Fatigue-related firing of distal muscle nociceptors reduces voluntary activation of proximal muscles of the same limb

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Kennedy DS, McNeil CJ, Gandevia SC, Taylor JL. Fatigue-related firing of distal muscle nociceptors reduces voluntary activation of proximal muscles of the same limb. J Appl Physiol 116: 385–394, 2014. First published December 19, 2013; doi:10.1152/japplphysiol.01166.2013.—With fatiguing exercise, firing of group III/IV muscle afferents reduces voluntary activation and force of the exercised muscles. These afferents can also act across agonist/antagonist pairs, reducing voluntary activation and force in nonfatigued muscles. We hypothesized that fatigued firing of group III/IV muscle afferents from a fatigued adductor pollicis (AP) contraction would decrease voluntary activation and force of AP and ipsilateral elbow flexors. In two experiments (n = 10) we examined voluntary activation of AP and elbow flexors by measuring changes in superimposed twitches evoked by ulnar nerve stimulation and transcranial magnetic stimulation of the motor cortex, respectively. Inflation of a sphygmomanometer cuff after a 2-min AP maximal voluntary contraction (MVC) blocked circulation of the hand for 2 min and maintained firing of group III/IV muscle afferents. After a 2-min AP MVC, maximal AP voluntary activation was lower with than without ischemia (56.2 ± 17.7% vs. 76.3 ± 14.6%; mean ± SD; P < 0.05) as was force (40.3 ± 12.8% vs. 57.1 ± 13.8% peak MVC; P < 0.05). Likewise, after a 2-min AP MVC, elbow flexion voluntary activation was lower with than without ischemia (88.3 ± 7.5% vs. 93.6 ± 3.9%; P < 0.05) as was torque (80.2 ± 4.6% vs. 86.6 ± 1.0% peak MVC; P < 0.05). Pain during ischemia was reported as Moderate to Very Strong. Postfatigue firing of group III/IV muscle afferents from the hand decreased voluntary drive and force of AP. Moreover, this effect decreased voluntary drive and torque of proximal unfatigued muscles, the elbow flexors. Fatigue-sensitive group III/IV muscle nociceptors act to limit voluntary drive not only to fatigued muscles but also to unfatigued muscles within the same limb.

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can excite nearby dorsal horn neurons that receive primarily input from another muscle that has not received noxious stimuli (26, 42).

The current study was undertaken to test the hypothesis that maintained firing of group III and IV muscle afferents in the hand after a fatiguing maximal contraction decreases voluntary drive not only to the fatigued distal muscle but also to proximal muscles in the same limb. First, we examined whether maintained firing of group III and IV muscle afferents decreased voluntary activation and force of adductor pollicis following a fatiguing adductor pollicis contraction. Next, we tested whether maintained firing of group III and IV muscle afferents in the hand following a fatiguing adductor pollicis contraction altered voluntary activation and torque production of the elbow flexors.

MATERIALS AND METHODS

Two experiments were conducted to determine whether firing of fatigue-sensitive group III and IV muscle afferents of adductor pollicis altered voluntary activation of adductor pollicis and of elbow flexor muscles. Ten healthy subjects participated in Experiment 1 (mean age: 39 years; male: 7, female: 3). Five subjects from Experiment 1 and five additional subjects participated in Experiment 2 (n = 10; mean age: 33 years; male: 6, female: 4). In both studies, subjects performed a sustained 2-min maximal voluntary contraction of adductor pollicis. In the first experiment, the 2-min contraction was followed by brief adductor pollicis MVCs performed either during maintained ischemia of the hand, which prevented recovery of the muscle from fatigue, or with the muscle allowed to recover. In the second experiment, brief elbow flexor MVCs were performed following the 2-min adductor pollicis contraction again with or without maintained ischemia of the hand. Visual feedback of adductor pollicis force and elbow flexor torque was provided with separate arrays of LEDs. The Human Research Ethics Committee at the University of New South Wales approved the study, and written informed consent was obtained. The study was conducted according to the Declaration of Helsinki.

