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Critical role of nociceptor plasticity in chronic pain

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Abstract

The transition from acute to chronic pain states may be the most important challenge in research to improve clinical treatment of debilitating pain. We describe a recently identified mechanism of neuronal plasticity in primary afferent nociceptive nerve fibers (nociceptors) by which an acute inflammatory insult or environmental stressor can trigger long-lasting hypersensitivity of nociceptors to inflammatory cytokines. This phenomenon, “hyperalgesic priming,” depends on the epsilon isoform of protein kinase C (PKC ϵ) and a switch in intracellular signaling pathways that mediate cytokine-induced nociceptor hyperexcitability. We discuss the impact of this discovery on our understanding of, and ultimately our ability to treat, a variety of enigmatic and debilitating pain conditions, including those associated with repetitive-injury, and generalized pain conditions like fibromyalgia.

Introduction

The notion that “chronic” pain is a phenomenon distinct from “acute” pain is widely accepted as common sense among both physicians and the lay public [1]. Yet, there is no definition of chronic pain that distinguishes it mechanistically from acute pain. Current working definitions of chronic pain, for the most part resort to fixed temporal cut-offs after which point acute pain switches in name to chronic pain. The arbitrariness of this approach is amply emphasized by the range of calendar-based periods that are used, for example: 1 month [2], 3 months [3], 6 months [1], or 1 year [4].

Clinical experience, however, suggests that the difference between acute and chronic pain is not arbitrary, and that there can be a functional transition of pain states from acute to chronic [5-8]. This transition seems to be associated with a time-dependent disconnection of the generation of pain from the initial tissue injury, and decrease of responsiveness to some therapies that successfully treat acute pain [9]. Alternatively acute pain may persist for long periods without ever undergoing a “chronicization” [10] of its underlying mechanism.

Understanding the cellular mechanisms underlying chronic pain states will be a critical step in the development of new therapies to specifically target the distinct mechanisms of chronic pain. Numerous studies have implicated plastic changes in central nervous system circuitry, driven by increased activity in nociceptive primary afferent nerve fibers [11]. However, until

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recently, very little was known concerning the cellular changes underlying these very long-lasting alterations in excitability of primary afferents associated with chronic pain states.

In this review, we summarize a growing body of evidence that a transient insult can trigger long-lasting changes in primary afferent nociceptors, which prime them to become hyperresponsive to future mild insults that would normally not evoke pain in the un-primed state. The epsilon isoform of protein kinase C (PKC ϵ) in the primary afferent nociceptor plays multiple crucial roles in this phenomenon [12], known as “hyperalgesic priming.” Emerging evidence suggests that hyperalgesic priming may be not only a basic pathophysiological mechanism of chronic re-injury pain, but may also be key to understanding some of the most perplexing chronic pain conditions, including pain syndromes that are stress-related (*e.g.*, fibromyalgia, irritable bowel syndrome, or post-traumatic stress disorder), and neuropathic (*e.g.*, associated with diabetes or chemotherapy for cancer or AIDS). Finally, we suggest that hyperalgesic priming is related to a broader range of other physiological phenomena in which excitable cells undergo PKC ϵ -dependent priming in response to diverse insults.

Discovery of hyperalgesic priming

Numerous animal models of *long-lasting* pain have been developed as a means to study mechanisms of chronic pain. However, most of these models are complicated by the presence of ongoing tissue injury (notably, a variety of models employ chronic inflammation induced by complete Freund’s adjuvant or carrageenan), preventing the distinction between mechanisms of ongoing acute pain and neuroplastic changes that specifically underlie chronic pain. Even commonly employed models of neuropathic pain involving mechanical damage to a peripheral nerve can involve ongoing post-operative irritation and inflammation of the nerve or spinal root [13].

Separating the mechanisms of acute and chronic pain was a key concern in initial investigations that led to the discovery of the phenomenon of hyperalgesic priming. The clinical observation that some chronic pain conditions can be initiated by one or more transient episodes of acute pain (*e.g.*, complex regional pain syndrome type I, occupational repetitive stress disorders), a protocol was developed to temporally isolate mechanisms that maintain chronic pain from those that produce an antecedent acute pain [14] (Figure 1). A short-lived inflammation was induced in rat hind paw by intradermal injection of a very low dose of the inflammogen, carrageenan. The resultant inflammation (localized redness with minimal swelling) is associated with acute hyperalgesia, detected as a decrease in threshold for the withdrawal response to a mechanical pressure stimulus applied to the inflamed paw. Both the acute inflammation and associated hyperalgesia resolve within 4 days, leaving the animal with no signs of ongoing inflammation or hyperalgesia (indeed, carrageenan injection is often used as a model of a simple acute inflammatory pain). However, when the paw is challenged with a new inflammatory stimulus, even weeks later, a dramatically enhanced hyperalgesic response is apparent. Thus, injection of a low dose of an inflammatory cytokine, *e.g.*, prostaglandin E₂ (PGE₂), which in a naïve rat paw would cause only a brief hyperalgesia lasting less than 4 hours, now evokes hyperalgesia lasting at least 24 hours. In addition to this prolongation, hyperalgesic priming also causes an increase in the magnitude of hyperalgesia: the dose-response relationship for PGE₂-induced hyperalgesia is shifted to the left by more than an order of magnitude [15]. Hyperalgesia induced by other endogenous inflammatory mediators, including serotonin and adenosine are similarly enhanced. This latent hyper-susceptibility to inflammatory hyperalgesia that is still present, undiminished, weeks later, is termed “hyperalgesic priming.” The potential clinical significance of this hypersensitivity to pro-inflammatory cytokines is emphasized by the fact that PGE₂ is a target of the most commonly used class of drugs for treating pain, the non-steroidal anti-inflammatory analgesics (NSAIDs).

