Afferents contributing to the exaggerated long latency reflex response to electrical stimulation in Parkinson’s disease

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SUMMARY Reflex pathways to tibialis anterior motoneurons from low threshold afferents of the common peroneal nerve were examined in 13 Parkinsonian subjects and 12 age-matched normals. Post-synaptic events occurring in single motoneurons were derived from changes in the firing probability of single voluntarily activated motor units during afferent stimulation. A period of increased firing probability of “monosynaptic” latency (about 33 ms) occurred in all subjects in both groups. A second, later, period of increased firing probability (latency about 64 ms) was seen in 2/12 normals and 8/13 Parkinsonian subjects. Neither of these responses could be produced by cutaneous stimulation. The electrical threshold of the afferents mediating the later effect was 0.82 of the threshold of alpha motoneuron axons which is similar to that of the afferents mediating the shorter latency response. Thus, large non cutaneous afferents contribute to this long latency response in man presumably through polysynaptic pathways. Transmission in these pathways is enhanced in Parkinson’s disease.

Perturbations of a limb in man can cause segmented reflex responses in the stretched muscles.1 The reflex response with the shortest latency, labelled M1 by Lee and Tatton,2 is attributed to the predominantly “monosynaptic” facilitation of motoneurons from primary spindle endings.3 A longer latency response, labelled M2 by Lee and Tatton,2 has a number of possible explanations which include two opposing theories; first, that the response is mediated by large, fast conducting afferents to the spinal cord and then by polysynaptic, and possibly “long loop” pathways to motoneurons. The main delay being in the central nervous system;4–7 second, that the response is mediated by slowly conducting afferents to the spinal cord then by oligosynaptic pathways to motoneurons the main delay being in the peripheral nervous system.8–9 These two possibilities cannot be distinguished by limb perturbation since this stimulus excites many different receptors whose afferents have different conduction velocities. Electrical stimulation of a peripheral nerve however, excites axons in approximate relation to their size, the larger axons having lower thresholds.10–11 If long latency responses could be elicited by electrical stimulation of low threshold afferents in peripheral nerves then polysynaptic pathways from these afferents must exist and these pathways might contribute to the late responses produced by stretch. To test for this possibility we examined the reflex effects produced in tibialis anterior motoneurons by electrical stimulation of low threshold afferents in the peroneal nerve in normal subjects.

In Parkinson’s disease the long latency response (M2) to limb perturbation is exaggerated.2 12–19 We also examined patients with Parkinson’s disease to determine whether any long latency responses obtained from electrical stimulation of low threshold afferents were exaggerated in these patients.

Methods

Observations were made on 12 normal subjects aged 32 to 83 years (mean = 57.8) and 13 patients with Parkinson’s disease...
aged 39 to 69 years (mean = 55.8). Patients with Parkinson’s
disease with bradykinesia and/or rigidity in the lower
extremities, but little or no tremor, were asked to volunteer
for the study and provided informed consent. Rigidity was
graded on a scale of 0-4 for each limb and for the trunk,
making the total possible score for the four limbs and trunk
between 0 and 20. The patients were classified as “mild” if
the rigidity score of the tested limb was zero and the total
score was less than 4, and “moderate” if the rigidity score for
the tested limb was one or more or the total score was 4 or
more.

The common peroneal nerve was stimulated with surface
electrodes (2-5 cm apart) at the head of the fibula using
square wave stimuli 0.5 ms in duration, delivered at 303 ms
intervals. The electrode was carefully positioned to stimulate
the alpha motoneuron axons innervating the tibialis anterior
at a lower voltage than that required to stimulate the alpha
motoneuron axons innervating the peroneous longus muscle.
The motor threshold (MT) for a given muscle was determined
by gradually increasing the stimulus voltage until the
first alpha motoneuron axons to that muscle were activated,
as judged by a movement of the muscle tendon and/or an
action potential on the surface EMG recording (surface
EMG was monitored using pairs of surface electrodes placed
4 cm apart over the tibialis anterior and peroneus longus
muscles). Stimulus strength was expressed in multiples of this
MT voltage. Local cutaneous afferents in the region of the
knee were stimulated by moving the stimulating electrode
from its position over the peroneal nerve to neighbouring
sites. Cutaneous afferents in the distribution of the peroneal
nerve were activated by stimulating the distal peroneal nerve
at the ankle and by stimulating the toes.

