Neuromuscular fatigue and the differentiation of moto-neurone and muscle unit properties

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Abstract It is well known that muscles consist of motor units with widely varying contractile properties. In the present survey an analysis is given of various ways in which the properties of the motoneurones are matched to those of their muscle units such as to help to minimize the risk for neuromuscular fatigue. This seems essentially to be done in two ways: (i) by matching the recruitment threshold of motoneurones to the fatigue-resistance of their muscle units, thus ensuring an appropriate choice of units for various types of motor task (*posture vs. movement match*); (ii) by matching the repetitive discharge properties of the motoneurones to those of their muscle units in ways that will serve to keep muscle units active, as much as possible, at low relative force levels (includes a *rate gradation match* between the minimum maintained firing rate of motoneurones and the contractile speed of their muscle units). Experiments with long-term stimulation of muscles suggest that part of the normally obtained matching between motoneurone and muscle unit properties may be caused and maintained by long-term effects of neuromuscular activity on muscle fibre properties (including endurance). In connection with the experiments on chronic stimulation it was noted that changes in fatigue sensitivity of muscles did not consistently occur in parallel with changes in the electromyographic behaviour of these muscles during fatigue tests.

Introduction

In the present context, neuromuscular fatigue will simply be defined as a decline of force taking place during a steady pattern of activation of some kind. Whether neuromusclar fatigue develops in a particular usage situation will depend on the combination of at least four major factors:

- (i) the properties and organization of the *muscle fibres* themselves, determining their fatigue-resistance (endurance) in various usage-contexts;
- (ii) the *kind of contraction* produced by the muscle fibres (isometric, concentric, excentric), depending on the force-balance between the target muscle, other muscles and external influences;
- (iii) the manner in which the fibres are activated by their *motoneurones* during the particular usage concerned;
- (iv) the extent to which the metabolic needs of the muscle fibres are adequately taken care of by relevant external supporting mechanisms (e.g. *(micro-)circulation, respiration, etc.*).

Below I will give a rather general survey centred on data concerning point (iii), i.e. I will primarily review in which ways the properties and the functional organization of the moto-neurones are differentiated to make them handle their various brands of muscle units such that fatigue problems might be minimized. There are at least two obvious manners in which the motoneuronal management of muscle units may serve to decrease the risk for fatigue:

- (iii-a) by using an appropriate *muscle unit selection*, i.e. chosing the right unit for the right task (*recruitment optimalization*);
- (iii-b) by using an appropriate *level of muscle unit drive*, i.e. essentially by keeping the activation level (impulse rate) of each unit as low as feasible for a given usage situation (*frequency optimalization*).
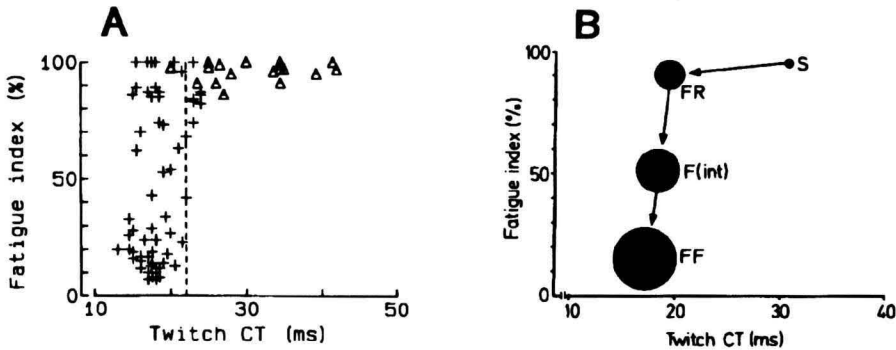
Figure 1. Graphs illustrating the co-variation between different contractile properties among muscle units of cat's peroneus longus muscle. Fatigue index (%) plotted versus twitch time-to-peak (ms) for 80 individual units (**A**) and for average values of the same units after categorization into types S, FR, F(int) and FF (**B**). In **B**, the diameter of each symbol is proportional to the maximum tetanic force of the respective unit category (mean force for FF units: 27.9 g). Reproduced with permission from Kernell et al. (1983) (**A**) and Kernell (1986) (**B**).

I will start by discussing the questions relating to muscle unit selection and that implies that I will first have to deal with a muscular problem, namely the normal degree of variability in contractile muscle unit properties (i.e. the functional range over which motoneurones might select different muscle units). With respect to muscle units as well as motoneurones, my overview will be illustrated with examples from our own experimental work, which has largely been performed on hindlimb muscles of cats and rats.

