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Review

The role of the innate immune system in psychiatric disorders

Kenneth A. Jones *, Christian Thomsen [1]

Lundbeck Research USA, Neuroinflammation Drug Biology Unit 215 College Road, Paramus, NJ 07652, USA

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ABSTRACT

There is by now substantial clinical evidence for an association between specific mood disorders and altered immune function. More recently, a number of hypotheses have been forwarded to explain how components of the innate immune system can regulate brain function at the cellular and systems levels and how these may underlie the pathology of disorders such as depression, PTSD and bipolar disorder. In this review we draw reference to biochemical, cellular and animal disease models, as well as clinical observations to elucidate the role of the innate immune system in psychiatric disorders. Proinflammatory cytokines, such as IL-1β IL-6 and TNFα, which feature prominently in the immune response to pathogen in the periphery, have unique and specific actions on neurons and circuits within the central nervous system. Effects of these signaling molecules on neurotransmission, memory, and glucocorticoid function, as well as animal behaviors such as social withdrawal and fear conditioning relevant to psychiatric disorders are elucidated. Finally, we highlight future directions for studies, including the use of peripheral biomarkers, relevant for developing new therapeutic approaches for treating psychiatric illnesses. This article is part of Special Issue entitled 'neuroinflammation in neurodegeneration and neurodysfunction'.

Contents

Abbreviations: PTSD, post-traumatic stress disorder; IL-1β, interleukin-1beta; IL-6, interleukin-6; TNFα, tumor necrosis factor alpha; IFNα, interferon alpha; TLR, toll-like receptor; LPS, lipopolysaccharide; CRP, C-reactive protein; NFκβ, nuclear factor kappa beta; HPA, hypothalamic-pituitary axis; MDD, major depressive disorder; SSRI, selective serotonin reuptake inhibitor; CNS, central nervous system; MC4, melanocortin receptor 4; BDNF, brain derived neurotrophic factor; IDO, indoleamine 2,3-dioxygenase; NMDA, N-methyl-D-aspartate; HPA, hypothalamic pituitary axis; PBMC, peripheral blood mononuclear cells; HDAC, histone deacetylase; TREM-1, triggering receptor expressed on myeloid cells-1.

* Corresponding author at: Forest Research Institute, Harborside Financial Center, Plaza V, Jersey City, NJ 07311, USA. Fax: +1 201 427 8200.
E-mail address: ken.jones@frx.com (K.A. Jones).
[1] Present address: H. Lundbeck A/S, Ottiliavej 9, 2500 Valby, Denmark.

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Introduction

Depression and other mood disorders are among the most common diseases worldwide and are associated with a tremendous burden to the people affected as well as high rates of suicide. Despite the fact that there has been substantial effort to develop new drugs and that modern, selective antidepressants represent significant therapeutic progress, there are still considerable unmet needs. To address those needs particularly related to therapeutic non-responders a rational approach would be to search for novel mechanisms of action. Most antidepressants function by modulating serotonergic and/or noradrenergic neurotransmission, and while this is an important mechanism therapeutically, its role in disease etiology is yet unclear.

As a result, the identification of additional pathophysiological changes associated with depressive disorders is an important goal. Growing evidence points to a significant role for elements of the immune system to dramatically influence brain function in ways that are relevant to facets of psychiatric and neurological diseases.

This review will not attempt to cover all psychiatric disorders but instead will focus on those, particularly depression, post-traumatic stress disorder, and bipolar disorder that appear to share manifestations of chronic maladaptive changes in central nervous system function by elements of the innate immune system ("neuroinflammation"). We will draw reference to biochemical, cellular, and animal disease models, as well as clinical observations to elucidate the role of the innate immune system in psychiatric disorders. Finally, we will point out potential new directions for future studies relevant for developing therapeutic approaches for treating psychiatric illnesses.

