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ORIGINAL ARTICLE

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Central and peripheral contributions to muscle fatigue in humans during sustained maximal effort

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Abstract The purpose of this study was to estimate the relative contributions of central and peripheral factors to the development of human muscle fatigue. Nine healthy subjects [five male, four female; age = 30 (2) years, mean (SE)] sustained a maximum voluntary isometric contraction (MVC) of the ankle dorsiflexor muscles for 4 min. Fatigue was quantitated as the fall in MVC. Three measures of central activation and one measure of peripheral activation (compound muscle action potential, CMAP) were made using electromyography (EMG) and electrical stimulation. Measures of intramuscular metabolism were made using magnetic resonance spectroscopy. After exercise, MVC and electrically stimulated tetanic contraction (50 Hz, 500 ms) forces were 22.2 (3.7)% and 37.3 (7.1)% of pre-exercise values, respectively. The measures of central activation suggested some central fatigue during exercise: (1) the central activation ratio [MVC/(MVC + superimposed tetanic force)] fell from 0.94 (0.03) to 0.78 (0.09), (2) the MVC/tetanic force ratio fell from 2.3 (0.7) to 1.3 (0.7), and (3) the integral of the EMG (iEMG) signal decreased to 72.6 (9.1)% of the initial value, while the CMAP amplitude was unchanged. Intramuscular pH was associated by regression with the decline in MVC force (and therefore fatigue) and iEMG. The results indicate that central factors, which were not associated with altered peripheral excitability, contributed approximately 20% to the muscle fatigue developed, with the remainder being attributable to intramuscular (i.e., metabolic) factors. The association between pH and iEMG is consistent with proton concentration as a feedback mechanism for central motor drive during maximal effort.

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Introduction

Human muscle fatigue, defined as a loss of maximum force-generating capacity, may develop for a variety of reasons. Failure of force production may occur at the various sites along the pathway from the central nervous system through to the intramuscular contractile machinery. The contribution of impaired central motor drive to muscle fatigue has been investigated, with some researchers finding little or no central failure (Bigland-Ritchie et al. 1986b; Merton 1954), and others reporting significant central activation failure during fatiguing exercise (Bigland-Ritchie et al. 1978; McKenzie et al. 1992).

Peripheral factors in fatigue primarily include metabolic inhibition of the contractile process and excitation-contraction coupling failure (Baker et al. 1993; Cady et al. 1989; Cooke et al. 1988; DeGroot et al. 1993; Miller et al. 1987, 1988; Weiner et al. 1990; Wilson et al. 1988). Prolonged low-intensity exercise has been associated with failure of excitation-contraction coupling (Baker et al. 1993; Moussavi et al. 1989), which has a very slow time course of recovery (Edwards et al. 1977). Accumulation of intramuscular metabolites has been implicated in the development of fatigue during high-intensity exercise, although agreement on which metabolite plays the most important role is still lacking (Baker et al. 1993; Cady et al. 1989; Miller et al. 1988; Weiner et al. 1990; Wilson et al. 1990). Reduced excitability of neuromuscular transmission has been reported to occur under some fatiguing conditions (Fuglevand et al. 1993; Miller et al. 1987; Stephens and Taylor 1972), however this does not appear to be a common occurrence, particularly during voluntary contractions.

Thus, although various sites along the pathway of force production have been implicated in human skeletal muscle fatigue, the relative roles of central and peripheral factors in the development of muscle fatigue remain

unclear. Previous studies have generally focussed on one or two sites along the pathway of force production, which thereby precludes a complete understanding of the mechanisms of fatigue. By combining existing technologies, methods are available for simultaneously quantifying the relative roles of central and peripheral factors in human muscle fatigue under a variety of conditions.

