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Review article

The effect of mood-stabilizing drugs on cytokine levels in bipolar disorder: A systematic review

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ABSTRACT

Objectives: Cytokine level alterations suggest a role for the immune system in the pathophysiology of bipolar disorder (BD). Pharmacotherapy is an important confounding factor in clinical research on cytokine levels. In this systematic review we collate the evidence on blood cytokine levels in medication-free BD and the effects of single mood-stabilizing drugs on these levels.
Methods: A systematic review was conducted according to the PRISMA statement. We searched the Pubmed and Embase databases for clinical studies reporting either on cytokine levels in medication-free BD or on the effects of single mood-stabilizing drugs on cytokine levels in BD.
Results: Of the 564 articles screened, 17 were included. Fourteen articles report on medication-free patients with BD and indicate state-related cytokine alterations. Six articles discuss the effect of lithium. Whereas no data on short-term effects of lithium were found, ≥ 2 months lithium use in euthymic populations is associated with normal cytokine levels. Two studies report no effect of valproate and no studies were found on carbamazepine, lamotrigine or antipsychotics.
Limitations: The available studies are characterized by a broad methodological heterogeneity and limited replication between studies.
Conclusions: This systematic review suggests the presence of state-related cytokine level alterations in medication-free BD with most evidence pointing to a proinflammatory cytokine response in mania. Euthymia and long-term lithium use are associated with normal cytokine levels. To improve our understanding of the impact of mood-stabilizing drugs on cytokine levels, longitudinal studies with medication-free baseline, randomized controlled single-drug treatment protocols and close mood state monitoring are needed.

Contents

Abbreviations: BD, Bipolar disorder; CRP, C-reactive protein; HCs, Healthy controls; IFN, Interferon; IL, Interleukin; LPS, Lipopolysaccharide; PHA, Phytohemagglutinin; PRISMA-P, Preferred reporting items for systematic review and meta-analysis protocols; sIL-R, Soluble interleukin receptor; sTNF-R, Soluble tumor necrosis factor receptor; TGF, Transforming growth factor; TNF, Tumor necrosis factor

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1. Introduction

Bipolar disorder (BD) is a group of affective disorders characterized by episodes of mania or hypomania, often alternating with depressive episodes and interspersed with euthymic intervals (Phillips and Kupfer, 2013). The disease is associated with a progressive decline in cognitive and psychosocial functioning, the latter aspects accounting for a significant reduced quality of life (Levy and Manove, 2012). In search of the neurobiological underpinnings of BD, abnormalities in brain structure, brain function, neurodevelopment, neurotransmission, inter- and intracellular signaling and (epi)genetics have been identified (Maletic and Raison, 2014). Recently gained insights emphasize the role of the immune system in the pathophysiology of BD (Goldstein et al., 2009; Maletic and Raison, 2014; Stertz et al., 2013). Several studies show raised levels of inflammatory markers, notably cytokines (Hornig et al., 1998; Modabbernia et al., 2013; Munkholm et al., 2013).

Cytokines are small soluble proteins crucial for immune response regulation. They can have pro- or anti-inflammatory characteristics and some have a broader regulatory role in the immune response. Typical proinflammatory cytokines are tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β and IL-6. They are mainly secreted by macrophages in response to noxious stimuli and contribute to a rapid local inflammatory response. Other important cytokines are interferon gamma (IFN-γ), IL-2, IL-4 and IL-10. These have a diverse set of functions. Basically, IFN-γ and IL-2 enhance the cellular immune response, while IL-4 and IL-10 activate the humoral immune response and have an anti-inflammatory effect through negative feedback on immune cell activation (Drexhage et al., 2010; Liao et al., 2011; Shabgah et al., 2014). Cytokines exert their function through binding to cytokine receptors. Both membrane-bound and soluble forms of cytokine receptors have been identified. Soluble cytokine receptors are readily detectable in peripheral blood samples and have been proposed as suitable markers of disease activity in various inflammatory diseases such as cancer, infections and autoimmune diseases (Barbosa et al., 2011; Cetin et al., 2012; Diez-Ruiz et al., 1995; Kronfol and Remick, 2000). Binding of the soluble receptors with their respective cytokines can result in both agonistic (soluble TNF receptor 1 and 2 (sTNFR1&2), sIL-6R) and antagonistic (sIL-2R) effects on cytokine signaling (Breunis et al., 2003; Wolf et al., 2014).

The repeated observation of elevated cytokine levels in both BD and major depressive disorder has put forward the 'cytokine-hypothesis of mood disorders'. According to this hypothesis, excessive production of cytokines due to chronic activation of macrophages, microglia, and T-cells is suggested to cause psychiatric signs and symptoms through effects on neurotransmission, neuroendocrine function and neural plasticity (Beumer et al., 2012; Haarman et al., 2014; Maes et al., 1995b; Miller et al., 2009; Rosenblat et al., 2014).

While several clinical studies and 2 recent meta-analyses (Modabbernia et al., 2013; Munkholm et al., 2013) show significant cytokine changes in BD, cautious interpretation of these results should be emphasized. The design of the individual studies is highly heterogeneous, generally small in sample size and often lacks control for important confounding factors. Indeed, age, gender, smoking habits, metabolic syndrome, somatic comorbidities and use of mood-stabilizing drugs are known to influence peripheral cytokine levels (Drexhage et al., 2010; Haack et al., 1999), but are often not accounted for. These confounders impede a conclusive interpretation of the current data on cytokine level alterations in BD. The severity and phasic course of BD often imposes complex psychotropic drug regimens on patients (Bauer et al., 2013). Consequently, the use of mood-stabilizing drugs at time of inclusion in clinical studies is often inevitable and unconfounded medication-free cytokine levels in patients with BD are therefore hard to obtain. Some *in vitro* studies on the influence of mood-stabilizing drugs (mainly lithium) on cytokine production are available. However, results are conflicting and translation to clinical populations is difficult (Himmerich et al., 2013, 2014; Kleinerman et al., 1989; Knijff et al., 2007; Petersein et al., 2015). Clinical studies on the other hand, rarely have patients on standardized treatment regimens and are therefore limited to a comparison of cytokine levels in 'medication-free and 'medicated' patients. However, as the individual mechanisms of action differ greatly between various mood-stabilizing agents, we can equally hypothesize different effects on the immune system. A separate evaluation of single drugs is therefore crucial.

This systematic review will focus on cytokine levels in medication-free patients with BD and the influence of single mood-stabilizing drugs on cytokine levels. We discuss limitations in the current body of literature and formulate suggestions for future research.

2. Methods

This systematic review was conducted and reported according to the PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) guideline (Moher et al., 2015). Objectives and eligibility criteria were specified in advance and documented in a protocol. For protocol details and PRISMA checklist, see Supplementary material.