Supraspinal factors in human muscle fatigue: evidence for suboptimal output from the motor cortex

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1. Voluntary activation of elbow flexor muscles can be optimal during brief maximal voluntary contractions (MVCs), although central fatigue, a progressive decline in the ability to drive the muscle maximally, develops during sustained or repeated efforts. We stimulated the motor cortex and motor point in human subjects to investigate motor output during fatigue.

2. The increment in force (relative to the voluntary force) produced by stimulation of the motor point of biceps brachii increased during sustained isometric MVCs of the elbow flexors. Motoneuronal output became suboptimal during the contraction, i.e. central fatigue developed and accounted for a small but significant loss of maximal voluntary force. During 3 min MVCs, voluntary activation of biceps fell to an average of 90·7% from an average of >99%.

3. The increment in force (relative to the voluntary force) produced by magnetic cortical stimulation was initially small (1·0%) but also increased during sustained MVCs to 9·8% (with a 2 min MVC). Thus, cortical output was not optimal at the time of stimulation nor were sites distal to the motor cortex already acting maximally.

4. A sphygmomanometer cuff around the upper arm blocked blood supply to brachioradialis near the end of a sustained MVC and throughout subsequent brief MVCs. Neither maximal voluntary force nor voluntary activation recovered during ischaemia after the sustained MVC. However, fatigue-induced changes in EMG responses to magnetic cortical stimulation recovered rapidly despite maintained ischaemia.

5. In conclusion, during sustained MVCs, voluntary activation becomes less than optimal so that force can be increased by stimulation of the motor cortex or the motor nerve. Complex changes in excitability of the motor cortex also occur with fatigue, but can be dissociated from the impairment of voluntary activation. We argue that inadequate neural drive effectively 'upstream' of the motor cortex must be one site involved in the genesis of central fatigue.

Fatigue is an exercise-induced decrease in the maximal force produced by a muscle. Most of the decline in maximal voluntary force occurs through processes in the muscle, distal to the neuromuscular junction (e.g. Merton, 1954; Westerblad, Lee, Lannergren & Allen, 1991). However, changes in the performance of any or all sites in the pathway from the motor cortex to the muscle fibre may contribute to fatigue, so that impairment of muscle performance is not necessarily the limiting factor in force production from a fatigued muscle. Under some conditions, neural activity does not drive the muscle to generate the full force of which it is capable (Mosso, 1904; Ikai & Steinhaus, 1960; Bigland-Ritchie, Jones, Hosking & Edwards, 1978; McKenzie, Bigland-Ritchie, Gorman & Gandevia, 1992).

During a maximal effort, the degree of voluntary activation of a muscle can be assessed by supramaximal electrical stimulation of the motor nerve (Merton, 1954). Motor units not recruited by volition, or not firing at optimal rates will produce extra force. The bigger the force produced by such a stimulus during a contraction, the greater the failure of voluntary activation. In well-motivated subjects receiving feedback and continuous encouragement, voluntary activation is high (Belanger & McComas, 1981; Bellemare, Woods, Johansson & Bigland-Ritchie, 1983; Gandevia & McKenzie, 1988; Gandevia, McKenzie & Plassman, 1990). However, voluntary activation in brief non-fatiguing maximal efforts is frequently less than 100% and is somewhat dependent on which muscle is activated (Belanger & McComas, 1981; McKenzie *et al.* 1992). During a sustained fatiguing contraction, voluntary activation declines progressively. This decline is termed 'central fatigue'.

