Psychoneuroendocrinology (2012) 37, 1397—1416

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

REVIEW

Neuroplastic changes in depression: A role for the immune system

Harris Eyre [a,b], Bernhard T. Baune [a,*]

[a] Discipline of Psychiatry, School of Medicine, University of Adelaide, North Terrace, Adelaide, South Australia 5005, Australia
[b] School of Medicine and Dentistry, James Cook University, 101 Angus Smith Drive, Townsville, Queensland 4811, Australia

Received 29 November 2011; received in revised form 15 March 2012; accepted 22 March 2012

KEYWORDS
Neuroplasticity;
Depression;
Immune system;
Humoral;
Cellular;
Recovery;
Treatment

Summary Accumulating evidence suggests that there is a rich cross-talk between the neuroimmune system and neuroplasticity mechanisms under both physiological conditions and pathophysiological conditions in depression. Anti-neuroplastic changes which occur in depression include a decrease in proliferation of neural stem cells (NSCs), decreased survival of neuroblasts and immature neurons, impaired neurocircuitry (cortical—striatal—limbic circuits), reduced levels of neurotrophins, reduced spine density and dendritic retraction. Since both humoral and cellular immune factors have been implicated in neuroplastic processes, in this review we present a model suggesting that neuroplastic processes in depression are mediated through various neuroimmune mechanisms.

The review puts forward a model in that both humoral and cellular neuroimmune factors are involved with impairing neuroplasticity under pathophysiological conditions such as depression. Specifically, neuroimmune factors including interleukin (IL)-1, IL-6, tumour necrosis factor (TNF)-α, CD4+CD25+T regulatory cells (T reg), self-specific CD4+T cells, monocyte-derived macrophages, microglia and astrocytes are shown to be vital to processes of neuroplasticity such as long-term potentiation (LTP), NSC survival, synaptic branching, neurotrophin regulation and neurogenesis. In rodent models of depression, IL-1, IL-6 and TNF are associated with reduced hippocampal neurogenesis; mechanisms which are associated with this include the stress-activated protein kinase (SAPK)/Janus Kinase (JNK) pathway, hypoxia-inducible factors (HIF)-1α, JAK-Signal Transducer and Activator of Transcription (STAT) pathway, mitogen-activated protein kinase (MAPK)/cAMP responsive element binding protein (CREB) pathway, Ras-MAPK, PI-3 kinase, IKK/nuclear factor (NF)-κB and TGFβ activated kinase-1 (TAK-1).

Neuroimmunological mechanisms have an active role in the neuroplastic changes associated with depression. Since therapies in depression, including antidepressants (AD), omega-3 polyunsaturated fatty acids (PUFAs) and physical activity exert neuroplasticity-enhancing effects potentially mediated by neuroimmune mechanisms, the immune system might serve as a promising target for interventions in depression.

* Corresponding author. Tel.: +61 8 8222 5141; fax: +61 8 8222 2865.
E-mail address: Bernhard.Baune@Adelaide.edu.au (B.T. Baune).

0306-4530/$ — see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.psyneuen.2012.03.019

Contents

1. Introduction

The increasing burden and prevalence of depression make the search for an extended understanding of the aetiology and pathophysiology of depression highly significant (WHO, 2008; Lepine and Briley, 2011). The pathophysiology of depression is hypothesised to be associated with various neurobiological changes (Baune, 2009; Miller et al., 2009a). An emphasis has been given to neuroimmune processes for directly and indirectly affecting other important neurobiological processes of depression (Garcia-Bueno et al., 2008; Maes et al., 2009; Kubera et al., 2010). Neuroinflammatory proteins such as TNF-α, IL-6, C-reactive protein (CRP), IL-1β, interferons alpha and gamma (IFN-α and γ) are affecting immunological mechanisms in the periphery and the central nervous system (CNS); they are potential mediators of symptoms of depression-like behaviour (Garcia-Bueno et al., 2008; Anisman, 2009; Maes et al., 2009; Kubera et al., 2010; Wager-Smith and Markou, 2011). These findings have lead to the formulation of the cytokine model of depression due to the capacity of pro-inflammatory cytokines to induce 'sickness behaviour', which closely resembles depression-like behaviour in humans (Dantzer et al., 2008; Capuron and Miller, 2011). Cells which are implicated in the production of pro-inflammatory cytokines include astrocytes, microglia, macrophages and T cells (Garcia-Bueno et al., 2008).

