Journal of
Alzheimer's Disease & Parkinsonism

McLarnon, J Alzheimers Dis Parkinsonism 2016, 6:5
DOI: 10.4172/2161-0460.1000273

Mini Review Open Access

Chemokine Interleukin-8 (IL-8) in Alzheimer's and Other Neurodegenerative Diseases

James G McLarnon*

The University of British Columbia, Vancouver British Columbia, V6T1W3, Canada

Abstract

Interleukin -8 (IL-8), a member of the CXC chemokine family, is well-documented as an important chemotactic signaling factor for recruitment of neutrophils to sites of infection and damage. However in neurodegenerative disease such as Alzheimer's disease (AD), it is the resident macrophage cells, microglia, which are primary responding cells to brain insult such as deposition of amyloid β peptide. IL-8 exhibits an autocrine interaction with microglia by inducing a recruitment of the cells to specific sites of inflammation and subsequent increased production of the chemokine from activated cells. This positive feedback process thus has the capacity to amplify and sustain inflammatory response and brain neuroinflammation. The net result is that a localized and enhanced inflammatory response is induced by accumulating activated microglia at sites of inflammation serving to exacerbate inflammatory reactivity in AD brain. Importantly, under certain conditions the chemotaxis and subsequent activation of microglia may be deleterious to bystander cells including neurons. This review summarizes work from selected studies concerning the involvement and contributions of IL-8 mobilization from activated microglia to brain neuroinflammation as documented in the neurodegenerative diseases Alzheimer's disease (AD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and Parkinson's disease (PD).

Keywords: Chemotaxis; Interleukin-8; Activated microglia; Alzheimer's disease; Neurodegenerative disease; Neuroinflammation

Introduction

Chemokine responses constitute an early and integral response from microglial cells to changes in parenchymal microenvironment in brain. The spatial localization and activation of the resident microglia comprises an immune response to brain insults. In theory, the process to mobilize microglia serves as a feedback mechanism to preserve homeostatic conditions in brain. In reality, under certain conditions including ones associated with disease, the inflammatory microenvironment arising from accumulated and reactive microglia may be detrimental to the viability of bystander cells including neurons.

The chemokine IL-8 is well known as an inflammatory factor which induces a chemotactic response involving infiltration of neutrophils through the blood-brain barrier [1]. However, in various neurodegenerative diseases mobilization of neutrophils in brain parenchyma may be highly restricted due to minimal permeability of the cells through BBB (for one exemption see below for recent findings showing neutrophil extravasation into brain in an animal model of Alzheimer's disease (AD)). Thus in neurodegenerative disease mobilized microglia constitute the primary cells which mediate chemotactic responses to brain insults and alterations in brain microenvironment [2]. Importantly, activated microglias are a potent secretory source of IL-8 and express CXCR2 receptor for the chemokine providing a positive feedback mechanism for sustained amplification of inflammatory response [3].

As noted, although chemotactic response could confer neuroprotection, considerable evidence has been presented to suggest that microglial activation in neurodegenerative disease is associated with excessive localized brain inflammation and neurotoxicity [4,5]. Much data regarding the proinflammatory activity of IL-8 in neurodegenerative disease has come from studies on Alzheimer's disease (AD) brain and these results provide a focus for this review. One reason for the more comprehensive results in AD is due to the more frequent use of in vitro studies on IL-8 cellular interactions which are relatively lacking in other neurodegenerative diseases. In particular, as discussed below the patterns of IL-8 mobilization and signaling associated with stimulation of microglia in culture have been detailed under conditions relevant to AD brain.

This review also considers evidence for IL-8-mediated chemotactic response in other neurodegenerative conditions including Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and Parkinson's disease (PD).

IL-8 in Alzheimer's Disease (AD)

Evidence obtained from in vitro studies on cultured human microglia suggests that IL-8 may play a relatively important role in promoting pro-inflammatory reactivity in AD. In one study a comprehensive microarray analysis was carried out on expression of a broad spectrum of factors following amyloid-beta (Aβ) treatment of cortical human microglia [6]. In excess of 100 genes were tested following microglial exposure to a low dosage of peptide (full length Aβ1-42 at 2.5 μM) including a number of pro-inflammatory chemokines and cytokines. Overall, chemokine family members demonstrated the highest induced gene expression relative to other inflammatory mediators. Of these, the expression of IL-8 showed the largest extent of upregulation (in excess of 10-fold compared with unstimulated cells) of the genes analyzed.

