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Impact of inflammation on neurotransmitter changes in major depression: An insight into the action of antidepressants

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ABSTRACT

This review summarises the evidence that chronic low grade inflammation plays an important role in the pathology of depression. Evidence is provided that pro-inflammatory cytokines, together with dysfunctional endocrine and neurotransmitter systems, provide a network of changes that underlie depression and may ultimately contribute to the neurodegenerative changes that characterise depression in the elderly.
Antidepressants attenuate the inflammatory changes and hypercortisolaemia by reducing the release of the pro-inflammatory cytokines from activated microglia, and by sensitizing the glucocorticoids receptors in the HPA axis. These effects correlate with an improvement in monoamine neurotransmitter function. The possible mechanisms whereby this cascade of changes occurs are outlined.
In conclusion, the mechanisms whereby antidepressants act should now consider the involvement of the immune and endocrine systems in addition to the central neurotransmitters. This may open up possibilities for a new generation of antidepressants in the future.

1. Introduction

Major depression is a chronic illness which results in functional impairment and frequently to a lifelong social and physical disability. Those with major depression commonly experience frequent relapses, incomplete recovery and residual symptoms and therefore it is not surprising that depression is one of the ten leading burdens of disease world-wide (Lopez et al., 2006). In addition to the adverse psychosocial dysfunction associated with depression, physical ill-health, such as heart disease, type-2 diabetes, autoimmune diseases and cancer, are often associated with the disorder (Leonard, 2013; McIntyre et al., 2012).

Of the various possibilities that have been posited to explain the link between physical and mental illness, a disruption of the immune-endocrine axis would appear to provide the most plausible explanation. The purpose of this review is to consider how such changes may account for the pathophysiology of depression and how an understanding of the psychoimmune changes caused by drugs that attenuate the symptoms may open up novel possibilities for the development of new therapeutic agents.

In recent years there has been an increasing interest by neuroscientists in the role that chronic low grade inflammation plays in the psychopathology of major psychiatric and neurological disorders. The expansion of experimental and clinical research into inflammation has been stimulated by knowledge that the pathological changes occurring in brain disorders are not limited to specific neurotransmitter abnormalities but reflect multifunctional changes in the immune, endocrine and neurotransmitter circuits in the brain. This has led to a reappraisal of the mechanisms whereby the hypothalamic-pituitary-adrenal (HPA) axis, and components of cell mediated immunity such as the pro- and anti-inflammatory cytokines, impact on the brain and thereby contribute to the pathological changes (Connor and Leonard, 1998; Pace and Miller,2001; Leonard, 2010).

There is now substantial experimental and clinical evidence to indicate that a combination of inflammation and oxidative stress plays a crucial role in the pathophysiology of major depression (Maes et al., 2011; Maes,1995; Song et al. 1994). At the level of the neuron, these changes result in the activation of excitotoxic pathways that contribute to the increase in apoptosis and a reduction in areas of the brain (such as the hippocampus, amygdala and pre-frontal cortex) which are critically involved in the pathology of depression. Smith (1991) was one of the first to hypothesise that the pro-inflammatory cytokines, exemplified by interleukins (IL-) 1 and 6, interferon gamma (IFN) and tumour necrosis factor alpha (TNF) in the serum, were associated with the principal symptoms of depression (Pariante and Miller, 2001) while the anti-inflammatory cytokines (such as IL-4,10 and 13) were reduced. Such observations formed the basis of the macrophage theory of depression, a concept that has been substantiated with additional evidence showing that the activated prostenoid pathway (leading to an increase in prostaglandin E2, PGE2) and nitric oxide sythase (resulting in an increase in nitric oxide) also played key roles in the damaging effects of chronic, low grade inflammation in the brain (see Connor and Leonard, 1998; Kubera et al., 2001; Janelidze et al., 2011; Maes, 1999; Kim et al., 2002; Leonard, 2001).

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The credibility of the macrophage theory was further supported by the effect of the pro-inflammatory cytokine IFN-alpha when administered therapeutically to treat hepatitis C and some types of leukaemia. It was reported that a substantial minority of these patients developed symptoms of major depression as a consequence of the treatment, effects which were attenuated by antidepressants (Capuron et al., 2002a,b) Thus the core symptoms of depression would appear to be linked to an increase in serum pro-inflammatory cytokines while a pro-inflammatory cytokine such as IFN-alpha can induce depressive-like symptoms in otherwise non-depressed patients. Furthermore, effective antidepressant treatment would appear to antagonise the adverse effects of the pro-inflammatory cytokine by increasing the concentration of anti-inflammatory cytokines, such as IL-10 (Colin et al., 2003).

The association of raised inflammatory markers, such as the pro-inflammatory cytokines and C-Reactive Protein (CRP) in the blood of patients with major depression, suggests that such factors may be potential markers of the disorder. An additional marker which has received attention recently is vascular endothelial growth factor (VEGF). VEGF is implicated in neuronal survival, neuroprotection, differentiation and axonal growth and has been reported to be reduced in the cerebrospinal fluid of severely depressed patients (Isung et al., 2012). This would support the hypothesis that neuronal repair is reduced in severe depression and thereby linked to the neurodegenerative changes found in the brain of such patients. However, Igo et al. (2007) reported that the mRNA of VEGF was increased in the lymphocytes from depressed patients and decreased in response to effective antidepressant treatment. Clearly it is necessary to be cautious in extrapolating from change in the blood and peripheral tissues to those occurring in the brain. There are a number of immune compartments in the periphery, and possibly also in the brain, and while they are interconnected, they may not reflect the same quantitative and qualitative changes.

