Psychopharmacology (2016) 233:1623–1636
DOI 10.1007/s00213-016-4214-0

REVIEW

Role of neuro-immunological factors in the pathophysiology of mood disorders

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Received: 17 May 2015 / Accepted: 12 January 2016 / Published online: 23 January 2016

Abstract Mood disorders, despite the widespread availability of monoamine-based antidepressant treatments, are associated with persistently high rates of disability, together with elevated rates of mortality due to suicide, cardiovascular disease, and other causes. The development of more effective treatments has been hindered by the lack of knowledge about the etiology and pathogenesis of mood disorders. An emerging area of science that promises novel pathways to antidepressant and mood stabilizing therapies surrounds evidence that immune cells and their signaling play a major role in the pathophysiology of major depressive disorder (MDD) and bipolar disorder (BD). Here, we review evidence that the release of neuroactive cytokines, particularly interleukins such as IL-1β, IL-6, and TNF-α, is altered in these disorders and discuss mechanisms such as the ATP-gated ion channel P2X7, through which cytokine signaling can influence neuro-glial interactions. Brain P2X7, an emerging target and antagonism of P2X7 holds promise as a novel mechanism for targeting treatment-resistant depression. We further discuss the role of microglia and astroglia in central neuroinflammation and their interaction with the peripheral immune system We present extant clinical evidence that bolsters the role of neuroinflammation and neuroactive cytokines in mood disorders. To that end, the role of clinical imaging by probing neuroinflammatory markers is also discussed briefly. Finally, we present data using preclinical neuroinflammation models that produce depression-like behaviors in experimental animals to identify neuroinflammatory mechanisms which may aid in novel neuroimmune target identification for the development of exciting pharmacological interventions in mood disorders.

Keywords Neuroinflammation · Neuroimmunology · Depression · Microglia · Astrocyte

Mood disorders comprise a set of clinically pleomorphic syndromes composed of symptoms within the emotional, cognitive, visceral, and behavioral symptom domains that show high heritability relative to other common medical conditions, but remain idiopathic with respect to etiology. The main mood disorders, major depressive disorder (MDD; aka unipolar depression) and bipolar disorder (BD), pose serious public health burdens partly due to their high lifetime prevalence rates (Kessler et al. 2003). Recent epidemiology data suggest that the prevalence of depression is increasing worldwide (Kessler and Bromet 2013), which appears at least partly attributable to the secular trend that the age at illness onset becomes progressively younger and the cumulative lifetime prevalence progressively higher across younger birth cohorts. Despite the availability of many antidepressant drugs, the World Health Organization (WHO) ranks MDD as the highest global cause of "years of life lived with disability" for all age groups, and projects that in 2030, MDD will rank first in global disease burden as measured in disability-adjusted life years (DALYs) (Ferrari et al. 2014; Kessler 2012; Whiteford et al. 2013). Mood disorders also are associated with elevated mortality rates, especially due to suicide (Bolton et al. 2015)

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and cardiovascular disease (Goldstein et al. 2015). In the USA, suicide rates increased over the past decade for some demographic groups (e.g., increasing 32 and 37 % among males ages 45–54 and 55–64, respectively) and on a global scale, suicide ranks second overall among causes for death for those aged 15–20. The persistently high magnitude of these global public health problems partly reflects the limited efficacy of extant therapies, as about one third of MDD patients do not achieve remission despite multiple trials using different treatments, while another third cannot maintain remission and suffer relapse despite continued adherence to initially effective treatments (Rush et al. 2006); as such, there has been a renewed drive within the neuroscience community to better understand the causality of such differences and target signaling pathways that may be beneficial in treatment-resistant depression (O'Leary et al. 2015; Papakostas and Ionescu 2015). A problem that has limited the success of novel therapeutic discovery for mood disorders is that the extant antidepressant pharmacotherapies—which essentially all target biogenic amine-based mechanisms—were discovered empirically, without clear knowledge of the pathogenic mechanisms that contribute to mood disorders. Based upon studies of biological differences between depressed patients who respond to monoamine reuptake-inhibiting agents versus those who do not, however, a recent set of biomarker findings consistently indicates that the non-responders manifest abnormal elevations in a variety of proinflammatory immunological markers (Carvalho et al. 2013; Cattaneo et al. 2013; O'Brien et al. 2007; Uher et al. 2014; Yoshimura et al. 2009). Over the past decade, a compelling body of evidence has emerged to suggest that factors within the innate and the adaptive immune system comprise pathological contributors to the expression and maintenance of MDD and BD, potentially thereby illuminating new targets for novel therapeutics in mood disorders (Haapakoski et al. 2016; Pariante 2015). This evidence includes the detection of elevated cytokines in the plasma and cerebrospinal fluid (CSF) of depressed individuals, the induction of depressive symptoms in humans by proinflammatory cytokines and low dose endotoxin, elevated markers of microglial activation (TSPO) in depressed patients and/or in subjects treated with endotoxin (Sandiego et al. 2015), and meta-analyses of genome-wide association study (GWAS) studies implicating immune pathway dysregulation. Many of these findings are corroborated preclinically by similar phenomena where immune activation produces or exacerbates depressive-like behaviors in stressed animals (see a later section), and these behaviors are prevented or reversed by anti-inflammatory treatments (Hodes et al. 2014). In addition, emerging science indicates that peripheral immune cells and those within the CNS, such as microglia, and their interplay with astrocytes and neurons play a major role in the pathophysiology of mood disorders (Fig. 1). Although the concept of psychoneuroimmunology is not new, recent preclinical and clinical literature has invigorated research aimed at elucidating the neurobiology underlying interactions between glia and neurons within the context of mood disorders.

What is neuroinflammation: interplay of the immune system and CNS?

