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Full Length Research Paper

Fluoxetine treatment for major depression decreases the plasma levels of cytokines

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Elevated levels of pro-inflammatory biomarkers have been reported in major depressive disorder (MDD). The aim of this study is to investigate the plasma levels of interleukin-18 (IL-18), macrophage-inflammatory protein-1α (MIP-1α), monocyte chemoattractant protein 1 (MCP-1), stromal cell derived factor-1 (SDF-1), and regulated upon activation, normal T cell expressed and secreted (RANTES) in patients with MDD before and after eight week treatment of fluoxetine hydrochloride in comparison with normal controls. All subjects were assessed before and after treatment with the Hamilton Depression Rating Scale (HDRS). Our results showed that the symptoms of forty healthy controls and thirty-four patients with MDD were correlated with their plasma levels of IL-18, MIP-1α, MCP-1, SDF-1α, and RANTES. The levels of all five cytokine of patients with MDD were significantly decreased after treatment. However, the levels remained significantly higher than those of the healthy controls ($p<0.001$). In the seven depressed subjects whose HDRS score fell to below seven after antidepressant therapy comparing with those subjects whose HDRS score larger than seven, the mean levels of IL-18 ($p=0.01$) and SDF-1α($p<0.05$) were significantly lower. Conversely, higher levels of cytokines correlated with a persistently increased severity of symptoms, as measured by the HDRS scores. In conclusion, these findings suggest that MDD is associated with activation of the immune system, and the antidepressant effect of fluoxetine may be mediated in part through its anti-inflammatory effects.

Key words: Fluoxetine hydrochloride, major depression, cytokine, chemokine, inflammation.

INTRODUCTION

Major depressive disorder (MDD), a common and sometimes fatal disorder is one of the leading causes of disability worldwide (Lopez et al., 2001). MDD is viewed as a disorder that involves abnormalities in the central monoaminergic neurotransmitter system and gives rise to behavioral changes and alterations in neurohormonal pathways. Antidepressants, which largely target monoamine pathways, can be effective. However, clinical improvement after treatment with antidepressants occurs in less than 70% of depressed patients, and the rate of relapse can be as high as 50% (Byrne and Rothschild, 1998; Nelson, 2003; Connor and Leonard, 1998).

Recently, it has been suggested that the behavioral deficits, central monoamine abnormalities, and activation of the hypothalamic-pituitary-adrenal (HPA) axis that are observed in MDD are associated with alterations in immune function (Maes et al., 1995). There is now evidence that MDD is accompanied by an immune response that results in an increased production of pro-inflammatory cytokines. One study has shown that markers of T cell activation, such as the soluble IL-2 receptor, are increased

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in patients with depression, which suggested that both the innate and acquired immune systems are involved in the pathogenesis of MDD (Merendino et al., 2002). Kokai et al. (2002) found that the mean plasma concentration of IL-18 was three-fold higher in non-medicated patients with MDD and four-fold higher for patients who had panic disorder when compared to normal controls. Piletz et al. (2009) reported that patients with MDD had significantly higher baseline levels of monocyte chemoattractant protein 1 (MCP-1), as compared to controls (Piletz et al., 2009). Merendino et al. (2004) detected no macrophage-inflammatory protein-1α (MIP-1α) expression in normal controls, while 20% of patients with depression expressed a detectable level of MIP-1α. Stress, which was mimicked by the administration of corticosterone in drinking water, correlated positively with higher plasma levels of regulated upon activation, normal T cell expressed and secreted (RANTES) (Sutcigi et al., 2007). Only rare studies have investigated the role of broad spectrum pre-cytokines such as stromal cell derived factor-1 (SDF-1) and RANTES. Even in this limited number of studies, conflicting results have also been described.

Serotonin, or 5-hydroxytryptamine (5-HT) has a well-described role in the central and peripheral nervous system. However, it is also a potent immunomodulator. It has been shown to upregulate the production of the pro-inflammatory cytokine, interleukin-6 (IL-6), and is a potent regulator of the function of human dendritic cells (Muller et al., 2009). Selective serotonin reuptake inhibitors (SSRI) decrease the amount of endothelial adhesion molecule expression induced by cytokines, the endothelial adhesiveness to monocytes, and circulating levels of vascular adhesion molecules (Lekakis et al., 2010). The serum concentrations of IL-6, IL-8, IL-10, MIP-1β and MCP-1 in women with psychological symptoms such as anxiety and mild depression were shown to be decreased significantly after they were treated with paroxetine, a type of SSRI (Yasui et al., 2009). It is also reported that serum il-1β and il-6 did not change significantly after intervention with fluoxetine (Jazayeri, 2010). The results are inconsistent.

