

CAFFEINE ATTENUATES DELAYED ONSET MUSCLE PAIN FOLLOWING ECCENTRIC EXERCISE

by

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(Under the Direction of Patrick O'Connor)

ABSTRACT

This randomized, double-blind, placebo-controlled, counterbalanced, repeated measures experiment examined the effects of a $5 \text{ mg} \cdot \text{kg}^{-1}$ body weight dose of caffeine on delayed onset muscle pain intensity and force loss in response to 64 eccentric actions of the dominant quadriceps induced by electrical stimulation. Low caffeine consuming college-aged females ($N = 9$) ingested caffeine or placebo 24 and 48 hours following electrically stimulated eccentric exercise of the quadriceps. One hour after ingestion, maximal voluntary isometric contractions (MVIC) and submaximal voluntary eccentric actions were used to determine whether caffeine attenuates muscle pain intensity or force loss during activation of damaged quadriceps. Pain intensity was measured using a 0 to 100 visual analog scale. Caffeine produced a large (12.7 raw VAS units; -58.4%; $d = -0.88$) statistically significant hypoalgesia during the MVIC ($t = -2.52$; $df = 8$; $P_{\text{one-tailed}} = 0.018$) and a smaller reduction in pain scores during submaximal voluntary eccentric movements (7.8 raw VAS units; -25%, $d = -.34$; $P_{\text{one-tailed}} = 0.179$). Caffeine produced a small increase in MVIC force (5.3%; $d = 0.12$; $P_{\text{one-tailed}} = 0.095$). The results suggest that adenosine contributes to delayed onset muscle pain and adenosine antagonists are useful in treating this type of muscle pain among low caffeine consumers.

KEY WORDS: adenosine antagonist, DOMS, force, electrical stimulation, isometric, soreness

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DEDICATION

Γεωργιος Μαριδακης:

Σας ευχαριστω για την ιστορια μας, την αρχη μας και την οικογενεια μας.

Μας λειψατε.

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CHAPTER 1

INTRODUCTION

Pain is a common experience that is defined as the perception of noxious stimuli that may identify a potential threat to tissues (Almeida, 2004). It seems logical that pain should occur during a physiological insult so as to prevent any further damage to the organism. However, it is known that intense, high-tension eccentric bouts of exercise can damage skeletal muscle and the resulting muscle pain follows a delayed time course. On average this delayed muscle pain reaches peak intensity between approximately 24 and 48 hours post-damage (Cheung et al., 2003; Clarkson & Hubal, 2002; Clarkson and Newham, 1995). Delayed onset skeletal muscle pain has been studied for decades and the available evidence implicates the inflammatory response that follows skeletal muscle damage as an important mechanism in delayed onset muscle pain (Smith, 1991).

Although delayed onset muscle pain may be an experience shared by a large number of people, the pain intensity varies greatly among individuals. Laboratory studies have shown that delayed onset muscle pain intensity ratings vary greatly among individuals who performed an identical, standardized eccentric exercise stimulus. The reasons for the wide variability in pain intensity ratings are poorly understood, but individual variations in muscle fiber recruitment patterns or inflammatory responses might be contributing factors. For example, individuals who experience more pain a day or two following voluntary eccentric exercise might recruit fewer fibers in performing a standard eccentric exercise stimulus compared to those who experience less pain. The use of electrical stimulation to induce muscle injury might minimize this potential

source of individual variation in pain ratings through consistent and localized skeletal muscle fiber activation throughout the exercise stimulus.

Neuromuscular electrical stimulation has often been employed in strength-training and rehabilitation protocols for skeletal muscle groups (Lake, 1992; Morrissey, 1988), but it has also been utilized in inducing eccentric movements in healthy humans with the aid of a dynamometer (Brown et al., 1996; Child et al., 1998; Dudley et al., 1990; Hortobagyi et al., 1999; Kues et al., 1996; Westing et al., 1990). Researchers have shown that electrically stimulated eccentric movements produce significantly more torque with increasing angular velocities than do voluntary movements (Dudley et al., 1990; Westing et al., 1990).

By using neuromuscular electrical stimulation to elicit high levels of force at a constant rate of angular velocity, and thereby maintaining high muscle fiber tension, there is more control over the activated muscle fibers and, thus, the extent of damage induced throughout the eccentric movement protocol. However, there are no studies that have looked at the role of neuromuscular electrical stimulation, eccentric actions and subsequent skeletal muscle damage, specifically focusing on delayed onset muscle pain.

There have been numerous attempts to test the efficacy of a number of hypoalgesic substances on delayed onset muscle pain. Many of these substances have focused on the acute inflammatory response that accompanies skeletal muscle damage through the use of nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs have inconsistent effects on delayed onset muscle pain (Cheung et al., 2003). Regardless of the dose and frequency of administration, the use of nonsteroidal anti-inflammatory drugs has not been shown to be consistently effective in the treatment of delayed onset muscle pain either as prophylactics or therapeutics. In addition, the

use of nonsteroidal anti-inflammatory drugs in large doses may delay the healing process in damaged tissue (Cheung et al., 2003).

The most consistent nonsteroidal anti-inflammatory drugs to reduce delayed onset muscle pain have been transdermally applied ketoprofen (Cannavino et al., 2003; Sayers et al., 2001) and naproxen (Dudley et al., 1997; Lecomte, et al., 1998). Ketoprofen is not commercially available in the United States (Cannavino et al., 2003)

Investigated alternatives to nonsteroidal anti-inflammatory drugs also have proven to be inconsistently effective in reducing delayed onset muscle pain. For example, prophylactic tolperisone (Bajaj et al., 2003), a centrally acting muscle relaxant, as well as fish oil and isoflavones (Lenn et al., 2002) provided no reduction in delayed muscle pain. Perhaps utilizing a substance that can achieve some of the analgesic actions of nonsteroidal anti-inflammatory drugs, but that also does not greatly influence the inflammatory process may prove useful in attenuating the delayed muscle pain that follows eccentric exercise induced skeletal muscle damage.

To date, no investigators have reported the results of experiments aimed at determining the role of adenosine in delayed onset muscle pain. Adenosine has been implicated as a nociceptive afferent activator (Myers et al., 1997) and it is present during inflammation (Levine & Reichling, 1994; Sawynok & Liu, 2003). Caffeine is a competitive, nonselective adenosine receptor antagonist (James, 1991; James, 1997) primarily acting on high affinity adenosine A₁ and A₂ receptors (Daly et al., 1999; Fredholm et al., 1999; James, 1997). These receptors are reported to be located in peripheral afferent nerves (Bryan & Marshall, 1999; Lynge & Hellsten, 2000), the dorsal horn of the spinal cord (Sawynok & Liu, 2003) as well as in higher brain areas associated with pain processing (Ribeiro et al., 2003; Sebastiao & Ribeiro, 1996).

Caffeine has been the subject of much research in part due to its common use (Barone & Roberts, 1996). There are a handful of human studies which have examined caffeine as a hypoalgesic. Reductions in ischemic forearm muscle pain have been found with a caffeine dose of 200 mg (Myers et al., 1997). Caffeine has also shown moderate to large hypoalgesic effects on quadriceps muscle pain during cycling exercise with pre-exercise doses of 5 and 10 mg · kg⁻¹, respectively (Motl et al., 2003; O'Connor et al., 2004).

The purpose of this experiment is to test the null hypothesis that a 5 mg · kg⁻¹ body weight dose of caffeine will not cause a significant change in two consequences of muscle damage (i.e., pain intensity ratings or maximal voluntary contraction force) 24 and 48 hours following electrically induced eccentric exercise of the quadriceps. The alternative hypotheses are that a 5 mg · kg⁻¹ body weight dose of caffeine will produce a (a) large ($d = .80$), statistically significant reduction in quadriceps muscle pain intensity ratings and (b) a large ($d = .80$) statistically significant change in maximal voluntary contraction force.

CHAPTER 2

LITERATURE REVIEW

INTRODUCTION

The review contains the following sections: (1) exercise induced skeletal muscle damage, (2) neuromuscular electrical stimulation, (3) the neurobiological basis for pain, focusing on the potential role of adenosine in delayed onset muscle pain and (4) caffeine; its metabolism and its influence on physiological functions.

