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The plasma levels of various cytokines are increased during ongoing depression and are reduced to normal levels after recovery

Johan Dahl [a,*], Heidi Ormstad [b], Hans Christian D. Aass [c], Ulrik Fredrik Malt [d,e], Lil Träskman Bendz [f], Leiv Sandvik [g], Lena Brundin [h,i], Ole A. Andreassen [j,k]

[a] Ringerike Psychiatric Center, Vestre Viken Hospital Trust, Norway
[b] Faculty of Health Sciences, Buskerud University College, Norway
[c] Department of Medical Biochemistry, Oslo University Hospital, Norway
[d] Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[e] Department of Psychosomatic Medicine, Oslo University Hospital, Rikshospitalet, Oslo, Norway
[f] Department of Clinical Sciences, Section for Psychiatry, Lund University, Lund, Sweden
[g] Center for Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway
[h] Division of Psychiatry and Behavioral Medicine, College of Human Medicine, Michigan State University, Grand Rapids, USA
[i] Van Andel Research Institute, Center for Translational Medicine, Grand Rapids, MI, USA
[j] NORMENT, KG Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[k] Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway

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Abstract
Background: Cytokines are implicated in the pathophysiology of major depressive disorder (MDD). However, the pattern of alterations in cytokine levels is still unclear. The current study investigated the plasma levels of a range of cytokines in a follow-up design, with the aim of determining their involvement in depression.
Methods: Fifty medication-free MDD patients with a depressive episode and 34 healthy controls were included at baseline; the patients were followed up after 12 weeks. Before initiating treatment, the patients were diagnosed and assessed for depressive symptoms and blood for cytokine analysis was obtained. The same clinical assessments and cytokine measurements were performed after 12 weeks of "treatment as usual."
Results: The cytokines interleukin (IL)-1β, IL-1 receptor antagonist (IL-1Ra), IL-5, IL-6, IL-7, IL-8, IL-10, granulocyte colony-stimulating factor (G-CSF), and interferon gamma (IFNγ) were significantly elevated ($p = 0.01$—0.047) in depressed patients at baseline compared to healthy controls.

* Corresponding author at: Vestre Viken HF, Ringerike Psychiatric Centre, Arnold Dybsjords vei 1, 3511 Hoenefoss, Norway. Tel.: +47 40029395.
E-mail address: johan.dahl@vestreviken.no (J. Dahl).

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After 12 weeks of treatment, the plasma levels of seven of these nine cytokines (IL-1Ra, IL-6, IL-7, IL-8, IL-10, G-CSF, and IFNγ had decreased significantly compared to baseline and did not differ from those in the healthy controls. The depressive symptoms were simultaneously significantly reduced. In addition, the reduction to normal cytokines levels occurred only in those who met the recovery criteria.

Conclusion: A more general pattern of elevated cytokine levels is described herein relative to what has been described previously shown in MDD. Furthermore, recovery from depression was associated with reduction to normal levels of the majority of the measured cytokines. These results strongly support the notion that a complex network of cytokines is involved in the pathophysiology of MDD.

1. Background

Several studies have suggested that immune dysregulation forms part of the pathophysiology of depression (Smith, 1991; Maes et al., 1993; Sluzewska et al., 1996; Dantzer and Kelley, 2007; Kim et al., 2007; Leonard and Maes, 2012). The macrophage hypothesis of depression put forward by Smith (1991) states that proinflammatory cytokines, which are produced by activated macrophages, contribute to many of the symptoms of depression. Their role in depression is supported by the high rate of clinical depression seen during treatment with cytokines, leading to the cytokine-induced depression model (Musselman et al., 2001; Raison et al., 2005). The link between immunity and depression is further supported by "sickness behavior," which is seen during both infection and depression (Dantzer, 2007).

