REVIEW

Depression: an inflammatory illness?

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ABSTRACT

Major depressive disorder (MDD) is associated with significant morbidity and mortality. Findings from preclinical and clinical studies suggest that psychiatric illnesses, particularly MDD, are associated with inflammatory processes. While it is unlikely that MDD is a primary 'inflammatory' disorder, there is now evidence to suggest that inflammation may play a subtle role in the pathophysiology of MDD. Most of the evidence that links inflammation to MDD comes from three observations: (a) one-third of those with major depression show elevated peripheral inflammatory biomarkers, even in the absence of a medical illness; (b) inflammatory illnesses are associated with greater rates of MDD; and (c) patients treated with cytokines are at greater risk of developing major depressive illness. We now know that the brain is not an immune privileged organ. Inflammatory mediators have been found to affect various substrates thought to be important in the aetiopathogenesis of MDD, including altered monoamine and glutamate neurotransmission, glucocorticoid receptor resistance and adult hippocampal neurogenesis. At a higher level, inflammation is thought to affect brain signalling patterns, cognition and the production of a constellation of symptoms, termed 'sickness behaviour'. Inflammation may therefore play a role in the aetiology of depression, at least in a 'cohort' of vulnerable individuals. Inflammation may not only act as a precipitating factor that pushes a person into depression but also a perpetuating factor that may pose an obstacle to recovery. More importantly, inflammatory markers may aid in the diagnosis and prediction of treatment response, leading to the possibility of tailored treatments, thereby allowing stratification of what remains a heterogenous disorder.

INTRODUCTION

Mental, neurological and substance use disorders account for a significant proportion of the global burden of disease, surpassing that of cardiovascular disease and cancer. Major depressive disorder (MDD) is the third leading cause of disease burden.[1]

Our understanding of the pathophysiology of MDD, while increasing, remains incomplete, despite major research funding over the past 20 years. A number of biological findings have been replicated and are proving fruitful in terms of research outcomes. However, bringing these findings together and translating those to effective treatments remain elusive.[2]

The past two decades have witnessed a burgeoning area of preclinical and clinical research linking psychiatric illnesses to inflammatory processes. Most of this has arisen from an attempt to link these illnesses—particularly MDD—with 'stress' biology, and have raised the possibility of an 'initial common pathway' whereby immune/inflammatory and stress biomarkers combine to cause changes in brain structure and function.[3]

Most of the evidence that links inflammation and MDD comes from three observations.[4]

1. MDD (even in the absence of medical illness) is associated with raised inflammatory markers.
2. Inflammatory medical illnesses—both CNS and peripheral—are associated with greater rates of major depression.
3. Patients treated with cytokines for various illnesses are at increased risk of developing major depressive illness.

In this review, we discuss briefly each of the above observations. We then go on to discuss the possible mechanisms involved in the aetiopathogenesis of MDD, in the context of inflammation. Finally, we discuss the possible translational implications of these findings.

MDD IS ASSOCIATED WITH INCREASED INFLAMMATORY MARKERS

Inflammation has been linked to depression in a number of ways.[4 5] More robust findings include:

1. Mean array value for inflammatory mediators/markers is higher in MDD than normal, non-depressed subjects.
2. Approximately one-third of people with MDD have higher levels of inflammatory markers compared with the normal, non-depressed population.
3. These increases are more modest than in autoimmune or infectious disease—for example, 2–3 times higher than in healthy controls. However, as Raison and Miller point out, small physiological differences can have profound consequences over time, especially if they change in a consistent direction. Similar findings have been found in cardiovascular disease, stroke and diabetes.

Alterations in serum and CSF concentrations of a number of inflammatory markers, including cytokines, chemokines and acute phase reactant proteins, have been found in patients with MDD, and exist in the absence of comorbid medical illness. The most replicated findings pertain to raised C reactive protein (CRP) and proinflammatory cytokines—tumour necrosis factor α (TNFα) and interleukin (IL)-6—confirmed by at least two recent meta-analyses.[6 7] Both meta-analyses found significant heterogeneity among the included studies; however, there was no evidence of publication bias. More interestingly, there is evidence to say that this abnormality is corrected to an extent in response to antidepressant treatment.

