Neural control in human muscle fatigue: changes in muscle afferents, moto neurones and moto cortical drive

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ABSTRACT
To understand the neural factors which contribute to fatigue, it is not satisfactory to regard fatigue as occurring only when a task can no longer be performed. Changes in muscle afferent feedback, moto neuronal discharge, moto cortical output, and perceived effort develop well before an endurance limit in limb muscles. During sustained maximal contractions the discharge of moto neurones declines, commonly to below the level required to produce maximal force from the muscle whose contractile speed is usually slowed. Thus, some 'central' fatigue develops. Recent findings using transcranial stimulation have revealed that the moto cortex is one site at which suboptimal output develops during human muscle fatigue. There is a need to study the reflex effects on moto neurones and the excitability of the moto cortex in experimental animals, as well as to apply rigorous methods to assess these processes in voluntary exercise in human subjects.

Keywords central fatigue, cortical stimulation, fatigue, inhibition, moto neurones, moto cortex, muscle spindles, reflexes.

Received 2 April 1997, accepted 16 June 1997

Fatigue is a time-dependent exercise-induced reduction in the maximal force generating capacity of a muscle. During a maximal voluntary contraction fatigue begins rapidly. It arises more slowly for weaker contractions but occurs even if a submaximal voluntary force is sustained. Manifestations of fatigue reflecting largely peripheral factors include the reduction in maximal force and power and also the slowing of muscle relaxation which often accompanies sustained high-intensity effort. However, the central nervous system is involved not only in driving moto neurones but also in the increased tremor of the exercising limb, the recruitment of muscles initially uninvolved in the task and the subjective increase in effort. Some of these 'central' features may disrupt performance more than the reduction in maximal muscle force. The increased perceived 'effort', a signal requiring the moto cortex, reflects the need to recruit more moto neurones and muscles, and to drive them harder (for review see Jones 1995, Gandevia 1996). However, the interaction between reflex inputs, moto neuronal properties and supraspinal factors during fatigue is not well understood (for review see Enoka & Stuart 1992, Fuglevand 1996).

There is a question as to what extent the available moto neurones are recruited in fatigue. Studies using sensitive forms of twitch interpolation (Hales & Gandevia 1988) have not confirmed the original prediction of Merton (1954) that moto units are fully recruited and discharging at rates sufficient for fusion at the onset of maximal voluntary isometric contractions. For several muscles in which identical methods have been used voluntary activation is usually above 85–90% during attempted maximal voluntary isometric contractions (including for the diaphragm) (e.g. Allen et al., 1993, Allen et al. 1995, Herbert & Gandevia 1996, for review see Gandevia et al. 1995). Averaged across one fatiguing 'maximal' contraction in several subjects, or several contractions in one subject, voluntary activation declines significantly. This is defined as 'central fatigue' (Gandevia et al. 1995). Its development should contribute to the decline in discharge rate of moto neurones during fatigue.

For maximal voluntary isometric contractions the moto neurone discharge rates after the initial peak force are about 20–50 Hz for upper limb muscles with variation between subjects and muscles (e.g. Bellemare et al. 1983). If the voluntary contraction continues for more than a few seconds, discharge rates decline and approach a plateau towards 60 s (e.g. Grimby et al. 1981, Bigland-Ritchie et al. 1983a, Gandevia et al. 1990).

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This decline in rate assists the output from the muscle because relaxation times for whole muscle usually lengthen during strong isometric contractions and thus lower discharge frequencies produce the same fraction of maximal force (Bigland-Ritchie et al. 1983b). The decline in moto unit rate has been called muscle ‘wisdom’ (Marsden et al. 1983) but given that the firing may fall too low to maintain full activation of the muscle and that muscle relaxation rate sometimes increases in fatigue (e.g. McKenzie & Gandevia 1991), the term is not appropriate. More irregular firing of moto neurones develops with fatigue (Gandevia et al. 1990, Garland et al. 1994). In fatiguing anisometric contractions moto units show variable discharge patterns (Miller et al. 1996).

An extreme example of the predominance of central factors in fatigue occurs when a task cannot be continued (‘task failure’) but the muscles can produce the required force when stimulated electrically. This possibility was recognized by Mosso, Waller, Lombard and others last century and a recent report supports the proposition: when subjects could no longer voluntarily plantarflex the ankle at 30% maximum, the force could be maintained by electrical stimulation of the nerve innervating the plantarflexors (Loescher et al. 1996a).

This phenomenon is likely to depend on the subjects, the degree of maximal voluntary drive for the muscle group, the peripheral muscle properties, and the intensity of the fatiguing task.