Therefore, the purpose of the present study was to quantitate the central and peripheral contributions to the development of muscle fatigue in healthy human volunteers during a sustained maximum voluntary isometric contraction (MVC). To estimate the changes that occur during fatigue at several sites along the pathway of force production, simultaneous non-invasive measurements of central activation, neuromuscular junction (NMJ) and muscle membrane excitability, and intracellular energy metabolites were made using electromyography (EMG), electrical stimulation and magnetic resonance spectroscopy (MRS) during ankle dorsiflexion exercise. To examine further the factors involved in fatigue, the relationships between the decline in force production and measures of activation and metabolism were determined.

Methods

Subjects

Nine (five male, four female) healthy subjects volunteered for this study. The subjects' physical characteristics were [mean (SE)]: age 30 (2) years, height 177.0 (3.7) cm, weight 68.5 (4.2) kg. The subjects ranged in physical activity level from sedentary to recreationally active. All volunteers signed consent forms as approved by the Committee on Human Research at the University of California, San Francisco.

EMG and electrical stimulation

These techniques have been described previously (Kent-Braun and LeBlanc 1996; Kent-Braun et al. 1993, 1994). All electrodes were non-magnetic disks of 10 mm in diameter and were applied with conducting gel. Two stimulating electrodes were taped longitudinally over the peroneal nerve, 1 cm distal to the fibular head. The recording electrode was taped to the belly of the tibialis anterior, and the reference electrode was placed on the medial malleolus. To reduce stimulus artifact, copper a ground plate was placed over the calf midway between the stimulating and recording electrodes. All electrodes were secured on the leg of the subject prior to positioning the leg in a Lexan exercise apparatus designed to hold the leg stationary during voluntary and electrically stimulated contractions of the dorsiflexor muscles (Kent-Braun and LeBlanc 1996).

Prior to and at the end of the exercise, the excitability of the NMJ and muscle membrane was assessed by examining the compound muscle action potential (CMAP). This was elicited by a single supramaximal stimulus (0.1 ms duration). In order to ensure that the stimulation was supramaximal throughout the experiment, the stimulation voltage used was 25 V (approximately 10–15%) above that necessary to produce a maximum-amplitude CMAP. This voltage was then used for all subsequent stimuli. The amplitude of the CMAP was measured as the peak-to-peak value and expressed in mV, and the duration of the negative peak is reported in ms.

To monitor changes in muscle electrical activity during the development of fatigue, the surface EMG was recorded continuously during exercise. The integral of the rectified EMG (iEMG) was calculated from a 500-ms sample of data extracted every 2.5 s during exercise. The change in iEMG is expressed relative to that obtained during the first 2.5 s of exercise.

Force measurements

MVC force was recorded before and continuously during exercise. Electrically stimulated tetanic force (50 Hz, 500 ms) and twitch tension were recorded before and at the end of exercise. Subjects were comfortably seated and the leg was fixed in the exercise apparatus. The foot was held firmly against a foot platform with an adjustable Velcro strap across the metatarsal heads. Force output was measured with a non-magnetic force transducer (West Coast Research, Los Angeles, Calif, USA) that was attached beneath the foot platform. The signal from the force transducer was amplified (TECA electromyograph TE-4, White Plains, N.Y., USA), converted to a digital signal and displayed using Labview software (National Instruments, Austin, Tex., USA). Prior to the start of exercise, three twitch responses, four MVCs (3–5 s each) and one tetanus were obtained, in that order, each separated by 1 min of rest. The highest force value for each type of measurement was recorded as the pre-exercise value. Pre-exercise force data are reported in Newtons (N).

Voluntary fatigue was quantitated as the change in force (MVC) during exercise. The change in tetanic force was used as the primary index of peripheral fatigue, with the change in twitch force used as an additional marker. Twitch contraction time, the maximum rates of tetanic force development and relaxation, and the half-relaxation time ($t_{1/2}$) of tetanic force were also calculated.

