Glia and immune cell signaling in bipolar disorder: insights from neuropharmacology and molecular imaging to clinical application

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Bipolar disorder (BD) is a debilitating mental illness characterized by severe fluctuations in mood, sleep, energy and executive functioning. Pharmacological studies of selective serotonin reuptake inhibitors and the monoamine system have helped us to clinically understand bipolar depression. Mood stabilizers such as lithium and valproic acid, the first-line treatments for bipolar mania and depression, inhibit glycogen synthase kinase-3 beta (GSK-3β) and regulate the Wnt pathway. Recent investigations suggest that microglia, the resident immune cells of the brain, provide a physiological link between the serotonin system and the GSK-3β/Wnt pathway through neuroinflammation. We review the pharmacological, translational and brain imaging studies that support a role for microglia in regulating neurotransmitter synthesis and immune cell activation. These investigations provide a model for microglia involvement in the pathophysiology and phenotype of BD that may translate into improved therapies.

**INTRODUCTION**

Bipolar disorder (BD) is a pervasive, psychiatric illness that affects 5.7 million people in the United States. BD is characterized by fluctuating mood states, cognitive impairment and functional disability. Depressive episodes are the major contributing factor to the disability associated with bipolar illness, often first presenting in later adolescence and early adulthood. Because the impulsivity and grandiosity in mania may be misdiagnosed as a behavioral problem or attributed to another mental disorder, there is an estimated 10-year delay between onset of BD and accurate diagnosis. Therefore, early pharmacological management of BD is critical in order to avoid long-term disability and the increased health service utilization often associated with the illness.

Although only marginally understood, the pathophysiology of BD has traditionally been attributed to deficits in monoamine neurotransmitters, with a focus on serotonin, based on the mechanism of action of antidepressants. In clinical practice, patients that fail to respond to an optimized regimen of mood stabilizers tend to respond to augmentation with selective serotonin reuptake inhibitors (SSRIs). Bipolar depression mistaken for major depressive disorder (MDD) and treated with SSRIs can cause a ‘switch’ effect where patients may become manic. Although the serotonin system in particular has been implicated in the pathophysiology of bipolar depression, a growing body of evidence is shifting from theories of simple deficits in serotonin to those based on effects secondary to abnormalities in neuronal plasticity. In this context, plasticity is defined as an experience-dependent change in synaptic strength, cell resilience and/or connectivity. Homeostasis, support and protection of neurons are maintained by glia (microglia and astrocytes) in the brain and peripheral nervous system. Although astrocytes are large stellate cells that provide biochemical support, microglia are specialized macrophages capable of phagocytosis in order to protect neurons in the central nervous system (CNS). Microglia appear to function as sensors and regulators of serotonin production through pro-inflammatory cytokines in the brain. One link between microglia and serotonin production may be inflammatory signaling in the kynurenine pathway (KYP), an alternate route of tryptophan metabolism that decreases serotonin neurotransmission (Figure 1). Changes in the cytokine environment and serotonin production mediated by microglia appear to lead to long-term changes in synaptic function and downstream effects of apoptosis, excitotoxicity, neurogenesis and neurotrophic production. Developmental, neuropathological and imaging data in basic science and clinical models of BD demonstrate that serotonin production and neuronal connectivity are dependent on immune cytokine pathways in the periphery and the brain.

Mood stabilizers such as lithium (Li) and valproic acid (VPA) are the first-line pharmaceutical agents used in both the depressed and manic phases of BD. Although the mechanism of action of Li and VPA are unclear, they both apparently allow immune cell signaling through inactivation of the enzyme glycogen synthase kinase-3 beta (GSK-3β) in the Wnt pathway. Li and VPA also inactivate other enzymes involved in inflammation, including cyclooxygenase 2 and aracadonic acid. Recent data suggest that the Wnt family of lipoglycoproteins signal microglia activation through pro-inflammatory cytokines and β-catenin signaling networks (Figure 2). Gene-expression profiling also reveals that Wnt-3A stimulation specifically increases the expression of pro-inflammatory immune response genes in microglia and exacerbates the release of interleukin (IL)-6, IL-12 and tumor necrosis factor (TNF-α).
Given the strength of the evidence for involvement of neuroinflammatory processes in integrating the serotonin system with the Wnt pathway, the focus of this article is to critically examine the role microglia have in BD. We will relate findings in these signaling pathways to pharmacological treatment and clinical systems, based on current data and translational models for investigating the pathology and physiology of BD.

