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R. A Howlett, K. M Kelley, B. Grassi, L. B. Gladden and M. C Hogan

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B.M. Meyers and E. Cafarelli

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G. R. Cox, B. Desbrow, P. G. Montgomery, M. E. Anderson, C. R. Bruce, T. A. Macrides, D. T. Martin, A. Moquin, A. Roberts, J. A. Hawley and L. M. Burke

J Appl Physiol, September 1, 2002; 93 (3): 990-999.

[Abstract] [Full Text] [PDF]

Opposite actions of caffeine and creatine on muscle relaxation time in humans

P. Hespel, B. O. 't Eijnde and M. Van Leemputte

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Caffeine potentiates low frequency skeletal muscle force in habitual and nonhabitual caffeine consumers

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Tarnopolsky, Mark and Cynthia Cupido. Caffeine potentiates low frequency skeletal muscle force in habitual and nonhabitual caffeine consumers. *J Appl Physiol* 89: 1719–1724, 2000.—The mechanism of action underlying the ergogenic effect of caffeine is still unclear. Caffeine increases the force of muscular contraction during low-frequency stimulation by potentiating calcium release from the sarcoplasmic reticulum. Studies have also suggested an enhancement of lipid oxidation and glycogen sparing as potential mechanisms. Given that several studies have found an ergogenic effect of caffeine with no apparent metabolic effects, it is likely that a direct effect upon muscle is important. Twelve healthy male subjects were classified as habitual ($n = 6$) or nonhabitual ($n = 6$) caffeine consumers based on a 4-day diet record analysis, with a mean caffeine consumption of 771 and 14 mg/day for each group, respectively. Subjects were randomly allocated to receive caffeine (6 mg/kg) and placebo (citrate) in a double-blind, cross-over fashion ~100 min before a 2-min tetanic stimulation of the common peroneal nerve in a custom-made dynamometer (2 trials each of 20 and 40 Hz). Tetanic torque was measured every 30 s during and at 1, 5, and 15 min after the stimulation protocol. Maximal voluntary contraction strength and peak twitch torque were measured before and after the stimulation protocol. Caffeine potentiated the force of contraction during the final minute of the 20-Hz stimulation ($P < 0.05$) with no effect of habituation. There was no effect of caffeine on 40-Hz stimulation strength nor was there an effect on maximal voluntary contraction or peak twitch torque. These data support the hypothesis that some of the ergogenic effect of caffeine in endurance exercise performance occurs directly at the skeletal muscle level.

fatigue; methylxanthines; tolerance

CAFFEINE IS A METHYLXANTHINE derivative that has been used for centuries due to its putative ergogenic (work enhancement) effects (29). Carefully controlled studies have demonstrated an ergogenic effect of caffeine in endurance exercise performance (7, 10, 13, 17). One of the mechanisms of action that may explain this ergogenic effect is an increase in free fatty acid (FFA) oxidation (7, 10) and a subsequent sparing of muscle glycogen (9, 10, 26). Caffeine likely exerts these effects through competitive antagonism of adenosine recep-

tors at physiological concentrations (16). However, there have been several studies that have raised doubts that an ergogenic effect of caffeine was due to the aforementioned metabolic effects (14, 22, 32). For example, one study found that a low dose of caffeine (3 mg/kg body wt) improved exercise capacity yet did not alter catecholamine or FFA/glycerol concentration in young men (14). A study in tetraplegic patients found that caffeine ingestion improved exercise performance but did not affect the respiratory exchange ratio (RER) and had minimal effects on catecholamines (22). Another study found that caffeine ingestion improved exercise capacity yet did not alter RER in young, habitual caffeine consumers in spite of a 2- and 4-day caffeine withdrawal (32). Together, these data cast doubts on the theory that the ergogenic effects of caffeine are mediated solely by enhanced FFA oxidation and raise speculation that the ergogenic effect of caffeine is mediated at the level of the skeletal muscle (14, 22).