Few studies have focused on the relationship between MDD and IL-18, MCP-1, MIP-1α, SDF-1α, and RANTES; we investigate the plasma levels of IL-18, MCP-1, MIP-1α, SDF-1α, and RANTES in major depression before and after 8-week fluoxetine hydrochloride treatment and their correlation with symptoms .The goals of this study are: (1) To determine the plasma concentrations of IL-18, MCP-1, MIP-1α, SDF-1α, and RANTES in a cohort of patients with depression; (2) to evaluate whether treatment with a SSRI, fluoxetine hydrochloride, affects the pathogenesis of MDD through causing decreased circulating levels of these cytokines; (3) whether cases of MDD that are refractory to treatment with fluoxetine hydrochloride correlate with different degrees of immuno-activation; and (4) to investigate the correlation of the level of these cytokines with the severity of depression, as measured by the Hamilton Depression Rating Scale (HDRS).

MATERIALS AND METHODS

Subjects

Seventy-four participants (40 healthy control subjects and 34 subjects with depression) were included in the present study. There was no significant difference between the groups with regards to age or sex. All of the subjects gave their written informed consent prior to commencing the trial. Participants were recruited from the outpatient and inpatient of Sir Run Run Shaw Hospital and all of them fulfilled the DSM-IV criteria for MDD. Subjects were between the ages of 18 and 66 years, with an average of 42.53± 12.1 years in patients group and 40.33± 10.1 in control group. 18 males and 16 females in patients group, 20 males and 20 females in control group. Forty healthy volunteers were included in the study as controls. The erythrocyte sedimentation rates (ESR) were all normal. Computed tomography (CT) or magnetic resonance imaging (MRI) scans of the head were normal in all patients with MDD.

The severity of the depression was quantified by the HDRS on, before and after the eight week monotherapy treatment course of fluoxetine hydrochloride (fluoxetine; 20 mg/day in first three weeks and 40 mg/day in last five weeks). No antidepressant medication was taken within the last one year in all subjects. Subjects received a thorough psychiatric assessment by a senior psychiatrist before and after treatment. The controls also took HDRS. Inter- and intra-assay coefficients of variation were reliably 10%. All ratings were evaluated by a psychiatrist, who was blinded to the immunological profiles. All parameters were repeated after treatment with fluoxetine.

The exclusion criteria applied to both the treatment and control groups of participants. They included the presence of any additional axis I or axis II DSM-IV diagnosis, current pregnancy, acute or chronic infections within the past month, dementia, autoimmune, allergic, neoplastic or endocrine diseases, and any other acute physical disorders, including surgery or myocardial or cerebral infarction within the past three months. Patients who had been exposed to any drug, which included antidepressants, oral steroids, nonsteroidal anti-inflammatory drugs, lithium, immunoregulants, and oral contraceptives within the six week period prior to the study were also excluded. Additionally, patients who had undergone electric shock therapy were excluded. The use of zolpidem was permitted for the treatment of insomnia. Healthy volunteers were interviewed and those with no lifetime or current diagnosis of any psychiatric disorders were included as the control group.

The current study utilized a prospective control design. The case collector, lab worker, and statistician were separate individuals.

Measurements

After an overnight fast, blood samples for the cytokine assays were collected at between 0700 am to 0800 am from patients with MDD and from the healthy controls. Venous blood samples were placed on ice immediately and transported to the laboratory. The serum samples were then aliquotted and stored at –70°C for later measurements of the levels of IL-18, MIP-1α, MCP-1, SDF-1α, and RANTES. All immunological parameters were determined by enzyme-linked immunosorbant assay (ELISA) techniques in accordance with the protocols of the manufacturers. After the colorimetric reaction was developed, the absorbance at 450 nm was quantified by an eight-channel spectrophotometer, and the absorbance readings were converted to pg/ml units based upon standard curves obtained with recombinant cytokines for each assay. If the absor-

Table 1. HDRS score before and after treatment.

