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# 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 varients, 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 neuropathological 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 Szot 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-6R 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.

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