

REVIEW ARTICLE

Muscle Pain: Mechanisms and Clinical Significance

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SUMMARY

Introduction: Muscle pain is common, but the understanding of its causes is still patchy. This article addresses the mechanisms of some important types of muscle pain.

Methods: Selective literature review, predominantly of data derived from neuroanatomical and electrophysiological experiments on anesthetized rats.

Results: Muscle pain is evoked by specialized nerve endings (nociceptors). Important stimuli for muscle pain are adenosintriphosphate (ATP) and a low tissue pH. Excitation of muscle nociceptors leads to hyperexcitability of spinal sensory neurones (central sensitization). Low frequency activity in muscle nociceptors is sufficient to induce central sensitization.

Discussion: Central sensitization leads to increased excitation in the spinal cord and to referral of muscle pain. The motoneurons of a painful muscle are centrally inhibited. Muscular spasm is mostly secondary to a painful lesion in another muscle or joint. The pain of fibromyalgia is assumed to relate to a dysfunction of central nociceptive processing. Psychosocial factors also contribute to pain.

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Key words: muscle pain, nociceptor, sensitization, myofascial trigger point, muscle spasm, fibromyalgia

Muscle pain is a major medical problem: in , the majority (60% to 85%) of the population has had (nonspecific) back pain of muscular origin at some time or other (lifetime prevalence) (1). Pain evoked by myofascial trigger points has a point prevalence of approximately 30% (2). More than 7% of all women aged 70 to 80 years suffer from the fibromyalgia syndrome (e1). In an Italian study, musculoskeletal pain was found to be the most common reason that patients consulted a doctor (3). Thus, treating physicians should be aware of the mechanisms of muscle pain, insofar as they are currently understood.

This article provides an overview of the more common types of muscle pain. It is not intended as a comprehensive guide to all that is known about muscle pain, including both basic research and clinical aspects. Psychosocial factors, in particular, are not discussed here, even though they often play an important role in chronic pain. Because most of the results discussed here were obtained in animal experiments, one must be cautious in assuming that they apply to human beings as well. Nevertheless, experience has shown that the pain mechanisms revealed by basic research fit in well with the corresponding clinical observations. Thus, we will draw a number of explicit parallels between experimental findings and clinical symptoms, even though these parallels will not be entirely free of speculative content. Only a small number of therapeutic recommendations can be made on the basis of the available data. The main purpose of this article is to deepen physicians' knowledge of the anatomical and physiological processes underlying muscle pain.

Muscle pain versus cutaneous pain

The scientific understanding of pain has changed. "Pain" is no longer a unitary entity; rather, there are different types of pain that come about through different mechanisms, and that accordingly must be treated in different ways.

Muscle pain differs in many ways from pain in the skin or viscera. These differences concern not just the underlying mechanisms, but also a number of subjective features. The main subjective differences between muscle pain and cutaneous pain are listed in the *table*. One example is that pain arising in muscle tends to be referred pain more often than does pain arising in the skin. Objective differences are found at all levels of the nervous system. Thus, one cannot simply assume that the mechanisms of cutaneous pain are shared by muscle pain.

Peripheral mechanisms

Muscle pain is produced by the activation of specific receptors (so-called nociceptors): these receptors are specialized for the detection of stimuli that are objectively capable of damaging tissue and that are subjectively perceived as painful. They consist of free nerve endings and are connected to the central nervous system (CNS) by way of unmyelinated (group IV) or thinly myelinated (group III) fibers. They can be sensitized and activated by strong mechanical stimuli, such as trauma or mechanical overloading, as well as by endogenous inflammatory mediators including bradykinin (BK), serotonin, and prostaglandin E2 (PGE2).

Two activating chemical substances are particularly important for the generation of muscle pain: adenosine triphosphate (ATP) and protons (H⁺ ions). These chemical irritants activate nerve endings by binding to receptor molecules located in the membrane of the nerve ending. ATP activates muscle nociceptors mainly by binding to the P2X3 receptor molecule, H⁺ mainly by binding to the receptor molecules TRPV1 (transient receptor potential vanilloid 1) and ASICs (acid-sensing ion channels) (4). These receptor molecules are channel proteins that span the membrane of the nerve ending and mainly permit Na⁺ ions to enter the neuron. These Na⁺ ions then induce neural excitation.