Skeletal Muscle Damage

Intense eccentric muscle actions cause muscle damage and delayed onset muscle pain, especially following unaccustomed physical activity. Two consequences of skeletal muscle damage will be examined: the force lost and the delayed muscle pain that results from intense, isokinetic and electrically induced eccentric exercises. Both isometric force loss and delayed muscle pain share a similar time course of recovery, but whether or not pain intensity plays a significant role in generating isometric force following skeletal muscle damage remains unclear.

Force loss

A significant reduction in force production has been observed immediately following muscle damaging eccentric exercises and is considered to be a reliable indirect measure of skeletal muscle damage (Brown et al., 1996; Child et al., 1998; Clarkson & Hubal, 2002; Radak et al., 1999; Stupka et al., 2001). Post-damage force reductions have been observed during isometric, concentric and eccentric movements with eccentrics showing the largest reduction (Cheung et al., 2003; Deschenes et al., 2000; MacIntyre et al., 1996). Across muscle groups, the

average force reduction following low and high-force eccentric exercises has been observed to be approximately 10-30% and 50-65%, respectively (Clarkson & Hubal, 2002).

Of the six studies that have evaluated force and torque production in the quadriceps using neuromuscular electrical stimulation, only two have provided information regarding the force lost immediately following electrically stimulated eccentric exercises (Brown et al., 1996; Child et al., 1998). In both of these studies stimulation amplitude was enough to produce 50% of maximal voluntary isometric contraction force. There was a 40-50% reduction in maximum voluntary isometric force production observed immediately following 60-70 electrically induced eccentric actions of the knee flexors and continuing until three days post eccentric exercise (Brown et al., 1996; Child et al., 1998).

Delayed onset muscle pain

Pain following eccentric exercise has been shown to increase in intensity during the first 24 hours post exercise, reach a peak intensity between 24 & 72 hours and subside within 5-7 days post exercise (Cheung et al., 2003; Clarkson et al., 1999).

The delayed onset of pain following unaccustomed eccentric exercise may be due to the time course of the inflammatory response following muscle damage. It has been proposed that aspects of the acute inflammatory response contribute to delayed onset muscle pain (Smith, 1991). A large number of inflammatory mediators sensitize or activate nociceptive afferents including bradykinin, serotonin, potassium, histamine, prostaglandins, leukotrienes, substance P, hydrogen ions and adenosine (Levine & Reichling, 1994). Dying cells, such as those found at sites of skeletal muscle damage, lyse and release intracellular stores of adenosine nucleotides that are rapidly metabolized to adenosine (Cronstein et al., 1990). The high concentration of

adenosine at or near sites of damage and inflammation increases the likelihood of nociceptive afferent activation.

There are conflicting opinions regarding the role of delayed muscle pain in force reduction following damaging exercises. Some researchers have shown an association between delayed muscle pain and post-damage force loss (MacIntyre et al., 1996; Radak et al., 1999) while others have not (Clarkson & Hubal, 2002; Newham et al., 1985). This discrepancy may be explained in part by two factors: bimodal force reduction and inhibition of nociceptive sensory processing at the central or peripheral level during skeletal muscle activation.

Bimodal force reduction

In addition to the significant and immediate reduction in force production following intense eccentric exercise, there is a second, smaller reduction in force 20-24 hours post damage (MacIntyre et al., 1996). This second reduction in force corresponds to the time course of delayed onset muscle pain, which has led some researchers to implicate the second reduction in force to delayed onset muscle pain through the infiltration of inflammatory mediators (Clarkson & Hubal, 2002; MacIntyre et al., 1996). The potential mechanisms responsible for the occurrence of bimodal force reduction seen following damaging exercises have not been well researched, but one study suggests that sex-related differences may exist (MacIntyre et al., 2000).

Nociceptive transmission inhibition

The gate control theory emphasizes the role of the brain in pain processing as well as the ability of neurons in the spinal dorsal horn to modulate sensory inputs (Melzack, 1999). It is known that activation of non-nociceptive afferents (i.e. Type I and II) inhibits nociceptive neuron activity (O'Connor & Cook, 1999). Application of the gate control theory can be observed

during exercise as non-nociceptive afferents in skeletal muscle are activated and modulate nociceptive transmission. For example, researchers found that during a sub-maximal isometric contraction, pressure pain threshold increased in the quadriceps compared to resting controls (Kosek & Ekholm, 1995). This type of finding is consistent with the gate control theory and suggests an explanation for the inconsistent relationship that has been observed between delayed onset muscle pain and force production during activation of damaged skeletal muscles.

Adenosine

The proposed investigation will use the non-selective adenosine antagonist caffeine as a possible analgesic. Adenosine and its receptors are located in numerous cell bodies, including those potentially relevant to nociception and pain. Adenosine A₁, A_{2A} and A_{2B} receptors are present in vascular cells of human skeletal muscle tissue (Lynge & Hellsten, 2000). Both adenosine and ATP stimulate Type IV nociceptive afferents from rat skeletal muscle via adenosine A₁ and P2X₃ receptors, respectively (Reinohl et al., 2003). Adenosine and A₁ receptors are present in the inner portion of lamina II of the rat dorsal horn of the spinal cord, a location where nociceptive afferents synapse (Schulte et al., 2003). Thus it is possible that skeletal muscle inflammation induced increases in adenosine in vascular cells of skeletal muscle, in nociceptive afferents from skeletal muscle or in lamina II of the spinal cord may contribute to delayed onset muscle pain. Adenosine antagonism via caffeine may reduce nociception and pain that is associated with damaged muscle fibers of the quadriceps when induced by electrically induced eccentric exercises.

Neuromuscular Electrical Stimulation

Neuromuscular electrical stimulation (NMES) is the process by which electrical current is applied percutaneously to elicit a skeletal muscular contraction (Lake, 1992). Specific NMES

elements that are needed for optimal activation have received limited attention in healthy human individuals, but some information is available about six areas of NMES: current amplitude, frequency, pulse duration, pulse wave shape, electrode size and electrode placement (Lake, 1992; Moreno-Aranda & Seireg, 1981a; Moreno-Aranda & Seireg, 1981b; Morrissey, 1988). Each of these elements will be considered in order to address which protocol might be best for inducing skeletal muscle damage through NMES.

There are only a handful of studies that evaluated the role of NMES in inducing eccentric movements in healthy human quadriceps, and the protocols from each of these studies have been similar (Brown et al., 1996; Child et al., 1998; Dudley, 1990; Hortobagyi et al., 1999; Kues & Mayhew, 1996; Westing et al., 1990).

Amplitude

A positive linear relationship has been reported between the amplitude of the electrical stimulation applied to the skin and force produced by skeletal muscle contraction (Lake, 1992). The absolute amplitude (current in milliamps) of the electrical stimulus employed varies and depends on interactions among the desired intensity (i.e., amplitude required to elicit a certain percentage of MVC) and factors that influence resistance to the electrical current such as thickness of skin and fat, and the participants' tolerance of the electrical stimulus.

Submaximal percentages (30-60%) of participant maximal voluntary contraction force have been utilized in order to adequately activate and damage skeletal muscle fibers but not harm joint or soft tissue during the eccentric actions (Brown et al., 1996; Child et al., 1998; Dudley et al., 1990; Kues & Mayhew, 1996).

Frequency

NMES studies inducing eccentric muscle actions in human quadriceps have used electrical stimulation frequencies of either 50 or 100 Hz (Brown et al., 1996; Child et al., 1998; Dudley et al., 1990; Hortobagyi et al., 1999). Lower frequencies, such as those between 20 and 35 Hz produce tetanus, but do not produce as much force as with higher frequencies (Lake, 1992; McNeal & Baker, 1988).

Pulse Wave Shape

There is no consensus that any specific pulse wave shape minimizes participant discomfort or produces more force than any other. NMES induced eccentric actions of the human quadriceps have used both sinusoidal (Dudley et al., 1990; Hortobagyi et al., 1999) or monophasic rectangle/square waves (Brown et al., 1996; Child et al., 1998).

