CHAPTER 60: Muscle Pain: Pathophysiology, Evaluation, and Treatment

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INTRODUCTION AND EPIDEMIOLOGY

INTRODUCTION

Muscles, representing approximately 50% of the body by weight, have long been recognized by clinicians as a source of common pain problems. Various terms have been applied to muscles and soft tissue pain, generally reflecting the prevailing concepts of muscle pain mechanisms or clinical observations of painful muscles. The changing concepts about the nature of muscle pain make it difficult to collect data on the incidence and impact of muscle-related pain. A brief review of the history of these concepts is presented.

DESCRIPTIVE TERMS

The terms *muscular rheumatism*[1] and *nonarticular rheumatism*[2] were used to suggest that pain and stiffness in the region of a joint were caused by soft tissue rather than articular dysfunction. Inflammation as the cause of muscle pain led to the terms *fibrositis* and *myofibrositis*,[3] which were abandoned with the awareness that inflammation could generally not be demonstrated in painful muscles.

The palpable changes in the muscles, revealing increased resilience, ropiness, and nodularity, led to the terms *Myogelosen* (muscle gelling),[4] *Muskelhärten* (hardened muscle),[5] and *Muskelschwiele* (muscle callus). The term *myofascial pain*, suggesting pain originating in muscle and connective tissue, first used by Reynolds in 1952, is now confusingly used interchangeably with *myofascial pain syndrome*, suggested by Travell and Simons,[6] referring to muscle pain originating in myofascial trigger points (TrPs).

PAIN DISTRIBUTION AND PUTATIVE ETIOLOGY AFFECT NOMENCLATURE

Littlejohn[7] suggests that the term *regionalized musculoskeletal disorders* be used for muscle pain when the causes appear to be inflammation, sprain, strain, or degeneration of muscles and tendons. When no obvious etiology is present to account for muscle pain, tenderness, stiffness, and often associated nonanatomic dysesthesias and autonomic disturbances, four overlapping and confusing diagnoses are often used: (1) regional pain syndrome, (2) complex regional pain syndrome, and when muscle pain is widespread, (3) chronic widespread pain (CWP), or (4) fibromyalgia syndrome (FMS). Central nervous system (CNS) dysregulation is generally thought to underlie these diagnoses rather than peripheral muscle pain generators.

MUSCLE PAIN AND NEUROPLASTICITY

When muscle nociceptors (discussed later in the chapter) are sensitized, they stimulate and may sensitize dorsal horn neurons, which may result in opening previously ineffective synaptic pathways, leading to stimulation of

neurons at adjacent and distant spinal levels. This mechanism may produce referred muscle pain. Sensitized CNS neurons and primary dysfunction in descending inhibitory pathways may lower the threshold for nociceptive stimulation and result in enhanced muscle pain. Pain from other tissue (nerve, joint, viscera) may refer to muscle and may result in the production of independently self-sustaining muscle pain and a confounded clinical presentation.

MUSCLE PAIN AS A CAUSE OF OR COEXISTING WITH OTHER SUSPECTED PAIN DIAGNOSES

Although diagnoses such as nonspecific low back, neck, and shoulder pain are often thought to be the result of sprains and strains of muscles and other soft tissue,[8,9] they would not show up in an epidemiologic survey as muscle-related pain. (The following discussion alludes to muscle pain as a representative for soft tissue pain, understanding that fascia, ligaments, and tendons are also sources of soft tissue pain.)

A large study showed that 70% or more of patients with acute low back pain (LBP) in an ambulatory setting were diagnosed as having nonspecific LBP, defined as sprains and strains of soft tissue,[8] so it is remarkable that muscles are not considered in the etiology of LBP in guidelines from important national and international organizations.[10] Pain presentations in a region of the body may be incorrectly labeled based on a body part (e.g., epicondylitis) and ignore the surrounding musculature,[11] which may be important in the total pain presentation.[12]

Tension-type headaches (TTHs) may be related to muscle-generated pain.[13] Ten percent of pain complaints in patients with cancer are unrelated to the cancer or treatment and are generally thought to be caused by soft tissue.[14] Therefore, statistics on the incidence and prevalence of muscle pain in the general population are confounded and we believe underestimate the clinical and economic importance of muscles in common pain syndromes.

EPIDEMIOLOGY

Fifty percent of adolescents reported previous lifetime incidence as well as prospectively for 1 to 5 years of LBP, CWP, FMS, shoulder pain, or musculoskeletal pain.[15] Associated significant reductions in health-related quality-of-life scores were noted when pain occurred at least once a week at more than one site.[16] A 2009 European study reported a 1-month period prevalence of LBP of nearly 40% in adolescents.[17]

Twenty-seven percent of adults reported LBP in the preceding 3 months, and 14% reported neck pain in the 2008 National Health Interview Survey Report.[18] A 2009 study showed a rising prevalence of chronic LBP across all age groups during a 14-year period.[19] In the United Kingdom, the lifetime prevalence of chronic LBP in the general population is estimated to be 6.3% to 11.1%.[20]

The 12-month prevalence of neck pain was 30% to 50% in 2008 in The Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders.[21] The 1-month period prevalence of shoulder pain is between 20% and 33%.[22]

U.S. and U.K. data for CWP show a 10% to 11% point prevalence, with women affected 1.5 times more often than men.[23–25] Point prevalence for FMS is 0.5% to 4% from the same data, with women affected 10 times more often than men. Data also show that patients with FMS frequently have a history of work-related neck and shoulder pain, whiplash, LBP, and muscle tension,[26,27] suggesting that many of these patients' diffuse pain problems may have begun in clinically or subclinically damaged muscles.

DIAGNOSIS

HISTORY

Muscles may be the cause of pains mistakenly attributed to other tissue and may contribute to the overall pain presentation in patients who have pain from other sources (e.g., HNP, rotator cuff tear, arthritis). Therefore, unless a muscle assessment is a standard part of the physical examination of the patient in pain, it may not be considered in the pain diagnoses. For example, a detailed work and social history may reveal factors that could produce overt or subclinical muscle injury.

Work-related factors may include recent changes in the physical demands in the work setting, prolonged positioning, repetitive movements, and consistently physically or psychologically demanding labor. Sports-related activity may include changes in activity, type, intensity, frequency, and equipment. Examples are playing tennis for longer than usual, incorporating a new serve, and using a new racket. Upper body activities associated with the initiation or perpetuation of neck and shoulder pain include use of the computer keyboard with an elbow angle of less than 90 degrees, a nonergonomic monitor position, regular use of a phone without using a headset or speaker, and reading or watching television in bed.

SIGNS AND SYMPTOMS

Muscle pain may occur in a discrete area or in multiple regions as an activity-related aching discomfort but at times also at rest. Patients typically complain of a dull, aching sensation that is made worse with more aggressive activity of the painful region and prolonged positioning. If pain occurs with prolonged positioning, movement tends to initially reduce the pain (e.g., standing in one spot causing LBP, which is then diminished with walking). The painful muscle generally has diminished ability for maximal effort (pain inhibition) related to suppressed activity in the painful agonist with associated problems in coordination and diminished flexibility related to increased activity in the antagonist.[28]

Because nerves traveling through or adjacent to contracted muscles may become compressed, the presentation may suggest a neuropathic problem. Piriformis syndrome is only one such example.[29]

BASIC NEUROANATOMY AND NEUROPHYSIOLOGY OF MUSCLE PAIN

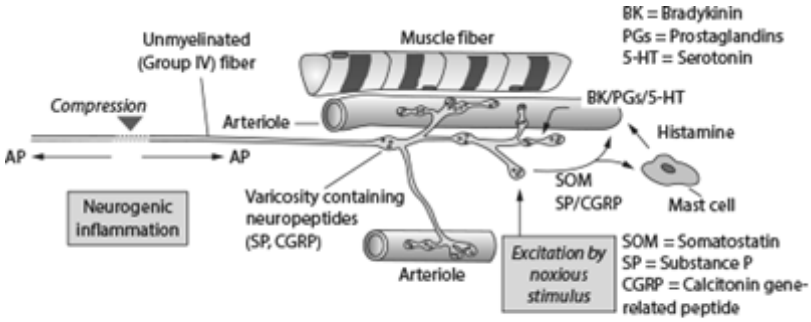
NEUROANATOMY OF MUSCLE NOCICEPTORS AND THEIR AFFERENT FIBERS

Small-diameter high-threshold afferent fibers have to be excited in order to elicit muscle pain. Histologically, they consist of thin myelinated (group III) and nonmyelinated (group IV)[30] fibers. The conduction velocity of these fibers is low: group IV fibers conduct at 0.5 to 2.5 m/s in a cat and group III fibers at 2.5 to 30 m/s. Group III fibers correspond to cutaneous Aδ- and group IV to C fibers. Not all of these small-caliber fibers are nociceptive; they also include thermoreceptive and mechanoreceptive fibers with a low threshold in the innocuous range.[31,32]

The typical structure mediating muscle pain is the free nerve ending.[33] The term indicates that in a light microscope, no corpuscular receptive structure can be recognized (**Fig. 60-1**). Free nerve endings, having a high mechanical threshold in the noxious range or responding to pain-producing chemicals, are called *nociceptors* or *nociceptive endings*. They are not excited by light deformation of the muscle or physiological movements. The expression “pain receptor” should be avoided because a nociceptor does not measure pain but the intensity of a painful stimulus. Pain is the sequela of a strong excitation of nociceptors and originates in the cortex.

Figure 60-1.

Structure of a muscle nociceptor and events occurring around the receptor during noxious stimulation. The nociceptor has several branches close to arterioles. The noxious stimulus (upward arrow) excites the nociceptor, leading to the release of neuropeptides from the ending, such as substance P (SP), calcitonin gene-related peptide (CGRP), and somatostatin (SOM). SP and CGRP cause vasodilation and increased capillary permeability in the small blood vessels in the vicinity of the ending. SP also degranulates mast cells; the released histamine is likewise a vasodilator. The release of neuropeptides from nociceptive endings can also occur when action potentials invade the ending retrogradely (against the normal direction of propagation) in neuropathy or radiculopathy (left part of figure). At the site of a nerve compression, action potentials originate in the nociceptive fiber and propagate both anterogradely (to the central nervous system, causing pain) and retrogradely (to the receptive ending, causing neurogenic inflammation through the release of neuropeptides). The neurogenic inflammation is a sterile inflammation around the nociceptive ending caused by an increase in blood vessel permeability followed by plasma extravasation. The plasma extravasation leads to the formation of bradykinin and other agents that sensitize the nociceptor. The result of a neurogenic inflammation is a local edema with sensitized nociceptors. (Modified from Mense and Gerwin.[34] Mense S, Gerwin R. *Muscle Pain: Understanding the Mechanisms. 1st ed*. Heidelberg: Springer; 2010.)



Whereas group III afferents terminate not only in free nerve endings but also in paciniform corpuscles, group IV fibers supply exclusively free nerve endings. The predominant location of free nerve endings is the adventitia of arterioles and venules. The muscle fibers proper are not supplied by free nerve endings.[35]

The density of free nerve endings in the peritendineum (the connective tissue around a tendon) of the rat calcaneal tendon was several times higher than that in the gastrocnemius-soleus (GS) muscle.[35] The dense innervation of the peritendineum may explain the high prevalence of tenderness or pain in the tissue around tendons and their insertion sites.

