Progress in Neuro-Psychopharmacology & Biological Psychiatry 54 (2014) 265–274

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

Review article

A phase-specific neuroimmune model of clinical depression

H.A. Eyre [a,b], M.J. Stuart [c], B.T. Baune [a,*]

[a] Discipline of Psychiatry, School of Medicine, University of Adelaide, Adelaide, Australia
[b] School of Medicine and Dentistry, James Cook University, Townsville, Australia
[c] School of Medicine, University of Queensland, Brisbane, Australia

ARTICLE INFO

Article history:
Received 20 May 2014
Received in revised form 17 June 2014
Accepted 25 June 2014
Available online 3 July 2014

Keywords:
Cytokine
Depression
Immune
Inflammation
Model
Staging

ABSTRACT

Immune dysfunction and pro-inflammatory states in particular have been implicated in the aetiology and pathogenesis of depression. Whilst the onset of an episode and certain symptoms of depression appear well explained by this inflammatory model, the underpinnings of the episodic and progressive nature, as well as relapse and remission status in depression require attention. In this review it is suggested that additional immune factors beyond pro- and anti-inflammatory cytokines may effectively contribute to the understanding of the neurobiology of clinical depression. Considering neurobiological effects of immunomodulatory factors such as T cells, macrophages, microglia and astrocytes relevant to depression, we suggest a neuroimmune model of depression underpinned by dynamic immunomodulatory processes. This perspective paper then outlines a neuroimmune model of clinical phases of depression in an attempt to more adequately explain depression-like behaviours in pre-clinical models and the dynamic nature of depression in clinical populations. Finally, the implications for immunomodulatory treatments of depression are considered.

Contents

Abbreviations: MDD, major depressive disorder; PIC, proinflammatory cytokine; AIC, anti-inflammatory cytokine; HC, hippocampus; LTP, long term potentiation; HPA, hypothalamus-pituitary-adrenal; 3-HK, 3-hydroxykynurenine; QA, quinolinic acid; IDO, indoleamine-2,3-dioxygenase; SSRI, selective serotonin reuptake inhibitor; SNRI, selective serotonin and noradrenaline reuptake inhibitor; ECT, electroconvulsive therapy; NSAID, Non-steroidal anti-inflammatory drug; PFC, prefrontal cortex.

* Corresponding author at: Discipline of Psychiatry; School of Medicine, University of Adelaide; Adelaide, SA 5005, Australia. Tel.: +61 8 8222 5141; fax: +61 8 8222 2865.
E-mail address: Bernhard.Baune@Adelaide.edu.au (B.T. Baune).

1. Introduction

Major depressive disorder (MDD) presents a major heath concern and challenge for clinical management. MDD is high in burden of disease and it is predicted to rise in the future (WHO, 2008). Moreover, clinical depression management is hampered by low rates of remission

http://dx.doi.org/10.1016/j.pnpbp.2014.06.011
0278-5846/

following initial treatment (~70%) (Trivedi et al., 2006), and nearly one-third will not achieve remission following several treatment steps (Rush et al., 2006a, 2006b).

Biological models of depression play an important role in etiological and pathophysiological research and clinical management of MDD. Amongst such biological models, factors of the immune system exerting effects on key processes such as neuroplasticity, neurotransmission, oxidative stress and neuroendocrinological functions are considered to be central to the development of depression (Dantzer et al., 2008; Eyre and Baune, 2012c; Haroon et al., 2012; McAfoose and Baune, 2009; Miller et al., 2009). Each of these models attempts to explain the complex interaction of environmental factors (i.e. stress), with underlying biological vulnerabilities (e.g. genetic/epigenetic) factors which converge to produce the observed spectrum of clinical presentations and associated anatomical, functional, and biochemical disturbances (Baune, 2009; Mahar et al., 2014; Moylan et al., 2014; Slavich and Irwin, 2014). These interactions between stress and the aforementioned biological systems are likely to be bi-directional and dynamic over the temporal progression of any individual's illness which confers additional complexity to any model of depression. A full description of the role of stress in the initiation and potentiation of depressive illness and its interactions with immune processes are beyond the scope of this review, and are extensively described elsewhere (see for reviews Mahar et al., 2014; Moylan et al., 2014).

The most established immune-based model of depression is the inflammatory or cytokine model of depression (Dantzer et al., 2008; McAfoose and Baune, 2009; Miller et al., 2009). This model postulates that a pro-inflammatory state characterised by elevations in pro-inflammatory cytokines (PICs) and reductions in anti-inflammatory cytokines (AIC) are involved in the development of depression-like behaviour in animals and clinical depression in humans. The net pro-inflammatory state is found to impair hippocampal (HC) neuroplasticity (e.g. neurogenesis, synaptic plasticity, long-term potentiation (LTP)), induce glucocorticoid insensitivity of the hypothalamo–pituitary–adrenal (HPA) axis, increase oxidative stress in the HC, reduce serotonin levels and create neurotoxic serotonergic metabolites (i.e. 3-hydroxykynurenine (3-HK) and quinolinic acid (QA)) (Dantzer et al., 2008; Eyre and Baune, 2012d; Leonard and Maes, 2012; Miller et al., 2009; Moylan et al., 2012). Although this model suggests that anti-inflammatory treatments could alleviate symptoms of depression by reducing the net pro-inflammatory state in the brain, recent findings appear to be inconclusive on the clinical efficacy of anti-inflammatory treatments (Gallagher et al., 2012; Muller et al., 2006, 2011; Raison et al., 2012; Warner-Schmidt et al., 2011).

