

Mini Review

On the enigma of pain and hyperalgesia: A molecular perspective

John J. Haddad¹

Molecular Signaling Research Group, Division of Biological Sciences, Departments of Biology and Biomedical Sciences, Faculty of Arts and Sciences, Lebanese International University, Beirut, Lebanon

Department of Biology, Faculty of Sciences, University of Balamand, Balamand, Tripoli, Lebanon

Department of Clinical Laboratory Sciences, Faculty of Health Sciences, University of Balamand, Aschrafieh, St. Georges Hospital and Medical Center, Beirut, Lebanon

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Abstract

Pain is a common symptom of injuries and inflammatory-related conditions. The perception of pain, commonly known as nociception, depends on integrated receptors and molecular pathways. Inflammatory mediators are involved in the genesis, persistence, and severity of pain. Noxious stimuli can trigger a cascade of inflammatory loops that feedback onto sensory modalities and domains of the CNS, in an attempt to alert the brain of deregulated homeostasis. Understanding the mechanisms of pain continue to make nociception and hyperalgesia a burgeoning field of research.

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Introduction and background

What is pain?

Pain is a common symptom of injuries and diseases [1]. Nerve cell endings or receptors, commonly known as nociceptors, are central to pain sensation. Nociceptors have the ability to relay information to the CNS, thus indicating the location, nature, and intensity of the ensuing pain [2].

Nociceptive signaling

A nociceptive stimulus unleashes a cascade of events throughout the nervous system, which can ultimately loop back to the site of injury. This response prompts cells in the injured area to release chemicals that trigger an immune

response, thus influencing the intensity and duration of pain [3–5].

The inflammatory lynchpin

The inflammatory milieu that usually precedes pain is transcriptionally regulated [6]. NF- κ B is a major transcription factor, essentially involved in mediating inflammatory processes [7,8], which exacerbate pain, hyperalgesia, and pain sensation [9].

Current strategies aiming at controlling the origin, and propagation, of pain, as well as its manifestations, reveal the crucial role that this transcription factor has in modulating pain and nociception [10].

Pain and nociception—current concepts

Nociceptive signaling can be considered as a correlate of motor reaction (reflex mainly) aiming at protecting the living tissue. Nerve endings of thinly myelinated and/or unmyelinated fibers are activated by excessive stimulation

¹ Retrospect address: Severenghaus-Radiometer Research Laboratories, Department of Anesthesia & Perioperative Care, Faculty of Medicine, University of California, San Francisco, CA, USA.

E-mail address: john.haddad@yahoo.co.uk

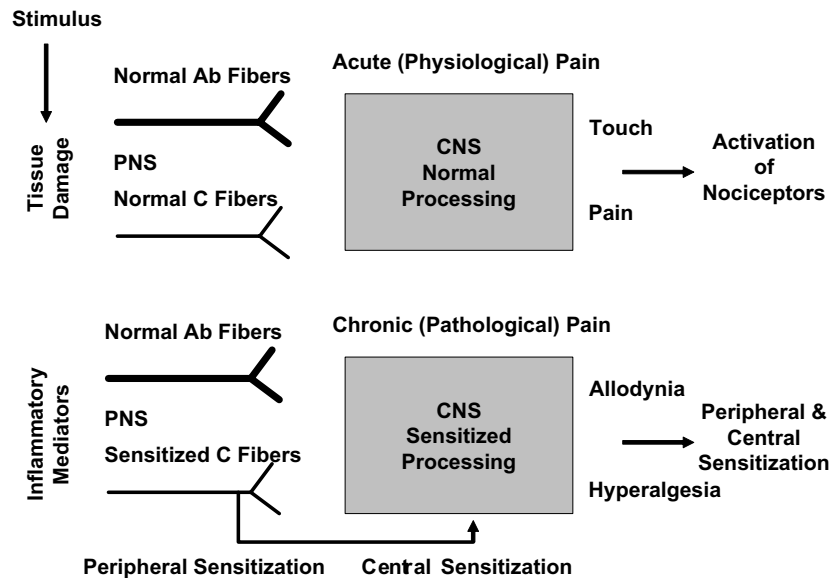


Fig. 1. A diagrammatic scheme exhibiting pain pathways, processing, and sensitization due to tissue damage and inflammatory mediators.

(e.g., mechanical, chemical, and thermal) that can lead ultimately to a damage or injury [3,11–13] (Fig. 1).

Pain as a sensory modality

The beneficial aspect of this signaling and its crucial role for survival are strongly suggested from the major deformities and limited life-span of individuals with congenital analgesia despite all measures made to compensate for this absence. From this aspect, acute nociception can be considered as a sensory modality like touch and taste, with the added survival value just alluded to Ref. [3].

When nociceptive signaling persists for a long period of time exceeding its determining causes, it becomes a pathological entity by itself to be potentially labeled as chronic pain [14]. The development of this entity can be considered as an end result of a persistent cross-talk between environmental and neurogenic factors leading, ultimately, to a vicious cycle.

This condition usually occurs following tissue injury, inflammation, and ischemic damage, which can result in transient or chronic changes in the environment of the nociceptors and in the function of the sensory nerve fibers [15].

