The neurobiology of muscle fatigue: 15 years later

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Synopsis This brief review summarizes progress that has been made in the study of muscle fatigue since a review published 15 years ago (Enoka RM, Stuart DG. 1992. Neurobiology of muscle fatigue. J Appl Physiol 72:1631–48.). The present review first discusses progress on the four themes identified in the 1992 review and then describes a new approach that can be used to identify the functionally significant physiological adjustments that occur during fatiguing contractions. As described in the previous review, it is currently not possible to develop a comprehensive model of muscle fatigue because the prevailing mechanism that impairs performance varies with the characteristics of the task that is being performed. An alternative approach is to focus on the mechanisms that cause failure to complete the task. This task-failure approach involves comparing two performances and identifying the adjustments that limit the rate for the more difficult condition. With this approach, initial studies have demonstrated that the time to failure of a sustained contraction can be influenced by such variables as the type of load supported by the limb, the posture of the limb, and the group of muscles involved in the task. The challenge is to identify the mechanisms that enable these different variables influence the time to task failure.

Introduction

The purpose of this brief review is to provide an update on progress made in the study of muscle fatigue since an earlier review (Enoka and Stuart 1992). At the time of the previous review, there was great excitement in this field, as expressed at international symposia in London (1980), Paris (1990), Amsterdam (1992), and Miami (1994). Due to the breadth of interest in this topic and the variety of viewpoints expressed by the participants, however, there was little consensus on some fundamental issues and the literature was quite confusing. The 1992 review attempted to summarize the field and to provide a framework for subsequent studies on muscle fatigue.

At the time, there was much discussion about the definition of muscle fatigue, without which there can be no agreement on how to measure fatigue and, therefore, how to identify the contributing mechanisms. An early definition was that fatigue represents an inability to maintain the required or expected force (Edwards 1981). Some investigators suggested, however, that it is necessary to indicate that fatigue is a transient phenomenon caused by physical activity, which led to the definition of fatigue as a reduction in the force-generating capacity of the neuromuscular system that occurs during sustained activity (Bigland-Ritchie et al. 1983). With this definition, fatigue was readily quantified as the decrease in the peak force of an isometric contraction during a maximal voluntary contraction (MVC). Because this definition accommodated neither the changes occurring during movement nor the sensations that accompanied fatiguing contractions (Jones 1993; McComas et al. 1995), Enoka and Stuart (1992) proposed that fatigue be defined as an acute impairment of performance that includes both an increase in the perceived effort necessary to exert a desired force and an eventual inability to produce this force.

Within this framework, the previous review identified four themes that synthesized much of the work being conducted on muscle fatigue: task dependency, relation between muscle force and endurance time, muscle wisdom, and perception of effort. The principle of task dependency states that there is no single cause of muscle fatigue and that the dominant mechanism depends on the details of the task being performed. This principle acknowledges that fatigue can be caused by multiple mechanisms and that the primary cause of fatigue varies across tasks. Significant variables that influence the prevailing mechanism include subject motivation, pattern of muscle activation, intensity and duration of activity, and continuous or intermittent activity. Enoka and Stuart (1992) suggested that a productive

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approach for subsequent studies would be to identify the boundary conditions that distinguished the domain of each mechanism. The second theme addressed the exponential relation between the time that a task can be sustained and the force of the contraction. It was suggested that studies conducted at different intensities of contraction would likely identify the contributions by different mechanisms; this concept is closely related to the issue of task-dependency. The third theme was "muscle wisdom", which refers to the reduction in the discharge rate of motor units to match the change in the mechanical state of the muscle during the fatiguing contraction. There was considerable interest in the mechanisms that mediated the decrease in discharge rate and the extent to which this adjustment was distributed across the population of motor units. The fourth theme was the sense of effort and the changes that occur during sustained contractions. That review discussed the derivation of the sense of effort from the corollary discharge and described observations arising from experimental and clinical studies.

