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DIFFERENT MECHANISMS UNDERLIE THE LONG-LATENCY STRETCH REFLEX RESPONSE OF ACTIVE HUMAN MUSCLE AT DIFFERENT JOINTS

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SUMMARY

1. Stretch of voluntarily activated human muscle results in a reflex response consisting of short-latency (M1) and delayed long-latency (M2) components. The mechanism of the M2 response remains the subject of controversy. The present study tested the universality of the hypothesis that the M2 response results from the transmission of low-threshold muscle afferent input travelling over a long-loop supraspinal pathway. Muscle reflex responses resulting from imposed stretch were obtained from the first dorsal interosseus (FDI), biceps brachii (BB), triceps brachii (TB) and triceps surae (TS) muscles.

2. Patients suffering from Huntington's disease (HD) show a selective loss of FDI-M2 responses, with sparing of the M1. This has been attributed to disruption of supraspinal pathways as a part of the disease pathology. Accordingly, HD has been used in the present study as a model to test the universality of the long-loop hypothesis: if this is so, then HD patients with an absent FDI M2 should also fail to show an M2 response in other muscles.

3. It is shown that a group of HD patients in whom the FDI-M2 response was absent or residual developed clear M2 responses in the TB, BB and TS muscles following stretch sufficient to invariably evoke this component in normal subjects.

4. It is thus concluded that longer-latency stretch reflex components are not invariably mediated over long-loop supraspinal pathways, but that this mode of control is dominant only in muscles, such as those of the hand, whose function depends largely on direct cortical control.

INTRODUCTION

Hammond (1954), working on the human biceps brachii muscle, was the first to demonstrate that, following stretch of voluntarily activated muscle, the evoked reflex response consisted of two components. The first, short-latency response (M1, in the terminology of Lee & Tatton, 1975) has generally been accepted to be the result of direct connections between muscle spindle Ia afferents and motoneurones

from the same muscle. The mechanism of the second, longer latency and more marked response (M2 in the terminology of Lee & Tatton, 1975), however, has remained the subject of controversy. Hammond suggested that the reason for the late appearance of the M2 could be that it travels over a longer pathway in the central nervous system (CNS), or that it is mediated by slower-conducting afferents. Supported by Phillips' (1969) description of a transcortical motor loop in the baboon hand muscles, the former suggestion gained the ascendency in the seventies (Marsden, Merton & Morton 1976). In recent years, however, in the face of accumulating evidence that M2 responses could survive after transection of the suggested transcortical reflex loops (Ghez & Shinoda, 1978; Miller & Brook, 1981), additional explanations of the M2 mechanism have been put forward. The more significant of these are (i) that the M2 response is mediated by slower conducting afferents, specifically muscle spindle secondary endings (Matthews, 1984) or cutaneous afferents (Darton, Lippold, Shahani & Shahani, 1985); (ii) segmentation of the Ia afferent volley by mechanical oscillations in the stretched muscle, the 'resonance' hypothesis (Eklund, Hagbarth, Hägglund & Wallin, 1982*a*, *b*); (iii) transmission of Ia afferent input over polysynaptic spinal pathways (Hultborn & Wigström, 1980).

All of these alternative theories have received partisan support and attracted fierce criticism, but it is noticeable that the most vocal contributors to the debate have been intent on pushing through one explanation to the exclusion of all others. But, as Marsden and his co-workers have pointed out (Marsden, Rothwell & Day, 1983), given the wide functional requirements made of different joints and their muscles, there is no intrinsic reason why only one mechanism should apply for all muscles, or even why a mixture of mechanisms might not be responsible for any given M2 response; while a transcortical reflex loop might be expected in muscles, such as those of the hand, which are predominantly under direct cortical control during much of their behavioural repertoire, it is possible that long-loop reflexes in muscles normally engaged in more automatic movements, such as stance and gait, would have reflex mechanisms which reflect the greater involvement of peripheral circuitry in their control. Indeed, much of the conflicting evidence that has fuelled the debate has been obtained from different muscles and further confusion has arisen from the application of 'long-latency' to a variety of electromyogram (EMG) responses occurring later than the interval to which this term was originally applied, that is the M2 response following immediately after the initial, M1 burst.

