Caffeine increases time to fatigue by maintaining force and not by altering firing rates during submaximal isometric contractions

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Meyers, B. M., and E. Cafarelli. Caffeine increases time to fatigue by maintaining force and not by altering firing rates during submaximal isometric contractions. *J Appl Physiol* 99: 1056–1063, 2005. —Caffeine increases time to fatigue [limit of endurance (Tlim)] during submaximal isometric contractions without altering whole muscle activation or neuromuscular junction transmission. We used 10 male volunteers in a randomized, double-blind, repeated-measures experiment to examine single motor unit firing rates during intermittent submaximal contractions and to determine whether administering caffeine increased Tlim by maintaining higher firing rates. On 2 separate days, subjects performed intermittent 50% maximal voluntary contractions of the quadriceps to Tlim, 1 h after ingesting a caffeine (6 mg/kg) or placebo capsule. Average motor unit firing rates recorded with tungsten microelectrodes were constant for the duration of contractions. Caffeine increased average Tlim by 20.5 ± 8.1% (P < 0.05) compared with placebo conditions. This increase was due to seven subjects, termed responders, who increased Tlim significantly. Two other subjects showed no response, and a third had a shorter Tlim. Neither the increased Tlim nor the responders’ performance could be explained by alterations in firing rates or other neuromuscular variables. However, the amplitude of the evoked twitch and its maximal instantaneous rate of relaxation did not decline to the same degree in the caffeine trial of the responders; this resulted in values 20 and 30% higher at the time point matching the end of the placebo trial (P < 0.05). The amplitude of the evoked twitch and the maximal instantaneous rate of relaxation were linearly correlated (caffeine r = 0.72, placebo r = 0.80, both P < 0.001), suggesting that the increase in Tlim may be partially explained by caffeine’s effects on calcium reuptake and twitch force.

contractile properties; ergogenic; calcium handling

THE LITERATURE CLEARLY INDICATES that when a submaximal isometric contraction is sustained, motor unit (MU) firing rates decline (18, 25, 44). In contrast, firing rates may be maintained during intermittent contractions (50) or decreased in low-threshold MUs (7). According to the muscular wisdom hypothesis (38), the slower firing rate is matched to slower contractile properties, and the decrease does not contribute to force loss during fatigue (6). A number of mechanisms are believed to be responsible for the reduction in MU firing rates. These include a metaboreflex (20, 56) and a decline in muscle spindle activity (35). However, muscular wisdom fails to explain firing rate adaptations in a number of conditions (19, 36). For example, the force-frequency relationship shifts rightward after fatigue (39). This indicates that increased firing rates may be required in fatigued muscle to offset force loss from an impairment of excitation-contraction coupling, specific to low frequencies (14). As a consequence, firing rates maintained at a constant rate in an intermittent task may not be sufficient to prevent a loss of force.

Caffeine has been studied extensively for its effect in delaying fatigue. Three theories have been advanced to explain its ergogenic action. These include: alterations in fat metabolism; a direct effect on calcium release from the sarcoplasmic reticulum and increased excitatory neurotransmitter activity as a consequence of adenosine receptor antagonism (22). Caffeine was thought to increase the duration of aerobic activity because it promoted free fatty acid utilization, and as a result it spared glycogen (22). However, caffeine increases time to fatigue [limit of endurance (Tlim)] in short-duration isometric tasks, when glycogen availability is not a limiting factor (30, 46, 53). It also potentiates twitch force in an in situ animal preparation by increasing calcium release from the sarcoplasmic reticulum (13, 37) at a dosage that is potentially lethal in humans (41), alleviates low-frequency fatigue (49), but has no effect on twitch amplitude during a voluntary fatigue task (30, 46). An alternative explanation for caffeine’s actions pertains to its role as an adenosine receptor antagonist using dosages safe for human consumption (43, 45). Adenosine has primarily inhibitory effects in both the central and peripheral nervous systems (11). Basal levels of adenosine decrease spontaneous and neurotransmitter-evoked firing of cortical neurons (34, 45) and inhibit the release of many other neurotransmitters, including acetylcholine, norepinephrine, serotonin, and dopamine (11). Thus adenosine has the capacity to alter α-motoneuron excitability (47) and, potentially, MU firing rates.