NEUROPEPTIDE CONTENT OF NOCICEPTIVE FREE NERVE ENDINGS

There is evidence from studies on dorsal root ganglion (DRG) cells that substance P (SP) and, to a lesser extent, calcitonin gene-related peptide (CGRP) are characteristic of nociceptive units.[36] Other neuropeptides, such as somatostatin (SOM), vasoactive intestinal polypeptide (VIP), and nerve growth factor (NGF), are also present in unmyelinated fibers in muscle[35] but are not as closely related to a nociceptive function as SP and CGRP. A strong argument supporting a nociceptive function of SP is that noxious stimulation in the body periphery is followed by a release of SP in the dorsal horn of the spinal cord where nociceptive endings terminate. Both SP and CGRP are presumably released together when the afferent fiber is active because they coexist in nociceptive units.

Generally, the neuropeptide content of nerve fibers from muscle is similar to that of cutaneous nerves.[37,38] However, compared with skin nerves, muscle nerves appear to contain less SP. In rats in which a chronic myositis had been induced, the innervation density of the muscle with free nerve endings containing SP and NGF was significantly increased.[35]

In the CNS, neuropeptides function as neuromodulators, substances that enhance or attenuate the action of neurotransmitters. Glutamate is the main neurotransmitter of nociceptive afferents in the spinal cord, and the neuropeptides enhance the central nervous effects of glutamate released by peripheral noxious stimuli.[39]

PHYSIOLOGICAL PROPERTIES OF MUSCLE NOCICEPTORS

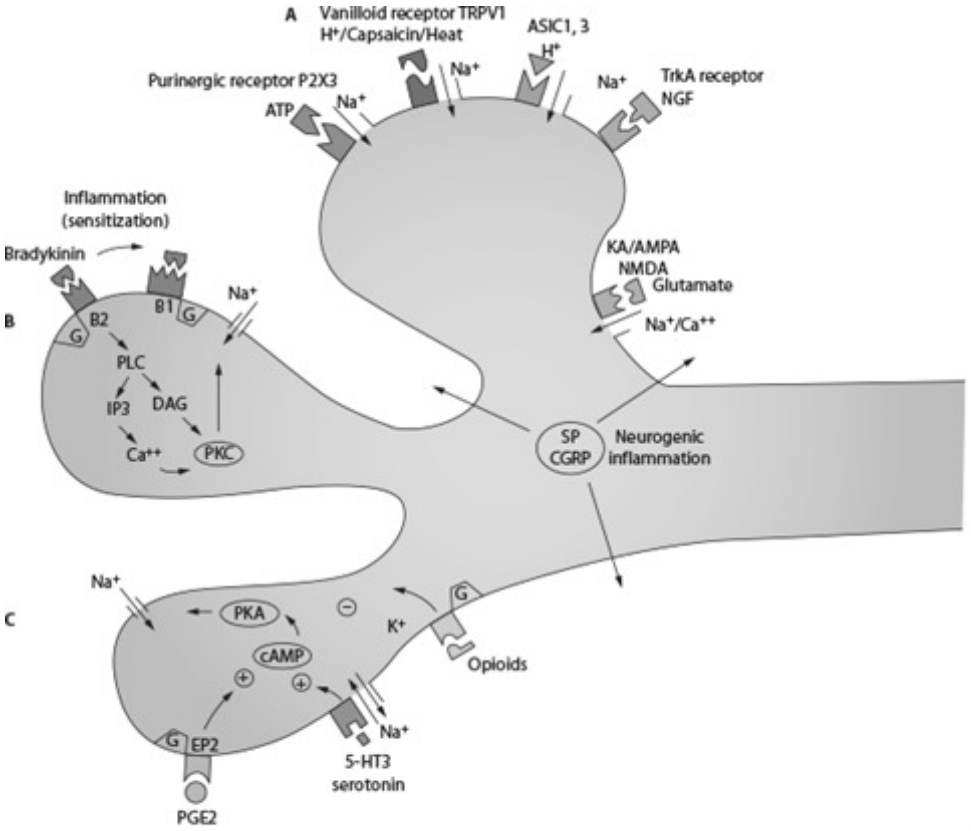
Whenever a nociceptor is excited, it releases the neuropeptides stored in its ending into the interstitial tissue. Many of these agents, particularly CGRP and SP, cause vasodilatation and an increase in vascular permeability of the blood vessels around the active ending. The result is a shift of blood plasma from the intravascular to the interstitial space. Here, bradykinin (BKN) is cleaved from plasma proteins, serotonin (5-HT) is released from platelets, and prostaglandin E_2 (PGE_2) is released from endothelial and other tissue cells. All of these substances sensitize nociceptors. Thus, the main tissue alteration induced by a noxious mechanical stimulus is a localized region of vasodilatation, edema, and sensitized nociceptors. These effects can also be evoked by the compression of a peripheral nerve or dorsal root, which triggers action potentials at the compression site. Action potentials traveling to the CNS cause neuropathic pain; those traveling to the body periphery lead to the release of sensitizing substances from the nociceptive ending. The result is a neurogenic inflammation (see Fig. 60-1) which may enhance the pain of patients with neuropathy.

SUBSTANCES EXCITING MUSCLE NOCICEPTORS

The membrane of a nociceptor is equipped with receptor molecules to which sensitizing or stimulating agents bind (**Fig. 60-2**) or that are sensitive to thermal or mechanical stimuli. The following substances are effective stimulants for muscle receptors, most of which are released together in damaged muscle.[40,41]

Figure 60-2.

Receptor molecules in the membrane of a nociceptive ending, which are important for muscle pain. Branch A: Receptor molecules that excite the ending by opening Na^+ channels. Three receptors are sensitive to H^+ ions: the transient receptor potential subtype V1 (TRPV1) and the acid-sensing ion channels (ASIC) 1 and 3. When H^+ binds to the receptor, an Na^+ channel opens, and positively charged ions (mainly Na^+) enter the cell. The purinergic receptor P2X3 binds adenosine triphosphate (ATP) that has a relatively high concentration in muscle cells. Branch B: Inflammation-induced change of the bradykinin receptor molecule. In intact tissue, bradykinin (BKN) excites or sensitizes the ending through the B2 receptor. In inflamed tissue, BKN acts on the B1 receptor. B1 is synthesized in the dorsal root ganglion (DRG), transported to the ending, and built in the membrane. BKN exerts its action by activating a G protein that regulates intracellular second messengers, such as protein kinase C (PKC). PKC increases the permeability of Na^+ channels and thus sensitizes the ending. Branch C: Receptors that mainly sensitize the ending. Prostaglandin E_2 (PGE_2) and serotonin (5-HT) increase the intracellular concentration of the second messengers cAMP and protein kinase A (PKA). PKA increases the permeability of the Na^+ channels and thus allows larger ion currents to enter the ending. This renders the ending more sensitive to external stimuli. The opioid receptor molecule inhibits the sensitization process. (Modified from Mense and Gerwin.[34] Mense S, Gerwin R. *Muscle Pain: Understanding the Mechanisms. 1st ed.* Heidelberg: Springer; 2010.)



Source: Zahid H. Bajwa, R. Joshua Wootton, Carol A. Warfield: *Principles and Practice of Pain Medicine*, 3rd Edition
www.accessanesthesiology.com

CAPSAICIN

Capsaicin, the active ingredient of chili peppers, is the specific stimulant for the transient receptor potential receptor subtype 1 (TRPV1), formerly called VR1.[42] The TRPV1 receptor is one of the most important molecules for the induction of pain; its endogenous ligands are H^+ ions. The receptor is also sensitive to heat. Acidity of the tissue increases this sensitivity. For instance, in tissue with an acidic pH, as occurs after strenuous exercise, the normal body temperature is sufficient for activating the receptor and causing pain.[43] With fever, stimulation of TRPV1 may explain the often accompanying total-body ache. In humans, muscle nociceptors were found that could be activated by injections of capsaicin,[44] indicating the presence of the TRPV1 receptor.

MECHANICAL STIMULI

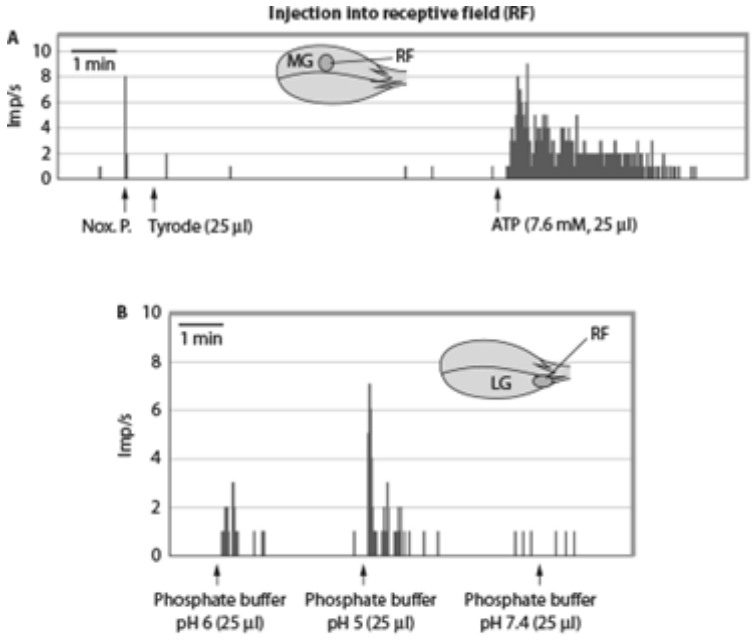
TRPV4 is a mechanoreceptor that is sensitive to both weak and strong (noxious) intensities of local pressure.[45] It may be the receptor for pain evoked by mechanical stimuli.

PROTONS (H^+)

Protons are a particularly important stimulus for muscle pain because almost all pathologic changes in muscle (e.g., exhausting exercise, ischemia, inflammation) are accompanied by a drop in tissue pH. In these conditions, the pH of the muscle tissue can drop to 5 to 6. Protons bind to acid-sensing ion channels (ASICs), with ASIC3 being particularly important for muscle pain,[46] reacting to small pH changes (e.g., pH 7.4–7.1).[47] Muscle nociceptors respond to pathophysiologic decreases in pH, with the magnitude of response depending on the degree of acidity (**Fig. 60-3**). Repeated intramuscular (IM) injections of acidic solutions have been reported to induce a long-lasting hyperalgesia.[48]

Figure 60-3.

Electrical activity of single muscle receptors tested with intramuscular injections of adenosine triphosphate (adenosine triphosphate [ATP]; A) and acidic solutions (B), respectively. The activity was recorded from the gastrocnemius-soleus (GS) nerve and transformed to time histograms by a computer. Both receptors also responded to noxious mechanical pressure (Nox.P; see left part of A); they probably were so-called polymodal nociceptors responding to all kinds of noxious stimuli. **A,** Response to ATP injected into the unit's mechanosensitive receptive field (RF) in the medial head of the GS muscle (MG). Note that ATP was injected at a concentration that exists in muscle cells and is released when these cells are damaged. Before the ATP injection, the solvent tyrode solution was injected as a control, without any effect. **B,** Stimulating effect of acidic buffer solutions on another muscle nociceptor. The ending was tested with intramuscular injections of buffer solutions, two acidic ones (pH 6 and 5) and one at a neutral pH (7.4). The unit responded with a larger response to pH 5 than to pH 6, the neutral solution had no effect. (Modified from Mense and Gerwin.[34] Mense S, Gerwin R. *Muscle Pain: Understanding the Mechanisms. 1st ed.* Heidelberg: Springer; 2010.)