Experiment 1: thumb adduction after a 2-min MVC of adductor pollicis with and without subsequent ischemia. The subject’s right hand was braced in a neutral forearm position with the fingers secured by a strap (Fig. 1A). The thumb was placed in a rigid cylinder attached to a force transducer to record force (XTran, Melbourne, Australia: linear to 250 N) such that the ulnar side of the thumb pressed against the cylinder just proximal to the distal phalanx. The thumb was positioned in abduction and half way between flexion and extension in the same plane as the second metacarpal. Surface EMG was acquired from the right adductor pollicis muscle through Ag-AgCl electrodes (Conmed ClearTrace ECG Sensor Electrodes Utica, NY) placed over the muscle belly and the lateral aspect of the first metacarpophalangeal joint following skin preparation. EMG signals were amplified (X100) and band-pass filtered (16–1,000 Hz) using CED 1902 amplifiers (Cambridge Electronic Design, Cambridge, UK). Force and EMG data were recorded to a computer with a 12-bit A/D converter (CED 1401 Plus) and Spike2 software (v 6.06, CED). Force was sampled at 1,000 Hz and amplified by 10 via a sample and hold amplifier. EMG was sampled at 2,000 Hz.

Ulnar nerve stimulation. To determine the maximal compound muscle action potential (Mmax), a constant-current stimulator (model DS7A, Digitimer, Welwyn Garden City, UK) delivered single stimuli (500 μs pulse width) through self-adhesive electrodes. The cathode was placed at the elbow lateral to the medial epicondyle along the postcondylar groove and the anode 1–2 cm distal to the cathode along the direction of the nerve. A single stimulus was delivered with increasing intensity until the peak-to-peak amplitude of the M wave from adductor pollicis showed no further increase. The stimulus intensity (13–60 mA) was set to 150% of the current required to elicit Mmax. Paired stimuli (doublet) with an interstimulus interval of 10 ms were delivered throughout the rest of the experiment. The resting twitch elicited by high-frequency paired stimuli is less susceptible to fatigue than that elicited by a single stimulus and is therefore more appropriate for estimating voluntary activation (2, 10, 57).

Experiment 2: elbow flexion after a 2-min MVC of adductor pollicis with and without subsequent ischemia of the hand. The subject was seated at a table with the right arm held in supination, 90° of shoulder flexion, and 90° of elbow flexion. The arm was fixed at the wrist to a stationary arm bar designed to measure torque about the elbow via a force transducer (XTran: linear to 1kN) (3). The alignment of the thumb was the same as in Experiment 1, except the thumb was placed against a concave, rounded knob attached to a force transducer (XTran: linear to 100 N). The device fitted between the thumb and the metacarpal heads and was designed to measure the force of thumb adduction generated by contraction of adductor pollicis (Fig. 1B). Tape secured the transducer to the hand to ensure that it did not slip. Forces and EMG signals for biceps and triceps brachii were sampled.
as in Experiment 1. Electrode placement for both muscles was in a belly-tendon configuration.

Brachial plexus stimulation. To determine Mmax for biceps and triceps brachii, the same constant-current stimulator was used (200 µs pulse width). The cathode was placed in the supraclavicular fossa over Erb’s point and the anode over the acromion. At the start of the experiment and prior to performing any contractions, single stimuli were delivered with increasing intensity until the peak-to-peak amplitude of M waves from biceps and triceps showed no further increase. No further brachial plexus stimulation was used.

Transcranial magnetic stimulation (TMS). TMS was delivered using a circular coil (13.5-cm outside diameter; Magstim 200, Magstim, Whitland, UK) oriented to preferentially activate the left motor cortex and the muscles of the right arm. TMS intensity was set for measurement of voluntary activation of the elbow flexor muscles. It was selected such that during an elbow flexor contraction of 50% MVC the amplitude of the motor evoked potential (MEP) in biceps brachii was 70% of Mmax or greater, whereas the triceps MEP was 15% of Mmax or less during an elbow flexor MVC (55). This intensity of stimulation (47–80% stimulator output) was used for each trial. The area of biceps brachii MEPs was normalized to that of Mmax obtained at the start of the experiment (e.g., 55).

