Chemokines in the brain: neuroimmunology and beyond

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Chemokines in the brain have been recognised as essential elements in neurodegenerative diseases and related neuroinflammation. Recent studies suggest that in addition to the orchestration of chemotaxis of immune cells, chemokines are also involved in neurodevelopment and neurophysiological signalling.

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Abbreviations

EAE	experimental autoimmune encephalitis
MS	multiple sclerosis

Introduction

Because of extensive research and rapid progress in the field, a variety of reviews on chemokines have appeared recently that address their function and localisation, including discussion of the central nervous system (CNS) [1–5]. Research on chemokines in the brain has primarily focused on immune responses and local inflammation. Recently, new functions of chemokines have been described, such as their involvement in neuronal development, nociception and synaptic transmission. This review discusses recent advances in understanding the physiological and pathophysiological functions and the localisation of chemokines and their receptors in the brain.

Chemokines and chemokine receptors: pharmacology and function

Chemokines constitute a superfamily of small proteins (8–14 kDa) that are instrumental for the trafficking of leukocytes in normal immunosurveillance as well as the coordination of infiltration of inflammatory cells under pathological conditions. Chemokines and their receptors form an elaborate signalling system. Currently, approximately 50 different human chemokines have been described and these chemokines interact with 18 different chemokine receptors [6•,7•].

Chemokines are classified by their structure on the basis of the number and spacing of conserved cysteine motifs in the NH_2 terminus. Thus, four groups, named the C, CC, CXC and CX3C families, have been distinguished. The classification of the chemokine receptors parallels the four subgroups designated for chemokines — these receptor subgroups have been designated XCR, CCR, CXCR and CX3CR. Most of these chemokine receptors recognise more than one chemokine. As the different types of immune cells express multiple chemokine receptors that overlap in their ligand specificity, chemokine receptor pharmacology is very complex. Because of this promiscuity and the lack of selective agonists and antagonists, the study of chemokine receptors in native systems is difficult.

Chemokines bind to seven-transmembrane spanning receptors [6•] and activate heterotrimeric G-proteins. Generally, the G-proteins activated by chemokine receptors belong to the $G_{\alpha i}$ family and are pertussis toxin sensitive. The signal transduction of most chemokine receptors involves inhibition of cAMP and transient increases in intracellular calcium. Furthermore, downstream activation of mitogen-activated protein kinases (MAPKs), phosphoinositide 3 kinase (PI3-K) and small GTP-binding proteins like RAC, RhoA and CDC42H, which presumably are involved in the cytoskeletal reorganisation necessary for cell migration, has been described [8,9].

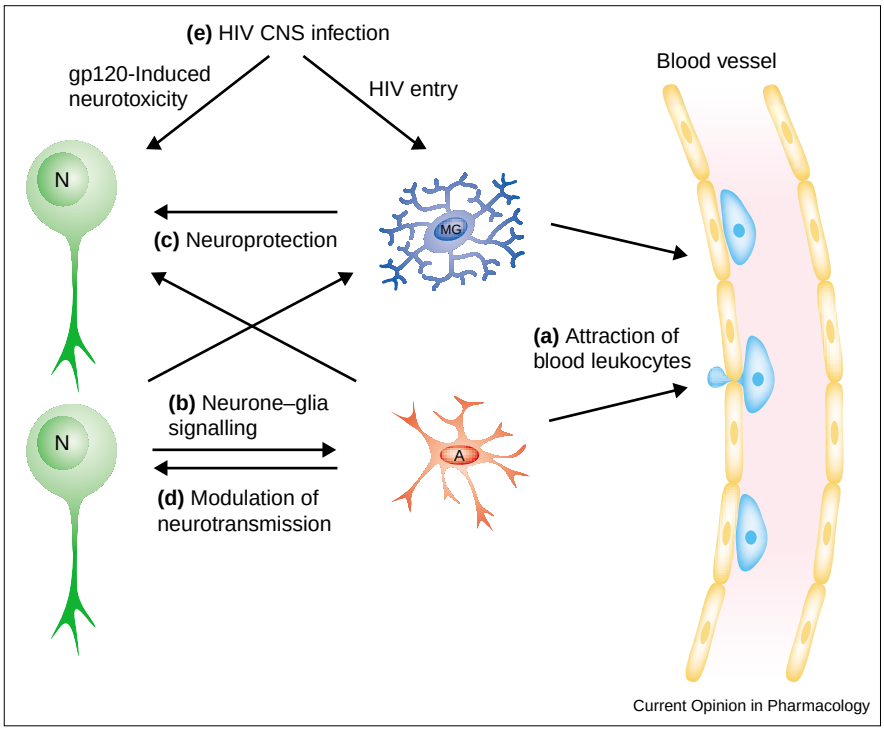
As mentioned previously, the most general response to chemokine stimulation is chemotaxis. The chemotaxis of different types of leukocytes is mediated by complex combinations of chemokine receptors. A clear distinction can be made between homeostatic chemokines, which are mainly involved in physiological traffic-like immune surveillance, and inducible chemokines, which are induced during inflammation. It is now becoming increasingly clear that distinct migration activity of lymphocytes, and presumably also monocytes and granulocytes at various stages of activation, are finely tuned by complex combinations of homeostatic and inducible chemokines [10]. In addition to chemotaxis, a number of other biological functions of chemokines have been observed, such as induction of cell adhesion, phagocytosis, T-cell differentiation and activation, apoptosis, angiogenesis, proliferation and cytokine secretion [11].