Although changes in motoneurone firing rates and spinal reflexes have been demonstrated during fatigue (Bigland-Ritchie, Johansson, Lippold, Smith & Woods, 1983; Kulkulka, Moore & Russell, 1986; Hayward, Breitbach & Rymer, 1988; Garland & McComas, 1990; Duchateau & Hainaut, 1993), such alterations are not themselves indications of central fatigue. Motoneurone firing rates decrease during a sustained voluntary contraction but this is a functionally useful change which matches activation to the slower contractile properties of the muscle (Bigland-Ritchie, Johansson, Lippold & Woods, 1983; Marsden, Meadows & Merton, 1983). However, too great a slowing of neuronal firing would constitute central fatigue. Altered feedback from large- and small-diameter muscle afferents during sustained contractions can influence the behaviour of α-motoneurones and the level of voluntary activation. In non-fatigued muscle, pain reduces voluntary activation (Rutherford, Jones & Newham, 1986; Gandevia & McKenzie, 1988) and, therefore, the small-diameter muscle afferent input during a sustained contraction may be expected to lead to a progressive failure of voluntary activation. The discharge of muscle spindle afferents decreases during a sustained contraction and may also be implicated in central fatigue (Macefield, Hagbarth, Gorman, Gandevia & Burke, 1991). Vibration of fatigued muscle during a prolonged maximal voluntary effort increases spindle firing and increases force output (Bongiovanni & Hagbarth, 1990). However, muscle afferents do not project only to spinal levels and, therefore, any contribution to central fatigue could be mediated supraspinally.

The excitability of the cortex in human subjects is altered during fatigue. When transcranial magnetic stimuli are delivered during fatiguing isometric contractions, both the size of the evoked compound muscle action potential (MEP) and the duration of the subsequent period of near-silence of the EMG (silent period) increase. These changes appear to occur supraspinally and may reflect increased voluntary drive to the motor cortex (Taylor, Butler, Allen & Gandevia, 1996). However, the relationship of these alterations to central fatigue is unknown.

We therefore stimulated different levels of the motor pathway during prolonged fatiguing contractions and have demonstrated that voluntary force in a maximal effort is often not limited by the ability of the motor cortex, α-motoneurones or muscle to generate additional output. Failure of voluntary activation can be dissociated from the complex changes in the excitability of the motor cortex which accompany muscle fatigue. This suggests that central fatigue is not causally linked with these changes. Hence, inadequate neural drive effectively 'upstream' of the motor cortex may be crucial in the genesis of central fatigue. Results have been presented in brief (Allen, Butler, Taylor & Gandevia, 1994).

METHODS

Terminology

Initially, we define six terms which we will use to describe voluntary force production: maximal voluntary contraction (MVC) – a contraction in which subjects, with continuous feedback and encouragement, believe their effort to be maximal; maximal voluntary force – the force produced during a MVC; maximal evocable force – force of a MVC which cannot be increased by interpolated supramaximal motor-point stimuli; voluntary activation – the level of motoneuronal drive during a contraction; optimal voluntary activation – level of motoneuronal drive that produces maximal evocable force; central fatigue – a progressive, exercise-induced decline in voluntary activation of a muscle.

Experimental arrangement

Eight normal volunteers (aged 25–42 years, 2 females) were studied. All procedures were undertaken with the approval of the local ethics committee and written informed consent from each volunteer was obtained. As described in the preceding manuscript, subjects sat with the right arm held at the wrist in an isometric myograph which measured the force of elbow flexion (Fig. 1*A* of Taylor *et al.* 1996). Visual feedback and verbal encouragement were given throughout all contractions.

Stimulation

Motor responses were elicited by stimulation at two sites in different experiments. (1) Motor point: pairs of supramaximal electrical stimuli (100 ms duration, 200–400 mA, interstimulus interval of 10 ms) were delivered by a Digitimer DS7 stimulator (modified to produce up to 1 A; Digitimer Ltd, Welwyn Garden City, Herts, UK) through surface electrodes (10 × 12 mm gauze-covered aluminium strips, soaked in saline and electrode gel) over biceps brachii. The cathode was positioned over the motor point and the anode over the distal tendon. (2) Transcranial magnetic cortical stimulation: stimuli were delivered via a round coil (13 cm o.d.) fixed over the vertex (stimulus intensities 70–100% output, Magstim 200; Magstim Co., Dyfed, UK). The coil was oriented to stimulate the left hemisphere preferentially.