**ANTIDEPRESSANTS, SEROTONIN AND THE KYP**

Serotonin and bipolar depression

Monoamines have been implicated in altered production, transport, storage, release, reuptake and degradation of neurotransmitters in BD. Excitatory N-methyl-D-aspartate receptor and inhibitory gamma-aminobutyric acid amino acids, cholinergic...
and noradrenergic systems, corticotrophin releasing factor, thyrotropin releasing factor and other neurotransmitters and neuromodulators have been linked to the depressive phase of BD. 22 SSRIs, in the form of commonly prescribed antidepressant drugs, have hel ped to expand our knowledge of both unipolar depression (MDD) and BD and the mechanisms behind these disorders. Serotonin is involved in mood, sleep, appetite and energy level, all of which are altered in BD. The il licit drug 3,4- methylene-dioxy-methamphetamine (ecstasy) inhibits the reuptake of serotonin through the serotonin transporter (5-HTT). In a mood state that resembles BD, the transient elevation in serotonin activity generates feelings of elation, followed by depressive feelings related to depleted serotonin when the drug wears off. Multiple animal studies suggest that serotonin signaling may be influenced by immune cytokine pathways in the brain and periphery through the KYP. 11,12 Activated microglia in the KYP trigger an alternate route of tryptophan metabolism that ultimately reduces overall serotonin availability in the brain (Figure 1). Cytokines such as IL-2 and IL-6, released in the periphery from macrophages and in interferon-gamma (IFN-γ) from activated microglia within the CNS, may provoke overstimulation of the KYP that effectively depletes CNS serotonin levels and alters trophic support from brain-derived neurotrophic factor (BDNF) and TNF-α.23–25 A systematic meta-analysis of cytokines in BD found evidence in support of peripheral inflammatory alterations. Significant increases were observed in several cytokines and receptors including soluble IL-2, IL-2 receptor, IL-4, IL-6 receptor and TNF-α.26 Signaling pathways involving pro-inflammatory cytokines have also been shown to increase the activity of the serotonin 5-HTT in the brain, with inflammatory mediators in the KYP specifically connected to 5-HTT in other organ systems.27,23,24 Genetic and postmortem studies demonstrate a higher propensity to develop affective illness in individuals with 5-HTT regulatory site promoter region length polymorphisms (5-HTTLPR-s allele), and the associated cytokine-induced fatigue and depression symptoms were observed.28–31 Within the context of stressful events, there appear to be different allelic frequencies in BD compared with MDD, with no interaction with stress in conferring susceptibility in BD.32–34 Although one rare, distinct 5-HTT gene polymorphism was associated with greater chance of developing MDD but not BD,35 data from a different series of studies using a genetic marker within the serotonin transporter found a 5-HTT-transporter polymorphism that occurs at a higher frequency in both MDD and BD.36,37

