Review article:

Molecular Regulation of Inflammatory Pain and Hyperalgesia - Is NF-κB the Lynchpin? Focus Article and Critical Review

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ABSTRACT

Inflammatory cells and inflammatory mediators are crucially involved in the genesis, persistence and severity of pain following trauma, infection or nerve injury. The mechanisms and pathways mediating pain and nociception are transcriptionally regulated. The transcriptional mediator nuclear factor (NF)-κB plays a major role in regulating the inflammatory milieu, ostensibly via the control of gene expression/suppression. An association has recently emerged to establish a possible link between NF-κB and pain/nociception, purportedly through the regulation of the inflammatory loop and the secretion (biosynthesis) of pro-inflammatory mediators. Current concepts conspicuously indicate that the effective inhibition of this transcription factor and associated upstream kinase(s) and the pathways that regulate its nuclear translocation could be major targets in a new strategy for the alleviation of inflammation and inflammatory-related pain. To better understand this relationship between NF-κB and the evolution of pain and hyperalgesia/nociception, it is imperative to unravel the molecular basis of this process. This survey definitively integrates current themes pertaining to the pivotal role that NF-κB shares in regulating pain through the decoding of implicated molecular pathways and signaling mechanisms.

Keywords: Hyperalgesia, inflammation, NF-κB, nociception, pain, transcription factors

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1. Introduction and Background

Pain is the most common symptom of injuries and diseases (Finnerup and Jensen, 2006; Haddad, 2007). Nerve cell endings or receptors, commonly known as nociceptors, are central to pain sensation. Nociceptors relay information to the CNS thus indicating the location, nature and intensity of the ensuing pain.

A nociceptive stimulus unleashes a cascade of events throughout the nervous system, which can ultimately lead (loop) back to the site of injury (Garry et al., 2004). This response prompts cells of a variety of types in the injured area to release chemicals that trigger an immune response and influence the intensity and duration of pain (Basbaum and Jessel, 2000; Saadé et al., 2000; Block et al., 2004).

The inflammatory milieu that usually precedes, and accompanies, pain is transcriptionally regulated (Sung and Ambron, 2004). Nuclear factor (NF)-κB is a transcription factor (TF) essentially involved with mediating the release of inflammatory mediators (Chen et al., 2002; Haddad, 2002a; Aggarwal, 2004; Gilroy et al., 2004; Isomura and Morita, 2006; Nam, 2006; Park and Christman, 2006), which may exacerbate pain, hyperalgesia and nociception (Tegeder et al., 2004; Rittner and Brack, 2006; Zhang and Huang, 2006).

Current strategies aiming at controlling the origin, and propagation, of pain, as well as its manifestations, reveal the crucial role that this TF has in modulating pain, following the ensuing inflammatory cascade (Park and Christman, 2006). Apart from establishing a burgeoning trend that stresses the involvement of NF-κB, however, the mechanisms implicated are still being elucidated (Fraser, 2006).

It is the purpose of this survey to amalgamate and integrate current concepts in the understanding of how this TF regulates pain/nociception, and to correlate NF-κB activity with the molecular control of pain.

2. NF-κB: Overview of an inflammatory TF and its integration into regulatory pathways

2.1. The nature of the Rel/NF-κB family of TFs

NF-κB or *Rel* proteins comprise a family of structurally-related eukaryotic TFs (Campbell and Perkins, 2006; Xiao et al., 2006). NF-κB mediates the expression of an array of genes that are critical for the regulation of apoptosis (Haddad and Land, 2000a; Anest et al., 2003; Hiscott et al., 2003; Lu et al., 2004; Takada et al., 2004; Haddad, 2004b; Piva et al., 2006), viral replication (Taddeo et al., 2003), tumorigenensis and cancer (Karin and Greten, 2005; Shishodia and Aggarwal, 2004; Karin, 2006; Pikarsky and Ben-Neriah, 2006), inflammation (Haddad and Land, 2001a; Haddad et al., 2001; Aggarwal, 2004; Gilroy et al., 2004), hematopoiesis (Bottero et al., 2006) and various autoimmune diseases (Iwahashi et al., 2004; Peng, 2004).

Rel/NF-κB proteins are related through a highly conserved DNA-binding/dimerization domain called the *Rel* homology (RH) domain (Xiao et al., 2006). The *Rel*/NF-κB proteins are divided into two major classes based on sequences C-terminal to the RH domain. Members of one class (p105, p100 and *Drosophila melanogaster* Relish) have long C-terminal domains that contain multiple copies of ankyrin repeats, which act to inhibit these molecules (Campbell and Perkins, 2006).

Members of this class become active, shorter DNA-binding proteins [p105 → p50 (NF-κB$_1$); p100 → p52 (NF-κB$_2$)] by limited proteolysis and/or arrested translation. As such, they are generally not activators of transcription, except when they form dimers with members of the second class of *Rel*/NF-κB TFs (Campbell and Perkins, 2006).

The second class includes c-*Rel* (p75) (and its retroviral homologue v-*Rel*), *Rel*B (p68), *Rel*A (p65) and the *Drosophila* Dorsal and Dif proteins. This class of *Rel* proteins contains C-terminal transcription activation domains, which are often not conserved at the sequence level across species, even though they can activate transcription in a variety of species (Campbell and Perkins, 2006).

