Receptors for Interleukins and Tumor Necrosis Factor are Important in Assessing their Roles in CNS Disorders

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Abstract

The immune-to-brain communication is still in its infancy but there is a great deal of data to suggest its importance in several central nervous system (CNS) disorders. There are three cytokines, interleukin-1 (IL-1), IL-6 and tumor necrosis factor alpha (TNFα), which have emerged to have a major role in the CNS and in different CNS disorders. The majority of the published work to date has been on examining changes in the levels of these proteins in the CNS with inflammation; but recent work from our laboratory has shown the receptors for these cytokines may also be an important factor in neuroinflammation mediated CNS disorders, because these receptors are solely localized to neurons and are modified when their ligands levels are elevated. For neuroinflammation and the increase in cytokine levels (either by glia or neurons) to influence neurons and consequently affect the development of CNS disorders, the location of these cytokines receptors on neuronal populations may be the key.

Keywords: Alzheimer’s disease; CNS disorders; Neuroinflammation

Introduction

Over recent year’s inflammation, specifically neuroinflammation, has received a great deal of attention especially in reference to central nervous system (CNS) disorders like Alzheimer’s disease (AD), Parkinson’s disease (PD), depression, and traumatic brain injury (TBI) [1-5]. It has become apparent that an immune response can regulate the CNS. This connection has been termed the immune-to-brain communication [6-9]. Understanding this connection between the immune system and CNS function is in its infancy. However, it is clear that an immune response by the peripheral administration of the inflammatory agent, lipopolysaccharide (LPS), can result in excitation in specific brain regions by detecting an increase in the expression of the neuronal immediate early gene Fos [10-16]. The immune response with the involvement of a neuroinflammatory response is complex and involves multiple proteins with a complex time course. Research has shown cytokines play an important role in mediating the effects of LPS, with specific interest in interleukin (IL)-1, IL-6 and tumor necrosis factor alpha (TNFα). Stimulation of Fos can be mediated by IL-1β (a subtype of IL-1) [17-19] and IL-6 [15,19] supporting the immune-to-brain communication. At the present time, the link between the immune system to CNS disorders appears to be strongest with depression and AD.

The behavior observed following LPS induced “sickness” (cytokine-induced sickness behavior) is similar to depression, such as withdrawal from physical and social environment, pain, malaise, and anhedonia [20-23]. The cytokines involved in mediating these behaviors are mainly IL-1β and TNFα, with IL-6 having some role [20,24,25]. In addition, administration of LPS or these cytokines ultimately results in depressive-like behavior in two common animals’ models of depression: the forced swim test and the tail suspension test [20].

Cytokines are proposed to mediate depression because administration of LPS, IL-1 or IL-6 can enhance the hypothalamic-pituitary-adrenal (HPA) axis, a major component in the development of depression; and LPS, IL-1 or IL-6 alters levels of norepinephrine (NE) and serotonin (5HT), two neurotransmitters systems mediating depression [21,26,27].

Neuroinflammation’s role in the progression of AD has been growing with the identification of TREM2 and CD33 variants, two markers indicating the presence of neuroinflammation, as major risk factors in the development of AD [28-32]. The role of neuroinflammation in AD is also apparent from epidemiological, retrospective studies that demonstrated nonsteroidal anti-inflammatory drugs to reduce the incidence of AD [33-36]. Some studies have detected elevated IL-1, IL-6 and TNFα protein in postmortem AD tissue in neuronal and non-neuronal cells [35,37], although there is no change in mRNA levels [38,39]. There is a relationship between inflammation and the generation of cytokines and the presence of β-amyloid (Aβ), a classic neuropsychological marker of AD [40,41]. Elevated levels of IL-1, IL-6 and TNFα the activity of neurons (long-term potentiation), specifically in the hippocampus, thereby impairing cognition/memory [42-48].

