IL-4, JAK-STAT signaling, and pain

Melanie Busch-Dienstfertig* and Sara González-Rodríguez

Department of Anesthesiology and Critical Care Medicine; Charité Campus Benjamin Franklin; Freie Universität Berlin; Berlin, Germany

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Abbreviations: IL, interleukin; JAK, Janus kinase; STAT, signal transducer and activator of transcription; TNF-α, tumor necrosis factor-α; NGF, nerve growth factor; NSAIDs, non-steroidal anti-inflammatory drugs; SOCS, suppressors of cytokine signaling; PIAS, proteins inhibitors of activated STATs; PGE₂, prostaglandin-E₂; ATP, adenosine triphosphate; CFA, complete Freund adjuvant; COX-2, cyclooxygenase-2; HSV, herpes simplex virus; Th, T helper cell; TGF-β, transforming growth factor-β

Pain and Inflammation

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage as defined by the International Association for the Study of Pain (IASP, http://www.iasp-pain.org). It is transmitted by sensory neurons called nociceptors, which are characterized by higher activation thresholds compared with other nerve fibers. These nociceptors are usually activated when there is a potentially harmful (noxious) stimulus (heat, cold, pressure, or acid) or an injury (wound, cut, or nerve lesion). Mediators of nociceptor activation include kininogens, lipids, endothehins, proinflammatory cytokines, growth factors, protons, and chemokines secreted by inflammatory, endothelial and immune cells (Fig. 1A). Encoding of noxious information is called nociception. The most important nociceptive behavioral symptoms measured in animal models are hyperalgesia (increased sensitivity to a noxious stimulus) and allodynia (increased sensitivity to a stimulus that does not normally provoke nociception). To closely mimic human pain, diseases and injuries are modeled mainly in rodents but these models fail to reproduce the emotional component characterizing human pain. There are many models but in general they can be attributed to three main pain groups according to their etiology: inflammatory, cancer, and neuropathic pain. Several drugs such as opioids,1-3 non-steroidal anti-inflammatory drugs (NSAIDs),4,5 IL-1 receptor antagonist,6 or antibodies, e.g., anti-nerve growth factor (NGF)7 and anti-tumor necrosis factor (TNF)-α,8 were studied in cancer pain models showing different efficacy. In neuropathic pain also opioids,9-11 purinergic receptor antagonist,12 and enkephalin-degrading inhibitors13 have been tested. Although inflammatory pain has its own etiology, both cancer and neuropathic pain share an inflammatory component, which makes inflammatory pain the broadest type of pain. Intense pain like postoperative and polytraumatism pain cannot be treated suitably with NSAIDs and opioids are required.14,15 In addition to their strong analgesic effect, it is well accepted that opioids also have anti-inflammatory effects such as elevating plasma corticosterone levels and reducing T-cell proliferation as reviewed by other authors.16 This may explain why opioids have been shown to be more potent under inflammatory conditions.17-19 The activation of opioid receptors located at peripheral nerve endings can inhibit pain by blocking noiception and these receptors are upregulated in injured tissue (for further references see ref. 20).

During the development of inflammation, multiple factors are released including cytokines, which can roughly be divided into pro- and anti-inflammatory ones. The earliest cytokines formed are usually IL-1β and TNF-α acting directly on specific receptors in neurons leading to the activation of a multitude of pathways and the accumulation of different effectors such as more cytokines, chemokines, prostanooids, neuropeptides, nitric oxide, lipids, and ATP. By that, a proliferative growth and hypertrophia of glial cells is induced in the CNS which in turn release more pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6 and thereby also contribute to the complex activation loop.20-22 TNF-α, IL-6, and IL-1β are potent COX-2 activators24 (see Fig. 1B) and consequently also prostaglandins accumulate in both injured tissue and spinal cord leading to an increased sensibility of neurons. Many activities of TNF-α and IL-1β are NGF-mediated. In inflamed tissue, NGF induces proliferation and degranulation of macrophages; among the factors released is also NGF. Moreover, NGF acts through posttranscriptional regulation of receptors and ion channels inducing mechanical and thermal hyperalgesia.25 In summary, there are several positive