Rel/NF-κB TFs bind to 9-10 base pair DNA sites, referred to as κB sites, as dimers. All vertebrate *Rel* proteins can form homodimers or heterodimers, except for *Rel*B, which can only form heterodimers. This combinatorial diversity contributes to the

regulation of distinct, but overlapping, sets of genes, in that the individual dimers have distinct DNA-binding site specificities (Vermeulin et al., 2006). The term 'NF-κB' specifically refers to a p50-p65 heterodimer, one of the most avidly forming dimers in most cells (Fig. 1A).
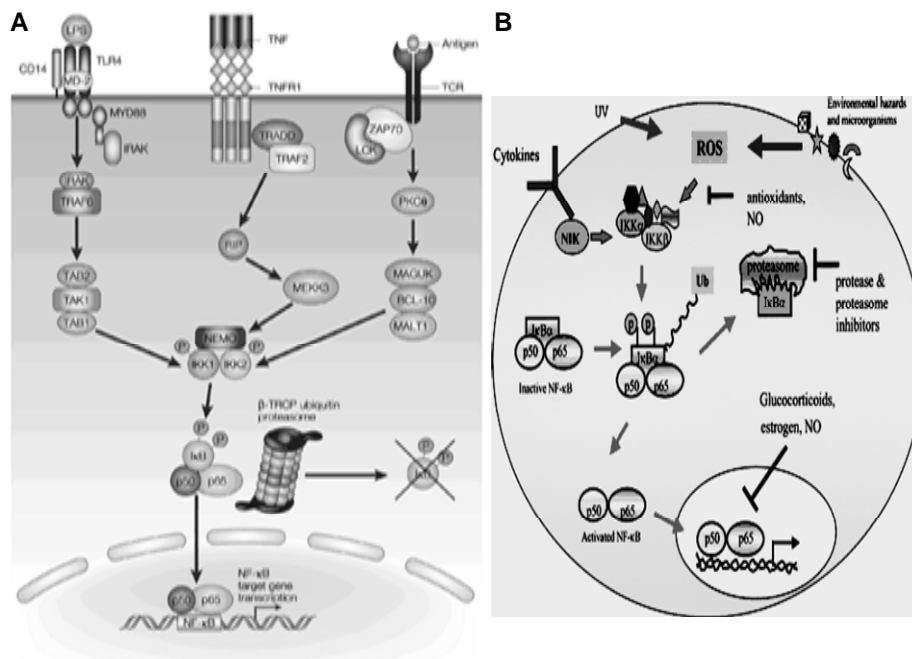

Figure 1: (A) A schematic illustration depicting the NF-κB signaling pathways in response to LPS, TNF and related antigens. (B) Various incoming signals converge on the activation of the IκB kinase (IKK) complex by reactive oxygen species (ROS) and NF-κB-inducible kinase (NIK). IKK then phosphorylates IκB at 2 N-terminal serines, which signals it for ubiquitination and proteolysis (proteasome). Freed NF-κB complex (p50/p65) enters the nucleus and activates gene expression. Inhibitors including glucocorticoids suppress the transcriptional activity of NF-κB (see Haddad, 2002a).

2.2. The zones and mechanisms of action of NF-κB

The activation of NF-κB is part of a stress response axis as it is activated by a variety of stimuli that include growth factors, cytokines, lymphokines, ultraviolet (UV), pharmacological agents and oxidants/reductants (DiDonato et al., 1997; Haddad et al., 2000; Haddad, 2002a; Haddad, 2004b; Chen and Greene, 2004; Karin et al., 2004) (Fig. 1B).

The activity of NF-κB is primarily regulated by interaction with inhibitory, IκB, proteins (Yamamoto and Gaynor, 2004). As with the *Rel*/NF-κB proteins, there are several IκB proteins that have discordant affinities for *Rel*/NF-κB complexes, are regulated differently and are expressed in a tissue-specific manner (Campbell and Perkins, 2006).

The best-studied NF-κB-IκB interaction is that of IκBα with the NF-κB p50-p65 dimer. This interaction blocks the ability of NF-κB to bind to DNA and,

subsequently, results in the NF-κB complex being primarily retained in the cytoplasm due to a strong nuclear export signal in IκBα (Karin, 2006). That is, the NF-κB-IκBα complex is continuously shuttling between the nucleus and the cytoplasm, but its rate of nuclear export exceeds its rate of import and thus the complex is generally cytoplasmic.

From biochemical studies and direct structural determinations, it is clear that IκBα makes multiple contacts with NF-κB (Karin, 2006). These interactions cover sequences of NF-κB that are important for DNA binding. In contrast, when IκBβ interacts with the NF-κB complex, the complex is retained in the cytoplasm (i.e., does not necessarily undergo nucleo-cytoplasmic shuttling).

NF-κB, thus, is present as a latent, inactive, IκB-bound cytosolic complex. When a cell receives any of a multitude of extracellular signals, NF-κB rapidly

enters the nucleus and activates gene expression. Therefore, a key step for controlling NF-κB activity is the regulation of the IκB-NF-κB interaction. Almost all signals that lead to the activation of NF-κB converge on the regulation of a high molecular weight complex that contains a serine-specific IκB kinase (IKK) (Karin, 2006).

In the classical or canonical pathway, activation of IKK complex leads to the phosphorylation by IKKβ of two specific serines near the N terminus of IκBα, which targets IκBα for ubiquitination (generally by a complex called β-TrCP) and degradation by the 26S proteasome complex.

In the non-canonical pathway, the p100-RelB complex is activated by phosphorylation of the C-terminal region of p100 by an IKKα homodimer (lacking IKKγ), which leads to ubiquitination followed by degradation of the p100 IκB-like C-terminal sequences to generate p52-*Rel*B (Karin, 2006).

In either pathway, the unmasked NF-κB complex can then enter the nucleus to activate target gene expression. In the canonical pathway, intriguingly, one of the target genes activated by NF-κB is that which encodes IκBα. Newly-synthesized IκBα can enter the nucleus, dissociate NF-κB from DNA and export the complex back to the cytoplasm to restore the original latency (Haddad et al., 2000). Thus, the activation of the NF-κB pathway is generally a transient process, roughly lasting from 30-60 minutes in most cells (Campbell and Perkins, 2006).

