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REVIEW ARTICLE

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Changes in muscle afferents, motoneurons and motor drive during muscle fatigue

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Abstract Fatigue is a reduction of maximal muscle force or power that occurs with exercise. It is accompanied by changes at multiple levels in the motor pathway and also by changes in the discharge patterns of muscle afferents. Changes in afferent firing can lead to altered perceptions and can also act on the efferent pathway. Changes in the motor pathway include slowing of motor unit firing rates during sustained maximal voluntary contractions (MVCs). Muscle responses to stimulation at different levels of the motor pathway also change. Transcranial magnetic stimulation of the motor cortex and stimulation of descending tracts in the spinal cord in human subjects show an increase in the response of the cortex and a decrease in response of the motoneuron pool during sustained MVCs. In addition, the silent period following magnetic stimulation is prolonged. During relaxation after fatiguing exercise, muscle responses to stimulation of the motor cortex are initially facilitated and are then depressed for many minutes, whereas responses to descending tract stimulation are initially depressed but recover over about 2 min. Although some of the loss of force of fatigue does occur through inadequate drive to the muscle, it is not clear which, if any, of the changes described in the cortex or the motoneurons are responsible for loss of maximal voluntary force and thus contribute to fatigue. Changes may be associated with muscle fatigue without causing it.

Key words Central fatigue · Muscle fatigue · Human · Motor cortex · Motoneuron

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Introduction

Fatigue is a reduction of maximal muscle force or power that occurs with exercise. In most tasks, most of the loss of force occurs because of changes within the muscle, but some loss of force can also occur because of changes within the central nervous system. Thus, the *total fatigue* induced by any task can only be measured by comparing the force or power of a maximal voluntary effort before and at the end of the exercise. In an isometric maximal voluntary contraction (MVC) loss of voluntary force occurs after a few seconds, but in submaximal or intermittent exercise, the onset of fatigue is more difficult to determine. However, few tasks can be carried out indefinitely and a finite endurance time for any task implies that the processes that underlie fatigue begin as soon as the task begins even if the loss of maximal voluntary force is not immediately apparent. In terms of sustained isometric contractions, perhaps only the very weakest contraction might be maintained for hours. With stronger submaximal contractions, the increasing amplitude and decreasing frequency content of the electromyogram (EMG) and the gradually increasing voluntary effort needed to maintain force output are markers of fatigue (e.g. Edwards and Lippold 1956; McCloskey et al. 1974; Jones and Hunter 1983; Bigland-Ritchie et al. 1986; Krogh-Lund and Jorgensen 1991; Löscher et al. 1996a).

In human subjects, supramaximal stimulation of the motor nerve can be used to divide fatigue into two components (Merton 1954). The first, exercise-related changes which are distal to the site of stimulation and which are seen as a decrease in twitch or tetanic force generated by the stimulus, is termed *peripheral fatigue*. Peripheral fatigue largely occurs within the muscle but may have components related to the neuromuscular junction or terminal branches of the motor axon. The second, exercise-related changes which occur proximal to the motor axons and which lead to a failure of voluntary activation and thus a decrease in maximal

voluntary force, is termed *central fatigue*. Central fatigue can be detected by supramaximal stimulation of the motor nerve during isometric MVCs and measurement of any increment in force generated by the stimulus (Belanger and McComas 1981; Hales and Gandevia 1988). An increment in force implies the presence of some motor units that have not been recruited by the voluntary effort or are not firing fast enough to achieve maximal force output. Voluntary activation is less than 100%. If the increment in force evoked by the stimulus to the motor nerve enlarges with exercise, then voluntary activation is decreasing. A progressive, exercise-related failure of voluntary activation indicates central fatigue (Gandevia et al. 1995). During a 3 min MVC of the biceps brachii muscle, voluntary activation falls from close to 100% down to 90%, whereas maximal voluntary force falls to around half its initial value (Gandevia et al. 1996).

During fatigue, contraction and relaxation of muscle fibres slow (e.g. Burke et al. 1973; Thomas et al. 1991; Fuglevand et al. 1999). Thus, contractions can become fused with lower firing rates in fatigued fibres than in unfatigued fibres (Edwards et al. 1975; Bigland-Ritchie et al. 1983b; Marsden et al. 1983). In such circumstances, lower rates of motoneuron firing and a decrease in EMG may continue to generate a weak force (Gooch et al. 1990). To hold a stronger level of force, additional motor units are recruited as those initially recruited become fatigued so that the firing rate of some motoneurons increases and of others decreases (Garland et al. 1994). In a sustained MVC, it is impossible to keep force output constant but decreased firing rates should still maximise force output. Thus, slowing of motoneuron discharge can be a useful adaptation to fatigue when continuation of unnecessary high firing rates might lead to block at the neuromuscular junction. However, whenever central fatigue can be demonstrated motor unit firing rates must be too low (Gandevia et al. 1995).