In line with a pro-inflammatory state in the depressed brain is the neuroprogression model recently published by Moylan et al. (2012). This model suggests that a neuroprogressive process occurs in some patients with MDD leading to poorer symptomatic, treatment and functional outcomes. In such patients, longer and more frequent episodes appear to increase vulnerability to develop further episodes (Kendler et al., 2001). The neuroprogressive nature of such a course of disease is believed to be associated with structural brain changes and changes in inflammatory, neurotransmission, oxidative and nitrosative stress pathways, neuroplasticity, HPA axis modulation and mitochondrial dysfunction (Maes et al., 2012b, 2012c; Moylan et al., 2012; Sheline et al., 2003; Videbech and Ravnkilde, 2004).

Whilst the inflammatory pathophysiology and neurobiology of depression may explain the progressive nature of depression in some patient groups, the complexity of the involvement of the immune system in clinical depression may go beyond pro- and anti-inflammatory compounds. This preliminary conclusion can be drawn from clinical observations such as the discordance between the essentially linear increase in systemic inflammatory milieu observed with increasing age and the bimodal peaks of incidence of depression in not only the elderly; but also early adulthood (Hein and O'Banion, 2012; Kessler et al., 2005), the paucity of efficacy of anti-inflammatory drug compounds (i.e. non-steroidal anti-inflammatory agents (Gallagher et al., 2012; Warner-Schmidt et al., 2011) and anti-cytokine molecules such as infliximab (Raison et al., 2012)) in depression. Moreover, immunomodulatory factors such as systemic immune cells (e.g. central nervous system-specific autoreactive CD4+ T cells, M2-type blood-derived macrophages and T regs) and microglia and astrocytes exert neuroprotective effects relevant to molecular mechanisms of neuroplasticity (Eyre and Baune, 2012c).

This body of research is suggestive of a complex relationship between neuroinflammation, neuroprogression and neuroprotection in the development of depression and in clinical states of depression such as relapse, remission and recovery. Hence, in this review we formulate a neuroimmune model of depression that encompasses both neuroprogressive, neuroinflammatory and immunomodulatory processes that help explain the complex clinical nature and variable natural history of MDD and that may aid the development of immunomodulatory treatments in MDD.

2. Clinical phases of a neuroimmune model of depression

We suggest three phases in the proposed neuroimmune model: *sub-syndromal*, acute *clinical* and *post-acute*. Together, these stages represent a potential range of clinical scenarios relevant to depression. The phases are represented by various interrelated neuroimmune, neuroplasticity and neuroprotection changes which will be outlined later in this paper.

The *sub-syndromal phase* encompasses factors relevant to depression prior to the onset of clinically significant symptoms. These include sub-threshold symptoms and risk factors for the development of depression. In this phase, a proportion of patients may not go on to develop a depressive episode, with their sub-threshold symptoms reducing shortly thereafter. Some patients may go on to develop a major depressive episode.

The *acute clinical phase* of the model encompasses the initiation and main duration of the clinically significant part of the depressive episode, when there is maximal symptomatology. Depressive symptoms may be mild, moderate or severe and may include melancholic, atypical, psychotic and non-melancholic symptomatology. This phase can be the first episode for an individual and may form a single episode with no life-time relapse; however, this phase may instead connote a recurrence of depression with a prior period of total or partial remission. Finally this stage may represent a progressive recurrence of depression whereby each episode can be associated with more severe symptomatology and a longer duration than the previous episode (Moylan et al., 2012).

The *post-acute phase* encompasses a period when depressive symptoms are generally improving. During this period there can be full recovery whereby the symptomatology of the affected individual is the same as before the depressive episode; alternatively, there can be partial recovery. The final possibility is there is no recovery and the affected individual's symptoms become chronic and neurocognitive decline is progressive.

3. Immune considerations for the neuroimmune model of depression

In the following sections we will outline how the neuroimmune factors are differentially disordered in the various clinical phases of the proposed model. There will also be a discussion of the neurobiological rationale for the role of these factors in each phase and highlighted areas for further investigation. Clinical studies will be utilised for evidence where possible.

3.1. Immune considerations in the sub-syndromal phase of depression

3.1.1. Pro-inflammatory cytokines in the sub-syndromal phase of depression

PICs and their associated neurobiological effects on neuroplasticity, neuroendocrine processes and neurotransmitters are thought to be