The various stimuli that activate NF-κB, therefore, cause the phosphorylation of IκB by upstream kinases, which is followed by its ubiquitination and subsequent degradation (Haddad et al., 2000; Haddad et al., 2002; Karin and Greten, 2005) (Fig. 2). This results in the exposure of the nuclear localization signals (NLS) on NF-κB$_1$ subunit (p50) and the subsequent translocation of the molecule (p50-p65 dimer) to the nucleus. NF-κB generally binds with a consensus sequence (5'-GGGACTTTCC-3') of various genes and thus activates their transcription (Karin et al., 2004; Karin, 2006).
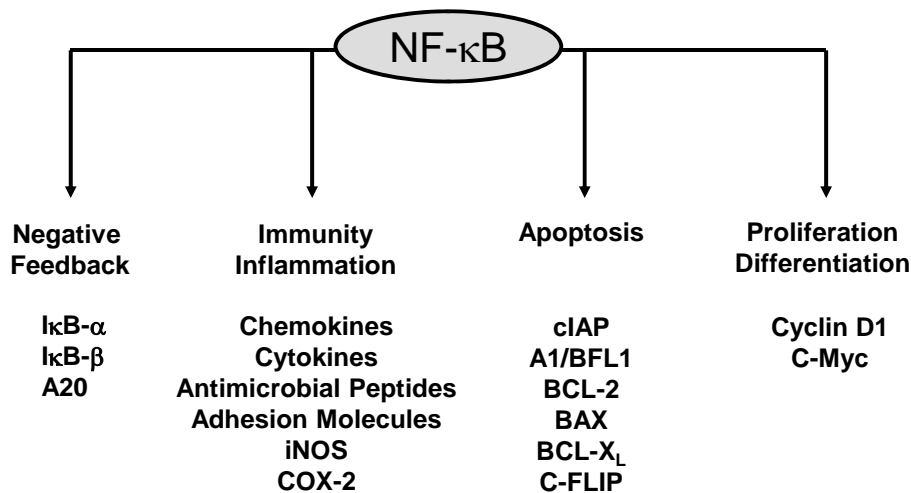

Figure 2: NF-κB and the regulation of specialized signaling pathways (see Haddad et al., 2002).

A more thorough discussion on NF-κB signaling pathways is beyond the scope of this survey (Fig. 3). For that particular reason, we have incorporated up-to-

date references particularly selected for their specific themes on NF-κB (Brennan and O'Neill, 1996; Zandi et al., 1998; Haddad et al., 2000; Haddad, 2002a;

Anest et al., 2003; Aggarwal, 2004; Krakauer, 2004; Wajant, 2004; Yamamoto and Gaynor, 2004; Karin et al., 2004; Campbell and Perkins, 2006; Karin, 2006).
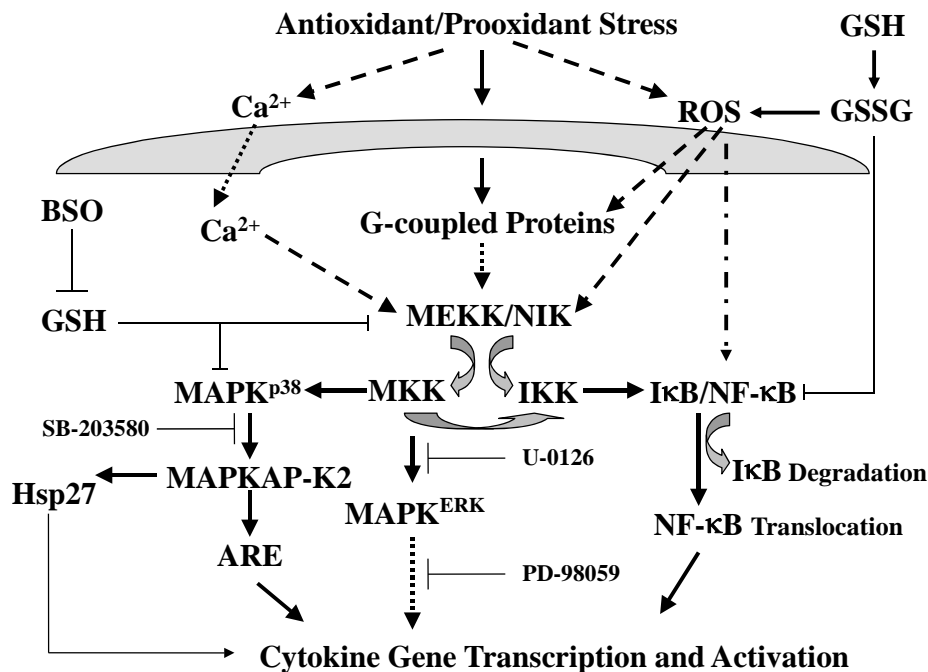

Figure 3: Antioxidant/prooxidant mechanisms in the regulation of inflammatory cytokines. Oxidative stress, mainly caused by the depletion of GSH by BSO or conversion onto GSSG, can cause the accumulation of ROS. ROS activates downstream effector mechanisms involving upstream kinases, such as MEKK/NIK, which regulates the phosphorylation of MKK and IκB/NF-κB complex. Both pathways have the potential to regulate genes implicated with cytokine biosynthesis (see Haddad et al., 2000).

The following section investigates major concepts of pain, nociception and hyperalgesia.

3. 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 (e.g., mechanical, chemical and thermal) that can lead ultimately to a damage or injury (Fig. 4) (Kanaan et al., 1996; Wall, 1998; Millan et al., 1999; Basbaum and Jessell, 2000; Baliki et al., 2003; Almeida et al., 2004; Woolf, 2004a, 2004b).

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 (absence of pain) despite all measures made to compensate for this absence (Loro et al, 1978; Dyck et al., 1983). From this aspect, acute nociception can be considered as a sensory modality like touch and taste, with the added survival value just alluded to (Cervero and Laird, 1991; Julius and Basbaum, 2001).

On the other hand, 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 (Cervero and Laird, 1991; Saadé et al., 1993a, 1993b; Millan et al., 1999; Julius and Basbaum, 2001). 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 (Wall, 1995; Zimmermann and Herdegen, 1996; Wall, 1998; Millan et al., 1999).
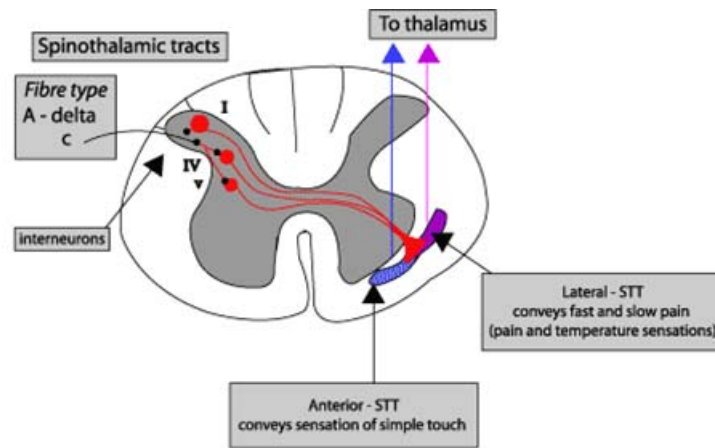
Figure 4: Pain fibers terminate mainly in the superficial dorsal horn (laminae I- II). Aδ fibers enter lamina I (and V) and synapse on a second set of neurons. These neurons will carry the signal to the thalamus and are part of the spinothalamic tract (STT). The C fibers enter the spinal cord and synapse on lamina I cells and lamina II interneurons - neurons that make synaptic connections with other cells within the local environment. The interneurons convey the signal to the STT cells that reside mainly in laminae I, IV and V. The axons of the STT cells project across the spinal cord to the STT, which is located in the ventrolateral quadrant of the contralateral spinal cord white matter (Adapted, courtesy of AnesthesiaUK).