Progress since 1992

Since the paper by Enoka and Stuart (1992) and the international symposium in Miami (Gandevia et al. 1995), the rate of progress in the field has not matched expectations expressed in the early 1990s. There has been progress, of course, and this has been summarized in several reviews (Allen 2004; Gandevia 2001; Nybo and Secher, 2004; Fitts 2006; Meeusen et al. 2006; Nordstrom et al. 2007). Because the purpose of the present Symposium was to honor the contributions of Professor Douglas G. Stuart to neurobiology, however, the current review briefly describes progress in the field based on the scheme outlined by Enoka and Stuart (1992).

Definition of muscle fatigue

In contrast to the 1992 suggestion that the study of muscle fatigue should address both the perceived effort and decline in force that occurs during sustained activity, the field has largely focused on the latter. The most common definition of fatigue in the past decade is that it corresponds to an exercise-induced reduction in the ability of the muscle to produce force or power, whether or not the task can be sustained. As a consequence of this definition, fatigue often begins soon after the onset of sustained activity, even though an individual can continue performing the task. This distinction, however, is not appreciated by many investigators who continue to confound the literature by describing the duration over which a task can be sustained as the "point of fatigue". Although the impairments that contribute to fatigue will eventually limit the capacity of the individual to continue that task, fatigue and task failure should be distinguished (Bigland-Ritchie and Woods, 1984).

At least since the seminal work of Angelo Mosso (Di Giulio et al. 2006), the typical strategy used by experimentalists has been to determine whether the mechanism responsible for fatigue is located in the exercising muscle or in the nervous system. Such an approach has resulted in distinguishing between central and peripheral fatigue or neural and muscular fatigue. These descriptors lead to further confusion in the literature because there is no obvious boundary between the nervous system and muscle, and adjustments that occur at one location can have a profound effect upon those that evolve at the other. For example, how should the increase in afferent feedback in response to changes in the metabolic and mechanical state of the muscle during a fatiguing contraction be classified? Is this a central or a peripheral mechanism? Due to the mutual interaction of central and peripheral mechanisms, the dichotomy is not particularly useful and should be avoided (Nybo and Secher 2004).

Task dependency

The influence of the task on the prevailing mechanism remains the central issue in the study of muscle fatigue. The significance of task can be illustrated by briefly describing three examples. First, consider the changes that occur in fatigability with advancing age. Baudry et al. (2006) had young and old adults perform a series of maximal shortening and lengthening contractions with the dorsiflexor muscles. The decline in peak torque during both types of contractions was greater for the old adults, indicating that they were more fatigable than were the young adults. In contrast, Hunter et al. (2005) found that old men could sustain an isometric contraction with the elbow flexor muscles at a force that was 20% of maximum for a longer duration than could young men. At the conclusion of the submaximal contraction, the two groups of men exhibited a similar amount of fatigue, as indicated by equivalent declines in the maximal force that they could exert. Hence, the old men were less fatigable when they performed this task. This comparison indicates that the influence of age on muscle fatigue depends on the task that is being performed.

The second example of task dependency is the difference in fatigability between men and women. When men and women perform fatiguing contractions under normal conditions, women are usually capable of a longer time to task failure (Hunter and Enoka 2001; Clark et al. 2005; Hunter et al. 2006). The typical explanation for this sex difference is that because men are often stronger than women, they experience a greater occlusion of blood flow and different metabolic activity when the task is performed at the same relative intensity (% of maximum). Consistent with this explanation, the time to failure when the elbow flexor and plantarflexor muscles performed the force task (20% MVC force) was similar for men and women who were matched for strength (Hatzikotoulas et al. 2004; Hunter et al. 2004a) and there was no difference in the time to failure of the force task (25% MVC force) between the sexes for the knee extensor muscles when blood flow was occluded (Clark et al. 2005).

