Role of inflammation and immunity in depression

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Abstract

Monoamine-based treatments of depression are only effective in a select population of patients. Understanding the pathogenesis and mechanisms of depression may offer novel therapies where typical monoamine treatments fail. We present evidence for the role of low-grade systemic activation of the innate immune system in the pathogenesis of depression, antidepressant response, anti-inflammatory treatment of depression, and physical comorbidities of depression. Cross-sectional studies have demonstrated a relationship between specific inflammatory blood biomarkers (IL-6, CRP and TNF-α) and depression. Longitudinal studies show inflammation is not an epiphenomenon of depression: inflammatory biomarkers precede depressive symptoms. Evidence from animal studies have detailed mechanisms whereby peripheral inflammatory signals are communicated to the brain, affecting mood, cognition and behaviour. Pharmacologically, a high IL-6 level predicts poor response to selective serotonin reuptake inhibitors and it remains elevated in non-responders, indicating inflammatory cytokines may underlie treatment resistance. Furthermore, anti-cytokine treatments have substantial antidepressant effects comparable to conventional antidepressant medication, at least in patients with co-morbid depression and high levels of peripheral inflammation. There is also evidence that inflammation links depression and physical illness, with elevated inflammatory markers mediating the relationship between depression and both childhood maltreatment and coronary heart disease. Clearly, the role of inflammation in depression is complex. To understand the relationship better, studies need to examine causality of the association and the efficacy of novel immunotherapies in depressed patients without chronic physical illness.

Introduction

Pathophysiological mechanisms and pharmacotherapy for depression are typically predicated on monoamine neurotransmitters (1) but a third of patients are resistant to these drugs for depression (2). Epidemiological, clinical and pre-clinical studies suggest a role of the immune system, particularly low-grade systemic inflammation as reflected by elevated circulating inflammatory markers such as acute phase proteins (e.g. C-reactive protein (CRP)) and cytokines (e.g. interleukin 6 or IL-6), in the pathogenesis of depression (for reviews see (3, 4)). The association between the immune system and the brain may offer new mechanistic understanding and insights for novel therapies for depression. In this article we present an overview of the evidence linking low-grade systemic activation of the innate immune system and depression. We also review the role of inflammation in antidepressant response, the effectiveness of anti-inflammatory treatment for depression based on recent systematic reviews and meta-analyses, and the potential role of inflammation in physical comorbidities for depression. For key concepts see Box 1, and for an accessible introduction to the field see Bullmore (5).

Evidence for a role of inflammation in depression

Depression is common in people with a chronic inflammatory disorder such as rheumatoid arthritis (6). About 30 - 50% of patients with the hepatitis C virus develop depression following treatment with interferon (INF), a potent inducer of inflammatory cytokines (7). Experimental immuno-activation in healthy volunteers leads to depressive symptoms and reduced cognitive performance (8, 9). Systematic reviews and meta-analyses of cross-sectional studies confirm elevated inflammatory markers in acutely depressed patients which are largely normalised after remission of symptoms with antidepressant treatment (10-12). The effect size for IL-6, CRP and tumour necrosis factor alpha (TNF-α), some of the key inflammatory markers, in patients with major depression compared with healthy controls are 0.54 (95% CI = 0.40–0.69),

0.47 (95% CI = 0.28–0.65) and 0.40 (95% CI = 0.15–0.65), respectively (11). However, an important caveat of these studies is that, due to their cross-sectional design, they cannot determine whether increase in inflammatory markers is a cause or consequence of illness. Recently, population-based longitudinal studies have demonstrated that elevated cytokine levels precede, and so could potentially cause, depressive symptoms (13, 14). A dose-response relationship between serum concentration of IL-6 in childhood at nine years and subsequent depressive symptoms in early-adulthood at 18 years, which is independent of sociodemographic and other potential confounders, has been reported in the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort (13). A longitudinal association between circulating IL-6 and CRP levels and subsequent depressive symptoms has been reported from the Whitehall II cohort (14). Taken together, the current evidence strongly supports the claim that elevated inflammatory markers could be a causal risk factor for depression rather than being a consequence of depression or epiphenomenal. Mechanisms underlying the association between inflammatory markers and depression have been identified using animal experimental studies. It has been shown that circulating inflammatory markers can communicate with the brain using a number of pathways leading to changes in mood, cognition and behaviour by affecting neurotransmitter metabolism, activating the hypothalamic-pituitary-adrenal (HPA) axis, increasing oxidative stress and reducing synaptic plasticity, possibly as a result of activation of microglia, the resident immune cells of the brain (for reviews see (3, 4)).