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, serotonine (5-hydroxytryptamine, 5-HT), nitric oxide (NO), prostanoids, neurotrophins, cytokines, ATP, protons and other mediators that are released by injured and/or affected (including immune) cells (Dray, 1995; Hunt, 2000; Hill, 2001; Hunt and Mantyh, 2001; Julius and Basbaum, 2001).

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 (Poole et al., 2000; Saadé et al., 2000; Hunt and Mantyh, 2001). The latter can contribute to the direct release of neuropeptides (SP, CGRP) (Saadé et al., 2002; Massaad et al., 2004), or indirect (reflex) release of catecholamines through the sympathetic efferents (Basbaum and Levine, 1991). Both neuropeptides and catocholamines are well known for

their vasoactive properties and their effects on various immune cells (Levine et al., 1986; Payan et al., 1987; Safieh-Garabedian et al., 2002) (Fig. 5).

The end result of the cross-talk between immunogenic and neurogenic inflammation (Zimmermann and Herdegen, 1996; Saadé, et al., 2002; Costa et al., 2006) is chronic pain, on one side, and the various breakdown products in the inflammatory 'soup' or milieu, on the other hand (Dray, 1994; Poole et al., 2000), 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 (Almeida et al., 2004). These include, as illustration: i) activation of silent or dormant nociceptors (McMahon and Koltzenburg, 1990); 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) (McMahon and Wall, 1984; Cervero and Laird, 1991; Gracely et al., 1992; Coderre et al., 1993); iii) changes in the ionic channels (Na$^+$ channels) (Dib-Hajj et al., 1999) and in the properties of membrane receptors (Zimmermann and Herdegen, 1996; Millan et al., 1999); and iv) significant alterations of the electrical signaling behavior of the injured and the intact neighboring fibers (Devor and Wall, 1990; Devor and Seltzer, 1999).
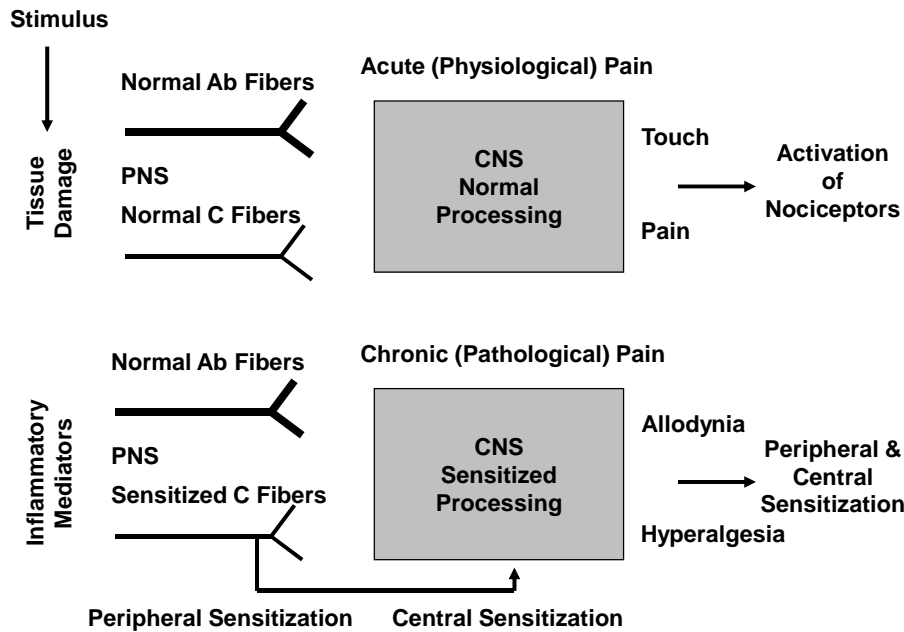

Figure 5: A diagrammatic scheme exhibiting pain pathways, processing and sensitization due to tissue damage and inflammatory mediators.

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 (Basbaum and Levine, 1991; Wall, 1998) (see Fig. 4).

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 (Marchand et al., 2005).

Because of the presence of a myriad of models alleged with pain and pain mechanisms, it is imperative, therefore, to dislodge (dissociate) 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 (Bennett, 1999; Chacur et al., 2001).

This implies that pro-inflammatory mediators (including cytokines) 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 (Deleo et al., 1996; Sommer, 2001; Saadé et al., 2002; Sommer, 2003).

In conclusion, various strategies have been adopted to stop the 'snow ball' phenomenon at the origin of chronic pain (Saadé et al., 1985; Wall, 1985; Saadé et al., 1990; Kanaan et al., 1997; Wall, 1998; Jabbur and Saadé, 1999; Hunt, 2000; Garry et al., 2004). 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 (Saadé et al., 1997; Safieh-Garabedian et al., 1997; Saadé et al., 1998; Massaad et al., 2004; Safieh-Garabedian et al., 2004).

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-κB.

The following sections will focus on the outcome of contemporary research as to understand the NF-κB-pain nexus and the alleviation of chronic pain through specific targeting of this TF potentiating mechanisms.