Experimental procedures. Subjects attended on 2 days at least 2 days apart for each experiment. On 1 day, a sphygmomanometer cuff was inflated at times to block blood flow to the hand. Subjects were randomly assigned to perform the “cuff” or “no-cuff” trial first. The cuff was 72 mm wide. For Experiment 1, the cuff was positioned on the upper third of the forearm just distal to the antecubital fossa (Fig. 1A). To minimize any compression of the muscles of the elbow and to eliminate metabolite accumulation from the forearm muscles, the cuff in Experiment 2 was placed just proximal to the strap securing the wrist to the arm bar (Fig. 1B). When required, the cuff was inflated to 300 mmHg using compressed air, which ensured inflation in ~1 s. After the 2 min of sustained ischemia, subjects were asked to rate the pain felt in the hand during the ischemic period on a 0–11 scale (9).

Experiment 1: thumb adduction after a 2-min MVC of adductor pollicis with and without subsequent ischemia. Subjects began the experiment with three brief (2–3 s) MVCs of adductor pollicis. A 90-s rest separated each control MVC to minimize fatigue. Doublets were delivered during each contraction and at rest, ~2 s after the contraction. On the day of the “cuff” trial, the cuff was inflated ~5 s before the start of each MVC and deflated after the resting doublet was delivered. Subjects then performed a 2-min sustained adductor pollicis MVC. Doublets were delivered every 10 s. All subjects were given verbal encouragement and visual feedback to provide maximal effort. During the “cuff” trial, the cuff was inflated 5 s prior to the end of the 2-min contraction. The cuff remained inflated for 2 min while subjects performed five brief MVCs of adductor pollicis with the first at 20 s after the end of the sustained contraction. The first, second, and third contractions were separated by 20 s and the remaining two contractions followed every 30 s thereafter until the end of the 2 min. A doublet was delivered during each brief MVC and followed by a resting doublet. The cuff was then deflated and subjects performed a further four contractions over the next 3 min (Fig. 2). For the “no-cuff” trial the procedure was the same but the cuff was not inflated prior to control MVCs or following the 2-min fatiguing contraction.

Experiment 2: elbow flexion after a 2-min MVC of adductor pollicis with and without subsequent ischemia of the hand. First, subjects performed six sets of control contractions of the elbow flexors, three with the cuff inflated about the wrist and three without. Each contraction set began with a brief MVC followed by two brief submaximal (75% and 50% MVC) contractions with ~8 s between contractions and with 90 s rest between sets to minimize fatigue. TMS was delivered during each contraction. The target forces for the submaxim-
mal contractions were always derived from the MVC of that set. For familiarization, subjects also performed three brief MVCs of adductor pollicis with 90-s rests. Subjects then performed a sustained 2-min adductor pollicis MVC but without stimulation. As in Experiment 1, during the “cuff” trial, the cuff was inflated 5 s prior to the end of the 2-min sustained contraction to maintain ischemia of the hand. The cuff remained inflated about the wrist for 2 min while the subject performed four of the same elbow flexor contraction sets as described above but with 10 s rest between sets. After the 2 min of ischemia, the cuff was deflated and subjects performed a further four contraction sets of the elbow flexors over the next 2 min (Fig. 2). For the “no-cuff” trial, the procedure was the same but the cuff was not inflated after the 2-min fatiguing adductor pollicis contraction.

Data analysis and statistics. All measures were analyzed off-line using Signal software (v. 4.06; CED). Mean force or torque of each contraction was measured over the 100 ms prior to stimulation. For each subject the highest measured force or torque in a control MVC was treated as the peak MVC force or torque. Forces and torques of other MVCs during that experiment were normalized to this value. Superimposed twitches of adductor pollicis during the 2-min sustained MVC were measured and expressed as a percentage of the ongoing MVC force. The amplitude of resting twitches of adductor pollicis was measured and also normalized to the peak MVC force. For Experiment 1, voluntary activation of adductor pollicis was calculated for each MVC by using the equation: voluntary activation (%) = [1-(superimposed twitch/resting twitch)] × 100. For Experiment 2, voluntary activation of the elbow flexor muscles was calculated for each MVC with the same equation but substituting the resting twitch with an estimated resting twitch which was derived from the y-intercept of the linear regression between the size of the evoked twitch from TMS and voluntary torque at MVC, 75% and 50% of that MVC (55, 56). Traces of superimposed twitches (both experiments) and resting twitches (Experiment 1) can be seen in Fig. 3. Biceps brachii MEP area was measured between cursors set from the initial deflection from baseline to the second crossing of the horizontal axis and normalized to the area of resting Mmax recorded at the start of the experiment.