Central activation

Changes in central activation during exercise were measured in three ways. The first method was to compare the change in the central activation ratio (CAR) before and after exercise. The CAR is defined as the peak MVC divided by the peak total force, where total force is the sum of the MVC plus the force from a superimposed train (50 Hz, 500 ms) of stimuli (Kent-Braun and LeBlanc 1996). The CAR was quantitated before and during the last seconds of exercise. The second method of measuring central fatigue was to compare the decline in voluntary force (MVC) with the decline in tetanic force (Bigland-Ritchie et al. 1978; Merton 1954) by examining the change in the MVC/tetanic force ratio. A decrease in this ratio, reflecting a relatively greater reduction in voluntary force, indicates central activation failure. The third method was to compare the change in the iEMG signal during exercise with the change in CMAP amplitude (iEMG/CMAP ratio). The iEMG is a measure of the total electrical signal sent from the central nervous system to the muscle (Enoka 1994; Miller et al. 1987). The CMAP amplitude is a measure of both the transmission of this signal across the neuromuscular junction and the excitability of the muscle membrane (Fuglevand et al. 1993; Garland and McComas 1990; Miller et al. 1987; Thomas et al. 1989; Woods et al. 1987). A reduction in the iEMG without a reduction in CMAP amplitude may be interpreted as central activation failure (Bigland-Ritchie et al. 1983; Garland and McComas 1990; Stephens and Taylor 1972).

Metabolic measurements

In six of the nine subjects, 31-phosphorus MRS was used to monitor changes in phosphocreatine (PCr), inorganic phosphate (Pi), diprotonated inorganic phosphate ($H_2PO_4^-$) and pH within the muscle during exercise. These methods have been described previously (Kent-Braun et al. 1993a, b, 1994). After placement of the EMG electrodes, a 3 × 5-cm elliptical MRS surface coil was taped

directly over the belly of the tibialis anterior muscle, approximately 1 cm proximal to the EMG recording electrode. The subject's leg was secured in the exercise apparatus and inserted into the 30-cm bore, 1.9-T Oxford magnet with GE-CSI spectrometer. The magnet was shimmed using the proton signal, and phosphorus data were subsequently acquired. The repetition time was 1.25 s, the nominal pulse angle was 50°, and the block size was 4000 Hz. The rest spectrum was averaged over 4 min (192 acquisitions), and the spectra obtained during exercise were averaged over 30 s (24 acquisitions). Data were processed using NMR 1 software (New Methods Research, East Syracuse, N.Y., USA) to fit the peaks for phosphomonoesters, Pi, phosphodiesters, PCr and the three peaks of adenosine triphosphate. By fitting all peaks in the spectrum, the inaccurate estimation of metabolite concentrations due to overlapping peaks was avoided. The results were transferred to a spreadsheet for calculations of millimolar concentrations and pH. Intracellular pH was calculated from the chemical shift of Pi to PCr, and $H_2PO_4^-$ was calculated according to the equation of Cady and coworkers (Cady et al. 1989).

Exercise protocol

After baseline measurements were made, the subjects performed a sustained isometric MVC of the dorsiflexor muscles for 4 min. Loud verbal encouragement was given to each subject throughout the exercise protocol. "Extra effort was requested before and during the superimposed tetanic stimulation at the end of the 4-min period.

Statistics

Differences between pre- and post-exercise values for each measure were assessed using the non-parametric Wilcoxon signed rank test. The association between changes during exercise in force and pH was determined using a Spearman rank order correlation. The associations between force and iEMG, and iEMG and pH were determined using second-order (non-linear) regression analyses. Significance for all statistical analyses was established when $P < 0.06$, as assigned by the non-parametric analyses. All data are presented as the mean (SE) (median, range).