There is substantive evidence that caffeine may also facilitate neuromuscular function at the level of the sarcoplasmic reticulum (SR) (5, 12, 18, 20, 27, 28, 34). In supraphysiological concentrations, caffeine potentiated the release of calcium from the SR and may have induced contracture in vitro (34). The potentiation of muscle contractile force has also been demonstrated at concentrations that are attainable with ergogenic doses of caffeine in humans (20, 27). Studies performed in vitro have demonstrated that caffeine directly potentiated calcium release from the ryanodine receptor (23) and that this was not occurring via adenosine antagonism (12).

Studies in humans have demonstrated a potentiation of submaximal skeletal muscle contraction force with caffeine doses ranging from 4 to 7 mg/kg body wt (20, 27). However, our laboratory has reported that caffeine (6 mg/kg body wt) did not potentiate electrically elicited twitch torque or maximal voluntary contractile force in six habitual caffeine-consuming men (30). Confounding the latter study (30) was the fact that maximal voluntary contraction strength (MVC) and twitch measurements are not likely to be sensitive

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or specific enough to detect a potentiation of calcium release during fatigue. It would also be predicted that the greatest effect of caffeine on skeletal muscle would occur during low frequency electrical stimulation in which the locus of fatigue is thought to be at the level of calcium release from the SR (4, 8) and not at maximal intensities in which the locus of fatigue is proximal and analogous to high stimulation frequencies (4, 8). The lack of an effect of caffeine on MVC torque (30) or at high stimulation frequencies (20) is consistent with the practical observation that caffeine does not appear to enhance high-intensity exercise performance (Ref. 15, for review see Ref. 29).

Another factor that must be considered in the evaluation of the effect of caffeine is a tolerance to the effects from habitual consumption. Tolerance to the adenosine receptor-mediated effects of epinephrine release (1), FFA release (11), and increased blood pressure (25) have been observed. Given that the dihydropyridine and ryanodine receptors form a macromolecular complex (21) and are not true receptors, it could be predicted that downregulation would not occur, as has been shown for the adenosine receptor-mediated effects (25).

Therefore, we examined the involuntarily elicited and volitional neuromuscular contractile and electrical properties of skeletal muscle in 12 men with habitual (caffeine intake >500 mg/day) and nonhabitual caffeine consumption (caffeine intake <50 mg/day) in response to an ergogenic dose of caffeine (6 mg/kg body wt). We hypothesized that caffeine would potentiate muscle force at low, and not high, stimulation frequencies and that this effect would be independent of habituation status.

METHODS

Subjects. Twelve healthy men were recruited to participate in the study (see Table 1). Written, informed consent for participation was obtained from each volunteer after ethical approval of the study was given by the McMaster University Medical Advisory Committee. All participants completed a medical history screening, were physically active (≥ 3 times/wk), and had previous experience participating in studies with similar testing protocols. History or signs of psychiatric,

renal, cardiac, or neurological diseases and/or use of any prescription medications were exclusion criteria. Four-day food records were obtained from potential candidates who had classified themselves as habitual or nonhabitual caffeine consumers and were analyzed using a computerized program (Nutritionist IV, Silverton, OR). We allocated subjects into habitual or nonhabitual caffeine consumer groups if their mean daily caffeine consumption was >500 or <50 mg/day, respectively. The subjects in each group had nearly identical habitual dietary intakes (except for caffeine intake), exercised similarly, and differed only in a slightly greater height for the nonhabitual group (see Table 1).

Experimental protocol. After being assigned to the habitual or nonhabitual group ($n = 6$ for each group), the participants were randomized in a double-blind, cross-over, counter-balanced study to receive caffeine (Caf = 6 mg/kg as caffeine citrate) and placebo (PL; citrate). All participants completed both stages of the trial. Each trial was 4 days long, with dietary adherence ensured with the use of a dietary checklist. Subjects were instructed to adhere strictly to their habitual type, intensity, and duration of physical activity for this period. In addition, the meal on the evening before testing (*day 3*) was kept constant (diet checklist), and no caffeine-containing foods or beverages were consumed for 12 h before testing. All participants reported to the testing center between 0730 and 1330 (each individual at the same time) on the fourth day of each trial, ≥ 6 -h postabsorptive, and ~ 90 min after consuming Caf or PL dissolved in artificially sweetened lemonade.