The simplest view of how motoneuron firing is controlled during voluntary contractions must include descending input to the motoneurons as well as input from muscle afferents and recurrent inhibition. All these inputs influence motoneuronal excitability and all interact at a segmental level by influencing the excitability of various interneurons (for reviews see Windhorst and Boorman 1995; McCrea 1996). Interactions will also occur at a supraspinal level where afferent inputs may modify descending drive. During sustained voluntary muscle contraction and fatigue, changes occur in each input to the motoneuron pool. This review will briefly describe the changes in afferent input that occur in fatiguing exercise and the way in which these affect proprioceptive sensations. It will then discuss the behaviour of motoneurons and the motor cortex during fatiguing contractions and how this behaviour relates to central fatigue.

Activity in muscle afferents and fatigue

Muscle afferents can be grouped by their function and by the conduction velocity of the fibres. Group Ia and some group II afferents innervate muscle spindles which lie in parallel to the muscle fibres and signal muscle length and changes in muscle length. Golgi tendon organs (group Ib afferents) are linked in series with a number of motor units and signal static and dynamic aspects of the force of contraction. Non-spindle group II fibres and many of the slower-conducting, thinly myelinated group III fibres are mechanically sensitive and respond to muscle contraction and/or stretch. Other group III fibres and group IV fibres respond to various metabolites produced during exercise or to noxious levels of mechanical strain.

Mechanisms through which fatigue might affect the firing of afferents arising from the contracting muscle include adaptation with repetitive firing and changes in the stiffness, temperature and chemical milieu of the muscle. Afferents from the muscle spindle are uniquely susceptible to alteration of sensitivity through the fusimotor system. The effects of fatigue on the discharge of afferents may depend on the fatiguing exercise.

During isometric voluntary contractions, muscle spindle firing initially increases as the fusimotor system is engaged along with α-motoneurons. However, recording in human subjects has shown that if the contraction is sustained at a moderate constant force, a decrease occurs in the firing of Ia fibres (Macefield et al. 1991). Animal studies have demonstrated a late increase in fusimotor drive as metabolites accumulate in fatigued muscle but it is not clear how this affects spindle firing in intact animals or humans (Ljubisavljevic and Anastasijevic 1994; Ljubisavljevic et al. 1994, 1997). Spindle firing will be quite different in exercise in which the muscle changes length. When the muscle is shortened, muscle spindles fire less and can be silenced with faster movements (Burke et al. 1978; Al Falahe et al. 1990). During eccentric contractions in which the muscle lengthens, spindles fire more than under isometric conditions. The effects of fatigue on spindle discharge during lengthening or shortening contractions are unknown.

After fatiguing contractions, Ia afferents show increased sensitivity to muscle stretch (Nelson and Hutton 1985) but these after-effects of contraction may be related to thixotropy of the intrafusal muscle fibres rather than to fatigue. Even when muscle is not fatigued the immediate history of contraction of the muscle is important to the sensitivity of muscle spindles (Gregory et al. 1988, 1998; Proske et al. 1993).

Individual Golgi tendon organs signal the tension produced by contraction of a sample of motor units. After an initial response to the onset of tension, tendon organ firing adapts quickly to signal ongoing force

(Macefield et al. 1991; Jami 1992). Although the firing of individual tendon organs is likely to alter during all fatiguing exercise because of changes in which motor units are being recruited to perform the task, it is likely that ensemble firing will continue to signal force production by the whole muscle. After strong contractions the stretch sensitivity of the tendon organs has been found to be decreased for 15–30 s and discharge rates to be decreased by 50% for the same level of force production (Hutton and Nelson 1986; Thompson et al. 1990). However, it is not clear how this effect arises or its influence on firing during sustained or intermittent fatiguing contractions. Presumably during a sustained MVC, as the force falls, tendon organ discharge rates will be lower than at the same force in a non-fatigued muscle.