Normal pattern of co-variation among muscle unit contractile properties

It is well known that, within the average limb muscle of commonly used experimental animals, there is a characteristic pattern of co-variation between the maximum force, speed and endurance of the muscle units. This is illustrated by Fig.1, which shows the typical 'inverted L-shape' for the relation between measures of endurance and isometric speed (cf., however, less marked co-variation and smaller endurance-range among human thenar motor units; Thomas et al. 1991). In A individual values are shown; these data illustrate that there is essentially a *continuous* variation among the muscle units in their physiological properties. In B the various units have been categorized, for descriptive purposes, into the four classes S, FR, F(int), FF as defined by Burke and coworkers (see Burke et al. 1973; Burke 1981). At one extreme of the distribution we have units that are weak, slow and highly resistant to fatigue. At the other extreme, the units are fast and strong and of low endurance.

The endurance data of Fig.1 emanate from measurements with the *Burke-type fatigue test* : 0.33 sec stimulation-bursts of 40 Hz were repeated once a sec for 2-4 min, and a fatigue index was calculated which essentially corresponded to the fraction of initial burst-force still being produced after 2 min test activation (y-axes of Fig.1). It should be noted that this test was originally designed for classification purposes, and it might then be considered as an advantage that the test tends to produce a bimodal distribution of fatigue indices (bimodality sometimes much more marked than in Fig.1, cf. Burke et al., 1973). Part of this bimodality is apparently the result of a 'saturation' of endurance-values at the upper end of the distribution; FR or S units with similarly high fatigue indices according to a Burke-test may be demonstrated to differ considerably in endurance according to other tests (Botterman & Cope 1988; Cope et al. 1991). Furthermore, in a more long-lasting series of contractions than that of the typical Burke-test, the maintenance of force generation generally tends to be markedly better for S units than for FR units (cf. Burke et al. 1973; Botterman & Cope 1988).

Optimalization of motoneuronal recruitment: 'Property-ranked recruitment' and the 'posture vs. movement match'

In most motor acts, the muscle units tend to become recruited in the general order indicated by the arrows in Fig.1B, i.e. in the sequence S ➜ FR ➜ F(int) ➜ FF. On average, this will be a recruitment in an order of increasing unit force and that does, of course, correspond to one aspect of the 'size principle' of Henneman (review: Henneman & Mendell 1981). This principle was originally formulated on basis of experiments in which the measurements concerned an aspect of *motoneuronal* size, namely the relative diameter of the motor axon, which is often monitored in terms of axonal conduction velocity. As measured over the whole range of motoneuronal and muscle unit properties both components tend to co-vary in relative 'size', i.e. there is typically (at least in the cat) a positive correlation between axonal conduction velocity and muscle unit maximum force (particularly evident for S+FR units; e.g. Emonet-Dénand et al. 1988). Also *within* single classes of units (at least for the S units), recruitment tends to occur in order of increasing axon size (Bawa et al. 1984).

Intracellular measurements from our own as well as from other laboratories have suggested that intrinsic differences in motoneuronal electrical excitability are important for the commonly appearing recruitment hierarchy (e.g. Kernell 1966; Kernell & Monster 1981; Fleshman et al. 1981; Gustafsson & Pinter 1985): weaker currents are needed for the activation of small-axoned slow-twitch motoneurones than for the fast-twitch ones with larger axons. The relatively high excitability of the slow-twitch small-axoned cells is mainly caused by the relatively high specific resistance of their membrane (for references and further discussion, see Kernell 1992). Thus, there is seemingly no obligatory linkage between the motoneuronal (or axon) size and the motoneuronal (recruitment) excitability, and this kind of co-variation is also not universally present. One of the best-documented 'aberrations' is of particular relevance for neuromuscular endurance: at least for motoneurones of some muscles of the cat's hindlimb, the size vs. excitability correlation is absent when comparing fast-twitch cells of fatigue-sensitive (FF) and fatigue-resistant (FR) units. These axon and cell body sizes vary over the same range for FR and FF cells in spite of the fact that the FR motoneurones have a markedly higher average degree of electrical excitability (i.e. lower electrical current needed for activation; Fleshman et al. 1981; Kernell & Monster 1981), presumably mainly caused by their higher input (and specific membrane) resistance (Fleshman et al. 1981; for further discussion and references, see Kernell 1992).

