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CHAPTER 5

Muscle Soreness and Damage and the Repeated-Bout Effect

Ken Nosaka, PhD

Unaccustomed exercise consisting of repeated or forced lengthening (eccentric) contractions induces muscle damage. The most noticeable symptom of this damage is the muscle soreness that we experience after performing such exercise, which is often referred to as delayed-onset muscle soreness (DOMS). Eccentric exercise-induced muscle damage is also characterized by morphological changes such as disruption of contractile and noncontractile proteins and the plasma membrane, increases in muscle proteins in the blood, prolonged loss of muscle function, swelling, and abnormality detected by ultrasound and magnetic resonance images. These are used as markers of muscle damage, but it is not clear how they are related to each other and are associated with DOMS. A bout of unaccustomed exercise confers a protective effect against DOMS and muscle damage in subsequent bouts of the same or a similar exercise. This effect, referred to as the repeated-bout effect, is a unique feature of eccentric exercise-induced muscle damage. This chapter focuses on the physiology of muscle soreness, the relationship between DOMS and muscle damage, and the repeated-bout effect.

Muscle Soreness

Pain originating from skeletal muscle is caused by an acute or overuse injury or by chronic syndromes such as fibromyalgia and muscular rheumatism. Muscle soreness refers to muscle pain felt after exercise when the muscle is palpated or moved, and is most com-

monly experienced after the performance of unaccustomed exercise consisting of lengthening (eccentric) contractions. The development of such muscle soreness is generally delayed. Although DOMS is an extremely common symptom, its underlying mechanisms are not clearly understood, nor are the reasons for the delay.

Understanding Pain

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey and Bogduk 1994, pg. 210). We experience various kinds of pain in association with injuries, illnesses, and diseases. We also experience pain in many other nonpathological conditions (e.g., when we hold a heavy object or climb up stairs). Pain is a crucial signal that informs us of an abnormality in the body or a potential risk, but it is difficult to appreciate its value when we are suffering from it. In some cases, pain has no physiological value and yields only suffering. Pain perception is influenced by many factors, such as age, gender, and social or cultural norms about acceptable behavior in relation to pain (Unruh et al. 2002). In addition, given the same magnitude of tissue damage, the magnitude of pain perception ranges widely among individuals, since pain is a subjective symptom. These factors add to the complexity of understanding pain.

Function of Pain

Pain is generally considered a warning signal of actual or perceived tissue damage, and one of its major functions is to protect the organism from injurious stimuli (Millan 1999; Unruh et al. 2002). In order for this to occur, (1) pain should be felt before injurious stimuli induce irreversible damage to tissue, (2) the magnitude of the pain should reflect the severity of tissue damage, and (3) the duration of the pain should match the process of tissue damage and recovery. However, pain often occurs without clear evidence of tissue damage; and its onset, magnitude, and duration do not necessarily correspond to tissue damage (Melzack 1982). In cancer, for example, pain does not exist in the developmental phase, but cancer patients often suffer from severe pain in the phase when the disease is no longer treatable.

There are two clinical states of pain: physiological (nociceptive) pain and neuropathic (intractable) pain (Kingsley 2002). The former results from the direct stimulation of pain receptors due to injury of tissue and inflammatory responses, and the latter results from injury to the nervous system that causes permanent changes in central nervous system connections (Kingsley 2002). Chronic pain may be associated with changes in the nervous system (Unruh et al. 2002). Neuropathic pain does not appear to have a useful physiological function (Millan 1999), and is not necessarily functioning as a warning signal.

Exercise and Muscle Pain

Muscle pain occurs in many situations in sport and exercise, ranging from stretching a stiff muscle to holding a heavy object to incurring a muscle cramp or muscle tear. The onset of muscle pain varies depending on the cause. Figure 5.1 shows changes in the magnitude of muscle pain relative to its peak in five different situations: The same person experienced a muscle tear of the biceps femoris while playing tennis, a muscle cramp in the knee flexors on a different occasion, pain in the knee extensors from running a marathon (42.195 km), pain in the knee extensors from playing soccer for 120 min, and pain from performing maximal eccentric exercise of the elbow flexors. Pain can occur either (a) only during exercise, (b) both during and after exercise, or (c) only after exercise.

Muscle pain is elicited by sustained or rhythmic muscle contractions, with occlusion of blood flow accelerating its onset and increasing the intensity; but it subsides quickly once muscle activity is terminated and normal blood flow is restored (Miles and Clarkson 1994). It seems likely that pain substances produced during muscle contractions, as well as increased intramuscular pressure, are associated with the pain.

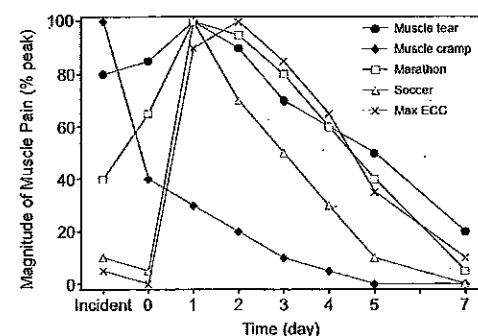


Figure 5.1 Changes in the magnitude of muscle pain relative to its peak (100%) in five different incidents. The pain level when the muscle tear and the muscle cramp occurred or during performance of exercises is shown as "Incident"; "0" is either 30 min after the occurrence of the muscle tear and the muscle cramp or immediately after the exercise. The peak pain level differed among the incidents, and the magnitude of pain was normalized relative to the peak value.

A muscle cramp—a sudden involuntary shortening of muscle—elicits sharp pain that appears to result from stimulation of mechanical receptors by excessive muscle tension (Miles and Clarkson 1994). It appears that muscle cramps can also be a consequence of prolonged low-intensity exercise, and many factors (e.g., fatigue, dehydration, electrolyte abnormality, environmental conditions) appear to be associated with the cause in this context. The pain disappears rapidly if the muscle stops cramping, but a residual pain is present after stretching of the cramping muscle (figure 5.1). Stretching of a cramping muscle is a forced lengthening (eccentric) muscle action that induces the "muscle damage" explained later in the chapter.

If muscle pain occurs during exercise, it may be a signal to stop or slow down. If the cause of the pain is a serious injury such as a laceration or contusion, we have no choice but to stop moving. Pain from these injuries is sustained and often aggravated in the days after the incident. Pain that continues after the cessation of exercise may indicate the need for treatment. Pain is generally one of the classic signs of inflammation (Hargreaves et al. 1989); therefore, anti-inflammatory treatment would be the first choice for relief.

As shown in figure 5.1, pain may develop during endurance events such as the marathon and triathlon, then continue and sometimes become aggravated the next day. In contrast, with other types of exercise, little or no muscle pain develops during performance but begins to develop several hours later. We experience this type of delayed-onset muscle pain especially when performing an unaccustomed exercise. This type of muscle pain is the main focus of this chapter.

Neurophysiology of Muscle Pain

Muscle pain has been less frequently documented than pain originating from cutaneous or visceral tissue. Most of the pain receptors appear to have a common physiological basis, but it appears that there are some differences between skeletal muscle nociceptors and others.

Pain Receptors (Nociceptors)

Pain receptors, referred to as nociceptors, respond to a noxious (tissue threatening) stimulus. Most of the data on the neuropathology of pain are from studies of cutaneous nociceptors; less information is available for muscle nociceptors. Muscle pain differs from cutaneous pain in that pain associated with muscle lesions is described as aching and cramping, while cutaneous pain is characterized by sharp, pricking, stabbing, or burning sensations (Mense 1993).

A large portion of the afferent nerve terminals lack encapsulated endings; these unencapsulated endings are called free nerve endings. The free nerve endings are nociceptors, which are highly branched and have large areas of sensitivity. This is why our idea of the place of origin of a pain sensation is often vague, particularly for muscle pain (Mense 1993). When we feel muscle pain, it is difficult to tell exactly where in the muscle the pain is originating without careful palpation of the muscle. It appears that the pain spreads beyond its actual site of origin.

Skeletal muscles contain four types of afferent fibers: types I (A α), II (A β), III (A δ), and IV (C). The free nerve endings of the latter two respond to noxious stimuli such as mechanical pressure, heat, cold, and algogenic substances (e.g., bradykinin, potassium, serotonin, histamine). A δ fibers have thin myelinated axons with a relatively fast conducting velocity (5–30 m/s); they respond to muscle stretch, contractions, and innocuous pressure and are sensitized by thermal and chemical stimuli (Millan 1999). In contrast, C fibers are thin and unmyelinated and transmit signals more slowly (0.5–2 m/s). Like A δ fibers, C fibers respond to thermal stimuli, ischemia, and hypoxia and are sensitized by chemical stimuli (Millan 1999). Stimulation of C fibers in muscle elicits dull, aching pain and cramping pain. The pain sensation from muscle is thought to be mainly mediated by C fibers and secondarily by A δ fibers (Hargreaves et al. 1989).

Muscle Nociceptor Locations

In skeletal muscle, the free nerve endings of A δ and C fibers are located along the walls of arterioles and in the surrounding connective tissue (Mense 1993). It is important to note that there are no pain receptors on the muscle plasma membrane. Therefore, even if some muscle fibers are damaged and stop functioning, we may not feel muscle pain if nociceptors located far from the damaged area are not affected. Interestingly, devastating

muscle dystrophies such as the Duchenne type are not painful (Marchettini 1993).

It seems that the sensation of muscle pain is activated by changes in the chemical environment surrounding muscle tissue, or by stimulation of fascia, rather than by primary muscle cell damage (Marchettini 1993). Weerakkody and colleagues (2001) reported that muscle mechanoreceptors (primary endings of muscle spindles) are involved in DOMS and argued against the likelihood that a simple sensitization process is responsible for DOMS. It has also been documented that the sympathetic nervous system contributes to the sensation of pain by augmenting or modifying the nociceptors (Hargreaves et al. 1989).

Muscle Nociceptor Stimuli

As already described, muscle nociceptors are polymodal, responding to mechanical, thermal, and chemical stimuli. Effective stimuli for nociceptors in skeletal muscle are strong mechanical forces and endogenous algogenic substances such as bradykinin, serotonin, and potassium ions (Mense 1993). The nociceptors are sensitized by prostaglandin E₂ (PGE₂) (Mense 1993) and hydrogen ions (not lactic acids) (O'Connor and Cook 1999). It appears that muscle nociceptors respond to weak mechanical stimuli when they are sensitized.