*Correspondence to: Melanie Busch-Dienstfertig; melanie.busch@charite.de
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feedback loops contributing to the establishment of painful inflammation. On the other hand, cytokines such as IL-1β also contribute to anti-inflammatory and antinociceptive processes by stimulating the synthesis of opioid receptors in dorsal root ganglia neurons which are then axonally transported toward the periphery.26 Opioid peptide expression and release is not limited to neurons, immune cells infiltrating inflamed tissue also contain such peptides: Chemokines induce an increase in the number of leukocytes containing opioid peptides in the inflamed tissue27 and the liberation of these endogenous pain inhibitors depends on pro-inflammatory cytokines like IL-1β and IL-6.28,29 Once released, immune cell-derived opioid peptides are able to activate opioid receptors on peripheral terminals and inhibit neuronal excitability, as a result, pain is reduced.30

**Pronociceptive Cytokines**

Several pro-inflammatory cytokines are involved in heightened pain sensitivity under inflammatory conditions as already reviewed by other authors.24,30 Therefore, we will point out only a few exemplary studies here. TNF-α can directly sensitize nociceptive fibers as shown in electrophysiological studies31,32 and enhances prostaglandin synthesis33 (see Fig. 1A). Accordingly, the knockout of TNF-α receptors resulted in reduced heat hyperalgesia after intraplantar injection of an adjuvant inducing inflammation (complete Freund adjuvant, CFA) in mice.33 Several so-called biologicals (antibodies, receptor antagonists, soluble receptors, and others) have been developed to block TNF-α and some of them are approved (infliximab, adalimumab, and etanercept) to treat inflammatory diseases like rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn disease, chronic psoriasis, and juvenile idiopathic arthritis in patients. In a rat model of arthritis, etanercept significantly decreased inflammation-induced locomotor and pain-related behaviors. The same study provided electrophysiological recordings performed in anesthetized rats showing reduced responses to noxious outward rotation of inflamed knees after etanercept treatment.34

As mentioned above and shown in Figure 1B, TNF-α enhances the production and release of several other pro-inflammatory cytokines and factors like IL-6, IL-8, IL-1β, NGF, and prostaglandins and by that amplifies the inflammatory response. The injection of TNF-α into healthy tissue of rats locally elevated the levels of IL-1β and NGF and produced a transient, dose-dependent mechanical hyperalgesia.35 In other experiments of the same study, TNF-α antiserum significantly delayed the onset of CFA-induced inflammatory hyperalgesia and reduced IL-1β but not NGF levels. In contrast to TNF-α, IL-1β shows less direct involvement in the pronociceptive context of inflammation although intraplantar injections of IL-1β in rats also produced short-lasting thermal hyperalgesia,36 probably by elevating the levels of prostaglandins and NGF (see Fig. 1A and B). Moreover, IL-1β seems a crucial mediator for inflammatory cartilage and bone degradation.37 A selective inhibitor of the IL-1 pathway, IL-1 receptor antagonist, significantly reduced joint destruction and offered a safe and well tolerated therapy for rheumatoid arthritis patients.38 Activation of TNF-α and IL-1β receptors is leading to the ultimate activation of the nuclear factor κB (NFκB) and to the transcription of NFκB-regulated genes mediated by a variety of adaptor proteins and kinases (see Fig. 1B).

