REVIEW: THE ROLE OF INFLAMMATION IN DEPRESSION

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SUMMARY

The role of inflammation in major depressive disorder (MDD) has been of growing interest over the past two decades and evidence suggests it plays a role in depression. Evidence linking inflammation to MDD comes from three different observations (a) elevated levels of inflammatory markers in patients with MDD, even in the absence of illness, (b) co-occurrence of MDD with inflammatory illnesses and (c) increased risk of MDD with cytokine treatment. Cytokines have been found to influence almost every pathway involved in the pathogenesis of depression including alterations to the expression of neurotransmitters, neuroendocrine function, synaptic plasticity and basal ganglia. The similarities between cytokine-induced sickness behaviour and MDD further support a role of inflammation in depression as well as the anti-inflammatory effects of successful antidepressant treatment. This account describes the inflammatory mechanisms thought to be involved in MDD and the evidence for this.

Key words: *major depressive disorder - cytokines – inflammatory - markers – interleukin - tumour necrosis factor - C-reactive protein - interferon*

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INTRODUCTION

Major depressive disorder (MDD) is the most common psychiatric illness and it is the leading cause of disability worldwide (Moussavi et al. 2008, Kiecolt-Glaser & Glaser 2002). ICD-10 (international classify-cation of disease 10) and DSM-IV (diagnostic and statistical manual of mental disorders IV) characterizes MDD as a persistent low mood, anhedonia, fatigue or low energy and at least one of these core symptoms, or a combination, must be present on most days for at least 2 weeks. Biological symptoms include disturbed sleep with early morning wakening, loss of appetite, diurnal mood variation and reduced libido. Cognitive symptoms include hopelessness, helplessness, worthlessness, poor concentration, low-self esteem, guilt and suicidal idea-tion. MDD consists of seven or more of these symptoms once they become pervasive and significantly affect daily functioning. The aetiology of MDD includes stressful life events, personality, gender, illness, family history, personal support, loneliness as well as alcohol and drugs abuse. Although the pathophysiology of MDD is poorly understood, it is thought to include changes in the expression of neurotransmitters, altera-tions to the hypothalamus-adrenal-pituitary (HPA) axis, genes and structural changes within the brain.

The role of inflammation in MDD has been of growing interest over the past two decades and it is now thought to play a role in the pathogenesis of depression. In the 1990s, the mind was considered to be immune from ailments in the body. This was described by Franz Kafka in one of his early letters to Milena whereby he described his experience of tuberculosis:

> *"It is my mind that is ill, the affection of my lungs is nothing else than the spillover of my ill mind…"*
>
> *(Kafka 1900)*

The relationship between the immune system and the brain was not protested until 1985, when a group of scientists discovered evidence that immune responses are suppressed in depressed patients (Stein et al. 1985). However, a number of immune components, such as inflammatory biomarkers, are in fact heightened in subgroup of depressed patients (Maes et al. 1991). This account explores the role of inflammation in depression and the possible inflammatory mechanisms involved, drawing evidence from the three observations: (a) elevated levels of inflammatory markers in patients with MDD, even in the absence of illness, (b) co-occurrence of MDD with inflammatory illnesses and (c) increased risk of MDD with cytokine treatment.

THE INFLAMMATORY HYPOTHESIS

It is now known that MDD involves both immune suppression which is indicated by a reduction in natural killer cell cytotoxicity and lymphocyte proliferation as well as immune activation which is indicated by an increase in inflammatory mediators (Blume et al. 2012). The current hypothesis is that excess inflammation is thought to play a role in the pathophysiology of MDD, however, the mechanism by which this occurs is unclear. In addition to this, it is not known whether inflammation causes depression or vice verse. A role of cytokines in depression is supported by the phenomeno-logical similarities between the symptoms of cytokine-induced sickness behaviour and depression such as behavioral inhibition, anorexia, weight loss, anhedonia, psycho-somatic symptoms, anxiety and neurocognitive symptoms (Maes et al. 2012). The initial acute immune response in sickness behaviour is thought to be beneficial to the individual since it enables them to cope better with illness or infection (Dantzer et al. 2008). Therefore, depression may simply be a maladaptation of

sickness behaviour as a result of chronic immune activation and consequential inflammation (Raison & Miller 2011). However, in order to establish this, the inflammatory mechanisms involved must first be explored. Inflammation occurs as a result of an imbalance between pro-inflammatory mediators such as cytokines, chemokines and acute phase proteins and anti-inflammatory mediators, the former being in excess (Irwin & Miller 2007, Blume, et al. 2012, Zorrilla et al. 2001).