Cellular mechanisms of hyperalgesic priming: two roles of PKC ϵ

Initial investigations into the mechanism underlying hyperalgesic priming revealed that, in the primed state, PGE₂-induced hyperalgesia is not only enhanced and prolonged, but it also involves a switch in intracellular signaling pathways. Mechanical hyperalgesia induced by PGE₂ is normally mediated largely by activation of the adenylyl cyclase — cyclic AMP — protein kinase A (PKA) second messenger signaling cascade in nociceptive primary afferents [16], and thus is strongly attenuated by injection of PKA antagonists into the peripheral receptive fields of those nerve fibers. Following induction of hyperalgesic priming, however, the new, prolonged component of the response to PGE₂ is not sensitive to PKA antagonism, but is instead greatly reduced by a selective inhibitor of the epsilon isoform of PKC (PKC ϵ). Of note, the PKC ϵ -mediated prolonged response to PGE₂ in the primed state does not *replace* the normal PKA-mediated transient response, but is *added* to it.

In addition to playing a key role in the expression of priming-enhanced mechanical hyperalgesia, PKC ϵ activity is also required to maintain the primed state (even when the state is latent, *i.e.*, there is no inflammatory mediator inducing hyperalgesia). To demonstrate this role of PKC ϵ , after carrageenan-induced hyperalgesic priming was established, antisense oligodeoxynucleotide was injected intrathecally to produce a transient (approximately 3- to 5-day) decrease in PKC ϵ expression in sensory neurons [12] (Figure 2). Priming-induced enhancement of PGE₂ hyperalgesia was not only blocked *during* this transient reduction in PKC ϵ level, but also failed to reappear after the antisense treatment was discontinued and PKC ϵ recovered [12]. Thus, ongoing PKC ϵ activity is essential to maintain, as well as initiate, the primed state.

The observation that PKC ϵ is necessary to maintain hyperalgesic priming, suggested the possibility that stimulating PKC ϵ activity could be *sufficient* to initiate priming. Indeed, hyperalgesic priming can be induced by a highly selective agonist of PKC ϵ (pseudo-receptor octapeptide for activated PKC ϵ , $\psi\epsilon$ RACK). The observation that hyperalgesic priming could be induced by doses of $\psi\epsilon$ RACK too low to produce any detectable hyperalgesia [12,17] suggests that a chronic state of hyperalgesic priming can be induced without an antecedent acute pain state.

Priming occurs in peripheral nerve endings

Consistent with its having a peripheral mechanism, hyperalgesic priming is induced by a localized stimulus and is topographically limited to that region, requires PKC ϵ activity in peripheral tissue, and is mimicked by selective stimulation of PKC ϵ activity in the skin. More specifically, this peripheral PKC ϵ -mediated mechanism must occur within the primary afferent nerve fiber itself because, among all the cells in the skin, only primary afferents are exposed to the spinally administered antisense oligodeoxynucleotides that reverse hyperalgesic priming.

Although the cellular mechanisms of hyperalgesic priming occur within the peripheral terminals of primary afferent nociceptors, the resultant abnormal afferent activity can trigger plastic changes in the central nervous system (“central sensitization”) that add an additional dimension of nervous system dysfunction to the chronic pain state. That initiation and maintenance of central sensitization is a consequence of primary afferent activity (whether evoked or spontaneous) is suggested by the ability of transient local anesthesia to terminate hyperalgesia both in animal models of central sensitization [18] as well as in pain patients whose conditions are thought to involve central sensitization, including chemogenic pain [19], surgical pain [20] and generalized pain syndromes (*e.g.*, irritable bowel [21] and fibromyalgia [22]). Therefore, from a therapeutic perspective, it may be useful to note that elimination of hyperalgesic priming in the primary afferent would also be expected to

ameliorate central sensitization; however, treatments directed at central sensitization are unlikely to provide lasting relief if priming of primary afferent nociceptor hyperexcitability is not addressed.

Potential insights into pathophysiology of “re-injury” pain conditions

A variety of poorly-understood and intractable chronic pain conditions can be characterized as an injury-induced state of hyper-responsiveness to subsequent insults (Figure 3). Pain may subside by avoidance of re-injury, but the latent state of hyper-responsiveness persists. In this regard there is a basic resemblance of such conditions to the phenomenon of hyperalgesic priming, and the comparison may yield important insights to advance our understanding of the underlying pathophysiological mechanisms of chronic pain.

For example, repetitive strain injury (also known as cumulative trauma disorder or occupational overuse syndrome) is a condition produced by repetition of movements resulting in chronic hyper-susceptibility to pain from future repetitions of these normally innocuous movements. Temporary pain relief can be achieved with injection of local anesthetic [23], suggesting the importance of abnormal primary afferent activity in generating the pain.