ADENOSINE TRIPHOSPHATE

Adenosine triphosphate (ATP) binds to the purinergic P2X3 receptor.[49] ATP is present in every tissue cell and is released during trauma and other pathologic cell changes. Therefore, ATP has been considered a general signal substance for pain.[50] ATP is particularly important for muscle pain because it is present in muscle cells in high concentrations.[51] The ATP concentration released from a damaged muscle is sufficient to excite muscle nociceptors (see Fig. 60-3). When injected into human muscle, ATP causes pain.[52]

NERVE GROWTH FACTOR

The receptor molecule for NGF is the tyrosine kinase A (TrkA) receptor.[53] NGF has a sensitizing action on peripheral nociceptors and neurons in the CNS. It has a close relationship to muscle: it is synthesized in muscle, and its synthesis is increased during pathophysiologic changes of the muscle (e.g., inflammation).[54] NGF appears to be the only substance that excites nociceptors exclusively without influencing non-nociceptive free nerve endings.[32] However, the excitatory action of NGF is restricted to a special subset of nociceptors that have a strong sensitizing effect on spinal neurons (see later discussion).

BRADYKININ

Bradykinin is cleaved from plasma proteins when blood plasma moves from blood vessels into the interstitium. In intact tissue, BKN excites nerve endings by binding to the receptor molecule B2; however, in inflamed tissues, the receptor B1 is the predominant one.[55] Many of the pain-producing substances, including BKN, excite not only nociceptors but also low-threshold mechanosensitive free nerve endings. Therefore, BKN is not a specific excitant of nociceptors.

SEROTONIN

Serotonin (5-hydroxytryptamine, 5-HT) is released from blood platelets during blood clotting. The action of serotonin on nociceptors in the body periphery is predominantly mediated by the 5-HT_3 receptor. The serotonin concentrations usually released are likely to sensitize nociceptors rather than exciting them.

PROSTAGLANDIN E_2

Prostaglandins are released in a pathologically altered muscle by the action of cyclooxygenases. PGE_2 binds to the prostanoid receptor (EP2) in the membrane of the nociceptive ending. Similar to serotonin, PGE_2 may sensitize nociceptors without exciting them.[56]

GLUTAMATE

Evidence indicates that receptor molecules for glutamate (e.g., *N*-methyl-D-aspartate [NMDA] receptors) exist on nociceptive endings in masticatory muscles.[57] In female rats, the responses of group III/IV muscle receptors to glutamate were greater than in male rats.[58] Thus, gender differences are present even at the level of the nociceptor. The NMDA receptor has been reported to be a mediator of inflammatory pain.[59] Hypertonic NaCl may excite free nerve endings indirectly through glutamate released by Na^+.[60]

SUBSTANCES EXCITING MUSCLE NOCICEPTORS INDEPENDENT OF MEMBRANE RECEPTORS

Hypertonic Saline

Hypertonic NaCl solutions (4.5%–6.0%) are often used to elicit pain from muscles in humans[61] (for a review, see Graven-Nielsen[62]). Injections of the hypertonic solution elicit a medium level of pain in healthy control participants. The mechanism of the pain produced by hypertonic saline is still obscure. Two members of the TRP receptor family appear to be sensitive to osmotic stimuli, named TRPV4[45] and TRPA1.[63]

The different behavior of the various functional types of free nerve endings (nociceptors, mechanoreceptors, thermoreceptors) is probably due to the expression of special combinations of receptor molecules in their cell membrane.[64]

Potassium Ions (K^+)

K^+ ions can excite nociceptors directly by depolarizing the membrane potential to threshold. This stimulus was used in many studies in the beginning of experimental pain research[65] but is no longer common. Nevertheless, K^+ can be the cause of muscle pain when muscle cells are damaged and the intracellular K^+ ions are set free.

CLINICAL PHENOMENA ASSOCIATED WITH MUSCLE-GENERATED PAIN

Tenderness

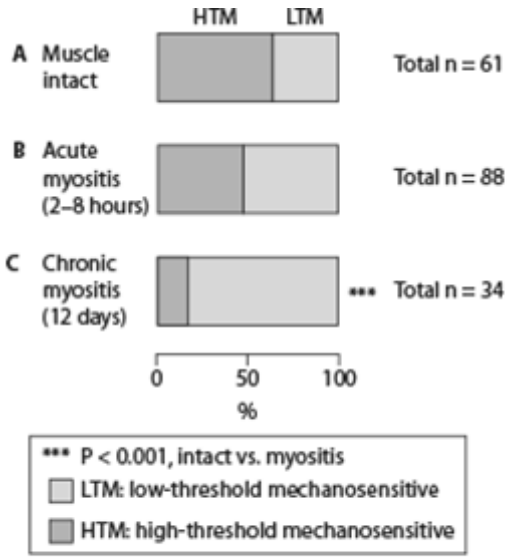
Pressure to muscles causing discomfort is the most obvious manifestation of common muscle pain. Such tenderness is found in acute muscle pain, for example, after blunt trauma or aggressive physical work or exercise. If additional provocations do not occur, the tenderness disappears.

Peripheral Sensitization

The reason for the tenderness is sensitization of the peripheral nociceptor by sensitizing inflammatory substances (the peripheral sensitization is, in most cases, combined with central sensitization; discussed later in the chapter). Many substances that are released from damaged muscle (e.g., BKN, PGE_2, NGF, tumor necrosis factor-α [TNF-α]) increase the mechanical sensitivity of nociceptors.[65,66] In intact tissue, a nociceptor has a high mechanical threshold, but when it is sensitized, it lowers its threshold into the innocuous range and is excited by everyday stimuli, such as weak muscle deformation. This transition from high- to low-threshold mechanosensitivity can be seen when an intact muscle is experimentally inflamed (**Fig. 60-4**). Some of the sensitizing effects are due to intermediate substances (e.g., TNF-α induces sensitization through the release of PGE_2).[67] Another example is the increased excitatory action of BKN after exposure to PGE_2 and serotonin.[56] A combination of BKN and 5-HT injected into the temporalis muscle in humans elicited stronger pain than that caused by each stimulant alone.[68]

Figure 60-4.

Myositis-induced change in mechanical responsiveness of mechanosensitive free nerve endings in muscle receptors in the gastrocnemius-soleus (GS) muscle of the rat. In **A** to **C**, the proportion of low-threshold mechanosensitive (LTM, mechanoreceptive) endings relative to high-threshold mechanosensitive (HTM, nociceptive) units is shown. **A,** In intact muscle, the proportion of HTM endings is close to 60%, and that of LTM units is 40%. **B,** In acutely inflamed muscle (2- to 8-hour duration), the proportion of HTM receptors was (nonsignificantly) decreased, presumably because of a beginning sensitization of the nociceptors. C, In chronically inflamed muscle, the proportion of HTM receptors had dropped to less than 20%, and that of LTM units was increased to more than 80%. Many of the LTM units in C must have been former HTM receptors that were sensitized and lowered their threshold into the innocuous range. (Modified from Mense and Gerwin.[34] Mense S, Gerwin R. *Muscle Pain: Understanding the Mechanisms. 1st ed*. Heidelberg: Springer; 2010.)



Central Sensitization

In the long run, every input from muscle nociceptors to the spinal cord probably sensitizes central nociceptive neurons. The central sensitization is associated with one or several of the following.

Appearance of New Receptive Fields

A receptive field (RF) of a central neuron is the body region from which the neuron can be excited or inhibited. In animal experiments, new RFs of a neuron can be induced by injecting a pain-producing agent into a muscle. For instance, a neuron that initially had a single high-threshold mechanosensitive RF in one muscle of the hindlimb acquired additional RFs in other muscles and tissues of that hindlimb.[69]

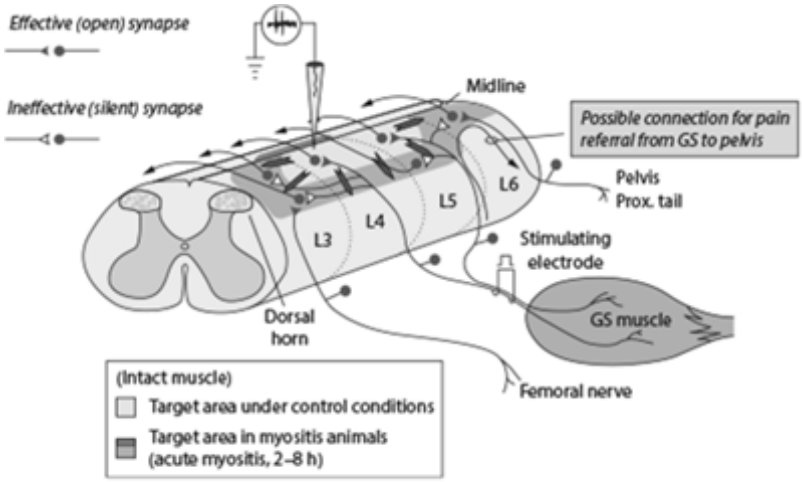
The appearance of new RFs is probably caused by the opening of formerly ineffective synapses on the neuron.[70] Probably, the newly induced RFs originally had ineffective synaptic connections with the neuron, but after painful stimulation of the muscle sensitized the neuron, these connections became effective.

This unmasking of synaptic connections represents pain-induced changes in the wiring of the dorsal horn. When an entire limb muscle is damaged, many spinal neurons acquire new RFs. The result is that the input from a given muscle excites more neurons in the spinal cord. Thus, the spinal target area in which input from the damaged muscle excites dorsal horn neurons expands. Such an effect can be induced by an experimental muscle inflammation in the rat (**Fig. 60-5**).[71] In these myositis animals, responses were obtained from neurons in the segment L3, where neurons do not normally respond to input from the inflamed GS muscle. The unmasking of ineffective synapses is partly due to neuromodulatory substances in the CNS (e.g., neuropeptides such as SP and CGRP or neurotrophins such as brain-derived neurotrophic factor).[72,73] When the central sensitization has become chronic, it is independent of further input from the damaged muscle.[48]

Figure 60-5.

Reorganization of the wiring in the spinal cord during an acute muscle inflammation. The figure shows the change in the target area of the gastrocnemius-soleus (GS) muscle nerve in the spinal cord. “Target area of a nerve” indicates the regions in the spinal cord where dorsal horn neurons can be excited by a standard electrical stimulus applied to the nerve. The dorsal horn neurons were searched in systematic microelectrode tracks in the

segments L3 to L6. Before induction of the myositis, neurons responding to electrical stimulation of the GS nerve were found only in the segments L5, L4, and caudal L3 (gray area). A few hours after induction of the myositis, the target area had expanded and included the entire segment L3 and L6. Apparently, the input from nociceptors in the inflamed GS muscle had opened formerly ineffective synaptic connections with the muscle in these segments. After expansion of the target area (right part of figure), there are effective synaptic connections between the GS muscle and neurons in L6, which supply the pelvic region. This newly opened connection may form the basis for the referral of pain from the GS muscle to the pelvic region. (Modified from Mense and Gerwin.[34] Mense S, Gerwin R. *Muscle Pain: Understanding the Mechanisms. 1st ed*. Heidelberg: Springer; 2010.)