A meta-analysis of 22 antidepressant treatment studies found that IL-1β and IL 6 levels (but not TNF-α) decreased in response to therapy, along with a reduction in depressive symptoms. This response was found to be specific for selective serotonin reuptake inhibitors (SSRIs), the most common firstline pharmacological treatments. These findings propose the possibility that inflammatory cytokines contribute to depressive symptoms, and that antidepressants block the effect of inflammatory cytokines in the brain.[8]

Despite these findings it is still difficult to justify describing MDD as a primary 'inflammatory' illness because inflammation is neither necessary nor sufficient to be the sole cause of MDD. This is complicated by the fact that immune/inflammatory disruption has been found in a number of other psychiatric conditions, including schizophrenia and post-traumatic stress disorder.[9 10] It is therefore more likely that inflammation and its mediators may play a more subtle role, as part of a generalised physiological response, or may act as a trigger to a cascade of events that ultimately leads to the depressive phenotype. Raison and Miller in this context have described a 'super-network', with immune response element amplification.[5] This includes multiple mechanisms through which inflammation may act in precipitating the depression phenotype. These include

- Insensitivity to glucocorticoid inhibitory feedback
- Reduced parasympathetic signalling
- Reduced production of brain derived neurotrophic factor
- Increased anterior cingulated cortex activity
- Reduced hippocampal volume

This resonates with the concept of 'allostatic load' described by McEwen.[11] Allostasis has been described as the process of adaptation to acute stress, involving activation of both the sympathetic adrenomedullary and hypothalamic–pituitary–adrenal (HPA) axes in order to restore homeostasis when faced with a challenge. 'Allostatic load' refers to the price the body pays for being forced to adapt to adverse situations—that is, the wear and tear that the body experiences as a result of activation of the above systems. This wear and tear represents either the 'excess' or the 'inefficient' operation of the above systems and can occur due to one of four mechanisms: repeated stress leading to repeated activations of these systems over time; failure of the systems to adapt to multiple stimuli; failure to shut down after being activated once; or the other extreme, where the systems do not get activated at all (eg, in autoimmune diseases). It is not surprising that, in this context, inflammation plays a key role in the process of allostasis. A number of studies have shown a significant association between allostatic load (measured using a composite score of inflammatory and metabolic markers) and medical health (eg, cardiovascular disease) and with mental ill health (such as major depression).[12]

If indeed inflammatory processes are important in the aetiopathogenesis of MDD, a number of important questions still remain unanswered.

- Are the suggested biomarkers important in the aetiopathogenesis of MDD or are they merely an epiphenomenon associated with MDD?
- Do peripheral markers of inflammation in humans correlate with brain markers in what is essentially an illness of the CNS?
- Does correcting peripheral inflammation also correct central inflammation?
- If inflammatory markers are involved in the pathogenesis of major depression, does a dose–response relationship exist between these markers and brain function?
- How stable are these markers and what is the normal variability associated with the measures?

Further studies are required to elucidate these processes.

Could inflammatory markers be helpful in diagnosing and predicting treatment response in MDD?

A continuing challenge in MDD is the lack of 'stratification'—that is, a clear way of classifying what is a highly heterogeneous disorder in order to aid diagnosis or predict treatment response. There has recently been an emphasis on the need to develop a 'biomarker' panel for depression that aims to profile diverse peripheral factors, including cytokine levels and peripheral growth factors that may provide a 'biological signature' that may help predict treatment response.[13]

Anti-inflammatory response has been associated with antidepressant effects, Persoons *et al* finding that those with Crohn's and MDD with higher pretreatment CRP levels had greater remission from MDD with infliximab.[14]

Very few studies have assessed the usefulness of cytokine levels in predicting treatment response in depression. Some of these studies have shown interesting patterns of findings.[15] O'Brien *et al* found that raised pretreatment plasma levels of IL-6 and TNFα were suggestive of poor response to antidepressants.[16] Similarly, Lanquillon *et al* found greater pretreatment IL-6 levels were associated with treatment resistance.[17] Eller *et al* found that higher levels of TNFα predicted non-response to treatment with escitalopram.[18] In a more recent study that combined pharmacogenetic and imaging genetics analysis, Baune *et al* found an association between the rs114643 variant of the *IL1B* gene and non-remission after antidepressant treatment and decreased amygdala and anterior cingulate cortex function.[19]

