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REVIEW

THE ROLE OF INFLAMMATION AND MICROGLIAL ACTIVATION IN THE PATHOPHYSIOLOGY OF PSYCHIATRIC DISORDERS

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Abstract—Psychiatric disorders, including major depressive disorder (MDD), bipolar disorder (BD) and schizophrenia, affect a significant percentage of the world population. These disorders are associated with educational difficulties, decreased productivity and reduced quality of life, but their underlying pathophysiological mechanisms are not fully elucidated. Recently, studies have suggested that psychiatric disorders could be considered as inflammatory disorders, even though the exact mechanisms underlying this association are not known. An increase in inflammatory response and oxidative stress may lead to inflammation, which in turn can stimulate microglia in the brain. Microglial activation is roused by the M1 phenotype, which is associated with an increase in interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α). On the contrary, M2 phenotype is associated with a release of anti-inflammatory cytokines. Thus, it is possible that the inflammatory response from microglial activation can contribute to brain pathology, as well as influence treatment responses. This review will highlight the role of inflammation in the pathophysiology of psychiatric disorders, such as MDD, BD, schizophrenia, and autism. More specifically, the role of microglial activation and associated molecular cascades will also be discussed as a means by which these neuroinflammatory mechanisms take place, when appropriate.

Key words: microglia, neuroinflammation, major depressive disorder, bipolar disorder, autism, schizophrenia.

Contents

INTRODUCTION

A growing body of evidence suggests that many psychiatric disorders, including major depressive disorder (MDD), bipolar disorder (BD), schizophrenia, and autism are associated with distinct inflammatory mechanisms in the periphery and in the central nervous system (CNS). The relevance of inflammation in these conditions has been proposed by several studies, linking them with alterations in cytokines and acute-phase reactants. Risk factors for MDD and BD include medical conditions associated with chronic inflammatory and immunological alterations, such as rheumatoid arthritis, obesity and diabetes (Leboyer et al., 2012). Moreover, peripheral immune modulators have been shown to induce psychiatric symptoms in humans and in animal models (Dantzer et al., 2008; Harrison et al., 2009; Eisenberger et al., 2010; Haroon et al., 2012). Inflammation in the context of the nervous system, termed

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Abbreviations: ADX, adrenalectomized; ASD, autism spectrum disorders; BD, bipolar disorder; CSF, cerebrospinal fluid; DAMPs, damage-associated molecular patterns; FS, forced swimming; HDACi, histone deacetylase inhibitor; HSP, heat shock protein; IDO, indoleamine 2,3 dioxygenase; IFN-γ, interferon-γ; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase; LH, learned helplessness; LPS, lipopolysaccharide; MDD, major depressive disorder; NMDA, N-methyl-D-aspartate; NO, nitric oxide; OB, olfactory bulbectomised; P2X7R, P2X7purinergic receptor; PET, positron emission tomography; PTSD, post-traumatic stress disorder; QUIN, quinolinic acid; SSRIs, selective serotonin reuptake inhibitors; TGF-β, transforming growth factor-β; Th1, T-helper 1; Th2, T-helper 2; TLRs, toll-like receptors; TNF-α, tumor necrosis factor-α; TS, tail suspension; VPA, valproate.

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'neuroinflammation', has been reported in patients with psychiatric disorders (Najjar et al., 2013), and is typically associated with microglial activation.

Microglia are CNS-resident cells that are usually the first to be activated in response to tissue damage or brain infections (Stertz et al., 2013). These small cells have several functions described, including (but not limited to): pathogen recognition, phagocytosis, antigen presentation, and synapse remodeling (reviewed in Boche et al., 2013). Non-activated microglia termed ''quiescent'' or ''resting'' microglia are constantly surveilling the surrounding environment in non-pathological conditions (Nimmerjahn et al., 2005; Marshall et al., 2013). In response to changes in the environment, microglial cells can be activated by changing their morphology and function (Marshall et al., 2013). Their activators include a range of different molecules, such as the P2X7purinergic receptor (P2X7R), and endogenous constituents that are normally released from injured cells, including adenosine 5′-triphosphate (ATP), S100 molecules, histones and heat shock protein (HSP), which are known as damage-associated molecular patterns (DAMPs) (Lu et al., 2014; Wiersinga et al., 2014). Specifically, P2X7R acts as a ''sensor of danger'' by responding to the so-called ''danger signal'' ATP, which is released from injured cells and activates microglia (Weisman et al., 2012; Gubert et al., 2013). The same goes for other DAMPs with their specific receptors.