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METHODS

Subjects

Ten men [age 23.5 ± 4.7 (SD) yr; height 1.8 ± 0.1 m; weight 74 ± 11.4 kg] who reported consuming <200 mg/wk of caffeinated foods and beverages were paid volunteers for the study. We controlled for several factors known to alter caffeine metabolism. Nonsmokers of average weight were selected, because nicotine and adiposity modify the rate of caffeine degradation (31, 43). Only men were recruited, because oral contraceptive use increases the half-life of caffeine and its clearance is diminished during the luteal phase of the menstrual cycle (1, 32). Neurological deficits or prescription medications were also criteria for exclusion. Subjects with low caffeine intake were selected, because chronic caffeine consumption upregulates adenosine receptors (58). Plasma adenosine is elevated severalfold on acute caffeine administration in chronic users, but the effect can be reversed with 12 h of caffeine withdrawal (8). Subjects were provided with a list of caffeinated foods, beverages, and drugs to avoid for 1 wk before and during the study. A preliminary session was used to familiarize the subjects with the protocol and techniques. All subjects read and signed an informed consent document. The York University Human Participants Review Committee approved all aspects of the experiment.

Experimental Protocols

We used a double-blind, repeated-measures design; caffeine and placebo conditions were randomized across two separate experimental sessions. Conditions were separated by at least 4 days to control for fatigue and muscle soreness and to allow for caffeine washout (42). Experiments were begun at approximately the same AM hour to control for circadian rhythms and to minimize sleeplessness. Subjects were instructed to refrain from strenuous activity for 24 h, eat the same meal, and maintain similar sleep patterns before each session. Compliance was confirmed by self-report before and after each experiment. The subjects were asked at the end of the experiment whether they had been given caffeine or the placebo capsule. We did not use a control group (no capsule), because they respond no differently from a placebo group (30).

Control protocol. At the beginning of each experiment, unpotentiated evoked twitches were recorded from the knee extensors. Next, maximal voluntary contractions (MVC) were repeated until three of these contractions within 10% of each other were obtained. These were averaged and used to express true maximum force. Subjects were then given a capsule containing either caffeine or placebo. The subjects were instructed to refrain from strenuous activity for 24 h, eat the same meal, and maintain similar sleep patterns before each session. Compliance was confirmed by self-report before and after each experiment. The subjects were asked at the end of the experiment whether they had been given caffeine or the placebo capsule. We did not use a control group (no capsule), because they respond no differently from a placebo group (30).

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For some time, we have noticed that MVCs performed with tungsten microelectrodes inserted into vastus lateralis are frequently smaller than those performed without microelectrodes in the muscle. We have not been able to attribute this to subject discomfort, microelectrode placement, or antagonist activity. Consequently, all comparisons in the control protocol used MVC amplitudes obtained without microelectrodes in vastus lateralis. All other MVC data are based on attempted maximal contractions performed with microelectrodes in the muscle.

Fatigue and recovery protocol. After the control protocol, all procedures were performed with intramuscular microelectrodes inserted into vastus lateralis, and maximal twitches were obtained in the potentiated state. The fatigue protocol consisted of intermittent isometric contractions held for 15 s at 50% of the control MVC with the target force displayed on a computer monitor. This protocol was based on that of Plaskett and Cafarelli (46). In the experimental design, it was not necessary that firing rates decline. On the basis of the force-frequency curve (39), firing rates must stay constant or increase for force to be maintained. We anticipated that the effect of caffeine would be apparent if firing rates stayed constant longer or even increased rather than gradually decreasing to maintain the target force during the protocol. Maximal twitches were evoked during the 2.5-s rest periods. Supramaximal shocks were delivered in the middle of each 50% MVC contraction to determine the degree of voluntary activation. The protocol was terminated when the target force fell below 45% MVC for >2 s. Recovery MVC were performed at 0, 2, 5, and 15 min after the fatigue protocol.

Procedures

Caffeine. US Pharmaceutical-grade caffeine (6 mg/kg, A&C American Chemicals, Montreal, PQ, Canada) or the same amount of all-purpose flour in gelatin capsules were administered after the pretest. A person not involved in the experiment arranged the order of the capsules and devised the key that described the order. This double-blind design was not broken until all the experiments were completed and all the data were analyzed.