INFLAMMATORY MECHANISMS

The innate immune system is thought to play an integral role in depression and it determines the type of adaptive immune response involving T helper (Th) 1 or Th2 lymphocytes. In Th1 response, macrophages release pro-inflammatory cytokines such as interferon gamma (INF-γ), tumour necrosis factor alpha (TNF-α), interleukin (IL)-1 and 2. This occurs in response to the recognition of pathogens, tissue damage or destruction via cell surface Toll-like receptors (TLRs) (Dinan 2009, Irwin & Miller 2007). There is currently no conclusive evidence for a role of TLRs in MDD in humans, even though they are thought to be the gatekeepers of innate immune activation (Gárate et al. 2011). Although there is no evidence for a role of infectious agents (such as the Borna virus) in MDD, lipopolysaccharides (LPS) and endotoxin have been shown to induce symptoms of MDD through peripheral immune activation (Steiner et al. 2012). TLRs activate nuclear factor–κB (NF-κB) which induces an innate inflammatory response involving the release of pro-inflammatory cytokines such as IL-1, IL-2, IL-6 and TNF-α (Figure 1a) (Raison et al. 2006, Dinan 2009, Irwin & Miller 2007). Once activated, microglia may remain activated for several months and release pro-inflammatory cytokines which could explain why patients who suffer from chronic physical illnesses often develop MDD. These cytokines provide a communication between the peripheral and central immune system by at least four different mechanisms in MDD (Figure 1b). Cytokines access the brain via leaky regions in BBB; active transport across the BBB; a neural pathway involving afferent nerve fibers such as the sensory vagus which relay information through the nucleus tractus solitarius; a humoral pathway, involving volume diffusion from circumventricular organs across the BBB (Steiner et al. 2012, Dantzer et al. 2008. Raison et al. 2006). The BBB may even be impaired in MDD, allowing the extravasation of leukocytes and upregulation of intracellular adhesion molecules (Steiner et al. 2012).

NEUROTRANSMITTER METABOLISM AND INFLAMMATION

Once inside the brain, cytokines influence the pathways involved in the pathophysiology of depression such as metabolic alterations of neurotransmitters including serotonin (5-HT), dopamine (DA), noradrenaline (NA). Tryptophan is an amino acid precursor of 5-HT and melatonin (Figure 1). In the Th1 response (Figure 1c), microglia and macrophages secrete IL-1, IFN-γ and TNF-α which induce indoleamine 2,3-dioxygenase (IDO) expression favoring conversion of tryptophan into quinolinic acid, a N-Methyl-D-aspartic acid (NMDA) agonist, and kynurenic acid, NMDA antagonist. This reduces tryptophan availability for 5-HT and melatonin synthesis. Confirming the presence of activated microglia in depression is the synthesis of quinoloic acid, since they are the only cells in the central nervous system (CNS) which express all the enzymes required for its synthesis, whereas multiple cell types express IDO (Saito et al. 1993). As a result, there is reduced availability of 5-HT which is implicated in the pathogenesis of MDD (Krishnadas & Cavanagh 2012, Mcnally et al. 2010, Müller & Schwarz 2007). Quinoloic acid is a NMDA agonist and therefore its accumulation may contribute to excitotoxicity as well as calcium-mediated cell death in MDD (Mcnally et al. 2010, Krishnadas & Cavanagh 2012). Although paroxetine has shown efficacy to treat INF-α-induced depression, kynurenine levels remain unaltered suggesting that increases in synaptic 5-HT by paroxetine compensate for the IDO favoring the kynurenic acid pathway (Capuron et al. 2003, Capuron & Miller 2011).

DA is another monoamine which is implicated in MDD, particularly with the symptoms of sickness behaviour and anhedonia. There is a reduction in DA in the basal ganglia in MDD and this may contribute to the blunted reaction to positive reinforces and abnormal response to negative feedback observed in depressed patients. As with 5-HT described previously, pro-inflammatory cytokines influence dopamine synthesis and reuptake. Kynurenine is converted into kynurenic acid, an NMDA antagonist, which antagonizes α7 nicotinic acetylcholine (ACh) receptors and can reduce striatal dopamine release. Dopamine reuptake is increased through phosphorylation of the dopamine transporter (DAT) by mitogen-activated protein kinase kinase (MAPKK) (Shelton & Miller 2011). NA is also thought to be involved in the pathogenesis of depression however the role of inflammation in the reduction of NA has not yet been established in humans with MDD.

