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Review

Involvement of chemokines in pain

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Abstract

It is well established that neuroinflammation plays an important role in neurodegenerative diseases like Alzheimer's disease, stroke, traumatic brain- and spinal cord injury and demyelinating diseases. Likewise, it has been suggested that neuroinflammation plays an important role in nociception and hyperalgesia. Most research concerning inflammatory aspects of pain has concerned the effects of proinflammatory cytokines, prostaglandins and growth factors. Recently, it has been suggested that chemokines play a role in inflammatory pain. Chemokines do not only attract blood leukocytes to the site of injury but also contribute directly to nociception.

Keywords: Chemokine; Nociception; Hyperalgesia; Inflammation

1. Introduction

Damage to the central and peripheral nervous system can range from traumatic injury to chemical intoxication to immunological challenge. These injuries often result in the development of acute or chronic algesia and allodynia. Both neuronal and humoral activity then leads to activation of astrocytes and microglia in the spinal cord leading to subsequent expression of immune factors. In this respect, neuroimmune signaling cascades of cytokines like interleukin-1β, tumor necrosis factor-α (TNF-α and interleukin-6 that result in production and release of prostaglandins have been reported (Wagner and Myers, 1996a; Sweitzer et al., 1999; DeLeo and Yezierski, 2001).

Whereas most pain research related to neuroimmune function has focussed on cytokines and growth factors, recently several reports concerning the involvement of chemokines in inflammatory pain and hyperalgesia have been published (Cunha et al., 1991; Oh et al., 2001; Serhan et al., 2001). Chemokines are a family of small chemoattractant cytokines. The involvement of chemokines in the pathogenesis of pain may in part be due to the chemoattraction of immune cells but may also result from direct involvement in nociceptive signal transduction. In this review, the current status of involvement of chemokines in nociception and hyperalgesia will be addressed.

2. Neuroinflammation and pain

The last years, it has been shown that both resident and infiltrating immune cells play an important role in the development of specific aspects of inflammation involving infiltration, edema, fever and hyperalgesia (Malaviya et al., 1996; Souza et al., 1988; DeLeo and Yezierski, 2001). Cytokines and growth factors have been strongly associated with pathological pain states both in the peripheral and the central nervous system (Clathworthy et al., 1995; Sommer et al., 1998; Woolf et al., 1997; Laughlin et al., 2000). Furthermore, it has been postulated that cytokines induce hyperexcitable sensory states that induce the development of hyperalgesia (Watkins et al., 1995, 1997). It thus has been shown that acute peripheral inflammation induces activation of astrocytes as well as cytokine expression of interleukin-1β in the spinal cord, which correlate with zymosan- and formalin-induced allodynia. Similarly, expression of the cytokine TNF-α correlates with the development of peripheral nerve injury and endoneurial injection of TNF-α induces neuropathic pain in rats (Wagner and Myers, 1996a,b).

3. Infiltration of immune cells involved in inflammatory pain

Under basal conditions, the brain vascular endothelium acts as a barrier to the immune system limiting the entry of blood leukocytes (Miller, 1999). Proinflammatory cy-

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tokines and eicosanoids induce upregulation of endothelial adhesion molecules like E-selectin and intracellular adhesion molecule-1 and thus induce leukocyte adhesion and migration (Wong et al., 1999). In addition, proinflammatory cytokines like interleukin-1β and TNFα increase membrane permeability of vascular endothelial cells (Gloor et al., 1997; Mark and Miller, 1999). In line with these observations, it was found in several models representing inflammatory pain states, following peripheral nerve injury, that the integrity of the blood–brain barrier was decreased and the expression of tight junctional proteins was altered (Huber et al., 2001). After injury to a peripheral nerve, the immune cells are recruited to the lesion (Clathworthy et al., 1995; Perry et al., 1987). These infiltrating cells are involved in removing cellular debris and facilitate regeneration. However, infiltrating immune cells also seem to contribute to hyperalgesia. This has been suggested because the infiltration of macrophages at the lesioned site correlates with the course of hyperalgesia (Ramer et al., 1997; Wagner et al., 1995). Furthermore, suppression of the inflammatory response suppresses hyperalgesia in a sciatic nerve lesion model in rats (Clathworthy et al., 1995; Wagner et al., 1998). This is presumably due to the fact that infiltrating immune cells release various algesic factors which sensitize or excite nociceptive afferents and induce hyperalgesia (Mizumura and Kumazawa, 1996; Rang et al., 1991; Taiwo and Levine, 1990). Neutrophils are the first cells that infiltrate and produce inflammatory factors including chemotactic factors specific for monocytes (Antony et al., 1985; Pereira et al., 1990; Territo et al., 1989). Accordingly, neutrophils are involved in the subsequent infiltration of the lesion by other immune cells.