The expansion of the spinal input area from a given muscle is the basis for the referral of muscle pain. When, for instance, rat neurons in the segment L6 are pathologically excited by input from the GS muscle (the normal target area of that muscle is L4 and L5), they send the signal “tissue-damaging stimulus in the pelvis” to higher centers because the neurons in L6 normally process input from the pelvis. Thus in humans, after opening of the formerly ineffective synaptic connections from the GS (triceps surae) muscle to the L5 and S1 segments, a patient may feel referred pain in the pelvis when the GS muscle is pathologically altered.

Central Sensitization by Subthreshold Potentials in Dorsal Horn Neurons

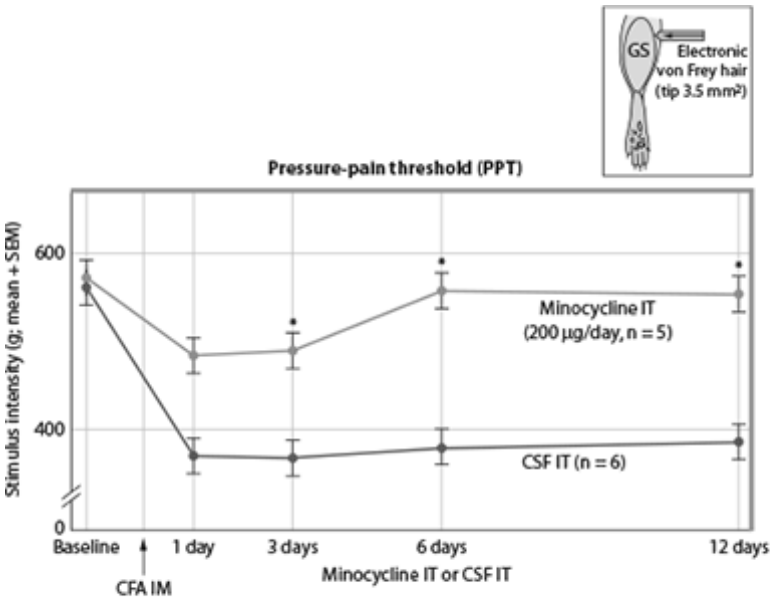
Many studies on central sensitization used high-frequency electrical stimulation (e.g., 100 Hz) to elicit the sensitization. However, one of the authors Mense has found that high-frequencies are not required for sensitization because in Mense's laboratory, in chronic pathophysiological muscle lesions, the afferent input does not reach mean frequencies exceeding 1 Hz. Recent data showed that even subthreshold synaptic potentials in dorsal horn neurons are sufficient to cause central sensitization. The subthreshold potentials were evoked by injection of NGF into the GS muscle. In single-fiber recordings, NGF was found to excite a large proportion of rat nociceptors,[32] but the animals did not show any immediate pain reactions. One day after IM injection of NGF, the rats exhibited a marked mechanical allodynia and hyperalgesia. Intracellular recordings from dorsal horn neurons in rats showed that NGF elicited mainly subthreshold synaptic potentials in dorsal horn neurons.[74] The NGF-induced central sensitization involved the activation of NMDA receptors because administration of ketamine (an NMDA antagonist) prevented the NGF-induced allodynia and hyperalgesia. Svensson and colleagues[75] likewise observed the combination of lack of immediate pain followed by allodynia when they injected NGF into the masseter muscle in humans.

Glial Cells and Central Sensitization

Approximately 90% of all cells in the CNS are glial cells, but only recently have they been systematically studied in pain mechanisms.[76] Glial cells can be activated by nociceptive input from muscle and, when activated, release substances that sensitize dorsal horn neurons.[73,77] Among the various types of glial cells, microglia appear to be a key factor in the pain-related behavior of rats in which a chronic muscle inflammation has been induced. When the microglial activation was prevented by intrathecal (IT) administration of minocycline, the myositis-induced allodynia (**Fig. 60-6**) and reduction of locomotor activity were largely normalized.[78]

Figure 60-6.

Effect of a microglia block on the myositis-induced reduction of the pressure-pain threshold (PPT). The PPT was determined by applying pressure to the gastrocnemius-soleus (GS) muscle with an electronic von Frey hair (inset in the upper right). The pressure was increased until a withdrawal reaction of the hindlimb occurred. The mean intensity of pressure that led to withdrawal was defined as PPT. Red line and data points, Animals in which a myositis had been induced by an intramuscular injection of complete Freund's adjuvant (CFA IM; upward arrow). The rats received artificial cerebrospinal fluid (CSF) but no microglia block (control). Blue line and data points, Myositis rats treated with intrathecal (IT) minocycline, a drug that blocks the activation of microglia cells. The drugs were administered continuously through an IT catheter connected to an implanted osmotic pump. Note that in the minocycline-treated animals, the PPT was largely normal 6 and 12 days after onset of the treatment, although the GS muscle was inflamed. Asterisks indicate statistically significant differences between untreated myositis animals and myositis animals treated with minocycline; $*P < 0.05$. (Modified after Chacur et al.[78])



In the clinical setting, it is difficult to distinguish between peripheral and central sensitization. The above animal data suggest that both forms of sensitization usually occur together. Therefore, when a patient presents with chronic muscle tenderness, often peripheral and central sensitization have already occurred.

Conditioned Pain Modulation

In contrast to CS, conditioned pain modulation (CPM; formerly known as diffuse noxious inhibitory control) is the phenomenon of one pain suppressing another pain. A painful stimulus can cause an increase in the threshold of spinal cord neurons outside the RF of the primary stimulus, which can result in decreased pain perception to a

second potentially painful stimulus.[79] CPM is mediated through a spinal-medullary spinal pathway but appears to be under cortical control.[80] Conceptually, a painful stimulus could be emotionally assessed for its potential harm and then be selectively inhibited. It has been demonstrated that CPM can be impaired in the presence of chronic pain,[81] such as osteoarthritis of the hip, and can be restored to normal after a hip replacement. An impaired CPM response has also been found in fibromyalgia,[82] chronic TTH,[83] and irritable bowel syndrome[84] but not in chronic LBP.[85]

Suboptimal CPM was found to be associated with an increased chance of developing chronic postthoracotomy pain.[86] Therefore, in the future, measurement of CPM could be found to be a useful factor in predicting persistent postprocedure pain.

Clinical Applications

Persistent tenderness occurs in muscles whose neurochemical and contractile apparatus is altered. Two common reasons for chronic muscle tenderness are TrPs and FMS (see later discussion). TrPs are tender nodules in the muscle and its attachments with altered neurochemistry that facilitates sensitization of muscle nociceptors. Sensitized nociceptors in the periphery stimulate nociceptive neurons in the dorsal horn and may cause central sensitization. Fibromyalgia, in contrast, is thought to be caused by an altered processing of nociceptive information in the CNS. One possible mechanism is a dysfunction in central pain-modulating pathways, resulting in lowered pain threshold to noxious stimuli with the associated phenomenon of tender points (TPs) in 11 of 18 areas. However, recent studies have shown the importance of peripheral pain generators in the genesis of FMS symptoms.[87]

Digital palpation is generally used to determine tenderness, but its use presents two major problems. First, varying amounts of pressure by the examiner diminish the reliability of the examination and contribute to poor interrater reliability. Use of pressure-recording devices may improve the accuracy of the amount of applied pressure necessary to elicit discomfort in the patient.[88–90] Structured training programs to teach palpation skills may increase interrater reliability in the identification of TPs and TrPs, but the results are inconsistent.[91] Second, palpation to elicit a subjective experience of pain is often performed on a sedentary muscle, but most functional muscle pain is experienced with activity rather than rest. Therefore, an examination of a resting muscle is likely to be less accurate in determining the muscle that is the source of the pain, frequently identifying a referred muscle pain, compared with an examination that is more consistent with a patient's experience, namely, muscle movement[92,93] causing pain (movement or muscle allodynia).

Pain During Contractions

Sensitized muscle nociceptors are excited at a lower than normal threshold, producing pain with everyday movement (muscle or mechanical allodynia), which is the usual clinical presentation of patients with painful muscles (vs. rest pain). Electrical stimulation has been reported to be more accurate than palpation in determining if a specific muscle is a source of regional pain.[92] Multiple mechanisms in the muscle and surrounding tissue contribute to the experience of pain. The entire muscle may be involved in pain production, not just TrPs, which are found in the muscle attachments as well as the muscle proper[94] (see later for a discussion of TrPs). Electrical stimulation of a muscle to induce contraction is thought to cause pain by two mechanisms. First is traction on the sensitized nociceptors in the entheses. As pointed out earlier, the peritendineum has been found to have a particularly dense innervation with free nerve endings, including nociceptive ones. A persistent pull at the entheses by a shortened or overloaded muscle or one harboring a TrP probably releases sensitizing substances (a mechanical tissue lesion is generally assumed to be associated with a sterile inflammation caused by sensitizing substances[73]). Second is deformation of the nociceptors in the muscle TrPs. Nociceptors in a TrP are likely to be sensitized because in the TrP, the concentration of sensitizing substances is high.[95] Because of their low mechanical threshold, sensitized nociceptors respond to light

deformation of the muscle. The evaluation assumes that if pain is produced by minimal physical contraction of the muscle along its entirety from origin to insertion and not in adjacent suspected muscles, it is the putative source of pain and a target of treatment.[94] In addition, if pain is produced initially but is gone with continued stimulation, it is assumed that the muscle in question is stiff or tense and would respond, as it just did to conservative measures, such as neuromuscular stimulation, to eliminate the cause of pain.

Restricted Range of Motion

Muscles that are painful during normal activities typically have diminished flexibility. Muscle flexibility is measured as a function of joint movement. Restrictions in motion can be the result of articular pathology (capsule, bone, ligaments, cartilage), nerve, or muscle–tendon dysfunction. In the absence of articular and nerve dysfunction as causes of pain, active range of motion assessment may reveal the possible source to be tension or stiffness in the related muscles. Other causes are painful alteration of the entheses by persistent muscle pull at the insertion zone or central inhibition of the α-motoneurons supplying the muscles (see discussion later in the chapter).

Simple tests that can be incorporated into the physical examination are, for the lower body, straight leg raising for hamstrings, finger to floor touch with knees locked for the low back and hamstrings, and assessment of the symmetry of the position of the right versus the left knee when one leg is crossed over the other to gauge the stiffness of the hip rotator muscles. For the upper body, tests include forward flexion and abduction of the extended arm and functional internal and external rotation of the shoulder by measuring asymmetry in touching the upper back from above and below (see Fig. 60-10). Findings of stiffness suggest muscle–tendon dysfunction; possible sources of current pain; and in some cases, predictors of pain in the course of physically demanding activity. For example, deficits in functional (scapular–humeral or scapular–thoracic) internal rotation in a patient with shoulder pain suggest that the examiner may find tenderness in the infraspinatus, teres major, or rhomboid muscles; increasing hamstring flexibility in army recruits appears to decrease the incidence of overuse lower extremity injuries;[96] and increased tightness in the hamstrings or quadriceps in elite athletes was associated with an increase in lower extremity muscle injuries.[97]

Weakness

Muscle weakness must be differentiated from neurogenic weakness associated with nerve compression or dysfunction. Painful muscles are frequently found to be weakened on muscle strength testing. It is assumed that the inability to perform a maximal contraction protects the “injured” muscle from further harm. Psychological distress also contributes to weakness.[98] The main mechanism underlying the weakness probably is the central inhibition of the α-motoneurons supplying the painful muscles. Because of impaired muscle coordination, weakness may result in damaged joints and thus form a source of additional pain. As early as 1984, Stokes and Young put forward a “vicious cycle” hypothesis of arthrogenous weakness describing reflex inhibition of muscles by joint input.[99] Elimination of the pain in the joint restores normal strength. Weakness over time may also be a function of endurance,[100] and rest in this case will restore strength.