Protocol

Motor-point stimulation. Biceps brachii was stimulated with the muscle relaxed, during short-duration maximal voluntary contractions (MVCs) and during a sustained 3 min duration MVC ($n = 6$ subjects). Initially, subjects performed three brief (2–3 s) maximal isometric elbow flexions, each contraction separated by 1 min. During and 5 s after each contraction, stimuli were delivered over biceps brachii. Then, after a 1 min rest, subjects performed a sustained MVC, during which stimuli were given approximately every 10 s. Immediately following the sustained MVC, three sets of stimuli were delivered over the relaxed muscle within 15 s. Force was sampled at 1 kHz for 25 ms prior to, and 475 ms after, each stimulus. Custom amplifiers measured the background force at the moment of stimulation and any increment in force generated by the resulting muscle twitch (Hales & Gandevia, 1988).

Transcranial magnetic stimulation. Subjects ($n = 6$) performed five brief maximal isometric elbow flexions (2–3 s duration) at intervals of approximately 1 min. These were followed by a 2 min sustained MVC. Finally, a series of brief MVCs were performed at 0·5, 1, 2 and 3 min after the sustained contraction to monitor

recovery. During each brief MVC, a single transcranial magnetic stimulus was given, whereas during the sustained effort, stimuli were delivered every 10–15 s. Force was sampled at 5 kHz from 50 ms before to 500 ms after each stimulus and was recorded on disk for off-line analysis (1401 interface; Cambridge Electronic Design, Cambridge, UK). EMG responses were recorded from biceps brachii and brachioradialis and are described in the preceding paper.

Cortical stimulation during muscle fatigue maintained by ischaemia

In four subjects, a sphygmomanometer cuff was placed around the upper arm prior to the sequence of elbow flexions. After 1·25–1·75 min of the sustained MVC, the cuff was inflated to block arterial blood flow, and maximal effort was maintained until one further transcranial stimulus had been delivered. The cuff remained inflated to 300 mmHg until two short-duration contractions, with superimposed magnetic stimuli, were performed

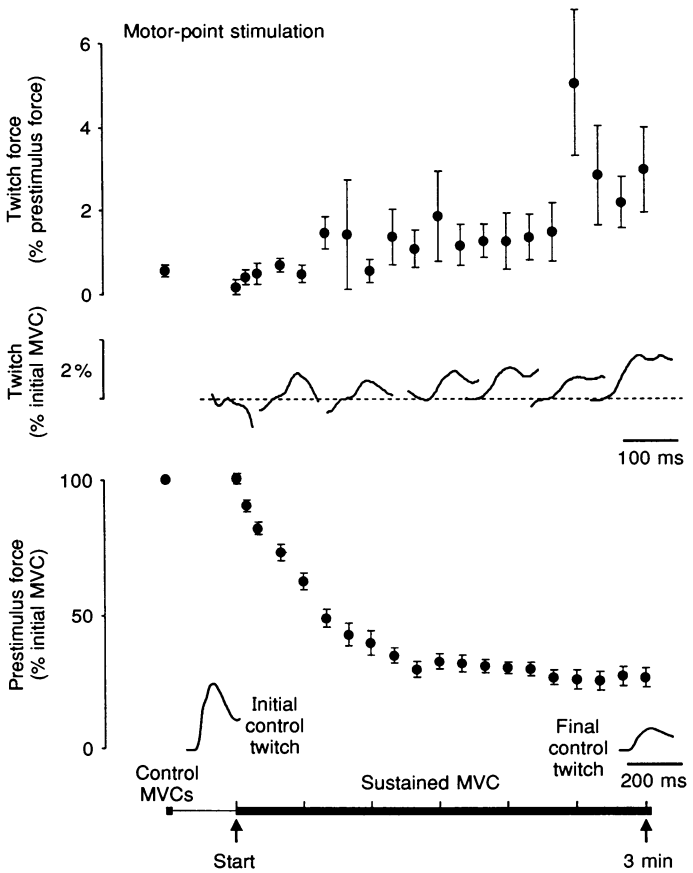

Figure 1. Reduction in voluntary force and increase in interpolated twitch size during a sustained MVC