ATP is found in all cells of the body and is released whenever bodily tissues of any type are injured. Rat muscle nociceptors can be activated by the injection of ATP in a concentration corresponding to that found in muscle cells (5) (figure 1). Weakly acidic solutions (pH 6 to 5) are also effective activators of muscle nociceptors (6). A drop in pH is probably one of the main activators of peripheral nociceptors, as many painful disturbances of muscle are associated with low pH in muscle tissue. Nerve growth factor (NGF) also has a connection to muscle pain: NGF is synthesized in muscle and activates muscle nociceptors (e2). NGF synthesis is increased when a muscle is inflamed (e3).

Muscle nociceptors contain neuropeptides, including substance P (SP) and calcitonin-gene-related peptide (CGRP). These peptides are released when nerve endings are activated and induce local edema by dilating the local blood vessels and increasing their permeability. Thus, a nociceptor can alter the microcirculation in its immediate neighborhood by releasing neuropeptides. Endogenous substances such as BK and E2 prostaglandins are released by muscle lesions of all kinds. BK is synthesized from plasma proteins by the action of the enzyme kallikrein, while prostaglandins are synthesized from arachidonic acid by the action of cyclooxygenase. These two activating substances increase the sensitivity of nociceptors to external stimuli (peripheral sensitization).

Clinical significance

Because ATP is released in any kind of tissue injury, it can be considered a universal pain-inducing substance (7). ATP is found in particularly high concentration in muscle cells; it can cause pain in muscle trauma (e.g., a

bruise or tear of muscle fibers) as well as in other types of pathological change in muscle (e.g., necrotizing myositis) (e4).

Acidic tissue pH is one of the main activating factors leading to muscle pain. Practically all pathological and pathophysiological changes of skeletal muscle are accompanied by a drop in pH, among them

- chronic ischemic states,
- tonic contractions or spasms,
- myofascial trigger points,
- (occupationally induced) postural abnormalities, and
- myositides.

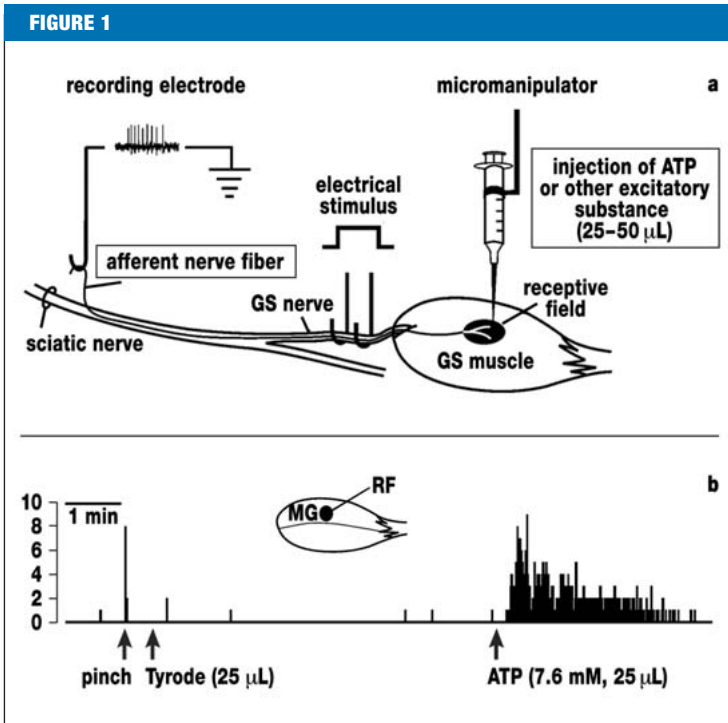
TABLE

Subjective differences between muscle pain and cutaneous pain

Muscle pain	Cutaneous pain
Electrical nerve stimulation induces only one pain	Electrical nerve stimulation induces a first pain and a second pain
Poorly localizable	Well-localized
Tearing, cramping, pressing quality	Stabbing, burning, cutting quality
Marked tendency toward referral of pain	No tendency toward referral of pain
Affective aspect: difficult to tolerate	Affective aspect: easier to tolerate