An increased sensitivity of nociceptors to a stimulus is termed hyperalgesia, and allodynia refers to the situation in which pain is induced by a stimulus that does not normally provoke pain (Calzà 2001). In normal conditions, palpating, stretching, or contracting muscles does not induce muscle pain; however, the same stimulus evokes pain when muscle damage has occurred. This indicates that muscle damage changes innocuous stimuli to noxious stimuli; muscle nociceptors become hyperalgesic, and the injured person experiences allodynia. It seems that in general, endogenous substances produced by muscle damage and inflammation do not stimulate muscle nociceptors directly (though some of them may to some extent) but instead increase the sensitivity of the nociceptors so that muscle contraction or stretching or palpation pressure becomes painful (figure 5.2). Swelling may also contribute to hyperplasia of the nociceptors.

Pain Pathways

A δ and C fibers bring signals from skeletal muscle to the spinal cord (figure 5.2). Most A δ and C fibers enter the dorsal root ganglion and synapse primarily in the dorsal horn of the spinal cord (Guyton 1994). From the spinal cord, pain signals take the spinothalamic pathways to the medulla, the midbrain, and the cerebral cortex. There are two different spinothalamic pathways: the neospinothalamic (lateral spinothalamic) tract and the paleospinothalamic (anterior spinothalamic) tract (O'Connor and Cook 1999). The neospinothalamic tract transmits signals primarily from A δ fibers and appears to be responsible for sharp, fast pain.

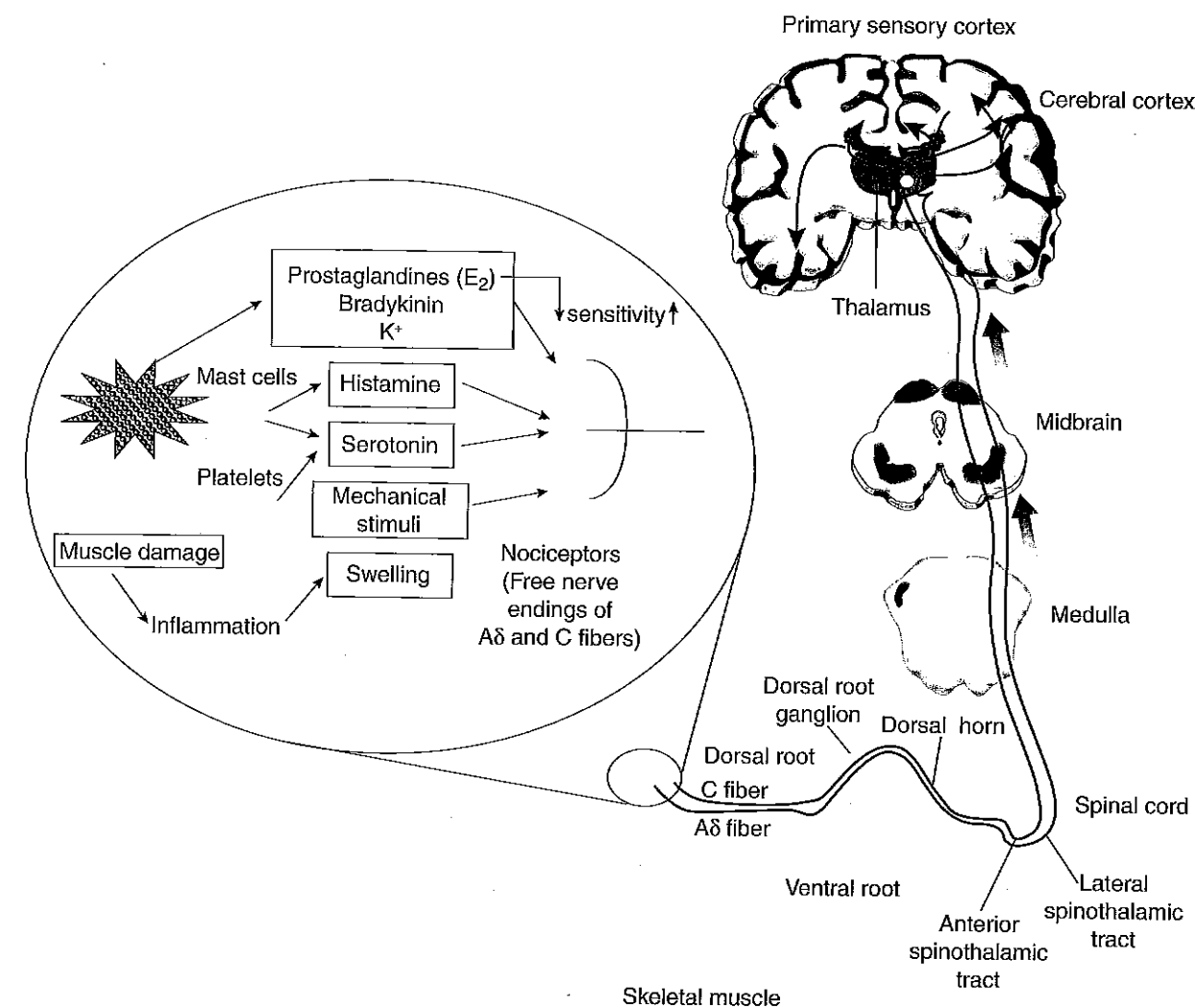


Figure 5.2 Pain pathways from skeletal muscle and a schematic view of the events at the site of skeletal muscle damage.

In contrast, pain signals from C fibers take the paleospinothalamic tract and terminate widely in the brainstem and thalamus. It seems that dull, aching pain is conveyed by this tract. The thalamus is the terminal of the spinothalamic pathways and transfers sensory information to the primary somatosensory areas of the cerebral cortex designated Brodmann's areas 3, 1, and 2 (Guyton 1994). In addition to these areas, multiple cortical areas such as the secondary somatosensory cortex, the anterior cingulate cortex, the insula, the prefrontal cortex, and the supplementary motor area are activated by pain stimuli (Kingsley 2002).

Modulation of Pain and Analgesia

The transmission of pain sensation from the nociceptors to the spinal cord to the cerebral cortex is modulated (Millan 1999). Stimulation of nociceptors does not necessarily reach consciousness and elicit pain. For example, it is often reported that athletes do not feel pain during

a match even if they have a serious injury. The nervous system can interact with the pain pathways to palliate the perception of pain under some conditions. In this pain control process, often called analgesia, not only the brain but also the spinal cord is involved (Millan 1999). Substances involved in analgesia include enkephalins, endorphins, and other opiate neuropeptides. Enkephalin is believed to cause presynaptic and postsynaptic inhibition of type Aδ and C fibers in the dorsal horns (Koltyn 2000). It is also known that multiple areas of the brain have opiate receptors, and opiates such as endorphins and enkephalins suppress pain signals (O'Connor and Cook 1999). Thus, the magnitude of pain does not directly reflect the magnitude of the stimulus to nociceptors.

It has been documented that exercise increases pain thresholds and pain tolerance; this phenomenon is often referred to as exercise-induced analgesia (Koltyn 2000; O'Connor and Cook 1999). Exercise-induced analgesia has

been found to occur following running, cycling, and swimming, but little is known about the effect from resistance exercise (Koltyn 2000). More than 100 years ago, Hough (1902) reported that performing a second bout of exercise on the day after an activity that induced muscle soreness caused excessive pain for the first 2 to 3 min, which disappeared over the course of 5 to 10 min of exercise. Armstrong (1984) stated that exercising a sore muscle appeared to provide the most effective way of reducing the soreness; however, the nature of exercise-induced analgesia for DOMS has not been investigated systematically. A later section of the chapter provides further details on this issue.

Delayed-Onset Muscle Soreness

Following unaccustomed or severe exercise, we experience the discomfort of a dull, aching pain, combined with tenderness and often stiffness, for several days. The "delay" in DOMS appears to vary among exercises or individuals, but the pain normally increases in intensity in the first 24 h after exercise, peaks from 24 to 72 h, then subsides and disappears by five to seven days postexercise. There is little or no discomfort at rest; the sensation of pain is elicited when mechanical stimuli such as pressure, stretching, or contraction are imposed on the affected muscles.

Muscle soreness develops during exercise such as long distance running or performance of a marathon, and often gets worse over the days of recovery (figure 5.1). This type of muscle soreness is different from that occurring only after exercise. It may be that the cause of the muscle soreness felt during exercise is not the same as that responsible for the muscle soreness after exercise. However, it seems likely that the cause of the soreness in the days following exercise is similar in the two scenarios. Muscle damage induced by lengthening (eccentric) contractions is associated with the muscle soreness felt over the subsequent days (Armstrong 1984).

Mechanism of DOMS

A number of theories have been proposed to explain DOMS; among these are theories involving lactic acid, muscle spasm, muscle damage, connective tissue damage, and inflammation (Cheung et al. 2003). Theories pertaining to lactic acid and muscle spasm are unlikely to explain DOMS, and there is evidence to refute these explanations (Cleak and Eston 1992; Miles and Clarkson 1994).

Delayed-onset muscle soreness was first described by Hough (1902), who concluded that DOMS was "fundamentally the result of ruptures within the muscle." Although "ruptures" of muscle fibers are not associated with DOMS, ultrastructural disruptions of myofibrils, especially at the Z-disc, characterized by broadening, streaming, or smearing of the Z-disc structure as observed under electron microscope, have been reported to accom-

pany DOMS (Friden et al. 1981, 1984; Yu and Thornell 2002). Connective tissue damage is also indirectly shown by increases in urine hydroxyproline (Abraham 1977) or plasma hydroxyproline and serum type 1 collagen concentration (Brown et al. 1999).

Therefore, the "damage" theory proposed by Hough is still valid with some modification, and it is most likely that muscle or connective tissue damage (or both) and subsequent inflammatory responses are associated with DOMS (Cheung et al. 2003). It may be that changes in connective tissue (endomysium or perimysium), rather than damage to muscle fibers, relate directly to DOMS. Jones and colleagues (1987) suggested that damage and shortening of muscle connective tissue would increase the mechanical sensitivity of muscle nociceptors and cause pain with stretching or palpation. One postulate is that the inflammatory response process leading to sensitization of muscle nociceptors takes time, and this would explain the delay (Smith 1991).

