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Chemokines, neuronal–glial interactions, and central processing of neuropathic pain

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ABSTRACT

Millions of people worldwide suffer from neuropathic pain as a result of damage to or dysfunction of the nervous system under various disease conditions. Development of effective therapeutic strategies requires a better understanding of molecular and cellular mechanisms underlying the pathogenesis of neuropathic pain. It has been increasingly recognized that spinal cord glial cells such as microglia and astrocytes play a critical role in the induction and maintenance of neuropathic pain by releasing powerful neuromodulators such as proinflammatory cytokines and chemokines. Recent evidence reveals chemokines as new players in pain control. In this article, we review evidence for chemokine modulation of pain via neuronal–glial interactions by focusing on the central role of two chemokines, CX3CL1 (fractalkine) and CCL2 (MCP-1), because they differentially regulate neuronal–glial interactions. Release of CX3CL1 from neurons is ideal to mediate neuronal-to-microglial signaling, since the sole receptor of this chemokine, CX3CR1, is expressed in spinal microglia and activation of the receptor leads to phosphorylation of p38 MAP kinase in microglia. Although CCL2 was implicated in neuronal-to-microglial signaling, a recent study shows a novel role of CCL2 in astroglial-to-neuronal signaling after nerve injury. In particular, CCL2 rapidly induces central sensitization by increasing the activity of NMDA receptors in dorsal horn neurons. Insights into the role of chemokines in neuronal–glial interactions after nerve injury will identify new targets for therapeutic intervention of neuropathic pain.

Contents

1. Introduction

Neuropathic pain is a common reason for a clinic visit. It can be associated with many types of injuries to the nervous system, such as trauma, nerve compression, inflammation, and infection or be a consequence of neurodegenerative diseases (e.g. diabetes and multiple sclerosis), tumor infiltration, surgeries, as well as side effects of drug treatment (e.g. chemotherapy and antiretroviral therapy) (Woolf & Mannion, 1999; Dworkin et al., 2003; Ji & Strichartz, 2004; Kehlet et al., 2006). Neuropathic pain can manifest as spontaneous pain, allodynia (pain evoked by a normally innocuous stimulus), and hyperalgesia (enhanced pain evoked by a noxious stimulus). Particularly, tactile allodynia is a cardinal symptom of neuropathic pain (Dworkin et al., 2003). Neuropathic pain can persist for months

Abbreviations: AD, Alzheimer's disease; AMPA, alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; CCI, chronic constriction injury; CNS, central nervous system; DRG, dorsal root ganglion; ERK, extracellular signal-regulated kinase; EPSC, excitatory postsynaptic currents; IL, interleukin; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MCP-1, monocytes chemoattractant protein-1; MS, multiple sclerosis; NMDA, N-methyl-D-aspartic acid; PNS, peripheral nervous system; SNL, spinal nerve ligation; TNF-α, tumor necrosis factor-alpha; TRPV1, transient receptor potential vanilloid type 1.

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and years, even after the primary tissue damage has healed. Current treatments have only produced limited relief of this pain in a portion of patients (Dworkin et al., 2003; Costigan et al., 2009b).

Based on the association of clinical neuropathic pain with the nervous system injuries, several animal models have been used to investigate the neuropathic pain mechanisms and test novel analgesics, in which the sciatic nerve, spinal nerve, or DRG is intentionally damaged. These models include transection of the sciatic nerve (Devor & Wall, 1981), chronic constriction of sciatic nerve (CCI) (Bennett & Xie, 1988), partial sciatic nerve ligation (PSNL) (Seltzer et al., 1990), spinal nerve ligation (SNL) (Kim & Chung, 1992), spared nerve injury (SNI) (Decosterd & Woolf, 2000), and chronic compression of the DRG (CCD) (Hu & Xing, 1998). Neuropathic pain was also induced by infection, inflammation, or demyelination of the sciatic nerve (Wallace et al., 2003), as well as by chemotherapy (e.g., Paclitaxel) (Polomano et al., 2001) and toxin [(e.g., 2′-3′-dideoxycytidine (ddC)] (Joseph et al., 2004).

Neuropathic pain is generally believed to be an expression of neural plasticity, which can occur as both peripheral sensitization, an increase in the sensitivity and excitability of primary sensory neurons in the peripheral nervous system (PNS), and central sensitization, an increase in the activity and excitability of nociceptive neurons in the spinal cord and brain in the central nervous system (CNS), and lead to the development and maintenance of neuropathic pain (Woolf & Salter, 2000; Julius & Basbaum, 2001; Ji et al., 2003). After nerve injury, inflammatory mediators such as proinflammatory cytokines, chemokines, prostaglandins, histamine, serotonin, bradykinin, and nerve growth factors are released from injured nerve fibers and adjacent immune cells (Ji & Strichartz, 2004; Sommer & Kress, 2004; Abbadie, 2005). These mediators can directly act on DRG neuronal cell bodies and axons leading to peripheral sensitization (Scholz & Woolf, 2002; Schafers et al., 2003; Sommer & Kress, 2004; Kawasaki et al., 2008b). Nerve injury-induced central sensitization can manifest as an increase in glutamate NMDA and AMPA receptors-mediated excitatory synaptic transmission in dorsal horn neurons. It can also manifest as a decrease in GABA and glycine receptor-mediated decrease or loss of inhibitory synaptic transmission (disinhibition) (Woolf & Mannion, 1999; Ji et al., 2003; Coull et al., 2005). In addition, an increase in descending facilitation also contributes to central sensitization after nerve injury (Porreca et al., 2002).