These findings imply that raised inflammatory parameters in patients with MDD may be biological markers of poor treatment response. More importantly, tackling this state of 'inflammation' may be important in treating MDD in those with high pretreatment levels of inflammatory markers. It is tempting here to hypothesise that addition of an anti-inflammatory medication may be a treatment option and, as discussed below, this seems to be the back bone of a number of translational endeavours. A few studies indeed have been successful in showing this.[20] However, the evidence pointing towards this direction is inconsistent. In contrast with the above mentioned findings, Harley *et al* found that patients treated with antidepressants with baseline CRP levels above 10 mg/l showed significantly better improvement than those who were within the normal range.[21] Furthermore, a recent study that analysed a dataset from a large scale real world pragmatic study (Sequenced Treatment Alternatives to Relieve Depression (STAR-D)) showed that anti-inflammatory drugs may have antagonistic effects on the antidepressant effectiveness of SSRIs, a finding that is in contrast with the above hypothesis.[22]

Studies are currently underway that aim to clarify the clinical and neurobiological phenotype of depressed patients with increased inflammation. It is hoped that if an 'inflammatory phenotype' of depression does emerge, this will help to individualise the diagnosis and treatment of patients with this particular phenotype.[23]

DEPRESSION IN THE CONTEXT OF INFLAMMATORY MEDICAL CONDITIONS

One possible way of improving our understanding of the relationship between inflammation and MDD is the study of MDD comorbid with physical (medical) illness. This paradigm allows us to explore how a known inflammatory pathophysiological process might impact on the brain.

MDD occurs at a 5–10 times higher rate in those with medical illness, and worsens prognosis and disability. This is

particularly true when the medical illness is associated with an autoimmune process. MDD is by far the most common psychiatric manifestation of multiple sclerosis, with a lifetime prevalence of around 50% and rates of suicide as high as 15%.[24] This association is also seen in peripheral (as opposed to only CNS) inflammation, in diseases such as psoriasis, rheumatoid arthritis (RA) and inflammatory bowel diseases. Conservative estimates of rates of MDD are between 13% and 17% in these patients.[25–27]

This is also true in cases of medical illness with 'low grade' inflammation—for example, cancer, stroke, coronary artery disease and epilepsy that are not traditionally considered to have a primary inflammatory aetiopathology. Acute brain ischaemia is associated with an inflammatory response that contributes to ischaemic damage.[28] Conservative estimates suggest that around 30% of people who survive a stroke experience clinical MDD.[29] Similarly, epilepsy is associated with significantly high rates of MDD. Proinflammatory cytokine mediated changes in glutamatergic neurotransmission are thought to be relevant in the aetiopathogenesis of seizure and epilepsy[30] (see below). Similar rates of MDD are seen in cancer and cardiovascular illness.[31]

In the context of medical illness, inflammation may trigger a major depressive episode in vulnerable individuals. Inflammation in this context may act as a precipitating and perpetuating factor in predisposed individuals. Katja *et al* in a recent meta-analysis found that those with a short allele (SS) functional polymorphisms (5-HTTLPR) of the promoter region of the serotonin transporter gene (predisposition) were more likely to develop an MDD episode in the presence of a specific medical condition (stressor).[32]

CYTOKINE THERAPY INDUCES DEPRESSIVE SYMPTOMS

Cytokines such as interferon α (IFNα) and IL-2 are used as immunotherapy for the treatment of chronic hepatitis C and cancer.[33 34] There is good evidence to suggest that those who undergo these treatments are more prone to develop MDD. Sockalingam *et al* recently reviewed nine prospective studies that used clinician rated measures to detect MDD in patients treated with IFNα for hepatitis C. They found that the prevalence of IFNα induced depression was in the range 10–40%, with more rigorous studies suggesting a prevalence approximating 20–30%.[35]

How these cytokines induce depressive changes is a matter of much debate. IFNα induced depressive symptoms are associated with changes in cytokine levels in serum. IFNα treatment may therefore directly or indirectly affect neurotransmitter systems in the CNS. A reduction in peripheral serotonin level has also been demonstrated in hepatitis C patients during IFNα treatment.[36] Several studies have demonstrated a positive correlation between increased depression symptoms during IFNα therapy and metabolites of indolamine deoxygenase enzyme (see below) in the blood and CSF of patients with hepatitis C.[37]

Another area of much interest has been trying to predict who will develop MDD in response to these treatments. Interestingly, the *short* allele of 5HTTLPR has been associated with an increased risk of depressive symptoms during IFNα therapy.[38] However, the findings are not consistent. A more recent study of hepatitis C patients demonstrated that those with the 'high transcription' serotonin genotype (LL) showed greater depressive symptoms during IFNα therapy compared with those with the short allele (SS).[39] Other studies have implicated polymorphisms in other genes (eg, IL-6) that may confer greater risk or protection from developing MDD in response to cytokine treatments.[38]

HOW MAY PROINFLAMMATORY CYTOKINES CAUSE MDD?