Results

Force and CMAP

Prior to exercise, the mean MVC was 105.0 (11.6)N (102.7 N, 63.6–168.2), the mean tetanic force was 66.6 (12.4)N (42.4 N, 17.8–132.4), and the mean twitch force was 4.1 (1.2)N (2.7 N, 1.4–12.2). At the end of exercise, the MVC was 22.2 (3.7)% (23.1%, 2.0–39.6) of the pre-exercise value, indicating the occurrence of severe muscular fatigue in the subjects (Fig. 1A). At the end of exercise, tetanic force was 37.3 (7.1)% (19.5%, 2.4–46.7) of the pre-exercise value. There was a decrease in twitch tension to 1.5 (0.3)N (1.2 N, 0.3–2.8), and a shortening of the twitch contraction time from 85.2 (5.7) ms (80.9 ms, 67.2–109.6) to 46.9 (9.6) ms (44.4 ms, 9.6–90.4). The shorter twitch contraction time is likely to be a result of the markedly reduced twitch force. The similar relative fall (≈37%) of both tetanic (50 Hz) and twitch tension (1 Hz) suggests that there was little or no frequency specific (i.e., low-frequency) fatigue. There were no significant changes in the maximum rate of tetanic force development, the $t_{1/2}$ of force relaxation or the maximum rate of force relaxation (data not shown). There appeared to be no difference in the degree of fatigue between the women (MVC fell to 22.5% of the pre-exercise value) and the mean (MVC fell to 22.5% and 24.0% of the pre-exercise value, respectively). Due to a technical problem, the time course data shown in Fig. 1 represent those of eight of the nine subjects.

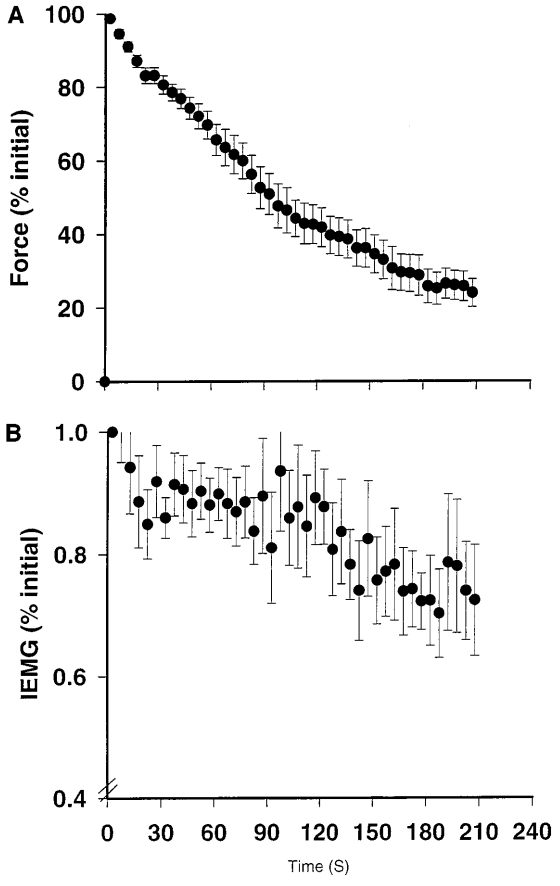

Fig. 1A, B The change in force (**A**) and rectified, integrated surface electromyograph (iEMG) (**B**) in eight healthy subjects during an isometric maximum voluntary contraction of the dorsiflexor muscles, sustained for 4 min. Data are the means ± SE

The amplitude of the CMAP did not fall significantly during exercise [from 10.6 (0.6) mV (9.8 mV, 8.7–13.5) to 10.3 (0.4) mV (9.8 mV, 4.3–11.9)]. There was an increase in CMAP duration from 15.4 (0.6) ms (15.7 ms, 13.9–19.8) pre-exercise to 17.8 (1.0) ms (18.4, 12.4–22.0) immediately following exercise. The CMAP data indicate no significant failure of neuromuscular excitability at the NMJ or muscle membrane during fatigue.