Eccentric Exercise and DOMS

Eccentric exercise, exercise mainly consisting of lengthening (eccentric) contractions, produces greater DOMS than exercise involving mainly shortening (concentric) or static (isometric) contractions (Newham et al. 1983; Talag 1973). It has been reported that isometric contractions at long muscle lengths induce greater DOMS than those at short muscle lengths; however, the magnitude of DOMS following isometric exercise is much less than that after eccentric exercise (Jones et al. 1989).

It appears that although pure concentric contractions do not induce DOMS, when people perform repeated concentric contractions in training they also unintentionally perform eccentric contractions, especially when muscles are fatigued. For example, when lifting a dumbbell using the elbow flexors, if we fail to produce a force larger than the dumbbell, our elbow flexors are lengthened while producing force. This may result in DOMS and muscle damage. In fact, concentric exercise of the elbow flexors with a 10 kg dumbbell may induce minor muscle soreness after exercise. However, the magnitude of the soreness is much less than it would be if the same person at the same level of training had engaged in eccentric exercise with the same weight (see figure 5.3f).

Unaccustomed eccentric exercise is known to induce greater damage to the internal membrane system, intermediate filaments, Z-discs, and contractile proteins than other types of exercises (Lieber and Friden 2002). This provides strong support for the damage and inflammation theory of the mechanism of DOMS. However, alteration of the Z-disc structure occurs to some degree even after concentric exercise (Gibala et al. 1995). The magnitude of ultrastructural alterations may not necessarily determine the magnitude of muscle damage (Nunenburg et al. 1992). It has also

been documented that morphological changes at the muscle fiber level (e.g., mononuclear cell infiltration) do not correspond with muscle pain (Jones et al. 1986; Newham 1988). Moreover, Yu and colleagues (2002) did not find muscle fiber degeneration or an inflammatory response in human skeletal muscle with DOMS. Thus, the exact relationships between damage and inflammation in muscle or connective tissue and DOMS are still not clearly understood.

Measurement of DOMS

There is no generally accepted single best measure of pain (O'Connor and Cook 1999). However, there are several methods for evaluating pain, including the pressure pain threshold and tenderness, and several ways to quantify the soreness level using a questionnaire (MacIntyre et al. 1995; O'Connor and Cook 1999; Ohbach and Gale 1989). Types of scales for assessing muscle soreness include visual analog scales (VAS), numerical rating scales, verbal rating scales, descriptor differential scales, and the McGill pain questionnaire. Ohnhaus and Adler (1975) reported that a VAS consisting of a line (50-200 mm) with "no pain" at the left end and "unbearable pain" at the right end reflected a subject's muscle-associated pain more precisely than a verbal rating scale.

A number of difficulties exist with use of the VAS to quantify soreness, although this type of scale has been used in many studies. The difficulties include questions regarding the sensitivity of the instrument. For example, subjects who mark "50," or "unbearably painful," for the peak DOMS level cannot indicate a greater pain level even if they experience greater soreness in subsequent days. This is a disadvantage of using a closed-ended scale. A better way of quantifying pain may be to use an open-ended scale in which subjects can choose any number to represent the pain associated with some intermediate level of stimulation and then scale all subsequent tests in relation to the initial reference stimulus (Jones and Round 1990).

It is also important to note that the pain sensation can vary among subjects. For example, some subjects may mark "40" even if their soreness level is medium; others may mark "10" even if the pain level is very severe. Because of the subjective and individual nature of the pain sensation, the question arises whether it is possible to compare levels of soreness between subjects, or even changes in DOMS over days in the same subject. Perception of a noxious stimulus may differ greatly between individuals and may also vary with a given person's mood, health, or hormonal status. Melzack (1982) stated that "pain is not simply a function of the amount of bodily damage alone, but is influenced by attention, anxiety, suggestion, and other psychological variables (pg. 148)."

For these reasons, it is important to be cognizant of the limitations in quantitatively assessing DOMS in experimental studies.

DOMS and Muscle Damage

As already discussed, DOMS is a symptom particular to eccentric exercise-induced muscle damage. Other symptoms of muscle damage include muscle weakness, stiffness, and swelling. Muscle damage is detected by histological changes, increases in muscle proteins in the blood, and abnormality shown by ultrasound and magnetic resonance images. It is important to note that DOMS does not necessarily represent muscle damage and that the level of DOMS and changes in muscle detected by the different methods are not necessarily correlated.

Defining Muscle Damage

Muscle is damaged when it receives a harmful physical, chemical, or biological stimulus. In relation to exercise and sport, muscle damage occurs as a result of physical trauma, which is also referred to as muscle injury. In relation to exercise, Safran and colleagues (1989) suggested that muscle injury can be divided into three major types based on clinical presentation. A Type I injury is characterized by muscle soreness that occurs 24 to 48 h after unaccustomed exercise (DOMS). A Type II injury is characterized by an acute disabling pain from a muscle tear, ranging from a tear of a few fibers, with fascia remaining intact, to a complete tear of the muscle and fascia. A Type III injury is associated with muscle soreness or cramping that occurs during or immediately after exercise. It may not be accurate to include the Type III injury, because actual injury to muscle does not occur in the case of muscle cramping, although muscle damage may be a part of the process of treating a muscle cramp (e.g., stretching the cramping muscle).

Again, the Type I injury is peculiar to eccentric exercise. Eccentric exercise-induced muscle damage is evident by morphological changes in the intracellular structure and extracellular matrix (Armstrong et al. 1991; Lieber and Friden 2002; Stauber and Smith 1998). The earliest events associated with the muscle damage are mechanical, and later events indicate muscle remodeling (Friden and Lieber 2001). Damage to muscle and connective tissue is followed by an inflammatory response that is necessary for regeneration (Kuipers 1994). During this process, neutrophils and macrophages infiltrate damaged muscle fibers and degrade damaged proteins (MacIntyre et al. 1995). However, it seems possible that this degradation process does not necessarily take place if the damage is not severe (Proske and Morgan 2001). The relationship between ultrastructural changes and the inflammatory process has not yet been clarified.

Strictly speaking, muscle damage should be verified only through morphological examination. However, the highly focal nature of damage to specific sarcomeres in individual fibers makes quantitative evaluations of the magnitude of muscle damage difficult (Faulkner et al. 1993). This is why symptoms are more frequently used as markers of muscle damage.

Indirect Markers of Muscle Damage

Two typical symptoms of eccentric exercise-induced muscle damage are muscle soreness and loss of muscle function, and these effects have been used as markers of muscle damage (Bär et al. 1997). Muscle damage is also assessed via increases in muscle-specific proteins in the blood such as creatine kinase (CK) or myoglobin (Clarkson et al. 1992). Swelling of muscles, detected by increases in circumference or magnetic resonance or ultrasound images, is often included among the markers of muscle damage (Howell et al. 1993; Nosaka and Clarkson 1996). Among indirect markers, muscle function measures such as muscle strength and range of motion (ROM) are considered the best tools for quantifying muscle damage (Warren et al. 1999).

Figure 5.3 shows changes in some indirect markers of muscle damage after eccentric and concentric exercise of the elbow flexors. Nonresistance-trained subjects performed a bout of eccentric exercise (ECC) of the elbow flexors with one arm and a bout of concentric exercise (CON) with the other arm; bouts were four to six weeks apart. In both exercises, six sets of five muscle contractions with 2 min rest between sets were performed with a dumbbell set at 40% of each arm's maximal isometric strength measured at an elbow joint angle of 90°. The average weight of the dumbbell used for both exercises was approximately 10 kg; the range of motion was 90° for both, with ECC starting from an elbow joint angle of 90° and CON from a fully extended position (180°). The time taken for each movement was 3 to 4 s for ECC and 2 to 3 s for CON. Significantly larger changes in maximal isometric strength, ROM, and upper arm circumference were evident following ECC compared to CON. A prolonged loss of muscle strength and ROM, profound swelling, DOMS, and increases in plasma CK activity and myoglobin concentration were peculiar to eccentric exercise.

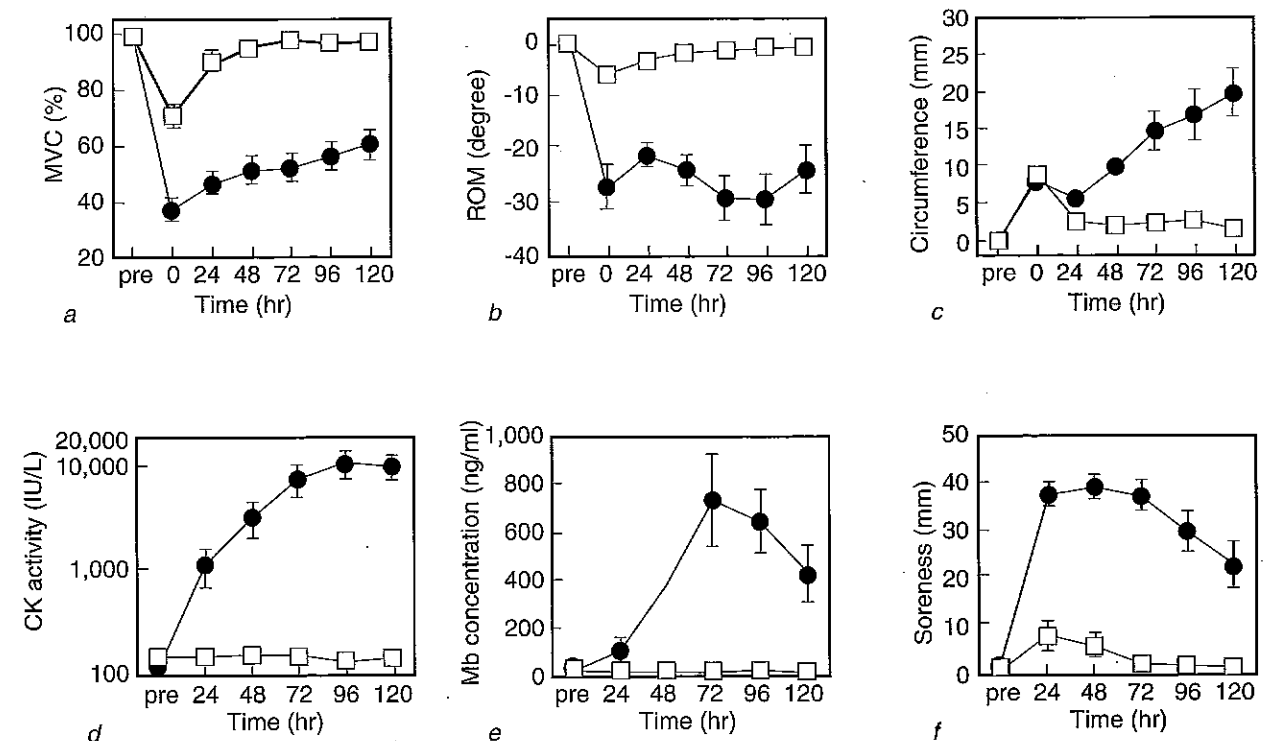


Figure 5.3 Comparison between eccentric (circles) and concentric (squares) exercise of the elbow flexors for changes in markers of muscle damage before (pre), immediately after (0), and 24 to 120 h after exercise. (a) Normalized changes in maximal isometric strength; (b) absolute changes in range of motion from baseline (pre); (c) absolute changes in upper arm circumference from baseline (pre); (d) plasma creatine kinase activity; (e) plasma myoglobin concentration; (f) muscle soreness as indicated on a VAS of 50 mm (0: no pain; 50: very painful).