The production of IL-8 has been examined in cultured microglia

***Corresponding author:** James G McLarnon, Department of Anesthesiology, Pharmacology and Therapeutics, The University of British Columbia, Vancouver British Columbia, V6T1W3, Canada, Tel: 1-604-2638813; E-mail: mclarnon@mail.ubc.ca

Received September 21, 2016; **Accepted** October 18, 2016; **Published** October 25, 2016

Citation: McLarnon JG (2016) Chemokine Interleukin-8 (IL-8) in Alzheimer's and Other Neurodegenerative Diseases. J Alzheimers Dis Parkinsonism 6: 273. doi: 10.4172/2161-0460.1000273

obtained post-mortem from AD and non-demented (ND) individuals [7]. Microglial cultured cells were isolated from tissue samples obtained from superior frontal gyrus for both groups. The adult cells were immunoreactive for a host of microglial markers including major histocompatibility complex class II marker. In addition, cultured cells demonstrated chemotactic responses in vitro induced by Aβ deposits. Cultured microglias were incubated with different levels of Aβ1-42 (range 10 nM to 10 μM). For both diseased and control human microglia, exposure to peptide increased levels of IL-8 in a dose-dependent manner. This work [7] also reported full length Aβ induced upregulation of other chemokines and proinflammatory cytokines indicating peptide stimulation of aged microglia was associated with a spectrum of inflammatory mediators.

The effects of incubation of human fetal microglia with full length Aβ peptide (5 μM Aβ1-42 for 8 h) was studied on expressions of IL-8 and a panel of pro-inflammatory cytokines cytokines IL-6, IL -1β and TNF-α [8]. In addition, the effects of adding IL-8 together with Aβ1-42 on expression of the inflammatory mediators were examined. Application of Aβ1-42 alone was found to significantly increase the expressions of IL-8 and the pro -inflammatory cytokines relative to controls (unstimulated cells and cells receiving reverse Aβ peptide (inactive form Aβ42-1) treatment). However, if IL-8 was applied together with Aβ1-42 the expression of IL-8 and the pro-inflammatory cytokines was further enhanced suggesting that the chemokine amplified inflammatory reactivity induced by peptide. This work also reported the production of the cytokines was significantly enhanced with IL-8 treatment of Aβ1-42–stimulated human microglia compared with peptide application alone. Interestingly, IL-8 priming of human microglia had no effect to alter levels of the anti-inflammatory cytokines IL-10 and TGFβ1.

The neurotoxic effects of IL-8 have been directly examined with chemokine treatment of neuronal cultures [9]. IL-8 application was found to induce neuronal death which was associated with changes in pro-apoptotic proteins and inflammatory mediators. In the latter case increased levels of the matrix metallo-proteinases MMP-2 and MMP-9 were implicated in neurotoxicity.

Several studies have examined levels of IL-8 in AD and control individuals. Cerebrospinal fluid levels of IL-8 were found significantly elevated in patients with mild cognitive impairment (MCI) and individuals diagnosed with AD compared with age -matched controls [10]. The increased IL-8 in MCI individuals was noteworthy in that MCI may serve as a progression to AD; indeed one-half of MCI patients developed AD within 3 years [10]. Interestingly, MCI individuals showed no changes in the intactness of blood-brain barrier (BBB) as demonstrated by permeability of the barrier to albumin and immunoglobulin.

A number of cytokines and chemokines have been analyzed in brain tissue extracts from genetic forms of AD [11]. The results showed that levels of IL-8 and monocyte chemo-attractant protein 1 (MCP-1) were significantly increased in brain tissue derived from AD patients relative to controls. A more recent work has also reported that levels of IL-8 were considerably elevated in AD patients compared to non-demented controls [12]. Importantly, the increased levels of IL-8 showed a correlation with a reduced performance on cell cognition tasks.

