Morphologic and Mechanical Basis of Delayed-Onset Muscle Soreness

Richard L. Lieber, PhD, and Jan Fridén, MD, PhD

Abstract

Muscle pain after unaccustomed exercise is believed to result from repetitive active lengthening of skeletal muscle. This "eccentric exercise" initiates a sequence of events that includes muscle cytoskeletal breakdown, inflammation, and remodeling such that subsequent exercise sessions result in less injury and soreness. Recent studies of eccentric exercise using well-defined animal models have identified the mechanical and cellular events associated with the injury-repair process. In addition, neurophysiologic studies have elucidated mechanisms of pain that operate in skeletal muscle. Taken together, these studies improve our understanding of the muscle injury process and will lead to rational therapeutic interventions to facilitate recovery.

J Am Acad Orthop Surg 2002;10:67-73

Delayed-onset muscle soreness (DOMS), or what is commonly described as postexercise muscle soreness, is the sensation of muscular discomfort and pain during active contractions that occurs in a delayed fashion after strenuous exercise. Usually, the initial symptoms are most evident at the muscle tendon junction and thereafter spread throughout the entire muscle. Skeletal muscle soreness and injury are associated with intense exercise. The soreness and accompanying muscle damage are even more pronounced if the exercise performed is new to the individual. Thus, even individuals who are in excellent athletic condition may experience muscle soreness and damage when performing exercise to which they are unaccustomed. The relationship between the development of DOMS and the loss of muscle strength has yet to be explicitly proven.

Symptoms

Sore muscles after exercise are usually described as stiff, tender, or aching. The stiffness associated with DOMS is not a function of antagonistic muscular action but is probably caused by edema occurring in the perimuscular connective tissue.[1] The symptoms of DOMS develop during the first 24 to 48 hours, peak between 24 and 72 hours, and disappear within 5 to 7 days,[2,3] usually without intervention. Regardless of the exact location of the palpable region of soreness, passive stretching and renewed activity aggravate the pain. Some controversy exists regarding the relationship between maximum voluntary force and symptoms of soreness. Ebbeling and Clarkson[3] suggested that there is very little or no relationship between the development of soreness and a decrease in muscle strength. Newham et al[4] demonstrated return of maximum quadriceps strength to pre-exercise levels within 24 hours after step exercise, while others have reported that a period of >2 weeks is necessary to recover maximum isometric strength. In addition to tenderness with palpation, the examiner also will find prolonged strength loss, a reduced range of motion, and elevated levels of serum creatine kinase (CK).

Many studies have reported that eccentric exercise results in a significant increase in CK levels 24 to 48 hours after the exercise session[5] that may peak between 3 to 6 days, depending on the precise nature of the exercise (Fig. 1, open circles). CK is an intramuscular enzyme responsible for maintaining adequate adenosine triphosphate levels during muscle contraction. Its appearance in the serum is interpreted as indicating an increased permeability or breakdown of the membrane sur-

Dr. Lieber is Professor of Orthopaedics and Bioengineering, Veterans Affairs Medical Center, and Department of Orthopaedics and Bioengineering, University of California, San Diego, Calif. Dr. Fridén is Professor of Hand Surgery, Department of Hand Surgery, Göteborg University, Göteborg, Sweden.

Reprint requests: Dr. Lieber, University of California San Diego School of Medicine, 3350 La Jolla Village Drive, San Diego, CA 92161.

