Central excitability does not limit postfatigue voluntary activation of quadriceps femoris

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Submitted 21 October 2005; accepted in final form 9 January 2006

Kalmar, J. M., and E. Cafarelli. Central excitability does not limit postfatigue voluntary activation of quadriceps femoris. J Appl Physiol 100: 1757–1764, 2006. First published January 19, 2006; doi:10.1152/japplphysiol.01347.2005.—After fatigue, motor evoked potentials (MEP) elicited by transcranial magnetic stimulation and cervicomедullary evoked potentials elicited by stimulation of the corticospinal tract are depressed. These reductions in corticomotor excitability and corticospinal transmission are accompanied by voluntary activation failure, but this may not reflect a causal relationship. Our purpose was to determine whether a decline in central excitability contributes to central fatigue. We hypothesized that, if central excitability limits voluntary activation, then a caffeine-induced increase in central excitability should offset voluntary activation failure. In this repeated-measures study, eight men each attended two sessions. Baseline measures of knee extension torque, maximal voluntary activation, peripheral transmission, contractile properties, and central excitability were made before administration of caffeine (6 mg/kg) or placebo. The amplitude of vastus lateralis MEPs elicited during minimal muscle activation provided a measure of central excitability. After a 1-h rest, baseline measures were repeated before, during, and after a fatigue protocol that ended when maximal voluntary torque declined by 35% (Tlim). Increased prefatigue MEP amplitude (P = 0.055) and cortically evoked twitch (P < 0.05) in the caffeine trial indicate the drug increased central excitability. In the caffeine trial, increased MEP amplitude was correlated with time to task failure (r = 0.74, P < 0.05). Caffeine potentiated the MEP early in the fatigue protocol (P < 0.05) and offset the 40% decline in placebo MEP (P < 0.05) at Tlim. However, this was not associated with enhanced maximal voluntary activation during fatigue or recovery, demonstrating that voluntary activation is not limited by central excitability.

Twitch interpolation (23), as well as surface and intramuscular electromyography (EMG) (6), are frequently used to assess fatigue-induced changes in central drive during voluntary muscle activation. Cortically evoked potentials, on the other hand, offer the opportunity to assess the effects of fatigue on the excitability of the central motor pathway during muscle activation as well as at rest (18). A prolonged decline in the amplitude of the resting motor evoked potential (MEP) elicited by transcranial magnetic stimulation (TMS) has been observed after fatiguing voluntary contractions (10, 28, 33, 51, 52). Because potentials evoked by transcranial electrical stimulation do not undergo the same long-lasting postexercise depression, the phenomenon has been attributed to a reduction in the excitability of the motor cortical neuron (9, 40, 52). Potentials evoked by cervicomедullary stimulation of the descending corticospinal tract (CMEP) are also transiently depressed after fatigue, suggesting that corticospinal transmission is impaired after strong or prolonged voluntary muscle activation (13, 21, 47, 58). Whereas it would seem that these impairments could account for voluntary activation failure, the postfatigue decline in MEP and CMEP recovers within seconds when assessed during high-intensity muscle activation (13, 47, 54–56). This suggests that strong voluntary drive may overcome the reductions in cortical excitability and corticospinal synaptic transmission that are evident at rest. Nonetheless, Petersen et al. (47) report that the reductions in corticospinal transmission do affect voluntary activation. We sought to manipulate the excitability of the central motor pathway, using a central nervous system stimulant such as caffeine, to determine the role of hypoexcitability in voluntary activation failure.

Our laboratory has previously demonstrated the effects of caffeine on the voluntary activation of a large locomotor muscle group (26, 48) and has advocated the use of this central nervous system stimulant as a tool to study central fatigue (27). In the first central fatigue investigation to use caffeine as a perturbation of central excitability, we observed a reduction in the amplitude of the first dorsal interosseous muscle MEP after repetitive submaximal isometric contractions that was offset by caffeine (28). However, the effect of caffeine on central excitability was not associated with a delay in task failure or enhanced maximal voluntary activation of this intrinsic hand muscle (28). Furthermore, substantial peripheral transmission failure made it difficult to interpret the fatigue-induced decline in MEP and surface EMG in this experiment. In this earlier study, we normalized the MEP to the M wave to account for peripheral transmission failure (28). However, we noted that the rapid and nonlinear decline in peripheral transmission over the course of the fatigue protocol limits the accuracy of the normalized MEP and surface EMG as measures of central excitability.