Much of the clearest evidence for a long-loop (possibly transcortical) explanation of M2 has been obtained in the small muscles of the hand (for review, see Wiesendanger & Miles, 1982), particularly from studies showing that central CNS lesions affect the M2 to a far greater extent than the M1 (Marsden, Merton, Morton & Adam, 1977). Stretch of the first dorsal interosseus (FDI) muscle in the voluntarily active state elicits, in normal subjects, the classic M1–M2 profile in the FDI EMG. Similar stretch in a patient suffering from Huntington's disease (HD), however, elicits a clear M1 response, but the M2 response is residual or absent in 70–80% of cases (Noth, Podoll & Friedemann, 1985). Closely associated with this loss of the FDI M2 is a reduction in the early somatosensory-evoked cortical potentials arising from stimulation of peripheral nerves in both the upper and lower limbs (Noth, Engel,

Friedemann & Lange, 1984; Bollen, Arts, Roos, Van der Velde & Buruma, 1985). CNS damage in HD is supraspinal in nature (Bruyn, Bots & Dom, 1979) and the loss of the M2 in HD has been widely accepted as resulting from disruption of a supraspinal, possibly transcortical Ia afferent reflex loop. Thus HD represents a useful model for demonstrating differences in the M2 mechanisms of different muscles: as afferent inflow from rapidly conducting fibres to the somatosensory cortex is uniformly affected in HD, and if M2 responses are invariable mediated by a supraspinal long-loop mechanism, then these responses should be absent or residual in all muscles of those HD patients who lack a M2 response in the FDI. Accordingly, we studied the stretch reflex responses of voluntarily activated FDI, triceps brachii (TB), biceps brachii (BB) and triceps surae (TS) muscles in a group of HD patients and in a group of age-matched normal subjects. While the FDI-M2 response was absent or residual in all the HD patients, the M2 of the other muscles was clearly present in all cases. Some quantative differences from the normal responses were, however, apparent. The significance of these changes is discussed. Some of the results of this study have been reported briefly elsewhere (Fellows, Töpper & Schwarz, 1991).

METHODS

This study concerned ten patients with a positive family history and clinical signs of Huntington's disease. Ten age-matched neurologically normal subjects acted as a control group. The HD patients were selected from an Out Patients list on the basis of possessing sufficient cognitive powers to perform the force-maintenance task required during displacement. Their choreatic movements were not so severe as to preclude quiet sitting. Clinical details are given in Table 1. The subjects gave their informed consent to all procedures, which had previously been approved by the local ethical committee.

Details of the joint displacement apparatus have been provided in full elsewhere: FDI (Noth, Schwarz, Podoll & Motamedi, 1991), BB and TB (Thilmann, Fellows & Garms, 1991), TS (Fellows & Thilmann, 1989). In brief, subjects were seated in a heavy, stable chair, with the limb under study supported by a moulded cast allowing rotation at the axis of the joint. They were required to maintain a constant level of contraction (10–15% of their maximum voluntary contraction (MVC)) in the muscle under study (with the aid of a force-level feedback monitor) while a torque motor applied displacements to stretch the muscle at random intervals between 1 and 3 s (FDI) or 5–8 s (all other muscles). Several velocities of stretch were applied at each joint. Full details of the movement parameters for each muscle are given in Table 2.

It should be noted that stretch parameters were chosen which elicited a clear M1–M2 pattern in all the normal subjects. Exact equivalence of stretch for the different muscles is not implied; what is of interest is whether a stretch which elicited an M2 response in all normal subjects elicited a similar response in the HD patients. During each stretch, the computer (DEC, PDP11/73) sampled position and surface EMG records (amplified up to $\times 10000$. Bandwidth 10–1000 Hz) from the stretched muscle at a rate of 1000 Hz per channel. EMG was then rectified and all sweeps at a given stretch velocity averaged (the number of trials, n, varies; see Table 2 for details). The average EMG level of the background activity occurring in the 50 ms before displacement was established. The area of the reflex responses above this level was then divided by the area below the mean level in the reflex interval to provide a measure of reflex activity as a ratio of the background contraction.

For the BB, TB and TS muscles, stretch was also applied with the muscle relaxed. In addition, with the limb fixed in the cast at an angle of 90 deg, the tendon jerk reflexes of BB, TB and TS muscles were also obtained using maximal manual percussion with a hammer which triggered computed sampling of force and EMG records. In these cases, where no initial activity was present in the muscle, the area of reflex responses (in μV s) was measured.

Statistical significance levels, where given, were assessed by variance analysis. Results are given as means $\pm$ standard error of the mean (S.E.M).

TABLE 1. Clinical details of HD patients

Case number	Age (years)	Sex	Disease duration (years)
1	53	f	10
2	22	m	1
3	41	f	3
4	42	m	4
5	34	f	3
6	58	f	7
7	60	f	4
8	30	m	7
9	48	f	5
10	32	m	7

TABLE 2. Parameters of applied stretch

Muscle	Amplitude (deg)	Velocities (deg/s)			Number of trials
FDI	5	400	300	200	128
BB	30	300	175	80	10
TB	30	300	175	80	10
TS	5	175	100	50	10

RESULTS

First dorsal interosseus

In agreement with previous studies (Noth *et al.* 1985) in which a small mechanical displacement was applied to the FDI, a rapid ramp displacement (5 deg) of the normal FDI during voluntary activation elicited a reflex response with two peaks of activity (upper trace, Fig. 1*A*).