To ensure blinding, the subjects were asked not to report any subjective feelings to the other participants or research assistants during testing. The testing sessions were separated by a period of 7 days. All but one of the habitual group correctly identified the Caf trial post hoc. The most commonly reported symptoms in the Caf trial were nervousness, tremor, and mild stomach upset.

Before the first session, each subject had the right and left leg randomized to be fatigued with either a 20-Hz (low frequency) or 40-Hz (high frequency) stimulation protocol. All testing was first performed on the right leg during the initial testing session and on the left leg during the second testing session. The stimulation frequency for each leg was kept constant between testing sessions. The following measurements were made for the dorsiflexor muscles of each leg. 1) Peak twitch torque (PTT) and compound muscle action potential (M-wave) amplitude using supramaximal stimulation (that used to evoke maximal PTT + 10%) were taken as baseline measurements. Then the MVC (5 s) and percent motor unit activation (%MUA) were determined using the interpolated twitch technique of Belanger and McComas (2). 2) During the tetanic fatigue protocol, tetanic torque (TETT) and M-wave characteristics were elicited with 2 min of supramaximal tetanic stimulation at either 20 or 40 Hz, with recordings made at 0–5, 25–30, 55–60, 85–90, and 115–120 s of continuous stimulation. 3) In the recovery period, PTT and M-wave area were measured at 2 s (IMM), and 15 min (+15 min) of recovery with MVC and %MUA measurements were taken 2 s later (+4 s; IMM) and ~ 15 min (+15 min) of recovery. A brief tetanic stimulation occurred at 1, 5, and 15 min of recovery, with a ramp from 20 to 40 Hz (2 s at each frequency).

Stimulation and recording. The torque measurements were made from the dorsiflexors, with evoked contractions elicited by indirect stimulation of the common peroneal nerve. The skin over the tibialis anterior muscle (10-cm distal to the tibial tubercle; stigmatic or G_1 electrode) and over the myotendinous junction (reference or G_2 electrode)

Table 1. *Subject characteristics*

	HAB, $n = 6$	NonHAB, $n = 6$	<i>P</i> Value
Weight, kg	76.8 \pm 7.1	76.9 \pm 12.9	NS
Height, cm	176 \pm 4	184 \pm 4	<0.05*
Age, yr	29 \pm 7	26 \pm 4	NS
Nutritional analysis			
Caffeine, mg	771 \pm 295	14 \pm 17	<0.001*
Energy, kcal	2,914 \pm 887	2,869 \pm 829	NS
Protein, g	101 \pm 15	107 \pm 35	NS
Protein, %	15 \pm 4	16 \pm 4	NS
Fat, %	28 \pm 3	24 \pm 7	NS
Carbohydrate, %	55 \pm 7	58 \pm 11	NS
Ethanol, %	2 \pm 1	2 \pm 2	NS

Values are means \pm SD. HAB, habitual caffeine consumers; NonHAB, nonhabitual caffeine consumers. *Significance determined with unpaired *t*-test. NS, not significant.

was prepared with shaving, sandpaper abrasion, and cleansing with isopropyl alcohol; electromyographic activity was recorded using disposable silver/silver-chloride electrodes (model 2248, 3M) at a sampling frequency of 2 kHz. The placement between testing sessions was ensured using an indelible marking pen. The stimulating electrodes consisted of a rubber anode (57 × 57 mm) and lead plate cathode (20 × 20 mm) placed over the patellar tendon and posteroinferior to the fibular head, respectively. A silver strip ground electrode (6 × 50 mm) was placed between the cathode and the G₁ electrode. The lower leg was then firmly secured to a custom-made dynamometer with the knee angle at 90° and the ankle at 10° of plantar flexion, as previously described (31).

Single, 100- μ s rectangular pulses were delivered to the stimulating electrodes using a high-voltage stimulator (model 3072, Devices Systems, Welwyn Garden City, Hertfordshire, UK). There were no differences in the stimulation intensities required to elicit PTT between groups and within trials. The timing of the single twitch and TETT stimuli were controlled by a laboratory controller (Stoelting, Wooddale, IL). PTT was measured at exactly 1 s into the 5-s recorded window during the stimulation, and MVC torque was measured at the peak of the voluntary effort. The electromyography signals were fed into amplifiers with bandwidths of 20 Hz to 1.5 kHz and were displayed in real time on an VGA computer monitor (model 2431PO, CTX). The data were also streamed continuously to disk using a Dataq waveform scrolling board (WFS-200DC, Dataq Instruments, Akron, OH) for analysis.