Serotonin signaling through the KYP
The KYP, activated by peripheral cytokines and mediated by microglia, is an increasingly attractive potential modulator of serotonin and BDNF. Serotonin and BDNF may also be connected through pro-inflammatory cytokines. Research focused at the interface between inflammatory cascades, neuroplasticity and depression have demonstrated that once peripheral cytokines gain access to the brain, they influence production, release and reuptake of serotonin, as well as noradrenaline and dopamine.12 In BD a decreased plasma ratio of tryptophan, the precursor to serotonin, to other large, neutral amino acids was demonstrated in acute mania.27,38 Those serotonin deficits in the manic phase of BD form the basis of an interesting hypothesis that overstimulation of the enzyme indoleamine 2,3-dioxygenase (IDO) by peripheral and central inflammatory mediators activates the consumption of tryptophan in the KYP (Figure 1) and leads to serotonin depletion.27,24,39,40 That pathway represents an alternative metabolic route for tryptophan.12,24,27,38 Activated microglia in the brain promote expression of cytokines that leads to increased IDO activity and CNS tryptophan depletion with a concurrent increase in brain quinolinic acid, a metabolite produced distally within the KYP. Another enzyme, tryptophan 2,3-dioxygenase, further metabolizes tryptophan in the periphery along the KYP.19 Because brain tryptophan levels depend on plasma levels, brain serotonin will be compromised by the systemic activity of these two enzymes. Overproduction of quinolinic acid, an excitotoxin, can further decrease BDNF, activate pro-apoptotic cascades by TNF-α and increase glutamate and N-methyl-D-aspartate receptor-activated excitotoxicity.39,41 Interestingly, brain imaging studies demonstrate a selective increase in glutamate in the occipital cortex during both acute exacerbation and remission of depression.42,43 We propose that a portion of the neuropsychiatric findings in both depression and mania may rely on that mechanism. Furthermore, activation of that pathway may lead to changes in synaptic resilience, connectivity of serotoninergic neurons and/or stress-related cell death. Some propose that the balance between production of quinolinic acid versus kynurenic acid may be more important than serotonin depletion in mediating symptoms in BD. Translational methods to study activated microglia and serotonin transmission, specifically the integrity of the presynaptic 5-HTT sites, may lend insight into the pathogenesis of BD-related symptoms.

Given that antidepressant treatments enhance monoamine function, to date translational research has focused on the serotonin (5-HT) system in unipolar depression with bipolar depression used as a comparison.32,44–46 However, results related to the serotonin transporter in BD have conflicted at times, due in part to the heterogeneity of the populations studied, the radio-pharmacological used, the acute or mood state of the patient and other methodological differences.32,45 Recent advances in radiotracer development and high-resolution molecular imaging of the brain provide an opportunity to evaluate the serotonin system, as well as innovative pathways involved in neuronal plasticity and neuroinflammation in BD.

MOOD STABILIZERS, LI AND VPA AND THE WNT PATHWAY
Mood stabilizers are linked to pro-inflammatory cytokine production
Mood stabilizers, the primary pharmacological treatments for BD, have been shown to affect neuroinflammatory pathways.46 Cell culture, animal models and clinical studies examining haloperidol, lamotrigine, carbamazepine, Li and VPA show changes in arachidonic acid, cytokines and other markers of inflammation in the presence of these medications.47–49 However, some of these studies have been contradictory because of the variability in the cell types studied, diagnosis of the subjects included (bipolar I, bipolar II and/or euthymic) and other medications taken during the study. Many of the studies include pretreatment scenarios with non-physiological dosages of the mood stabilizers, which can also skew the interpretation of the results.18 However, the trend is that Li and VPA, in particular, dampen the pro-inflammatory response in BD and may stimulate inflammatory markers in euthymic patients.50

Both Li and VPA appear to affect inflammatory pathways by downregulating and/or skewing markers of T-cell activation, IL-2 and IFN-γ and by reducing lipopolysaccharide (LPS)-induced dopaminergic neurotoxicity by inhibiting microglial over-activation.19,50 In a recent study of the effects of Li on LPS-induced inflammation on rat primary glia cells, Li decreased expression of cyclooxygenase 2 and iNOS.51 Li also decreased secretion of TNF-α, IL1-β and PGE(2), although only in the presence of supra-therapeutic dosages of Li. In monocytes from healthy control subjects, Li increased IL-1 in a dose dependent manner and decreased levels of LPS, with no effect on IL-6.52 In contrast, another study in euthyemic bipolar patients compared to healthy controls showed lower levels of IL-2, IL-6, IL-10 and IFN-γ in the bipolar group only.53 The VPA pretreatment of glia cells is also suggested to reduce LPS-induced pro-inflammatory responses by limiting microglial activation
through the enzyme histone deacetylase, thus decreasing dopamine-related neurotoxicity.50