Pulse Duration

Pulse duration of 0.5 ms has been used consistently in NMES based eccentric actions of the human quadriceps. It has been found that, regardless of pulse shape, 0.5 ms is an adequate width of time for the pulse wave to effectively activate this muscle group (Brown et al., 1996; Child et al., 1998; Dudley et al., 1990).

Electrode Size

A compromise between too small and too large electrodes must be made with NMES. Small electrodes produce a high density of current, which is painful (Alon, 1994; Lake, 1992; Patterson & Lockwood, 1993). As the electrodes increase in size, however, there is an increased chance of activating muscles other than the target muscles. Thus, the electrodes should be large enough to activate the target muscle(s) as well as accommodate the participants' comfort levels, but not so large as to activate non-target muscles. Studies of quadriceps muscles have used

electrode areas ranging from as small as 36.08 cm² (Dudley et al., 1990) to as large as 150 cm² (Child et al., 1998) for each electrode.

Electrode Placement

Studies using NMES to activate the quadriceps muscles have placed electrodes distally on the vastus medialis and proximally on the vastus lateralis (Dudley et al., 1990) or vice versa (Hortobagyi et al., 1999).

NMES versus voluntary muscle actions

To my knowledge, no studies have directly compared the perceptual or physiological consequences of NMES induced versus voluntary exercise induced muscle damage. However, there are hypothetical advantages and disadvantages to each method for the study of eccentric exercise induced muscle damage and pain. The primary advantage of using NMES to induce muscle damage is that the damage could be induced with more control than with voluntary contractions. Muscle activation is more localized with NMES because of a consistent activation of only a certain number of fibers rather than the cycling effect of fibers seen during voluntary actions (Westing et al., 1990; Lieber, 2002). A second advantage of NMES induced eccentric actions is the significantly greater production of torque than voluntary actions as angular velocity increases (Dudley et al., 1990; Westing et al., 1990). Although there are no studies that have directly compared electrically induced and voluntary eccentrics and the resulting delayed muscle pain, differences in force production at different angular velocities have been reported. At an angular velocity of 60 degrees · second⁻¹, average quadriceps torque during NMES eccentrics has been observed to be approximately 20% greater than voluntary (Westing et al., 1990).

There are at least three disadvantages of using NMES compared to voluntary muscle action in studying eccentric exercise. First, NMES lacks generalizability. Under normal skeletal

muscle conditions, consistent activation of only a certain number of muscle fibers does not occur. Second, NMES is uncomfortable and it can be painful. It is possible that the perceived pain and discomfort could either result in fewer potential participants being willing to volunteer for a study involving electric stimulation or result in the dropout rate being higher compared to studies that involve voluntary exercise. Third, NMES requires specialized and expensive equipment that may not be available in all laboratories.

Neurobiology of Pain and Nociception

Pain refers to an unpleasant perception associated with actual or potential tissue damage. Nociception refers to the activation of neural tissues involved in transmitting information about actual or potential damage. It is well established that nociception can occur without pain, and this is thought to be due to biological mechanisms attenuating nociceptive signals (Almeida et al., 2004).

Nociceptive Afferents

Muscle pain usually occurs as a result of muscle damage, such as muscle fiber disruption or tears. Biochemical and physiological consequences of muscle fiber injury stimulate specific nociceptive afferents. These nociceptive afferents have been classified into two types based on their size and presence of myelin (Almeida et al., 2004). Type III nociceptive afferents are thinly myelinated fibers that best respond to noxious pressure (Almeida et al., 2004) that occurs with localized swelling and inflammation after muscle injury. Type IV nociceptive afferents are smaller unmyelinated fibers and can be specific to algescic chemicals or polymodal. Polymodal refers to a fiber's ability to respond equally well to thermal, pressure and chemical noxious stimuli (Almeida et al., 2004).

There are numerous chemicals that are known to stimulate nociceptive afferents either by sensitization or activation. Those chemicals that sensitize are less potent than activators because they only decrease activation threshold of nerves rather than directly causing nerves to depolarize. Sensitizers of nociceptive afferents include prostaglandins, leukotrienes, substance P and hydrogen ions. Activators of nociceptive afferents include bradykinin, serotonin, potassium, histamine and adenosine (Levine & Reichling, 1994; Myers et al., 1997).

Peripheral levels of many of the activators and sensitizers listed above increase in interstitial fluid surrounding skeletal muscle nociceptive afferents in response to inflammation (Mense, 2003). Both neuronal (nociceptive afferents and sympathetic nerves) and non-neuronal (muscle and vascular cells) sources of adenosine contribute to increases in peripheral adenosine (Sawynok, 1998). An increase in peripheral adenosine has been attributed to (1) the release of adenosine triphosphate (ATP) into the extracellular medium following cell damage from which adenosine is generated (Mense, 2003), (2) enhanced catabolism of ATP inside cells in response to toxins or inflammatory mediators that increases the transport of adenosine outside of the cell (Lynge et al., 2001) or (3) by alterations of the activity of adenosine kinase and adenosine deaminase induced by inflammatory mediators (Sawynok & Liu, 2003).

Most algogenic chemicals, including adenosine, have been shown to contribute to nociception by binding to receptors located on the surface of the Type IV afferent (Sylvén et al., 1988). There is evidence that adenosine may have complex effects on pain signaling and inflammation that are mediated by different receptors. For example, adenosine A₁ receptor activation has been implicated in inhibitory neuromodulation and neuroprotection while adenosine A_{2A} receptors on neurons produce excitatory actions (Sawynok & Liu, 2003).

Adenosine A₃ receptor activation can have pro-nociceptive actions mediated by mast cell action, histamine and 5-HT release (Sawynok, 1998).

Spinal Cord

Nociceptive afferents from the limbs have their cell bodies in the dorsal root ganglia. Type IV nociceptive afferents generally terminate in lamina II of the dorsal horn while Type III nociceptive afferents usually terminate in laminae I and V (Sawynok & Liu, 2003). Within the dorsal horn of the spinal cord nociceptive afferents communicate using the neurotransmitter glutamate and excitatory amino acids such as substance P, neurokinin A and calcitonin gene-related peptide (Sawynok & Liu, 2003). Adenosine is also involved in nociception-related neural transmission in the spinal cord. A number of studies have demonstrated that the spinal administration of adenosine produces analgesia in a broad range of nociceptive, inflammatory and neuropathic pain tests (Sawynok & Liu, 2003). These studies have shown that spinal analgesia can be mediated by adenosine A₁ receptors (Sawynok & Liu, 2003). Autoradiographic studies using selective ligand binding approaches revealed the presence of adenosine A₁ receptors in the superficial layers of the dorsal spinal cord, which corresponds to the area of termination of small diameter sensory afferents (Sawynok & Liu, 2003). It seems contradictory that spinally administered adenosine would induce analgesia as adenosine infusion produces algesia when administered peripherally via the A₁ receptors (Myers et al., 1997; Sawynok & Liu, 2003). It has been hypothesized that the inverse action of adenosine at the spinal and peripheral levels may be explained by a multireceptor complex that is linked via a second messenger system as seen with the μ -opioid receptors (Sawynok & Liu, 2003). It is plausible that those factors within the multireceptor complex for opioids can also affect the inhibitory or excitatory actions of adenosine A₁ receptors, though the specifics of the factors for adenosine are not well

understood. There is, at present, little evidence that adenosine A_{2A}, A_{2B} or A₃ receptors in the spinal cord are involved in modulating pain transmission.

Brain

From the spinal cord, nociceptive information is transmitted to the brain by several nerve tracts. The spinothalamic tract is most well described, but the spinoreticular and spinomesencephalic tracts play important roles as well. Briefly, the spinothalamic tract carries nociceptive information from the dorsal horn of the spine to the lateral thalamus and then to a number of brain areas, but the heaviest projections are to somatosensory cortices I and II and the hypothalamus (Derbyshire, 1999; Kupers et al., 2004). The spinoreticular tract carries nociceptive information from the dorsal horn of the spine to the reticular formation at the levels of the pons and medulla before synapsing at the medial thalamus (Almeida, 2004). The spinomesencephalic tract travels from the dorsal horn to mesencephalic areas as well as the locus coeruleus.

