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Differences in immunomodulatory properties between venlafaxine and paroxetine in patients with major depressive disorder

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ABSTRACT

Inflammatory processes play a crucial role in the pathophysiology of depression, and identifying the specific cytokines targeted by different antidepressants is important for personalized treatment. The aims of this study were to examine whether venlafaxine and paroxetine cause different immunomodulatory effects when used to treat patients with major depression and to clarify the relationships between plasma cytokine levels and the therapeutic effectiveness of these drugs. A total of 91 Han Chinese patients with major depression completed the 8-week paroxetine or venlafaxine treatment and 90 healthy controls were recruited. A multiplex assay was used to measure cytokines levels in patients with major depression before and after an 8-week venlafaxine and paroxetine treatment. Cytokine levels were measured in healthy controls at the baseline. The 21-item Hamilton Depression Rating Scale was used to assess the changes in psychopathological symptoms from the baseline to the end point in each patient. Venlafaxine treatment caused greater decreases in the levels of interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), interleukin 4 (IL-4), IL-5, IL-1β, and IL-8 than did paroxetine. Paroxetine treatment increased the levels of proinflammatory cytokines IFN-γ, TNF-α, and IL-6 and decreased Th2 cytokine levels. After paroxetine treatment, IL-6 levels increased more in the non-remitter group than in the remitter group. In the remitter group, IL-4 and IL-5 levels decreased to values seen in the healthy controls. After venlafaxine treatment in both the remitter and non-remitter groups, IL-1β levels decreased to values seen in the healthy controls. Our results suggest that venlafaxine and paroxetine have different immunomodulatory properties and that venlafaxine has greater anti-inflammatory effects than paroxetine.

1. Introduction

Inflammation may play an important role in the pathophysiology of depression, and monitoring the therapeutic efficacy of drugs used to treat depression at the level of the immune system and immune-targeted therapies may be helpful for identifying unique patient populations (Haapakoski et al., 2016; Miller et al., 2009). Experimental and clinical evidence has emerged to suggest that activation of proinflammatory cytokines, including interleukin 1 (IL-1), IL-6, interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α), may contribute to depression. The possible mechanisms to explain a role of proinflammatory cytokines in depression are as follows. Proinflammatory cytokines can inhibit serotonin synthesis in the brain by activating the enzyme indoleamine 2,3-dioxygenase, which catalyzes the metabolism of tryptophan, the primary precursor for serotonin, into kynurenine. These cytokines also reduce the availability of monoamines

Abbreviations: ANOVA, analysis of variance; ANCOVA, analysis of covariance; BMI, body mass index; CNS, central nervous system; ELISA, enzyme-linked immunosorbent assay; GM-CSF, granulocyte–macrophage colony-stimulating factor; HDRS, The 21-item Hamilton Depression Rating Scale; HPA axis, hypothalamic–pituitary–adrenal axis; IFN-γ, interferon gamma; IL, interleukin; MDD, major depressive disorder; NF-κB, nuclear factor-kappa B; SADS-L, Schedule of Affective Disorder and Schizophrenia-Lifetime; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; Th, T helper; TNF-α, tumor necrosis factor alpha; 5HT, 5-hydroxytryptamine; 5HTT, 5-hydroxytryptamine transporter

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such as serotonin, dopamine, and noradrenaline by increasing the expression and function of the presynaptic reuptake pumps (transporters). Proinflammatory cytokines may reduce monoamine synthesis by decreasing enzymatic cofactors expression, such as tetrahydrobiopterin, which is rate limiting for the biosynthesis of monoamines (Miller and Raison, 2016; Raison et al., 2009; Raison et al., 2010).

Peripherally increased levels of the proinflammatory cytokines IL-1β, IFN-γ, and TNF-α can be induced by lipopolysaccharide, typhoid vaccine (Harrison et al., 2009), or IFN treatment in patients with hepatitis C (Raison et al., 2009). Increased levels of these cytokines have been linked to depressive-like symptoms in animal and human studies (Haapakoski et al., 2016). The peripheral immune system can transduce immune signals to the brain through different humoral, cellular, and neural pathways. Moreover, peripheral cytokines can pass through leaky regions in the blood–brain barrier (BBB) into the brain parenchyma in association with pathological etiologies that involve increased BBB permeability or volume diffusion, such as major depressive disorder (MDD). Cytokines may also affect the central nervous system (CNS) via mediators such as prostaglandins or nitric oxide, which are released in response to cytokines or from afferent vagal nerve fibers (Dantzer et al., 2008; Felger and Lotrich, 2013).

Vaccination such as immunization with myelin-derived peptide, which activates self-reactive T cells, has been shown to ameliorate depressive behavior in murine models by restoring the levels of hippocampal brain-derived neurotrophic factor and neurogenesis. It has been suggested that immune-based therapies should be considered for treatment of depression (Lewitus et al., 2009). Peripheral cytokine levels may be useful biomarkers for the clinical evaluation of the therapeutic efficacy and immunomodulatory effects of antidepressants in the treatment of depressed patients. Cumulative meta-analyses have reported higher concentrations of peripheral proinflammatory cytokines, such as IL-6 and TNF-α, in patients with MDD compared with non-depressed controls (Dowlati et al., 2010; Haapakoski et al., 2015). Recent studies have also examined the variation in circulating cytokine levels after selective serotonin reuptake inhibitor (SSRI) treatment for MDD and whether these drugs modify the balance between T helper 1 (Th1) and Th2 cells and between innate and adaptive cytokines (Hernandez et al., 2008; Ho et al., 2015).