The interplay of immune system and the central nervous system involving proinflammatory cytokines, chemokines leading to microglial activation, and astrogliosis is called *neuroinflammation*. The *Journal of Neuroinflammation* defines neuroinflammation as "innate immunological responses of the nervous system, involving microglia, astrocytes, cytokines, chemokines, and related molecular processes." We propose that the term "inflammation" in this context is a misnomer, as in the CNS the fingerprints of an inflammatory state are unique and different from conventional inflammation involving peripheral immune cells. A recent review on CNS myeloid cells discusses different signatures of central immunity in this context (Biber et al. 2015). In the literature, *Neuroimmunology* has been widely used interchangeably with *Neuroinflammation*; we see *Neuroimmunology* as the science of peripheral immune system modulating central neurophysiology, whereas *Neuroinflammation* is a discipline of immune system of CNS, primarily dictated by the resident CNS immune cells called microglia. In the CNS, microglia and astrocytes are important cell types that play a critical role in neuroimmune interactions in several CNS diseases which have a "neuroinflammatory" component. For example, whereas it is relatively well accepted that neuroinflammation contributes to the causal mechanisms underlying multiple sclerosis, Parkinson's disease, and epilepsy, *debate remains whether neuroinflammation plays pathological or adaptive/compensatory roles in the pathophysiology underlying Alzheimer's and mood disorders.* In the CNS, bone marrow-derived immune cells have a restricted access due to an intact blood–brain barrier (BBB) and blood-CSF barrier; during an injury or infection when this barrier is compromised, peripheral immune cells can penetrate the CNS causing neuroinflammation. Nevertheless, other conditions exist in which macrophages and monocytes from the periphery can migrate into the CNS (Capuron and Miller 2011; Wohleb et al. 2014), and the recent discovery of CNS lymphatics may serve as the conduit of such body to brain cellular migration (Louveau et al. 2015). In addition, and probably more pertinent to the topic of neuroinflammation, microglia are the critical cell types that change from a "normal surveillance of the brain" mode to a "response" mode during injury and disease pathology. Resting microglia manifest a distinct "ramified" morphology whose function is to sense local environment within the brain and maintain homeostasis with neighboring neurons, astrocytes, and oligodendrocytes which participate in synaptic function