Key brain areas related to nociception are the periaqueductal gray, anterior cingulate and the amygdala. Studies using human brain imaging have shown that the most consistently activated brain areas in response to noxious stimuli are the thalamus, somatosensory cortices I and II, the anterior cingulate cortex, prefrontal cortices and dorsal posterior insula (bilaterally) (Derbyshire, 1999; Kupers et al., 2004).

Adenosine receptors are widely distributed in the brain and spinal cord. The highest density of A₁ receptors has been found in the brain cortex and dorsal horn of the spinal cord (Sebastiao & Ribeiro, 1996). The highest density of A_{2A} receptors has been found in the cerebral cortex (Sebastiao & Ribeiro, 1996). The brain areas with a high density of adenosine receptors of most relevance to nociception and pain appear to be the cortical regions (Ribeiro et al., 2003).

Caffeine

Caffeine, also known as 1,3,7 trimethylxanthine, is a member of the family of methylated xanthines (James, 1997). The analgesic potential of caffeine is described in terms of its pharmacokinetics following ingestion (i.e., absorption, distribution, metabolism & excretion), its action as a non-selective, competitive adenosine antagonist and a potential ergogenic aid.

Absorption

Following oral ingestion, caffeine is rapidly absorbed into the bloodstream from the gastrointestinal tract; however, variations regarding peak plasma concentration exist. Peak concentrations have been reported within 40-60 minutes and 15-120 minutes (Arnaud, 1998). This variation has been hypothesized to be due to delayed gastric emptying by factors such as contents of the stomach and intestine, amount of caffeine ingested, source of caffeine (James, 1997) and Ph (Spiller, 1998). Absorption appears to be independent of age, sex (Arnaud, 1987), genes and disease of the subject (Arnaud, 1998). Higher absorption rates have been reported in obese subjects (Kaminori et al., 1987).

Distribution

Studies have shown that caffeine can readily permeate all tissues throughout the body including crossing the blood-brain barrier. There is no evidence of caffeine being sequestered in specific organs (James, 1991; James, 1997).

Metabolism

Caffeine is metabolized by the hepatic microsomal cytochrome P-450 enzyme system. Any significant contribution by any other organ(s) has not been demonstrated (Arnaud, 1998). Post-ingestion breakdown of caffeine results in a host of metabolites, the most important being the dimethylxanthines paraxanthine, theobromine and theophylline (Arnaud, 1998; James, 1997;

Spiller, 1998). Theobromine and theophylline increase to relatively low levels (12% and 4% respectively) while the level of paraxanthine is significantly higher (84%) (Arnaud, 1998; James, 1997). Unique to human adults, caffeine is almost completely transformed with approximately 2% of the ingested sample observed unchanged in urine (Arnaud, 1998; James, 1997).

Excretion

In humans, the half-life of caffeine varies between 3-7 hours but may be influenced by a variety of factors such as gender, contraceptive use and pregnancy (James, 1991).

Adenosine

The most plausible mechanism of action for methylxanthines and hypoalgesia is the competitive nonselective blockade of adenosine A₁ and A₂ receptors (Daly et al., 1999; Fredholm et al., 1999; James, 1997). Both caffeine and theophylline have been observed to have analgesic effects while paraxanthine and theobromine have not.

It has been reported that high affinity adenosine receptors are located in brain areas involved in nociceptive and anti-nociceptive actions (Ribeiro et al., 2003), but adenosine receptors are also located at the level of skeletal muscle. Until recently it has been unclear if the receptors are located within skeletal muscle itself or on the vascular tissue. Recently, evidence for the direct existence of only adenosine A_{2A} and A_{2B} receptors within skeletal muscle has been found in the rat (Bryan & Marshall, 1999) while adenosine A₁, A_{2A}, and A_{2B} receptors have been found to exist in the vascular cells of human skeletal muscle (Lynge & Hellsten, 2000).

Ergogenic aid

The primary mechanism by which caffeine exerts its ergogenic effects is unclear. Most of the studies that have evaluated the ergogenic effects of caffeine have examined time to exhaustion in endurance exercises lasting between 30 and 60 minutes (Graham, 2001). The

ergogenic effect of caffeine during short-term intense exercise has not been well explored, but the current evidence shows effects only in exercises lasting at least 60 seconds (Graham, 2001). Based on these findings, caffeine should not exert any profound ergogenic effect during a brief, intense exercise such as a maximal voluntary contraction of the quadriceps.

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CHAPTER 3

CAFFEINE ATTENUATES DELAYED ONSET MUSCLE PAIN FOLLOWING ECCENTRIC EXERCISE¹

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ABSTRACT

This randomized, double-blind, placebo-controlled, counterbalanced, repeated measures experiment examined the effects of a $5 \text{ mg} \cdot \text{kg}^{-1}$ body weight dose of caffeine on delayed onset muscle pain intensity and force loss in response to 64 eccentric actions of the dominant quadriceps induced by electrical stimulation. Low caffeine consuming college-aged females ($N = 9$) ingested caffeine or placebo 24 and 48 hours following electrically stimulated eccentric exercise of the quadriceps. One hour after ingestion, maximal voluntary isometric contractions (MVIC) and submaximal voluntary eccentric actions were used to determine whether caffeine attenuates muscle pain intensity or force loss during activation of damaged quadriceps. Pain intensity was measured using a 0 to 100 visual analog scale. Caffeine produced a large (12.7 raw VAS units; -58.4%; $d = -0.88$) statistically significant hypoalgesia during the MVIC ($t = -2.52$; $df = 8$; $P_{\text{one-tailed}} = 0.018$) and a smaller reduction in pain scores during submaximal voluntary eccentric movements (7.8 raw VAS units; -25%, $d = -.34$; $P_{\text{one-tailed}} = 0.179$). Caffeine produced a small increase in MVIC force (5.3%; $d = 0.12$; $P_{\text{one-tailed}} = 0.095$). The results suggest that adenosine contributes to delayed onset muscle pain and adenosine antagonists are useful in treating this type of muscle pain among low caffeine consumers.

KEY WORDS: adenosine antagonist, DOMS, force, electrical stimulation, isometric, soreness

INTRODUCTION

Dozens of experiments have tested the effectiveness of pharmacological (e.g., non-steroidal anti-inflammatory medications), physical (e.g., massage, stretching), and other potential therapies (e.g., anti-oxidants, ultrasound) for reducing delayed onset muscle pain caused by eccentric exercise. In general, these treatments have been inconsistent in attenuating delayed onset muscle pain or had small or no effect (12).

Investigators have not reported the results of experiments aimed at determining the role of adenosine in delayed onset muscle pain, yet increased adenosine release with inflammation plausibly could contribute to this type of pain (25). Adenosine moderates the function of various cells by acting on adenosine receptors. Adenosine receptors are located in numerous tissues, including peripheral nociceptive afferent nerves (4, 26), the dorsal horn of the spinal cord (35) and higher brain areas associated with pain processing (34).

One method for safely manipulating adenosine receptors in humans is by ingesting caffeine. Caffeine is a competitive, nonselective adenosine receptor antagonist primarily acting on high affinity adenosine A₁ and A_{2A} receptors (13, 16, 20). Ingested caffeine acts on the peripheral nervous system and because caffeine crosses the blood brain barrier it acts on the central nervous system as well. Habituation and withdrawal effects occur with chronic use and disuse of caffeine and these effects are associated with up and down regulation of adenosine receptors (21).

Both hypoalgesic and ergogenic effects of caffeine are documented. Caffeine significantly increases the exercise test duration to onset of angina (30) and reduces experimentally induced ischemic forearm muscle pain (28) as well as quadriceps muscle pain that occurs naturally during cycling exercise (27, 29). Caffeine in doses above 3 mg · kg⁻¹ body

weight has been shown to repeatedly improve endurance (17). Less attention has been paid to whether caffeine ingestion has ergogenic effects on muscular strength and no studies have reported on the effect of caffeine on the strength loss that follows muscle injury induced by eccentric exercise.

