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EFFECTS OF ISCHAEMIA UPON REFLEX ELECTROMYOGRAPHIC RESPONSES EVOKED BY STRETCH AND VIBRATION IN HUMAN WRIST FLEXOR MUSCLES

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SUMMARY

1. The reflex electromyographic responses evoked in a wrist flexor muscle, flexor carpi radialis (f.c.r.), by forcible extension of the wrist ('stretch') and by vibration of the flexor tendon have been studied in normal subjects. Reflexes were elicited during the maintenance of a low level of voluntary flexor contraction (5% maximum). Stretch regularly produced a relatively prolonged (*ca.* 100 ms duration) increase in e.m.g. activity which was usually divisible into short-latency (*ca.* 25 ms, M1) and long-latency (*ca.* 50 ms, M2) peaks. Vibration produced a single, phasic peak, at short latency, with no sign of an accompanying long-latency wave comparable to the M2 stretch response.

2. Ischaemia was induced by inflation of a blood-pressure cuff around the upper arm and its effects upon the reflex patterns were studied. During ischaemia M1 stretch responses showed a more rapid and pronounced decline than did M2 responses and were abolished before voluntary power was appreciably affected. Vibration-evoked short-latency peaks changed in an essentially parallel manner to M1 stretch reflexes. During recovery from ischaemia M2 reflexes were restored before short-latency responses.

3. The patterns of reflex reductions in e.m.g. upon withdrawal of stimulation were also studied. Such troughs in activity, under non-ischaemic conditions, regularly commenced at short latency and were of relatively small amplitude. The records of several of the subjects, and particularly ones obtained during ischaemia, suggested that release of stretch (with concomitant stretch of antagonists) could elicit an additive, long-latency decline in e.m.g. The existence of any such separate, delayed component was never observed upon termination of vibration.

4. Measurements of changes in the latencies and durations of reflex components, accompanying the progression of ischaemia, indicated that depression of early reflex activity resulted in part from increases in the latencies of these initial peaks but predominantly reflected simultaneous and separate reductions in their amplitudes.

5. The generation of short-latency reflexes by stretch and vibration, both of which stimuli powerfully excite muscle spindle primary endings, and the marked susceptibility of these responses to ischaemia supports their being mediated by group Ia

afferents. The contrasting behaviour of M2 stretch responses, both regarding their absence with vibration and their resistance to ischaemia, suggests that they depend crucially upon a separate group of reflex afferents. On the basis of collateral control experiments, in which M2 responses were largely unchanged when the hand and lower forearm were rendered insentient (by the prolonged application of a pressure cuff just below the belly of f.c.r.), the responsible reflex afferents seem almost certain to be of intramuscular origin, e.g. spindle group II afferents.

INTRODUCTION

Stretch of a voluntarily contracting human muscle, applied by rotation of its joint, typically evokes a reasonably prolonged (*ca.* 100 ms) increase in electromyographic activity which is often divisible into short- and long-latency reflex components (often respectively termed 'M1' and 'M2' responses; cf. Tatton & Lee, 1975). The short-latency stretch responses are generally agreed to result from the spinal reflex excitatory action of muscle spindle group Ia afferents. In contrast, the neural mechanisms, including the sensory receptors, their afferent fibres and the central neural pathways, responsible for long-latency responses remain equivocal.

The 'transcortical' (Phillips, 1969; Marsden, Merton & Morton, 1972) and 'resonance' (Eklund, Hagbarth, Hagglund & Wallin, 1982) hypotheses both suggest that M2 components depend upon activation of muscle spindle primary endings and their large-diameter, rapidly conducting group Ia afferents. Reflex delay is seen to arise, respectively, due to 'long loop' central transmission and segmentation of afferent discharge. The 'group II' hypothesis (Matthews, 1984) also attributes M2 reflexes to spindle receptors in the stretched muscle but proposes that the responsible endings are secondaries and that the long latency of their spinal excitatory action arises from the relatively slower conduction of their smaller-diameter group II afferents.

Alternatively, non-muscular (e.g. skin and joint) proprioceptors, simultaneously excited by the mechanical stimulus, could contribute to long-latency responses (Marsden, Merton & Morton, 1971, 1976) a view expressed most forcibly by Darton, Lippold, Shahani & Shahani (1985) who argue that M2 responses consist solely of polysynaptic, spinal reflexes mediated by large-diameter, cutaneous afferents.

We have addressed the issue of the afferent origin of the stretch reflexes of f.c.r. by comparing the reflex e.m.g. patterns evoked by vibration and stretch (Matthews, 1984) and studying the effects upon these of ischaemia. Any changes induced by ischaemia may be expected to result predominantly from a progressive block of conduction of nerve fibres of successively smaller diameter (Lewis, Pickering & Rothschild, 1937; Leksell, 1945) due both to local pressure (Bentley & Schlapp, 1943*a*; Torebjork & Hallin, 1973) and hypoxia (Bentley & Schlapp, 1943*b*) and from derangements of sensory receptor function (Matthews, 1933). An earlier investigation of alterations in stretch-evoked reflexes, in f.c.r., during and following ischaemia (Jaeger, Gottlieb, Agarwal & Tahmoush, 1982) indicated differential actions upon short- and long-latency responses, which were especially evident during recovery. M1 reflexes tended to be suppressed earlier in ischaemia (see Fig. 5, Jaeger *et al.* 1982) and showed a typically delayed re-emergence after cuff release. These authors sug-

gested that, whilst both M1 and M2 reflexes depended upon muscle spindle group Ia activity, the two responses were mediated by separate neural pathways. They attributed the greater vulnerability of M1 responses to their transmission by a route which required a more intense afferent input for its operation and was, therefore, more susceptible to ischaemia-induced depression of group Ia discharge.

The current experiments extend these observations in two main respects: first, by the additional use of vibration and secondly, by the study of reflex responses elicited at the termination as well as commencement of stimulation. The rationale for employing vibration is that it is an extremely potent stimulant of spindle primaries in man which can generate a high-frequency, group Ia-dominated afferent barrage (Burke, Hagbarth, Lofstedt & Wallin, 1976). Thus, application of vibration has allowed a more detailed exploration of the changes produced by ischaemia in reflexes mediated by group Ia afferents and hence a greater insight as to the contribution of these afferents to normal reflex patterns. Furthermore, vibration characteristically evokes, in f.c.r., a single major e.m.g. response, analagous to the M1 stretch reflex, which lacks a long-latency wave comparable to the M2 component (Cody, MacDermott, Matthews & Richardson, 1986*b*). Therefore, changes in the time course, particularly duration, of short-latency reflex action during ischaemia, as might result from slowing of peripheral nerve conduction, could be measured with greater reliability than for corresponding stretch responses. The significance of investigating 'off responses' is that cessation of vibration and release of stretch must both cause immediate and monotonic reductions in firing of group Ia (and any other contributory, excitatory) afferents. Such relatively simple decreases in afferent discharge potentially provide a more dependable basis for analysis than the uncertain temporal patterns of increased sensory input evoked by the application of stimulation, and which for stretch are more likely to be segmented and to involve a greater variety of receptors.

Our findings of differential behaviour of short- and long-latency reflexes, both regarding the mode of afferent stimulation necessary for their appearance and their susceptibility to ischaemia, are most readily interpreted as indicating that they are mediated by separate reflex mechanisms which depend crucially upon different sources of sensory input arising from different receptor types and transmitted by afferents of different diameter. Preliminary observations have been reported briefly (Cody, Goodwin & Richardson, 1986*a*).

