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Review

Chemokines/chemokine receptors in the central nervous system and Alzheimer's disease

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Alzheimer's disease (AD) is the most common cause of dementia in the elderly, and the fourth leading cause of death in the United States. Its pathological changes include amyloid beta deposits, neurofibrillary tangles and a variety of 'inflammatory' phenomenon such as activation of microglia and astrocytes. The pathological significance of inflammatory responses elicited by resident central nervous system (CNS) cells has drawn considerable attention in recent years. Chemokines belongs to a rapidly expanding family of cytokines, the primary function of which is control of the correct positioning of cells in tissues and recruitment of leukocytes to the site of inflammation. Study of this very important class of inflammatory cytokines may greatly help our understanding of inflammation in the progress of AD, as well as other neurodegenerative diseases. So far, immunoreactivity for a number of chemokines (including IL-8, IP-10, MIP-1β, MIPα and MCP-1) and chemokine receptors (including CXCR2, CXCR3, CXCR4, CCR3, CCR5 and Duffy antigen) have been demonstrated in resident cells of the CNS, and upregulation of some of the chemokines and receptors are found associated with AD pathological changes. In this review, we summarize findings regarding the expression of chemokines and their receptors by CNS cells under physiological and pathological conditions. Although little is known about the potential pathophysiological roles of chemokines in CNS, we have put forward hypotheses on how chemokines may be involved in AD.

Keywords: cytokines; inflammation; neuron; glial; neurodegeneration; amyloid

Introduction

Alzheimer's disease (AD) is a devastating illness affecting the elderly. It is the most common cause of dementia and the fourth leading cause of death in the USA. Its clinical features include progressive dementia with gradual loss of cognitive function. Its main neuropathological features include neurofibrillary tangles, senile plaques, and loss of neurons and synapses (reviewed in Hyman, 1997). A marked astrocytosis and microglial activation occurs throughout the cortex. Substantial evidence has implicated the involvement of 'inflammatory' responses in AD pathogenesis (Hull *et al*, 1996; Mrak *et al*, 1995; Rogers *et al*, 1996; Sheng *et al*, 1996), and anti-inflammatory treatment has shown a promising effect in delaying the disease progression (McGeer and Rogers, 1992; Rich *et al*, 1995). Based on the above reasons, we focused our attention on a very important family of inflammatory cytokines, the chemokine family in the CNS, and systematically studied their expression in both normal and AD brains.

Four structural brances of human chemokines, α (CXC), β (CC), γ (C) and δ (CX_3C) have been described, based on variations in a shared cysteine motif. Chemokine receptors are correspondingly named CXCR (1–5), CCR (1–8), CR and CX_3CR. All of them are members of the seven transmembrane domain receptor superfamily. Table 1 lists chemokine receptors and their corresponding ligands that have been reported so far.

In the hematopoetic system, the primary function of chemokines is control of the correct positioning of cells in tissues and recruitment of leukocytes to

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Table 1 Chemokine family in human

Branches	*Receptors*	*Ligands*
CXC (α)[1,2]		
	CXCR1 (IL-8RA)	IL-8
	CXCR2 (IL-8RB)	IL-8, GROα, β, γ, NAP-2, ENA78, GCP-2
	CXCR3	IP-10, Mig
	CXCR4	SDF-1
	CXCR5[5]	BCA-1
CC (β)[1,2]		
	CCR-1	Rantes, MIP-1α, MCP-2, MCP-3
	CCR2a/b	MCP-1, 2, 3, 4
	CCR3	eotaxin, Rantes, MCP-3, 4, eotaxin-2
	CCR4	Rantes, MIP-1α, TARC[6], MDC[6]
	CCR5	Rantes, MIP-1α, MIP-1β
	CCR6[7,8]	MIP-3α, LARC
	CCR7[9]	6Ckine[10], MIP-3β[10]
	CCR8[11,12]	I-309, TARC[13], MIP-1β[13]
C (γ)[3]	CR	Lymphotactin
CX_3C (δ)[4]	CX_3CR	Fractalkine
Promiscuous	Duffy antigen	MGSA, IL-8, Rantes, MCP-1, etc.
	Others	

