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Chemokines as Pain Mediators and Modulators

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Abstract

Purpose of review—Chemokines are central to the innate immune response following tissue damage, injury and some diseases. The function of chemokines in nervous system autoimmune diseases has been long recognized. There is also growing evidence that disease-associated of injury-induced functional expression of chemokines/receptors in both neural and non-neural elements of the peripheral nervous system play crucial roles in the pathophysiology of chronic pain.

Recent findings—Chemokine involvement in neuropathic pain processing has recently been established in animal models. Evidence of chemokine contribution to chronic pain includes the upregulation of monocyte chemoattractant protein-1 (MCP-1/CCL2) and its respective receptor, CCR2, in many subpopulations of sensory neurons. Activation of CCR2 by MCP-1 elicits membrane depolarization, trigger action potentials and sensitizes nociceptors via transactivation of transient receptor potential channels TRPA1 and TRPV1. Increased signaling by stromal-derived factor-1 (SDF-1/CXCL12) and its receptor, CXCR4, has been shown to contribute to chronic pain behavior. The use of specific chemokine receptor antagonists for CCR2 and CXCR4 successfully reverses nociceptive pain behavior.

Summary—Our results suggest that specific chemokines/receptors are up-regulated by sensory neurons following peripheral nerve injury and appear to participate in neural signal processing leading to chronic pain states. Taken together, chemokines and their receptors are potential targets for development of novel therapeutics.

Keywords

chemokines; receptors; pain; models

Introduction

Our incomplete understanding of the mechanisms underlying chronic pain hypersensitivity accounts for the general ineffectiveness of currently available options for the treatment of chronic pain syndromes. Despite its complex pathophysiology, it is clear that many aspects of neuropathic pain are associated with short- and long-term changes in the excitability of sensory neurons in the dorsal root ganglia (DRG). Neuromimmune interactions are increasingly recognized as important elements in nociceptive processing and recent evidence suggest that the upregulated expression of inflammatory chemotactic cytokines (chemokines) in association with tissue damage or infection serve not only in the capacity of leukocyte chemotaxis, but also in the generation of hyperexcitable sensory neurons. In this review discuss the diverse

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changes produced by inflammatory chemokines in the context of disease-associated and injury-induced chronic pain syndromes.

A complex biological process that has largely been ignored by the field of pain research is the concept of persistent acute (or chronic) inflammation within the nervous system also known as neuroinflammation. For many years, the nervous system was considered to be 'immune privileged', neither susceptible to nor contributing to inflammation. It is now appreciated that the nervous system does indeed exhibit inflammatory processes in response to injury, infection, or disease. To date, many of the inflammatory processes that are studied in the nervous system are associated with neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, prion diseases, multiple sclerosis and HIV-dementia. Additionally, the resident immune cells that secrete a variety of proinflammatory and neurotoxic factors are thought to induce and/or exacerbate neurodegeneration (1). This state of neuroinflammation can also facilitate or directly produce pain by releasing cytokines, reactive oxygen intermediates, proteinases and complement proteins which in turn recruit immune cells, and activate glial cells (2,3). Many of these events induce the expression of a family of factors known as chemokines. Chemokines functional largely to orchestrate the migration of leukocytes to inflamed tissue. Injury or disease-induced *de novo* chemokine/receptor expression within the nervous system, however, is linked to glial activation states and neuronal hyperexcitability and has been implicated in the development and persistence of many pathologic pain states (4).

Chemokines, Chemokine Receptors and Intracellular Signaling

Chemokines constitute a large family of relatively low molecular weight proteins classified by the presence of a cysteine motif in the N-terminal region of the protein. Initial characterization of chemokines divided the family into α- and β-chemokines. In α chemokines, one amino acid separates the first two cysteine residues (cysteine-X amino acid-cysteine or CXC), whereas in β-chemokines, the first two cysteine residues are adjacent to each other (cysteine-cysteine, or CC). Two additional classes were added for the chemokines, lympotactin (single cysteine, XC) and fractalkine (first two cysteines are separated by three amino acids, CX3C). The chemokine nomenclature herein utilizes both the original ligand name and the systematic name. The systematic name uses XC, CC, CXC and CX3C, indicating the class to which the chemokine belongs, followed by the letter "L"(for ligand) and then a number. The numbering system corresponds to that already in use to designate the genes encoding each chemokine (See Table 1).