Inflammatory pain

In the case of inflammation or tissue damage, various inflammatory mediators and products of tissue breakdown are released within a time period ranging from minutes to hours.

These include bradykinin, proteases, histamine, serotonin (5-hydroxytryptamine, 5-HT), nitric oxide (NO), prostanooids, neurotrophins, cytokines, ATP, protons, and other mediators that are released by injured and/or affected (including immune) cells [3].

Most of these inflammatory products can irritate or sensitize the nerve terminals in the affected area, which can lead to two main consequences: nociceptive signaling and neurogenic inflammation [16]. The latter can contribute to the direct release of neuropeptides (SP, CGRP) [17], or indirect (reflex) release of catecholamines through the sympathetic efferents [18].

Both neuropeptides and catecholamines are well known for their vasoactive properties and their effects on various immune cells [19].

Neurogenic pain

The end result of the cross-talk between immunogenic and neurogenic inflammation [15] is chronic pain, on one side, and the various breakdown products in the inflammatory ‘soup’ or milieu, on the other hand [20], thus leading to the perpetuation of inflammation and to induction of critical changes in the properties of nerve terminals.

Several important changes in the properties of afferent and efferent neurons are observed during chronic pain and inflammation [12].

These include, as illustration: (i) activation of silent or dormant nociceptors [21]; (ii) peripheral and central sensitization, leading to hyperalgesia (increased reactivity to nociceptive stimuli) and allodynia (nociceptive signaling and/or reaction induced by innocuous stimuli under normal conditions) [22]; (iii) changes in the ionic channels (Na^+ channels) [23] and in the properties of membrane receptors [15]; (iv) significant alterations of the electrical signaling behavior of the injured and the intact neighboring fibers [24].

This constellation of events can occur totally, or in part, in various clinical and experimental situations leading to chronic pain, thus losing its survival value as an alarm signal.

Chronic pain—is it spontaneous?

An important focus of pain research has been the study of chronic pain mechanisms, particularly the processes that lead to the abnormal sensitivity—spontaneous pain and hyperalgesia—that is associated with these states.

For some time it has been recognized that inflammatory mediators released from immune cells can contribute to these persistent pain states. However, it has only recently become clear that immune cell products might have a crucial role not just in inflammatory pain, but also in neuropathic pain caused by damage to peripheral nerves or to the CNS [25].

Because of the presence of a myriad of models alleged with pain and pain mechanisms, it is imperative, therefore, to dislodge the concepts applied with experimental models of pain from those associated with pain in humans, likely to be perceived, psychologically, physiologically, and mechanistically, at differential levels.

Recent reports include the inflammatory mediators in the special category of neuropathic pains, that are initially classified as resulting from discrete or obvious damage to the central or peripheral nervous systems. These reports are based on animal experimentations showing an attenuation of neuropathic manifestations by treatment with anti-inflammatory drugs and especially specific antagonists to pro-inflammatory cytokines [26].

This implies that pro-inflammatory mediators can constitute an end product of neurogenic inflammation and can contribute further to the neuropathic pain by increasing the inflammatory component of the vicious cycle [27].

Designed strategies for combating pain

Various strategies have been adopted to stop the ‘snow ball’ phenomenon at the origin of chronic pain [28]. These include targeting of various mediators, considered to play a key role in the inflammatory cascade, and based on the use of specific antagonists to prostanoids, histamine, neurotrophins, and cytokines [29].

A new strategy has recently emerged and is based on targeting the transcription factors at the origin of expression of several pro-inflammatory mediators and cytokines. The transcription factor of immense interest is, undoubtedly, NF- κ B.

The following section will focus on the outcome of contemporary research to understand the alleviation of chronic pain through specific targeting of NF- κ B potentiating mechanisms.

Molecular regulation of pain

NF- κ B and the regulation of pain—molecular aspects: is NF- κ B a lynchpin?

Nociception and the molecular regulation of pain involve NF- κ B and related cofactors.

However, the precise mechanisms by which NF- κ B regulates pain-related pathways are yet to be unraveled. Accumulating mounting evidence thereby indicates an integral role for this transcription factor in the regulation of pain signaling pathways [30].

With this in mind, in the upcoming sections there will be specific elaboration on the molecular mechanisms and pathways associated with NF- κ B-mediated regulation of pain.

The repercussions of NF- κ B activation at localized and centralized nervous sites

Members of the Rel/NF- κ B family of eukaryotic transcription factors are activated within the CNS in pathological settings of apoptosis and neurological diseases [31]. The effect of NF- κ B activation on pain signaling pathways varies with the versatility of the site of activation.

Certain drugs and/or pain killers can act centrally to inhibit NF- κ B activation in peripheral acute inflammation via a descending neural pathway [32]. Conversely, it was shown that IL-1 β -induced NF- κ B activation may play a major role in transmission of immune signals from the periphery to the brain [33]. This bidirectional influence of NF- κ B is central to deciphering the molecular codes associated with pain and nociception at different levels of hierarchy of nervous sites.