The first component (M1 in the scheme of Lee & Tatton (1975)) occurred with a mean onset latency of $32{\cdot}0 \pm 0{\cdot}87$ ms (mean $\pm$ S.E.M.) and lasted for $17{\cdot}2 \pm 0{\cdot}86$ ms. It was succeeded by a larger component (M2) with a mean latency of $54{\cdot}5 \pm 1{\cdot}33$ ms and duration of $34{\cdot}9 \pm 1{\cdot}84$ ms. In some cases the termination of the M2 response and the onset of subsequent activity was not so clearly defined as in the subject shown in the figure, but in all cases a major reflex component was apparent during the M2 time interval. If an identical series of displacement was applied to a patient with HD, however, a different picture was obtained (middle trace, Fig. 1*A*). Whereas the M1 response was not only apparent, but even exaggerated over normal values ($P < 0{\cdot}05$), no increase in activity over background EMG levels was observed during the M2 interval in 60% of HD patients and in the remainder only a minimal increase in activity was apparent, in no case reaching even the smallest value seen for M2 in the normal subjects. Taken as a whole for the HD group, the M2 response values lay close to zero and were depressed from normal values at the highest level of significance ($P < 0{\cdot}001$).

Figure 1*B* shows the group averages for the FDI-M1 and -M2 responses obtained at three rates of stretch. It is apparent that the exaggeration of the M1 response and the profound depression of the M2 component in HD patients is visible ($P < 0{\cdot}05$ and

