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Research Article

Acetaminophen's Impact on Skeletal Muscles in Young Adults

Goncalves, J., Patel, S., Merrill, G.F *

Cell Biology and Neuroscience, Nelson Biological Laboratories, 604 Allison Road, Piscataway, NJ 08855.

***Corresponding Author:** Merrill, G.F, Department of Cell Biology and Neuroscience, Division of Life Sciences, School of Arts and Sciences, Rutgers University, New Brunswick/Piscataway, New Jersey 08855.

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Abstract

Globally, acetaminophen has been widely used as an analgesic and antipyretic. However, its role has been expanding in recent years through the use of new surgical approaches such as the Enhanced Recovery after Surgery protocol. In the current experiment we sought to identify differences in muscle strength when university students were treated with acetaminophen as opposed to placebo. The experiment was double blinded. Notably, males were found to have a statistically significant increase ($P<0.05$) in strength of grip when they were asked to sustain a maximal grip in the presence of acetaminophen. A similar trend was seen in females but results did not achieve statistical significance ($P>0.05$). We conclude that acetaminophen has previously unreported effects on human skeletal muscle performance that might have important sex-based variability. In addition, with the cost-effective nature of acetaminophen, and with its increasing use in the clinical arena, further work must be done. A few aims of such work should be to discover the medication's differential actions on various muscle groups under differing conditions and in both sexes.

Keywords: muscle strength; muscle fatigue; myoprotective

Introduction

Acetaminophen is a widely used and inexpensive analgesic and antipyretic, but its potential for other uses is becoming more broadly understood. For example, in patients undergoing cardiac surgery, acetaminophen minimizes acute kidney injury (AKI) (1). Additionally, research in the Merrill Laboratory at Rutgers University has found cardioprotective (2-14), cerebroprotective (15), mitoprotective (15), and myoprotective (16) effects in animals. However, not all these effects have been corroborated in humans.

Even though acetaminophen's mechanisms of cytoprotection are not fully understood, other research (3, 4) in combination with investigations in cell biology suggest a few possibilities. These include antioxidant scavenging. Acetaminophen is a monophenol and most phenols have antioxidant properties (13). By attenuating the effects of peroxynitrite (5, 8), hydroxyl radical (2), superoxide anion and hydrogen peroxide (10), acetaminophen reduces apoptosis and tissue necrosis (12). Cytotoxic actions of oxidants, left unblocked, can lead to activation of intracellular matrix metalloproteinases (e.g., MMP-2) causing downstream cleavage of troponin-I and impairment of myocardial diastolic function (11, 13, 15).

Furthermore, by reducing plasma concentrations of peroxynitrite, acetaminophen attenuates the ischemia/hypoxia-induced opening of mitochondrial permeability transition pores (MPTP) (10). This helps protect the physiological homeostasis of mitochondrial acid/base balance. Treatment of the tissues with acetaminophen also stabilizes ATPase activity of the sodium-potassium pump, leading to protection/preservation of the transmembrane distribution of anions and cations (7, 11-13).

It is reasonable to infer that the above mechanisms might also be beneficial to skeletal muscle, which is the premise of this experiment. Therefore, we sought to explore if acetaminophen has any impact on forearm skeletal muscle exhaustion. We also hypothesized that acetaminophen-treated participants would be able to sustain grip strength longer than placebo-treated participants.

The aim of this study was to investigate the effects of acetaminophen young adult skeletal muscle, specifically assessing intermittent and sustained conditions. In this experiment, the null hypothesis (H0) stated there will be no statistically significant difference in skeletal muscle function between placebo and acetaminophen treatments. The alternative hypothesis (HA) proposed a statistically significant difference.

Materials and Methods Experimental Subjects

Rutgers University students (n = 10) visited the Merrill Laboratory on two separate occasions. Participants were asked to maintain their usual daily

routines by not altering their diets, exercise, sleep, or other lifestyle behaviors. All participants agreed to the requirements and remained compliant throughout the study.

Experimental Protocol

Hand grip was used as the measure of skeletal muscle performance. The forearm and hand muscles were involved when performing hand grip exercises during this experiment (Figure 1).