The purpose of the present experiment was to determine whether a decline in central excitability contributes to central fatigue. To facilitate the interpretation of the MEP and surface EMG, we utilized the quadriceps femoris, a muscle group that has not demonstrated peripheral transmission failure in previous experiments (26, 48). In so doing, the cortically evoked MEP should provide an estimate of central excitability that is unencumbered by peripheral failure. We hypothesized that, if the voluntary activation of muscle is limited by a decline in resting central excitability, then a caffeine-induced increase should delay task failure and enhance postfatigue voluntary activation and maximal voluntary torque.
MATERIALS AND METHODS

Subjects

Eight men [22.5 yr (SD 1.9), 72.4 kg (SD 13.8)] participated in this repeated-measures, randomized, double-blind study. Because habitual caffeine consumption diminishes the effects of an acute dose (4), only subjects with a self-reported caffeine intake of <250 mg/wk were accepted. Because we did not measure plasma caffeine directly in this study, we used a pool of subjects that was homogenous with respect to a number of variables known to alter caffeine pharmacokinetics. We used only nonsmoking men of average body mass because smoking (46) and obesity (29) increase the rate of caffeine degradation. We did not use women in this study because cortical excitability fluctuates during the menstrual cycle (53) and because caffeine clearance is diminished during the luteal phase of the menstrual cycle (31) and by oral contraceptive use (1). Applicants with neurological pathologies or symptoms (loss of sensation, altered sensation, weakness, pain) and those using medications, nutritional supplements (other than multivitamins), or ergogenic aids were also excluded from the study.

Participants were introduced to the experimental apparatus as well as the electrical and magnetic stimuli and practiced making maximal voluntary contractions (MVCs) during an orientation session. At the end of the orientation, subjects were instructed to abstain from consuming caffeine-containing foods, beverages, and medication from 1 wk before and throughout the duration of the study. They were also asked to avoid alcohol and exhaustive exercise the day before each session. Finally, subjects were instructed to eat the same breakfast on each experimental day and asked to reschedule if they were ill or slept poorly the night before an experiment. Each subject read and signed an informed consent document and was paid for their participation in the study. The investigation conformed to the Declaration of Helsinki and was approved by the institutional human subjects review committee.

Apparatus

A custom-built dynamometer (York University Machine Shop) was adjusted to position both the hip and knee at 90° of flexion. A cast aluminum cuff attached to a force transducer was clamped ~2 cm above the lateral malleolus of the right leg. The dynamometer was tilted back 45° to provide full back and head support, and a lap belt was used to maintain hip angle during isometric knee extension. To prevent head movement during TMS, a padded strap was placed over the forehead and secured to either side of the headrest. Throughout the experiment, target force levels and visual feedback of force output were displayed on a large computer monitor mounted high enough to be easily viewed from the reclined position.

Protocol

Each subject attended two sessions that were 1 wk apart. Each session consisted of a precapsule test, followed by the oral administration of a gelatin capsule containing either caffeine (6 mg/kg, US Pharmacopeia-grade, A&C American Chemicals, Montreal, PQ, Canada) or a placebo (all-purpose flour). An identical postcapsule test took place 1 h after capsule administration to allow caffeine to reach peak plasma concentrations (22). The postcapsule test was followed by the fatigue task and a 15-min recovery period.