NF- κ B seems to be able to modulate inflammation and associated pain mechanisms at the level of the spinal cord. For example, the spinal activation of NF- κ B induced cyclooxygenase (COX)-2 upregulation and contributed to inflammatory pain hypersensitivity [30]. Conversely, inhibition of NF- κ B activation by the antioxidant/prooxidant chemical pyrrolidine dithiocarbamate (PDTC) [34] attenuated inflammation and oxidative stress after experimental spinal cord trauma [35].

Recent work also provided evidence that NF- κ B may participate in the regulation of neuronal activity-dependent transcription and behavior under pathophysiologic conditions. At the level of the brain, for example, it was noted that the inhibition of an upstream kinase associated with the phosphorylation of I κ B (IKK) decreased LPS-induced COX-2 gene expression in C6 rat glioma cells [36], implicating a potential mechanism for anti-inflammatory pain therapy. The anti-inflammatory theory on the alleviation of pain is subsequently further promoted below.

The effect of NF- κ B on inflammatory mediators and inflammatory pain

The association between NF- κ B and the regulation of inflammatory pain essentially emerged with the role of the inflammatory enzyme COX and arachidonic acid (AA) [37]. To cite an example, I refer to acetylsalicylic acid (aspirin), which is well known to inhibit COX and the release of AA; aspirin is purportedly the drug that is most

commonly self-administered to reduce inflammation, swelling (edema), and pain [38].

NF- κ B-mediated upregulation of COX is crucial for the release PGs, which in turn exacerbate inflammatory pain and hyperalgesia. Acetylsalicylic acid may also contribute to the regulation of apoptosis associated with inflammation. Conversely, inhibition of COX expression by various mediators alleviates NF- κ B-dependent inflammatory pain.

NF- κ B-mediated pain transcriptional mechanisms

The effect of NF- κ B on galanin receptors

The signaling pathways mediating pain and nociception are, purportedly, transcriptionally controlled [39].

In support of this concept, the chromosomal location and transcriptional regulation of the human galanin-1 receptor gene (GALN1R), which mediates the effects of galanin as a neuroendocrine peptide in modulating pain processing and perception, revealed the existence of two NF- κ B sites [40].

These NF- κ B-related sites are located –269 and –809 bp upstream from the translational start site of NF- κ B. This indicates that GALN1R gene expression can be regulated as a consequence of inflammatory conditions associated with pain in a NF- κ B-dependent mechanism [40].

The effect of NF- κ B on kinin receptors

Inflammatory kinins (bradykinin and kallidin) are produced at sites of injury and inflammation; they serve a critical role in signaling tissue distress as well as organizing tissue responsiveness to injury [41].

The acute activation and prolonged sensitization of fine afferents are important in the protective responses that occur to minimize further tissue injury. However, the excessive release of inflammatory kinins may, in an effect similar to cytokines, exacerbate tissue injury and damage.

These inflammatory effects occur through the activation of B₂ receptors present on sensory neurons, resulting in a change of membrane excitability and altered cellular neurochemistry. B₂ receptor activation of a variety of tissues, including postganglionic sympathetic fibers, stimulates the production of several pro-inflammatory mediators, such as prostanoids and cytokines, which further interact with kinins and thus contribute to inflammation and hyperalgesia [16].

Similar to the effect of B₂ receptors, it has been shown that the increased expression of B₁ receptors may play a prominent role in inflammatory pain and hyperalgesia [42]. The B₁/B₂ kinin receptors, therefore, play a major role in the mediation of inflammatory and pain-related responses [41].

Molecular and pharmacological evidences show that the B₁ kinin receptor expression can be regulated through endogenous glucocorticoids by a mechanism dependent on NF- κ B activation [43]. For instance, paw edema and contraction of portal vein, mediated by B₁ agonist des-Arg(9)-BK in adrenalectomized (ADX) rats, were inhibited

by dexamethasone or COX-2 inhibitor, meloxicam and with PDTC, a NF- κ B inhibitor.

Interestingly, treatment of ADX rats with dexamethasone, PDTC or a combination of dexamethasone/PDTC blocked NF- κ B activation caused by the absence of endogenous glucocorticoid [43]. This mechanism supports the notion that NF- κ B-mediated regulation of kinin receptors can modulate inflammation and inflammatory pain. To recapitulate, kinins and kinins' receptors are potent mediators of inflammatory pain, ostensibly via the regulation of NF- κ B.

The effect of NF- κ B decoys on pain

Pro-inflammatory cytokines and related mediators have been reported to be involved in the genesis, persistence, and severity of neuropathic pain, following nerve injury, as discussed above.

The theme that emerges quickly is focused on the mechanisms that 'non-classically' blockade NF- κ B. Decoys are at the forefront.

In illustration, for example, in a neuropathic pain model, NF- κ B inhibition using a specific decoy has been shown to decrease thermal hyperalgesia via the suppression of the expression of mRNA of inflammatory cytokines, inducible NOS (iNOS), and adhesion molecules at the site of nerve injury [44].

Another NF- κ B decoy was also reported to downregulate inflammatory pain associated with restenosis in coronary heart disease [45].