All the information discussed above address changes mainly in the protein or mRNA (mainly determined by PCR) levels of cytokines in specific regions of the CNS and the resultant effect on the functioning brain. However, for these cytokines to produce their effect it is important to determine where the receptors for the cytokines are localized and how they respond to the changing protein levels. Work recently published from my laboratory examined IL-6, 7 and 10 mRNA in the brain following multiple injections of LPS, plus the receptors for IL-6 and -7 (IL-6R and IL-7R) [49]. Our work demonstrated that IL-6, -6R, -7, -7R and -10 mRNA, under basal conditions, are localized to neurons in specific brain regions (cortex, hippocampus and cerebellum); indicating that LPS-induced inflammation can have...
direct effect on CNS neurons. Following administration of multiple LPS injections, there was a significant increase in IL-6 mRNA in the spleen and in the brain of 5 of the 9 animals. The increase in IL-6 mRNA in the brain due to LPS administration was observed only in non-neuronal cells throughout the brain, the neuronal expression remained unchanged. Interestingly, the receptor for IL-6, IL-6R mRNA was not observed in the non-neuronal population that expressed IL-6 mRNA following LPS. IL-6R mRNA was significantly elevated in all the brain regions that exhibited neuronal expression, except for the cerebellum ONLY in the animals that exhibited non-neuronal IL-6 mRNA in response to LPS, indicating that a non-neuronal response to LPS can directly (or indirectly) affect neurons which express the receptor for IL-6 [49]. In the hippocampus however, IL-6R mRNA was elevated in all the animals that were administered LPS, even the LPS treated animals that did not exhibit IL-6 non-neuronal expression, suggesting the hippocampus to be sensitive to LPS. This data supports the relationship between inflammation due to LPS and depression that was discussed above. Also, the Szoł et al., study indicates that the peripheral response of IL-6R mRNA following multiple LPS injections was different from the central response; in the spleen IL-6 mRNA was reduced in response to elevated IL-6 mRNA, but in the brain IL-6R mRNA was elevated in most but not all brain regions in response to elevated IL-6 mRNA expressed [49].

Similarly, a change in TNFα, no matter if TNFα is generated in non-neuronal or neuronal cells in the brain, will directly affect neuronal cells because TNFα receptor 1 mRNA is solely localized to neurons [6]. The same applies for IL-1, there are two variants of IL-1 (α and β), but both of these variants of IL-1 bind to the IL-1 receptor (IL-1R), which is expressed in neurons, particularly in the hippocampus [50,51]. Little is known about alterations in these receptors under different conditions including inflammation.

As our knowledge concerning the role of neuroinflammation in different CNS disorders is increasing, and that specific cytokines like IL-1, IL-6 and TNFα are extremely important in mediating these changes in behavior or neuronal activity; however, it is apparent that their receptors are also extremely important in mediating their effects and producing the neuronal alterations that are associated with these CND disorders.

