Differences in accommodative properties of median and peroneal motor axons

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Abstract

Objectives—To investigate whether accommodation to depolarising and hyperpolarising currents differs for motor axons of human upper and lower limb nerves.

Methods—The threshold tracking technique was used to measure threshold electrotonus for median and peroneal motor axons. The threshold current that produced a compound muscle action potential 50% of maximum was measured, and membrane potential was altered using subthreshold polarising currents of 330 ms duration but of variable intensity, from +40% (depolarising) to –100% (hyperpolarising) of the unconditioned threshold.

Results—The maximal threshold changes (the peak of the S1 phase of threshold electrotonus) were significantly greater in median axons for both depolarising and hyperpolarising currents. The subsequent phases of accommodation to depolarising currents (S2) and to hyperpolarising currents (S3) were also significantly greater in median axons. These findings raised the possibility that greater accommodation in median axons resulted from greater changes in membrane potential.

However, regression of S2 against S1 to depolarising currents disclosed significantly greater accommodation (27.8%) for median axons, suggesting that slow K+ conductances may be more prominent on median than peroneal axons. By contrast, the relation between S3 and S1 to hyperpolarising currents was similar for the two nerves, suggesting that the difference in inward rectification was merely because the conductance varies with the extent of hyperpolarisation.

Conclusions—Slow K+ conductances are more prominent for median motor axons than for peroneal axons. It would therefore be expected that axons innervating the lower limbs have less protection from depolarising stress and could develop ectopic activity more readily.

(J Neurol Neurosurg Psychiatry 2001;70:372–376)

Keywords: threshold electrotonus; threshold tracking; slow K+ channel; inward rectification

There are subtle differences in axonal properties in different human nerves, presumably reflecting adaptation to the discharge patterns normally carried by axons. For example, sensory axons have different strength-duration properties, presumably due to a more prominent Na+ conductance which is active at resting membrane potential, and greater inward rectification than motor axons. In addition, it has recently been reported that there are significant differences in axonal properties between nerves in the upper and lower limbs.

Positive and negative symptoms in patients with polyneuropathy are more prominent in the lower limbs, and this may partly result from differences in axonal properties between nerves in the upper and lower limbs. It is not surprising that there may be biophysical differences in motor axons innervating muscles in the hand and foot, because their maximal discharge rates and discharge patterns probably differ.

A previous study comparing median and peroneal motor axons suggested that accommodation to prolonged depolarising stimuli (presumably reflecting slow K+ channel activity) and accommodation to hyperpolarising stimuli (probably reflecting inward rectification) are more prominent in median axons. However, the study also found that median axons have greater threshold changes to both depolarising and hyperpolarising conditioning currents. Assuming that threshold varies with membrane potential, this raises the possibility that the more prominent accommodation on median axons was merely the result of a greater change in membrane potential. To demonstrate that there are differences in internodally located conductances responsible for accommodation to depolarising and hyperpolarising currents would require studies in which accommodation is measured in response to similar changes in membrane potential.

The present study was undertaken to investigate whether there are quantitative differences in accommodation between median and peroneal motor axons, by comparing the accommodative changes in threshold in response to currents of graded intensity. The data suggest that the two nerves respond differently to prolonged subthreshold currents and, accordingly, it might be expected that they have different behaviour under stress.