Cytokines and cellular mediators of neuroinflammation—peripheral/central interactions

There is a growing appreciation of the profound interrelationship between the central nervous system (CNS) and immune systems, and this is perhaps best exemplified within the context of the innate immune system. In contrast to the more highly evolved adaptive immune system which is able to recognize and remember specific pathogens, and to mount stronger attacks each time the pathogen is encountered, the innate immune system is genetically encoded to stereotypically respond to specific signals derived from pathogens or other danger signals. These signals derive from common pathogens, such as bacterial cell wall components (lipopolysaccharides, LPS), and components from tissue damage, such as ATP, uric acid, and heat shock proteins. The recently discovered family of toll-like receptors (TLRs — Gay and Keith, 1991) binds some of these components and initiates a signal transduction cascade which results in the release of pro-inflammatory cytokines and chemokines in order to neutralize pathogen and initiate tissue repair.

Of the inflammatory mediators, the most well-studied are the cytokines interleukin 1beta (IL-1β, interleukin 6 (IL-6) and tumor necrosis factor alpha (TNFα). All of these are released by macrophages, other peripheral immune cells, and microglia, as part of the early acute phase reaction which provides defense against invading pathogens. These cytokines are robustly stimulated by molecules associated with pathogens, such as LPS and viral nucleic acids, that bind to TLRs and activate the NFκβ pathway (Fig 1). IL-1β is considered the "master cytokine" because its release is an early event that triggers release of others components of the acute phase response, including IL-6 (Dinarello, 2009). The production, maturation and release of IL-1β are controlled by dual pathways that involve TLRs, which activate transcription, and the interaction of the P2X7 receptor, pannexin-1 and caspase-1, which process the mature form of IL-1β prior to release (Abbracchio et al., 2009; Di Virgilio, 2007). These cytokines also serve to signal tissue injury, both locally, in the case of microglia, and systemically, in the case of IL-6. Major sources of IL-6 are liver and muscle as a result of hepatotoxicity and muscle damage, respectively. Strenuous exercise also elevates IL-6, and as a result it can show great variability as a plasma biomarker. TNFα, together with IL-1β and IL-6 have well described actions on the hypothalamus including induction of fever, suppression of appetite, and stimulation of the hypothalamic pituitary axis (HPA) to release corticotropin-releasing factor (Goshen et al., 2008; Goshen and Yirmiya, 2009; Layé et al., 2000). TNFα in particular is involved in

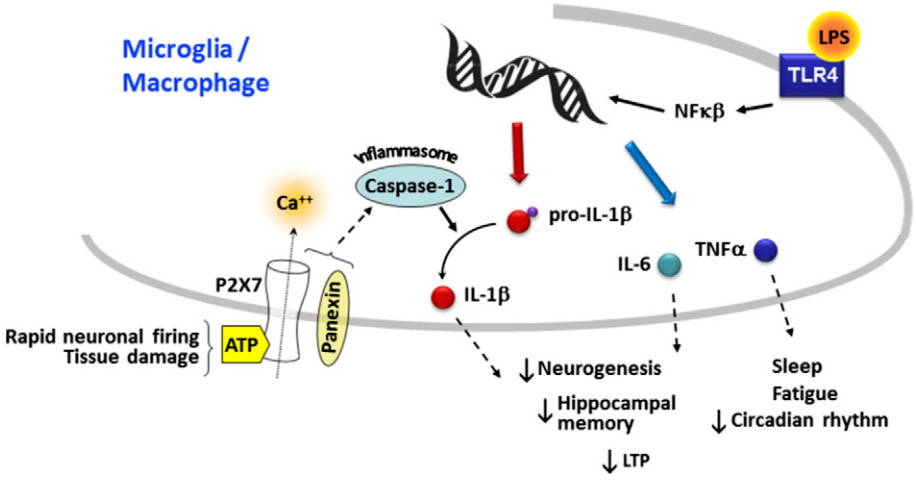

Fig. 1. Pathways for regulation and secretion of IL-1β and other neuroactive cytokines and their effects on the nervous system. Regulation of IL-6, TNFα and IL-1β is primarily via the NFκβ pathway through transcriptional activation. Inactive pro-IL-1β (as well as pro-IL-18 — not shown) requires further processing by the inflammasome component caspase-1. Endogenous stimulants include extracellular ATP and bacterial LPS. There are many other endogenous and exogenous inflammatory mediators that cause acute inflammation via other TLR subtypes and additional components of the inflammasome (not shown). See text for details on specific roles of each cytokine on cellular and behavioral effects.