3.1. Chemokines in the brain

Chemokines are small chemotactic cytokines of approximately 10 kDa, which mediate the infiltration of leukocytes to sites of inflammation and control the homing of dendritic cells, T cells and B cells (for review see: Rollins, 1997; Rossi and Zlotnik, 2000). Chemokines and their receptors, all of which are G-protein coupled, are subdivided into four families: CXC-, CC-, C- and CX3C-chemokines (Murphy et al., 2000). Based on mouse and human genome projects and expressed sequence tag databases, a large number of chemokines and chemokine receptors have been identified (Rossi and Zlotnik, 2000). In humans, more than 40 chemokines and 18 chemokine receptors are known (Murphy et al., 2000). Beyond their functions in immune and inflammatory reactions, chemokines mediate a variety of different processes throughout the body. It has been reported that chemokines and their receptors are also involved in the development, maturation of leukocytes, angiogenesis, metastasis, wound healing and allograft rejection (Rossi and Zlotnik, 2000; Sallusto et al., 1998; Hancock et al., 2000).

Chemokines and their receptors are not only found in peripheral tissue. It has been shown extensively that chemokines and their receptors are also expressed in the central nervous system (CNS) during development and pathology (Asensio and Campbell, 1999; Glabinski and Ransohoff, 1999; Bacon and Harrison, 2000; De Groot and Woodroofe, 2001). Several lines of evidence indicate that chemokine expression in the CNS is prominently involved in the infiltration of the CNS by blood leukocytes in response to CNS diseases (Wu et al., 2000; Asensio and Campbell, 1999; Mennicken et al., 1999; Ransohoff and Tani, 1998). It has been shown that neurons and most glial cell types also express chemokine receptors. This has raised the suggestion that chemokines, in addition to immune activity, may contribute to an intercellular signaling system related to pathological conditions within the CNS (Hesselgesser and Horuk, 1999; Bacon and Harrison, 2000). For example, the effects of chemokines on neuronal survival and short-term effects on synaptic transmission (Meucci et al., 1998; Limatola et al., 2000; Meucci et al., 2000) have been reported.

Over 70% of the cell population of the central nervous system (CNS) consists of glia cells (microglia, astrocytes and oligodendrocytes). Glia are currently considered as the neuroimmune cells in the CNS. In the peripheral nervous system, acute neuroinflammation is initiated by infiltrating macrophages and the activation of these cells leads to the release of chemokines which then recruit other immune cells. In the CNS microglia, the macrophages of the brain (Hickey and Kimura, 1988) initiate the first immune responses to nerve injury (Kreuzberg, 1996). Thus, glia cells are closely involved in the neuroimmune response following peripheral nerve or central injury that results in pain (Sweitzer et al., 1999; DeLeo and Yezierski, 2001).

Chemokines are synthesized locally at the sites of inflammation and establish a concentration gradient to which immune cells migrate. In case of neuroinflammatory pain, the chemokines most likely are produced by resident and infiltrating macrophages and by glia cells. However, further research concerning the cell types producing chemokines during the course of neuropathy remains to be done.

3.2. Chemokines and pain

As mentioned previously, both local and infiltrating cells are involved in the production of factors chemoattracting immune cells towards the site of injury and mediate nociceptive effects. In addition to chemotaxis, chemokines may be directly involved in the mediation of pain.

The most elaborate data concerning chemokine-involvement in pain concern the effects of the chemokine interleukin-8 (CXCL8) which attracts and activates neutrophils and lymphocytes. A hyperalgesic effect of CXCL8 was measured in a rat paw pressure test (Cunha et al., 1991).