[1]Baggiolini *et al*, 1997; [2]Premack and Schall, 1996; [3]Yoshida *et al*, 1998; [4]Bazan *et al*, 1997; [5]Legler *et al*, 1998; [6]Imai *et al*, 1998; [7]Baba *et al*, 1997; [8]Greaves *et al*, 1997; [9]Yoshida *et al*, 1997; [10]Campbell *et al*, 1998; [11]Tiffany *et al*, 1997; [12]Roos *et al*, 1997; [13]Bernardini *et al*, 1998.

inflammatory sites. In many central nervous system (CNS) diseases such as multiple sclerosis (MS), brain trauma, infections, or focal ischemia and reperfusion, the blood brain barrier is breached, and leukocyte infiltration is found at the lesion sites (Eng *et al*, 1996; Ghirnikar *et al*, 1998; Glabinski *et al*, 1995a; Ransohoff, 1997; Ransohoff and Tani, 1998). Clearly, we would expect a role of chemokines in the pathology of these diseases. What we would like to emphasize here is that in AD, and many other neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Huntington disease (HD), etc., the blood brain barrier is intact, and no infiltration of inflammatory cells is present. The chronic 'inflammatory' responses implicated in these diseases are believed to be caused by resident CNS cells. So far, an impressive number of chemokines and receptors have been found in resident CNS cells, and there is growing evidence showing that some of them are upregulated in AD brains. Some interesting questions have therefore been raised: Could these inflammation-related chemokines expressed by resident CNS cells play a role in the neurodegeneration process in AD and even other neurodegenerative diseases? Do they also have a role for the normal brain development and function? In this review, we will focus on the chemokines and their receptors that are expressed by CNS cells and their potential roles in mediating neuronal-neuronal, neuronal-glial and glial-glial interactions in the CNS under physiological and pathological situations, particularly AD.

Chemokines and their receptors in the CNS

Chemokines and their receptors that have been detected under physiological or pathological conditions in brain tissues or neuronal and glial cultures by immunohistochemistry, by *in situ* or by reverse transcriptase-polymerase chain reaction (RT–PCR) are summarized in Table 2. Although the autoimmune disease model EAE is not directly relevant to AD pathology, we have also included some data obtained from this animal model to provide supporting evidence as to which cell types can be the source of chemokine expression *in vivo*. So far, chemokines detected by immunohistochemistry in brain tissue include IP-10 in a subpopulation of resting and reactive astrocytes (MengQi Xia *et al*, manuscript in preparation); IL-8 on astrocytes (Sanders *et al*, 1998); MIP-1β in some resting and reactive astrocytes (Xia *et al*, 1998) and MIP-1α in neurons and weakly on some microglia (Ishizuka *et al*, 1997a; Xia *et al*, 1998); and MCP-1 in some reactive microglia (Ishizuka *et al*, 1997b). Immunoreactivity for a number of chemokine receptors has also been detected in CNS cells: three (CXCR2, CXCR3, CXCR4) out of the five CXCRs have been detected on neurons, and two (CCR3 and CCR5) out of eight CCRs have been detected mainly on microglia cells and weakly on neurons.

Alzheimer's disease

AD neuropathology contains two major features: intraneuronal paired helical filament containing neurofibrillary tangles which occur in neuronal cytoplasm and processes, and complex extracellular lesions called senile plaques. Senile plaques consist of a deposit of Amyloid β (Aβ), a 40–42 amino acids peptide derived from amyloid precursor protein (APP). Frequently, plaques are surrounded by reactive microglia, reactive astrocytes and several types of dystrophic neurites. In AD brains, we and other investigators have observed certain abnormal patterns of chemokine and their receptor expression often associated with senile plaques (Xia *et al*, 1997; Horuk *et al*, 1997; Xia *et al*, 1998; Ishizuka *et al*, 1997b). These findings are summarized in Table 2.

We have reported the constitutive presence of CXCR2 on a subpopulation of neurons in cortical and subcortical regions with its expression particular strong in pyramidal neurons of CA regions and neurons of the dentate gyrus (Figure 1). Upregulation of CXCR2 expression was observed on some dystrophic neurites of senile plaques (Xia *et al*, 1997). Simultaneous work by Horuk and colleagues (Horuk *et al*, 1997) concurred with this finding. We have demonstrated by double staining and confocal microscopic analysis that CXCR2

expression on dystrophic neurites correlates with APP expression. Almost all CXCR2 positive neuritic plaques correspond to APP positive neuritic plaques, and most of those dystrophic neurites are negative for PHF tau, a marker of degenerating neurites. Interestingly, APP positive neuritic plaques (at least a substantial proportion) are believed to represent aberrant regenerating neurites (Geddes *et al*, 1986; Masliah *et al*, 1991; 1992) and APP has been shown to play a role in promoting neurite outgrowth and neuronal survival *in vitro* (Mattson, 1997; Milward *et al*, 1992). Therefore, we speculate that CXCR2 positive dystrophic neurites represent aberrant regenerating neurites.