In contrast to TNF-α and IL-1β, IL-6 largely mediates its effects via the janus kinase/signal transducer and activator of transcription (JAK-STAT) pathway used by several cytokines and growth factors.39 The route starts with the binding of the ligand to its receptor, which dimerizes followed by the association and autophosphorylation of usually two out of four known JAK proteins (JAK1, JAK2, JAK3, and TYK2) and the subsequent docking of certain STAT proteins comprising a family of seven members (STAT1, STAT2, STAT3, STAT4, STAT5A/B, and STAT6). Once bound to the receptor, SH2 domains of the STATs connect to the phosphotyrosines on the tail of the receptor and STAT phosphorylation by JAKs occurs. Then, activated STAT proteins dissociate from the receptor, dimerize and translocate to the nucleus where they recognize and bind to specific DNA sequences of their target genes and inhibit or induce gene expression. IL-6 binding to the IL-6 receptor typically results in the phosphorylation of JAKs 1 and 2 and of STAT3 (see Fig. 1B). There is evidence that IL-6 and STAT3 activation are the key mediators of both chronic inflammation and joint destruction in rheumatoid arthritis.40 By inhibiting STAT3 the authors found reduced inflammation and joint destruction in a model of collagen-induced arthritis through a significant reduction in the expression of IL-6 family cytokines and NFκB, indicating pro-inflammatory action of IL-6. The pronociceptive properties of IL-6 became overt in IL-6 knockout mice.41 These animals showed reduced thermal and mechanical hyperalgesia after injection of carrageenan into the hindpaws and after nerve lesion as compared with wild-types. Additionally, the blockade of JAK-STAT3 activity by lentiviral-mediated production of the suppressor of cytokine signaling (SOCS) 3 prevented the strong expression of IL-6 and of other factors induced in the spinal cord after nerve lesion in rats and substantially attenuated mechanical allodynia.42 In vitro experiments indicated that TNF-α induces

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**Figure 1.** Modulation of hyperalgesia. (A) Several different classes of molecules can directly induce hyperalgesia in inflammation, while opioids can potentially block it. (B) The antinociceptive effect of anti-inflammatory cytokines is largely mediated via JAK/STAT activation resulting in the inhibition of the production or release of pro-inflammatory cytokines. Most pro-inflammatory cytokines indirectly contribute to hyperalgesia by enhancing the synthesis or release of prostaglandins, sympathetic amines, endothelin, and NGF. The cytokine signaling is mediated via various adaptor proteins and include pathways such as MAPK, JAK-STAT, and NFκB. Boxes, factors inducing hyperalgesia; diamonds, pro-inflammatory cytokines; circles, anti-inflammatory cytokines/proteins; AP-1, activator protein 1; ATP, adenosine triphosphate; BP, binding protein; H+, protons; iFN, interferon; iKKα, iκB kinase complex; IL, interleukin; IRAKs, IL-1 receptor-associated kinases; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; MyD88, myeloid differentiation factor 88; NFκB, nuclear factor κB; NGF, nerve growth factor; STAT, signal transducer and activator of transcription; TNF, tumor necrosis factor; TRAF, TNF receptor-associated factor.
the synthesis and release of IL-6 via JAK-STAT3 and different mitogen activated kinase (MAPK) pathways in C6 glia cells. On the other hand, IL-6 is not a classical pro-inflammatory cytokine and exerts several anti-inflammatory actions such as downregulation of IFN-γ, IL-1β, and TNF-α. However, to the best of our knowledge there are no reports on antinociceptive action of IL-6, despite the IL-6-mediated liberation of opioid peptides from leukocytes already mentioned above.

Two other cytokines with predominantly pro-inflammatory action, namely IL-12 and IL-18, also contribute to hyperalgesia by elevating the endothelin levels and by enhancing pro-inflammatory cytokines such as TNF-α (see Fig. 1B). Both IL-12 and IL-18 signal via TYK2 and STAT4; IL-18, however, mainly mediates its effects via MAPK and other adaptor proteins to activate NFκB and AP-1. Taken together, TNF-α, IL-1β, IL-6, IL-12, and IL-18 seem to be directly or indirectly relevant for the initiation and maintenance of hypersensitivity toward painful stimuli in inflammation, which is to some extent mediated via JAK-STAT.