Custom-designed, computer-driven oscilloscope and data analysis software (CODAS, Dataq Instruments, Akron, OH) were used for subsequent analysis of the stored mechanical and electrical data. The mechanical data included PTT, MVC, and TETT, whereas the electrical data included the M-wave amplitude. The amplitude was measured from the negative to the positive peak (31).

Analysis and statistics. All data were analyzed using ANOVAs. Most ANOVAs were four-way, between-within, split-plot designs {factor 1 = [2 levels (Caf, PL)]; factor 2 = time [several levels]; factor 3 = frequency [2 levels (20, 40 Hz)]; and factor 4 (between-group factor) = habituation [2 levels (habitual, nonhabitual)]}. When significant interactions were observed, Tukey's post hoc analysis was used to make pair-wise comparisons. A level of $P < 0.05$ was considered to be statistically significant. All values in text, tables, and figures are means \pm SD.

RESULTS

Tetanic stimulation data. We found no main effects or interactions for any of the measured outcome variables with respect to caffeine consumption status (habitual vs. nonhabitual). Therefore, we combined the data across groups for clarity of presentation. The major finding in the present study was a significantly ($P < 0.05$) higher TETT for the Caf compared with PL trial at 60, 90, and 120 s during the 20-Hz tetanic contraction (Fig. 1). There was no effect of caffeine on TETT during the 40-Hz stimulation and a slight trend toward recovering force more quickly ($P = 0.09$) in the PL trial. As expected, the initial torque was higher for the 40- vs. 20-Hz stimulation frequency and declined more rapidly for the 40-Hz stimulation. The 40-Hz force had recovered to baseline values by 1 min of recovery, whereas the torque had still not recovered to basal values by 15 min of recovery for the 20-Hz stimulation

