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Review

Chemokines and chemokine receptors in CNS pathology

AR Glabinski[1] and RM Ransohoff[2]

[1]*Department of Neurology, Medical University of Lodz, Szp.im.N.Barlickiego, ul, Kopcinskiego 22, 90-153, Lodz, Poland;* [2]*Department of Neurosciences, The Lerner Research Institute, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA*

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Chemokines, chemokine receptors and CNS pathology-background

Chemokines are small proinflammatory cytokines which stimulate migration of inflammatory cells *in vitro* and *in vivo*. They can be divided according to structure, function and gene localization into four different subfamilies. Chemokines have been ascribed diverse additional functions, including regulation of angiogenesis, control of cell proliferation and developmental tissue patterning.

The suspicion that chemokines could be involved in CNS pathology emerged from considering their target-cell specificity, in light of the selective recruitment of leukocyte populations to the intrathecal compartment in diverse disease processes. Initial studies of chemokine expression in the CNS were performed in models including experimental autoimmune encephalomyelitis (EAE), stroke and meningitis. Early results from these investigations provided the exciting insight that parenchymal CNS cells were among the most abundant sources of chemokines, both *in vitro* and *in vivo*. A landmark observation from Karpus *et al* (1995) was that EAE could be abrogated by passive immunization with antibodies to a single chemokine, MIP-1α.

Chemokine receptors have also found a place in the unique pathologies of the nervous system. Evident relationships between chemokines that function in specific processes and response by appropriate hematogenous receptor-bearing cells have been demonstrated. Of more novelty (if less well understood) has been the finding that chemokine receptors such as CXCR4, CXCR2, CX3CR1 and the Duffy antigen receptor for chemokines (DARC) are expressed by resident neuroepithelial cells. These varied observations point to a fascinating, diverse and complex array of biological roles for these products in the CNS. Preliminary results in this field are reviewed in this manuscript and summarized in the Tables.

Correspondence: M Ransohoff
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Chemokines in experimental autoimmune encephalomyelitis (EAE)

EAE is a model of organ-specific autoimmunity, and is a useful experimental system for examining certain aspects of the human disorder multiple sclerosis (MS). The disorder is induced in susceptible animals (mice, rats, guinea pigs or nonhuman primates) with injections of myelin antigens in emulsion. The most common practice at present is to immunize with either whole spinal cord homogenate, myelin protein preparations or peptides derived from myelin proteins. The cardinal encephalitogenic proteins of myelin are myelin basic protein (MBP), myelin proteolipid protein (PLP) and myelin oligodendroglial glycoprotein (MOG).

It has been shown that chemokine upregulation occurs in EAE and correlates with disease appearance (Hulkower *et al*, 1993; Ransohoff *et al*, 1993; Godiska *et al*, 1995; Glabinski *et al*, 1996a). Godiska and coworkers observed increased expression of mRNA for several chemokines including RANTES, MIP-1α, MIP-1β, TCA3, IP-10 MCP-1 KC, and MCP-3 in spinal cord before clinical signs appeared. They reported also that encephalitogenic T cells expressed transcripts for RANTES, MIP-1α, MIP-1β and TCA3 (Godiska *et al*, 1995). We observed very transient expression of MCP-1 and IP10 at the beginning of acute EAE (Ransohoff *et al*, 1993).

Analysis of chemokine gene expression and histological findings suggested that chemokines amplify but not initiate invasion of CNS by inflammatory cells from the blood (Glabinski *et al*, 1996a). *In situ* hybridization showed that several chemokines are expressed by astrocytes in near vicinity of inflammatory cuffs (Ransohoff *et al*, 1993; Glabinski *et al*, 1996a; Tani *et al*, 1996b).

In chronic-relapsing EAE we observed increased expression at the mRNA and protein level of five chemokines (MCP-1, IP-10, MIP-1alpha, GRO-alpha, RANTES) during spontaneous relapse of the disease (Glabinski *et al*, 1997). Three of them were expressed by astrocytes (MCP-1, IP-10 and GRO-alpha), two others (MIP-1 alpha and RANTES) by inflammatory cells (Glabinski *et al*, 1997).