Precapsule and postcapsule tests (Fig. 1A). The precapsule test began with three attempts to produce a MVC of the knee extensors; each was followed by a 60-s rest period. A supramaximal pulse was applied to the femoral nerve (see below) during and immediately after each attempted MVC to quantify percent voluntary activation (%activation) using the twitch interpolation technique (2) and to assess maximal mass action potential (M wave) and contractile properties. Percent activation was calculated as \[ \frac{1 - (SIT/POT)}{100} \], where SIT is the amplitude of the superimposed twitch and POT is the amplitude of the potentiated twitch evoked at rest immediately after the MVC. After the third MVC, 10 TMS stimuli were applied at a rate of 0.3 Hz and at an output 10% of maximal stimulator output higher than active motor threshold (AMT; assessed at 3% MVC). The participant was then given a capsule containing either caffeine or placebo, and he rested in another room with the recording and stimulating electrodes left in place. One hour later, postcapsule recordings were made in a protocol identical to the precapsule test. Sample data are shown for the region in Fig. 1A depicted by the asterisk (Fig. 2).
Fatigue test (Fig. 1B). The fatigue protocol began immediately after the postcapsule test and consisted of sets of 10 4-s knee extension contractions made in response to voice commands played from an audiocassette. The 1st and 10th contraction of each set were MVCs, and the others were at a target force of 50% MVC displayed for the subject on a computer monitor. There was a 2-s rest between each contraction, and a 12-s rest between sets. Between each set of contractions, four TMS stimuli were applied at a rate of 0.3 Hz during minimal activation of the knee extensors (3% MVC). Supramaximal electrical stimuli were applied to the femoral nerve during and after all MVCs to assess %activation, M-wave, and contractile properties. This protocol was repeated until task failure (Tlim), defined as the point at which MVC declined by 35% of the initial MVC, despite verbal encouragement.

Recovery test (Fig. 1C). Recovery measures were made at 0 (Tlim), 5, 10, and 15 min from the point of task failure. Recovery measures included MVC followed by 10 TMS stimuli applied at a rate of 0.3 Hz during minimal (3% MVC) knee extension. Supramaximal electrical stimuli were applied to the femoral nerve during and after all MVCs to assess %activation, M-wave, and contractile properties.

TMS

The optimal coil position for eliciting a MEP in the vastus lateralis was determined on arrival at the laboratory each day. This was accomplished by setting the transcranial magnetic stimulator (model MES-10, Cadwell Laboratories, Kennewick, WA) at 80% maximal output and moving an angled figure-8 coil (Cadwell Laboratories, Kennewick, WA) over the vertex to locate the position eliciting the largest MEP in the vastus lateralis. This position was marked on a tight-fitting swim cap, or directly onto the scalp of subjects with very short hair.

Resting motor threshold is typically higher for lower extremity muscles than for distal hand muscles (12), which are more frequently used in TMS studies. During pilot work, we found that resting motor threshold of quadriceps MEPs was frequently greater than 90% maximal stimulator output and that, in some subjects, it was not possible to evoke MEPs in the resting quadriceps. We also found that quadriceps MEP amplitude was extremely inconsistent with the muscle at rest. Therefore, in the present study, we had subjects hold a very low level contraction (3% MVC) during TMS to facilitate the MEP. This low level of activation does not offset postexercise depression of the MEP (47). AMT [on average, 60.2% (SD 9.5) maximal stimulator output] was determined at the beginning of both the precapsule and postcapsule tests by reducing the stimulator output in 2% increments until an MEP exceeding 50 µV was elicited by 5 of 10 stimuli. The stimulator was then set at AMT + 10% maximal stimulator output. During analysis, MEPs were excluded if force output deviated from the 3% MVC target.

Electrical Stimulation

The femoral nerve was stimulated using a 2.5 × 2.5-cm cathode over the femoral nerve in the femoral triangle and a 12.5 × 7-cm anode placed midway between greater trochanter and the iliac crest. Both electrodes were made of carbonized rubber, coated with electroconductive gel, and held in place with a Hypafix dressing retention sheet (Smith & Nephew, St. Laurent, Canada). Square pulses with a 200-µs pulse duration were applied at a current 120% of that which produced a maximal twitch (model DS7A, Digitimer, Hertfordshire, UK). The stimulus required to evoke a maximal twitch was assessed at the beginning of both the precapsule and postcapsule test, but it varied no more than 5% from pre- to postcapsule for any subject.

EMG

Bipolar silver-silver chloride recording electrodes with a 0.8-cm diameter and interelectrode distance of 2.0 cm (EQ, Chalfont, PA) were centered over the vastus lateralis ~7 cm proximal to the superior border of the patella. The skin under both electrodes was shaved, exfoliated, and swabbed with 70% isopropyl alcohol. A water-soaked strap electrode was wrapped around the leg and covered with plastic wrap to serve as a ground. The surface EMG was preamplified at the source and passed through a variable-gain second-stage amplifier.