In recent years, it is increasingly recognized that non-neuronal cells such as immune cells (macrophages and lymphocytes) and glial cells in the PNS (e.g., Schwann cells and satellite cells) and CNS (e.g., astrocytes and microglia) also play a critical role in chronic pain processing (Ji et al., 2006; Scholz & Woolf, 2007; Milligan et al., 2008; Romero-Sandoval et al., 2008; Milligan & Watkins, 2009; Mcmahon & Malcangio, 2009). Nerve injury induces substantial changes in both microglia and astrocytes in the spinal cord (Jin et al., 2003; DeLeo et al., 2004; Zhuang et al., 2006). Inhibition of microglial activation by minocycline prevents/delays neuropathic pain development (Raghavendra et al., 2003; Hua et al., 2005; Ledeboer et al., 2005). Intrathecal injection of astroglial toxin fluorocitrate (Milligan et al., 2003; Hosoi et al., 2004) and L-alpha-aminoadipate (Zhuang et al., 2006) also reverses nerve injury- or nerve inflammation-induced mechanical allodynia. Further, inhibition of microglial signaling by inhibiting the action of P2X4 and p38 MAPK or activating cannabinoid receptor type-2 or inhibition of astroglial signaling by inhibiting c-Jun-N-terminal kinase (JNK) or matrix metalloproteae-2 also attenuates neuropathic pain (Jin et al., 2003; Tsuda et al., 2003; 2004; Zhuang et al., 2006; Kawasaki et al., 2008a; Romero-Sandoval et al., 2009). These data support an important role of spinal microglia and astrocytes in enhancing neuropathic pain.

It is generally believed that spinal glial cells enhance and maintain neuropathic pain by releasing potent neuromodulators, such as proinflammatory cytokines and chemokines and growth factors (Watkins & Maier, 2002; Abbadie, 2005; Inoue, 2006; White & Wilson, 2008; Milligan & Watkins, 2009; Trang et al., 2009; Abbadie et al., 2009; Gao et al., 2009). While the role of proinflammatory cytokines (e.g. TNF-α, IL-1β, and IL-6) in neuropathic pain sensitization has been well demonstrated (Arruda et al., 1998; Milligan et al., 2003; Lee et al., 2004; Ohtori et al., 2004; Ledeboer et al., 2005; Moalem & Tracey, 2006) and the mechanisms of these cytokines in central sensitization have also been explored (Guo et al., 2007; Kawasaki et al., 2008b), the role of chemokines in neuropathic pain is far from clear. Chemokines are small proteins that were initially characterized as chemotactic peptides controlling the trafficking of leukocytes (Charo & Ransohoff, 2006). Increasing evidence suggests that chemokines are involved in neuroinflammation at different anatomical locations, including injured nerve, dorsal root ganglion (DRG), spinal cord, and brain (Mennicken et al., 1999; Scholz & Woolf, 2007; White et al., 2007; Miller et al., 2008) and contribute to chronic pain processing (Abbadie et al., 2009). In this article, we review the evidence for the involvement of chemokines and chemokine receptors in neuropathic pain, with emphasis on their central role in regulating neuronal–glial interactions and neural plasticity.

2. Chemokines, chemokine receptors, and neurodegeneration

2.1. Chemokines

Chemokines are a family of functionally related small secreted molecules (8–14 kDs) named “chemokine” because of leukocyte chemoattractant and cytokine-like activities (Asensio & Campbell, 1999). This family is composed of about 50 related molecules in humans, with close homologues in other mammalian species (Charo & Ransohoff, 2006). Each chemokine contains 70–100 amino acids, with 20–95% sequence identity to others including conserved cysteine residues (Bonecchi et al., 2009). According to cysteine's number and spacing, four chemokine subfamilies have been defined: CC, CXC, XC, and CX3C subfamilies (Luster, 1998; Bajetto et al., 2002; Laing & Secombes, 2004). The CC chemokines form the largest subfamily that is characterized by the adjacent positions of the first two of a total of four cysteine residues. The CC family has 28 members with a large spectrum of actions and attracts monocytes, eosinophils, basophils, T lymphocytes, natural killer (NK) cells, and dendritic cells (Ubogu et al., 2006; Savarin-Vuaillat & Ransohoff, 2007).

The CXC chemokines is the second largest group that is characterized by the intervention of a single amino acid between the first two cysteine residues. Depending on the presence or absence of the sequence motif glutamic acid–leucine–arginine (ELR) near the N-terminus, the CXC subfamily can be divided into two groups: ELR-positive and ELR-negative, displaying different functions. The CXC chemokines with ELR motif bind and activate CXCR2, specifically acting on neutrophils and other CXCR2-positive cells, but those without the ELR motif act primarily on lymphocytes and monocytes (Ubogu et al., 2006; Savarin-Vuaillat & Ransohoff, 2007).

The C chemokine family includes two molecules with only two cysteine residues. They can act on lymphocytes, but not on neutrophils or monocytes. The CX3C family has only one member with three intervening amino acids in-between the first two cysteine residues. CX3CL1 (fractalkine) can be soluble as well as membrane-bound and acts as an adhesion molecule or a chemoattractant for T cells and NK cells (Ubogu et al., 2006; Savarin-Vuaillat & Ransohoff, 2007).

Chemokines were initially named by its biological function. Since 2000, a new chemokine classification system has been used, in which chemokines are considered as chemokine ligands (L) (Zlotnik & Yoshie, 2000). Therefore, each chemokine has a designation of CCL, CXCL, XCL, or CX3CL. Most chemokines have two names, one reflecting a particular biological aspect, such as monocyte chemoattractant protein-1 (MCP-1) and another reflecting its structure, such as CCL2 (Bajetto et al., 2002). In this review, we choose to use structural