Mechanically-sensitive non-spindle group II and group III afferents respond to muscle contraction, stretch or non-noxious pressure. They have low background discharge rates. During a sustained submaximal contraction, firing tends to decrease after the initial response to contraction. However, if the contraction continues for several minutes firing rates pick up again (Hayward et al. 1991). This late increase in firing is enhanced by ischaemia of the muscle. Stretch and pressure sensitivity of the afferents follow similar patterns. Enhanced sensitivity to mechanical stimuli can persist after 20 min of rest. Although some group IV afferents are also sensitive to mechanical stimuli, more of them, along with some group III afferents respond to mechanical stimuli only at noxious levels. During a strong 1–2 min contraction, mechanically-sensitive afferents have been found to fire initially and then drop their rates as muscle force drops whereas group IV afferents tend to increase firing rates later in the contraction as fatigue develops (Kaufman et al. 1983; Mense and Stahnke 1983; Kaufman and Rybicki 1987). The firing of these afferents is also enhanced by ischaemia. The introduction of metabolites such as potassium, lactic acid, bradykinin and arachidonic acid into the muscle activates many groups III and IV afferents and sensitises others (e.g. Mense 1977; Kniffki et al. 1978; Rotto and Kaufman 1988; Sinoway et al. 1993).

Changes in perception during fatigue

Muscle spindle afferents play an important role in the perception of joint movement and position. A recent study in cats showed that the ensemble firing of groups of muscle spindles became less distinctive for different size stretches when the muscle was fatigued (Pedersen et al. 1998). This suggests that the ability to detect imposed movements might be impaired, and one study in human subjects has reported a small increase in the displacement needed for movement detection with fatigue (Carpenter et al. 1998). Testing of position sense at the shoulder, knee and elbow after fatiguing exercise has shown small inconsistent changes (Marks and Quinney 1993; Sharpe and Miles 1993; Voight et al. 1996).

Judgements about force exerted are made in a complex way. Most subjects are biased by their sense of effort when they are asked to match heaviness or force and the sense of effort is related to the magnitude of descending commands (for reviews see McCloskey 1981, Gandevia 1996). During fatiguing exercise more motor units are recruited to produce the same force. The sense of effort is increased and objects feel heavier and forces produced are judged to be greater than they really are (e.g. McCloskey et al. 1974; Gandevia and McCloskey 1978; Jones and Hunter 1983). However, increasing effort and perception of force are not related in a one-to-one way (Jones and Hunter 1983). The force produced by maximal effort of a fatigued muscle is judged to be less than that produced by a maximal effort of the unfatigued muscle. The perception of force or heaviness is probably biased by signals of muscle tension from tendon organs. With instruction, it is possible for subjects to attend to muscle tension rather than effort (for review see Jones 1995). Furthermore, when tendon organs are desensitised after an MVC errors occur in the estimation of small forces. The errors are consistent with a perception of force signalled by the discharge of tendon organs (Thompson et al. 1990).

Late in fatiguing contractions, particularly those in which the muscle is ischaemic, pain develops in the muscle. This sensation probably arises from firing of the groups III and IV afferents that are sensitive to metabolic products and ischaemia. Intraneural microstimulation of groups III and IV afferents in human subjects have been shown to elicit deep muscle pain (Simone et al. 1994). Injection of hypertonic saline, capsaicin or levo ascorbic acid into the muscle results in similar pain (Kellgren 1938; Simone et al. 1992; Graven-Nielsen et al. 1997; Rossi and Decchi 1997).

Motoneuron activity during fatigue

During a sustained MVC, motor unit firing rates decrease (see Fig. 1). At the same time, the contraction and relaxation of muscle fibres slow and so that tetanic tension can be achieved by less frequent firing (Grimby et al. 1981; Bigland-Ritchie et al. 1983a, b; Marsden 1969, 1983). The mechanism by which the slowing of motoneuron firing occurs has been the subject of much investigation but remains unclear. The possible contributors to the changes in motoneuron firing include the intrinsic properties of the motoneurons, recurrent (Renshaw cell) inhibition, reflex inhibition or disfacilitation and changes in descending drive to the motoneuron pool.

With stimulation by intracellular or extracellular currents, motoneuron firing rates decline. During 4 min of injection of constant current, many cells which initially fire repetitively stop this discharge while others continue firing but at slower rates (Kernell and Monster

