results

Muscle fatigue and repetitive stimulation

Muscle fatigue was tested in patients 2–5 by comparing the force recordings during MVC for 60 s for the affected muscle and the homonymous muscle on the normal side (Fig. 1). Because both median nerves were affected in patient 1, the fatigue test in patient 1 was compared with data obtained from the same muscle in a normal subject (Fig. 5). The initial force or the mean force during 5–10 s after the onset (F1) of MVC and the end force averaged over the last 5 s of MVC (F2) was measured. F1 and F2 were 1.88 ± 0.28 kg (mean ± standard deviation) and 1.77 ± 0.19 kg,
Fig. 2 (A) Serial recordings of distal and proximal compound EMG responses before the MVC, during the MVC and after the MVC of patient 2 (same muscle as in Fig. 1B). The waveform at MVC30" (30 s after onset) was obtained during the 60 s MVC by interrupting the contraction for 5–6 s and that at MVC60" was obtained at its end. Note the shift in the latency of a late EMG component (arrowheads). (B) Activation study in the patient with ALS whose force measurements are shown in Fig. 1C. Note no changes in the proximal responses except for a slight latency change (arrowheads). Also note the different time bases in A and B.

respectively, for the control muscles and 0.54 ± 0.59 and 0.24 ± 0.32 kg for the affected muscles (Fig. 3A). The ratio F2/F1 represents the degree of fatigue, and was 95 ± 7% (mean ± standard deviation) for the normal muscles, but was significantly lower for the affected muscles (42 ± 19%, $P = 0.01$, paired $t$-test; $P = 0.04$, Wilcoxon signed rank test).

Repetitive stimulation studies at the wrist were performed before and after MVC for 60 s in the affected muscles, all of which showed normal results. At 3 Hz, the amplitude decrement of the third response ranged from −3 to +2% before the MVC and from −5 to +5% after the MVC. The CMAP amplitudes were also unchanged (4.8 ± 3.8 versus 5.0 ± 3.9 mV; peak to peak).

**Monitoring of conduction block**

Figure 2 depicts the serial changes in the degree of conduction block before and after MVC in patient 2 (panel A), and the corresponding findings in a patient with ALS (panel B). Patient 2 showed substantial changes, with latency shifts and increased temporal dispersion in the proximal response waveform, immediately after MVC. Moreover, a late component (arrowheads in Fig. 2) had developed prolongation of latency at 30 s of MVC, and had disappeared by the end of the MVC. This component reappeared 30 s after the MVC, but with a slightly prolonged latency, which gradually returned to the baseline over 60–90 s. These graded findings are not compatible with artificial reduction of CMAP amplitude due to an inadequate stimulus intensity, but point to the decreased safety factor for transmission through the lesion site, initially prolonging latencies, then blocking conduction. By contrast, the patient with ALS exhibited no changes in the proximal and distal responses except for slight latency changes.
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Fig. 3 Summary of muscle fatigue testing (A) and serial changes in P/D ratio before (controls 1–3), during (MVC) and 30, 60, 90 and 120 s after the MVC (B). In A, F1 and F2 represent the averaged force over 5–10 s after the onset of the MVC and over the last 5 s of the MVC, respectively. For subjects who underwent multiple trials, the values for MVC represent the ratios with the greatest contraction-induced change. Although two peaks are shown for patient 1 in B, only peak 1 was used for statistical analysis. The amplitude measurement was made off-line with manual adjustment of the cursors, and the values may differ from those in automatic measurement as shown in Fig. 5.

A summary of serial changes in the P/D ratio is shown in Fig. 3B. Two peaks were analysed in patient 1 because the later peak, which presumably resulted from slower-conducting axons with a lower safety factor than those responsible for the first peak, would be suitable for monitoring serial amplitude changes induced by voluntary activation. Because the first peak recovered rapidly in amplitude and latency, the second peak could not have been affected by phase cancellation caused by the first peak.