It should be stressed that one of the most important and general messages contained in the concept of Henneman's 'size principle' is that recruitment typically takes place in a functionally adequate relation to the various contractile properties of the muscle units (e.g. Henneman & Mendell 1981; see further comments below); this remains valid also for cases in which aspects of motoneuronal size show little co-variation with other functional properties. There is a need for a more general term than 'size principle' when referring to motoneuronal behaviour in which the recruitment hierarchy is ordered in relation to contractile unit properties (but not necessarily in relation to axon size); one possibility would be the term '*property-ranked recruitment*' (Kernell 1992).

When analyzing the functional relevance of relationships between motoneuronal recruitment and muscle unit properties it is useful to consider them as representing two major types of motoneurone vs. muscle unit match (Fig.2):
- (a) The match between recruitment hierarchy (ascending-force-order of recruitment) and muscle unit maximum force represents a '*recruitment-gradation match* '. This match primarily serves to optimize the smoothness of force gradation by letting strong units be used mainly in muscle contractions of high total muscle force; thereby the *relative* force-magnitude of each recruitment step will be minimized (Henneman & Mendell 1981).
- (b) The match of recruitment hierarchy vs. fatigue-resistance and speed represents an endurance-related association, a '*posture vs. movement match*'. Posture is typically maintained by contractions of weak to moderate force and potentially very long duration. The units that primarily will become engaged in the execution of such contractions are the easily recruited S units. The high endurance of these units makes them, of course, eminently suited for postural tasks. Furthermore, the slow contractile speed of the S units would be of particular value in postural near-isometric contractions because the maintenance of force takes place at less metabolic expense in slow than in faster muscle (e.g. Crow & Kushmerick 1982). On the other hand, very strong contractions that mobilize much of the total resources of a muscle might mainly be needed for the transient acceleration phase of rapid movements and, in this situation, the fast contractile speed (and great power capacity) of the late-recruited FF units would clearly be of value. In strong
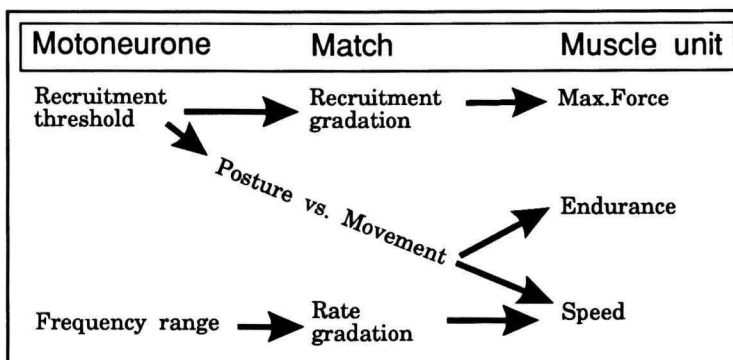
Figure 2. Scheme illustrating commonly occurring types of matching between motoneuronal behaviour and muscle unit properties.

contractions, capillaries will become compressed by surrounding activated muscle fibres and the local blood supply will become minimal or absent; hence, the poor oxidative capacity of fibres characteristic for FF units (cf. Burke 1981) might not matter much in their typical usage situations. On the other hand, it should be remembered that these 'fatigue-sensitive' fibres have a potentially relatively *high* endurance under ischaemic conditions because the anoxic metabolism of glycogen is more effective in fibres of type IIB (typically FF units) than in those of type I (typically S) (for refs., see Burke 1981).

The two recruitment-related matches of Fig.2 are to some degree potentially independent of each other, i.e. there is no obligatory linkage between the maximum force of a muscle unit and its speed or fatigue resistance. The extent to which all these three contractile properties tend to co-vary would be expected to be related to, for instance, the degree to which a particular muscle is actually used for postural support and/or rapid movement, thus motivating the appropriate kind of 'posture vs. movement match' between recruitment behaviour and endurance/speed-related unit properties. Maintained postural contractions are likely to be largely produced by S units. Hence, for instance, in the hindlimb it is appropriate that the percentage of S units indeed tends to be higher for the post-tibial anti-gravity muscles of the ankle than for their counterparts on the pre-tibial side (see literature-data compiled in Table 3 of Kernell et al. 1983).

