Published in final edited form as:
Curr Pain Headache Rep. 2008 October ; 12(5): 338–343.

Central Mechanisms in the Maintenance of Chronic Widespread Noninflammatory Muscle Pain

Josimari M. DeSantana, PhD and **Kathleen A. Sluka, PhD**

Abstract

Chronic widespread pain (CWP) conditions such as fibromyalgia and myofascial syndromes are characterized by generalized pain, tenderness, morning stiffness, disturbed sleep, and pronounced fatigue. However, CWP pathophysiology is still unclear. A number of hypotheses have been proposed as the underlying pathophysiology of CWP: muscular dysfunction/ischemia, central sensitization, and a deficit in endogenous pain-modulating systems. This article reviews the current and emerging literature about the pathophysiology and neurobiology of chronic widespread musculoskeletal pain. Widespread musculoskeletal pain results in changes in the central nervous system in human subjects and animal models. These changes likely reflect alterations in supraspinal modulation of nociception, and include increases in excitatory and decreases in inhibitory modulation pathways. These alterations in excitation and inhibition likely drive changes observed in the spinal cord to result in central sensitization, and the consequent pain and hyperalgesia.

Introduction

Chronic pain is an abnormal and nonprotective response. It has been defined as pain that outlasts normal tissue healing time, pain that is out of proportion to the inciting incident, or pain that lasts longer than 6 months. Approximately 14% of the US population suffers from chronic widespread muscle pain (CWP) conditions such as fibromyalgia (FM) [1]. It is estimated that FM affects 6 million Americans (2%−7% of the population), making it a common pain condition [1,2]. FM syndrome is characterized by generalized pain, tenderness, morning stiffness, disturbed sleep, and pronounced fatigue [3]. The diagnostic criteria proposed by the American College of Rheumatology include widespread pain in conjunction with tenderness on palpation of 11 or more of 18 specified tender points [2].

Pathophysiology of CWP in Humans

Several hypotheses have been proposed as the underlying pathophysiology of CWP: muscular dysfunction/ischemia [4,5], central sensitization [1,6,7], or a deficit in endogenous pain-modulating systems [8,9•]. Deficits in the central processing and central sensitization are suggested by studies showing a generalized decrease in mechanical thresholds [10-12], temporal summation to thermal and deep mechanical stimulation [12-14], larger areas of referred pain after infusion of hypertonic saline into the muscle [13], and alterations in descending modulation that are interpreted as decreased endogenous pain inhibition [15]. Temporal summation in patients with FM is enhanced compared with normal control subjects

Corresponding author Kathleen A. Sluka, PhD Physical Therapy and Rehabilitation Science, 1−242 MEB, University of Iowa, Iowa City, IA 52252, USA. E-mail: kathleen-sluka@uiowa.edu.

Disclosures
No potential conflicts of interest relevant to this article were reported.

and is followed by exaggerated after-sensations and temporal summation at low stimulus frequencies [16]. Blockade of N-methyl-D-aspartate (NMDA) receptors with systemic ketamine in people with FM reduces the local and referred pain associated with intramuscular infusion of hypertonic saline [10]. However, blockade of NMDA receptors with dextromethorphan in FM subjects produces an effect similar to that in healthy controls, suggesting that enhanced activity at NMDA receptors does not contribute to the differences in central pain processing between FM and healthy subjects [16]. However, other neural mechanisms may contribute to the pain associated with FM. Patients with FM have increased concentrations of substance P and nerve growth factor, and decreases in serotonin in the cerebrospinal fluid [17,18], suggesting that increased excitation and a simultaneous decrease in inhibition can be found in FM. Taken together, there appears to be substantial support for increased central sensitization in people with FM. However, recent evidence also supports a potential role of the peripheral nervous system in the mechanisms underlying development of CWP [19•,20].

Animal Model of CWP

Musculoskeletal pain syndromes such as FM and myofascial pain syndrome can be difficult to treat, and until recently, basic science studies focused on cutaneous pain. Recent works have established both inflammatory and noninflammatory models of muscle pain that result in widespread, long-lasting hyperalgesia [21-23]. Inflammatory models typically involve intramuscular injection of carrageenan, which produces an initial acute inflammatory response that converts to a chronic inflammatory response by 1 week [23]. This model is associated with the development of heat and mechanical hyperalgesia, as well as central hyperexcit-ability of dorsal horn neurons (central sensitization) [23]. However, widespread hyperalgesia without tissue injury is common and likely distinctly different from that associated with muscle inflammation.