Li and VPA also upregulate the expression of the neurotrophic factors BDNF and glial cell line-derived neurotrophic factor from astrocytes that promote cell survival, differentiation and growth.60,54–57 Another group demonstrated that monocytes of a large proportion of bipolar patients and offspring of bipolar parents showed an inflammatory gene expression signature.12,58 Those treated with Li and VPA appear to have a downregulated expression of a series of inflammatory genes. This body of literature supports investigating biomarkers for inflammatory mediators as a logical next step to identify both manic and depressed states in patients. In addition to gaining insight into the pathophysiology of BD, information obtained from additional investigations may eventually help with therapeutic monitoring.

The Wnt/GSK-3β pathway is a target for mood stabilizers

A growing body of literature suggests that Li and VPA also target GSK-3β in the Wnt signaling pathway. The Wnt pathway is a highly conserved signaling cascade that is critical for synaptic plasticity, circadian rhythms and cell survival59 (Figure 2). GSK-3β is the principal enzyme in the Wnt pathway and appears to share a common link between proteins involved in immune response and clinical characteristics of BD, as well as schizophrenia and unipolar depression.60–62 Therefore, inflammatory cytokines, working through this signal transduction mechanism, may be a potential target for therapeutic intervention in BD. Medication induced and transgenic mouse models suggest that Li and VPA directly inhibit GSK-3β by upregulating expression of BDNF and glial cell line-derived neurotrophic factor from astrocytes and microglia that promote cell survival, differentiation and growth.63,64 In vitro studies using neuronal cell lines also demonstrate that Li and VPA inhibit GSK-3β, that leads to an accumulation of β-catenin. β-catenin, as a transcription factor, stimulates other neurotrophic factors and attenuates the activation of microglia.12,47,65 Therefore, the Wnt pathway is important for mood stabilizer activity and inflammatory signaling.

Genetic studies of Wnt proteins in inflammation and BD

An emerging body of literature supports the hypothesis that genetic aberrations or polymorphisms in the Wnt signaling pathway may be involved in BD.6 In studies of monzygotic twins discordant for BD, 292 genes were found to be differentially expressed in BD, with eight genes in the Wnt signaling pathway.66 Family-based association studies of 554 offspring with BD and their parents from 317 families found evidence for an association of BD susceptibility within the peroxisome proliferator-activated receptor (PPAR) gene family in the Wnt signaling pathway.55,67 Specifically, one group observed an association with a single-nucleotide polymorphism repeat that was within a single-haplotype block that spanned exons 3–7 of the gene on chromosome 6p. BD patients with a higher degree of functional impairment and carrying an allele in Wnt-2B or Wnt-7A were more strongly associated with this single-nucleotide polymorphism.68 Chromosome 6p has not been implicated directly by linkage studies of BD, although this region contains several interesting candidate genes that have been associated with both schizophrenia and psychotic BD.68–71

Inflammation, cell proliferation and peroxisomal functioning are modulated by the PPAR family of nuclear hormone receptors.72 However, members of the PPAR gene family have not been widely investigated in association with either bipolar depression, bipolar mania or psychotic disorders. Murine brain, skin and adipose tissue have significant gene expression of PPAR, with higher expression in the hippocampus, hypothalamus, entorhinal cortex, as well as within the corpus callosum and neostriatum.72–73 In rat models of neurodegeneration and ischemia, agonists of PPARD were neuroprotective.74 Several studies utilizing the Global Assessment of Functioning Scale, which captures both social-occupational and interpersonal functioning, identified unemployment and functional impairment as the most highly familial features of BD among 40 variables tested.75 The association of PPARD gene with poor functioning is consistent with a potential role for Wnt dysfunction in moderate to severe BD. Taken together, these findings suggest that Wnt polymorphisms may confer vulnerability for developing BD, and may act through inflammatory cascades to regulate trophic support to brain structures. Future studies that examine why BD symptoms cluster in families with Wnt gene polymorphisms and how this relates to serotonergic signaling will enhance our understanding of the Wnt cascade in BD.