Proinflammatory cytokines may provoke changes in brain structure and function, leading to the development of MDD. The mechanisms by which these peripheral inflammatory responses signal the brain is unclear. Cytokines can directly modulate pathways implicated in the aetiology and treatment of depression. Suggested mechanisms include the effect of cytokines on the HPA axis, on neurotransmission and a direct action on hippocampal neurogenesis.

Cytokines exist in the brain and may therefore exert an effect on the brain

Traditionally, the brain was considered an 'immune privileged' organ. However, it is now known that the brain is indeed susceptible to immune mediated insult. Cytokines are large proteins—proteins, peptides or glycopeptides—that form part of a large family of cell signalling molecules. They are formed and released as a 'cascade' where induction of one of the molecules can trigger the activation of a number of molecules. In the brain, cytokines are produced by neurons, microglia and astrocytes. Cytokines in the brain are 'gliotransmitters' that act on a number of receptors and are thought to be key in a number of brain functions. They may be activated in a number of ways. Where the primary focus of immune activity is the brain (eg, post-stroke depression, multiple sclerosis), it is thought that cytokines are produced in the brain itself. Additionally, we now know that peripheral cytokines can signal the brain through at least five mechanisms.[4]

a. Passage of cytokines through 'leaky' regions in the blood brain barrier (BBB)—for example, the circumventricular organ
b. Active transport across the BBB
c. Transmission of signals along the afferent vagal pathway
d. Entry of activated monocytes from periphery into the brain—chemokines are increasingly seen as having a role here
e. Second messenger signals from the endothelial lining of the BBB which in turn leads to an excess production of cytokines by glia.

Action on HPA axis: HPA axis overactivity and glucocorticoid resistance

HPA axis abnormalities have been reported in MDD.[40] Overactivity of this system has been attributed to glucocorticoid receptor (GR) resistance, secondary to either reduced expression of GR or decreased functionality of GR. There is some evidence that proinflammatory cytokines, including TNFα, induce glucocorticoid resistance through the above mechanisms. Functional inhibition is induced by preventing the entry of the cortisol–GR receptor complex into the nucleus (by inducing Jun amino-terminal kinase) and also by preventing the binding of the complex to the DNA (by inducing nuclear factor κB).[41] This in turn leads to altered expression of GR in cells. Change in expression and functionality of the system can be measured in vitro, pre- and post-treatment, with TNFα blockers. Recent work by Anacker *et al* links glucocorticoid mechanisms to neurogenesis (a process thought to be key in mediating the action of antidepressants). They suggest that activation of GR is necessary for the antidepressant induced modulation of neurogenesis in humans.[42]

Action on neurotransmitters

Monoamine neurotransmitters

Monoamine pathways have been implicated in the aetiology of depression for a number of years. SSRI antidepressants have been reported to be effective in inducing and sustaining

remission of inflammation in patients with RA.[43] There seems to be a bidirectional relationship between serotonergic systems and inflammation. A key site of action of antidepressants is the serotonin transporter (SERT) which regulates serotonergic neurotransmission. There are increasing data in animal and humans to suggest that inflammation is associated with neuronal SERT activity. We have previously shown that treatment with the TNF blocking agent adalimumab led to a decrease in SERT binding by up to 20% using [123I]beta CIT-SPECT.[44]

There is evidence that proinflammatory cytokines, including TNFα, induce glial indoleamine dioxygenase. This activates the kynurenine pathway, thus channelling the available dietary tryptophan (the substrate for serotonin synthesis) to form kynurenine (Kyn), 3 hydroxy kynurenine (3HK) and quinolinic acid (QUIN), rather than serotonin (5HT). In addition to decreasing serotonin availability in the neuron, the accumulating 3HK and QUIN—both N-methyl-D-aspartate (NMDA) receptor agonists—contribute to excitotoxicity and calcium mediated cell death.[45]

