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Review

Cytokines in bipolar disorder: A systematic review and meta-analysis

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ABSTRACT

Background: Current research and hypothesis regarding the pathophysiology of bipolar disorder suggests the involvement of immune system dysfunction that is possibly related to disease activity. Our objective was to systematically review evidence of cytokine alterations in bipolar disorder according to affective state.

Methods: We conducted a systemtic review of studies measuring endogenous cytokine concentrations in patients with bipolar disorder and a meta-analysis, reporting results according to the PRISMA statement.

Results: Thirteen studies were included, comprising 556 bipolar disorder patients and 767 healthy controls, evaluating 15 different cytokines-, cytokine receptors- or cytokine antagonists. The levels of tumor necrosis factor-α (TNF-α), the soluble tumor necrosis factor receptor type 1 (sTNF-R1) and the soluble inlerleukin-2 receptor (sIL-2R) were elevated in manic patients compared with healthy control subjects ($p < 0.01$ for each). Levels of sTNF-R1 and TNF-α were elevated in manic patients compared to euthymic patients ($p=0.01$ and $p=0.04$, respectively). sTNF-R1 levels were elevated in euthymic patients compared with healthy control subjects ($p < 0.01$). There were no significant findings for other comparisons, including intra-individual alterations of cytokine levels.

Limitations: Stratification according to mood state resulted in small study numbers for some cytokines. Findings were limited by heterogeneity, small sample sizes and a lack of control for confounding factors in individual studies.

Conclusions: This meta-analysis found some support for immune dysregulation in bipolar disorder. Future research is warranted to elucidate the role of endogenous cytokine alterations in bipolar disorder. Clinical studies examining longitudinal changes within individuals are recommended.

Contents

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1. Introduction

Multiple lines of evidence indicate that bipolar disorder is a systemic disease, with widespread biochemical alterations occurring in and beyond the central nervous system (Berk et al., 2010; Kapczinski et al., 2008). Current hypotheses regarding the neurobiological background for bipolar disorder point towards defects in both cellular energy regulation, the immune system and expression of neurotrophic factors along with epigenetic alterations as core elements in the pathophysiology of the disorder (Gardner and Boles, 2010; Grande et al., 2011). These components, along with epigenetic alterations, have accordingly been proposed to be central to the neuroprogressive changes observed in bipolar disorder (Berk, 2009; Berk et al., 2010).

Several areas of research have pointed to immune system dysregulation and inflammation in bipolar disorder (Goldstein et al., 2009). More specifically, immune system aberrations have been demonstrated in both in-vitro studies (Kim et al., 2007; Knijff et al., 2007) and in clinical studies showing both alterations of peripheral markers of inflammation (Brietzke et al., 2009b; Cunha et al., 2008; Dickerson et al., 2007) and alterations of inflammation related gene signatures (Drexhage et al., 2010b; Padmos et al., 2008). In addition, preclinical studies have indicated anti-inflammatory properties as a possible role of action for mood stabilizers (Bosetti et al., 2002; Lee et al., 2008; Maes et al., 1999; Rapaport and Manji, 2001).

Cytokines are key signalling molecules in inflammation, exerting a regulatory effect in both the innate and the adaptive immunological response. They are produced by immune cells as well as non-immune cells and exert their effects beyond strictly the immune system. Cytokines bind to either specific cellular receptors or soluble receptors capable of modulating the immunological effect of cytokines. The immune response is further moderated by cytokine receptor antagonists, also binding to cytokine receptors (Drexhage et al., 2010a). Importantly, the role of cytokines in metabolism extend beyond the inflammatory system, impacting also on neurotransmitter metabolism, neurogenesis and the neuroendocrine system (Haroon et al., 2012).

Alterations of the inflammatory system appear to be related to disease state. Peripheral markers related to inflammation, oxidative stress and neurotrophins have been proposed as mediators of systemic toxicity, specifically related to mood episodes and illness activity (Grande et al., 2011; Kapczinski et al., 2010a, 2010b). In unipolar depression, inflammatory markers elevated in depressed patients have been demonstrated to normalize after successful treatment (Miller et al., 2009) and in schizophrenia some cytokines have been indicated to be state markers for acute exacerbations (Miller et al., 2011). While mood-state related inflammatory system alterations have been demonstrated in individual clinical studies in bipolar disorder, mainly indicating elevated levels of pro-inflammatory markers during manic and depressive episodes, results have been inconsistent and the association between altered cytokine levels and mood state remains unclear for a number of cytokines (Goldstein et al., 2009).

Taken together, current evidence suggests that core pathological processes underlying bipolar disorder and the possible detrimental effects resulting from mood episodes are closely related to illness activity and alterations between affective states.

Meta-analysis has the potential to bring further clarity to an area of research where single studies are generally of low power and to improve the strength of evidence while also examining sources of heterogeneity among studies and whether this influences the observed effects.

The purpose of the present study was therefore to perform a meta-analysis of peripheral blood cytokine-, cytokine receptor and cytokine antagonist levels in bipolar disorder according to clinical state. First, we examined alterations of endogenous immune activity in bipolar disorder patients according to clinical state (i.e., manic, depressive and euthymic state) in comparison to healthy controls. Comparisons between bipolar patients in different clinical states and evaluation of intra-individual alterations of immune activity were also performed. Second, we performed a qualitative assessment of the effect of symptom severity, medication status and clinical characteristics (i.e., smoking status and body mass index) on cytokine-, cytokine receptor and cytokine antagonist levels.

We specifically refrained from including a global analysis of cytokine levels in bipolar patients compared with healthy controls, as this does not inform on cytokine levels according to mood state and illness activity.

This is the first meta-analysis of cytokines in bipolar disorder.

2. Methods and materials

The meta-analysis was conducted and reported according to the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) (Moher et al., 2009). A protocol for the review was prepared and is available by contact to the first author.

2.1. Eligibility criteria

Original studies reporting on cytokine concentrations, cytokine receptor concentrations or cytokine antagonist concentrations in bipolar disorder were eligible for review. Further criteria were (1) adult subjects >18 years of age, meeting DSM-III-R, DSM-IV or ICD-10 criteria for bipolar disorder; studies confirming diagnosis by several individual trained psychiatrists were also evaluated; (2) cross-sectional studies comparing levels in bipolar disorder patients with either control subjects or bipolar disorder patients in a different affective state (case-control studies) or longitudinal studies comparing cytokine-, cytokine receptor or cytokine antagonist levels in bipolar disorder patients in a specified state and subsequent remission; where studies evaluated a therapeutic intervention the baseline clinical state and corresponding cytokine parameter levels were used for comparison with healthy controls if a control group was studied; (3) clinical status of bipolar disorder patients in a well defined affective state (euthymia, hypomania, mania, depression or remission); (4) studies assessing blood levels of cytokine-, cytokine receptor or cytokine antagonist levels; (5) studies published in English. If the study population included patients in various affective states, authors were contacted in order to obtain stratified data if these were not available in the manuscript. Exclusion criteria were (1) studies of in vitro cytokine production in stimulated peripheral blood mononuclear cells as they assess the response to immune challenge and do not likely inform about endogenous immune activity; (2) studies not reporting mean and standard deviation of cytokine parameter levels. If these data were not available in the