Furthermore, since cytokine imbalance in acute coronary syndrome was a major cause of inflammatory pain associated with this condition, it was postulated that the downregulation of cytokine release via transcriptional control could be of therapeutic value [46].

In corroboration, another report indicated that the modulation of peripheral inflammation in sensory ganglia by NF- κ B decoy oligodeoxynucleotide [47] is dependent on the regulation of the activity of c-Src kinase, a member of the non-receptor tyrosine kinase super family, a decreased level of p65 (RelA) NF- κ B subunit and an inhibition of COX-2 protein expression.

These observations may represent novel pathways for unraveling the molecular mechanisms of inflammatory pain. Therefore, amplifying intrinsic anti-inflammatory mechanisms may constitute potential avenues for the therapeutic intervention of inflammatory pain.

The effect of NF- κ B-related kinases on pain

I have touched previously on the significant role of upstream kinases in the regulation of NF- κ B and NF- κ B-mediated regulation of downstream pathways. Here, I talk in brevity about the role that upstream kinases play in the regulation of inflammatory pain.

The specific inhibition of IKK, the upstream kinase which phosphorylates I κ B thus leading to NF- κ B activation [34] (Fig. 2), was shown to downregulate hyperalgesia in inflammatory and neuropathic pain models [10]. Furthermore, inhibition of IKK activity was shown to prevent

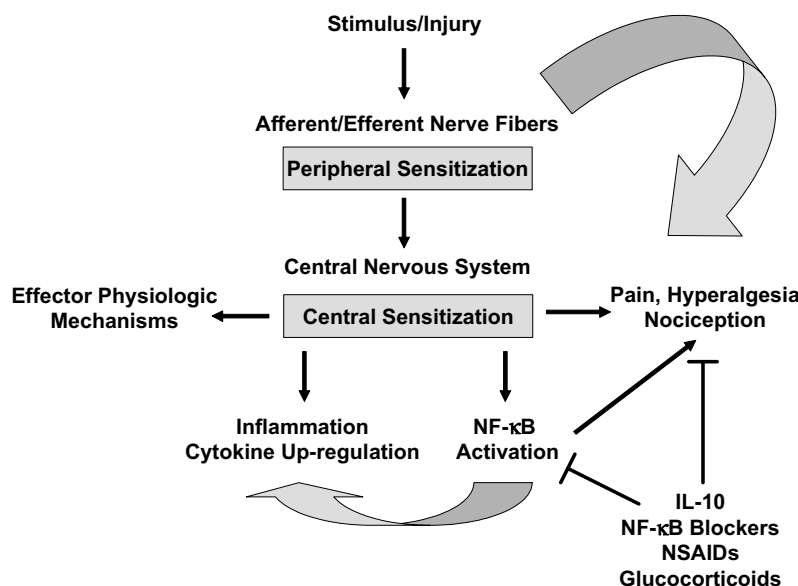


Fig. 2. NF- κ B and the regulation of putative pain signaling pathways.

injury, infection and stress-induced upregulation of pro-inflammatory genes, and reduce hyperalgesia and inflammation.

The involvement of IKK in pain-related mechanisms suggests that this kinase may prove to be a novel target in the treatment of pathological pain and inflammation.

To reinforce this theme, the inhibition of IKK activity was similarly shown to downregulate LPS-induced COX activation and associated inflammatory pain. For example, γ -mangostin, an extract purified from the fruit hull of the medicinal plant *Garcinia mangostana*, reduced PGE₂ release and COX-2 gene expression *in vitro* [36]. Furthermore, an *in vitro* IKK assay using immunoprecipitated IKK protein showed that γ -mangostin inhibited IKK activity in a concentration-dependent manner.

Consistently, γ -mangostin was also observed to decrease the LPS-induced I κ B degradation and phosphorylation. In addition, luciferase reporter assays showed that γ -mangostin reduced the LPS-inducible activation of NF- κ B- and human COX-2 gene promoter region-dependent transcription [36].

Taken together, therefore, the inhibition of IKK, and subsequently NF- κ B target genes, may decrease inflammatory pain and, essentially, may be a useful mechanism for theorizing anti-inflammatory drug development.

Another family of kinases that is crucial in the regulation of NF- κ B is MAPKs. For instance, the activation of the MAPK^{ERK} signaling cascade by excitotoxic spinal cord injury has been shown to implicate NF- κ B [48]. The mechanisms involved a series of transcriptional activators, including ELK-1 and CREB. These results clearly indicated that injury-induced activation of the MAPK^{ERK}/NF- κ B signaling cascade and the transcriptional upregulation of receptors critical in the development of chronic pain may be offset by the blockade of intracellular kinase cascades involved with pain-related behavior.

NF- κ B and the regulation of analgesia/anti-nociception mechanisms

NF- κ B, then, is a major regulator of analgesia and related mechanisms of pain regulation too. For instance, it has been observed that there was a decrease of the electroacupuncture (EA)-induced analgesic effects in NF- κ B₁ (p50) knockout mice (p50^{-/-}), suggesting that this transcription factor may play a crucial role in both low and high frequency EA-induced analgesia [49]. This was in concert with the intriguing role of NF- κ B in neuronal and immune cells mediating inflammation-induced analgesia [50].