Conversely, serotonergic systems have been found to significantly impact on inflammatory pathways. Descending spinal serotonergic pathways have been implicated in the physiology of pain modulation. Zhao *et al* showed that knockout mice that lacked these descending serotonin pathways in the brain exhibited enhanced inflammatory pain (but normal visceral and thermal pain) compared with their littermate control mice. They showed that the analgesic effects of SSRI antidepressants were absent in this strain of mice, suggesting that serotonergic pathways play an important role in modulating inflammatory pain compared with mechanistic pain.[46] Recent findings suggest that antidepressants have anti-inflammatory and analgesic properties. O'Brien *et al* showed that CRP levels decreased following treatment with antidepressant.[47] Piletz *et al* found that raised proinflammatory biomarkers in patients with MDD showed a decrease in response to treatment with venlafaxine (a serotonin and norepinephrine reuptake inhibitor, exhibiting serotonin reuptake inhibition at lower doses and norepinephrine reuptake inhibition at higher doses) at the serotonergic (lower) dose range rather than the norepinephrine (higher) dose range, suggesting that sertonergic pathways mediate the anti-inflammatory response to antidepressants.[48]

Recent experimental data show that the peripheral activation of 5-HT2A receptors in primary aortic smooth muscle cells leads to an extremely potent inhibition of TNFα mediated inflammation, another possible mechanism of action of SSRIs in mediating the anti-inflammatory action. SSRIs, including escitalopram, are thought to increase extracellular serotonin concentrations at these receptors. However, SSRIs are thought to downregulate 5HT2A in the long run. Surprisingly, blockade of 5HT2A receptors also has the same effect—that is, downregulation. However, it is possible that downregulation of these receptors decreases with age, suggesting that SSRI antidepressants may have a potential role in treating inflammatory conditions, at least in the older population.[49] In spite of the good evidence for the use of tricyclic antidepressants and venlafaxine in the treatment of neuropathic pain (number needed to treat=3), data regarding the use of SSRI in neuropathic pain are inconclusive.[50] Evidence for the use of antidepressants in inflammatory conditions is even less promising, largely due to the lack of good quality data. Richards *et al* reviewed the available evidence for the efficacy of antidepressants in pain in patients with RA and found no conclusive evidence.[51] They reviewed eight randomised controlled trials looking at tricyclic antidepressants and two trials evaluated an SSRI as a comparator. The quality of the studies included was poor, and there were insufficient data for a number needed to treat to be calculated for the primary outcome measure of pain. They concluded that there was currently insufficient evidence to support the routine prescription of antidepressants as analgesics in patients with RA and that the use of these agents may be associated with greater adverse events. Similarly, Micocka-Walus in a review of 12 non-randomised controlled studies of antidepressants in inflammatory bowel disease found no conclusive evidence of the efficacy of antidepressants on disease prognosis.[52] They found that although there was some benefit in the use of antidepressants in inflammatory bowel disease, the quality of the data available to reach a conclusion was not good enough. The authors of both of the above reviews proposed that better conducted prospective studies are required to address this issue. Another monoamine that has been implicated in major depression is dopamine, particularly in symptoms associated with anhedonia and sickness behaviour. As with serotonin, proinflammatory cytokines influence the synthesis and reuptake of dopamine.[53 54]

Glutamate neurotransmission

Glutamate induced excitotoxicity—excess activation of neuronal glutamate receptors that ultimately leads to cell death—has been implicated in mediating neuronal death in many disorders, including stroke and neurodegenerative disorders. Glutamate induced excitotoxicity has also been implicated in psychiatric disorders such as depression.[55] Excessive accumulation of intracellular calcium is thought to be the major step that leads to neuronal cell death. The type of receptor that has been most implicated in glutamate excitotoxicity is the NMDA subtype. It is thought that overstimulation of these receptors leads to an overload of calcium and, in turn, neuronal death. Other receptors, such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kaininate receptors, are also thought to play a role in excitotoxicity as their ion channels are partially permeable to calcium.[56]

Inflammatory processes have been found to be associated with an increase in glutamate induced neurotoxicity. Proinflammatory cytokines are thought to mediate this process. Mechanisms by which these inflammatory mediators cause an increase in glutamate neurotransmission include:

- Upregulation and augmentation of NMDA function
- Increased release and reuptake inhibition of glutamate
- Action on AMPA receptors
- Activation of kynurenine pathway

Upregulation and augmentation of glutamatergic pathway

It has been recognised that hippocampal neurons exposed to IL-1β and TNFα intensify the excitotoxic neuronal damage induced through NMDA and AMPA receptors.[57] The action of IL-1β on the glutamatergic system is thought to be through its action on the IL-1 R1 receptor. These receptors colocalise with NMDA receptors on hippocampal neurons. NMDA receptors consist of two subunits, NR1 and NR2. NR2 subunits have further isoforms. It is proposed that IL-1β induces phosphorylation of the NR2B isoform, which leads to upregulation of NMDA receptor function. This leads to an increase in Ca^{2+} influx into the neuron and consequent cell death.[58]

