Available online at www.sciencedirect.com

SciVerse ScienceDirect

Current Opinion in Neurobiology

Neuroimmune signaling: a key component of alcohol abuse

Jody Mayfield, Laura Ferguson and R Adron Harris

Molecular and behavioral studies corroborate a pivotal role for the innate immune system in mediating the acute and chronic effects of alcohol and support a neuroimmune hypothesis of alcohol addiction. Changes in expression of neuroimmune genes and microglial transcripts occur in postmortem brain from alcoholics and animals exposed to alcohol, and null mutant animals lacking certain innate immune genes show decreased alcohol-mediated responses. Many of the differentially expressed genes are part of the toll like receptor (TLR) signaling pathway and culminate in an increased expression of pro-inflammatory immune genes. Compounds known to inhibit inflammation, microglial activation, and neuroimmune gene expression have shown promising results in reducing alcohol-mediated behaviors in animal models, indicating that neuroimmune signaling pathways offer unexplored targets in the treatment of alcohol abuse.

Address
Waggoner Center for Alcohol and Addiction Research, The University of Texas at Austin, TX 78712, USA

Corresponding author: Harris, R Adron (harris@austin.utexas.edu)

Current Opinion in Neurobiology 2013, **23**:513–520

This review comes from a themed issue on **Addiction**

Edited by **Barry Everitt** and **Ulrike Heberlein**

For a complete overview see the Issue and the Editorial

Available online 22nd February 2013

0959-4388/$ – see front matter,

http://dx.doi.org/10.1016/j.conb.2013.01.024

Introduction

The interplay between brain, behavior, and immunity in the etiology and progression of drug abuse is a rapidly expanding area of interest for addiction research. Evidence is accumulating that the neuroimmune system, encompassing innate immune responses within the peripheral and central nervous systems, contributes to drug abuse and dependence. Recent studies point to a role for immune responses in all three stages of the addiction model, from binge/intoxication, withdrawal/negative affect, to preoccupation/anticipation or craving [1•,2,3].

In the case of alcohol abuse, there is strong evidence for a neuroimmune role of addiction, with the innate immune system being linked to brain changes associated with acute and chronic alcohol exposure. An array of behavioral and genetic studies within the past several years supports a role for innate immunity in alcohol abuse and also highlights neuroimmune pathways as potential targets in the treatment of alcohol addiction.

Innate immunity

The innate immune system is also known as the non-specific immune system and is the first line of defense against pathogens. It defends the host in a rather generic, albeit immediate manner, by acting as a physical or chemical barrier to infection but does not provide long-lasting immunity, which is the role of the adaptive immune system.

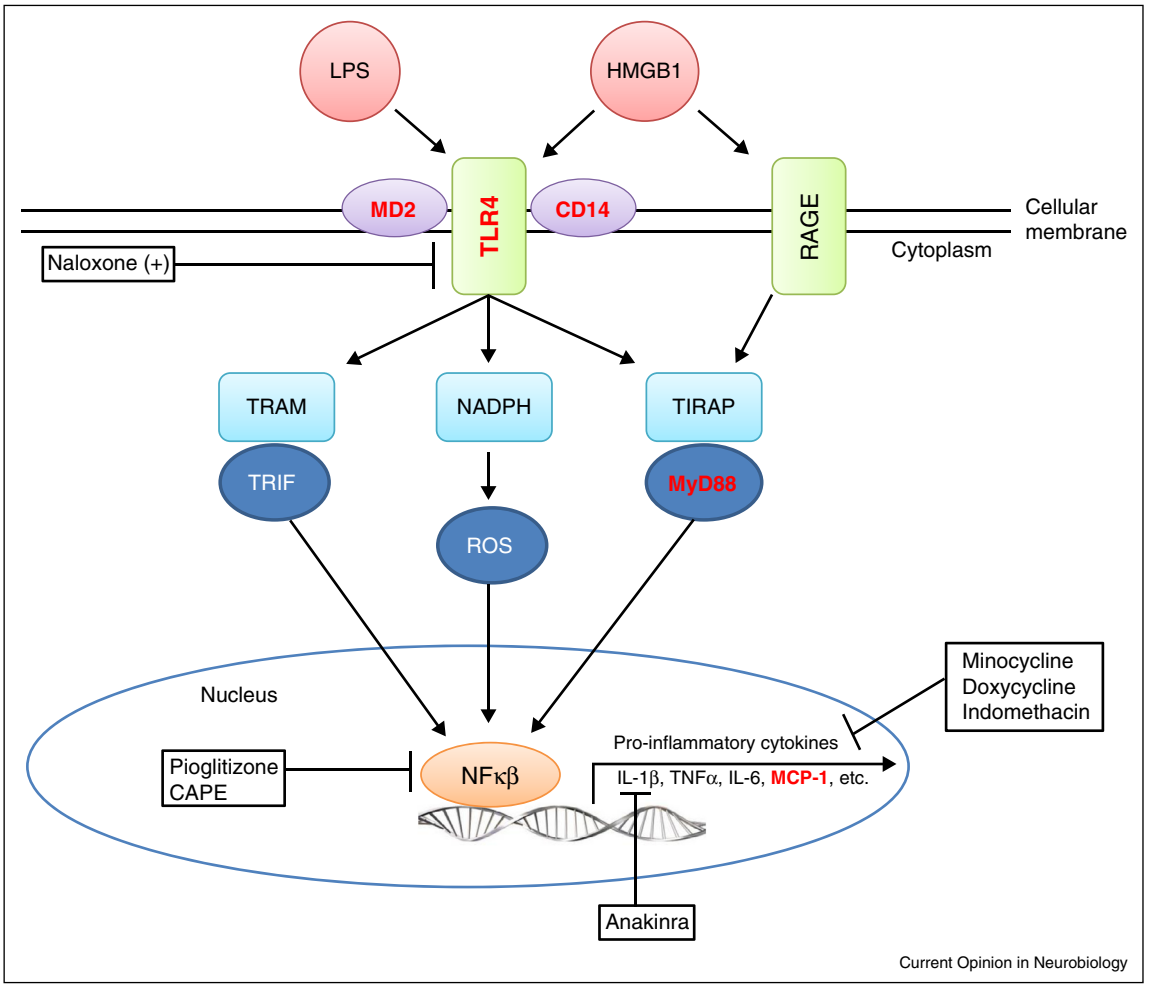
Innate immune cells outside of the brain consist of macrophages (including liver Kupffer cells), dendritic cells, mast cells, neutrophils, and other leukocytes. Microglia are brain-specific macrophages and are the main immune-derived cells in the brain while astrocytes, a subtype of glial cells, are also involved in mediating innate immunity in the CNS. Although microglia activation can be pro-inflammatory or anti-inflammatory, it is the pro-inflammatory mechanisms induced by alcohol that will be discussed here. Innate immune signaling pathways are shared among major tissues; thus brain microglia respond to and initiate innate immune signaling via similar pathways to immune cells in the liver, intestines, and lungs.