Optimalization of motoneuronal discharge frequency

In muscles consisting of mammalian twitch fibres, it is of major importance for the gradability of force as well as for the realization of an endurance-promoting 'frequency optimalization' that the muscle is not commanded by a single neurone but by a *multi-unit motoneurone pool*. The twitch elicited by a single action potential is often quite large in comparison to the maximum tetanic force (twitch vs. tetanus ratio commonly 0.15-0.30) and, if a whole muscle were managed by a single command-neurone, a smooth and steady level of contraction would only be obtained by activation rates high enough to cause near-fusion. However, the use of such nearly-fused contractions would be quite ineffective from various other points of view: endurance would low, circulation would be ineffective, and there would be little or no possibility for grading the force. In mammalian twitch muscle, the only way to combine a smoothness of force production with a reasonable degree of endurance and gradability of tension is to subdivide the muscle into different units that can be active *asynchronously* to each other. Thus, one might say that the evolutionary 'invention' of the twitch muscle fibre would in itself have produced sufficient motivation for a subsequent invention of the motoneurone pool as a commanding device (if not already invented for other reasons).

Slow and faster muscle units differ in the range of stimulation rates needed for the effective modulation of force (steep portion of tension-frequency curve), and the slow and faster

motoneurones show corresponding differences in their intrinsically possible range of discharge rates. This represents a third kind of match between motoneuronal and muscle unit features, a *'rate-gradation match'* (Fig.2). Of particular relevance in this context is the minimum rate of maintained firing, i.e. the rate at which a neurone will tend to start firing when just barely recruited. This rate depends to an important extent on the time course of the post-spike afterhyperpolarization (AHP), which is of a duration about equal to that of the twitch (Kernell 1983; Bakels & Kernell, in preparation); besides the AHP, other factors may contribute as well to the setting of the minimum rate (cf. Carp et al. 1991). The rate-gradation match is typically such that, on recruitment, muscle units tend to start firing at discharge rates slow enough to produce almost completely unfused contractions (for references, see Kernell 1992). In maintained submaximal contractions, fatigue commonly develops less rapidly at low total forces than at higher output levels (Bigland-Ritchie & Woods 1984; Botterman & Cope 1988; Cope et al. 1991; cf. also Garland et al. 1988). Thus, for such reasons, the rate-gradation match is presumably important for the maintenance of an optimum degree of neuromuscular endurance during motor functions.

Differences in the minimum rate of maintained firing (as caused by differences in AHP duration) are of interest also in relation to yet another aspect of motoneuronal rhythmic behaviour: the frequency-adaptation. During the long-lasting intracellular activation of a motoneurone with a steady injected current, discharge rate declines continuously during at least the initial 1/2 - 1 minute of firing (Kernell & Monster 1982a). The precise mechanisms producing this *'late adaptation'* are still uncertain; AHP-related factors are not necessarily involved. For a given motoneurone, the late adaptation is more marked the higher the rate of firing at the onset of the discharge. When comparing different motoneurones that were activated by the same weak amount of suprathreshold current, the starting rate was (as expected) found to be lower in motoneurones of slow-twitch units and, correspondingly, these slow motoneurones also showed less late adaptation (Kernell & Monster 1982b). Thus, the slow-twitch motoneurones seemed particularly well suited for the production of steady postural contractions. In discharges at higher force levels and impulse rates, the late adaptation might in itself help to produce an endurance-promoting optimalization of discharge frequency. During the course of maintained contractions there is often a progressive slowing of contractile speed (Bigland-Ritchie & Woods 1984), and in relatively strong contractions the highest degree of average force output is actually produced by a steadily *declining* activation rate (Jones et al. 1979), such as is also seen to occur during the initial minute of a maximum voluntary contraction (Bigland-Ritchie & Woods 1984). Experimental evidence indicates that, in voluntary contractions, much of this rate decline is produced by reflexes (Woods et al. 1987; see also present symposium: Bigland-Ritchie, Gandevia, Stuart & Callister). The intrinsic motoneuronal properties associated with the late adaptation would, however, be likely to add to the rate drop as well, thereby in certain situations helping to minimize neuromuscular fatigue. In other cases, the late adaptation might conceivably instead *contribute* to central aspects of neuromuscular fatigue (see discussion in Kernell & Monster 1982b).