Baseline measures and measures during sustained MVCs were compared using paired sample t-tests. Two-way repeated-measures ANOVAs were used to examine the effect of ischemia during the 2 min following the sustained MVC on voluntary activation, MVC force, and resting twitch amplitude of adductor pollicis in Experiment 1 and voluntary activation, MVC torque, and estimated resting twitch amplitude for the elbow flexor muscles in Experiment 2. For Experiment 1, factors in the 2 × 6 analyses were trial (ischemia/no ischemia) and time (mean value for control MVCs and data for five MVCs in the 2 min with or without ischemia). For Experiment 2, the same factors were examined in 2 × 5 analyses, as only four MVCs were performed during the 2 min after the sustained MVC. Pairwise multiple comparisons were made using a Tukey’s HSD test. Data are given in the text as mean ± SD and shown in the figures as mean ± SEM. Significance was set at *P* < 0.05.

RESULTS

Experiment 1: thumb adduction after a 2-min MVC of adductor pollicis with and without subsequent ischemia. On separate days, subjects performed brief MVCs of adductor pollicis with and without maintained ischemia (“cuff”/“no-
The 2-min contraction was lower than the mean voluntary during the first, second, and third of the five brief MVCs after
main effects of trial (F1,9 = 0.001). Asterisk indicates statistically significant difference between the contractions performed with the cuff inflated and corresponding contractions when blood flow was allowed (filled rectangle).
analysis showed that the resting twitch was smaller in the “cuff” vs. the “no-cuff” trial for all five brief MVCs after the 2-min contraction (P = 0.02 to P < 0.001). In both trials the size of the resting twitch during the five brief MVCs after the 2-min contraction was smaller compared with those during control trials (P < 0.001).

Pain perception on the Borg scale (0–11) during the “cuff” trial ranged from 2.5 (Weak to Moderate) to 5.5 (Strong) with a mean rating of 5.3 (Strong). Pain was described as being localized to the right hand and/or the thumb. Perceived pain during the “no-cuff” trial was rated from 0 (Nothing at all) to 0.5 (Extremely weak).

**Experiment 2: elbow flexion after a 2-min MVC of adductor pollicis with and without subsequent ischemia of the hand.** Subjects performed a 2-min sustained MVC of adductor pollicis. In contrast to Experiment 1, subjects then performed brief elbow flexor MVCs with (“cuff” trial) and without (“no-cuff” trial) maintained ischemia of the hand. Elbow flexor MVC torque prior to the sustained contraction of adductor pollicis did not differ on the 2 trial days (“cuff” trial, 64.6 ± 22.4 Nm; “no-cuff” trial, 66.0 ± 22.8 Nm; P = 0.15), nor did voluntary activation of elbow flexors (95.2 ± 2.3% vs. 95.9 ± 3.0%; P = 0.32) or the size of the estimated resting twitch (10.6 ± 3.3% vs. 10.8 ± 2.7% peak MVC torque; P = 0.8). The area of biceps brachii motor evoked potentials recorded during MVCs also did not differ on the 2 trial days (57.1 ± 20.0% Mmax, vs. 59.1 ± 22.5% Mmax; P = 0.73). Adductor pollicis force during the 2-min sustained MVC declined a similar amount (51.1 ± 14.7% and 56.4 ± 13.6% peak MVC force decrease; P = 0.17) during the “cuff” and “no-cuff” trials, respectively.