To model CWP, our laboratory developed and characterized an animal model of chronic muscle hyperalgesia induced by two intramuscular injections of acidic saline [21]. This model is unique from other muscle pain models because 1) there is long-lasting bilateral mechanical hyperalgesia of the paw, muscle, and viscera; 2) there is no peripheral tissue damage; and 3) hyperalgesia is maintained by changes in the central nervous system (CNS) [21,24-28].

Characterization of the CWP model

Initial characterization of the model showed that repeated injection of pH 4.0 saline into the gastrocnemius muscle produced a long-lasting, widespread mechanical hyperalgesia without motor deficits or tissue damage. This hyperalgesia was dependent on dose and time of injection such that the lowest pH tested (pH 4.0) produced the greatest hyperalgesia, and interinjection intervals of 2 and 5 days (pH 4.0 saline) produced equivalent and significant decreases in mechanical withdrawal threshold bilaterally. However, inter-injection intervals of 10 days did not produce hyperalgesia [21], suggesting there is a critical window for the induction of hyperalgesia by the second injection.

Pharmacologic characterization of the acidic saline model shows similarities to that of people with FM. Specifically, the hyperalgesia is reversed by opioid agonists delivered spinally, spinal NMDA antagonists, as well as systemic pregabalin, NMDA antagonists, potassium channel openers, and sodium channel blockers [27,29,30]. However, there is no effect on the hyperalgesia with cyclooxygenase-2–specific inhibitors, anticonvulsants such as lamotrigine, or anxiolytic drugs such as diazepam [29]. Further, aerobic exercises reverse the hyperalgesia in this model [31] as in human subjects with FM [32•], and muscle fatigue enhances the development of hyperalgesia [33•].

Experimental Models of Muscle Pain in Human Subjects

Decreasing pH increases activity of nociceptors and produces a painful response in humans [34-36]. The infusion of acidic buffer into the tibialis anterior muscle produces pain at the site of infusion as well as referred pain at the ankle, a site distal to the infusion. Further, there are decreases in pressure pain threshold (hyperalgesia) at both sites of infusion (primary hyperalgesia) and at the referred pain site (secondary hyperalgesia) [35]. Similarly, single infusions of hypertonic saline into the anterior tibialis muscle of human subjects produce pain at the site of hypertonic saline infusion and distal to the site of infusion at the ankle; however, hyperalgesia is not present in this model [37-39]. The distal spread was dependent on volume of infusion such that lower volumes did not produce a referred pain area; increasing the volume of infusion increased the referral of distal pain [37]. Thus, in human subjects, stimulation of deep tissue with acidic buffer or hypertonic saline produces local and referred pain, and stimulation with an acidic buffer also produces primary and secondary hyperalgesia.

Spinal Mechanisms in CWP

Increased release of glutamate

Excitatory amino acids (EAAs) glutamate and aspartate play an essential role in nociception transmission through the spinal cord [39,40]. In the model of noninflammatory muscle pain induced by repeated acid intramuscular injections, spinal blockade of ionotropic glutamate receptors, both NMDA and AMPA/kainate receptors, reversed the hyperalgesia [24]. Further, blockade of NMDA (but not AMPA/kainate) receptors during the second injection of acidic saline delayed the onset of mechanical hyperalgesia [24], suggesting a role for increased glutamate release in the development of mechanical hyperalgesia associated with repeated acid injections. In parallel, there was an increased release of the EAAs glutamate and aspartate in the dorsal horn of the spinal cord in response to the second injection of acidic saline, compared with the first injection or controls injected with pH 7.2 saline [25]. In addition, 1 week after the second injection of acidic saline, baseline concentrations of glutamate and aspar-tate were increased in the dorsal horn of the spinal cord, suggesting long-lasting increases in excitatory neurotransmitter release at the level of the spinal cord. The increases in deep dorsal horn EAA concentrations after the second intramuscular injection of acid paralleled the development of mechanical hyperalgesia and central sensitization in this model of noninflammatory muscle-induced hyperalgesia [21,41].