At present, pharmacological testing for modulation of IL-8 signaling in AD animal models has not been examined in detail. In one study, pharmacological inhibition of CXCR2 receptor was examined in vivo following Aβ1-42 injection into rat hippocampus [13]. This animal model showed elevated expression of IL-8 and CXCR2 in peptide-injected rats compared to animals receiving vehicle or reverse peptide. Blockade of CXCR2 was effective in reducing microgliosis and was found to be neuroprotective. It was suggested that the neuroprotection conferred from block of IL-8 receptor could be due to a reduced microglial production of oxidative species.

Recent work has raised the interesting possibility that neutrophil migration may be involved in inflammatory response in AD brain. Using transgenic AD models, the extravasation of neutrophils into brain parenchyma to areas of amyloid plaques has been demonstrated [14,15]. At this time it is not known how IL-8 signaling contributes to the patterns of neutrophil infiltration in the AD animal models.

IL-8 in other Neurodegenerative Diseases

Huntington's disease (HD)

Inflammation in HD is characterized by microglial activation and migration of cells in response to abnormal mutant protein [16]. The use of positron emission tomography (PET) has shown activation of microglia as an early event in the pathology of HD [17]. Microglial activation also demonstrated both temporal and spatial correlations with neuronal damage and dysfunction. Importantly, microglial activation and brain inflammation was associated with the severity in the progression of the disease [18]. Increased levels of IL-8 have been reported in HD brain [19] and in post-mortem samples from HD patients [20]. In the latter work, the chemokine was found elevated in cortex and cerebellum in addition to striatum. A transgenic porcine model, using fragments of human huntingtin protein, has been used as an animal model of HD. Elevated levels of IL-8 (and IL-1β) were found in transgenic animals [21] with activated microglia producing the increased levels of the chemokine. Since IL-8 was increased in serum, it was suggested that the chemokine could have utility as a biomarker for immunopathology in HD [22]. At present, the effects of pharmacological inhibition of IL-8 signaling pathways has not been reported in animal models of HD.

Amyotrophic lateral sclerosis (ALS)

Levels of IL-8 (and MCP-1) were considerably increased in cerebrospinal fluid (CSF) and serum from ALS patients compared to controls [23]. The expressions of both chemokines were higher in CSF relative to serum. The authors suggested that the elevation in IL-8 was mediated by activated microglia leading to a pro-inflammatory cascade in ALS brain. Levels of cytokines and chemokines have been measured in peripheral blood samples taken from ALS patients and controls [24]. A number of inflammatory mediators including IL-8 exhibited significant increases in blood from ALS individuals. Importantly, levels of IL-8 were found to be correlated with progression of the disease. The findings from this work suggested levels of IL-8 could serve as a systematic biomarker for severity of disease. Analysis of lumbar puncture of CSF samples from ALS and controls has also identified IL-8 as a candidate biomarker for progression of the disease [25]. In another study IL-8 levels in CSF were compared between sporadic ALS patients and individuals with non-inflammatory disease [26]. Amounts of the chemokine were found to be significantly elevated in the ALS patients relative to controls and considerably higher in males compared to females. The results from this work suggested a prominent role for IL-8 in mediating neuroinflammation in ALS brain.

Parkinson's disease (PD)

A number of reviews have provided evidence for roles of neuroinflammation in the pathogenesis of PD [27,28]. Activated microglias in the substantia nigra of PD patients have been implicated as cellular sources of inflammatory reactivity. At present, few studies have examined levels of IL-8 in PD brain. In one work serum levels of the chemokine were measured in individuals diagnosed with idiopathic PD and in controls [29]. The results showed IL-8 concentrations were doubled in diseased brain compared with control; this difference in levels of the chemokine was significant. However, a contrary finding has recently been reported. Levels of IL-8 and cytokine TNF-α were found reduced in serum from Indian PD patients relative to controls [30]. Overall, despite the relevance of neuroinflammation in the pathophysiology of PD, data is lacking on roles of IL-8 and other chemotactic factors in the progression of the disease.