As noted above, Karpus and colleagues provided support for the functional importance of chemokine expression in EAE by passive immunization studies. Anti-MIP-1α blocked initial attacks of EAE after adoptive transfer of activated antigen-specific T-cells blasts (Karpus *et al*, 1995). Interestingly, anti-MCP-1 antibodies, which were inert towards initial attacks, significantly reduced relapses of disease, which were unaffected by anti-MIP-1α (Karpus *et al*, 1997). These results indicated complex and nonredundant functions of individual β-chemokines in EAE (Karpus *et al*, 1998).

Chemokines in nonimmunologic CNS injury

Shortly after mechanical trauma to the CNS inflammatory cells migrate from the blood to the injury site and begin the process of tissue repair. The cellular signals for that migration are not known. The functions of chemokines suggest that they are attractive candidates for that role. We analzyed four models of CNS trauma: nitrocellulose membrane stab or implant injury to the adult or neonatal cortex. In the models of mechanical injury to the adult brain we observed increased expression of the mRNA for MCP-1 3 h after injury (Glabinski *et al*, 1996b). MCP-1 protein was detected at 12 h postinjury. In the neonatal stab injury model characterized by lack of inflammation MCP-1 expression was significantly lower than in other models. Other analyzed chemokines (IP-10, MIP-1α, GRO-α) were not detected at the mRNA or protein level. *In situ* hybridization experiments combined with immunocytochemistry showed that astrocytes in the vicinity of the injury site were the cellular source of MCP-1 (Glabinski *et al*, 1996b). Similar kinetics of MCP-1 expression was described in rat models of mechanical injury (Berman *et al*, 1996). It has been shown also in rat stab wound brain injury that reactive astroyctes may express MIP-1β following trauma (Ghirnikar *et al*, 1996). After cryogenic lesion to the cerebral cortex MCP-1 mRNA expression peaked at 6 h, remained elevated for 24 h and then declined by 48 h. IP-10 expression was not upregulated in that brain injury model (Grzybicki *et al*, 1998). Compatible results were reported by Hausmann and colleagues, who found selective upregulation of MCP-1 expression after sterile but not LPS-augmented cerebral trauma (Hausmann *et al*, 1998).

There are several reports showing increased expression of some chemokines in experimental models of brain ischemia. This may suggest that locally produced chemokines may stimulate inflammatory cell migration to the ischemic area and contribute to brain injury in ischemic stroke. Kim and coworkers observed increased expression of mRNA for two chemokines (MCP-1 and MIP-1α) 6 h after induction of cerebral ischemia, with peak expression at 24–48 h (Kim *et al*, 1995). Immunostaining suggested that MCP-1 positive cells were endothelial cells and macrophages in the ischemic area. The morphology of MIP-1α positive cells was similar to GFAP-positive astrocytes (Kim *et al*, 1995). Contradictory results were published by others who showed by double *in situ* hybridization that MIP-1α is produced by Mac-1 positive microglial cells with peak of expression 4–6 h after onset of occlusion (Takami *et al*, 1997). Increased MCP-1 mRNA expression at 6 h after occlusion of middle cerebral artery (MCAO) has also been reported. The kinetics of MCP-1 expression was similar after permanent MCAO or MCAO reperfusion (Wang *et al*, 1995).

Astrocytes were the cellular source of MCP-1 from 6 h to 2 days after MCAO, as reported by Gourmala *et al* (1997). At later time points MCP-1 was detected in macrophages and reactive microglia in the ischemic area (Gourmala *et al*, 1997). Increased MCP-1 expression has been observed as early as 1 h after reperfusion in the rat forebrain reperfusion model (Yoshimoto *et al*, 1997). Chemokine CINC (cytokine-induced neutrophil chemoattractant) which belongs to IL-8 family and is a potent neutrophil chemoattractant in rats, was overexpressed in the cerebral cortex of rats 6–12 h after MCAO (Liu *et al*, 1993). Another group observed increased CINC expression in the brain and serum 3–12 h after reperfusion. One hour of ischemia without reperfusion did not produce increase in CINC expression in the brain (Yamasaki *et al*, 1995).