NEUROENDOCRINE FUNCTION AND INFLAMMATION

Inflammatory cytokines have been found to activate the HPA axis and increase in corticotropin-releasing hormone (CRH) and glucocorticoid activity in depressed patients. The HPA axis is involved in regulation of cortisol levels in response to stress. In response to psychological stress in cortical brain regions and prostaglandin E2 (PGE2) release from activated microglia, the hypothalamus releases CRH and adrenocorticotropic hormone (ACTH) (Figure 1d). CRH stimulates the pituitary gland to release corticotropin which induces the release of cortisol from the zona fasciculata of adrenal gland into the plasma (Ruhé et al. 2007, Krishnadas & Cavanagh 2012).
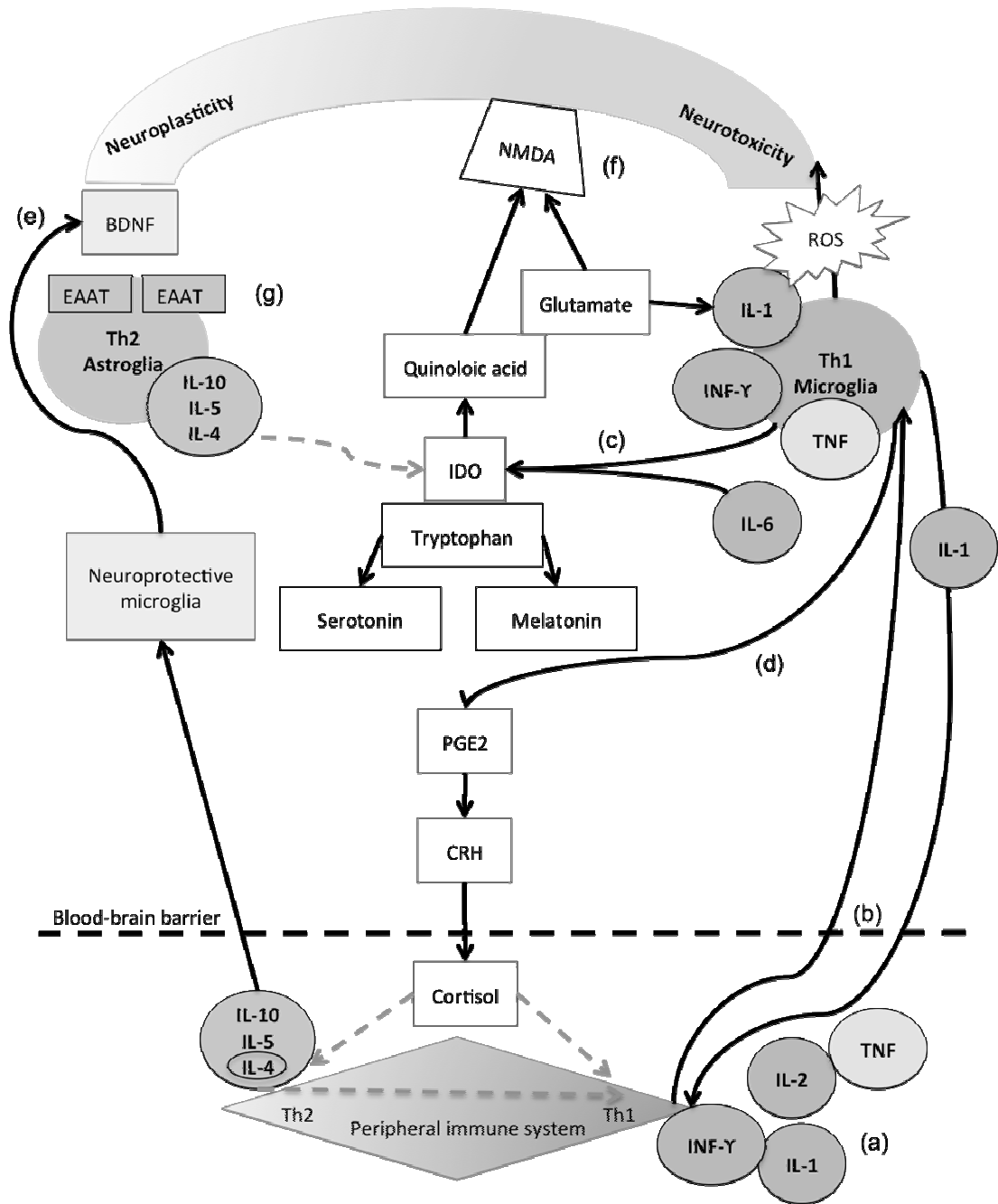
Figure 1. Inflammatory mechanisms in MDD (Adapted from Mcnally et al. 2010)