Electrical stimulation. We used a constant-current stimulator (model DS7, Digitimer, Welwyn Garden City, Hertfordshire, UK) to deliver 200-µs square-wave pulses to the right femoral nerve. The cathode (4 × 4 cm) was positioned directly over the femoral nerve in the inguinal crease, and the anode (12.5 × 7 cm) was placed over the iliac crest and the lateral border of the gluteus maximus. All supramaximal stimulation used paired pulses separated by 20 ms (50 Hz) to increase the sensitivity of the twitch interpolation technique (17).

Force. Isometric force was measured in a fully adjustable custom-made dynamometer (York Machine Shop). The device was equipped with a full back and head support and with a seat belt to stabilize the hips at 90° of flexion. The unit was tilted back to 45°, and the subject’s arms were folded over his chest during all contractions. The right knee joint was positioned at 90° of flexion. An aluminum cuff was placed 2.5 cm proximal to the lateral malleolus and attached to a strain gauge load cell.

Surface electromyography. Electrical activity was recorded with bipolar Ag-AgCl surface electrodes (EQ, Chalfont, PA) over the vastus lateralis muscle belly, 10 cm proximal to the superior border of the patella and on the long head of the biceps femoris midway between the ischial tuberosity and the popliteal fossa. A Hypafix retention sheet was applied over the biceps femoris electrode to hold it in place. A water-soaked ground electrode was placed around the upper thigh and covered in plastic wrap to prevent evaporation.

Intramuscular microelectrodes. High-impedance (6 – 8 MΩ) tungsten microelectrodes (FHC, Bowdoinham, ME) were used to record single MU discharges from vastus lateralis. Before the recording was begun, the skin was shaved and cleaned with a 70% ethanol solution, and a 25-gauge hypodermic needle was used to puncture the skin and fascia over the midbelly of the muscle. The recording electrode was inserted through this puncture into the muscle, and the reference microelectrode was inserted subcutaneously into the adipose tissue 2 cm proximal to the patella. Using the technique of Bellemare et al. (4), the recording electrode was advanced manually at ~0.5 mm/s during contractions to sample the discharge frequency of several MUs. When the electrode had been completely inserted into the muscle (5–7 cm), it was withdrawn and reinserted at a different angle.

Action potential trains were manually sorted by amplitude, shape, and interspike interval (Fig. 1E). To accept a train of spikes, a minimum of five interspike intervals was required during a constant level of force and the mean interspike interval had to have a coefficient of variation ~30% (15). Trains with long interspike intervals of >200 ms or doublets with interspike interval of <20 ms were excluded. The superimposed shock temporarily interrupted the intramuscular signal for ~30 ms, eliminating this region from analysis.

Signal Processing

Biopotentials were preamplified at the source and then passed through a second-stage variable-gain amplifier with a frequency response that was essentially flat from 0 to 1 kHz. All signals were
simultaneously displayed on a computer monitor and recorded on cassette (Vetter PCM 4000A, Rebersberg, PA; Sony VCR SLV-N80) for offline analysis in Spike2 (version 4.1, CED, Cambridge, UK). The force signal was analog-to-digital converted at 500 Hz and low-pass filtered at 50 Hz. The surface electromyograph (EMG) interference signal was sampled at 1 kHz and high-pass filtered at 17 Hz. The intramuscular signal was amplified and band-pass filtered between 1 and 2.5 kHz (Neurolog Digitimer, Medical Systems, Greenvale, NY) and sampled at 10 kHz.

Control measures. Maximal potentiated twitches were used to determine contractile properties, including peak twitch amplitude (Twamp), and the maximum instantaneous ascending (dF/dt) and descending (−dF/dt) rates of force. The peak-to-peak amplitude of the M wave was used to assess any changes in the efficacy of neuromuscular transmission and action potential propagation across the neuromuscular junction and sarcolemma. The paired pulse necessitated that only the second M wave was used, because the second-pulse stimulus artifact truncated the negative phase of the first M wave.

MVC peak force was averaged across the three highest trials within 10% of each other. Maximal vastus lateralis voluntary activation was assessed with twitch interpolation and root mean square amplitude of the surface EMG. Percent voluntary activation of the MU pool was quantified from the superimposed twitch at peak force, relative to the twitch immediately after the contraction: percent activation = [1 − (superimposed Twamp/potentiated Twamp) × 100] (3).

Fatigue and recovery. Tlim was the point at which force fell to ≤45% MVC for >2 s. Tlim was calculated from the beginning of the first contraction to the point of force failure, but the final attempt at 50% MVC continued until 15 s had elapsed. Changes in contractile properties were analyzed from the twitches evoked between contractions. Root mean square EMG was measured in 2-s epochs before and after the superimposed twitch during each contraction. Recovery data were derived from a single MVC at each time point.