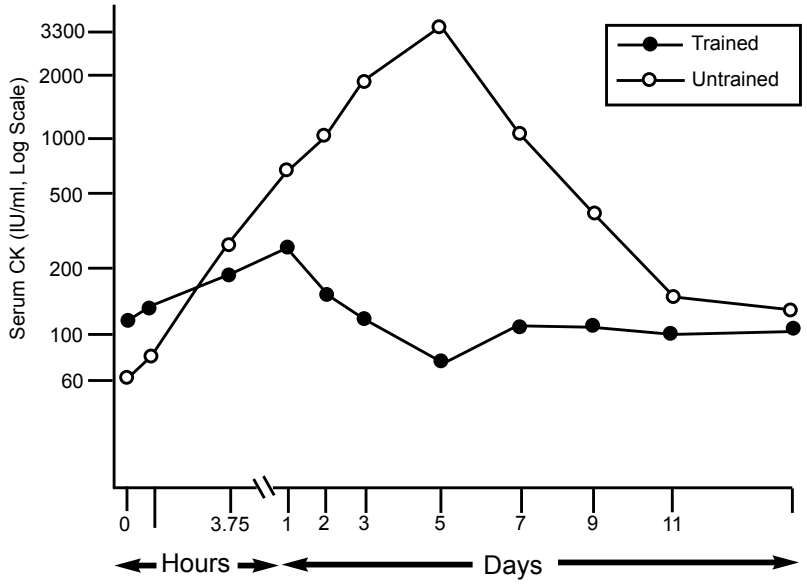

Figure 1 Time course of serum CK levels after a session of eccentric exercise in untrained and trained young men. Note that the delayed and prolonged increase in CK levels in untrained individuals is attenuated after training. (Reproduced with permission from Lieber RL [ed]: *Skeletal Muscle Structure and Function: Implications for Rehabilitation and Sports Medicine*. Baltimore, Md: Williams & Wilkins, 1992.)

rounding the muscle cell. Increased CK levels resolve in 7 to 14 days. In a similar delayed fashion, muscle pain accompanying eccentric exercise peaks 24 to 48 hours after the exercise session but resolves more rapidly compared with CK levels. Interestingly, peak CK levels are not strongly correlated with either the timing of increased muscle pain or the magnitude of tissue injury.

Another widely agreed-on finding is that training prevents or at least attenuates the magnitude of muscle injury that occurs after eccentric exercise (Fig. 1, solid circles). This training effect is produced only after eccentric training of the specific muscle group being tested. In other words, there is a very high degree of specificity regarding the protective effect of exercise. General increased aerobic fitness neither prevents nor attenuates eccentric contraction-induced muscle injury.

Skeletal Muscle Injury

Injury to muscle fibers can occur as a result of direct trauma, disease, application of myotoxic agents (such as local anesthetics), inflammatory processes, or intense exercise. The association between the type of injury and the nature of the pain that accompanies it has been studied using a number of experimental models. Results from these studies clarify the various mechanisms of muscle fiber injury and factors that influence the type and duration of pain associated with it. The model most commonly used to study DOMS is the eccentric contraction model.

Muscle Injury Resulting From Eccentric Contractions

Among the variety of types of muscle action are the eccentric, concentric, and isometric. During an eccentric action, an activated muscle is forced to elongate while producing tension. Its counterpart, concentric action, produces tension during muscle shortening. The intermediate, isometric contraction produces tension while the muscle remains essentially at a constant length. All three actions are common components of daily movement. The tension generated during eccentric action is higher than that for either of the other actions. Asmussen[6] established that DOMS was primarily associated with the eccentric component of exercise. A muscle injury model utilizing eccentric contraction, in which the muscle is actively generating force during the lengthening maneuver, has been implemented in animals as well as humans.

Based on experimental studies of skeletal muscles directly subjected to eccentric exercise, investigators believe that the very early events causing muscle injury are mechanical in nature.[7,8] For example, during cyclic eccentric exercise of the rabbit tibialis anterior, significant mechanical changes were observed in the first 5 to 7 minutes of exercise. After this period, histologic examination revealed that a small fraction of muscle fibers appeared to be larger, more rounded, and more lightly stained compared with surrounding normal muscle fibers. Interestingly, recent immunohistochemical studies have revealed structural disruption of the cytoskeleton within the fibers at these very earlier time periods[9] that may provide further insights into the damage mechanism. Such pathologic changes also can be seen following either sprint or distance running in humans and after resistance training.[10,11]

Fiber Type-Specific Damage

Both animal and human studies have provided evidence for selective damage of fast fiber types after eccentric exercise.[12,13] In human studies, this damage was confined

to the type 2 muscle fibers in general (Table 1), but in animal studies, damage has been further localized to the type FG (often equated to type 2B) fast fiber subtype. In one study,[12] 231 "enlarged" rabbit tibialis anterior fibers were observed from six different muscles; all were of the FG fiber type. Their average size was about four times the normal muscle fiber area. For some fibers observed in serial section, the area and shape of the fiber changed dramatically from one section to the next[12] (Fig. 2). Because FG fibers are the most highly fatigable muscle fibers, it has been speculated that the high degree of fatigability of these fibers may predispose them to injury, but this has not been supported in detailed animal studies.[14]

At the ultrastructural level, the most commonly reported morphologic abnormality is the loss of the regular orientation of Z bands with the fibers. The most subtle form of injury is the slight "wavy" appearance of the Z band, while more severe injury is manifest by complete Z band or A band disruption (Fig. 3). Despite the numerous reports of this phenomenon, a mechanistic explanation for selective Z band damage is not available.