Overactivity of the HPA axis in MDD causes hyper-cortisolemia which may either result in decreased expression of the glucocorticoid receptor (GR) or decrease functionality of the GR, both ultimately resulting in glucocorticoid resistance. Through these mechanisms, there is evidence for a role of pro-inflammatory cytokines such as TNF-α in glucocorticoid resistance. The peripheral immune cells no longer respond to cortisol due to glucocorticoid resistance and the negative regulation on the immune response is lost which may increase inflammation. Glucocorticoid mechanisms have been recently linked to neurogenesis and it is thought that GR activation is necessary for its modulation by antidepressants (Anacker et al. 2011).

SYNAPTIC PLASTICITY AND INFLAMMATION

A number of studies have implicated neurotoxicity and a loss of neuroplasticity in MDD and evidence suggests inflammation may contribute this. Neuro-plasticity involves the Th2 response which involves antibody production and the release of anti-inflammatory cytokines such as IL-4, IL-5, and IL-10 which inhibit the Th1 response. These activate neuroprotective microglia which result in increased expression of brain-derived neurotrophic factor (BDNF), a growth factor involved in neurogenesis. An imbalance between the Th1 and Th2 response has been

found in some patients with MDD and this could impair neuroplasticity. Pro-inflammatory mediators activate microglia in the brain and this leads to the release neurotoxic substances in (Figure 1e) such as reactive oxygen species (ROS), positive feedback to the peripheral Th1 immune arm to increase the release of IL-2, IFN-γ and IL-1. Neurotoxic substances are released in excess of neurotrophic factors and therefore, a loss of plasticity and an increase in excitotoxicity is observed in patients with MDD (Raison et al. 2006, Martinowich et al. 2007). Activated microglia cause oxidative stress and nitric oxide production which increases inflammation. IL-1β activates nitric oxide production and this results in glutamate release and consequent excessive NMDA agonism. (Krishnadas & Cavanagh 2012). Successful treatment with antidepressants inhibit IFN-γ-induced microglial production of IL-6 and nitric oxide and this reduces depressive symptoms in MDD (Hashioka et al. 2007).

Over the past few years, it has also been demonstrated that excessive NMDA agonism by quinoloic acid may be implicated in MDD through excitotoxicity and calcium-mediated neuronal death (Figure 1f) (Sublette & Postolache 2012). Exposure to IL-1β and TNF-α enhances excitotoxicity through NMDA and AMPA receptor agonism in hippocampal neurons. IL-1β is thought to act through R1 receptors via phosphorylation of the NR2B subunit. This results in upregulation of the NMDA receptor (Viviani et al. 2003). TNF-α induces the production of AMPA receptors which lack GluR2 subunit. This is thought to predispose the neuron to further excitotoxicity and cell death (Krishnadas & Cavanagh 2012). Treatment with a non-competitive NMDA antagonist, ketamine, has been shown to have depressogenic effects with immediate onset as well as inhibit TNF-α synthesis in microglia after treatment with endotoxin (Shibakawa et al. 2005). Excessive NMDA receptor agonism also leads to glutamate release and further microglial activation and release of pro-inflammatory cytokines. IL-1β also activates nitric

oxide production which also results in glutamate release (Krishnadas & Cavanagh 2012). Although glutamate is known to cause neurotoxicity in excess, it has not been unequivocally demonstrated in MDD. Glutamate increases endotoxin activation of microglia and direct activation of microglia, and its effects can be inhibited by memantine (Mcnally et al. 2010).