Conclusion

Neuroinflammation is a critical component in the pathogenesis of neurodegenerative diseases. Evidence suggests that activated microglia serve as a primary source for a host of inflammatory mediators which in assemblage can lead to neurotoxicity in inflamed brain. Mobilization of chemokine factors is a response to changes in brain homeostatic conditions leading to localized accumulation of reactive microglia at target sites. In particular, levels of the chemokine IL -8 are significantly elevated in neurodegenerative disease. The putative roles of IL-8-mediated chemotactic responses in neuroinflammation have been most extensively examined in AD brain. Evidence from in vitro studies relevant to AD, use of AD animal models and analysis of IL-8 levels in human brain suggest that resident brain microglia are the primary cell both responding to, and producing, the chemokine. Thus autocrine responses to brain insults from activated microglia include increased levels of IL -8 which contribute to a positive feedback process amplifying and sustaining inflammatory reactivity in AD brain. Localized and chronic microglial activation in response to Aβ deposits is associated with sustained cellular production of a milieu of inflammatory mediators including pro-inflammatory cytokines, reactive oxygen species and matrix metalloproteinases which in assemblage can cause abnormalities to blood vessels and neurotoxicity. Pharmacological modulation of IL-8 signaling pathways, including inhibition of CXCR2 receptor in microglia, is suggested as a clinical strategy to reduce chemotactic-dependent inflammation and provide neuroprotection in neurodegenerative disease.

Acknowledgement

Grants from Pacific Alzheimer's Research Foundation, Canadian Alzheimer's Society and Canadian Institute for Health Research have provided support for research on AD carried out in my laboratory. Many individuals have contributed to the success of in vivo and in vitro studies relevant to AD with special thanks to Jae K Ryu and Hyun B Choi for their expertise.

