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Emerging role of the P2X7-NLRP3-IL1β pathway in mood disorders

Anindya Bhattacharya[a,*], Declan N.C Jones[b]

[a] Janssen Research & Development, Neuroscience Therapeutic Area, 3210 Merryfield Row, San Diego, CA 92121, United States
[b] Neuroscience External Innovation, Johnson & Johnson Innovation Centre, One Chapel Place, London, W1G 0BG, United Kingdom

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ABSTRACT

The science of neuroimmunopsychiatry has evolved rapidly in the last few years with the hope of tackling the unmet need in mood disorders. This article focuses on an inflammatory pathway, highly conserved in myeloid cells that may play a role in neuroinflammatory disorders including depression. Within the brain tissue, microglia are the myeloid cells that express the P2X7 ion channel that is connected through the NLRP3 inflammasome complex leading to release of IL-1β and IL-18. We present, in the way of reviewing relevant literature, the preclinical data and scientific rationale supporting the role of the P2X7-NLRP3-IL-1β pathway in mood disorders. We also highlight recent advances in drug discovery and development of P2X7 small molecule antagonists and P2X7 PET ligands which provide optimism that clinical tools are availableto address critical proof-of-concept experiments in mood disorders.

1. Depression and neuroimmunology: call for a renewed thinking and 'out of the box' approach to help patients

It is now well established that mood disorders such as major depressive disorder (MDD) and bipolar disorder (BD) show high lifetime prevalence rates resulting in significant impact on quality of life to patients and their families (Hirschfeld, 2012). This is compounded by the negative social stigma associated with mental health, resulting in delayed medical assistance, causing debilitating neuropsychological conditions, sometimes leading to suicidal ideation and death. When patients with mood disorders do seek medical attention, a large proportion of the patient pool either do not respond adequately or with only a very limited response to current medications; as such, less than ideal improvements in quality of life accompanied by side effect burden reduces the motivation for patients to maintain the treatment regimen for a sufficient time. Hence, the unmet need (fast onset of action, maintenance therapy, relapse prevention, efficacy in treatment resistant depression, efficacy in bipolar depression) is high and there is an overwhelming need for innovation and investigation of novel mechanisms of action for new medications in psychiatry (O'Leary et al., 2015). Unfortunately, despite the high unmet need, a number of pharmaceutical & biotechnology organizations decided to stop drug discovery work in psychiatry, due to the number of failed clinical trials, challenges in patient selection, clinical trial methods, and the associated financial risk (Cook et al., 2014). Rational drug discovery and development has been challenging in this space due to insufficient knowledge of the etiology of mood pathology resulting in poor animal modeling and a consequent lack of confidence in pre-clinical target validation approaches (O'Donnell and Ehlers, 2015). There is now growing appreciation that not all mood disorder patients present with similar domains of pathology, and as such 'one size fits all' approach to treatments in psychiatry is inappropriate. Perhaps, with the advent of genomics and biomarkers correlating and/or predicting disease susceptibility and treatment response, one can hope that the days of meaningful precision medicine in psychiatry (Amare et al., 2017) are not far away, perhaps analogous to the medical advances made in personalized treatment of certain cancers (Barnes et al., 2017).

Why do most mood disorder patients fail to adequately respond to current medications and, if they do respond, why do they so often fail to remit (Gaynes et al., 2009). It is well appreciated in neuropsychiatry that there is a lack of detailed understanding of the causality of mood disorders; at least, it is not as refined as some other diseases (psoriasis, diabetes, breast & lung cancer). Perhaps, it time to challenge the traditional "neuron-centric" view of neuropsychiatric disorders and to appreciate that brain circuitry is defined by both neurons and glia, important cellular partners that may account for some component of the mood pathology (Mechawar and Savitz, 2016; Ongur et al., 2014). Glial cells, notably microglia play an important role in maintaining innate immunity and are the drivers of inflammation within the CNS (Li and Barres, 2018). One recent area of focus is the link between inflammatory disorders as a co-morbidity to mood disorders. Although this story is not new (Maes et al., 2016), a robust body of data is

* Corresponding author.
E-mail address: abhatta2@its.jnj.com (A. Bhattacharya).

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emerging suggesting an important role for an imbalance of the immune system and the central nervous system (CNS), leading to the hypothesis that mental health, especially depression, may be modulated by systemic inflammatory tone (D'Mello and Swain, 2017; Pfau et al., 2018). For example, it is now known that administration of pro-inflammatory cytokines such as interferon-α (IFN-α) or low dose endotoxin (LPS) can induce depressive symptoms in man and preclinical species. In one of the clearest examples indicating that elevated cytokine signaling can cause depressive symptoms, immune challenge with IFN-α during the treatment of hepatitis C reliably induces the major depressive syndrome (and less commonly manic symptoms) in 30%–40% of previously non-depressed humans (Hepgul et al., 2016; Hoyo-Becerra et al., 2014; Pace and Miller, 2009). The neuropsychiatric sequelae of IFN-α converges with other types of evidence to suggest that elevated signaling of some neuroactive cytokines (TNF-α, IL-6, IL-1β) can play a causal and/or a maintenance role in depressive symptomology (Dantzer, 2018; Pfau et al., 2018). The neuroactive cytokine hypothesis of depression has been corroborated pre-clinically, specifically by showing that immune activation produces depression-like behaviors in repeatedly stressed animals and that these behaviors can be prevented or reversed by targeting factors such as IL-6 and IL-1β (Miller et al., 2017; Remus and Dantzer, 2016).