Expression of chemokines in the CNS of transgenic mice

Most of the early information about chemokines and their physiological roles came from *in vitro* studies. Those results could not be directly extrapolated to the *in vivo* situation. This problem has been addressed by the demonstration that pro-

grammed expression of chemokine genes in the CNS can trigger the recruitment of leukocytes *in vivo* (Lira *et al*, 1997). MCP-1 transgene expressed in oligodendrocytes under control of MBP promoter was able to induce accumulation of inflammatory cells within the CNS (Fuentes *et al*, 1995). Immunohistochemical staining showed that infiltrating cells were monocytes/macrophages and they were localized mainly in perivascular areas with minimal parenchymal infiltration. MCP-1 immunoreactivity was detected at the abluminal surface of cerebral microvessels. The mononuclear cell accumulation was massively amplified at that model by intraparenchymal injection of lipopolysaccharide (LPS). Despite monocyte accumulation no neurological or behavioral signs were observed (Fuentes *et al*, 1995).

CNS-specific expression of α-chemokine KC, which is a potent neutrophil chemoattractant *in vitro* produced impressive neutrophil infiltration into perivascular, meningeal and parenchymal CNS sites (Tani *et al*, 1996a). KC expression was detected in oligodendrocytes and colocalized with infiltrating neutrophils. Three weeks old mice were healthy and behaviorally normal despite remarkable neutrophil accumulation. Beginning at 40 days of age MBP-KC mice developed a neurological syndrome of pronounced postural instability and rigidity. The major neuropathological findings at that time were microglial activation and blood-brain barrier disruption (Tani *et al*, 1996a). Results obtained from these experiments suggested that chemokines are potent inducers of inflammatory cell migration into the CNS *in vivo*. Moreover, their activities were target cell-specific *in vivo* and restricted mainly to triggering migration but not activation (Ransohoff *et al*, 1996).

Chemokines in human CNS pathology

Migration of inflammatory cells from the blood to the CNS compartment is the principal pathological feature of bacterial meningitis. Most information about chemokine involvement in human CNS pathology comes from studies analyzing chemokine levels in the CSF of patients with meningitis. Spanaus and collaborators analyzed by ELISA concentrations of several chemokines in the CSF of patients with pyogenic meningitis (Spanaus *et al*, 1997). They found significantly increased levels of IL-8, GRO-α, MIP-1α, and MIP-1β but not RANTES, when compared with noninflammatory CSF controls. The CSF from meningitis patients was chemotactic *in vitro* for neutrophils and mononuclear leukocytes and the migration was diminished by specific anti-chemokine antibodies (Spanaus *et al*, 1997). In another study elevated levels of IL-8, GRO-α and MCP-1 were found in the CSF from patients with bacterial and aseptic meningitis but not in parallel blood serum specimens (Sprenger *et al*, 1996). Number of granulocytes in the CSF from bacterial meningitis patients correlated with IL-8 and GRO-α levels, whereas MCP-1 level correlated well with mononuclear cell count in aseptic meningitis (Sprenger *et al*, 1996). In another study IL-8 concentration in the CSF was higher than 2.5 ng/ml in all samples from patients with pyogenic meningitis, but also in some samples from patients with nonbacterial meningitis (Lopez-Cortes *et al*, 1995). In patients with nonpyogenic meningitis a significant correlation between IL-8 levels and CSF granulocyte counts was found (Lopez-Cortes *et al*, 1995). These results suggest that chemokines are involved in inflammatory cell accumulation in the subarachnoid space.

MIP-1α in the CSF was reported to be increased in multiple sclerosis patients during relapse as well as in CSF from patients with Behcet's disease and HTLV-1 associated myelopathy. MIP-1α level in that study correlated with leukocyte and protein concentration in the CSF (Miyagishi *et al*, 1995). Increased level of IL-8 was also detected in CSF of patients with severe brain trauma, at higher levels in CSF than in corresponding serum and correlated directly with blood-brain barrier dysfunction (Kossmann *et al*, 1997).