CXCL8 evoked dose-dependent hyperalgesia, which was blocked by CXCL8 specific anti-serum, β-adrenoceptor antagonists and dopaminergic antagonist but not by the cyclooxygenase inhibitor indomethacin. This suggests the involvement of the sympathetic nervous system in CXCL8-induced hyperalgesia. It was thus concluded that CXCL8 causes hyperalgesia by a prostaglandin-independent mechanism. This was one of the first suggestions for a neuroimmune component in hyperalgesia. In addition, Ribeiro et al. (2000) showed that the zymosan- and acetic acid-induced nociceptive writhing response is dependent upon the activation of resident macrophages and mast cells, which release TNF-α, interleukin-1β and CXCL8. Intraperitoneal administration of a specific anti-serum against CXCL8 partly blocked the nociceptive response. Whereas, intraperitoneal injection of TNF-α, interleukin-1β or CXCL8 separately did not induce the nociceptive effect, the injection of a mixture of the three recombinant cytokines caused a significant writhing response, suggesting that the nociceptive effect results from a synergistic effect of the three cytokines. In clinical situations, the role of CXCL8 is less evident. In patients suffering from endometriosis, a clear upregulation of CXCL8 was observed (Gazvani et al., 1998). Complaints of abdominal pain, however, did not correlate with CXCL8 concentrations in the peritoneal fluid. Similarly, in chronic pelvic pain syndrome (prostatitis) elevated levels of the chemokines CXCL8 and ENA-78 (CXCL5) were found in prostatic secretions of prostatitis patients (Hochreiter et al., 2000). From these examples, it is clear that the clinical relevance of the involvement of CXCL8 in nociception needs to be further explored.

It has been suggested recently that dorsal root ganglion neurons are actively involved in chemokine signaling and that chemokines thus act as messengers between peripheral immune cells and sensory afferent neurons at inflamed sites (Oh et al., 2001). Using immunocytochemistry and reverse transcriptase polymerase chain reaction (RT-PCR) assays, Oh et al. (2000) claim that isolated dorsal root ganglion neurons express the chemokine receptors CCR4 and CCR5 as well as CXCR4 and CX3CR-1. Stimulation of these chemokine receptors in isolated sensory neurons induced calcium mobilization, a lowering of the threshold for action potential generation, and a weak release of Substance P. Particularly, the localization of CXCR4 on peripheral terminals suggests the possible signaling of chemokines released in inflamed tissue. Thus, because axon terminals of dorsal root ganglion neurons widely express CXCR4 receptors they may be able to respond to signals generated by peripheral immune cells and deliver them to the brain via ascending spinal routes. Furthermore, based on calcium responses in isolated dorsal root ganglion neurons induced by chemokines, Oh et al. (2000) suggested that also the chemokine receptors CCR2/CCR3/CCR6/CCR7/CCR8/CXCR1/CXCR2/CXCR3/CXCR5 are expressed in these cells. 84.7% of these chemokine responsive neurons responded to nociceptive stimuli like bradykinin or capsaicin. In addition, Oh et al. (2000) showed that the injection of the chemokines macrophage-derived chemokine (MDC; CCL22), stromal cell-derived factor-1 (SDF-1α; CXCL12) and regulated on activation normal T cell expressed and secreted (RANTES; CCL5) in the hindpaw caused allodynia. Oh et al. (2000) thus claim that chemokines may produce enhanced sensitivity to pain via direct actions on chemokine receptors expressed by nociceptive neurons. Accordingly, chemokines released from leukocytes in inflammatory infiltrates could be directly responsible for increased pain sensitivity observed during inflammation.

Nociceptin is a novel factor that acts at the opioid-like receptor ORL1 (Noci-R) which is involved in the processing of pain signals (Meunier et al., 1995; Boom et al., 1999; Noda et al.,1998). It was reported by Serhan et al. (2001) that ORL1 is functionally expressed by peripheral blood polymorphonuclear monocytes. Furthermore, Serhan et al. (2001) showed that nociceptin at picomolar concentrations induces chemotaxis of neutrophils in vivo. Aspirin-triggered lipid mediators inhibit the chemotactic effect of nociceptin. Due to its pronounced effect in pain and its pronounced chemotactic effect nociceptin may become an important drug target for the treatment of inflammatory pain.

4. Conclusions

Infiltration of blood leukocytes is one of the hallmarks of neuroinflammation and associated peripheral and neuropathic pain. Since chemokines are instrumental for leukocyte infiltration, these molecules are relevant for the development of the inflammatory process during nociception. In addition, direct involvement of chemokine receptor activation in nociception and hyperalgesia has been suggested in several reports. Although clear evidence for the involvement of chemokines in nociception and hyperalgesia is available, a number of issues such as the exact localization of chemokine expression, the receptors involved and the underlying signal transduction require more research. This research and the emerging clinical potential for anti-nociceptive therapy will be greatly helped by the currently ongoing development of specific antagonists for chemokine receptors.

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