In contrast, when men and women of equal strength performed intermittent contractions (6-s contraction, 4-s rest) to a target force of 50% MVC force with the elbow flexor muscles, the time to task failure was longer for the women (Hunter et al. 2004b). Despite the two groups of subjects exerting a similar net muscle torque, electromyogram (EMG) activity increased more rapidly for the men and they reached task failure sooner than did the women. Similarly, the decline in MVC torque of the elbow flexor muscle after a series of MVCs was greater for men than for women, and this difference was not attributable to a greater impairment of voluntary activation during the fatiguing contractions (Hunter et al. 2006). Furthermore, because the amount of fatigue experienced by men and women during intermittent contractions is similar when blood flow is occluded (Russ and Kent-Braun 2003), the sex difference is likely caused by one or more factors located within the muscle. One possibility is that the relative contributions of the metabolic pathways used to supply ATP during a muscle contraction can differ for men and women during fatiguing contractions and contribute to differences in the time to task failure (Russ et al. 2005).

The third example of task dependency involves the role of afferent feedback delivered by group III-IV afferents in modulating the output from the spinal cord during fatiguing contractions. The receptors innervated by group-III afferents are sensitive to changes in both the mechanical state and the metabolic environment of the muscle, whereas group-IV afferents are most responsive to the chemical milieu in the muscle. A common strategy used to study the influence of fatigue on the feedback delivered by group III-IV afferents is to compare the recovery of function, when blood flow is normal and when it is impeded. When blood flow is occluded, the metabolites that accumulate in the fatigued muscle will continue to provide a stimulus that sustains the discharge of group III-IV afferents (Hayes et al. 2006). With this approach, Bigland-Ritchie et al. (1986b) found that the depression of discharge rate for motor units in the *biceps brachii* after a sustained MVC did not recover during the 3 min that blood flow was occluded but did recover to control values within 3 min after blood flow was restored. This result led to the conclusion that a peripheral reflex mediated by group III-IV afferents from the fatigued muscle contributed to the decrease in discharge rate during this protocol. Conversely, feedback from the afferents that are sensitive to an occlusion of blood flow did not contribute to the decrease in voluntary activation of muscle after an MVC that was sustained by the elbow flexor muscles for 2 min (Taylor et al. 2000; Butler et al. 2003).

The central connections of group III-IV afferents, however, can evoke diverse responses. Martin et al. (2006) examined the contribution of feedback by group III-IV afferents to the fatigue experienced during sustained 2 min MVCs with the elbow flexor and extensor muscles. The protocols involved comparing the amplitude of potentials evoked in muscle with transmastoid stimulation of the corticospinal tract during the MVCs and during recovery, when blood flow to the muscle was occluded and when it was not. When a muscle is kept ischemic, the accumulated metabolites enhance the feedback delivered by group III-IV afferents (Kaufman et al. 1984; Rotto and Kaufman 1988; Hayes et al. 2006). By comparing the amplitude of the evoked potentials in the presence and absence of enhanced feedback by groups III-IV afferents, it is possible to estimate the influence of these afferents on the excitability of motor neurons. When the fatiguing contraction was performed with the *triceps brachii* muscle, the amplitude of the evoked response decreased during the MVC and remained depressed during ischemia, but recovered within 15 s after the removal of ischemia. The amplitude of the evoked potentials in *triceps brachii* also decreased after the fatiguing contraction was performed with the elbow flexor muscles. In contrast, the amplitude of the evoked potentials in *biceps brachii* increased after a fatiguing contraction with *triceps brachii*. These results indicate

that group III-IV afferents depressed the excitability of the motor neurons of *triceps brachii*, but facilitated those that innervate *biceps brachii*. Thus, the contribution of feedback from group III-IV afferents to the decline in motor unit activity during a fatiguing contraction probably differs for flexor and extensor muscles.

From these three examples, it is obvious that the issue of task dependency discussed by Enoka and Stuart (1992) remains a major obstacle to formulating a coherent model of muscle fatigue. Some generalizations, however, do seem warranted. For example, the capacity of the nervous system to sustain an adequate activation of the muscles involved in the task appears to become impaired as the duration of the activity increases (Löscher et al. 1996; Søgaard et al. 2006). Conversely, the fatigue that occurs during brief maximal efforts appears not to be caused by an inadequate activation (Bigland-Ritchie et al. 1982). Furthermore, the insufficiency of the activation can be exacerbated by such conditions as a decline in the levels of blood glucose and exercise in hot environments (Nybo and Nielsen 2001; Nybo 2003). Nonetheless, most of the work that has demonstrated differences across tasks has not identified the boundary conditions that trigger a change in the prevailing mechanism, as suggested by Enoka and Stuart (1992).