P/D ratios from the five patients with MMN, including only the first peak from patient 1, were analysed statistically. Overall, the P/D ratio decreased to 19 ± 14% (mean ± standard deviation) of the precontraction ratio, and the duration of recovery was up to 120 s. The ratios before MVC were already low (0.16 ± 0.11), indicating conduction block at rest. Following MVC, they decreased further to 0.04 ± 0.05, a change that was significant (P = 0.01, paired t-test; P = 0.04, Wilcoxon signed rank test). The same activation study resulted in no significant changes in the ratio in the control muscles (94 ± 3.8% of those before MVC) or in ALS patients (95 ± 6.7%).

On the whole, the extent of P/D ratio reduction was similar to that of muscle fatigue for each patient with MMN (Fig. 3A).

Monitoring of nerve excitability
To investigate the mechanism of conduction block, nerve excitability near the site of the lesion was monitored in patient 1 before and after MVC for 120 s (Figs 4 and 5). Serial changes in the distal and proximal responses in two trials, performed at an interval of >15 min, are illustrated in Fig. 4. Because the distal responses did not change, only those of the first trial are shown. The changes were reproducible in the two trials; the proximal responses were almost abolished immediately after MVC, and the first peak recovered within 6–24 s. The second peak reappeared after 30–36 s and gradually recovered its latency and amplitude over 1 min.

The physiological parameters obtained in trial 2 are shown in Fig. 5A. The force measurement showed prominent fatigue within 1 min. Thumb abduction was still possible through the abductor pollicis longus muscle, which was intact in this patient. Immediately after the muscle activation, the threshold at the lesion site (S3) increased by ~48% in parallel with an increase in supernormality (~135%), changes that indicate axonal hyperpolarization. A control trial in a normal subject (Fig. 5B) revealed similar increases in threshold (~38%) and supernormality (~115%), but with no conduction block or
Serial recordings of distal and proximal responses before and after a 120 s MVC in patient 1. The illustration on the left shows electrode locations in relation to the extent and size of the lesion, as measured on MRI in a previous study (Kaji et al., 1993). R = recording site over APB; S1 = stimulation for distal response; S2 = stimulation for proximal response; S3 = stimulation for nerve excitability monitoring. The EMG waveforms from two trials are shown (trial 1 and trial 2) for the proximal responses, but only those for trial 1 are shown for distal responses because they remained the same in trial 2. Note that the contraction-induced changes in the proximal responses were similar in the two trials. Separate analyses of the amplitudes of the peaks designated as (1) and (2) are shown in Fig. 5. The latencies of peak (2) returned gradually to the baseline after MVC.

Fatigue. In Fig. 5A, the time course of the contraction-induced changes in threshold and supernormality are similar to that of recovery of the second peak of the proximal EMG response following a similar MVC.

Discussion

The present study has documented activity-dependent conduction block in MMN, and provides evidence that axonal hyperpolarization precipitated the block. The same activation study showed no significant changes in patients with ALS. In MMN, muscle fatigue occurred in parallel with the conduction block. No other causes of fatigue were identified; normal repetitive stimulation studies and lack of fatigue in other muscles within the same patient indicate that neuromuscular transmission defects or fatigue of central or muscle origin are unlikely. It is therefore reasonable to conclude that the activity-dependent conduction block produced the muscle fatigue in MMN.

A technical limitation applies to delivering a stimulus at an intensity sufficient to evoke a maximal response, particularly at Erb’s point, and this is the major problem in the correct identification of conduction block. The threshold for excitation at a demyelinated site may be substantially increased and, because the brachial plexus is the favoured site of the lesion in MMN, it can be quite difficult to determine the degree of conduction block. To avoid this, we used magnetic stimulation at the spinal nerve roots, a site that is usually proximal to the lesion (Kaji et al., 1993).