Diminished muscle strength is typically assumed in clinical discussions of common pain syndromes such as LBP (i.e., core weakness), leading to the conclusion that core strengthening exercises would be helpful.[101] However, the construct validity and treatment protocols for core strengthening programs have been questioned.[102] Various nonspecific exercises have been associated with long-term improvement in patients with nonspecific low back pain (NSLBP).[103,104] The absence of subgroupings of patients[105] based on psychosocial variables and specific assessments for level of conditioning (strength and flexibility) may contribute to the failure to find any one exercise protocol superior to another. The muscle fasciae may also be a possible source of nociceptive stimuli resulting in NSLBP.[106]

The clinician will generally not have equipment to measure the strength of postural muscles. Norman J. Marcus uses the KW test, which is a simple means to test for minimal muscle strength and flexibility of key postural trunk muscles.[107] In a large uncontrolled study, elimination of the deficiencies was correlated with improvement in LBP.[108] This is in contrast to a February 2011 Cochrane review showing no relationship between a positive clinical outcome and the putative target of the exercise for chronic NSLBP.[109]

Spasm and Cramp

Involuntary long-lasting contraction of striated muscle accompanied by increased electromyography (EMG) activity is defined as spasm, which may or may not be associated with pain. Cramps are brief, self-limiting, and generally painful contractions of a muscle or muscle group, also accompanied by increased EMG activity.

Muscle spasm is often misunderstood because of (1) prior incorrect explanations of its pathophysiology and (2) other conditions that present clinical similarities to spasm. The classical understanding of the pain–spasm–pain cycle has been disproved. Although spasm, present for a long enough time, may result in muscle ischemia and pain, the pain does not in turn produce muscle contraction. On the contrary, painful muscles typically show diminished or absent EMG activity, but an antagonistic muscle typically shows increased EMG activity.[34] This phenomenon is thought to limit movement in an injured region to prevent further damage and facilitate healing.

The pain–spasm–pain concept states that the input from muscle nociceptors excites the homonymous α-motoneurons, causing a tonic (ischemic) contraction of the painful muscle. The ischemic contraction is painful and activates muscle nociceptors, which in turn excite the α-motorneurons.[110] However, in clinical experiments on myofascial LBP, the low back muscle activity was reduced in the phase associated with normally high EMG activity.[111] This finding speaks in favor of an inhibition, rather than activation, of homonymous α-motoneurons. γ-Motoneuron activity was likewise not facilitated during nociceptive input from muscle.[112] Thus, the pain–spasm–pain hypothesis is not supported by recent experimental findings and has to be considered a misconception.

To date, the pain-adaptation model of Lund and colleagues[113] has largely replaced the pain–spasm–pain vicious cycle. The model predicts decreased muscle activity in agonistic contraction phases and increased muscle activity in antagonistic phases of a painful muscle (i.e., contraction to inhibit motion). Collectively, the recent data show that a muscle spasm is not caused by a painful lesion in that muscle but by a lesion somewhere else. The true source of pain may be located in another muscle, a joint that is moved by the muscle, an inflamed nerve, or an internal organ, helping explain the frequent failure to obtain long-term benefit from injections into a muscle with painful spasm. The rigid abdomen that accompanies an inflamed appendix is an example of a spasm caused by a painful internal organ. The examiner has to find the original source of pain; otherwise, the treatment will not be successful.

Physical examination may detect a hardened, stiffened muscle. This may be the result of inappropriate muscle contraction (tension) or neurogenic involuntary muscle contraction (spasm), both associated with increased EMG activity. Tension may respond to a variety of biobehavioral approaches.[114–116] Hardened muscles may also be the result of increases in muscle tone or decreases in elasticity (from stiffness, contractures, or myofascial TrPs) that occur without accompanying increases in EMG activity, presenting a diagnostic and subsequently a treatment challenge. The absence of an animal model to study the various conditions associated with increases in muscle hardness and a testable pathophysiological mechanism further challenges our understanding and interferes in the development of effective treatment. A recent study suggests that an animal model may be possible for FMS.[117]

Because multiple overlapping mechanisms can contribute to spasm-like regional pain, it is understandable that a wide variety of pharmacologic interventions are thought to be possibly effective with as yet no demonstrated

superiority between classes of medication[118,119] and no clear evidence of effectiveness for injection and denervation procedures for back pain thought to be related to painful muscles.[120]

Cramps

Although cramps generally occur after age 60 years, they have also been observed in young exercisers.[121] In elderly adults, they most often occur at night and involve the lower extremities. Movement of the painful part generally quickly diminishes and then eliminates the cramp. Cramps may be the result of a variety of neurologic diseases, including amyotrophic lateral sclerosis.[122] The majority are from unknown causes but are thought to involve the spinal α-motoneuron, which appears to have a lowered electrical stimulation threshold frequency to produce cramping.[123] Two other possible mechanisms for the cramp pain are (1) not the whole muscle but only parts of it contract at the transition zone between cramping and inactive muscle parts (sheering forces may excite nociceptors), and (2) motor and nociceptive fibers are entrapped in the contracting muscle. The compressed motor fibers maintain the cramp, and the nociceptive fibers elicit pain.

Quinine has been the drug of choice for nonspecific cramping, but the U.S. Food and Drug Administration banned its use for anything but the treatment of malaria because of concerns about serious albeit nonfatal side effects. Comparisons of quinine with other possible treatments still favor quinine.[124] Nonpharmacologic treatments have not been found to be effective,[125] and a recent Cochrane review[126] opines that quinine is still the treatment of choice despite the chance of side effects.

Pain Affects Muscle Function and Patterns of Coordination

Painful muscles and joints affect our ability to perform tasks. Maximal effort, ability to sustain the effort, and coordinated movement are all detrimentally affected by pain. As a corollary, some physical activities can produce muscle pain.

Altered patterns of muscle activity may precede or follow the appearance of regional muscle pain (see later discussion). Patients have a decrease of the maximal voluntary contraction of a painful muscle and a variety of changes in the static (contraction without movement), resting, and dynamic activity level of regionally painful muscles compared with normal control participants. Exploring the mechanisms of these alterations may facilitate effective treatment.

Muscle activity may produce movement through a shortening muscle contraction (concentric contraction, e.g., quadriceps contraction going up stairs) or by a lengthening contraction (eccentric contraction, e.g., quadriceps contraction going down stairs). It is actually more demanding of our muscles to go down than upstairs. Prolonged eccentric contractions are often followed by delayed-onset muscle soreness (DOMS) with the pain peaking 1 or 2 days after the exercise.

When a painful muscle is activated, decreased activity in the agonist phase and increased activity in the antagonist phase occur.[113] Such changes reduce the ability of the muscle to produce maximum contractions. It also leads to recruitment of adjacent muscles to substitute for the reduced capacity of the muscle proper to the task. The changes in muscle activation may be adaptive to promote healing by minimizing the work of the painful muscle but may also lead to additional and ongoing pain by using muscles that are inappropriate for a task and creating suboptimal conditions for joint movement and stability.[127]

CHANGED PATTERN OF LOCOMOTION

IMPACT OF MUSCLE PAIN ON LOCOMOTION

The physiologic basis of the influence of muscle pain on locomotion is related to the synaptic connections between (nociceptive) group III and IV muscle afferents and the α-motoneurons in the ventral horn.[128,129] Normally, the activity in the many thousands of synapses on the surface of a single α-motoneuron is predominantly inhibitory, and as such, the motor unit supplied by the neuron is silent (i.e., a normal resting muscle has no EMG activity).

ELECTROMYOGRAPHIC ACTIVITY OF A RESTING PAINFUL MUSCLE

In patients with myofascial pain, both increased and unchanged resting EMG activities have been found. In fibromyalgia, Elert et al.[130] observed an increase in the resting EMG activity. The same finding was reported in temporomandibular pain,[131] neck pain,[132] and LBP.[133,134] DOMS can occur with EMG activity at rest[135] or without any EMG activity.[136,137]

Thus, the overall evidence for increased resting EMG activity in humans during muscle pain is weak. Rather, there is an inhibition of α-motoneurons, which is partly attributable to a facilitated homonymous recurrent inhibition during experimental muscle pain.[138]

However, in animal experiments on masticatory muscles, there was an increase in EMG activity during painful stimulation.[139] In these studies, the jaw-opening muscles showed the strongest activity. These findings cannot be transferred to limb muscles because the central wiring of the masticatory muscles differs from that of muscles supplied by spinal nerves. In the masticatory muscles, opening of the jaw is a protective pain reflex as is the reduced activity in painful limbs.

INFLUENCE OF MUSCLE PAIN ON STATIC CONTRACTIONS

During acute experimental muscle pain, the MVC is significantly lower than in control conditions.[140–142] Likewise, in localized clinical pain conditions such as lateral epicondylalgia, reduced MVC is also found in the sore arm.[143] In fibromyalgia, the reduction in strength is assumed to be caused by impaired central activation of motor units. In these patients, when the ulnar nerve is supramaximally stimulated, there is no reduced MVC of the adductor pollicis muscle.[144] In addition to reduced MVC, patients with muscle pain exhibit a decreased endurance during submaximal contractions.[145,146]

It is worth noting that during static contractions, muscle pain decreases not only the activity of the painful muscle but also that of synergistic muscles.[147,148] Because of the inhibition of the painful muscle, the required force can be achieved only by a changed muscle recruitment pattern and eventual overload of otherwise nonpainful muscles. Spinal motoneurons as well as motor cortex motoneurons may be inhibited by nociceptive input from muscle.[149]

MUSCLE PAIN AND DYNAMIC MUSCLE ACTIVITY

Experimental and clinical low back muscle pain influence muscle activity during gait. Such an influence was found in recordings of the activity of low back muscles on a treadmill. Muscle activity was increased in phases during which there is normally no EMG activity, and there was no or decreased activity in movement phases when pain-free subjects exhibited strong EMG activity.[150] Moreover, when pain is induced in the low back muscles, the feedforward response of the abdominal muscles is reduced. This effect may impair spinal stability.[151]

Muscle pain can also have a strong impact on joints, particularly in the legs. Gait analyses during experimental pain in the vastus medialis muscle showed that the pain resulted in impaired knee joint control and joint

instability during walking.[152] The impaired joint control may render the knee joint prone to injury and may perpetuate the chronicity of musculoskeletal pain.

