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REVIEW

Inflammation and clinical response to treatment in depression: A meta-analysis

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Abstract
The depressive state has been characterised as one of elevated inflammation, which holds promise for better understanding treatment-resistance in affective disorders as well as for future developments in treatment stratification. Aiming to investigate alterations in the inflammatory profiles of individuals with depression as putative biomarkers for clinical response, we conducted a meta-analyses examining data from 35 studies that investigated inflammation before and after treatment in depressed patients together with a measure of clinical response. There were sufficient data to analyse IL-6, TNFα and CRP. Levels of IL-6 decreased with antidepressant treatment regardless of outcome, whereas persistently elevated TNFα was associated with prospectively determined treatment resistance. Treatment non-responders tended to have higher baseline inflammation, using a composite measure of inflammatory markers. Our findings suggest that elevated levels of inflammation are contributory to treatment resistance. Combining inflammatory biomarkers might prove a useful tool to improve diagnosis and detection of treatment refractoriness, and targeting persistent inflammation in treatment-resistant depression may offer a potential target for the development of novel intervention strategies.
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1. Introduction

An aberrant inflammatory profile has been widely demonstrated in depressive disorders and is believed to contribute to some of the biological mechanisms associated with disease onset and treatment response (Dowlati et al., 2010; Miller et al., 2009; Smith, 1991). Recent evidence suggests that levels of inflammation might be modifiable with pharmacological treatment (Hannestad et al., 2011; Hiles et al., 2012; Janssen et al., 2010) and preliminary evidence indicates that treatment resistance might be associated with heightened inflammation. Additionally, non-steroidal anti-inflammatory drugs might be beneficial as adjunctive treatments in unipolar (Akhondzadeh et al., 2009; Muller et al., 2006) and bipolar (Nery et al., 2008) disorders and the TNFα antagonist infliximab may particularly benefit depressed individuals with a history of treatment resistance and high inflammation (Raison et al., 2013). Treatment non-response contributes greatly to the burden of affective illnesses (Gibson et al., 2010); it is common, affecting at least a third of patients (Warden et al., 2007), and is generally associated with poorer long-term outcomes (Fekadu et al., 2009). To improve the rate and robustness of clinical response in depression there is a need for novel treatment strategies (Kupfer et al., 2012), including enhancing the personalisation of treatment provision using stratification. As such, research has been increasingly focusing on the importance of effectively screening for predictors of response across depressed populations, and using putative biomarker signatures prior to treatment provision may help to identify objective biological differences between patients who do or do not respond to treatments. Measuring 'panels' of biomarkers may assist with the discovery of biological signatures for disorders such as depression (Schmidt et al., 2011), which also may be supported using meta-analytic techniques that provide enhanced statistical power than individual studies. Combining these two approaches may be useful for identifying inflammatory relationships with depressed state and response to treatment, particularly as studies measuring different (but similar) data points cannot otherwise be compared in a high-powered analysis. We describe a new methodology of combining inflammatory data from different biomarkers together to enable a substantially higher statistical power.

Another important factor in this relationship is whether inflammatory profiles within a depressed state might differ between individuals with unipolar and bipolar diagnoses: although this has not been established there is some indicative evidence that inflammation is not elevated in bipolar depressed state (Munkholm et al., 2013), as opposed to mania and euthymia.

1.1. Aim of the study

With the aim of expanding on previous work, we investigated studies measuring inflammatory biomarkers in depression in relation to treatment response and hypothesised that (a) non-responsive patients would have higher levels of inflammation at baseline than responders; (b) patients would show a decrease in levels of inflammation after a course of treatment, but that; (c) treatment refractoriness would be characterised by persistently high levels of inflammation.

2. Experimental procedures

2.1. Criteria for study inclusion

A systematic search of the literature was conducted to obtain all studies that measured inflammatory responses in depression at baseline and following a course of treatment, and that also assessed treatment response. A priori inclusion criteria required eligible studies to be in English, measure in vivo at least one peripheral biomarker purporting to measure inflammation in human subjects classified as being in a depressive episode according to a clinician-rated standardised measure of depression symptomatology (e.g. HRSD, MADRS, IDS) alongside a standardised measure of clinical response to a treatment (and where relevant, a comparison of inflammation between responder and non-responder groups at one timepoint or more). To ensure we measured naturally occurring inflammation we excluded any studies which included a psychological or physiological stressor, or induced inflammation either by a targeted agent or by specific immunomodulatory drugs (e.g. non-steroidal anti-inflammatory drugs would be excluded, but not psychotropic medications). For this reason we also excluded papers reporting relevant comparisons in specifically physically ill samples (though we included studies which did not necessarily exclude individuals who had physical illnesses). Subjects were required to be of any adult age to be considered eligible.

2.2. Systematic search

We searched the databases PubMED (1960-), EMBASE (1974-), and PsycINFO (1967-), with the aim of eliciting all studies measuring peripheral markers of inflammation in patients with unipolar or bipolar depression and in relation to treatment response and/or clinical improvement, fulfilling our inclusion criteria. The full search process is depicted in Figure 1. Studies were retrieved by RS and inclusion/exclusion of studies agreed by consensus (with AC, AP). Studies were also scrutinised for potentially relevant citations. In case of incomplete information study authors were contacted to request additional data not available in the original manuscript.

2.3. Assessment of quality

Research reports were assessed using seven criteria, adapted from those developed by the Evidence-Based Medicine Working Group that had been modified for use in prognostic investigations (Fekadu et al., 2009) and the Cochrane Collaboration's Risk of Bias tool for trial designs (Higgins et al., 2011). Studies can score either positively (+1), negatively (−1) or neutrally (no score change) on each of the following domains: Cohort formation, sample size, trial/follow-up length, collection of biological data, study completion data, design of treatment provision, objective clinical assessment. This resulted in a ranking from −7 to +7 (see Table 1), which we used as a brief indicator of methodological rigour in individual studies, within the limitations of this approach.

2.4. Composite biomarker calculation

It was clear that the variation between studies of inflammatory biomarkers investigated would lead to low-powered meta-analyses of individual biomarkers. Based on the consideration that all selected biomarkers should measure the same latent construct (inflammation) and thus be correlated, we planned analyses to incorporate all possible available data. This novel method should at present be considered a preliminary test of the predictive validity of a combination of biomarkers as a measure of overall inflammatory response. The 'composite

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