Microglial activation can be divided into two distinct types: a classical M1 and an alternative M2 activation. In the M1 activation, microglial cells may become hyperramified or ameboid/phagocytic (Boche et al., 2013), and may synthesize proinflammatory molecules (interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and IL-6, among others), superoxide radicals, glutamate (Barger et al., 2007; Takaki et al., 2012), nitric oxide (NO) and ultimately clear infections and repair tissues. Alternatively, M2 activation, which can be triggered by cytokines such as IL-4, IL-13 or IL-25 (Boche et al., 2013; Maiorino et al., 2013), has been associated with a release of anti-inflammatory cytokines such as IL-10, insulin-growth factor-1(IGF-1), transforming growth factor-β (TGF-β), and neurotrophic factors (Ekdahl, 2012; Boche et al., 2013; Hu et al., 2015), which facilitate healing and limit neuronal injury (Najjar et al., 2013). The nature and the magnitude of the injury, along with several other factors, can influence the development of these distinct microglial phenotypes (Marshall et al., 2013). In addition to this dichotomous phenotype classification, a graded level of microglia activation has also been proposed, in which cells can go from a resting stage, to an alert, homing, phagocytic stage and finally to bystander activation, which can be differentiated by morphological features and the levels of cytokines and growth factors secreted (Raivich et al., 1999). Most importantly, identifying activated microglia in a pathological condition, although being a marker of inflammation, does not allow for an understanding of the inflammatory process. Thus, only by determining the phenotype of microglia can one identify its role in cytotoxicity and/or neuroprotection (Colton and Wilcock, 2010; Graeber et al., 2011; Marshall et al., 2013).

Several studies in the past year speculated that alterations in the number and/or morphology of microglial cells are involved in cognitive and behavioral changes observed in psychiatry disorders (Di Benedetto and Rupprecht, 2013; Muller et al., 2014; Nakagawa and Chiba, 2014; Watkins et al., 2014; Zeidan-Chulia et al., 2014; Najjar and Pearlman, 2015). However, although activation of microglia is a typical hallmark of brain pathology, the extent to which it has beneficial or detrimental functions in the brain in different psychiatric disorders remains to be elucidated (Dheen et al., 2007). Specifically, given that microglia can be activated in either a cytotoxic or a neuroprotective way, characteristics of the microglial activation assessed in a specific condition need to be taken into account. This review article aims to summarize evidence of inflammation and in major psychiatric disorders, such as major depression, BD, schizophrenia, and autism, including the role it plays in their progression and therapeutics. More specifically, the role of microglial activation and polarization, as well as associated molecular cascades, will also be discussed as a means by which these neuroinflammatory mechanisms take place, when appropriate.

THE ROLE OF MICROGLIA IN STRESS AND DEPRESSION

MDD is considered a critical public health problem, and it is estimated that approximately 350 million individuals are affected worldwide (WHO, 2012). In addition, almost 1 million lives are lost yearly due to suicide, which translates to 3000 suicide deaths every day (WHO, 2012). Until recently, the monoaminergic hypothesis appeared to be the most widely accepted theory for depression. However, a series of new studies have shown that other pathways involved with neuroplasticity or intracellular signaling cascades would be directly or indirectly responsible for the mood dysregulation, as well as to the mechanism of action of antidepressant drugs (Reus et al., 2013a, 2014; Abelaira et al., 2014a,b; Hoyo-Becerra et al., 2014; Ignacio et al., 2014).

Since patients with autoimmune and inflammatory disorders, such as diabetes and fibromyalgia, present with depressive symptoms, it has been proposed that depression may be linked to inflammation (Ceretta et al., 2012; Abelaira et al., 2014a,b; Hoyo-Becerra et al., 2014; Iseme et al., 2014; McInnis et al., 2014). In fact, patients with depression have been shown to present an increase in serum levels of proinflammatory cytokines, such as IL-1, IL-6, IL-8, IL-12, interferon-γ (IFN-γ) and TNF-α (Schiepers et al., 2005; O'Brien et al., 2007). In addition, elevated plasma levels of IL-1β, IL-1 receptor antagonist, IL-5, IL-6, IL-7, IL-8, IL-10, granulocyte colony-stimulating factor (G-CSF), and IFN-γ have been reported in patients during ongoing depression. Of note, cytokines were reduced to normal levels after 12 weeks of treatment with antidepressants (Dahl et al., 2014). On this same vein, Song et al. (2009) showed an increase in serum IL-1β and a decrease in IL-10 levels (proinflammatory cytokine) in depressed patients. In addition, T-helper 1 (Th1) and T-

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