Table 2 Chemokines/receptors evaluated in the CNS

	Human	*Rodent*
CXCR1	Not detectable[1]	
CXCR2	Neurons and some neuritic plaques in AD[1,2]	
IL-8	Constitutively present in astrocytes[3] Induced in fetal microglia culture by LPS, IL-1β or TNF-α[4] or bacteria[5] Induced in astrocytes by TNF-α and IL-1β[6] or by reduced microenvironmental oxygen pressure[7] mRNA detectable in neoplastic astrocytes[8a,b]	
CXCR3	Neurons including purkinje cells[9]	Inducible in both astrocytes and microglia culture by LPS, TNF-α and IFN-γ[11] or noninfectious NDV[12]
IP-10	Constitutively present in some astrocyte[9] elevated in some reactive astrocytes in AD[9] present in 79% in the CSF of viral meningitis patients[10]	also induced in neuroblastoma by MV[13] The most prominently induced chemokine mRNA Induced in resident CNS cells in LCM[14] In mouse EAE, mRNA accumulated in a striking, transient burst within astrocytes near the inflamed sites[15] and only detectable in the early phase of EAE[16]
Mig	Not available	mRNA inducible in rat astrocytes and microglia by IFN-γ[17]
CXCR4	Neurons and microglia[18]	Gene deficient mice showed abnormal cerebellum development[19]
SDF-1	Not available	Gene deficient mice showed abnormal cerebellum development[19,20]
CCR1	Not available	mRNA detected in mouse astrocyte by PCR, mediate astrocyte chemotaxis to MIP-1α[21]
CCR2	Not available	
MCP-1	Reactive microglia of mature senile plaques in AD[22] present in 97% in the CSF of viral meningitis patients[10] CSF levels markedly higher in CMV encephalitis[23]	Protein inducible in rat and mouse glial culture by LPS[11] mRNA or protein induced in rat CNS cells after focal ischemia[24] and excitotoxic injury[25] In mouse EAE, accumulated in a striking, transient burst within astrocytes near the inflamed sites[15] sharply induced in astrocytes near mechanical injury[26]
CCR3	Upregulated in some reactive microglia in AD[27]	
Eotaxin	Not detectable	
CCR5	Upregulated in some reactive microglia in AD[27]	mRNA upregulated in rat focal ischemia model[28]
MIP-1α	Neurons and some microglia[27,29] mRNA and protein inducible by LPS, TNFα or IL-1β in human fetal microglia culture[30]	mRNA induced in mouse resident CNS cells after spinal cord injury[31] and in rat CNS cells after focal ischemia[24,32]
MIP-1β	Upregulated in reactive astrocytes of AD[27] mRNA and protein inducible by LPS, TNFα or IL-1β in human fetal microglia culture[30]	mRNA induced in mouse resident CNS cells after spinal cord injury[31]
Rantes	Not detectable[27]	mRNA induced in rat astrocytes and microglia by noninfectious NDV[12]
MCP-3	Not detectable[27]	
CX_3CR	Not available	mRNA detected in rat microglia by in situ[33]
Fractalkine	Not available	mRNA detected in rat neurons by in situ[33]
Duffy antigen	Exclusively Purkinje cells in cerebellum[2]	