Statistics

We analyzed the data with one- or two-way repeated-measures ANOVA and with Tukey post hoc tests when needed (Statistica version 6.0, Statsoft, Tulsa, OK). Data from the control protocol were expressed as a posttest-to-pretest ratio and compared between drug conditions. Linear regression was performed on dependent variables from the fatigue protocol (percent voluntary activation, Twamp, dF/dt). Data from each subject were individually plotted using SigmaPlot 2000 (version 6.0, SPSS, Chicago, IL). Averaged slopes and y-intercepts from these analyses were compared between drug conditions. All variables from the fatigue protocol except the firing rates were normalized to their initial value (percent of initial). The duration for both conditions was expressed as a percentage of placebo Tlim. Data from the fatigue protocol were compared at three different time points: placebo Tlim, at the time point in the caffeine trial that corresponded to placebo Tlim, and caffeine Tlim. The three subjects who did not increase Tlim with caffeine did not have data at the time point in the caffeine trial that corresponded to placebo Tlim. To perform a repeated-measures ANOVA, the missing values were replaced with those from the caffeine Tlim. Our laboratory has used this method previously because it is the most conservative approach for dealing with data from “nonresponders” (46). Data from recovery were analyzed with a two-factor [drug (caffeine, placebo) × time (prefatigue and 0, 2, 5, and 15 min)] ANOVA. All data are presented as means ± SE.

RESULTS

Control Protocol

The MVC and twitch contractile properties from the pre- and posttests are shown in Table 1. Caffeine had no effect on these
measures. Although increases in MVC and percent activation have previously been reported (30, 46), these particular responses to caffeine have not always been observed (49).

Fatigue Protocol

Figure 1 shows typical recordings made from the knee extensors (A and B), biceps femoris (C), and vastus lateralis (D) during a caffeine trial. These are consistent with the pattern of fatigue that our laboratory has seen previously during intermittent isometric contractions (46). Activation of vastus lateralis and coactivation of biceps femoris increased as Tlim was approached. Examples of intramuscular recordings (Fig. 1E), at both fast and slow sweep speeds, show the activation of individual MUs during contraction.

Tlim. Figure 2 shows the distribution of how caffeine altered Tlim in the sample of 10 subjects. On average, caffeine resulted in a 20.5 ± 8.1% increase (P < 0.05) in Tlim. Mean Tlim was 109.1 ± 11.6% s in placebo and 130.4 ± 13.3 s in the caffeine condition (P < 0.05). The seven subjects who increased Tlim in the caffeine condition were termed “responders.”

Voluntary activation. Vastus lateralis surface EMG amplitude increased at approximately the same rate in each condition as a function of time (Fig. 3). There was no significant effect of caffeine on the EMG amplitude at Tlim. Biceps femoris EMG increased by 50.8 ± 23.9% but was not altered by caffeine. The M-wave amplitude did not change during the fatigue protocol and also was not altered by caffeine.

Percent activation was calculated from the ratio of the superimposed to the potentiated twitch (57). These data were averaged at 15, 30, and 60% of placebo and caffeine Tlim, and regression lines were calculated for each individual subject. There were no significant differences between the regression slopes or y-intercepts (caffeine r = 0.8; placebo r = 0.71). There was no significant difference in voluntary activation at Tlim between the two conditions.

MU firing rates. We recorded a total of 441 MU trains during the fatigue protocol (Fig. 4A). Individual firing rates were determined at 20% increments of Tlim and were not significantly different as a function of either time or drug. For the pooled data, averaged firing rates were 13.6 ± 1.0 Hz at onset and 12.3 ± 1.1 Hz at Tlim. Figure 4, B and C, are histograms showing the combined caffeine and placebo firing rate distributions during the first and last 40% of Tlim.