All chemokines exert their biological effects through the activation of an extended family of seven transmembrane G-protein-coupled receptors (GPCRs). Nineteen chemokine receptors have been cloned including six CXC receptors (CXCR1-6), 10 CC receptors (from CCR1-10) and lympotactin (XCR1) and fractalkine (CXC3CR1). Chemokine receptors are notoriously promiscuous, i.e. single chemokines can activate several different chemokine receptors (See Table 1). There are, however, instances when a chemokine receptor is activated by a single chemokine. For example, the CXCR4 receptor has only one known ligand, stromal-derived factor-1 alpha (SDF1α/CXCL12).

A common response of all non-excitable cells to chemokine stimulation is chemotaxis. The presence of chemokine receptors on neurons often trigger downstream signaling cascades via dissociation of G proteins which induce the phosphoinositidine 3-kinase pathway (PI3K) or activates phospholipase C resulting in Ca^{2+} influx and protein kinase C activation (5). Knockout experiments in mice have revealed the central role played by PI3K in cellular responses to chemokines (6,7) while transient Ca^{2+} elevations are one of the most well-characterized effects of chemokines (8,9). It is important to note that most responses to chemokines are blocked with pertussis toxin, indicating that many chemokine receptors are

$G_{i/o}$ coupled. Recent functional characterizations of chemokine receptors suggest these proteins form dimers that could further regulate their signaling (10,11). In addition, evidence also suggests that chemokines may activate mitogen-activated protein kinase (MAPK) by either G_a or G-protein independent signaling (10,12).

Although chemokines usually have a beneficial effect in limiting responses to cellular and organ damage, a breakdown in the regulation of the inflammatory response may result in a wide range of chronic diseases. This chemokine mediated component is also likely to extend to the pathogenesis and maintenance of chronic pain in both disease-related conditions (e.g. multiple sclerosis, HIV-1 and herpes simplex) and following trauma, all of which are associated with innate immune responses and prolonged expression of chemokines and their receptors by the cellular elements of the nervous system (4). As such, interference with chemokine function is a promising approach for the development of both novel anti-inflammatory medications for disease and chronic pain conditions.

CHEMOKINES/RECEPTORS IN ACUTE AND CHRONIC PAIN

Tissue damage, inflammation or injury of the nervous system may result in chronic neuropathic pain characterized by hyperalgesia (increased sensitivity to painful stimuli), allodynia (innocuous stimuli perceived as painful) and spontaneous pain. Immune and non-immune cells associated with the injury response release pro-inflammatory mediators such as prostaglandins, histamine, serotonin, protons, bradykinin, nerve growth factor, and pro-inflammatory cytokines that can sensitize primary afferent neurons and contribute to pain hypersensitivity. There is also adequate evidence demonstrating that like other inflammatory mediators, chemokines elicit hypernociception. For example, Oh and colleagues (2001) demonstrated that the simple injection of SDF1α/CXCL12, Regulated upon Activation, Normal T-cell Expressed, and Secreted (RANTES/CCL5) or macrophage inflammatory protein-1α (MIP1α/CCL3) into the un-inflamed adult rat hind paw produces dose-dependent tactile allodynia. These behavioral experiments in combination with accompanying RT-PCR, calcium imaging studies and immunohistochemistry confirmed the presence and functionality of the respective chemokine receptors, CXCR4, CCR5 and CCR4 in rodent dorsal root ganglion (DRG) sensory neurons (8). Similar behavioral effects were observed following the introduction of interleukin-8 (IL-8 CXCL8) (13) and intrathecal introduction of fractalkine (CX3CL1) (14).

Peripheral sensitization as influenced by chemokines may be due to receptor activation and downstream signaling and/or to a sensitization of transient receptor potential (TRP) cation channels such as the capsaicin-sensitive TRPV1 (15) or the mechanosensitive variant,TRPA1 (16,17). For example, recent investigations revealed MIP-1α/CCL3 enhanced the response of TRPV1-positive neurons to capsaicin by inducing calcium influx and protein kinase C (PKC) activation (18). The activation of both TRPV1 and TRPA1 by monocytes chemoattractant protein-1 (MCP-1/CCL2) signaling has also been observed in previously-injured nociceptive DRG neurons (19).