METHODS

Subjects

The study was made on ten subjects (seven male, three female). Their mean age was 36·9 years ±7·5 (S.E. of mean). All subjects participated in the experiments with their informed consent (Code of Ethics of the World Medical Association, Declaration of Helsinki) and protocols were approved by the University of Manchester Ethical Committee. None of the subjects had any history of neurological or cardiovascular disease. Each of the ten subjects was studied in the main series of experiments, in which ischaemia was induced by an upper arm blood-pressure cuff; nine of these were studied on a single occasion and one on two occasions (separated by an interval of two weeks). The right arm was studied routinely. Control experiments, in which the hand and lower part of the arm were made anaesthetic by inflation of a blood-pressure cuff just below the belly of f.c.r. were performed on two of the subjects.

Experimental arrangements

Detailed accounts of the general techniques and equipment used have been reported previously (Cody *et al.* 1986*b*).

Subjects exerted a constant wrist flexor torque (typically about 0·5 N m) of approximately 5% of their individual maximum throughout the experiment, aided by an oscilloscope display of their force production. They were required not to react voluntarily to stimuli, neither to 'resist' nor to 'let go', and to ignore the transient fluctuations in the force record which occurred upon stimulation.

Mechanical stimulation

Stretch. Subjects grasped a handle coupled to a powerful electromagnetic vibrator which incorporated length and force transducers and operated as a positional servo. The forearm was held, just proximal to the wrist joint, by two vertical, padded bars. 'Ramp and hold' movements of the handle of the vibrator, of 10 mm extent, were used forcibly to extend the wrist through a rotation of approximately 10 deg. Velocities of movement, which were selected for each subject so as to evoke responses featuring both prominent M1 and M2 components, were within the range 100–300 deg s^{-1}. In all cases stretch and release of stretch were of identical rate.

Vibration. A small, electromagnetic vibrator was used to apply high-frequency (123 or 145 Hz) sinusoidal displacements, which were symmetrical about the starting position, percutaneously to the tendon of f.c.r. The vibrator was suspended from a cantilever system so that its grooved, plastic head pressed upon the tendon, about 5 cm above the wrist crease, with a force of 2·5 N. Displacement waveform was monitored by a length transducer attached to the shaft of the vibrator and was regulated by adjusting the profile of the driving signal. Peak-to-peak amplitudes, which were selected for each subject to elicit a short-latency peak of comparable amplitude to their corresponding M1 stretch response, were in the range 0·3–1·0 mm. Each train of vibration commenced and terminated at the mid-point of a releasing stroke so that each stretching stroke, including the first and the last, was of full size (cf. Fig. 6).

Stretch and vibration stimuli, of similar duration (which for stretch included its rising, maintained and falling phases), were applied alternately and continuously throughout each experiment. Precise durations of the stimuli varied (range 300–1000 ms) somewhat between individual subjects as did repetition rates (range 0·6–0·3 s^{-1}).

Electromyography

Differential surface recordings were made from the belly of f.c.r. using pairs of electrodes placed 5 cm apart. Signals were filtered (bandpass 0·1 Hz to 3 kHz) and rectified (time constant 1 ms) before on-line averaging (Neurolog NL 750, bin-width 2 ms).

Unrectified e.m.g. signals, displacement waveforms of stretch and vibration mechanical stimuli and trigger pulses were recorded on a 7-channel FM tape-recorder (Philips Analogue 7, bandpass d.c. to 1·25 kHz). These signals were replayed to allow averaging (using different bin widths to improve resolution) of responses elicited at the beginning and end of stimulation, for different numbers of trials and during selected phases of the experiment.

Ischaemia

After collection of control data, ischaemia of the lower arm and hand was induced by inflation of a standard blood-pressure cuff, applied just proximal to the elbow, to a pressure of 6·6 kPa (50 mmHg) above the subject's systolic blood pressure. The subject's blood pressure was monitored regularly, using a second sphygmomanometer, from the contralateral arm. Ischaemia was maintained until voluntary power began to decline (typically 20–25 min) when the cuff was rapidly deflated.

Measurement and analysis of data

Areas of rectified, e.m.g. averages were made by tracing the relevant sections of enlarged records using a graphics tablet linked to an Apple II computer. The areas of M1 responses were measured over a period of 25 ms commencing at the control (pre-ischaemic) latency of individual subjects. M2 stretch reflex areas were measured over a period starting 5 ms after the end of the M1 measurement interval and continuing until the excitatory response returned to background levels.

Areas of responses were expressed in two ways: 'absolute' values were the areas above pre-stimulus background levels of e.m.g. whilst 'normalized' values or fractional increases over background were calculated by dividing absolute values by the background area for an equivalent time interval.

Latency measurements were made from oscilloscope displays, at fast sweep speed, of individual responses or averages. In each case, time zero was obtained from the requisite length transducer waveform. The latencies of vibration 'on' responses were measured as in Fig. 1 from the beginning of the initial stretching stroke (which followed a quarter-cycle of release from the starting mid-position) since this corresponded to the onset of tendon extension and thus of muscle stretch. Time zero for withdrawal of vibration was taken as completion of the last, full instroke since this corresponded to the end of the final stretching phase. This was followed by a quarter-cycle of release to the rest mid-position. Times of termination of response components were measured from the point at which declining activity crossed the background e.m.g. level (or occasionally by extrapolation of the falling edge of the peak to background).

Statistics

In addition to the use of conventional parametric tests for calculation of mean values and their standard errors, three non-parametric analyses were also widely applied. The Friedman two-way analysis of variance by ranks was employed to determine whether any changes in reflex parameters (e.g. amplitudes, latencies, durations and times of termination) were associated with the progression of the experiment. For this purpose matched data derived for each of the individual subjects from six standard averaging periods (one pre-ischaemia or control period and five subsequent, successive periods, three of which were during ischaemia and two during recovery from ischaemia) were compared in the test. Wilcoxon's matched-pairs, signed-ranks test was utilized to establish whether systematic differences existed between the measures of reflex parameters, obtained from individual subjects, collected at two separate averaging periods during the course of the experiment. Tests of correlation of M1 and M2 response amplitudes were made using Spearman's rank correlation coefficient.

RESULTS

The records of Fig. 1 present the principal findings of the current study. They illustrate the characteristic effects of ischaemia (upper arm cuff) upon patterns of rectified, e.m.g. reflexes elicited in f.c.r. by stretch and tendon vibration. The time courses of responses are shown relative to the onsets of stimulation as determined from the respective length transducer waveforms. Time zero for vibration was taken as the beginning of the first full stretching stroke upon the tendon, i.e. commencement of the initial stretching phase (see Methods).

Control recordings of stretch reflexes (Fig. 1*A*, top line), obtained prior to inflation of the cuff, feature the familiar, fairly prolonged e.m.g. response comprising short-latency (*ca.* 25 ms, M1) and long-latency (*ca.* 50 ms, M2) excitatory waves. The simultaneous average of the responses to tendon vibration (Fig. 1*B*, top line) shows, in contrast, increased activity at short latency only. This is of similar amplitude to the M1 component of the stretch reflex. The markedly bifid form of the short-latency peaks, evoked both by vibration and stretch, reflects rectification of highly synchronized, biphasic compound muscle action potentials.

Following induction of ischaemia there is a marked and progressive decline in e.m.g. evoked at short latency, by both modes of mechanical stimulation, whilst the later wave of activity produced by stretch is relatively less affected. Thus, after a period of 16·5 min short-latency reflexes were virtually abolished whereas a substantial long-latency stretch-evoked response survived. At this stage of ischaemia no difficulty was encountered in maintaining target force and there was no apparent

diminution of voluntary power. Subsequently the remaining reflex activity disappeared, an occurrence which approximately coincided with a waning of voluntary e.m.g. activity.