Twitch contractile properties. Contractile properties were obtained from the maximal twitch evoked between contractions. Twamp and +dF/dt declined at the same rates during fatigue in both conditions, but −dF/dt declined at a slower rate (P < 0.05) in the caffeine condition. Tlim is plotted as a function of the −dF/dt slope in Fig. 5A. There was a difference in the average −dF/dt values of the caffeine responders and nonresponders. *

Table 1. Effects of placebo and caffeine ingestion on control measurements

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prefatigue</th>
<th>Postfatigue</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVC, N</td>
<td>632.4±50.0</td>
<td>582.1±51.1</td>
<td>0.92±0.04</td>
</tr>
<tr>
<td>% Activation</td>
<td>94.5±1.6</td>
<td>92.8±1.9</td>
<td>0.98±0.01</td>
</tr>
<tr>
<td>EMG, mV</td>
<td>0.32±0.05</td>
<td>0.30±0.05</td>
<td>1.0±0.09</td>
</tr>
<tr>
<td>Twamp, N</td>
<td>202.6±10.8</td>
<td>195.3±9.1</td>
<td>0.97±0.03</td>
</tr>
<tr>
<td>+dF/dt, N s⁻¹</td>
<td>2.651±103.9</td>
<td>2.548±88.3</td>
<td>0.97±0.03</td>
</tr>
<tr>
<td>−dF/dt, N s⁻¹</td>
<td>−1.530±108.5</td>
<td>−1.578±118.8</td>
<td>1.03±0.04</td>
</tr>
<tr>
<td>M wave, mV</td>
<td>6.1±1.0</td>
<td>5.6±1.0</td>
<td>0.9±0.03</td>
</tr>
<tr>
<td>Drug, % correct</td>
<td>70</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. MVC, maximal voluntary contraction; EMG, electromyograph; Twamp, peak twitch amplitude; +dF/dt and −dF/dt, maximum instantaneous ascending and descending rates of force, respectively.
Fig. 4. A: MU firing rates from the PL (○) and CF (▲) fatigue protocols. Firing rates did not differ at any point in the trials. The number of MU trains counted at each point is listed below the graph. Distributions were similar for all MUs during the first (B) and last (C) 40% of $T_{lim}$.

nonresponders ($P < 0.005$). Contractile properties from the caffeine responders ($n = 7$) are shown in Fig. 5B. There was a slower rate of decline in the $-dF/dt$ (slope = $-0.24$) compared with placebo (slope = $-0.65$), and $-dF/dt$ was $\sim 30\%$ higher with caffeine at placebo $T_{lim}$ ($P < 0.05$). At caffeine $T_{lim}$, $-dF/dt$ did not differ from the placebo trial. There was no difference in the behavior of $+dF/dt$ between conditions.

Figure 5C shows the decline in $T_{wamp}$, using only the data from the caffeine responders. Although the averages of the individual regression slopes were not different between trials (caffeine slope = $-0.46 \pm 0.09$; placebo slope = $-0.58 \pm 0.09$), $T_{wamp}$ was significantly larger in the caffeine trial at placebo $T_{lim}$ ($P < 0.05$), but it was not different at the end of both trials. Because $-dF/dt$ and $T_{wamp}$ relate to calcium handling (52) and caffeine had an effect on both of these measures, we plotted $T_{wamp}$ as a function of $-dF/dt$ (Fig. 6).

As expected, caffeine treatment did not alter the basic relationship (caffeine $r = 0.72$; placebo $r = 0.80$), but it attenuated the decline in these measures. The data points at 20 and 50% $T_{lim}$ are similar between drug conditions. The interesting finding is that, at placebo $T_{lim}$, the caffeine value has not declined to the same degree as placebo and is similar to the averaged values at 50% $T_{lim}$.

Recovery Protocol

Recovery of MVC was followed at 0, 2, 5, and 15 min after $T_{lim}$ (Fig. 7). At the beginning of recovery, MVC was 70% of prefatigue ($P < 0.001$), and it had recovered to initial levels by 5 min. Although the caffeine trial was 21% longer, MVC was not further reduced as we had anticipated. There was a main effect of drug ($P < 0.05$); mean caffeine recovery MVC was 8% larger than placebo (465.0 vs. 431.3 N). Negative $dF/dt$ was only depressed at 0 min ($P < 0.001$; data not shown), and there was a main effect of drug ($P < 0.05$). Caffeine $-dF/dt$ values were 7% greater than placebo ($-1,561.6$ vs. $-1,454.8$ N/s). There were no differences between the caffeine and placebo trials for measures of voluntary activation or any of the other contractile properties.
similar between conditions, but CF attenuated the decline in
fatigue task. However, we found that rates did not decline
during intermittent contractions in the control condition and
that the increase in $T_{lim}$ in the caffeine condition could not be
explained by changes in firing rates. The increase in $T_{lim}$ is
consistent with our laboratory’s previous studies (30, 46) and
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novel finding from this experiment is that caffeine ingestion is
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during an isometric fatigue protocol. This suggests an effect of
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Firing Rate Adaptations in Response to Intermittent
Contractions and Caffeine

