Immune influences on the brain: new findings and implications for treatment

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The European Behavioural Pharmacology Society (EBPS) sponsors a biennial workshop to promote scientific exchange and present the latest advances in behavioural neuroscience discovery related to neuropsychiatric disorders and pharmacological interventions. The current special issue of *Psychopharmacology* arose from an EBPS-sponsored workshop on immune influences on the brain and behaviour held at the University of Sussex in June 2014.

This meeting represented, we believe, the first international conference on immunopsychiatry. It brought together leading researchers from the USA, Europe and Israel. Key themes included the following: (1) the role of immune modulators in memory and the progression of neurodegenerative disorders, (2) the contribution of prenatal and perinatal infection and/or inflammation to common mental illnesses and (3) targeting the immune system to treat mental illnesses, including depression, schizophrenia and alcohol dependence. The special issue brings together papers covering a number of these themes.

Over recent years, there has been an explosion of interest in the role of the immune system in depression. Pro-inflammatory cytokines can acutely depress mood, and when given chronically (e.g. during the treatment of hepatitis C) induce major depressive episodes. Interestingly, the article by Fialho et al. in the special issue provides evidence that some antidepressant treatments may also influence interferon alpha treatment for hepatitis C (Fialho et al. 2015). The evidence for the role of the immune system in the pathogenesis of depression is expertly reviewed in the article by Bhattacharya et al. (Bhattacharya et al. 2016), which draws together the multiple lines of evidence and considers their implications for understanding unipolar affective disorders and their treatment. Two original investigations published in the special issue add to this literature, showing that inflammation is linked to the persistence of depressive symptoms (Zalli et al. 2015), and indicate a role for IL-6 acting on the locus coeruleus in the development of depressive-like behaviour (Kurosawa et al. 2015). The latter paper, in particular, indicates that the inflammatory system has effects on a number of neurotransmitter systems relevant to depression. The review by Boorman et al. in the special issue considers this further, focusing on the endocannabinoid system (Boorman et al. 2015), and discusses the therapeutic implications for developing new treatment for depressive disorders.

It has also become apparent over recent years that existing therapeutic agents have effects on inflammatory pathways, and this was the subject of a previous editorial (Mondelli and Howes 2013). Baumeister et al. review this literature for antidepressants and the other major classes of psychotropic drugs (Baumeister et al. 2015). Several other papers extend this literature by investigating the role of inflammation in therapy for affective disorders (Fialho et al. 2015; Grosse et al. 2015; Herteleer

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et al. 2016; Hung et al. 2015), and psychotic disorders (Hefner et al. 2015; Da Cruz Jung et al. 2015).

Early life infection and inflammation has long been implicated in the aetiology of a number of common mental illnesses including depression, anxiety and schizophrenia. Khandaker and Dantzer review this for schizophrenia, as well as drawing on other recent data to discuss the potential role of inflammation in the pathoaetiology of psychotic disorders (Khandaker and Dantzer 2015). Autoantibodies to neuroreceptors, in particular to glutamatergic and dopaminergic receptors, have emerged in the last few years as a new potential immune pathoaetiological mechanism for psychotic disorders, so it is timely for Pollak et al. to review this growing literature and consider the many outstanding issues (Pollak et al. 2015).

Stress is another factor that can predispose to the future development of mental illness. A growing literature has investigated the effect of a variety of stressors on microglia, the brain's resident immune cells. Evidence for microglial activation has been reported in vivo in patients with depression as well as schizophrenia, but also those at risk of mental disorders (Setiawan et al. 2015; Bloomfield et al. 2016). The review by Calcia et al. in this issue finds that a variety of stressors are associated with upregulation of a marker for microglia, suggesting that stress could be a common mechanism underlying microglial changes across these disorders (Calcia et al. 2016).

The immune system has also been implicated in addiction. Prof Fulton Crews spoke at the EBPS meeting on how neuro-immune signalling contributes to the neurobiology of alcohol addiction, and has distilled this into a review in this issue (Crews and Vetreno 2015).

Finally, Leboyer et al. raise the question of whether the role for the immune system in mental disorder is sufficiently established for therapeutic trials in their provocative paper in the special issue (Leboyer et al. 2016). Ultimately, the success of immunopsychiatry will be judged on its ability to deliver new or repurposed immunotherapies that meaningfully enhance the lives of patients suffering from mental illnesses. The finding from Yu et al. that the cysteinyl leukotriene receptor 1 mediates the link between stress and inflammation and depressive behaviour is one example where new mechanistic insights could identify novel treatment targets (Yu et al. 2015).

Together, the papers in this special issue highlight the growing body of evidence linking systemic and central inflammation to a range of common mental illnesses including disorders of mood, schizophrenia and alcohol dependence. This evidence coupled with the active engagement of partners from the pharmaceutical industry suggests a bright future for the nascent field of immunopsychiatry and the promise of immunotherapeutics for mental illness in the not-too-distant future.

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