The neuropeptides stored in muscle nociceptors are released not only when peripheral stimuli activate the nerve endings, but also when spinal nerves are compressed. In this type of neuropathic pain, action potentials are generated at the site of compression and spread not only centripetally, i.e., toward the central nervous system, but also centrifugally, i.e., toward the nociceptive endings, where they induce the release of vasoactive neuropeptides. In this way, neurogenic inflammation comes about, characterized by hyperemia, edema, and the release of inflammatory mediators (8). The inflammatory mediators sensitize the muscle nociceptors and thereby increase neuropathic pain.

The sensitization of the muscle nociceptors by endogenous mediators such as BK and PGE2 is one of the reasons why patients with muscle lesions suffer from tenderness to pressure on the muscle, and from pain on movement or exercise. It is also the reason why many types of muscle pain respond well to the administration of non-steroidal anti-inflammatory drugs (NSAID), which block prostaglandin synthesis. Sensitization manifests itself clinically in two closely related phenomena: stimuli that normally do not cause pain are perceived as painful (allodynia), while stimuli that are normally painful cause more severe pain than before (hyperalgesia). The principal mechanism for allodynia and hyperalgesia, however, is thought to be located in the central nervous system.



The activation of a single muscle nociceptor by adenosine triphosphate (ATP). a) The impulse-firing activity of single nociceptors was recorded from sciatic nerve filaments in anesthetized rats. The gastrocnemius-soleus (GS) muscle was dissected free, the receptive nerve ending was localized within it with mechanical stimuli, and the excitatory substance was injected in the vicinity of the nerve ending. b) The nociceptive ending was found in the medial head of the gastrocnemius muscle (MG; black spot). The injection of the solvent Tyrode (control substance) had no effect, but the injection of a 7.6 mM solution of ATP induced activity lasting for minutes (modified after [5]). RF, receptive field.

In general, physicians should become more aware of possible muscular causes for symptoms affecting the musculoskeletal system, e.g., back pain.

Central nervous mechanisms

Mechanisms of chronification

An influx of nervous impulses from muscle nociceptors into the spinal cord increases the excitability of posterior horn neurons to a greater extent than one from cutaneous nociceptors (9). Persistent muscle nociceptor activation in experimental myositis in rats leads within a few hours to an increase in the number of neurons that can be activated by impulses coming from muscle (10) (figure 2). This spread of excitation is due in part to an overexcitability of the sensory neurons of the spinal cord, which, in turn, is brought about by the effect of glutamate on NMDA (N-methyl-D-aspartate) receptors and of substance P on NK1 (neurokinin 1) receptors in the membranes of the spinal neurons (central sensitization).

Two main mechanisms underlie the overexcitability of spinal nociceptive neurons:

A structural change of ion channels, rendering them more permeable to Na⁺ and Ca²⁺, is the short-term result of an influx of nociceptive impulses into the spinal cord. Among other effects, this causes originally

ineffective ("silent" or "dormant") synapses to become effective. A silent synapse cannot generate an action potential in the postsynaptic neuron; at most, synaptic activity in it leads to only a small excitatory postsynaptic potential. One of the mechanisms by which silent synapses become functional is an upward shift in the membrane potential of the postsynaptic cell that is brought about by a steady stream of action potentials impinging on it. This persistent depolarization activates intracellular enzymes, which, in turn, increase the permeability of the ion channels. The result is that sub-threshold potentials become larger and exceed the excitation threshold. This process can generate new functional connections in the CNS. Because the membrane potential of the depolarized cell is near its excitation threshold, the cell is overexcitable and can become activated – producing pain – even in response to a weak stimulus.

A change of gene transcription in the neuronal nucleus, leading to a modification of synthetic processes, causes new ion channels to be synthesized and incorporated into the nerve cell membrane. The long-term result of central sensitization is a nociceptive cell whose membrane contains a higher density of ion channels that are also more permeable to ions. This explains the hyperexcitability of the cell. Glial cells, too, particularly microglia, can contribute to the sensitization of central neurons by secreting substances such as tumor necrosis factor α (TNF-α) (8).