Functional expression of chemokine/receptors in the damaged nervous system may both participate in the etiology and symptomology of diverse pathological pain states. To date the evidence in animal models includes the upregulation of chemokine/receptors in partial ligation of the sciatic nerve (20–23), chronic constriction injury of the sciatic nerve (24–26), chronic compression of the L_4L_5 DRG (CCD; a rodent model of spinal stenosis) (27,28), spinal cord contusion (29), chemically-induced focal nerve demyelination (30,31), bone cancer pain (32), zymosan or adjuvant-induced inflammatory pain (33–37) and the chemotoxic effects of some anti-HIV therapeutics (38). Despite the potential importance of these factors for clinical pain syndromes, only a few studies have been designed to investigate the presence of altered levels of chemokines. These include the measurement of chemokine levels in prostatic secretion from

individuals diagnosed with chronic pelvic pain syndrome (39), herniated lumbar intravertebral disc specimens (40) and the cerebral spinal fluid taken (CSF) from individuals diagnosed with chronic regional pain syndrome (CRPS) (41–43) . Although these studies did not reveal a specific molecule that could serve as a diagnostic marker of a chronic pain syndrome, it was notable that CSF from patients afflicted with CRPS did reveal a common pattern of elevated cytokines and chemokines in 11 of 22 individuals tested (42).

ROLE OF MCP-1/CCR2 IN NOCICEPTIVE SIGNALING

Of the many chemokines induced by injury or disease, the chemokine receptor CCR2 and its preferred ligand, MCP-1/CCL2 consistently appears to be of special importance in peripheral nerve and neuronal hyperexcitability. The importance of this chemokine/receptor pairing in neuropathic pain states was first demonstrated in CCR2 knockout mice. Testing of acute pain behavior in CCR2 knockout mice does not differ from wild type mice. Following partial ligation of the sciatic nerve, a model known to induce hypernociception, CCR2 knockout mice failed to display mechanical hyperalgesia (20), while overexpression of glial MCP-1 by transgenic mice produced enhanced nociceptive responses (44). Additional confirmation of a *de novo* role for MCP-1/CCR2 signaling in injured neurons was observed following chronic compression of the dorsal root ganglia (a model of spinal stenosis). In this investigation, the injury produced neuronal upregulation of both MCP-1 and CCR2 in the DRG while exogenous administration of MCP-1/CCL2 produced a depolarized resting membrane potential and increased firing in the neuronal cell bodies (27). Subsequent studies demonstrated that not only did sensory neurons following peripheral nerve injury exhibit chronic upregulation of functional MCP-1/CCR2 signaling in neurons, but a CCR2 specific receptor antagonist could reverse hypernociceptive behavior in the injured animal (30). Further investigations into the excitatory effects of MCP-1/CCR2 signaling in sensory neurons have revealed that i) regulation of the CCR2 chemokine receptor expression in neurons is activity-dependent on the signal transcription factor, nuclear factor in activated T cells (NFAT) (45) and ii) MCP-1 activates a non-cation selective voltage-independent, depolarizing current and inhibited a voltage-dependent outward current (28). Moreover, MCP-1 protein expression by DRG neurons following nerve injury is colocalized with calcitonin gene-related peptide in large dense core vesicles and release of MCP-1 vesicles could be induced from the soma by depolarization in a Ca^{2+}-dependent manner (19).

The role of MCP-1/CCR2 signaling is not limited to the DRG soma. Zhang and De Koninick (25) recently demonstrated that MCP-1/CCL2 is also present in central afferent fibers in the spinal cord. Electrical activity due to peripheral nerve injury may serve to stimulate central afferent release of MCP-1/CCL2 into the spinal cord dorsal horn activating CCR2 bearing glial cells or neurons (20,23,25). Notably, neuronally-derived chemokines that activate glial cells also include the chemokine, fractalkine/CX3CRL1. Both endogenous and exogenous fractalkine/CX3CL1 serve to activate microglial cells following peripheral nerve injury (24, 33). Perhaps more importantly, CX3CR1 antagonists can both prevent and attenuate ongoing neuropathic pain behavior (24).