Data Acquisition and Processing

Amplified torque and EMG signals were pulse-code modulated (model 4000A, Vetter Digital, Rebersberg, PA) and stored on video-cassette (model SLV-N80, Sony VCR) for offline analysis. Stored signals were analog-to-digital converted (micro1401, CED, Cambridge, UK) and analyzed using Spike2 for Windows (version 4, CED, Cambridge, UK). Torque was digitized at a rate of 1,000 Hz and low-pass filtered (50-Hz cutoff). Vastus lateralis EMG was digitized at a rate of 2,500 Hz and high-pass filtered (20-Hz cutoff).

Statistical Analysis

Statistical analysis was performed using Statistica, version 6 (StatSoft, Tulsa, OK). The effects of caffeine and placebo before the
fatigue protocol (i.e., see Fig. 4) were compared using dependent $t$-tests. The fatigue and recovery data were analyzed using two-way (drug/time) ANOVA to test for main effects and interactions. Contrast analysis was used to test for differences when ANOVA revealed a significant main effect or interaction. An $\alpha$-value of 0.05 was adjusted using the modified Bonferroni method [(0.05/degrees of freedom for effect) x number of comparisons] to reduce the incidence of type I error. For the fatigue protocol, only those sets completed by all subjects, including set 1, set 2, and the final set ($T_{lim}$) were included in statistical analysis and figures. Data are presented as means (SD), unless otherwise indicated.

RESULTS

Contractile Properties and Peripheral Transmission

Caffeine did not alter maximal M-wave amplitude ($M_{amp}$; A), peak twitch tension (PTT; B), or the maximal instantaneous rate of twitch relaxation ($-dF/dt$; C) are expressed as a percentage of the prefatigue [postcapsule (postcap)] value during the caffeine (▼) and placebo (▲) trials. M waves and contractile properties evoked immediately after the final MVC of the first 2 sets of the fatigue protocol are shown because all subjects were able to complete these sets. *Significant difference from the postcap value for the pooled caffeine and placebo data, $P < 0.05$.

Central Excitability and Maximal Voluntary Activation

Prefatigue effects of caffeine. There was a precapsule to postcapsule change in MEP amplitude of 40.9% (SD 31.68) in the caffeine trial and 0.6% (SD 14.14) in the placebo trial. Caffeine $\Delta$MEP was not significantly higher than placebo $\Delta$MEP ($P = 0.055$); however, the $P$ value should be noted. The pre- to postcapsule change in the accompanying cortically evoked twitch was significantly greater in the caffeine trial ($P < 0.05$; Fig. 4A). The pre- to postcapsule change in maximal voluntary torque and change in %activation were also higher in the caffeine trial compared with the placebo (Fig. 4B). However, the pre- to postcapsule change in the root mean square of the maximal surface EMG (RMS$_{max}$) did not differ

fatigue protocol but showed no evidence of peripheral transmission failure (Fig. 3A). Identical statistical procedures revealed a main effect of time for PTT [$F = 12.93(6,42), P < 0.01$; Fig. 3B] as well as $-dF/dt$ [$F = 13.83(6,42), P < 0.01$; Fig. 3C]. Both declined over the course of the fatigue protocol and remained depressed throughout the recovery period. There was no main effect of drug or interaction between drug and time for any of these analyses; thus caffeine did not alter $M_{amp}$, PTT, or $-dF/dt$ at any time point during fatigue or recovery (Fig. 3).

Fig. 3. Changes in peripheral transmission and contractile properties during fatigue and recovery M-wave amplitude ($M_{amp}$; A), peak twitch tension (PTT; B), and the maximal instantaneous rate of twitch relaxation ($-dF/dt$; C) are expressed as a percentage of the prefatigue [postcapsule (postcap)] value during the caffeine (▼) and placebo (▲) trials. M waves and contractile properties evoked immediately after the final MVC of the first 2 sets of the fatigue protocol are shown because all subjects were able to complete these sets. *Significant difference from the postcap value for the pooled caffeine and placebo data, $P < 0.05$.