4. NF-κB and the regulation of pain – molecular aspects: Is NF-κB a lynchpin?

Nociception and the molecular regulation of pain involve key transcription factors, particularly NF-κB and related cofactors. The intricate relationship between NF-κB and pain is, consequently, rapidly evolving. However, the precise mechanisms by which NF-κB 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 (Lee et al., 2004; Tegeder et al., 2004; Liuzzo et al., 2007) (Fig. 6).
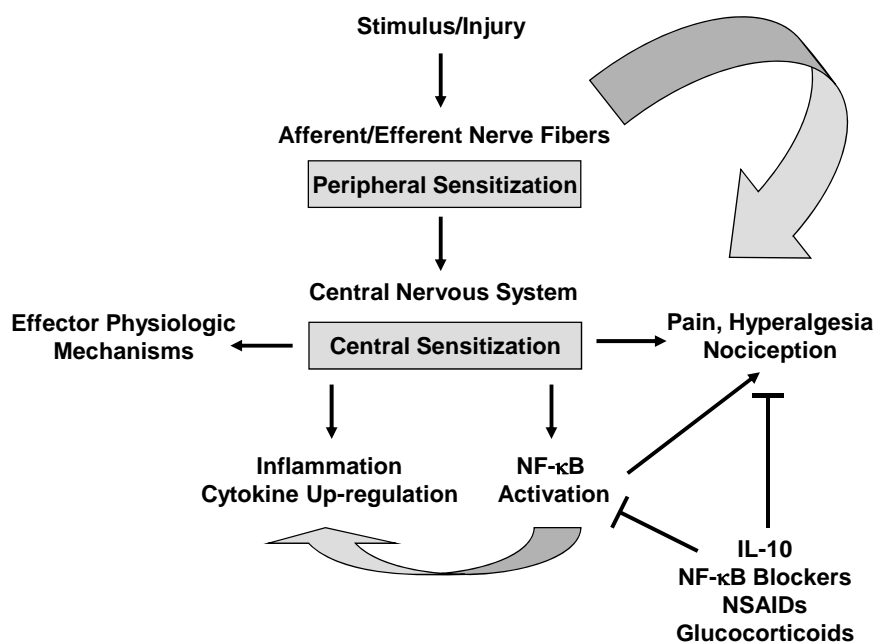
Figure 6: NF-κB and the regulation of putative pain signaling pathways.

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

4.1. The repercussions of NF-κB activation at localized and centralized nervous sites

Members of the *Rel*/NF-κB family of eukaryotic transcription factors are activated within the CNS in pathological settings of apoptosis and neurological diseases (Meffert and Baltimore, 2005). The effect of NF-κB activation on pain signaling pathways varies, however, with the site (locality) of activation.

Certain drugs and/or pain killers can act centrally to inhibit NF-κB activation in peripheral acute inflammation via a descending neural pathway (Ichiyama et al., 1999). Conversely, it was shown that IL-1β-induced NF-κB activation may play a role in the transmission of immune signals from the periphery to the brain (Nadjar et al., 2005). This bidirectional influence of NF-κB is central to deciphering the molecular codes associated with pain and nociception at different levels of hierarchy of nervous sites.

To cite another example of the role of NF-κB in the aforementioned bidirectional regulatory mechanisms, it is worth mentioning that this transcription factor is at the center of responses of the peripheral nervous system (PNS) to inflammatory cytokines. For instance, NF-κB activity was purportedly increased in rat dorsal root ganglia (DRG) neurons by tumor necrosis factor (TNF), nerve growth factor (NGF) (Wood, 1995) and partial sciatic nerve injury (Ma and Bisby, 1998). Since these cytokines and/or injurious events are at the heart of pain, it appears that the regulatory effect of NF-κB is essentially crucial, at least in part, for developing the symptoms associated with pain and nociception.

This observation is reinforced by another study showing that cytokine-mediated activation of NF-κB could be a potential component of the signaling pathway responsible for the maintenance of adult sensory neuron survival following axon damage (Fernyhough et al., 2005). In addition, peripheral inflammatory pain in sensory ganglia has been shown to have been modulated by a specific NF-κB decoy (Igwe, 2005). The discussion on the effect of decoys on NF-κB-mediated pain will ensue in a subsequent section.

Having now investigated the effect of NF-κB on central and peripheral inflammatory sites associated with pain, it remains of particular interest to indicate that NF-κB also 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-κB induced cyclooxygenase (COX)-2 upregulation and contributed to inflammatory pain hypersensitivity (Lee at al., 2004). Conversely, inhibition of NF-κB activation by the antioxidant/prooxidant chemical pyrrolidine dithiocarbamate (PDTC) (Haddad et al., 2000) attenuated inflammation and oxidative stress after experimental spinal cord trauma (La Rosa et al., 2004).

This is corroborated with the observation that manganese-dependent superoxide dismutase (MnSOD – the antioxidant enzyme that leads to the dismutation of the superoxide radical) as induced by TNF-β is regulated transcriptionally by NF-κB following spinal cord injury (Yune et al., 2004). Similarly, inhibition of astroglial NF-κB reduced inflammation and improved functional recovery after spinal cord injury (Brambilla et al., 2005). Furthermore, it was reported that there is involvement of spinal cord NF-κB activation in models of cytokine-induced pain (Ledeboer et al., 2005). In short, it seems likely to indicate that the activation of NF-κB at the level of the spinal cord facilitates inflammatory-mediated pain and nociception.

Recent work also provided evidence that NF-κB may participate in the regulation of neuronal activity-dependent transcription and behavior under pathophysiologic conditions. At the level of the CNS *in vitro*, for example, it was noted that the inhibition of IKK decreased LPS-induced COX-2 gene expression a glioma cell line (Nakatani et al., 2004), implicating a mechanism for anti-inflammatory pain therapy. The anti-inflammatory theory on the alleviation of pain is subsequently further promoted below.

Based on the aforementioned, we can conclude the following: i) the localized activation of NF-κB is central to the development of inflammatory pain; ii) the central activation of this transcription factor modulates peripheral pain; and iii) the bidirectional effect of NF-κB spanning the range of the spinal cord is also essential for the development of inflammatory pain (see Fig. 6).

4.2. The effect of NF-κB on inflammatory mediators and inflammatory pain

It has been perceived so far that inflammatory mediators are at the center of the effect of NF-κB on the evolution of inflammatory pain and nociception. In this section I tackle the effect of select inflammatory mediators and their role in the development of pain.