Chemokines and chemokine receptors in the CNS

The first findings showing prominent expression of chemokines and their receptors in brain tissue were published approximately 10 years ago (see for example: [12,13]). Since then, numerous detailed studies on CNS chemokines and chemokine receptors have been published, and it is now clear that the endogenous cells of the CNS synthesise distinct chemokines and might respond to chemokine stimulation by chemokine receptor expression [1–5].

Several lines of evidence indicate that all types of endogenous cells of the CNS (astrocytes, oligodendrocytes, microglia and neurones) express functional

Figure 1



A working hypothesis of chemokines as mediators of several functions in the brain. Experimental evidence now indicates that chemokines might have a variety of different functions in the physiology and also in the pathology of the CNS. It is likely that at least three different endogenous brain cell types participate in chemokine signalling; neurones (N), astrocytes (A) and microglia (MG). **(a)** Several lines of evidence, including chemokine and chemokine receptor knockout models, suggest that chemokines like CCL2, CCL3, CCL5 and CXCL10 (thought to be derived from glial cells) might be crucial molecules for the attraction of blood leukocytes into the CNS. **(b)** Recent evidence has shown fast expression of neuronal chemokines like CCL2, CCL21 and CXCL10 in response to neuronal damage. It has been suggested that these chemokines are involved in the communication between damaged neurones and surrounding glial cells. **(c)** *In vitro* evidence shows that several chemokines (CCL2, CCL5, CXCL8 and CXCL10) have direct neuroprotective properties and it is tempting to speculate that these chemokines released from glial cells may have similar effects *in vivo*. **(d)** It has been shown that CXCL12 influences neurotransmission via direct and indirect effects *in vitro*. If CXCL12 is released from astrocytes and has similar effects *in vivo*, this modulation of neurotransmission may be another facet to chemokine activity in the brain. **(e)** Chemokine receptors like CXCR4 and CCR5, which are expressed in microglia and neurones, seem to be directly involved in the infection of microglia with HIV and in gp120 induced neurotoxicity.

chemokine receptors [14•,15–18]. A variety of publications show that the expression of chemokine receptors in CNS cells is regulated by inflammatory mediators like transforming growth factor β1 or interferon γ [19,20] but most reports indicate that chemokine receptors are also expressed by unchallenged cells.

In contrast, the expression of chemokines in the CNS is mostly inducible by inflammatory stimuli, meaning that constitutive chemokine expression is hardly observed in normal brain. The two chemokines that are constitutively found in CNS are CX3CL1 (fractalkine) and CXCL12 (stromal-cell-derived factor 1α), which are expressed by neurones and astrocytes, respectively [21–23].