Fig. 4. Pre- to postcapsule changes in TMS-evoked responses and voluntary activation. Percent change from precapsule to postcapsule is shown for MEP amplitude and TMS-evoked twitch (PTT$_{TMS}$) amplitude (A) and for maximal voluntary torque and %activation (B) in the caffeine trial (solid bars) and placebo trial (shaded bars). NS, not significant. *Significant difference between caffeine and placebo, $P < 0.05$. 

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between the caffeine (3.0% (SD 10.9)) and placebo (3.1% (SD 13.6)) trials.

**Effects of caffeine during fatigue and recovery.** There was a significant correlation \((r = 0.74, P < 0.05)\) between the pre- to postcapsule increase in central excitability and the number of sets completed in the caffeine trial (Fig. 5). On average, the number of sets completed in the fatigue protocol was the same in the caffeine and placebo trials with 5.0 (SD 3.7) and 5.1 (SD 2.5) sets, respectively. It should be noted, however, that the postcapsule MVC, and therefore the 50% target, was higher in the caffeine trial. ANOVA for MEP amplitude during fatigue and recovery revealed a significant interaction between drug and time \([F = 5.15(6, 42), P < 0.01]\). Planned comparisons therefore included postcapsule vs. set 1, set 2, 0 min, 5 min, 10 min, and 15 min for each of the two drug conditions and caffeine vs. placebo at each of the fatigue and recovery time points (18 comparisons in total). Accordingly, significance was set to \(P < 0.016\) using the modified Bonferroni correction factor. During the fatigue protocol, placebo MEP amplitude was significantly depressed at Tlim, but it fully recovered within 5 min (Fig. 6). Caffeine MEP amplitude was significantly potentiated at the end of the second set of contractions and returned to prefatigue amplitude by Tlim (Fig. 6). There was a main effect of time for maximal voluntary torque \([F = 12.56(6, 42), P < 0.01; \text{Fig. 7A}]\) and maximal root-mean-square amplitude \([F = 5.04(6, 42); \text{Fig. 7B}]\) as well as %activation \([F = 3.33(6, 42), P < 0.01; \text{Fig. 7C}; P < 0.01]\), but there was no effect of drug and no interaction. Because caffeine had no effect on voluntary activation RMSmax, or %activation, the two drug conditions were pooled. Contrasts included postcapsule vs. set 1, set 2, 0 min, 5 min, 10 min, and 15 min (6 comparisons), and significance was \(P < 0.05\) using the modified Bonferroni correction factor. Maximal voluntary torque was depressed from the first set of the fatigue protocol up until 10 min of recovery. Maximal voluntary EMG was depressed only at 5 min of recovery, whereas %activation was depressed at Tlim and 5 min of recovery.

![Fig. 5](image-url)  
**Fig. 5.** Number of sets completed expressed as a function of precapsule to postcapsule change in MEP amplitude. Linear regression reveals a significant correlation between the prefatigue increase in MEP amplitude and the number of sets completed in the caffeine trial but not the placebo trial. The line is fit to the caffeine data points only because there was no correlation between the variables in the placebo trial.

![Fig. 6](image-url)  
**Fig. 6.** Changes in central excitability during fatigue and recovery MEP amplitude are expressed as a percentage of the postcapsule value during the caffeine and placebo trials. Set 1 and set 2 data correspond to the MEPs evoked after the final MVC of these sets, which were completed by all subjects. *Significant difference from the postcapsule value within a drug treatment, \(P < 0.05\). §Significant difference between drug treatments, \(P < 0.016\).**

![Fig. 7](image-url)  
**Fig. 7.** Changes in maximal voluntary activation and torque during fatigue and recovery. Maximal voluntary contraction (A), the maximal surface EMG [maximal root mean square (RMSmax); B], and percent activation (C) are expressed as a percentage of the prefatigue (postcapsule) value in the caffeine trial (●) and placebo trial (○). Set 1 and set 2 data correspond to the final MVC of each set. SIT, amplitude of superimposed twitch; POT, amplitude of the potentiated twitch evoked at rest immediately after MVC. *Significant difference from the postcapsule value for the pooled caffeine and placebo data, \(P < 0.05\).**
DISCUSSION