The purpose of this randomized, double-blind, placebo-controlled, counterbalanced, repeated measures experiment was to test whether a $5 \text{ mg} \cdot \text{kg}^{-1}$ body weight dose of caffeine attenuates either muscle pain or maximal isometric force loss following eccentric exercise.

METHODS

Participants

University of Georgia female undergraduates were recruited. Participants were able to earn extra course credit for participation. Eligibility required one to be, or report being: (a) non pregnant, (b) a non-smoker, (c) not overweight, defined as a body mass index (BMI) < 25 , (d) not involved in any lower body resistance exercise program that included knee extensions/flexions more than once per week, (e) not currently training for any competitive athletic event, (f) a low daily caffeine consumer ($< 100 \text{ mg} \cdot \text{day}^{-1}$), (g) free from known hypersensitivity to caffeine, (h) not taking any prescription medicine or over the counter stimulants, (i) free from contraindication for performing leg exercises and (j) without a pre-existing knee injury. Participants were informed of risks associated with the project and each provided written consent in accordance with the University of Georgia Institutional Review Board guidelines for use of human subjects.

Ten volunteers completed testing. One participant reported no delayed onset muscle pain 24- to 48-hours after eccentric exercise and was excluded from the analysis. One participant completed 16 of 64 eccentric muscle actions because of equipment failure but her data were

included in the analysis because the delayed force loss (ranging from 3.5% to 8.5%) and muscle pain intensity responses (VAS scores ranging from 9 to 14) observed prior to the intervention were adequate to test the experimental hypotheses. Selected characteristics of the nine participants are presented in Table 1.

Procedures

Day 1. Potential participants completed four questionnaires to establish eligibility: an exercise history and injury questionnaire, a medical history questionnaire, a 7-day caffeine recall and a caffeine sensitivity questionnaire.

Participants were measured for height and weight using a calibrated DETECTO scale. Next, maximal voluntary isometric contraction (MVIC) strength of the dominant quadriceps was assessed. Subjects were seated in a custom-built chair with the hip and knee secured at $\sim 70^\circ$ of flexion. The leg was firmly secured to a rigid lever arm with an inelastic strap to ensure that the knee extensors could only perform isometric contractions. Isometric mode contractions were used to minimize the potential for skeletal muscle injury. The moment arm was established by placing a load cell (model 2000A, Rice Lake Weighing Systems, Rice Lake, WI) parallel to the line of pull and perpendicular to the lever arm. Torque was recorded from the load cell by using a MacLab analog-to-digital converter (model ML 400, ADInstruments, Milford, MA) sampling at 100 Hz and interfaced with a portable Macintosh computer (Apple Computer, Cupertino, CA). Torque was calculated by multiplying the peak force (in pounds) by the length of the lever arm (1 foot) and then converting foot-pounds to Newton-meters. Three MVICs, separated by one minute, were performed. Participants were instructed to perform each MVIC as quickly and explosively as possible. These instructions and methods were used for all subsequent tests of MVIC strength.

Participants next were fitted to and familiarized with the Kin-Com dynamometer (Isokinetic International, Harrison, TN). The dominant leg was attached to the Kin-Com lever arm at the ankle and positioned so the axis of rotation was aligned with the knee joint. The length of the lever arm was measured for each individual and maintained during all subsequent testing.

Day 2. Participants were required to report no quadriceps pain in order to complete the testing on day 2 and no participant reported quadriceps pain. Two 6.98 x 10.16 cm electrodes were placed distally on the vastus medialis and proximally on the vastus lateralis of the dominant quadriceps. A Rich-Marr TheraMINI electrical stimulator was used to elicit 8 sets of 8 eccentric actions of the dominant quadriceps while participants were positioned in the Kin-Com dynamometer. The electrical stimulus consisted of a biphasic sinusoidal wave with a 0.450 ms pulse duration elicited at 100 Hz. The absolute current applied varied among participants, but each received a current that resulted in force produced of approximately 50% MVIC. Fifty percent of MVIC was selected in order to adequately activate and damage skeletal muscle fibers but not harm joint or soft tissue during the eccentric actions. One participant who completed the study did report a knee injury. Whether the injury was caused by the exercise protocol, a pre-existing condition or physical activities performed outside the laboratory was unclear. There was nothing remarkable about this participant's reduction in MVIC force following eccentric exercise (ranging from 2% to 16%) or the quadriceps pain intensity ratings (VAS score ranging from 3 to 30) on either day of testing that would suggest the injury biased the outcome of this study.

The eccentric actions were performed from 10 to 80 degrees below horizontal (70 degree range of motion). The start force at 10 degrees was set at 50 Newtons. The eccentric actions were performed at a constant angular velocity of $120 \text{ degrees} \cdot \text{sec}^{-1}$. Electrical stimulation of the

quadriceps was elicited using a 1 second “ on ”, 1 second “ off ” protocol. The primary researcher plugged in the stimulator wire to elicit each eccentric movement and then unplugged the wire once the 70 degree range of motion was completed. After each eccentric movement was completed, the researcher returned the lever arm back to 10 degrees below horizontal starting position at a controlled rate of $200 \text{ degrees} \cdot \text{sec}^{-1}$ for each movement. Each set was separated by 1 minute.

Following the eccentric exercise protocol, participants performed three maximal voluntary isometric contractions, each separated by one minute.

Days 3 and 4. Participants reported for testing at 24 and 48 hours after the eccentric exercise protocol. The procedures were identical on these days except that on one day caffeine was ingested and the other a placebo was ingested.

Three MVICs were completed, both to determine maximal force and to stimulate delayed onset muscle pain. The highest pain intensity experienced during the three MVICs was reported immediately after the three exercises were completed. Two subsequent submaximal eccentric actions were also used to stimulate pain. The participants voluntarily activated the Kin-Com from 10 degrees to 80 degrees below horizontal at a speed of $90 \text{ degrees} \cdot \text{sec}^{-1}$. The participants needed to overcome 50 N of preset load force in order to initiate the eccentric action and were instructed to resist against the load cell throughout the entire range of motion. Immediately after the second eccentric action the participant reported the highest pain intensity experienced during the two exercises. Next, the participants consumed either a caffeine pill or a placebo pill. One hour after ingestion, the MVIC and submaximal eccentric tests were repeated and associated pain ratings obtained.

Participants were randomly assigned to the order in which they received caffeine or placebo. Twenty-four hours after eccentric exercise, four of the participants ingested $5 \text{ mg} \cdot \text{kg}^{-1}$ of caffeine (Caffeine Anhydrous, USP, Meridian, Decatur, AL) and the other five participants received placebo (flour). Caffeine and placebo were delivered in gelatin capsules (No. 0, NOW Foods, Bloomingdale, IL). Forty-eight hours after eccentric exercise, those who previously consumed caffeine received placebo and those who had consumed placebo received caffeine. All participants consumed caffeine or placebo with 500 mL of water and then sat and read quietly in a sound-dampened, thermoneutral environmental chamber maintained at 23 ± 2 degrees (Celsius) and $\sim 50\%$ relative humidity. Caffeine and placebo pills were administered using a double blind, counterbalanced procedure to minimize participant/investigator expectancy and order effects.

Quadriceps muscle pain intensity ratings were obtained using a visual analog scale. Participants placed a vertical mark with a pen on a 10 cm horizontal visual analog scale. The left and right ends of the scale were anchored with the phrases 'no pain' and 'most intense pain imaginable,' respectively. Pain intensity was scored from 0 to 100 measured in millimeters from the left end of the scale. Substantial evidence supports the validity of scores using this visual analog scale as measures of pain intensity (31).

After testing was completed, both the participants and the blinded investigator recording the exercise and pain data were asked to indicate which day they thought caffeine was ingested.

Statistical analysis

Raw data were entered into the Statistical Program for Social Sciences (SPSS version 13.0 for Windows), which was used for data analysis.