To record motor unit activity, a concentric needle elec-
trode (cross sectional area = 0.65 mm², central electrode
surface area = 0.07 mm²) was inserted into the tibialis ante-
or muscle 10 cm below the tibial tuberosity and 1 cm lateral
to the tibial crest, and positioned close to a motor unit
activated by gentle voluntary contraction. The signal was
amplified 5000-10,000 times and filtered using a band pass of
10 Hz to 30 kHz. A window discriminator and peak detector
were used to select a given motor unit action potential. The
subject was provided with auditory and visual feedback of
the motor unit discharges, and was instructed to keep the
unit discharging at a constant rate. Peristimulus time histo-
grams (nth order) with 400 μs bins (a 30 ms prestimulus
period and a 170 ms poststimulus period) of the occurrences
of the single motor unit’s action potentials in response to
more than 2000 stimuli were generated using a lab computer.
A five bin running average was used prior to the analysis to
reduce bin to bin variation. The thresholds for detection of a
response (see below) were established from unsmoothed histograms to permit the comparison with previous data.

The mean background firing probability of the motor unit
was calculated from the 30 ms prestimulus period. A period
of increased firing probability was accepted if the firing
probability in three or more adjacent bins exceeded the mean
background firing probability plus 2 standard deviations.

A “satisfactory recording” was defined as a run in which
a motor unit’s spike train had been recorded without con-
tamination from other motor units or artifact during the
delivery of more than 2000 stimuli. The “threshold” for
detection of a facilitatory effect was determined in the fol-
lowing way. Consecutive recordings of the same motor unit
were obtained using different stimulus intensities until “satisfactory recordings” above and below the stimulus intensity
required for the observed effect were obtained (with a stim-
ulus separation of not more than 0.05 MT). Paired stimuli (5
ms apart and of equal intensity) were used to ensure that
small late responses were not overlooked when searching for
the threshold to detection of the long latency response. The
time of the motor unit action potential was subtracted from
the response latency to obtain the actual or “corrected”
latency (for further details of the method see Mao et al20).

All experiments were recorded on magnetic tape for fur-
ther analyses. First order peristimulus histograms, which
record only the first time a unit fires in relation to a stimulus,
were also constructed from these tapes to exclude double
discharges of motor units.

Student’s t test and Chi-square analysis were used for
statistical analysis. Probabilities of less than 0.05 (two-tailed)
were considered to be significant.

Results

In the normal subjects (fig 1, top histogram), all of the
units studied (49 units in 12 subjects) had a short
latency period of increased firing probability which
will be referred to as the “short latency response”. The
mean corrected latency was 33.1 ms (SD = 2.3 ms).
A second, longer latency response was also seen in two
of the 12 normal subjects. The mean corrected latency
was 65 ms (SD = 3.24 ms).

In the Parkinsonian patients (fig 1, bottom histo-
gram) all except one of the units given an adequate

Fig 1 Peristimulus time histograms (PSTH) of a tibialis anterior motor unit in a normal subject (top) and a Parkinsonian subject (bottom) during stimulation of the deep peroneal nerve (at time zero) at an intensity of 0.9 x the threshold of the alpha motor neuron axons (0.9 MT). Bin width = 400 μs. The histograms have been smoothed using a five bin running average. Vertical scale indicates the number of counts in each bin. Note the short latency period of increased firing probability in both histograms at about 40 ms, and, the additional longer latency peak in the bottom histogram at about 68 ms. The gap near time zero in the bottom histogram results from stimulus artifacts.
Long latency reflex in Parkinson's disease

Fig 2  A comparison of the effectiveness of the short and long latency facilitation of tibialis anterior motor units produced by stimulation of the deep peroneal nerve in normal subjects (left), and Parkinsonian subjects (right). Abscissa: stimulation intensity expressed in terms of the threshold of the alpha motoneuron axons (MT). Ordinate: the number of extra counts normalised to 1,000 stimuli in the short latency period of increased firing probability (short latency response) (top) and in the longer latency response (bottom).