Upon release of the pressure cuff a reversed sequence of changes in reflex patterns

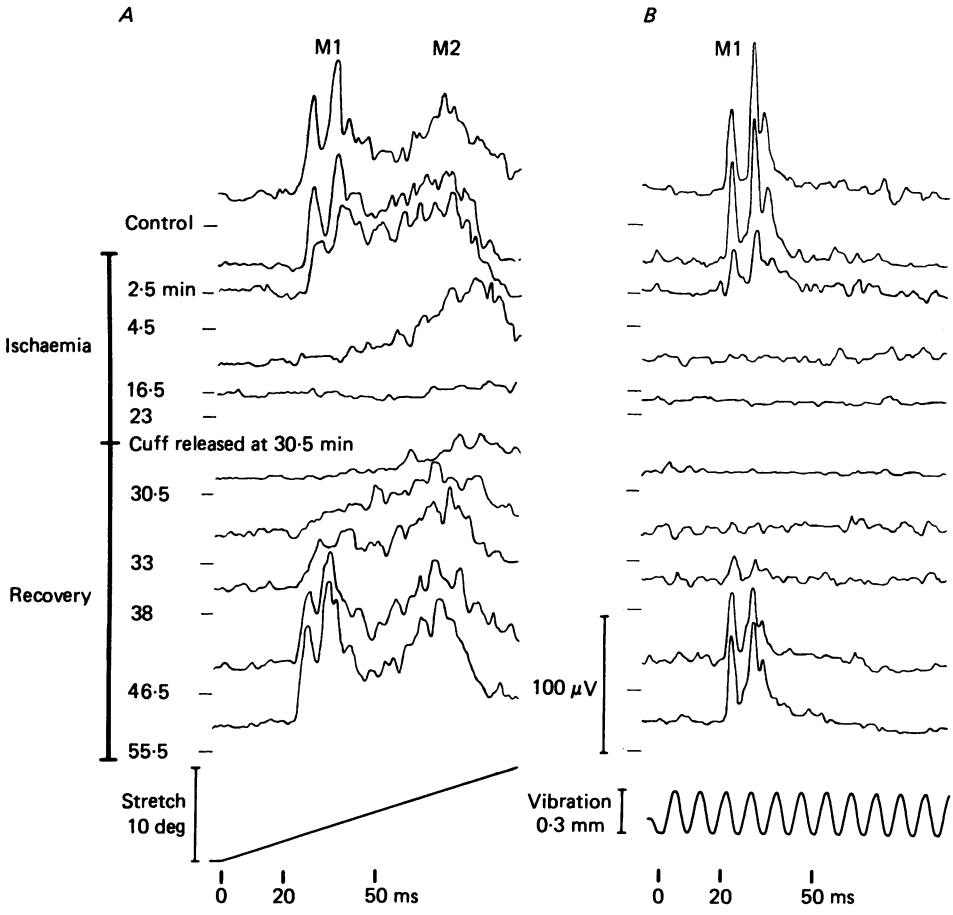

Fig. 1. Changes in the patterns of reflex e.m.g. responses evoked in f.c.r. by stretch (*A*) and flexor tendon vibration (*B*) during ischaemia and recovery from ischaemia. The horizontal bar at the start of each averaged (64 sweeps, repetition rate 0·33 s^{-1}), rectified record indicates zero e.m.g. level. The times shown on the left are the mid-points of averaging periods and are relative to initial inflation of the blood-pressure cuff.

was observed. Long-latency stretch reflexes quickly recovered, as did voluntary power, and were restored to control amplitudes within about 10 min. Short-latency stretch reflexes re-emerged more gradually and did not achieve normal levels until approximately 20 min had elapsed. Changes in short-latency vibration responses essentially paralleled those of M1 stretch reflexes.

Quantitative changes in short-latency reflex activity during ischaemia

In order to obtain quantitative measures of alterations in short-latency reflexes, for a range of subjects, the areas of rectified e.m.g. responses occurring within a 25 ms period commencing at control M1 latencies were computed. Values were

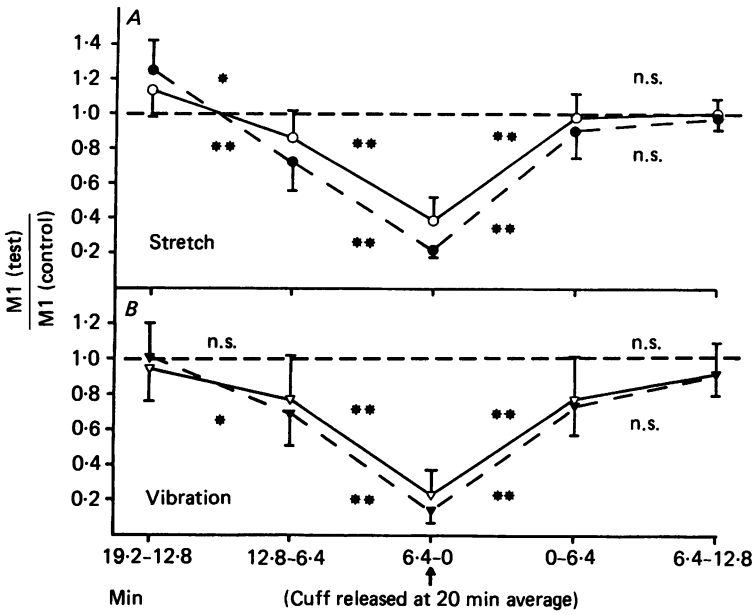

Fig. 2. Changes in the amplitudes of short-latency (M1) reflexes evoked by stretch (*A*) and vibration (*B*) during ischaemia and recovery from ischaemia. Data points are mean values (±S.E. of means), obtained from ten subjects (eleven observations) and are expressed as fractions of control values. Response amplitudes are presented as 'normalized' (○—○, ▽—▽) and 'absolute' (●---●, ▼---▼) areas. Mean control amplitudes of reflex responses are indicated by the horizontal dashed lines. The abscissa shows the durations of five standard averaging periods (128 sweeps, 0·33 s^{-1}) relative to the time of cuff deflation (time zero). Friedman's two-way analysis of variance by ranks indicated that both normalized and absolute measures of reflex activity were affected systematically during the course of the experiment ($P < 0·006$). Levels of significance of the difference between adjacent data points, according to Wilcoxon's matched-pairs, signed-ranks test, are indicated (** $P < 0·01$; * $P < 0·05$; n.s. (not significant) $P > 0·05$).

expressed both as absolute excitatory responses above pre-existing background levels and as responses normalized with respect to background e.m.g., i.e. fractional increases above background levels (see Methods).