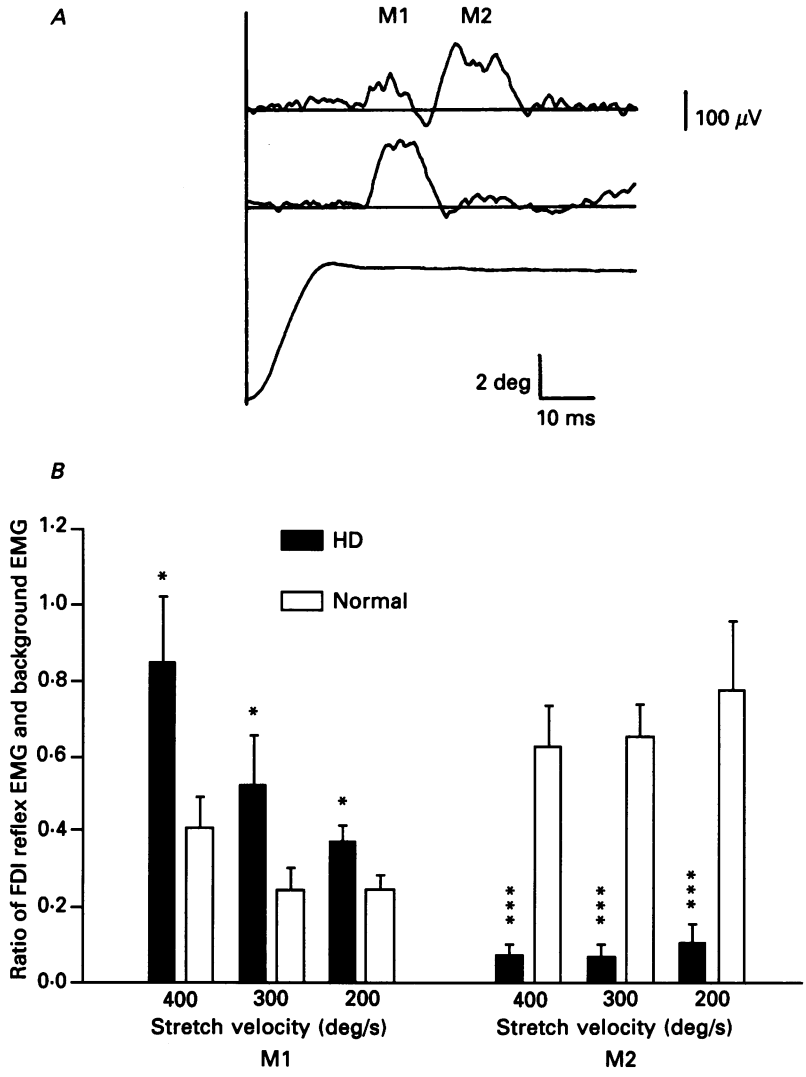

Fig. 1. *A*, rectified and averaged ($n = 128$) EMG record obtained following stretch (5 deg, 400 deg/s) of the FDI of a normal subject (upper trace) and a patient (case 4) with HD (middle trace). The lower trace shows the imposed displacement. It should be noted that the same normal subject and HD patient are shown in all subsequent EMG records. Background voluntary force of 15% MVC. Baseline represents mean background EMG during 50 ms before stretch. *B*, group averages ($n = 10$, ± S.E.M.) for the FDI reflex EMG obtained during the M1 and M2 interval following 5 deg abduction of the finger at three stretch velocities for the normal subjects (open bars) and the HD patients (filled bars). All EMG values are expressed as the ratio of increase over background EMG levels. Asterisks indicate the level of significance for differences between HD patients and normal subjects (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$).

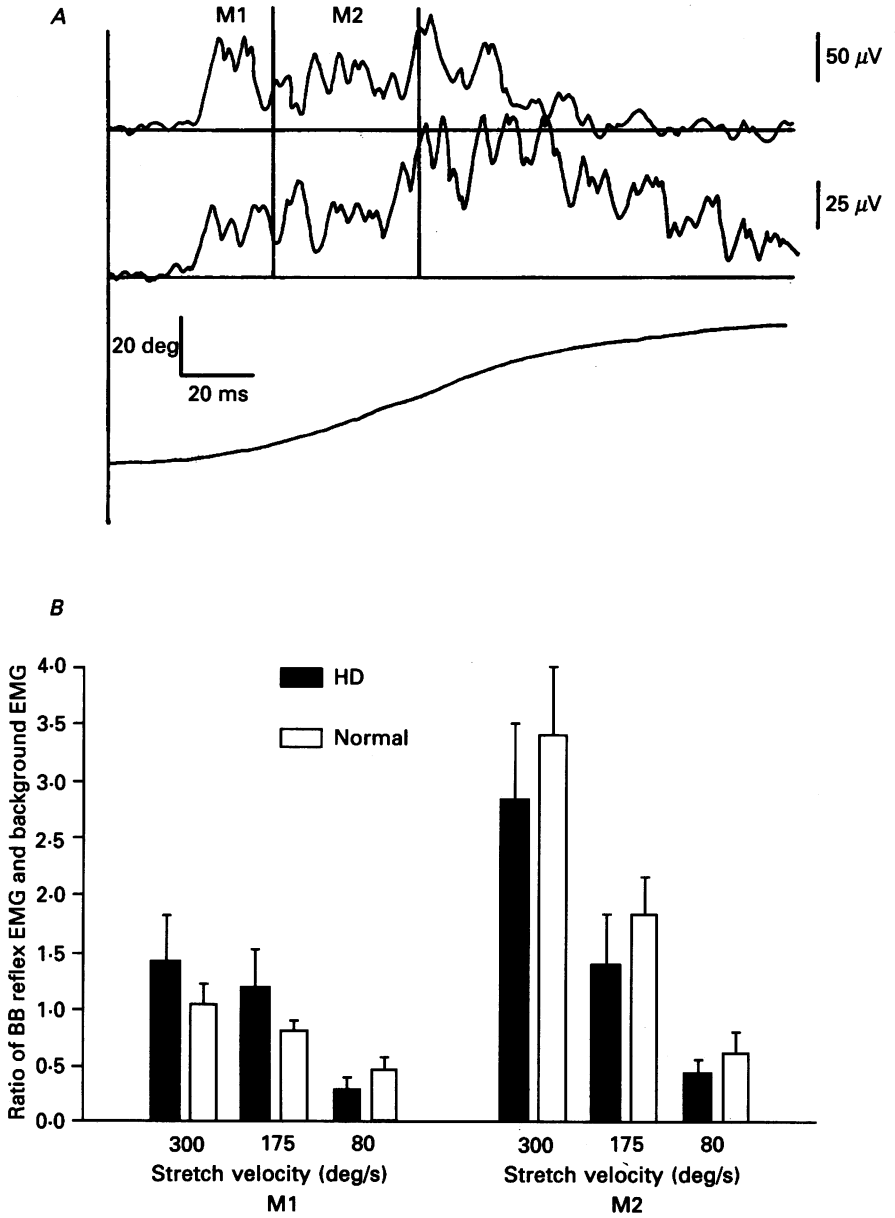

Fig. 2. *A*, rectified and averaged ($n = 10$) EMG record obtained following stretch (30 deg, 300 deg/s) of the BB of a normal subject (upper trace) and a patient (case 4) with HD (middle trace). The vertical lines indicate the M2 interval (45–85 ms). The lower trace shows the imposed displacement. Background voluntary force of 4 Nm. Baseline represents mean background EMG during 50 ms before stretch. *B*, group averages ($n =$ 7 (HD) or *10* (Normal) $\pm$ S.E.M.) for the BB reflex EMG obtained during the M1 and M2 interval following 30 deg elbow extension at three stretch velocities for the normal subjects (open bars) and the HD patients (filled bars). All EMG values expressed as the ratio of increase over background EMG levels.