Muscle wisdom

The concept of muscle wisdom arose from the observation that the force exerted by a muscle declined more rapidly when it was evoked with stimuli delivered at a constant rate compared with a gradual decrease in the stimulation rate (Jones et al. 1979; Marsden et al. 1983). The rationale was that the decrease in stimulation rate mimicked the decline in discharge rate of motor units that occurs during voluntary contractions. The functional advantages of the decrease in discharge rate include a reduction in the likelihood of activation failure (e.g., axonal branch-point failure, impairment of excitation–contraction coupling) and optimization of the activation rate to the contractile state of the muscle. Because the relaxation rate of the twitch decreases and the duration of the twitch increases as fatigue occurs, the same degree of fusion in the force during a tetanus can be achieved with a lower rate of activation. Although the mechanism responsible for the slowing down of the rate of discharge during a sustained voluntary contraction is not known, Marsden et al. (1983) entertained the idea that there were possible contributions by reflexes, motor neuron properties, and descending drive.

Two lines of evidence, however, suggest that muscle wisdom is not an overall activation strategy during fatiguing contractions. First, electrical stimulation of a hand muscle with a rate that declined from 30 Hz to 15 Hz evoked a more rapid decline in force than that elicited by a constant rate of 30 Hz (Fuglevand and Keen 2003). The explanation for the opposite result to that obtained in the original muscle-wisdom experiments was that a stimulation rate of 30 Hz is more similar to the discharge rates of motor units during strong contractions than is the 80–100 Hz used previously (Jones et al. 1979; Marsden et al. 1983). The finding of a lesser decrease in force with a constant stimulation rate indicates that the decline in stimulation rate did not optimize muscle activation and actually contributed to the decrease in force during the fatiguing contraction. Second, the discharge rate of motor units during submaximal fatiguing contractions does not always decrease and those units that are recruited during the contraction invariably exhibit an increase in discharge rate (Nordstrom and Miles 1991; Garland et al. 1994; Carpentier et al. 2001; Kuchinad et al. 2004). Taken together, these results suggest that the adjustments experienced by motor units during a fatiguing contraction vary across the population, presumably depending on the details of the task being performed.

The task-failure approach

Due to the task dependency of muscle fatigue, it is not possible to answer the question "What causes muscle fatigue?" Enoka and Stuart (1992) recognized this limitation and they suggested that by delineating the boundary conditions associated with a change in the prevailing mechanism progress could be made toward a comprehensive model of muscle fatigue. Instead, we have adopted another strategy. Following the advice of Professor Stuart, we decided to ask a different question when we could not answer the question about the cause of muscle fatigue. For about the past 8 years we have addressed the question, "What causes task failure?" Our recent work has focused on the mechanisms that limit the duration a task can be sustained. Because multiple adjustments occur during fatiguing contractions, we have attempted to identify the rate-limiting adjustments by comparing the changes that occur during two tasks. Such an approach emphasizes the functional significance of the changes that occur during fatiguing contractions because it identifies the

adjustments that limit the duration of the more difficult task. In addition to examining one group of subjects performing two similar tasks, comparisons made with the task-failure approach also can include two groups of subjects sustaining the same task and one group of subjects performing the same task before and after an intervention. To illustrate the task-failure approach, we briefly describe work on the influence of load type on the duration that a task can be sustained, and address how this effect can be altered by varying the posture of the limb or the muscle group that performs the task.