Central activation

During exercise, the CAR fell significantly from 0.94 (0.03) (1.0, 0.76–1.0) to 0.78 (0.09) (0.81, 0.11–1.0). A comparison of the decline in MVC and tetanic force (to 22% vs 37% of the initial values, respectively) revealed

that voluntary fatigue was greater than stimulated fatigue. Consistent with this result was the decrease in the MVC/tetanic force ratio observed during exercise, from 2.34 (0.71) (1.60, 0.88–7.47) to 1.25 (0.69) (0.69, 0.04–6.36). There was a significant decrease in the iEMG from the first 5 s of exercise to the last 5 s of exercise (Fig. 1B). Overall, the iEMG fell to 72.6 (9.1)% (71.5%, 39–117) of the pre-exercise value during exercise. The lack of change in CMAP amplitude and the significant decrease in iEMG resulted in a fall of iEMG/CMAP from 3.29 (0.32) (3.60, 1.8–4.4) to 0.74 (0.09) (0.73, 0.5–1.3). These results suggest that central factors contributed to the muscle fatigue that developed during this exercise protocol.

Metabolites

Intracellular energy metabolites (n = 6) were significantly altered during exercise (Fig. 2). PCr fell from 38.2 (0.5) mM, (38.4 mM, 36.3–39.5) to 8.7 (1.5) mM (9.2 mM, 3.9–14.1), while Pi increased from 4.3 (0.5) mM (4.2 mM, 3.0–6.2) to 33.8 (1.5) mM (33.3 mM, 28.4–38.6), and $H_2PO_4^-$ increased from 1.5 (0.2) mM (1.4 mM, 1.0–2.1) to 21.4 (1.6) mM (21.4 mM, 15.3–25.4). Intracellular pH fell from 7.01 (0.01) (7.01, 6.99–7.04) at rest to 6.49 (0.05) (6.44, 6.36–6.66) at the end of the 4-min exercise protocol.

Factors associated with fatigue

Changes in force (MVC) and pH were linearly associated during exercise (r_s = 0.95, Fig. 3A), while the relationships between force and both Pi and $H_2PO_4^-$ were non-linear during this protocol (Fig. 3B, C). That is, as force continued to fall during exercise, there was no further increase in either Pi or $H_2PO_4^-$.

There was a strong, although non-linear, relationship between the changes in force and iEMG during exercise (r = 0.92, Fig. 4A), consistent with a role for diminished central motor drive in the development of muscle fatigue. This effect can be attributed to central, rather than peripheral activation failure because there was no change in the amplitude of the CMAP during exercise.

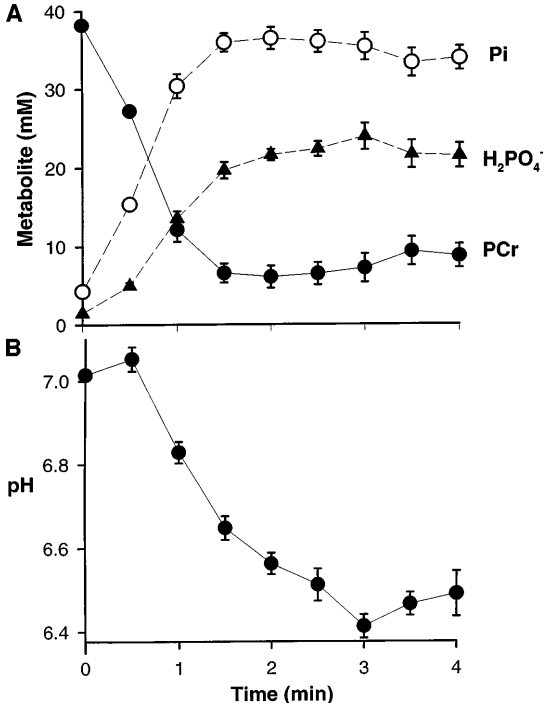

Fig. 2A, B The change in intramuscular metabolites and pH during exercise in six healthy subjects: **A** Phosphocreatine (PCr; in mM, *closed circles*), inorganic phosphate (P_i, in mM, *open circles*), and diprotonated inorganic phosphate ($H_2PO_4^-$; in mM, *closed triangles*); **B** pH. Data are the means ± SE