Excess synaptic glutamate is usually taken up by astrocytes via excitatory amino acid transporters (EAATs) to prevent excitotoxicity in neurons, however, IL-1β released from activated microglia impairs astroglial removal of synaptic glutamate which is corrected by riluzole, an antidepressant (Figure 1g) (Vercellino et al. 2007). There is a correlation between the activation of microglia and loss of EAAT1 or EAAT2 in astrocytes in multiple sclerosis patients with focal loss and cortical lesions, resulting in excitotoxicity (Rothstein et al. 1996).

ELEVATED PRO-INFLAMMATORY MEDIATORS IN MDD

In a third of patients with MDD, the most replicated alterations to serum and cerebrospinal fluid (CSF) concentrations of inflammatory markers include an elevation of IL-6, TNF-α, and C-reactive protein compared to non-depressed patients (Dantzer et al. 2008, Raison et al. 2012, Dowlati et al. 2010, Liu et al. 2012, Dinan 2009). This occurs even in the absence of physical illness or infection and therefore the increase in inflammatory markers can only be accounted for by depression (Irwin & Miller 2007). In a meta-analysis of 22 cross-sectional studies, the standard mean difference (SMD) of sIL-2R, TNF-α, and IL-6 (all studies) in patients with MDD were significantly higher than those of healthy controls with a p value of less than 0.05 (Table 1) (Liu et al. 2012). DSM was used to elicit depressive symptoms of MDD in included studies and heterogeneity was evaluated by the Cochran Q test (l^2).

Table 1. Sensitivity analyses indicating correlation of sIL-2R, TNF-α, and IL-6 (Liu et al. 2012)

		All studies	Plasma studies	Serum studies
sIL-2R	SMD	0.555	0.917	0.281
	l^2	57.483	46.709	0
	n	8	4	4
	p	<0.001	<0.001	0.01
TNF-α	SMD	0.562	0.46	0.616
	l^2	89.707	80.308	91.602
	n	15	5	10
	p	0.01	0.195	0.023
IL-6	SMD	0.68	0.627	0.641
	l^2	63.896	82.027	0
	n	18	8	10
	p	<0.001	0.015	<0.001
IL-1β	SMD	-0.525	0.381	-1.139
	l^2	93.13	82.192	96.675
	n	10	4	6
	p	0.221	0.391	0.066

There was no significant increase in IL-1β (-0.525) in both serum and plasma studies and this casts doubt on its role in NMDA agonism and nitric oxide release in MDD. Different methods of measuring the pro-inflammatory markers were used in the included studies and some subjects had a dual diagnosis of depression and substance misuse which may have affected the results. This study indicates an association between inflammatory markers and depression and no causal relationship has been found since the severity of depression was not included in the analysis (Dowlati et al. 2010, Liu et al. 2012).

A 22 study meta-analysis on antidepressant treatment supports a role of inflammation in MDD by indicating a reduction in IL-1 and IL-6 as well as depressive symptoms in response to antidepressant treatment. This response was specific for serotonin-selective reuptake inhibitors (SSRIs) which is the most common first-line treatment for MDD suggesting that antidepressants block the effect of inflammatory cytokines and relieve depressive symptoms (Hannestad et al. 2011). However, other studies have failed to find a correlation between inflammation and the severity of depressive symptoms (Schlatter et al. 2004). In addition to this, some studies have found incongruent and opposite correlations for different pro-inflammatory markers as well as failure to identify an association between inflammation and the pathogenesis of depression (Schlatter et al. 2004, Levin et al. 1999) (Steptoe et al. 2003). In addition to this, other studies show that this association has been attenuated when factors such as body mass index, personality or gender have been included in the analyses (Bouhuys et al. 2004).

Copeland et al in 2012 was the first to carry out a longitudinal study for MDD on a targeted population consisting of children. Interviews were carried out to elicit depressive symptoms rather than self-reports and CRP levels in blood spots were measured to identify the degree of inflammation in each individual. This study demonstrated depression was associated with later levels of CRP from measurements in blood spots and therefore depression promotes inflammation. In addition to this, an elevation in CRP from a young age may increase the risk of late life recurrent depressive episodes, or even increase the risk of treatment-resistant depression. The level of inflammation promoted by depression in this case may also increase the risk of ailments such as cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM) associated with increased age (Copeland et al. 2012). Therefore, inflammation is not primary in MDD and inflammatory processes may take place after there is reduced immunocompetence in depressed patients.