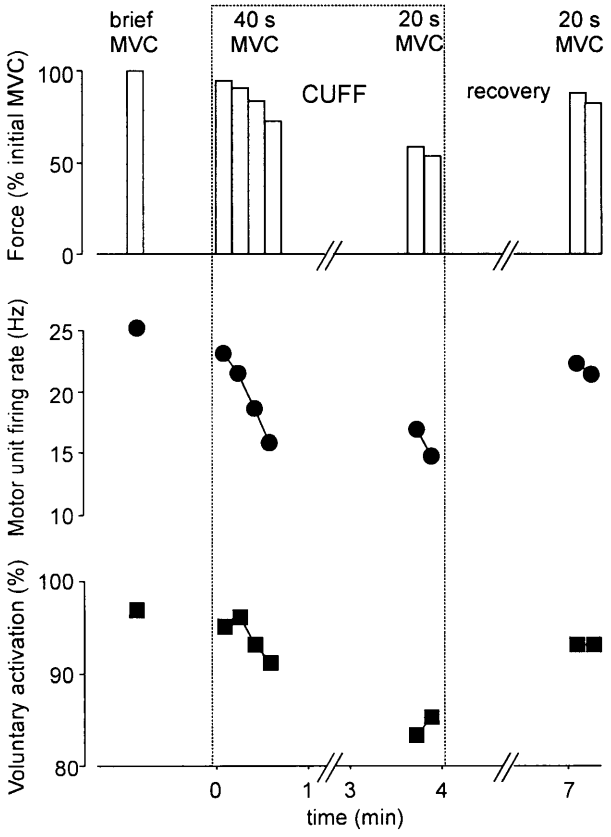

Fig. 1 Force, motor unit firing rates and voluntary activation during maximal voluntary contractions (*MVC*) of quadriceps muscle in human subjects. Data are replotted from Woods et al. (1987). While blood flow to and from the leg was blocked, subjects performed a 40 s maximal knee extension, rested for 3 min and then performed a 20 s MVC. After blood flow was allowed to resume and after a further 3 min rest, a final 20 s MVC was performed. Mean data are plotted for each 10 s period during the voluntary contractions. Force, motor unit firing rates and voluntary activation all decline during the initial fatiguing MVC, do not recover while the limb is ischaemic despite 3 min rest, but do recover with 3 min rest when blood flow resumes

1982a, b; Spielmann et al. 1993; Sawczuk et al. 1997). This process of "late adaptation" is more pronounced in the neurons innervating the larger, faster and more fatiguable motor units (Spielmann et al. 1993) and this is consistent with the changes in motor unit firing rates recorded during voluntary contractions. However, it is not clear if adaptation to synaptic inputs occurs in a similar way during voluntary activation. Furthermore, after injection of current, motoneurons recover given 2 min rest. In contrast, when the muscle is held ischaemic at the end of a MVC, motor unit firing rates have been shown to remain low despite a rest of 3 min (Woods et al. 1987; see Fig. 1). Blocking blood flow to and from the muscle prevents the recovery of muscle force and minimises the dispersion of metabolic products. It should allow recovery from any effects of repetitive firing of the motoneurons. This observation strongly suggests that feedback from afferents is important in controlling motoneuron firing rates during fatigue. The decreased firing rates that occur in voluntary contractions after muscle has been fatigued by electrical stimulation of the motor nerve also support this conclusion (Garland and McComas 1990).

Groups III and IV muscle afferents fire late in fatiguing contractions in response to the accumulation of metabolites and continue to fire when the muscle is held ischaemic after a contraction (Kaufman et al. 1984). Thus, these afferents are very likely to be involved in the control of motor unit firing rates. However, groups III and IV afferents from muscle have mixed excitatory and inhibitory effects on α-motoneurons with more frequent excitation in flexor and more frequent inhibition in extensor muscles (Kniffki et al. 1979, 1981a, b) so that the mechanism of slowing motoneuron rates is unclear. Although groups III and IV afferents may act at a segmental level, action at a supraspinal level could also slow motor unit firing by reducing descending drive.

The most direct reflex inputs come from the Ia afferents from muscle spindles which excite homonymous motoneurons through oligosynaptic pathways. Spindle discharge supports motoneuron firing during voluntary activation. Activation of spindle endings through vibration can increase motoneuron firing acutely during a fatiguing contraction but fails with longer applications (Bongiovanni and Hagbarth 1990; Bongiovanni et al. 1990). Direct recording of spindle firing during sustained voluntary contractions has indicated that discharge rates fall, although at around 30% MVC for 1 min, the contractions were minimally fatiguing (Macefield et al. 1991). Thus, disfacilitation of motoneurons through a decline in muscle spindle discharge might contribute to decreasing motor unit firing rates. Recent evidence in the spinalised rat suggests that the discharge of capsaicin-sensitive groups III and IV muscle afferents during fatigue may further decrease spindle support to the motoneurons by presynaptic inhibition of the Ia volley (Pettorossi et al. 1999). However, changes in presynaptic inhibition related to voluntary control of movement are also likely to alter the efficacy of this afferent input (e.g. Meunier and Pierrot-Deseilligny 1989; Iles 1996).