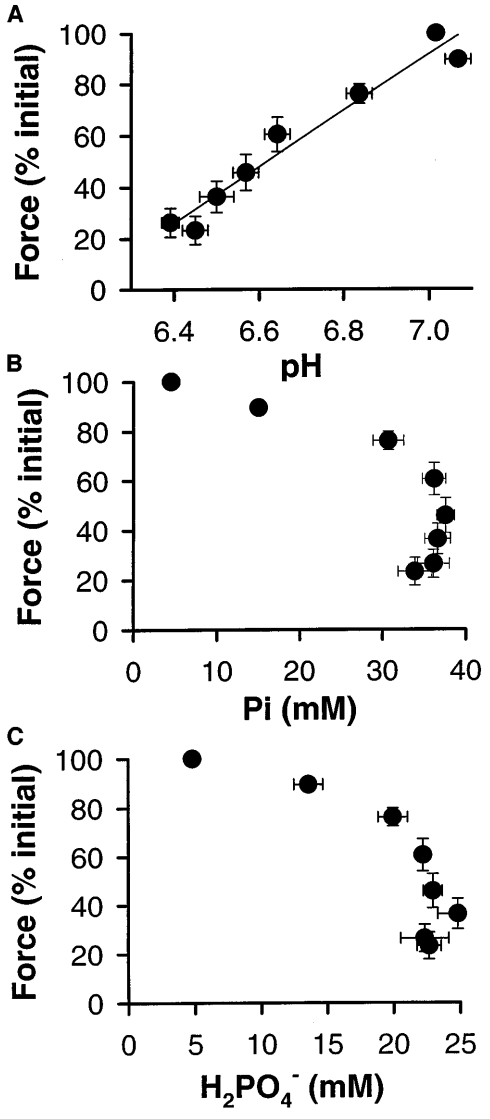

Fig. 3A–C The associations between mean force and (**A**) pH, (**B**) Pi and (**C**) $H_2PO_4^-$ during exercise. The relationship between force and pH was highly linear by Spearman rank order (non-parametric) correlation analysis (r_s = 0.95). Data are the means ± SE

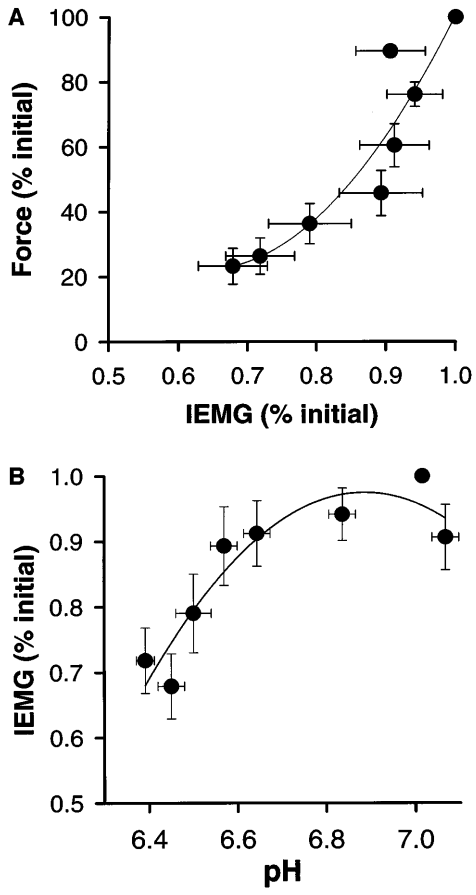

Fig. 4A, B The associations between mean iEMG and force (**A**) and pH (**B**) during exercise. Non-linear (second-order) regression analysis indicated strong relationships between these variables (r = 0.92 and 0.93, respectively) during fatiguing exercise. Data are the means ± SE

Finally, the iEMG and pH were also associated by second-order regression (r = 0.93, Fig. 4B), demonstrating a link between the intramuscular milieu and central motor drive.