Fig. 2 shows the changes in such short-latency reflex activity evoked by stretch (Fig. 2*A*) and by vibration (Fig. 2*B*) during ischaemia and recovery from ischaemia. The precise parameters of stimulation and time courses of the effects of ischaemia varied somewhat from subject to subject. Therefore, to allow comparison of data between subjects, averaging periods were aligned in relation to the time of cuff release, which corresponded to a noticeable reduction in voluntary e.m.g. and power and on average occurred about 20 min after cuff inflation. Pooled data derived from

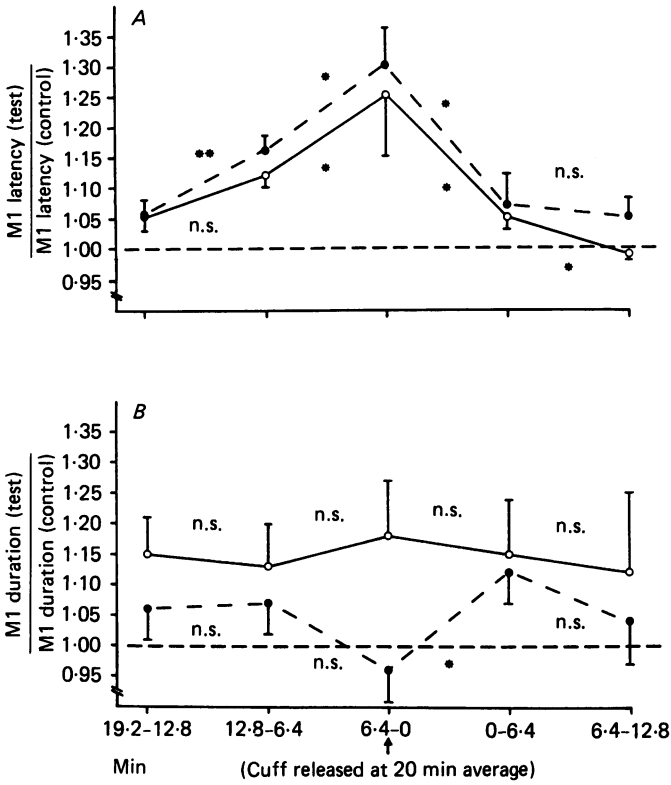

Fig. 3. Changes in the latencies (*A*) and durations (*B*) of the initial peaks of e.m.g. activity evoked by stretch (●---●) and vibration (○---○) during ischaemia and recovery from ischaemia. Data points are mean values (±S.E. of mean), obtained from ten subjects (eleven observations), and are expressed as fractions of control values. The averaging periods are identical to those of Fig. 2. Mean control levels are indicated by the horizontal dashed lines. The mean control latencies of responses to stretch and vibration were, respectively, 21·2±0·5 and 20·8±0·5 ms, whilst the mean control durations were 26·8±1·1 and 20·0±1·5 ms. The latencies of responses, both to stretch and vibration, were affected systematically during the course of the experiment ($P < 0·004$, Friedman) but their durations were not. Levels of significance of differences between adjacent data points are indicated (** $P < 0·01$; * $P < 0·05$; n.s. $P > 0·05$). Latencies of stretch and vibration reflexes in the first averaging period were increased compared to control values ($P < 0·05$) but had returned to normal by the final period. Durations of responses in neither the first nor the final averaging period differed significantly from control values.

five sequential averaging periods (128 trials, 0·33 s^{-1}), three leading up to cuff release and two during recovery, are shown. Mean values are expressed as proportions of pre-ischaemia, control amplitudes.

There was a decline in the mean areas of short-latency reflex activity, elicited both by stretch and vibration, as ischaemia progressed and a return to control values following cuff release. Statistical analysis, using Wilcoxon's matched-pairs, signed-ranks test, confirmed that the amplitudes of the stretch reflex responses for each of the sequential averaging periods differed significantly (see legend, Fig. 2) from those of the immediately preceding and succeeding periods, with the sole exception of the

final periods. This finding applied equally to absolute and normalized measures of reflex activities. Similarly, statistically significant changes in absolute and normalized measures of vibration-evoked responses were found, varying only in that the absolute response did not differ significantly between the first and second averaging periods.

The close correspondence of changes in normalized and absolute reflex e.m.g. activities indicates that the observed trends cannot have arisen fortuitously as a result of any systematic fluctuations in background levels of e.m.g. occurring over the course of the experiments. Direct support for this assertion was provided by statistical analyses of the levels of voluntary e.m.g. measured over successive averaging periods, which showed that they did not change significantly until about 20 min after the onset of ischaemia. Indeed, the onset of the reduction in e.m.g. which then regularly occurred served as a signal for cuff release.

Additional quantitative measurements were made of alterations in the latencies and durations of the earliest excitatory e.m.g. responses occurring during ischaemia. Such data were collected in order to assess the extent to which a temporal dispersion of sensory and/or motor discharge (due to receptor failure or changes in peripheral nerve conduction velocity) could be held responsible for the observed decline in short-latency reflex activity (i.e. reflex activity occurring within 25 ms of control latency). Fig. 3*A* presents the mean latencies of the initial components of stretch- and vibration-evoked reflexes for each of the five standard averaging periods. The sequential periods over which averages were made were again aligned, for different subjects, upon the time of cuff release. Latencies are expressed as fractional increases over pre-ischaemia control values.

The mean latencies both of stretch- and vibration-evoked reflexes tended to increase progressively during ischaemia. Accordingly, the latencies of the reduced, initial peaks, elicited by these two forms of stimulation for the second averaging period during ischaemia, were respectively 16% and 12% greater than control values and were significantly delayed ($P < 0{\cdot}01$, Wilcoxon; see legend of Fig. 3 for details of statistical significance of other changes). In the subsequent averaging period (i.e. immediately prior to cuff release) the latencies of corresponding responses were further increased, now by respectively 30% and 25%, compared to pre-ischaemia values. Upon restoration of the circulation the reflex latencies were rapidly restored to normal.

It should be noted, however, that despite these increases in mean latencies which occurred during ischaemia, the e.m.g. peaks always commenced within about 30 ms of the onset of stimulation and thus may be regarded, unequivocally, as being of 'short' rather than 'long' latency.

Complementary measurements were made of the durations of the earliest, identifiable e.m.g. peaks evoked by the two forms of stimulation. This was considered to be particularly important for vibration reflexes which essentially comprised a single, phasic excitatory response whose end-point was well defined; terminations of short-latency stretch responses were inevitably less clear since these peaks usually merged with later waves of activity. Fig. 3*B* shows the changes in the mean durations of initial, phasic, vibration-evoked responses, measured over identical averaging periods to those from which the data upon latencies were derived. There was a weak trend for responses to become more prolonged as ischaemia progressed. Such increases

in mean duration were invariably small (always < 4 ms), however, and at no stage did values differ significantly (Wilcoxon) from control data. Equivalent measurements upon the durations of M1 stretch reflexes (Fig. 3*B*), which were obtained by extrapolation of the falling edge of the peak until it crossed background e.m.g. level, were inherently of less certain accuracy. These too failed to show either any consistent trend or significant alterations between sequential averaging periods during the course of the experiment, except for the averaging period directly following cuff release, for which the duration was increased at the 5% level (Wilcoxon). Additionally, these e.m.g. peaks remained essentially symmetrical throughout (see Fig. 1).

Overall, therefore, whilst initial reflex responses were delayed during ischaemia they did not become longer lasting.

Considering the reductions in areas of e.m.g. activity measured within the 'M1 epoch' (Fig. 2) occurring during ischaemia, and the accompanying increases in latencies of responses (Fig. 3), it is evident that the two effects are of quite different magnitudes. The normalized amplitudes of responses to stretch and vibration declined, respectively, by 61% and 77% of control values, whilst corresponding responses were delayed by only 30% and 25% of their pre-ischaemia latencies. Equally pertinent, however, is whether the relatively small changes in latencies could have led to appreciable sections of initial response peaks falling beyond the standard M1 measurement epoch, and so have been solely or mainly responsible for the reductions in short-latency response areas. Inspection of individual records indicated that the fixed measurement period usually continued to provide a reasonable sample of M1 reflex activity and thus made this possibility improbable.