**MICROGLIA: THE KEY CELLS WHERE ACTIONS OF ANTIDEPRESSANTS AND MOOD STABILIZERS CONVERGE**

Microglia and immune signaling

Based on pharmacological evidence, microglia appear to have a functional role in serotonin neurotransmitter signaling through inflammatory mechanisms that ultimately affect the Wnt/GSK-3β pathway and mood in BD.76 Gial cells have become increasingly important in understanding neurplasticity and cellular resilience mechanisms. Astrocytes and microglia are subtypes of glial cells in the CNS. Microglia, as the resident macrophages of the brain, adapt rapidly and respond to changes in the CNS environment by regulating cytokine production and neuronal plasticity and neurotransmitter synthesis. Microglia are considered ‘activated’ after interacting with macrophages and undergo a morphological change. Activated microglia proliferate, express the 18-kDa translocator protein (TSPO) and release cytokines and other signal systems.76 Postmortem studies in BD suggest a decreased number and size of microglia.77,82,84,108 The deficit in density and overall number of glia were most notable in the prefrontal cortex and anterior cingulate cortex of participants with mood disorders.82,84,108 Collectively, this reduction in microglial growth argues for a mood disorder-specific glial pathology where decreased proliferation occurs before BD or as a result of a protracted course of degeneration where extensive gliosis has not yet been processed. Bipolar patients are proposed to have a higher inflammatory load of circulating monocytes at the transcriptome level involving various inflammatory transcripts, regulated by microglia and related to the Wnt signaling pathway.13 However, little is known about the role of activated microglia in BD in manic versus depressed mood episodes. Given that microglia are thought to play a protective role, the clinical evidence in the literature and our preliminary studies, there is increased support for investigating activated microglia and inflammatory cytokines as potential biomarkers for predicting disease exacerbation in both the manic and depressed states of the illness.12,26,47,77 Therefore, activated microglia may be a potential biomarker for mood states and a measure of pharmacological response in BD therapy.

Serotonin signaling promotes inflammation through glial signaling

Multiple SSRIs have been proposed to have an effect on microglia with both pro-and anti-inflammatory properties reported.78 The disparate findings of decreased TNF-α production,79 increased and no effect84 on serotonergic production may be because of the differences in experimental approach. One group recently demonstrated that at dosages consistent with pharmacological treatment, fluoxetine, sertraline, paroxetine and fluvoxamine significantly increased LPS-induced production of TNF-α.78 They also found that exposure over 24-h and concentrations < 5 M of antidepressants actually created a pro-inflammatory environment. At the molecular level, serotonin production is also modulated by...
microglia. As mentioned above, activated microglia promote expression of inflammatory cytokines that stimulate IOD activity and deplete CNS tryptophan. Activated microglia signaling cascades, because of enzyme activation in the KYP, ultimately lead to lower levels of serotonin and alterations in 5-HTT availability (Figure 1).\(^1\),\(^4\),\(^8\)-\(^14\) Further tryptophan metabolism leads to overproduction of excitotoxins and additional cytokine activation, ultimately resulting in glutamate and N-methyl-D-aspartate receptor excitotoxicity. Interestingly, brain imaging studies demonstrate a selective increase in glutamate in the occipital cortex during both acute exacerbation and remission of depression.\(^1\),\(^15\) We hypothesize, as have others, that a portion of the neuropsychiatric findings in both depression and mania may rely on microglia acting through KYP mechanisms.

Wnt proteins interact with microglia to promote inflammation
The Wnt pathway is of interest in BD and molecular imaging investigations (Figure 2). We reviewed the role of Wnt-glial interactions in the section 'The Wnt/ GSK-3β pathway as a target for mood stabilizers', in our discussion, and their possible involvement in mood disorder. Although some argue that lack of sufficient clinical and postmortem data to support Wnt alterations in any mood disorder,\(^1\)\(^6\) pharmacological, neurodevelopmental and behavioral data point to the possibility of involvement of the Wnt pathway through glial-neuronal signaling. A recent series of studies provide strong evidence that Wnt-3A and Wnt-5A proteins act directly on β-catenin and drive a pro-inflammatory transformation of microglial cells.\(^2\),\(^2\),\(^3\),\(^4\) The Wnt family of lipoglycoproteins appear to direct response genes in microglia and generate de novo IL-6, IL-12 and TNF-α. Future clinical studies of microglia are needed that also incorporate β-catenin and GSK-3β genotypes and or signaling networks in order to understand pathogenic significance of microglia in BD.