In the top and bottom panels, each point represents the mean ± S.E.M. of data from six subjects. The initial point indicates the mean ± S.E.M. of values from three brief MVCs for each subject, whereas each subsequent point consists of one value from each subject. The top panel shows the increment in force generated by a twitch evoked by motor-point stimulation of biceps brachii. Twitch force is expressed as a percentage of the voluntary force measured at the time of stimulus (bottom panel). The twitch force superimposed on the 3 min MVC increases progressively during the contraction. The middle panel shows typical raw traces of elbow torque recorded from one subject. Traces show the twitch response to the stimuli delivered at the start and each 30 s through the contraction. Each trace shows 25 ms prior to the stimulus and has been truncated after the peak of the twitch. Twitches have been aligned so that the dotted line crosses each trace at the moment of stimulation. The bottom panel shows the decline in voluntary force, expressed as a percentage of the initial maximal voluntary force, during the sustained MVC. Force was measured just prior to delivery of each stimulus during brief control MVCs and during the sustained contraction. Traces inset in the bottom panel show twitches elicited from the relaxed muscle before (trace on left) and after (trace on right) the sustained MVC. Their amplitudes are scaled to the percentage of initial MVC (i.e. y-axis). The decrease in amplitude of the control twitch after the sustained MVC shows the degree of peripheral fatigue.

at 0·5 and 1 min after the end of the sustained MVC. Additional cortical stimuli were delivered during brief maximal flexions at 0·5, 1 and 2 min after the cuff was deflated.

Data analysis

Increments in force produced by motor-point stimulation (superimposed twitches) during brief maximal efforts, and at the beginning and end of the sustained MVC, were used to calculate the levels of voluntary drive:

$$\text{voluntary activation (\%)} = \left(1 - \frac{\text{superimposed twitch}}{\text{mean control twitch}}\right) \times 100,$$

where the control twitch is the force evoked by stimulation of the relaxed muscle. To estimate the relative levels of voluntary drive *during* sustained maximal contractions, force produced by the superimposed twitch was expressed as a fraction of the background force (maximal voluntary force at the time of stimulation). An increase in this fraction represents a decrease in voluntary activation. For motor-point stimulation, the fraction compares incremental force of biceps brachii alone with the voluntary force of all elbow flexors. However, similar analysis of superimposed twitches following cortical stimulation compares incremental force from all elbow flexors with the voluntary force of all elbow flexors, and may allow a reasonable estimate of voluntary activation (see Discussion).

RESULTS

Level of voluntary activation during a sustained maximal effort

Stimulation of the motor point of biceps brachii assessed the ability of six subjects to activate the flexors of the elbow during a sustained isometric maximal voluntary contraction (MVC). As the contraction proceeded, voluntary force declined to 25·9 ± 8·6% (S.D.) of initial MVC (Fig. 1), and immediately following contraction, stimulation of the resting muscle generated 29·5 ± 5·1% of the force generated by control twitches before the contraction. Thus, most of the decline in voluntary force is accounted for by fatigue in the muscle. However, this decline in peripheral