Discussion

The results of this study indicate that central activation failure plays a significant, although modest, role in the development of muscle fatigue during an isometric MVC sustained for 4 min. By examining both the net decrease in CAR (16%) and the difference between tetanic and voluntary fatigue (37% − 22% = 15%), it can be estimated that 15–16% of the 78% fall in MVC was due to central fatigue. Thus, approximately 20% of the fatigue developed was due to central factors. Because the CMAP data indicated no failure of neuromuscular transmission, the remainder of the fatigue developed (≈80%) was apparently due to intramuscular sources, primarily increased proton concentration ($[H^+]$). The associations between pH and both iEMG and the decline in force are consistent with the presence of a feedback loop between intramuscular metabolism and central motor drive during fatigue.

The decrease in CAR during exercise indicates that there was a small degree of central activation failure during the exercise protocol. This result is of a similar magnitude (Δ = 0.13) to that from a different group of healthy volunteers studied previously using the same muscle group and exercise protocol (Kent-Braun et al. 1993). The CAR is a measure of the completeness of central activation during a MVC. Prior to exercise, there was a small (6%) degree of incomplete activation in these subjects. In general, complete activation of the dorsiflexors may be expected (Belanger and McComas 1981), but in some circumstances a small degree of incomplete activation can be observed (Kent-Braun and LeBlanc 1996). The superimposed train of stimuli employed in the present study has been shown to be more sensitive in detecting central activation failure than that of a single superimposed twitch (Kent-Braun and LeBlanc 1996). This may explain the discrepancy between the results of this study and those of others examining central activation during voluntary contractions (Belanger and McComas 1981; Bigland-Ritchie et al. 1986b).

The significant decrease in MVC/tetanic force observed in the present study also provides evidence of central activation failure during this protocol. As described previously, central fatigue can be detected by comparing voluntary (MVC) with electrically-stimulated (tetanus) force-generating capacity after fatiguing exercise (Bigland-Ritchie et al. 1978; Merton 1954; Vollestad et al. 1988); a fall in this ratio after exercise is an indication of central activation failure (Bigland-Ritchie et al. 1986b; Thomas et al. 1989). Some (Bigland-Ritchie et al. 1978; Thomas et al. 1989), but not all (Vollestad et al. 1988) previous studies that have used this method have detected central fatigue during exercise. The variability of results is likely to be due to differences in the type of exercise performed and the muscle studied, as well as the adequacy of the stimulated force response. The observation that tetanic force does not equal MVC is rather common. Tetanic force has been reported to be 30% of MVC in the soleus (Bigland-Ritchie et al. 1986b), 52% in the quadriceps (Bigland-Ritichie et al. 1986b), and 75% in the triceps surae group (Davies and White 1983). In the present study, pre-exercise tetanic force was approximately 65% of MVC, most likely reflecting some inadvertent activation of the plantar flexor muscles during stimulation of the peroneal nerve. Thus, while experimental conditions in which tetanic force is less than MVC may not be optimal for ruling out central activation failure, the observation of activation failure in the present study suggests that tetanic force MVC ≥65% may be adequate for assessing central activation using this method.

Finally, in order to examine separately central and peripheral activation during exercise, the changes in iEMG and CMAP amplitude were compared. The results indicate a significant reduction in iEMG with no decline in CMAP. Decreased iEMG during a sustained

MVC may be attributed to a decrease in motor neuron firing rates rather than a reduction in the extent of motor unit recruitment (Bigland-Ritchie et al 1983, 1986a). Others argue that a decrease in the number of motor units recruited could also be responsible for a decrease in iEMG (Stephens and Taylor 1972). In the present study, the precise mechanism for the decrease in central activation cannot be ascertained.

The results of this study indicate a decrease in central activation during exercise. However, the magnitude of this activation failure was modest. In contrast, the changes in peripheral factors, primarily energy metabolism, were striking.