Tendon organs influence α and γ motoneurons through both inhibitory and excitatory interneurons. These interneurons receive input from other afferents including Ia afferents as well as through descending systems of control. During sustained voluntary contractions, there is a reduction in Ib inhibition to the contracting muscle. This may occur through presynaptic influences on the Ib afferents or through changes in inputs to the interneurons (Jankowska 1992; LaFleur et al. 1992). Activation of groups III and IV afferents through intramuscular injection of levo ascorbic acid further reduces Ib inhibitory action (Rossi and Decchi 1997; Rossi et al. 1999). Thus, Ib afferents are not likely to contribute to motoneuron slowing.

During voluntary contractions, the interaction of inputs to the motoneuron pool in intact animals and humans is complex. In addition to the changing descending and afferent inputs, qualitative changes in

motoneuron behaviour are also apparent during some voluntary movements. After-hyperpolarisation is greatly reduced during fictive locomotion and the induction of plateau potentials by serotonergic pathways from the midbrain might result in repetitive firing with minimal synaptic input (e.g. Brownstone et al. 1992; Kiehn and Ekn 1997, 1998; Gorassini et al. 1998). During fatigue, interactions at the segmental level mean that not only are afferent inputs from the muscle altered, but the pattern of their transmission to the motoneurons and the properties of the motoneurons also change.

Stimulation of motor pathways during exercise

One way to examine changes in motor control during fatigue in human subjects is to stimulate the motor pathway at different levels. Transcranial magnetic stimulation over the motor cortex has been shown to evoke complex descending volleys in corticospinal neurons (for review see Rothwell et al. 1991). The short-latency responses elicited in muscle are known as motor evoked potentials (MEP). Their size is influenced by excitability of cortical and corticospinal neurons, as well as by the state of the motoneurons and finally by the muscle fibre action potential. The axons of the corticospinal tract (and probably other descending tracts) can be stimulated directly by an electrical pulse passed between the mastoid bones or a magnetic shock over the back of the head (Ugawa et al. 1991, 1994; Gandevia et al. 1999). Given the relatively strong monosynaptic corticospinal connections to many motoneuron pools in human subjects (Palmer and Ashby 1992) and the lack of presynaptic inhibition at these synapses (Nielsen and Petersen 1994), this stimulus gives a very direct access to the motoneurons. Responses to descending tract stimulation are unaffected by intracortical changes in excitability but will alter with the excitability of motoneurons and with any peripheral change in the muscle fibre action potential. Stimulation of the peripheral motor nerve can demonstrate changes in the muscle fibre action potential. Comparison of the responses that the different stimuli evoke in the muscle allows identification of the level at which changes occur during fatigue.

Recent studies have demonstrated changes in the responses to transcranial magnetic stimulation both during and after exercise. Voluntary contraction immediately increases the excitability of the motor cortex so that stimulation evokes more and larger descending volleys and the size of the MEP recorded from the muscle is increased (e.g. Hess et al. 1987; Di Lazzaro et al. 1998). However, some of the increase is also due to increased responsiveness of α-motoneurons to the descending input (Ugawa et al. 1995; Kaneko et al. 1996).

If exercise continues, the MEP becomes even larger. This occurs both during sustained submaximal contractions and during sustained or intermittent MVCs (Mills and Thomson 1995; Taylor et al. 1996, 1999; Ljubisavljevic et al. 1996; McKay et al. 1996; Sacco et al. 1997). An increase in size of the MEP can be seen in the second pair of traces in Fig. 3. During sustained MVCs, the size of responses to stimulation of the descending tracts decreases. That is, α-motoneurons become more difficult to activate (Butler et al. 1999). The growth of the MEP despite this "inhibition" of the motoneurons indicates an increase in the output evoked from the cortex by the magnetic stimulus during fatigue. Although the MEP can double in size during a sustained MVC, its onset latency increases. This delay may reflect a delay in activation of inhibited motoneurons by the descending volleys (Taylor et al. 1999). During submaximal exercise, the site of change is less clear. To sustain a submaximal force as the muscle becomes