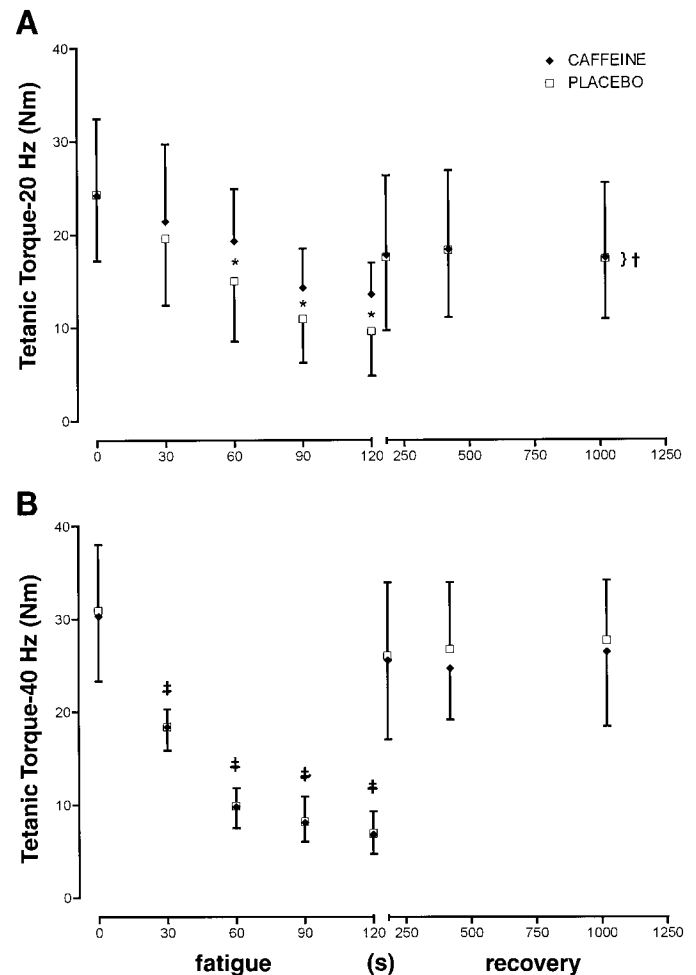


Fig. 1. Torque measurements during (fatigue) and after (recovery) 2 min of tetanic stimulation. A: 20-Hz stimulation. B: 40-Hz stimulation. Time scale is from the start of stimulation, with the 3 recovery times corresponding to 1, 5, and 15 min after stimulation. *Significantly higher for caffeine vs. placebo at 60, 90, and 120 s ($P < 0.05$); †torque did not recover to baseline values during the entire 15-min recovery period ($P < 0.001$); ‡torque declined rapidly and similarly for both caffeine and placebo trials ($P < 0.001$) compared with baseline and recovered rapidly to values that were not different from those at rest (time = 0) by the first recovery measurement (time = +1 min).

trial ($P < 0.001$ for interaction; Fig. 1). We found no effect of Caf treatment on the M-wave amplitude during either the 20- or 40-Hz stimulation protocol. As expected, there was a significant reduction in M-wave amplitude for the 40-Hz stimulation that was significant by the 60-s time point and persisted throughout the tetanic stimulation protocol ($P < 0.01$). The M-wave amplitude was higher for the 20-Hz stimulation trial compared with the 40-Hz trial from the 30-s time point until the end of the stimulation. The M-wave amplitude was not significantly reduced during the 20-Hz stimulation until the 90- and 120-s time points (time × stimulation frequency interaction, $P < 0.01$; Fig. 2). These torque and M-wave characteristics during the fatigue trial were expected and represent the well-described phenomena of low and high fatigue as

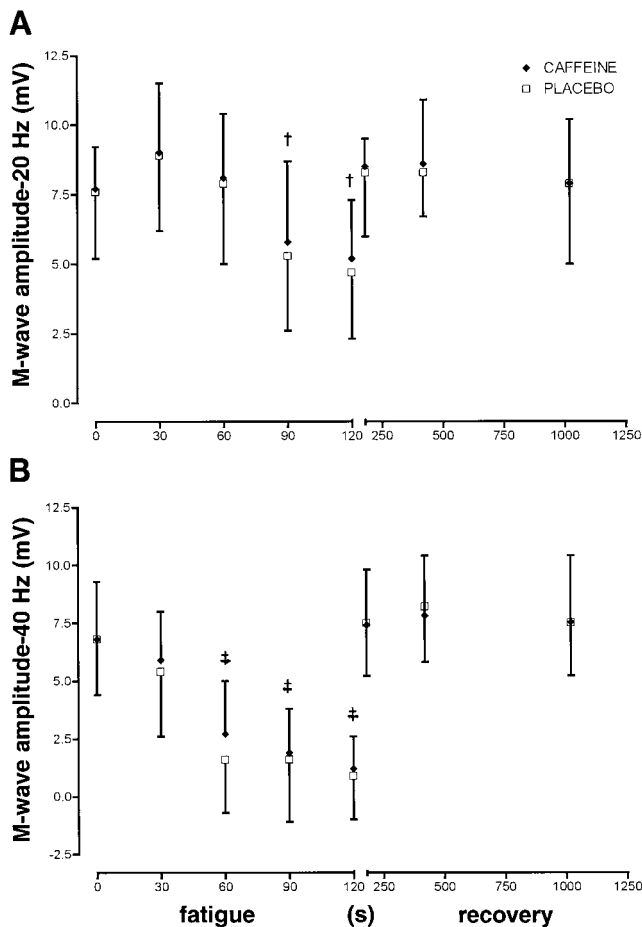


Fig. 2. M-wave amplitude measurements during and after 2 min of tetanic stimulation. A: 20-Hz stimulation. B: 40-Hz stimulation. M-wave amplitude was lower for the 40- vs. 20-Hz stimulation trial at all time points from 30 s until the end of the fatigue trial ($P < 0.01$ for time \times stimulation frequency interaction). †M-wave amplitude declined similarly for both caffeine and placebo trials and was significantly lower than resting values at 90 and 120 s ($P < 0.01$); ‡M-wave amplitude declined similarly for both caffeine and placebo trials and was significantly lower than resting values at 60, 90, and 120 s ($P < 0.01$).

described by Edwards et al. (8) and as shown by our laboratory in the past (31).