The matter was tested further by calculation of the changes in area of an isosceles triangle, chosen to simulate an e.m.g. peak, encompassed by a standard measurement period equivalent to its base upon progressively shifting the triangle to the right. It can be shown that upon displacement of such a triangle by a fraction K of its base the proportion of its area now falling beyond the measurement interval equals $2K^2$. Considering an increase in latency of 7 ms, which corresponds to the extreme extent encountered experimentally, and a measurement epoch of 25 ms (i.e. $K = 0{\cdot}28$), the section of the triangle no longer encompassed by the measurement boundaries is 15·7% of its area. Thus, whilst delay in onset of responses must have contributed to the observed reductions in areas of e.m.g. activity occurring within 25 ms of control latency, the extent of this effect is likely to have been fairly limited. Instead, the marked decline in amplitudes of M1 responses during ischaemia seems certain to have resulted predominantly from a reduction in the heights of these reflex peaks.

Quantitative changes in long-latency reflex activity during ischaemia

The pronounced long-latency (*ca.* 50 ms) waves of e.m.g. which were such a conspicuous feature of normal stretch-evoked reflex patterns were absent following flexor tendon vibration (see Fig. 1). Quantitative analysis of late reflex components has, therefore, been confined to M2 stretch responses. Areas of M2 peaks were computed over periods which commenced 5 ms after the termination of the M1 measurement epoch and continued until the excitatory responses returned to background levels. This method of measurement was adopted to provide a reasonable overall sample of M2 activity throughout the course of the experiment, despite any changes in its precise waveform. The peak, whilst remaining a clearly identifiable entity, tended to rise less steeply and to become somewhat prolonged during ischaemia.

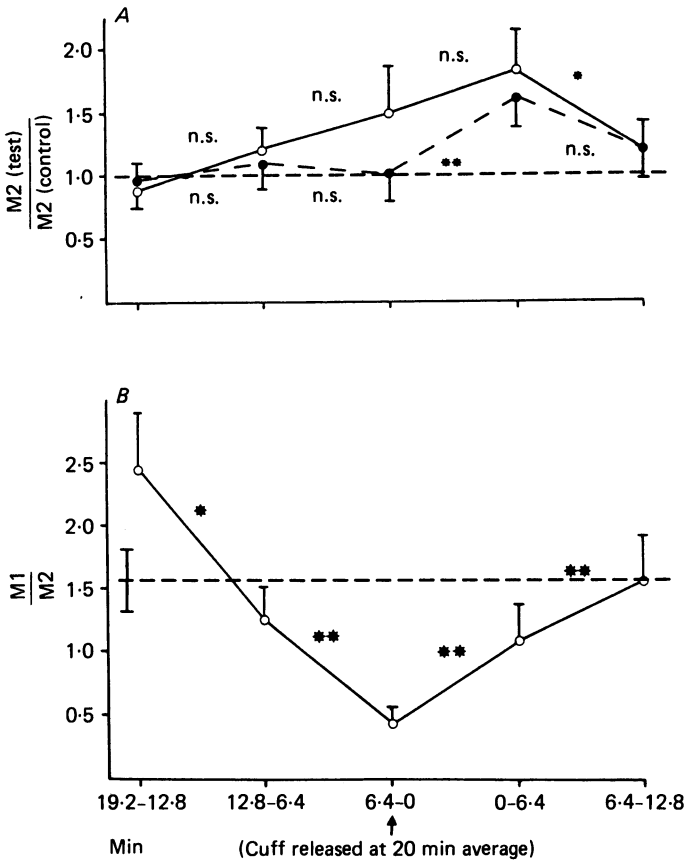

Fig. 4. *A*, changes in the amplitudes of long-latency (M2) stretch reflexes during ischaemia and recovery from ischaemia. Responses are presented as 'normalized' (○—○) and 'absolute' (●---●) areas. *B*, changes in the ratio of M1 and M2 stretch response amplitudes. The dashed horizontal lines indicate mean control levels (which for the M1/M2 ratio is 1·57, rather than unity, since M1 responses were on average of greater area than M2 responses). All data points are mean values (±S.E. of mean) obtained from ten subjects (eleven observations). Averaging periods are identical to those of Fig. 2. Neither normalized nor absolute measures of M2 response amplitudes were affected systematically during the course of the experiment ($P > 0·1$, Friedman) whereas M1/M2 ratios were significantly affected ($P < 0·0005$). Levels of significance of differences between adjacent data points are indicated (** $P < 0·01$; * $P < 0·05$; n.s. $P > 0·05$).

Changes in the durations of M2 stretch reflexes were assessed by measurement of the times of termination of these excitatory peaks, i.e. the time relative to stimulus application at which e.m.g. activity fell back to background level. The mean times of termination of M2 responses increased incrementally during ischaemia and decreased during recovery. Prolongation of responses was maximal for the averaging period immediately prior to cuff release when the mean time of termination was 132% of the control value and was significantly delayed ($P < 0·01$, Wilcoxon).

Fig. 4*A* shows the changes in mean M2 response amplitudes which occurred during ischaemia and recovery from ischaemia. Response amplitudes are expressed both as absolute and normalized areas and the averaging periods are identical to those

previously used to assess short-latency responses. Mean M2 absolute response amplitude remained fairly constant throughout ischaemia, and statistical analyses (Wilcoxon) indicated that no significant differences existed between adjacent data points. Corresponding mean normalized values did tend to increase progressively during ischaemia, but such changes were also not significant. Following release of the pressure cuff, however, the mean M2 absolute area did show a significant increase above that obtained in the immediately preceding period (final ischaemic period) and was, at this stage, greater than that of control recordings. Similarly, the corresponding normalized area was increased over its control value. These transiently elevated M2 responses, observed immediately after cuff release, then declined to within pre-ischaemia levels over the subsequent, final averaging period. Thus, unlike M1 responses, M2 responses were not reduced in amplitude during ischaemia and in the early recovery phase; indeed they were somewhat enhanced upon restoration of the circulation.

The contrasting behaviour of short- and long-latency stretch reflexes is further emphasized by the data plotted in Fig. 4*B* which present changes in the ratio of M1 and M2 areas observed during ischaemia. The mean M1/M2 ratio in the first of the averaging periods shown was slightly higher than that for the pre-ischaemia, control level (dashed horizontal line). Thereafter, the mean M1/M2 ratio showed a symmetrical fall as ischaemia progressed and a rise during recovery. The differences between each of the successive data points were significant at the 2% level (Wilcoxon). Control values of M1/M2 had been re-established by the final averaging period. Thus, the alterations of M1/M2 ratios largely reflected the fluctuations occurring in M1 responses.

A supplementary observation was that the M1 and M2 response amplitudes of individual subjects were not significantly correlated (Spearman), either during control recordings or at any stage of ischaemia or recovery from ischaemia.

Reflex patterns upon release of stretch and termination of vibration

Fig. 5 illustrates examples of the effects of the release of stretch (*A*, *C* and *E*) and termination of flexor tendon vibration (*B*, *D* and *F*) observed under control conditions, after 20 min ischaemia and 20 min following cuff deflation. Each averaged display of such 'off' responses is accompanied by its simultaneously recorded 'on' response. The vibration waveform (not shown) ended with a quarter-cycle of release to its mid-position. Time zero for cessation of stimulation was taken as the completion of the final full stretching stroke upon the tendon (see Methods).

