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A shift toward T helper 2 responses and an increase in modulators of innate immunity in depressed patients treated with escitalopram

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Abstract Depression is hypothesized to involve inflammatory processes, and identifying the key cytokines targeted by antidepressant drugs is critical for tailoring treatment to specific cases. However, investigating a limited number of cytokines at one time cannot provide a broad picture of antidepressant-associated immunomodulation. Cytokines act in a network where one could demonstrate pleiotropism, redundancy, synergy, and antagonism with other cytokine functions. This study was aimed at determining whether escitalopram functions as an anti-inflammatory agent and, if so, how it influences cytokine networks. A total of 24 healthy controls and 26 patients with clinical depression requiring inpatient treatment were recruited. A multiplex assay, an efficient tool to simultaneously measure 27 cytokines, was applied in patients with depression before and after 4-week escitalopram treatment. Healthy controls did not take escitalopram and completed cytokine analyses once. We demonstrated that escitalopram increased the levels of interleukin (IL)-1 receptor antagonist and IL-2. Moreover, escitalopram contributed to a shift toward T helper 2 responses and an increase in modulators

Abbreviations: ELISA, enzyme-linked immunosorbent assay; SSRIs, selective serotonin reuptake inhibitors; IL, interleukin-1; TNF-α, tumor necrosis factor alpha; IFN-γ, interferon gamma; IL-1RA, interleukin-1 receptor antagonist; Th, T helper; HDRS, Hamilton Depression Rating Scale; FGF, fibroblast growth factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IP-10, interferon gamma-induced protein 10; MCP-1, monocyte chemotactic protein 1; MIP-1α, macrophage inflammatory protein-1 alpha; PDGF, platelet-derived growth factor; RANTES, regulated on activation** normal T cell expressed and secreted; VEGF, vascular endothelial growth factor; 5-HT, 5-hydroxytryptamine.

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of innate immunity, leading to a decrease of immune system activation, both innate and adaptive. We suggest that escitalopram modulates the balance of IL-1 and IL-1 receptor antagonist and improves the function and number of T regulatory cells. However, diverse conclusions could be drawn if only a few cytokines were assessed or different significance levels were used. Further studies should investigate a wide range of cytokines in a reliable and valid way, which is key to disentangling the effects of different antidepressants on inflammatory processes.

1. Introduction

A better understanding of the neurobiology of major depressive disorder, the third leading cause of disease burden, offers hope for novel targeted therapies. The striking comorbidity of depression with several modern maladies, such as cardiovascular diseases and diabetes, brings psychiatry and medicine in lockstep for the search for potential shared etiological mechanisms (Katon, 2003). There is increasing recognition that inflammation is a primary pathophysiological determinant of these modern maladies, prompting researchers to raise the questions of whether and to what extent inflammatory process affect depression (Ridker, 2007). Indeed, preclinical and clinical studies into this issue have sprung up, followed by an avalanche of evidence making a case for the inflammatory hypothesis of depression.

Supporting the inflammatory hypothesis of depression are studies showing elevated levels of a variety of inflammatory biomarkers in depressed persons and observations that inflammatory cytokines induce a syndrome of sickness behavior, characterized by multiple features overlapping with clinical depression (Berk et al., 2013; Dowlati et al., 2010; Haroon et al., 2012; Miller et al., 2009). New evidence against such a burgeoning backdrop has emerged suggesting that inflammation is not generally present in, but only restricted to particular subgroups of, depressed persons (Haroon et al., 2012; Raison and Miller, 2011). One critical issue is the complex and varied repertoire of effects each antidepressant has on inflammatory processes. Evidence clearly shows that the changes cytokine levels are not consistently tied to positive outcomes during depression treatment (Hannestad et al., 2011). Successful management of depression requires identification of the cytokines that drive pathogenesis in depression and pinpointing which cytokines are targeted by each antidepressant agent.

The surveying of a limited number of cytokines at one time may have led to conflicting findings on the association between antidepressants and cytokines. Cross sectional single cytokine measurements, such as enzyme-linked immunosorbent assay (ELISA), might not decipher the cytokine network involved in an antidepressant's pharmacological underpinnings because most cytokines tend to act in networks or cascades, within which a cytokine could demonstrate pleiotropism, redundancy, synergy, and antagonism with other cytokine functions (Elshal and McCoy, 2006; Richens et al., 2010; Wong et al., 2008). A technology that simultaneously quantifies multiple cytokines with reproducibility, precision, and accuracy across studies might be essential to creating a global picture of antidepressant-associated immunomodulation. A meta-analysis of 22 studies reported that selective serotonin reuptake inhibitors (SSRIs) consistently reduced levels of interleukin-1 beta (IL-1β), IL-6, and tumor necrosis factor alpha (TNF-α) (Hannestad et al., 2011); however, 19 out of these 22 studies used conventional ELISA measurements. This anti-inflammatory effect appears contradictory to data from several studies in which antidepressants were shown to elicit systemic inflammation as demonstrated by increased levels of C-reactive protein (Hamer et al., 2011), IL-1β, IL-6, and interferon gamma (IFN-γ) (Marques-Deak et al., 2007). It is clear that a holistic approach for cytokine assay can advance our understanding of each antidepressant's unique cytokine fingerprint.

Escitalopram is the most selective of the SSRIs (Owens and Rosenbaum, 2002), and its effects on the interrelationships between different cytokines have not been extensively investigated. Two studies have addressed this issue, one that recruited patients with major depressive disorder and healthy controls (Eller et al., 2008), and a second that enrolled healthy first-degree relatives of patients with clinical depression (Haastrup et al., 2012). A total of six cytokines, including IL-1 receptor antagonist (IL-1RA), soluble IL-2 receptor, IL-6, IL-8, IL-10, and TNF-α, were examined in these two studies. Eller et al. (2008) reported that changes in serum levels of soluble IL-2 receptor were different for responders and non-responders during escitalopram treatment. On the contrary, Haastrup et al. (2012) did not find any effect of escitalopram on cytokine levels, and therefore did not support the hypothesis of escitalopram's anti-inflammatory effect. However, these two studies examined a limited number of cytokines, which may have hampered the exploration of escitalopram's effects on the orchestration of inflammatory processes.

We applied a multiplex assay to detect a panel of 27 cytokines, providing a comprehensive depiction of *in vivo* changes in cytokine profiles. This study aimed to investigate: (1) escitalopram's anti-inflammatory effect for patients with clinical depression, (2) differences in cytokine levels between healthy controls and patients with depression before and after escitalopram treatment, and (3) the association between cytokine changes and depression symptom improvement. In addition to cytokine levels, this study also examined cytokine ratios, which can determine escitalopram's ability to shift the immunity balance towards T helper (Th)1 or Th2 response.