Activation of the cyclic AMP pathway

Activation of the cyclic AMP (cAMP) pathway in the spinal cord and supraspinal pathways plays a crucial role in the transmission of the nociceptive input. Spinal activation of the cAMP pathway produces mechanical hyperalgesia and increases the response of spinothalamic tract neurons to noxious but not innocuous mechanical stimuli [22,42,43]. In mice that lack adenylate cyclase 1 and 8, hyperalgesia does not develop after intramuscular carrageenan [44]. Furthermore, blocking adenylate cyclase or protein kinase A (PKA) prevents the mechanical hyperalgesia and allodynia produced by intradermal, intramuscular, or intraarticular injection of capsaicin, and repeated intramuscular acidic saline injections [22, 26,45].

The catalytic subunit of PKA translocates to the nucleus and phosphorylates cAMP-response-element-binding protein (CREB) at serine-133, which is necessary for gene transcription. After repeated intramuscular injections of acidic saline, there is an increase in CREB and phosphorylated CREB (p-CREB), bilaterally in the spinal cord dorsal horn; the increases in p-CREB are prevented by blockade of the cAMP pathway [26]. Although p-CREB is found in spinothalamic tract cells, the increases observed in p-CREB occur in nonspinothalamic tract

neurons [45]. The increases in p-CREB after repeated acid injections are time dependent such that increases occur 24 hours but not 1 week after induction of hyperalgesia [26]. Similarly, the effects of blockade of the cAMP pathway are also time dependent such that hyperalgesia is reversed 24 hours but not 1 week after the induction of deep tissue hyperalgesia [22,26]. Thus, activation of the cAMP pathway after deep tissue injury occurs in a time-dependent manner to initiate long-term hyperalgesia potentially through activation of gene transcription by p-CREB.

PKA also phosphorylates the NMDA receptor at serine-897 of the NR1 subunit (p-NR1). Increases in phosphorylation of the NR1 subunit of the NMDA receptor occur after repeated intramuscular acid injection in lamina X spinothalamic tract neurons in the spinal cord [45]. Other protein kinases could also underlie the hyperalgesia associated with repeated acid injections. Numerous studies support a role of protein kinase C (PKC) and the calcium/calmodulin pathway in models of tissue injury [46], and activation of the PKC pathway with phorbol esters in the spinal cord produces mechanical hyperalgesia [47]. However, blockade of PKC has no effect on the hyperalgesia produced by repeated acid injections [47], suggesting that the PKC pathway is not involved at the spinal level in CWP. Involvement of other intracellular mechanisms has not been tested in this unique model of noninflammatory muscle pain.

Glia are not activated

Glial cells in the CNS, particularly the spinal cord, play a critical role in processing of nociceptive information [48,49]. Glia express receptors for many neurotransmitters (including glutamate receptors) and are involved in the clearance of neurotransmitters from the synaptic cleft. Activation of astrocytes and microglia occurs in a number of pain models, including neuropathic and inflammatory [50,51]. However, after repeated intramuscular acid injections, the hyperalgesia is not affected by single or repeated blockade of interleukin-1, a glial metabolic inhibitor, or interleukin-10 [52]. Further, using immunohistochemistry there was no activation of glial cells in the spinal cord after repeated intramuscular injections of acid [52].

Supraspinal Mechanisms in CWP

There is evidence that secondary hyperalgesia is maintained by changes in the CNS [53], which is facilitated and maintained by two distinct areas in the rostral ventral medulla (RVM) that have been implicated in a number of studies on descending inhibition: the nucleus raphe magnus (NRM) and the nucleus gigantocellularis (Gi) [54-56]. In the noninflammatory model of CWP, reversible blockade by ropivacaine (local anesthetic) of the NRM or Gi bilaterally during the second, hyperalgesia-inducing intramuscular injection of pH 4.0 saline prevents the development of primary muscle and secondary cutaneous mechanical hyperalgesia 24 hours later [28]. Moreover, if the hyperalgesia has already developed, ropivacaine microinjected into NRM or Gi reverses the completely developed primary (muscle) and secondary (paw) mechanical hyperalgesia [28]. This suggests that cells in the NRM and Gi (or axons passing through these RVM cell groups) are critical for the development and maintenance of mechanical hyperalgesia after muscle insult [28]. Clinical studies show that deficits in the descending pain inhibitory systems are impaired in chronic conditions such as FM [9•,15,57]. However, it is unknown in these studies if there is an increase in facilitation or a decrease in inhibition. The animal studies suggest an increase in facilitation because blockade of neuronal activity reverses the hyperalgesia. Thus, as in animal models, pain in people with CWP may be due to a shift in the balance between endogenous inhibitory and facilitatory influences, representing a dysfunction within endogenous systems of modulation.