Inflammation After Muscle Injury

Direct evidence of inflammatory cells within skeletal muscle after eccentric exercise has been reported in both animals and humans.[5,15] The early mechanical events are followed by infiltration of circulating monocytes that become macrophages after entering the tissue (Fig. 4). In a study of the rabbit tibialis anterior,[12] the time course of torque generation in rabbit dorsiflexors was measured after a single eccentric exercise session; there was a measurable progressive decline in force that was delayed and occurred over a 2- to 3-day period. The mechanism for the progressive decline in force was hypothesized by the authors to be the infiltration of inflammatory cells and associated proteolytic degradation of muscle tissue. In this model, the progressive force decline was about the same order of magnitude as the force decline that occurred as a result of the mechanical injury itself. Cellular infiltration was uniquely associated with the eccentric exercise itself in that isometrically exercised muscles were devoid of infiltrating cells, and the same force decrement was not observed after isometric exercise of the same duration. A similar scenario has been proposed in human exercise studies.[16]

Because the inflammatory process itself can cause damage in excess of that caused by the exercise, it is possible that prevention of inflammation would improve muscle status following injury. Based on this assumption, nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed to provide analgesia and to improve performance. The specific objective effects of the NSAIDs on muscle function are, however, poorly understood, and it is difficult to test muscle function in humans because the analgesic effect of NSAIDs may itself permit improved performance by lessening or eliminating pain. The anti-inflammatory medication flurbiprofen was tested in the rabbit muscle injury model described above. Muscles were exercised with a single eccentric exercise session, after which the anti-inflammatory medication was given for 7 days.[17] Muscle contractile properties were measured for the 28 days following the exercise; interestingly, muscles treated with the NSAID demonstrated a significant short-term improvement in contractile function

Table 1
Characteristics of Human Skeletal Muscle Fiber Types

	Type I	Type IIA	Type IIB
Other names	Red, slow twitch (ST) Slow oxidative (SO)	White, fast twitch (FT) Fast oxidative glycolytic (FOG)	Fast glycolytic (FG)
Speed of contraction	Slow	Fast	Fast
Fatigability	Fatigue-resistant	Moderately fatigue-resistant	Most fatigable
Aerobic capacity	High	Medium	Low
Anaerobic capacity	Low	High	High
Motor unit size	Small	Medium	Large
Capillary density	High	Medium	Low

(Adapted with permission from Garrett WE, Jr, Best TM: "Anatomy, Physiology, and Mechanics of Skeletal Muscle," in Buckwalter JA, Einhorn TA, Simon SR [eds]: *Orthopaedic Basic Science: Biology and Biomechanics of the Musculoskeletal System*, ed 2. American Academy of Orthopaedic Surgeons, Rosemont, Ill: 2000, p. 692.)