### IL-4 and Antinociceptive Properties of Anti-inflammatory Cytokines

Several anti-inflammatory cytokines also signal via JAK-STAT including IL-4, which is one of the best known anti-inflammatory cytokines due to its widespread biological roles in diverse processes such as T-cell proliferation, activated B-cell stimulation, activation of macrophages, chronic inflammation, and wound repair. IL-4 is mainly produced by activated T cells and its overexpression is associated with allergies. IL-4 can produce its effects via two types of receptor complexes (IL-4R-I and IL-4R-II) as reviewed in detail by others. Type I is a heterodimer formed by the IL-4R-α chain in association with the common cytokine receptor gamma chain (γc), while type II is composed of IL-4R-α in association with IL-13R-α1. The first type is expressed on hematopoietic cells of the lymphoid (T and B cells) and myeloid (monocytes, macrophages, and fibroblasts) lineage and its stimulation by IL-4 induces activation of the JAKs and finally of STAT6 (see Fig. 1B). In addition, the IL-4R-I associates with insulin receptor substrate 2 and by that activates the PI3K/Akt and Ras/MEK/Erk pathways involved in cell proliferation, survival and translational control. IL-4R-I is strongly involved in regulating the maturation and proliferation of type 2 T helper (Th2) cells and in IgE synthesis by B cells. The type II receptor is expressed on hematopoietic cells of the myeloid lineage and on nonhematopoietic cells (smooth muscle and epithelial cells), can bind both IL-4 and IL-13, and also leads to STAT6 activation; STAT3 can also be phosphorylated. The JAKs linked to the type II receptor are JAK1, JAK2, and TYK2 (see Fig. 1B). In contrast to IL-4R-I, the type II receptor does not associate with insulin receptor substrate 2 and consequently the PI3K/Akt and Ras/MEK/Erk pathways are not activated. IL-4R-II is involved in respiratory airway processes and mucus secretion.

IL-4 deficiency has been described to exacerbate inflammation in collagen-induced arthritis and its overexpression or exogenous administration has been shown to delay the development and/or establishment or gravity of diseases such as Alzheimer, encephalomyelitis, and collagen-induced arthritis in transgenic mice. Moreover, IL-4 is involved in antileukemia immune responses, which in line with previous findings. Besides IL-4, IL-1 receptor antagonist reversed hyperalgesia with similar efficiency (see also Fig. 1B). The same group corroborated the antinociceptive action of IL-4 in two other models of inflammatory pain. They showed that cytokine pretreatment inhibited the writhing response induced by the intraperitoneal administration of acetic acid or zymosan in mice and reduced the knee joint incapacitation induced by intra-articular injection of zymosan in rats. Consistently, IL-4 antibodies potentiated hyperalgesia induced by zymosan. Injection of other anti-inflammatory cytokines (IL-10 and IL-13) produced similar antinociceptive effects as IL-4. The common pathway activated by IL-4, IL-13, and IL-10 is JAK-STAT (see Fig. 1B), indicating that the antinociceptive effect of anti-inflammatory cytokines is mediated via this signaling cascade. Since IL-4 can bind to type I and II IL-4-R and IL-13 binds to type II IL-4-R, both receptors seem to contribute to the antinociceptive effects observed in the studies mentioned above.