Force is maintained during repeated submaximal contrac-
tions either by recruiting additional MUs or increasing firing
rates, or both. When contractions are sustained, it is clear that
firing rates decline in both maximal (6, 38, 56) and submaximal
(18, 25, 44) contractions. However, there is some confusion
about the firing rate behavior of MUs during intermittent
contractions. For example, some authors (50) report that firing
rates are constant in an intermittent isometric fatigue task, but
others show that firing rates increase during low-level inter-
mittent contractions (5, 9). Examination of the frequency-
relationship of fatigued muscle indicates that slightly in-
creased, but still suboptimal, firing rates contribute to force
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have shown here, may be insufficient to prevent the eventual
decrease in force. Nevertheless, the divergent firing rate be-
behavior between sustained and intermittent tasks suggests that
different strategies are evoked within the central nervous sys-
tem during fatigue.

It should be noted that the number of MUs activated during
a maintained contraction is not constant, but rather it increases
during the course of the protocol. This is shown in Fig. 3,
where there is a continuous increase in the surface EMG signal
during the fatigue protocol in both conditions. Although we
cannot specify the different MU types being activated, at the
beginning of the protocol the contraction is 50% of maximal,
whereas at the end it is closer to 100% of the force that can be
generated. It is therefore likely that larger MUs were not
activated at the beginning of the 50% MVC contraction but that
they were recruited toward the end where the contractions are
near maximal.

Maintaining firing rates during intermittent isometric tasks
could involve either increased 1a input or increased blood flow
such as occurs during dynamic contractions (25, 50). It is
known that 1a activity decreases in the first 30 s of a sustained
contraction (35) but that adding vibration can provide enough
of a stimulus to prevent the decline in firing rate (24). In the
present experiment, contraction and relaxation occurred with
an 86% duty cycle (15 s on, 2.5 off). This short rest period may
have avoided the loss of 1a input to the MU pool, but we have
no other data to support this speculation.

The occurrence of rest periods during intermittent muscle
activity may play a role in enhancing muscle endurance. At
50% MVC, quadriceps blood flow is minimal, but it increases
severalfold during a 5-s rest period (48). In sustained contrac-
tions, the lack of blood flow triggers a metaboreflex that is
thought to depress MU firing rates (20, 56). Although the rest
period in the present study was only 2.5 s, it is likely that some
metabolites were removed during these periods of increased
flow. For example, we compared the total time the muscle was
active in the control condition (94.6 s) to our previous work
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endurance time suggests that the 2.5-s rest interval was ben-
eficial, possibly due to improved blood flow. In addition, Du-
chateau and colleagues (10) recently reported that intermittent

Fig. 6. Relationship between $T_{wamp}$ and $-dF/dt$ during fatigue. Linear regression
was calculated from the CF responders data. $T_{wamp}$ and $-dF/dt$ were
linearly related ($P < 0.001$). The relationship was no different for PL (solid line) and
CF conditions (dashed line). Pooled means are shown at 20 and 50%
and at and PL $T_{lim}$ for PL (●) and CF trials (○). Values at 20 and 50% $T_{lim}$ were
similar between conditions, but CF attenuated the decline in $-dF/dt$ and $T_{wamp}$
at PL $T_{lim}$.

**DISCUSSION**

We examined average MU firing rates of vastus lateralis
during intermittent isometric contractions, and we tested the
hypothesis that the ergogenic effect of caffeine occurs because
MU firing rates are either maintained or increased during a
fatigue task. However, we found that rates did not decline
during intermittent contractions in the control condition and
that the increase in $T_{lim}$ in the caffeine condition could not be
explained by changes in firing rates. The increase in $T_{lim}$ is
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Fig. 7. MVC prefatigue and at 0, 2, 5, and 15 min postfatigue for PL (black bars) and CF (gray bars) trials. MVC force was depressed at 0 and 2 min,
compared with prefatigue (⁎$P < 0.05$, **$P < 0.001$). There was also a main
effect of drug, with CF MVCs being larger than PL ($P < 0.05$).
tasks do not depress the Hoffmann and long-latency reflexes, as do sustained contractions. Given these observations, the metaboreflex may not be evoked during intermittent contractions, thus allowing firing rates to be maintained.