Relationship of Chemokines to Disease-Related Chronic Pain

Neuropathic pain is a topic of some concern for individuals with autoimmune or life-threatening diseases as the pain syndromes are difficult to treat and significantly detract from the quality of life. A prime example is the pain syndrome called distal symmetrical polyneuropathy (DSP), that affects as many as one third of all HIV infected individuals (46). This painful sensory neuropathy frequently begins with paresthesias in the fingers and toes progressing over weeks to months, followed by the development of pain, often of a burning and lancinating nature, which can make walking very difficult. Measurements of pain

hypersensitivity have demonstrated allodynia and hyperalgesia in HIV-1 infected individuals despite the absence of productive viral infection in the peripheral neurons. Subsequently, indirect effects of HIV-1 must lead to the development of this pain state (e.g. viral coat protein gp120 binding to the HIV-1 co-receptors CCR5 or CXCR4 present on neurons) (47). Given these parameters, there are two ways in which HIV-1-induced DSP may occur: (1) viral protein shedding in the peripheral nervous system enables gp120 to produce painful neuropathy via glial/non-neuronal signaling in the DRG and/or spinal cord (48,49) or (2) gp120 directly activates sensory neurons (8,50).

Complicating matters further, AIDS patients who are treated by highly active, anti-retroviral therapeutical (HAART) agents can also develop a painful sensory neuropathy. Intriguingly, the symptoms of this syndrome are clinically indistinguishable from those of HIV-induced DSP, including a burning sensation in the hands and feet and hypersensitivity to pain. In fact, these two syndromes are usually seen in association with one another making diagnosis more difficult.

Recent studies in rat shed new light on the mechanisms of HAART-induced DSP (38). These studies found that the HAART drug, 2',3'-dideoxycytidine (ddC) produced neuropathic pain behavior, increased CXCR4 mRNA expression in the DRG and significantly increased SDF1/CXCL12-dependent neuronal activation. Moreover, ddC-induced rodent pain behavior could be attenuated using the highly specific CXCR4 receptor antagonist, AMD3100 (38).

PNS and CNS inflammatory demyelinating diseases such as Guillain-Barre syndrome, Charcot-Marie Tooth disease type 1 and 4, and multiple sclerosis can also be accompanied by neuropathic pain (51). Epidemiological studies suggest that chronic pain syndromes afflict 50–80% of patients with multiple sclerosis and 70–90% of individuals with Guillain-Barre syndrome (52). Disease-related components that may be central to this neuropathic pain symptomology may include axon degeneration and the resulting Wallerian degeneration (53) and/or the upregulation and chronic expression of chemokines and their cognate receptors (54–56).

There is presently little direct evidence of chemokines contributing to neuropathic pain in acute and chronic inflammatory demyelinating disorders in humans. However, direct study of several rodent models of demyelinating diseases known to elicit neuropathic pain behavior (including late-developing peripheral axon demyelination in *periaxin* knockout mice (57), chemically-induced transient focal demyelination of the sciatic nerve in mice and rats (30,58) and the late, acute clinical phase of experimental autoimmune neuritis [EAN; unpublished data; (59)] may be instrumental in determining the possible role of chemokine-influenced chronic pain. Moreover, recent studies of rats and mice subjected to transient focal demyelination of the sciatic nerve exhibit chronic upregulation of MCP-1/CCL2 and interferon γ producing protein-10 (IP-10/CXCL10) and the chemokine receptors, CCR2, CCR5 and CXCR4 in primary sensory neurons (30). These chemokines/receptors may effectively modulate the accompanying chronic pain behavior by modifying the manner in which these sensory neurons respond to peripheral stimuli.

CONCLUSIONS

Chemokines are responsible for specific recruitment of leukoctyes during inflammation and disease. Besides the well-established role of chemokines in the immune system, a number of chemokines and their receptors directly or indirectly exert their activity on adult neurons and glial cells where they are involved in intercellular communication. Many chemokines exhibit *de novo* expression in the nervous system following the induction of disease and nerve injury, and may play a distinct role in chronic pain syndromes. There is uncertainty about the exact

mechanism by which chemokines act in these pain states, as the effect of chemokines could impact neurons in either a direct or indirect manner. Nonetheless, the data suggest that strategies aimed at limiting the actions of chemokines may result in an important new direction of therapy.