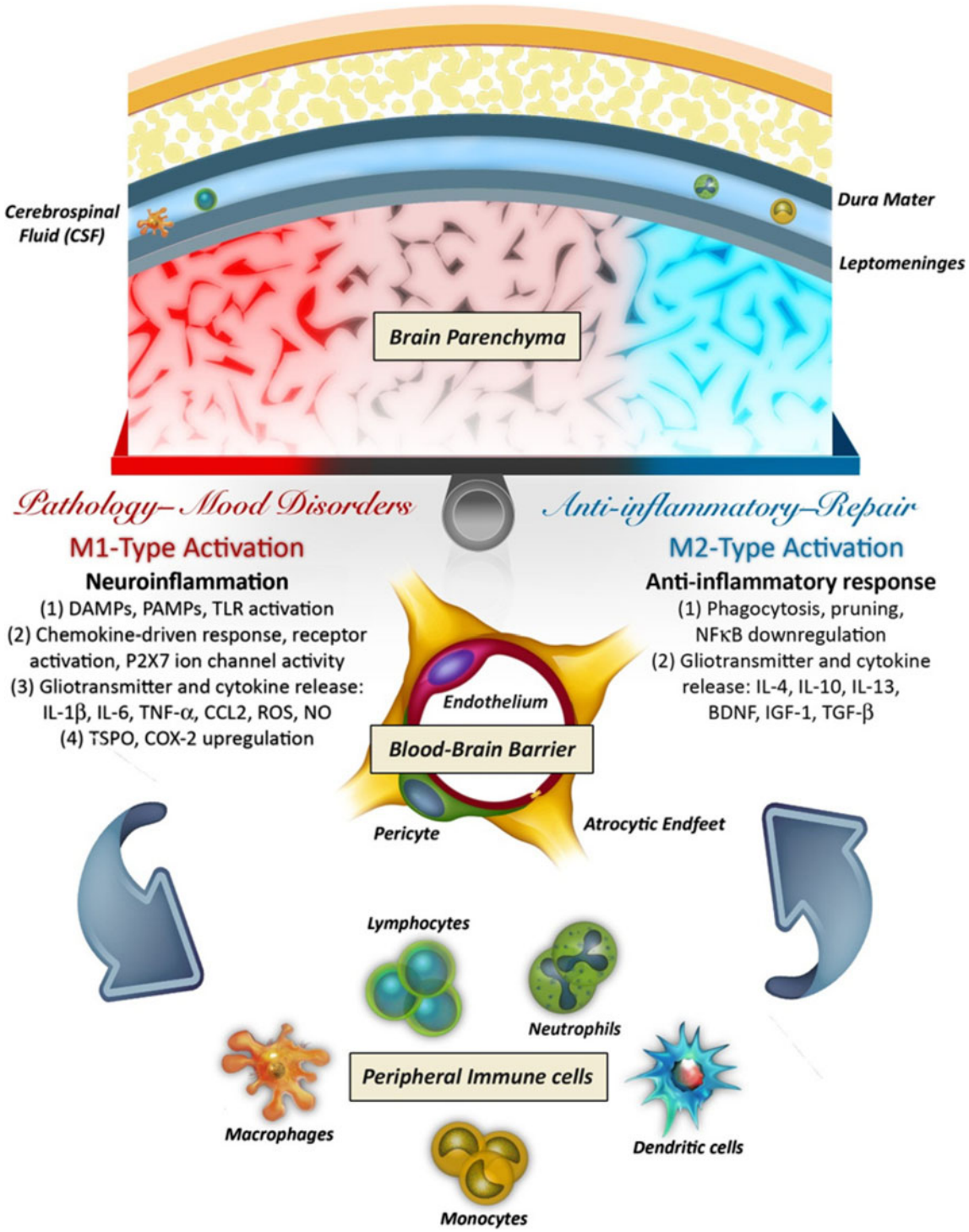

Fig. 1 Schematic representation of the interplay between peripheral immune cells (lymphocytes, neutrophils, macrophages, monocytes, and dendritic cells), the blood–brain barrier (predominantly endothelial cells), and microglia–astrocytes within the brain to drive neuroinflammation. These cells and their signaling partners play a role to maintain a homeostatic balance in the brain; a balance between the proinflammatory (M1) and the anti-inflammatory (M2) state. During chronic episodes of mood disorders, the balance is shifted toward the M1 proinflammatory state defined by increased activity of cytokines (IL-1β, IL-6, TNF-α), chemokines (CCL2), and their cognate receptors, P2X7 activation, TSPO upregulation and activation of toll-like receptors (TLRs) caused by danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). In parallel, the system tries to reset itself by stimulating the M2 repair process as indicated in the cartoon (increased microglial phagocytosis, increased synaptic pruning, release of anti-inflammatory cytokines etc.). The current hypothesis in the field is that the imbalance between M1 and M2 (M1 > M2) state of microglial activation results in mood disorders; this remains a clinically untested mechanism. Restoration of the balance (toward M2 by dampening M1 signaling) ought to be a therapeutic strategy to tackle mood disorders

and transmission. During CNS pathology associated with neuroinflammation, microglia respond by adopting an amoeboid morphology and, in the process, release gliotransmitters such as proinflammatory cytokines such as interleukin 1β (IL-1β), interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), interferon γ (IFN-γ), chemokines (CCL2), glutamate, adenosine triphosphate (ATP), nitric oxide (NO), reactive oxygen species, and reactive nitrogen species (ROS/RNS) that may cause enhanced signaling leading to an imbalance of the neuro-glia connectivity (Ben Achour and Pascual 2010). The proinflammatory (M1) phenotype occurs in response to tissue injury, stress, and infection (bacterial/viral) as part of the adaptive immunity response resulting in release of IL-1β, TNF-α, IL-6, CCL2, NO, etc. (Fig. 1). The repair is mediated by microglia, predominantly of the anti-inflammatory (M2) phenotype, which are more phagocytic in nature than their M1 counterparts. During this phase of repair, microglia release anti-inflammatory interleukins (ILs) such as IL-4, IL-10, IL-13, etc. (Fig. 1). Notably, the microglia can exist in a range of phenotypes that are intermediate in their morphologies between M1 and M2 as well (Orihuela et al. 2015; Tang and Le 2015). Several recent reviews have expanded on the different roles of M1/M2 microglia and their role in CNS (patho)physiology (Cherry et al. 2014; Prinz and Priller 2014). In addition, emerging science has brought to light the important role of microglia in synaptic pruning that restores normal connectivity (Aguzzi et al. 2013; Chung and Barres 2012; Zhan et al. 2014) as there is growing appreciation that the tripartite synapse is "out of tune" during neuroinflammation. *The process of microglial activation is a central component of neuroinflammation.* Microglial activation is a phenomenon that involves some of the following features: (a) changes in microglial morphology from ramified to amoeboid; (b) upregulation of cellular markers such as ionized calcium-binding adapter molecule 1 (Iba-1), cluster of differentiation molecule 11b (CD11b), translocator protein (TSPO), inducible nitric oxide synthase (iNOS), cannabinoid receptor 2 (CB-2), and cyclooxygenase 2 (COX-2); (c) shifting the balance toward M1: proinflammation; (d) increased microglial proliferation and migration. The central question and debate that engulfs this topic is the chicken and egg question: is microglial activation a result of a repair response or is it a central culprit to glial pathology that initiates disruption of normal physiology precipitating in several CNS diseases including mood disorders (Fig. 1)? While the process of microglial activation is a central component of neuroinflammation, in mood disorders and several other CNS diseases, a question that remains unanswered is whether microglial activation constitutes the result of a reparative response or instead comprises a pathological mechanism that initiates disruption of normal physiology. The extant data suggest that neuroinflammation can play pathological roles under some conditions and adaptive/restorative roles in others, with both roles potentially coexisting within the context of some CNS disease states. Chronic and uncontrolled neuroinflammation eventually contributes to a CNS pathological phenotype. Glial factors released from microglia and astrocyte during neuroinflammation modulates synaptic plasticity and neurogenesis and has a profound impact on circuitry in the context of symptomology for mood disorders.

The role of peripheral immune cells in modulating central neuroinflammation

In recent years, we have witnessed the birth of an increasingly nuanced understanding of the role of the immune system as a mediator of CNS function during health and disease. As has already been detailed, microglia—the resident macrophages of the brain—are able to play direct influence on surrounding neural cells via their production of soluble immune factors and also by phagocytosis of pathogens, debris, synapses, or even entire neural cells. However, peripheral immune cells also play roles in CNS function ranging from the sublime—supporting learning and memory in mice (Brynskikh et al. 2008; Derecki et al. 2010; Kipnis et al. 2004; Wolf et al. 2009; Ziv et al. 2006) and, more recently, humans (Jiang et al. 2014) via release of factors like interleukin (IL)-4—to the protective, as evidenced by IFN-γ-mediated control of *Toxoplasma gondii* (Yarovinsky 2014), to the catastrophic, as in the case of multiple sclerosis (MS), largely promulgated by autoreactive T cells running amok. Indeed, as supported largely by MS studies, it has long been taken more or less dogmatically that the presence of the immune system either close to or within the brain parenchyma is a situation to be avoided at all costs. However, this view has been modified by a number of recent works—many in high-profile journals—suggesting that the immune system can also play a beneficial role in CNS pathology. For example, a controlled amplification of the autoimmune response was associated with improved neuronal survival in rodent models of acute CNS injury (Moalem et al. 1999) and chronic neurodegenerative conditions (Hofstetter et al. 2003; Kipnis et al. 2002). These were followed by findings that indeed revealed a far more complex interplay (Kigerl et al. 2009) than previously considered between the peripheral immune system and the CNS and studies suggesting a key beneficial component of the immune response to CNS pathology (Cronk et al. 2015; Shechter et al. 2009).