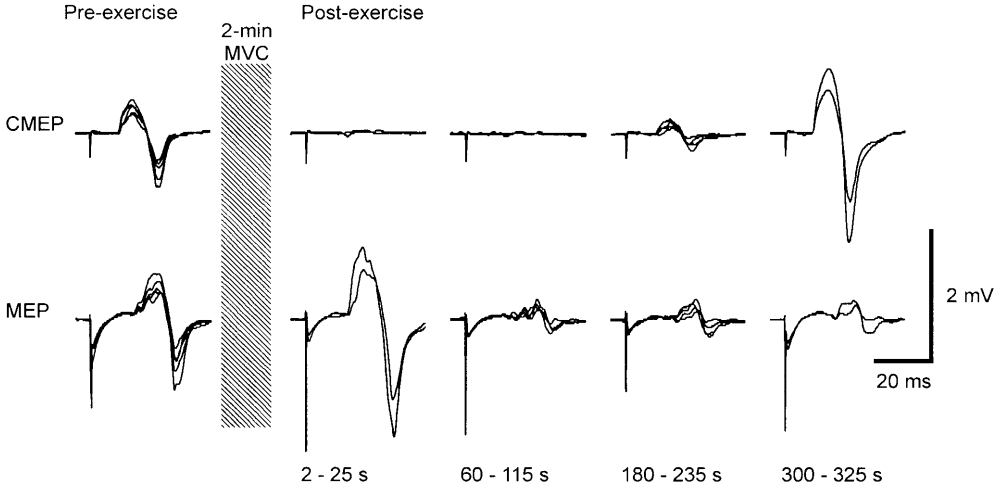

Fig. 2 Responses recorded from biceps brachii muscle after transcranial magnetic stimulation and stimulation of the descending tracts in one subject. Compound muscle action potentials were evoked by transcranial magnetic stimulation (motor evoked potentials, *MEP*) or by electrical stimulation of the descending tracts at the level of the cervicomedullary junction (cervicomedullary motor evoked potentials, *CMEP*). Responses were elicited in the relaxed muscle before and after a 2 min maximal elbow flexion. Whereas CMEPs are initially depressed after the maximal voluntary contraction (*MVC*) and recover over about 2 min, MEPs are facilitated immediately post-contraction and then become depressed for many minutes. Figure is reprinted from Gandevia et al. (1999)

fatigued, more motoneurons are recruited. This increased activation of motoneurons is accompanied by a perception of increased effort and probably reflects extra descending drive to the motoneurons. Responsiveness at both the cortical and spinal level are likely to increase. This is consistent with the observation that when MEPs increase in size during a sustained 20% MVC, responses to transcranial electrical stimulation also increase (Sacco et al. 1997).

After brief or fatiguing maximal or submaximal contractions, MEPs in the relaxed muscle are increased in size compared to those elicited before the contraction (Brasil-Neto et al. 1993; Liepert et al. 1996; Ljubisavljevic et al. 1996; Samii et al. 1996b) This facilitation lasts for 2–4 min and is indicative of a continuing increase in intracortical excitability (Samii et al. 1996b). Surprisingly, immediately after even brief MVCs responses to stimulation of the descending tracts at the level of the cervicomedullary junction are reduced (Gandevia et al. 1999). This reduction does not occur after tetanic stimulation of the peripheral nerve with its consequent reflex synaptic and antidromic activation of the motoneurons and thus may indicate a decreased efficacy of the corticospinal-motoneuronal synapse. The reduction recovers during 2 min of rest. These opposing changes of increased "excitability" of the cortex and decreased "excitability" of the motoneurons have also been demonstrated after repetitive transcranial magnetic stimulation of the motor cortex (Modugna et al. 1998). Post-contraction facilitation of the MEP is impaired in some patients with symptoms of fatigue. These include patients with depression, cerebellar degeneration and chronic fatigue syndrome although not those with prior polio (Samii et al. 1996a, 1997b, 1998).

If fatigue develops during exercise, the post-contraction facilitation of the MEP is followed by a depression in magnitude that can last for more than 30 min (Brasil-Neto et al. 1993; McKay et al. 1995; Zanette et al. 1995; Liepert et al. 1996; Samii et al. 1996b, 1997c; Gandevia et al. 1999). The duration of the depression is related to the intensity and duration of exercise and, thus, is correlated with fatigue (Samii et al. 1997c; Gandevia et al. 1999). It can develop after submaximal or maximal contractions. This effect reflects a decrease in cortical excitability that is confined to the muscle that has been contracting (McKay et al. 1995; Zanette et al. 1995; Ljubisavljevic et al. 1996; Samii et al. 1997a). The response elicited by stimulation of the descending tracts after a 2 min MVC has shown that the motoneurons are not inhibited at this time (Gandevia et al. 1999). Figure 2 compares the MEP and the response to descending tract stimulation in one subject after a 2 min MVC. The functional consequences of these changes in cortical and spinal excitability that are observed when muscles are relaxed after contractions are not clear. When transcranial magnetic stimuli are delivered *during* brief voluntary contractions performed in the recovery period, MEPs have recovered to control size by 15–30 s after the fatiguing exercise (Taylor et al. 1996, 1999). Similarly, the response to stimulation of the descending tracts has also recovered (Butler et al. 1999). Thus, the post-contraction facilitation and depression of the MEP and any decrease in the efficacy of corticospinal input to the motoneurons can be abolished by voluntary effort.