Some forms of headache may also be interpreted as chronic re-injury pain conditions that are consistent with the mechanism of hyperalgesic priming. For example, the most common headache disorder, tension-type headache, can transition from an episodic form to a much more intractable chronic form [24]. A recent longitudinal study has shown that this transition is associated with a decrease in the threshold for pain evoked by pressure stimuli [25]. This observation seems consistent with the induction of hyperalgesic priming by muscle tension, leading to subsequent hyper-susceptibility to future pain in those muscles. Tonic decrease in pressure pain threshold could result from hyperresponsiveness of primed primary afferent nociceptors to ambient levels of cytokines. Central sensitization, which is often suggested as a mechanism of chronic tension-type headache could be a consequence of such hyperalgesic priming of muscle afferents.

Hyperalgesic priming induced by stress

While the ability of stressful stimuli to cause analgesia is well-known, it is also clear that repeated environmental stressors can induce a persistent hyperalgesic state [26]. The hypothesis that PKC ϵ -dependent hyperalgesic priming underlies long-lasting stress-induced enhancement of hyperalgesia was recently tested in animal experiments [27]. Rats exposed to non-habituating sound stress exhibited marked increases in mechanical hyperalgesia evoked by local injections of prostaglandin E₂ or epinephrine. This enhancement, which lasted for weeks, required concerted action of glucocorticoids and catecholamines at receptors located in the periphery on sensory afferents. The altered response to pronociceptive mediators involves a switch in G-protein coupling of their receptors from G_s to G_i [28,28], and for prostaglandin, emergence of novel dependence on PKC ϵ and loss of dependence on protein kinase A [29] (Figure 3). Thus, stress induces a sustained condition of increased sensitivity to the hyperalgesic effects of pro-inflammatory cytokines that is indistinguishable from the phenomenon of hyperalgesic priming that is induced by inflammation. Because ongoing stress can cause a lasting elevation of circulating pro-inflammatory cytokines [30], hyperalgesic priming of primary afferents in stressed individuals might produce tonic pain.

Stress-induced hyperalgesic priming in chronic generalized pain conditions?

Generalized pain syndromes (including fibromyalgia, irritable bowel and chronic fatigue) are very common clinical pain syndromes (see Table 1) characterized by widespread chronic musculoskeletal pain without overt clinical signs of underlying pathophysiology. Because of

our lack of understanding of the underlying etiology, currently accepted therapies are symptomatic (*e.g.* antidepressants, muscle relaxants, anticonvulsants, exercise, cognitive therapy), and are able to relieve pain in only about half of patients [31].

We propose that a key mechanism underlying generalized pain syndromes is stress-induced hyperalgesic priming of primary afferent nerve fibers. Prominent clinical characteristics of generalized pain conditions like fibromyalgia are consistent with this idea. For example, symptoms are characterized by waxing and waning episodes of pain, between which patients remain in a latent state of hypersensitivity to future insults [32]. Also consistent with a priming-like latent hyperexcitability of primary afferents, pain in fibromyalgia patients may be relieved by injection of local anesthetics at tender points [33] or even at symptom-free trigger points [34]. Finally, stress can dramatically exacerbate symptoms in generalized pain syndromes—even the earliest descriptions of these conditions noted their obvious link to both stress and inflammatory conditions [35]. Approximately half of all fibromyalgia patients report that initial onset of their chronic pain followed a traumatic event [36], and it has been suggested that fibromyalgia should be considered primarily as a stress disorder [37]. Furthermore, it has also been suggested that due to the close association of fibromyalgia with conditions like rheumatoid arthritis, the concept of “primary” fibromyalgia (versus secondary fibromyalgia) may not be justified [38].

The hypothesized role of stress-induced hyperalgesic priming may help illuminate a peculiar clinical observation in fibromyalgia; although systemic steroids are generally effective in the treatment of acute inflammatory musculoskeletal pain [39], fibromyalgia patients treated with glucocorticoids have been reported to show *worsened* outcomes [40]. This result is consistent with expected exacerbation of hyperalgesic priming by steroid drugs. Beyond its theoretical interest, this insight has practical importance, as one study reported 40% of elderly fibromyalgia sufferers received corticosteroids on the mistaken assumption that they had polymyalgia rheumatica or an inflammatory joint disease [41].

Hyperalgesic priming increases the response of nociceptive nerve fibers to pro-inflammatory cytokines, and therefore, our hypothesis predicts that these cytokines play a role in the pathogenesis of generalized pain syndromes like fibromyalgia. In fact, the observation of a much higher incidence of fibromyalgia in patients with inflammatory diseases (*e.g.*, approximately half of patients with systemic lupus erythematosus [42] and one sixth of rheumatoid arthritis patients [43]) or infectious diseases (*e.g.*, approximately one third of patients infected with human T cell lymphotropic virus type I [44]) suggests that proinflammatory cytokines may be an important factor [45,46]. Furthermore, many patients with fibromyalgia exhibit increased levels of proinflammatory cytokines (including prostaglandin E₂, interleukins and tumor necrosis factor α) in plasma and tissues [47,48], and cytokine levels correlate with the severity of their pain [49]. The observation that effective treatment of associated inflammatory disease (*e.g.*, rheumatoid arthritis) may improve fibromyalgia pain [50], suggests that normalizing cytokine levels may correct the underlying pathology of fibromyalgia. Thus, cytokine antagonists might prove to be a useful novel tool in fibromyalgia therapy; in fact, intravenous immunoglobulin therapy (IVIg), one effect of which is reduction of cytokine levels [51], has yielded promising results in a small trial in fibromyalgia patients [52].