While these data support a key role for immune factors in pathologies involving frank infiltration of the CNS by peripheral cells, intriguing recent studies also suggest that changes in peripheral immune cell populations can be correlated with "sterile" CNS pathologies—i.e., disorders that do not feature clear penetration of the blood–brain or blood–CSF barrier by circulating cells. It has been understood for some time that chronic stress leads to dysregulation of glucocorticoid-

associated factors. Similarly, a large volume of data has been compiled suggesting that proinflammatory cytokines released during peripheral infection are associated with behavioral correlates of depressive mood—termed sickness behavior (Kelley et al. 2003). Links between sickness behavior and a tryptophan metabolizing enzyme, namely indoleamine 2,3 dioxygenase (IDO), have even been demonstrated (Dantzer et al. 2011), thus establishing potential association between cytokines and monoamine deficiency. However, it is only recently that these tantalizing—but separate—lines of evidence have begun to converge in findings regarding posttraumatic stress disorder (PTSD). PTSD has risen to the fore in terms of results that strongly link CNS pathology, stress, and immune system dysregulation at the level of inflammatory cascades and gene networks. In a recent publication, Breen et al. (Breen et al. 2015) examined blood samples by RNAseq from $N = 188$ marines before and after deployment in areas of active conflict, and then a second, non-overlapping cohort of $N = 96$. This combination of within-subject design, large sample size, and study replication lends strong credence to the results, which unambiguously highlight not only proinflammatory gene networks as upregulated in PTSD sufferers, but specifically type-a and type-b interferon-induced genes—a particularly striking finding given the frequently seen emergence of depressive symptoms in cancer patients receiving IFN-α therapy. Moreover, the authors detected a highly significant signature of CD14+ monocyte-associated factors as differentially regulated in PTSD sufferers; this finding is particularly notable given that monocytes are the primary producers of IL-6, IL-1β, and TNF-α, three major factors linked to mood disorder in preclinical studies and clinical populations. CD14+ monocytes are mobilized into circulation primarily by CCL2, a prototypical chemokine produced by glial (Glabinski et al. 1996) and blood–brain barrier cells (Andjelkovic and Pachter 2000) during neuroinflammation. Thus, these findings highlight a possible link between glial activation and loss of peripheral immune homeostasis leading to chronic feedback between the CNS and periphery in PTSD. Much circumstantial and phenomenological evidence exists to suggest that peripheral immune dysfunction is tied to CNS pathology; however, mechanisms linking the two are only recently coming to light (Fig. 1). A particularly striking example of previously unanticipated links between the CNS and peripheral immune system is the discovery of lymphatic vessels within the dura mater that provide a clear and defined pathway for immune cells to traffic along the borders of the brain. It was previously suggested that T cells, dendritic cells, and antigen traced a somewhat meandering route out of the CNS, passing through the arachnoid granulations, following the olfactory nerves, traveling through the cribriform plate, through the nasal mucosa, and ultimately reaching the deep cervical lymph nodes. However, Louveau et al. (2015), and subsequently, Aspelund et al. (2015), identified a more direct route alongside the superior sagittal and transverse sinuses (Aspelund et al. 2015; Louveau et al. 2015). Although fluorescence-activated cell sorting (FACS) labeling of single-cell meningeal suspensions had previously shown the presence of T lymphocytes in these para-parenchymal tissues (Derecki et al. 2010), only microscopic analysis of meninges in whole-mount revealed the concentrated presence of the several classical molecular markers of lymphatic vasculature, including Lyve-1, Prox-1, and podoplanin. Labeling of these using immunofluorescence and fluorescent reporter strains allowed researchers to visualize in exquisite detail the precise route of the vessels and the corresponding lymphatic efflux from the brain. The discovery of CNS lymphatics is profoundly important in that their presence indicates a clear and unambiguous relationship between the brain and peripheral immune system, rather than one defined solely by pathology. In the following section, we attempt to connect the dots by highlighting clinical observations suggesting molecular factors that link immune factors with CNS function.

Astute clinical observations indicating a role of immunological factors in mood disorders: paradigm change and renewed hope in neuropsychiatry to target treatment resistant depression?

There is growing appreciation of the role of immune system and neuroinflammation in the pathophysiology of mood disorder (Najjar et al. 2013; Noto et al. 2014; Rosenblat et al. 2014; Walker et al. 2014). This has resulted in targeted and rationale drug discovery efforts with a view to intervene immune modulators thought to be causal to mood disorders. Immune mediators for which the mean concentrations are increased in the blood and CSF of patients with mood disorders versus healthy controls, both when assessed at baseline and after exposure to stressors, include IL-6, IL-1β, IFN-α, TNF-α, prostaglandin E2, and the chemokine CCL2 (Dowlati et al. 2010; Jones and Thomsen 2013; Pace and Miller 2009; Soderlund et al. 2011; Young et al. 2014). The mRNA transcripts for these cytokines and for other related innate immune system proteins also have been elevated in peripheral blood cells in mood disorder patients relative to controls (Carvalho et al. 2014; Cattaneo et al. 2013; Jansen et al. 2015; Padmos et al. 2008; Powell et al. 2014; Savitz et al. 2013). The clinical significance of these findings has been bolstered by replicated findings that patients with MDD or