In this brief review I consider the effects of feedback from muscle and the role of supraspinal sites on the changing behaviour of moto neurones during fatigue. Much of the data derive from isometric exercise in which electrophysiological measures can be made without interference from movement. Deficiencies in techniques used to assess human muscle fatigue are mentioned.

**MUSCLE AFFERENT INPUTS DURING MUSCLE FATIGUE**

During maximal voluntary contractions of a human muscle, the input from specialized muscle mechanoreceptors (innervated by large-diameter afferents) and from chemosensors and nociceptors (innervated by small-diameter afferents) will change. Based largely on data from animal studies, the probable changes in muscle afferent input are shown in Figure 1.

### Muscle spindle afferents

During isometric contractions the fusimotor system recruits human muscle spindle endings but their discharge frequency declines with time if the contraction is sustained beyond 1–2 s and fatigue develops (e.g. Macefield et al. 1991). Neglecting the effect of presynaptic inhibition, spindle-mediated facilitation of moto neurones will decline during a sustained isometric contraction, i.e. disfacilitation develops. However, in concentric contractions the spindle afferents’ role will differ because fusimotor drive may be insufficient to overcome muscle shortening and spindle afferents in the contracting muscle may fall silent (Burke et al. 1978, Al Falahe et al. 1990). In eccentric contractions spindle input may be accentuated as animal studies indicate that spindle afferents increase their responsiveness to stretch during fatigue (e.g. Nelson & Hutton 1985, Hayward et al. 1991).

### Golgi tendon organ afferents

Tendon organs respond to active muscle forces generated by the moto units which insert into them (Jami 1992, cf. Hulliger et al. 1995). However, their discharge adapts during the first seconds of force production. Thereafter, the ensemble input from tendon organs is

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**Figure 1** Schematic representation of the likely changes in muscle afferent input during a sustained maximal voluntary contraction of a limb muscle. Data compiled mostly from studies in animals.
well suited to signal force produced by the muscle. The stretch sensitivity of individual tendon organs varies with fatigue (Hutton & Nelson 1986, Thompson et al. 1990, Hayward et al. 1991). The practical consequences of changes in stretch sensitivity of muscle spindle and tendon organ afferents during muscle fatigue are uncertain, particularly as their reflex effects may be attenuated at a spinal level, and because the effects are small compared with those in the more numerous group III and IV afferents (Hayward et al. 1991).

Non-spindle group II and groups III and IV muscle afferents

During muscle fatigue the discharge of small-diameter muscle afferents (groups III and IV) increases according to the temperature, chemical and the mechanical environment of their free nerve endings (e.g. Paintal 1960, Kniffki et al. 1978, Kaufman et al. 1983, Hayward et al. 1991). They have little or no background discharge and, because they are so numerous, small changes in their discharge will produce massive increases in their ensemble input to the central nervous system (CNS). Following fatiguing contractions most group II non-spindle afferents and group III mechanosensitive afferents have increased discharge rates, increased sensitivity to stretch and palpation but reduced responsiveness to additional contractions (Hayward et al. 1991). Group III afferents increase their discharge by about 1 Hz within the first 10 s of an isometric contraction but this is not sustained (Sinoway et al. 1993). Metabolites produced by prolonged muscle contraction reduce the mechanical thresholds of group III and IV afferents (e.g. Rotto et al. 1988). Some group III afferents discharge during slow locomotion in decerebrate cats (Pickar et al. 1994), but there are no data on the discharge of human group III and IV afferents in voluntary contractions. Some recordings in animals may be of limited guidance because contractions are produced by electrical stimulation without distributing it in a more natural asynchronous way to motor units.

Changes at the moto neuronal level during muscle fatigue

Intrinsic moto neuronal properties, reflex inhibition and disfacilitation, Renshaw cell inhibition, and insufficient drive from supraspinal sites may all contribute to the decline in moto unit firing rate in fatigue. Theoretically, it would be optimal if each moto neurone had its output individually controlled to produce the highest force from its muscle fibres depending on their contractile state. However, a compartmentalized reflex machinery which modulates each moto neurone's output based on local reflex inputs from group III and IV afferents surrounding its muscle fibres is highly unlikely. Systematic changes in the intrinsic properties of moto neurones with increasing threshold and size (Kernell & Monster 1982, Binder & Mendell 1990), along with nonhomogeneous distribution of reflex inputs within the moto neurone pool, will aid optimization of the whole pool's output.