Peripheral Mechanisms in CWP

ASIC3 is important for induction

There are four acid-sensing ion channels found in the mammalian nervous system: ASIC1, ASIC2, ASIC3, and ASIC4. Of these, ASIC3 appears to play a critical role in the development of hyperalgesia after repeated intramuscular acid injection or deep tissue inflammation. In ASIC3 knockout mice, the secondary mechanical hyperalgesia that normally occurs after repeated intramuscular acid injections, muscle inflammation, or joint inflammation does not develop [41,58,59]. However, primary hyperalgesia after paw or joint inflammation still develops, similar to controls [59-61]. Further, ASIC3 expression in peripheral tissues is critical for the development of the hyperalgesia because re-expression of ASIC3 in muscle tissue (but not skin) of ASIC3 knockout mice restores the development of hyperalgesia after carrageenan muscle inflammation [58]. In parallel, central sensitization of dorsal horn neurons, measured as a bilateral spread of receptive fields and increased mechanical sensitivity, does not develop in ASIC3 knockout mice [41]. Further, there is an upregulation of ASIC3 in joint afferents innervating the synovium and their cells bodies (dorsal root ganglion) after joint inflammation [59]. However, in ASIC1 knockout mice, secondary hyperalgesia develops similarly to controls [41]. Together these data suggest that ASIC3 is critical for development of secondary hyperalgesia and central sensitization that occurs after insult to deep tissues.

Neurotrophin-3 in muscle is protective

The neurotrophins are a family of secreted factors (nerve growth factor [NGF], brain-derived neurotrophic factor, neurotrophin-3 [NT-3], and neurotrophin-4/5) that have trophic activity on different classes of dorsal root ganglion neurons. The NGF-related neurotrophins signal via tyrosine kinase (Trk) receptors and bind a common receptor with low affinity (p75), and the subtype TrkC shows high affinity for NT-3 [62]. All of these neurotrophins are expressed in the muscle [63]; most muscle afferents express TrkC and are responsive to NT-3 [64]. Mice that overexpress NT-3 do not develop hyperalgesia after repeated injection of acidic saline [65]. Similarly, injection of NT-3 into muscle during the development of hyperalgesia prevented the onset of hyperalgesia; however, NT-3 was ineffective when delivered after the development of hyperalgesia [65]. Further, intrathecal or systemic delivery of NT-3 had no effect on the development of hyperalgesia, suggesting that activation of TrkC in muscle is protective. Thus, the protective effects of NT-3 are important in induction of hyperalgesia, but it does not have a role after induction.