Data from Lavender and Nosaka, 2006.

Connections Between DOMS and Muscle Damage

As already discussed, although DOMS is one of the symptoms associated with muscle damage, it may not be a direct reflection of muscle damage. It is possible for severe DOMS to develop with little or no indication of muscle damage, and severe muscle damage does not necessarily result in severe DOMS. The dissociation between DOMS and other indicators of muscle damage has been documented (Newham 1988; Rodenburg et al. 1993; Nosaka et al. 2002a).

Time Course

Although unaccustomed eccentric exercise results in DOMS and a number of functional, structural, and biochemical changes, it is important to note that the time courses of these changes differ (figure 5.4). After maximal eccentric exercise of the elbow flexors, muscle soreness does not develop immediately whereas muscle strength shows its largest decrease at this point. Range of motion is more affected a couple of days after exercise but recovers more quickly than muscle strength. When muscle soreness subsides, swelling of the upper arm peaks, and abnormality in magnetic resonance or ultrasound images is greatest around this time period. Plasma CK activity peaks around five days after exercise and returns to baseline two to three weeks later. Not only do the time courses of changes in the markers of muscle damage differ from one another, but also none of them match the time course of muscle soreness (Newham 1988). All this clearly shows that muscle soreness is not a cause of loss of muscle function, swelling is not a direct stimulus for muscle soreness, and muscle soreness does not peak when plasma CK peaks.

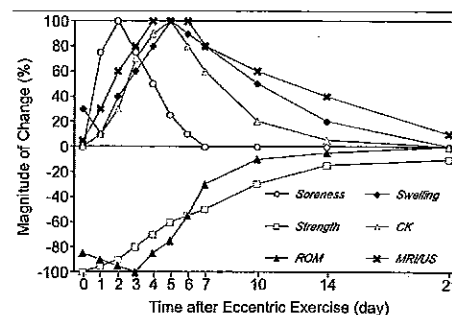


Figure 5.4 Time course of changes in markers of muscle damage after maximal eccentric exercise of the elbow flexors: muscle soreness, upper arm circumference (swelling), maximal isometric strength (strength), creatine kinase (CK), range of motion (ROM), and magnetic and ultrasound images (MRI/US).

Data from Nosaka and Clarkson, 1996.

Correlations Between DOMS and Other Markers Among Subjects

It has been reported that the level of DOMS correlates poorly with the magnitude of changes in other indicators of muscle damage (Nosaka et al. 2002a; Rodenburg et al. 1993). As shown in figure 5.5, the peak muscle soreness score does not correlate strongly with other markers. It is generally thought that the larger the decrease in muscle strength following eccentric exercise, the greater the magnitude of muscle damage. However, subjects who show large decreases in maximal isometric strength do not necessarily have severe soreness.

It is also interesting that resistance-trained subjects and untrained subjects reported a similar magnitude of peak muscle soreness after performing maximal eccentric exercise of the elbow flexors, although changes in other markers of muscle damage such as maximal isometric strength and plasma CK activity were significantly larger for untrained compared to trained subjects (figure 5.6). This suggests that the magnitude of muscle damage is less for resistance-trained than for untrained individuals after eccentric exercise, but that resistance-trained individuals may feel a similar magnitude of DOMS with significantly less muscle damage.

The Magnitude of DOMS and Muscle Damage in the Same Subject

The examples shown so far are based on groups of subjects. It may be that findings of little or no relationship between DOMS and muscle damage are due to differing pain perception among subjects. However, there is evidence to support the idea that DOMS does not reflect

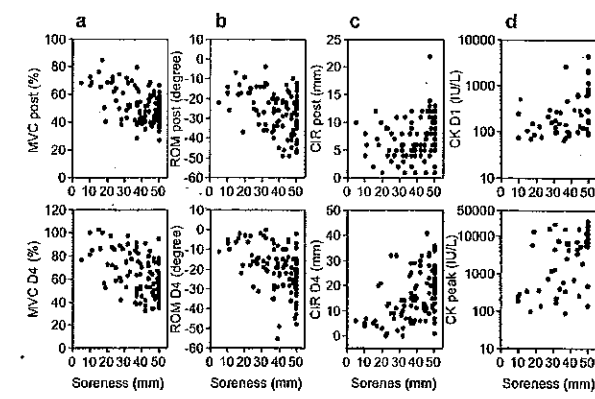


Figure 5.5 Correlations between peak muscle soreness (VAS, 0-50 mm scale) and other markers of muscle damage. (a) Percent changes in maximal isometric strength immediately or four days after exercise; (b) changes in range of motion immediately or four days after exercise; (c) changes in upper arm circumference from baseline immediately or four days after exercise; (d) plasma creatine kinase activity at one day postexercise and peak.

Data from Nosaka and Clarkson, 1996.

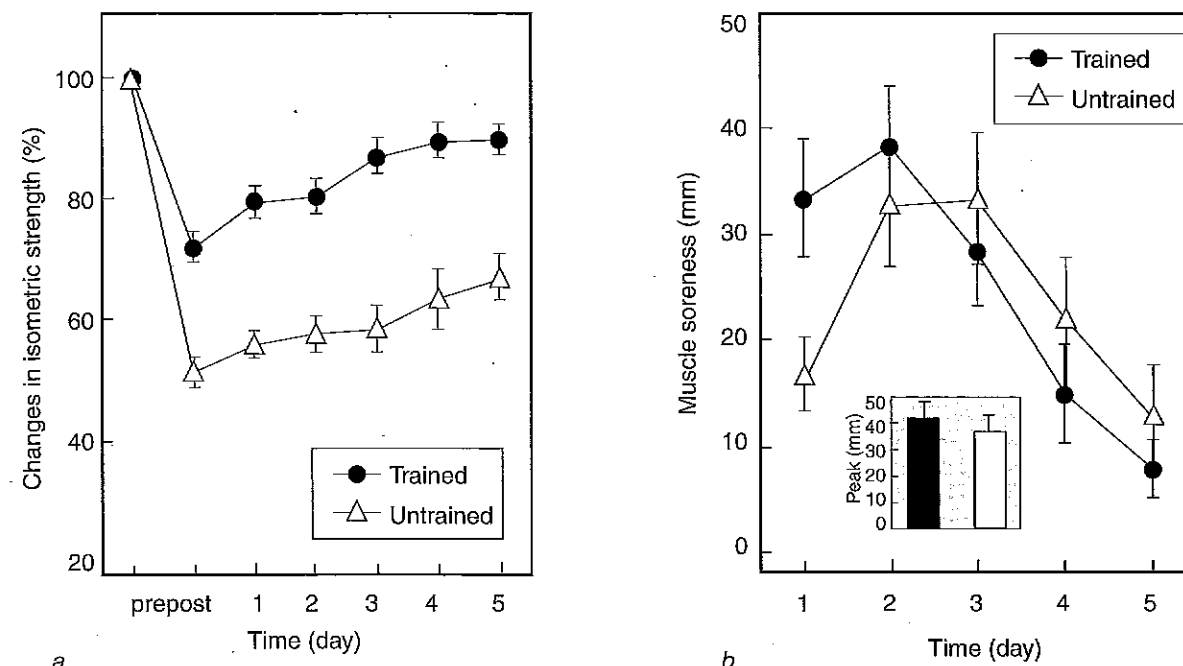


Figure 5.6 Comparison between trained (circles) and untrained (triangles) subjects on changes in (a) maximal isometric strength and (b) muscle soreness after eccentric exercise of the elbow flexors. The muscle soreness graph also shows the peak soreness value for each group.

Data from Newton et al., 2007.

the magnitude of muscle damage even within a given individual, depending on the type and intensity of exercise as well as on which muscles are being used.

• **Type and intensity of exercise.** When the same subject performed two different intensities of eccentric exercise using the same muscle group, all of the indirect markers of muscle damage showed larger changes for maximal intensity than for 50% intensity. However, no significant difference in muscle soreness was observed between the exercises (Nosaka and Newton 2002c). Moreover, two different types of exercise of the elbow flexors (maximal eccentric exercise in which 24 forced eccentric muscle actions were performed under maximal force generation; endurance exercise in which elbow flexion and extension movements were repeated for 30 min) performed by the same subject induced a similar magnitude of muscle soreness, but the magnitudes of changes in other markers of muscle damage such as muscle strength and plasma CK activity were significantly different (figure 5.7). These findings also support the notion that the magnitude of DOMS does not necessarily reflect the magnitude of muscle damage.

• **Difference between arm and leg muscles.** The responses to eccentric exercise differ between the leg and arm muscles. Having subjects perform both arm and

leg exercises, Jamurtas and colleagues (2005) compared effects of an eccentric exercise of the elbow flexors with those of an eccentric exercise of the knee extensors, matching the number of eccentric actions (six sets of 12 reps) and the relative intensity using 75% of predetermined maximal eccentric torque. The arm eccentric exercise induced larger decreases and slower recovery of strength, as well as larger increases in blood markers of muscle damage (CK, myoglobin), than the leg exercise. However, DOMS did not differ between the two exercises (figure 5.8). These findings again support the idea that the magnitude of DOMS does not represent the magnitude of muscle damage.

