Progress in Neuro-Psychopharmacology & Biological Psychiatry 35 (2011) 760–768

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Cytokines mediated inflammation and decreased neurogenesis in animal models of depression

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ARTICLE INFO

Article history:
Received 13 May 2010
Received in revised form 15 June 2010
Accepted 23 June 2010
Available online 30 June 2010

Keywords:
Depression
Animal models
Cytokines
Neurogenesis
Neurotrophic system
Omega-3 fatty acids

ABSTRACT

In patients with major depression or in animal models of depression, significantly increases in the concentrations of pro-inflammatory cytokines have been consistently reported. Proinflammatory cytokines can stimulate the hypothalamic-pituitary-adrenal (HPA) axis to release stress hormone, glucocorticoids. As a consequence of excessive inflammatory response triggered by pro-inflammatory cytokines in the periphery, free radicals, oxidants and glucocorticoids are over-produced, which can affect glial cell functions and damage neurons in the brain. Indeed, decreased neurogenesis and the dysfunction of neurotrophic system (up- or down-regulations of neurotrophins and their receptors) have been recently found. Effective treatments for depressive symptoms, such as antidepressants and omega-3 fatty acids can increase or modulate neurotrophic system and enhance neurogenesis. However, the relationship between glial cells; microglia (mostly involved in neuroinflammation) and astrocytes (producing neurotrophins), and the contribution of inflammation to decreased neurogenesis and dysfunction of neurotrophic system are almost unknown. This review first introduces changes in behavior, neurotransmitter, cytokine and neurogenesis aspects in depressed patients and several animal models of depression, secondly explores the possible relationship between pro- and anti-inflammatory cytokines and neurogenesis in these models, then discusses the effects of current treatments on inflammation, neurotrophic system and neurogenesis, and finally pointes out the limitations and future research directions.

1. Introduction

Major depression is a severe psychiatric disorder that has lifetime prevalence in excess of 15%, and is the fourth leading cause of disability worldwide (Maes et al., 2009) as well as the second largest contributor to the global burden of disease by the year 2020 (aan het Rot et al., 2009). About one third (36%) of Canadians have suffered from depression or anxiety themselves. This makes depression a major healthy concern to the personal and economic welfare (Sobocki et al., 2006).

Over the last two decades, new developments in psychiatric research have led to the hypothesis that inflammatory processes and brain-immune interactions are involved in the pathogenesis of major depression, and may contribute to the dysfunction of serotonergic and noradrenergic systems. Increased levels of pro-inflammatory cytokines e.g. interleukin (IL)-1, IL-6, IL-8, IL-12, interferon (IFN)-γ and tumor necrosis factor (TNF)-α have consistently been reported in patients with depression (Schiepers et al. 2005; Raison et al., 2006; Mossner et al., 2007). Systemic exposure to inflammatory challenges, such as lipopolysaccharide (LPS), not only causes a systemic inflammation, but also induces a central neuroinflammation, reflected by activation of brain microglia with a chronically elevated production of pro-inflammatory mediators, such as TNF-α in the brain, which may remain elevated for 10 months (Qin et al. 2007). It is well-known that LPS administration (either peripheral or central) induces neuroinflammation and increases pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α, and may induce specific symptoms, labeled as the sickness behavior syndrome (Dantzer, 2009). These behavioral changes, including lethargy, decreased libido, psychomotor retardation and impairment in memory, anorexia and weight loss or eating disorder, anxiety and stress-like behavior, sleep disturbances and hopeless behavior, are similar to those observed in depressed patients. The neuroendocrine changes after an inflammation challenge, such as the dysfunction of the hypothalamic-pituitary and

Abbreviations: ACh, acetylcholine; AChE, acetylcholinesterase; BDNF, brain-derived neurotrophic factor; ChAT, choline acetyl transferase; cPLA2, calcium-dependent cytoplasmic phospholipase A2; CRF, corticotrophin-releasing factor; DGNF, glial-derived neurotrophic factor; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FGF, fibroblast growth factor; HPA, hypothalamic-pituitary-adrenal; i.c.v., intracerebroventricular; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; NGF, nerve growth factor; NA, noradrenaline; NR, NMDA receptor subunit; OB, olfactory bulbectomized; n, omega; PGE2, prostaglandin E2; Th, T helper; TNF, tumor necrosis factor; 5-HT, serotonin.