Conclusions

Widespread musculoskeletal pain results in CNS changes in human subjects and animal models. Peripherally, activation of ASIC3 is necessary for development of widespread muscle pain, and NT-3 prevents development of hyperalgesia. Central changes are also critical for development of widespread muscle pain and likely reflect alterations in supraspinal modulation of nociception; these include increases in excitatory and decreases in inhibitory modulation pathways. These alterations in excitation and inhibition likely drive changes observed in the spinal cord to result in central sensitization and the consequent pain and hyperalgesia.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Clauw DJ, Crofford LJ. Chronic widespread pain and fibromyalgia: what we know, and what we need to know? Best Pract Res Clin Rheumatol 2003;17:685–701. [PubMed: 12849719]
2. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. Arthritis Rheum 1990;33:160–172. [PubMed: 2306288]
3. Boissevain MD, McCain GA. Toward an integrated understanding of fibromyalgia syndrome. I. Medical and pathophysiological aspects. Pain 1991;45:227–238. [PubMed: 1876432]
4. Bengtsson A, Henriksson KG. The muscle in fibromyalgia--a review of Swedish studies. J Rheumatol Suppl 1989;19:144–149. [PubMed: 2691674]
5. Henriksson KG, Bengtsson A. Fibromyalgia--a clinical entity? Can J Physiol Pharmacol 1991;69:672–677. [PubMed: 1863919]
6. Staud R, Vierck CJ, Mauderli A, et al. Abnormal temporal summation of second pain (wind-up) in patients with the fibromyalgia syndrome. Arthritis Rheum 1998;41:S353.
7. Price DD, Staud R, Robinson ME, et al. Enhanced temporal summation of second pain and its central modulation in fibromyalgia patients. Pain 2002;99:49–59. [PubMed: 12237183]
8. Kosek E, Ekholm J, Hansson P. Modulation of pressure pain thresholds during and following isometric contraction in patients with fibromyalgia and in healthy controls. Pain 1996;64:415–423. [PubMed: 8783304]
9•. Julien N, Goffaux P, Arsenault P, et al. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain 2005;114:295–302. [PubMed: 15733656]• Of importanceThis study shows loss of descending inhibitory controls in people with FM.
10. Graven-Nielsen T, Aspegren KS, Henriksson KG, et al. Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. Pain 2000;85:483–491. [PubMed: 10781923]
11. Vierck CJ Jr, Staud R, Price DD, et al. The effect of maximal exercise on temporal summation of second pain (windup) in patients with fibromyalgia syndrome. J Pain 2001;2:334–344. [PubMed: 14622813]
12. Staud R, Carl KE, Vierck CJ, et al. Repetitive muscle stimuli result in enhanced wind-up of fibromyalgia patients. Arthritis Rheum 2001;44:S395.
13. Sörensen J, Graven-Nielsen T, Henriksson KG, et al. Hyperexcitability in fibromyalgia. J Rheumatol 1998;25:152–155. [PubMed: 9458220]
14. Staud R, Vierck CJ, Cannon RL, et al. Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. Pain 2001;91:165–175. [PubMed: 11240089]
15. Kosek E, Hansson P. Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia patients and healthy subjects. Pain 1997;70:41–51. [PubMed: 9106808]
16. Staud R, Vierck CJ, Robinson ME, et al. Effects of the N-methyl-D-aspartate receptor antagonist dextromethorphan on temporal summation of pain are similar in fibromyalgia patients and normal control subjects. J Pain 2005;6:323–332. [PubMed: 15890634]
17. Russell IJ, Orr MD, Littman B, et al. Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome. Arthritis Rheum 1994;37:1593–1601. [PubMed: 7526868]
18. Giovengo SL, Russell IJ, Larson AA. Increased concentrations of nerve growth factor in cerebrospinal fluid of patients with fibromyalgia. J Rheumatol 1999;26:1564–1569. [PubMed: 10405946]
19•. Vierck CJ Jr. Mechanisms underlying development of spatially distributed chronic pain (fibromyalgia). Pain 2006;124:242–263. [PubMed: 16842915]• Of importanceGood review of potential mechanisms underlying FM.
20. Staud R, Rodriguez ME. Mechanisms of disease: pain in fibromyalgia syndrome. Nat Clin Pract Rheumatol 2006;2:90–98. [PubMed: 16932662]
21. Sluka KA, Kalra A, Moore SA. Unilateral intramuscular injections of acidic saline produce a bilateral, long-lasting hyperalgesia. Muscle Nerve 2001;24:37–46. [PubMed: 11150964]
22. Sluka KA. Stimulation of deep somatic tissue with capsaicin produces long-lasting mechanical allodynia and heat hypoalgesia that depends on early activation of the cAMP pathway. J Neurosci 2002;22:5687–5693. [PubMed: 12097520]