To our knowledge, few previous studies have investigated the immunomodulatory and anti-inflammatory effects of venlafaxine, a serotonin–norepinephrine reuptake inhibitor (SNRI), in patients with MDD. The aims of this study were as follows: (1) to compare the immunomodulatory effects of venlafaxine (an SNRI) or paroxetine (an SSRI) in patients with MDD; (2) to compare the changes in plasma cytokine levels between patients with MDD and heathy controls; (3) to determine whether plasma cytokine levels are related to the severity of depression; and (4) to determine whether changes in plasma cytokine levels are related to the therapeutic effectiveness of venlafaxine and paroxetine treatment. We also calculated cytokine ratios to help clarify whether venlafaxine and paroxetine can alter the balance toward the Th1/Th2 or innate/adaptive response. We measured the concentrations of Th1 cytokines (IL-2, TNF-α, and IFN-γ), Th2 cytokines (IL-4, IL-5, IL-6, and IL-10), and other cytokines with no established Th1 or Th2 inflammatory function (IL-1β, IL-8, and granulocyte–macrophage colony-stimulating factor (GM-CSF)). We also calculated the ratios between Th1 cytokines and Th2 cytokines; and the ratios between innate immunity mediators (IL-1β, IL-6, IL-8, and TNF-α) and adaptive immunity mediators (IL-2, IL-4, and IFN-γ) (Haapakoski et al., 2016; Ho et al., 2015).

2. Materials and methods

2.1. Participants

Patients with MDD were recruited from the outpatient and inpatient populations, and the control group included healthy volunteers, who were recruited from the community. All participants gave written informed consent after the procedures of the study were explained completely. This study design was approved by the Institutional Review Board of the Tri-Service General Hospital (TSGH) for the Protection of Human Subjects (TSGHIRB 096-05-009). The TSGH is a medical teaching hospital that belongs to the National Defense Medical Center, Taipei, Taiwan. To minimize the effect of ethnic differences, all participants were unrelated Han Chinese who were born and living in Taiwan, and all of their biological grandparents were of Han Chinese ancestry. Each participant was assessed initially by an experienced attending psychiatrist and subsequently interviewed by a well-trained psychologist using the Chinese version of the modified Schedule for Affective Disorders and Schizophrenia-Lifetime (SADS-L) (Endicott and Spitzer, 1978; Merikangas et al., 1998). The interrater reliability κ values of the SADS-L were good to excellent for MDD, bipolar disorder, anxiety disorder, schizophrenia, and substance abuse/dependence (Huang et al., 2004). A family history of MDD was defined as the presence of one or more first-degree relatives with a history of MDD.

The inclusion criteria for the patients were as follows: (1) diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (American Psychiatric Association, 2000); (2) a severity rating on the 21-item Hamilton Depression Rating Scale (HDRS) score of ≥18 (Hamilton, 1960); (3) being drug naïve or drug free of antidepressant or other psychotropic medications for ≥1 month; (4) age between 20 and 65 years; and (5) absence of other psychiatric axis I disorders. The exclusion criteria were: (1) significant active physical illness; (2) organic brain disease or epilepsy; (3) any concomitant major psychiatric disorder; (4) history of substance use disorder; (5) thyroid disease; or (6) women who were pregnant or lactating. An 8-week, open-label, flexible-dose antidepressant treatment (including venlafaxine 75–300 mg or paroxetine 10–40 mg) was instituted, and the dosage was adjusted according to the patient's symptoms. Patients with MDD who started using other antidepressants or who added mood stabilizers or antipsychotics to their treatment regimens were dropped from the study.

Age- and sex-matched control subjects were selected. The exclusion criteria for both the control subjects and patients were: (1) use of antibiotics or nonsteroidal anti-inflammatory drugs, either during the study or within 1 month before enrollment; (2) the presence of any physiological disease such as diabetes, cardiovascular disease, rheumatic arthritis, thyroid disease, obesity (body mass index (BMI) $> 30\ kg/m^2$), cancer, liver cirrhosis, or women who were pregnant or lactating. Healthy controls did not have any psychiatric disorder nor take antidepressants and their cytokine levels were obtained only at the baseline. Tobacco use and alcohol consumption were not allowed.

2.2. Psychometric assessment and cytokines measurement

The 21-item HDRS score (Hamilton, 1960) was used to assess the severity of psychopathological symptoms by the same experienced attending psychiatrist from the baseline to the end point (week 8). A higher score on the HDRS indicated an overall greater severity of depression. A remitter was defined as having an HDRS score of ≤7 in week 8 of antidepressant treatment.

To measure cytokine levels, venous blood samples were obtained by venipuncture from subjects who had fasted for more than 8 hours. To standardize the measurements and to ensure that the values reflected the basal fasting morning cytokine levels, all samples were obtained between 7:30 and 10:00 am. Peripheral blood samples were collected within 24 hours after recruitment for both healthy controls and patients with MDD. In week 8 of antidepressant treatment, blood samples were collected from patients only, and cytokine levels were measured as described below. Blood samples were collected in EDTA-containing tubes (BD Vacutainer® K2E (EDTA) 18.0 mg Plus Blood Collection Tube (10 ml) Ref: 367525) which were turned upside down 10–15 times and then placed on ice and centrifuged (3500 rpm for 15 min, at 4 °C)