Inflammation and antidepressant response

About a third of depressed patients have elevated circulating CRP levels (15, 16), while a third of patients are antidepressant resistant (2) - this may not be a coincidence. Indeed, activation of the inflammatory system as reflected by elevated serum concentrations of IL-6 and other cytokines predicts poor response to antidepressant drugs (17, 18). Patients who do not respond to selective serotonin reuptake inhibitors (SSRIs) and other antidepressant drugs continue to show elevated levels of IL-6, CRP and other inflammatory markers (19, 20). It is thought that depressed patients with elevated inflammatory markers display resistance to antidepressants because these drugs do not rectify inflammation-related pathologies such as activation of the kynurenine pathway (21). Inflammatory cytokines such as gamma-interferon (IFN-gamma) and IL-6 activate the tryptophan-metabolising enzyme indoleamine 2,3-dioxygenase (IDO), which shifts tryptophan metabolism towards kynurenine leading to increased production of neurotoxic and potentially depressogenic metabolites such as 3-hydroxykynurenine (3-HK) and quinolinic acid (for a review see (22)). Therefore, in a clinical setting, peripheral immuno-phenotyping may be a helpful tool for predicting antidepressant response and for identifying patients who are likely to benefit from immunomodulatory treatments.

Evidence for effectiveness of anti-inflammatory drugs in depression

Meta-analysis of randomised controlled trials (RCTs) of non-steroidal anti-inflammatory drugs (NSAIDs), administered as sole treatment or as adjunct to antidepressants, indicates that they are more effective than placebo in treating depression (23). Celecoxib, a selective inhibitor of the cyclooxygenase 2 pathway, has been studied most extensively. A meta-analysis of 10 RCTs involving 2750 patients has reported a small to medium effect size for celecoxib monotherapy or adjunct therapy in depression; standardised mean difference (SMD) = −0.29 (95% CI, −0.49 to −0.08). NSAIDs were generally well tolerated; there was no evidence of an increased number of gastrointestinal or cardiovascular events after six weeks of celecoxib treatment (23). However, there are important issues regarding the interpretation of these results. NSAIDs are broad-spectrum anti-inflammatory agents that also act on other targets, such as glucocorticoid receptors (24). These receptors are themselves relevant for depression pathophysiology (25), so the extent to which the antidepressant effect of NSAIDs is due solely to anti-inflammatory action is unclear. Cyclooxygenase-2 inhibitors increase risk of cardiovascular disease (26), a known comorbidity for depression, so their use in depression may be problematic. Many trials of anti-inflammatory drugs for depression are based on people with chronic physical illness (23) and it is unclear whether the improvement in depression is due to the improvement in physical illness.

More recently, studies have been examining the effectiveness of a newer class of anti-inflammatory drugs for depression. These are cytokine modulators (e.g. monoclonal antibodies and cytokine inhibitors) which target specific cytokines or cytokine receptors and are therefore more mechanistically specific than