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doi:10.1016/j.pnpbp.2010.06.020

adrenal (HPA) axis, and hypercortisolism, are also similar to those observed in depressed patients. Conversely, in depression, there is a strong correlation between the depressed symptoms and the presence of peripheral inflammation (Bremmer et al., 2007).

The hypercortisolism and excessive inflammatory responses have been reported to contribute to neuronal apoptosis and death (Zhu et al., 2010; Woodman and Lockette, 2009). Indeed, several lines of evidence indicate that mood disorders are characterized by a decreased neurogenesis (Rajkowska and Miguel-Hidalgo, 2007; Frodl et al., 2006; Hajsza et al., 2005). Structural brain changes detected by MRI in depressed patients have been reported in several brain regions, including volumetric changes in the hippocampus, amygdala, prefrontal cortex, anterior cingulate and basal ganglia (Campbell and MacQueen, 2006). Cellular changes in the postmortem hippocampus and neuronal and glial modifications have also been observed (Stockmeier et al., 2004). The selective and persistent loss of hippocampal volume is not only induced by hippocampal neuronal death, but also by decreased neurogenesis (Sapolsky, 2004). The precise role of new neurons in the hippocampus is still unclear. Since new neurons are easily excitable and plastic, they may be recruited into the hippocampal circuitry upon demand during various behaviors such as learning, exploring a new environment, running, undergoing stress etc. Becker and Wojtowicz, 2007 postulated that new neurons may involve into a unique generation of distinctive episodic memories without interference of their turnover. In the depressed patients, their recall of episodic memories, particularly for positive events, is overly general and lacking details (Brittelbank et al., 1993). As well, the hippocampus is not only widely known to be critical in memory, it is also in a key position to indirectly influence responses to stress and emotion by connecting and regulating limbic regions, such as the hypothalamus and amygdala. Thus, the reduction of hippocampal neurogenesis may contribute to other depressive symptoms. Indeed, increasing evidence has indicated a link between reduction of hippocampal neurogenesis and depression: 1) stress, as a trigger or cause of depression has been found to increase inflammatory responses (Maes et al., 2002) but reduce neurogenesis (Rothman and Mattson, 2010). Early stress (in the childhood) may induce developmental abnormalities in the amygdala, hippocampus, anterior cingulate cortex, and corpus callosum (Bremner and Narayan, 1998). In adult tree shrews, stressful conditions decrease neurogenesis in the dentate gyrus (Gould et al., 1997); 2) many factors that are beneficial in treating the behavioral symptoms of depression have been shown to enhance neurogenesis in laboratory animals; these include electroconvulsive therapy (ECT), exercise, environmental enrichment and effective antidepressant treatments (Kempermann et al., 1997; Bjornebekk et al., 2005; Zhu et al., 2006; Malberg et al., 2000). Furthermore, significant decreases in neurotrophins, particularly brain-derived neurotrophic factor (BDNF); have been detected in depression and in stress-induced animal models of depression (Angelucci et al., 2005). In several rodent models of depression, reduced hippocampal neurogenesis were reported (Goshen et al., 2008; Koo and Duman, 2008) along with decreases in the levels of BDNF in brain regions (Schmidt and Duman, 2007; Fuchs et al., 2004). Recent evidence suggests the involvement of other neurotrophic factors, fibroblast growth factor (FGF) and glial-derived neurotrophic factor (GDNF), in depression since a reduced activity in the FGF system during brain development may result in a predisposition or vulnerability to depression (Turner et al., 2006), while reduced GDNF in depression (Michel et al., 2008) may be related to glial-mediated neuroimmune condition.