23. Radhakrishnan R, Sluka KA. Spinal muscarinic receptors are activated during low or high frequency TENS-induced antihyperalgesia in rats. Neuropharmacology 2003;45:1111–1119. [PubMed: 14614954]
24. Skyba DA, King EW, Sluka KA. Effects of NMDA and non-NMDA ionotropic glutamate receptor antagonists on the development and maintenance of hyperalgesia induced by repeated intramuscular injection of acidic saline. Pain 2002;98:69–78. [PubMed: 12098618]
25. Skyba DA, Lisi TL, Sluka KA. Excitatory amino acid concentrations increase in the spinal cord dorsal horn after repeated intramuscular injection of acidic saline. Pain 2005;119:142–149. [PubMed: 16297556]
26. Hoeger-Bement MK, Sluka KA. Phosphorylation of CREB and mechanical hyperalgesia is reversed by blockade of the cAMP pathway in a time-dependent manner after repeated intramuscular acid injections. J Neurosci 2003;23:5437–5445. [PubMed: 12843242]
27. Yokoyama T, Maeda Y, Audette KM, Sluka KA. Pregabalin reduces muscle and cutaneous hyperalgesia in two models of chronic muscle pain in rats. J Pain 2007;8:422–429. [PubMed: 17293165]
28. Tillu DV, Gebhart GF, Sluka KA. Descending facilitatory pathways from the RVM initiate and maintain bilateral hyperalgesia after muscle insult. Pain 2008;136:331–339. [PubMed: 17764841]
29. Nielsen AN, Mathiesen C, Blackburn-Munro G. Pharmacological characterisation of acid-induced muscle allodynia in rats. Eur J Pharmacol 2004;487:93–103. [PubMed: 15033380]
30. Sluka KA, Rohlwing JJ, Bussey RA, et al. Chronic muscle pain induced by repeated acid injection is reversed by spinally administered mu- and delta-, but not kappa-, opioid receptor agonists. J Pharmacol Exp Ther 2002;302:1146–1150. [PubMed: 12183674]
31. Bement MK, Sluka KA. Low-intensity exercise reverses chronic muscle pain in the rat in a naloxone-dependent manner. Arch Phys Med Rehabil 2005;86:1736–1740. [PubMed: 16181935]
32•. Busch AJ, Barber KA, Overend TJ, et al. Exercise for treating fibromyalgia syndrome. Cochrane Database Syst Rev 2007:CD003786. [PubMed: 17943797]• Of importanceSystematic review with meta-analysis data showing the effectiveness of exercise in treating FM.
33•. Yokoyama T, Lisi TL, Moore SA, et al. Muscle fatigue increases the probability of developing hyperalgesia in mice. J Pain 2007;8:692–699. [PubMed: 17627895]• Of importanceInitial study showing that exercise-induced fatigue enhances the development of muscle pain.
34. Reeh PW, Steen KH. Tissue acidosis in nociception and pain. Prog Brain Res 1996;113:143–151. [PubMed: 9009732]
35. Frey Law, LA.; Sluka, KA.; McMullen, T., et al. Acidic buffer induced muscle pain evokes referred pain and mechanical hyperalgesia in humans [abstract].. Presented at the 12th World Congress on Pain, International Association for the Study of Pain.; Glasgow, Scotland. August 17−22, 2008;
36. Graven-Nielsen T, Arendt-Nielsen L, Svensson P, et al. Quantification of local and referred muscle pain in humans after sequential i.m. injections of hypertonic saline. Pain 1997;69:111–117. [PubMed: 9060020]
37. Graven-Nielsen T, Arendt-Nielsen L, Svensson P, et al. Experimental muscle pain: a quantitative study of local and referred pain in humans following injection of hypertonic saline. J Musculoskelet Pain 1997;5:49–69.
38. Graven-Nielsen T, Arendt-Nielsen L, Svensson P, et al. Stimulus-response functions in areas with experimentally induced referred muscle pain--a psychophysical study. Brain Res 1997;744:121–128. [PubMed: 9030420]
39. Dougherty PM, Willis WD. Enhanced responses of spinothalamic tract neurons to excitatory amino acids accompany capsaicin-induced sensitization in the monkey. J Neurosci 1992;12:883–894. [PubMed: 1545244]
40. Sluka KA, Westlund KN. Spinal cord amino acid release and content in an arthritis model: the effects of pretreatment with non-NMDA, NMDA, and NK1 receptor antagonists. Brain Res 1993;627:89–103. [PubMed: 7904887]
41. Sluka KA, Price MP, Breese NM, et al. Chronic hyperalgesia induced by repeated acid injections in muscle is abolished by the loss of ASIC3, but not ASIC1. Pain 2003;106:229–239. [PubMed: 14659506]