Parameter	Healthy controls (*n*=40)	MDD before therapy (*n*=34)	MDD after therapy (*n*=34)
Total score	3 .04±0.12	24.13 ± 4.39*#	10.08 ± 3.03*
Anxiety/somatization	1.02±0.06	7.68 ± 2.09*#	3.33 ± 1.73*
Dysfunction of cognition	0.71±0.02	2.45 ± 1.83*#	0.35 ± 0.66*
Retardation	0.59±0.04	10.75 ± 3.94*#	6.43 ± 3.75*
Body weight	0.44±0.01	0.65 ± 0.83*#	0.25 ± 0.44*
Insomnia	1.55±0.08	3.98 ± 1.17*#	1.05 ± 0.71*

*p<0.01 vs. healthy controls; # p<0.01 vs. MDD after therapy.
Values are mean±SD.

Table 2. IL-18, MIP-1α, MCP-1, SDF-1α, and RANTES levels in treatment and control groups.

Parameter (pg/ml)	Healthy controls (n=40)	MDD before treatment (n=34)	MDD after treatment (n=34)
IL-18	55.93 ± 7.98	115.73 ± 12.23*#	90.33 ± 2.94*
MIP-1 α	290.42 ± 33.61	688.75 ± 110.72*#	452.36 ± 8.91*
MCP-1	144.08±19.90	479.18 ± 33.64*#	275.84 ± 13.37*
SDF-1α	1301.33 ± 134.20	2788.00 ± 104.76*#	2129.67 ± 81.29*
RANTES	1.77 ±0.19	3.89 ± 0.09*#	2.60 ± 0.18*

*p<0.01 vs. healthy controls; # p< 0.01 vs. MDD after treatment.
Values are mean±SD.

bance readings exceeded the linear range of the standard curves, the ELISA assay was repeated after serial dilution of the supernatants. Each serum sample was tested in at least two independent ELISA experiments, and the data were calculated from the mean of between two to four tests for each sample. The same procedures were applied for the assessment after treatment.

Statistical analysis

Data were analyzed with the Statistical Programme for the Social Sciences (SPSS Inc., Ill, USA). The data were expressed as the mean ± SD. The lifetime duration of MDD, the duration of this current episode of MDD, changes in HDRS before and after treatment, and the immune measurements were analyzed. Pearson's correlation coefficients were calculated to examine the relationship of the severity of MDD with the levels of the cytokines. Before and after values of the parameters were compared with the use of paired samples t tests. The cytokine levels of the control and treatment groups before and after treatment were subjected to a one-way analysis of variance (ANOVA) followed by an independent t test to compare the values in the control and treatment groups. A p-value of less than or equal to 0.05 was evaluated as being statistically significant.

RESULTS

The mean and standard deviation (SD) duration of the episode of MDD was 29 ± 13.50 months. The mean age of onset of the disease is 40.03±11.78. 17/34 of patients were first-onset, another 17/34 of patients were relapsed. The HDRS score in the normal controls were all below four. The HDRS scores were all ≥17 in the depressed subjects, and were ≥24 in 22 of these cases. In 33 cases, the HDRS score decreased by more than 50% after therapy, and this decrease was more than 75% in one case. The HDRS score was ≤7 in eight cases after treatment, which is viewed as evidence of clinical recovery. The HDRS score showed that anxiety/ somaticzation, cognition, retardation, body weight, and sleep disorder scores all decreased significantly after treatment with fluoxetine (Table 1). The HDRS scores of healthy group was 3 .04±0.12 as shown in Table 1.

The immunological characteristics of the patients with MDD and healthy controls and the results of the comparisons between the two groups are shown in Table 2. The ANOVA detected statistical significances among the control and the patients pre- and posttreatment of IL-18 ($F[2,105]=36.52$, $p<0.001$), MIP-1α ($F[2,105]=26.82$, $p<0.001$), MCP-1 ($F[2,105]=150.31$, $p<0.001$), SDF-1α($F[2,105]=140.33$, $p<0.001$), and RANTES ($F[2,105]=138.30$, $p<0.001$). The differences between the groups were confirmed by Duncan's test ($p<.001$). The mean levels of IL-18 ($p<0.01$), MIP-1α ($p<0.01$), MCP-1 ($p<0.01$), SDF-1α ($p<0.01$), and RANTES ($p<0.01$) were significantly lower in subjects with MDD after antidepressant therapy than before therapy (Table 2). The mean levels of IL-18, MIP-1α, MCP-1, SDF-1α, and RANTES remained significantly higher ($p<0.001$) in depressed subjects after antidepressant therapy than in normal control subjects (Table 2).