IL-4 links the immune system to the opioid system by inducing mu- and delta-opioid receptors (MOR, DOR) and pro-opiomelanocortin (POMC) transcription. Opioid receptor gene expression in T cells thereby was STAT6-dependent while POMC gene expression in lymphocytes was mediated via JAK-STAT activation and involved STAT3 but not STAT6. These findings point toward the importance of the JAK-STAT pathway in the upregulation of the opioid system by IL-4. Reciprocally, opioid peptides seem to be factors involved in the Th1–Th2 balance, where POMC-derived β-endorphin and opioid receptors can be considered as Th2 activators and IL-4 transcription in T cells can be stimulated by endogenous and exogenous opioids. However, Ferreira and colleagues found that the injection of the opioid receptor antagonist naloxone did not affect the acute cytokine-induced antinociception, e.g., in the acetic acid test, indicating that the endogenous opioid system was not involved. Thus, although IL-4 and the opioid system are intimately connected with each other, IL-4 seems to exert its acute antinociceptive function also solely by the inhibition of pro-inflammatory cytokines and factors (see Fig. 1B).

The relevance of IL-4 in pain was more recently supported by an investigation of IL-4 deficiency in mice. Healthy IL-4
knockout mice displayed tactile allodynia, while responses to heat and cold stimuli and to muscle pressure were normal. However, under neuropathic conditions IL-4 deficient animals were indistinguishable from wild types and did not show further enhanced pain. Gene expression analysis demonstrated overexpression of IL-10 and IL-13 in the spinal cord, which may have had a compensatory action and could explain the lack of differences between the two genotypes in their pain behavior after nerve lesion. Others investigated the effect of IL-4 on neuropathic pain using in vivo gene transfer. In animals overexpressing IL-4 in non-replicating herpes simplex virus (HSV)-infected dorsal root ganglia, thermal hyperalgesia and mechanical allodynia due to nerve ligation were decreased. Moreover, levels of IL-1β, PGE₂, and p-p38 in the spinal cord dorsal horn, which usually increase after nerve lesion, were decreased in IL-4 overexpressing animals. Similarly, HSV vector-mediated IL-4 expression reduced the inflammatory response, bladder overactivity and nociceptive behavior induced by bladder irritation in rats. Overexpression of other anti-inflammatory factors using HSV vectors encoding the soluble (p55) TNF receptor or adeno-associated viral vector encoding IL-10 also successfully reduced neurophatic pain.

Although there are not many experimental studies regarding potential IL-4 effects on pain, the search for new therapeutic strategies for the treatment of pain or prevention of chronic inflammation development has increased during the last years focusing on either increasing the function or expression of anti-inflammatory cytokines or on blocking pro-inflammatory cytokines. Some studies provided new information related to IL-4, which might lead to a better understanding of its involvement in human diseases and could improve future drug design. For example, a synthetic IL-4 α-helix C-derived peptide termed Ph8 was designed, which is a partial agonist of IL-4R-1 and an antagonist of IL-4R-II. In rats with collagen-induced arthritis Ph8 delayed the manifestation of chronic inflammation by inhibiting TNF-α secretion and by inducing apoptosis of Th1 cells. Interestingly, Ph8 did not promote the shift toward a Th2 response and its effect was reversible after discontinuation of the treatment, indicating that no activation of IRS-2 linked pathways occurred after binding of Ph8 to IL-4R-I. Nociception, however, was not investigated in this study.

Despite the broad range of investigations focusing on IL-4, little attention has been directed on its splice variants so far. As Luzina and colleagues recently reported, splice variants of IL-4 are expressed in humans (spleen and bone marrow) and in other species. One splice variant, namely IL-4β2, induced higher levels of pro-inflammatory (TNF-α, IL-1, and monocyte chemotactic protein-1) and Th1-related cytokines (IL-12 and IFN-γ) in rodent lungs, indicating that IL-4β2 has different effects than IL-4 although both peptides seem to bind to the same receptors. At present, there is only one specific antibody without cross-reactivity with full-length IL-4 protein and such antibodies are necessary to distinguish between the two peptides. More studies on this splice variant are required including revision of already published data to clearly assign the observed effects to the different forms of IL-4.

How Does Inhibition of the JAK-STAT Pathway Affect Pain?