Finally, it is clear that different individuals are differentially susceptible to developing generalized pain syndromes during their lifetimes [53]. The observation that exposure of humans to stress early in life, or even before birth, can induce life-long chronic susceptibility to develop pain syndromes, for example, migraine headaches [54], raises the intriguing possibility that early stress could trigger permanent changes in pain pathways in the nervous system. Consistent with this idea, recent studies found that maternal separation of neonatal rats

can cause the animals in adulthood to exhibit pain symptoms resembling irritable bowel syndrome [55]. Whether stress-induced hyperalgesic priming could underlie such long-term changes is not known since, at present, the persistence of hyperalgesic priming has only been studied up to 3 weeks[14].

Stress-induced hyperalgesic priming and other chronic pain conditions

Although not ordinarily classified as generalized pain syndromes, other chronic conditions could also involve a component of stress-induced hyperalgesic priming. For example, stress-induced exacerbation of pain in rheumatoid arthritis³⁷ and colitis³⁸ is well recognized, and this effect might arise from stress-induced priming of nociceptors making them more susceptible to the hyperalgesic effect of the elevated levels of inflammatory cytokines present in these inflammatory diseases [56,57]. In addition, stress itself increases cytokine levels [30], which would further exacerbate pain.

A number of other stress-related psychological disorders that are not ordinarily thought of as primarily pain conditions are, however, associated with generalized pain. For example, generalized pain may be the major debilitating symptom in post-traumatic stress disorder (PTSD) [58,59], chronic fatigue syndrome [60] and depression [61]. The tight linkage between such stress-related psychological disorders and pain (*e.g.*, the “depression-pain dyad”) may reflect that stress not only induces psychological symptoms, but may also directly activate the neuropathological mechanism of hyperalgesic priming.

Other chronic pain disorders, classified as “neuropathic” because they are caused by damage or dysfunction in the nervous system, are notoriously resistant to treatment even with potent narcotic analgesics [62]. Much research into the stress-induced exacerbation of neuropathic pain has focused on direct interaction of stress-activated sympathetic nerve fibers with sensory nerve fibers at sites of nerve injury [63,64], and consistent with this idea, destruction of sympathetic nerve fibers (sympathectomy) relieves symptoms in some of these patients. However, sympathectomy is often ineffective [65], and recent experimental evidence suggests that the dominant effect of stress in some neuropathic pain conditions may be the induction of hyperalgesic priming -- painful peripheral neuropathy induced by alcohol consumption in rats is abolished when stress axes are ablated [66].

Our proposal that hyperalgesic priming is a principal mechanism in an array of chronic pain syndromes might appear to result in an incongruous grouping of pain conditions that have traditionally been considered to be separate entities. To the contrary, however, this proposal conforms with a growing awareness that the attempt to create specific diagnostic categories has under-emphasized commonalities among these conditions. Thus, for example, in view of the difficulty in separating them diagnostically, and that their coexistence within patients is so common, it has also been suggested that fibromyalgia and irritable bowel syndrome should be considered different expressions of a single pathogenetic process [67], and it has been questioned whether posttraumatic stress disorder, tenderness, and fibromyalgia syndrome are in fact different entities [58]. Even repetitive stress disorders, which seem more localized and linked to more specific injuries, are now recognized to share with generalized pain syndromes a very strong pathophysiological component of psychosocial stress [68].

A wider role for PKC ϵ -dependent “priming” in other stress-induced states of altered reactivity?

This review is primarily concerned with the role of PKC ϵ -dependent changes in neuronal excitability in the transition from acute to chronic pain, which has been termed “hyperalgesic priming.” However, it seems unlikely that this cellular mechanism has evolved specifically to

modulate pain sensitivity, and thus it may be informative to view it in the wider context of excitable cells in general. We speculate that “hyperalgesic” priming constitutes one aspect of a more basic phenomenon in which PKC ϵ in excitable cells responds to stressful events by altering the cells’ reactivity to future insults. This idea converges with the emerging concept of PKC ϵ signaling as a “stress-sensing” cellular mechanism [69].

Probably the most intensively investigated function of PKC ϵ is its role in cardiac preconditioning [70], a phenomenon that conforms well with the concept of PKC ϵ as a stress-sensing trigger of altered excitability. In cardiac preconditioning a brief episode of ischemia followed by reperfusion induces changes in cardiac myocytes, lasting for weeks, that enable them to survive a future, more severe, ischemic event. Activation of PKC ϵ is both required and sufficient to trigger the cascade of signaling pathways that ultimately alter the response of calcium handling mechanisms to ischemic stress.