Mean elbow flexor torque during the four brief MVCs after the sustained 2-min adductor pollicis contraction was lower in the “cuff” trial (80.2 ± 4.6% of peak MVC in control trials) than in the “no-cuff” trial (86.6 ± 1.0%) and both were decreased from the mean torque in control trials (93.7 ± 3.4%; Fig. 5A). Two-way repeated-measures ANOVA examining MVC torque showed significant main effects of trial (F1,9 = 5.64, P < 0.05) and time (F4,36 = 40.87, P < 0.001) and a significant interaction (F4,36 = 2.69, P = 0.05). Post hoc analysis showed that the final three brief elbow flexor MVCs after the 2-min sustained contraction were lower in the “cuff” vs. the “no-cuff” trial (P = 0.04 to P = 0.006). In the “cuff” trial, torque during all four brief MVCs after the 2-min contraction was lower compared with the mean torque in control trials (P = 0.003 to P < 0.001). In the “no-cuff” trial, torque in all but the first brief MVC following the sustained contraction was reduced relative to the mean torque in control trials (P = 0.12 for the first MVC; P < 0.001 for the second, third, and fourth MVCs).

Mean voluntary activation of the elbow flexors during the four brief MVCs after the sustained 2-min adductor pollicis contraction was also lower in the “cuff” trial vs. the “no-cuff” trial (88.3 ± 7.5% vs. 93.6 ± 3.9%; Fig. 5B). Two-way repeated-measures ANOVA showed significant differences between voluntary activation in the two trials (F1,9 = 11.63, P = 0.006).
trials (F1,9 = 5.44, \( P = 0.002 \)), with a significant interaction (F1,9 = 2.65, \( P < 0.05 \)). Post hoc analysis shows that the final three brief MVCs after the 2-min sustained contraction were lower in the “cuff” trial compared with the “no-cuff” trial (\( P = 0.05 \) to \( P = 0.001 \)). In the “cuff” trial, voluntary activation was lower for the final three brief MVCs after the 2-min contraction compared with mean voluntary activation during control MVCs (\( P = 0.006 \) to \( P < 0.001 \)). In the “no-cuff” trial, there were no differences in voluntary activation from the control MVCs.

The mean size of the estimated resting twitch during the four brief MVCs after the sustained 2-min adductor pollicis contraction was 9.9 ± 3.1% peak MVC torque in the “cuff” trial and 11.3 ± 3.5% in the “no-cuff” trial (Fig. 5C). Two-way repeated-measures ANOVA showed no differences between trials (F1,9 = 2.69, \( P = 0.14 \)) or over time (F4,36 = 1.24, \( P = 0.67 \)). Likewise, there were no differences between the biceps brachii MEP areas in brief MVCs between trials (F1,9 = 0.16, \( P = 0.7 \)) or over time (F4,36 = 1.45, \( P = 0.24 \)).

Ratings of pain during the “cuff” trial ranged from 3 (Moderate) to 8 (Very strong) with a mean rating of 4.5 (Moderate to Strong). Pain was described as being localized to the right hand and/or the thumb. Perceived pain during the “no-cuff” trial was rated from 0 (Nothing at all) to 0.5 (Extremely weak).

**DISCUSSION**

The main finding of this study is that maintained firing of group III and IV muscle afferents in the hand after a fatiguing contraction of adductor pollicis contributes to decreased voluntary activation and torque of the unfatigued elbow flexor muscles. In addition, maintained firing of these afferents decreased voluntary activation and force production of the fatigued adductor pollicis. These findings extend those of our recent study, which demonstrated that maintained firing of fatigue-sensitive afferents of antagonist muscles impairs voluntary activation of the agonist elbow flexors (32). The data indicate that fatigue-induced nociceptive group III and IV muscle afferent feedback leads to widespread decreases in central drive to muscles in the same limb.