An intrinsic property of moto neurones which could mediate the decline in moto neuronal discharge rates during fatigue is that firing rates adapt when moto neurones are stimulated with intracellular or extracellular current (e.g. Kernell & Monster 1982, Spielmann et al. 1993, Sawczuk et al. 1995). The reduction in firing rate (‘late adaptation’) is appropriately more pronounced for type F than type S moto units. Additional changes develop with repeated bursts of stimulation (Spielmann et al. 1993). The precise pattern of moto neuronal discharge can influence the force produced (see Bevan et al. 1992), but whether the observed increase in irregularity of firing actually increases force production in fatigue is unclear.

In intact preparations, moto neuronal behaviour during fatigue will be modulated by: (i) supraspinal commands to interneurones and moto neurones; (ii) control by brainstem serotonergic pathways of the ‘gain’ and possible bistable behaviour of moto neurones (e.g. Hultborn & Kiehn 1992); (iii) classical reflex and recurrent inputs to α- and γ-moto neurones; (iv) presynaptic modulation specific classes of reflex inputs to moto neurones (e.g. Jankowska 1992). Some of these factors are shown in Figure 2. To determine how the whole system will behave during fatigue is daunting because of the many inputs to the moto neurone pool, their combined monosynaptic and nonmonosynaptic effects on moto neurones, and their changes in size with time and with fatigue. Some reflex effects on moto neurones are considered briefly below (see Windhorst & Boorman 1995).

The connection between Ia afferents and the moto neurone is well studied but its behaviour during fatigue is not established. Indirect evidence reveals that muscle afferents provide significant excitation to the moto neurone pool (up to 30%) during sustained fatiguing isometric contractions (e.g. Gandevia et al. 1990, Macefield et al. 1993). However, presynaptic inhibition will attenuate the reflex effectiveness of any Ia input in some movements, at least in the lower limb (e.g. Capaday & Stein 1987, Meunier & Pierrot-Deseilligny 1989). Effective transmitter depletion at the Ia-moto neurone synapse (homosynaptic depression) may also develop (e.g. Curtis & Eccles 1960, Bongiovanni & Hagbarth 1990, Lev-tov & Pinco 1992).

As indicated earlier, muscle spindle discharge decreases during fatiguing static contractions in human subjects (Macefield et al. 1991), irrespective of any reflex excitation of fusimoto neurones (e.g. Ljubisavljevic
et al. 1992, Ljubisavljevic & Anastasijevic 1994, Ljubisavljevic et al. 1995). It is not established whether late increases in fusimotor firing in the cat are relevant to voluntary fatigue of human muscles. As the unloading reflex seems reduced in fatigue of human finger extensor muscles, any excitation of homonymous fusimotor neurones is insufficient to maintain the prefatigue levels of spindle-mediated facilitation. Any attenuation of ‘stretch’ reflexes will reduce the ability of spinal reflexes to oppose length changes (e.g. Hagbarth et al. 1995). However, methodological difficulties abound in the interpretation of studies of human reflexes in fatigue (see below).

Golgi tendon organ afferents are traditionally believed to reflexly reduce moto neurone output (Jami 1992). The picture is more complex in fatigue because of spindle afferent convergence on Ib inhibitory interneurones (see Jankowska 1992), such that Ib effects can be excitatory (e.g. Pratt 1995). In a sustained contraction, the Ib inhibitory postsynaptic potentials in moto neurones decline so that the gain of force feedback is reduced (Zytnicki et al. 1990, see also Kirsch & Rymer 1987).

While there seems no doubt that inputs from small-diameter muscle afferents reflexly alter moto outputs, the way it is achieved in fatiguing voluntary contractions is unresolved. The inputs will act at spinal and supraspinal sites. In the anaesthetized cat the spinal machinery exists to mediate inhibition among synergist muscles during fatigue (Hayward et al. 1988). Many have implied that these afferents exert their inhibitory effects at a spinal level (e.g. Bigland-Ritchie et al. 1986, see also Garland & McComas 1990) but the evidence is circumstantial. The decline in moto neurone discharge in strong contractions is present when muscles contract voluntarily after fatigue produced by electrical stimulation (Garland & McComas 1990), but absent when muscle afferents are blocked by local anaesthesia (Gandevia et al. 1990, Macefield et al. 1993).

Additional inhibition of moto neurones derives from Renshaw cells which receive excitatory inputs from moto neurones, particularly those of high threshold (Hultborn et al. 1988) as well as descending and peripheral inputs. In the cat the rapid discharge of Renshaw cells declines nonlinearly when moto neurone frequency declines so that their output can contribute to the adaptation of moto neurone rates during fatigue (Windhorst & Boorman 1995). Studies using indirect H-reflex methods in humans suggest that recurrent inhibition (and/or prolongation of the after-hyperpolarization) increases in maximal efforts (Kukulka et al. 1986), but declines in submaximal ones (Loescher et al. 1996b).