In a similar phenomenon, termed neuronal preconditioning, a variety of sublethal cellular stressors can prepare neurons to respond to a subsequent episode of lethal ischemia via PKC ϵ -dependent mechanisms [71]. Perhaps more closely related to the *hyperexcitability* which is the hallmark of hyperalgesic priming, ischemic stress can also induce long-term hyperexcitability of hippocampal neurons that involves the activation of L-type calcium channels and NMDA receptors [72]. It has been suggested that PKC ϵ activity may be crucial to this hyperexcitability, and as such is a potential target of anti-epileptic therapy [73].

Finally, anxiety may be viewed as another type of chronic hyper-reactive state in which repeated stressors induce exaggerated fear responses to future stress. From this perspective, it is intriguing to note that knockdown of PKC ϵ in the amygdala can reduce anxiety-like behavior in mice (induced by exposure to open field or elevated maze) [74]. Perhaps affective disorders characterized by excessive anxiety, like post-traumatic stress disorder, represent a central nervous system correlate of PKC ϵ -dependent hyperalgesic priming of primary afferent nerve fibers.

Conclusion

In summary, an understanding of PKC ϵ -dependent hyperalgesic priming may provide fundamental insights into the cellular mechanisms that underlie a diverse range of pain conditions, including what may be the most important single issue for improving the clinical treatment of pain: cellular mechanisms that cause the transition from acute to chronic pain states. PKC ϵ presents a promising target for the development of novel pharmacological strategies for the treatment of pain: expression of PKC ϵ is preferentially expressed in nociceptive neurons, and it plays a crucial role in chronic hyperexcitability but its inhibition causes little disruption in normal sensory function.

In addition to the possibility of defining a key mechanism of nociceptor hyperexcitability in chronic pain, research into hyperalgesic priming might help illuminate other puzzling issues in nociceptor physiology. For example, opioid-induced hyperalgesia is a paradoxical increase in pain associated with the development of tolerance to opiate analgesic drugs, which complicates opiate withdrawal and is thought to underlie analgesic rebound headache. That opioid-induced hyperalgesia has been found to be PKC-dependent and to involve a switch in G-protein-coupling (of the μ -opioid receptor) [75] suggests a possible mechanistic relationship to hyperalgesic priming.

Finally, recognizing parallels between hyperalgesic priming and a broad range of other stress-induced states of altered cellular reactivity, may not only encourage new lines of investigation in these disparate fields of investigation, but perhaps lead to a more unified concept of the physiological role of PKC ϵ .

Glossary

Cytokine, The term “cytokine” historically referred to proteins, like interleukins and TNF- α , released from immune cells to modulate local cellular responses to injury, infection and inflammation. The current view of cytokines has broadened considerably. For example, in the context of hyperalgesic priming, epinephrine that is released in inflamed tissues where it sensitizes primary afferent nociceptors is considered to act as a cytokine.; **Fibromyalgia**, The principal symptoms of fibromyalgia are chronic widespread pain and painful response to touch. The American College of Rheumatology defines the diagnosis of fibromyalgia by the presence of both: 1) history of widespread pain lasting more than three months—in all four quadrants of the body, i.e., both above and below the waist on both sides of the body, and 2) pain can be elicited from at least 11 of 18 pre-defined points on the body (“tender points”) upon stimulation with 4 kilograms of force.; **Generalized Pain Syndrome**, Generalized pain syndromes are a diverse group of disorders in which chronic pain is present in widespread areas of the body in the absence of any clear noxious stimulus. Some of the most prevalent generalized pain syndromes are fibromyalgia, irritable bowel syndrome, and interstitial cystitis. Generalized pain is also an important and debilitating symptom in other disorders in which pain is not the foremost defining characteristic, including chronic fatigue syndrome and post-traumatic stress disorder. Many of these disorders are comorbid conditions, often occurring together in individual patients.; **Hyperalgesic Priming**, An operational definition of hyperalgesic priming is: a neuroplastic change in the primary afferent nociceptor that causes PGE₂-induced hyperalgesia to last at least 24 hours and to become dependent on PKC ϵ .; **Nociceptor**, A nociceptor is a sensory neuron giving rise to a small-diameter nerve fiber that is activated by noxious (potentially tissue damaging) stimuli. Activity in nociceptors usually elicits the human perception of pain.; **PKC ϵ** , A member of the “novel” class of protein kinase C isoforms that are activated by diacylglycerol or phorbol ester, but not by calcium..

References

1. International Association for the Study of Pain Task Force on Taxonomy: Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. 1994. p. 222
2. Magni G. On the relationship between chronic pain and depression when there is no organic lesion. *Pain* 1987;31:1–21. [PubMed: 3320879]
3. Croft P, et al. The prevalence of chronic widespread pain in the general population. *J Rheumatol* 1993;20:710–713. [PubMed: 8496870]
4. Brekke M, et al. Severity of musculoskeletal pain: relations to socioeconomic inequality. *Soc Sci Med* 2002;54:221–228. [PubMed: 11824927]
5. Casey, C. Young, et al. Transition from acute to chronic pain and disability: A model including cognitive, affective, and trauma factors. *Pain*. 2007
6. Kovacs FM, et al. The transition from acute to subacute and chronic low back pain: a study based on determinants of quality of life and prediction of chronic disability. *Spine* 2005;30:1786–1792. [PubMed: 16094282]
7. Cahana A, Forster A. Mechanisms by which acute orofacial pain becomes chronic. *Rev Stomatol Chir Maxillofac* 2006;107:156–160. [PubMed: 16804482]
8. Fransen M, et al. Risk factors associated with the transition from acute to chronic occupational back pain. *Spine* 2002;27:92–98. [PubMed: 11805644]
9. Biondi DM. Is migraine a neuropathic pain syndrome? *Curr Pain Headache Rep* 2006;10:167–178. [PubMed: 18778570]
10. Cerbo R, et al. The importance of anxiety and depression as factors in chronicization of primary headaches. *J Headache Pain* 2000;1:S45–S48.
11. Kayser V, et al. Sensitization of the nervous system, induced by two successive hindpaw inflammations, is suppressed by a local anesthetic. *Brain Res* 1998;794:19–27. [PubMed: 9630485]