Load type

Our initial studies compared two tasks that both involved sustained isometric contractions and required the same submaximal net muscle torque and joint angle yet differed in the type of feedback provided to the subject and the type of load supported by the muscles (Hunter et al. 2004; Maluf and Enoka, 2005). In one task, referred to as the force task, the limb was attached to a restraint and the subject was required to maintain a constant force for as long as possible while viewing force feedback on a monitor (Fig. 1). In the other task, referred to as the position task, the subject supported an inertial load that was equivalent to the force exerted during the force task and was required to maintain a constant joint angle for as long as possible while viewing position feedback on a monitor. The time to failure of the position task was briefer in the position shown in Fig. 1C when a hand muscle (first dorsal interosseus) performed the two tasks at a target force of 20% of maximum (Table 1).

The difference in the time to failure was caused by a more rapid recruitment of the motor unit pool during the position task as indicated by a quicker increase in the amplitude of the surface EMG for the hand muscle (Fig. 2). Because the net muscle torque exerted by each subject was similar for the two tasks, the load on the muscle fibers did not differ initially. As the fatiguing contractions progressed, however, the more rapid recruitment of motor units during the position task should have reduced the load experienced by the active muscle fibers. Consequently, the more rapid recruitment of motor units during the position task was not caused by a more substantial decrease in the force produced by the active muscle fibers, which suggests that the difference in recruitment rate was a consequence of the control strategy used by the central nervous system (CNS). To underscore this interpretation, there was no difference in the time to failure or the rate of motor unit recruitment for the force and position tasks, when the target force exceeded the upper limit of motor unit recruitment (60% of maximal force) for the muscle (Table 1).

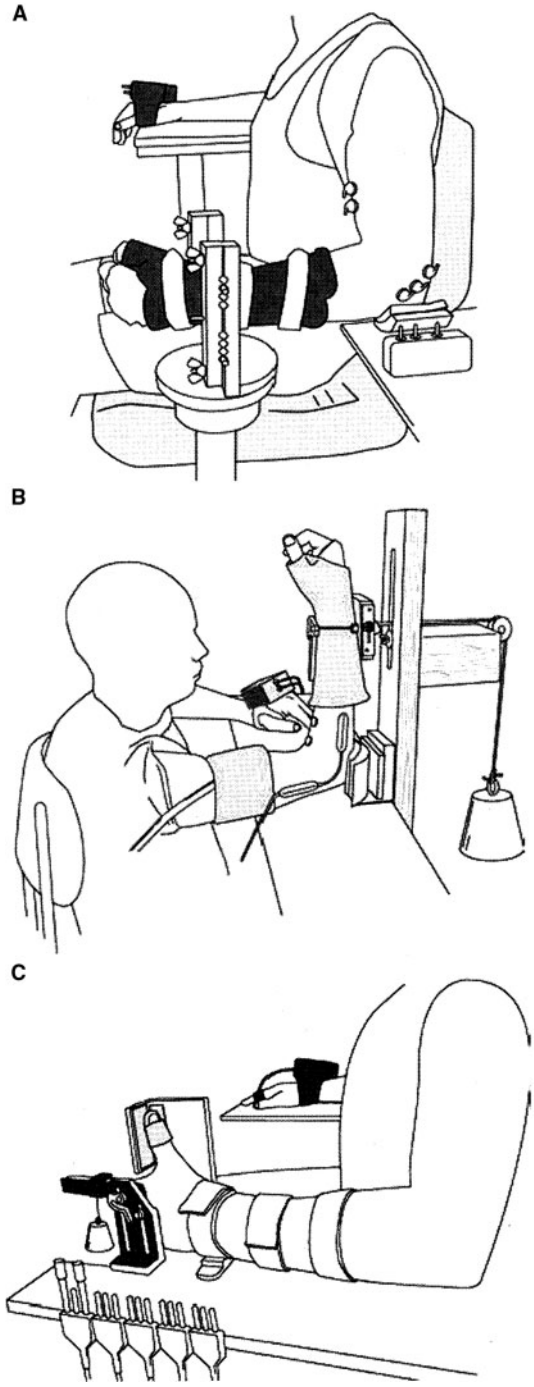

Fig. 1 Limb position and test muscle for task-failure studies. Experimental arrangement for the force (**A**) and position (**B, C**) tasks as performed by the elbow flexor (**A, B**) and first dorsal interosseus (**C**) muscles. Reprinted from Maluf and Enoka (2005).