$P < 0{\cdot}001$, respectively) at all three rates of displacement. Furthermore, the magnitude of the M1 response of the HD patients showed a significant positive correlation with the displacement velocity ($P < 0{\cdot}025$).

Given the exaggerated values of M1 in the HD patients, it is possible that the depressed M2 values result from the refractoriness of the FDI motoneurone pool. If this was the case, reduction of the M2 response should be positively correlated with M1 magnitude. Accordingly, a regression analysis was performed between the magnitude of M1 and M2 responses in this group. No correlation was observed ($r = 0{\cdot}0735$, P was not significant).

Biceps brachii

Figure 2*A* shows the BB reflex EMG response of a normal subject (upper trace) and a HD patient (middle trace) obtained following 300 deg/s extension of the elbow applied while the subject maintained a moderate (4 Nm) flexing contraction.

Although the M1–M2 segmentation is, as would be expected from earlier studies, less clear than in the FDI, it is apparent that in the period following the M1 response (later than 45 ms) and well before the earliest time for any possible voluntary activation, a clear burst of activity is visible in both subjects. For purposes of quantification, the M2 response was defined as the activity occurring between 45–85 ms, for both normal subjects and HD patients. Activity in this time interval was observed in all the normal subjects and in all of the seven HD patients in whom the BB was examined. Quantification of M1 and M2 magnitudes revealed no significant differences between the HD patients and the normals at any of the three displacement velocities (Figure 2*B*). The reflex magnitudes of the M1 and M2 components were positively correlated with stretch velocity for both HD patients and normals ($P < 0{\cdot}005$, M1; $P < 0{\cdot}025$, M2).

The BB tendon jerk reflexes and the responses to imposed stretch of the relaxed BB showed no differences between the two groups.

Triceps brachii

Figure 3*A* shows the TB EMG response obtained following 300 deg/s flexion of the elbow during maintenance of a moderate (4 Nm) extending force for a normal subject (upper trace) and a HD patient (middle trace).

It may be seen that qualitatively, the responses are identical, with a clear burst of activity in the M2 interval (45–85 ms) in both cases. When the group averages for the integrated EMG occurring in this interval were examined, however, quantitative differences became apparent, as may be seen in Fig. 3*B*. While M1 values were largely identical for the two groups, the M2 response of the HD patients, although clearly present in all cases, was significantly smaller than the M2 of the normal subjects at all three velocities of stretch applied. It should be noted that, as was the case for the BB, both M1 and M2 magnitude increase with increasing stretch velocity.

With the TB relaxed, no differences were seen between the HD patients and the normals in either the reflex response to displacement or in the tendon jerk reflex.