The Message of DOMS

Delayed-onset muscle soreness may play a protective role by acting as a warning to reduce muscle activity and prevent further injury. However, we may find that further activity, although causing more pain initially, in fact then alleviates muscle soreness. Hough (1902) reported that performing a second bout of exercise with a sore muscle caused excessive pain for the first 2 to 3 min but that the pain disappeared over the course of 5 to 10 min. Saxon and Donnelly (1995) investigated the effect of submaximal (50%) concentric exercise performed one to

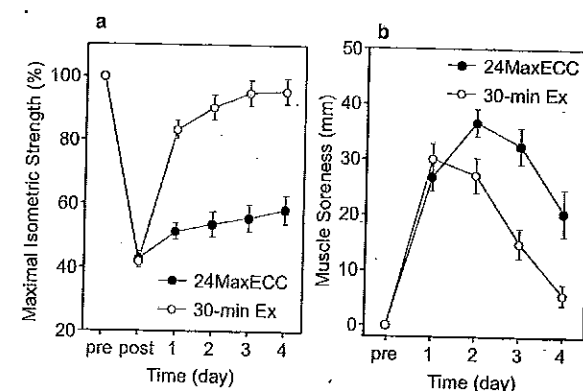


Figure 5.7 Comparison between two different types of exercise of the elbow flexors for changes in (a) maximal isometric strength and (b) muscle soreness. Each subject performed the two types of exercise using a different arm: 24 maximal eccentric actions of the elbow flexors (24MaxECC, filled circles) and repeated elbow flexion (1 s) and extension (1 s) movements for 30 min (30 min Ex: open circles) using a light dumbbell.

Nosaka et al. Unpublished data.

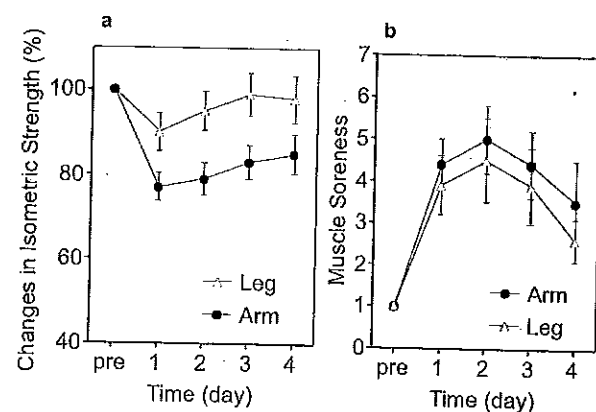


Figure 5.8 Comparison between eccentric exercise of knee extensors (leg: triangles) and elbow flexors (arm: circles) for changes in (a) maximal isometric strength and (b) muscle soreness after exercise.

Modified from Jamutas et al., 2005.

four days following a bout of maximal eccentric exercise on DOMS. They reported that DOMS was significantly reduced immediately after performing the concentric exercise on day 2, but no significant effect on DOMS was found on the other days.

A recent study by Zainuddin et al. (2006) demonstrated that muscle soreness was palliated significantly ($\approx 40\%$) immediately after performance of light concentric exercise on each of days 1 through 4 following eccentric exercise that induced muscle

soreness and damage (figure 5.9a). This suggests that the light concentric exercise was effective for attenuating DOMS. However, the palliative effect of the light exercise was temporary and did not influence changes in overall muscle soreness (figure 5.9b). No adverse effects of the light concentric exercise on recovery of muscle function were evident, either. Thus, it seems unlikely that DOMS is a warning sign not to use the affected muscle.

Several studies have shown that performing eccentric exercise in the early recovery days after the initial bout (two to three days) with sore muscles does not exacerbate muscle damage or retard the recovery process (Chen 2003; Nosaka and Newton 2002c, 2002d). These results suggest that muscle soreness is not necessarily a warning signal not to use the muscle. Such muscle pain may be telling us that we should not use the muscle, but we find that the pain is reduced when we use the sore muscle anyway. Thus it is still unclear how we should treat this type of muscle pain. We often face a situation in which we need to consider whether to ignore and overcome pain or accept and try to remove it.

Repeated-Bout Effect

Once an individual has experienced severe DOMS after performing an unaccustomed exercise, the exercise is no longer unaccustomed. After the person performs a similar exercise a couple of weeks later, severe DOMS no longer develops. It is as if muscles adapt to exercise rapidly to

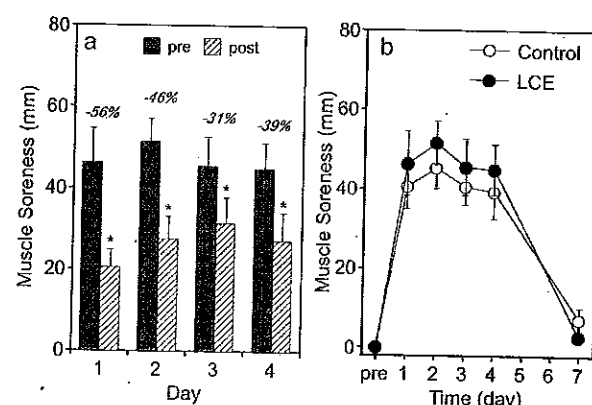


Figure 5.9 (a) Changes in muscle soreness with extension of the elbow joint before (pre) and immediately after (post) light concentric exercise performed on days 1 to 4 after maximal eccentric exercise; (b) changes in soreness following eccentric exercise for control and light concentric exercise (LCE) conditions. Asterisk indicates significant ($p < 0.05$) difference from the pre value. The left graph also shows changes from pre to post.

Based on Zainuddin et al., 2006.

protect themselves from muscle damage. This phenomenon of a protective effect against muscle damage has been termed the repeated-bout effect (McHugh 2003).

Along with attenuated DOMS after the exercise, the repeated-bout effect is characterized by faster recovery of muscle strength and range of motion, reduced swelling and muscle soreness, and smaller increases in muscle proteins (e.g., CK, myoglobin) in the blood following the second bout of a given eccentric exercise compared to the first (figure 5.10). It has also been demonstrated that immune responses are attenuated in the second bout (Pizza et al. 1999). Fewer abnormalities in ultrasound or magnetic resonance images are evident after the subsequent bout as well (Foley et al. 1999).

It is important to note that the protective effect conferred by the initial bout of eccentric exercise does not necessarily "prevent" muscle damage, but attenuates the magnitude of changes in markers of muscle damage or enhances the recovery process. It appears that the adaptation is more specific to the muscles involved in the exercise, as evidenced by a study in which subjects performed the second eccentric exercise bout with a different arm from the initial bout. No significant difference in the changes in isometric strength is evident between the right and left arm bouts separated by two weeks, but the first and second bouts performed by the same arm show a distinct difference in strength recovery (figure 5.11). Howatson and van Someren (2007) reported that changes

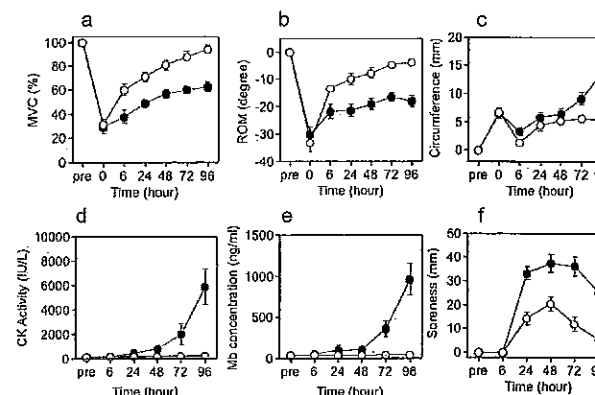


Figure 5.10 Comparison between first (filled circles) and second (open circles) bout of exercise of the elbow flexors for changes in markers of muscle damage before (pre), immediately after (0), and 24 to 120 h after exercise. (a) Normalized changes in maximal isometric strength; (b) absolute changes in range of motion from baseline (pre); (c) absolute changes in upper arm circumference from baseline (pre); (d) plasma creatine kinase activity; (e) plasma myoglobin concentration; and (f) muscle soreness as indicated by a VAS (50 mm line: 0, no pain; 50, very painful).

Based on Hirose et al., 2004.

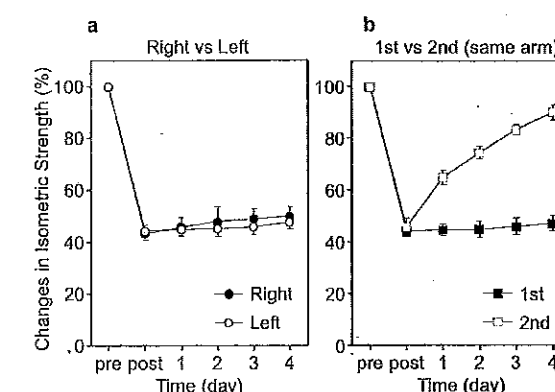


Figure 5.11 Comparison between (a) right- (filled circles) and left- (open circles) arm bouts and (b) first (filled squares) and second (open squares) bouts, using the same arm, of changes in maximal isometric strength following eccentric exercise of the elbow flexors. The two exercise bouts were separated by two weeks.

Nosaka et al. Unpublished data.

in maximal isometric strength, serum CK activity, and muscle soreness were attenuated when a second bout of eccentric exercise of the elbow flexors was performed by the contralateral arm two weeks later; however, the magnitude of protection in the contralateral arm was much less than that shown in the ipsilateral limb. Newton et al. (2007) compared changes in the markers of muscle damage between arms after maximal eccentric exercise of the elbow flexors separated by four weeks by counterbalancing the use of dominant or nondominant arm for the first bout among subjects. Changes in maximal isometric strength, range of motion, upper arm circumference, plasma CK activity, and muscle soreness measures were not significantly different between arms, but a significant difference between the bouts was evident for maximal isometric torque, circumference, and plasma CK activity, such that the changes were significantly smaller after the second bout compared with the first bout. These suggest that some effect is transferred from one arm to the other, but the effect is weak, and the repeated bout effect appears more strongly for the muscle that previously performed the same eccentric exercise.

Characteristics of Repeated-Bout Effect

The repeated-bout effect occurs whenever unaccustomed exercise is repeated within a certain period of time. However, many factors influence the magnitude of the effect, such as time between bouts, the number of eccentric contractions, muscle length, and exercise mode. Additionally, it seems that intersubject variability exists in relation to

this effect, and the magnitude of the effect differs among the markers of muscle damage.

Effect of Time Between Bouts

If the time period between the unaccustomed and subsequent exercise bout is too long, the repeated-bout effect does not occur. However, it appears that the repeated-bout effect lasts for at least several weeks and that its length is dependent on markers of muscle damage (Nosaka et al. 2005a). It was reported that changes in indirect markers of muscle damage following exercise were suppressed more when the interbout interval was 6 weeks compared to 10 weeks (Nosaka et al. 1991). As shown in figure 5.12, faster recovery of strength and range of motion, reduced swelling, less development of muscle soreness, and smaller increases in muscle proteins in the blood following a second eccentric exercise bout compared with the initial bout persisted for more than six months for eccentric exercise of the elbow flexors. However, the magnitude of the protective effect appears to decrease gradually as the time between bouts increases, and the time course of attenuation of the protective effect varies among the measures. No protective effects seem to last more than a year.