Table 3. IL-18, MIP-1α, MCP-1, SDF-1α, and RANTES levels in patients of HDRS score ≤7 and >7 after treatment and control groups.

Parameter (pg/ml)	Healthy controls (n=40)	HDRS score ≤7 (n=7)	HDRS score>7 (n=27)
IL-18	55.93 ± 7.98	75.32 ± 2.52*#	92.96 ± 8.47*
MIP-1 α	290.42 ± 33.61	429.86 ±40.36*	461.81 ± 6.31*
MCP-1	144.08±19.90	264.87 ± 18.66*	279.96 ± 26.39*
SDF-1α	1301.33 ± 134.20	1993.67 ±17.62*#	2152.67 ± 22.14*
RANTES	1.77 ±0.19	2.41 ±0.30*	2.74 ± 0.38*

*p<0.01 vs. healthy controls; # p<0.05 vs. HDRS score >7.
Values are mean±SD.

In the seven cases of patients whose HDRS score was ≤7 after antidepressant therapy, the mean post-treatment levels of IL-18 (p<0.001), MIP-1α (p<0.001), MCP-1 (p<0.001), SDF-1α (p<0.001), and RANTES (p<0.001) were significantly higher than in normal control subjects. In these patients, the mean post-treatment levels of IL-18 (p<0.05) and SDF-1α (p<0.05) were significantly lower compared to other depressed subjects whose HDRS score >7 after antidepressant therapy (Table 3).

The levels of each cytokine were correlated with the HDRS scores in both groups (p<0.001). The lifetime duration of depression was significantly correlated with the levels of IL-18 (p<0.01), MIP-1α (p<0.01), SDF-1α(p<0.01) in patients with MDD before treatment. Conversely, the duration of the current episode of MDD did not correlate with cytokine level (p>0.05). There was no difference in cytokine levels between genders in either group (p>0.05).

DISCUSSION

Our results showed that the pro-inflammatory cytokines and chemokines were significantly higher in patients with MDD than those of healthy controls. After antidepressant treatment, these cytokines decreased but remained higher in patients with MDD than in the healthy controls. The levels of each cytokine were significantly correlated with the HDRS score. It seems likely that the treatment course of fluoxetine hydrochloride might have exerted immunomodulatory effects through a consequent decrease in the circulating levels of pro-inflammatory cytokines and chemokines. However, although the cytokine concentrations decreased after the eight-week course of fluoxetine, they remained higher than the healthy controls. The refractory nature of symptoms of depression to antidepressant treatment, as assessed by the HDRS score, appeared to be correlated with high plasma levels of cytokines. IL-18 and SDF-1α may be biomarkers of antidepressant treatment resistance.

IL-18, which is a pro-inflammatory cytokine that plays an important role in the helper T-cell type 1 response, is a new member of the family of cytokines that is known to be produced within the brain. MIP-1 is chemoattractive of monocyte,and T cell CD4+T cell,CD3+ T cell and memory T cell (Taub, 1993). MCP is monocyte chemotactic protein. SDF-1 was first described as a factor produced by bone marrow stromal cells that induces proliferation of B cell progenitors and regulates B cell maturation (Nagasawa, 1996). SDF-1 is the unique biological ligand for CXCR4. Acting on CXCR4, SDF-1 exerts chemoattractant effects on target cells and mediates critical retentive functions towards pre-B cells, IL-1, and tumor necrosis factor (TNF) which regulate the expression of SDF-1 (Fedyk, 2001). SDF-1 induced expression of TNF-α, IL-1, RANTES in primary astrocytes (Han, 2001). RANTES is a monocyte chemoattractant. Most histone may release RANTES induced by IL-1β or TNF-α (Marfaing-Koka, 1995). Coexpression of RANTES or MCP-1 resulted in the enhanced expression of TNF-α (Kim, 1998). These cytokines are chemoattractive of different inflammatory cells. So we measured these cytokines to investigate activation of immuno network.

Merendino et al. (2004) demonstrated that serum IL-18 levels of patients with MDD were significantly higher than those of healthy individuals. These data are consistent with our results. Lehto et al. (2010) reported that the MDD group had lower levels of MCP-1 than the healthy controls. The current study found that levels of IL-18, MIP-1α and MCP-1 were higher in patients with MDD than in normal controls (Kokai et al., 2002; Piletz et al., 2009).