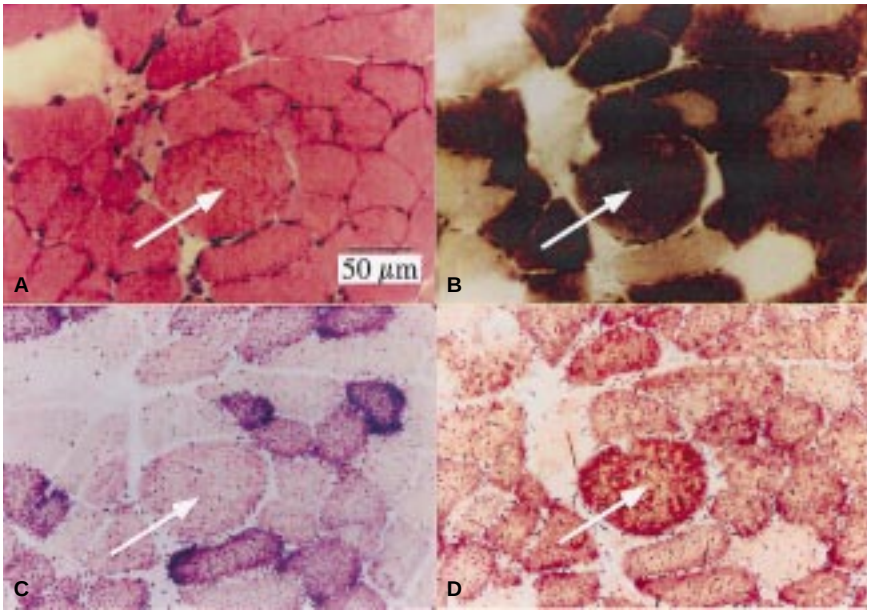

Figure 2 Cross-sectional light micrographs of rabbit tibialis anterior muscle under different staining conditions. Enlarged fiber, shown with arrows, is of the FG fiber type. **A,** Hematoxylin-eosin. **B,** Myofibrillar adenosine triphosphate following preincubation at pH = 9.4. **C,** Succinate dehydrogenase. **D,** α-Glycerophosphate dehydrogenase.

but a subsequent loss in function (Fig. 5). These data may have significant implications for the use of NSAIDs in pain treatment associated with neuromuscular injury.

Skeletal Muscle Pain

Numerous studies have documented the existence of pain after blunt trauma, eccentric exercise, injection of noxious agents, and peripheral nerve disease in skeletal muscles. It is clear, however, that muscle fiber damage does not necessarily cause pain. This statement is based on the observation that muscle biopsies obtained from patients with primary muscle diseases such as Duchenne muscular dystrophy reveal major disruptions of the myofibrillar and sarcotubular apparatus, yet the patients themselves remain pain free. Thus, pain within muscle that occurs after fiber injury probably results from secondary events that occur after the damage itself. Based on this evidence and extrapolation of experimental data obtained from muscles, tendons, and joints, muscle pain is thought to result from stimulation of nociceptors within the muscle itself.

Skeletal Muscle Innervation

Muscles are supplied by a rich and extensive network of receptors that are innervated by small myelinated (group III) and unmyelinated (group IV) afferent nerve fibers. These fibers conduct much more slowly (Table 2) than do either the α-motoneurons that project to the muscle fibers (i.e., extrafusal muscle fibers), the γ-motoneurons that project to the muscle spindles (intrafusal muscle fibers), or even the Ia afferents that feed back from muscle spindles to the spinal cord.

Nociception in Skeletal Muscle

Although the bulk of the data on the neurophysiology of pain has been obtained from studies of cutaneous receptors, studies of muscle and visceral pain are much more clinically relevant. The extensive studies by Mense et al[18-20] provide a wealth of understanding regarding these nociceptive mechanisms in muscle and viscera. They delineated several important differences between muscle and visceral pain compared with cutaneous pain. First, cutaneous pain is localized with great accuracy, and muscle pain is difficult to localize. Second,

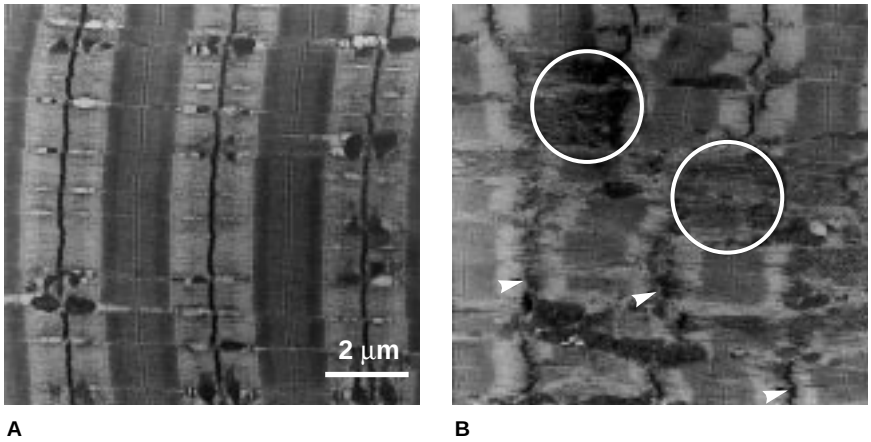

Figure 3 Longitudinal electron micrographs of rabbit tibialis anterior muscle after 30 min of eccentric contractions. **A,** Sample from normal muscle showing clean alignment of myofibrils across the field. **B,** Sample from muscle showing smearing of the Z band material (small arrowheads) and extension of the Z bands into adjacent A bands (circled regions).