It was once thought that posterior horn neurons could only be sensitized by high-frequency activation. This is not so: action potentials, or even subthreshold postsynaptic potentials, at low frequency can still suffice to make posterior horn cells overexcitable (11, 12).

Clinical significance

Tenderness to pressure and pain on movement or exercise. The overexcitability of nociceptive neurons in the CNS is considered the main cause of allodynia and hyperalgesia in patients with chronic muscle pain. The persistent depolarization of the sensitized cells has recently become the target of medications that open potassium channels and thus remove positive charge from the cell (e5). In this way, the membrane potential becomes increasingly negative, and thus further away from the neuron's excitatory threshold.

The increased excitability of spinal neurons and the spread of excitation within the CNS are the first steps in the process of chronification of muscle pain. The endpoint of chronification consists of structural remodeling processes in the CNS that open up new pathways for nociceptive information and cause pain to persist over the long term. Patients with chronic muscle pain are difficult to treat, because the functional and structural changes in the CNS need time to regress. The fact that not all muscle pain becomes chronic implies that chronification requires not only the mechanisms just discussed, but also other ones, e.g., a genetic predisposition.

Referred pain arising in muscle. Pain arising in muscle is more likely to be referred pain than pain arising

in the skin. Referred pain is pain that is felt not (only) at its site of origin, but at another site some distance away. A possible mechanism of referred pain is the spread, within the spinal cord, of excitation due to the muscle lesion (9) (figures 2 and 3). As soon as the excitation reaches sensory posterior horn neurons that innervate an area beyond the site of the original muscle lesion, the patient feels referred pain in that area, even though none of the nociceptors in it are activated (13).

An example is shown in figure 3: a stimulus delivered to the myofascial trigger point (MTrP) in the soleus muscle causes only mild local pain, while the patient feels more severe (referred) pain in the sacroiliac joint. No conclusive answers are yet available to the questions of why muscle pain is more likely than cutaneous pain to be referred, why it is usually not referred to both proximal and distal sites, and why pain referral is often discontinuous. There is, however, a well-known discontinuity of spinal topography between the C4 and T2 dermatomes.

Changes of muscle tone as a cause of pain

Muscle spasm can be defined as persistent, involuntary muscle contraction (not including spasticity, a phenomenon of central nervous origin). The main reason why pain arises in muscle spasm is muscle ischemia, which leads to a drop in pH and the release of pain-producing substances such as bradykinin, ATP, and H⁺.

The vicious-circle concept of muscle spasm – muscle pain causes spasm, which causes more pain, etc. – should now be considered obsolete. Most studies have shown that muscle pain lowers the excitability of the α -motor neurons innervating the painful muscle (14) (a "pain adaptation" model) (15).

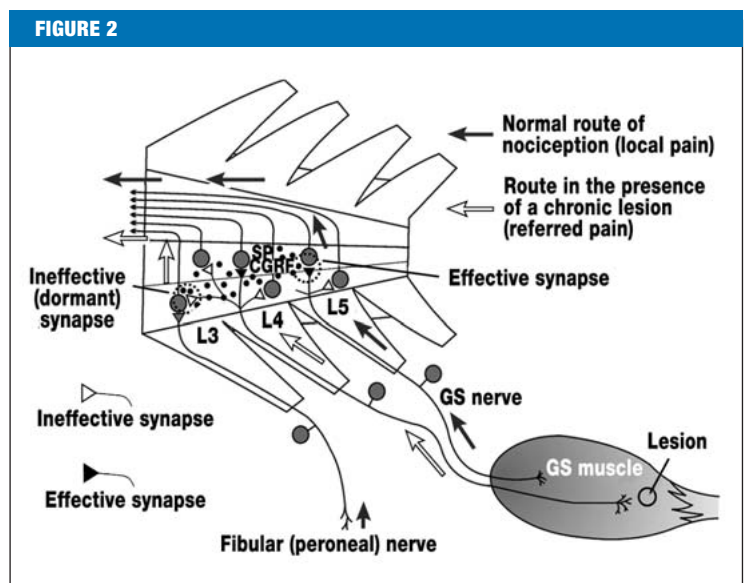
Clinical significance

Muscle spasm can be precipitated by, among other things, pain in another muscle. Thus, a spasm-like increase EMG activity in the trapezius muscle has been described in response to painful stimulation of the biceps brachii muscle (16). Another source of muscle spasms is pathological changes in a neighboring joint. These sources of pain must be deliberately sought.