FUNCTIONAL BRAIN IMAGING: NEUROTRANSMITTERS AND MICROGLIA
Advantages of in vivo imaging models
Investigation of therapeutic pathways and microglia related mechanisms for BD has been challenging because there are few animal models that fully recapitulate the disease. Most of the current information comes from postmortem studies.\(^2\),\(^8\),\(^1\) One limitation of postmortem tissue investigation is that the tissue is usually obtained after a person died or at the end stage of the disease. Despite the potential to understand BD noninvasively and therefore in a highly relevant milieu in human subjects, BD has received only limited attention in molecular imaging studies. Functional neuroimaging modalities such as positron emission tomography (PET), single-photon emission computed tomography and functional magnetic resonance imaging offer powerful, noninvasive methods to examine brain structure and neurochemical correlates involved in mood. Animal systems that combine cellular and molecular observations with imaging are being applied to the study of psychotic illnesses. One potential caveat of in vivo brain imaging is its sensitivity in identifying biological mechanism at the protein and receptor level in human subjects in either the depressed or manic phase of the illness.

Imaging the serotonin transporter in BD
In human subjects research, structural and functional studies are emerging in mood disorders, with the most consistent neuroimaging data related to alterations in serotonergic signaling in unipolar depression (MDD).\(^3\),\(^5\),\(^6\),\(^8\),\(^9\) However, translating observations in unipolar depression with findings in bipolar depression\(^9\) have not always been consistent. Studies with the 5-HTT ligand [\(^1\)C]DASB have shown increased serotonin transporter binding in bipolar patients and unipolar depressed patients with bipolar relatives\(^9\),\(^1\)\(^0\). The 5-HTT radiopharmaceutical [\(^1\)C]3-aminoo-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile, [\(^1\)C]DASB has enabled sensitive detection of alterations in serotonergic transmission.\(^9\),\(^9\),\(^1\)\(^0\)\(^1\) [\(^1\)C]DASB was found to be a more effective radioligand for the serotonin transporter owing to its fast kinetics, reversibility, higher selectivity, greater specific binding and higher reproducibility.\(^9\),\(^9\) In vivo evaluation of 5-HTT with [\(^1\)C]DASB has been used by several groups in the setting of alcoholism, tryptophan depletion, occupancy studies of different SSRI medications and most recently in our lab in HIV-associated depression.\(^9\),\(^8\),\(^1\)\(^1\)\(^2\)\(^3\) Interestsing studies in unipolar depression showed increased binding to 5-HTT and a return to normal 5-HTT availability in recovered depressed patients in a euthymic mode.\(^9\),\(^8\),\(^1\)\(^1\)\(^2\),\(^3\) However, in bipolar-depressed patients, the data from several studies to date have not been so consistent.\(^9\),\(^8\),\(^1\)\(^1\)\(^2\),\(^3\) One study genotyped for bi- and triallelic 5-HTTLPR polymorphisms in bipolar-depressed patients demonstrated lower 5-HTT binding in BD and no difference in 5-HTTLP in BD compared with controls.\(^4\) However, imaging was done with a radiopharmaceutical that some believe has less specific binding than [\(^1\)C]DASB.\(^9\),\(^8\),\(^1\)\(^0\)\(^4\) The other study used PET imaging with [\(^1\)C]DASB in BD, unipolar depression and controls. Unipolar depression and BD were both associated with elevated 5-HTT binding in the insula, thalamus and striatum, but showed distinct abnormalities in the brainstem.\(^3\) The BD finding could be explained by potential medication effects, the varied genetic background of the patients studied or conceivably because of underlying differences in the pattern of symptoms between MDD and BD.\(^3\) To address some of the confounding factors that have appeared in the neuroimaging literature, future studies are needed that focus on imaging families with BD or individuals with common genetic polymorphisms.