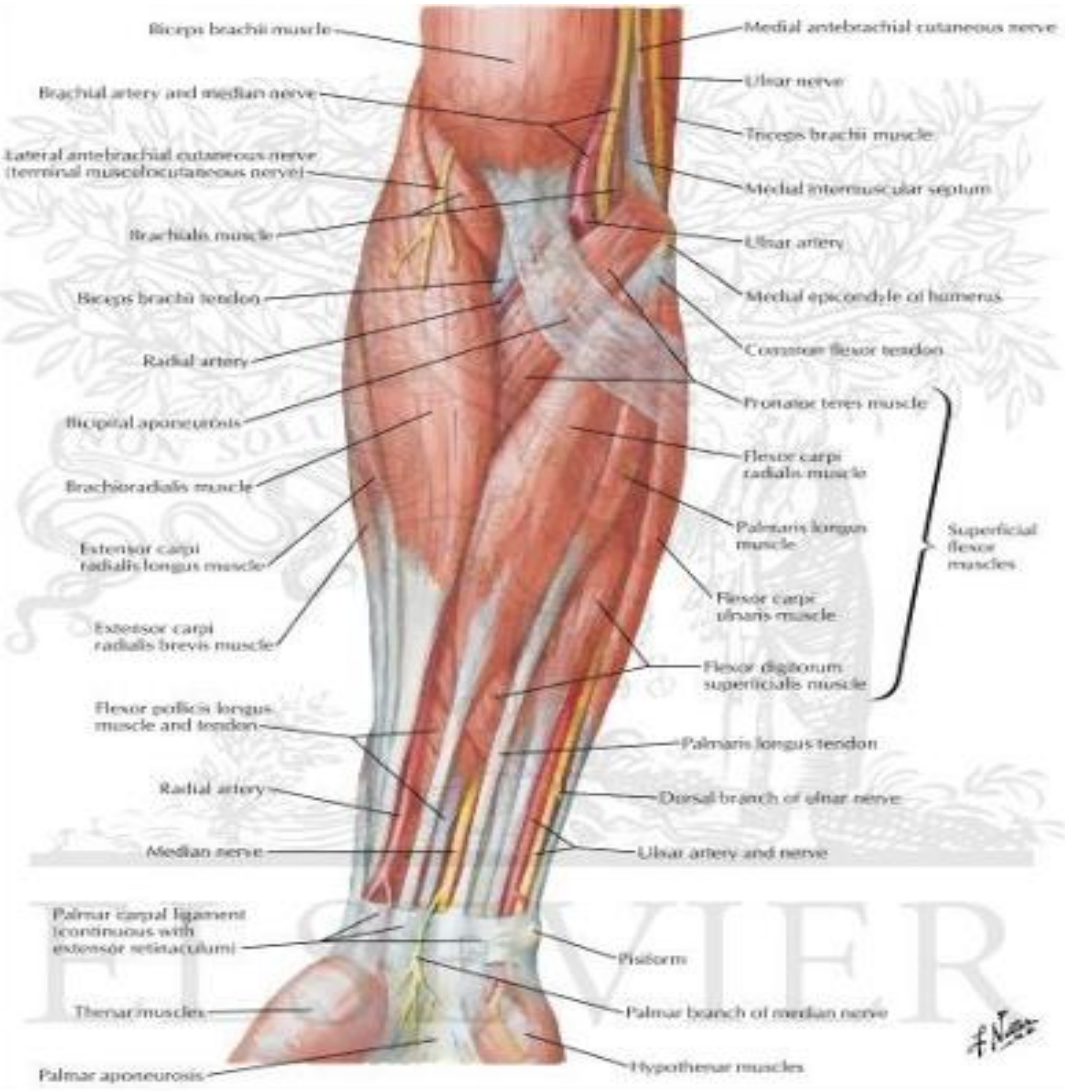

Figure 1: Forearm flexor muscles and other tissues involved in experiment with acetaminophen and young adults. Illustrated by F. Netter (see: Atlas of Human Anatomy 6th Edition 25th Anniversary Edition, F. Netter, M.D. Elsevier, 2014).

These muscles consist mostly of type II fast-twitch fibers, which fatigue more easily than type I slow-twitch fibers that are designed for sustained endurance (18). Three exercises were conducted each time the participants came to the lab. Throughout each experiment, participants assumed a boxer's stance and faced away from the computer. Participants used their dominant hand to grip instruments.

A baseline grip exercise was conducted using a manual grip force transducer, and these baseline values helped with calibration of a digital dynamometer. In a boxer's stance, and upon a research assistant's audible cadence 3, 2, 1, GO, participants were instructed to grip the transducer with their maximum strength. This was exercise number 1.

Following this activity, participants conducted an intermittent grip exercise performed using an electronic model MLT004ST grip force transducer. Data were collected using the electronic grip transducer, which was attached to a data acquisition system paired to a desktop PC computer running LabChart software (v. 8.1.30, 2024). Participants were instructed to grip the transducer for six cycles while following verbal cues (18). This was exercise number 2.