There is little information about cellular sources of chemokine production during human CNS pathology. MCP-1 immunoreactivity was detected in reactive microglia and mature but not in immature senile plaques in autopsy specimens from five Alzheimer disease patients (Ishizuka *et al*, 1997). Simpson and coworkers demonstrated expression of MCP-1 protein by astrocytes bordering active MS lesions, compatible with prior observations in EAE, trauma and cerebral ischemia models (Simpson *et al*, 1998). Hvas *et al* showed that RANTES mRNA was expressed by perivascular inflammatory cells in MS brain sections as previously reported in EAE (Hvas *et al*, 1997).

Chemokine expression by CNS cells *in vitro*

MCP-1 was originally purified in 1989 from the culture supernatant of a glioma cell line (Yoshimura *et al*, 1989). Since that time numerous studies on chemokine expression by CNS cells *in vitro* have been published. Many human glioma cell lines were shown to produce IL-8 and MCP-1, while none of neuroblastoma cell lines expressed these cytokines (Morita *et al*, 1993). In other studies IL-8 was produced by five astrocytoma cell lines (Nitta *et al*, 1992) and also in some glioblastoma cell lines (Kasahara *et al*, 1991). Cultured astroyctes stimulated by cytokines TNFα and TGFβ express MCP-1 mRNA and protein (Hurwitz *et al*, 1995). IFNγ can also stimulate MCP-1 expression by astrocytoma cell line (Zhou *et al*, 1998). Additionally, stimulated

astrocytes can express MIP-1α and MIP-1β (Peterson *et al*, 1997) and RANTES (Barnes *et al*, 1996). LPS, IL-1β and TNF-α stimulate production of MCP-1 by astrocytes but not microglia (Hayashi *et al*, 1995). HIV-1 transactivator protein Tat significantly increase astrocyte production of MCP-1, but not RANTES, MIP-1α and MIP-1β suggesting that HIV may induce monocyte infiltration in the CNS via astrocyte stimulation (Conant *et al*, 1998). IP-10 and RANTES expression can be upregulated in primary rat astrocytes and microglia by the infection of neurotropic paramyxovirus NDV (Fisher *et al*, 1995). Beta amyloid peptide is able to stimulate expression of IL-8 by human astrocytoma cells (Gitter *et al*, 1995).

Microglial cells are critical for CNS response to varied forms of injury. When stimulated *in vitro* by LPS, IL-1β and TNFα they can produce IL-8. Pretreatment with IL-4, IL-10 or TGF-beta 1 inhibited the stimulatory effects of these proinflammatory cytokines (Ehrlich *et al*, 1998). Cryptococcal polysaccharide was also capable of inducing IL-8 production by human fetal microglial cells showing that some fungi can stimulate endogenous CNS cells to express chemokines (Lipovsky *et al*, 1998).

Human cultured microglia produce MIP-1α, MIP-1β and MCP-1 in response to LPS, TNFα or IL-1β (McManus *et al*, 1998). Moreover MCP-1 expression by brain macrophages can be also stimulated by IL-6 and CSF-1 (Calvo *et al*, 1996) as well as the active fragment of beta amyloid (Meda *et al*, 1996). This last observation gives new insight into mechanisms underlying amyloid plaque formation in the CNS during Alzheimer disease. Microglial cells infected by SIV *in vitro* can produce more IL-8 than uninfected cultures (Sopper *et al*, 1996).

TNFα treatment of mixed human brain cell cultures stimulated higher expression of RANTES and MIP-1β than observed after similar stimulation of microglial cells (Lokensgard *et al*, 1997). Cultured brain endothelial cells were shown to express mRNA for MCP-1. Treatment with TNFα increased MCP-1 expression in a dose-dependent manner (Zach *et al*, 1997). Bovine brain microvessel endothelial cells showed increased expression of IL-8 after infection with bacterial parasite *C. ruminantium* (Bourdoulous *et al*, 1995).