References
1. Stoll G, Jander S, Schroeter M (2000) Cytokines in CNS disorders: neurotoxicity versus neuroprotection. J Neural Transm Supp 59:81-89.
2. Vitkovic L, Bockaert J, Jacque C (2000) "Inflammatory" cytokines: neuromodulators in normal brain? J Neurochem 74: 457-471.
3. Strie K, Zhou JH, Shen WH, Broussaud SR, Johnson RW, et al. (2001) Interleukin-10 in the brain. Crit Rev Immunol 21: 427-449.
4. Orr CE, Rowe DB, Halliday GM (2002) An inflammatory review of Parkinson's disease. Prog Neurobiol 68: 325-340.
5. McCusker RH, Kelley KW (2013) Immune-neural connections: how the immune system's response to infectious agents influences behavior. J Exp Biol 216: 84-98.
6. Williamson L, Bilbo SD (2013) Chemokines and the hippocampus: A new perspective on hippocampal plasticity and vulnerability. Brain Beh Immun 30:186-194.
7. Quan N (2014) In-depth conversation: spectrum and kinetics of neuroimmune afferent pathways. Brain Behav Immun 40: 1-8.
8. Rummel C (2016) Inflammatory transgene factors as activation markers and functional readouts in immune-to-brain communication. Brain Beh Immun 54:1-14.
9. Belevych N, Buchanan K, Chen Q, Bailey M, Quan N (2010) Location-specific activation of the paraventricular nucleus of the hypothalamus by localized inflammation. Brain Beh Immun 24:1137-1147.
10. Brady LS, Lynn AB, Herkenham M, Gottesfeld J (1994) Systemic interleukin-1 induces early and late patterns of c-fos mRNA expression in the brain. J Neurosci 14:4951-4964.
11. Elmhquist JK, Ackermann MR, Register KB, Rimler RB, Ross LR, Jacobson CD (1993) Induction of Fos-like immunoreactivity in the rat brain following Pasteurella multocida endotoxin administration. Endocrinology 133: 3054-3057.
12. Freino F, Moreau M, O'Connor J, Lawson M, Micon C, et al. (2007) Lipopolysaccharide induces delayed FosB/DeltaFosB immunostaining within the mouse extended amygdala, hippocampus and hypothalamus, that parallel the expression of depressive-like behavior. Psychoneuroendocrinology 32:516-531.
13. Kurusawa N, Shimiizu K, Seki K (2016) The development of depression-like behavior is consolidated by IL-6-induced activation of locus coeruleus neurons and IL-1β-induced elevated leptin levels in mice. Psychopharmacology 233:1725-1737.
14. Sagar SM, Price KJ, Kasting NW, Sharp FR (1995) Anatomic patterns of FOS immunostaining in rat brain following systemic endotoxin administration. Brain Res Bull 36:381-392.
15. Chan RRW, Brown ER, Ericsson A, Kovacs KJ, Sawchenko PE (1993) A comparison of two immediate-early genes, c-fos and NGFI-B as markers for functional activation in stress-related neuroendocrine circuitry. J Neurosci 13:5126-5138.
16. Ericsson A, Kovacs KJ, Sawchenko PE (1994) A functional anatomical analysis of central pathways subserving the effects of interleukin-1 on stress-related neuroendocrine neurons. J Neurosci 14: 897-913.
17. Niimi M, Sato M, Wada Y, Takahara J, Kawamishi K (1997) Effect of central and continuous intravenous injection of interleukin-1 beta on c-fos expression in the brain: involvement of prostaglandins. Neuroimmunomodulation 2-3:87-92.
18. Niimi M, Wada Y, Sato M, Takahara J, Kawamishi K (1997) Effect of continuous intravenous injection of interleukin-6 and pretreatment with cyclooxygenase inhibitor on brain c-fos expression in the rat. Neuroendoecrinology 66: 47-53.
19. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW (2008) From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 9: 46-56.
20. Dunn AJ, Swiergiel AH, de Beaurepaire R (2005) Cytokines as mediators of depression: what can we learn from animal studies? Neurosci Biobehav Rev 29: 891-909.
21. Schiepers Ol, Wichers MC, Maes M (2005) Cytokines and major depression. Prog Neuropsychopharmacol Biol Psychiatry 29: 201-217.
22. Smith RS (1991) The macrophage theory of depression. Med Hypotheses 35: 298-306.
23. Yimira R, Weidenfeld J, Pollak Y, Morag M, Morag A, et al. (1999) Cytokines, "depression due to a general medical condition," and antidepressant drugs. Adv Exp Med Biol 461:283-316.
24. O'Brien SM, Scott IV, Dinan TG (2004) Cytokines: abnormalities in major depression and implications for pharmacological treatment. Hum Psychopharmacol Clin Exp 19:397-403.
25. Schiepers Ol, Wichers MC, Maes M (2005) Cytokines and major depression. Prog Neuropsychopharmacol Biol Psychiatry 29: 201-217.
26. Guerreiro R, Wojiotas A, Bras J, Carraquillo M, Rogaeva E, et al. (2013) TREM2 variants in Alzheimer's disease. N Engl J Med 368: 117-127.