After the intermittent exercise, participants were given a five-minute break, during which time they were permitted to sit down. After the break, participants assumed the boxer's stance for the final exercise. As per the instructor's command, participants used the same digital dynamometer and data acquisition system to perform a fatigue exercise. Participants were instructed to perform a maximal grip of the electronic force transducer, and

to maintain it for as long as possible. When participants felt fatigue increasing and the need to stop, they notified the instructor approximately ten seconds before releasing their grip. Maximum forces were monitored at the onset and termination of the activity using the data acquisition system (18). This was exercise number 3.

Acetaminophen vs Placebo

Students participated in the above protocol on two separate occasions, occurring no less than 24 hours apart. Four hours prior to arrival, the participant consumed either an oral dose of placebo or acetaminophen (1000 mg). Doses were determined based on pilot data from the Merrill lab collected from a similar population of students (19). Such doses are also used in some hospitals for relief of pain following cardiac surgical procedures (20).

Statistics

All data were separated by gender as previous reports suggest men experience an accelerated metabolism of the medication (21). All data are expressed as means plus or minus one standard error of the mean ($\bar{X} \pm$ S.E.M). Analysis of Variance (ANOVA) was used to identify differences in variability, and statistical significance was defined as $P < 0.05$.

Results

Figures 1 and 2 are images of forearm anatomy and equipment used during the experiment, respectively.

Figure 2: Equipment used in current experiment. Both manual and electronic (calibrated) hand-held dynamometers were used. Also shown are the data acquisition system (ADInstruments, Colorado Springs, CO) and a desktop computer running LabChart software (v. 8.30.24).

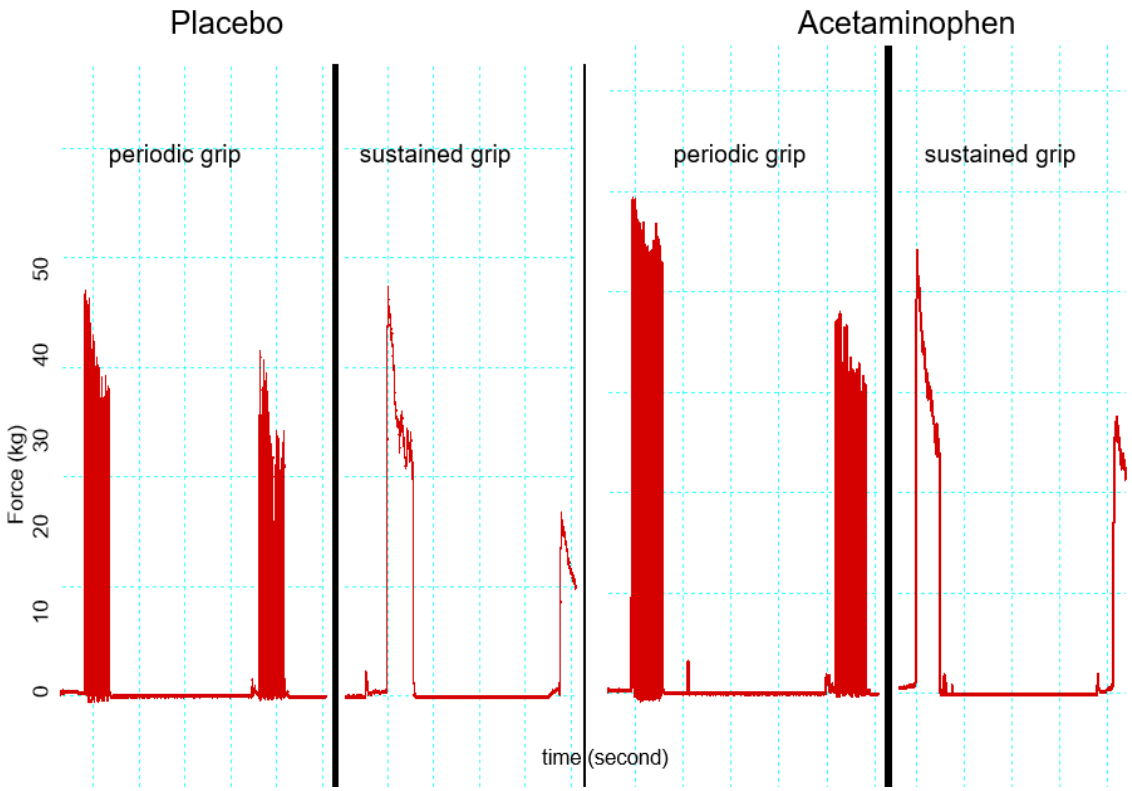

Figure 3: Sample of both periodic and sustained handgrip exercise in a conditioned, competitive young female gymnast. Note the improvement in muscle function in the presence of acetaminophen.