Methods

SUBJECTS

Fourteen experiments were performed on seven normal volunteers (aged 24 to 55 years, mean 36 years), who had no clinical or electrophysiological evidence of a peripheral nerve disorder. The subjects gave informed consent to the experimental procedures, which had been approved by the committee on experimental procedures involving human subjects of the University of New South Wales.
METHODS
In all studies, the current required to produce a compound muscle action potential (CMAP) that was 50% of maximum was determined using a computerised threshold-tracking program (QTRAC20, Institute of Neurology, Queen Square, London, UK). The median CMAP was recorded from the abductor pollicis brevis, and the peroneal CMAP from the extensor digitorum brevis. The peroneal nerve was chosen in the lower limb because it innervates only one intrinsic muscle of the foot, such that the EMG recording would not be contaminated by activity from other muscles. For nerve stimulation, the active electrode was over the nerve at the wrist for the median nerve and at the ankle for the peroneal nerve, and the reference electrode was 10 to 20 cm proximal to the active electrode. Skin temperature was measured near the stimulus site, and was maintained at or above 30°C using blankets and a heater when necessary. Temperatures were 32.1 (0.8)°C at the wrist, and 31.4 (1.1)°C at the ankle (mean (SD)). It should be noted that threshold electrotonus is relatively insensitive to temperature, at least within the range 30°C-34°C.

To investigate the effects of changing membrane potential, subthreshold depolarising or hyperpolarising DC of 300 ms duration was used to activate the accommodative conductances. Figure 1 shows the changes in threshold for the test CMAP produced by the polarising currents (threshold electrotonus) from one subject. Threshold currents required to produce an unconditioned CMAP of 50% maximum were measured using a test stimulus of 1.0 ms duration. The strength of the polarising current was varied systematically from +40% (depolarising) to –100% (hyperpolarising) of the unconditioned threshold. Threshold measurements were made from 10 ms before the onset of the polarising currents to 50 ms after their end. The peaks of the maximal threshold changes occurred at ~25 ms with depolarising currents and at ~100 ms with hyperpolarising currents (fig 1).

-Based on the threshold electrotonus curves in fig 1, the changes in threshold for the test potential were measured 25 ms, 100 ms, and 300 ms after the onset of subthreshold polarising currents lasting 330 ms, using a 1.0 ms test stimulus. The strength of the polarising current was varied systematically from +40% (depolarising) to –100% (hyperpolarising) of the unconditioned threshold in 10% steps. The changes in threshold produced by the DC polarising current were normalised to the threshold for an unconditioned CMAP, and were defined as follows (fig 1):

\[ F = \text{the abrupt threshold change corresponding to the first electrotonic response to the polarising current.} \]

\[ S_1 = \text{first slow phase of threshold electrotonus to depolarising current=}T_{300d}−T_{25d}. \]

\[ S_2 = \text{accommodation to depolarising potential changes=}T_{25d}−T_{100d}. \]

\[ S_3 = \text{accommodation to hyperpolarising potential changes=}T_{100h}−T_{300h}. \]

where \( T_{25d}, T_{100d}, T_{300d}, T_{25d}, T_{100d}, T_{300d} \) represent normalised threshold values measured 25 ms, 100 ms, and 300 ms after the onset of depolarising (d) or hyperpolarising (h) currents, respectively.

Although the onsets of \( S_2 \) and \( S_3 \) occur at ~25 ms and ~100 ms respectively, this does not imply that the conductances responsible for the accommodative threshold changes are inactive until these intervals. However, the change in membrane potentials driving the conductance are probably maximal at or near these intervals.

-Results
The threshold changes produced by DC lasting 300 ms are illustrated for one subject in fig 1. For equivalently strong currents, accommodation to both depolarising current (\( S_2 \)) and hyperpolarising current (\( S_3 \)) was greater for median axons than peroneal axons. However, the maximal threshold changes (\( S_1 \) and \( S_1h \)) were also greater for median axons.