The role of SDF-1α and RANTES in depression is uncertain. MDD is accompanied by a variety of immunomodulatory processes that affect both the innate and the acquired immune responses. IL-18, MIP-1α, MCP-1, SDF-1α, and RANTES may be potential biomarkers of MDD. The plasma level of these cytokines is significantly correlated with HDRS.

Previous investigations have reported increased levels of IL-6 during an acute depressive episode, which normalized after an eight-week period of treatment with fluoxetine (Maes et al., 1995). Maes et al. (1997) reported that treatment with antidepressants had no significant effects on serum IL-6, IL-1Ra, CC16 or sCD8. These previous study findings have been somewhat inconsistent. In our

research, cytokines decreased after antidepressant treatment. Therefore, we hypothesize that antidepressants may alleviate the symptoms of depression by inhibiting cytokine secretion from immune cells *in vivo.*

In seven cases of patients whose HDRS score was ≤7 after antidepressant therapy. The mean levels of IL-18 ($p<0.001$), MIP-1α ($p<0.001$), MCP-1 ($p<0.001$), SDF-1 ($p<0.001$), and RANTES ($p<0.001$) were significantly higher than in normal controls. However, the activation of the immune system could not be suppressed by medication to a normal state after such a short period of treatment. This may be one of the reasons why patients with MDD need long periods of antidepressant treatment to prevent relapses, even after the symptoms are relieved. Further research is needed to assess whether the immune response, which appears to produce an increased level of pro-inflammatory cytokines, will be normalized after long periods of treatment with antidepressants. If this can be normalized by pharmaceuticals; cytokines may become important biomarkers to assist in the decisions regarding treatment levels and cessation.

Clinical improvement after treatment with antidepressants generally occurs in less than 70% of depressed patients with rates of relapse as high as 50%. Coincidentally, the HDRS score reduced by more than 75% in one case and to ≤7 points on the HDRS in eight cases after treatment, which was viewed as remission. There is a paucity of information with regards to the etiology of MDD that is resistant to treatment despite such a high occurrence of relapse. Treatment-resistant patients have been reported to have elevated plasma levels of IL-6, sIL-6R, IL-1Ra and sIL-2R (Bosker et al., 2004). In seven cases of depressed subjects whose HDRS score was ≤7 after antidepressant therapy, the mean levels of IL-18 ($p=0.01$) and SDF-1α($p<0.05$) were significantly lower compared to the patients whose HDRS score >7 after treatment. The activation of cell-mediated immunity may be one probable explanation for decreased response to drug therapy in some patients. Consequently, IL-18 and SDF-1α may be biomarkers of antidepressant treatment resistance.

A novel psychoneuroimmunological perspective on the treatment of depressive illness may be required for the successful treatment of this condition, and the current prevalent views on depression may need to change. Understanding the role that pro-inflammatory mediators play in response to drug therapy in depressed patients may aid in the explanation of treatment resistance and assist in designing more effective pharmacotherapy. Immunomodulatory treatment may be a promising target for such therapies, and our study sustained this perspective.

We showed in our study that the concentrations of IL-18, MCP-1, MIP-1α, SDF-1α, and RANTES were elevated in patients with MDD. Our results suggest that treatment with the SSRI, fluoxetine hydrochloride, may exert its effects on MDD through decreasing these cytokines, at least in part.Treatment resistance of patients with MDD to fluoxetine hydrochloride correlated with immunoactivation, and IL-18 and SDF-1α may be biomarkers of antidepressant treatment resistance. The severity of depression, as measured by HDRS, was correlated with the level of these cytokines. Yet, these cytokines may be not trait-specific; they may be a sign of immunoactivation in major depression.

Administration of proinflammatory cytokines in animals induces 'sickness behaviour'' (Alesci et al., 2005) which is a pattern of behavioural alterations that is very similar to the behavioural symptoms of depression in humans, we presume that higher cytokines induce depression.