MOTOR CORTICAL AND SUPRASPINAL FACTORS IN MUSCLE FATIGUE

In fatiguing exercise, there are changes in central enkephalinergic, dopaminergic and serotonergic systems (e.g. Hoffman et al. 1990, Bailey et al. 1993, Persson et al. 1993, cf. van Hall et al. 1995). These presumably control vigilance and motivation, pain and its tolerance, while other neuroendocrine changes alter availability of substrates for muscle contraction. Manipulation of these factors should alter centrally mediated components of fatigue. A challenge is to isolate direct roles for these systems in both central fatigue and subsequent task failure.

Given the behavioural changes that accompany muscle fatigue (including changes in subjective effort, attention and pain), there must be many associated supraspinal changes measurable at an electrophysiological and biochemical level, but, as for events at a spinal level, it is difficult to determine which are sec-
ondary to peripheral fatigue and which contribute to central fatigue and eventual task failure. As indicated earlier, intrinsic moto neuronal, spinal and supraspinal factors could all generate central fatigue. However, we must examine the roles the moto cortex and supraspinal drive play in the decline in moto neurone firing frequency in fatigue. Particularly in humans, cortical output monosynaptically excites most spinal moto nuclei (e.g. Porter & Lemon 1993) without the effects of presynaptic inhibition (Nielsen & Petersen 1994). Hence supraspinal centres which alter corticomoto neuronal output will affect moto neurones in a most direct way.

Some recent studies have focused on the development of changes in the corticospinal system during fatigue. In monkeys trained to fatigue their elbow flexors there were variable changes in the discharge of corticomotor neuronal cells (Maton et al. 1994). In humans performing repetitive submaximal contractions, the size and area of electromyographic (EMG) responses to transcranial magnetic stimulation of the cortex decline after cessation of exercise (Brasil Neto et al. 1993, McKay et al. 1995, Zanette et al. 1995). We recently examined the changes in the EMG and force responses to transcranial stimulation of the motor cortex during sustained maximal voluntary isometric contractions of the elbow flexors lasting 1–3 min (Figure 3). Voluntary activation was monitored during exercise with twitch interpolation from the moto point and by measurement of force twitches evoked by transcranial stimulation (Gandevia et al. 1996, Taylor et al. 1996).

The silent period in the EMG following high-intensity cortical stimulation lengthened by about 50 ms from its control value (see also McKay et al. 1996) within 30 s of a maximal voluntary contraction or when an initially submaximal contraction later required maximal effort. The short-latency excitatory response to cortical stimulation appeared to increase in maximal contractions by about 50% (Figure 3a). One factor which could underlie this is the recruitment of additional corticospinal cells, not simply those with a projection to the elbow flexors, but others with a divergent projection to several arm muscles including the elbow flexors (Mills and Thomson 1995). If present, such progressive spread of recruitment would lead to the contraction of additional related muscles during the task, a phenomenon commonly observed with strong isometric efforts (Figure 4b).

Three pieces of evidence suggest that these changes were focal cortical events. Firstly, the changes could not be prevented by vibration of the muscles designed to make up for diminished spindle input. Secondly, if the sustained maximal contraction involved one muscle group, the cortical ‘silent period’ lengthened only in that group and not in nearby muscles. Finally, the growth of the excitatory response to cortical stimulation was not present when the corticospinal axons were stimulated distal to the cortex at the cervicomedullary junction.

Despite their robustness, changes in moto cortical excitability probed by artificial stimulation do not directly affect the central fatigue during sustained efforts. First, these changes in cortical excitability recovered within 30 s, even when the contracting elbow flexors were maintained ischaemic, a manoeuvre assumed to maintain the chemically mediated input via group III and IV afferents (see above). However, during ischaemia maintained after a sustained maximal contraction with a sphygmomanometer cuff, central fatigue persisted. Thus, moto cortical stimulation at the start of