Table 1 Time to failure for the force and position tasks shown in Fig. 1

	Target force (%)	Force task (s)	Position task (s)	Ratio (%)
Elbow flexors (Fig. 1A)	15	1402 ± 728	702 ± 582	51 ± 26
Elbow flexors (Fig. 1B)	20	609 ± 250	477 ± 276	77 ± 21
1st dorsal interosseus (Fig. 1C)	20	983 ± 1328	593 ± 212	63 ± 28
1st dorsal interosseus (Fig. 1C)	60	93 ± 41	86 ± 31	96 ± 17

Note. Data (mean ± SD) from Hunter et al. (2002), Rudroff et al. (2005) and Maluf et al. (2005). Target force is expressed as a percentage of the peak force achieved during a maximal voluntary contraction. The Ratio (%) indicates the duration of the position task relative to the force task.

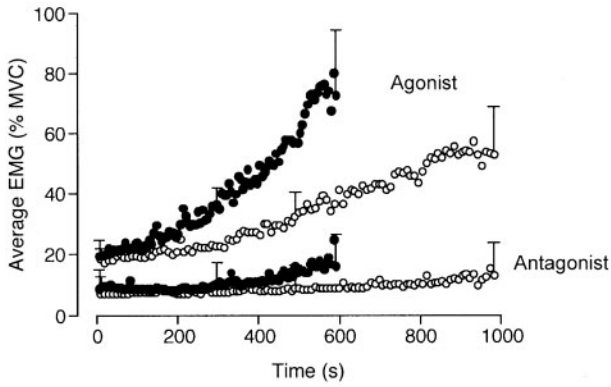

Fig. 2 Amplitude of the electromyogram (EMG) during the force (open circles) and position (filled circles) tasks performed with the first dorsal interosseus (hand) muscle. The antagonist muscle was the second palmar interosseus. Data from Maluf et al. (2005). The 95% confidence intervals are shown in the middle and at the end of each set of average EMG data.

The behavior of single motor units during the force and position tasks was examined directly by Mottram et al. (2005). They recorded the discharge of the same motor unit in *biceps brachii*, when subjects sustained the two contractions with the same load (~20% MVC force) for about 3 min. The contraction was not performed to task failure so that it was possible to record the discharge of the same motor unit in a single experimental session. The average discharge rate (13 pps) and coefficient of variation for discharge rate (22.8%) were similar at the beginning of the two contractions, but discharge rate decreased more and the coefficient of variation increased more during the position task. Furthermore, Mottram et al. (2005) observed the recruitment of the same 26 units during the two tasks, and six different motor units during the force task and 20 different motor units during the position task. Thus, the synaptic inputs received by the motor unit pool differed during the two tasks, presumably due to the difference in load type, even though the magnitude of the load and the net muscle torque was the same. One possibility is that position task involved heightened activity in reflex pathways to maintain the position of the limb (Hunter et al. 2004). Consequently, the briefer duration for the position task was attributable to a more rapid activation of motor units in the muscle.

In the performance of everyday activities, humans encounter loads with a wide variety of mechanical properties. Pressing against the rigid arm of a chair to stand up is an example of interacting with a purely static resistance, while carrying a glass of water requires careful compensation for the inertia of the load to avoid spilling the water. Although we transition from interacting with one type of load to another with minimal effort, it is likely that there occurs some compensation in the motor system to manage these different mechanical properties. Indeed, a series of studies examining motor learning have demonstrated that the motor system is exquisitely sensitive to load compliance (Shadmehr and Mussa-Ivaldi 1994). The influence of type of load on the time to task failure during a sustained contraction is consistent with this sensitivity. However, the magnitude of the effect of load type on the difference in the time to failure for the force and position tasks was much greater than expected. The observation that type of load can influence time to task failure across different limbs and postures indicates that the change in the motor unit activity to accommodate the different loads may be a common strategy used by the nervous system (Maluf and Enoka 2005). To date, however, few studies have examined the influence of load type on either the characteristics of the motor output or the underlying control strategy (Buchanan and Lloyd, 1995; Mackey et al. 2002).