The JAK-STAT pathway is strongly regulated as reviewed by Kiu and Nicholson. JAK-STAT regulation thereby aims at controlling the magnitude and duration of cytokine signaling and includes different mechanisms such as receptor internalization by vesicles and subsequent receptor degradation, dephosphorylation by phosphatases (PTPs), and posttranslational modifications of STAT proteins. Furthermore, there are two classes of endogenously expressed negative regulators. The SOCS interfere with STAT binding to cytokine receptors and with STAT phosphorylation by JAKs, while the inhibitors of activated STATs (PIAS) block STAT-mediated gene activation. To what extent these endogenous inhibitory mechanisms are involved in inflammatory pain remains to be elucidated in detail. As has been already pointed out above, interference with IL-6 signaling via SOCS3-overexpression reduced mechanical hyperalgesia after nerve lesion in rats indicating that the negative regulators may represent promising targets for the treatment of pain. Synthetic JAK inhibitors act at the same level as SOCS proteins and prevent STAT activation. Among the JAK inhibitors under clinical investigation to treat e.g., rheumatoid arthritis, tofacitinib (CP-690550, predominantly inhibits JAK3 but at higher doses also JAK1 and 2) was approved and baricitinib (LY3009104, inhibits JAK1 and 2) reached phase II trial. In rheumatoid arthritis, tofacitinib, besides improving physical functioning and health status, also reduced pain, which became apparent already one week after the beginning of the medication and further improved until the end of the study (6 wk). In contrast to biologicals that mainly have to be delivered intravenously, JAK inhibitors are administered orally, which is more comfortable for the patients. Based on such observations, the implication of JAK inhibitors in pain management will probably gain more attention in the future although both pro- and anti-inflammatory cytokine actions are affected alike. Interestingly, there is evidence that the immunosuppressive effect of morphine may be a consequence of SOCS and PIAS expression induced by morphine treatment of virus-infected human blood monocyte-derived macrophages in vitro. Conclusively, the authors also found reduced expression of JAK-STAT-induced cytokines (IFN-α, IFN-β, and IFN-γ) and of IFN-inducible genes. These findings may spawn new therapeutic interventions using morphine and other opioids.

Conclusions

The experimental studies described above raise the question if pain is simply an outcome of the balance between pro- and anti-inflammatory cytokines. Only few studies have addressed this question so far. In patients with complex regional pain syndromes, TNF-α and IL-2 serum levels were higher and IL-4, IL-10, and TGF-β levels were lower than in the controls. In another patients cohort with chronic widespread pain including fibromyalgia, serum levels of IL-4 and IL-10 were also lower than in healthy controls but no significant differences were observed between the plasma levels of IL-2, IL-8, TNF-α, or TGF-β of
patients and controls. In these two patient groups, a relative elevation of the ratio of pro- to anti-inflammatory cytokines seems to coincide with pain. Similarly, IL-2 and TNF-α protein levels in serum were higher in patients with painful neuropathy as compared with healthy control subjects and also when compared with the levels determined in patients with less painful neuropathy. In both painful and painless neuropathies however, serum levels of IL-4 were substantially higher than in healthy control subjects and the ratio of pro- to anti-inflammatory cytokines was not elevated with respect to painful neuropathy. Further studies are necessary to work out if serum cytokine levels could clearly indicate a painful disease state. Moreover, pain studies in patients are complicated by the subjective experience of pain and new instruments to objectively measure pain are desirable. Recent research demonstrated that pain can be visualized using functional magnetic resonance imaging (MRI). This method measures blood oxygen level-dependent signals in the brain. Activity in brain areas involved in nociception (thalamus, somatosensory cortex, and the limbic system) was defined to be indicative for pain and was blocked after infusion of a monoclonal antibody to TNF-α in arthritis patients and in arthritic mice. This method promises to be a valuable tool to investigate the antinociceptive effect of conventional and new pain therapies including JAK inhibitors. In addition, correlation of functional MRI-determined pain and cytokine levels may help to identify pain biomarkers in the future.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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