-POLARISING LEVEL AND \( S_1 \)
Figure 2 shows the relation between the strength of the polarising currents and the change in threshold produced by prolonged subthreshold depolarising and hyperpolarising currents. The maximal threshold changes measured 25 ms after the onset of depolarisation (equivalent to \( F+S_{1d} \)) were greater for median motor axons than for peroneal motor axons in all seven subjects (\( p=0.0008 \) for the 40% depolarising current, paired \( t \) test; fig 2

![Figure 1 Threshold electrotonus of median (filled circles) and peroneal (open circles) motor axons from a normal subject. Threshold currents required to produce a compound muscle action potential of 50% maximum were measured using test stimulus of 1.0 ms duration. Polarising currents were of 300 ms duration, and their intensity was set +40%, –40%, and –80% of the unconditioned threshold. The \( F, S_1, S_2, \) and \( S_3 \) phases are defined as in Vagg et al (see also text), for the 40% depolarising current and the 80% hyperpolarising current. In accordance with convention, threshold reduction is plotted on the y axis so that responses to depolarising and hyperpolarising currents are upwards and downwards, respectively. The interrupted vertical lines are at 25 ms and 100 ms—that is, at the peaks of \( S_1 \) and \( S_{1h} \), respectively.](http://jnnp.bmj.com/ on July 6, 2017 - Published by group.bmj.com)
The relations were roughly linear and the slopes of the regression lines for the two nerves differed significantly (p<0.05, t test for slope). For the response to depolarising currents, the peak threshold change (F+S1d) was measured because the accommodative conductance (a slow K+ conductance, Gk) is located on both the nodal and internodal membrane. The findings were similar whether F+S1d or only S1d was used to reflect the threshold change during S2.

With hyperpolarising currents, only the slow (S1) phase of threshold electrotonus was measured, excluding the initial rapid threshold change (F), because inward rectification is located in the internode. It should be noted that the findings were similar whether F+S1h or S1h was used to reflect the threshold change driving S3. The extent of S1 on hyperpolarisation was again greater for median axons for six of seven subjects and identical in the seventh, a difference that was significant (p=0.009 for the 100% hyperpolarising current, paired t test; fig 2 B). The differences between the nerves were greater the stronger the depolarising or hyperpolarising current. These findings showed that depolarising and hyperpolarising currents produce greater changes in membrane potential for median motor axons, presumably because they produce greater changes in membrane potential after the onset of the prolonged subthreshold depolarising current. The S2 accommodative phase was estimated by subtracting the threshold change at 300 ms from the threshold change at 25 ms. S2 was greater in median axons.

To measure S3, the threshold change produced by a subthreshold hyperpolarising current at 300 ms was subtracted from the threshold change at 100 ms. For six of seven subjects both S2 and S3 accommodation were greater in response to the same polarisation level in median axons, and they were the same in the seventh subject (fig 3 A and B). These differences in the S2 and S3 phases of the threshold electrotonus raise the possibility that median motor axons have a greater slow K+ conductance and greater inward rectification than peroneal motor axons. However, these differences might be explained by greater changes in membrane potential produced by the conditioning current. To determine whether this was the case, the relation between the accommodative responses and S1 was investigated.

RELATION BETWEEN ACCOMMODATION AND THE DRIVING THRESHOLD CHANGE

Figure 4 A shows the relation between the driving threshold change measured as F+S1d, and the S2 accommodation. There was a linear relation for both median and peroneal motor axons. The slope was significantly steeper for median motor axons than for peroneal axons (p=0.04, t test for slope). With median axons, a
Accommodation in median and peroneal axons

This study has documented driving threshold change, $S_1$, during prolonged hyperpolarising currents. There was a similar relation for median motor axons and peroneal motor axons, apart from the greater maximal $S_1$ threshold increase in median axons. This finding suggests that the difference in $S_3$ accommodation in fig 3 B can be fully explained by the difference in $S_1$, in fig 2 B.

**Discussion**

This study has documented differences between motor axons in the median and peroneal nerves. Firstly, the applied currents produced greater changes in threshold ($S_1$) and presumably greater changes in membrane potential for median axons. Secondly, in response to the same change in threshold (and presumably the same change in membrane potential), the $S_2$ phase of threshold electrotonus was significantly greater in median motor axons than in peroneal axons. Thirdly, the $S_3$ phase was similar between the two nerves when the driving threshold changes were matched. The $S_2$ phase of threshold electrotonus mainly reflects nodal and internodal slow $K^+$ conductances, whereas $S_3$ is largely due to inward rectification, a conductance located in the internode. The results therefore provide evidence that there is an internerve difference in the expression of slow $K^+$ conductances but not in inward rectification.