12. Parada CA, et al. Transient attenuation of protein kinase C epsilon can terminate a chronic hyperalgesic state in the rat. *Neuroscience* 2003;120:219–226. [PubMed: 12849754]
13. Clatworthy AL, et al. Role of peri-axonal inflammation in the development of thermal hyperalgesia and guarding behavior in a rat model of neuropathic pain. *Neurosci Lett* 1995;184:5–8. [PubMed: 7739805]
14. Aley KO, et al. Chronic hypersensitivity for inflammatory nociceptor sensitization mediated by the epsilon isoform of protein kinase C. *J Neurosci* 2000;20:4680–4685. [PubMed: 10844037]
15. Parada CA, et al. Chronic hyperalgesic priming in the rat involves a novel interaction between cAMP and PKCepsilon second messenger pathways. *Pain* 2005;113:185–190. [PubMed: 15621379]
16. Levine, JD.; Reichling, DB. Textbook of Pain. Wall, P.D. and Melzack, R.; Churchill Livingstone: 2005. Peripheral mechanisms of inflammatory pain.
17. Joseph EK, et al. Hyperalgesic priming in the rat demonstrates marked sexual dimorphism. *Pain* 2003;105:143–150. [PubMed: 14499430]
18. Taylor BK, et al. Persistent cardiovascular and behavioral nociceptive responses to subcutaneous formalin require peripheral nerve input. *J Neurosci* 1995;15:7575–7584. [PubMed: 7472508]
19. Koltzenburg M, et al. Nociceptor modulated central sensitization causes mechanical hyperalgesia in acute chemogenic and chronic neuropathic pain. *Brain* 1994;117:579–591. [PubMed: 8032867]
20. Cervero F. Visceral pain: mechanisms of peripheral and central sensitization. *Ann Med* 1995;27:235–239. [PubMed: 7632420]
21. Price DD, et al. Peripheral and central contributions to hyperalgesia in irritable bowel syndrome. *The Journal of Pain* 2006;7:529–535. [PubMed: 16885007]
22. Staud R, et al. Enhanced central pain processing of fibromyalgia patients is maintained by muscle afferent input: A randomized, double-blind, placebo-controlled study. *Pain*. 2009
23. Sheon RP. Repetitive strain injury. 2. Diagnostic and treatment tips on six common problems. *The Goff Group. Postgrad Med* 1997;102:72–78. [PubMed: 9336597]
24. Bendtsen L, Jensen R. Tension-type headache: the most common, but also the most neglected, headache disorder. *Curr Opin Neurol* 2006;19:305–309. [PubMed: 16702840]
25. Buchgreitz L, et al. Increased pain sensitivity is not a risk factor but a consequence of frequent headache: A population-based follow-up study. *Pain* 2008;137:623–630. [PubMed: 18061350]
26. Imbe H, et al. Stress-induced hyperalgesia: animal models and putative mechanisms. *Front Biosci* 2006;11:2179–2192. [PubMed: 16720304]
27. Khasar SG, et al. Repeated sound stress enhances inflammatory pain in the rat. *Pain* 2005;116:79–86. [PubMed: 15936144]
28. Dina OA, et al. Activation of Gi induces mechanical hyperalgesia poststress or inflammation. *Neuroscience* 2009;160:501–507. [PubMed: 19275929]
29. Khasar SG, et al. Stress induces a switch of intracellular signaling in sensory neurons in a model of generalized pain. *J Neurosci* 2008;28:5721–5730. [PubMed: 18509033]
30. Maes M, et al. The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety. *Cytokine* 1998;10:313–318. [PubMed: 9617578]
31. Bruckle W, Zeidler H. Fibromyalgia. *Internist (Berl)* 2004;45:923–934. [PubMed: 15309316]
32. Gupta A, et al. Pressure pain thresholds and tender point counts as predictors of new chronic widespread pain in somatising subjects. *Ann Rheum Dis* 2007;66:517–521. [PubMed: 17012291]
33. Hong CZ, Hsueh TC. Difference in pain relief after trigger point injections in myofascial pain patients with and without fibromyalgia. *Archives of Physical Medicine and Rehabilitation* 1996;77:1161–1166. [PubMed: 8931529]
34. Hong CZ, Simons DG. Pathophysiologic and electrophysiologic mechanisms of myofascial trigger points. *Archives of Physical Medicine and Rehabilitation* 1998;79:863–872. [PubMed: 9685106]
35. Manningham, R. The symptoms, nature, causes, and cure of the febricula, or little fever. *J Robinson; London*: 1750.
36. Staud R. Fibromyalgia pain: do we know the source? *Curr Opin Rheumatol* 2004;16:157–163. [PubMed: 14770104]