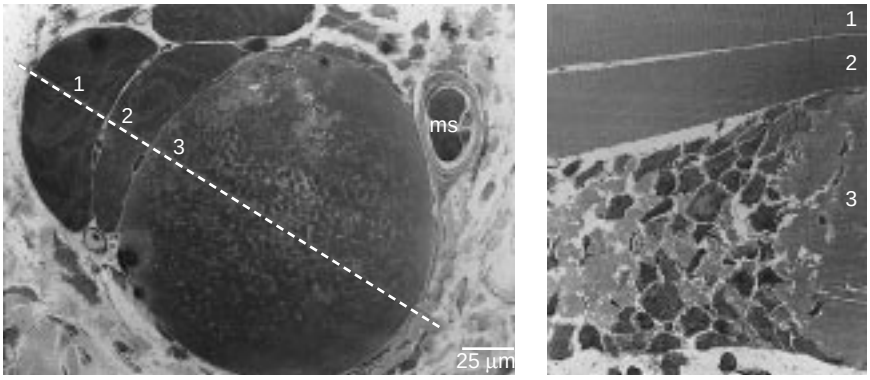

Figure 4 **A,** Cross-section of muscle fibers showing enlarged fiber (3) and two normal fibers (1 and 2), and muscle spindle (ms). **B,** Longitudinal section of muscle along plane shown in panel *A* (white dotted line) revealing the inflammatory process that leads to the enlarged fiber type (3) and size variation observed (compare with Fig. 2). Enlarged fibers thus represent "supercontracted" cells being digested by inflammatory cells close by. (Reproduced with permission from Fridén J, Lieber RL: Segmental muscle fiber lesions after repetitive eccentric contractions. *Cell Tissue Res* 1998;293:165-171.)

while increasing the activation intensity of cutaneous receptors does not change the size of the receptive field, increasing muscular pain intensity results in referral to remote sites such as other muscles, fascia, tendons, joints, or ligaments. Third, muscle pain is associated with symptoms mediated through the autonomic nervous system, such as decreased blood pressure, nausea, and sweating, whereas cutaneous pain is not.

In contrast to results produced from analogous studies of the skin, repetitive electrical stimulation of muscle afferents results only in painful sensations. Increasing the intensity does not modify the subjective nature of the pain and serves only to elicit the description of a "cramp" as well as a decreased ability to localize the site of pain source.[21] Additionally, the magnitude of referred pain is positively correlated to the stimulation frequency of deep nociceptive fibers.

Factors That Modulate Nociception in Skeletal Muscle

The type III and IV nociceptors in skeletal muscle have been studied extensively in the cat hindlimb preparation.[18,19] The percentages of motor and sensory nerves innervating the lateral gastrocnemius-soleus muscles have been shown to be approximately 60% and 40%, respectively. Of the sensory nerves, about 40% of them can be classified as nociceptive, suggesting an overall high sensibility within these muscles (15% to 20% of the innervating axons).

Experimental demonstration of factors affecting nociception is obtained by using single nociceptive afferents from anesthetized cats and experimentally perturbing the system. For example, Mense and Meyer[18] measured the discharge activity of these group III afferents and saw almost no activity on light touch with a painter's brush (Fig. 6), some activity on moderate touch, and high activity with noxious touch (pinching the muscle with forceps). No activity was observed on passive stretch of the muscle within the physiologic range (6 mm in this case), but when the muscle was stretched 9 or 12 mm, a moderate level of activity was recorded. This makes teleologic sense because nociceptors are designed not only