Chemokine receptors – overview

Chemokines act on target cells via seven-transmembrane-domain receptors that signal through GTP-binding proteins. Two main subgroups of chemokine receptors have been described: CXC chemokine receptors (CXCR) with 36–77% and CC chemokine receptors (CCR) with 46–89% identical amino acids (Baggiolini *et al*, 1997). Lately a receptor for CX_3C chemokine-fractalkine/neurotactin was identified (Imai *et al*, 1997), so far there is no known receptor for C chemokine lymphotactin. The largest family of chemokine receptors are CCR receptors consisted of ten receptor types in human (CCR1–CCR10). CXCR receptor family includes four types of receptors in humans (CXCR1–CXCR5). Chemokine receptors can be categorized into four different subgroups: shared, specific, promiscuous and viral (Premack and Schall, 1996). Most of the chemokine receptors can bind more than one chemokine ligand belonging to the same chemokine subfamily (shared group). CXCR2 binds several CXC chemokines that contain a canonical glutamate-leucine-arginine (ELR) motif. CXCR3 binds non-ELR CXC chemokines including β-R1/I-TAC (Cole *et al*, 1998; Rani *et al*, 1996), IP-10 and Mig. All CCR receptors have several ligands. There is a promiscuous chemokine receptor designated as DARC which is identical to Duffy blood group antigen on erythrocytes. It binds chemokines from CC and CXC subfamilies and it is postulated that it works in the blood as a 'sink' for chemokines because of the lack of signaling. Two (among several other) viruses encode chemokine receptors: *Cytomegalovirus* (CMV US28) and *Herpes virus saimiri* (HSV ECRF3) (Murphy, 1996; Premack and Schall, 1996). The role of virally encoded chemokine receptors is unknown but preservation of signaling function is of considerable interest (Murphy, 1996).

Chemokine receptors in CNS pathology

Expression of several different chemokine receptors has been detected in the normal CNS as well as in cultured cells derived from CNS components (Tables 1 and 2). The fractalkine receptor CX3CR1 was detected at surprisingly high levels in normal brain and spinal cord in both human and rodent specimens before its response to the fractalkine ligand was described (Combadiere *et al*, 1995; Harrison *et al*, 1994; Imai *et al*, 1997). Fractalkine was also demonstrated to be highly abundant in normal CNS tissues and upregulated in pathology, suggesting important functions for this ligand-receptor system in neural physilogy (Bazan *et al*, 1997; Pan *et al*, 1997). Horuk and coworkers detected the DARC receptor on cerebellar Purkinje cells in archival human brain sections (Horuk *et al*, 1996) and CXCR-2 on projection nuerons in diverse regions of the brain and spinal cord (Horuk *et al*, 1997). The same group reported detection of chemokine receptors CCR1, CCR5, CXCR2 and CXCR4 by immunohistochemistry in cultured human neurons (Hesselgesser *et al*, 1997). Transcripts for CXCR4 were identified also by Northern blot (Heesen *et al*, 1996a; Nagasawa *et al*, 1996) and RT–PCR (Heesen *et al*, 1997) in cultured primary mouse astrocytes. Cultured astrocytes were shown to express also CCR1 (Tanabe *et al*, 1997), but not

CCR2 and CXCR2 (Heesen *et al*, 1996b). Other studies confirmed that CXCR4 is expressed by microglia in human and mouse brain (He *et al*, 1996). The single unequivocal demonstration that chemokine receptors are important for developmental neural patterning comes from the finding that CXCR4 knockout mice exhibit abnormal formation of the CNS (Littman, 1998). Two alternatively spliced forms of mouse CXCR4 have been identified both of which are expressed by cultured astrocytes and microglia (Heesen *et al*, 1997). Several orphan chemokine receptor-like proteins were detected in the CNS. They have structure similar to chemokine receptors but their ligands