Cytokines constitute a diverse group of low-molecular-weight proteins that form a network that controls not only local and systemic immune and inflammatory responses but also wound healing, hematopoiesis, and other biologic processes (Brunton et al., 2013). Cytokines also mediate normal cellular processes, with the actions of certain cytokines counteracting each other, thereby providing a fine-tuned balance (Kim et al., 2007). Cytokines are pleiotropic, in that they can have more than one effect, with these effects depending upon the concentration of the particular cytokine and the prevailing state of the immune system (Ozaki and Leonard, 2002; Cavaillon, 2001).

There are different ways to classify cytokines: based on their effect on the immune system they can be grouped as pro- and anti-inflammatory cytokines or as T-helper (Th)1 (stimulate cellular immunity) and Th2 (stimulate humoral immunity) cytokines (Brunton et al., 2013).

While a role for cytokines in the etiology of major depressive disorder (MDD) seems plausible, two recent meta-analyses of cytokine levels in MDD revealed that the reviewed studies did not provide a clear picture of the cytokine profile (Dowlati et al., 2010; Liu et al., 2012). Dowlati et al. (2010) concluded that only two proinflammatory cytokines [interleukin (IL)-6 and tumor necrosis factor alpha (TNFα)] were consistently elevated in depression. IL-6 and TNFα are markers of activity in the upstream inflammatory pathways (Aukrust et al., 1996). Liu et al. (2012) also found elevated levels of IL-6 and TNFα, but also elevated levels of IL-2R, which is a soluble IL-2 receptor that is known to be a marker of cell-mediated activation (Maes, 2011). Many of the findings of the individual studies included were not confirmed in these two meta-analyses (Dowlati et al., 2010; Liu et al., 2012). Furthermore, there are some inconsistent findings regarding the balance between Th1 and Th2 cytokines. Pavon et al. (2006) found a decreased Th1/Th2 cytokine ratio in depression, whereas Myint et al. (2005) found an increased Th1/Th2 cytokine ratio. These studies used both serum and plasma (Dowlati et al., 2010; Liu et al., 2012), and cytokines seem to be robustly detected whether measured in plasma or serum.

Most individual studies of cytokine alterations in depression have investigated a restricted number of cytokines. The studies included in the meta-analyses of Dowlati et al. (2010) and Liu et al. (2012) involved a total of ten cytokines, with an average of 2.6 cytokines per study. In the meta-analysis of Hannestad et al. (2011), the mean number of cytokines analyzed per study was 1.4, with a maximum of 3. The inclusion of only a small number of cytokines in an individual study can give the false impression of a very specific immune activation. This is supported by a study of 20 cytokines in the serum of MDD patients, in which 15 cytokines were found to be elevated (Simon et al., 2008). Those authors described an abundant increase in both pro- and anti-inflammatory markers as a generalized inflammatory state. This may be missed if only a restricted set of markers is analyzed. In order to obtain a better picture of the pattern of inflammatory changes in MDD, a range of immune markers should be investigated in the same experimental groups.

While about half of the studies included in the meta-analysis of Dowlati et al. (2010) and Liu et al. (2012) were longitudinal, only baseline data were reported that compared depressed patients and controls. It is not possible to draw any conclusions regarding causative factors in such cross-sectional studies; in contrast, longitudinal studies may provide more detailed information. A reduction in cytokine levels after pharmacotherapy has been reported previously for TNFα (Tuglu et al., 2003), IL-1β (Himmerich et al., 2010), IL-6 (Basterzi et al., 2005), and IL-12 (Sutcigil et al., 2007). Moreover, increased levels of IL-4 and transforming growth factor beta (TGFβ) have also been observed after pharmacotherapy (Sutcigil et al., 2007). However, there are some inconsistencies in this field. Hannestad et al. (2011) found that antidepressant treatment reduced the levels of IL-1β, and possibly also those of IL-6, but had no effect on TNFα. Those authors concluded that the levels of inflammatory cytokines do not decrease significantly even when patients exhibit symptom improvement.

The aim of the current study was to further determine the alteration in cytokine levels in depression. A broad spectrum