Several studies showed that when the second eccentric exercise was performed two weeks after the first bout, prior to full recovery of muscle function, prolonged decreases in muscle function and development of muscle soreness, but no increases in CK activity, occurred (Clarkson and Tremblay 1988; Newham et al. 1987; Nosaka et al. 2005b). When the second bout was performed within a week of the initial exercise, in the early recovery phase,

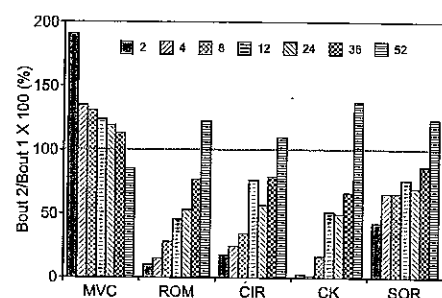


Figure 5.12 Magnitude of repeated-bout effect for maximal isometric strength (MVC), range of motion (ROM), upper arm circumference (CIR), plasma creatine kinase activity (CK), and muscle soreness (SOR) when the interval between bouts was 2, 4, 8, 12, 24, 36, or 52 weeks. For MVC, ROM, and CIR, the values at four days postexercise in relation to the preexercise values were compared between bouts. For CK and SOR, peak values after exercise were compared between bouts.

Data from Nosaka et al., 2001a, Nosaka et al., 2001b, Nosaka et al., 2005a, and Nosaka et al., 2005b.

no adverse effects on markers of damage were observed, although acute decreases in muscle function occurred immediately after exercise (Chen 2003; Ebbeling and Clarkson 1989; Nosaka and Newton 2002c, 2002d).

Effect of Number of Eccentric Contractions

Muscles do not appear to require the same exercise stimuli in the two bouts in order to show the repeated-bout effect. It has been reported that performing an initial eccentric bout with a relatively small number of eccentric actions produced the repeated-bout effect. An initial bout of 24 maximal eccentric repetitions reduced plasma CK activity and the magnitude of the strength loss and DOMS when a 70-repetition bout was performed two weeks later (Clarkson and Tremblay 1988). It has also been demonstrated that 10, 30, or 50 eccentric actions provided equal protection for a bout of 50 eccentric actions three weeks later, in which increases in plasma CK activity were attenuated and the magnitude of isometric force loss was reduced (Brown et al. 1997).

Nosaka and colleagues (2001b) investigated whether a small volume of an initial eccentric exercise bout could still confer the repeated bout effect on a second bout of a larger volume eccentric exercise that was performed two weeks later. The volume for the initial exercise bout was less than 10% (two maximal eccentric actions: 2ECC), of the number of contractions to be performed in the second bout (24 maximal eccentric actions: 24ECC). All variables changed significantly after 2ECC, but the amount of change in isometric strength and muscle soreness after for the 2ECC was significantly smaller than that for 24ECC (figure 5.13). After the second bout, the group that performed 24ECC initially showed a profound repeated-bout effect that was indicated by a faster recovery of isometric strength and less development of muscle soreness. The group that initially performed 2ECC (2-24ECC) also demonstrated the repeated-bout effect, although the magnitude of the effect was not as strong as that of the 24-24ECC. These results suggest that the repeated-bout effect can be produced by two maximal eccentric actions, and it is not necessary to perform a high number of eccentric actions in the first bout to elicit a repeated-bout effect.

Effect of Muscle Length

It is known that changes in markers of muscle damage are significantly smaller following eccentric exercise of the elbow flexors in which the elbow joint is not fully extended compared to when it is fully extended (Nosaka and Sakamoto 2001). An interesting question is whether eccentric exercise without full extension movements can protect against muscle damage induced by eccentric exercise with full extension.

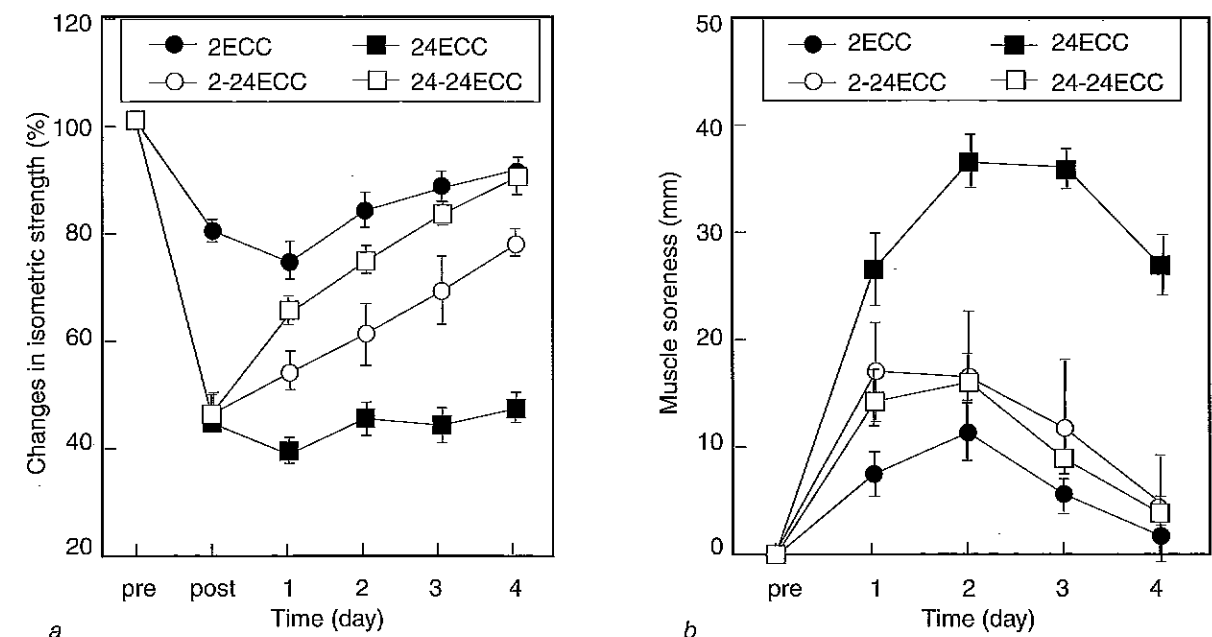


Figure 5.13 Changes in (a) maximal isometric strength and (b) muscle soreness following two (2ECC: filled circles) or 24 (24ECC: filled squares) maximal eccentric actions of the elbow flexors and in the subsequent bout of exercise (in which 24 maximal eccentric actions of the same muscle group were performed by the arm that previously performed 2ECC [2-24ECC: open circles] or 24ECC [24-24ECC: open squares]).

Modified from Nosaka et al., 2001b.

To address this question, Nosaka and colleagues (2005b) compared two groups of subjects. One group (L-L) performed eccentric exercise at a long starting length for both a first and a second bout separated by four weeks; the other group (S-L) performed eccentric exercise at a short starting length followed four weeks later by eccentric exercise at the long starting length (figure 5.14). The eccentric exercise at a long muscle length induced greater muscle damage than an equivalent bout performed at a short muscle length, as shown by the study mentioned in the preceding paragraph. In addition, results showed that eccentric exercise at the short muscle length produced a partial protective effect against muscle damage induced by exercise at the long muscle length. Although the short muscle length exercise induced an appreciable degree of protection against the effects of the more demanding bout, the magnitude of protection varied among the criterion measures. In general, this amounted to a "partial" protection of around 50% for most of the criterion variables. A possible explanation for this result is that the adaptation of the brachialis was more pronounced following the short muscle length exercise, resulting in an enhancement of the protective effect for that muscle compared to that for the biceps brachii.

Strategies to minimize the degree of damage associated with eccentric exercise should include consideration

of not only the number of actions, but also the range of motion of the activity, with particular regard to the portion of the range of motion associated with full muscle extension. However, this may not generalize, since McHugh Pasiakos (2004) did not find such an effect for the knee extensors. It may be that arm muscles are different from leg muscles not only in their susceptibility to eccentric exercise-induced muscle damage (Jamurtas et al. 2005) but also with regard to the repeated-bout effect.

Effect of Exercise Mode

Whitehead and colleagues (1998) reported that the susceptibility of muscle to damage from eccentric exercise (downhill running) was increased after subjects performed concentric exercise (450 plantarflexion movements with a 10 kg weight) for five days prior to the eccentric exercise. These authors speculated that the concentric exercise reduced the number of sarcomeres in series and shifted the length-tension relationship in the direction of shorter muscle lengths, which makes the muscle more susceptible to eccentric exercise-induced muscle damage. Conversely, Nosaka and Newton (2002a) showed that eight weeks of concentric training of the elbow flexors using a submaximal dumbbell weight did not exacerbate muscle damage induced by maximal