As mentioned above, depression is associated with an increased inflammatory processe and reduced neurogenesis. Even though the direct effect of neuroinflammation on neurotrophic system and neurogenesis is unknown, increasing evidence may suggest that proinflammatory cytokines and neuroinflammation are through three ways to reduce neurogenesis by 1) stimulating the HPA axis to release glucocorticoids that suppress neurogenesis (Liu et al., 2003); 2) changing glial cell functions, in which changes in astrocyte-produced neurotrophins could make significant contribution, and 3) overproduction of oxygen radicals and pro-inflammatory cytokines can directly damage neurons.

It is well-known that inflammation can increase the production of oxygen radicals, and such an increase was also found in depressed patients (Sarandol et al., 2007; Forlenza and Miller, 2006; Maes et al., 2007). The brain and the nervous system are prone to oxidative stress since they are inadequately equipped with antioxidant defense systems to prevent oxidative damage (Halliwell, 2006). The neurodegenerative effects of oxidative stress may be explained by increased generation of reactive oxygen species, which overwhelms the antioxidant defenses in the brain causing oxidative damage (Pong, 2003). The latter together with subsequent mitochondrial dysfunctions and accumulation of oxidized proteins can causes damages to DNA and membrane fatty acids, which can disrupt lipid signaling and enhance lipid peroxidation. Moreover, oxidative stress can adversely affect gene expression and proteolysis, which also contribute to neurodegeneration (Halliwell, 2006; Mancuso et al., 2006; Bazan et al., 2005; Potashkin and Meredith, 2006). Indeed, in animal models, administration of pro-inflammatory cytokine inducers, LPS, or pro-inflammatory cytokines can result in marked suppression of hippocampal neurogenesis (Ekdahl et al., 2003; Monje et al., 2003; Goshen et al., 2008; Koo and Duman, 2008).

Inflammation-reduced neurogenesis may be via the activation of microglia (Kempermann and Neumann, 2003) since both pro-inflammatory cytokines and oxidative stress is produced by activated microglia. As sequence of microglial activation, the other glial cells, astrocyte functions, especially the production of neurotrophins may be changed. Neurotrophins and their receptors compose a major neuroprotective system in the brain because they stabilize and maintain homeostasis (protection and repair), control and clean neurotoxins, regulate neurotransmission and modulate neuronal regenesis and degenesis (Meyer et al., 2001; Cadete-Leite et al., 2003; Kerschensteiner et al., 2009). However, the relationship between neuroinflammation and neurotrophin functions is unclear in depression research. Obviously, to understand this relationship will be very important for knowing the role of inflammation in the decreased neurogenesis in depressive illness. Thus, this article reviews recent findings in inflammation and neurogenesis aspects from studies in animal models and try to find the link and correlation between these two pathological factors.

2. Findings from animal models of depression

Several animal models have been used to study the neuropathology of depression; these include olfactory bulbectomized (OB) rats (Song and Leonard, 2005), chronic or sub-chronic IL-1 administration in rats (Song et al., 2006), psychosocial stress in tree shrews (Czeh et al., 2001), social defeat in rats (Czeh et al., 2010), foot-shock stress in rats (Malberg and Duman, 2003) and LPS-induced model (Brown, 2007). Among these models, the OB rat is the most studied depression model in terms of the link between inflammation and neurodegeneration (Song and Leonard, 2005; Wang et al., 2007a, b; Wang et al., 2010). Many studies in the past 25 years have demonstrated that changes in behavior, neurotransmission, neuroendocrine and the immune system in OB rats are qualitatively similar to those observed in depressed patients. The OB rat is also a popular model for evaluating the effects of various treatments for mood disorders (Tsunekawa et al., 2008).

2.1. OB model

Bilateral removal of the olfactory bulbs in rats produces a complex constellation of behavioral, neurochemical, neuroendocrine and immune alterations, which are qualitatively similar to those observed in patients with major depression. OB-induced changes can be