NSAIDs. A proof-of-concept RCT has examined the effectiveness of infliximab, a monoclonal antibody that binds specifically to TNF-α and thus blocks pro-inflammatory signalling by this pathway, in treating resistant depression. While overall, no benefit of infliximab was observed, there was evidence that depressive symptoms were likely to improve in subjects with immuno-activation at baseline (i.e. elevated CRP levels) (16). Supported by a large number of RCTs, cytokine modulators are well established treatments for chronic inflammatory conditions such as rheumatoid arthritis (27) and psoriasis (28). Many of these clinical trials have also reported on secondary psychosocial outcome measures, including depression. A systematic review and meta-analysis of these clinical trials has found that anti-cytokine treatment has a significant antidepressant effect (29). Based on 7 RCTs, involving 2370 participants, the effect size for antidepressant action of anti-cytokine treatment compared to placebo is 0.40 (95% CI, 0.22-0.59), which is comparable to estimates for common antidepressants (29). Crucially, the antidepressant effect is not associated with improvement in primary physical illness, suggesting that the mood improvement is not simply a consequence of physical health improvement after anti-cytokine treatment. The antidepressant effect was also not associated with the age or sex of participants, but was associated with baseline depression severity, as seen in RCTs of monoaminergic drugs (30) and psychotherapy (31). In addition, the study showed that adjunctive treatment with anti-cytokine therapy and eight non-randomised and/or non-placebo studies yielded similar small-to-medium effect estimates favouring anti-cytokine therapy; SMD = 0.19 (95% CI, 0.00-0.37) and 0.51 (95% CI, 0.34-0.67), respectively (29). With regard to specific drugs, anti-TNF antibodies were most commonly studied (five RCTs); SMD = 0.33 (95% CI, 0.06-0.60). Adalimumab, infliximab and tocilizumab (an anti-IL-6 receptor monoclonal antibody) all showed statistically significant improvements in depression (29). Taken together, these findings indicate a potentially causal role for peripheral pro-inflammatory cytokines in depression and that cytokine modulators may be a novel class of antidepressants for patients with systemic inflammation.

Inflammation as a common link between depression and physical illness

Low-grade systemic inflammation could be a common mechanism underlying the high comorbidity between depression and coronary heart disease. Patients with depression are twice as likely to develop heart disease after controlling for effects of smoking and hypertension (32, 33). Large scale population-based longitudinal studies have reported associations between higher serum levels of IL-6, CRP and future risks of heart disease (34), depression and psychosis (13). The findings could be linked with early-life factors influencing inflammatory regulation, such as impaired foetal development or childhood maltreatment. This idea is consistent with the common-cause or developmental-programming hypothesis. Developmental programming refers to permanent alteration in physiological system(s) following exposure to adversity during a chronologically restricted developmental window. The physiological alterations, in combination with genetic and/or other environmental factors, can increase risks of several diseases in adulthood (35). Empirical evidence from longitudinal studies supports the developmental-programming hypothesis. Low birth weight (a marker of suboptimal foetal development), is associated with increased circulating CRP levels (36) as well as risks of heart disease (35), diabetes (35) depression and schizophrenia (37). Furthermore, evidence from the Dunedin birth cohort suggests higher levels of CRP mediate the association between childhood maltreatment and risk of depression in adulthood (38).

Conclusion

A better understanding of the role of inflammation could be paradigm changing for depression by providing novel mechanisms and treatments for this disorder, which is a leading cause of morbidity worldwide. The field now needs studies examining causality of association, and RCTs of novel immunotherapies in depressed patients without chronic physical illness. Immuno-therapeutic strategies based on current evidence might include immuno-phenotyping of patients to predict antidepressant response and anti-inflammatory adjunct treatment for patients with evidence of inflammation.

Box 1: Key concepts

- Depression is common in people with a chronic inflammatory disorder
- Immuno-activation leads to depressive symptoms in patients and healthy volunteers
- Depressed patients show evidence of inflammation as reflected by elevated circulating pro-inflammatory cytokines and acute phase proteins
- Elevated peripheral pro-inflammatory markers increase future risk of depression in healthy people
- Systematic inflammation can influence the brain, leading to altered mood, cognition and behaviour
- Inflammation is associated with antidepressant resistance
- Anti-inflammatory drugs may reduce depression, particularly in patients with evidence of activation of the innate immune system
- Inflammation may be a common mechanism underlying the comorbidity between depression and coronary heart disease

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