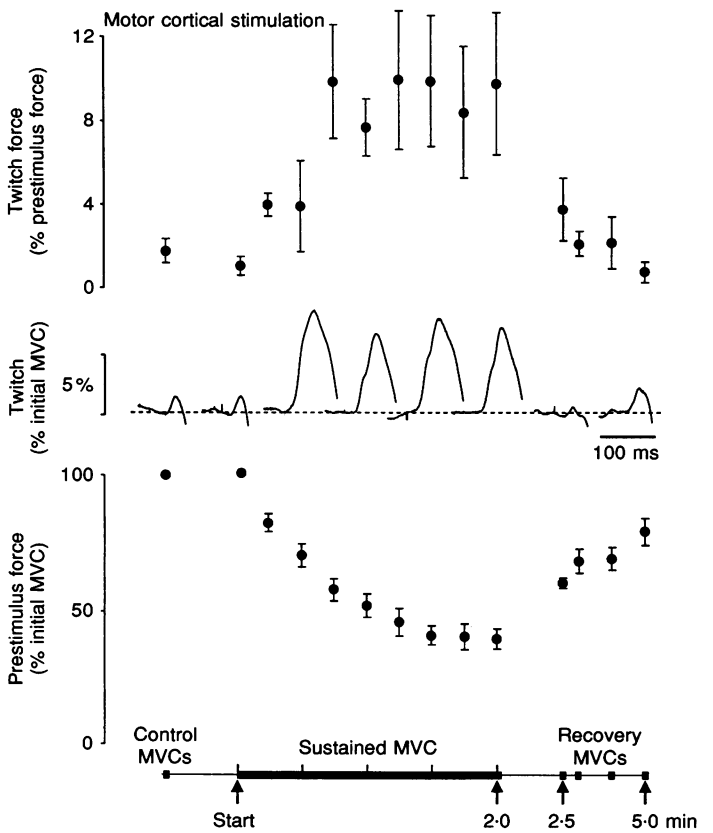

Figure 2. Reduction in voluntary force and increase in superimposed cortically evoked twitches during a sustained MVC

First point is the mean ± S.E.M. of five control values from each subject (same subjects and similar display as Fig. 2). The top panel shows the additional force resulting from magnetic stimulation of the motor cortex during the MVC. Twitch force is expressed as a percentage of the voluntary force at the time of stimulation. The initial value was measured during brief non-fatiguing MVCs. Twitch force increases during the sustained maximal effort and recovers quickly after it stops. The middle panel shows typical traces of elbow flexor torque for twitches recorded from a single subject. They come from stimuli during a control MVC, at the start and each 30 s during the sustained effort, and from two contractions during recovery. The bottom panel shows voluntary force prior to each stimulus and is expressed as a percentage of the maximal force produced when the muscle is not fatigued.

force-generating capacity was accompanied by an increase in the increment in force produced by the stimuli superimposed on the voluntary contraction. Thus, the mean force increment produced by the first stimulus during sustained contraction was 0·7 ± 1·7% of the control twitch force (before the sustained contraction), whereas the final superimposed twitch produced a much larger fraction (9·3 ± 7·9%) of the force of the twitch which followed the contraction. Figure 1 shows examples of control and superimposed twitches in one subject. On average, subjects initially had greater than 99% voluntary activation of biceps brachii and this dropped to about 90% by the end of a 3 min maximal effort. Despite the high initial level of voluntary activation (see Allen, Gandevia & McKenzie, 1995), central fatigue occurred in all subjects.

Magnetic cortical stimuli evoked muscle 'twitches' during a sustained MVC in separate studies in the same subjects. Again, as the MVC progressed, the increment in force generated by the stimulus increased (Fig. 2). At the end of the 2 min MVC, voluntary force decreased to 39·2 ± 9·1% of its initial maximum. At the beginning of the sustained MVC, the additional force evoked by cortical stimulation was 1 ± 1·1% of the voluntary output at the time of stimulation, whereas by the end it had increased to 9·8 ± 8·3%. With brief contractions during recovery, the increments in force evoked by stimulation returned to control levels. Because cortical stimulation contracts all elbow flexors, not solely biceps brachii, the size of the force increments cannot be compared directly with that obtained by motor-point stimulation. However, despite the continuing maximal voluntary effort, cortical stimulation increased motor cortical output and produced increased force from the elbow flexors. Thus, it is likely that the motor cortex was not optimally activated by volition at the moment of stimulation.