37. Van Houdenhove B, Egle UT. Fibromyalgia: a stress disorder? Piecing the biopsychosocial puzzle together. *Psychother Psychosom* 2004;73:267–275. [PubMed: 15292624]
38. Forslind K, et al. Does primary fibromyalgia exist? *Br J Rheumatol* 1990;29:368–370. [PubMed: 2224406]
39. Markman M, et al. Use of low-dose oral prednisone to prevent paclitaxel-induced arthralgias and myalgias. *Gynecol Oncol* 1999;72:100–101. [PubMed: 9889038]
40. Clark S, et al. A double blind crossover trial of prednisone versus placebo in the treatment of fibrositis. *J Rheumatol* 1985;12:980–983. [PubMed: 3910836]
41. Yunus MB, et al. Fibromyalgia syndrome among the elderly. Comparison with younger patients. *J Am Geriatr Soc* 1988;36:987–995. [PubMed: 3171051]
42. Staud R. Are patients with systemic lupus erythematosus at increased risk for fibromyalgia? *Curr Rheumatol Rep* 2006;8:430–435. [PubMed: 17092442]
43. Wolfe F, Michaud K. Severe rheumatoid arthritis (RA), worse outcomes, comorbid illness, and sociodemographic disadvantage characterize ra patients with fibromyalgia. *J Rheumatol* 2004;31:695–700. [PubMed: 15088293]
44. Cruz BA, et al. Higher prevalence of fibromyalgia in patients infected with human T cell lymphotropic virus type I. *J Rheumatol* 2006;33:2300–2303. [PubMed: 17086610]
45. Wallace DJ. Is there a role for cytokine based therapies in fibromyalgia. *Curr Pharm Des* 2006;12:17–22. [PubMed: 16454720]
46. Sommer C, et al. Etiology and pathophysiology of fibromyalgia syndrome and chronic widespread pain. *Schmerz* 2008;22:267–282. [PubMed: 18470541]
47. Thompson ME, Barkhuizen A. Fibromyalgia, hepatitis C infection, and the cytokine connection. *Curr Pain Headache Rep* 2003;7:342–347. [PubMed: 12946286]
48. Hedenberg-Magnusson B, et al. Pain mediation by prostaglandin E2 and leukotriene B4 in the human masseter muscle. *Acta Odontol Scand* 2001;59:348–355. [PubMed: 11831483]
49. Wang H, et al. Circulating cytokine levels compared to pain in patients with fibromyalgia -- a prospective longitudinal study over 6 months. *J Rheumatol* 2008;35:1366–1370. [PubMed: 18528959]
50. Hench PK. Secondary fibrositis. *Am J Med* 1986;81:60–62. [PubMed: 3464209]
51. Le Pottier L, et al. Intravenous immunoglobulin and cytokines: focus on tumor necrosis factor family members BAFF and APRIL. *Ann N Y Acad Sci* 2007;1110:426–432. [PubMed: 17911457]
52. Caro XJ, et al. A subset of fibromyalgia patients have findings suggestive of chronic inflammatory demyelinating polyneuropathy and appear to respond to IVIg. *Rheumatology (Oxford)* 2008;47:208–211. [PubMed: 18208823]
53. Affleck G, et al. Person and contextual features of daily stress reactivity: individual differences in relations of undesirable daily events with mood disturbance and chronic pain intensity. *J Pers Soc Psychol* 1994;66:329–340. [PubMed: 8195989]
54. Maneyapanda SB, Venkatasubramanian A. Relationship between significant perinatal events and migraine severity. *Pediatrics* 2005;116:e555–8. [PubMed: 16199683]
55. Coutinho SV, et al. Neonatal maternal separation alters stress-induced responses to viscerosomatic nociceptive stimuli in rat. *Am J Physiol Gastrointest Liver Physiol* 2002;282:G307–16. [PubMed: 11804852]
56. Feldmann M, et al. Role of cytokines in rheumatoid arthritis. *Annu Rev Immunol* 1996;14:397–440. [PubMed: 8717520]
57. Gotteland M, et al. Local and systemic liberation of proinflammatory cytokines in ulcerative colitis. *Dig Dis Sci* 1999;44:830–835. [PubMed: 10219845]
58. Amital D, et al. Posttraumatic stress disorder, tenderness, and fibromyalgia syndrome: are they different entities? *J Psychosom Res* 2006;61:663–669. [PubMed: 17084145]
59. Cohen H, et al. Prevalence of post-traumatic stress disorder in fibromyalgia patients: overlapping syndromes or post-traumatic fibromyalgia syndrome? *Semin Arthritis Rheum* 2002;32:38–50. [PubMed: 12219319]