During and following a sustained maximal effort there is a reduction in the ability of the muscles to generate force. A contribution of central mechanisms to this fatigue is indicated by a progressive increase in superimposed twitch size during the sustained effort and a reduced voluntary activation in the recovery period afterward. Voluntary activation is calculated by comparing the additional force (superimposed twitch) evoked by a supramaximal stimulus during a maximal voluntary contraction to the force evoked from the resting muscle by the same stimulus (22, 45). In the present study we used ulnar nerve stimulation to show that a fatiguing voluntary contraction of adductor pollicis results in central fatigue. After the fatiguing sustained MVC, when blood flow to the hand was not occluded, voluntary activation and force increased progressively despite the performance of multiple brief MVCs. In contrast, when the hand was held ischemic after the end of the fatiguing contraction, voluntary activation was lower than when blood flow was allowed. Concomitantly, peripheral fatigue was also increased during the 2 min of ongoing ischemia as demonstrated by the smaller resting twitch. These results are consistent with previous studies using similar protocols to prevent muscle recovery after a fatiguing contraction (e.g., 10, 59). However, while impaired voluntary activation of adductor pollicis during postfatigue ischemia has previously been reported, the specific effect of the ischemia was unclear as the influence of fatigue without subsequent ischemia was not reported (59). In the current study both the preceding fatigue produced by a 2-min MVC and the subsequent ischemia reduced voluntary activation. The increase in central fatigue with ischemia is likely due to feedback from group III and IV muscle afferents. As we used peripheral nerve stimulation to determine voluntary activation, we cannot ascertain at what level in the motor pathway group III and IV muscle afferent effects occurred. Hence, contributions from spinal inputs to central fatigue cannot be ruled out. However, a similar effect of group III and IV muscle afferent feedback has been shown for the elbow flexors and this effect is supraspinal (13, 32). Thus it would be predicted that group III and IV afferents innervating the hand muscles also act at a supraspinal level to increase central fatigue.

Our results also show that when ischemia of the hand is maintained after a fatiguing contraction of adductor pollicis, voluntary activation of nonexercised elbow flexors decreases and this decrease in central drive contributes to an overall reduction in torque. The decrease in voluntary activation of the nonexercised elbow flexors was less (~5%) than the effect of ongoing postfatigue ischemia of the hand on voluntary activation of the fatigued adductor pollicis (~20%). Likewise, this effect of group III and IV afferents from small, distal hand muscles on nonexercised elbow flexors was not as large as that shown previously for afferents from large, proximal muscles, the elbow extensors (~14%; 32). It is not clear whether the progressive decline in voluntary activation of the elbow flexors over the period of ischemia should be called central fatigue, as it did not come about through exercise of the elbow flexors. However, it does depend on fatiguing exercise even though this was performed by other muscles. We have shown previously that voluntary activation of the elbow flexors is unchanged by ischemic contractions without prior fatigue (32). In the current study, maximal voluntary torque of unfatigued elbow flexors was reduced in the “no-cuff” as well as the “cuff” trial in the 2 min after the sustained MVC, but voluntary activation in the “no-cuff” trial was not significantly decreased. This slight fatigue is probably due to the large number of strong contractions over the short period of time and, consistent with our previous findings, the lack of change in voluntary activation suggests a negligible contribution from central mechanisms.