Activation of the inflammatory response system involves not only specific immune and metabolic alterations but also neuroendocrine changes, such as hyperactivity of the hypothalamus-pituitary-adrenocortical axis and the peripheral and central turnover of 5-HT. The central action of cytokines may account for the HPA axis hyperactivity that is frequently observed in depressive disorders (Wang and Dunn, 1999). Pro-inflammatory cytokines may cause HPA axis hyperactivity by disturbing the negative feedback inhibition of circulating corticosteroids on the HPA axis. With regards to the deficiency in 5-HT neurotransmission that is concomitant with MDD, cytokines may reduce 5-HT levels by lowering the availability of its precursor tryptophan (TRP) through the activation of the enzyme that metabolizes TRP, indoleamine-2,3-dioxygenase (Brown et al., 1991) Curran and O'Connor, (2001) reported that IL-18 impair the induction of long-term potentiation (LTP); IL-18 significantly depressed the amplitude of pharmacologically isolated N-methyl d-aspartate (NMDA) receptor mediated fEPSP, IL-18 may affects NMDA-dependent LTP in the hippocampus, a main target structure in depression. It however, needs further investigation. Although the central effects of pro-inflammatory cytokines appear to account for most of the symptoms that occur in depression, it remains to be established whether cytokines play a causal role in depressive illness or represent epiphenomena of the disorder without a major causative influence.

Antidepressants may alleviate depressive symptoms by inhibiting cytokine secretion from immune cells *in vivo* or by decreasing the concentration of cytokines in the brain, and thereby blocking the action of cytokines in the central nervous system (Taler et al., 2008; Zhu et al., 2009).

Some potential limitations of the current study should be noted. Firstly, the duration of treatment was only eight weeks. Further research is needed to investigate the level of these cytokines after longer periods of therapy. If the levels of cytokines continue to decline, it is possible that the levels of these cytokines are markers of the efficacy of antidepressant therapy and may help to determine when to stop treatment for MDD. Secondly, it remains unclear whether altered cytokine and chemokine levels are responsible for the etiology of depression or merely represent secondary features of the illness.

Thirdly, normal controls did not take the antidepressant, and so we do not know whether the cytokine levels would have dropped in these patients after the administration of fluoxetine. There are also some questions that has not being clarified clearly. For example, did depression induced higher cytokine levels or did higher cytokines induce depression? In addition, a placebo-controlled design would be better to show if antidepressants will decrease cytokine levels in controls. Moreover, it would be better to include the anti-inflammatory factors in future research.

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Abbreviations

MDD, Major depressive disorder; **HPA,** hypothalamic-pituitary-adrenal; **MCP-1,** monocyte chemoattractant protein 1; **SDF-1,** stromal cell derived factor-1; MIP-1α, macrophage-inflammatory protein-1α; **RANTES,** regulated upon activation, normal T cell expressed and secreted; **5-HT,** 5-hydroxytryptamine; **IL-6,** interleukin-6; **SSRI,** Selective serotonin reuptake inhibitors; **HDRS,** Hamilton depression rating scale; **ESR,** erythrocyte sedimentation rates; **ELISA,** enzyme-linked immunosorbant assay; **TNF,** tumor necrosis factor; **TRP,** tryptophan; **LTP,** long-term potentiation; **NMDA,** N-methyl d-aspartate.

REFERENCES

Alesci S, Martinez PE, Kelkar S, Ilias I, Ronsaville DS, Listwak SJ, Ayala AR, Licinio J, Gold HK, Kling MA, Chrousos GP, Gold PW (2005). Major depression is associated with significant diurnal elevations in plasma interleukin-6 levels, a shift of its circadian rhythm and loss of physiological complexity in its secretion: clinical implications. J. Clin. Endocrinol. Metab. 90: 2522-2530.

Bosker FJ, Westerink BH, Cremers TI, Gerrits M, van der Hart MG, Kuipers SD, van der Pompe G, ter Horst GJ, den Boer JA, Korf J (2004). Future antidepressants: what is in the pipeline and what is missing? CNS Drugs, 18: 705-732.

Brown RR, Ozaki Y, Datta SP, Borden EC, Sondel PM, Malone DG (1991). Implications of interferon-induced tryptophan catabolism in cancer, auto-immune diseases and AIDS. Adv. Exp. Med. Biol. 294: 425-435.

Byrne SE, Rothschild AJ (1998). Loss of antidepressant efficacy during maintenance therapy: possible mechanisms and treatments. J. Clin. Psychiatry, 59:279-288.

Connor TJ, Leonard BE (1998). Depression, stress and immunological activation: the role of cytokines in depressive disorders. Life Sci. 62: 583-606.

Curran B, O'Connor JJ (2001). The pro-inflammatory cytokine interleukin-18 impairs long-term potentiation and NMDA receptor-mediated transmission in the rat hippocampus *in vitro*. Neuroscience, 108: 83-90.

Plasma interleukin-18 levels in patients with psychiatric disorders. J. Immunother. 25: 68-71.