Voluntary activation during muscle fatigue maintained by ischaemia

Brachioradialis was maintained in its fatigued state at the end of the voluntary effort by inflating a sphygmomanometer cuff around the upper arm to block arterial

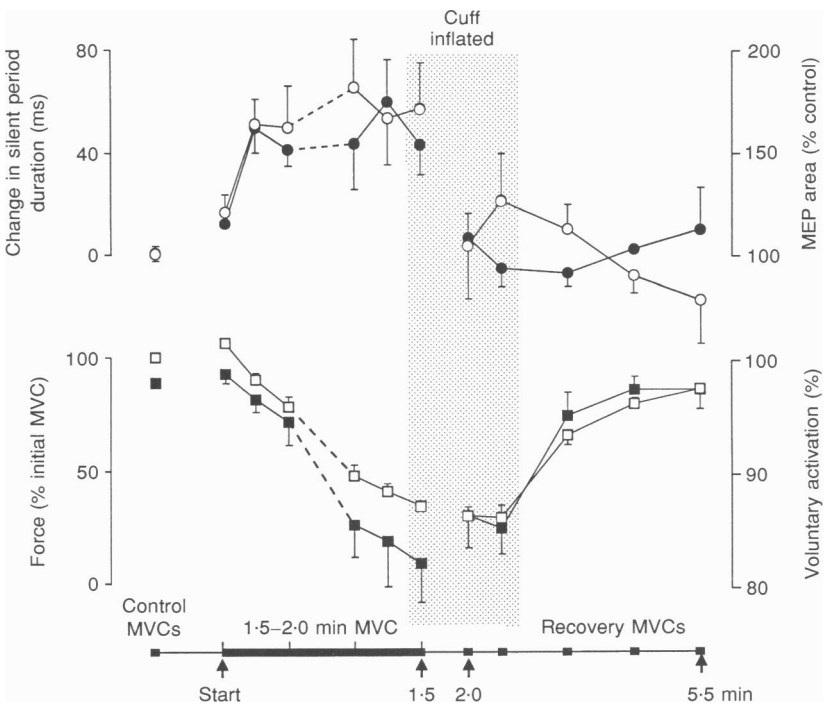

Figure 3. Effect of maintained ischaemia on recovery of silent period duration, MEP area, voluntary activation and voluntary force

Upper panel shows the EMG responses to cortical stimulation. Left axis shows the change in silent period duration (○) and the right axis the MEP area (●). Lower panel shows the maximal voluntary force (left axis, □) and voluntary activation (right axis, ■). Voluntary activation is estimated from the increment in force produced by cortical stimuli. It assumes that the MVC at the time of stimulation represents 100% activation and from this subtracts twitch force. This method of calculation will slightly underestimate the true level of voluntary activation (see Discussion). Shaded area indicates when blood flow was occluded. During the sustained MVC, silent period duration and MEP area grow, whereas voluntary force and voluntary activation fall. After the sustained MVC, ischaemia prevents recovery of force production by the muscle. However, silent period duration and MEP area recover quickly to control levels. Voluntary activation does not recover until blood flow resumes. Voluntary activation and force are scaled to emphasize their parallel changes.

supply ($n = 4$). During recovery with the cuff inflated, the increments in force evoked by the cortical stimuli which were superimposed on brief MVCs, stayed at the same level as at the end of the sustained effort (18·0 ± 7·1% voluntary force at MVC end and 15 ± 4·7% 1 min later). Neither voluntary activation nor force improved while the muscle was held fatigued (Fig. 3, lower panel). This contrasts with the behaviour of EMG responses to magnetic stimulation. Changes in the area of MEPs and the duration of the silent period during these experiments are illustrated in the upper panel of Fig. 3 and reported in detail in the preceding paper. Despite maintained ischaemia, evoked EMG responses quickly return to control levels at the end of the sustained contraction. Thus, the failure of voluntary activation during a sustained MVC (i.e. central fatigue) can be dissociated from the changes in the EMG responses to motor cortical stimulation.