27. Jonsson T, Stefansson H, Steinberg S, Jonsdottir I, Jonsson PV, et al. (2013) Variant of TREM2 associated with the risk of Alzheimer's disease. N Engl J Med 368: 107-116.
28. Naj AC, Jun G, Beecham GW, Wang LS, Vardarajan BN, et al. (2011) Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. Nat Genet 43: 436-441.
29. Nazem A, Sankowski R, Bacher M, Al-Abed Y (2015) Rodent models of neuroinflammation for Alzheimer's disease. J Neuroinflammation 12: 74.
30. Wyss-Coray T, Rogers J (2012) Inflammation in Alzheimer disease—a brief review of the basic science and clinical literature. Cold Spring Harb Perspect Med 2: a006346.
31. Andersen K, Launer LJ, Ott A, Hoes AW, Breteler MM, et al. (1995) Do nonsteroidal anti-inflammatory drugs decrease the risk for Alzheimer’s disease? The Rotterdam Study. Neurology 45: 1441-1445.
32. Klegeris A, McGeer PL (2005) Non-steroidal anti-inflammatory drugs (NSAIDs) and other anti-inflammatory agents in the treatment of neurodegenerative disease. Curr Alzheimer Res 2:353-365.
33. McGeer PL, McGeer E, Rogers J, Sibley J (1990) Anti-inflammatory drugs and Alzheimer disease. Lancet 335: 1037.
34. Stewart WF, Kawas C, Corrada M, Metter EJ (1997) Risk of Alzheimer’s disease and duration of NSAID use. Neurology 48: 626-632.
35. McGeer PL, Sibley J (2005) Sparing of age-related macular degeneration in rheumatoid arthritis. Neurobiol Aging 26: 683-695.
36. Sokolova A, Hill MD, Rahimi F, Warden LA, Halliday GM, et al. (2008) Monocyte chemoattractant protein-1 plays a dominant role in the chronic inflammation observed in Alzheimer's disease. Brain Pathol 19:392-398.
37. Loring JF, Wen X, Lee JM, Seilhamer J, Somogyi R (2001) A gene expression profile of Alzheimer’s disease. DNA Cell Biol 20: 115-124.
38. Ferretti MT, Cuello AC (2011) Does a pro-inflammatory process precede Alzheimer's disease and mild cognitive impairment? Curr Alzheimer Res 8:164-174.
39. Ferretti MT, Bruno MA, Ducatenzeiler A, Klein WL, Cuello AC (2012) Intracellular Aβ-oligomers and early inflammation in a model of Alzheimer's disease. Neurobiol Aging 33: 1329-1342.
40. McGeer EG, McGeer PL (2010) Neuroinflammation in Alzheimer’s disease and mild cognitive impairment: a field in its infancy. J Alzheimers Dis 19: 355-361.
41. Bellinger FP, Madamba SG, Campbell IL, Siggins GR (1995) Reduced long-term potentiation in the dentate gyrus of transgenic mice with cerebral overexpression of interleukin-6. Neurosci Lett 198: 95-98.
42. Cunningham AL, Murray CA, O'Neil LAJ, Lynch MA, O’Connor JJ (1996) Interleukin-1β (IL-1β) and tumor necrosis factor (TNF) inhibit long-term potentiation in the dentate gyrus in vitro. Neurosci Lett 203:17-20.
43. Deak T (2007) From hippocampus to dorsal horn: the pervasive impact of IL-1 on learning and memory spans the length of the neuroaxis. Brain Behav Immun 21: 746-747.
44. Del Rey A, Balschun D, Wetzel W, Randolf A, Besedovsky HO (2013) A cytokine network involving brain-borne IL-1β, IL-1ra, IL-18, IL-6 and TNFα operates during long-term potentiation and learning. Brain Behav Immun 33:15-23.
45. Kahl MS, Kranjac D, Alonzo CA, Haase JH, Cedillos RO, et al. (2012) Prolonged elevation in hippocampal Aβ and cognitive deficits following repeated endotoxin exposure in the mouse. Behav Brain Res 229:176-184.
46. Katsuki H, Nakai S, Hirai Y, Akai K, Kiso Y, et al. (1990) Interleukin-1 beta inhibits long-term potentiation in the CA3 region of mouse hippocampal slices. Eur J Pharmacol 181: 323-326.
47. Vereker E, O'Donnell E, Lynch A, Kelly A, Nolan Y, et al. (2001) Evidence that interleukin-1β and reactive oxygen species production play a pivotal role in stress-induced impairment of LTP in the rat dentate gyrus. Eur J Neurosci 14:1809-1819.
48. Szot P, Franklin A, Figlewicz DP, Petru Beuca T, Bullock K, et al. (2017) Multiple lipopolysacharride (LPS) injections alter interleukin 6 (IL-6), IL-7, IL-10 and IL-6 and IL-7 receptor mRNA in CNS and spleen. Neuroscience 335:9-21.
49. Ban E, Milon G, Prudhomme N, Fillion G, Haour F (1991) Receptors for interleukin-1 (a and b) in mouse brain: mapping and neuronal localization in hippocampus. Neuroscience 43:21-30.
50. Cunningham ET Jr, Wada E, Carter DB, Tracey DE, Battey JF; et al. (1992) In situ histochemical localization of type I interleukin-1 receptor messenger RNA in the central nervous system, pituitary, and adrenal gland of the mouse. J Neurosci 12: 1101-1114.