Increased release and reuptake inhibition of glutamate

IL-1β has also been found to inhibit the reuptake of glutamate by glial cells. This is thought to be mediated through the action of these proinflammatory cytokines on expression of the glutamate transporter. This malfunction of the transporter leads to

an increase in extracellular glutamate and further NMDA mediated excitotoxicity. In addition to this, IL-1β has been found to activate nitric oxide synthase which leads to an increase in production of nitric oxide and hence an increase in glutamate release.[59]

Action on AMPA receptors

TNFα has been shown to influence the trafficking of AMPA glutamate receptors in inflammatory conditions. Normally AMPA receptors have four subunits, GluR1–4. The presence of TNFα leads to production of AMPA receptors lacking the GluR2 subunit. This receptor conformation is said to facilitate calcium influx into the neuron. This predisposes the neuron to glutamate induced excitotoxicity.[60]

Kyneurenine pathway

The impact of the Kyn pathway on excitotoxicity was described above. This activation of the Kyn pathway by proinflammatory cytokines thus channels the available tryptophan to form Kyn, 3HK and QUIN. 3HK and QUIN are NMDA receptor agonists. High concentrations of these compounds are thought to contribute to excitotoxicity and calcium mediated cell death.[61]

Cytokine mediated neurogenesis and neuronal loss

Neurogenesis in the hippocampus of the adult brain is thought to contribute to memory and learning. While a pathogenic role for reduced hippocampal neurogenesis in depression is unclear, there is now considerable experimental evidence that the generation of new neurons in the dentate gyrus of the hippocampus is enhanced by antidepressant treatment.[62]

There is a body of evidence to suggest that inflammation induces a decrease in neurogenesis. As mentioned above, this decrease may in part be due to HPA axis abnormalities which, when corrected, restores neurogenesis.

Cytokine mediated regulation of hippocampal neurogenesis in experimental animals is indicated by several pieces of evidence:

- Monje *et al* reported that neuroinflammation inhibits neurogenesis and that inflammatory blockage with a non-steroidal anti-inflammatory drug restores neurogenesis.[63]
- In exploring a potential mechanism underlying depression induced by IFNα treatment, Kaneko *et al* found that IFNα suppressed neurogenesis in the dentate, and that IL-1β played an essential role in that suppression.[64]
- Stress induced reduction in hippocampal neurogenesis is attenuated by blockade of the IL-1β receptor.
- Mice deficient in TNF receptor 1 (responsible for neuronal damage) exhibit enhanced hippocampal neurogenesis.[65]

There are some data to suggest that inflammatory cytokines may affect the expression of trophic and growth factors. However, the results are inconsistent.[66] In spite of the above studies, there is still a dearth of data on the involvement of inflammatory mediators in decreasing neurogenesis. There are very few studies that have looked at the effect of anti-inflammatory drugs on neurogenesis and depression.

Cytokine induced inflammation modulates sickness behaviour and neuronal activation

Systemic inflammation is known to elicit symptoms in healthy mammals, collectively called 'sickness behaviour'. This consist of behavioural changes, including disturbance in sleep, appetite, psychomotor slowing, memory impairment and behaviour, that are thought to be very similar to biological symptoms of depression in humans.[67 68] Interferon therapy is associated with sickness-like symptoms, including lack of sleep, loss of appetite, weight loss and fatigue, usually occurring during the first 2–4 weeks of therapy, that can be early indicators of depression which usually develops 1–3 months after treatment.[69 70] Capuron *et al* found that in spite of considerable overlap in symptoms between cytokine induced depression and idiopathic depression in medically healthy subjects, psychomotor symptoms were much greater in the cytokine induced MDD group while cognitive distortions were greater in those with idiopathic MDD.