Our hypothesis that caffeine would maintain higher firing rates during a fatigue protocol because the drug is a well-known adenosine receptor antagonist (12) was not supported by the data. This finding is consistent with the observation that the drug does not alter average firing rates during brief, unfatigued submaximal contractions (30). Although caffeine increases spinal excitability in the unfatigued state (54), this apparently does not result in increased motor outflow at the level of the α-motoneuron. In a similar intermittent task, it was demonstrated that, whereas firing rates remained constant at submaximal forces, maximal firing rates declined steadily (50). Thus our firing rates were approaching a greater percent of maximum during fatigue. This may have limited any potential for caffeine to increase relative firing rates any further.

Effect of Caffeine on Contractile Properties

Muscle contractile properties in unfatigued muscle are not affected by an acute dose of caffeine (27, 46, 49). However, during progressive fatigue, maximal Twamp and −dF/dt both decline because of a reduction in calcium handling by the sarcoplasmic reticulum: force falls because of a reduced calcium release (2), and the relaxation rate decreases because both calcium reuptake and rate of cross-bridge detachment are slowed [in humans (21) and in single fibers (55)]. Tarnopolsky and Cupido (49) have speculated that during low-frequency fatigue, when calcium release is thought to be impaired, caffeine maintains force output by maintaining calcium release; however, they provide no evidence to support this idea. Our data therefore appear consistent with a decreased sarcoplasmic reticulum calcium release and reuptake (33). Because caffeine administration was associated with an attenuated decrease in −dF/dt and Twamp, we suggest that caffeine maintains calcium reuptake and as a result improves calcium release and force through some unknown mechanism. The action of caffeine on −dF/dt does not seem to involve changes in cross-bridge kinetics, but this idea requires further examination. Thus it may be that caffeine increases Tlim in part by maintaining the force output of the muscle secondary to improvements in calcium handling.

In an in situ muscle preparation, caffeine potentiates twitch force by directly increasing calcium release through its effects on the ryanodine receptor (13, 37), but the dosage required for this effect is potentially lethal to humans (41). Using a caffeine dosage equivalent to ours (6 mg/kg), intracellular calcium levels and muscle force do not change (26, 29). However, Tarnopolsky et al. (49) demonstrated that caffeine maintained evoked force approximately midway through an involuntary fatigue protocol. Their data suggest that caffeine given orally at doses tolerable to humans may alter calcium handling and force production in human muscle, once a certain degree of fatigue has occurred. We did not make this observation in a previous study from our laboratory (46). The discrepancy can be explained by differences in the way the twitch technique interpolation was employed. Over the course of the fatigue task, the Twamp evoked with double pulses declined by 50% in placebo conditions, and MVC declined by 30%. In contrast, Twamp from the previous study, evoked with single pulses, declined to a greater extent (70%; Ref. 46). Because the double-pulse Twamp declined more in parallel with MVC, the technique may provide greater sensitivity to fatigue-related changes in contractile properties.

The absence of changes in contractile properties of the nonresponders suggests that some Tlim variability is due to differing effects at the muscle after an acute dose of caffeine. On the basis of this, we removed the nonresponders from the contractile property analyses. When we included the nonresponders, the effect of caffeine was masked. Mohr and coworkers (40) electrically stimulated limbs of paralyzed subjects, and they reported a distribution of Tlim responses similar to that of the present study. Without volitional drive, the range in Tlim could not be explained by subjectively determined factors, such as motivation, or tolerance to discomfort (16). The amount of caffeine one consumes does not alter its actions at the muscle (49) and would not be a factor in the present study. Because there is minimal variability in plasma caffeine after an acute dose (23), differences in its metabolism are unlikely to account for the observed range in Tlim. We suggest that the increase in Tlim depends to some extent on caffeine’s actions at the muscle, but we also recognize that other factors may be involved.

In summary, caffeine extends Tlim during repeated submaximal contractions of the quadriceps with no apparent change in central drive or evidence of neuromuscular transmission failure. Caffeine was associated with changes in Twamp and −dF/dt, suggesting that fatigue may be delayed by maintaining calcium reuptake and force production. The absence of a relation between Tlim and −dF/dt suggests that other mechanisms are also involved.

GRANTS

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REFERENCES