Table 1a Chemokines upregulated in experimental infectious CNS pathology

Upregulated chemokine	*CNS pathology*	*Animal*	*Cellular source*	*Reference*
MIP-1α, MIP-1β, RANTES, MCP-3, IP-10	SIV-induced AID, encephalitis	Monkey	Endothelial cells, Monocytes, Microglia	Sasseville *et al*, 1996
IP-10, RANTES, MCP-1, MIP-1β, MCP-3, Lymphotactin, C10, MIP-2, MIP-1α	Lymphocytic, Chorio-meningitis	Mouse	Brain homogenate	Asensio and Campbell, 1997
MIP-1α, MIP-2	Listeria *meningo-encephalitis*	Mouse	Granulocytes, Monocytes	Seebach *et al*, 1995
IP-10, RANTES, MCP-1, MCP-3, MIP-1β, MIP-2	Hepatitis virus encephalomyelitis	Mouse	Astrocytes	Lane *et al*, 1998

Table 1b. Chemokines upregulated in experimental noninfectious CNS pathology

MCP-1, RANTES, MIP-1α, MIP-1β, TCA-3, IP-10, MCP-1, KC, MCP-3, Fractalkine	EAE, ChREAE	Mouse, Rat	CNS, homogenate astrocytes, microglia, lymphcytes, macrophages, endothelial cells	Hulkower *et al*, 1993; Ransohoff *et al*, 1993; Godiska *et al*, 1995; Glabinski *et al*, 1996; Karpus *et al*, 1995; Tani *et al*, 1996; Pan *et al*, 1997; Glabinski *et al*, 1997; Berman *et al*, 1996; Miyagishi *et al*, 1995
MCP-1, MIP-1α, MIP-1β	Mechanical injury	Mouse, Rat	Astrocytes, macrophages, endothelial cells, microglia	Glabinski *et al*, 1996; Berman *et al*, 1996; Ghirnikar *et al*, 1996; Hausmann *et al*, 1998; McTigue *et al*, 1998; (JNR in press)
MCP-1	Freeze injury	Mouse	Homogenate	Grzybicki *et al*, 1998
MCP-1	Chemical injury	Rat	Astrocytes, macrophages	Calvo *et al*, 1996; Hausmann *et al*, 1998; McTigue *et al*, 1998; (JNR in press)
MCP-1, MIP-1α, CINC	Brain ischemia	Rat	Brain homogenate, endothelial cells, microglia, macrophages, astrocytes	Wang *et al*, 1995; Lu *et al*, 1993; Yamasaki *et al*, 1995; Kim *et al*, 1995; Takami *et al*, 1997; Gourmaia *et al*, 1997; Ivacko *et al*, 1997

Table 2 Chemokines upregulated in human CNS pathology

Upregulated chemokine	*CNS pathology*	*Tissue source*	*Reference*
IL-8	Astrocytoma, glioblastoma	Tumor cells	Van Meir *et al*, 1992; Nitta *et al*, 1992
IL-8, Gro-α, MCP-1, MIP-1α, MIP-1β	Bacterial and aseptic meningitis		Sprenger *et al*, 1996; Spanaus *et al*, 1997; Lopez-Cortes *et al*, 1995
MIP-1α	Multiple sclerosis, Behcet's disease, HTLV-1, myelopathy		Miyagishi *et al*, 1995
IL-8	Brain injury		Kossman *et al*, 1997
MCP-1	HIV-1 associated dementia		Conant *et al*, 1998
MCP-1	Alzheimer disease	Microglia, senile plaques	Ishizuka *et al*, 1997; Hvas *et al*, 1997; Simpson *et al*, 1998
RANTES	Multiple sclerosis	Perivascular leukocytes	Hvas *et al*, 1997
MCP-1	Multiple sclerosis	Astrocytes	Simpson *et al*, 1998

have not been identified so far. One of them is CXCR5 receptor isolated initially from Burkitt's lymphoma cells but expressed also in mature B cells and in brain neurons (Kaiser *et al*, 1993). Another example of orphan chemokine-like receptors in a family of LCR-1 receptors identified initially in bovine locus coeruleus, later rat and sheep homologs were found (Wong *et al*, 1996).