MEDICAL ILLNESSES AND DEPRESSION

MDD occurs at a 5-10 times higher rate in patients with a physical illness, suggesting that immune dys-regulation may be a central feature common to de-pression and to its co-morbidity. These diseases can be classified as either inflammatory involving auto-immunity or immune activation, or non-inflammatory (Shelton & Miller 2011). Autoimmune diseases which occur with MDD include rheumatoid arthritis (RA) whereby depression worsens prognosis and disability (Krishnadas et al. 2011). In addition to this, MDD is associated with diseases with 'low' grade inflammation such as cancers, coronary artery disease, stroke and epilepsy. Even though these diseases are not traditionally associated with inflammation, it occurs secondary to initial ischaemia (Hackett & Anderson 2005).
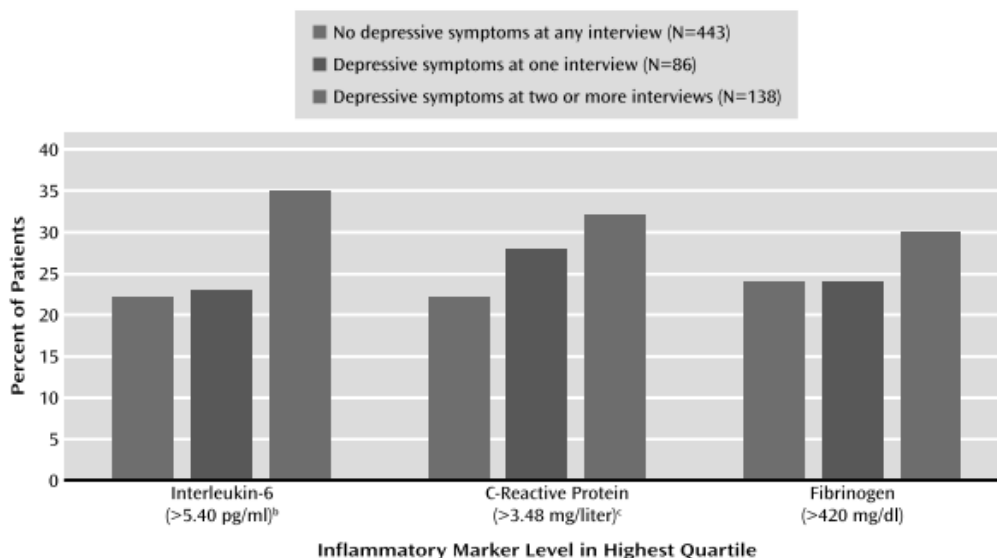
In patients with coronary heart disease, the proportions of participants with levels of IL-6, CRP and fibrinogen were 22-24% in those without depressive symptoms at any interview, 23-28% in those with depressive symptoms at one interview and 30-35% in patients with depressive symptoms at two or more interviews in a 5 year follow-up (Figure 2) (Jonge et al. 2011).

Despite a significant association of pro-inflammatory mediators and depressive symptoms in coronary heart disease, this study showed that there was no effect of inflammation on depressive symptoms after adjustment for age, race, gender, education, history of diabetes or myocardial infarction, congestive heart failure, use of aspirin and the baseline levels of inflammatory markers (Jonge et al. 2011). In addition to this, a Patient Health Questionnaire was used to elicit 9 depressive symptoms and this is not a reliable method for diagnosis of MDD. Therefore, this suggests that inflammation in medical illnesses does not cause MDD even though co-morbidity of MDD is associated with excess peripheral inflammation in diseases such as multiple sclerosis, psoriasis, Crohn's disease, human immunodeficiency disease (Lo Fermo et al. 2010).

IMMUNOTHERAPY AND DEPRESSION

Immunotherapy involves the systemic injection of cytokines such as INF-α and IL-2 in the treatment of infectious diseases such as hepatitis C and cancer. Immunotherapy is a potent inducer of pro-inflammatory cytokines, especially IL-6, and INF-α treatment is strongly associated with the onset of depressive symptoms. It induces neurovegetative symptoms associated with sickness behaviour within 1-8 weeks of therapy suggesting inflammation has an initial beneficial role (Maes et al. 2012). This can be an early indication of depression which usually occurs 1-3 months after treatment whereby changes in mood and cognition occur after 8 weeks (Raison & Miller 2011, Capuron & Miller 2011).