During a voluntary contraction, transcranial magnetic stimulation causes an EMG silence which follows the MEP. This silent period can last for more than 200 ms. It is thought to be the result of inhibition of cortifugal drive through the activation of inhibitory neurons within the cortex by the magnetic stimulus (e.g. Fuhr et al. 1991; Inghilleri et al. 1993; Triggs et al. 1993). Recurrent inhibition of the motoneurons is also likely to contribute to its early part. During a sustained MVC, the silent period increases in duration progressively (Taylor et al. 1996, 1999; Fig. 3). In contrast, during a sustained submaximal contraction, the silent period initially does not change in duration. Only when, with increasing fatigue of the muscle, subjects need to make an effort which is close to maximal to maintain the target force does the silent period increase in duration (Taylor et al. 1996; Sacco et al. 1997). Like the changes in the MEP, changes in the silent period are confined to the contracting muscle and recover quickly after the fatiguing exercise.

When the muscle is held ischaemic at the end of exercise so that metabolites are retained in the limb, motoneuron firing rates do not recover despite the pause in repetitive activation of motoneurons and contraction-sensitive afferents (see Fig. 1). Although H-reflexes have been shown to remain depressed (Garland and McComas 1990), responses to stimulation of the descending tracts are unaffected by the maintained ischaemia. Neither the inhibition of the responses seen during a sustained MVC nor the immediate post-contraction depression of responses in the relaxed muscle have been found to be maintained (Butler et al. 1999; Taylor et al. 2000). This strongly suggests that the firing of groups III and IV afferents in fatigue does not inhibit α-motoneurons. Depression of the H-reflex may result from inhibition of the presynaptic volley (Pettorossi et al. 1999). Furthermore, responses to cortical stimulation are also unaffected by maintained muscle ischaemia. Both the increased duration of the silent period and the increased size of the MEP recover to control levels whether or not blood flow to the muscle is restricted (Gandevia et al. 1996; Butler et al. 1999). In Fig. 3, the third pair of traces from the top shows recovery of the MEP and silent period despite maintained ischaemia.

Association of changes in motoneurons and motor cortex with central fatigue

During maximal voluntary efforts, stimulation of the motor nerve can often elicit a small increment in force output from the contracting muscle (e.g. McKenzie and Gandevia 1991; Allen et al. 1995; Herbert and Gandevia