Preliminary analyses. Preliminary analyses were performed to determine the trial-to-trial reliability of the MVIC force measures. The intraclass correlation (ICC) model used was a one way (3 Trials) random effects model. The ICC model also used consistency as the type of agreement and the single measures option. High reliability was found for each of the six sets of MVIC force assessments (day 1 Baseline = 0.980; day 2 post eccentric = 0.995; 24 hour pre-ingestion = 0.986; 24 hour post-ingestion = 0.986; 48 hour pre-ingestion = 0.985; and 48 hour post-ingestion = 0.990). The associated means for each trial were: day 1 Baseline = 183.4, 185.1, 188.0 Nm; day 2 post-eccentric = 153.0, 154.3, 154.9 Nm; 24 hour pre-ingestion 159.2, 159.0, 158.2 Nm; 24 post-ingestion = 157.4, 161.1, 160.3 Nm; 48 hour pre-ingestion = 155.9, 161.2, 164.7 Nm; and 48 hour post-ingestion = 159.8, 166.4, 166.7 Nm. These preliminary analyses supported the use of the average of three MVICs as the criterion measure of maximal force in the primary analysis.

Primary analyses. Descriptive data are reported as means and standard deviations in tables. Standard errors are used in the figure. Effect size calculations were made using Cohen's d ; that is, the difference in two means divided by the pooled standard deviations (10). Dependent t-tests using pre- to post-ingestion change scores comparing the caffeine and placebo conditions were used to test the hypotheses. Because the literature shows caffeine reduces pain and increases muscular performance, one-tailed tests were used.

RESULTS

Effect of caffeine on pain.

Descriptive pain data are presented in Table 2 and Figure 1. One hour after caffeine ingestion, pain intensity during the maximal voluntary isometric contractions was decreased by 12.7 raw VAS units (-58.4%, $d = -0.88$ SD_{pooled}). This reduction in pain intensity was

statistically significantly greater than the 1.9 VAS score decrease found after placebo ingestion ($t = -2.52$; $df = 8$; $P_{\text{one-tailed}} = 0.018$). Eight of nine participants reported larger decreased MVIC pain scores following caffeine ingestion compared to placebo.

One hour after caffeine ingestion, pain intensity stimulated by voluntary lengthening of the quadriceps during submaximal eccentric actions decreased by 7.8 raw VAS units (-25%, $d = -.34 SD_{\text{pooled}}$). Six of the nine participants reported larger decreased pain scores following caffeine ingestion compared to placebo during submaximal eccentric actions. Two participants reported no change in pain scores. This reduction in pain intensity was not statistically greater than the 1.9 VAS score decrease found after placebo consumption ($t = -.975$; $df = 8$; $P_{\text{one-tailed}} = .179$).

Effect of caffeine on force.

Descriptive MVIC force data are presented in Table 2. One hour after caffeine ingestion, force increased by a small magnitude compared to pre-ingestion (5.3%; $d = 0.12 SD_{\text{pooled}}$). Five of nine participants reported an increase in force production following caffeine ingestion compared to placebo. One participant reported no change in force. This increase in force was not statistically significantly greater than the 1.47% reduction in force found after placebo ingestion ($t = 1.43$; $df = 8$; $P_{\text{one-tailed}} = 0.095$).

Force loss after eccentric exercise.

Baseline (day 1) MVIC torque was 185.4 ± 48.1 Nm. Following eccentric exercise on day 2, MVIC force was reduced by 31.4 Nm (~17%; $d = 0.59 SD_{\text{pooled}}$). The reduction in force was significantly different than baseline ($t = 4.77$; $df = 7$; $P = 0.001$).

Participants were 100% correct in estimating which day they received caffeine and the blinded investigator was 89% correct.

DISCUSSION

The primary novel finding from this study was the large pain reduction during maximal voluntary isometric contraction following caffeine ingestion. Because the release of adenosine, a potent algescic agent, is increased during inflammation following injury (25) and caffeine is an adenosine antagonist, it is plausible that the findings resulted from caffeine attenuating nociceptive activity induced by adenosine in the periphery. Indeed, four to eight hours following eccentric exercise, the expression of the gene for the adenosine A₁ receptor is increased by nearly six times in human skeletal muscle (7). The precise mechanism for the reduction in pain found in this experiment is uncertain because caffeine is a non-selective adenosine receptor antagonist with high affinity for both A₁ and A_{2A} receptors. Also, the locus within the nervous system for the antinociceptive effect is uncertain because of the widespread location of adenosine receptors. In addition to being localized within nociceptive afferent fibers, adenosine receptors are present in, and caffeine has access to, the dorsal horn of the spinal cord (34, 35) and brain areas involved in pain such as primary and secondary somatosensory, insular, anterior cingulate and prefrontal cortices (1).

The magnitude of the hypoalgesic effect of caffeine during MVICs generally is greater than what has been previously reported in experiments testing other treatments for delayed onset muscle pain. Naproxen doses of 500 mg twice daily or 220 mg · day⁻¹ produced a 22% and 30% reduction in muscle soreness, respectively (approximately -0.46 and -0.60 SD, respectively) and ketoprofen produced a 10% and 17% reduction in muscle soreness with doses of 25 and 100 mg in participants reporting high pre-drug pain intensity scores of 40-77 on a 100 mm visual analog scale (14, 23, 36). A study examining topical ketoprofen, in which the mean pre-drug pain intensities were more similar to those in the present study, found a 33% reduction in muscle pain

(0.71 SD). A 25% reduction in pain following 2600 mg of aspirin has been reported (15), though no placebo group was used. In addition, inconsistent results from ibuprofen have been reported with a wide range of doses (1200-2400 mg) and treatment periods (5 days pre-damage – 10 days post-damage) (12). The efficacy of non-steroidal anti-inflammatories in reducing delayed onset muscle pain has been inconsistent.

The effect of caffeine on reduced pain intensity in response to MVICs was observed despite relatively low pre-ingestion pain scores. Prior studies examining therapeutic interventions for delayed onset muscle pain often have used methods that result in higher mean visual analog pain ratings (14, 23, 36), and some investigators contend that therapeutic interventions cannot be tested validly without moderate or higher (> 40 on a 0-100 scale) pain intensity ratings (1). The present findings show the inaccuracy of that contention at least with caffeine. Moreover, it is possible that the failure to find treatments that consistently reduce delayed onset muscle pain may be due in part to the focus of most of the prior research on eccentric exercise protocols resulting in muscle damage that is too severe and intensely painful to be effectively treated with a single, readily available intervention (e.g., over-the-counter medicine). In the present study, caffeine's hypoalgesic effects were revealed at relatively low mean pain intensities that may be more consistent with the delayed onset muscle pain intensity experienced by most individuals performing activities of daily living outside of a laboratory environment.

In addition to adenosine receptor antagonism, several alternative explanations for the results exist that cannot be ruled out based on the design of the present investigation including differences in pre-treatment pain scores and blood pressure responses to caffeine. Mean MVIC pain scores prior to caffeine ingestion were ~8 raw VAS units higher than pre-placebo ingestion.

It is well known that the magnitude of change in many physiological variables is dependent in part on the initial values and by analogy this might have occurred for the MVIC pain results. This possibility is discounted by the smaller decrease in pain ratings with the submaximal eccentric actions despite higher mean pre-caffeine ingestion pain scores in that condition compared to the MVIC condition (i.e. 30.1 vs. 26.6). With regard to blood pressure, caffeine increases blood pressure and increased systolic blood pressure can be hypoalgesic (3). Blood pressure was not assessed here; however, blood pressure has been found to be weakly correlated with pain ratings following unaccustomed eccentric exercise (31).

A second novel finding from this study was the smaller pain reduction with submaximal eccentric movements compared to the MVIC stimulated pain. It is not clear why the hypoalgesic effects of caffeine would differ between these two movements and there are several possible explanations including small sample bias and differing physiological responses to the two types of movements. Compared to the submaximal eccentric actions, maximal exercise (MVICs) likely would be associated with higher intramuscular adenosine and intramuscular pressure. Both these effects may have resulted in caffeine having a larger hypoalgesic effect; the high intramuscular pressure hypothesis is based on reduced blood flow in the maximally contracting muscle contributing to a higher concentration of adenosine. It is possible that larger hypoalgesic treatment effects are revealed when maximal exercise is used as the noxious stimulus. To date, few muscle injury studies have used maximal exercise as a noxious stimulus.