BD show elevations of these cytokines in the plasma and CSF relative to controls matched for age, BMI, smoking, and comorbid medical conditions and that the levels of these cytokines have correlated with illness severity and/or suicidality ratings in some studies. Moreover, successful treatment with conventional antidepressant drugs lowers the cytokine levels in depressed patients, although non-responsiveness to conventional antidepressants is correlated with higher IL1-β, IL-6, and CRP levels (Cattaneo et al. 2013; Hannestad et al. 2011; Yoshimura et al. 2009). In one of the clearest examples of elevated levels of a cytokine causing depressive symptoms, immune challenge with interferon-α (IFN-α) during treatment of hepatitis C is well known to induce the major depressive syndrome and/or manic symptoms in 30 to 40 % of patients (Hoyo-Becerra et al. 2014; Pace and Miller 2009). The neuropsychiatric sequelae of IFN-α administration merit comment because they converge with other types of evidence to suggest that elevations may exert a causal role for depressive symptoms in mood disorders (Baraldi et al. 2012). Within the days following IFN-α administration, individuals show a behavioral complex that includes anorexia, fatigue, lower mood, reduced social interaction, and reduced engagement in pleasurable activities, known as "sickness behavior". In addition, however, 30 to 40 % of individuals treated with IFN-α for various medical conditions additionally develop a major depressive episode (MDE) that appears indistinguishable from that observed in MDD or BD (Miller et al. 2009). The MDE arises later than the initial appearance of sickness behavior, and the likelihood of developing an MDE continues to rise as the time spent receiving IFN-α increases. The symptoms of the MDE differ from those of sickness behavior by magnitude in some cases (e.g., more severely depressed mood and pervasive anhedonia in MDE) and by quality in others (e.g., guilt ruminations, pathological anxiety, and suicide ideation appear uniquely characteristic of MDE). The prevailing hypothesis holds that IFN-α-induced MDEs constitute an example of a "proinflammatory state-induced mood disorder," which manifest in some individuals exposed to IFN-α on the basis of a biological predisposition and that a subset of the "primary" MDD population also manifests depressive symptoms due to the influence of elevated neuroactive cytokine signaling caused via other etiologies. For example, a single nucleotide polymorphism (SNP) in the IL-6 receptor gene resulting in lower IL-6 expression was associated with decreased susceptibility to the development of depressive symptoms during IFN-α treatment. Notably, some patients who manifest IFN-α-induced MDE improve during SSRI treatment leading physicians to prophylactically initiate SSRIs in the weeks prior to initiating IFN-α for some patients (Udina et al. 2014). Of the symptom domains affected by IFN-α, however, the depressed mood symptom dimension is most responsive, whereas the anxiety, cognitive dysfunction, and neurovegetative symptom dimensions are less responsive (or unresponsive) to prophylactic SSRI treatment (McNutt et al. 2012). These observations hold intriguing therapeutic implications, because in patients with primary mood disorders, higher blood levels of proinflammatory cytokines or their mRNA transcripts predict future response to treatment with SSRIs or other conventional antidepressants (Cattaneo et al. 2013; O'Brien et al. 2007; Uher et al. 2014; Yoshimura et al. 2009).

Conversely, some data suggest that directly reducing the signaling of some cytokines can induce an antidepressant effect. For example, patients with psoriasis who received the anti-TNF-α agent etanercept showed significant improvement in depressive symptoms in response to drug versus placebo as assessed using conventional depression rating scales, and this difference was evident earlier than the associated changes in pain or skin lesions (Tyring et al. 2006). In this study, patients treated with etanercept also had significant improvements in fatigue; while the improvements in fatigue correlated with decreasing joint pain, the improvements in symptoms of depression were less correlated with objective measures of skin clearance or joint pain. Nevertheless, these clinical findings suggest that the relationship between immune function and the pathophysiology of mood disorders is complex. Despite the consistent findings that mean concentrations of cytokine levels are elevated between depressed and control samples, the data from individual studies suggest that these differences may be attributable to a subset(s) of the depressed patients. An unanswered question, therefore, is the extent to which activation of certain elements of the innate immune system may pertain specifically to the pathophysiology of mood disorders. Alternatively or additionally, such directional differences in immune system function may reflect biological heterogeneity within the mood disorder population. For example, Grosse et al. (2015) reported *increased* expression of monocyte genes and decreased expression of glucocorticoid receptor (GR) α versus β subunits (see below) ratio in MDD patients aged ≥28 years (Grosse et al. 2015). However, in patients <28 years of age, two subgroups were evident: one who manifested a severe course of depression (recurrent type, onset <15 years, additionally characterized by panic/arousal symptoms and childhood trauma) that had a monocyte gene expression similar to healthy controls and a second subgroup with a milder illness course (73 % first episode depression, onset ≥15 years, additionally characterized by the absence of panic symptoms) that exhibited a strongly *reduced* inflammatory monocyte activation compared to controls. The question of subtypes is particularly germane to treatment considerations, as multiple studies report that *higher* levels of C-reactive protein (CRP) or of cytokine proteins or mRNA transcripts in blood are correlated with poorer response to conventional antidepressant drugs (see above). Nevertheless, other studies have shown that a biomarker signature composed of multiple immunological factors is able to discriminate a majority of patients in mood disorder samples from healthy controls. For example, Padmos

et al. (2008) performed whole-genome expression profiling on microarrays using purified CD14+ monocytes and reported elevated mRNAs of inflammatory (e.g., TNF, PDE4B, IL-1β, IL6, TNF), trafficking, survival (e.g., BCL2A), and mitogen-activated protein kinase pathway (e.g., MAPK6, ATF3) genes in BD subjects in various illness phases and in affected offspring of other BD subjects (Padmos et al. 2008). Notably, in stored peripheral blood mononuclear cells (PBMCs) from the same subjects (38 BD patients and 22 HCs) assessed via FACS analysis, the percentages of anti-inflammatory CD4+ CD25highFoxP3+ regulatory T cells were higher in BD patients <40 years of age, while percentages of Th1, Th2, and Th17 cells were normal. Together, these results thus showed enhancement of both proinflammatory monocyte and anti-inflammatory T cell mediators in BD (Drexhage et al. 2010). In summary, there seems to be general acceptance that proinflammatory mediators contribute to the etiology and/or maintenance of mood disorders.