Lehto SM, Niskanen L, Herzig KH, Tolmunen T, Huotari A, Viinamäki H, Koivumaa-Honkanen H, Honkalampi K, Ruotsalainen H, Hintikka J (2010). Serum chemokine levels in major depressive disorder. Psychoneuroendocrinology, 5: 226-232.

Lekakis J, Ikonomidis I, Papoutsi Z, Moutsatsou P, Nikolaou M, Parissis J, Kremastinos DT (2010). Selective serotonin re-uptake inhibitors decrease the cytokine-induced endothelial adhesion molecule expression, the endothelial adhesiveness to monocytes and the circulating levels of vascular adhesion molecules. Int. J. Cardiol. 139: 150-158.

Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ (2006). Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet, 367: 1747-1757.

Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E (1997). Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. Cytokine, 9: 853-858.

Maes M, Meltzer HY, Bosmans E, Bergmans R, Vandoolaeghe E, Ranjan R, Desnyder R (1995). Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. J. Affect Disord. 34: 301-309.

Maes M, Meltzer HY, Buckley P, Bosmans E (1995). Plasma-soluble interleukin-2 and transferrin receptor in schizophrenia and major depression. Eur. Arch. Psychiatry Clin. Neurosci. 244: 325-329.

Merendino RA, Di Pasquale G, De Luca F, Di Pasquale L, Ferlazzo E, Martino G, Palumbo MC, Morabito F, Gangemi S (2004). Involvement of fractalkine and macrophage inflammatory protein-1 alpha in moderate-severe depression. Mediators Inflamm. 13: 205-207.

Merendino RA, Di Rosa AE, Di Pasquale G, Minciullo PL, Mangraviti C, Costantino A, Ruello A, Gangemi S (2002). Interleukin-18 and CD30 serum levels in patients with moderate-severe depression. Mediators Inflamm. 11: 265-267.

Muller T, Dürk T, Blumenthal B, Grimm M, Cicko S, Panther E, Sorichter S, Herouy Y, Di Virgilio F, Ferrari D, Norgauer J, Idzko M (2009). 5-hydroxytryptamine modulates migration, cytokine and chemokine release and T-cell priming capacity of dendritic cells *in vitro* and *in vivo*. PLoS One, 4: e6453.

Nelson JC (2003). Managing treatment-resistant major depression. J. Clin. Psychiatry, 64: 5-12.

Piletz JE, Halaris A, Iqbal O, Hoppensteadt D, Fareed J, Zhu H, Sinacore J, DevaneCL(2009). Pro-inflammatory biomakers in depression: treatment with venlafaxine. World J. Biol Psychiatry, 10: 313-323.

Shini S, Kaiser P (2009). Effects of stress, mimicked by administration of corticosterone in drinking water, on the expression of chicken cytokine and chemokine genes in lymphocytes. Stress, 12: 388-399.

Sutcigi L, Oktenli C, Musabak U, Bozkurt A, Cansever A, Uzun O, Sanisoglu SY, Yesilova Z, Ozmenler N, Ozsahin A, Sengul A (2007). Pro- and anti-inflammatory cytokine balance in major depression: effect of sertraline therapy. Clin. Dev. Immunol. 2007: 76396.

Taler M, Bar M, Korob I, Lomnitski L, Baharav E, Grunbaum-Novak N, Weizman A, Gil-Ad I (2008). Evidence for an inhibitory immunomodulatory effect of selected antidepressants on rat splenocytes: possible relevance to depression and hyperactive-immune disorders. Int. Immunopharmacol. 8: 526-533.

Wang J, Dunn AJ (1999). The role of interleukin-6 in the activation of the hypothalamo-pituitary-adrenocortical axis and brain indoleamines by endotoxin and interleukin-1 beta. Brain Res. 815: 337-348.

Yasui T, Yamada M, Uemura H, Ueno S, Numata S, Ohmori T, Tsuchiya N, Noguchi M, Yuzurihara M, Kase Y, Irahara M (2009). Changes in circulating cytokine levels in midlife women with psychological symptoms with selective serotonin reuptake inhibitor and Japanese traditional medicine. Maturitas, 62: 146-152.

Zhu J, Wei X, Liu J, Hu Y, Xu J (2009). Interaction of glia activation and neurotransmission in hippocampus of neuropathic rats treated with mirtazapine. Exp. Clin. Psychopharmacol. 17: 198-203.