Twitch contraction characteristics. As with the tetanic stimulation variables, there were no main effects or interactions for any of the measured outcome vari-

ables with respect to caffeine consumption status (habitual vs. nonhabitual) and, therefore, we combined the data across groups for clarity of presentation. Furthermore, the values taken during the 20- and 40-Hz trials were nearly identical (<4% difference), and thus the values were averaged across stimulation frequency trials. The MVC and PTT were significantly lower ($P < 0.01$) immediately after the tetanic stimulation (+1 min) compared with values taken before (Pre) and at 15 min after the tetanic stimulation protocol (+15 min; Table 2). Neither caffeine treatment nor time affected the %MUA, which was always close to 100% (Table 2).

DISCUSSION

The major finding of this study was a potentiation of the contraction force during low frequency (20 Hz) stimulation with acute caffeine ingestion (6 mg/kg). Furthermore, there was no effect of tolerance with respect to the increase in low frequency contraction force. These findings support the suggestion that the ergogenic effect of caffeine is at least partially mediated by a direct effect on skeletal muscle (14). It is also important to note that the enhancement of low frequency force in the current study occurred at a caffeine dose that was similar to that found to be ergogenic in endurance sports (7, 13, 14, 17) and at a dose that would be considered "legal" under the current guidelines of the International Olympic Committee (13).

The potentiation of contraction force with electrical stimulation at low, but not high, stimulation frequencies has previously been demonstrated (20). That study found a potentiation of low frequency tetanic contraction force in five men in response to 500 mg of caffeine in a randomized, double-blind study; however, the habitual caffeine consumption status was not reported (20). Another study found that caffeine (600 mg, ~8 mg/kg) also potentiated evoked diaphragm muscle contraction force in response to twitch contractions elicited via indirect phrenic nerve stimulation (27). This group also found an increased time until fatigue and a lower perceived exertion at both 80 and 90% maximal inspiratory pressure-loaded breathing (26). This potentiation of lower frequency force, but not contraction velocity, has also been observed in response to physiologically obtainable methylxanthine concentrations (50–100 $\mu\text{mol/l}$) in frog skeletal muscle (5). Although

Table 2. Dorsiflexion twitch and MVC data

	Caffeine			Placebo			P Value
	Pre	IMM	+15 min	Pre	IMM	+15 min	
PTT	3.4 \pm 1.4	1.1 \pm 1.0*	3.2 \pm 1.2	3.5 \pm 1.6	1.4 \pm 1.4*	3.0 \pm 1.5	NS†
MVC	47.7 \pm 8.3	26.5 \pm 8.9*	44.1 \pm 4.7	48.1 \pm 6.2	26.7 \pm 9.2*	44.1 \pm 5.7	NS†
%MUA	98.9 \pm 2.2	99.5 \pm 1.2	98.7 \pm 2.3	98.6 \pm 2.3	99.3 \pm 1.5	99.1 \pm 3.1	NS†

Values are means \pm SD. Values are combined across caffeine intake status and are the mean of 2 values taken during the 20- and 40-Hz stimulation. There were no interactive effects of stimulation frequency nor caffeine intake status on the measured variables. Pre, before tetanic stimulation protocol; IMM, immediately after tetanic stimulation; +15 min, 15 min after tetanic stimulation; PTT, peak twitch torque; MVC, maximal voluntary contraction; %MUA, percent motor unit activation. *MVC and PTT were significantly lower ($P < 0.01$) immediately after tetanic stimulation compared with Pre and +15-min values. †Main effect for the effect of caffeine vs. placebo treatment (NS for all variables measured).

plasma caffeine concentrations were not obtained in the present study, they would be expected to be in the range of 40–50 $\mu\text{mol/l}$ (32), which is at, or slightly lower than, a dose shown to potentiate skeletal muscle force in vitro (5). It is also important to note that many studies have not used physiological doses in vitro and that the reproducibility of tetanic force measurements are rarely provided in these types of experiments. As a result, subtle alterations in tetanic force in response to an intervention may not be as sensitive as in vivo measurements across time.