4.2.1. NF-κB and cyclooxygenase regulation

The association between NF-κB and inflammatory pain essentially emerged with the role of COX and arachidonic acid (AA) (Mitchell et al., 1997). 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 (Yin et al., 1998; Vane and Botting, 2003).

Now I should come to a thought on the role of cytokines in the regulation of COX, as perceived from the tripod nexus of NF-κB, inflammation and pain. The identification of a cytokine-inducible isoform of COX, known as COX-2 (Mitchell et al., 1997), has led to the suggestion that salicylic acid can produce its anti-inflammatory actions by downregulating COX-2; of particular interest the conception that this inhibitory effect is mediated via the downregulation of NF-κB (Wu, 2003; Broom et al., 2004). This reinforces the suggestion that NF-κB-mediated inflammatory pain is COX-dependent.

On a related front, we report a key role of prostaglandins (PGs) in the development of pain and inflammatory hyperalgesia, an effect that has been well documented (Ferreira, 1986; Dray, 1994; Dray, 1995; Safieh-Garabedian et al., 1997; Ma and Eisenach, 2003). For instance, it has been noted that interleukin (IL)-1β-mediated induction of COX-2 and PGE_2 synthesis is dependent on the involvement of a mitogen-activated protein kinase (MAPK)[p38] and NF-κB (Fiebich et al., 2000).

Furthermore, the inhibition of NF-κB is reported crucial in the treatment of inflammatory pain associated with the expression of RANTES (regulated on activation, normal T cell expressed and secreted), one of the most potent chemokines in allergic and infectious disease associated with the expression of COX (Zhao et al., 2002) and in clinical models of nociception and pain (Valen et al., 2000; Johnson-Pais et al., 2003).

Clinically speaking, Rofecoxib, a selective COX-2 inhibitor approved for the treatment of rheumatoid arthritis (RA), inflammatory pain and osteoarthritis, has been shown to have proven efficacy in alleviating pain and inflammation, ostensibly via the downregulation of NF-κB and, to a lesser extent, activating protein (AP)-1, another transcription factor (Niederberger et al., 2003; Krakauer, 2004; Niederberger et al., 2004; Koppert et al., 2004).

COX-2, the major inducer of the release of PGE_2 (Vane and Botting, 2003), has also been reported to augment the processing of nociceptive stimuli following peripheral inflammation (Ferriera, 1986; Lai et al., 2001). The activation of NF-κB is associated with the induction of COX-2, thereby contributing to the evolution of inflammatory hyperalgesia (Balakin et al., 1994; Lee et al., 2004).

Recently, Brummelkamp and coworkers (2003) have identified a mechanism implicating acetylsalicylic acid in the regulation of NF-κB-mediated apoptosis in patients suffering the condition of cylindromatosis (familial cylindromatosis is a rare genetic disorder, giving rise to neoplasms of the skin appendages.) The familial cylindromatosis tumor suppressor gene (CYLD) is purported to enhance the activation of NF-κB by specific binding with IKKγ. The authors indicate that inhibition of CYLD increases resistance to apoptosis, suggesting a mechanism through which loss of CYLD contributes to oncogenesis. This is because the loss of the CYLD gene leads to activation of NF-κB, a transcription factor having antiapoptotic activity. Furthermore, this effect can be relieved by aspirin derivatives that inhibit NF-κB activity, suggesting a therapeutic intervention strategy to restore growth control in patients afflicted with familial cylindromatosis (Brummelkamp et al., 2003).

The aforementioned jibes with a clinical trial undertaken to treat cylindromatosis patients with salicylic acid (Oosterkamp et al., 2006). In cell-based assays, salicylate can prevent NF-κB activation caused by loss of the cylindromatosis gene, suggesting that salicylic acid application might be a potential treatment for cylindromatosis. The application of salicylate exhibited control over the lesion's size and degree of remission, indicating that the effective inhibition of NF-κB may resemble a potential therapeutic approach to treating cylindromatosis (Oosterkamp et al., 2006).

In summary, NF-κB-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-κB-dependent inflammatory pain.

4.2.2. NF-κB and cytokine regulation

As has been previously conferred, inflammatory molecules regulated by NF-κB exacerbate the pathophysiology of pain-related conditions (Sommer and Kress, 2004) (see Fig. 5). The secretion of inflammatory mediators through NF-κB activation is required, for instance, for the induction of allodynia (Deleo et al., 1996) and inflammatory pain (Poole et al., 2000; Safieh-Garabedian et al., 2002).

To further illustrate this concept, it has been reported that IL-10, an anti-inflammatory cytokine, and IL-1ra, a soluble IL-1 receptor antagonist, may impede the development of dynorphin-induced allodynia via the down-regulation of NF-κB and the central pro-inflammatory cascade (Laughlin et al., 2000). This mechanism suggests that NF-κB-dependent production of cytokines is required for the induction of allodynia. Modulation of NF-κB activity may, therefore, prove to be an effective therapeutic strategy for the treatment of chronic pain and pain associated with inflammation (Safieh-Garabedian et al., 2004).

Nociceptive processing also implicates TNF-α, which is regulated by NF-κB (Friedman, 2000; Tegeder et al., 2004). Furthermore, cytokines can modulate pain in patients with myocardial infarction (MI) and unstable nociceptive angina through NF-κB (Ritchie, 1998; Jenkins, 1999).

In corroboration, this was reinforced with the observation that *Pseudomonas aeruginosa* quorum-sensing mechanisms were implicated in inducing inflammatory pain via the release of cytokines in a NF-κB-dependent mechanism (Smith et al., 2002).

IL-1β and TNF-α also induced signs of neuropathic pain, associated with the upregulation of p65 (*Rel*A) NF-κB subunit in dorsal root ganglia (Zelenka et al., 2005), thereby indicating a possible central mechanism of the algesic effects of cytokines in pain.

Taken together, these observations stress the notion that NF-κB-mediated regulation of inflammatory cytokines is significant in controlling the processing of pain, allodynia, nociception and hyperalgesia related mechanisms.

4.3. NF-κB-mediated pain transcriptional mechanisms

The reader's attention is now diverted to focus on a thorough discussion on the molecular mechanisms associated with NF-κB-dependent regulation of inflammatory pain.