INF-α-induced depression is associated with changes in 5-HT metabolism via IL-6 which induces IDO and increases the plasma levels of kynurenine, alterations in CRH function which occurs as a result of a heightened response of ACTH and cortisol (Capuron et al. 2003). In a study of 30 patients who received 3 months of 3MU INF-α treatment for chronic active

Figure 2. Correlation between inflammatory mediators and depressive symptoms in patients with coronary heart disease (Jonge et al. 2011)

Table 2. MARDS scores in patients before and after INF-α treatment (Bonaccorso et al. 2002)

Items	Baseline	End-point	F-value	P-value
Expressed sadness	0.93 (1.17)	1.70 (1.38)	7.5	0.010
Unexpressed sadness	0.96 (1.25)	1.81 (1.61)	7.8	0.009
Irritability	0.88 (0.97)	1.81 (1.52)	10.0	0.004
Insomnia	0.59 (0.84)	1.33 (1.30)	5.4	0.03
Loss of appetite	0.15 (0.53)	0.62 (1.11)	6.6	0.02
Lack of concentration	0.62 (1.24)	1.22 (1.69)	3.2	0.08
Asthenia	0.40 (0.97)	1.74 (1.43)	22.3	0.0002
Anhedonia	0.48 (0.84)	0.88 (1.67)	2.0	0.2
Pessimistic thoughts	0.55 (0.84)	0.55 (1.05)	0.0	0.99
Suicidal thoughts	0.22 (0.80)	0.07 (0.26)	6.8	0.6

hepatitis C, 40.7% were diagnosed with MDD with significantly higher Montgomery Asberg Depression Rating Scale (MADRS) scores for insomnia, sadness, irritability, loss of appetite and asthenia compared to baseline scores (Table 2). Diagnosis of MDD was elicited by 2 psychiatrists using DSM-IV. This study did not include a control group due to ethical considerations and this could have hampered interpretation of the results (Bonaccorso et al. 2002).

This is simply an correlation between depressive symptoms and INF-α treatment and no casual relationship has been established. Positron emission tomography suggests INF-α disrupts metabolic activity in the basal ganglia affecting both psychomotor speed and anhedonia in patients with MDD (Juengling et al. 2000). INF-α may also alter processing within the dorsal anterior cingulate cortex which has increased activity to negative events in patients with MDD compared to controls, a possible mechanism of inducing depressive symptoms.

CONCLUSION

The role of inflammation in MDD has been of growing interest over the past two decades, however, there are inconsistencies in evidence. Cytokines and other pro-inflammatory mediators, including IL-6, IL-1β, and TNF-α, interact with almost every patho-physiologic area involved in mood regulation such as neurotransmitter metabolism, neuroendocrine function, anterior cingulate cortex activity, basal ganglia, and synaptic plasticity. However, MDD is not an inflammatory disorder since it is neither necessary, nor sufficient, to be the sole cause of MDD and it only occurs in a subgroup of patients. These individuals may be predisposed to develop MDD coupled with inflammation as suggested by studies on genetic variations in serotonin transporter gene or those genes affecting T-cell function (Wong et al. 2009, Karg et al. 2011). In addition to this, there is also a polymorphism in the promoter region of IDO 1 (rs9657182) which predicts

the development of moderate or severe depression in Caucasian individuals undergoing INF-α therapy for Hepatitis C (Smith et al. 2012). It has also been proposed that childhood adversity may predispose individuals to develop depression with inflammation. Therefore, inflammation may contribute to some cases of depression acting simply as a trigger to a cascade of events which ultimately leads to depression or as an underlying physiological response as a result of a heightened sensitivity of the immune system to stress (Krishnadas & Cavanagh 2012). Inflammation may even occur secondary to the reduced immunocompetence observed in patients with MDD, rendering them more vulnerable to invasion and proliferation of pathogens. Difficulties with studying this topic is heterogeneity of depressed patients as they may have differences in the immune profiles as well as in symptom profiles or demographic features. It is difficult to establish which factor occurs first in middle-aged or elderly subjects since the chances of being free of an episode of depression or inflammation significantly decrease with age and a large population is required to have sufficient power. The relationship between depression and inflammatory-driven illnesses is bidirectional and is driven by several biological processes, including immune dysregulation. In this context, inflammation may precipitate a depressive episode in a vulnerable individual with a medical illness. However, inflammation may also act as a perpetuating factor and prevent recovery from depression in these predisposed individuals.

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