What is the likely explanation for this sudden NF- κ B anti-inflammatory, analgesic effects? In order to understand this discrepancy and to reconcile the inflammatory and anti-inflammatory effects of this transcription factor, we have to decipher yet another code pertaining to the key regulatory elements associated with the expression of NF- κ B. Opioids are, of course, legitimate targets.

Analgesic opioids and their receptors are key players in a cross-talk between the nervous and immune systems (bidirectional neuro-immune interactions) [51]. For example, it is established that the endogenous opioid system is activated during inflammation as a physiological feedback mechanism to attenuate inflammatory pain. Nonetheless, what is the exact role of opioids in NF- κ B-dependent analgesia?

Among six putative NF- κ B binding sites on the μ -opioid receptor gene promoter, three *cis*-active elements at nt -174, -557, and -207 were identified using transfection experiments of reporter gene constructs, EMSA and *in vivo* binding studies with decoy oligonucleotides [50].

Allelic variation within the -557 element was reported to reduce its *trans*-activating potency, which may affect regulation of the μ -opioid receptor gene in persons carrying this mutation, suggesting a regulatory function of

inflammatory mediators in opioid-mediated processes in neuronal and immune cells, with possible impact on the complex of inflammation-induced analgesia [50].

Interestingly, excluding the effect of NF- κ B with the specific NF- κ B inhibitor sulfasalazine, two AP-1 elements, which differ in one nucleotide each from the classic AP-1 binding site, are delineated to positions –2388 and –1434 of the promoter of the human μ -opioid receptor gene [52]. This suggests that a potential cross-talk exists between NF- κ B and AP-1 sites in the regulation of opioid-related sites in inflammation.

Molecular events that result in loss of pain perception also implicate NF- κ B. For example, the receptor for advanced glycation end products (RAGE), which is associated with sustained NF- κ B activation in neuropathy, has a central role in sensory neuronal dysfunction [53].

Interestingly, NF- κ B activation was blunted in RAGE^{-/-} mice, demonstrating that the RAGE-NF- κ B axis may operate by mediating functional sensory deficits and that its inhibition may provide a therapeutic approach in neuropathy [53].

Anti-nociception was also reported to be associated with the downregulation of NF- κ B and other inflammatory mediators [54], thus reinforcing the aforementioned observation.

In contrast with the aforementioned, Frassdorf and colleagues [55] reported that NF- κ B was involved with morphine-induced myocardial protection and pain downregulation. Similar to the effect of LPS, morphine induced late preconditioning and activation of this transcription factor in the heart *in vivo*, suggesting the involvement of NF- κ B in the suppression of pain-related pathways implicated with acute coronary syndromes. This discrepancy in NF- κ B dual behavior as far as pain and hyperalgesia/analgesia is concerned has to do likely with the mechanisms and pathways involved with the regulation of this transcription factor.

In summary, it is observed that the inflammatory milieu, which initially is triggered as a protective mechanism, may untimely and unexpectedly evolve into a cascade of events and injuries exacerbated by the expression of NF- κ B and related cofactors.

This assumption of the duality of NF- κ B is squared on the complexity of the inflammatory cascade and its ramifications that may equally dissect into protective and/or injurious events, depending on selective pathways being activated. This may shed light on why pain perception, at least in humans, is so complex yet predictable! The mechanisms involved have yet to be deciphered.

NF- κ B-independent mechanisms in the regulation of pain

Despite the central role of NF- κ B in regulating pain and hyperalgesia, as noted, it has been reported that there likely exist NF- κ B-independent mechanism(s). For instance, sodium salicylate was shown to inhibit PGE₂ release when added together with IL-1 β , an effect that was independent

of NF- κ B activation, or COX-2 transcription/translation [37]. Whether other pathways are implicated has yet to be determined.

In corroboration, it has been postulated that sodium salicylate, at least in this specific model, was an effective inhibitor of COX-2 activity at concentrations far below those required to inhibit NF- κ B, a pathway that is displaced by AA signaling.

It seems likely that the duality of the nature of NF- κ B in regulating hyperalgesia and analgesia may pave the way for the emerging of other significant cofactors that have their share in controlling the mechanisms of pain and inflammatory-related pain.

I already have witnessed a role for MAPKs. My colleagues and I have previously reported NF- κ B-independent mechanisms in the regulation of inflammatory mediators; MAPKs were attracting alternatives [56].

Conclusions, summary, and prospects

The possible involvement of NF- κ B signaling pathways in regulating the molecular mechanisms of nociception has relative repercussions on inflammatory-related pain behavior, sensation, and perception. Evolving, yet burgeoning, research on the relationship existing between NF- κ B and pain (hyperalgesia/analgesia) continues apace, but hitherto the race into deciphering the molecular mechanisms is even more rapidly developing.