Upon stopping both forms of mechanical stimulation there followed reductions in e.m.g. The precise onsets of these troughs, as judged against fluctuating existing e.m.g. levels (which for vibration often included small, sinusoidal reflex components at stimulus frequency), were invariably more difficult to measure than those of excitatory peaks elicited at the commencement of stimulation. In control recordings (Fig. 5*A* and *B*), nevertheless, such reductions obviously began within 30 ms of the termination of both stretch and vibration and thus corresponded in onset to the short-latency increases in activity found in the paired 'on' response records.

After 20 min ischaemia (Fig. 5*C* and *D*) a well-defined fall in e.m.g. upon release of stretch is still apparent but now occurs at about 55 ms, i.e. unequivocally of long latency and with no sign of any earlier reduction in activity (Fig. 5*C*). The M1 wave

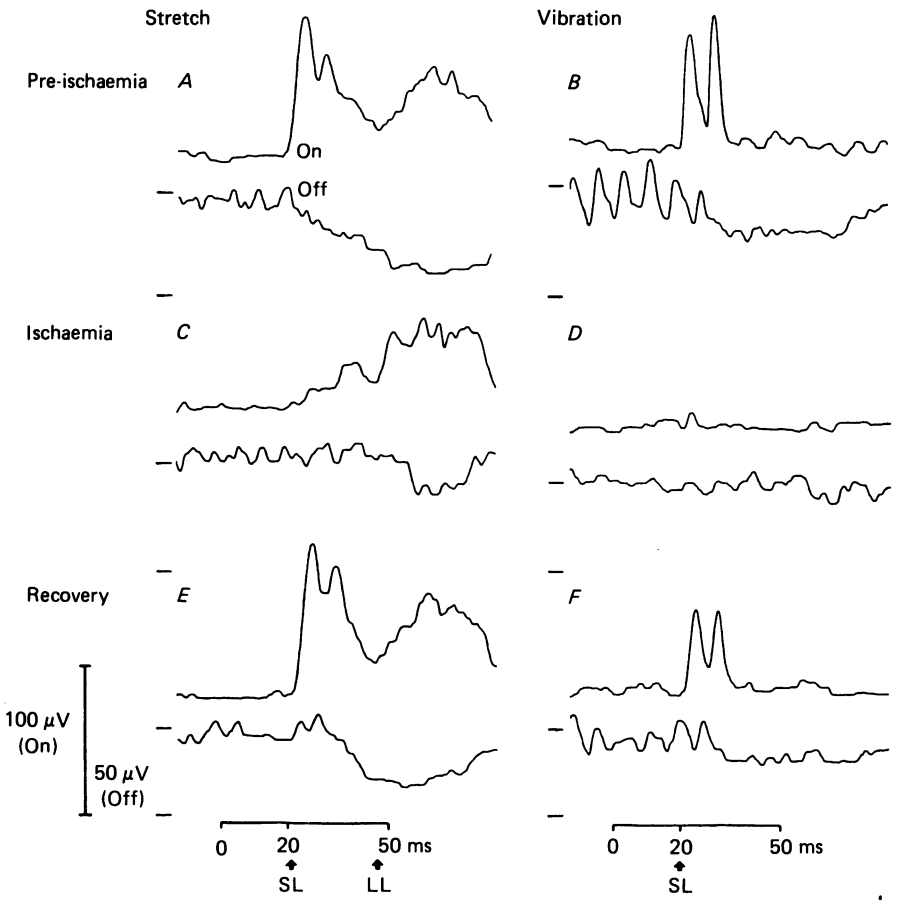

Fig. 5. Comparison of reflex e.m.g. responses evoked in f.c.r. by the application and release of stretch (left-hand series) and onset and termination of vibration (right-hand series). Each pair of averaged (64 sweeps, 0·33 s^{-1}), rectified records represents corresponding 'on' and 'off' responses obtained prior to ischaemia (*A* and *B*), after approximately 20 min ischaemia (*C* and *D*) and about 20 min following deflation of the cuff (*E* and *F*). Stretch and release were each of 100 deg s^{-1} and vibration was of 0·3 mm peak-to-peak amplitude. 'On' and 'off' responses were of different magnitudes and are displayed using separate voltage scales. The commencements, during control recording, of short-latency (SL) and long-latency (LL) 'on' responses are indicated by labelled arrows beneath the records. Same subject as Fig. 1. Zero e.m.g. indicated by horizontal bar at start of each record.

of the corresponding stretch response is markedly depressed. At this stage of ischaemia both 'on' and 'off' responses to vibration had disappeared (Fig. 5*D*).

Following restoration of the blood supply (Fig. 5*E* and *F*) the patterns of reflex response evoked both at onset and termination of stimulation returned to their initial forms. It is noteworthy that in this subject changes in the patterns of 'off' responses during ischaemia essentially paralleled those of simultaneously recorded 'on' responses, both in the suppression of short-latency effects (evoked by each form of mechanical stimulation) and persistence of long-latency action (seen only with stretch and its release).

Two further lines of evidence suggested that release of stretch could produce

distinct, long-latency reductions in e.m.g., whose presence was normally masked by their superimposition upon ubiquitous short-latency ones. In control recordings from two additional subjects the profile of the falling edge of the e.m.g. trough appeared to be subdivided into two elements; the initial component was small, of shallow slope and disappeared during ischaemia, whereas the long-latency component was more

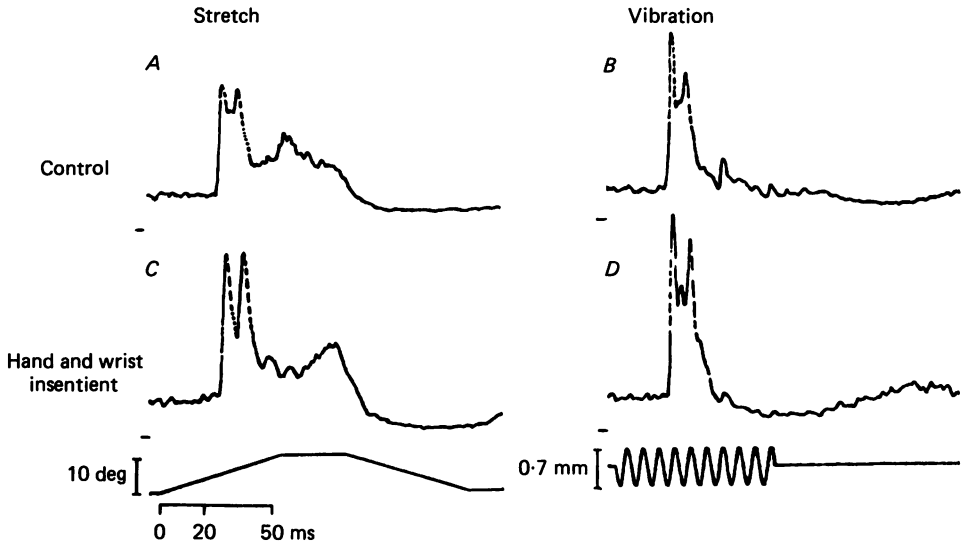

Fig. 6. Comparison of the reflex e.m.g. responses evoked in f.c.r. by stretch and vibration under normal conditions (*A* and *B*) and when the hand and lower forearm were insentient following prolonged (70 min) inflation of a blood-pressure cuff just below the belly of the muscle (*C* and *D*). The records are averages (64 sweeps, 0·33 s^{-1}) of rectified activity. During recordings the subject maintained a steady voluntary contraction of 20% MVC but relaxed between averaging periods. Zero e.m.g. indicated by horizontal bar at start of each record.

pronounced, of steeper slope and remained throughout the experiment. Secondly, for each of the six subjects whose 'off' responses were of sufficient amplitude and clarity to permit analysis, the latencies of reductions in e.m.g. upon release of stretch approximately doubled, although this occurred when reasonably large short-latency stretch reflexes persisted.