FEAR THAT MOVEMENT WILL BE HARMFUL

Kinesiophobia, defined by Kori et al. as "an excessive, irrational, and debilitating fear of physical movement and activity resulting from a feeling of vulnerability to painful injury or re-injury,"[153] is a major impediment to recovery in patients with persistent pain.[154–156] Patients equate "hurt" with "harm" and avoid fear-producing activities.[157] This affects a patient's capacity to resume social activities after an injury[158] as well as the ability to maximally rehabilitate after surgeries.[159] It has been shown that in patients with negative beliefs about movement and exercise, even the thought of a specific movement can produce pain and swelling.[160]

POSTURE

Posture, defined as the position or bearing of the body, whether characteristic or assumed for a special purpose when deviating from a theoretically healthy stance, has been thought to be a result of and a contributing factor to muscle pain.[161–163] Experimentally induced pain in the muscles surrounding the knee alters postural stability and may be associated with an increased likelihood of falling.[164] Awkward postures are a factor in work-related back, neck, and temporomandibular joint pain.[165,166] Postural changes, such as those observed in patients with an "antalgic" gait, are minimized with programs encouraging movement and use of the painful part.[158,167,168] Based on assuming a relationship between posture and pain, it is surprising that a systematic review of adults and a longitudinal study of children and adolescents did not find any association between posture and the occurrence of LBP,[169,170] and reviews of workplace interventions to diminish neck pain found no evidence of effectiveness on neck pain or sickness absence.[171] Postural dysfunction appears to be related to multiple factors. Inactivity in adolescents was found to be associated with poor posture and the report of LBP.[172] LBP inhibits anticipatory muscle contractions mediated through the anterior cortex.[173,174] Psychosocial factors may be associated with the production of muscle tension patterns resulting in postural changes and pain.[83,175–178] Because no standard of care exists for the physical and psychological examination to describe the patient in pain, identify painful muscles, or provide an accepted exercise routine, it is not surprising that no clear evidence has yet emerged supporting the widespread use of specific interventions to promote healthy postures.

OCCUPATIONAL MUSCLE PAIN (CHRONIC WORK-RELATED MYALGIA, REPETITIVE STRAIN INJURY)

Work-related myalgias (WRMs) contribute to loss in productive work time. In a 2002 U.S. study of more than 20,000 workers, 13% experienced pain-related reduced productivity at an estimated value of $61 billion,[179] representing the largest category of work-related illness in the United States, the Nordic countries, and Japan and accounting for the largest number of work absences and disabilities in the United States, Canada, Finland, Sweden, and England.[180,181]

Physical factors include (1) high-intensity contractions to address jobs requiring high degrees of muscle strength; (2) continuous demands for output with minimal ability to rest, relax, and stretch fatigued muscles; (3) awkward posturing resulting in sustained muscle contraction; and (4) tasks requiring fine motor skills that rely on the coactivation of muscles to stabilize the extremity.[182] Psychological factors are related to both the cognitive demands of the job and the emotional experience working in a particular job setting, both contributing to psychosocial tension and stress and resulting in myalgia-related physiologic effects.

OVERLOAD RELATED TO JOB DEMANDS

STRENUOUS WORK

Overload, subjecting muscle fibers to forces beyond their capacity, can produce pain and damage. This typically occurs in physically demanding jobs in industries such as manufacturing, mining, and agriculture. The muscles of a worker with the strength to manage most job demands may become strained in the event of the need to lift a heavier than usual object or with an awkward movement. A worker is best protected by being able to lift as much as 100% more than is typically demanded by the job task. But muscle strength alone is not sufficient to protect against pain and injuries. In relationship to back pain, the concept that strengthening (core strengthening) certain weakened deep paraspinal muscles could diminish or eliminate back pain has been challenged.[102,183] Repetitive demands on strong muscles without sufficient recovery time can produce muscle fatigue, dysfunction, and pain.

MONOTONOUS WORK AT A LOW WORKLOAD

Workers who perform seemingly nonstrenuous activity may develop muscle pain. Jobs that require repetitious muscle movement in a small range may be associated with a higher incidence of muscle pain and spasm. Hägg[184] observed that all muscle fibers do not contract at the same time. Some fibers may be recruited, and others in the same muscle are quiescent. At a low workload, muscle contraction typically involves recruitment of the type Ia muscle fibers first,[185] and these fibers are also the last to be derecruited, thus overworking the Ia fibers and possibly producing fatigue, dysfunction, and pain. At the suggestion of a colleague Mats Bjurvald, Hägg named his theory the *Cinderella hypothesis*.

NONSPECIFIC LOW BACK PAIN

Nonspecific low back pain is the most costly chronic pain condition facing our health care system.[186] Despite advances in our understanding of pain mechanisms and various treatments, we remain challenged by patients with persistent back pain. The pain generator remains controversial, frequently chosen on the basis of clinician's specialty and mode of practice.[187,188] Because muscle and other soft tissue is presumed to frequently account for NSLBP, it is surprising that the evaluation and treatment of muscular causes of LBP are not addressed in the American or European guidelines.[189,190]

Of the wide variety of treatments commonly used, the most promising seem to be cognitive-behavioral interventions encouraging activity and exercise. Almost all other interventions have not demonstrated clear effectiveness when analyzed in rigorous, systematic reviews.[172,189–209] Of all the putative pain generators that might respond to exercise—remaining active, massage, and relaxation approaches—logic suggests that muscle is a major target of these interventions and thus a source of pain. However, translating the concept of muscle-related NSLBP to successful treatment interventions has been a challenge. Attempts to incorporate proper ergonomic principles to proactively address musculoskeletal disorders in the workplace have not been effective.[210] Even the consensus that remaining active and at work is beneficial for patients with NSLBP has not dissuaded most physicians from advising patients not to work.[211]

Exercise, defined as a “series of movements to promote good physical health,” allows almost any activity to be defined as an exercise protocol. Indeed, a systematic review has concluded that various nonspecific exercises have produced long-term results in patients with NSLBP.[212] However, idiosyncratic provision of exercise protocols without patient subclassification may confound outcome data and eliminate the possibility of meta-analyses. Systematic reviews of the effects of published exercise interventions[213,214] revealed that although most were statistically significant, many were not clinically meaningful.[9] A much needed head-to-head study is currently under way to compare the effects of two different exercise protocols.[215]

A suggested reason for the inability to show effectiveness in many exercise programs is the general absence of subgroups of patients[216] based on psychosocial variables and specific assessments for level of conditioning (strength and flexibility). Conversely, another hypothesis is that the effects of exercise are more related to central phenomena, such as improvement in coordination and reductions in kinesiophobia, than to any specific exercise effect.[217]

Nonspecific LBP is assumed to originate in the soft tissues of the low back such as muscles, ligaments, and fascia.[218] Back muscles are relatively well established as a source of NSLBP, for instance, when they harbor myofascial TrPs[219] (see discussion later in the chapter). In contrast, the fascia have attracted much less interest.

THE THORACOLUMBAR FASCIA AS A POSSIBLE CAUSE OF NONSPECIFIC LOW BACK PAIN

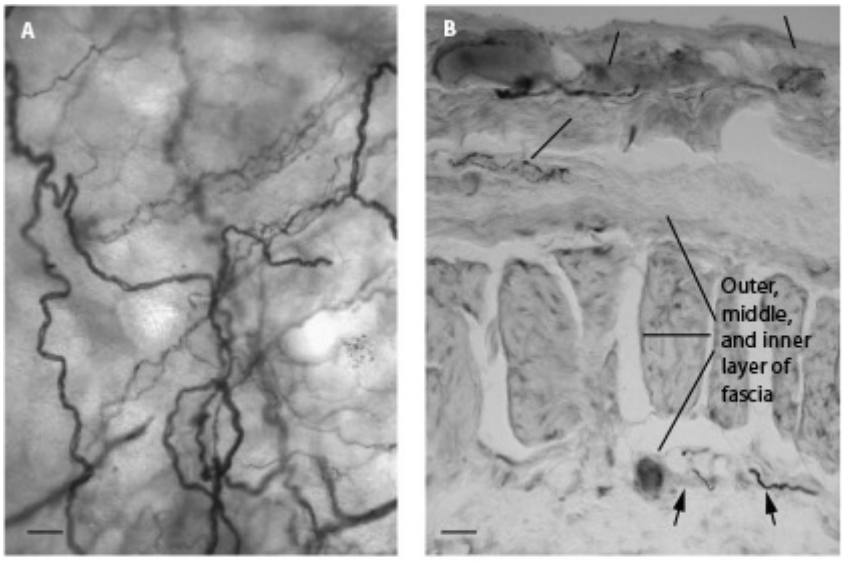
The thoracolumbar fascia (TLF) is the largest fascia of the low back and wraps the genuine back muscles with a posterior and anterior lamina. It thus forms a sheath around the muscles which reduces friction during movements. Its role in the biomechanics of the lumbar spine is well established. The TLF transfers loads among the arm, spine, pelvis, and lower limbs. Actually, it links the legs and arms crosswise; that is, it is part of a biomechanical chain between the fascia latae of the leg and the fascia of the contralateral latissimus dorsi muscle that attaches to the upper arm. Moreover, it is the insertion site for the broad abdominal muscles and thus further stabilizes the trunk. The TLF contains myofibroblasts and therefore has contractile properties.[220] It is a plastic structure and adjusts to altered tensions and forces that occur during long-lasting changes in posture and movement patterns.

FASCIA INNERVATION AND NEURONAL DATA PROCESSING OF INPUT FROM THE FASCIA

Little information is available about a possible sensory role of the TLF, particularly in NSLBP. If it really performs such a function, the TLF should have a dense innervation with sensory fibers, including nociceptors. However, the results of existing studies are inconsistent and partly contradictory. The group of Bednar and colleagues[221] did not find any sensory end organs in the TLF of patients with LBP and stated that in these patients, the fascia was “deficiently innervated.” In contrast, another group[222] demonstrated that the TLF is innervated. A recent study on the innervation of the fascia in rats and humans presented evidence for a possible contribution of the TLF to NSLBP.[223] The main histologic findings were that (1) the fascia is densely innervated (**Fig. 60-7**); (2) it exhibits SP-containing free nerve endings, which are assumed to be nociceptors; and (3) it has an abundant innervation with efferent sympathetic nerve endings, accounting for more than 30% of all nerve fibers of the fascia. The purpose of this dense innervation with sympathetic fibers is obscure. Because the thickest layer of the fascia is not supplied by blood vessels, these fibers are probably not vasoconstrictors. Possibly, the sympathetic fibers modulate pain sensations from the fascia[224] and may explain why some patients with NSLBP report that their pain is worse when they are under psychological stress.

Figure 60-7.

Innervation of the thoracolumbar fascia of the rat. **A,** Whole-mount preparation of the fascia at the level of the vertebral body L5. The figure shows a dense network of nerve fiber bundles and single fibers, many of which outlined blood vessels (upper half of panel). The fibers were stained with antibodies to protein gene product (PGP) 9.5, which stains all fibers irrespective of their function. **B,** Cross-section in the coronal plane through the fascia at the same level as panel A. The main layer of the fascia consists of massive collagen fiber bundles (cross-sectioned) that appear as bricklike structures in the figure. On both sides, thin layers of connective tissue connect these collagen bundles to the subcutaneous tissue and underlying muscle, respectively. Nerve fibers are mainly present in the subcutaneous tissue and in the layer between the fascia and muscle. A free nerve ending is visible in the upper left of the panel (open arrow). It has a granular structure because of many axonal expansions that contain neuropeptides. Filled arrows indicate small-diameter fibers of passage.