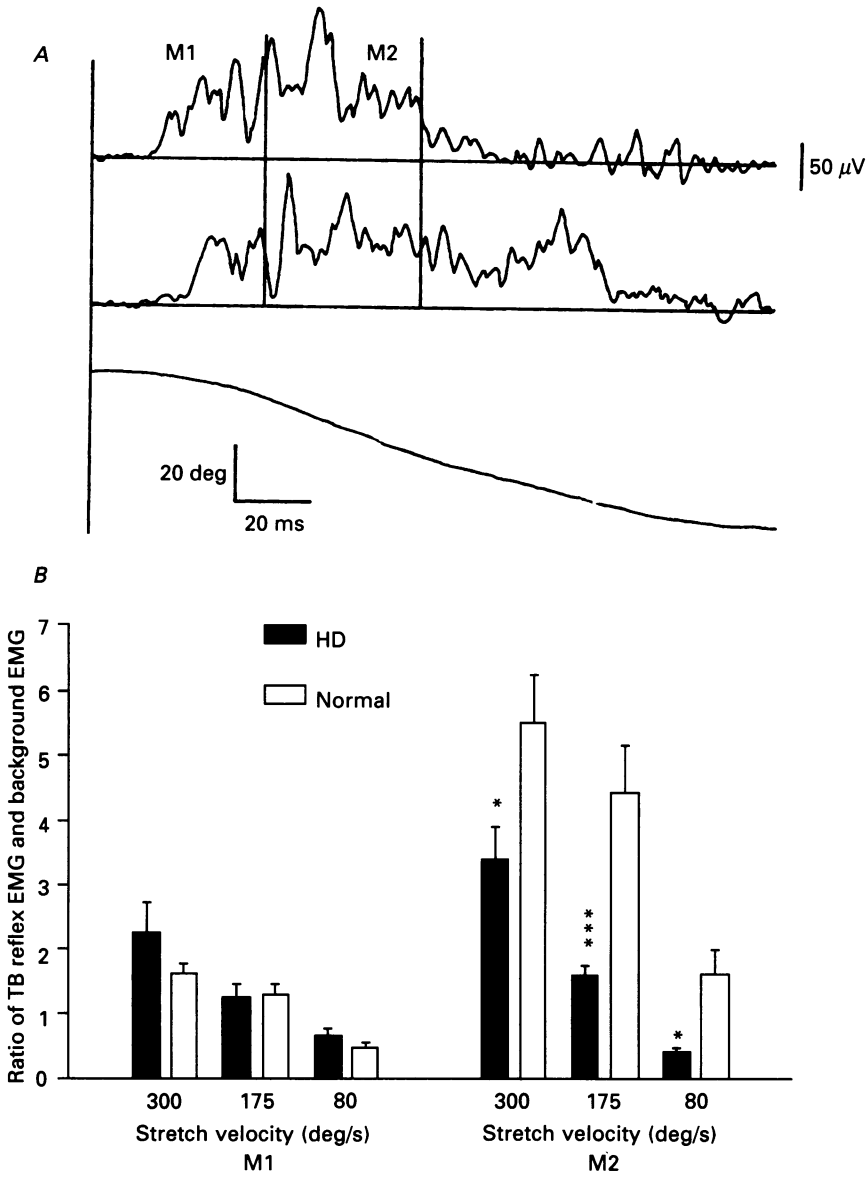

Fig. 3. *A*, rectified and averaged ($n = 10$) EMG record obtained following stretch (30 deg, 300 deg/s) of the TB of a normal subject (upper trace) and a patient (case 4) with HD (middle trace). Vertical lines define the M2 interval. The lower trace shows the imposed displacement. Background voluntary force of 4 Nm. Baseline represents mean background EMG during 50 ms before stretch. *B*, group averages ($n = 10$, ± S.E.M.) for the TB reflex EMG obtained during the M1 and M2 interval following 30 deg elbow flexion at three stretch velocities for the normal subjects (open bars) and the HD patients (filled bars). All EMG values expressed as the ratio of increase over background EMG levels. Asterisks indicate the level of significance for differences between HD patients and normal subjects (*$P < 0{\cdot}05$; ***$P < 0{\cdot}001$).