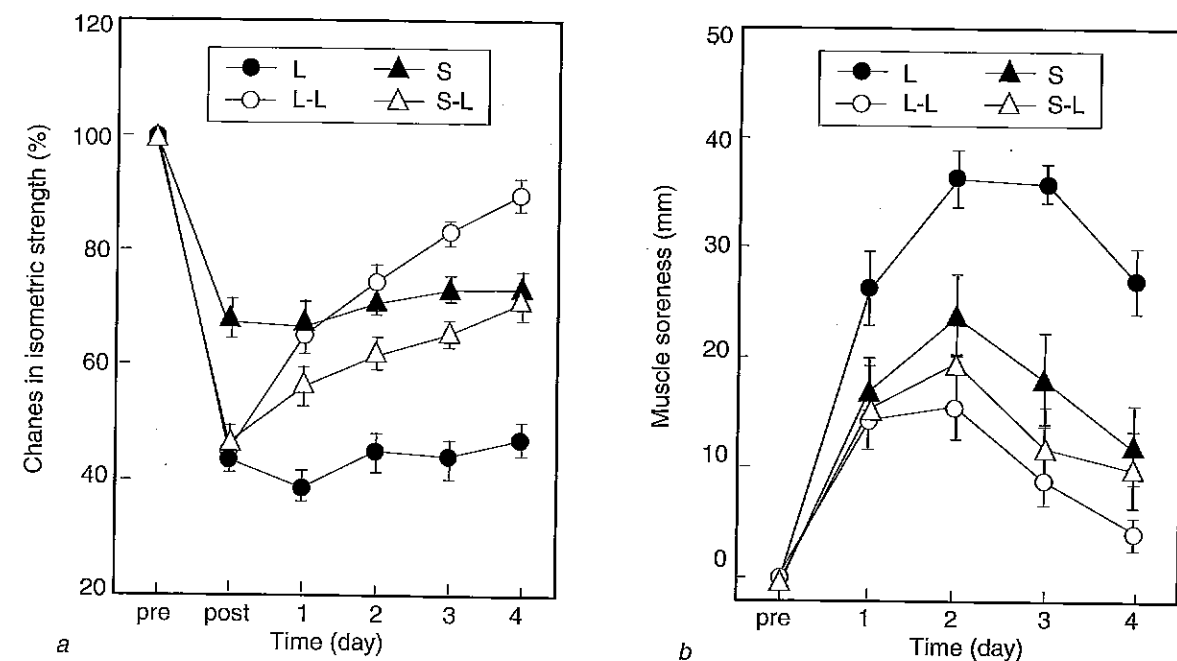


Figure 5.14 Comparison between long and short muscle length eccentric exercise of the elbow flexors for changes in (a) maximal isometric strength and (b) muscle soreness following the first bout (L: filled circles; S: filled triangles) and the second bout (L-L: open circles; S-L: open triangles) from the preexercise value (100%). In the second bout, performed four weeks after the first, both groups (one having performed long and the other having performed short muscle length eccentric exercise) performed the long muscle length eccentric exercise.

Modified from Nosaka et al., 2005b.

eccentric exercise of the same muscle. They suggested that to prevent or reduce eccentric exercise-induced muscle damage, it seems necessary to stimulate the muscles using the same muscle actions and intensity as in the damaging exercise.

Eston and colleagues (1996) showed that muscle soreness, strength loss, and increases in plasma CK activity after a downhill run were reduced when 100 maximal isokinetic eccentric actions had been performed two weeks earlier. This suggests that a different mode of exercise of the same muscle group confers the repeated-bout effect. It is not clear yet how much of a protective effect is conferred by a different mode of exercise of the same muscle.

One unpublished study addressed the extent of protection conferred by a submaximal elbow flexor endurance task against the effects of maximal eccentric exercise of the same muscle group. A group of subjects flexed (1 s) and extended (1 s) their elbow joint rhythmically for 30 min (900 actions) with a wristband load set at 10% of their maximal isometric strength and then, four to six weeks later, performed maximal eccentric exercise of the elbow flexors consisting of 24 forcible extensions of the elbow joint from a flexed (90°) to an extended position (180°). Another group

performed the two bouts of maximal eccentric exercise with the same arm.

Changes in indicators of muscle damage were significantly smaller following the endurance exercise compared with the maximal exercise (figure 5.15). After the maximal eccentric exercise, the subjects who had performed the endurance exercise initially showed smaller changes in the indicators of muscle damage compared with those observed after the first bout of maximal eccentric exercise performed by the other group of subjects. However, the magnitude of the protective effect against the effects of maximal eccentric exercise in the subjects who had initially performed the endurance exercise was not as strong as that shown by the subjects who repeated the maximal eccentric exercise. This suggests that protection against the effects of maximal eccentric exercise can be partially conferred to the elbow flexors using submaximal endurance exercise that results in minor damage.

Protective Effect Induced by Isometric or Nondamaging Exercise

It seems that severe muscle damage is not necessary in order to confer a protective effect on subsequent exercise.

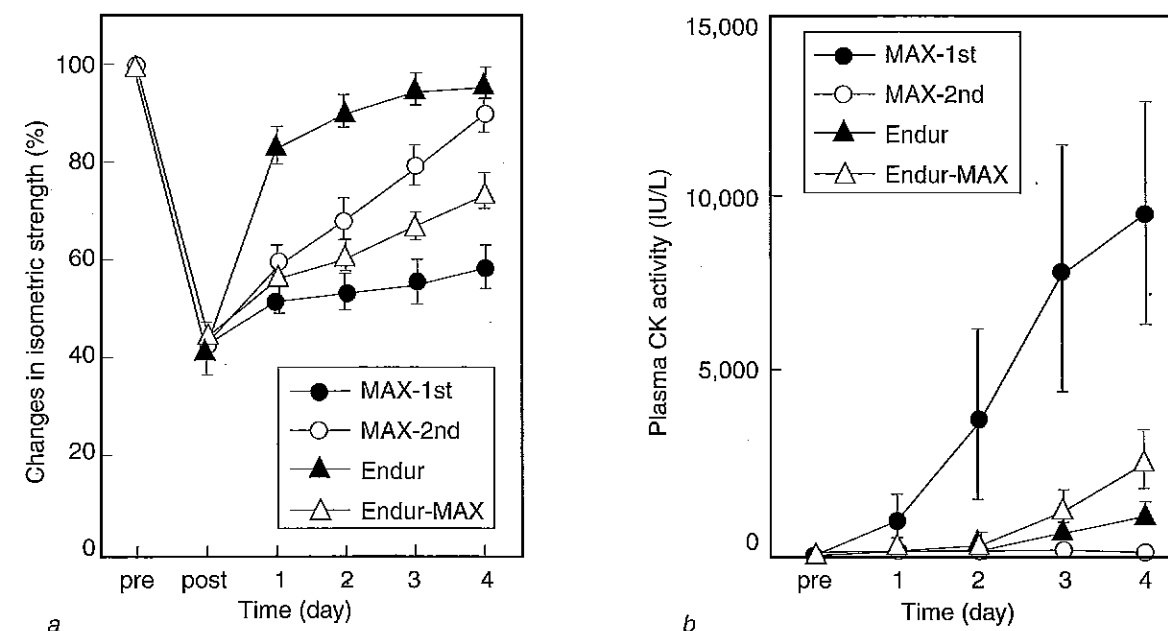


Figure 5.15 Effect of endurance exercise of the elbow flexors (Endur) on maximal eccentric exercise of the same muscles (Max) in comparison to the effect when the maximal eccentric exercise was performed in both the first (Max-1st) and the second bout (Max-2nd). Changes in (a) maximal isometric strength and (b) plasma CK (creatine kinase) activity following the first (filled circles) and second (open circles) bout of the maximal eccentric exercise and after the endurance exercise (filled triangles) and then the maximal eccentric exercise (open triangles).

Nosaka et al. Unpublished data.

As already mentioned, low-intensity (40%) eccentric exercise could confer protection of 20% to 60% on the indices of muscle damage following a subsequent 100% exercise bout performed two to three weeks later (Chen et al. 2007). Lavender and Nosaka (2007) have shown recently that light eccentric exercise (with a dumbbell set at 10% of maximal isometric strength) induces some protection against the effects of a subsequent bout of eccentric exercise with a heavier weight (a dumbbell set at 40% of maximal isometric strength) carried out two days later. However, whether the protective effect conferred by 10% eccentric exercise lasts longer, say for two weeks, has not been confirmed. Some animal studies have shown that isometric exercise can produce protective effects against the effects of eccentric exercise. Koh and Brooks (2001) reported that maximal isometric contractions or passive stretches of the extensor digitorum longus (EDL) muscles in mice did not cause degeneration of muscle fibers but induced protection against muscle damage from maximal eccentric actions performed three days later. McArdle and colleagues (2004) also reported that nondamaging isometric contractions of the soleus and EDL muscles via electrical stimulation, conducted 4 or 12 h prior to a damaging protocol, reduced CK

release from the muscles of mice. However, no human studies have yet shown the extent of the protective effect conferred by isometric exercise against the effects of eccentric exercise.

Mechanisms of Repeated-Bout Effect

The mechanisms underlying the repeated-bout effect have yet to be fully elucidated, although several potential mechanisms have been addressed. McHugh (2003) reviewed studies associated with the repeated-bout effect and categorized the potential mechanisms as neural, mechanical, and cellular adaptations (table 5.1). He concluded that "there may be several mechanisms for the repeated bout effect and those mechanisms may complement each other or operate independently of each other (McHugh 2003, p. 96)."

The neural adaptations include more efficient recruitment of motor units, increased synchrony of motor unit firing, better distribution of the workload among fibers, improved usage of synergist muscles, and increased slow-twitch fiber recruitment. To investigate any neural adaptations associated with the repeated-bout effect,

Table 5.1 Potential Mechanisms for the Repeated-Bout Effect

Neural adaptations (spinal cord, CNS)	Mechanical adaptations (noncontractile elements)	Cellular adaptations (contractile machinery)
Increased recruitment of slow-twitch motor units	Increased passive or dynamic muscle stiffness	Longitudinal addition of sarcomeres (shift in the length-tension relationship)
Activation of larger motor unit pool	Remodeling of intermediate filament system to provide mechanical reinforcement (desmin, titin, etc.)	Adaptation in inflammatory response
Increased motor unit synchronization	Increased intramuscular connective tissue	Adaptation to maintain excitation-contraction coupling
Learning effect		Strengthened plasma membrane
		Increased protein synthesis
		Increased stress proteins (heat shock proteins, etc.)
		Removal of stress-susceptible fibers and replacement by stronger fibers

Nosaka and colleagues (2002b) compared two bouts of stretching of muscles receiving percutaneous electrical stimulation. Since the electrical stimulation bypasses the involvement of central motor drive, the expectation was to examine whether the central nervous system is involved in the repeated-bout effect. The results showed that the repeated bout of exercise resulted in less damage than the first bout, with all of the indirect markers of muscle damage showing smaller changes, and that recovery was significantly faster following the second bout (figure 5.16). If neural adaptations were primarily responsible for the repeated-bout effect, similar effects on the criterion measures would have been observed following the two eccentric exercise bouts. The findings thus suggest that the repeated-bout effect did not result from changes in the motor output of the central nervous system. Some evidence exists to support the neural adaptation theory. Howatson and van Someren (2007) reported a significant attenuation of muscle damage in the second bout of eccentric exercise performed by the contralateral arm two weeks later. Newton et al. (2007) also showed that changes in maximal isometric torque, upper arm circumference, and plasma CK activity were significantly smaller after the second bout performed by the opposite arm than the first bout. A possible explanation for how the attenuation of the changes in some of the criterion measures was conferred by the first bout performed by the contralateral arm may lie in the phenomenon of cross education effect or some learning effect (Howatson and van Someren 2007; Newton et al. 2007).