In subjects with MDD or BD one of the more highly replicated biomarker abnormalities is an elevation in peripheral blood IL-6 concentrations (Hodes et al., 2016). Notably during IFN-α treatment the magnitude of the increase in plasma and CSF IL-6 levels correlates positively with depressive symptom severity (Hofer and Campbell, 2016). 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). In a preclinical model of depression, it was elegantly demonstrated that increased peripheral IL-6 contributed to the depressogenic behavior, and systemic administration of an IL-6 antibody was effective in modulating such behavioral phenotypes, indicating that targeting circulating IL-6 maybe an alternate strategy in depression (Hodes et al., 2014). Sun et al (2017) explored whether IL-6 neutralizing monoclonal antibodies (mAb) may show antidepressant activity in humans by analyzing the clinical trial data from studies using sirukumab in rheumatoid arthritis (RA) and siltuximab in multicentric Castleman's Disease (MCD) (Sun et al., 2017). These studies showed that among patients who exhibited high-depressive symptoms at baseline, administration of an anti-IL-6 mAb significantly improved mood relative to placebo, even after co-varying for changes in primary medical illness severity and in subgroups whose primary medical illness had not improved. In the sirukumab RA study, the pre-treatment plasma levels of the soluble IL-6 receptor (sIL-6R) correlated with the magnitude of improvement in depression ratings under sirukumab. Conversely, a study that used tocilizumab, a mAb against IL-6 receptor, proved ineffective at improving depressive symptoms, although significant improvements in anxiety measures were seen (Traki et al., 2014). It is important to point out that the clinical study in question was not designed to measure symptomatic improvements in depression as the primary endpoint; rather it was a RA study where mood symptom changes were also captured. Preclinically, efficacy of IL-6 receptor antibody has been demonstrated in a social defeat model of stress-induced anhedonia (Zhang et al., 2017). Whether the efficacy in preclinical models is due to central IL-6 or IL-6 receptor blockade remains speculative; it remains more likely that the effects seen in these models are primarily due to dampening of peripheral IL-6/IL-6 receptor signaling. A Phase 2a clinical study is ongoing to directly assess the effects of sirukumab as an adjunctive treatment in MDD who have had a suboptimal response to the current standard oral antidepressant therapy and have elevated C-Reactive Protein (CRP) ≥ 3 mg/l (https://clinicaltrials.gov/ct2/show/NCT02473289).

TNF-α is another pro-inflammatory cytokine that has been linked to the pathology of depression (Tyring et al., 2006) and a clinical study of the efficacy of infliximab (mAb TNF-α) in depressed patients generated negative results on depressive symptoms rating using a conventional depression rating scale (Raison et al., 2013). However, a post hoc investigation of data from this study revealed a significant positive correlation between clinical improvement and pre-treatment levels of the nonspecific inflammation marker, CRP, raising the possibility that antidepressant effects may be limited to individuals who manifest a pro-inflammatory 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 (since very low proportions of peripherally administered monoclonal antibodies enter the brain following acute treatment), or whether therapies that reduce TNF-α signaling must instead directly engage targets in the CNS. As such, the strategy to treat depression by targeting peripheral inflammatory factors, such as IL-6 and TNF-α, is yet to be unequivocally demonstrated in the clinic and additional clinical studies in the most appropriate populations are required to effectively test these mechanisms.

A second approach is to target neuroinflammatory mediators directly in the brain (Najjar et al., 2013). IL-1β is another immune derived signaling molecule that is related to mood pathology and several lines of scientific evidence points to the potential vulnerability of the IL-1β pathway in mood disorders, and converging data points to the importance of targeting IL-1β in the brain (Koo and Duman, 2009). Within the brain parenchyma, microglia are analogous to macrophages of the immune system and play a role in guarding the immune health of the brain. Microglia can sense danger signals and generate pro-inflammatory factors causing neuroinflammation. As such, microglial targets which are amenable to small molecule drug discovery may represent a new set of targets to drug hunters (Biber et al., 2016). In addition, several lines of recent data point to the critical role of microglia in neurodegenerative conditions; one concept that has been discussed recently is the role of 'disease associated microglia' (Keren-Shaul et al., 2017) and 'border associated macrophages' (Mrdjen et al., 2018) in the brain, a significant evolution of the M1 (pro-inflammatory) and M2 (anti-inflammatory) phenotype proposal. While we are scratching the surface with regards to this line of inquiry and the relevance to disease, there is tremendous excitement in the field to prosecute targets in both neurology and psychiatry in this space. Several companies, including Janssen, have attempted to identify drug-like molecules (and now clinical candidates) targeting microglial ATP-gated ion channel P2X7, that is known to cause IL-1β release (see subsequent section). A rapidly expanding scientific literature suggests that alterations in immune system function and neuroinflammation play major roles in the pathophysiology of at least some subtypes of mood disorders. How do these cytokines impact symptoms in patients that may manifest clinically as a mood disorders? Emerging literature suggests that immune cells in the periphery and/or the brain (*i.e.* microglia and/or perivascular macrophages and/or infiltrating monocytes) interact with neurons in the CNS to play roles in the pathophysiology of mood disorders in animal models (Hodes et al., 2015), although this is yet to be clinically proven. 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. Recently the discovery of CNS lymphatics in the brain meninges has provided a new insight into possible mechanisms by which immune cells at the borders sense and react to brain health