Compared with the large number of chemokines described in the periphery, relatively few chemokines have been found in the brain under pathological conditions. These few chemokines, however, seem to play a crucial role in neurodegeneration, because most neurodegenerative diseases known are accompanied by chemokine expression. The most prominent chemokines described in the injured CNS are CCL2, CCL3, CCL4, CCL5, CCL8, CXCL8 and CXCL10 ([1–5]; see Table 1). Recent publications showed that glial chemokines are crucial mediators of infiltration in CNS inflammation [24••,25•,26••,27••]. This suggests that inhibiting glial chemokine expression may provide new, more sophisticated therapies for neurodegenerative diseases. Experiments performed in cultured glial cells show that the expression of glial chemokines is regulated by different pro-inflammatory and anti-inflammatory factors, such as cytokines, bacterial toxins, β-amyloid or viral proteins. Interestingly, these factors induce the expression of specific chemokines, suggesting that the expression of glial chemokines is dependent on distinct pro-inflammatory and anti-inflammatory factors [15,28•,29,30]. Thus, chemokine expression and immune cell infiltration in particular disease pathologies may depend on the pro-inflammatory and anti-inflammatory factors associated with the disease. Unfortunately, little is known yet about the regulatory mechanisms of glial chemokine expression *in vivo*.

CNS chemokines are not only expressed in glial cells; it has been shown recently that chemokines such as CCL2, CCL3, CXCL10 and CCL21 (secondary lymphoid tissue chemokine [SLC]) are also inducibly expressed in neurones under conditions of neuronal degeneration [31,32••,33–35]. However, the induction of neuronal chemokines is generally fast compared with the expression of the same chemokine in glial cells. Whereas it takes 1–3 days after neuronal damage before glial chemokine expression is detectable, chemokines are expressed in neurons within 6–12 hours [31,32••,33–35]. This rather early expression time-point indicates a special function of

neuronal-derived chemokines. It makes it tempting to speculate that neuronal chemokines might contribute to the early communication system that has been suggested between neurones and glial cells after neuronal damage [36].

Functions of chemokines and chemokine receptors in the CNS

Neuroinflammation

In the brain, chemokines mediate local immune responses and also attract leukocytes, which are believed to migrate along a concentration gradient of chemokines across the blood–brain barrier to their target (Figure 1). Astrocytes and microglia are CNS-resident immune cells that can produce different kinds of chemokines. Because these glia cells are closely associated with the blood–brain barrier, it has been suggested that these cells regulate leukocyte infiltration into the brain [37•]. In addition, chemokine-binding sites on human brain microvessels have been described [38].

As mentioned previously, almost all neurodegenerative diseases have been associated with the expression of chemokines (see Table 1), the activation of local glia cells and the attraction of leukocytes. The type of chemoattraction may involve specifically local immune cells or predominantly blood leukocytes [39] — this is most likely to depend on the types of chemokines expressed in different pathologies. The most elaborately investigated neurodegenerative disease characterised by leukocyte infiltration is multiple sclerosis (MS). Distinct chemokines are involved in the attraction of leukocytes; thus, using the experimental autoimmune encephalitis (EAE) model of MS in rodents, it has been shown that CCR2 knockout mice developed no signs of MS pathology [25•,26••]. Furthermore, they found no localised macrophage infiltration. Similarly, CCL2 knockout mice show a clear reduction of EAE pathology and a strong reduction of macrophage infiltration into the brain [27••].

A prominent example of localised neuroinflammation is Alzheimer's disease [40]. It is suggested that chemokines expressed in the vicinity of amyloid plaques initially attract and/or activate local glia cells. The local inflammatory response of chemoattracted microglia seemingly remains restricted to a small area around the β-amyloid plaques. In addition, the involvement of chemokines in host defence against bacterial and viral infections of the CNS has been suggested [41,42•].

HIV and gp120-induced neurotoxicity

Chemokine receptors in the brain are likely to be crucial for different aspects of CNS HIV infection (Figure 1), as HIV uses chemokine receptors like CXCR4 or CCR5 as co-receptors to infect cells. It is suggested that the expression of these receptors enables HIV to infect brain microglia, which are the brain endogenous virus reservoirs (for review, see [43]). New results, moreover, indicate that chemokine receptors are not only responsible for the HIV infection of target cells but might also play an important role in the development of AIDS-related dementia [43]. It is clear today that the glycoprotein gp120 from the envelope of HIV-1 has direct neurotoxic effects [43,44,45••,46•]. Because gp120 binds directly to chemokine receptors, it has been suggested that they also mediate the neurotoxic effects of gp120 [43]. This assumption is corroborated by the findings that hippocampal neurones from patients with HIV encephalitis had higher expression levels of chemokine receptors than hippocampal neurones from HIV patients without encephalitis or from control (uninfected) patients [47].

Table 1

Chemokines and receptors implicated in human CNS disease*.