Myofascial trigger points

Myofascial trigger points (MTrP's) are palpable, punctate areas of hardening in the muscle tissue that are painful on movement and palpation (17). Light-microscopic studies performed many years ago already revealed so-called contraction knots within MTrP's (18): these are local thickenings of individual muscle fibers brought about by the contraction of a small number of sarcomeres.

In a widespread hypothesis on the origin of MTrP's (19), it is supposed that a muscular lesion damages the neuromuscular endplate so that it secretes an excessive amount of acetylcholine. The ensuing depolarization of the muscle cell membrane produces a contraction knot that compresses the neighboring capillaries, causing local ischemia. Ischemia, in turn, leads to the release of



The mechanism of generation of referred muscle pain. Normally, the L4 and L5 segments are the main area in which the GS nerve exerts its effects in the rat (GS, gastrocnemius-soleus muscle), characterized by effective synapses (grey triangles) that reliably excite the post-synaptic neurons. Local pain arising in these segments is felt at the site of the lesion (black arrows). In animals with an inflamed GS muscle, the area of influence of the GS nerve was found to have expanded into the L3 segment, which contains only ineffective synapses (open triangles) of GS afferent fibers. These synapses do not normally induce any action potentials in the L3 neurons. In the presence of a lesion in the muscle, the muscle afferents in the L4 and L5 segments secrete substances (e.g., SP = substance P, black dots) that diffuse to the L3 segment and convert the ineffective synapses there into effective ones. Thus, it was newly possible for impulses from GS nociceptors (open arrows) to excite the L3 neurons, ultimately giving rise to referred pain that was felt in the distribution of the fibular nerve (lateral calf and foot).

substances into the tissue that sensitize nociceptors, accounting for the tenderness of MTrP's to pressure. Substances of this type have been found to be present within the MTrP's of these patients (20). This supposed mechanism leaves many questions unanswered but is currently the only comprehensive hypothesis on the origin of MTrP's.

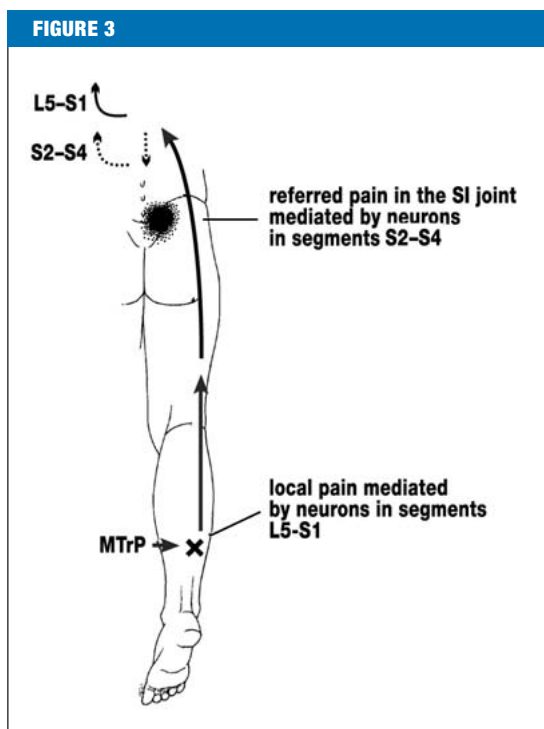
Clinical significance

Patients with MTrP's often have pain in three locations:

- at the site of the MTrP itself,
- at the origin or insertion of the affected muscle, because of pulling by the muscle fibers that have been stretched by the contraction knots,
- and referred pain outside the MTrP (figure 3).