A common clinical experience is people receiving flu or typhoid vaccination developing symptoms of fatigue, psychomotor slowing and depressed mood. Clinical studies have shown that these changes are significantly associated with increased IL-6 levels.[71] On functional MRI, these people have also been shown to activate brain regions thought to be important in modulating mood. Areas that have been shown to be activated include the insula, an area thought to be important in body representation and subjective emotional experience, and the substantia nigra, that correlated with measures of fatigue and psychomotor slowing, findings that are consistent with the clinical findings of Capuron *et al* described above.[72 73]

Cytokine mediated cognitive dysfunction

Neurocognitive function reflects the functional integrity of neuronal structures. Patients suffering from MDD show a number of cognitive deficits during periods of illness, particularly in the domains of attention, memory and executive function. In patients who have recurrent episodes of MDD, deficits on performance on tests of executive function have been shown to persist into periods of recovery, suggesting that these deficits may be trait markers of the illness.[74] Cognitive dysfunction has been shown to correlate positively with the presence of proinflammatory cytokines and other inflammatory mediators in various illnesses.[75] There is considerable evidence to show that proinflammatory cytokines play an important role in cellular mechanisms underlying cognition, including synaptic plasticity.[76] IL-1β and TNFα play an important role in long term potentiation and depression. It is postulated that while normal levels of cytokines are essential for the consolidation and integration of AMPAs on the neuron, in excess they tend to have a detrimental effect. In addition, TNF seems to play an important role in synaptic scaling (homeostatic plasticity) in hippocampal neurons. Any imbalance in the normal milieu of TNF is said to affect long term synaptic plasticity and hence cognition. In this respect, measures of neurocognition before and after treatment with TNFα antagonists may provide us with some clue to the effect of the treatment on neuronal (structural/functional) integrity in various circuits/parts of the brain involved in these tasks.[77] Recent reports show that the TNF antagonist etanercept administered intrathecally has been used in the treatment of patients with Alzheimer's disease.[78] Currently, there is one randomised controlled study underway looking at the effects of subcutaneous etanercept in the treatment of Alzheimer's disease. (http://Clinicaltrials.gov NCT01068353).

TRANSLATIONAL IMPLICATION

Given the numerous links that have been shown to exist between inflammation and depression, it would be reasonable to surmise that treatment with anti-inflammatory agents may be beneficial in depression. There is tentative evidence that anti-inflammatory agents have antidepressant properties. Specifically, TNF blocking agents have been shown to improve mood, independent of improvement in the inflammatory condition. Tyring