A possible mechanism to explain group III and IV afferent feedback from distal muscles affecting proximal muscles comes from animal studies investigating referred pain. These studies suggest that there is convergence and divergence of muscle nociceptive connections at the spinal cord (51, 60). Afferents from one muscle may have connections to dorsal horn neurons that receive signals primarily from other nearby muscles. This input may excite these dorsal horn neurons in the absence of noxious input from their primary muscles and convey nociceptive signals to higher centers (25, 26, 42). In addition, this divergent excitation of dorsal horn neurons appears to spread rostrally, which may account for nociceptive signaling of more proximal muscles when distal muscles are stimulated (24, 42, 52). A 2-min maximal contraction followed by 2 min of ischemia may provide sufficient nociceptive...
In addition, increased lactate concentrations can also enhance high concentrations of these metabolites (e.g., 30, 38, 41, 43). Occlusion will have prevented their clearance. Group III and IV of interstitial muscle ATP, H^+ sustained contraction should have resulted in high concentrations levels suggesting high nociceptive input. The maximal susceptibility measured during maximal voluntary efforts was unaffected even with continued ischemia and feedback from group III and IV muscle afferents. While there is no direct evidence for an effect of group III and IV afferents from the hand muscles on motoneurons of the elbow flexors, this motoneuron pool has been shown to be facilitated by afferents from both the elbow flexors and extensors (39, 40). In spite of this facilitation, insufficient motor cortical drive and impaired voluntary activation of the elbow flexors occurs after a fatiguing contraction of either the elbow flexors or extensors when group III and IV muscle afferent firing is maintained (32). Thus it is probable that group III and IV muscle afferents from hand muscles, like those of the elbow flexors and extensors, act at a supraspinal level and do not directly inhibit the motoneurons of the elbow flexors. In the present study the combination of maximal isometric exercise and subsequent ischemia likely activates a subset of group III and IV muscle afferents classified as nociceptors responding strongly to noxious stimuli similar to other forms of high-intensity exercise (11, 28) and ischemic exercise that is painful, like that in patients with vaso-occlusive disease (17, 35, 48). During the 2 min of ongoing ischemia, subjects reported Moderate to Strong pain levels suggesting high nociceptive input. The maximal sustained contraction should have resulted in high concentrations of interstitial muscle ATP, H^+, and lactate, and circulatory occlusion will have prevented their clearance. Group III and IV muscle afferents classified as nociceptors respond strongly to high concentrations of these metabolites (e.g., 30, 38, 41, 43). In addition, increased lactate concentrations can also enhance acid-sensing Na^+ channels in nociceptive group III and IV muscle afferents, increasing their responses to ischemia (29). The reduction of voluntary activation and force for adductor pollicis and torque for elbow flexors during the 2 min of ongoing ischemia of the hand was not seen immediately. Voluntary activation and force or torque during the first contraction in the “cuff” trial was not statistically different from that in the “no-cuff” trial in either experiment. After a fatiguing contraction of adductor pollicis voluntary activation and force of adductor pollicis in the “no-cuff” trial steadily recovered while in the “cuff” trial both remained low until blood flow was restored. Elbow flexor voluntary activation in the “no-cuff” trial was unchanged during the 2 min after the sustained adductor pollicis contraction, whereas in the “cuff” trial voluntary activation was reduced ~40 s into the 2 min of ischemia and remained low until blood flow was restored. This delayed effect may be due to the duration of nociceptive input (temporal summation) needed to excite nearby dorsal horn neurons in the spinal cord as discussed above (26, 42). Given the high pain responses from our subjects and the use of maximal contractions followed by maintained ischemia, it is likely that the afferents responsible for the decrease in central drive to both the fatigued adductor pollicis and the unfatigued elbow flexors are nociceptive group III and IV muscle afferents. However, it should be noted that experimental muscle pain, produced through intramuscular injection of hypertonic saline, had little effect on voluntary activation of the elbow flexors (33). Hence the effect on voluntary drive may require specific classes or firing patterns of afferents activated by fatigue-producing exercise.

The broad effect of fatigue-sensitive nociceptive group III and IV muscle afferent feedback to limit central drive to muscles other than the exercised muscle has implications for whole-body exercise. During cycling to exhaustion, spinal injection of fentanyl, which likely blocks both mechano- and nociceptive subtypes of group III and IV muscle afferents and probably reduces contraction-evoked release of substance P (a neuropeptide that is released by small diameter afferents and that can excite multiple sites, particularly in the dorsal horn of the spinal cord) (58), increased central motor drive, attenuated cardiorespiratory responses, and increased peripheral muscle fatigue (4). These findings suggest that group III and IV muscle afferent feedback can reduce voluntary drive and contribute to cardiorespiratory responses during high-intensity cycling. This complements our finding that the effects of nociceptive group III and IV muscle afferents on central motor drive are not confined to a fatigued muscle and its synergists. Our finding raises the possibility that nociceptive feedback from multiple muscles in the one limb may have additive effects on central drive so that high-intensity multijoint exercise may be particularly prone to central fatigue. In addition, it suggests between-muscle interactions, in which feedback from more fatigued muscles can alter performance of less fatigued muscles. Such an effect could be particularly relevant when vascular pathology results in muscle pain with exercise. For example, foot or calf pain during walking may impair drive to the knee or hip muscles and thus impair gait.

In conclusion, activity in group III and IV muscle afferents from fatigued adductor pollicis can decrease central drive and voluntary force during a maximal contraction of this muscle. This effect also limits neural drive to and torque production of proximal, unfatigued muscles in the same limb, the elbow flexors. The responsible afferents are probably muscle nociceptors given the maximal fatiguing contraction with subsequent ischemia and the high level of subjective pain. This has implications for high-intensity exercise and for painful exercise in patients with vaso-occlusive disorders.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

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