Neuroinflammatory mechanisms in depression are thought to negatively interact with various pathways and can lead to monoamine dysfunction e.g. lowering serotonin levels, creation of neurotoxic tryptophan-like by-products (3-hydroxykynurenine (3-HK) and quinolinic acid (QA)), hypothalamo—pituitary—adrenal (HPA) axis dysfunction (e.g. hypercortisolaemia and reduced glucocorticoid receptor density), neurogenesis dysfunction (e.g. apoptosis and reduced neurotrophin production), neurocircuitry dysfunction (cortical—striatal—limbic circuits) and neuroimmune dysfunction (e.g. decreased T cell proliferation, increased apoptotic rate and impaired T cell function) (Caruso et al., 1993; Maes et al., 1995; Mellor et al., 2003; Clark et al., 2005; Miller et al., 2009a; Kubera et al., 2010; Piser, 2010; Bloch and Qawasmi, 2011).

The neurogenesis hypothesis of depression posits the following: (1) neurogenesis in the subgranular zone of the dentate gyrus is negatively affected by stress and (2) alterations in the rate of neurogenesis play a significant role in the pathophysiology of depression (Hanson et al., 2011). Functional and volumetric magnetic resonance imaging (MRI) studies provide a clinical correlation to pre-clinical findings (Ahdidan et al., 2011; Arnone et al., 2011; Delgado y Palacios et al., 2011; Rowland, 2011). Depression-related hippocampal pathology is found in clinical studies and is indicated by reduced volume (Hanson et al., 2011). In the pre-clinical setting depression-like behaviour is found to have negative effects on neurogenesis in the adult hippocampus (HC) including a reduction in the proliferation rate of NSC and other markers of neurogenesis (e.g. impaired neurocircuitry and decreased survival of neuroblasts) (Fournier and Duman, 2011; Hanson et al., 2011; Petrik et al., 2011).

Accumulating evidence suggests that there is a rich cross-talk between the neuroimmune system and NSCs to regulate neuroplasticity under physiological and pathological conditions. Understanding the neuroimmune mechanisms regulating neuroplasticity will assist in understanding the interaction of immune cells, cytokines and chemokines with the pathways and systems of the brain that regulate neurodevelopment, neuroprotection and neurorepair. The precise role of neuroimmune regulation of neural plasticity is largely unknown, although in vivo and in vitro studies suggest a beneficial effect of certain neuroimmune mediators (Molina-Holgado and Molina-Holgado, 2010). Mediators such as interleukins IL-1, IL-6, IFN and TNF-α play a role in these processes (Gonzalez-Perez et al., 2010; Molina-Holgado and Molina-Holgado, 2010). Cellular neuroimmune mechanisms such as various subtypes of T cells are involved in regulating neurogenesis across physiological and pathological conditions (Huang et al., 2010; Schwartz and Shechter, 2010a,b; Capuron and Miller, 2011). For example, T reg cells are shown to enhance HC neurogenesis via increasing glial cell-derived neurotrophic factors (GDNFs) and transforming growth factor beta (TGF-β); moreover, in a pathological stroke model, absence of T reg cells confer reduced HC neurogenesis (Kipnis et al., 2004; Reynolds et al., 2007; Ziv et al., 2007). A clinical study has shown that serum T reg numbers are decreased in the depressed state, and the cell population increased following successful antidepressant therapy (Himmerich et al., 2010). However, the exact role of T regs in depression is not known since T regs appear to exert complex regulatory and counter-regulatory effects in neurobiological processes.

It has been suggested that therapies in depression may exert neuroplasticity enhancing effects mediated by neuroimmune mechanisms (Capuron and Miller, 2011; Hanson et al., 2011; Haroon et al., 2011; Kubera et al., 2011; Shie