trial (that is with stimulus strengths as high as 1 MT before the run was classified as negative) had a short latency response (61/62 units 13 subjects). The mean corrected latency was 32.7 ms (SD = 5.1 ms). The responses were similar in magnitude (in extra counts per 1000 sweeps) to those of the normal subjects (t = 1.91 p > 0.05) (fig 2). Long latency responses occurred in eight of the 13 Parkinsonian subjects (fig 2), which is a significantly greater proportion than for normal subjects (Chi-square = 5.23; p < 0.025). The mean corrected latency was 61.3 ms (SD = 5.1 ms). The mean of the differences in latency between the short and the long latency responses in Parkinsonian subjects was 25 ms. A long latency response was seen in seven of eight patients with moderate rigidity but in only one of the five patients with mild rigidity. The thresholds of the axons mediating the long latency response were established in six Parkinsonian subjects. Paired stimulation (see Methods) was used in two of these studies (fig 3). The mean threshold of the long latency response was 0.82 x MT (range 0.675-0.85 MT). This is similar to the mean threshold for the axons mediating the short latency response in this muscle (mean 0.79 MT, range 0.76-0.85 MT) established in this laboratory.90 The possibility that cutaneous afferents contributed to the late responses was excluded by additional studies on a normal subject and on the Parkinsonian subject who showed the largest late responses. Long latency responses could not be elicited by stimulating the skin near the head of the fibula. Stimulation of the deep peroneal nerve at the ankle (at an intensity just below motor threshold to extensor digitorum brevis muscle) produced only

Fig 3  PSTHs of a tibialis anterior motor unit in a Parkinsonian subject during stimulation of the deep peroneal nerve at (top down) 0.76, 0.7, 0.68, 0.65 x MT. Paired stimuli (5 ms apart) were used in the lower three recordings. A long latency period of increased firing probability (long latency response) was observed with a "threshold" (see Methods) less than 0.65 MT., which is similar to the threshold for the short response.
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Fig 4  Stimulation of the common peroneal nerve (at 120
ms (●)) below the threshold of the alpha motoneuron
axons produces a short latency facilitation at 35 ms
(corrected latency) and, in the Parkinsonian subject (second
and third trace), a long latency facilitation at 63 ms
(corrected latency) following the stimulus.

Stimulation of the deep peroneal nerve at the ankle at
time zero (●) (at an intensity equal to the threshold of the
alpha motoneuron axons to the extensor digitorum brevis
muscle) produced an inhibition at 70 ms in the normal
subject (top trace) and in the Parkinsonian subject (bottom
trace).

Stimulation of the skin near the head of the fibula (middle
trace at time zero (●)) produced no response. The
stimulation intensity was the same as that used over the
common peroneal nerve (●).

inhibition (fig 4). Electrical stimulation of the skin of
the toes (applied with ring electrodes around
the second and fifth toes) did facilitate tibialis anterior
motor units but stimuli of 2-5 to 3 times the threshold
of perception (which are painful) were necessary for
this effect.

The range of firing rates of the motor units during
the recordings was 5.1–10.4 Hz (mean 7.3 Hz) for the
normal subjects and 6.3–10.6 Hz (mean 6.5 Hz) for the
subjects with Parkinson's disease. There was no cor-
relation (either positive or negative) between the mag-
nitudes of the short latency and the long latency
responses. The long latency responses were also
observed in first order peristimulus time histograms
and were not, therefore, the result of double dis-
charges of the motor unit.

Discussion

We observed short latency facilitation (onset 27–37
ms) of tibialis anterior motor units following peroneal
nerve stimulation. This facilitation likely represents
the “monosynaptic” action of primary spindle
afferents because: (a) it occurs with stimulation of
muscle nerves well below the threshold of the alpha
motoneuron axons, (b) the facilitation is seen only in
the homonymous muscle or close synergists,20 (c) a
similar facilitation of comparable latency follows
tendon taps,21 (d) the effect is suppressed by muscle
vibration,20 and (e) the estimated rise time of the
underlying EPSP is short.22

We also recorded long latency (onset 50–70 ms)
facilitation of tibialis anterior motor units following
electrical stimulation of the peroneal nerve. What can
be deduced about the receptors and mechanisms of
this response? The threshold of the responsible
afferents was well below the threshold of the alpha
motoneuron axons and was similar to that of the
presumed group I afferents responsible for the short
latency response. Electrical stimulation of cutaneous
afferents, either near the head of the fibula or in the
distribution of the peroneal nerve, failed to produce
an appropriately timed facilitatory effect. Thus the
long latency response appears to be generated by
large, fast conducting afferents other than cutaneous
afferents. A similar conclusion was reached by Iles23
who observed both early and late responses of similar
latencies in recordings of surface EMG over tibialis
anterior following electrical stimulation of the pero-
neal nerve, ramp stretch of the anterior tibial muscles
and taps to the tibialis anterior tendon.