The possibility that factors such as axonal size and skin resistance affected the results of threshold electrotonus cannot be excluded. However, a difference in the threshold changes during polarising currents is unlikely to be explicable by such differences. Refractoriness after a conditioning stimulus is inversely related to axonal size, but there is no significant difference in refractoriness of median axons at the wrist and of peroneal axons at the ankle. Skin resistance would have little or no effect on the results because the changes in threshold current were normalised to the unconditioned threshold.

$S_1$ is thought to reflect changes in membrane potential of the internodal axolemma, caused by current passing through or under the myelin sheath. The magnitude of $S_1$ depends on the access resistance to the internodal axolemma and also membrane potential. For example, when an axon is depolarised, the resistance of the internodal axolemma falls, due to activation of voltage dependent potassium channels, and $S_1$ decreases significantly. The differences seen in the present study are unlikely to be due to differences in membrane potential because axonal excitability parameters sensitive to the membrane potential (refractoriness and strength-duration time constant) do not differ for median and peroneal motor axons. The differences in $S_1$ could reflect the resistance of the internodal axolemma, although whether this is due to a difference in expression of ion channels or passive membrane properties is unknown at present.

Slow $K^+$ channels are voltage dependent: ~30% are open at resting membrane potential and more are activated as the axon is depolarised but, as mentioned above, a significant difference in membrane potential is unlikely. We therefore suggest that median motor axons have more functional slow $K^+$ channels than peroneal motor axons. The difference in expression of nodal and internodal slow $K^+$ conductances could be related to differences in the habitual discharge patterns of median and peroneal motor axons. Maximal firing rates in thenar motor units are about 30 Hz, though they may reach 100 Hz. Maximal firing rates of 25–30 Hz have been reported for motor axons of tibialis anterior, but there are limited data on the discharge patterns during common daily tasks. The thenar muscles are used more than the muscles in the foot for discrete movements, and habitual discharge patterns are likely to differ significantly, even if...
motor axons innervating both muscles can be driven to similar rates.

In some human peripheral neuropathies such as in diabetes mellitus or vasculitic disorders, depolarising stresses are created by nerve ischaemia or paralysis of the Na⁺-K⁺ pump. A lesser accommodation to depolarisation in motor axons innervating the lower limb muscles would provide less protection from depolarising stress. This could be a factor in the greater tendency for lower limb motor axons to become ectopically active, thus explaining why fasciculation, myokymia, and cramp are more prominent in lower limb muscles, both in normal subjects and in patients with peripheral neuropathy.

Our results showed that the extent of inward rectification was not significantly different for median and peroneal motor axons. Inward rectification is activated by prolonged hyperpolarisation, and produces a depolarising accommodation, limiting the extent of hyperpolarisation. Inward rectification could become significant when the axons conduct impulse trains. During prolonged impulse trains, human axons undergo substantial hyperpolarisation and this can lead to conduction block at the sites of impaired safety margin for impulse conduction. Our results, however, do not support the hypothesis that a difference in the extent of inward rectification in motor axons of the different nerves contributes to more prominent weakness in the distal lower limbs of patients with polyneuropathy.

We conclude that slow K⁺ conductances are not identical in different motor axons. It can therefore be expected that upper and lower limb axons will respond differently to depolarising stress, and this may contribute to the geographic differences in positive motor symptoms.

This study was supported by the National Health and Medical Research Council of Australia, the National Multiple Sclerosis Association of Australia, and the Uehara Memorial Foundation (Japan).

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J Neurol Neurosurg Psychiatry 2001 70: 372-376
doi: 10.1136/jnnp.70.3.372

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