This paper has unraveled several major potential roles for NF- κ B in the molecular regulation of pain: (i) NF- κ B is a major regulator of the gene expression of inflammatory mediators, which are at the epicenter of the evolution of inflammatory pain; (ii) NF- κ B-mediated inflammatory pain and nociception is a regulated process, which involves related transcriptional factors and/or cofactors such as AP-1, c-fos and MAPKs; (iii) Inflammatory pain is not necessarily an NF- κ B-exclusive event; NF- κ B promoted analgesia, neuropathic (neurogenic) pain and the expression of opioid receptors too; (iv) NF- κ B dual nature as a promoter of hyperalgesia and, probably, analgesia requires thorough understanding of the underlying molecular pathways and related cofactors (Fig. 2).

Whether the inhibition of this transcription factor, while downregulating the protracted inflammatory processes likely tarnished with the seal of inflammatory mediators, is of real therapeutic value for patients with evolving or debilitating pain conditions remains fascinating. Undoubtedly, unraveling the molecular association, therefore, would create well grounds for understanding the pain process and paves the way for a preventative, alleviating therapy for inflammatory-mediated pain.

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References

- [1] P.D. Wall, Pain and animals, *Nature* 316 (1985) 672.
- [2] P.D. Wall, The mechanisms by which tissue damage and pain are related, *Pain Mechanisms and Management* 1 (1998) 252–259.
- [3] A.I. Basbaum, T.M. Jessell, The perception of pain, *Principles of Neural Science* 4 (2000) 473–491.
- [4] B.M. Block, R.W. Hurley, S.N. Raja, Mechanism-based therapies for pain, *Drug News Perspect.* 17 (2004) 172–186.
- [5] N.E. Saadé, C.A. Massaad, S.A. Kanaan, B. Safieh-Garabedian, S.J. Jabbur, S.F. Atweh, Pain and neurogenic inflammation: A neural substrate for neuroendocrine-immune interactions, *Pain and Neuro-immune Interactions* 1 (2000) 111–123.
- [6] Y.J. Sung, R.T. Ambron, Pathways that elicit long-term changes in gene expression in nociceptive neurons following nerve injury: contributions to neuropathic pain, *Neurol. Res.* 26 (2004) 195–203.
- [7] I. Isomura, A. Morita, Regulation of NF- κ B signaling by decoy oligodeoxynucleotides, *Microbiol. Immunol.* 50 (2006) 559–563.
- [8] G.Y. Park, J.W. Christman, Nuclear factor κ B is a promising therapeutic target in inflammatory lung disease, *Curr. Drug Targets* 7 (2006) 661–668.
- [9] J.H. Zhang, Y.G. Huang, The immune system: a new look at pain, *Chin. Med. J. (Engl.)* 119 (2006) 930–938.
- [10] I. Tegeder, E. Niederberger, R. Schmidt, S. Kunz, H. Guhring, O. Ritzeler, M. Michaelis, G. Geisslinger, Specific inhibition of I κ B kinase reduces hyperalgesia in inflammatory and neuropathic pain models in rats, *J. Neurosci.* 24 (2004) 1637–1645.
- [11] M. Baliki, H.A. Al-Amin, S.F. Atweh, M. Hawwa, S.J. Jabbur, A.V. Apkarian, N.E. Saadé, Attenuation of neuropathic manifestations by local block of the activities of the ventrolateral orbito-frontal area in the rat, *Neuroscience* 120 (2003) 1093–1104.
- [12] T.F. Almeida, S. Roizenblatt, S. Tufik, Afferent pain pathways: a neuroanatomical review, *Brain Res.* 1000 (2004) 40–56.
- [13] C.J. Woolf, Dissecting out mechanisms responsible for peripheral neuropathic pain: implications for diagnosis and therapy, *Life Sci.* 74 (2004) 2605–2610.
- [14] F. Cervero, J.M.A. Laird, One pain or many pains - A new look at pain mechanisms, *News Physiologic. Sci.* 6 (1991) 268–273.
- [15] M. Zimmermann, T. Herdegen, Plasticity of the nervous system at the systemic, cellular and molecular levels: a mechanism of chronic pain and hyperalgesia, *Progress in Brain Research* 110 (1996) 233–259.
- [16] S. Poole, F.Q. Cunha, S.H. Ferreira, Bradykinin, cytokines and inflammatory hyperalgesia, *Pain and Neuroimmune Interactions* 1 (2000) 31–54.
- [17] C.A. Massaad, B. Safieh-Garabedian, S. Poole, S.F. Atweh, S.J. Jabbur, N.E. Saadé, Involvement of substance P, CGRP and histamine in the hyperalgesia and cytokine upregulation induced by intraplantar injection of capsaicin in rats, *J. Neuroimmunol.* 153 (2004) 171–182.