The methods in this study allow for more specific
conclusions on the mechanism of the long latency
response recorded here. Since electrical stimulation
produces only a single afferent volley in a peripheral
nerve24 the long latency response in this study cannot
be attributed to repetitive firing of primary
afferents.25–28 (It is remotely possible that the volley
passing antidromically in large afferents could result
in a resurgence of impulses after a silent period.
However, the lengths of the various afferents from
the point of stimulation to the individual muscle receptors
is variable making such synchronisation unlikely.) We
observed both the short latency and long latency
responses in the same tibialis anterior motor unit. The
long latency responses therefore do not arise from two
different subpopulations of motor units.29 30 A
double discharge of motoneurons31 cannot account
for the long latency response because it was estab-
that the motor unit did not fire twice in response to a single stimulus. The reactivation of peripheral receptors (for example as a consequence of the initial reflex response) is also an unlikely explanation for the long latency response for two reasons: (a) The 25 ms delay between the two responses is shorter than the mono- 
synaptic reflex loop time and (b) the size of the long latency response was not, in any way, dependent on 
the size of the short latency response. The present 
findings thus lead to the conclusion that the responses 
arise from fast conduct, non-cuttaneous afferents and that the “extra time” for the long latency response was taken within the central nervous system presumably in a polysynaptic pathway.24–7 32–35

Fast conducting, non-cutaneous afferents may not be the only afferents that can give rise to long latency 
responses. In the upper extremity long latency 
responses have been observed following electrical stimulation of low threshold afferents in purely cutaneous nerves.36–41 In the lower extremity, however, long latency responses have not been consistently demonstrated following electrical stimulation of low threshold cutaneous afferents although long latency facilitation of flexor muscles may follow stimulation of high threshold afferents. For example Choa et al42 reported that electrical stimuli to the second toe “just below the pain threshold” produced a “short latency” increase in surface EMG over tibialis anterior fol-

Explaination for the exaggerated long latency response in Parkinsonian subjects

We found that the long latency responses occurred in a greater proportion of patients with Parkinson’s disease than in normal subjects. This cannot be attribu-
ted to an increase in the excitability of alpha motor 
neurons. Changes of firing probibility of individual 
 motoneurons that are discharging regularly reflect 
subthreshold events in those motoneurons.22–44 There 
was no parallel increase in the short latency period of 
facilitation, and the firing rate of the motor units was 
not higher in the Parkinsonian patients. Tatton et al7 
reached a similar conclusion regarding the long latency response to limb perturbation (M2) by showing that the M2 (and not the M1) was increased 
in Parkinsonian patients even when the background level of muscle activity was matched by normal con-
trols.

It is unlikely that different populations of motor 
units were sampled in the two groups since in both 
groups the observations were made on single motor 
units which were among the first to be recruited and 
which showed sustained firing for at least 10 minutes. In 
any case the muscle and cutaneous afferent 
projections to tibialis anterior motor units in man 
differ little with recruitment threshold.45 

Nor can the exaggerated long latency response in 
the present study be explained by an increase in fusi-

motor drive or spindle sensitivity. Electrical stimu-
lation of spindle afferents bypasses the effects of such 
changes in spindle excitability and spindle afferent 
discharges in Parkinsonian subjects are considered to 
be similar to those of normal subjects maintaining an 
equivalent muscle contraction.46 Thus it appears that 
an increased transmission in a polysynaptic pathway 
from large muscle afferents to motoneurons is the 
most plausible explanation for the increased long 
latency responses that we observed in Parkinsonian 
patients. This, of course, does not exclude additional 
mechanisms from contributing to the long latency 
response to muscle stretch.

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