The reflex reductions in e.m.g. observed upon termination of vibration differed in two main respects: first, whilst recognizable responses remained, they were universally of short latency and secondly, they failed to exhibit any definite sign of a long-latency contribution.

Effects of anaesthesia of the hand and lower forearm upon reflex patterns

The possibility that mechanical stimulation, either vibration or stretch, produced its reflex effect by activation of receptors in the skin overlying the flexor tendon or wrist or those of the joint itself was tested in two subjects. A blood-pressure cuff was again utilized to induce ischaemia but now placed around the forearm just distal to the belly of f.c.r. to abolish sensation arising from more distal structures. This effect required relatively protracted (> 1 h) periods of ischaemia.

Fig. 6 compares recordings of stretch and vibration reflexes obtained before inflation of the cuff with those evoked after a prolonged period (70 min) of ischaemia. At the time of the latter recordings cutaneous sensation in the hand and around the wrist had been almost completely abolished. The presence of the vibrator probe, including its local high-frequency stimulation, as it pressed over the flexor tendon could no longer be detected with certainty. The occurrence of the large amplitude, forcible rotations of the wrist, applied by the stretcher, could still be identified, but with reduced appreciation of speed and extent.

The patterns of the reflexes evoked under these two conditions are, in the event, very similar. Thus, despite the impairment of cutaneous and joint position sense, vibration continued to elicit its characteristic short-latency phasic response, whose amplitude was virtually unaffected, whilst both M1 and M2 stretch reflexes survived largely unchanged.

DISCUSSION

The striking finding of the present investigation was of clearly differential behaviour of the long- (M2) and short-latency (M1) e.m.g. responses of wrist flexor muscles. First, vibration, both at its onset and termination, evoked solely short-latency responses (Matthews, 1984; Cody *et al.* 1986*b*). These vibration reflexes lacked accompanying long-latency components, such as those which were regularly produced by the application of stretch and which could be revealed for some subjects at the release of stretch following a period of ischaemia. Secondly, short-latency responses, whether elicited by vibration or stretch, were highly susceptible to ischaemia, whereas, confirming the observations of Jaeger *et al.* (1982), M2 stretch reflexes were relatively resistant.

We interpret such dualism of properties as simultaneously suggesting that the short-latency responses evoked by stretch and by vibration share a basically similar afferent origin, whilst the long-latency stretch reflex is mediated by an essentially separate group of receptors and sensory fibres. This general conclusion applies regardless of the particular afferent mechanisms underlying M1 and M2 reflexes.

Afferent origin of short-latency reflexes

All of the present evidence is entirely consistent with the generally accepted view that M1 responses result predominantly from the excitatory spinal reflex action of muscle spindle group Ia afferents. Stretch and tendon vibration both produced well-developed M1 reflexes; both stimulus modes are known to excite human spindle primary endings powerfully (Burke *et al.* 1976) and seem certain to generate potent autogenetic (including monosynaptic) excitation of motoneurones. Equally, group Ia afferents are amongst the largest-diameter, most rapidly conducting myelinated fibres, and as such may be expected to be particularly vulnerable to ischaemic nerve block (Lewis *et al.* 1937). Such an early ischaemia-induced depression of group Ia input would readily account for the high susceptibility of M1 responses under these conditions. The view that alterations in sensory rather than motor processes were responsible for the observed reduction in short-latency reflexes is supported by the finding that M1 responses declined before any appreciable fall in either later reflex components or voluntary power.

Several of the present findings, and especially those with vibration, argue against the depression of M1 reflexes during ischaemia having resulted primarily from a temporal dispersion of the build-up of afferent discharge as might follow from slowing of nerve conduction or failure of sensory receptors. In such a situation the reflex could be apparently lost as its latency and duration increased and it merged with later components. The current investigation of changes in the form of vibration-evoked reflex patterns during ischaemia allowed this issue to be tested more rigorously than has hitherto been possible in studies (Jaeger *et al.* 1982) in which stretch stimuli alone were employed. At its commencement, vibration may normally be expected to stimulate a powerful, highly synchronized and relatively selective group Ia barrage. More importantly, in the present context it elicits in f.c.r. a reflex which usually comprises a single, phasic peak which is uncontaminated by later, large excitatory components. Thus, in contrast to M1 stretch reflexes which are regularly accompanied by later responses, any prolongation of vibration-elicited, short-latency peaks may be viewed without the complication of their blending with ensuing responses. Additionally, measurement of the time courses of vibration reflexes provide a valuable reference for interpretation of changes of stretch-evoked e.m.g. waveforms since the underlying reflex mechanisms are presumed to be analogous.

In the event, the latencies of onset of the earliest, identifiable e.m.g. peaks, elicited both by vibration and stretch, did show small but significant increases during ischaemia. The durations of vibration-evoked, phasic peaks, in contrast, remained fairly constant, as did those of M1 stretch responses. These combined findings of increased latency and constant duration (with consequent delay of terminations of responses) are most readily explained by ischaemia having produced a loss of and/or reduction in conduction velocity of the fastest nerve fibres (e.g. spindle group Ia afferents) and simultaneous, but less marked, slowing of the less rapidly transmitting elements (e.g. A_α motor fibres). It should be stressed, however, that ischaemia acted principally to reduce the amplitudes of M1 peaks. This effect seems certain to have resulted from failure of transmission of the sensory volleys normally responsible for short-latency responses, either by complete fibre block or a preferential interference with the conduction of high-frequency bursts of discharge (i.e. Wedensky inhibition) in a substantial proportion of group Ia afferents.

Observations upon the parallel behaviour of reflex reductions in e.m.g. upon termination of vibration lead to a similar conclusion. Under normal conditions, withdrawal of this mode of reflex stimulation produced small but distinct short-latency decrements in activity whose latency showed rather little change during ischaemia before their eventual extinction.

Overall, each of these various lines of evidence combine to support the view that M1 stretch- and vibration-evoked reflexes share an essentially common afferent origin and are crucially dependent for their mediation upon muscle spindle group Ia activity.

Afferent origin of long-latency stretch reflexes

The finding that the characteristics of M2 stretch reflexes in f.c.r. differ from those of M1 responses, both regarding the form of stimulation necessary for their production and their susceptibility to ischaemia, is most simply explained in terms of independent reflex afferent mechanisms.

The differential behaviour of long-latency reflexes cannot plausibly have arisen from the involvement of a separate subpopulation of motoneurones, motoneuronal refractoriness or Renshaw inhibition. Recent recordings, in man, from single motor units of f.c.r. (Calancie & Bawa, 1985) have shown that individual units may contribute both to M1 and M2 stretch reflexes. These findings refute the notion that different groups of motoneurones underlie the two response components. Since the M1 peaks elicited by stretch and vibration were initially of similar amplitude, reflecting comparable strengths of motor discharge, the responsible motoneurones may be assumed to have been influenced to broadly equivalent extents by refractoriness and recurrent inhibition. Thus neither of these inhibitory processes could account for the lack of M2 responses with vibration. The decline of M1 responses, during ischaemia, and consequent reduction in refractoriness and recurrent inhibition, will have inevitably favoured the persistence or appearance of later reflex activity of whatever origin. Several factors, however, make it improbable that such effects could have been major determinants of the reflex patterns observed. The waning of short-latency vibration responses was generally unaccompanied by the emergence of any appreciable long-latency activity. Equally, M1 and M2 response amplitudes were not negatively correlated prior to ischaemia, as would have been expected if the occurrence of large initial responses had caused marked suppression of delayed activity.