42. Sluka KA. Activation of the cAMP transduction cascade contributes to the mechanical hyperalgesia and allodynia induced by intradermal injection of capsaicin. Br J Pharmacol 1997;122:1165–1173. [PubMed: 9401782]
43. Dolan S, Nolan AM. Biphasic modulation of nociceptive processing by the cyclic AMP-protein kinase A signalling pathway in sheep spinal cord. Neurosci Lett 2001;309:157–160. [PubMed: 11514065]
44. Vadakkan KI, Wang H, Ko SW, et al. Genetic reduction of chronic muscle pain in mice lacking calcium/calmodulin-stimulated adenylyl cyclases. Mol Pain 2006;2:7. [PubMed: 16503978]
45. Bement MK, Sluka KA. Co-localization of p-CREB and p-NR1 in spinothalamic neurons in a chronic muscle pain model. Neurosci Lett 2007;418:22–27. [PubMed: 17395373]
46. Sluka, KA.; Skyba, DA.; Hoeger Bement, MK., et al. Molecular Pain. Higher Education Press, Springer; China: 2008. Second messenger pathways in pain..
47. Sluka KA, Audette KM. Activation of protein kinase C in the spinal cord produces mechanical hyperalgesia by activating glutamate receptors, but does not mediate chronic muscle-induced hyperalgesia. Mol Pain 2006;2:13. [PubMed: 16584564]
48. Watkins LR, Milligan ED, Maier SF. Glial activation: a driving force for pathological pain. Trends Neurosci 2001;24:450–455. [PubMed: 11476884]
49. Watkins LR, Maier SF. Beyond neurons: evidence that immune and glial cells contribute to pathological pain states. Physiol Rev 2002;82:981–1011. [PubMed: 12270950]
50. Fu KY, Light AR, Matsushima GK, et al. Microglial reactions after subcutaneous formalin injection into the rat hind paw. Brain Res 1999;825:59–67. [PubMed: 10216173]
51. Sweitzer SM, Colburn RW, Rutkowski M, et al. Acute peripheral inflammation induces moderate glial activation and spinal IL-1beta expression that correlates with pain behavior in the rat. Brain Res 1999;829:209–221. [PubMed: 10350552]
52. Ledeboer A, Mahoney JH, Milligan ED, et al. Spinal cord glia and interleukin-1 do not appear to mediate persistent allodynia induced by intramuscular acidic saline in rats. J Pain 2006;7:757–767. [PubMed: 17018336]
53. Willis WD, Sluka KA, Rees H, et al. Cooperative mechanisms of neurotransmitter action in central nervous sensitization. Prog Brain Res 1996;110:151–166. [PubMed: 9000723]
54. Terayama R, Dubner R, Ren K. The roles of NMDA receptor activation and nucleus reticularis gigantocellularis in the time-dependent changes in descending inhibition after inflammation. Pain 2002;97:171–181. [PubMed: 12031790]
55. Vera-Portocarrero LP, Xie JY, Kowal J, et al. Descending facilitation from the rostral ventromedial medulla maintains visceral pain in rats with experimental pancreatitis. Gastroenterology 2006;130:2155–2164. [PubMed: 16762636]
56. Vera-Portocarrero LP, Zhang ET, Ossipov MH, et al. Descending facilitation from the rostral ventromedial medulla maintains nerve injury-induced central sensitization. Neuroscience 2006;140:1311–1320. [PubMed: 16650614]
57. Staud R, Robinson ME, Vierck CJ Jr, et al. Diffuse noxious inhibitory controls (DNIC) attenuate temporal summation of second pain in normal males but not in normal females or fibromyalgia patients. Pain 2003;101:167–174. [PubMed: 12507711]
58. Sluka KA, Radhakrishnan R, Benson CJ, et al. ASIC3 in muscle mediates mechanical, but not heat, hyperalgesia associated with muscle inflammation. Pain 2007;129:102–112. [PubMed: 17134831]
59. Ikeuchi M, Kolker SJ, Burnes LA, et al. Role of ASIC3 in the primary and secondary hyperalgesia produced by joint inflammation in mice. Pain. Mar 13;2008 (Epub ahead of print)
60. Chen CC, Zimmer A, Sun WH, et al. A role for ASIC3 in the modulation of high-intensity pain stimuli. Proc Natl Acad Sci U S A 2002;99:8992–8997. [PubMed: 12060708]
61. Mogil JS, Breese NM, Witty MF, et al. Transgenic expression of a dominant-negative ASIC3 subunit leads to increased sensitivity to mechanical and inflammatory stimuli. J Neurosci 2005;25:9893–9901. [PubMed: 16251436]
62. Snider WD. Functions of the neurotrophins during nervous system development: what the knockouts are teaching us. Cell 1994;77:627–638. [PubMed: 8205613]
63. Nagano M, Suzuki H. Quantitative analyses of expression of GDNF and neurotrophins during postnatal development in rat skeletal muscles. Neurosci Res 2003;45:391–399. [PubMed: 12657452]

64. McMahon SB, Armanini MP, Ling LH, Philips HS. Expression and co-expression of Trk receptors in subpopulations of adult primary sensory neurons projecting to identified peripheral targets. Neuron 1994;12:1161–1171. [PubMed: 7514427]

65. Gandhi R, Ryals JM, Wright DE. Neurotrophin-3 reverses chronic mechanical hyperalgesia induced by intramuscular acid injection. J Neurosci 2004;24:9405–9413. [PubMed: 15496676]