Limb posture

Time to task failure can also depend on the posture of the limb due to differences in the load placed on accessory muscles and changes in the relative contributions to the net muscle torque by the synergist muscles. When the force and position tasks are performed with the elbow flexors while the elbow is at a right angle, the time to task failure differs, depending on the orientation of the shoulder joint (Rudroff et al. 2006). The difference in the time

to task failure for the force and position tasks is much greater (Table 1), when the upper arm is vertical (Fig. 1A) than when the shoulder joint is flexed so that the upper arm is horizontal (Fig. 1B). When the upper arm was vertical, it was abducted from the trunk by about 0.4 rad and it was necessary for the subjects to activate the external rotator muscles at the shoulder (*supraspinatus*, *infraspinatus*, *teres minor*) to prevent internal rotation of the arm about the shoulder joint during the position task, but not during the force task when the arm was attached to the apparatus. Accordingly, Rudroff et al. (2007) found that the rate of increase in average EMG of the rotator cuff and posterior deltoid muscles was greater during the position task compared with the force task and that the load experienced by the accessory muscles contributed to the much greater reduction in the time to failure of the position task. This effect was not observed when the forearm was vertical and there was no difference in the load placed on the accessory muscles during the two tasks. This finding indicates that the demands experienced by postural muscles can limit the duration a task can be sustained.

Even changing the orientation of the forearm, while maintaining the same shoulder and elbow joint angles can dramatically influence the relative duration of the force and position tasks (Rudroff et al. 2005, 2007). Presumably, this effect arises either directly from a change in the mechanical stability at the joint, requiring a greater amount of muscle activity to maintain the posture or, more precisely, a mechanically less efficient pattern of activation of the muscle is required. Alternatively, the influence of changing the posture of the forearm might arise indirectly from the different engagement of muscles that occurs when the pronation–supination posture of the forearm is changed (Buchanan et al. 1989), such as might be mediated by the reflex pathways between the elbow flexor muscles (Naito et al. 1996, 1998; Riley et al. 2006). By this means, the demand on the CNS to maintain drive to the active muscles may vary with the change in posture (Le Bozec and Bouisset 2004).

Muscle group

When performing sustained contractions with different muscle groups, the time to failure with a given relative load varies substantially. For example, a submaximal contraction at 20% MVC can be sustained for about 30% longer when performing abduction of the index finger (Maluf et al. 2005) compared with flexion of the elbow (Rudroff et al. 2005, 2007). It is to be expected that the capacity to generate sustained contractions will vary across muscle groups, considering the different mechanical arrangement of muscles at any given joint, and differences in the fatigability of the constituent muscle fibers. Indeed, our motor system has evolved to optimize the configuration of our limb musculature for different actions. For example, the greater relative strength of the wrist flexors compared with the wrist extensors emphasizes grip strength (Lieber et al. 1990), and the evolution of the human hand has enhanced dexterity (Lemon 1999). Differences in both muscle morphology (Cheng and Scott, 2000; Ogihara et al. 2005) and the neural connections to a muscle group (Illert and Kummel 1999; Lemon, 1999) underlie these specializations. For example, recent work has shown that the projection of group III-IV afferents differs for the motor neuron pools of the elbow flexor muscles (Butler et al. 2003) and the elbow extensor muscles (Martin et al. 2006). As metabolites accumulate during a fatiguing contraction, the feedback delivered by the group III-IV afferents depresses the activity in extensor motor neurons, but facilitates the activity of flexor motor neurons (Martin et al. 2006). However, no studies have yet compared the times to task failure and the associated adjustments across muscle groups in the same individuals.

Conclusion

The initial studies with the task-failure approach suggest that it provides a strategy to identify the functional significance of the physiological adjustments that occur during fatiguing contractions. Importantly, the approach should provide a foundation for the systematic evaluation of the task dependency of muscle fatigue and the extent to which the limiting factors generalize across muscles, postures, types of contractions, and between healthy and diseased individuals.

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