Relationship of cytokine function to *clinical* and *preclinical* phenomenology of mood disorders: focus on TNF-α, IL-6, IL-1β signaling

TNF-α TNF-α signaling appears to play a major role in mood disorders (Dantzer et al. 2008). In meta-analyses of clinical studies, plasma TNF-α correlated with depression severity and level of resistance to conventional antidepressants (Dowlati et al. 2010; Miller et al. 2009). A causal relationship between TNFα elevation and depressive symptoms was suggested by observations that in patients with immunological diseases such as rheumatoid arthritis and psoriasis, anti-TNFα treatment alleviates depressed mood, and these antidepressant effects do not appear attributable simply to improvement in sickness symptoms, such as fatigue, or in the underlying autoimmune disorder (Krishnan et al. 2007; Tyring et al. 2006). Consistent with these observations, the TNFα receptor 1, TNFα receptor 2, and TNFα knockout mouse models all show antidepressant-like phenotypes (Simen et al. 2006; Yamada et al. 2000). Nevertheless, a clinical study of the efficacy of infliximab (a monoclonal antibody against TNF-α) in depressed patients generated negative results on a conventional depression rating scale score (Raison et al. 2013). A post hoc investigation of data from this study revealed a significant positive correlation between clinical improvement and pretreatment levels of the nonspecific inflammation marker, CRP, raising the possibility that antidepressant effects may be limited to individuals who manifest a proinflammatory diathesis. Nevertheless, because the test of the a priori hypothesis in this study was negative, the question remains whether targeting TNF-α via large molecules introduced in the periphery alone can produce an antidepressant effect (very low proportions of peripherally administered monoclonal antibodies enter the brain following acute treatment), or whether therapies targeted at TNF-α signaling must instead directly engage targets in the CNS.

IL-6 In subjects with MDD or BD, one of the more highly replicated biomarker abnormalities has been an elevation in peripheral blood IL-6 concentrations (Maes et al. 2014). Notably, during IFN-α treatment, the magnitude of the increase in plasma and CSF IL-6 levels correlates positively with depressive symptom severity. Conversely, a functional polymorphism in the promoter region of the IL-6 gene (rs1800795) that results in decreased IL-6 expression is associated with a significantly lower risk for developing major depressive episodes during IFN-α treatment (Bull et al. 2009). The relationship to IL-6 function is compatible with findings that, in patients with primary mood disorders, higher IL-6 levels in CSF correlated with suicidality, and elevated IL-6 levels in plasma correlated with non-responsiveness to conventional antidepressant drugs (Bay-Richter et al. 2015). In contrast, during the euthymic (i.e., asymptomatic) phase of BD, the CSF concentration of IL-6 was decreased with respect to healthy controls, despite the same BD subjects showing an abnormal elevation in the CSF levels of IL-1β (Soderlund et al. 2011). Although IL-6 can be released by immune cells in the CNS as well as in the periphery, preclinical evidence suggests that elevated IL-6 release from peripheral immune cells is sufficient to induce depressive behaviors, irrespective of central immune system activation. In studies conducted by Hodes and colleagues (Hodes et al. 2014), to elucidate the biological basis of susceptibility to depression-like behaviors under stress, mice that developed a persistent depression-like phenotype in response to social defeat stress (SDS) were compared to genetically identical mice that did not develop depression-like behaviors under SDS. The susceptible animals differed from the resilient animals by showing elevated basal IL-6 levels in the pre-SDS condition and higher IL-6 release in response to the stressed condition. In addition, white blood cells sampled pre-SDS from susceptible mice showed higher LPS-induced IL-6 release ex vivo than cells obtained from resilient mice. Crucially, the susceptibility to the depression-like phenotype could be altered toward either susceptibility or resilience by generating bone marrow chimeras that had hemopoetic stem cells transplanted from high IL-6 expressing mice or IL-6 knockout mice, respectively. The bone marrow recipients in these studies had received radiation to their bodies while the head was shielded, so the hemopoetic stem cells in periphery conferred the susceptibility to the depression-like phenotype under stress.

IL-1β In contrast to the therapeutic potential offered by neutralizing IL-6 predominantly in the periphery, the extant data suggest that for the proinflammatory cytokine IL-1β, reducing signaling in the brain may prove critical to achieving

antidepressant effects. IL-1β is probably the most potent pro-inflammatory cytokine released from microglia in the brain. Clinical studies found that IL-1β is present at abnormally higher levels in plasma, CSF, and postmortem brain tissue of individuals with mood disorders and that IL-1β levels are correlated positively with severity of depression (Jones and Thomsen 2013; Soderlund et al. 2011). Anisman and colleagues reported increased IL-1β production from lymphocytes in patients with dysthymic disorder, and a modest correlation existed between the cytokine and depressive symptoms (Anisman et al. 1999). IL-1β has been linked with geriatric depression as well as symptomology associated with postpartum depression (Corwin et al. 2008; Diniz et al. 2010). In animal models of stress-induced depression-like behaviors, several groups showed that IL-1β signaling is critical to acquisition of the depressed phenotype (Koo and Duman 2009; Maes et al. 2012). These depression-like phenotypes can be blocked by IL-1 receptor antagonists and are absent in IL-1R receptor knockout mice (Koo and Duman 2008). In addition, manipulation of central IL-1β, either by exogenous administration or by selective ablation of signaling via pharmacology or genetics, produced behavioral analogs of depression when IL-1β was increased, or antidepressant-like effects when IL-1β was decreased (Goshen et al. 2008; Zhang et al. 2015). IL-1β-driven changes in the brain caused decrease in neurogenesis in the brain (Koo and Duman 2008) and also increase stress response in the periphery as measured by increase in plasma cortisol (Song et al. 2003), indicating an interplay of stress-IL-1β and the HPA axis.