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**Figure 3**

(a) Biceps brachii EMG during maximal voluntary contractions (MVCs) of elbow flexors. Upper five traces during brief control MVCs. Middle traces during a sustained 2 min MVC and lower traces during recovery. The first vertical dashed line shows time of the transcranial magnetic stimulation. Second vertical dotted line shows the time of return of continuous EMG and marks the end of the silent period in control trials. This lengthens during the sustained MVC and recovers quickly. The moto evoked potential (MEP, just right of dashed line) is variable but grows during the sustained contraction and recovers rapidly. (From Taylor et al. 1996.) (b) Force during the sustained MVC shown in panel (a). Arrows indicates the time of a cortical stimulus. Corresponding force increments are shown sequentially in a raster below. (Panel (b), unpublished records from Gandevia et al. 1996.)
the maximal contraction increased ongoing voluntary force by about 1%, but as central fatigue evolved, the same cortical stimulus produced progressively more force (Figure 3b). Hence, the voluntary motor output became progressively less than optimal. The evoked force increments were followed immediately by a decrement: its duration increased with that of the silent period but its amplitude diminished due to the slowing in muscle relaxation rate. The presence of cortically evoked ‘twitches’ late in the prolonged contractions show that no site distal to the motor cortex was working at its absolute maximum. The most parsimonious explanation for the development of central fatigue is not that it reflects changes in motor cortical excitability, but that drive effectively ‘upstream’ of cortical output declined (such that it could be augmented by superimposed artificial stimulation). This reduction in drive may be mediated by supraspinal effects of group III and IV afferents. If so, a crucial question is not why motor neurones fail to fire fast enough but why the motor cortex does not work as hard as it could. The failure of motor cortical drive to remain sufficient during fatigue raises questions about the role of the cortical and subcortical areas projecting to the primary motor cortex and other cortical areas with direct corticospinal projections.

TECHNICAL LIMITATIONS TO THE STUDY OF HUMAN MUSCLE FATIGUE

Experimental methods are no better than their weakest link. Because it is difficult to make the ‘cleanest’ measurements to deduce changes in neural control during strong contractions, experimenters have often accepted conditions which are not ideal. Three examples are given to highlight problems that occur in measurements of force, EMG, and motor neuronal ‘excitability’. Any conclusions about central control of muscle during fatigue must survive rigorous assessment of the methods on which they are based.

(i) Twitch responses to electrical stimulation are used to monitor peripheral fatigue. The twitch is very susceptible to the ‘history’ of contraction with fatigue usually reducing the twitch more than tetanic force (e.g. Edwards et al. 1977). If submaximal stimulus intensities are used (e.g. with knee extensors) the same motor units are not tested with each stimulus. Furthermore, with fatigue, such a stimulus will activate fewer motor axons because of activity-dependent reductions in axonal excitability (Bergmans 1973). Hence, for force measurements in fatigue stimulus intensities must be supramaximal.

(ii) Levels of EMG are commonly used as surrogate measurements of neural drive to the fatiguing muscle. Problems arise because the size of the intracellular action potential is not constant with fatigue (Sandercoc et al. 1985): maximal compound muscle action potentials initially growth and then decline during a sustained contraction (Hicks et al. 1989, see also Fuglevand et al. 1993). The latter change reflects slowing in the conduction velocity of muscle fibres. Furthermore, surface EMG will not necessarily measure ‘drive’ to one muscle as it is easily contaminated by activity in nearby muscles.

(iii) Tests of motor neuronal excitability can only be conducted indirectly with H-reflexes and stretch and unloading responses. None of these reflexes is purely monosynaptic in humans (Burke et al. 1984) and reflex size must therefore depend on the activity of interneurones. These reflexes could only provide valid tests of motor neurone behaviour if exactly the same afferent volley were evoked and all other reflex and descending inputs were unaltered. These conditions are not easily achieved. Ideally the reflex behaviour of single motor units should be tested, as has been done for firing properties during fatigue (e.g. Enoka et al. 1989, Gar-
land et al. 1994). Finally, any apparent change in reflex behaviour must be interpreted in the light of the known reduction in moto neurone firing rate during sustained isometric contractions.

CONCLUSIONS

With intense brief exercise, force is likely to depend largely on muscle and biomechanical factors. If maximal exercise continues beyond about 10 s, central factors including deficient drive ‘upstream’ of moto cortical output attenuate performance and eventually stop it. If contractions are sufficiently intense, the threshold of the moto cortex appears reduced for both inhibitory and excitatory processes. There is a need to study in experimental animals the neural processes controlling activity of moto neurones and moto cortical neurones, and to apply rigorous methods to assess these processes in voluntary exercise in humans.

The author’s laboratory is supported by the National Health and Medical Research Council and the Asthma Foundation of New South Wales. Comments on the manuscript by Janet Taylor, Jane Butler and Gabrielle Allen are gratefully acknowledged. I regret that space limitations prevented citation of additional references.

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