Unless otherwise specified, all the results of brain tissues were obtained by immunohistochemistry. LCM: lymphocytic choriomeningitis. NDV: the neurotropic paramyxovirus, Newcastle disease virus. MV: Measles virus. [1]Xia *et al*, 1997; [2]Horuk *et al*, 1997; [3]Sanders *et al*, 1998; [4]Ehrlich *et al*, 1998; [5]Lipovsky, *et al* 1998; [6]Aloisi *et al*, 1995; [7]Desbaillets *et al*, 1997; [8a]Nitta *et al*, 1992; [8b]Van Meir *et al*, 1992; [9]MengQi Xia *et al*, manuscript in preparation; [10]Lahrtz *et al*, 1997; [11]Sun *et al*, 1997; [12]Fisher *et al*, 1995; [13]Nazar *et al*, 1997; [14]Asensio and Campbell, 1997; [15]Glabinski *et al*, 1995b; [16]Tanti *et al*, 1996; [17]Vanguri *et al*, 1995; [18]Lavi *et al*, 1997; [19]Zou *et al*, 1998; [20]Nagasawa *et al*, 1996; [21]Tanabe *et al*, 1997; [22]Ishizuka *et al*, 1997b; [23]Bernasconi *et al*, 1996; [24]Kim *et al*, 1995; [25]Szaflarski *et al*, 1998; [26]Glabinski *et al*, 1996; [27]Xia *et al*, 1998; [28]Spleiss *et al*, 1998; [29]Ishizuka *et al*, 1997a; [30]McManus *et al*, 1998; [31]Bartholdi and Schwab, 1997; [32]Takami *et al*, 1997; [33]Nishiyori *et al*, 1998.

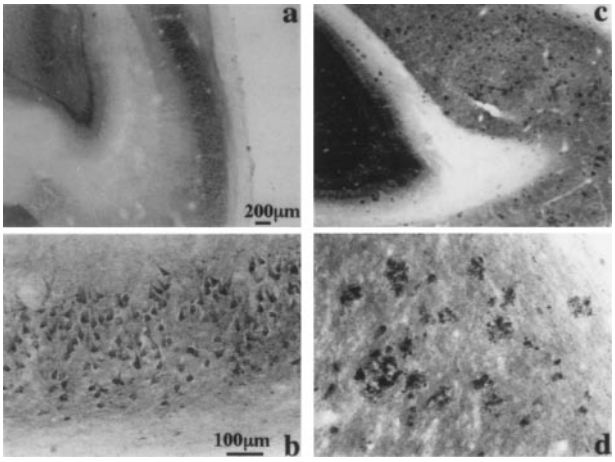

Figure 1 IL-8RB (CXCR2, Mab 6C6) immunoreactivity in (**a** and **b**) and the hippocampal formation of a 66 year old male control patient showing that (**a**) neurons and neutrophil of the dentate gyrus and CA region are strongly immunoreactive; (**b**) phyramidal neurons in CA 1 region are clearly stained; in (**c** and **d**) the hippocampal formation of a 74 year-old male AD patient showing that (**c**) a similar pattern of gray matter staining and an increased immunoreactivity on a subpopulation of plaques; and (**d**) a higher power view of some of the neuritic plaques in CA1 region. These neuritic plaques were later shown by double immunofluorescent staining and confocal microscopic analysis to be positive for APP but not tangles. Images (**a**) and (**c**), (**b**) and (**d**) share the same magnifications respectively. Modified with permission (Xia *et al*, 1997).

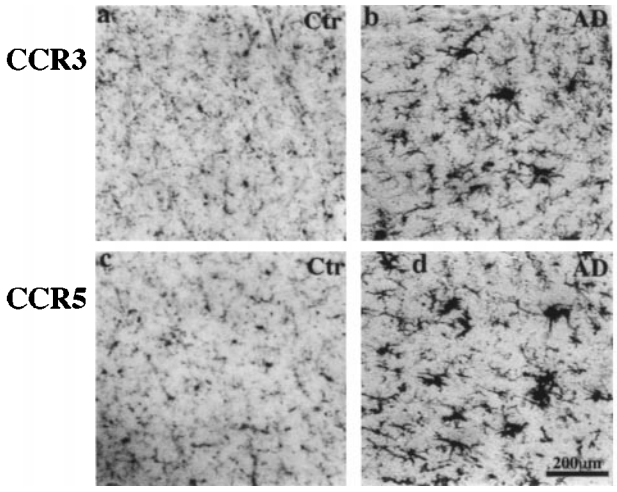

Figure 2 CCR3 (7B11) and CCR5 (3A9) immunoreactivity in the inferior temporal lobes of a 58 year-old control patient and an 81 year-old AD patient with duration of illness for 12 years. CCR3 (**a** and **b**) and CCR5 (**c** and **d**) immunoreactivitities are clearly seen on microglia of both cases. In the control case, the majority of cells stained are resting microglia; while in the AD brain both resting and reactive microglia cells are clearly stained, some reactive microglia appears in clusters. All images have the same scale of magnification. Adapted with permission (Xia *et al*, 1998).