So far I have only talked about recruitment- and rate-gradation separately. Normally, these two strategies of force modulation are used in parallel, although their coupling may differ quantitatively between different muscles. The relative contribution from either one of the two mechanisms over a certain force range (cf. Milner-Brown et al. 1973) has to do with the balance between the ease of recruitment gradation ('recruitment gain', cf. Kernell & Hultborn 1990) and the ease of rate gradation (steepness of slope for relation between discharge rate and intensity of activating synaptic (or injected) current; cf. Kernell 1992). Over the range of weak muscle forces used for postural control it would be advantageous to have the motoneurones discharging at frequencies relatively close to their minimum rates because: (i) the first-recruited units tend to be slow-contracting, having a comparatively limited frequency-range for the rate-modulation of force; (ii) low relative rates and unit tensions would generally be expected to promote endurance. A preponderance of relatively slow rates might be attained by having the thresholds of consecutively recruited neurones close to each other, thus allowing but little rate gradation to take place in parallel with the recruitment of additional cells. If such a close spacing of recruitment thresholds were primarily dependent of intrinsic motoneuronal properties (i.e. as opposed to synaptic distribution, cf. Kernell & Hultborn 1990), one would expect to find more densely clustered intracellular current-thresholds for the 'postural' S-motoneurones than for the more movement-associated FR or FF cells. Our data for intracellularly investigated rat and cat motoneurones have shown that this is also actually the case (Bakels & Kernell, in preparation; cf. data of Kernell & Monster 1981; Fleshman et al. 1981; Gustafsson & Pinter 1985). After ranking the motoneurones according to their current-threshold, the average threshold *difference* between successive S-

motoneurones was smaller than that between successive FF-motoneurones (rat: 0.3 nA for S, 2.2 nA for FF; cat: 0.8 nA for S, 1.9 nA for FF; small steps significantly more common among S than among FF units, chi-square analysis, $P<0.05$).

The long-term matching perspective: Usage-dependent neuromuscular plasticity

It is well known that also during adult life the motoneurones determine, to a significant degree, the properties of their muscle units. Since the chronic stimulation experiments of Salmons & Vrbová (1969), it is known that many of these effects may be caused by long-term effects of motoneuronal activity patterns on muscle fibre properties. Thus, the fact that various aspects of motoneuronal activity are normally well adapted to contractile muscle unit properties (see Fig.2) leads naturally to the question of whether this matching is based on direct causal relationships, e.g. on long-term 'training effects' of motoneuronal discharge patterns on muscle unit properties. We have looked into this question using chronic electrical stimulation of muscle nerves to study the long-term effects of different activation patterns on muscle properties (for references, see Kernell & Eeerbeek 1989, 1991; Kernell 1992). The experiments were performed on ankle dorsiflexor muscles of the cat hindlimb (mainly peroneus longus). Chronic stimulation was given to the deafferented peroneal nerve (no pain or reflexes) in different patterns during 4-8 weeks. Thereafter the muscle properties were investigated in a final acute experiment. With respect to endurance these experiments showed that, irrespective of the pulse rate of stimulation (cf. Hudlická et al. 1982), activation during 5% of total time per day was sufficient for producing a marked increase of fatigue resistance (Burke-test) whereas 0.5% 'extra' activity left the muscle with a normal sensitivity to fatigue. These amounts of imposed daily activity are of interest in relation to published evidence that, at least in the rat, motoneurones that were likely to have fatigue-resistant muscle fibres were normally active more than 0.5% of total time per day (range 1.6-5.0%, for presumed FR motoneurones, Hennig & Lømo 1985; cf. also present symposium: Hensbergen & Kernell). In short, our results supported the general idea that, within a preset "adaptive range", long-term effects of motoneuronal activity are important for *contributing* to the normal kinds of endurance-related matching between muscle unit and motoneurone properties (for a more complete discussion, see Kernell & Eerbeek 1989; Kernell 1992).

During our chronic stimulation studies we also investigated how strict the linkage was between usage-evoked changes in fatigue-resistance and concurrent alterations in parameters that are commonly assumed to be closely related to neuromuscular endurance: (a) the electromyographic (EMG) behaviour during fatigue tests; and (b) the oxidative enzyme activity, as studied histochemically (staining for succinate dehydrogenase, SDH). Much to our surprise we found that the 0.5% and the 5% series of chronic stimulation, which gave markedly different effects on endurance, produced identical results with regard to both kinds of presumed fatigue correlate (Kernell et al. 1987). Furthermore, following a period of intense chronic stimulation, the rate of recovery toward normal properties was much slower for the EMG- than for the force-related behaviour during fatigue tests (Kernell & Eerbeek 1991). These findings are not meant to imply that EMG-changes and SDH-activities would be without any importance for fatigue-resistance in general. Our observations serve to underline, however, that it is still an open question which *types of fatigue* are critically dependent on EMG-associated parameters and/or on aspects related to the efficiency of oxidative metabolism.

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