Physical and/or psychological stress plays a significant role in activating the HPA axis and the autonomic nervous system. The activation of the adrenoceptors on the macrophages in the periphery, and on the microglia in the brain, increases the inflammatory signalling pathway in which nuclear factor kappa beta (NF-kB) plays a crucial role. This results in an increase in cell mediated immunity even in the absence of an antigen challenge. The activation of the T-lymphocytes increases the Th1 lymphocytes to release IFN-gamma and IL-2; IL-2 then induces Th cells to further increase the inflammatory response. The rise in IFN-gamma triggers the release of neopterin, a marker of cell- mediated immunity. Similar changes are thought to occur in the brain as a consequence of the activation of the endothelial cells which line the blood–brain barrier and also by the activation of the vagus nerve which signals the central nicotinic receptors to activate the inflammatory response in the brain. In the brain such changes result in a multitude of pro-inflammatory cytokines, chemokines, PGE2 and reactive nitrogen and oxygen species.

Hitherto, the therapeutic actions of psychotropic drugs have been described in terms of their ability to counteract aberrant neurotransmitter changes, particularly those affecting the biogenic amines. There is some controversy whether the changes in biogenic amines associated with the action of antidepressants are the primary cause of the therapeutic response or whether the therapeutic response is more a reflection of a network of interacting processes involving neurotransmitters, hormones and immune modulators. This short review will discuss the role of the pro-inflammatory cytokines in depression and how antidepressants may modulate the inflammatory changes associated with these cytokines.

2. Relationship between the immune, endocrine and neurotransmitter systems in depression

Cytokines act in an autocrine, paracrine and endocrine fashion to control the proliferation, differentiation and the activity of immune cells. Although there are several types of immune cells that secrete cytokines, attention has been directed to the T-helper (Th) cells in particular. Thus the Th-1 cells secrete mainly pro-inflammatory cytokines, such as interferon-gamma (IFN-gamma), tumour necrosis factor-alpha (TNF-alpha) and interleukin-2 (IL-2) and promote cellular immunity whereas the Th-2 cells mainly secrete the anti-inflammatory cytokines (IL-4,IL-10 and IL-13) and promote humoral immunity (Mosman and Sad, 1996). The Th-1 and Th-2 cells are derived from activated Tho (naïve CD4 + cells) while IL-12, derived from macrophages, monocytes and dendritic cells, is the primary inducer of Th-1 cell differentiation. This explains why the stress induced activation of macrophages and monocytes in peripheral blood, and microglia in the brain, induces Th-1 cells to synthesise and release pro-inflammatory cytokines as a component of the stress response. In addition to the involvement of Th- 1 cells in cellular immunity, the Th-1 derived cytokines together with IL-12 stimulate the synthesis of the gaseous transmitter nitric oxide from nitric oxide synthase thereby enhancing the chronic delayed type inflammatory response Fearon and Locksley, 1996).

Th-1 and Th-2 responses are largely antagonistic in that IFN-gamma, and IL-12, inhibit the activity of Th-2 cells while anti-inflammatory cytokines from Th-2 cells inhibit Th-1 cell activity. This implies that an important property of Th-2 cells is to inhibit macrophage and microglia activation, T-cell proliferation and the synthesis of pro-inflammatory cytokines (Fearon and Locksley, 1996). In chronic depression, there is abundant evidence that pro-inflammatory cytokines predominate and thereby contribute to the pathological changes which characterise the disorder (Smith, 1991). In addition, the elevation in plasma cortisol and the increase in the sympathetic drive, which characterises major depression, also contribute to the inflammatory load as it is now apparent that the increased activity of the sympathetic system enhances the synthesis of the pro-inflammatory cytokine IL-6 (Coros et al., 2002) depressed patient.

3. Pro-inflammatory cytokines and depression

The macrophage theory of depression, as conceived by Smith (1991), postulated that the cardinal symptoms of depression are a reflection of the increase in pro-inflammatory cytokines. Clinical evidence in favour of this theory is based on the association of pro-inflammatory cytokines with the depressed mood, anhedonia, sleep disturbance, anorexia, decreased libido and fatigue. Further support for the theory is provided by the response of a substantial minority of non-depressed patients with hepatitis or leukaemia being treated therapeutically with IL-2 or IFN-alpha. These cytokines initiate a severe depressive episode in a substantial minority of the patients, effects which are largely attenuated by appropriate treatment with SSRI antidepressants (Capuron et al., 2002a,b, 2004).Such changes correlate with the activation of the anterior cingulated nucleus, a region of the brain that has been implicated in the major symptoms of depression (Capuron et al., 2005).

It is of interest that the inflammatory changes associated with depression, or initiated by pro-inflammatory cytokines, are attenuated by antidepressants. It is perhaps not surprising therefore to find clinical evidence that non-steroidal anti-inflammatory drugs, such as the cyclo-oxygenase (COX)-2 inhibitor celecoxib and even the non-selective COX inhibitor aspirin, have antidepressant effects as shown by the augmentation of the antidepressant response (Mendlewicz et al., 2006; Mueller et al., 2006) and even when administered alone to depressed patients (Akhondzadeh et al., 2009).The possible mechanism whereby celecoxib enhances the therapeutic effect of antidepressants has been investigated experimentally to determine if there was a link between the inhibition of COX-2 and changes in the release of noradrenaline and serotonin in the rat cortex when it is administered concurrently with the selective noradrenaline reuptake inhibitor reboxetine or the SSRI fluoxetine. Johanssen et al. (2012) showed that celecoxib enhanced the cortical release of noradrenaline and dopamine, but not serotonin,