- [18] A.I. Basbaum, J.D. Levine, The contribution of the nervous system to inflammation and inflammatory disease, *Can. J. Physiol. Pharmacol.* 69 (1991) 647–651.
- [19] B. Safieh-Garabedian, S. Poole, J.J. Haddad, C.A. Massaad, S.J. Jabbur, N.E. Saadé, The role of the sympathetic efferents in endotoxin-induced localized inflammatory hyperalgesia and cytokine upregulation, *Neuropharmacology* 42 (2002) 864–872.
- [20] A. Dray, Tasting the inflammatory soup: The role of peripheral neurones, *Pain Rev.* 1 (1994) 153–171.
- [21] S.B. McMahon, M. Koltzenburg, The changing role of primary afferent neurons in pain, *Pain* 43 (1990) 269–272.
- [22] T.J.Coderre, J. Kats, A. Vaccarino, R. Melzack, Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence, *Pain* 52 (1993) 259–285.
- [23] S.D. Dib-Hajj, J. Fjell, T.R. Cummins, Z. Zheng, K. Fried, R.H. LaMotte, J.A. Black, S.G. Waxman, Plasticity of sodium channel expression in DRG neurons in the chronic constriction injury model of neuropathic pain, *Pain* 83 (1999) 591–600.
- [24] M. Devor, P.D. Wall, Cross-excitation in dorsal root ganglia of nerve - injured and intact rats, *J. Neurophysiol.* 64 (1990) 1733–1746.
- [25] F. Marchand, M. Perretti, S.B. McMahon, Role of the immune system in chronic pain, *Nat. Rev. Neurosci.* 6 (2005) 521–532.
- [26] M. Chacur, E.D. Milligan, L.S. Gazda, C. Armstrong, H. Wang, K.J. Tracey, S.F. Maier, L.R. Watkins, A new model of sciatic inflammatory neuritis (SIN): induction of unilateral and bilateral mechanical allodynia following acute unilateral peri-sciatic immune activation in rats, *Pain* 94 (2001) 231–244.
- [27] N.E. Saadé, C.A. Massaad, C.I. Ochoa-Chaar, S.J. Jabbur, B. Safieh-Garabedian, S.F. Atweh, Upregulation of proinflammatory cytokines and nerve growth factor by intraplantar injection of capsaicin, *J. Physiol.* 545 (2002) 241–253.
- [28] S.J. Jabbur, N.E. Saadé, From electrical wiring to plastic neurons: evolving approaches to the study of pain, *Pain* 6 (1999) S87–S92.
- [29] B. Safieh-Garabedian, J.J. Haddad, N.E. Saadé, Cytokines in the central nervous system: Targets for therapeutic intervention, *Curr. Drug Targets CNS Neurol. Disord.* 3 (2004) 271–280.
- [30] K.M. Lee, B.S. Kang, H.L. Lee, S.J. Son, S.H. Hwang, D.S. Kim, J.S. Park, H.J. Cho, Spinal NF- κ B activation induces COX-2 upregulation and contributes to inflammatory pain hypersensitivity, *Eur. J. Neurosci.* 19 (2004) 3375–3381.
- [31] M.K. Meffert, D. Baltimore, Physiological functions for brain NF- κ B, *Trends Neurosci.* 28 (2005) 37–43.
- [32] T. Ichiyama, T. Sakai, A. Catania, G.S. Barsh, S. Furukawa, J.M. Lipton, Inhibition of peripheral NF- κ B activation by central action of a-melanocyte-stimulating hormone, *J. Neuroimmunol.* 99 (1999) 211–217.
- [33] A. Nadjar, V. Tridon, M.J. May, S. Ghosh, R. Dantzer, T. Amedee, P. Parnet, NF- κ B activates in vivo the synthesis of inducible Cox-2 in the brain, *J. Cereb. Blood Flow Metab.* 25 (2005) 1047–1059.
- [34] J.J. Haddad, R.E. Olver, S.C. Land, Antioxidant/pro-oxidant equilibrium regulates HIF-1 α and NF- κ B redox sensitivity. Evidence for inhibition by glutathione oxidation in alveolar epithelial cells, *J. Biol. Chem.* 275 (2000) 21130–21139.
- [35] G. La Rosa, S. Cardali, T. Genovese, A. Conti, R. Di Paola, D. La Torre, F. Cacciola, S. Cuzzocrea, Inhibition of the nuclear factor- κ B activation with pyrrolidine dithiocarbamate attenuating inflammation and oxidative stress after experimental spinal cord trauma in rats, *J. Neurosurg. Spine* 1 (2004) 311–321.
- [36] K. Nakatani, T. Yamakuni, N. Kondo, T. Arakawa, K. Oosawa, S. Shimura, H. Inoue, Y. Ohizumi, g-Mangostin inhibits inhibitor- κ B kinase activity and decreases lipopolysaccharide-induced cyclooxygenase-2 gene expression in C6 rat glioma cells, *Mol. Pharmacol.* 66 (2004) 667–674.
- [37] J.A. Mitchell, M. Saunders, P.J. Barnes, R. Newton, M.G. Belvisi, *Mol. Pharmacol.* 51 (1997) 907–912.