DISCUSSION

Central fatigue refers to a progressive decline in the ability to activate muscles voluntarily and it is attributable to impairment at sites proximal to the neuromuscular junction. We have demonstrated, using twitch interpolation, that practised subjects generate close to their maximal evocable force in brief maximal efforts, but during sustained maximal efforts, they become progressively worse at activating biceps brachii. Thus, voluntary activation becomes less than optimal. However, twitch interpolation by motor-point stimulation gives no clue as to which levels of the central nervous system are involved in central fatigue. The EMG responses that result from transcranial magnetic stimulation reflect changes in the behaviour of the motor cortex as well as more distal parts of the motor pathway. Both excitatory and inhibitory responses to transcranial stimuli are altered during sustained MVCs (Taylor *et al.* 1996). We also report for the first time that cortical stimuli can generate additional muscle force despite maximal 'voluntary' activation. This suggests that subjects are sometimes unable to drive the motor cortex optimally by voluntary effort.

If stimulation of the motor cortex produces no force in addition to a subject's voluntary output, some part of the motor pathway at, or distal to, the site of stimulation is operating at its maximal capacity. However, when we stimulated the motor cortex during sustained maximal elbow flexion, additional flexor force occurred. No part of the motor pathway from the motor cortex to the myofibril was operating at its limit despite maximal voluntary effort. Thus, some degree of fatigue occurred 'upstream' of the output of the motor cortex.

Voluntary activation assessed with stimulation of the motor cortex cannot be quantitatively compared with that with motor-point stimulation. Many muscles acting at the elbow contract following high-intensity cortical stimulation. Thus, twitches of antagonist muscles may have added extension forces and decreased the apparent failure of activation. A second concern with transcranial magnetic stimulation in the estimation of central fatigue is the variability of the corticofugal activity produced by the stimulus and the difficulty of obtaining a control value. With motor-point or peripheral nerve stimulation, a supramaximal stimulus can be used so that the twitch of relaxed muscle gives a standard by which to judge the size of twitches superimposed on voluntary contractions. In contrast, magnetic stimulation of the cortex generates a sequence of corticofugal volleys, the timing and amplitude of which depend on cortical excitability (Edgley, Eyre, Lemon & Miller, 1990; Burke, Hicks, Gandevia, Stephen, Woodforth & Crawford, 1993). Even if identical cortical output could be produced, the actions of these volleys would vary according to the state of the α-motoneurones. Hence, the force elicited from relaxed muscles by a magnetic cortical shock is not useful in quantifying the level of voluntary activation. Here, we used the voluntary force at the time of stimulation as a measure of force available from the muscle and compared the cortically evoked twitch with it. Because of central fatigue, maximal voluntary force will actually be less than the maximal evocable force, so that any evoked twitch force would be a larger percentage of maximal voluntary force than it would be of the maximal evocable force. This would overestimate failure of activation but the effect is small. The error can be assessed from the values for voluntary activation obtained from motor-point stimulation of biceps brachii when the evoked increment is expressed as a fraction of that produced by stimulation of the same motor axons at rest. This technique showed approximately 90% activation by the end of a 3 min sustained MVC. If this level of central fatigue occurred in all elbow flexors, maximal voluntary force would underestimate maximal evocable force by 10% so that the 10% failure of activation demonstrated by magnetic stimulation by the end of a 2 min MVC would convert to ~9%.