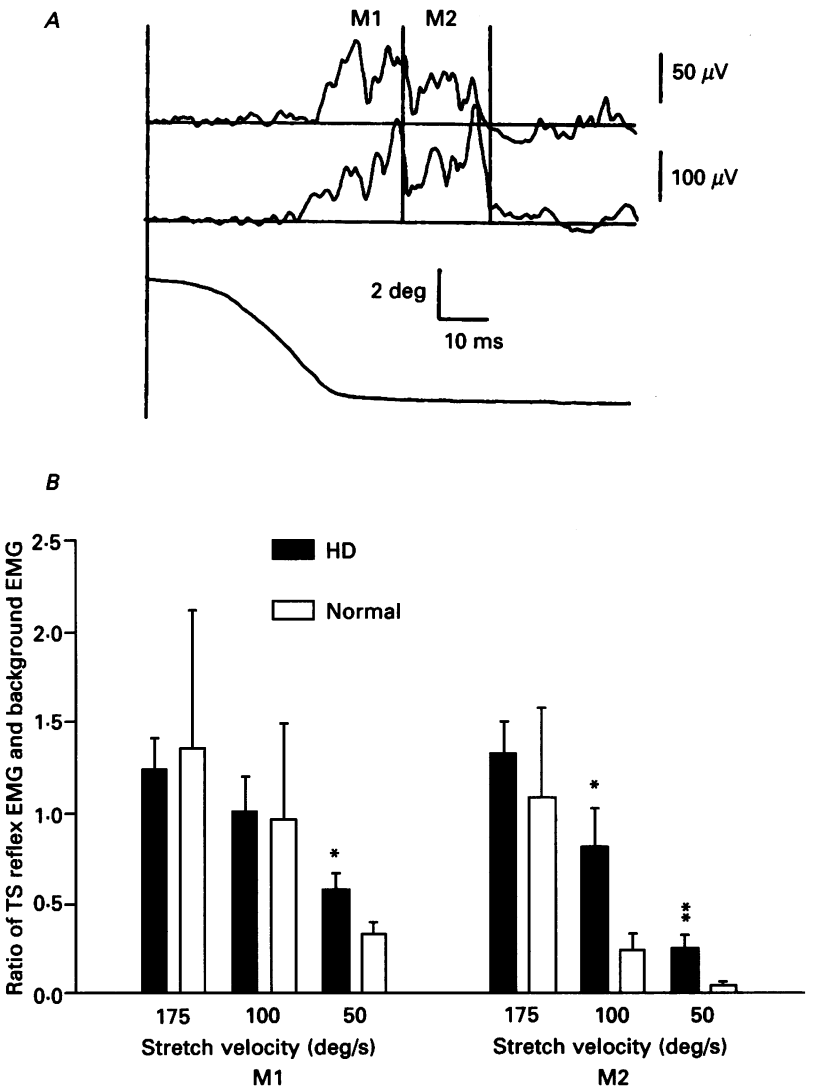

Fig. 4. *A*, rectified and averaged ($n = 10$) EMG record obtained following stretch (5 deg, 175 deg/s) of the TS of a normal subject (upper trace) and a patient (case 4) with HD (middle trace). Vertical lines define the M2 interval. The lower trace shows the imposed displacement. Background voluntary force of 4 Nm. Baseline represents mean background EMG during 50 ms before stretch. *B*, group averages ($n = 10$, ± S.E.M.) for the TS reflex EMG obtained during the M1 and M2 interval following 5 deg ankle dorsiflexion at three stretch velocities for the normal subjects (open bars) and the HD patients (filled bars). All EMG values expressed as the ratio of increase over background EMG levels. Asterisks indicate the level of significance (* $P < 0{\cdot}05$; ** $P < 0{\cdot}01$).

Triceps surae

Figure 4*A* shows the EMG response of the TS muscle to imposed dorsiflexion of the ankle during maintenance of a 4 Nm plantarflexing torque for a normal subject (upper trace) and a HD patient (middle trace).

It may be seen that a M1–M2 response pattern is present in both cases. Indeed, the magnitude of the M2 response of the HD patient in this case exceeds that of the normal subject. If reflex magnitude was standardized as a ratio of the background EMG, such differences persisted, as is shown in Fig. 4*B*. Considering first the M1, largely identical values were obtained at the two most rapid stretch velocities, but the HD M1, obtained with a 50 deg/s stretch was significantly larger than that of the normal subjects ($P < 0{\cdot}05$). With the M2, the differences were clearer. While the increase in M2 in the HD patients at the fastest rate of displacement did not reach significance, the patients showed significantly higher response levels at the two slower displacements speeds (100 deg/s, $P < 0{\cdot}025$; 50 deg/s, $P < 0{\cdot}005$).

As was the case for the BB and TB muscles, no differences were seen between the two groups in the relaxed state following either imposed displacement or tendon tap.

DISCUSSION

It is widely accepted that the loss of the later reflex component following mechanical (Noth *et al.* 1985) or electrical (Deuschl, Lücking & Schenck, 1989) stimulation of the hand muscles in HD patients occurs as the result of disruption of a long-loop, possible transcortical, reflex pathway. Thus HD represents a useful model to test the universality of the long-loop theory as a mechanism for the M2 responses of other muscles. The major finding of the present study is that in a group of HD patients in whom the M2 reflex response of the FDI muscle is abolished or residual, the M2 response in other muscles of the upper and lower limb is preserved. Thus it follows that the M2 reflex response of these other muscles cannot be mediated predominantly over a transcortical pathway, as has often been suggested (see, for example, Matthews, 1991).

The present study, has, however, also shown that the M2 response in muscles of the upper limb of HD patients, while clearly present, may be reduced in magnitude compared to those of normal subjects. Minor involvement of a transcortical pathway in the M2 response of upper arm muscles cannot, therefore be ruled out. In an earlier study of the wrist flexor muscles of HD patients, Thompson and his co-workers (Thompson, Berardelli, Rothwell, Day, Dick, Benecke & Marsden, 1988) noted that M2 responses were present in a far higher proportion (88%) of patients than the M2 of hand muscles (40% for flexor pollicis longus; also 30% for FDI (Noth *et al.* 1985)). The magnitude of the wrist flexor M2 was reduced, when present, to 50% of the normal value, a finding confirmed by a more recent study (Abbruzzese, Dall'Agata, Morena, Spadavecchia, Ratto & Favale, 1990). In the present study the TB M2, while seen in 100% of HD patients, was reduced in amplitude by, on average, 35%, while the FDI M2 was usually absent or, when present (30%), residual (< 10% of the normal value). It would thus appear that a proximal-to-distal progression occurs in the arm, with the M2 most often absent and most severely reduced in distal hand muscles, less so in the wrist muscles, and least of all in the muscles of the elbow joint (particularly the BB, an anti-gravity muscle). At first sight, it is tempting to link this progression to the extent of direct cortical projection, which in animal studies has been reported to decrease in a distal-to-proximal direction (Baldissera, Hultborn & Illert, 1981). A recent study using cortical magnetic stimulation in humans, however, has shown that at least some proximal arm muscles receive a degree of direct cortical