4.3.1. The effect of NF-κB on galanin receptors

The signaling pathways mediating pain and nociception are transcriptionally controlled (Mogil and McCarson, 2000; Hunt, 2000; Hill, 2001; Hunt and Mantyh, 2001; Julius and Basbaum, 2001). For example, 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-κB sites (Lorimer et al., 1997). This indicates that GALN1R gene expression can be regulated as a consequence of inflammatory conditions associated with pain in a NF-κB-dependent mechanism.

4.3.2. The effect of NF-κB on kinin receptors

Inflammatory kinins (bradykinin, 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 (Dray, 1997). The acute activation and prolonged sensitization of fine afferents, to produce pain and hyperalgesia, 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 B_2 receptors present on sensory neurons, resulting in a change of membrane excitability and altered cellular neurochemistry. B_2 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 (Poole et al., 2000).

Similar to the effect of B_2 receptors, it has been shown that the increased expression of B_1 receptors may play a prominent role in inflammatory pain and hyperalgesia (Ueno and Oh-ishi, 2003; Marceau and Regoli, 2004; Calixto et al., 2004). The B_1/B_2 kinin receptors, therefore, play a major role in the mediation of inflammatory and pain-related responses (Dray, 1997).

Molecular and pharmacological evidences show that the B_1 kinin receptor expression can be regulated through endogenous glucocorticoids by NF-κB activation (Cabrini et al., 2001). For instance, paw edema and contraction of portal vein, mediated by B_1 agonist des-Arg(9)-BK in adrenalectomized (ADX) models, were inhibited by dexamethasone or COX-2 inhibitor, meloxican, and with PDTC, a NF-κB inhibitor (Haddad and Land, 2000b; Haddad et al, 2000).

Interestingly, treatment with dexamethasone, PDTC or a combination of both blocked NF-κB activation caused by the absence of endogenous glucocorticoid (Cabrini et al., 2001). This mechanism supports the notion that NF-κB-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-κB.

4.3.3. The effect of NF-κB on c-fos and NO expression

After having tackled the role of galanin receptors and kinins in inflammatory pain, we shift gear to pinpoint the effective role of fos-related cofactors in the regulation of pain and hyperalgesia.

The involvement of c-fos and neuronal nitric oxide synthase (nNOS) in hyperalgesia induced by complete Freund's adjuvant (CFA) has been reported. The activation of NF-κB was shown to be pivotal for the expression of c-fos (early expression) and nNOS (late expression) proteins in response to CFA. Furthermore, the behavioral testing of hyperalgesia demonstrated that CFA reduced the thresholds for mechanical and thermal hyperalgesia, an effect that is NF-κB-dependent (Chan et al., 2000) (see Fig. 5).

The aforementioned strongly reinforces the ability of NF-κB to transcriptionally control the expression of cofactors that are essential in the evolution of inflammatory pain and hyperalgesia.

4.3.4. The effect of NF-κB 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 (Costa et al., 2006). The theme that emerges quickly is focused on the mechanisms that 'non-classically' blockade NF-κB. Decoys are at the forefront (Inoue et al., 2006; Sun et al., 2006).

In illustration, for example, in a neuropathic pain model, NF-κB inhibition using a specific decoy has been shown to decrease thermal hyperalgesia via the suppression of inflammatory cytokines, inducible NOS (iNOS) and adhesion molecules at the site of nerve injury (Sakaue et al., 2001).

Another NF-κB decoy was also reported to downregulate inflammatory pain associated with restenosis in coronary heart disease (Jun-Ichi et al., 2004). Furthermore, since cytokine imbalance in acute coronary syndrome was a major cause of inflammatory pain, it was postulated that the downregulation of cytokines via transcriptional control could be of therapeutic value (Alam et al., 2004).

In corroboration, another report indicated that the modulation of peripheral inflammation by NF-κB decoy oligodeoxynucleotide (Igwe, 2005) is dependent on the regulation of c-Src kinase, a member of the non-receptor tyrosine kinase super family, a decreased level of p65 (RelA) NF-κB subunit expression and COX-2 inhibition. These observations may represent novel pathways for unraveling the molecular mechanism of inflammatory pain. Therefore, amplifying intrinsic anti-inflammatory mechanisms may constitute potential avenues for the therapeutic intervention of inflammatory pain.

4.3.5. The effect of NF-κB-related kinases on pain

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

The specific inhibition of IKK (Rothwarf et al., 2000; Haddad et al., 2000; Karin, 2006) was reported to downregulate hyperalgesia in neuropathic pain models (Tegeder et al., 2004). Furthermore, inhibition of IKK activity was shown to prevent 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 PGE_2 release and COX-2 gene expression *in vitro* (Nakatani et al., 2004). Furthermore, an *in vitro* IKK assay showed that γ-mangostin inhibited IKK activity in a concentration-dependent manner.

Consistently, γ-mangostin was also observed to decrease LPS-induced IκB degradation and phosphorylation. In addition, luciferase reporter assays showed that γ-mangostin reduced the LPS-inducible activation of NF-κB- and human COX-2 gene promoter region-dependent transcription (Nakatani et al., 2004). Taken together, therefore, the inhibition of IKK, and subsequently NF-κB target genes, may decrease inflammatory pain and, essentially, may be a useful mechanism for anti-inflammatory drug development.

Another family of kinases that is crucial in the regulation of NF-κB is MAPKs (see Fig. 2). For instance, the activation of the MAPK^{ERK} signaling cascade by excitotoxic spinal cord injury has been shown to implicate NF-κB (Yu and Yezierski, 2005). 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-κB 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. The observation is corroborated with the role of MAPK^{P38} and MAPK^{JNK}

in NF-κB related induction of pain through C-fibers (Liu et al., 2007).

4.4. NF-κB and the regulation of analgesia/anti-nociception mechanisms

For now, I have focused on the role of NF-κB in the evolution of inflammatory-related pain and hyperalgesia. Being a multifaceted TF, it has not escaped my attention that this modulator may also be involved with antagonistic, analgesic effects.

NF-κB, 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-κB$_1$ (p50) knockout mice (p50$^{-/-}$), suggesting that this TF may play a crucial role in both low and high frequency EA-induced analgesia (Park et al., 2002). This was in concert with the intriguing role of NF-κB in neuronal and immune cells mediating inflammation-induced analgesia (Borner et al., 2002; Kraus et al., 2003).