In the present study, the proximal responses met the criteria for supramaximal stimulation set by the AAEM (Sumner, 1997) for elbow stimulation, as well as those set by ourselves for root stimulation, but it is still conceivable that not all axons were stimulated. In fact, the maximum response after root stimulation in a patient with ALS was approximately half of the distal response (Fig. 2B). This may be due to the difficulty of targeting both C8 and T1 roots, which innervate small hand muscles, by the magnetic coil. Otherwise the maximum output of the stimulator may be insufficient to attain the supramaximal level, and the proximal magnetic
in this axon and that the activity-dependent threshold increase was due to hyperpolarization. The inference that the nearby conduction block in other fibres, which we were unable to test directly, was also due to membrane hyperpolarization is compelling. Not only are demyelinated fibres more sensitive to the same load of hyperpolarization, due to their reduced safety factor, but also the activity-dependent hyperpolarizing current at sites of demyelination is much stronger than normal, (Bostock and Grafe, 1985; Inglis et al., 1998). The pattern of recovery seen in Figs 2 and 4, with conspicuous latency changes, is consistent with conduction failing at a site of demyelination, rather than stimulation failure at the proximal site. Therefore, it is unlikely that the changes observed in MMN are caused by technical factors. These activity-dependent changes, together with decreased amplitudes of the proximal response, may be useful in establishing the presence of a demyelinating lesion at the proximal site for differentiating MMN from ALS.

We obtained solid evidence for membrane hyperpolarization that developed after activity in an intact axon near the lesion, in which the increases in threshold and supernormality were similar to those in the control. Supernormality provides a useful index of membrane potential, provided that potassium channels are functioning normally (Bostock and Grafe, 1985; Bostock et al., 1998). The supernormality measurements therefore indicate both that the resting membrane potential was normal stimulation alone is unable to establish the presence of conduction block. However, significant changes in P/D ratios were found only in patients with MMN, not in ALS patients who had advanced chronic partial denervation in the small hand muscles. A characteristic of activity-dependent conduction block at sites of demyelination is that it is preceded by markedly prolonged internodal conduction times (Bostock and Grafe, 1985; Inglis et al., 1998). The pattern of recovery seen in Figs 2 and 4, with conspicuous latency changes, is consistent with conduction failing at a site of demyelination, rather than stimulation failure at the proximal site. Therefore, it is unlikely that the changes observed in MMN are caused by technical factors. These activity-dependent changes, together with decreased amplitudes of the proximal response, may be useful in establishing the presence of a demyelinating lesion at the proximal site for differentiating MMN from ALS.

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sensory axons (Vagg et al., 1998). This hypothesis is based in part on the assumption that hyperpolarization is involved in symptom production, which our new results confirm. As argued elsewhere (Waxman, 1996; Burke et al., 1997; Kaji and Kimura, 1999), such biophysical properties could protect sensory axons from conduction block, but at the expense of a greater disposition to ectopic activity. Despite having less propensity to ectopy, motor fibres may undergo preferential blockage in other demyelinating neuropathies, such as Guillain–Barré syndrome and chronic inflammatory demyelinating polyneuropathy, which often present with predominantly motor symptoms.

No previous studies have demonstrated muscle fatigue induced by conduction block within a nerve trunk, though there is a report of block at axonal branch points near their terminals (Lagueuy et al., 1998). The activity-dependent conduction block was demonstrated in animal models of central demyelination (McDonald and Sears, 1970; Kaji et al., 1988), and may account for the central fatigue in patients with multiple sclerosis. Indeed, the present finding of muscle fatigue associated with activity-dependent block provides a model for gaining insight into the complex process of fatigue in CNS disease.

As for the mechanism of hyperpolarization, activation of the sodium–potassium pump is likely to be the main cause because the fatigue lasted for minutes after MVC. This raises therapeutic opportunities because the administration of digitalis, a specific blocker of the pump, can reverse activity-dependent block in experimental models (Kaji and Sumner, 1989a, b).

In conclusion, we have provided evidence that conduction block in multifocal motor neuropathy is exacerbated by voluntary motor activity, due to hyperpolarization by the electrogenic sodium pump, and that this activity-dependent conduction block can cause muscle fatigue. The relative sparing of sensory axons may be due, at least in part, to their greater resistance to this type of block.

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