Nevertheless, it is evident that spindle group Ia afferents must normally exert a sustained facilitatory action upon motoneuronal excitability during protracted stretch or vibration. Such an action was clearly demonstrated by the finding of short-latency reductions in e.m.g. ('off' responses) upon cessation of stimulation. This sort of short-latency facilitation cannot, however, be essential for M2 generation since long-latency reflexes persisted largely unaltered following the abolition, by ischaemia, of both short-latency 'on' and 'off' responses. This observation argues strongly against M2 stretch reflexes originating from segmented group Ia volleys acting via short-latency spinal pathways to evoke successive e.m.g. peaks ('resonance hypothesis'; Eklund *et al.* 1982). It also undermines the suggestion that M2 reflexes are group Ia-mediated responses transmitted by long-loop central routes ('transcortical hypothesis': Phillips, 1969; Marsden *et al.* 1972).

A further possibility, and one proposed by Jaeger *et al.* (1982) to account for the greater susceptibility of M1 than M2 reflexes to ischaemia, is that whilst both responses arise from group Ia activity they are mediated by separate pathways which require different strengths of afferent input. It could be envisaged, for example, that short-latency reflexes were especially dependent upon high-frequency group Ia discharges and that selective suppression of such bursts, by receptor failure or Wedenksy inhibition of axonal transmission, during ischaemia would produce preferential loss of M1 responses. The suggestion that such a M2 route needs only a relatively weak group Ia volley for its operation is, however, hard to reconcile with the finding that the powerful group Ia discharge evoked by vibration in the non-ischaemic limb, and capable of producing well-developed short-latency responses, regularly fails to evoke long-latency ones.

Accepting that the balance of evidence is against muscle spindle group Ia afferents being primarily responsible for M2 stretch responses, elicited in f.c.r. during the maintenance of a steady voluntary effort, the immediate issue is whether our

findings allow any distinction to be made between the principal alternative groups of reflex afferents postulated to have this role, namely group II afferents (Matthews, 1984) and cutaneous and/or joint afferents (Marsden *et al.* 1971, 1976; Darton *et al.* 1985).

The case for attributing the M2 stretch reflexes of f.c.r. to group II action, based on comparison of responses to stretch and vibration (cf. Matthews, 1984), has already been made in detail (Cody *et al.* 1986*b*) and need not be restated. The comparative sensitivities of joint and cutaneous receptors to these two modes of stimulation are uncertain and presumably depend greatly upon the particular category of receptor concerned and its precise anatomical distribution. It could be envisaged, however, that some, at least, of the receptors of the wrist joint and of the skin overlying it might behave in an appropriately differential and directional manner. The occurrence of late e.m.g. reflexes, in muscles of the hand, which are elicited by stimulation of digital nerves (Jenner & Stephens, 1982) or cutaneous branches (Deuschl, Schenck & Lucking, 1985) is well documented. Indeed, cutaneous reflexes appear to be particularly pronounced in hand muscles where they may be of special functional importance, e.g. control of the precision grip (Johannson & Westling, 1984).

Available evidence, however, indicates that any contribution to reflexes in f.c.r. from skin afferents activated by wrist rotation or tendon vibration is modest. In control experiments for the present study short-latency responses (evoked by both modes of stimulation) and long-latency reflexes (elicited by stretch) persisted largely unchanged following inflation of a blood-pressure cuff just below the belly of the muscle so as to induce anaesthesia of the hand and lower part of the forearm. This finding provides independent support for the earlier conclusion of Bawa & McKenzie (1981), from the use of local anaesthetic to render the hand insentient, that both M1 and M2 reflexes of f.c.r. arise predominantly from intramuscular receptors. A variety of workers have obtained similar results from comparable studies upon a number of other muscles acting upon several different joints (e.g. thumb: Marsden, Merton & Morton, 1977; Matthews, 1984; Loo & McCloskey, 1985; Prochazka & Trend, 1986; great toe: Marsden *et al.* 1977; ankle: Iles, 1977; Chan, Jones & Catchlove, 1979) and agree that muscle afferents are responsible for both response components. Darton *et al.* (1985) are the sole dissenters from this general conclusion and contend that 'component M2 arises solely from skin, and/or subcutaneous stimulation and does not depend on muscle stretch'.

Modes of action of ischaemia

We view our findings as providing tentative support for the mediation of long-latency components by relatively smaller-diameter, more slowly conducting reflex afferents than group Ia fibres. This interpretation depends upon ischaemia, as applied under the present conditions, acting mainly to produce conduction block of progressively smaller peripheral nerve axons, either by hypoxia or pressure or a combination of these effects (Gasser & Erlanger, 1929; Lewis *et al.* 1937; Bentley & Schlapp, 1943*a*, *b*; Leksell, 1945; Laszlo, 1966; Torebjork & Hallin, 1973).

This view may, however, be too simple since ischaemia could potentially simultaneously influence a complex mixture of processes at different sites and to varying degrees. The most likely alternative to axonal block is that local hypoxia could

induce prior or additive changes in sensory receptor transduction. For example, asphyxia induced in the muscles of experimental animals by ligation of their blood vessels can have powerful effects upon spindle receptors, including high-frequency discharges initially with subsequent inexcitability (Matthews, 1933; Paintal, 1964). It seems unlikely that such dramatic alterations in transducer function, either of intramuscular or other types of receptors, will have occurred under the present less severe experimental conditions, but some degree of receptor failure cannot be excluded. Hence, ischaemia could, at least in principle, exert its main effects either upon receptors themselves or upon their axons, and the balance could vary between different categories of sensory unit.

Accordingly, whilst observations during ischaemia provide a basis for discrimination of the reflex actions of different types of sensory units they do not permit a definitive distinction between mediation by afferents of varying conduction velocity. The fact that rapidly conducting reflex afferents can contribute to the long-latency responses of some muscles, in particular abductor digiti minimi, has been shown by recent experiments in which the long-latency reflex evoked in this muscle by displacement of the little finger, and the F wave elicited by maximal stimulation of the ulnar nerve, were similarly delayed by cooling the arm (Matthews, 1987).

Overall, the present findings form a powerful and further argument against long-latency stretch reflexes, evoked in f.c.r. during maintenance of a steady voluntary effort, having arisen from spindle group Ia afferent input. The identity of the afferents actually responsible for M2 stretch reflexes, however, remains in doubt, as does the related issue of whether reflex delay results from slow peripheral conduction or prolonged central processing. However, the possibility exists that there is no unique, satisfying answer, but rather that the central nervous system utilizes varying combinations of available sensory information in the genesis of reflex patterns according to the functional roles of individual muscles and the nature of the tasks being undertaken.

Note added in proof. In agreement with the present findings and those of Jaeger *et al.* (1982) in f.c.r., Davies (1987) has recently reported that M1 stretch reflexes of the human abductor digiti minimi are more susceptible to ischaemia than are M2 components. Conversely, however, Hayashi, Becker, White & Lee (1987) conclude that long-latency stretch reflexes, of f.c.r., show greater ischaemia-induced suppression. Differences in data analysis (e.g. periods over which M1 and M2 components were measured, especially the use of a very narrow time interval for M2) and experimental techniques (e.g. stimulus parameters and resulting relative M1 *vs.* M2 sizes, instructions to subjects, cuff pressures) may have contributed to the contradictory results of Hayashi *et al.* (1987).

C.N.G. held a SERC postgraduate training studentship.

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