Although the increment in force from cortical stimulation during sustained MVCs demonstrates suboptimal cortical output, it does not indicate whether decreased excitability of spinal motoneurones contributes to impaired voluntary activation during fatigue. H-reflexes and short-latency responses to stretch are depressed in muscles held ischaemic after fatiguing exercise (Garland, 1991; Balestra, Duchateau & Hainaut, 1992). This may be due to inhibition of the afferent volley rather than the motoneurone (Duchateau & Hainaut, 1993), but still suggests diminished spinal excitation by Ia afferents during a fatiguing contraction. Motoneurone firing rates are decreased and this is reflected in decreased maximal EMG in fatigued muscle (Garland & McComas, 1990). Yet, voluntary activation has been reported as optimal in some subjects despite evidence of decreased spinal excitability (Garland & McComas, 1990; Garland, 1991). Near the end of fatiguing contractions, we measured similar levels of voluntary activation with stimulation of the motor point and the motor cortex. This is consistent with changes in α-motoneurone excitability contributing little to the decline in force production during fatigue. However, because of the uncertainties associated with the size of the corticofugal volley produced by cortical

stimulation, we cannot quantify the degree to which changes in the motoneurone pool might impair force production.

Relationship between motor cortical behaviour and central fatigue

Merton (1954) stimulated the ulnar nerve and showed that the adductor pollicis could be fully activated by voluntary effort. As ischaemia of the fatigued muscle prevented recovery of voluntary force, he concluded that fatigue was in the muscle. Subsequently, more sensitive measurements of twitches superimposed on maximal voluntary contractions have shown that a muscle is rarely optimally activated (see introduction), and, although the majority of fatigue is in the muscle during short-duration high-intensity contractions, some central fatigue also develops. In our studies, when the fatigued muscles were held ischaemic, voluntary force did not recover but the changes in EMG responses to cortical stimulation did. Not only does this confirm that the peripheral fatigue in these tasks arises beyond the sarcolemma, but the recovery of MEP area implies that the motor cortex and motoneurones returned to their effectively non-fatigued state when the MVC stopped. However, stimulation of the cortex continued to elicit increments in force during the subjects' brief maximal efforts, and thus voluntary activation of the muscle remained less than optimal. This dissociation implies that: (1) the continued failure of voluntary activation occurred as a result of failure of drive to corticospinal neurones with normal excitability, and (2) this failure to drive the motor cortex was a direct consequence of the muscle remaining fatigued. We postulate that the mechanism of the failure of drive involves fatigue-related firing of afferents from muscles, joints and tendons. Analysis of the responses of individual subjects shows that the greatest changes in EMG responses to cortical stimuli occurred in subjects with the highest levels of voluntary activation, and this is an additional dissociation of changes in motor cortical excitability from failure of voluntary activation.

If muscle fatigue is maintained by ischaemia after a contraction or is generated by peripheral nerve stimulation, then muscle fatigue is not accompanied by voluntary effort. Previous studies have assumed that cortical output is normal under such conditions, so that changes in α-motoneurone behaviour have been attributed to segmental reflex effects (Bigland-Ritchie, Dawson, Johansson & Lippold, 1986; Garland & McComas, 1990). However, if afferents from fatigued muscle do influence voluntary drive to the motor cortex, effects of altered corticospinal output on motoneurone excitability cannot be excluded while muscle is fatigued. Even if voluntary activation is shown to be optimal for the fatigued muscle, this does not necessarily mean that corticospinal output is the same as that required for full activation of the unfatigued muscle. Thus, there is no indication as to whether changes in spinal motoneurone firing are the consequence of altered afferent feedback, altered descending commands or both.

In conclusion, motor cortical stimulation may provide insight into neural drive during maximal voluntary contractions. For the elbow flexors, but not all respiratory muscles (Gandevia *et al.* 1990), cortical output is close to optimal in brief maximal efforts. During sustained maximal efforts, cortical output becomes suboptimal. At the same time, the threshold for excitatory and inhibitory events within a restricted cortical region appears to decrease. However, the cortically evoked EMG responses in the fatigued muscle can return to normal while voluntary force and voluntary activation remain impaired. The demonstration of suboptimal cortical output during fatigue, and the dissociation of impaired voluntary activation from changes in the responses of the motor cortex, suggest that sites effectively driving the motor cortex may play a major role in the development of central fatigue.

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