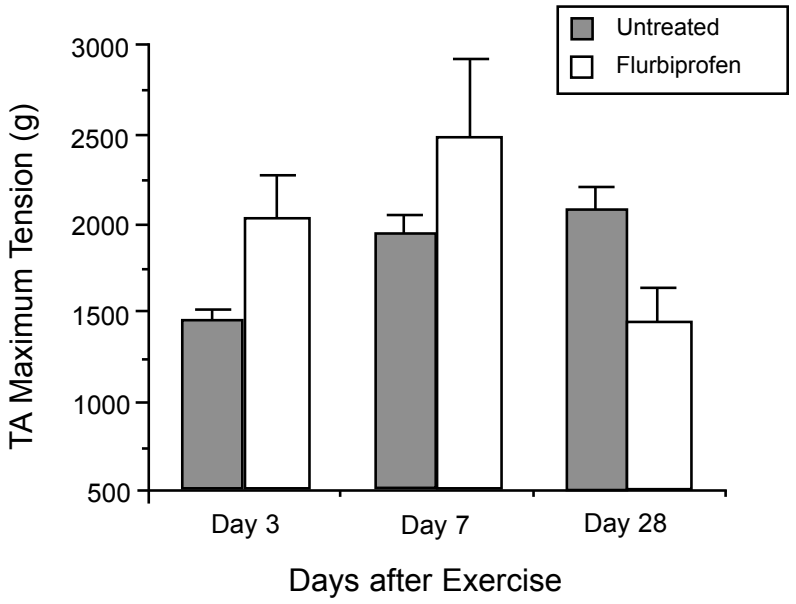

Figure 5 Maximum tetanic tension of tibialis anterior (TA) muscles from flurbiprofen-treated versus untreated animals. The flurbiprofen-treated animals generated higher muscle forces early in the treatment and lower muscle forces later in the treatment. (Adapted with permission.[17])

Table 2
Properties of Afferent Fibers in Peripheral Nerve

Fiber Group	Myelinated	Axon Diameter (μm)	Average Conduction (m/s)
I	Yes	15	90-100
II	Yes	10	40-50
III	Yes	5	20-30
IV	No	<1	1

to signal tissue damage but also to prevent it.

Inflammatory Factors

Other factors that caused increased output from nociceptors were injection of factors presumed to be involved in the inflammatory response, such as bradykinin ([BK] cleaved from precursor plasma proteins), 5-hydroxytryptamine (released from platelets after vascular damage), and prostaglandins ([PGs] a byproduct of the cyclooxygenase pathway). All receptors studied showed clear signs of BK-induced sensitization characterized by a lowered threshold to local pressure stimulation. Because BK is known to release PGE_2 from cells, it can actually potentiate its own action. This finding has led to the idea that compounds that block the effect of PG synthesis (e.g., acetylsalicylic acid [ASA]) might reduce or abolish the stimulatory action of BK. This was, in fact, the case. There was a complete lack of effect of BK within 15 minutes of injection of ASA, demonstrating the peripheral effect of ASA in that connections with the central nervous system were cut in this preparation.

Ischemia

Ischemia for prolonged periods (up to about 15 minutes) is not painful and does not evoke sympathetic reflexes. However, if a muscle contracts under ischemic conditions, pain rapidly develops. Most likely BK is involved in this response because kinin is released from plasma proteins during ischemia. Mense and Stahnke[19] demonstrated activation of group IV muscle receptors during ischemic contractions. Muscle contraction alone did not elicit the response, but afferent activity increased fourfold when the same contraction was performed while occluding the nutrient artery.

Reflex-Mediated Pain

Reports in some of the older clinical literature suggest that increased activity or excitability of the γ-motor system causes the painful spasms that sometimes appear in skeletal muscle. Increased activity of the γ-motor system would then lead to increased discharge frequency in muscle spindle afferent fibers that would, in turn, lead to increased activation of α-motoneurons. By this mechanism, a vicious cycle could result that would be strong enough to lead to ischemic contractions and pain by any one of a number of the mechanisms described above. Unfortunately, experimental evidence supporting this concept is lacking.[20] The main finding of these studies was that resting activity of the γ-motoneurons was significantly reduced by inflammation and that the reflex excitability of the neurons was likewise inhibited. These results demonstrated that nociceptive muscle afferents actually inhibit homonymous γ-motoneurons, which may represent an advantage to the muscle in that it could reduce potentially damaging forces on it.

Summary

DOMS represents a time-varying cascade of events that are uniquely associated with eccentric training of a skeletal muscle. Currently, there is not an adequate explanation for the relationship between muscle damage observed and clinical symptoms of pain. Intramuscular pain, similar to that observed after application of inflammatory factors to

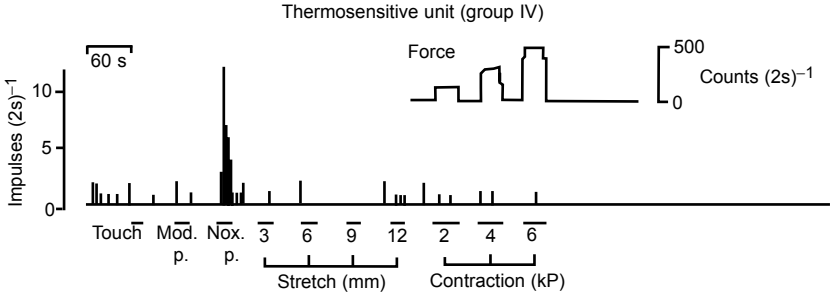

Figure 6 Recording from intramuscular type III afferents with pressure of different levels (left portion of panel) and with stretch above and beyond the physiological range (6 mm in this case). (Reproduced with permission.[18])

muscle, is likely to account for some of the DOMS observed. In addition, it is possible that reflex-mediated pain also contributes to DOMS. In the future, investigators will establish objective human models for DOMS and perform more sophisticated neurophysiologic analysis and noninvasive imaging of the neuromuscular system to define the mechanism and prevention of DOMS after athletic endeavors.