Magnetic stimulation of the motor cortex during fatiguing muscle activation reveals an increase in superimposed MEP amplitude and cortical silent period duration that indicate a concurrent increase in excitability of the motor cortical neuron and cortical inhibition (39, 50, 54–56). In contrast, there is a decline in the amplitude of superimposed potentials evoked by cervicomacular stimulation of corticospinal motor axons during a fatiguing contraction that has been attributed to a reduction in spinal motoneuron excitability (13, 21). When the muscle is at rest immediately after fatigue, however, TMS-evoked MEPs are briefly facilitated and then depressed for up to 20 min (10, 28, 33, 51, 52). CMEPs also decline in amplitude when assessed with the muscle at rest after fatigue, but they recover within 2 min (21, 47). These observations are consistent with postfatigue reductions in cortical excitability (9, 40, 52) and corticospinal synaptic transmission (21, 47).

At first glance, the pronounced fatigue-induced depression in corticomotor excitability and corticospinal transmission observed in resting muscle seem to provide an obvious explanation for the accompanying decline in voluntary activation and task failure. However, there are several lines of evidence which suggest that voluntary activation failure and reduced central excitability may not be causally linked. In the first place, failure to maximally activate muscle after exercise may occur, despite maintained or increased central excitability (37, 60). Furthermore, the cortical silent period (54), MEP (55, 56), and CMEP (13, 47) measured during brief postfatigue voluntary contractions, rather than with the muscle at rest, return to prefatigue values within seconds. It has been suggested that increased drive to the motor cortical neuron during moderate to maximal voluntary activation may offset reductions in central excitability and corticospinal transmission observed at rest and during low levels of activation (47, 55, 56). This hypothesis has been based, primarily, on the dissociation between the recovery times of MEPs and CMEPs evoked at rest vs. those evoked during strong contractions. Despite the fact that brief maximal effort may overcome the postfatigue decline in central excitability, hypoxic excitability of the motor pathway would require increased cortical drive to maintain a target force, which may result in increased sense of effort and hasten task failure. We proposed to test the hypothesis that central excitability does not limit voluntary activation more directly by manipulating central excitability using the central nervous system stimulant, caffeine.

It has been convincingly argued that adenosine receptor antagonism is the primary mechanism of caffeine’s actions at the micromolar concentrations elicited in human studies (16). In addition, caffeine’s effects on motor activity and fatigue resistance have been attributed to this mechanism in an animal study (15). Our laboratory has previously summarized a number of human studies that demonstrate the effects of caffeine on voluntary muscle activation (25) and have proposed that the ergogenic properties of the drug are due largely to central effects (27). We have previously reported an increase in resting first dorsal interosseous MEP amplitude at the onset of a fatigue protocol. This increase in central excitability may be due to either cortical or spinal mechanisms. Our laboratory has previously demonstrated a caffeine-induced increase in the slope of the soleus H-reflex recruitment curve (61) and self-sustained firing of tibialis anterior motor units (62) in nonfatigued muscle. These data suggest that caffeine may increase resting MEP amplitude via increased excitability of the spinal motoneuron.

Although caffeine has offset a decline in low-frequency tetanic force in two human studies, it had no effect on contractile properties in the present study or previous studies (26, 28, 48). This is not surprising given that plasma caffeine concentrations achieved in human studies are typically less than 70 μM; a level too low to increase the development of muscle tension, even when applied directly to isolated, fatigued muscle (24). Similarly, caffeine did not alter the M wave in the present study, and it may therefore be concluded that the drug did not improve neuromuscular transmission. Accordingly, the present study suggests that the effects of caffeine on MEP amplitude and the cortically evoked twitch are most likely due to a central mechanism.

Before the fatigue protocol, we observed caffeine-induced increases in maximal knee extension torque and percent activation that were similar in magnitude to previous observations (26, 48). The most novel finding in the present study; however, was a caffeine-induced increase in central excitability before fatigue. In addition to this, the drug significantly facilitated central excitability before task failure during the fatigue protocol, as demonstrated previously in an intrinsic hand muscle (28). If a decline in central excitability limits maximal voluntary activation, then the increase in MEP amplitude after the second set of contractions in the caffeine trial should have offset voluntary activation failure and increased MVC compared with the placebo. However, this was not the case. Furthermore, at the point of task failure, when maximal voluntary force had declined by 35% for all subjects, central excitability was only depressed in the placebo trial. Thus voluntary activation failure was not due to the accompanying decline in resting central excitability.