What is the likely explanation for this sudden NF-κB anti-inflammatory, analgesic effect? In order to understand this discrepancy and to reconcile the inflammatory and anti-inflammatory effects of this TF, we have to decipher yet another code pertaining to the key regulatory elements associated with the expression of NF-κB. 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 neuroimmune interactions) (DeLeo et al., 2004; Chen et al., 2007). 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-κB-dependent analgesia?

Among six putative NF-κB 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 (Kraus et al., 2003).

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 (Kraus et al., 2003).

Interestingly, excluding the effect of NF-κB with the specific 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 (Borner et al., 2002). This suggests that a potential cross-talk exists between NF-κB 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-κB. For example, the receptor for advanced glycation end products (RAGE), which is associated with sustained NF-κB activation in neuropathy, has a central role in sensory neuronal dysfunction (Bierhaus et al., 2004).

Interestingly, NF-κB activation was blunted in RAGE$^{-/-}$ mice, demonstrating that the RAGE-NF-κB axis may operate by mediating functional sensory deficits and that its inhibition may provide a therapeutic approach in neuropathy (Bierhaus et al., 2004). Anti-nociception was also reported to be associated with the downregulation of NF-κB and other inflammatory mediators (Kim et al., 2005), thus reinforcing the aforementioned observation.

Furthermore, it was recently shown that spinal glucocorticoid receptors through NF-κB may play a significant role in the regulation of EAAC1 (glutamate transporter) expression after peripheral nerve injury, a cellular pathway that may contribute to the development of neuropathic pain and related behaviors in rodents (Wang et al., 2006). This suggests that the downregulation of glutamate receptor expression and NF-κB are likely mechanisms in the effect of glucocorticoids on neuropathic pain (Hermoso and Cidlowski, 2003).

In jibe with this concept, it was reported that NF-κB activation following peripheral nerve injury could contribute to the generation of neuropathic pain. For example, it was noted that reciprocal regulation of this transcription factor and its inhibitor ZAS3, a zinc finger protein, is associated with the development of neuropathic-like pain (Wu et al., 2006).

Since ZAS3 is expressed in nervous tissues involved in cognitive function and pain modulation, the down-regulation of ZAS3 after peripheral nerve injury may lead to activation of NF-κB, allowing Wallerian regeneration and induction of NF-κB-dependent gene expression, including pro-inflammatory cytokines. This correlates with the observation that betamethasone, a corticosteroid, modulates neuropathic pain by altering cerebral expression of NF-κB and cytokines (Xie et al., 2006).

In contrast with the aforementioned, Frassdorf and colleagues (2005) reported that NF-κB 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-κB in the suppression of pain-related pathways implicated with acute coronary syndromes (Frassdorf et al., 2005).

This discrepancy in NF-κB 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-κB and related cofactors.

Our assumption of the duality of NF-κB 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-κB and pain pathways are schematized in Fig. 6.

4.5. NF-κB-independent mechanisms in the regulation of pain

Despite the central role of NF-κB in regulating pain and hyperalgesia, as noted, it has been reported that there likely exist NF-κB-independent mechanism(s). For instance, sodium salicylate was shown to inhibit PGE_2 release when added together with IL-1β, an effect that was independent of NF-κB activation, or COX-2 transcription/translation (Mitchell et al., 1997). Whether other pathways are implicated has yet to be determined. In corroboration, it has been postulated that sodium salicylate was an effective inhibitor of COX-2 activity at concentrations far below those required to inhibit NF-κB, a pathway that is displaced by AA.

It seems likely that the duality of the nature of NF-κB 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 (talking as the first author) have previously reported NF-κB-independent mechanisms in the regulation of inflammatory mediators; MAPKs were attracting alternatives (Haddad, 2002b; Haddad, 2004a; Haddad and Harb, 2005).

5. Conclusions, summary and prospects

The possible involvement of NF-κB in regulating the molecular pathways of nociception has relative repercussions on inflammatory-related pain behavior, sensation and perception. Evolving research on the relationship existing between NF-κB 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-κB in the molecular regulation of pain: i) NF-κB is a major regulator of the gene expression of inflammatory mediators, which are at the epicenter of the evolution of inflammatory pain; ii) NF-κB-mediated inflammatory pain and nociception is a regulated process, which involves related TFs and/or cofactors such as AP-1, c-fos and MAPKs; iii) Inflammatory pain is not necessarily an NF-κB-exclusive event; NF-κB promoted analgesia, neuropathic (neurogenic) pain and the expression of opioid receptors too; and iv) NF-κB dual nature as a promoter of hyperalgesia and, probably, analgesia requires thorough understanding of the underlying molecular pathways.

Whether the inhibition of this TF, while down-regulating 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 (D'Acquisto et al., 2002; Haddad, 2007). Undoubtedly, unraveling the molecular association between NF-κB and pain, therefore, would create solid grounds for understanding the pain process and paves the way for a preventative, alleviating therapy for inflammatory-mediated pain.

Abbreviations

Activating protein, AP; Adrenalectomized, ADX; Advanced glycation end products, RAGE; Arachidonic acid, AA; Central nervous system, CNS; Complete Freund's adjuvant, CFA; Cyclooxygenase, COX; Dorsal root ganglia, DRG; Electrophoretic mobility shift assay, EMSA); Galanin-1 receptor gene, GALN1R; Hydroxytryptamine, HT; Inducible NOS, iNOS; Inhibtory-κB, IκB; IκB kinase, IKK; Interleukin, IL; IL-1 receptor antagonist, IL-1ra; Manganese-dependent superoxide dismutase, MnSOD; Mitogen-activated protein kinase, MAPK;

Myocardial infarction, MI; Nerve growth factor, NGF; Neuronal nitric oxide synthase, nNOS; Nitric oxide, NO; NO synthase, NOS; Nuclear factor-κB, NF-κB; Prostaglandin, PG; Pyrrolidine dithiocarbamate, PDTC; Regulated on activation, normal T cell expressed and secreted, RANTES; Rel homology, RH; Rheumatoid arthritis, RA; Transcription factor, TF; Tumor necrosis factor, TNF; Ultraviolet, UV.

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