References

1. Hammond ME, Lapointe GR, Feucht PH, Hilt S, Gallegos CA, et al. (1995) IL-8 induces neutrophil chemotaxis predominantly via Type 1 IL-8 receptor. J Immunol 155: 1428-1433.
2. Kreutzberg GW (1996) Microglia: A sensor for pathological events in the CNS. Trends Neurosci 19: 312-318.
3. McLarnon JG (2012) Microglial chemotactic signaling factors in Alzheimer's disease. Am J Neurodegener Dis 1: 199-204.
4. Dheen ST, Kaur C, Ling EA (2007) Microglial activation and its implication in the brain diseases. Curr Med Chem 14: 1189-1197.
5. Kettenmann H, Hanisch UK, Noda M, Verkhratsky A (2011) Physiology of microglia. Physiol Rev 91: 461-553.
6. Walker DG, Lue LF, Beach TG (2001) Gene expression profiling of amyloid beta peptide-stimulated human post-mortem brain microglia. Neurobiol Aging 22: 957-966.
7. Lue LF, Rydel R, Brigham EF, Yang LB, Hampel H, et al. (2001) Inflammatory repertoire of Alzheimer's disease and non-demented elderly microglia *in vitro*. Glia 35: 72-79.
8. Franciosi S, Choi HB, Kim SU, McLarnon JG (2005) IL-8 enhancement of amyloid-beta (Aβ1-42)-induced expression and production of pro-inflammatory cytokines and COX-2 in cultured human microglia. J Neuroimmunol 159: 66-74.
9. Thirumangalakudi L, Rao HV, Grammas P (2007) IL-8 induces expression of matrix metalloproteinases, cell cycle and pro-apoptotic proteins and cell death in cultured neurons. J Alz Dis 11: 305-311.
10. Galimberti D, Schoonerboom N, Scheltens P, Fenoglio C, Bouwman F, et al (2006) Intrathecal chemokine synthesis in mild cognitive impairment and Alzheimer's disease. Arch Neurol 63: 538-543.
11. Sokolova A, Hill MD, Rahimi F, Warden LA, Halliday GM, et al. (2009) Monocyte chemo-attractant protein-1 plays a dominant role in the chronic inflammation observed in Alzheimer's disease. Brain Pathol 19: 392-398.
12. Alsadony MA, Shehata HH, Mohamad MI, Mahfouz RG (2013) Histone deacetlyases enzyme, copper and IL-8 levels in patients with AD. Am J Alzheimers Dis Other Demen 28: 54-61.
13. Ryu JK, Cho T, Choi HB, Jantaratnotai N, McLarnon JG (2015) Pharmacological antagonism of interleukin-8 receptor CXCR2 inhibits inflammatory reactivity and is neuroprotective in an animal model of Alzheimer's disease. J Neuroinflamm 12: 144.
14. Baik SH, Cha MY, Hyun YM, Cho H, Hamza B, et al. (2014) Migration of neutrophils targeting amyloid plaques in Alzheimer's disease mouse model. Neurobiol Aging 35: 1286-1292.
15. Zenaro E, Pietroniavo E, Della Bianco V, Piacentino G, Marongia L, et al. (2015) Neutrophils promote Alzheimer's disease-like pathology and cognitive decline via LFA-1 integrin. Nature Med 21: 880-886.
16. Ellrichmann G, Reick C, Saft C, Linker RA (2013) The role of the immune system in Huntington's disease. Clin Dev Immunol: 541219.
17. Tai YF, Pavese N, Gerhard A, Tabrizi SJ, Barker RA, et al. (2007) Imaging microglial activation in Huntington's disease. Brain Res Bull 72: 148-151.
18. Pavese N, Gerhard A, Tai YF, Ho AK, Turkheimer F, et al. (2006) Microglial activation correlates with severity in Huntington disease: A clinical and PET study. Neurology 66: 1638-1643.
19. Björkqvist M, Wild EJ, Thiele J, Silvestroni A, Andre R, et al (2008) A novel pathogenic pathway of immune activation detectable before clinical onset in Huntington's disease. J Exp Med 205: 1869-1877.
20. Silvestroni A, Faull RL, Strand AD, Moller T (2009) Distinct neuroinflammatory profile in post-mortem human Huntington's disease. NeuroReport 20: 1098-1103.
21. Valekova I, Jarkovska K, Kotrcova E, Bucci J, Ellederova Z, et al. (2016) Revelation of the IFNα, IL-10, IL-8 and IL-1β as promising biomarkers reflecting immune-pathological mechanisms in porcine Huntington's disease model. J Neuroimmunol 293: 71-81.
22. Kovarova H, Jarkovska K, Valekova I, Kotrcova E, Juhas S, et al. (2016) Emerging roles of IFNα, IL-10, IL-1 and IL-8 in central nervous inflammation and immune response imbalance in transgenic porcine model of neurodegenerative Huntington's disease. J Immunol 196 (1 supplement).
23. Kuhle J, Lindberg RL, Regeniter A, Mehling M, Steck AJ, et al. (2009) Increased levels of inflammatory chemokines in amyotrophic lateral sclerosis. Eur J Neurol 16: 771-774.
24. Ehrhart J, Smith AJ, Kuzmin-Nichols N, Zesiewicz TA, Jahan I, et al. (2015) Humoral factors in ALS patients during disease progression. J Neuroinflamm 12: 127.
25. Mitchell RM, Freenan WM, Randazzo WT, Stephens HE, Beard JL, et al. (2009) A CSF biomarker panel for identification of patients with amyotrophic lateral sclerosis. Neurology 72: 14-19.
26. Mennini T, Giordano L, Mengozzi M, Glezzi P, Tonelli R, et al. (2009) Increased IL-8 levels in the cerebrospinal fluid of patients with amyotrophic lateral sclerosis. Eur J Inflammation 7: 39-44.

27. Hirsch EC, Vyas S, Hunot S (2012) Neuroinflammation in Parkinson's disease. Parkinsonism Relat Disord 18 Suppl 1: S210-S212.

28. Tufekci KU, Meuwissen R, Genc S, Genc K (2012) Inflammation in Parkinson's disease. Adv Protein Chem Struct Biol 88: 69-132.

29. Szlufik S, Koziorowski D, Tomasiuk R, Friedman A (2012) Serum level of inflammatory factors in patients with Parkinson's disease. Movement Disorders 27: 17-21.

30. Gupta V, Garg RK, Khattri S (2016) Levels of IL-8 and TNF-α decrease in Parkinson's disease. Neurol Res 38: 98-102.