Imaging studies that target microglia
Molecular imaging methods to study activated microglia as a marker of neuroinflammation may lend insight into the pathogenesis of BD-related symptoms. Structural imaging studies report lower glial and neuronal cell volume and density in the dorsolateral prefrontal cortex and amygdala of patients with MDD,\(^1\)\(^0\) and the subgenual cortex in familial BD.\(^9\),\(^8\),\(^1\)\(^0\)

TSPO is an 18-kDa, mitochondrial membrane protein that is involved in a wide variety of functions including induction of apoptosis, cholesterol transport and modulation of inflammatory responses.\(^1\)\(^1\) Known recently as the peripheral benzodiazepine receptor (PBR), but expressed in the brain and the periphery, TSPO has been linked to in vivo monitoring of glial cell activation.\(^3\),\(^1\)\(^0\),\(^1\)\(^1\)\(^1\) Specifically, glial cells that are inactive have low expression of TSPO, whereas active cells have increased expression.\(^1\)\(^2\),\(^1\)\(^3\) As glia cells can be activated by a variety of brain insults, the measurement of TSPO binding is arguably a potential inflammatory marker in PET imaging is [\(^1\)C]-R-PK11195.\(^1\)\(^9\),\(^1\)\(^1\)\(^8\) However, [\(^1\)C]-R-PK11195 is characterized by high nonspecific binding, high protein binding and low brain uptake.\(^1\)\(^5\) To address those limitations, our group and
others used the PET ligand \[^{11}\text{C}]\text{N,N-diethyl-2-}[2-(4-methoxyphenyl)-5,7-dimethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-acetamide, \[^{11}\text{C}]\text{DPA-713, which appears to bind to the TSPO, as a plausible way to study microglial activation and implied neuroinflammation in vivo,119 with \[^{11}\text{C}]\text{DPA-713-PET as a developing method by which to evaluate inflammation.120 We examined the cerebral uptake of \[^{11}\text{C}]\text{DPA-713 in healthy human control subjects and found that \[^{11}\text{C}]\text{DPA-713 had substantially greater delivery and increased specific binding compared with \[^{11}\text{C}]\text{-R-PK11195.120 Those results indicate that \[^{11}\text{C}]\text{DPA-713 is a promising TSPO ligand for investigating what is likely neuroinflammation with PET. Whole-body PET/computed tomography of \[^{11}\text{C}]\text{DPA-713 shows an uptake pattern that is consistent with the biodistribution of TSPO and yields a dose burden that is comparable to that of other \[^{11}\text{C}]\text{-labeled PET tracers.121 Our preliminary studies with \[^{11}\text{C}]\text{DPA-713 show increased volume of distribution in the anterior, and posterior cingulated gyrus and the ventral lateral thalamus.77 Other TSPO ligands are emerging as promising imaging agents for the practical quantification of microglia. \[^{11}\text{C}]\text{PBR28 binds to TSPO and has been used in PET imaging to assess potential microglial activation.122,123,125 Other second-generation TSPO ligands evaluated in major psychiatric illnesses include \[^{11}\text{C}]\text{vinpocetine,126 \[^{18}\text{F}]\text{-FEPPA, \[^{11}\text{C}]\text{DAA1106,127 \[^{18}\text{F}]\text{-PBR06,128 and several other pharmacological probes.117 To date, many of the second-generation TSPO ligands have been used to study TSPO binding in Alzheimer’s disorder, with no studies reported to date in mood or psychotic disorders.126,127,129}

Clinical correlates of glial and immune signaling

Pro-inflammatory cytokines in both the peripheral and signaled by microglia in the CNS appear to operate in parallel and are involved in clinically relevant aspects of BD, including neuronal plasticity, neurotransmitter synthesis and neuroendocrine processes.12,15,137 There are several lines of clinical and pharmacological evidence that are consistent with microglia involvement in the inflammatory hypothesis of BD. They include:

(1) Patients with systemic inflammatory disorders such as coronary artery disease, multiple sclerosis, Crohn’s disease, cancer,
HIV and rheumatoid arthritis have a higher incidence of mood disorders compared with medically healthy individuals.\textsuperscript{137–139} BD is associated with a greater prevalence of diabetes mellitus, thyroid disease, obesity and other neuroendocrine diseases associated with inflammation.\textsuperscript{140,141}

(3) Increased production of pro-inflammatory cytokines IL-2, IL-2 receptor IL-6 (P < 0.01), TNF- \( \alpha \) (P < 0.05) and markers of inflammation, chemokines, C-reactive protein and adhesion molecules have been demonstrated in the blood and CSF in both the manic and depressive phases of BD compared with healthy subjects.\textsuperscript{25,45,126,142}

(4) Acutely ill BD patients with systemic inflammation and non-hepatic tissue damage have a higher risk for early natural death, which is reduced with Li treatment.\textsuperscript{138}

(5) Targeted therapies with anti-inflammatory agents such as eicosanoids, cyclooxygenase 2 inhibitors and antagonists to TNF- \( \alpha \) have been shown to ameliorate symptoms in MDD and BD patients.\textsuperscript{143}

Studies in patients on chronic IFN- \( \alpha \) therapy have been some of the most compelling in identifying neuroanatomical targets for cytokine effects.\textsuperscript{12,144} Previously euthymic hepatitis C and cancer patients undergoing chronic IFN- \( \gamma \) treatment have been observed to exhibit hypomimic-type symptoms of hypervigilance, irritability and anxiety, as well as full-blown mania.\textsuperscript{12,145} These studies suggest a particular vulnerability in the dorsal anterior cingulate cortex compared with non-IFN- \( \gamma \) treated control subjects.\textsuperscript{146}

Neuroimaging data demonstrate that BD as well as high anxiety, obsessive-compulsive traits and difficulty with conflict resolution have been associated with the dorsal anterior cingulate cortex.\textsuperscript{93,147,148} Prospective studies further identified an occurrence of depression of 30–50% in cancer patients treated with IFN- \( \gamma \) and chemotherapeutic agents.\textsuperscript{135,145,149} These clinical correlations combined with a translational research approach from lessons in pharmacology and neuroimaging will hopefully lead to more studies designed to understand the pathophysiology of BD.

SUMMARY

BD is a prevalent illness with significant disability and early mortality through suicide. The mechanisms through which both depression and BD develop are poorly understood. The monoamine hypothesis of mood disorders suggests that one of the biological bases of bipolar depression is a deficiency in serotonin. As glial cell activation (Figure 3) represents a potential common pathway for serotonin synthesis and neuronal plasticity, the available data strongly support translational, \textit{in vivo} imaging of inflammation as an encouraging area of investigation for the proposed examination of the pathophysiology of BD.\textsuperscript{117,118} The relevance of these studies is emphasized by the prevalence of BD and the need to implement early diagnostic and improved treatment interventions in order to decrease the morbidity and mortality associated with the illness. Molecular imaging research on the pathophysiology of BD and mechanisms pertaining to inflammation, alterations in serotonergic transmission and neuroplasticity are sparse. So far, PET studies to evaluate transporter availability in BD have focused on monoamine systems, including serotonin (5-HT) and the serotonin transporter (5-HTT), with both null and positive results depending on the demographics of the population studied. Important information will be acquired regarding the interactions of genetic factors and inflammatory mediators in bipolar patients, as well as the specific role of 5-HTT in the regulation of cellular plasticity cascades in BD. With experimental limitations from animal models and postmortem tissue for BD, we believe that future brain imaging studies in combination with translational methods will address the unmet needs for a coherent and comprehensive clinical model of BD. There is also a need to identify relevant inflammatory targets for improved therapeutic interventions. A growing body of literature also supports an increased appreciation for the integrated role of microglia in mood disorders research. An understanding of glia and immune signaling will potentially enhance discovery in the brain and behavioral sciences and fuel research on the causes of mental disorders.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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