60. Fukuda K, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med* 1994;121:953–959. [PubMed: 7978722]
61. Bair MJ, et al. Depression and pain comorbidity: a literature review. *Arch Intern Med* 2003;163:2433–2445. [PubMed: 14609780]
62. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet* 1999;353:1959–1964. [PubMed: 10371588]
63. Levine JD, et al. Clinical response to regional intravenous guanethidine in patients with rheumatoid arthritis. *J Rheumatol* 1986;13:1040–1043. [PubMed: 3550071]
64. Devor M. Neuropathic pain and injured nerve: peripheral mechanisms. *Br Med Bull* 1991;47:619–630. [PubMed: 1794075]
65. Mailis A, Furlan A. Sympathectomy for neuropathic pain. *Cochrane Database Syst Rev*. 2003CD002918
66. Dina OA, et al. Alcohol-induced stress in painful alcoholic neuropathy. *Eur J Neurosci* 2008;27:83–92. [PubMed: 18093169]
67. Veale D, et al. Primary fibromyalgia and the irritable bowel syndrome: different expressions of a common pathogenetic process. *Br J Rheumatol* 1991;30:220–222. [PubMed: 2049586]
68. Tjepkema M. Repetitive strain injury. *Health Rep* 2003;14:11–30. [PubMed: 14608793]
69. Barnett ME, et al. Protein kinase C as a stress sensor. *Cell Signal* 2007;19:1820–1829. [PubMed: 17629453]
70. Saurin AT, et al. Targeted disruption of the protein kinase C epsilon gene abolishes the infarct size reduction that follows ischaemic preconditioning of isolated buffer-perfused mouse hearts. *Cardiovasc Res* 2002;55:672–680. [PubMed: 12160964]
71. Chou WH, Messing RO. Protein kinase C isozymes in stroke. *Trends Cardiovasc Med* 2005;15:47–51. [PubMed: 15885569]
72. Godukhin O, et al. Neuronal hyperexcitability induced by repeated brief episodes of hypoxia in rat hippocampal slices: involvement of ionotropic glutamate receptors and L-type Ca(2+) channels. *Neuropharmacology* 2002;42:459–466. [PubMed: 11955517]
73. Toth M. The epsilon theory: a novel synthesis of the underlying molecular and electrophysiological mechanisms of primary generalized epilepsy and the possible mechanism of action of valproate. *Med Hypotheses* 2005;64:267–272. [PubMed: 15607553]
74. Lesscher HM, et al. Amygdala protein kinase C epsilon regulates corticotropin-releasing factor and anxiety-like behavior. *Genes Brain Behav*. 2007
75. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology* 2006;104:570–587. [PubMed: 16508405]

Figure 1. Chronic hyperalgesia associated with inflammation-induced hyperalgesic priming
(A) In the normal (unprimed) paw, a small intradermal injection of prostaglandin E₂ (PGE₂) causes an episode of acute hyperalgesia (decreased threshold for paw withdrawal from a pressure stimulus) lasting less than 4 hours. **(B)** Injection of the inflammogen, carrageenan, causes an episode of hyperalgesia that lasts less than 4 days (gray-filled curve). After carrageenan-induced hyperalgesia is no longer present, the paw remains in a latent state of hyperalgesic priming. In this state, an injection of PGE₂, which would cause only acute hyperalgesia in the normal (unprimed) paw, now induces an additional chronic hyperalgesia. In comparison to the unprimed paw, this hyperalgesia is greater in magnitude and is greatly prolonged, lasting at least 3 weeks.

Figure 2. PKC ϵ -dependence of hyperalgesia in the primed state demonstrated by antagonism antisense oligonucleotide

PKC ϵ is synthesized in cell bodies of sensory neurons in the dorsal root ganglia (purple dot) and transported along the sensory nerve axons (purple line) to nerve endings in the paw where it plays a role in nociception. To reduce expression of PKC ϵ in the sensory nerve, oligonucleotide antisense to PKC ϵ (blue) is injected into the intrathecal space of the spinal cord where it is taken up by dorsal root ganglion neurons. The resultant reduction in PKC ϵ transported to the sensory nerve ending eliminates the priming-induced enhancement of hyperalgesia induced by PGE $_2$ (red) in the paw.

Figure 3. Priming-induced switch in second messenger pathways of cytokine hyperalgesia

This simple schematic illustrates the switch in hyperalgesia induced by prostaglandin E_2 (PGE_2) acting on a prostaglandin E receptor (EP-R) on the surface of a nociceptive primary afferent nerve ending (purple). In the normal (unprimed) paw PGE_2 -induced hyperalgesia is mediated by G_s G-protein activation of protein kinase (PKA) activity which ultimately causes an acute episode of hyperalgesia (green-filled curve) by presumed modulation of ion channels (sinusoidal arrow). In the primed paw, PGE_2 acts on the same EP-R receptors, but in addition to the normal PKA-mediated pathway to acute hyperalgesia, an additional pathway involving $G_{i/o}$ G-protein activation of $PKC\epsilon$, leading to an amplified and prolonged chronic hyperalgesia (red-filled curve) in addition to the PKA-mediated acute hyperalgesia.

Table 1

Prevalence of chronic pain conditions possibly involving hyperalgesic priming

Condition	Approx Prevalence in General Population
Undifferentiated Chronic Widespread Pain	4-55%
Irritable Bowel	10-15%
Carpal tunnel syndrome	14%
Fibromyalgia	2-4%
Chronic Fatigue Syndrome	0.1-3%
Post-Traumatic Stress Disorder	1-2%
Interstitial Cystitis	0.3-0.4%