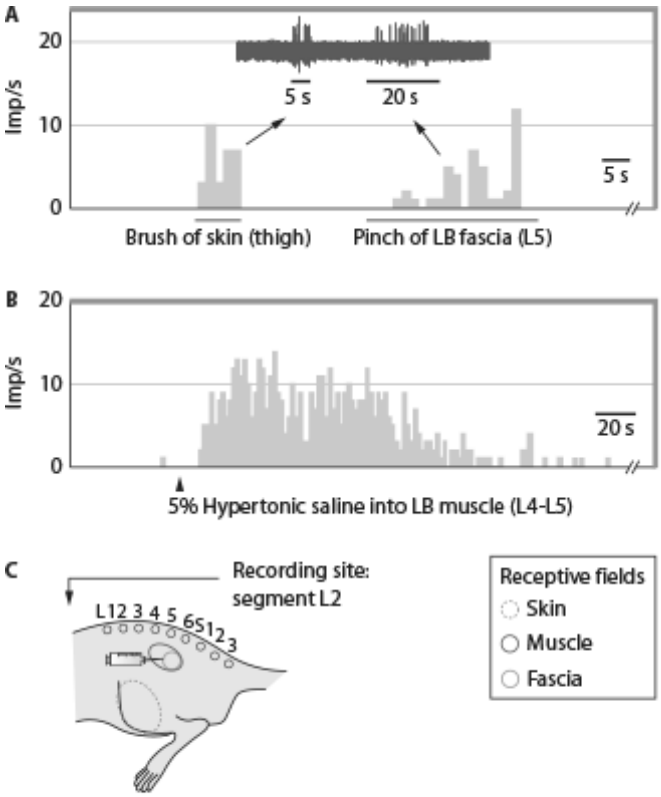


Sensory endings in fascia have been found in the iliolumbar ligament[225] and the fascia of the arm[226] in addition to the TLF.

In another study of the group of Siegfried Mense,[106] the electrical activity of spinal neurons processing input from sensory endings in the TLF was recorded. Most neurons had no exclusive input from the fascia but showed a marked input convergence from the multifidus muscle and the skin (**Fig. 60-8**). The input from most tissues was dominated by nociceptors; that is, the neurons were excited by painful stimulation of their RFs (pinching, squeezing, injections of hypertonic saline). The neurons behaved like typical wide-dynamic range (WDR) neurons, one of the nociceptive spinal cell types. The input convergence from many tissues and receptor types of the low back may explain why the subjective nature of NSLBP is usually described as diffuse. An interesting finding was that an experimental inflammation of the multifidus muscle increased not only the proportion of neurons responding to stimulation of the inflamed muscle but also the proportion of those neurons that responded to input from the fascia.[106] This finding suggests that the fascia becomes more sensitive even if the original pain source is located in the low back muscles.

Figure 60-8.

Electrical activity of a single dorsal horn neuron that had input from the thoracolumbar fascia and other tissues. Recording site: spinal segment L2. **A,** Response to brushing of the skin of the thigh and pinching of the fascia at the level of vertebra L5. LB, low back. **B,** Response to the injection of hypertonic saline (5%, 50 μL) into the erector spinae muscle at the level of vertebrae L4 to L5. The neuron also responded to weak deformation and noxious pressure of the same muscle (not shown). **C,** Approximate location and size of the receptive fields (RFs) of the neuron. Note the marked input convergence of this neuron from many tissues (fascia, skin, muscle) and receptor types (low-threshold mechanoreceptors and nociceptors). The neuron was dominated by input from nociceptors and behaved like a nociceptive wide-dynamic range (WDR) neuron. It may mediate pain from the soft tissues of the low back. (Modified after Taguchi et al.[106])



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Recent human data underpin a nociceptive role of fascia tissue. For instance, DOMS in the lower leg appears to be partly attributable to nociceptors in the fascia of the anterior tibial muscle.[227] In that study, the authors made systematic injections of a painful dose of hypertonic saline into the anterior tibial muscle and the overlying tissues after induction of DOMS in that muscle. When the hypertonic solution was injected directly underneath the fascia, it caused more pain than after injection into the muscle itself. These results show that the fascia of the human anterior tibial muscle is supplied with nociceptors and that these nociceptors are probably involved in DOMS.

PAIN CAUSED BY MYOFASCIAL TRIGGER POINTS

Trigger points are considered by many clinicians to be synonymous with myofascial pain syndrome and to account for most muscle pain, but others believe them to be nonsignificant epiphenomena.[228–231] TrPs are defined as palpable tender nodules in muscles that refer pain or discomfort to adjacent or distant muscles. Treatments are varied but usually involve needle placement (dry needling), the injection of one of a number of substances into the TrP, or both.

HISTORICAL PERSPECTIVE

Kellgren was the first to demonstrate muscle pain referral with his experiments with hypertonic saline,[232–234] but Travell and Simons described the typical patterns of referred pain from specific muscles.[235] Shah[236] has found biochemical alterations in the TrP that support the assumption that TrPs are a source of pain.

CURRENT HYPOTHESES OF TRIGGER POINT MORPHOLOGY AND FORMATION

Generally, the palpable myofascial TrP is assumed to consist of several contraction knots surrounded by normal muscle fibers.[237] A contraction knot is a localized (segmental) contraction of only part of an individual muscle

fiber. Actually, it is a contracture in the physiological sense (i.e., a contraction of a muscle fiber without electrical activation of the endplate). Therefore, a TrP is silent in the surface EMG. One of the few good histologic figures of a contraction knot was published long ago.[238] The knot was found in the gracile muscle of a dog; it was located in a palpable TrP. The typical histologic feature of the contraction knot was a close packing of the A bands within the contracted region so that no individual A bands can be recognized. In the region of the contraction knot, the affected muscle fibers are swollen and therefore probably compress the accompanying capillaries.

It is unknown if a human TrP exhibits the same features, but evidence points in that direction. One of the few systematic studies on the morphology of human TrPs was performed by Reitinger and colleagues.[239] The biopsy specimen were obtained from fresh cadavers that still exhibited palpable TrPs. Cross-sections showed large muscle fibers, which may have represented contraction knots. In electron microscopic sections, the I-band configuration was missing, which likewise indicates a contraction. The findings indicate that the cross-sectioned large muscle fibers were contracted and therefore had a greater diameter.

To date, there are no data on the TrP histology from living patients. Knowledge about the time course of TrP formation and morphologic differences between latent and active TrPs is completely missing. Large-scale open biopsies of TrPs would allow us to observe their evolution and help refine the understanding of the pathophysiological process. Therefore, the following considerations on the formation of a TrP, which are based on the minimally available scientific data, are largely hypothetical.

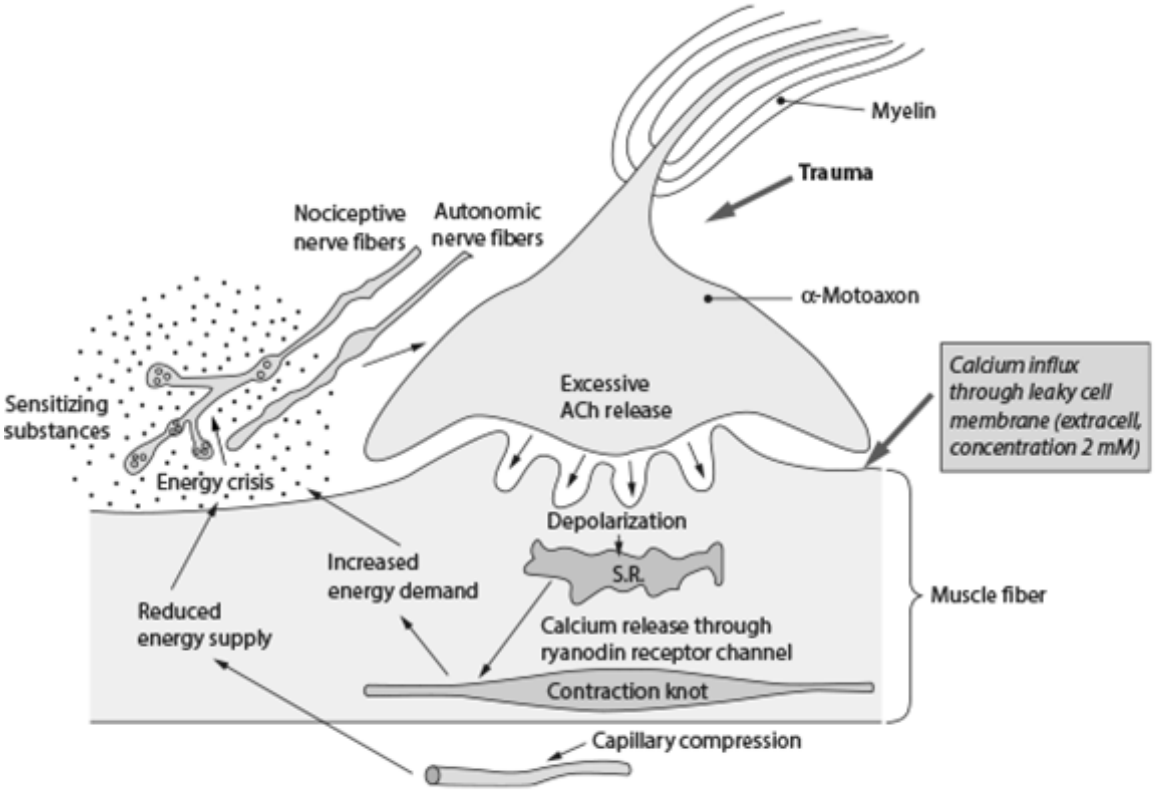
From clinical inspection, it appears that the first stage of TrP formation is the taut band, which often exhibits a latent TrP that exists without spontaneous pain but causes local, and sometimes referred, pain when mechanically stimulated. The next stage is the active TrP, which is spontaneously painful. Thus, there may be a sequence from the latent to the active TrP; that is, first there is a muscle lesion that does not cause pain, and then the active TrP develops.[240]

The integrated hypothesis of TrP formation was put forward by Simons[241] and later modified by Gerwin and colleagues.[242] The steps of this hypothesis are still not proven, but to date, there are no better hypotheses (**Fig. 60-9**). The formation of a TrP starts with trauma to the muscle, such as overuse, which mainly damages the endplate region of the neuromuscular junction. The damaged endplate releases excess amounts of acetylcholine (ACh), which release Ca^{++} from the sarcoplasmic reticulum and cause contraction knots in some of the muscle fibers underneath the endplate. The key factor of TrP formation and maintenance appears to be localized ischemia of the muscle, probably caused by capillary compression by the contraction knots. Ischemia is known to release BKN and other inflammatory agents and sensitize muscle nociceptors (see earlier discussion). This explains the pain and tenderness of the TrP. Using a microdialysis needle, Shah[238] has measured the concentration of inflammatory substances and H^+ ions in active and latent TrP and found significantly higher concentrations for most of these agents in active TrPs. The ischemia in the TrP is also important for maintaining the contracture because ischemia results in diminished production of ATP, which is necessary for the relaxation of the myosin and actin filaments.

Figure 60-9.