Because the MTrP is cut off from its blood supply by compression of the local microcirculation, oral NSAID's are not very effective against TrP pain. Therapeutic injections into the trigger point presumably work by diluting the sensitizing substances that are present here (among other mechanisms), as normal saline injections have been found to be just as effective as local anesthetic injections (13).

The referred symptoms associated with an MTrP often lead patients to localize their pain incorrectly. In such cases, the physician must deliberately search for



Pain referral from a myofascial trigger point (MTrP) in the soleus muscle to the sacroiliac (SI) joint. As shown in figure 2, referral of pain to the SI joint can be explained as follows: first, nociceptors in the trigger point induce local pain. The nociceptive impulses arising from the trigger point are then carried over spinal cord neurons belonging to the segments L5–S1, which are the normal relay stations for impulses from the soleus muscle. As excitation spreads in the spinal cord (in this case, mainly in the caudal direction), the normally ineffective connections between the soleus muscle and the neurons of the S2–S4 segments become effective. Impulses from the trigger point nociceptors can now activate neurons in S2–S4 that otherwise provide sensory innervation to the SI joint. The individual therefore feels pain referred to the SI joint.

the actual source of the pain by palpation of the muscle, and then treat it accordingly.

Descending nociceptive inhibition and the fibromyalgia syndrome

An important symptom of the fibromyalgia syndrome (FMS) is generalized pain that is mainly felt in the musculature (21). Two main models have been proposed to account for generalized muscle pain:

- An increased influx of nociceptive stimulation into muscle nociceptors leads to sensitization of neurons in the central nervous system, and thereby to generalized hypersensitivity to pain (22). In the muscles of FMS patients, however, only nonspecific changes have been found, which in all likelihood do not excite the muscle nociceptors. It remains an open question whether the changes in muscle histology that were seen in one study (e6) have any relevance to the pain of FMS.
- The descending pain-modulating systems (i.e., pain-inhibiting and pain-promoting systems) are

dysfunctional. The most important of these is the pain-inhibiting system that normally tonically dampens the activity of spinothalamic tract neurons (23), which constitute the main spinal nociceptive pathway. The neurons of origin of this pain-inhibiting system lie in the midbrain. The neural impulses of this system travel, by way of a relay station in the medulla, to the nociceptive cells of the spinal cord, where the actual inhibition takes place. The activity of the descending system is influenced by connections to the prefrontal cortex, the hypothalamus, and the limbic system. The descending system employs endogenous opioids as well as serotonin and noradrenaline as neurotransmitters (24). The descending pain-inhibiting system exerts a particularly strong effect on neurons that mediate muscle pain (e7); thus, dysfunction of this system would be expected mainly to cause muscle pain.

Clinical significance

The model of increased peripheral nociceptive activity leading to central sensitization can explain cases in which a local trauma, e.g., a whiplash injury of the cervical spine (e8), develops into a generalized fibromyalgia syndrome.

Many authors favor a primary cause in the central nervous system in the form of a dysfunctional processing of nociceptive information. The dysfunction might consist, for example, of an insufficient degree of activity in the descending pain-inhibiting pathways, or of excessive activity in the descending pain-promoting pathways (24). Connections to the limbic system explain the fact that psychosocial influences play a major role in the pain of FMS. If the descending inhibition of pain is insufficient, i.e., if the neurons of the spinothalamic tract are disinhibited, then pain may arise even in the absence of a painful stimulus in the periphery.

Clinical examination reveals sites of excessive sensitivity to palpation (tender points, TeP), at which mild externally applied pressure causes pain. Many of these TeP's are located at the myotendinous junction, rather than near the belly of the muscle, where MTrP's are more likely to be found. These TeP's are not associated with any local pathological changes (as far as is known) but are rather the expression of a generalized hypersensitivity to pain. FMS patients have a low pain threshold in the skin and subcutaneous tissue as well as in muscle (25).

Dysfunction of the descending pain-inhibiting system is suggested by the fact that the pain of FMS usually does not respond to morphine, which exerts its analgesic effect mainly by activating the pain-inhibiting pathways.

Conflict of interest statement

The author states that he has no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors.

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