The third finding in this study was the small increase in MVIC force production. Previous studies that examined the effect of caffeine during short-term, intense exercise reported ergogenic effects in exercises lasting longer than 60 seconds. Because of variations among studies in samples used (athletes vs. non-athletes), rest intervals between maximal exercises and

caffeine doses used, there is no consensus regarding the ergogenic effect of caffeine during short-term, intense exercise. Improvements of approximately 5.5% of maximal torque in highly trained male athletes have been reported with a dose of $7 \text{ mg} \cdot \text{kg}^{-1}$ body weight when single repetition maximal exercise protocols with adequate rest durations were used (19). An experiment using a dose of $6 \text{ mg} \cdot \text{kg}^{-1}$ body weight of caffeine with untrained males found that mean knee extensor strength increased by approximately 5% and maximal voluntary activation, determined using the twitch interpolation technique, increased by 3.5% (22). Other studies have found no effect of caffeine on maximal voluntary contractions (38). Using an electrically stimulated supramaximal ($\text{MVC} + 10\%$) muscle fatigue protocol lasting 120 seconds, a $6 \text{ mg} \cdot \text{kg}^{-1}$ body weight dose of caffeine potentiated the force of contraction in untrained males at low (20 Hz; mean of 25%), but not high (40 Hz; no effect) stimulation frequencies suggesting that caffeine lacks an ergogenic effect upon high intensity exercises (38). These findings along with that of the present study suggest that in some circumstances caffeine can enhance maximal isometric force, but often by a small percentage. It is unclear whether the increase in MVIC force in this study occurred as a result of reduced pain.

There are mixed findings concerning force generation and muscle function on days following damaging eccentric exercise. Some investigators contend that muscle function and force are affected by muscle pain (6, 33). Recently there have been studies that examined participants' ability to perceptually match and maintain maximal force following damaging eccentric exercise. The large errors reported indicate that participants may be attempting to match effort rather than force, suggesting nociceptive input has a central action that reduces motor cortical excitability (6, 33). However, most of the evidence supports the idea that damaged muscles can be fully activated regardless of the existence of muscle pain (9, 10, 37).

The *in vivo* administration of caffeine in rodents can cause calcium release from the sarcoplasmic reticulum through the ryanodine/SR calcium release channel and increase force (18). However, in humans the caffeine dose needed to produce a similar effect would be toxic (23). Therefore, in humans, it may be the case that caffeine's ergogenic effects occur by acting on the nervous system rather than directly on muscle excitation-contraction mechanisms.

There are several delimitations of the results of the present investigation. A small sample of young, healthy, low caffeine consuming women was tested. A larger sample size would have increased the likelihood of statistically significant finding extending to both the hypoalgesia with the submaximal eccentric pain stimulus and the attenuated MVIC force loss after eccentric muscle damage. The hypoalgesic effect observed with the $5 \text{ mg} \cdot \text{kg}^{-1}$ dose used here may not generalize to other samples, especially among groups with above average caffeine consumption. This is likely because many of the effects of an acute dose of caffeine are attenuated with chronic caffeine consumption (22). The magnitude of the hypoalgesic effect also may be dependent on the caffeine dose. It is unknown whether smaller or larger caffeine doses would produce smaller, similar or larger effects on pain ratings following eccentric exercise. Studies involving smaller caffeine doses might eliminate one of the potential limitations of the present investigation. That is, that despite the double-blind nature of the caffeine administration all the participants were able to accurately discern the day on which they consumed caffeine. This observation was not unexpected given the caffeine dose, the prior caffeine consumption history of the study participants and the known psychophysiological effects of caffeine. A smaller dose might be less discernible by the participants and also produce a hypoalgesia

CHAPTER 4

SUMMARY AND CONCLUSIONS

Caffeine has been utilized as an analgesic adjuvant in some clinical pain pathologies, as a mild stimulant in many foods and beverages and as an ergogenic aid in some athletic events. The plausibility of caffeine to attenuate pain resulting from intense damaging exercise is valid, yet the mechanisms behind this effect remain unknown.

This thesis was conducted in order to test the magnitude of caffeine's effect in attenuating delayed onset muscle pain and force production on days following damaging eccentric exercise. Nine, college-aged, low caffeine-consuming females performed 64 electrically induced eccentric exercise of the quadriceps. Following the ingestion of 5 mg · kg⁻¹ body weight dose of caffeine or placebo, participants performed maximal voluntary isometric and submaximal eccentric exercises to test the effect of caffeine on pain intensity and force production during these exercises.

The primary findings of this study support the use of caffeine as a hypoalgesic and a mild ergogenic aid during brief high intensity isometric exercise following damaging eccentric exercise. It is of potential interest to the application of this experiment's findings to note not only how muscle pain intensity was affected during testing and after intervention, but to speculate on how participants' daily activities might be affected as well. Although subjective ratings of everyday functions were not measured in this study, before testing began on Days 3 & 4, participants were quick to anecdotally report a change in abilities to perform everyday activities such as walking, ascending and descending stairs and attempting to sit down, which

they attributed to their delayed quadriceps muscle pain. Following caffeine ingestion, the participants appeared to show noticeable changes in behavior (e.g., an improved gait; less discussion about pain) suggesting that caffeine would have positive effects on activities of daily living. This is a potentially important direction for future research because improved functional outcomes may be as, or more, important than hypoalgesia.

In conclusion, following a caffeine dose of $5 \text{ mg} \cdot \text{kg}^{-1}$ body weight, delayed onset muscle pain intensity of the quadriceps was greatly reduced during maximal voluntary isometric contractions, but only moderately reduced during submaximal eccentric exercises. In addition, force production was increased by approximately 4% on the days following damage.

TABLE 1. Characteristics of the 9 female participants (mean \pm SD)

Age (y)	21.3 \pm 1.6
Height (cm)	169 \pm 6.0
Mass (kg)	59.8 \pm 6.9
Daily caffeine consumption (mg \cdot day ⁻¹)	55.1 \pm 30.9
BMI	20.9 \pm 1.8
Caffeine dose	298.9 \pm 34.4

TABLE 2. Pain intensity ratings and maximal voluntary isometric contraction (MVIC) torque (mean \pm SD)

	<u>MVIC pain (0-100)</u>		<u>SVEA pain (0-100)</u>		<u>MVC torque (Nm)</u>	
	<u>Placebo</u>	<u>Caffeine</u>	<u>Placebo</u>	<u>Caffeine</u>	<u>Placebo</u>	<u>Caffeine</u>
Pre-ingestion	18.2 \pm 10.8	26.6 \pm 15.6	28.1 \pm 11.3	30.1 \pm 11.9	162.8 \pm 58.7	156.9 \pm 51.9
Post-ingestion	16.3 \pm 8.9	13.9 \pm 13.1*	26.2 \pm 9.9	22.3 \pm 16.8	160.4 \pm 54.6	163.4 \pm 56.9
Effect size d	-0.19	-0.88	-0.12	-0.34	-0.04	0.12
Avg. % change	14.2 \pm 82.8	-52.8 \pm 34.9	-1.8 \pm 39.2	-25 \pm 35.2	-0.33	3.8

SVEA = submaximal voluntary eccentric action

* = statistically different change versus placebo ($p < 0.05$)