According to another theory, suggested by Proske and Morgan (2001), increases in sarcomere number in series are associated with the protective effect. The increases in sarcomere number in series are indirectly assessed by a shift in optimum angle toward a longer muscle

length (Proske and Morgan 2001). Philippou and colleagues (2004) recently reported a shift in the optimum angle of the elbow joint for producing maximal force by approximately 16°. If the shift could last for more than several weeks, this theory is attractive; however, the duration of this adaptation has yet to be determined. Chen and colleagues (2007) compared the effect of four different intensities (100%, 80%, 60%, and 40%) of initial eccentric exercise (ECC1) on optimum angle shift and the extent of muscle damage induced by subsequent maximal eccentric exercise (ECC2) performed two to three weeks later with a 100% load. A rightward shift of the optimum angle following ECC1 was significantly greater for the 100% and 80% than for the 60% and 40% exercises, and decreased significantly from immediately to five days postexercise. By the time ECC2 was performed, only 100% exercise retained a significant shift (4°). Although the magnitude of the repeated-bout effect following ECC2 was significantly smaller for the 40% and 60% groups, all groups showed significantly reduced changes in criterion measures following ECC2 in comparison to the ECC1 100% bout. This suggests that the repeated-bout effect is not dependent on the shift in optimum angle. Thus, it seems unlikely that the protective effect can be explained solely by increases in the number of sarcomeres in series.

Ingalls and colleagues (2004) recently showed that the enhanced strength recovery of mouse foot dorsiflexor muscles with repeated lengthening exercise could be attributed to elevated rates of protein synthesis. This could explain the faster recovery of muscle function after a second bout compared with an initial bout as seen in human studies. Newham and colleagues (1987) have postulated that muscle fibers become more resilient and are able to withstand a given eccentric exercise after stress-susceptible fibers are removed and replaced by regenerated fibers. This theory

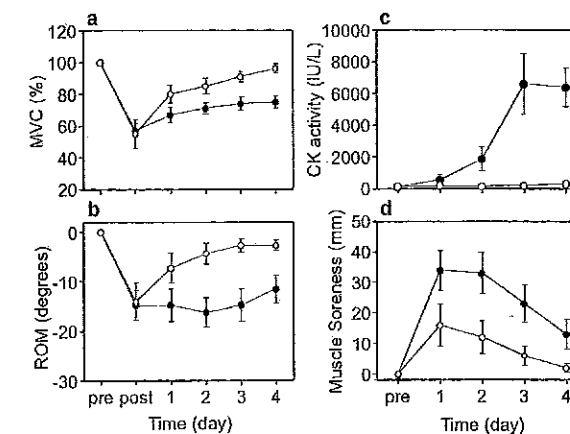


Figure 5.16 Comparison between first (filled circles) and second (open circles) bout of stretching of electrically stimulated muscles of the elbow flexors for changes in (a) maximal isometric strength, (b) range of motion, (c) plasma creatine kinase activity, and (d) muscle soreness.

Modified from Nosaka et al., 2002b.

appears to explain the repeated-bout effect very well if the newly regenerated fibers become susceptible again to eccentric exercise in 8 to 12 weeks. Figure 5.17 presents a graphic image of the stress-susceptible fiber hypothesis, which proposes six stages in the repeated-bout effect:

- **Stage 1:** Before performing the first eccentric exercise bout (ECC1), some of the muscle fibers are stress-susceptible fibers.
- **Stage 2:** These fibers are likely to be damaged by ECC1 and to degenerate, and severe muscle damage is induced, but other fibers may survive.
- **Stage 3:** After ECC1, the damaged fibers are regenerated and may be remodeled and become "strong" fibers.
- **Stage 4:** When the second bout of eccentric exercise (ECC2) occurs at this stage, the number of stress-susceptible fibers is small, and less muscle damage is produced.
- **Stage 5:** No stress-susceptible fibers exist and little muscle damage is induced when eccentric exercise is performed at this stage. When eccentric exercise is performed regularly, it may be that muscles are in the Stage 5 condition.
- **Stage 6:** Because of protein turnover, some muscle fibers become stress-susceptible fibers again.

Understanding the mechanisms underlying the repeated-bout effect may be the key to understanding eccentric exercise-induced muscle damage.

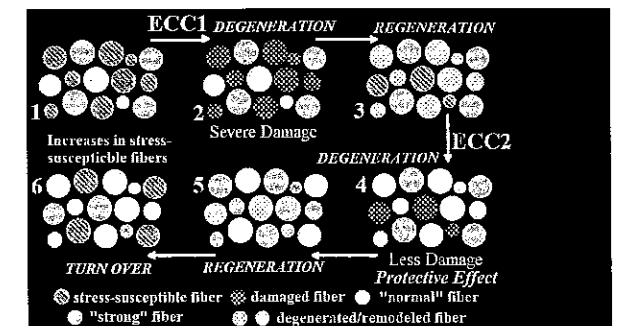


Figure 5.17 Stress-susceptible fiber hypothesis.

According to Koh (2002), heat shock proteins (HSPs) may be involved in protecting skeletal muscle fibers from eccentric exercise-induced muscle damage. A microwave diathermy treatment that increased muscle temperature to over 40° C, 16 to 20 h prior to exercise, resulted in a significantly faster recovery of muscle strength, a smaller change in ROM, and less muscle soreness; however, the protection afforded by the diathermy treatment was significantly less effective than in the second bout, performed four to six weeks after the initial bout (Nosaka et al. 2007). McArdle and colleagues (2004) proposed that activation of the heme oxygenase-1 (HO-1) gene resulting from increased reactive oxygen and nitrogen species (ROS) production was associated with the protective effect. Mikkelsen and colleagues (2006) have recently shown that stimulation of the Na⁺-K⁺ pump with β₂-adrenoceptor agonists improved force recovery in rat EDL muscles by 40% to 90% following a 30 min electrical stimulation protocol. It is possible that these proteins are associated with protective effects. Further studies are necessary to advance understanding of the mechanisms underlying the repeated-bout effect.

Summary

This chapter has focused on DOMS, muscle damage, the relationship between DOMS and muscle damage, and the repeated-bout effect. Despite advances in our understanding of eccentric exercise-induced muscle damage, we still do not have a complete picture of the phenomenon. More than a century ago, Hough (1902) carefully observed "muscular soreness" and thought creatively in an attempt to explain the cause of DOMS. He stated, "The abnormal condition of the muscle frequently escapes notice, unless attention is specially directed to it by making it work or by over extension." We still need to pay more attention to the condition of muscles so as not to miss what they can tell us. The key points of this chapter can be summarized as follows:

- Muscle soreness is sensed in the brain as a signal from muscle; however, the stimuli that prompt nociceptors or other receptors to evoke muscle soreness have not been fully elucidated.
- Delayed-onset muscle soreness is associated with eccentric exercise-induced muscle damage; however, it is still unclear how a sequence of events in the process of muscle damage induces DOMS.
- Physiological changes used as indicators of eccentric exercise-induced muscle damage include decreases in muscle function, swelling, increases in muscle proteins in the blood, and abnormalities shown by ultrasound and magnetic resonance images.
- The magnitude of DOMS does not necessarily reflect the extent of muscle damage, and the time course of DOMS does not represent the time course of changes in indicators of muscle damage.
- Muscle adapts rapidly after eccentric exercise to prevent muscle damage, and this effect (repeated-bout effect) lasts for several weeks to several months.
- The repeated-bout effect is produced even if the initial bout is less demanding than the second bout in terms of the number of eccentric actions, muscle lengths, and the force generated during eccentric exercise; and conferral of the protective effect does not necessarily require muscle damage.
- Neural, mechanical, and cellular adaptations are likely involved in the mechanisms underlying the repeated-bout effect; however, a unified theory explaining the mechanisms remains elusive.

CHAPTER 6

Satellite Cells and Muscle Repair

Karin Shortreed, MSc; Adam Johnston, MSc; and Thomas J. Hawke, PhD

The skeletal muscle of adult mammals displays a remarkable ability for growth and repair throughout the life span. This adaptability is largely the result of a population of stem cells, termed myogenic satellite cells, resident within the skeletal muscle itself. This chapter focuses on the capacity of skeletal muscle for growth and repair and the role of these unique cells in the regenerative process. The regulation of myogenic satellite cells in health and disease, as well as the role of various extrinsic factors in affecting myogenic satellite cell function, is also discussed.

Skeletal Muscle Stem Cell Populations

Adult skeletal muscles contain various cell populations that display stem cell-like characteristics, including the capacity for self-renewal, proliferation, and plasticity (capacity to become multiple lineages). In particular, the myogenic satellite cell and the muscle side-population (SP) cell are the most well characterized of the skeletal muscle stem cell populations to date.

Myogenic Satellite Cells

The myogenic satellite cell was named on the basis of its location at the periphery of the adult muscle fiber. Although these undifferentiated stem cells were identified over 40 years ago (Mauro 1961) and are the most thoroughly characterized of the resident muscle stem cell populations, a great deal of attention has recently been refocused on these

cells as we begin to further appreciate their stem cell-like capacities.

In unperturbed muscle, the quiescent myogenic satellite cell resides outside of the muscle fiber plasma membrane but underneath the overlying basal lamina (figure 6.1, *a* & *c*). In this resting state, the nuclei of these cells comprise approximately 2% to 5% of all muscle nuclei and display dense heterochromatin (genetically inactive region of chromosomes), reduced organelle content, and high nuclear to cytoplasmic volume ratio, consistent with their low transcriptional activity (figure 6.1*b*). Satellite cells exit their quiescent state and enter a proliferative phase in response to stressors such as trauma (figure 6.1*d*). Studies of rodent skeletal muscles have demonstrated a relationship between myogenic satellite cell content and muscle fiber types (see Hawke and Garry 2001 for review), with oxidative muscle fibers demonstrating a five to six times greater myogenic satellite cell content than glycolytic muscle fibers (table 6.1). As human skeletal muscle displays a more heterogeneous fiber type composition, this phenomenon is less observed in humans.

In response to cellular and extracellular cues associated with intense exercise or muscle damage, the myogenic satellite cells exit their quiescent state (become "activated"), proliferate, and migrate to the site of injury to repair or replace damaged muscle fibers by fusing together, fusing to existing muscle fibers, or both. Although it has been suggested that other stem cell populations contribute to skeletal muscle regeneration, the evidence to date suggests that myogenic satellite

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