Activation of innate immune cells stimulates endogenous toll like receptors (TLRs), a family of highly conserved pattern recognition receptors found in invertebrates and vertebrates. TLRs have been implicated in everything from neural plasticity to disease, demonstrating their dichotomous role from neurogenesis to pathogenesis [4]. The most widely studied TLR to date is TLR4 (the receptor for bacterial endotoxin), although 13 TLRs have now been identified [5]. Microglial cells express high levels of TLR4 and respond rapidly to the Gram-negative bacterial endotoxin lipopolysaccharide (LPS) to produce inflammatory mediators [6]. Microglial activation of TLR4 is required for astrocyte pro-inflammatory responses [7•]. Neurons have also been shown to express TLR4 [4,8–10] and propagate LPS-induced signaling [11], indicating an unexpected role for neurons in innate immunity and eluding to significant cross-communication among microglia, astrocytes, and neurons that likely characterize innate immune signaling in the CNS. Brain endothelial cells also express TLR4 and are able to receive neuroimmune stimulation from the brain side and secrete cytokines into the blood or receive stimulation from the blood and secrete cytokines into the brain, suggesting that the blood–brain barrier (BBB) may be a fourth component involved in the cross-talk between

neurons, microglia, and astrocytes [12]. Further study is needed to determine the exact cellular location of TLR4 in the brain and to decipher the contribution of neurons versus glia in innate immune responses. Nonetheless, the diverse roles of TLRs no doubt depend on the specific TLR, its agonists, mediators, and cellular location.

In addition to recognizing conserved molecular components of microbes (such as the endotoxin LPS), TLRs across the innate immune system respond to other cellular stressors called danger signals [13]. Danger signals include endogenous TLR agonists, such as high-mobility group box 1 (HMGB1) protein (Figure 1). HMGB1 is a nuclear protein with cytokine-like actions that activates microglia-TLR signaling, further fueling expression of innate immune genes via activation of NF-κB, nuclear factor κ light-chain-enhancer of activated B cells (Figure 1). Pro-inflammatory signals spread through signaling loops that amplify within and across peripheral and central immune cells. The extent to which CNS

Figure 1



Summary diagram of TLR4 signaling cascade. TLRs signal as dimers and heterodimers that recruit adaptor proteins such as CD14 and MD2. Depending on the adaptors recruited by the activated TLR, different pathways can be triggered, all of which culminate in activation of the pro-inflammatory transcription factor NF-κB. One pathway involves MyD88 and TIRAP and results in activation of NF-κB via IκB kinase. Another pathway uses NADPH oxidase that can activate NF-κB through ROS. TRIF and TRAM signaling proteins also initiate signal cascades, culminating in the activation of NF-κB and other pro-inflammatory transcription factors. RAGE is another transmembrane receptor operating in innate immune cells that is known to respond to HMGB1, and this pathway also induces pro-inflammatory gene transcription via NF-κB activation. The release of cytokines such as TNF-α, HMGB1, IL-1β, chemokines, proteases, and ROS activate adjacent cells. These cytokines affect the brain and are thought to contribute to the etiology, progression, and persistence of alcohol addiction. 'Off-the-shelf' FDA-approved drugs (shown here in boxes along with their site of action) are anti-inflammatory and interfere with the TLR4 signaling cascade. These examples are discussed in the text and represented here because they have been shown to decrease alcohol consumption and modify other alcohol behaviors. Bold red font indicates a gene that has been manipulated and shown to affect ethanol-related behavior. NF-κB: nuclear factor κ light-chain-enhancer of activated B cells; MyD88: myeloid differentiation primary response gene 88; TIRAP: toll-interleukin 1 receptor (TIR) domain containing adaptor protein; ROS: reactive oxygen species; TRIF: TIR-domain-containing adaptor-inducing IFNβ; TRAM: TRIF-related adaptor molecule; RAGE: receptor for advanced glycation endproducts; TNF-α: tumor necrosis factor-α; IL-1β: interleukin-1β; IL-6: interleukin-6; MCP-1: monocyte chemoattractant protein-1.