Integrated hypothesis of trigger point formation by Simons. The hypothesis assumes that a muscle lesion (e.g., overuse) mainly damages the presynaptic portion of the neuromuscular endplate. The result is an excessive release of acetylcholine (ACh), which causes a depolarization of the postsynaptic muscle cell membrane. This leads to the release of calcium ions from the sarcoplasmic reticulum (SR). The calcium ions produce a local contracture (the contraction knot) underneath the endplate. The contraction knot compresses capillaries, and the resulting ischemia together with an increased energy demand by the contraction knot causes an “energy crisis” associated with the release of inflammatory substances that sensitize nociceptors. This is the reason for the tenderness of a trigger point. The ACh release is under the control of autonomic (sympathetic) nerve fibers. The red arrow at the right indicates a speculative alternative mechanism for the formation of the contraction knot,

namely, the influx of calcium ions from the interstitial space through lesion-induced leaks in the muscle cell membrane. The interstitial calcium concentration is more than 100 times higher than that needed for the sliding of the myosin and actin filaments. (Modified after Simons and Travell.[93])



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There are also ways of releasing Ca^{++} from the intracellular sarcoplasmic reticulum independent of the neuromuscular junction: (1) dysfunctional ryanodine receptor calcium channels that control the release of Ca^{++} from the sarcoplasmic reticulum into the sarcoplasm[243,244] or (2) damage to the muscle cell, which produces small leaks in the membrane. Rhabdomyolysis after strenuous exercise has been described in the literature,[245] and it is conceivable that overuse of a muscle or part of a muscle damages its cell. Small leaks in the cell membrane would allow Ca^{++} ions to enter the cell and cause sliding of the actin and myosin filaments underneath the leaky membrane. The basis of these considerations is that in the interstitial fluid around the muscle cell, the Ca^{++} concentration is approximately 2 mM, but 0.01 mM is sufficient (see Fig. 60-9) for filament sliding to occur. It has to be emphasized that these hypothetical mechanisms have not yet been tested.

Even in healthy normal control participants, the region of the endplate has been found to be particularly sensitive to painful stimuli.[246] This finding suggests a high density of nociceptors in that region and may explain—besides the location of the contraction knots underneath the endplate—why in many muscles, TrP pain is worst in the endplate region.

Even with an enhanced understanding of TrP pathophysiology, clinicians' ability to identify TrPs is inconsistent.[247–252] Although the interrater reliability increases significantly with experienced versus novice clinicians, the experts' intrarater reliability curiously diminishes with repeated assessments.[253] Multiple criteria have been proposed to identify TrPs with palpation, such as finding a taut band, local tenderness, patient pain recognition, pain referral, a local twitch response, and a jump sign. In addition to not being applied uniformly across studies, the interrater identification of the criteria has proved to be generally unreliable.[254] Further confounding the accurate identification of muscles harboring TrPs, Simons noted that TrPs also exist at the

muscle attachment sites,[255] but the usual examination for TrPs is solely in the muscle tissue, resulting in overlooking sources of pain and targets for treatment.[94]

Various treatment protocols have been suggested to treat TrPs, including manual techniques, physical therapy modalities, and injections.[237] Trigger point injections (TPIs) are done with a variety of injectates or with none (dry needling). Use of local anesthetics versus dry needling is reasonable because it results in diminished postinjection pain.[256] Although all local anesthetics have been shown to be myotoxic (most profoundly with bupivacaine and chloroprocaine), they do not affect satellite cells. Damaged cells rarely produce clinically significant effects and generally regenerate in 4 to 6 weeks.[257,258] The cell damage from the injectate (and needling) may actually enhance the treatment effect through the elimination of dysfunctional fibers and by allowing the regeneration of normal fibrils. Although some studies suggest that there may be sustained benefit in the treatment of LBP with use of botulinum toxin or corticosteroids, systematic reviews[201,208] cannot support or reject their use. In a Cochrane review of neck pain,[259] botulinum toxin was found to be no better than saline. Considering the cost and potential risks, the routine use of botulinum toxin or corticosteroids for TrPs does not appear to be justified.

It is not surprising that with lack of agreement on criteria for diagnosis, poor interrater reliability to find TrPs, varied treatments, and the absence of any consistent postinjection protocol,[260] the outcomes for the treatment of TrPs do not rise to the level of evidence in the treatment of NSLBP (with or without sciatica).[261] To validate current approaches to assess and treat TrPs, head-to-head studies of competing methods to evaluate and treat muscle pain must be done to establish the most effective standard of care for identification of tender areas of muscles, injection techniques, injectates and their dosages, and postinjection protocols.

Two technologies to image muscles thought to harbor taut bands and TrPs have been suggested as possible means to more objectively identify the presence of pain-generating structures. Magnetic resonance elastography (MRE) allows visualization and identification of tissues with varied elasticity and has been shown to be capable of identifying taut bands that have diminished elasticity compared with normal muscle tissue. MRE appears to offer greater reliability than palpation in identifying taut bands.[262] Visualization of TrPs is more elusive, but recent studies have demonstrated the use of ultrasound in identifying TrPs.[263,264] Both of these techniques may help objectify the identification of taut bands and TrPs but have not yet been clinically tested to determine if they will improve the effectiveness of treatment for muscle pain.

Muscle pain is complicated. It is found as a sole source of common pain presentations and occurs as a result of painful phenomena in other tissue. More attention to the presence of muscle pain will facilitate refinement of our understanding of the initiation and perpetuation of common pain syndromes. It should therefore be included in our routine pain assessments and treatments. Absent a consensus opinion for addressing functional muscle pain, the below plan that incorporates many of the variables necessary to manage muscle pain is suggested by Norman J. Marcus.

Any patients with persistent pain should undergo a thorough examination of all muscles that could possibly contribute to the pain complaint.

A. Distinguish injectable muscle pain from pain related to tension, deficiency (weakness, stiffness, or both), and spasm. The KW test for strength and flexibility of key postural muscles for LBP and lower extremity pain identifies patients who are deconditioned (decreased strength and flexibility of postural muscles). Standard tests of upper body strength, along with assessment of forward elevation, abduction of the arm, and functional internal and external rotation of the shoulder (scapulohumeral and scapulothoracic motion) may find asymmetries of motion in the shoulder girdles, suggesting which muscle(s) may be involved (**Fig. 60-10**).

B. Attempt to identify primary versus referred muscle pain. (Identification through muscle stimulation appears to be more accurate than palpation.[265])

C. Use a standardized exercise program to correct muscle deficiencies. Norman J. Marcus provides the Kraus exercises: 8 for the upper body and 21 for the lower body.[266]

D. Suggest conditioning exercises (i.e., all patients, if possible, gradually increase their daily walking up to 2 to 3 miles each day).

E. Marcus identifies a specific muscle as a pain source rather than a TrP, and calls the identified muscle "Muscle Pain Amenable to Injection (MPAI)" and the muscle injection is called "Muscle-Tendon Injection (MTI)" rather than a TPI. When injecting a specific muscle, pay particular attention to the entheses of the identified muscle rather than just TrPs and taut bands. Consider injecting only one muscle during a given injection session (**Fig. 60-11**).

F. If you use an injection procedure (MTI) that targets the entire muscle, 3 days of a postinjection physical therapy protocol will minimize postinjection soreness and stiffness.[267]

G. If more than one MPAI is identified and multiple treatments are planned, reassess the patient for continued presence of MPAI before injecting the next planned muscle. It is possible that changes may have taken place as a result of successful injections. These changes may be related to diminished central sensitization, resulting in the next muscle no longer being painful to manual or electrical stimulation or conversely the ability to discern a new muscle as painful after the previous, most severely painful muscle was successfully treated.

Figure 60-10.

Assessment of shoulder functional (scapulohumeral and scapulothoracic) internal and external rotation. Compare the points of maximal excursion of the two hands reaching over the shoulder and down the back for external rotation and from below up toward the scapula for internal rotation. The differences represent the relative deficits.

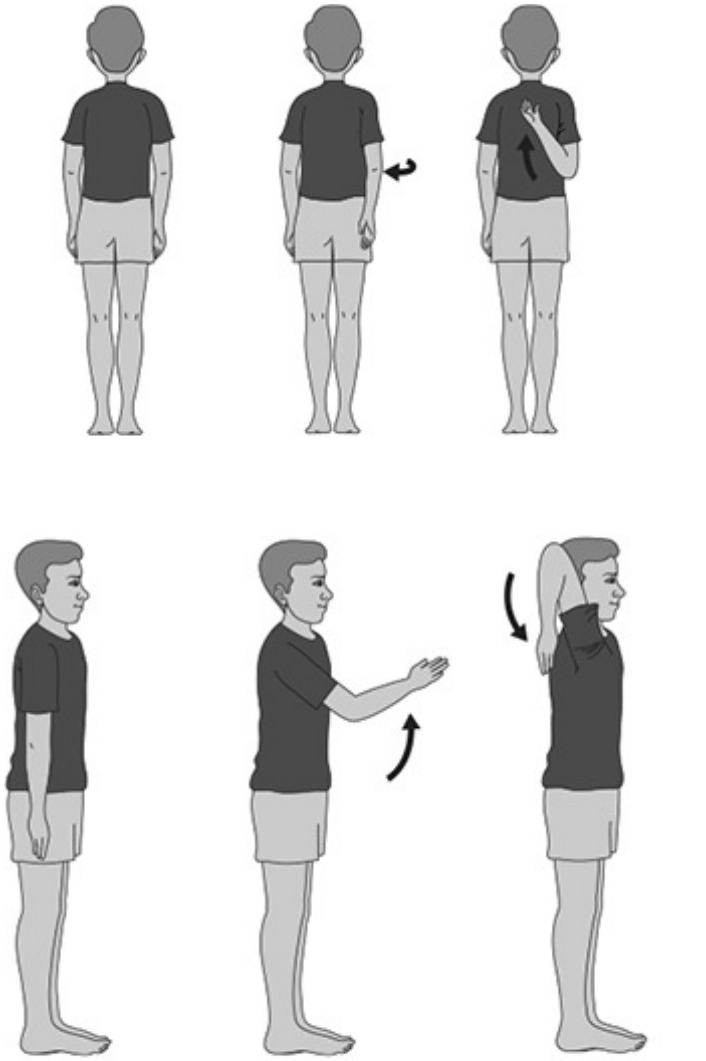
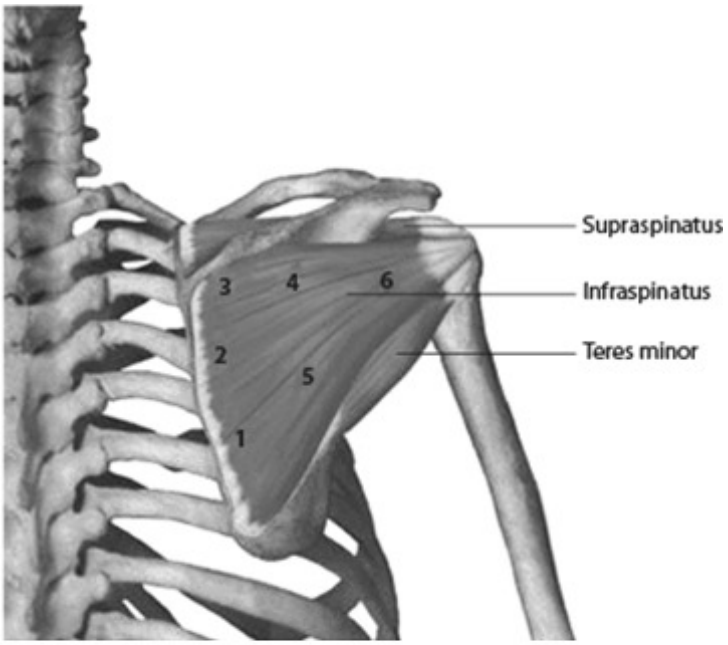


Figure 60-11.

The numbers represent the suggested sequence of muscle tendon injections into the infraspinatus muscle.



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