There were significant changes in the intramuscular energy metabolites during exercise (Fig. 2). In particular, the fall in pH was strongly correlated to the fall in force (Fig. 3). The importance of intramuscular energy metabolites in the development of muscle fatigue in humans has been documented previously (Baker et al. 1993; DeGroot et al. 1993; Miller et al. 1988; Weiner et al. 1990; Wilson et al. 1988). Pi, $H_2PO_4^-$ and protons (H^+) have all been implicated as factors causing fatigue, presumably acting by inhibition of the contractile process, including calcium kinetics. In the present study, the significant reduction in tetanic and twitch forces, particularly in light of the lack of peripheral activation failure (no decrease in CMAP amplitude), suggests that metabolic inhibition of the contractile process is likely to have occurred during this protocol. Previous research has indicated mainly that $H_2PO_4^-$ and Pi are responsible for muscle fatigue (Miller et al. 1988; De Groot et al. 1993; Weiner et al 1990; Wilson et al 1990), although agreement on this point remains elusive (Cady et al. 1989).

The role of H^+ in muscle fatigue has sometimes been considered to be a minor one. However, in both the present study and in previous research by Cady et al. (1989), [H^+] was observed to be best related to the decline in force. Likewise, Miller et al. (1988) observed a linear relationship between [H^+] and fatigue. Examination of Fig. 3 in the study reported here reveals that the relationships between force and both Pi and $H_2PO_4^-$ were non-linear. As force fell below ≈60% of its pre-exercise value, there was little further change in either Pi or $H_2PO_4^-$, suggesting that these metabolites did not influence the further development of muscle fatigue.

The differences between the present study and previous reports of Pi and $H_2PO_4^-$ as mediators of muscle fatigue may be attributable to differences in the muscle groups or exercise protocols utilized. In addition, several of these previous studies used the recovery from fatiguing exercise to draw conclusions regarding the mechansims of muscle fatigue. Given that H^+ production continues immediately after exercise as a result of the resynthesis of PCr, it is not surprising that the relationship between H^+ and force is not linear during the recovery period. It seems likely, therefore, that fatigue and recovery from fatigue may involve distinct processes, and that more than one metabolite may have a controlling influence on the development of fatigue under various conditions. Overall, then, the ability to quantitate the relative role of intramuscular metabolism in conjunction with the other sites along the pathway of force production may prove more feasible than the assignment of a single metabolite as a cause of fatigue under all conditions.

The strong association between fatigue and pH during exercise provides support for the interpretation of a dominant role for peripheral factors (≈80%) in the fatigue developed during this protocol. The associations between force and iEMG, and pH and iEMG (Fig. 4), are consistent with the role of pH in feedback to the central nervous system and a subsequent alteration in central motor drive during the development of fatigue (Bigland-Ritchie et al. 1986a; Garland and McComas 1990; Miller et al. 1996; Woods et al. 1987). It is of note that these latter associations, unlike that between fatigue and pH, were best fit by a non-linear model.

The methods used in this study are a combination and refinement of techniques developed by others for the study of various aspects of human muscle fatigue. The combination of metabolic and neurophysiologic measures provided by EMG and MRS allows assessment of the various sites along the pathway of force production during the development of muscle fatigue. Previous studies have generally been limited to information from only one or two sites along this pathway. Surface EMG data are difficult to interpret without corresponding CMAP data. Metabolic data are more fully interpretable when information regarding muscle activation is available. Using these non-invasive methods, it is possible to both separately and simultaneously quantitate the central and peripheral causes of muscle fatigue.

In conclusion, we have shown that high-intensity isometric exercise results in fatigue that is attributable to both central and peripheral factors. The relative contribution of these factors to fatigue may be estimated using a combination of voluntary and electrically stimulated force measures, EMG and measures of intramuscular energy metabolism by MRS. This approach improves our understanding of the mechanisms of human muscle fatigue by simultaneously assessing function at the various sites along the pathway of force production. In the present study, central fatigue contributed approximately 20% to the reduction in MVC, while the intramuscular metabolic milieu ([H^+]) was responsible for the remainder of the fatigue. The strong association between intramuscular metabolism and central motor drive illustrates the link between central and peripheral factors.

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