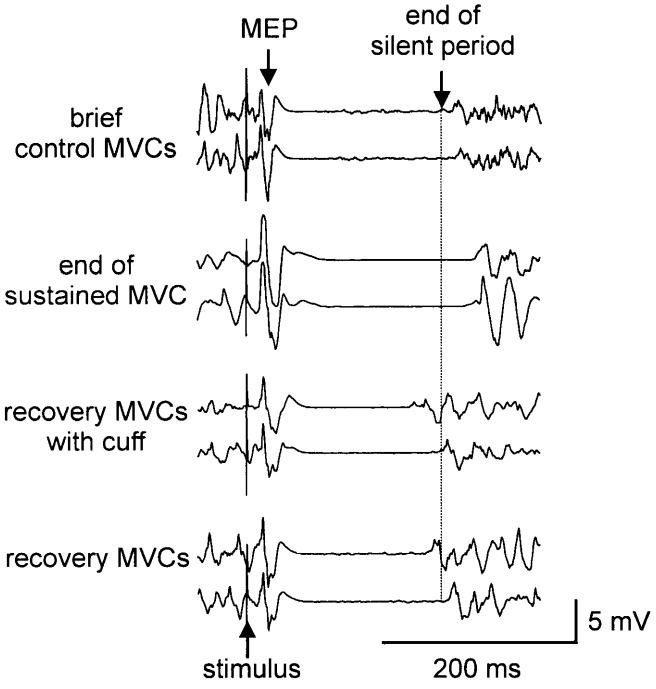

Fig. 3 Responses to transcranial magnetic stimulation recorded from brachioradialis muscle in one subject. All stimuli were delivered during maximal voluntary elbow flexions. In each trace, the MEP can be seen after the stimulus artefact and is followed by a long silent period. In this experiment, control data were recorded while the subject performed brief (2–3 s) MVCs of the elbow flexor muscles (*initial two traces*). The subject then performed a sustained fatiguing 2 min MVC. At the end of the contraction the arm was held ischaemic so that the muscle was not allowed to recover despite relaxation. Blood flow was allowed to resume after 1 min of recovery. During the ischaemic and non-ischaemic recovery, stimuli were delivered during brief MVCs. During the sustained MVC, the MEP increased in size and the silent period increased in duration (*second pair of traces*). Both the MEP and the silent period recovered to control levels after 30 s of rest despite maintained ischaemia. For definitions see Fig. 2

1996). This means that voluntary drive at the moment of stimulation is not sufficient to activate the muscle fibres maximally. During many kinds of exercise, including sustained MVCs, this increment in force elicited by nerve stimulation increases. This progressive failure of voluntary activation indicates the development of central fatigue and means that some of the decrease with fatigue in the force that subjects generate by a maximal voluntary effort is due to processes within the central nervous system (for review see Gandevia et al. 1995; Gandevia 1998). Central fatigue occurs with submaximal as well as maximal exercise. If subjects perform a sustained submaximal contraction until they can no longer voluntarily maintain the target force, an electrically evoked contraction of the muscle can generate forces above the target level (Löscher et al. 1996b). Although the muscle can still generate the target force, task failure occurs through a failure of voluntary drive. Failure of voluntary drive also occurs in the diaphragm during inspiratory resistive loading. Here it has been shown that the task is stopped voluntarily with no or minimal peripheral fatigue (McKenzie et al. 1997).

Transcranial magnetic stimulation over the motor cortex can also produce increments in force during contractions of some muscle groups. If increments are seen during maximal voluntary efforts it indicates that motor cortical output at the moment of stimulation is not maximal (Gandevia et al. 1996). The stimulus elicits corticofugal output additional to that being produced voluntarily. Furthermore, it indicates that voluntary output is not sufficient to activate motoneurons or muscle fibres maximally. The extra descending input to the motoneurons evokes extra force from the muscle. No site in the pathway from motor cortex to the muscle is working maximally. When the increments in force evoked by transcranial magnetic stimulation are measured during a sustained MVC, they increase in size. Thus, some central fatigue occurs because of processes that occur "upstream" of motor cortical output (Gandevia et al. 1996). However, this supraspinal fatigue does not appear to be related either to the changes in the motor cortex represented by the growth of the MEP and the duration of the silent period, or to the decreased responsiveness of the α-motoneurons. When the muscle is held ischaemic after a sustained MVC, the EMG responses to stimulation of the motor cortex and descending tracts recover, whereas motor unit firing rates and voluntary activation remain low until blood flow is allowed to resume. This is true for voluntary activation measured by both peripheral nerve stimulation and by stimulation of the motor cortex (see Fig. 1; Woods et al. 1987; Gandevia et al. 1996). Thus, although the responsiveness of the motor cortex and motoneurons to stimulation appears normal (Gandevia et al. 1996; Butler et al. 1999), drive to the motoneurons is suboptimal and could be improved by extra corticofugal volleys. Similar findings have been reported when nociceptive muscle afferents are activated by infusion of hypertonic saline into the muscle (Zedka et al. 1999). Thus, one action of groups III and IV muscle afferents may be at a supraspinal site to reduce descending drive to the motoneurons.

Despite the additional information about the behaviour of motor cortical cells and motoneurons gained by stimulation of the motor cortex and the descending tracts, it is still not clear how motoneuron firing rates are controlled in response to their changing properties during fatigue. The depression of motoneuronal responses during sustained MVCs and the changes in the motor cortex are not directly linked to the state of the muscle and probably result from the repetitive activation of neurons in the motor pathway. On the contrary, the effect of muscle ischaemia in holding motor unit firing rates low remains compelling evidence that feedback from the muscle is important in the control of motoneurons. However, the importance of afferent inputs may lie not in their reflex effects on the motoneurons but in their supraspinal actions. Here it should be remembered that although groups III and IV afferents are activated

and sensitised in the ischaemic muscle, other afferents may be better suited to dynamic adjustments of descending drive. For example, signals from tendon organs or those group III and non-spindle group II afferents which respond with contractions could be used to titrate voluntary drive to counter variations in force output from the muscle.

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