We have added to previous findings by demonstrating that the potentiation of force at low stimulation frequencies occurs in both habitual and nonhabitual caffeine consumers. These findings are consistent with those of VanSoren and Graham (32), who demonstrated an increase in cycling endurance after caffeine administration that was unrelated to hormonal/metabolic effects or previous caffeine habituation. These observations are important, for several investigations have found that the adenosine receptor-mediated responses to caffeine [i.e., FFA (11), heart rate, and blood pressure increase (25) and epinephrine response (1, 33)] are attenuated by chronic caffeine consumption (habituation). Together with the data from the present study, these data indirectly imply that the ryanodine-dihydropyridine receptor complex (21) is not down-regulated in response to chronic caffeine consumption.

The fact that caffeine only potentiated the low (20 Hz) and not the high (40 Hz) stimulation frequency muscle contraction force likely relates to the mechanism of low frequency fatigue and to the action mechanism of caffeine. Low-frequency stimulation is felt to result in a reduction in expected muscle force (fatigue) due to an impairment of excitation-contraction coupling (E-C coupling) (36). Recent evidence has demonstrated that this type of fatigue is due to an impairment of calcium release from the SR ryanodine receptor (36). In contrast, higher stimulation frequencies resulted in a more rapid force decrement that paralleled the reduction in electrical activity of the muscle (reduction in M-wave amplitude) (4, 8). It has been demonstrated that caffeine acts at the level of the ryanodine receptor (23) and not through adenosine antagonism (34). For example, ryanodine receptor cDNA that was transfected into Chinese hamster ovary cells released calcium in response to caffeine (23). We do not feel that caffeine could have altered other neuromuscular variables in the present study. First, the electrical stimulation removes the influence of supratentorial motivational and arousal mechanisms. Second, conduction velocity has never been shown to alter nerve conduction velocity, and, furthermore, an alteration of conduction velocity would not influence force output within the physiological range. Third, we do not feel that caffeine could have altered neuromuscular junction transmission, sarcolemmal excitability, or t-tubule propagation due to the fact that the M-wave was not affected by caffeine treatment. Together, these data are most consistent with the in vitro evidence demonstrating that caffeine can potentiate calcium

release from the SR. From a practical standpoint, the aforementioned phenomena support the practical observations that caffeine has an ergogenic effect in endurance and not high-intensity/power-type activities (15, for review see Ref. 29).

In our study, we found a classical pattern of fatigue, with the 40-Hz torque decreasing more rapidly than the 20-Hz contraction force and with a parallel drop in M-wave amplitude for the 40-Hz stimulation frequency (4, 8, 35). The fatigue at higher frequencies probably occurs at a locus proximal to E-C coupling, such as K^+ accumulation in the transverse tubules, that causes a failure of conduction propagation (4, 8, 35). Caffeine has been reported to reduce plasma K^+ concentrations during endurance cycling, possibly by stimulating the Na^+ - K^+ -ATPase pumps (19). However, this effect was thought to be due to an effect on inactive muscle, which would not likely alter the t-tubule K^+ concentration under the experimental paradigm used in the present study. It is probable that caffeine potentiated calcium release from the ryanodine receptor and attenuated low frequency fatigue (20 Hz) and that the 40-Hz stimulation caused a more rapid fatigue at a locus proximal to E-C coupling [t-tubule K^+ accumulation (35)]. Again, these observations are consistent with the concept that the locus of the effect of caffeine is at the level of calcium release from the SR (23, 34).

In summary, we have found that physiological doses of caffeine potentiate muscle force output during low stimulation frequencies and that there was no effect of tolerance. These findings may partially explain the apparent discrepancy between the consistently documented ergogenic effect of caffeine in endurance exercise performance and the inconsistent results regarding the mechanism(s) of such an effect (metabolic/hormonal). Furthermore, the lack of an effect of caffeine on MVC and higher stimulation frequency force is consistent with the lack of effect of caffeine upon maximal strength and high intensity activities.

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