A sample tracing of the experiment is shown in Figure 3, where the left side illustrates a placebo sample tracing for both intermittent and sustained exercises. The right side indicates the same exercises under acetaminophen conditions. One can observe an increase in both intermittent and sustained grips when the participant is taking 1000 mg of acetaminophen in the sample tracing. For the sustained grip exercise, males (n = 5) had a significantly greater ($P<0.05$) force when taking acetaminophen (42.8 ± 3.4) compared to placebo (34.2 ± 4) (Figure 4).

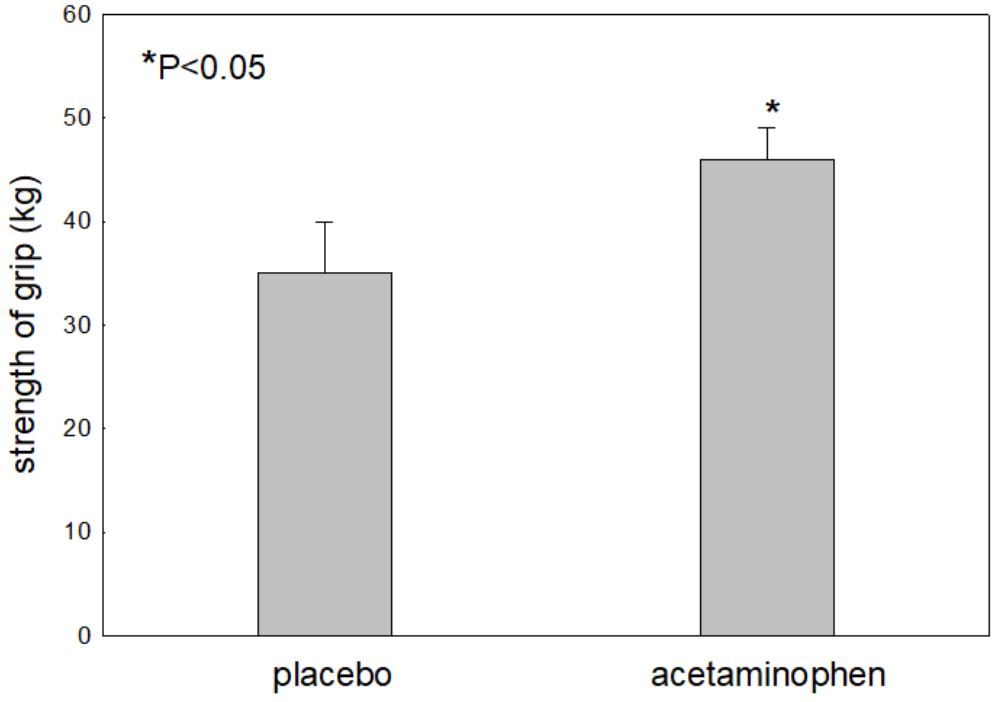

Figure 4: Histogram showing maximum strength of grip in male subjects in the absence and presence of acetaminophen (1000 mg, oral).

Females did not display a similar trend.

Trends in both males and females suggested a higher average maximum force during intermittent exercise under the placebo conditions. For example, males had a maximum force of 44 ± 2.5 (placebo) and 39.8 ± 2.9 (acetaminophen). Similar trends are seen in the female sample. Both males and females had higher minimum grip strengths under acetaminophen conditions during the intermittent exercise. When the female sample tested intermittent grip under placebo conditions, maximum force was 14.2 ± 0.8, while the same group of females under acetaminophen had a maximum force of 15.4 ± 1.6. This trend is replicated within the male sample. In spite of the general variability, there was no statistically significant difference between acetaminophen and placebo during the intermittent grip exercise for both male and female groups.

Discussion

Previous studies have demonstrated that over-the-counter doses of acetaminophen, when consumed in combination with resistance training, appear to enhance muscle hypertrophy and gains in strength in older adults (22).

Acetaminophen has many potential mechanisms for myoprotection (17) that could ultimately lead to increased time to fatigue and increase in magnitude of force both before and after fatigue. Acetaminophen's ability to act as an antioxidant/oxygen scavenger is particularly notable during ischemia and reperfusion, such as during sustained, strenuous, strength-training exercises (e.g., heavy lifting) when muscle contraction can actually reduce blood flow (23). Contraction-induced, extravascular compression, can partially occlude blood flow leading to transient tissue ischemia. Such temporary occlusion of blood flow to a working muscle substantially decreases time to fatigue and reduces development of maximal force (24).