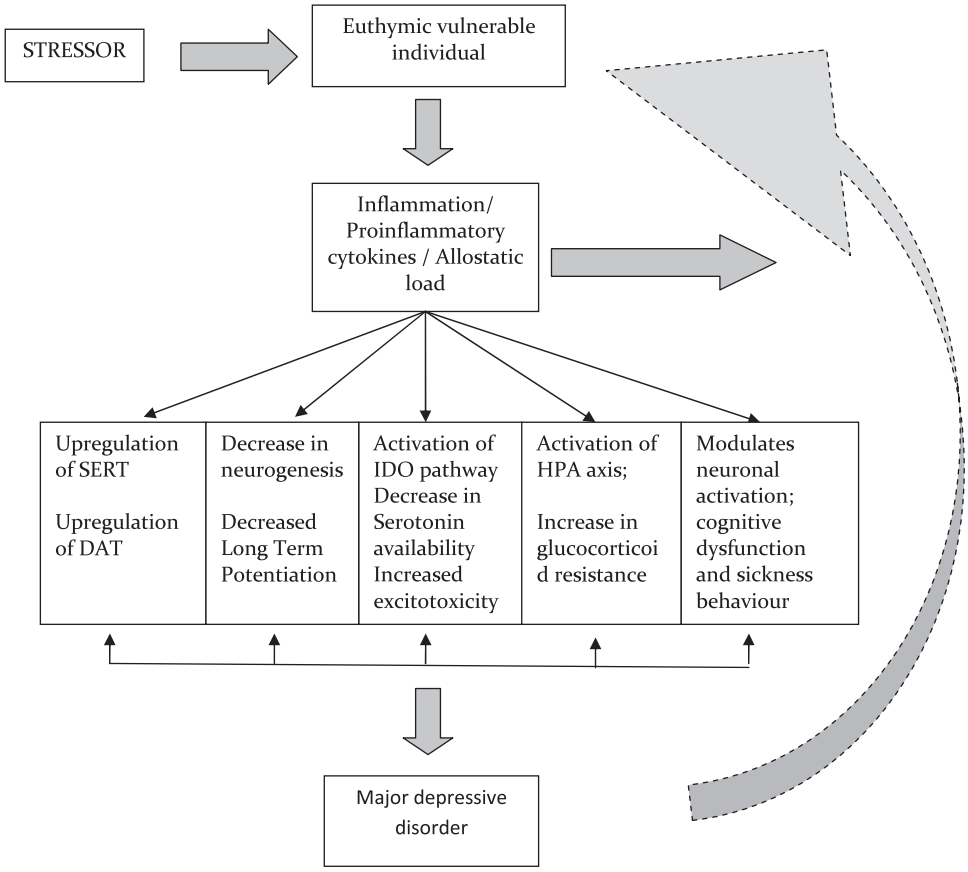

Figure 1 Potential pathways through which inflammation may play a part in the pathogenesis of major depression. Inflammation is activated in response to a stressor—endogenous (medical illness) or exogenous (psychological/ medication). This acts as a precipitating factor in those who are vulnerable (predisposing). This not only precipitates but also perpetuates and maintains the major depressive phenotype by preventing recovery. DAT, dopamine transporter; HPA, hypothalamic—pituitary—adrenal; IDO, indoleamine dioxygenase; SERT, serotonin transporter.

et al found that 55% of patients with psoriasis who were treated with etanercept showed a 50% reduction in Beck's depression inventory scores compared with 39% on placebo, an effect size comparable with antidepressants. This improvement was found to be independent of improvement in psoriasis.[79] Muller *et al* showed that addition of celecoxib (a COX-2 inhibitor which inhibits prostaglandin E2) to reboxetine (a norepinephrine reuptake inhibitor) showed significant additional effects on depressive symptoms compared with reboxetine alone.[20] A number of trials are in progress both in the UK and the USA exploring the utility of anti-inflammatory medications in MDD. Studies examining the effectiveness of biological agents such as infliximab that specifically target TNF in treating patients who have not responded to conventional antidepressants, who may have higher levels of inflammatory markers, are currently underway. (http://clinicaltrials.gov NCT00463580).

It should be noted that TNF blocking agents such as infliximab and etanercept are large molecules that do not cross the BBB. Bearing in mind that MDD is primarily an illness of the CNS, how these drugs bring about their antidepressant action is not clear.[80] At least in animal models, manipulating peripheral inflammatory cytokines has been shown to reflect changes in cytokine CNS expression. A possible mechanism is that the trafficking of immune cells that are already affected by HPA axis dysregulation into the CNS is being blocked by these anti-inflammatory agents. This area of research has however not been explored as much.

Anti-inflammatory agents targeting novel neurotransmitter systems (including glutamate) have been found to have some efficacy in treating psychiatric conditions. Two drugs of note are riluzole and ketamine, both of which have significant anti-inflammatory effects and have been found to be effective in treating depression. Riluzole is a glutamatergic modulator which has both neuroprotective and anticonvulsant properties due to its ability to inhibit glutamate release and enhance both glutamate reuptake and AMPA trafficking. The non-competitive, high affinity NMDA antagonist ketamine is a phencyclidine derivative that prevents excess calcium influx and cellular damage by antagonising NMDA receptors.[81] Ketamine has been shown to have a very fast onset of action in relieving depressive symptoms and is currently the focus of a number of studies in mood disorders. Other novel anti-inflammatory agents that may have promise include dietary omega 3 fatty acids, particularly eicosapentanoic acid and docosahexaenoic acid, which have been found to have significant anti-inflammatory action. Clinically important anti-inflammatory effects are suggested by trials demonstrating the benefits of n-3 fatty acids in RA, psoriasis, asthma and inflammatory bowel disorders. The addition of n-3 fatty acids to existing antidepressant therapy has been found to be effective in recurrent MDD.[82] Finally, drugs targeting the Kyn pathway have shown preliminary encouraging results in phase 1 trials.[83]

CONCLUSION

In this review we have tried to examine the links between MDD and inflammation. A significant number of the findings presented with regards to these are reasonably established 'facts', however, none of these generalisations applies to all individuals suffering from MDD and therefore may not be universally 'true'. Inflammation seems to be associated with MDD and may indeed play a role in the aetiology of MDD, at least in a 'cohort' of vulnerable individuals. Inflammation may not only act as a precipitating factor that pushes a person into depression, but

also as a perpetuating factor that may pose an obstacle to recovery (figure 1). Inflammatory markers may be potential biomarkers, aiding diagnosis or even helping to predict prognosis. Future work will focus on cementing the precise role of inflammation in depressive illness through more sophisticated animal models and clinical neuroscience, and will hopefully result in beneficial treatments for what remains a significantly disabling psychiatric illness.

Contributors RK and JC made equal contributions to this article.

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