Most recently, we have also demonstrated that CCR3 and CCR5 are present on microglia of both normal and AD brains (Figure 2, and their expression is increased on some reactive migroglia in AD (Xia *et al*, 1998). Some of the CCR3$^+$ or CCR5$^+$ reactive microglia are found associated with amyloid deposits. Among the tested CCR3 and CCR5 ligands, including MIP-1β and MIP-1α, RANTES, eotaxin and MCP-3, only immunoreactivities for MIP-1β and MIP-1α were observed. MIP-1β was predominantly found in a subpopulation of reactive astrocytes which were more widespread and more strongly stained in AD than control brains. MIP-1α stained predominantly in neurons and weakly in some microglia particularly in the white matter of both AD and controls. Thus one cell type produces ligand, and another cell type has receptor, suggesting a role for this class of chemokines in cell-cell communication in the CNS. Some of the CCR3$^+$ or CCR5$^+$ reactive microglia and MIP-1β^+ reactive astrocytes were found associated with amyloid deposits. An interesting part of the CCR3 and CCR5 story was that these two receptors are the recently found co-receptors for HIV entry into cells (Broder and Collman, 1997; Choe *et al*, 1996; Deng *et al*, 1996). Microglia, the primary target of HIV infection in the CNS, also use these receptors for the viral entry (He *et al*, 1997; Ghorpade *et al*, 1998). HIV infected patients may develop a progressive dementia, with motor and behavioral impairment termed 'AIDS-dementia complex'. The apparent activation of these β chemokine systems in AIDS-dementia complex (Nuovo and Alfieri, 1996; Schmidtmayerova *et al*, 1996), may have a detrimental role to neuronal function. We speculate that their apparent activation in AD brain may also play a role in this disease process.

Our ongoing experiments have shown overwhelming upregulation of IP-10 in reactive astrocytes despite the weak presence of this chemokine constitutively in a subpopulation of resting astrocytes. CXCR3 immunoreactivity was found on a subpopulation of cortical neurons (MengQi Xia *et al*, manuscript in preparation). Unlike CXCR2, its expression did not appear to be associated with AD pathology.

Ishizuka and colleagues have reported the presence of MCP-1 (a CCR2 ligand) in mature senile plaques and reactive microglia but not in immature senile plaques of brain tissues from five AD patients by immunohistochemistry (Ishizuka *et al*, 1997b).

Regulation of chemokine production

As summarized in Table 2, various stimuli such as LPS, cytokines, reduced oxygen pressure, some viral infections, etc., either alone or in combination, can stimulate different type of chemokines from different cell types. *In vitro*, although some

chemokines are more predominantly expressed in one cell type than another, virtually any cell type may have the capacity to express chemokines. However, chemokine expression *in vivo* appears to be more restricted to particular cell types.

Non-inflammatory activities of chemokines

Studies in the hematopoietic system show that binding of chemokines to their receptors leads to changes in the coupling of G proteins to the receptor (Baggiolini *et al*, 1997). A number of downsream signal transduction pathways become activated, including calcium mobilization, phospholipase C, phosphatidylinositol (PI)3-kinase, mitogen-activated protein (MAP) kinases and serine/threonine and tyrosine kinases. The exact mechanism of chemokine action in the CNS and the subsequent events after receptor activation await further study.