input comparable with that of intrinsic hand muscles (Colebatch, Rothwell, Day, Thompson & Marsden, 1990). Nevertheless, wide functional differences exist between distal and proximal muscles: hand muscles are involved predominantly in manipulative movements, under conscious control, while the muscles of the elbow joint are much more heavily involved in automatically regulated postural movements, as, of course is the TS, in which no reduction at all was apparent in the M2 responses of the HD patients, a finding supported by a study on standing HD patients, where M1–M2 values evoked at the ankle by platform tilt (SL1/SL2 in the nomenclature used in that study) were found to be normal (Huttenen & Hömberg, 1990). It is thus likely that the longer latency responses of the hand muscles, which will largely be evoked during consciously controlled movements, should be regulated via a transcortical loop, allowing a far greater degree of integration in conscious motor programmes, while the M2 responses of more postural muscles, such as those of the elbow and ankle, should be mediated over spinal pathways, allowing optimum integration in the automatic motor programmes (such as those of posture and gait) in which they are largely active.

In addition to the loss or marked reduction of the M2 response, it was also apparent that the M1 response in the HD patients was significantly larger than that of the normal subjects. It could therefore be argued that the absence of M2 in the HD patients was the result of refractoriness in the FDI motoneurone pool. That this is unlikely to be the case is indicated by the extremely poor correlation between the magnitude of the increase of the M1 response and of the reduction of the M2 response in the HD patients. Furthermore, in an earlier study (Noth *et al.* 1985) in which small perturbations of the finger were made, the FDI-M1 response of HD patients and normal subjects was identical, but the FDI-M2 response was nevertheless absent or residual in HD patients. The increase in the M1 component does not, therefore, explain the loss of M2 in the FDI in HD patients.

Another possible explanation for the lack of a M2 response in the FDI of the HD patients may lie in reflex habituation to repeated stimulation. Due to the larger number of trials required to build a stable average in the FDI than in the other muscles studied, it was necessary to use a higher repetition rate in order to avoid possible fatigue effects, coupled with problems with attention span of the HD patients, that might have arisen over the considerable period necessary to apply displacement at a lower rate. However, Rothwell and co-workers (Rothwell, Day, Berardelli & Marsden, 1986) found that with fixed repetition rates of greater than 0·2 Hz, marked habituation of the M2 response was apparent in muscles of the wrist and, less clearly, of the thumb. Alone, this could not explain the present findings, as the same stimulus rate was applied to patients and normals, but it is also reported that the habituation rate of a cutaneous evoked response, the 'blink reflex', is greater in HD patients (Caraceni, Avanzini, Spreafico, Negri, Broggi & Girotti, 1976). Thus it could be argued that the loss of the FDI M2 in HD patients arose from an enhanced habituation at the relatively high repetition rate used. However, it is also known (Rothwell *et al.* 1986) that use of randomized intervals, which were employed in the present study, greatly reduces the habituation of the M2 response seen with fixed intervals. Furthermore, it has recently been shown that muscle stretch reflexes in HD, rather than showing more rapid habituation, actually demonstrate impaired habituation of the M2 component (Abbruzzese *et al.* 1990). The higher repetition rate

employed for the FDI cannot, therefore, explain the selective loss of the M2 component of this muscle in HD patients.

While the present study has demonstrated that a transcortical loop is not a satisfactory mechanism for long-latency reflexes in all muscles, it can provide no direct positive evidence for the alternative explanations. It does, however, demonstrate that evidence for a particular long-latency reflex mechanism is not necessarily contradicted by findings obtained from a different muscle, particularly when one lies distal and the other proximal in a given limb. It does not, for example, automatically follow that the results obtained by cooling of distal hand muscles (Matthews, 1989) are contradictory to results supporting a role of secondary muscle afferents in the genesis of the M2 response which were obtained from more proximal arm muscles (Matthews, 1984). Given the differences in reflex behaviour between various muscles demonstrated in the present study, it would seem safe to infer that conflicting evidence is truly contradictory only when the relevant studies concern the same muscle. Furthermore, given the wide differences in the functional requirements made of the various muscles of the upper and lower limbs, it is unlikely that a universal mechanism underlies the M2 response, but rather, that a variety of solutions have been found to a range of problems in motor control.

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