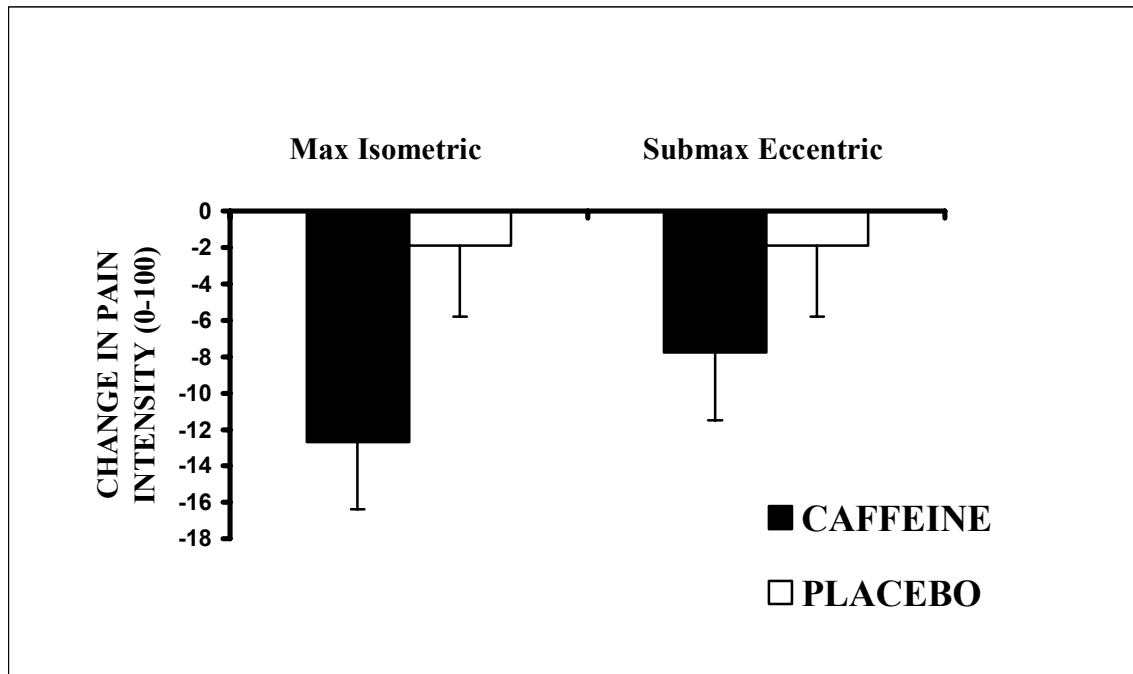


Figure 1 --- Pain intensity change scores following caffeine or placebo ingestion during maximal isometric (MVIC) and submaximal eccentric movements. Values are means \pm standard error.

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APPENDIX
QUESTIONNAIRE MATERIALS

7-day Caffeine Consumption Recall

Instructions: How many of the following caffeinated beverages or products that contain caffeine did you consume per day last week?

Beverage	Mon.	Tues.	Wed.	Thurs.	Fri.	Sat.	Sun.
Brewed coffee (cups)	_____	_____	_____	_____	_____	_____	_____
Instant coffee (cups)	_____	_____	_____	_____	_____	_____	_____
Decaffeinated coffee (cups)	_____	_____	_____	_____	_____	_____	_____
Tea (cups)	_____	_____	_____	_____	_____	_____	_____
Cocoa/Chocolate Milk (cups)	_____	_____	_____	_____	_____	_____	_____
Coffee ice cream (cups)	_____	_____	_____	_____	_____	_____	_____
Coffee yogurt (cups)	_____	_____	_____	_____	_____	_____	_____
Cola (cans)	_____	_____	_____	_____	_____	_____	_____
Cola (glasses)	_____	_____	_____	_____	_____	_____	_____
Mountain Dew (cans)	_____	_____	_____	_____	_____	_____	_____
Energy drinks (e.g. Red Bull)	_____	_____	_____	_____	_____	_____	_____
	_____	_____	_____	_____	_____	_____	_____
Product							
Chocolate (grams)	_____	_____	_____	_____	_____	_____	_____
Dexatrim (pills)	_____	_____	_____	_____	_____	_____	_____
Tylenol (pills)	_____	_____	_____	_____	_____	_____	_____

Excedrin (pills) _____ _____ _____ _____ _____ _____ _____

Anacin (pills) _____ _____ _____ _____ _____ _____ _____

Other products or herbal supplements that may have had caffeine in them:

Caffeine Sensitivity Questionnaire

Instructions: We are interested in knowing how sensitive you are to caffeine. Caffeine sensitivity refers to the degree to which you feel various physical or psychological symptoms in response to taking caffeine. Please answer as honestly and completely as you can.

1. The most common symptoms associated with caffeine consumption are feelings of anxiety or nervousness, muscle tension, shakiness or tremors and insomnia. If you have never experienced the above symptoms after taking a large amount of caffeine then you have below normal caffeine sensitivity. If you experience intense symptoms after taking caffeine then you have above normal caffeine sensitivity. Which of the following best describes you? (check one)

My sensitivity to caffeine is below normal_____

My sensitivity to caffeine is about normal_____

My sensitivity to caffeine is above normal_____

2. Have you ever used Nodoz or other caffeine pills?_____ If yes, did this elicit any negative side effects?_____

Explain._____

3. What is the greatest quantity of caffeine you have ever consumed in one day?_____

Did this quantity elicit any negative side effects?_____

Explain._____

4. Have you ever experienced negative side effects from caffeine?_____

Explain_____

Exercise/Injury History Questionnaire

Instructions: The purpose of this questionnaire is to obtain information about you and your current participation in exercise/sports and any history of injury. It is important that you answer each question honestly and completely. Please ask the investigator if you need clarification about any of the questions.

1. Are you currently training for any physically competitive event? YES NO
2. During a typical week, how many days do you exercise?
 - a. ≤ 1 days
 - b. 2 days
 - c. 3-4 days
 - d. ≥ 5 days
3. During a typical week, how long do you exercise per day?
 - a. ≤ 30 minutes
 - b. Between 30 and 45 minutes
 - c. Between 45 minutes and 1 hour
 - d. Greater than 1 hour
4. During a typical week, how many days do you participate (at least 20 minutes) in the following activities?
 - a. Sports (university, club or intramural team) _____
 - b. Endurance training (jogging, running, swimming) _____
 - c. Resistance training (lifting weights) _____
 - d. Yoga/Pilates _____
 - e. Other _____
5. For resistance training, which of the following exercises do you perform during the week? How often?
 - a. Squats _____
 - b. Leg Extensions _____
 - c. Leg Press _____
 - d. Hamstring Extensions _____
 - e. Lunges _____
 - f. Calf Raises _____
6. Have you ever been seriously injured while exercising? If so, what body location?
 - a. Head
 - b. Arms
 - c. Upper body/torso
 - d. Legs
 - e. Other _____

7. Have you ever undergone an operation for an exercise/sports related injury? If so, describe?
8. Have you ever undergone an operation for a non-exercise/sports related injury? If so, describe?

Medical History Questionnaire

1. _____ Gender
 - a. _____ If female, number of days since the start of your last menstrual cycle
 - b. _____ If female, are you taking any contraceptive medications?
 - c. _____ If female, are you pregnant?
2. _____ Age
3. _____ Height
4. _____ Weight
5. Do you regularly smoke cigarettes? YES NO
6. Are you currently taking any medication for pain? (Advil, Motrin, Aleve, Aspirin, Ibuprofen, Tylenol)

YES NO
7. Does your mother or father have high blood pressure? (i.e., hypertension)
8. Do you now have, or have you ever had high blood pressure?
9. Has any member of your family died of a heart attack prior to the age of 50?
10. Do you have, or have you ever had any heart trouble?
11. Have you ever had an unexplained episode of irregular heartbeats, trembling, sweating, difficulty breathing or intense anxiety?
12. Do you frequently suffer from pains in your chest?
13. Do you often feel faint or have spells of severe dizziness?
14. Have you ever fainted during exercise?

15. Do you have a bone or joint problem, such as arthritis, that has been or might be made worse with exercise?

16. Have you ever had a seizure? At rest? _____ or during exercise? _____

17. Do you have any pain that you have been experiencing for more than a month?

18. Is there any good reason not mentioned above why you should not engage in vigorous physical activity? If so, describe it:

Pain Intensity Scale

Instructions: Rate the intensity of pain you experienced while your leg was being moved by placing a vertical mark through the line below. If you experienced no pain at all put a mark at the left edge of the line. If you experienced the highest pain intensity that you can imagine then put a mark at the right edge of the line. Use the distance from the left edge to indicate the pain intensity that you feel for intensities between the two extremes. Rate your pain intensity accurately and honestly.

No Pain _____ Most Intense Pain
Imaginable