Under pathological situations (necrosis, neurodegeneration, microglial phagocytosis, astroglial pruning of synapse), brain IL-1β release is under the direct supervision of the ATP-gated P2X7 ion channel. P2X7 is expressed predominantly in glial cells of the CNS and is believed to be a central mediator of IL-1β release, which in turn communicates with neuronal IL-1 receptors to modulate neurophysiology. There is growing evidence that strengthens the role of P2X7-induced IL-1β signaling in the pathophysiology of mood disorders (Iwata et al. 2016; Sperlagh and Illes 2014). Several human genetic studies have associated the highly polymorphic *P2RX7* gene with both bipolar disorder and depression, and some of these mutations have been linked to a modulation of P2X7 channel function in vitro (Chrovian et al. 2014). In addition, several independent laboratories have demonstrated a protective phenotype of P2X7 knockout mice in models of depression and mania, strengthening the hypothesis that P2X7 antagonism may be therapeutically beneficial in mood disorders (Basso et al. 2009; Boucher et al. 2011; Csolle et al. 2013a). The phenotype of the knockout animals has since been validated using P2X7 selective antagonists (Wilkinson et al. 2014). In a model of sucrose consumption that is more reflective of anhedonic behavior, pharmacological antagonism of P2X7 (by AZ-10606120 and A-804598) restored the deficit observed in drinking sucrose water (anhedonia) either under chronic stress or by systemic administration of lipopolysaccharides (LPS) (Csolle et al. 2013b). Recently, two independent groups further demonstrated that centrally permeable P2X7 antagonists reverse anhedonic deficits induced by chronic stress in rats (Iwata et al. 2016; Lovenberg 2015). Taken together, it remains plausible that a selective and brain penetrant P2X7 antagonist may be therapeutically beneficial in neuropsychiatric conditions. Such a mechanism would be a novel treatment for psychiatric disorders. We can only remain optimistic that brain permeant P2X7 antagonists will proceed to proof of concept studies in neuropsychiatric disorders including depression and bipolar.

Imaging brain neuroinflammation: much needed biomarker for mood disorders

One of the challenges of drug development in neuropsychiatry is lack of tractable central biomarkers for disease and/or drug response or drug–target engagement in the human brain. To that end, emerging science linking the 18-kDa translocator protein TSPO (aka PBR for peripheral benzodiazepine receptor) to microglial activation has brought renewed excitement to CNS drug discovery and development. TSPO has been widely accepted in the field as a surrogate of neuroinflammation that involves an activated state of microglia in the brain. There are several reviews that focus on the biology of TSPO and upregulation of this protein in the context of microglial activation (Liu et al. 2014; Venneti et al. 2013). TSPO has generated tremendous interest in neuroscience drug discovery and several PET ligands for TSPO have been optimized as clinical imaging tools to probe neuroinflammation of normal versus diseased brain (Doorduin et al. 2008; Pulli and Chen 2014; Venneti et al. 2006). For example, using PET tracers for TSPO, the state of neuroinflammation has been established in patients suffering from schizophrenia (Bloomfield et al. 2016; Doorduin et al. 2009), multiple sclerosis (Oh et al. 2011; Vowinckel et al. 1997), Parkinson's disease (Gerhard et al. 2006), and Alzheimer's disease (Zimmer et al. 2014). Very recently, it was nicely demonstrated that LPS caused enhanced [^{11}C]-PBR28 signal in human brains, indicating a neuroinflammatory state of the human brain (Sandiego et al. 2015). LPS is an artificial stimulus, but very effective in eliciting proinflammatory cytokine release and has been now studied for TSPO in rodents (Ory et al. 2016), baboons (Hannestad et al. 2012), and now in humans (Sandiego et al. 2015). Recently, the first peer-reviewed study was published (Setiawan et al. 2015) indicating enhanced TSPO PET uptake in several brain regions of patients with a clinical diagnosis of major depressive episode. A similar study has been presented by two independent groups in recent scientific conferences (Holmes et al. 2014; Richards et al. 2015). Even though these

two studies indicate a neuroinflammatory tone in depressed patients, it is more than likely that all clinical depression is not neuroinflammation. The state of the patients' clinical profile, depression-related medications, response status, remission versus relapse, and the general state of inflammation burden may dictate whether TSPO PET may be a clinical biomarker for depression. It is therefore not surprising that a negative TSPO PET study also exists as it relates to clinical depression (Hannestad et al. 2013), although in this study, the patients were mild-to-moderate type and it is likely that TSPO upregulation is a surrogate of chronic high-grade neuroinflammation that may reside in severe depression. In fact, the hope would be to use TSPO PET imaging to stratify patients in an effort to enrich enrollment of depressed patients with neuroinflammation to in a proof-of-concept clinical study targeting signaling of microglial activation mechanisms. To that end, in addition to TSPO, PET ligands for other targets (CB-2, COX-2, P2X7) known to be involved in neuroinflammation are emerging as well (Gao et al. 2015; Hortala et al. 2014; Janssen et al. 2014; Ory et al. 2014; Slavik et al. 2015).