References

1. Howell JN, Chleboun G, Conatser R: Muscle stiffness, strength loss, swelling and soreness following exercise-induced injury in humans. *J Physiol* 1993;464:183-196.
2. Fridén J: Muscle soreness after exercise: Implications of morphological changes. *Int J Sports Med* 1984;5:57-66.
3. Ebbeling CB, Clarkson PM: Exercise-induced muscle damage and adaptation. *Sports Med* 1989;7:207-234.
4. Newham DJ, Mills KR, Quigley BM, Edwards RH: Pain and fatigue after concentric and eccentric muscle contractions. *Clin Sci (Lond)* 1983;64:55-62.
5. Evans WJ, Meredith CN, Cannon JG, et al: Metabolic changes following eccentric exercise in trained and untrained men. *J Appl Physiol* 1986;61:1864-1868.
6. Asmussen E: Observations on experimental muscular soreness. *Acta Rheum Scand* 1956;2:109-116.
7. Lieber RL, Fridén J: Muscle damage is not a function of muscle force but active muscle strain. *J Appl Physiol* 1993;74:520-526.
8. Warren GL, Hayes DA, Lowe DA, Armstrong RB: Mechanical factors in the initiation of eccentric contraction-induced injury in rat soleus muscle. *J Physiol* 1993;464:457-475.
9. Lieber RL, Thornell LE, Fridén J: Muscle cytoskeletal disruption occurs within the first 15 minutes of cyclic eccentric contraction. *J Appl Physiol* 1996;80:278-284.
10. Nimmo MA, Snow DH: Time course of ultrastructural changes in skeletal muscle after two types of exercise. *J Appl Physiol* 1982;52:910-913.
11. Warhol MJ, Siegel AJ, Evans WJ, Silverman LM: Skeletal muscle injury and repair in marathon runners after competition. *Am J Pathol* 1985;118:331-339.
12. Lieber RL, Fridén J: Selective damage of fast glycolytic muscle fibres with eccentric contraction of the rabbit tibialis anterior. *Acta Physiol Scand* 1988; 133:587-588.
13. Fridén J: Changes in human skeletal muscle induced by long-term eccentric exercise. *Cell Tissue Res* 1984;236:365-372.
14. Patel TJ, Cuizon D, Mathieu-Costello O, Fridén J, Lieber RL: Increased oxidative capacity does not protect skeletal muscle fibers from eccentric contraction-induced injury. *Am J Physiol* 1998;274(5 pt 2):R1300-R1308.
15. Armstrong RB, Ogilvie RW, Schwane JA: Eccentric exercise-induced injury to rat skeletal muscle. *J Appl Physiol* 1983;54:80-93.
16. Cannon JG, Orencole SF, Fielding RA, et al: Acute phase response in exercise: Interaction of age and vitamin E on neutrophils and muscle enzyme release. *Am J Physiol* 1990;259(6 pt 2):R1214-R1219.
17. Mishra DK, Fridén J, Schmitz MC, Lieber RL: Anti-inflammatory medication after muscle injury: A treatment resulting in short-term improvement but subsequent loss of muscle function. *J Bone Joint Surg Am* 1995;77: 1510-1519.
18. Mense S, Meyer H: Different types of slowly conducting afferent units in cat skeletal muscle and tendon. *J Physiol* 1985;363:403-417.
19. Mense S, Stahnke M: Responses in muscle afferent fibres of slow conduction velocity to contractions and ischaemia in the cat. *J Physiol* 1983;342: 383-397.
20. Mense S, Skeppar P: Discharge behaviour of feline gamma-motoneurones following induction of an artificial myositis. *Pain* 1991;46:201-210.
21. Torebjörk HE, Ochoa JL, Schady W: Referred pain from intraneural stimulation of muscle fascicles in the median nerve. *Pain* 1984;18:145-156.