Apart from their chemotactic ability, chemokines have also been demonstrated to have other activitites in hematopoietic and other systems. For example, MIP-1α has been shown to inhibit the proliferation of hematopoietic stem cells *in vitro* and *in vivo* (Cook, 1996). IL-8 has been shown to have angiogenic activity (Kumar *et al*, 1998). IP-10 is known to be angiostatic; it has been suggested that an imbalance of IP-10 and IL-8 favors angiogenesis in idiopathic pulmonary fibrosis (Keane *et al*, 1997). IP-10 and MIP-1α were able to block growth factor induced protein synthesis and proliferation in hematopoietic MO7e cells (Aronica *et al*, 1997); IP-10, and another CXCR3 ligand Mig are both antitumor agents that promote damage in established tumor vasculature and cause tissue necrosis in human Burkitt lymphomas (Sgadari *et al*, 1996; 1997; Yu *et al*, 1997). Mice lacking the CXCR2 homologue were apparently healthy despite increased B cells, metamyelocytes and neutrophils (Cacalano *et al*, 1994). CCR5-deficient mice showed reduced efficiency in macrophage function (Zhou *et al*, 1998). CCR2 knockout mice developed apparently normally, but have a selective decrease of monocyte/macrophage response to MCP-1, and reduced granulocyte and IFN-γ response to stimuli (Boring *et al*, 1997); The only evidence of a physiological role of chemokines and chemokine receptor in the CNS come from data that mice deficient of CXCR4 or SDF-1 (ligand for CXCR4), in addition to haematopoietic and cardiac defects, showed a different pattern of cerebellum development with many proliferating granule cells invading the cerebellar anlage (Zou *et al*, 1998; Nagasawa *et al*, 1996). These studies demonstrate the involvement of a G-protein coupled chemokine receptor in neuronal cell migration and patterning in CNS. It remains to be tested whether other chemokine receptors play any physiological roles in CNS.

Factors that may induce chemokine production in the CNS

CNS resident cells such as microglia and astrocytes are activated in AD and other neurodegenerative diseases (Dickson *et al*, 1993; Lue *et al*, 1996; Mrak *et al*, 1995; Sheng *et al*, 1996). In AD, the activated glia tend to surround senile plaques presumably through active chemotaxis. The chemotactic ability of both migroglia and astrocytes to several factors has been demonstrated (Maeda *et al*, 1997; Peterson *et al*, 1997; Tanabe *et al*, 1997). Microglia have been shown to be chemotactic towards Aβ 25–35 (Maeda *et al*, 1997) and some β-chemokines such as MIP-1α, MIP-1β and MCP-1 (Peterson *et al*, 1997), and astrocytes have also been shown to migrate towards MIP-1α (Tanabe *et al*, 1997). Activated microglia also demonstrate increased phagocytosis, secretion of cytokines, activation of the respiratory burst and induction of nitric oxide synthase (NOS) (reviewed in Zielasek and Hartung, 1996). These responses could be directly or indirectly responsible for neuronal injury.

Chemotactic potential of Aβ

Aβ has been shown to stimulate the chemotactic response of monocytes and microglia (Maeda *et al*, 1997). There is even evidence suggesting that Aβ itself may behave as a chemokine (Lorton, 1997). Another interesting piece of information shows that serum amyloid A (although different from Aβ in its primary structure) has the ability to promote chemotaxis of human monocytes, and this effect was mediated through a pertussis toxin-sensitive signaling pathway, similar to the chemokine receptor signaling pathway (Badolato *et al*, 1995). It remains to be tested whether Aβ itself can bind to any chemokine receptor, and whether Aβ-induced cytokine release and chemotaxis is due to the same pertussis toxin-sensitive signaling pathway.

Induction of cytokines and chemokines by Aβ

Amyloid fragments have been shown to induce production of certain inflammatory cytokines, such as IL-1, IL-6, as well as some chemokines such as IL-8. In addition to the fact that cytokines in their own right may induce more cytokine/chemokine production, the presence of Aβ could greatly further potentiate their production. For example, Aβ 25–35, fibrillar Aβ 1–40 or Aβ 1–42 are able to induce IL-1β production from the activated monocyte cell line THP-1 (Lorton *et al*, 1996), and Aβ 25–35 is able to strongly induce IL-1β in astroglia (Del Bo *et al*, 1995). Aβ can also induce secretion of IL-6 and IL-8 from human astrocytoma cells (U-373 MG) and monocytes (Gitter *et al*, 1995; Meda *et al*, 1995).

Proinflammatory stimuli such as LPS, IL-1β or TNF-α can stimulate synthesis of IL-8 by microglial cells (Ehrlich *et al*, 1998). Moreover, in the presence of IL-1β, aged Aβ markedly potentiated (3–8-fold) production of IL-6 and IL-8 by astrocytoma cells (Gitter *et al*, 1995). Interestingly, Aβ-induced IL-1β release from monocytic cell line THP-1 is calcium-dependent and requires the activation of specific G-proteins, similar to chemokines receptor activation (Lorton, 1997).