Animal models of neuroinflammation and behaviors akin to depression

In neuropsychiatry, a major challenge in translation physiology and pharmacology is lack of suitable animal models that elicit behaviors similar to clinical depression. Hence, the need for biomarkers of drug action in the brain (example, PET imaging) is critical in CNS drug discovery and development, particularly for proof of concept studies of novel mechanisms in the clinic. As noted in the previous section, TSPO and emerging imaging markers of neuroinflammation offer optimism for modeling neuroinflammation in animal models of depression due to the clinical translation of imaging endpoints. For example, in models that are known to cause neuroinflammation and depression-like behaviors (loss of pleasure as measured by decreased intake of sucrose water), several groups have reported hallmark features of neuroinflammation (microglia and astrocyte reactive morphology, microglial proliferation, increase in proinflammatory cytokines, TSPO upregulation, etc.). Recognizing that several modalities and variances of animal models exist that may cause depression-like behaviors, secondary to neuroinflammation, we would like to focus on three stimuli in this section: LPS, BCG, and stress.

Bacterial LPS has been probably the most studied animal model of neuroinflammation associated with depression. Acute and chronic administration of LPS in rodents has been reported to elicit anhedonia and markers of inflammation and stress in the periphery and in the CNS (Bay-Richter et al. 2011; Kubera et al. 2013). LPS produces a transient sickness behavior followed by depressive-like symptoms, which is also a case of concern in this model as it is possible that the sickness syndrome may result in anhedonic behaviors and changes in proinflammatory cytokines, which may be independent from biology related to cause a true "depression." Nonetheless, in LPS-challenged models, several groups have reported microglial activation, either by assessing TSPO changes by PET imaging in non-human primates (Hannestad et al. 2012) or by using minocycline and doxycycline (agents believed to cause dampening of microglial activation) efficacy in rodent models. For example, doxycycline prevented and reversed LPS-induced changes in immobility and brain IL-1β (Mello et al. 2013). Likewise, minocycline also attenuated LPS-induced behavioral changes and markers of neuroinflammation in mice (Henry et al. 2008). Recently, it was elegantly demonstrated that peripheral LPS also produces astrogliosis by measuring changes in bioluminescence of a reporter under GFAP promoter in mice (Biesmans et al. 2015).

Bacillus Calmette-Guerin (BCG) is an attenuated TB vaccine that is used to drive depression-like behaviors in mice (Moreau et al. 2008). A huge advantage of this model over LPS is the temporal resolution of depression over sickness like symptoms. While the sickness behaviors resolve within a week after BCG inoculation in mice, deficits of sucrose intake persist over 2–3 weeks helping in interpretation of drug action or elucidating signaling mechanisms in play. The BCG model is dependent of proinflammatory cytokines such as IL-6, TNF-α, IFN-γ and is also sensitive to TSPO upregulation as assessed by ex vivo autoradiography (Vijaya Kumar et al. 2014). All of these points to LPS and BCG as stimuli of neuroinflammation associated with depression.

More pathologically relevant models are where animals are stressed under different paradigms: acute restraint stress, shock stress, chronic unpredictable stress, chronic mild stress, and chronic social defeat stress. Some of these models have been carefully studied to probe the role of neuroinflammation in the brain while others have ancillary data suggestive of the same. None of the stress models have direct evidence of microglial activation by PET imaging of TSPO, which is a gap in the field. Acute restraint stressors have been used to drive depressogenic behaviors in rodent models, but there is scant literature of the role of a central neuroinflammation in such models. Models such as shock-induced stress (foot shock and tail shock) are probably more accepted as models of inflammation in the periphery with emerging data to support a neuroinflammatory component in the pathology (Arakawa et al. 2009; Weber et al. 2015). Models of chronic stress are probably relevant to studying the role of neuroinflammation associated with depression. For example, in a model of chronic stress, the authors demonstrated increased microglial activation and IL-1β, IL-6, and TNF-α in the substantia nigra (de Pablos et al. 2014). In another variation of chronic stress protocol, the results indicated that microglial activation was significantly increased in the infralimbic, cingulate, and medial

orbital cortices, nucleus accumbens, caudate putamen, amygdala, and hippocampus of the mouse brain (Farooq et al. 2012). Indirect lines of evidence (IL-1β blocking in the brain) would suggest that in chronic unpredictable stress paradigms, there is an element of inflammation in the brain (Koo and Duman 2008). Likewise, in chronic mild stress protocol of stress, indirect evidence of neuroinflammation exists as brain IL-1β levels were increased and blockade of capsase-1 caused a decrease of brain IL-1β and also reversed the deficit of sucrose intake (Zhang et al. 2015).

Conclusions

Taken together, these data support the hypothesis that elevated cytokine levels contribute to the pathophysiology of depression and the neurobiological mechanisms underlying resistance to conventional antidepressant drugs, in at least a subpopulation of depressed patients. They also suggest that specific cytokines and their effectors and regulators may constitute novel therapeutic targets for depression. Nevertheless, the extant postmortem data also indicate that mood disorders are not associated with classical neuroinflammation. Neither do all patients suffering from mood disorders have an inflammatory component; with the aid of diagnostic biomarkers (such as blood cytokine analysis or clinical PET imaging of neuroinflammation), it may be possible to target defined patient population suffering from depression and neuroinflammation, for clinical proof-of-concept studies with novel mechanism of action compounds that target signaling of microglia, astrocytes, or even peripheral cytokines/chemokines. Nevertheless, the field awaits definitive evidence that more targeted modulation of neuroactive cytokine signaling can exert antidepressant effects in primary mood disorders. Moreover, understanding whether centrally, as opposed to peripherally, acting therapies are needed to achieve antidepressant effects and determining the specificity of clinical populations likely to benefit from such treatments are key to mitigating safety concerns raised by using therapies that influence immunological function for mood disorders.

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