- [38] J.R. Vane, R.M. Botting, The mechanism of action of aspirin, *Thromb. Res.* 110 (2003) 255–258.
- [39] J.S. Mogil, K.E. McCarron, Identifying pain genes: bottom-up and top-down approaches, *J. Pain* 1 (2000) 66–80.
- [40] D.D. Lorimer, K. Matkowskj, R.V. Benya, Cloning, chromosomal location, and transcriptional regulation of the human galanin-1 receptor gene (GALN1R), *Biochem. Biophys. Res. Commun.* 241 (1997) 558–564.
- [41] A. Dray, Kinins and their receptors in hyperalgesia, *Can. J. Physiol. Pharmacol.* 75 (1997) 704–712.
- [42] J.B. Calixto, R. Medeiros, E.S. Fernandes, J. Ferreira, D.A. Cabrini, M.M. Campos, Kinin B1 receptors: key G-protein-coupled receptors and their role in inflammatory and painful processes, *Br. J. Pharmacol.* 143 (2004) 803–818.
- [43] D.A. Cabrini, M.M. Campos, K.S. Tratsk, V.F. Merino, J.A. Silva Jr., G.E. Souza, M.C. Avellar, J.B. Pesquero, J.B. Calixto, Molecular and pharmacological evidence for modulation of kinin B1 receptor expression by endogenous glucocorticoids hormones in rats, *Br. J. Pharmacol.* 132 (2001) 567–577.
- [44] G. Sakaue, M. Shimaoka, T. Fukuoka, T. Hiroi, T. Inoue, N. Hashimoto, T. Sakaguchi, Y. Sawa, R. Morishita, H. Kiyono, K. Noguchi, T. Mashimo, NF- κ B decoy suppresses cytokine expression and thermal hyperalgesia in a rat neuropathic pain model, *Neuroreport* 12 (2001) 2079–2084.
- [45] S. Jun-Ichi, I. Hiroshi, G. Ryo, M. Ryuichi, E. Kensuke, I. Mitsuaki, Initial clinical cases of the use of a NF- κ B decoy at the site of coronary stenting for the prevention of restenosis, *Circ. J.* 68 (2004) 270–271.
- [46] S.E. Alam, S.S. Nasser, K.E. Fernainy, A.A. Habib, K.F. Badr, Cytokine imbalance in acute coronary syndrome, *Curr. Opin. Pharmacol.* 4 (2004) 166–170.
- [47] O.J. Igwe, Modulation of peripheral inflammation in sensory ganglia by nuclear factor κ B decoy oligodeoxynucleotide: involvement of SRC kinase pathway, *Neurosci. Lett.* 381 (2005) 114–119.
- [48] C.G. Yu, R.P. Yezierski, Activation of the ERK1/2 signaling cascade by excitotoxic spinal cord injury, *Brain Res. Mol. Brain Res.* 138 (2005) 244–255.
- [49] H.J. Park, H.S. Lee, H.J. Lee, Y.M. Yoo, H.J. Lee, S.A. Kim, K. Leem, H.C. Kim, J.C. Seo, E.H. Kim, S. Lim, J.H. Chung, Decrease of the electroacupuncture-induced analgesic effects in nuclear factor- κ B1 knockout mice, *Neurosci. Lett.* 319 (2002) 141–144.
- [50] J. Kraus, C. Borner, E. Giannini, V. Holtt, The role of NF- κ B in tumor necrosis factor-regulated transcription of the human m-opioid receptor gene, *Mol. Pharmacol.* 64 (2003) 876–884.
- [51] J.A. DeLeo, F.Y. Tanga, V.L. Tawfik, Neuroimmune activation and neuroinflammation in chronic pain and opioid tolerance/hyperalgesia, *Neuroscientist* 10 (2004) 40–52.
- [52] C. Borner, V. Holtt, J. Kraus, Involvement of activator protein-1 in transcriptional regulation of the human m-opioid receptor gene, *Mol. Pharmacol.* 61 (2002) 800–805.
- [53] A. Bierhaus, K.M. Haslbeck, P.M. Humpert, B. Liliensiek, T. Dehmer, M. Morcos, A.A. Sayed, M. Andrassy, S. Schiekofer, J.G. Schneider, J.B. Schulz, D. Heuss, B. Neundorfer, S. Dierl, J. Huber, H. Tritschler, A.M. Schmidt, M. Schwaninger, H.U. Haering, E. Schleicher, M. Kasper, D.M. Stern, B. Arnold, P.P. Nawroth, Loss of pain perception in diabetes is dependent on a receptor of the immunoglobulin superfamily, *J. Clin. Invest.* 114 (2004) 1741–1751.
- [54] I.T. Kim, H.J. Park, J.H. Nam, Y.M. Park, J.H. Won, J. Choi, B.K. Choe, K.T. Lee, In-vitro and in-vivo anti-inflammatory and antinociceptive effects of the methanol extract of the roots of *Morinda officinalis*, *J. Pharm. Pharmacol.* 57 (2005) 607–615.
- [55] J. Frassdorf, N.C. Weber, D. Obal, O. Toma, J. Mullenheim, G. Kojda, B. Preckel, W. Schlack, Morphine induces late cardioprotection in rat hearts in vivo: the involvement of opioid receptors and nuclear transcription factor κ B, *Anesth. Analg.* 101 (2005) 934–941.
- [56] J.J. Haddad, H.L. Harb, L-g-Glutamyl-L-cysteinyl-glycine (glutathione; GSH) and GSH-related enzymes in the regulation of pro- and anti-inflammatory cytokines: a signaling transcriptional scenario for redox(y) immunologic sensor(s)? *Mol. Immunol.* 42 (2005) 987–1014.