Exercise-induced muscle damage increases free radical production, leading to oxidative damage to biomolecules (25). During ischemia and reperfusion, including that caused by exhaustive, heavy exercise, reactive oxygen species such as superoxide anion (O2), hydrogen peroxide (H2O2), hydroxyl radical (OH-), and peroxynitrite (ONOO-) are synthesized and released at greater rates. This can trigger cell death (apoptosis), tissue injury, and necrosis when these induce cellular calcium overload by impairing uptake, accelerating release, and/or a combination of alterations in calcium homeostasis (13). It is hypothesized that acetaminophen can act as an oxidant scavenger due to the structure of the acetaminophen phenolic ring, and thereby blocking cellular cascades that lead to apoptosis and necrosis (12, 26).

Acetaminophen can also attenuate the activation of intracellular MMP-2 and subsequent cleavage of troponin I by reducing the circulating levels of peroxynitrite. Although peroxynitrite itself is damaging to myocardial and endothelial tissue, it has also been shown to activate mediators of cellular damage (e.g., the matrix metalloproteinases). Studies have shown that the intracellular actions of matrix metalloproteinase-2 (MMP-2) is responsible, at least in part, for the injury observed from acute release of peroxynitrite following myocardial ischemia and reperfusion (27). Activation of myocardial MMP-2 causes increased proteolysis of troponin-I (TnI), and results in a decrease in overall cardiac mechanical function (10).

Ischemia and reperfusion cause a significant increase in opening of the mitochondrial permeability transition pore (MPTP), with subsequent mitochondrial swelling, and release of mitochondrial cytochrome c. Experiments on Langendorff-perfused guinea pig hearts revealed that treatment with acetaminophen preserved contractile function (particularly diastolic function) after peroxynitrite administration. Western blotting of heart homogenates showed increased degradative products of TnI in vehicle-treated versus acetaminophen-treated hearts. This physiology and observed inhibition of cytochrome c release in acetaminophen-treated subjects, which is likely a response to the complete upstream inhibition of MPTP opening in the presence of acetaminophen, reveals that acetaminophen is cardioprotective, at least in part, by attenuating peroxynitrite-activated, MMP-2-mediated cleavage of TnI. (10, 12).

The above mechanisms potentially play a part in the results found in this experiment, although they probably do not account for males having the only significantly higher strength of grip. However, the gender-based differences in drug absorption are well documented in the literature (21). And, if this is the case, then there could also be gender-based differences in acetaminophen's distribution, metabolism, and elimination from the tissues. Additionally, pharmacokinetics in women is affected by lower body weight, slower gastrointestinal motility, and reduced intestinal enzymatic activity, (21). Further study of such prospective differences in acetaminophen's efficacy and potency in men vs women is warranted.

The need for myoprotective drugs is vast. Everything from Lou Gehrig's disease, to sports injuries, sepsis, and organ protection during surgery could yield potential benefits from broader and more intense research on acetaminophen. As mentioned above, a recent study demonstrated an association between acetaminophen and reduced postoperative acute renal injury in adults undergoing cardiac surgery. Investigators theorized this to be due to a reduction in hemoglobin-induced oxidation of arachidonic acid and subsequent attenuation of intraoperative plasma isofuran concentrations (28). This has significant implications for patients undergoing cardiac surgery and any major surgery with a potentially long ischemic time of organ or muscle.

Limitations

The hand-held electronic dynamometer which was used to measure grip strength was reported to have caused mild discomfort for some participants. In turn, the discomfort could have influenced participant effort, thus introducing bias or performance variability across testing sessions. The sample size of the experiment was ten total students, five male and five female. This sample size could have limited the ability to identify trends in females. Additionally, the study focused on forearm and hand muscles in a seated, non-weight-bearing position. The above position allows for the testing of small muscle groups, but limits the ability to apply the findings to postural muscles used in whole-body movements. As a result, the effects of acetaminophen on lower-limb, core, or full-body muscular performance remain unknown and should be the focus of future studies.

Conclusion

Acetaminophen has previously unreported effects on human skeletal muscle performance that might have important sex-based variability. In addition, with the cost-effective nature of acetaminophen, and with its increasing use in the clinical arena, further research must be conducted on this topic. A few aims of such work should be to discover the medication's differential actions on various muscle groups under differing conditions and in both sexes.

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