Taken together, we believe that Aβ deposition may directly or indirectly induce cytokine/chemokine production which in turn may facilitate more Aβ deposition, and these cytokines and chemokines may exert detrimental effects on neuronal function.

Potential chemokine pathogenesis in AD and other CNS degenerative diseases

There has been very little information on the role of chemokines in the CNS. Since a number of these seven transmembrane surface molecules are constitutively present on neurons, it suggests that they have a physiological role in the CNS. Several general mechanisms may warrant further investigation:

Direct/indirect effects on neurons (growth promoting or toxicity)
Aside from the report that IL-8 has a neurotrophic effect on long term rat hippocampal neuronal culture (Araujo and Cotman, 1993), information regarding the direct effect of chemokines on neurons has been very scarce. Nevertheless, some cytokines such as IL-1β have been shown to increase neuronal vulnerability to Aβ toxicity (Fagarasan and Aisen, 1996), and IL-1β also selectively enhances neuronal damage caused by AMPA receptor activation in striatum (Lawrence *et al*, 1998). IL-6 has been shown to selectively enhance the calcium response of neurons to excitotoxic stimuli (Qiu *et al*, 1995). IL-6 has been shown to selectively enhance the calcium response of neurons to excitotoxic stimuli (Qiu *et al*, 1995). Moreover, cytokines by themselves can be neurotoxic: for example, IFN-γ plus IL-1β were shown to mediate neurotoxic effect in mixed neuronal/glia cell culture via an apoptotic mechanism (Hu *et al*, 1997; Lipton, 1996). It is conceivable that chronically increased expression of cytokines and chemokines in brain may play an important role in mediating neuronal toxicity in a direct and/or indirect fashion.

Chemokines may modulate APP processing or Aβ production
Both IL-1 and IL-6 induce neuronal APP mRNA expression significantly (Del Bo *et al*, 1995). IL-1β has been shown to increase the maturation of APP and cause enhanced processing of the full length APP isoforms and secretion of APP (Dash and Moore, 1995), which may presumably cause more Aβ production. Although there has been no report on the effect of chemokines on APP processing, since IL-1β has been shown to induce or potentiate the production of some chemokines such as IL-8 (Ehrlich *et al*, 1998; Gitter *et al*, 1995), it is possible that some chemokines may also play a role in modulating Aβ production.

Activation of kinase pathway
As all chemokine receptors are seven transmembrane G protein coupled molecules, we would expect their roles in cell signaling and protein phosphorylation through activation of kinase pathways. For the receptors found on neurons, their activation may result in the activation of MAP kinases, which in turn may well contribute to the hyperphosphorylation of tau in neurofibrillary tangles (Drewes *et al*, 1992; Hyman *et al*, 1994). In non-neuronal cell or cell lines, there has been evidence showing that binding of IL-8 or GRO-α with CXCR2 and binding of SDF-1 with CXCR4 resulted in MAP kinase activation (Jones *et al*, 1995; Popik *et al*, 1998). Clearly, this area can be a very important dimension of new research.

Effect on neuronal physiology
Pro-inflammatory cytokines such as IL-1β and IL-6 has recently been suggested to be responsible for the reduction of long term potentiation (LTP) in rodents (Bellinge, 1995; Murray and Lynch, 1998). Even in a situation when neuronal morphology is not obviously affected, chemokines may affect neuronal functions by affecting their LTP.

Conclusions and future directions

From the widespread expression of chemokine receptors in the normal CNS, and upregulation of some chemokines in resident CNS cells in AD, it seems likely that chemokines are playing a previously unexpected role in CNS physiology and pathophysiology.

From the many possible ways in which chemokines may affect CNS biology, one may conclude that we know little about the roles of this very important superfamily of inflammatory cytokines in the CNS. We hypothesize that chemokines, individually or in combination, may be important for normal communication among microglia, astrocytes and neurons and may help mediate activation of cells under stress conditions. In AD, Aβ deposits appear to serve as a focal point for chemokine upregulation, chemokines potentially play a role in primary or secondary pathological events that lead to neuronal death.

Many questions remain, but tools are now available to directly assess the role of specific chemokines in the CNS. Moreover, since chemokines can be detected by sensitive ELISAs, they may prove important in monitoring disease activity and potentially as a 'read out' for therapeutic efficacy of anti-inflammatory agents.

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