CNS pathology	Chemokines	Chemokine receptors
Alzheimer's disease	MCP-1/CCL2 IP-10/CXCL10 MIP-1β/CCL4	CCR3 CCR5 CXCR2 CXCR3
Multiple sclerosis	MCP-1/CCL2 MCP-2/CCL8 MCP-3/CCL7 RANTES/CCL5 MIP-1α/CCL3 MIP-1β/CCL4 IP-10/CXCL10 MIG	CCR2 CCR3 CCR5 CXCR3
HIV-1-associated dementia	MCP-1/CCL2	CCR5 CXCR4
HIV encephalitis	MCP-1/CCL2 MIP-1α/CCL3 MIP-1β/CCL4	CCR2 CCR5 CXCR4
Meningitis	MCP-1/CCL2 MIP-1α/CCL3 MIP-1β/CCL4 Gro-α IL-8/CXCL8 IP-10/CXCL10	
Brain trauma	MCP-1/CCL2 IL-8/CXCL8	
Behcet's disease	MIP-1α/CCL3	
Myelopathy	MIP-1α/CCL3	
Spinal cord contusion injury	MCP-1/CCL2 MIP-1α/CCL3 Gro-α	

*Data compiled from [1–5,15,60]. IL-8, interleukin 8; IP-10, interferon-inducible protein 10; MCP, monocyte chemoattractant protein; MIG, monokine induced by interferon γ; MIP, macrophage inflammatory protein; RANTES, regulated on activation, normal T cells expressed and secreted.

Neuroprotective effects of chemokines

Co-stimulation with chemokines (CX3CL1, CXCL12, CCL3 and CCL5) prevents gp120-induced apoptosis in neurones [44,45••,46•]. Recent data, moreover, indicate that chemokines like CXCL8, CXCL12, CCL5 and CCL2 also protect neurones from other forms of damage; for example, NMDA-induced or β-amyloid-induced neuronal

death ([48•]; Figure 1). Although there are conflicting reports on the neuronal chemokine receptor subtypes that are involved (CX3CR versus CXCR4 and CCR5; see, for example, [44,46•]), these results strongly indicate that glial-derived chemokines may have a significant impact on the survival of neurones and underline the function of chemokines in the communication between glial cells and neurones. In line with this assumption are the fascinating results, most recently published by Bezzi and colleagues [49••], that suggest that signalling based on CXCL12, CXCR4, tumour necrosis factor α and glutamate between neurones, astrocytes and microglia has a direct influence on the viability of the neurones in the system.

Chemokines and neurodevelopment

It has been suggested that chemokine receptor expression on neurones plays a role in the developmental organisation of the brain by regulating the migration of neuronal progenitors. In rodents, the developmental expression of chemokines has been demonstrated [50]. Accordingly, the activation of the chemokine receptor CXCR4 by CXCL12 seems to be crucial in CNS development, as knockout mice die soon after birth and show abnormalities in brain morphology [51]. In humans, developmental expression of neuronal CCL2 [52] and astrocytic CXCR3 [53] was demonstrated in foetal nervous tissue. The role of these proteins in neurodevelopment, however, remains to be established.

Effects of chemokines on neurotransmission

Because astrocytes and synapses are intimately associated, a functional role for astrocytes in modulating synaptic transmission has recently been extensively studied (Figure 1). It was reported that glutamate released from astrocytes controls the efficacy of synaptic transmission [54••], and recent findings suggest that chemokines regulate the glutamate release from astrocytes. It was shown that CXCL12 not only stimulated calcium transients in cultured granule cells but also modulated spontaneous synaptic activity in Purkinje cells in cerebellar slices [55]. This modulation of synaptic activity was mediated by glutamate released from astrocytes after stimulation with CXCL12 [49••,55]. Presumably, chemokinergic modulation of neuronal activity via astrocytic glutamate release may not be the only mechanism, as a direct influence of chemokines on the electrophysiology of neurones has been published [56•,57].

Conclusions

It is now believed that complex combinations of chemokines are involved in the specific recruitment of immune cells in the brain. Although the involvement of a large number of chemokines with overlapping biological activity suggests redundancy of this signalling system, the specific knockout of chemokine genes has been shown to prevent pathological processes in disease models in experimental animals. In addition, novel functions concerning intercellular signalling may be involved in maintaining CNS homeostasis, neurodevelopment, synaptic transmission, ageing [58] and the development of tumours [59]. Given the broad spectrum of chemokine functions in the periphery, additional novel effects of chemokines in the brain may be expected.

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