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Table 1

Chemokine nomenclature

Receptor	Systematic Name	Original Name
CCR1	CCL3	Macrophage Inflammatory Protein-1alpha (MIP-1α)
	CCL5	Regulated on Activation Normal T cell expressed and secreted (RANTES)
	CCL7	Macrophage Chemoattractant Protein-3 (MCP-3)
	CCL9	Macrophage Inflammatory Protein-1gamma (MIP-1γ)
	CCL14	Hemofiltrate CC Chemokine-1 (HCC-1)
	CCL15	Hemofiltrate CC Chemokine-2 (HCC-2)
	CCL16	Hemofiltrate CC Chemokine-4 (HCC-4)
	CCL23	Myeloid Progenitor Inhibitory Factor-1 (MIPF-1)
CCR2	CCL2	Macrophage Chemoattractant Protein-1 (MCP-1)
	CCL7	Macrophage Chemoattractant Protein-3 (MCP-3)
	CCL8	Macrophage Chemoattractant Protein-3 (MCP-2)
	CCL11	Eotaxin
	CCL13	Macrophage Chemoattractant Protein-4 (MCP-4)
	CCL16	Hemofiltrate CC Chemokine-4 (HCC-4)
	CCL27	Cutaneous T cell attracting chemokine (CTACK)
CCR3	CCL5	Regulated on Activation Normal T cell expressed and secreted (RANTES)
	CCL7	Macrophage Chemoattractant Protein-3 (MCP-3)
	CCL8	Macrophage Chemoattractant Protein-2 (MCP-2)
	CCL11	Eotaxin
	CCL13	Macrophage Chemoattractant Protein-4 (MCP-4)
	CCL14	Hemofiltrate CC Chemokine-1 (HCC-1)
	CCL24	Eotaxin-2
	CCL26	Eotaxin-3
CCR4	CCL17	Thymus and Activation-Regulated Chemokine (TARC)
	CCL22	Macrophage Derived Chemokine (MDC)
CCR5	CCL3	Macrophage Inflammatory Protein-1alpha (MIP-1α)
	CCL4	Macrophage Inflammatory Protein-1beta (MIP-1β)
	CCL5	Regulated on Activation Normal T cell expressed and secreted (RANTES)
	CCL8	Macrophage Chemoattractant Protein-2 (MCP-2)
CCR6	CCL20	Macrophage Inflammatory Protein-1alpha (MIP-1α)
CCR7	CCL19	Macrophage Inflammatory Protein-1beta (MIP-1β)
	CCL21	Secondary Lymphoid tissue Chemokine (SLC)
CCR8	CCL1	I-309 (TCA-3, SIS-f)
CCR9	CCl25	Thymus Expressed Chemokine (TECK)
CCR10	CCL27	Cutaneous T cell Attracting Chemokine (CTACK)
	CCL28	Mucosae-associated Epithelial Chemokine (MEC)
CCR11	CCL19	Macrophage Inflammatory Protein-1beta (MIP-1β)
	CCL21	Secondary Lymphoid tissue Chemokine (SLC)
	CCL25	Thymus Expressed Chemokine (TECK)
CXCR1	CXCL1	Growth Related Oncogene alpha (GRO-α)

Receptor	Systematic Name	Original Name
	CXCL6	Granulocyte Chemotactic Protein-2 (GCP-2)
	CXCL8	Interleukin-8 (IL-8)
CXCR2	CXCL1	Growth Related Oncogene-alpha (GRO- α)
	CXCL2	Growth Related Oncogene-beta (GRO-β)
	CXCL3	Growth Related Oncogene-gamma (GRO-γ)
	CXCL5	Epithelial cell-derived Neutrophil activating factor-78 (ENA-78)
	CXCL6	Granulocyte Chemotactic Protein-2 (GCP-2)
	CXCL7	Neutrophil Activating Protein-2 (NAP-2)
	CXCL8	Interleukin-8 (IL-8)
CXCR3	CXCL9	Monokine Induced by Gamma-interferon (MIG)
	CXCL10	Gamma-interferon-Inducible Protein-10 (IP-10)
	CXCL11	Interferon inducible T cell alpha Chemoattractant (I-TAC)
CXCR4	CXCL12	Stromal cell Derived Factor-1alpha/beta (SDF-1α/β)
CXCR5	CXCL13	B Cell Activating chemokine-1 (BCA-1)
CXCR6	CXCL16	Scavenger Receptor for Phosphatidylserine and oxidized LDLs (SRPSOX)
CX3CR1	CX3CL1	Fractalkine (Neurotactin)
XCR1	XCL1	Lymphotactin-alpha (SCM-1α)
	XCL2	Lymphotactin-beta (SCM-1β)