Table 3 Chemokines expressed by cultured cells

Chemokine	*CNS cells*	*Species*	*Reference*
MCP-1, IL-8	Glioma, astrocytoma, glioblastoma	Human	Morita *et al*, 1993; Van Meir *et al*, 1992; Nitta *et al*, 1992; Kasahara *et al*, 1991; Zhou *et al*, 1997
MCP-1, IL-8, MIP-1α, MIP-1β, RANTES, IP-10	Activated astrocytes	Human, rat murine	Gitter *et al*, 1995; Peterson *et al*, 1997; Conant *et al*, 1993; Barnes *et al*, 1996; Sun *et al*, 1997; Hurwitz *et al*, 1995; Fisher *et al*, 1995; Hayashi *et al*, 1995
MIP-1α, MIP-1β, MCP-1, IL-8, RANTES, IP-10	Activated microglia, brain macrophages	Human simian rat murine	McManus *et al*, 1998; Peterson *et al*, 1997; Ehrlich *et al*, 1998; Lipovsky *et al*, 1998; Lokensgard *et al*, 1997; Sopper *et al*, 1996; Sun *et al*, 1997; Hurwitz *et al*, 1995; Fisher *et al*, 1995; Hayashi *et al*, 1995; Meda *et al*, 1996; Calvo *et al*, 1996
MCP-1, IL-8	Stimulated cerebral endothelium	Human, bovine, porcine, murine	Zach *et al*, 1997; Lou *et al*, 1997; Bourdoulous *et al*, 1995
RANTES	Infected neurons	Mouse	Halford *et al*, 1996
RANTES, MIP-1α	Mixed brain cell cultures	Human	Lokensgard *et al*, 1997

Table 4 Chemokine receptors detected in normal CNS *in vivo*

Receptor	*Localization*	*Species*	*Reference*
CXCR-2	Projection neurons	Human autopsy brain	Horuk *et al*, 1997; Xia *et al*, 1997
DARC	Purkinje cells	Human autopsy brain	Horuk *et al*, 1996
CCR-3	Microglia	Human autopsy brain	He *et al*, 1996
CXC_3CR-1		Human brain RNA	Combadiere *et al*, 1995; Harrison *et al*, 1994
CCR-3, CCR-5, CXCR4	Pyramidal neurons, glial cells	Macaque	Westmoreland *et al*, 1998
RLCR-1	Neurons, ependymal cells	Rat	Wong *et al*, 1996
CCR-5	Normal brain	Rat	Jiang *et al*, 1998
CXCR5	Granule and Purkinje cell layer	Mouse	Kaiser *et al*, 1993

Table 5 Chemokine receptors upregulated in CNS pathology

Upregulated receptor	*CNS disease*	*Cellular source*	*Reference*
CXCR-2, CCR3	Alzheimer disease	Neurons	Horuk *et al*, 1997; Xia *et al*, 1997; He *et al*, 1996
CCR3, CCR5, CXCR53, CXCR4	SIV encephalomyelitis	Perivascular infiltrates	Westmoreland *et al*, 1998
CCR2, CCR5, CXCR4, CX_3CR1	EAE	Spinal cord homogenate	Jiang *et al*, 1998

Table 6 Chemokine receptors expressed by cultured CNS cells

Receptor	*CNS cells*	*Species*	*Reference*
IL8R, CXCR-4, CCR-1, CX_3CR-1	Astrocytes	Human, mouse, rat	Tanabe *et al*, 1997; Jiang *et al*, 1998; Heesen 1997
IL8R, CXCR-4, CCR-3, CCR-5, CX_3CR-1	Microglia	Human, mouse, rat	He *et al*, 1996; Tanabe *et al*, 1997; Jiang *et al*, 1998
CXCR-2, CXCR-4, CCR-1, CCR-5	Neurons	Human	Hesselgesser *et al*, 1997

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