In human studies, isolating the events that contribute to central fatigue is difficult and, by necessity, indirect. Furthermore, a decline in resting MEP amplitude may be due to a reduction in corticospinal motoneuronal excitability, transmission at the corticospinal-motoneuronal synapse, spinal motoneuronal excitability, as well as peripheral transmission failure. In the present study, there are a number of events that are not likely to have contributed to fatigue. Because M AMP did not decline, neuromuscular and sarcolemmal transmission failure did not contribute to the decline in maximal voluntary activation. Furthermore, our laboratory has found that voluntary activation failure is not offset by a caffeine-induced increase in spinal excitability assessed postfatigue in resting soleus muscle (28a). Thus the segmental mechanisms that suppress the monosynaptic reflex at rest are not likely to contribute to voluntary activation failure. Although it is possible that voluntary activation declines due to a withdrawal of 1α afferent input to the spinal motoneuron pool (8, 20), the resting measures of central excitability made in the present experiment do not test this hypothesis.

Gandevia, Taylor, and colleagues (21, 54, 57) have presented considerable evidence that the decline in motor unit activation is due, at least in part, to failure “upstream” of the motor cortical neuron. On the other hand, Petersen et al. (47) provide psychophysical evidence to suggest that reductions in...
corticospinal transmission may have some effect on voluntary movement. Thus transmission at the corticospinal-motoneuronal synapse as well as failure proximal to the motor cortical neuron may have contributed to voluntary activation failure in the present study. These possibilities cannot be confirmed because we did not use TMS-evoked twitch interpolation or cervicomedullary stimulation to assess these sources of failure.

Given the complexity of the events that precede execution of the motor command and resultant activation of motor cortical neurons (14), there is certainly ample opportunity for upstream failure (for reviews, see Refs. 19, 44). Although paired-pulse TMS (5, 59), functional magnetic resonance brain imaging (34, 35), positron emission tomography (30), as well as pathophysiological (36, 49) and pharmacological (3, 11) models have all been used to investigate the cerebral events that precede corticospinal activation, identifying specific sites of failure remains complicated by task specificity (7, 32, 38) and the indirect methodologies inherent in human fatigue investigations.

The correlation between time to task failure and the caffeine-induced increase in central excitability prior to the fatigue protocol was not due to a delay in voluntary activation failure, as percent activation and maximal torque declined to the same extent over the first two sets of fatiguing contractions. It is possible; however, that the correlation represents a range of “caffeine responders.” If this is the case, then rather than reflecting a causal relationship, the increase in central excitability and increased endurance time may be due to entirely different mechanisms. For example, caffeine is known to decrease force sensation (48) and muscle pain sensation (42, 43, 45) in humans. Many of the neurotransmitters affected by caffeine in vitro (17) have been implicated in central fatigue (41). For example, the drug increases dopaminergic function, suggesting that the effects of this neurotransmitter on arousal, motivation, and motor performance may contribute to the ergogenic effects of caffeine (17). Accordingly, subjects who responded to caffeine, exhibiting increased central excitability and increased endurance time, may have experienced less discomfort or reduced force sensation or have been more able to tolerate the fatigue protocol.

In summary, we observed a decline in the amplitude of MEPs evoked during very low level contractions at the end of a submaximal intermittent fatigue protocol. Caffeine potentiated MEP amplitude before task failure and offset MEP depression at Tlim. However, caffeine’s effects on central excitability were not associated with enhanced maximal voluntary activation. This suggests that voluntary activation of this large locomotor muscle is not limited by central excitability. Nonetheless, there was a correlation between the caffeine-induced increase in central excitability observed before the fatigue protocol and time to task failure, which may reflect a range of caffeine responders.

REFERENCES

CENTRAL EXCITABILITY AND FATIGUE

35. Liu JZ, Zhang L, Yao B, Sahgal V, and Yue GH. Fatigue induced by intermittent maximal voluntary contractions is associated with significant losses in muscle output but limited reductions in functional MRI-measured brain activation level. *Brain Res* 1040: 44–54, 2005.